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Dehydrated Hereditary Stomatocytosis Causing Sever Ascites Leading to Pulmonary Hypoplasia and Respiratory Insufficiency in a Neonate

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ABSTRACT

Introduction: Dehydrated hereditary stomatocytosis (DHS) is a rare, autosomal dominant disease primarily causing chronic anemia. However, DHS has been associated with perinatal ascites and edema. We report a unique case of DHS associated with severe ascites leading to pulmonary hypoplasia with resultant respiratory insufficiency in a neonate.
Case Presentation: EM is a 32.5-week EGA infant who was born with severe congenital ascites (following repeated prenatal paracentesis) identified on prenatal ultrasound. Initial chest-abdomen imaging is shown in Figure 1. He required CPAP at delivery but was weaned to high flow nasal cannula with intermittent episodes of prolonged intubation during repeat paracentesis. Paracentesis demonstrated simple ascites rather than chylous fluid. Lymphangiograms demonstrated transient lymphatic leakage with resolution. Genetic evaluation revealed a pathogenic mutation in the PIEZO1 gene for autosomal dominant DHS. This disorder has reduced penetrance and variable expressivity and symptoms range from absence of clinical features to lethal perinatal edema. During his first year of life EM developed severe chronic obstructive pulmonary disease with hypoxemia and a requirement for supplemental oxygen, restrictive lung disease secondary to thoracic dystrophy, and chronic lung disease of prematurity. He remained on supplemental oxygen for the first year and a half of life.
Discussion: DHS is a rare form of autosomal dominant hemolytic anemia reported in 26 individuals among 7 families worldwide. Clinical presentation varies significantly and includes chronic anemia, neonatal edema and ascites, and lymphatic malformations. Symptoms may develop in utero, during the perinatal period, or later in adulthood. Pulmonary hypoplasia and respiratory insufficiency caused by pre/perinatal ascites have not been reported. DHS is caused by gain-of-function mutations in the PIEZO1 (16q24.3) gene, as was demonstrated in our patient. Mutations result in increased red cell cation membrane permeability, particularly potassium, leading to depletion, dehydration, and shortened red cell survival. Expression of PIEZO1 in lymphatics may explain pre/perinatal edema and ascites. EM developed severe prenatal ascites leading to abnormal abdominal musculature and impaired diaphragm movement and fetal breathing causing pulmonary hypoplasia with subsequent respiratory insufficiency at birth. The pathophysiology in this case is similar to that of prune belly, where abnormal abdominal musculature is a known cause of impaired lung growth and development and subsequent respiratory compromise. Respiratory complications are primarily managed with supplemental oxygen and ventilatory support, if needed, until the lungs mature.
Conclusion: This case highlights a previously unreported extremely rare disease, DHS, leading to abnormal fetal breathing, marked pulmonary hypoplasia, and subsequent respiratory insufficiency.

INTRODUCTION

Dehydrated hereditary stomatocytosis (DHS) is a rare, autosomal dominant (AD) disease primarily associated with chronic anemia. DHS is known to cause perinatal edema and ascites, which may be severe. Severe ascites can cause impaired fetal breathing with resultant pulmonary hypoplasia and secondary thoracic abnormalities. Additionally, severe ascites can lead to profound abnormalities of abdominal wall development and pulmonary function abnormalities similar to those seen in prune-belly syndrome. We report a unique case of DHS associated with severe ascites leading to pulmonary hypoplasia, chronic respiratory insufficiency, and long term respiratory compromise.

CASE PRESENTATION

EM was born at 32.5 weeks estimated gestational age via planned Cesarean section secondary to severe, refractory congenital ascites despite five prenatal paracenteses. His mother received two doses of betamethasone prior to delivery. His initial chest-abdomen imaging is shown in Figure 1. He required CPAP at delivery and had APGAR scores of 4 and 8. Non-invasive positive pressure ventilation (NIPPV) was required prior to weaning to high-flow nasal cannula (HFNC), oxygen supplementation (OS), and room air by six days of life. EM required intermittent intubation for invasive procedures and required intermittent NIPPV, HFNC, and OS until he was 2½ months of age.

CASE PRESENTATION (cont.)

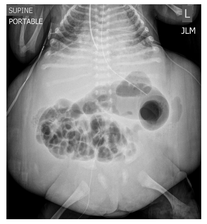

Figure 1: Chest-abdomen image at 2 months of age.

