Peer Reviewed

Bilateral Pulmonary Aplasia Diagnosed at Delivery

Elisa Zhang, MD, Alexandra Iacob, MD, Yona Nicolau, MD

Introduction:

Pulmonary aplasia is defined as the absence of lung parenchyma in the presence of bronchial buds, whereas pulmonary agenesis is defined by the absence of lung parenchyma, bronchus, and pulmonary vasculature. (1) Bilateral pulmonary aplasia or agenesis is a rare and lethal condition. Several cases associated with bilateral pulmonary agenesis have been previously reported, (1-5)most detected prenatally on advanced imaging but can be missed by routine prenatal ultrasounds (US). (1) Here, we report an unusual case of a term neonate found to have bilateral pulmonary aplasia postnatally, despite weekly ultrasounds starting at 26 weeks gestation and fetal MRI.

"Here, we report an unusual case of a term neonate found to have bilateral pulmonary aplasia postnatally, despite weekly ultrasounds starting at 26 weeks gestation and fetal MRI."

Case Report:

A 29-year-old primigravida had prenatal US scans at 19 and 20 weeks, indicating bilateral hydronephrosis, heterotaxy, cardiomegaly, and VSD. At 25 weeks, her US noted dextrocardia with an abnormal four-chamber view, subtle cranial lemon shape, pulmonary hypoplasia, hyperextension of the neck, small orbits, and pericardial effusion. Pregnancy was complicated by obesity (BMI 34) and severe polyhydramnios. Maternal prenatal labs were unremarkable. Amniotic fluid microarray was negative. A fetal MRI obtained at 31 weeks gestation showed polyhydramnios, dextrocardia, structurally normal heart, normal lung size, left-sided stomach, and hyperextension of the fetal neck, as seen in Figure 1. However, imaging was limited by increased amniotic fluid and significant fetal motion. Due to the numerous anomalies, the mother underwent weekly US scans starting at 26 weeks until delivery. They revealed a persistently hyperextended fetal neck. Due to concerns for airway patency, the infant was delivered at 38 weeks via Cesarean in coordination with Pediatric Anesthesia and Pediatric ENT. Physical exam revealed normal head and neck position, normal neck mobility, good respiratory effort, grimacing, but the absence of audible cry. The rest of the physical exam was otherwise unremarkable. Neonatal resuscitation guidelines were followed. Bag-mask ventilation was initiated due to bradycardia, cyanosis, and the development of retractions.

"However, imaging was limited by increased amniotic fluid and significant fetal motion. Due to the numerous anomalies, the mother underwent weekly US scans starting at 26 weeks until delivery. They revealed a persistently hyperextended fetal neck."

Minimal chest rise was observed despite adequate peak inspiratory pressures. Laryngoscopy performed by Pediatric ENT via rigid bronchoscope showed normal-appearing larynx with a normal epiglottis, arytenoids, and vocal cords, but the subglottis appeared collapsed entirely. Distal trachea and mainstem bronchi bilaterally could be opened briefly with significant positive pressure. The endotracheal tube was inserted, but there was no color change on capnography. Despite aggressive ventilation efforts, the baby remained hypoxic and bradycardic. The endotracheal tube was removed, and bronchoscopy was used to visualize the distal airway. The trachea was completely collapsed with the bronchoscope stenting open the proximal trachea. Notably, there was a complete loss of structure and no identifiable cartilaginous rings in the trachea or bronchi. An emergent tracheostomy was performed; tube position was confirmed via a bronchoscope. Ventilation continued with high pressures via tracheostomy with no response. At 35 minutes of life, parents agreed with discontinuation of life support. An autopsy was performed, which revealed:

1. Normal length and body weight
2. Normocephalic head but poorly calcified calvarium—6cm circular regions of ossification over bilateral parietal lobes but otherwise unmineralized
3. Extremely large and connected fontanelles
4. Grossly and histologically unremarkable fetal brain
5. Normally facies, palmar creases, extremities, digits
6. Bilateral pulmonary aplasia: tracheal tube bifurcated 3cm below the larynx; both distal segments ended in a blind pouch (Figure 2). Microscopic sections of the blind-ending right bronchus revealed cartilage plates, bronchial glands, and respiratory epithelium with no sign of alveolar structure development
7. Absent tracheal cartilage rings

