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Axenfeld-Rieger syndrome as a rare cause of umbilical abnormality

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Letter to the editor

We present the case of a 20-year-old primiparous woman with an ultrasound at 30 weeks demonstrating a male fetus with symmetrical intrauterine growth restriction (IUGR) (head circumference <1%, abdominal circumference 6%, femur <1%) and oligohydramnios (AFI 8.6cm, <5th centile). There was an elongated, tubular cord cystic structure measuring 50 x 29 x 24 mm, that was avascular, had an echogenic border and contained sparse echogenicities. It did not appear to be an abdominal wall defect as it arose at a distance from the insertion of the cord (Figure 1A, B). The ultrasound appearances were thought to be most consistent with an umbilical cord cyst.

Due to the association of umbilical cysts with chromosomal anomalies and no aneuploidy screening this pregnancy, the patient was offered amniocentesis for karyotyping. She declined, however, but disclosed a personal history of glaucoma and hypodontia, previously diagnosed as Axenfeld-Rieger abnormality by an ophthalmologist and that her father and brother were similarly affected. She was counselled that umbilical abnormalities, in particular redundant umbilical skin are a feature of Axenfeld-Rieger syndrome (ARS), and that this likely explained the

ultrasound findings.

Further monitoring of the pregnancy identified progressive deterioration in the fetal doppler indices, IUGR and oligohydramnios. A non-reassuring cardiotocograph prompted emergency Caesarean section at 31+6 weeks. The male infant was delivered in good condition and was small for gestational age (1400 grams) and had an unusual omphalocele that arose at a distance from the cord insertion (Figure 1C). The infant underwent surgical repair. Findings included small bowel in the umbilical cord with Meckel's diverticulum attached to the omphalocele sac. Ophthalmological examination was consistent with a diagnosis of Axenfeld-Rieger syndrome.

Genetic testing in the mother identified a novel mutation in the *PITX2* gene, c.271C>G, p.(Arg91Gly). Familial studies confirmed that the mutation was present in the infant and maternal grandfather, and thus segregates with ARS in the family.

ARS is an autosomal dominant disorder of neural crest development that results in a spectrum of abnormalities including ocular anterior segment dysgenesis, glaucoma, dental abnormalities, craniofacial dysmorphism, growth retardation, cardiovascular malformations and redundant periumbilical skin[1] . ARS is a genetically heterogenous

condition, with mutations in three genes (*PITX2*, *FOXC1,* and *FOXO1A)* having been identified to date[2].

The association between ARS and omphaloceles has previously been described; the birth prevalence of omphalocele is 4.3% in ARS versus 0.03% in the general population[3,4]. It is hypothesised that mutations in *PITX2* in particular may cause omphaloceles, as *PITX2* knockout mice exhibit failure of ventral wall closure[3,5]. We hypothesise that redundant periumbilical skin and ventral wall defect gave rise to an unusual appearing omphalocele in our patient and explains the atypical appearance on antenatal ultrasound.

Clinical and genetic findings of ARS are well described in the literature, but to our knowledge, this is the first report of antenatal ultrasound findings in ARS. Confirmation of the diagnosis in the mother allowed for accurate prognostication, recurrence risk counselling, and for appropriate surveillance for complications to be instituted in the infant following delivery.

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Figure legend:

A) Transverse view, arrow showing tubular cord cyst measures 50 x 29 x24 mm with echogenic border ,avascular and sparse echogenicities

B) Sagittal view. Arrows showing anechoic abdominal wall cyst which appeared to be a continuation of the the bladder (star) and extended till the level of the umbilicus (still < 50mm).

C) Image of infant after birth, with the omphalocele (red arrow) and redundant periumbilical skin (white arrow)