Index of Suspicion in the Nursery

1 Primary Neonatal Respiratory Failure

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INITIAL CASE PRESENTATION

A 2.91-kg male infant is born to a 31-year-old gravida 3, para 2 woman via repeat cesarean section at 39.1 weeks' gestation. The pregnancy had been complicated by polyhydramnios with normal anatomy noted on ultrasonography. Family history includes neonatal loss of a male infant with primary respiratory failure and pulmonary hypoplasia on autopsy. The mother's serologic findings, including group B *Streptococcus*, are negative. At delivery the neonate has poor respiratory effort and requires intubation. Apgar scores are 5, 6, and 6 at 1, 5, and 10 minutes. He is admitted to the NICU on a conventional ventilator. His cord blood gas findings are normal, and his complete blood cell count is not concerning for infection. A blood culture specimen is obtained, and he is started on empiric antibiotics. Given the profound hypoxemia, echocardiography is performed, which reveals normal structure and estimated suprasystemic pulmonary pressures. He is diagnosed with persistent pulmonary hypertension and is started on inhaled nitric oxide and continuous infusions of dopamine and dexmedetomidine. Around 12 hours after birth, he develops a left-sided pneumothorax requiring chest tube placement. He makes a transition to the high-frequency jet ventilator (HFJV) and is transferred for extracorporeal membrane oxygenation (ECMO) evaluation.

Physical examination reveals an infant who is intubated and sedated, but breathing over HFJV with retractions, no murmurs, cap refill 3 to 5 seconds, minimal spontaneous movement when stimulated, and decreased tone throughout.

LABORATORY STUDIES

Chest radiography shows expansion of 8 ribs. Arterial blood gas reveals a pH of 7.11, P_{CO_2} 64 mm Hg (8.5 kPa), P_{aO_2} 41 mm Hg (5.4 kPa), bicarbonate 20 mEq/L (20 mmol/L), and base deficit −11. Oxygenation index (OI) is 24. Cranial ultrasonography reveals normal structure. Karyotype and microarray are normal.

PATIENT COURSE

On day 1 after birth, oxygenation improves with maximization of therapy including continued inhaled nitric oxide and HFJV support, increase in sedation, paralytics, fluid resuscitation, blood products, blood pressure support, and

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intravenous milrinone infusion. He is incidentally found to have a right-sided tension pneumothorax on repeat chest radiography to evaluate chest expansion. Chest tube placement results in resolution of pneumothorax, and he remains hemodynamically stable, with oxygen saturation greater than 95%. Based on his severe pulmonary hypertension, primary respiratory failure and presumed pulmonary hypoplasia, as well as the family history, whole exome sequencing (WES) is ordered to evaluate for a potentially inherited condition. Hours later, he experiences acute decompensation and has an increasing OI. Chest radiography indicates good placement of bilateral chest tubes with expanded lungs. Arterial blood gas at that time reveals a pH of 7.25, P_{CO_2} 53 mm Hg (7.0 kPa), $P_{a}O_2$ 11 mm Hg (1.4 kPa), bicarbonate 19 mm Hg (19 mmol/L), and base deficit of −10, with an OI of 130. The ECMO team is notified of worsening status, but before cannulation, his heart rate drops and cardiopulmonary resuscitation is begun. He continues to deteriorate despite maximal resuscitative efforts. The parents and medical team decide to transition the goals of care from aggressive life-prolonging therapies to comfort measures only. He dies in his mother's arms.

DISCUSSION

Differential Diagnosis

The differential includes congenital lobar emphysema, alveolar capillary dysplasia, surfactant protein deficiencies, primary pulmonary alveolar proteinosis, congenital pulmonary lymphangiectasis, congenital myotonic dystrophy, autosomal dominant/recessive centronuclear myopathy, spinal muscular atrophy type 1.

Actual Diagnosis

WES reveals a pathogenic variant of the *MTM1* gene. The mother and father are referred to genetics and further testing reveals that the mother is a carrier for X-linked myotubular myopathy.

The Condition

X-linked myotubular myopathy or centronuclear myopathy is a rare inheritable disease caused by a mutation in the *MTM1* gene that encodes the enzyme myotubularin, which helps differentiate muscle cells. (1) It is characterized by muscle weakness that ranges in severity. The incidence is 1 in 50,000 male newborns. (2)(3) The most severely affected can die in utero or present prenatally with decreased fetal movement and maternal polyhydramnios. (4) Severely affected newborns have hypotonia and muscle weakness, which often leads to respiratory failure requiring mechanical ventilation. (2) Long term, severely affected boys have delayed motor milestones and are frequently unable to walk. (2) Muscle weakness may lead to myopathic facies, characterized by dolichocephaly, high forehead, long face with midface hypoplasia, and a narrow high-arched palate with subsequent malocclusion. (2)(3) Mildly to moderately affected individuals are less likely to require respiratory support, to have motor delays, or to develop myopathic facies. (2) Female carriers are typically asymptomatic; however, rare cases of symptomatic heterozygotes have been described. (2)

Diagnosis is based on muscular histopathologic changes, family history, and genetic testing. Genetic testing detects variants in 60% to 98% of cases. (2) Muscle biopsy cannot be exclusively used for diagnosis because of a lack of specificity. (2)

Because this disorder is X-linked, determining maternal carrier status is important. If the mother is a carrier, there is a 50% inheritance chance for each future child. Approximately 10% to 20% of cases have a de novo mutation. (2)(3) It is believed that penetrance is 100% in affected boys. (2)(3)

Treatment is based on symptomatology. Currently, there are no enzyme replacement therapies, and those who survive frequently require equipment such as tracheostomy, ventilator, feeding tubes, and assistive communication devices. (2)(5)

Ethics

ECMO is considered for diagnoses that are deemed recoverable, and candidacy can sometimes be questioned. The current patient had a history that was suspicious for a genetic condition and a possibility that he inherited a potentially life-limiting condition that would preclude ECMO; however, uncertainty remained because of lack of definitive testing on the sibling. Given the uncertainty, the medical teams decided ECMO would be reasonable while pursuing a definitive diagnosis. In cases with such uncertainty, it is imperative that the family receive extensive counseling that ECMO may prolong the child's life while a potential diagnosis is sought but may not meaningfully extend the child's life.

In addition, in the absence of a definitive diagnosis, obtaining blood specimens for WES can be helpful and have long-lasting implications for the health and well-being of the family and future children. This is important to consider despite the potentially high cost of WES that may discourage a health care institution from performing the test.

Lessons for the Clinician

- Primary neonatal respiratory failure/pulmonary hypertension can be caused by malformation of the airways, lungs, or brain; cardiac defects; skeletal anomalies; pulmonary

hypoplasia resulting from mass effect; protein deficiencies; or neuromuscular diseases.

- WES offers the opportunity to find diagnoses in rare presentations that can affect family well-being.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features and differential diagnosis of persistent pulmonary hypertension.
- Know the management of persistent pulmonary hypertension including assisted ventilation, pharmacologic approaches, and ECMO.

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Case 1: Primary Neonatal Respiratory Failure

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