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Prenatal Diagnosis of Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins

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Abstract

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) is a rare, lethal cause of neonatal respiratory failure and persistent pulmonary hypertension. We present a presumptive prenatal diagnosis of ACDMPV based on chorionic villus sampling of a *FOXF1* mutation in a fetus with extra-pulmonary anomalies often associated with ACDMPV.

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) OMIM# 265380 is a rare, lethal cause of neonatal respiratory failure associated with pulmonary hypertension.¹ Patients with ACDMPV have lungs with malposition of the pulmonary vein branches next to the pulmonary arteries, medial hypertrophy of small pulmonary arteries, thickened alveolar septa, and decreased pulmonary capillary density.² They usually develop progressive, irreversible hypoxemia and respiratory failure within the first 48 hours of life and die in the neonatal period. Recently, heterozygous point mutations or genomic deletions involving the *FOXF1* gene have been identified in most infants diagnosed with ACDMPV.^{3–5} Extra-pulmonary manifestations are found in up to 80% of infants with ACDMPV, most commonly gastrointestinal, genitourinary, and cardiovascular anomalies.² There is one reported case where prenatal suspicion for ACDMPV was confirmed by postnatal lung biopsy.⁶ We present a case in which a presumptive prenatal diagnosis of ACDMPV was made based on identification of a microdeletion of the *FOXF1* gene in a fetus with extra-pulmonary anomalies commonly associated with ACDMPV.

Case

A 37-year-old woman, gravida 1 with an unremarkable past medical and obstetric history, was referred to maternal fetal medicine for cystic hygroma evaluation at 11 weeks gestation. Chorionic villus sampling identified a normal female 46,XX karyotype, and a chromosome

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16q24.1 microdeletion, containing the *FOXF1* gene by genomic copy-number variants using chromosomal microarray analysis (CMA).⁵ Subsequent polymerase chain reaction and DNA sequencing revealed that the deletion was 1.171 Mb in size and was Alu-Alu mediated (chr16:86,027,014–87,198,727, hg19). Parental origin could not be determined because the paternal sample was unavailable.

Serial obstetric ultrasounds and fetal echocardiograms demonstrated an atrioventricular septal defect (AVSD), bilateral superior vena cavae, a low-normal-sized aortic valve, inability to demonstrate normal pulmonary venous return by pulse Doppler ultrasound, and suspected bowel atresia. Based on the chromosome 16q microdeletion in a fetus with anomalies commonly associated with ACDMPV, the mother was counseled prenatally about the provisionary diagnosis of ACDMPV and its poor prognosis, with a plan to avoid futile invasive therapies if her infant's respiratory course was consistent with ACDMPV.

A 3130-gram, female infant was delivered by cesarean section for nonreassuring fetal status at 39 weeks gestation. Following delivery, the infant's respiratory status declined within 24 hours of life, requiring 100% FiO₂, inhaled nitric oxide, and high-frequency oscillatory ventilation by 48 hours. Postnatal echocardiogram confirmed a partial AVSD with a large primum atrial septal defect, mild atrioventricular valve insufficiency, bilateral superior vena cavae, a mildly hypoplastic distal transverse aortic arch, normal pulmonary venous return, and suprasystemic right ventricular pressure. Her respiratory course was consistent with the presumed diagnosis of ACDMPV.

Given the prenatally identified *FOXF1* gene deletion, extracorporeal membrane oxygenation (ECMO) was considered to be a futile invasive intervention and was not offered, and surgical evaluation of suspected intestinal atresia was not performed. With the goal of compassionate care, as directed by extensive prenatal counseling, lung biopsy was not recommended, and the mother agreed with this plan. Comfort care was provided; the baby was extubated and died on day of life 2. Lung histologic exam on a limited chest autopsy confirmed the diagnosis of ACDMPV.

Discussion

There have been 2 case reports of prenatal diagnosis of chromosome 16 deletion in the *FOXF1* region. Parris et al described a patient prenatally diagnosed with an AVSD, bowel atresia, and a pericentric inversion of chromosome 16 on fetal karyotype, with ACDMPV confirmed at autopsy.⁶ Garabedian et al presented a fetus with cystic hygroma, fetal hydrops, and a single umbilical artery, with CMA demonstrating "interstitial deletion of chromosome 16 at position 16q24.1"⁷; the diagnosis of ACDMPV was not confirmed by lung histology postnatally.

In our case, we demonstrate how a presumptive prenatal diagnosis of ACDMPV can guide postnatal management. Although ACDMPV can currently only be confirmed by lung biopsy, suspecting ACDMPV prenatally from the CMA allowed our patient's family to prepare for her death. It also allowed the medical team to plan her postnatal care, including timing of lung biopsy and limiting futile, invasive interventions should her clinical course be

consistent with ACDMPV. Postmortem tissue confirmation of the diagnosis was important for the medical team as well as for the family.

