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Role of Next-Generation Sequencing in Deciphering Congenital Hemolytic Anemia: A Case of Multiple Mutations Leading to Dual Congenital Hemolytic Anemia

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Abstract

Before the widespread availability of next-generation sequencing (NGS), the diagnosis of hereditary spherocytosis (HS) and dehydrated hereditary stomatocytosis (DHS) was predominantly clinical. Here, we describe a patient with both HS and DHS who was initially treated for HS until NGS revealed that she had concomitant HS and DHS, leading to a pivot in clinical management. A 21-year-old female patient presented for evaluation of hemolytic anemia during pregnancy. The patient was clinically diagnosed with HS and treated with as-needed transfusions, with a plan for splenectomy. NGS revealed both HS and DHS. Thus, splenectomy was canceled, and aspirin was started. While treatments for HS and DHS differ greatly, in this case, where the patient has both, it is critical that treatment for DHS is prioritized because of the high risk of thromboembolic events following splenectomy. Early genetic evaluation is critical to provide an accurate diagnosis and to guide appropriate management.

Categories: Hematology

Keywords: anemia, congenital hemolytic anemia, dehydrated hereditary stomatocytosis, hereditary spherocytosis, next-generation sequencing

Introduction

Hereditary spherocytosis (HS) and hereditary elliptocytosis are characterized by membrane structural defects, while dysregulated membrane permeability is the hallmark of dehydrated hereditary stomatocytosis (DHS). Here, we focus our discussion on HS and DHS.

HS results from defects in genes encoding the red blood cell (RBC) membrane skeleton [1]. It is characterized by the presence of spherocytes in peripheral blood smears, which are small, dense spherical RBCs that lack the central pallor seen in normal RBCs [2]. Ankyrin and spectrin are the two most frequently affected membrane proteins, with mutations in SPTA1 (alpha-spectrin) being the most common [3]. HS has both autosomal dominant and recessive inheritance [4]. These defects render RBCs less resistant to stress and rupture. The abnormal RBCs are engulfed by phagocytes within the spleen, resulting in chronic hemolytic anemia. The incidence rate generally ranges from one in 2,000 to 5,000 people [5].

DHS is an autosomal dominant congenital hemolytic anemia characterized by the presence of stomatocytes, which are abnormal RBCs that exhibit a unique mouth-like shape [6]. Hemolytic anemia is characterized by premature destruction of RBCs that can be immune-related or immune system-independent. HS and DHS are both non-immune-mediated structural maladies. The prevalence of DHS is approximately one in 8,000 to 50,000 individuals [7]. DHS is typically caused by a gain-of-function mutation in PIEZO1 [8]. This results in increased permeability to sodium and calcium cations, leading to the formation of stomatocytes. DHS can often be misdiagnosed as other hemolytic disorders due to overlapping clinical features and laboratory findings [9].

Significant advances have been made in the diagnosis and clinical management of inherited red cell membrane disorders that result in hemolytic anemia. Before the widespread availability of next-generation sequencing (NGS), the diagnosis of HS and DHS was predominantly clinical. Diagnosis was made through an amalgamation of symptomatology, family history, characteristic peripheral smear findings of spherocytes and stomatocytes, and specialized laboratory tests such as osmotic fragility or eosin-5'-maleimide (EMA) binding assays. Molecular diagnosis of inherited red cell membrane disorders, used for rare presentations, was done with Sanger sequencing (to identify single-nucleotide variants and small deletions), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) (to detect known mutations), multiplex ligation-dependent probe amplification (MLPA) (to detect large, copy number variations), and single-strand conformation polymorphism (SSCP) (to detect unknown mutations) [10]. Diagnostic ease has boomed with NGS, which has helped with the rapid and comprehensive identification of pathogenic variants across multiple RBC genes [11]. NGS is a high-throughput method of sequencing DNA that aligns millions of

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short DNA sequences to build full libraries, allowing for characterization of genetic variants, including single-nucleotide polymorphisms, insertions, deletions, copy number variants, and structural variants. NGS is now commonly used in cancer genomics and genetic counseling, as well as the diagnosis of rare genetic disorders, as in this case.