A comprehensive evaluation for potential causes of EM's severe edema and ascites was undertaken. This included repeat paracentesis, lymphangiogram, echocardiogram, complete abdominal imaging, and infectious diseases workup, all of which were non-diagnostic. Complete genome sequencing identified a pathogenic mutation in the *PIEZO1* gene, c.6058G>A (p.A2020T), confirming a diagnosis of autosomal dominant DHS.

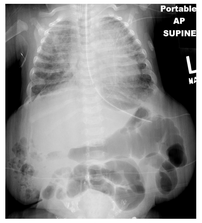

Figure 2: Chest-abdomen image at 4 months of age.

EM required hospitalization for respiratory failure at 4 months of age. Imaging at that time is shown in Figure 2. Pleural effusions responsive to diuretic therapy were identified on subsequent imaging. He was eventually weaned from mechanical ventilation and OS and was discharged on room air. EM had two hospital admissions at 6 months of age which were again associated with variable degrees of distress and hypoxemia. He was discharged on ¼ liter per min OS.

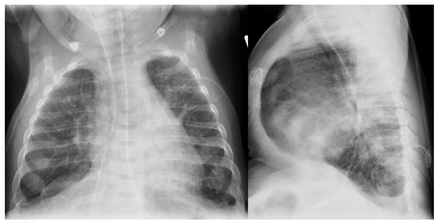

Figure 3 : CXR at18 months of age

EM remained on supplemental oxygen until approximately 16 months of age. He was then hospitalized with bronchiolitis at 18 months of age. He transiently required OS but was discharged after five days without OS.

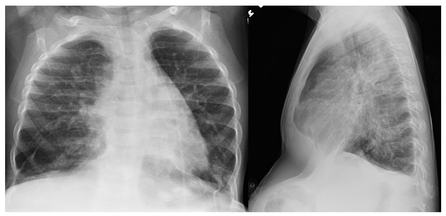

Figure 4 : CXR at 40 months of age

EM remained well from a respiratory standpoint until 40 months of age. He was again hospitalized with bronchiolitis associated with respiratory distress and hypoxemia. He was rapidly weaned from OS and discharged home.

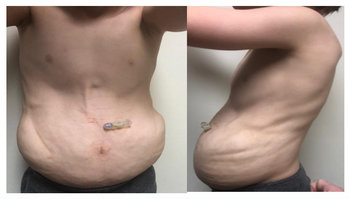

Figure 5 : Chest and abdomen photographs at 40 months of age

During ambulatory follow up, EM was doing well clinically. He did continue to demonstrate significant sternal bowing from air trapping and ongoing abdominal muscle abnormality with weak cough.

DISCUSSION

DHS is an AD hemolytic anemia caused by mutations in the *PIEZO1* gene. It is often difficult to diagnose due to its highly variable clinical presentation, which ranges from absence of clinical features to lethal perinatal complications. Advanced genetic testing is generally required for definitive diagnosis. Prenatal and perinatal ascites and edema, sometimes massive, have been reported in newborns with DHS.[1,2] Although lymphatic abnormalities have been associated with DHS, ascites fluid obtained from EM did not indicate lymphatic involvement.[3-5] A potential hepatic etiology was suggested.[6] We hypothesize that massive abdominal ascites and edema led to impaired fetal breathing with subsequent pulmonary hypoplasia. This, in turn, resulted in repeated episodes of postnatal respiratory failure, the need for prolonged OS, and long term respiratory compromise. Additionally, EM has the functional equivalent of Prune Belly syndrome (PBS). PBS has been associated with marked thoracic gas trapping and a restrictive pattern on spirometry.[7] As demonstrated in Figures 2-5, EM has had significant hyperinflation on chest imaging and thoracic dysmorphia on physical examination. He is not yet old enough to perform spirometry. Furthermore, EM has a markedly diminished cough, which may predispose him to additional respiratory compromise. EM has shown gradual clinical improvement. This is presumably due to ongoing pulmonary growth and development, which is anticipated to continue through at least six to ten years of age and potentially longer.

CONCLUSIONS

- DHS may result in massive abdominal ascites and edema leading to multiple pulmonary morbidities as discussed above.
- Symptoms should improve over time given ongoing postnatal lung growth and development .

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