A Large Stomach on Fetal Ultrasound: More than Intestinal Obstruction

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Dear Editor,

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV), caused by variants in the *FOXF1* gene, is a rare disorder mainly involving the vascular development of the lungs.[1] Affected infants present with severe, life-threatening respiratory distress and pulmonary hypertension. Other associated features may include malformations of the heart, gastrointestinal tract, and genitourinary system. The prenatal diagnosis is challenging since the involved pulmonary histological anomalies are undetectable on ultrasound. We, here, report a prenatal case of ACDMPV identified by exome analysis because of a large fetal stomach.

A 24-year-old female had a normal ultrasound at 12 weeks' gestation with a nuchal translucency of 1.2 mm. Her first-trimester screening test based on cell-free DNA was negative. The second-trimester scans at 22 weeks showed normal fetal biometrics and morphology. A third ultrasound at 28 weeks, however, showed a large stomach [Figure 1], with no evidence of fluid filling of the pyloric duct observed during the 30-min examination. The amniotic fluid index (AFI) was 190 mm. The fetal echocardiogram showed a normal heart. Amniocentesis was performed, and considering the negative cell-free DNA testing, exome sequencing was used as the first-tier diagnostic method. This approach identified a heterozygous *de novo* nonsense variant – c.231C>G (p.Phe77 Leu) of *FOXF1* in the fetus [Figure 1], which was classified as likely pathogenic according to ACMG guidelines. Serial obstetric ultrasounds demonstrated normal fetal growth and no additional anomalies except mild polyhydramnios (AFI 250 mm) occurring at 37 weeks. The pregnancy ended in 39 weeks.

A 2680-g female infant was delivered spontaneously. Apgar scores were 9-9-9. The infant's respiratory status deteriorated within 24 h of life, requiring 100% fraction of inspired oxygen, inhaled nitric oxide, and high-frequency oscillatory ventilation. The echocardiography documented a severe pulmonary hypertension in the absence of congenital structural abnormalities. Her postnatal course was consistent with the diagnosis of ACDMPV. Given the prenatally identified *FOXF1*

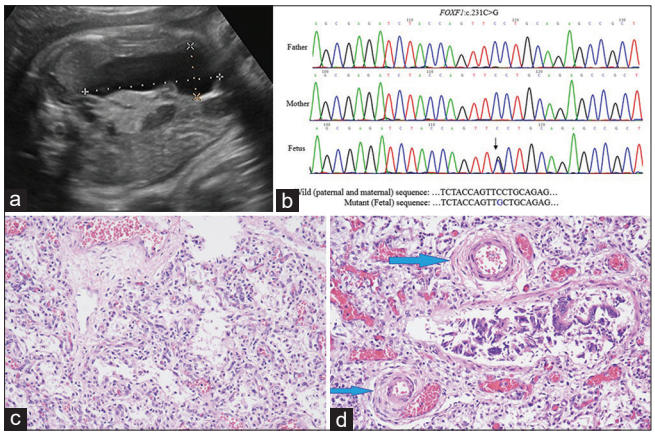

Figure 1: A fetus with alveolar capillary dysplasia with misalignment of the pulmonary veins caused by a *FOXF1* variant. (a) A scan image showing a large fetal stomach (56 mm × 26 mm) at 28 weeks' gestation; (b) DNA sequencing shows a heterozygous *FOXF1* c. 231C>G variant in the fetus and the absence of this variant in both parents. (c) Lung histology (H and E, ×20) demonstrates the characteristic histological features of the alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV): thickened alveolar septa with scarce dilated pulmonary capillaries. (d) Lung histology (H and E, ×20) demonstrates features of ACDMPV: congested pulmonary veins malpositioned, adjacent to the pulmonary arteries in the same adventitial sheath (arrow)

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variant and due to the irreversible nature of this disease, further invasive rescue measures were not attempted, and surgical evaluation of the suspected intestinal atresia was not performed. Comfort care was provided; the girl was extubated and died on the day 2 of life. The histopathological study at the autopsy showed diffuse-deficient capillarization of the lung with extensive misaligned pulmonary veins, confirming the diagnosis of ACDMPV [Figure 1]. A duodenal volvulus was also noted.

Although extrapulmonary malformations involving cardiovascular, gastrointestinal, and urogenital systems have been reported in ACDMPV cases,[2] these defects are nonspecific, and ACDMPV is rarely suspected prenatally. This present case caught our attention due to the enlargement of the fetal stomach which was assumed to result from pyloric obstruction. To date, only several patients with prenatally detected ACDMPV have been reported; all were incidentally identified to have 16q24.1 microdeletions containing *FOXF1* gene using microarray because of fetal nonspecific structural anomalies, including cystic hygroma, cardiac defect, esophageal dilation, lymphedema, and hydronephrosis.[3,4] Our case is the first one in which a *FOXF1* variant was detected by exome sequencing before birth. This case indicates that the detection of signs of intestinal obstruction in routine scans should alert physicians to considering ACDMPV in differential diagnoses. Since ACDMPV is very challenging to detect by fetal ultrasound, the more widespread implementation of prenatal genetic testing is warranted to facilitate early diagnosis.[5] This case is another example for the importance of obtaining a fetal genetic diagnosis from exome sequencing in affecting clinical decisions and managements.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent form. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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