NGS today is generally more cost-effective in cases where multiple genes or unknown mutations are being identified simultaneously compared to historic methods like Sanger sequencing or PCR. While PCR and Sanger are less expensive for a single, specific target, NGS provides a massively lower cost per base pair, saving time and money in complex diagnostic scenarios.

Management for HS and DHS also differs. According to the British Committee for Standards in Hematology guidelines, splenectomy is recommended for patients with moderate-to-severe HS who experience symptomatic anemia, growth delay, or frequent transfusion requirements, as it significantly reduces hemolysis and improves anemia [10]. Folic acid supplementation is recommended in severe and moderate HS to sustain erythropoiesis in the setting of chronic hemolysis [10].

In DHS, splenectomy is contraindicated because it is associated with a significantly increased risk of thromboembolic events [12]. A minority of patients require regular transfusions. Iron overload happens frequently and needs to be monitored in patients regardless of whether or not they get transfusions in order to avoid organ failure. Patients with evidence of iron overload can be treated with chelation or therapeutic phlebotomy.

Management of a patient with a diagnosis of DHS in the event of pregnancy has additional considerations, as fetal complications have been observed. DHS has been associated with fetal ascites and hydrops, where there is excessive fluid accumulation in the abdomen of the fetus, which can lead to organ failure [13]. In utero, exchange transfusions or drainage of excess amniotic and ascites fluid during pregnancy may be necessary to prevent demise.

For patients diagnosed with HS perinatally, there are increased risks of fetal anemia, similar to maternal [14]. Increased frequency of fetal growth monitoring may be needed, and there is an elevated risk of postpartum hemorrhage.

Multi-locus inheritance involving variants associated with both HS and DHS has been previously described, most notably in a large case series by Andolfo et al., which demonstrated that combined genotypes are not uncommon when comprehensive NGS panels are applied [15]. However, detailed descriptions of how such findings alter immediate clinical decision-making, particularly in situations such as pregnancy and consideration of splenectomy, remain limited. We fill this gap in the literature by describing the assessments and interventions provided in the case of a pregnant 21-year-old female patient presenting for evaluation of hemolytic anemia who was found to have both HS and DHS.

Case Presentation

A 21-year-old African American female patient presented with recurrent symptomatic anemia that required transfusion during pregnancy. A timeline of events is illustrated in Figure 1.

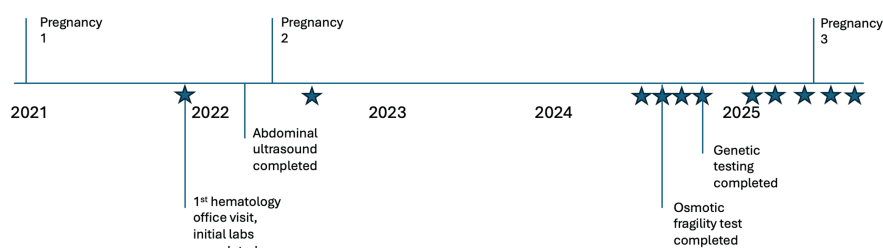


FIGURE 1: A timeline of events including pregnancies, hematology office visits, and key workup.

Blue stars represent individual office visits. The patient experienced some barriers to follow-up, leading to a gap in care between 2022 and 2024 and a delay in diagnosis.

The patient had a positive family history of venous thromboembolism in her mother at the age of 50 years, which led to a stroke in the setting of a patent foramen ovale. Workup revealed evidence of hemolysis with

undetectable haptoglobin and elevated lactate dehydrogenase (LDH) and bilirubin levels with spherocytes and polychromasia on peripheral smears (Figure 2).