8. Intact and normally-positioned diaphragm
9. Levocardia with severe cardiomegaly, right ventricular hypertrophy, interventricular septal hypertrophy, enlarged patent foramen ovale, and large patent ductus arteriosus
10. Enlarged pulmonary trunk with no pulmonary arteries and no pulmonary venous return
11. Normal gastrointestinal tract
12. Thymus and liver weight each at 84-95th percentile
13. Accessory spleen
14. Combined kidney weight at 5-16th percentile, left kidney pelviectasis
15. Normal male genitalia

"To our knowledge, this is the first case of bilateral pulmonary aplasia described to be associated with massive polyhydramnios, congenital absence of tracheal rings, persistent hyperextension of the neck on prenatal ultrasound, and poorly calcified calvarium."

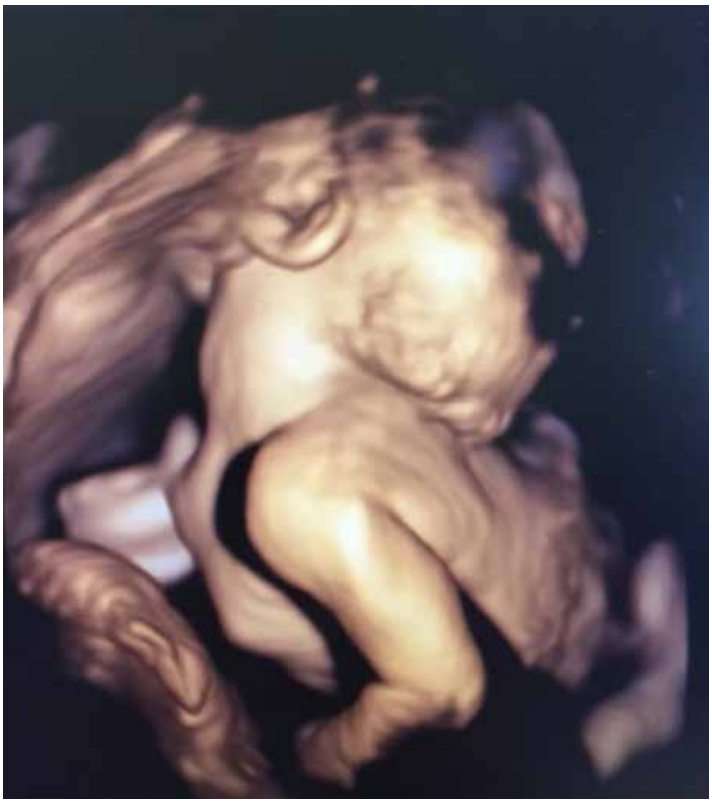

Figure 1. Fetal MRI depicting neck hyperextension.

Discussion:

This case of bilateral pulmonary aplasia associated with primary tracheobronchomalacia due to congenital absence of tracheal cartilage rings was undetected on prenatal ultrasounds as well as fetal MRI. To our knowledge, this is the first case of bilateral pulmonary aplasia described to be associated with massive polyhydramnios, congenital absence of tracheal rings, persistent hyperextension of the neck on prenatal ultrasound, and poorly calcified calvarium. Many similar cases in the literature were first detected via elevated diaphragm on prenatal ultrasound. (3-4) Our case was not detected prenatally, possibly due to the enlarged thymus filling the thoracic cavity or the lack of diaphragmatic elevation. Given the unknown etiology of our case, we explore the embryologic, molecular, and syndromic pathways that could offer an explanation.

