

Clinically Diagnosed Diamond-Blackfan Anemia with Negative Whole Exome Sequencing in an Infant with Crossed Renal Ectopia: A Case Report

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Case Report

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Abstract

Background

Diamond-Blackfan anemia (DBA) is a rare congenital bone marrow failure syndrome presenting with early-onset anemia and reticulocytopenia. Approximately 30–40% of clinically typical cases remain genetically unresolved on exome sequencing, and a diagnosis can still be established on clinical and morphological grounds when the phenotype is characteristic.

Case presentation:

We report an 80-day-old female infant of non-consanguineous parentage who presented with pallor, poor feeding, and severe transfusion-dependent anemia with reticulocytopenia since birth. Bone marrow examination showed a normocellular marrow with marked erythroid paucity and an elevated myeloid-to-erythroid ratio, with adequate megakaryocytes and no fibrosis or malignancy. Whole exome sequencing targeting RPS19, GATA1, and TSR2 was non-diagnostic, revealing only a heterozygous variant of uncertain significance in KMT2D. Contrast-enhanced CT urography incidentally identified a non-fused crossed ectopic left kidney. Alternative nutritional, infectious, and inherited marrow failure causes were excluded, and a clinical diagnosis of DBA was made. The infant was managed with packed red blood cell transfusion and supportive care.

Conclusion

This case illustrates that DBA can be diagnosed on clinical and morphological grounds despite a negative exome sequencing result, and describes non-fused crossed renal ectopia as an anomaly not previously reported in association with DBA, broadening the recognized spectrum of congenital anomalies in this disorder.

Introduction

Diamond-Blackfan anemia (DBA) is a rare inherited bone marrow failure disorder characterized by failure of red blood cell production. It usually presents during the first year of life with anemia and a low reticulocyte count (1, 2). DBA affects approximately 7 per million live births and occurs due to defects in ribosome production, which make developing red blood cell precursors more prone to cell death (3). In addition to anemia, affected individuals may have growth impairment, congenital abnormalities, and an increased risk of malignancies (2).

DBA most commonly results from reduced function of ribosomal proteins (ribosomal protein haploinsufficiency). Mutations in the RPS19 gene were the first identified genetic cause and remain the most common, accounting for approximately one-quarter of cases(4). Although DBA is usually inherited

in an autosomal dominant manner, no causative genetic variant is identified in about 30–40% of clinically typical cases(5).

Diagnosis of DBA is based on early-onset anemia, reticulocytopenia, and reduced erythroid precursors in an otherwise normocellular bone marrow, supported by findings such as elevated erythrocyte adenosine deaminase (eADA) activity, increased fetal hemoglobin, congenital anomalies, and genetic findings when available (1). The 2024 international consensus statement emphasizes that a diagnosis can be established on clinical and morphological grounds when the phenotype is characteristic, even in the absence of an identifiable pathogenic variant (6). Elevated eADA activity is a useful supportive marker but lacks specificity and may be unreliable after transfusion.

Congenital malformations occur in approximately 30–50% of patients with DBA and commonly involve the craniofacial structures, upper limbs, heart, and genitourinary system (1, 2). Crossed renal ectopia, characterized by migration of one kidney across the midline with ureteral insertion on the normal side, is a rare congenital anomaly that is usually detected incidentally; the non-fused form is less common than the fused form (7). To our knowledge, crossed renal ectopia has not previously been reported in association with DBA. We report an infant with early-onset, transfusion-dependent anemia and non-fused crossed renal ectopia, in whom WES was non-diagnostic but DBA was diagnosed based on clinical and morphological findings.

Case History/Examination

An 80-day-old female infant presented to the pediatric department with pallor and poor feeding. Generalized pallor had been noted since birth, and she had a two-month history of vomiting after feeds, occurring once daily. She was the second child born to non-consanguineous parents, a singleton, term, post-dated infant delivered at 41 weeks of gestation by emergency lower segment cesarean section for fetal distress. She cried immediately after birth, with a birth weight of 2600 g. Antenatal ultrasonography had shown non-visualization of the left kidney. Her elder sibling, a 2-year-old male, was healthy, and there was no family history of blood transfusion, recurrent abortion, or sibling death.