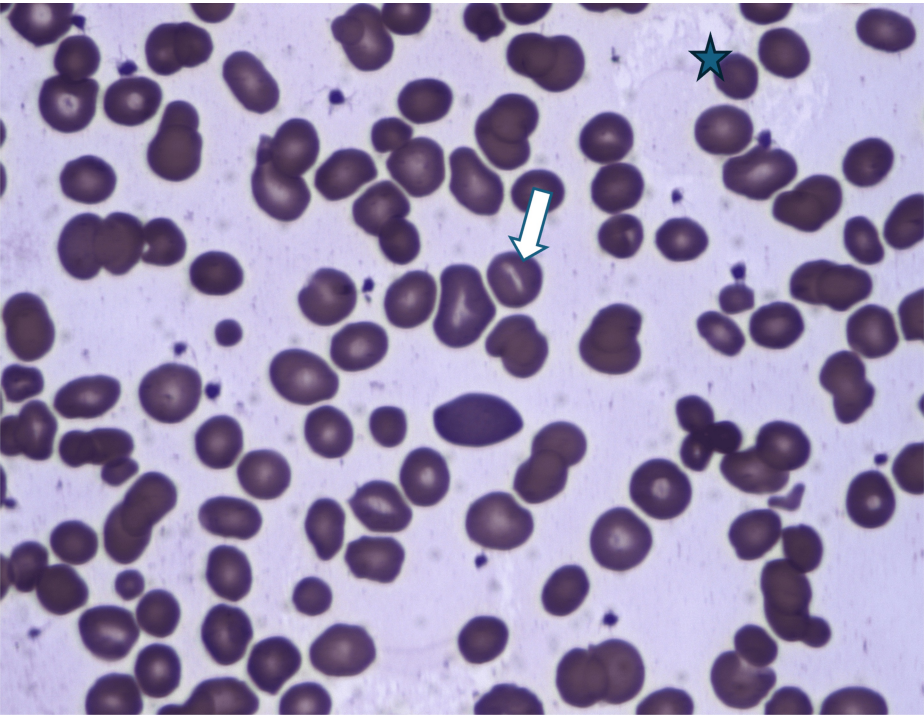


FIGURE 2: Patient's peripheral blood smear.

Peripheral blood smear (Wright-Giemsa stain) showing a stomatocyte, which is identified by the white arrow, characterized by a uniconcave morphology with a distinctive slit-like or mouth-shaped central pallor. A spherocyte is indicated by the blue star, appearing as a small, densely stained, hyperchromatic erythrocyte with complete loss of central pallor, reflecting a reduced surface-area-to-volume ratio. The background population shows prominent anisocytosis, with variation in red cell size evident across the field.

Osmotic fragility showed increased RBC fragility in some cells and decreased fragility in others, which is consistent with HS. RBC enzyme levels, including glucose-6-phosphate dehydrogenase (G6PD), were within normal limits. The direct antiglobulin test result was negative, and anti-Kell antibodies were detected. Pertinent laboratory values are illustrated in Table 1.

Lab	Lab values	Reference range	Comments
Leukocyte (x10 ³ /μL)	9.7	3.4-10.8	
Erythrocyte count (x10 ⁶ /μL)	2.97 (low)	3.77-5.28	Schistocytes present, polychromasia present, elliptocytes present, spherocytes present
Hemoglobin level (g/dL)	8.0 (low)	11.1-15.9	
Hematocrit (%)	24.4 (low)	34.0-46.6	
MCV (fL)	82	79-97	
MCH (pg)	26.9	26.6-33.0	
MCHC (g/dL)	32.8	31.5-35.7	
RDW (%)	24.6 (high)	11.7-15.4	
Platelet			

