Prenatal Detection of Heterotaxy Syndrome with Multisystem Fetal Anomalies in a Couple with Recurrent Pregnancy Loss: A Case Report

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***Abstract*—Background Heterotaxy syndrome is a rare disorder characterized by abnormal arrangement of thoracoabdominal organs along the left-right axis and is commonly associated with complex congenital cardiac anomalies and multisystem malformations. Recurrent pregnancy loss associated with fetal structural anomalies warrants detailed genetic evaluation.**

Case Presentation

We report a case of prenatal detection of heterotaxy syndrome with multisystem fetal anomalies in a non-consanguineous couple with recurrent pregnancy loss. The fourth pregnancy, achieved through in vitro fertilization (IVF) with preimplantation genetic testing for aneuploidy (PGT-A), demonstrated multiple fetal anomalies on prenatal ultrasonography and fetal echocardiography including right-sided stomach, absent pulmonary artery, and abnormal cardiac anatomy. Fetal autopsy revealed facial dysmorphism, left-sided pre-axial polydactyly, heterotaxy syndrome, and complex congenital cardiac anomalies.

Investigations

Chromosomal microarray analysis (CMA) performed on a previous products of conception detected Turner syndrome. Couple karyotyping was normal. Sperm DNA fragmentation assay demonstrated 50% DNA fragmentation in the husband. Whole exome sequencing (WES) of products of conception identified variants of uncertain significance in DNAH9 and TRIO genes. Expanded carrier screening did not identify any clinically significant shared pathogenic variants.

Conclusion

This case highlights the importance of detailed prenatal imaging, fetal autopsy, and advanced genetic investigations in recurrent pregnancy loss associated with fetal structural anomalies.

***Index Terms*—Congenital heart defects, Heterotaxy syndrome, Prenatal diagnosis, Recurrent pregnancy loss, Whole exome sequencing**

I. INTRODUCTION

Heterotaxy syndrome is a rare developmental disorder caused by abnormal left-right axis patterning during embryogenesis, resulting in abnormal arrangement of thoracoabdominal organs (1,2). It is commonly associated with congenital cardiac malformations, splenic abnormalities, intestinal malrotation, and other laterality defects (1,2). The estimated incidence ranges from approximately 1 in 10,000 to 1 in 20,000 live births. (1)

Advances in prenatal ultrasonography, fetal echocardiography, and molecular genetic testing have improved the detection of fetal structural anomalies and associated genetic etiologies. Recurrent pregnancy loss with congenital anomalies may indicate underlying chromosomal abnormalities, monogenic disorders, or ciliopathies (2–5). Comprehensive prenatal evaluation including fetal autopsy and genomic testing is important for recurrence risk assessment and genetic counselling.

Here, we report a prenatal case of heterotaxy syndrome with multisystem fetal anomalies in a non-consanguineous couple with recurrent pregnancy loss.

II. CASE PRESENTATION

A non-consanguineous couple with no known family history presented with a significant bad obstetric history (BOH) in view of four pregnancy losses over

seven years of marriage. The wife was gravida 4, abortion 4 (G4A4).

Obstetric History

- G1: Fetal heart beat loss at 12 weeks of gestation.
- G2: Spontaneous abortion.
- G3: Biochemical pregnancy.
- G4: Pregnancy achieved through in vitro fertilization (IVF). Preimplantation genetic testing for aneuploidy (PGT-A) was performed. Pregnancy termination was carried out at 17.2 weeks of gestation in view of multiple fetal anomalies detected on prenatal imaging.

Prenatal ultrasonography during the fourth pregnancy revealed a two-vessel umbilical cord and poor visualization of the left kidney. Nuchal translucency scan was suggestive of cardiac abnormalities. Fetal echocardiography demonstrated complex congenital anomalies including right-sided stomach, absent pulmonary artery, and abnormal cardiac anatomy.