Tracheal and pulmonary embryology begins during the third gestational week. (2) Pulmonary agenesis arises from the failure of lung bud formation. This process is critically dependent on the local expression of Fgf10 in the foregut mesoderm, which activates signaling in tracheal and respiratory progenitor cells. (6) Studies have shown that Fgf10-null mice die at birth and have multiple defects; lungs do not form, but tracheal development occurs. (6) There is increasing evidence in mice studies that Fgf10 expression is regulated by vitamin A-derivative retinoic acid (RA) signaling at the onset of lung development. (7) Vitamin A deficiency, genetic disruption of the RA pathway, or the presence of RA inhibitors have been associated with multiple developmental abnormalities, including lung agenesis in mice studies. Interestingly, tracheal cartilage development, which occurs at ten weeks, also relies on signaling by a variety of molecules, including RA.(6) Thus, vitamin A deficiencies or disruption of RA signaling may be a unifying cause for the findings seen in this patient with bilateral pulmonary aplasia and congenital absence of tracheal rings.

"Several syndromes, associations, and chromosomal anomalies have also been associated with pulmonary hypoplasia or agenesis. (5) Our patient's karyotype and microarray were normal. However, the remaining dysmorphology—poorly calcified skull and lack of tracheal cartilage—do not describe a known syndrome."

Several syndromes, associations, and chromosomal anomalies have also been associated with pulmonary hypoplasia or agenesis. (5) Our patient's karyotype and microarray were normal. However, the remaining dysmorphology—poorly calcified skull and lack of tracheal cartilage—do not describe a known syndrome. Spear syndrome, PDAC syndrome (pulmonary hypoplasia/agenesis, diaphragmatic hernia/eventration, anophthalmia/microphthalmia, and cardiac defect), PMD syndrome (pulmonary agenesis, microphthalmia, and diaphragmatic defect), Meckel syndrome, Hydrolethalus syndrome, Ellis-van Creveld syndrome, Opitz G/

Figure 2. Autopsy depicting trachea opened posteriorly and two probes showing the blind-ended lobar bronchi.

BBB syndrome, Smith-Lemli-Opitz syndrome, C syndrome, Fryn syndrome, Goldenhar syndrome, VACTERL, and Tracheal Agenesis Association are all conditions which can involve pulmonary hypoplasia/aplasia. However, these syndromes have characteristic musculoskeletal and multi-organ anomalies not present in this patient. Finally, viral infections, genetic factors, and folic acid may also be implicated in pulmonary anomalies. (3)

Bilateral pulmonary aplasia is associated with the absence of main pulmonary artery branches and pulmonary veins because pulmonary vasculature development depends on pulmonary mesenchyme stimulation to grow. (1,3) Thus, the suspicion for bilateral pulmonary aplasia or agenesis increases if color Doppler of pulmonary vasculature is absent, and several cases have been confirmed in utero with this test. (3) Pulmonary vasculature anomalies were not noted prenatally in this patient but confirmed on autopsy.

The cause of the patient's poorly-calcified calvarium and large fontanelles is unclear. Joints and marrow were noted to be grossly normal. X-rays were not done to assess ossification. The differential for large fontanelles includes hypophosphatemia and hypothyroidism. Trisomies, osteogenesis imperfecta, congenital rubella or syphilis, and cleidocranial dysplasia (5) are also possible but less likely given the karyotyping results, prenatal labs, and autopsy results.

Intriguingly, there is a temporal overlap of when this patient's major anomalies likely developed in utero. An interesting unifying etiology to consider would be a disruptive event in-utero around 7-10 weeks gestation, at which time the parietal bones should start to ossify(10), and the visceral lung pleura and tracheal cartilage should start to develop. Fgf10, the molecule necessary for lung development in mice, has also been implicated in skeletal disorders, (8) leading to the possibility that abnormal Fgf10 signaling may have a yet unknown role in both the pulmonary genesis and skull ossification.

The cause of the fetus' hyperextended neck also remains unclear. In a retrospective study of six fetuses with polyhydramnios and head hyperextension on prenatal ultrasound, five had neurologic malformations such as anencephaly or craniorachischisis. (9) This was not the case for our patient. The persistent in-utero hyperextended neck resolved by delivery and with no apparent structural cause could suggest an abnormal joint laxity. A connective tissue etiology may be another unifying explanation for this patient's pathology given the poorly-ossified skull, lack of tracheal rings, and constellation of the persistently hyperextended neck in utero.