(x10 ³ /μL)	392	150-450	
Iron (mcg/dL)	77	40.0-170.0	
Transferrin level (mg/dL)	174 (low)	200-330	
Transferrin saturation level (%)	31		
Iron binding capacity, total, calculated (mcg/dL)	248.8 (low)	250.0-450.0	
Ferritin level (ng/mL)	481 (high)	15-150	
ABO & RH	O negative		
ABSC-SP3	Positive		
Antibody identification	Anti-Kell		
Reticulocytes (%)	7.0 (high)	0.5-2.0	
Reticulocyte, absolute (%)	4.3 (high)	0.2-2.6	
G6PD	381	155-399	
Reticulocytes and immature fractions (%)	35.2 (high)	3.0-15.9	
Reticulocyte hemoglobin equivalent (pg)	28.9	28.2-36.6	
Total bilirubin (mg/dL)	2.0 (high)	0.2-1.3	
Haptoglobin (mg/dL)	<20 (low)	30-200	
Lactate dehydrogenase level (U/L)	702 (high)	300-600	
Hgb F (%)	1.6	0.0-2.0	Normal hemoglobin present; no hemoglobin variant or thalassemia was observed
Hgb A (%)	96.1 (low)	96.4-98.8	
Hgb A2 (%)	2.3	1.8-3.2	
Hgb S (%)	0	0	
Vitamin B12 (pg/mL)	342	232-1,245	
Folate (ng/mL)	7.2	>3.0	
Prothrombin time (seconds)	14.1	12.3-15.0	
INR	1.11		
Activated partial thromboplastin	34	23.8-37.6	

time (seconds)			
Fibrinogen level (mg/dL)	357	200-500	
D-dimer (µg/mL FEq units)	0.31	0.20-0.38	
Osmotic fragility, RBC			Patient RBCs show increased and decreased osmotic fragility. Dimorphic population of RBCs with a subset showing increased osmotic fragility and a subset showing decreased osmotic fragility. These findings are non-specific but have been described in thalassemia or can be seen after transfusion

TABLE 1: Initial presenting labs.

The most clinically significant laboratory abnormalities are highlighted here. Hemolysis was confirmed by low haptoglobin, markedly elevated LDH (702 U/L), elevated total bilirubin (2.0 mg/dL), and a reticulocyte percentage of 7.0%. Anemia was moderate with Hgb of 8.0 g/dL and hematocrit of 24.4%. Elevated RDW (24.6%) reflected significant red cell size heterogeneity consistent with a mixed red cell population. Ferritin was elevated at 481 ng/mL despite normal serum iron, raising concern for iron sequestration in the setting of chronic hemolysis.

ABSC-SP3: antibody screen for specificity protein 3; G6PD: glucose-6-phosphate dehydrogenase; Hgb: hemoglobin; INR: international normalized ratio; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; RBC: red blood cell; RDW: red cell distribution width; RH: Rhesus; LDH: lactate dehydrogenase

Abdominal ultrasound revealed mild splenomegaly (Figure 3).