In the immediate neonatal period, she was admitted to the neonatal intensive care unit for meconium aspiration syndrome and required mechanical ventilation for three days. Laboratory evaluation on the first day of life revealed severe anemia (hemoglobin 4.5 g/dL, RBC count 1.09 million/cumm, TLC 9100/cumm with neutrophils 29% and lymphocytes 66%, platelet count 134,000/cumm), with a normal echocardiogram. She received packed red blood cell (PRBC) transfusion with supportive care and was discharged.

At 80 days of age, she was re-evaluated for persistent pallor and decreased feeding, prompting the present admission.

Differential Diagnosis, Investigations, and Treatment

Investigations

Complete blood count showed severe anemia (hemoglobin 2.0 g/dL, RBC count 0.70 million/cumm, hematocrit 6.4%, MCV 91.5 fL, TLC 4200/cumm with neutrophils 10%, lymphocytes 85%, monocytes 5%, platelet count 181,000/cumm, absolute neutrophil count 420/cumm). Reticulocyte count was 1.5% (corrected 0.2%). Peripheral blood smear showed anisocytosis with normocytic, normochromic red cells, normal white cell morphology and maturation without atypical cells or hemoparasites, and adequate platelets with normal morphology.

Workup for nutritional, metabolic, and infectious causes showed serum iron 167.2 µg/dL, TIBC 312 µg/dL, transferrin saturation 53.6%, ferritin 1000 ng/mL, vitamin B12 599 pg/mL, and folic acid > 20 ng/mL. Thyroid function was normal (FT3 5.96 pmol/L, FT4 17.6 pmol/L, TSH 3.749 µIU/mL). Arterial blood gas and coagulation profile were normal. TORCH screening showed no active congenital infection (negative Toxoplasma, CMV, HSV; rubella IgG positive, IgM negative).

Renal function was normal. Liver function tests showed mild transaminase elevation (SGOT 80 U/L, SGPT 47 U/L) with reduced albumin (3.26 g/dL) and total protein (4.89 g/dL). Contrast-enhanced CT intravenous urography, performed for the antenatal renal finding, confirmed a non-fused crossed ectopic left kidney with an empty left renal fossa, preserved morphology, and normal contrast excretion in both kidneys without obstruction, calculus, mass, or pelvicalyceal dilatation (Fig. 1).

Ophthalmological examination was normal; audiological evaluation revealed mild bilateral hearing abnormality, with follow-up advised after three months. Forearm and hand radiography and echocardiography were normal.

Bone marrow aspiration and biopsy showed normocellular marrow (~ 90% cellularity) with erythroid paucity (erythroid precursors 9% of nucleated cells, myeloid-to-erythroid ratio 7.78:1), active myelopoiesis through all stages with relative eosinophil prominence, adequate megakaryocytes with normal morphology, and no fibrosis, granuloma, or malignancy.

Nutritional deficiencies, congenital infections, and transient erythroblastopenia of childhood were considered and excluded on clinical, biochemical, and morphological grounds. Other inherited bone marrow failure syndromes, Fanconi anemia and Shwachman-Diamond syndrome were also considered but felt less likely given the selective erythroid involvement, with active myelopoiesis, adequate megakaryocytes, and no persistent pancytopenia, in contrast to the multilineage abnormalities typical of those conditions.

Whole exome sequencing targeting RPS19, GATA1, and TSR2 identified no pathogenic or likely pathogenic variant. A heterozygous variant of uncertain significance was detected in KMT2D (c.3701G > T, p.Gly1234Val; NM_003482.4; sequencing depth 92×, alternate allele fraction 62%).

PRBC transfusion was administered with supportive care. eADA activity and fetal hemoglobin estimation could not be performed due to recent transfusion.

Conclusion and Results (Outcome and Follow-up)

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Following transfusion, repeat complete blood count showed hemoglobin improvement to 12.6 g/dL, TLC 6740/cumm (neutrophils 22%, lymphocytes 56%, monocytes 18%, eosinophils 4%), RBC count 3.99 million/ μ L, and platelet count 110,000/cumm.

Based on early-onset severe anemia, reticulocytopenia, erythroid paucity on bone marrow examination, exclusion of alternative causes, and a compatible clinical phenotype despite negative genetic testing, a clinical diagnosis of Diamond-Blackfan anemia was made. The KMT2D variant of uncertain significance was not attributed to the phenotype in the absence of supportive functional or segregation evidence and will require reassessment on longitudinal follow-up.

Planned follow-up includes audiological reassessment at three months for the mild bilateral hearing abnormality, surveillance of the non-fused crossed renal ectopia, structured monitoring of iron status (given the elevated ferritin) with timely chelation if needed, and longitudinal surveillance for the recognized predisposition to bone marrow failure and hematological/solid malignancies associated with DBA.