Conclusion:

Our case illustrates bilateral pulmonary aplasia diagnosed at birth with prenatal findings of persistent neck hyperextension and massive polyhydramnios. Prenatal diagnosis of bilateral pulmonary aplasia was missed despite several ultrasounds and fetal MRI, likely due to lack of previously described associated findings—elevated diaphragm, enlarged thymus—as well as visual limitations due to polyhydramnios. Given the link between vitamin A-derivative RA signaling, lung bud formation, and tracheal cartilage development, maternal vitamin A deficiency or disruption of the RA signaling pathway should be considered when presented with isolated, non-syndromic pulmonary aplasia and congenital absence of tracheal rings. Additionally, the absence of the main pulmonary artery and vein branches on prenatal imaging or absent color Doppler of these structures should also raise suspicion for this fatal condition. Given our patient's course, persistent fetal neck hyperextension with polyhydramnios could represent a new association in future prenatal diagnosis of bilateral pulmonary aplasia.

"Given our patient's course, persistent fetal neck hyperextension with polyhydramnios could represent a new association in future prenatal diagnosis of bilateral pulmonary aplasia."

References:

1. *Nguyen LN, Parks WT. Bilateral Pulmonary Agenesis: A Rare and Unexpected Finding in a Newborn. AJP Rep.*

2016;6(2):e246-e249. doi:10.1055/s-0036-1584530
2. Sandu K, Monnier P. Congenital tracheal anomalies. Otolaryngologic Clinics of North America. 2007;40(1):193-217.
3. Lee KA, Cho JY, Lee SM, et al. Prenatal diagnosis of bilateral pulmonary agenesis: a case report. Korean J Radiol. 2010;11(1):119-122. doi:10.3348/kjr.2010.11.1.119
4. Ramanah R, Martin A, Guigue V, et al. Recurrent prenatally diagnosed isolated bilateral pulmonary agenesis. Ultrasound Obstet Gynecol. 2012;40(6):724-725.
5. Toriello HV, Bauserman SC. Bilateral pulmonary agenesis: association with the hydrolethalus syndrome and review of the literature from a developmental field perspective. Am J Med Genet. 1985;21(1):93-103. doi:10.1002/ajmg.1320210114
6. Cardoso WV, Yang Y, Lu J. Chapter 4: Molecular Regulation of Lung Development. In: Grippi M et al., eds. Fishman's Pulmonary Disease and Disorders. 5th Edition. McGraw Hill. 2015: p. 73-82
7. Desai TJ, Malpel S, Flentke GR, et al. Retinoic acid selectively regulates Fgf10 expression and maintains cell identity in the prospective lung field of the developing foregut. Developmental Biology. 2004;273(2):402-415.
8. Moosa S, Wollnik B. Altered FGF signaling in congenital craniofacial and skeletal disorders. Semin Cell Dev Biol. 2016;53:115-125. doi:10.1016/j.semcdb.2015.12.005
9. Shipp TD, Bromley B, Benacerraf B. The prognostic significance of hyperextension of the fetal head detected antenatally with ultrasound. Ultrasound Obstet Gynecol. 2000;15(5):391-396. doi:10.1046/j.1469-0705.2000.00120.x
10. Jin SW, Sim KB, Kim SD. "Development and growth of the normal cranial vault: an embryologic review." J Korean Neurosurg Soc. 2016; 59(3): 192–196. doi: 10.3340/jkns.2016.59.3.192

Acknowledgments: Thank you to Dr. Edwards and Dr. Uy for their review of the manuscript and input on the pathology findings.

Ethics Statement: Institutional ethical committee approval is not required for case reports. The patient's parents consented to the publication of the case report.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Funding/Support: No funding was secured for this study.

NT

Elisa Zhang MD
Clinical Instructor
Department of Pediatrics, Division of Critical Care
Stanford School of Medicine
Palo Alto, California
Email: elisaz@stanford.edu

Alexandra Iacob, MD
Clinical Instructor
Department of Pediatrics, Division of Neonatology
Miller Children's Hospital
Long Beach, California
Email: alexandra.iacob@pediatrix.com

Corresponding Author

Yona Nicolau, MD
Associate Clinical Professor
Department of Pediatrics, Division of Neonatology
University of California - Irvine
Orange, California
Email: ynicolau1@hs.uci.edu