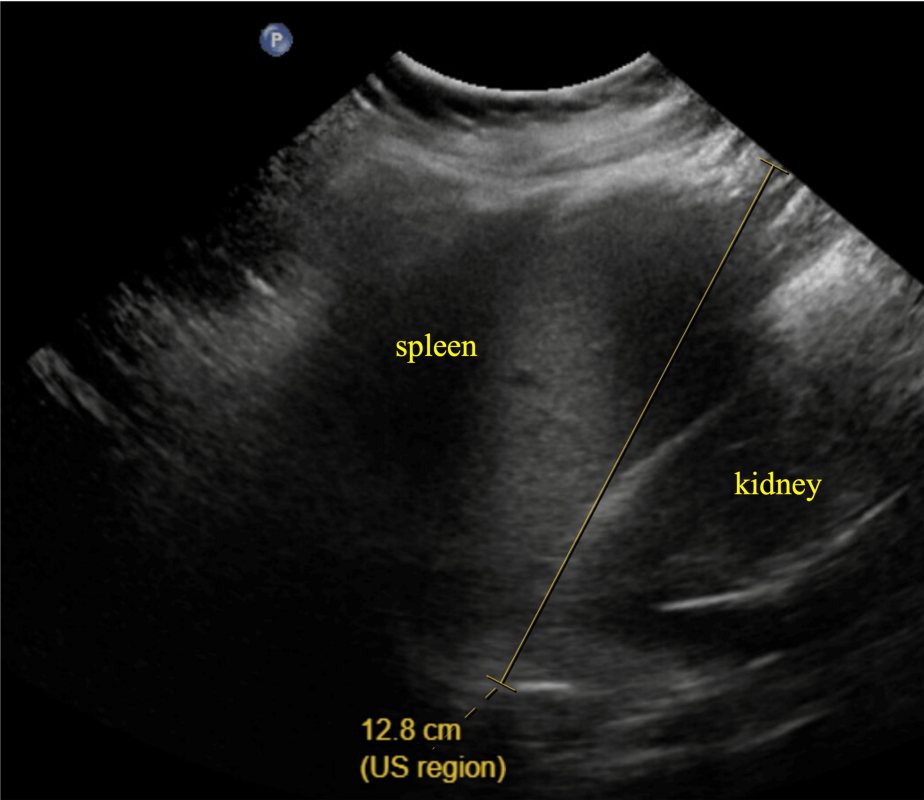


FIGURE 3: Abdominal ultrasound of the left upper quadrant showing mild splenomegaly with spleen measuring 12.8 cm.

During that time, the patient’s anemia was optimized prior to delivery. It was recommended that she receive a transfusion on admission to labor and delivery. Briefly, on admission, the patient’s hemoglobin was 7.7. The patient received 1 U packed red blood cell (PRBC), then had a vaginal normal spontaneous vaginal delivery at 37 weeks. Her hemoglobin dropped to 7.2, she was transfused another unit, and her hemoglobin responded appropriately and increased to 8.5. The patient gave birth to a healthy girl. Splenectomy was planned initially. However, genetic testing revealed multi-locus inheritance of mutations in SPTA1 and one mutation in PIEZO1. Specifically, the patient was found to have SPTA1 (DNA: c.83G>A) (pathogenic variant),

SPTA1 (DNA: c.4339-99C>T) (pathogenic alpha-LEPRA allele), SPTA1 (DNA: c.5572C>G;6521-12C>T) (benign alpha-LELY allele), PIEZO1 (DNA: c.328C>G) (pathogenic variant), and SLCO1B1 (DNA: c.481 +1G>T) (pathogenic variant). Genetic testing was performed using the Revvity AnyPanel hereditary anemia NGS platform (Revvity Signals Software, Waltham, MA, USA) with deletion and duplication analysis. Given these genetic findings, splenectomy was canceled. When the patient became pregnant again, transfusions were provided as needed for hemoglobin < 7; she continued folic acid supplementation and delivered a healthy baby. Subsequently, with the third pregnancy, the patient was again provided with as-needed transfusions for hemoglobin < 7, and the patient delivered a healthy baby. Of note, the patient required more transfusions with each subsequent pregnancy. At this time, with the dual diagnosis of HS and DHS based on genetic findings, the patient was counseled to avoid iron supplementation due to the risk of iron overload and to take aspirin to reduce the risk of thrombosis.

Although HS was initially suspected, genetic testing allowed for a more specific diagnosis of HS and DHS to be provided, allowing for tailored management of the patient in this case to avoid iron over-supplementation and manage the increased risk of thrombosis. Genetic testing analysis and results informed the cancellation of the splenectomy, reiterating the importance of early genetic testing in patients with hemolytic anemia who clinically appear to have HS. Notably, there were delays in the diagnostic process due to issues with specimen processing, requiring the patient to return multiple times for blood draws and irregular follow-up when the patient was experiencing personal difficulties.

Discussion

HS and hereditary elliptocytosis are characterized by membrane structural defects, while dysregulated membrane permeability is the hallmark of DHS. An overview of the various types of congenital hemolytic anemia is presented in Table 2.