Discussion

Our patient fulfilled the clinical diagnostic criteria for DBA, presenting with severe anemia in early infancy, profound reticulocytopenia (corrected reticulocyte count 0.2%), and normocellular bone marrow with marked erythroid paucity and an increased myeloid-to-erythroid ratio. Alternative nutritional, metabolic, infectious, and other acquired causes of red cell failure were excluded (6). These findings were consistent with the classical DBA phenotype and supported the diagnosis despite the absence of an identifiable pathogenic variant.

An atypical feature in our patient was the normocytic, normochromic red cell morphology, whereas macrocytosis is commonly described in DBA. However, macrocytosis is not universal and may be absent in early infancy or influenced by factors such as prior transfusion; therefore, its absence does not exclude the diagnosis (1, 2). The recognized phenotypic variability of DBA further supports this observation (2).

Diagnostic evaluation was further limited by the inability to perform eADA activity and fetal hemoglobin estimation because of recent transfusion. Although elevated eADA is a useful supportive marker for DBA, it lacks specificity and may be influenced by transfused donor erythrocytes (8, 9). Therefore,

diagnosis in our patient relied primarily on the characteristic clinical presentation and bone marrow findings.

A careful exclusion of alternative causes of anemia was central to the diagnostic evaluation. Acquired causes, including nutritional deficiencies, congenital infections, and transient erythroblastopenia of childhood, were excluded based on clinical, biochemical, and morphological findings (3). Distinguishing DBA from other inherited bone marrow failure syndromes, such as Fanconi anemia and Shwachman-Diamond syndrome, was also important, as these conditions typically involve multilineage hematopoietic abnormalities and progressive cytopenias. In contrast, our patient demonstrated selective erythroid involvement, with active myelopoiesis showing maturation through all stages, adequate megakaryocytes with normal morphology, and no persistent evidence of pancytopenia. This erythroid-restricted marrow abnormality in an otherwise normocellular marrow, together with very early-onset severe anemia and reticulocytopenia, strongly supported a diagnosis of DBA over other inherited or acquired marrow failure disorders.

The negative WES result in our patient does not exclude DBA, as a pathogenic variant remains unidentified in approximately 30–40% of clinically typical cases(5, 10). Exome sequencing has inherent limitations, including inability to reliably detect non-coding variants, deep intronic variants, and certain structural or copy-number abnormalities that may contribute to disease(11, 12). Therefore, a non-diagnostic WES result should be interpreted in the context of the clinical phenotype rather than considered evidence against the diagnosis.

In patients with a compatible DBA phenotype but negative initial genetic testing, additional approaches such as periodic reanalysis of sequencing data may help identify previously unrecognized pathogenic variants as genomic databases and bioinformatic tools continue to improve.18–20 Such reinterpretation should be performed in the context of detailed clinical findings and multidisciplinary evaluation rather than relying on sequencing results alone(13, 14).

Whole genome sequencing may provide additional diagnostic yield in patients with DBA who remain genetically unresolved after exome sequencing, as it can detect variants in genomic regions not captured by conventional approaches (15, 16). In our patient, future whole genome sequencing or periodic reanalysis of existing sequencing data may help identify a molecular diagnosis(15, 17). Sequencing also identified a heterozygous variant of uncertain significance in the KMT2D gene; however, in the absence of supportive functional or segregation evidence, this finding could not be attributed to the patient's phenotype and did not alter the clinical diagnosis. Its significance will require reassessment during longitudinal follow-up.

The finding of a non-fused crossed ectopic kidney is of particular interest in this case. Crossed renal ectopia is a rare congenital anomaly that is often asymptomatic and detected incidentally, as in our patient, where it was suspected antenatally and confirmed by contrast-enhanced computed tomographic urography; the non-fused subtype is less common than the fused form(7). Genitourinary abnormalities are recognized among the congenital manifestations of DBA, and their presence may provide additional

phenotypic support when the hematological features are compatible. Although congenital anomalies are well described in DBA and may occasionally be the presenting feature (18), we are not aware of any previous report linking DBA with crossed renal ectopia. While this single observation cannot establish causality, the coexistence of these findings expands the spectrum of associated anomalies and warrants further recognition.

