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Case Report

Fetal SPTA1-Related Hemolytic Anemia Presenting in the Mid-Trimester with Ascites

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Abstract

Nonimmune hydrops fetalis is diagnosed when two or more of the following findings are identified on prenatal ultrasound: fetal ascites, pleural effusion, pericardial effusion, skin edema or polyhydramnios. We report on a rare case of fetal hydrops resulting from hereditary hemolytic anemia in association with a novel variant in the SPTA1 gene.

Introduction

Nonimmune hydrops fetalis is diagnosed when two or more of the following findings are identified on prenatal ultrasound: fetal ascites, pleural effusion, pericardial effusion, skin edema or polyhydramnios. The etiology is vast and includes chromosomal or single gene syndromes, anemia of various causes, congenital heart abnormalities, and in utero infections, amongst others [1]. We report on a rare case of fetal hydrops resulting from hereditary hemolytic anemia in association with a novel variant in the *SPTA1* gene. *SPTA1*-related hemolytic anemias are a subtype of the hereditary spherocytoses affecting the red cell membrane protein alpha-spectrin, which is important in maintaining red cell shape and deformability. Few reported cases describing intrauterine management of fetal hydrops caused by anemia in association with *SPTA1* variants were found in the literature [2-4]. In our case, the fetus initially presented with isolated ascites and Doppler evidence of anemia in the early mid-trimester at 20 weeks. Fetal anemia was treated with in utero transfusions until 29 weeks' gestation, when preterm birth was indicated for abnormal antenatal testing. The newborn demised on day of life three with multisystem organ failure related to severe anemia.

Case Presentation

Twenty-six-year-old Hispanic G1P0000 was seen in consultation for fetal ascites at 20 1/7 weeks' gestation. The patient had no significant medical history and denied illness in the pregnancy. Ultrasound revealed fetal ascites and elevated middle cerebral artery Doppler-Peak Systolic Velocity (MCA-PSV) at 50.6 cm/s or 1.97 MoMs (normal less than 1.5), consistent with severe fetal anemia. A fetal echocardiogram was within normal limits. The patient's antibody screen was negative, and testing for infectious etiologies (syphilis, Parvovirus B19, and cytomegalovirus) was negative. The patient was offered Percutaneous Umbilical Sampling (PUBS) and Intrauterine Transfusion (IUT). A fetal paracentesis was performed, with removal of 20 mL of peritoneal fluid. Paracentesis fluid was sent for genome wide SNP-microarray which revealed male with normal copy number, but with regions of homozygosity in chromosome 1 at 1p31.3p31.1 (15.5 Mb) and 1q21.1q23.2 (16.3 Mb). Due to the difficulty of accessing the umbilical vein, an intraperitoneal transfusion of 12 mL concentrated Packed Red Blood Cells (PRBCs) was performed.

Upon further interview, the patient and her husband reported they were both from the same small town in Mexico and could be distant cousins, increasing our suspicion for an autosomal recessive condition affecting the fetus. Candidate genes in the identified homozygous regions included PKLR, associated with pyruvate kinase deficiency of the red cell; UBE2T, associated with Fanconi anemia, complementation group T; and *SPTA1*, associated with pyropoikilocytosis and spherocytosis, type 3. With no remaining fetal peritoneal fluid DNA available for further molecular evaluation, *PKLR* gene sequence analysis of patient's blood was offered as a start for assessment of carrier status of candidate genes, and this returned negative. The patient's health insurance denied coverage for any further molecular work-up beyond this. As an alternative, we planned for whole exome sequencing to be performed in the neonate after delivery.

At 21 3/7 weeks, MCA-PSV was still abnormal (55.5 cm/s, 2.06 MoM), consistent with persistent severe fetal anemia. A second IUT was performed after PUBS confirmed severe fetal anemia with an initial hematocrit of 9.6%. The fetus was transfused with 12 mL of PRBCs intracardiac and 20 mL intraperitoneally. The MCA-PSV normalized after transfusion was completed (PSV 33 cm/s).

At 23, 3/7 weeks, the fetus had persistent moderate to severe ascites, slightly increased from the prior examinations. In addition, a small pericardial effusion was noted, and the fetus was diagnosed with nonimmune hydrops. Ultrasound at 25, 1/7 weeks showed marked fetal ascites, thus the patient was admitted for a third PUBS/IUT. The initial fetal hematocrit was 12.6%, confirming persistent fetal anemia. Fetal paracentesis was performed with removal of approximately 200 mL of brown fluid. The fetus was transfused with 36 mL of PRBCs intravenously and 30 mL intraperitoneally.