Types of congenital hemolytic anemia	Racial predominance in the US	Incidence in the US	Inheritance pattern	Associated mutations	Treatment pattern*
Sickle cell disease	93.4% Black, 4.8% Hispanic, 1.8% White	2,000 per year	AR	Point mutations in the beta globin gene	Hydroxyurea ± L-glutamine, crizanlizumab, or voxelotor; HSCT
Alpha thalassemia (AT)	Most common in people of African, Southeast Asian, Mediterranean, and Middle Eastern descent	1 in 10,000 newborns	AR	Gene deletions in alpha globin genes	Silent carrier: no treatment; AT trait: avoid iron; HbH: blood transfusions as needed; AT major: aggressive blood transfusion, iron chelation
Beta thalassemia	More common in Mediterranean, Middle Eastern, South Asian, and African populations	3,665 per year	AR	Mutations that result in decreased or absent beta globin production	Blood transfusions, iron chelation; luspatercept; HSCT; gene therapy
Hereditary spherocytosis	Most common in individuals of Northern European ancestry	1 in 2,000 to 5,000 people	AD	ANK1, EPB42, SLC4A1, SPTA1, and SPTB mutations	Erythropoietin treatment; splenectomy
Dehydrated hereditary stomatocytosis	No well-established racial predominance	1 in 8,000 to 50,000	AD	PIEZO1 and KCNN4 mutations	Monitor for iron overload; avoid splenectomy
Hereditary elliptocytosis	Most common among people of African, Southeast Asian, and Mediterranean descent	Ranges from 1 in 2,000 to 1 in 4,000	AD	SPTA1, SPTB, and EPB41 mutations	Asymptomatic patients: no treatment; patients with hemolysis or anemia: blood transfusions, splenectomy, and appropriate vaccinations for encapsulated organisms
G6PD deficiency	More common in people of African, Asian, and Mediterranean descent	78,010 per year	X-linked recessive	G6PD mutations	Mild to moderate: eliminate triggers, treat concurrent infections, ensure adequate hydration, and ensure close monitoring; severe: blood transfusion and correction of electrolyte and acid-base disturbances
Pyruvate kinase deficiency	No well-established racial predominance	NA	AR	PKLR mutations	Splenectomy; blood transfusion; monitor for iron overload; mitapivat

TABLE 2: Types of congenital hemolytic anemias.

AD: autosomal dominant; ANK1: ankyrin-1; AR: autosomal recessive; EPB41: erythrocyte membrane protein band 4.1; EPB42: erythrocyte membrane protein band 4.2; G6PD: glucose-6-phosphate dehydrogenase; HbH: hemoglobin H disease; HSCT: hematopoietic stem cell transplantation; NA: not applicable; SLC4A1: solute carrier family 4 member 1, commonly known as band 3; SPTA1: alpha-spectrin; SPTB: beta-spectrin

*Focuses on treatment in adults rather than children

Table 2 provides a concise, clinically oriented overview of the major inherited congenital hemolytic anemias, integrating their epidemiology, genetic basis, inheritance patterns, and disease-specific management strategies. While these disorders often present with overlapping features of chronic hemolysis, anemia, and splenomegaly, the table highlights key distinctions that are critical for accurate diagnosis and appropriate treatment selection. In particular, it underscores that conditions such as HS and DHS, despite similar clinical presentations, have fundamentally divergent management pathways, with splenectomy playing a therapeutic role in HS but being contraindicated in DHS due to the risk of severe thromboembolic complications.

This case underscores the complexity of diagnosing rare hematological conditions, particularly when

overlapping phenotypes coexist. The diagnosis of DHS can be challenging, especially when stomatocytes are difficult to detect in peripheral blood smears. In this patient, only spherocytes were observed in the blood smear, highlighting the potential of a missed diagnosis of DHS. This poses an important diagnostic challenge, as an inaccurate diagnosis can lead to inappropriate management given the different treatment pathways. Splenectomy is contraindicated in DHS because of the increased risk of thromboembolic events such as deep vein thrombosis, pulmonary embolism, and portal vein thrombosis. This increased risk is due to dehydrated and subsequently rigid stomatocytes that persist in the circulation due to a lack of splenic destruction [16]. However, patients with moderate-to-severe HS benefit from splenectomy, which reduces the burden of hemolysis [10]. Supportive management with daily folic acid supplementation is recommended for both disorders to sustain erythropoiesis in the setting of chronic hemolysis. Iron supplements should be avoided in patients with DHS because when the body is ineffectively conducting erythropoiesis, there is no mechanism to excrete excess iron, which leads to its accumulation and deposition in the tissues. Patients with evidence of iron overload should start iron chelation to prevent toxic deposit formation [17]. While the treatments for HS and DHS differ, in the rare case of dual diagnosis, it is critical to prioritize treatment for DHS because thromboembolic events after splenectomy are a major life threat.