From a management perspective, transfusion support remains the mainstay for infants who present with severe, symptomatic anemia, as in our patient, whereas a trial of corticosteroids is generally deferred in early infancy because of the risks associated with steroid exposure at this age (19). Chronic transfusion carries a predictable burden of iron overload, and the elevated ferritin observed in our patient reinforces the need for structured monitoring of iron status and timely chelation. Longitudinal surveillance is essential given the recognized predisposition to bone marrow failure and to hematological and solid malignancies, and follow-up should also encompass the associated renal anomaly and the previously noted mild hearing abnormality(20).

Conclusion

This case highlights that a diagnosis of Diamond-Blackfan anemia can be established on clinical and morphological grounds when the phenotype is characteristic, even in the absence of a pathogenic variant on whole exome sequencing. The presence of non-fused crossed renal ectopia, an association not previously reported in DBA, adds to the expanding spectrum of congenital anomalies observed in this disorder and emphasizes the importance of recognizing extra-hematological manifestations. Continued clinical surveillance, along with future genomic reanalysis or whole genome sequencing, may help identify the underlying molecular cause in genetically unresolved cases.

Abbreviations

DBA
Diamond-Blackfan anemia
WES
Whole exome sequencing
eADA
Erythrocyte adenosine deaminase
PRBC
Packed red blood cell
RBC
Red blood cell
TLC
Total leukocyte count
MCV
Mean corpuscular volume

TIBC
Total iron-binding capacity
ANC
Absolute neutrophil count
CT
Computed tomography
SGOT
Serum glutamic-oxaloacetic transaminase
SGPT
Serum glutamic-pyruvic transaminase
FT3
Free triiodothyronine
FT4
Free thyroxine
TSH
Thyroid-stimulating hormone
IgG/IgM
Immunoglobulin G/M
NICU
Neonatal intensive care unit; RPS19/GATA1/TSR2/KMT2D:Gene names as discussed in text

Declarations

Consent:

Written informed consent for publication of this case report and accompanying images was obtained from the patient's legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-chief of this journal on request.

Ethical approval:

Not required.

Availability of data and materials:

The dataset(s) supporting the conclusions of this article is(are) included within the article.

Research registration number:

Not applicable

Note: no patient and author details are included in the figure.

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Authors' contributions:

NK managed the patient clinically, supervised the diagnostic workup, and critically reviewed the manuscript. SKJ contributed to literature review and drafting of the manuscript. SP conceived the case report, drafted the manuscript, coordinated revisions, and served as corresponding author. All authors read and approved the final manuscript.

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Figures

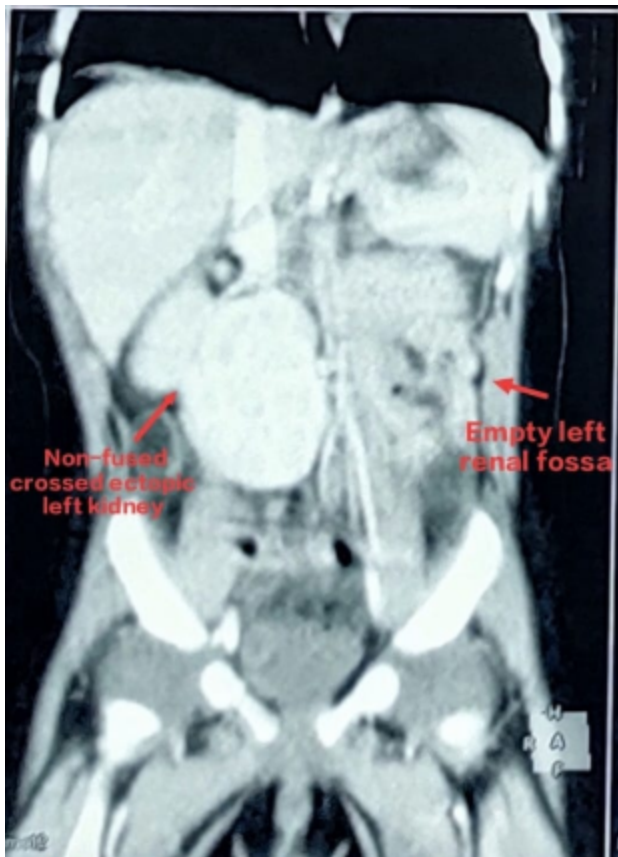


Figure 1

Contrast-enhanced CT urography demonstrating non-fused crossed left renal ectopia with preserved renal morphology and contrast excretion.