At 29 1/7 weeks, marked fetal ascites persisted. There was new polyhydramnios with an AFI of 28 cm. No pleural or pericardial effusions were noted at this time. Upon admission to labor and delivery for a planned fourth PUBS/IUT, the patient was found to

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have a category III fetal heart rate tracing. She had a primary cesarean section with delivery of a viable male infant weighing 1680 gm with APGAR scores of 2 at 1 minute and 4 at 5 minutes. The newborn demised on day of life 3 from multiorgan system failure and severe anemia. Blood smear was significant for anisocytosis, poikilocytosis, polychromasia, schistocytes, acanthocytes. Autopsy was significant for anasarca and splenomegaly at >99th centile for gestational age.

Whole exome sequencing was performed on the infant and identified a homozygous pathogenic variant in *SPTA1* gene c.4106dup p.(L1370Afs*10) located on chromosome 1q23. and a heterozygous Variant of Uncertain Significance (VUS) in the *MYBPC3* associated with autosomal dominant *MYBPC3*-related cardiomyopathy. Exome trio confirmed the infant's parents are both heterozygous for the c.4106dup p.(L1370Afs*10) variant in the *SPTA1* gene and the VUS in *MYBPC3* was maternally inherited. The couple was counseled that the infant had *SPTA1*-related hemolytic anemia that manifested very early in pregnancy causing severe fetal anemia and hydrops and they were given a 25% recurrence risk in each pregnancy. Maternal echocardiogram was ordered to assess for cardiomyopathy given the VUS finding in *MYBPC3*, and was normal.

Discussion

The hereditary spherocytoses are hemolytic anemias affecting the red cell cytoskeleton. They involve quantitative defects in the membrane proteins α-spectrin, β-spectrin, ankyrin, protein 4.2, and band 3.4. Among these, the spectrin-associated anemias have been previously reported as presenting with fetal hydrops. We report on a case of severe fetal anemia with initial finding of ascites very early in the pregnancy, at 20 1/7 weeks, with eventual progression to hydrops (transient pericardial effusion and then polyhydramnios along with persistent ascites). The couple was consanguineous and had fetal chromosomal microarray notable for regions of homozygosity on chromosome 1. Whole exome sequencing performed on the infant revealed the underlying etiology to be a novel homozygous pathogenic frameshift variant (c.4106p.Leu1370 Alafs*10) in *SPTA1* located on chromosome 1q23.1 resulting in deficiency of α-spectrin. Given the severity of hemolysis and marked fragmentation of the red blood cells on blood smear, the phenotype was consistent with autosomal recessive hereditary pyropoikilocytosis [5].

Review of the literature identified cases of hereditary pyropoikilocytosis with hydrops fetalis and severe anemia being recognized and treated with intrauterine transfusions as early as 25 weeks and until planned late preterm birth. In some of those cases, a prior history of fetal demise of a sibling was reported [2-4]. Other previously reported cases of hereditary pyropoikilocytosis with documented *SPTA1* variants included infants with severe anemia during neonatal life managed with transfusions and eventual splenectomy, and children with chronic transfusion requirement and clinical improvements or resolution with splenectomy or bone marrow transplant. [4,6-8]. In the cases with the most severe phenotypes (life-threatening anemia in utero leading to hydrops fetalis), particularly those requiring management with intrauterine transfusions, homozygous frameshift variants in *SPTA1* were identified, as was in our case, demonstrating greater impact to functional spectrin quantity. [2-4]. Interestingly, among cases with later onset of clinically identified anemia and good response to splenectomy, several had compound heterozygous variants in *SPTA1*, with a common genotype being a c.4339-99C>T allele paired with other variable point mutations on the opposite allele [4].

Our case study is consistent with recently published reports of an increasing frequency of underlying genetic etiologies being recognized in nonimmune hydrops fetalis when exome sequencing is used for definitive genetic diagnosis. Exome sequencing might also be informative in cases of unexplained fetal ascites [9]. Potential future treatments of severe hereditary hemolytic anemias presenting in fetal life may include stem cell transplantation (as is being used for in utero treatment of fetuses with alpha thalassemia major) in the hope of definitively addressing the condition prenatally.

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