With respect to the diagnostic screening process, the pathogenic SPTA1 variants help explain the patient's membrane structural defect and classic HS phenotype, including spherocytosis and increased red cell fragility. In contrast, the pathogenic PIEZO1 variant causes altered cation permeability of the membrane and erythrocyte dehydration, which is highly characteristic of DHS. This can explain the atypical laboratory findings and the subsequent contraindication to splenectomy. One important illustration is that the coexistence of these mutations explains the mixed clinical phenotype that could not be fully characteristic of either disorder alone. Table 3 highlights the key findings and their clinical implications.

Finding	Clinical implication
Spherocytes and splenomegaly	Early indicator of hereditary spherocytosis
Mixed osmotic fragility	Overlapping membrane disorders
Pathogenic SPTA1 variants	Confirmation of hereditary spherocytosis
Pathogenic PIEZO1 variant	Confirmation of dual hereditary spherocytosis, which results in contraindication of splenectomy
NGS results	Changed diagnosis and prevented inappropriate splenectomy
Increasing transfusion needs across pregnancies	Supports closer monitoring in subsequent pregnancies

TABLE 3: Summary table highlighting key findings and their clinical implications.

NGS: next-generation sequencing; SPTA1: alpha-spectrin

The advent of NGS has allowed for greater diagnostic accuracy for congenital hemolytic anemias and enhanced patient outcomes. NGS has enabled the identification of concomitant membrane and cation channel defects that are not discernible in purely morphological or osmotic tests. Subsequent genetic counseling and family screening are recommended to identify at-risk relatives and to guide anticipatory management.

With each pregnancy, the patient required more transfusions. For the first, second, and third pregnancies, the patient required two, three, and five transfusions, respectively. Of note, during the third pregnancy, the patient's hemoglobin was found to be 5.5 at 12 weeks of pregnancy, and later on, 6.1 at 37 weeks of pregnancy. The increasing transfusion requirement across pregnancies suggests that the physiological stress of pregnancy exacerbated the underlying hemolytic anemia. This trend underscores the importance of surveillance of blood counts and anticipatory transfusion planning in pregnant patients diagnosed with congenital hemolytic anemia. Checking symptoms and hemoglobin levels every four weeks for mild disease and 1-2 weeks for moderate-severe cases would help manage the symptoms and anemia, particularly during the third trimester when the fetus is experiencing the fastest growth.

Limitations of this case report are that causal inferences and generalizability are inherently limited. Larger series or systematic studies are needed to confirm the clinical implications of dual HS/DHS diagnoses.

Conclusions

Clinically diagnosing congenital hemolytic anemias can be challenging, particularly when overlapping phenotypes obscure the underlying etiology. In this case, early genetic evaluation was critical in arriving at an accurate dual diagnosis of HS and DHS and in redirecting clinical management away from a potentially harmful intervention. While splenectomy is typically indicated for patients with moderate-to-severe HS to reduce the burden of hemolysis, it is contraindicated in patients with DHS due to the significantly increased risk of thromboembolic complications. When both conditions are present, management of DHS should be prioritized, given this life-threatening risk. This case suggests that NGS-based genetic evaluation may be a valuable early step in the workup of patients with hemolytic anemia who present atypically or fail to respond as expected to standard management. However, given the inherent limitations of a single case report, these observations should be interpreted cautiously. Causal inferences cannot be drawn, and the generalizability of these findings to broader clinical practice remains to be confirmed through larger case series and prospective studies.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Acquisition, analysis, or interpretation of data: Lisa Liu, Aparna Nanduru, Amy D. Stringer, Maher Ali

Drafting of the manuscript: Lisa Liu, Aparna Nanduru, Amy D. Stringer

Critical review of the manuscript for important intellectual content: Maher Ali, Samah Nassereddine

Supervision: Samah Nassereddine

Disclosures

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