In a subsequent case at our institution, an infant was diagnosed with ACDMPV postnatally, following cardiac surgery for prenatally diagnosed hypoplastic left heart syndrome. After lung biopsy on ECMO confirmed ACDMPV, life support was withdrawn and the patient died on day of life 13, having had a protracted postoperative course. A heterozygous c.235C>T (p.Q79X) mutation in the *FOXF1* gene was demonstrated on a pre-ECMO blood sample after a normal microarray at delivery.

Although fetal ultrasound cannot resolve abnormalities of microscopic pulmonary vasculature as seen in ACDMPV, the presence of extra-pulmonary anomalies commonly found in ACDMPV indicates the diagnosis prenatally when combined with known mutations or deletions in *FOXF1*. Cardiac lesions have been reported in up to 25% of children with ACDMPV,² with the 2 predominant heart conditions being left-sided obstructive lesions and AVSDs.⁸ Less commonly described are anomalies in the pulmonary veins.^{9,10} However, in both of our cases of ACDMPV, we had difficulties identifying expected pulmonary vein Doppler patterns on fetal echocardiograms performed for evaluation of congenital heart disease. These findings suggest that unresolved pulmonary vein Doppler patterns in utero could be an additional prenatal feature of ACDMPV.

Currently, genetic testing for *FOXF1* can identify 70%–90% of potential ACDMPV cases.⁴ Given that approximately 25% of patients with histopathologically verified ACDMPV have relatively small deletions upstream to *FOXF1* that may not be well covered by the commercially available arrays, a custom region-specific array or high resolution genome-wide array should be used in the clinical diagnosis of patients with ACDMPV who are negative for point mutations in *FOXF1*. A negative genetic test does not exclude the diagnosis, and lung biopsy remains the diagnostic gold standard. However, abnormal genetic testing for *FOXF1* is helpful in guiding care postnatally, especially when the clinical course is consistent with ACDMPV. For infants with congenital heart disease and hypoxemia due to severe, refractory pulmonary hypertension out of proportion to that expected from their heart disease, a diagnosis of ACDMPV should be considered.³

Glossary

ACDMPV	Alveolar capillary dysplasia with misalignment of pulmonary veins
AVSD	Atrioventricular septal defect
CMA	Chromosomal microarray analysis
ECMO	Extracorporeal membrane oxygenation

References

1. Janney CG, Askin FB, Kuhn C III. Congenital alveolar capillary dysplasia—an unusual cause of respiratory distress in the newborn. *Am J Clin Pathol.* 1981; 76:722–7. [PubMed: 7293984]
2. Bishop NB, Stankiewicz P, Steinhorn RH. Alveolar capillary dysplasia. *Am J Respir Crit Care Med.* 2011; 184:172–9. [PubMed: 21471096]

3. Lane JR, Siwik E, Preminger T, Stork E, Spector M. Prospective diagnosis of alveolar capillary dysplasia in infants with congenital heart disease. *Am J Cardiol.* 1999; 84:618–20. A9–10. [PubMed: 10482172]
4. Sen P, Yang Y, Navarro C, Silva I, Szafranski P, Kolodziejska KE, et al. Novel *FOXF1* mutations in sporadic and familial cases of alveolar capillary dysplasia with misaligned pulmonary veins imply a role for its DNA binding domain. *Hum Mutat.* 2013; 34:801–11. [PubMed: 23505205]
5. Szafranski P, Dharmadhikari AV, Brosens E, Gurha P, Kolodziejska KE, Zhishuo O, et al. Small noncoding differentially methylated copy-number variants, including lncRNA genes, cause a lethal lung developmental disorder. *Genome Res.* 2013; 23:23–33. [PubMed: 23034409]
6. Parris T, Nik AM, Kotecha S, Langston C, Helou K, Platt C, et al. Inversion upstream of *FOXF1* in a case of lethal alveolar capillary dysplasia with misalignment of pulmonary veins. *Am J Med Genet Part A.* 2013; 161A:764–70. [PubMed: 23444129]
7. Garabedian MJ, Wallerstein D, Medina N, Byrne J, Wallerstein RJ. Prenatal diagnosis of cystic hygroma related to a deletion of 16q24.1 with haploinsufficiency of *FOXF1* and *FOXC2* genes. *Case Rep Genet.* 2012; 2012:490408. [PubMed: 23074687]
8. Laux D, Malan V, Bajolle F, Boudjemline Y, Amiel J, Bonnet D. FOX gene cluster defects in alveolar capillary dysplasia associated with congenital heart disease. *Cardiol Young.* 2013; 23:697–704. [PubMed: 23331759]
9. del Val VA, Avila-Alvarez A, Schteffer LR, Santos F, Deiros L, Del Cerro MJ. Alveolar capillary dysplasia with misalignment of the pulmonary veins associated with aortic coarctation and intestinal malrotation. *J Perinatol.* 2014; 34:795–7. [PubMed: 25263726]
10. Sen P, Thakur N, Stockton DW, Langston C, Bejjani BA. Expanding the phenotype of alveolar capillary dysplasia (ACD). *J Pediatr.* 2004; 145:646–51. [PubMed: 15520767]