Fetal autopsy revealed multiple dysmorphic features including mild brachycephaly, micro retrognathia, depressed nasal bridge with flat nasal tip, and left-sided pre-axial polydactyly. Internal examination demonstrated heterotaxy syndrome associated with major congenital cardiac anomalies. The heart was abnormal in shape with the apex sharply tilted towards the left side and mild displacement towards the right side of the midline. Poor interventricular grooving was noted. A monoventricle appearance was observed due to a large ventricular septal defect (VSD). Enlarged right atrium and right ventricle were present. Abnormal outflow tracts were identified with the aorta appearing larger in caliber compared to the hypoplastic pulmonary artery.

Autopsy Impression

The fetus showed facial dysmorphism with left-sided pre-axial polydactyly along with heterotaxy syndrome and major complex congenital cardiac anomalies.

In view of recurrent pregnancy loss and multisystem fetal anomalies, the couple was advised whole exome sequencing (WES) on products of conception (POC) to evaluate for a possible monogenic etiology.

III. INVESTIGATIONS

Routine Maternal Investigations

The female partner underwent evaluation for thrombophilia and autoimmune etiologies associated with recurrent pregnancy loss, including:

- Thrombophilia panel testing
- Homocysteine levels
- IgM and IgG antibody testing
- Lupus anticoagulant testing

All investigations were within normal limits.

IV. FAMILY HISTORY

Male Partner

The male partner had a positive family history of malignancies:

- Lung cancer in paternal grandfather
- Throat cancer in paternal uncle
- Oral cancer in another paternal uncle

Female Partner

No significant family history was reported.

V. GENETIC INVESTIGATIONS

Chromosomal Microarray Analysis (CMA)

Chromosomal microarray analysis performed on the first products of conception detected Turner syndrome.

Couple Karyotype

Karyotype analysis of both partners revealed normal results.

Sperm DNA Fragmentation

Sperm DNA fragmentation assay of the husband demonstrated 50% DNA fragmentation.

Whole Exome Sequencing (WES) of Products of Conception

Whole exome sequencing performed on the products of conception did not identify any pathogenic or likely pathogenic variants explaining the fetal phenotype. However, the following variants of uncertain significance (VUS) were identified:

1. DNAH9 gene
   - Exon 3: c.770G>A; p. Ser257Asn
   - Associated condition: Primary ciliary dyskinesia 40 (Autosomal recessive)
2. DNAH9 gene
   - Exon 5: c.1064C>T; p. Pro355Leu
   - Associated condition: Primary ciliary dyskinesia 40 (Autosomal recessive)
3. TRIO gene
   - Exon 40: c.5996T>C; p. Met1999Thr

- Associated condition: Intellectual developmental disorder with microcephaly (Autosomal dominant)

The identified variants were classified as variants of uncertain significance. Couple carrier screening and further genetic counselling were recommended.

Expanded Carrier Screening

Expanded carrier screening was subsequently performed for the couple. No clinically significant shared pathogenic or likely pathogenic variants associated with autosomal recessive disorders were identified on carrier screening analysis. Genes associated with laterality defects, ciliopathies, and congenital malformation syndromes, including DNAH9, ZIC3, PKD1L1, and CRELD1, were adequately covered in the carrier screening panel.

In view of recurrent pregnancy loss and fetal findings suggestive of a possible ciliopathy-related laterality disorder, detailed genetic counselling regarding recurrence risk and future reproductive options was provided to the couple.

VI. DISCUSSION

Heterotaxy syndrome comprises a spectrum of disorders caused by abnormal left-right axis development during embryogenesis (2,4). It is frequently associated with complex congenital cardiac defects and extracardiac anomalies including splenic abnormalities, intestinal malrotation, and laterality defects (1,2). Prenatal diagnosis primarily relies on detailed fetal ultrasonography and fetal echocardiography.

The present case is notable due to recurrent pregnancy loss associated with multisystem fetal anomalies including heterotaxy syndrome, complex congenital heart disease, facial dysmorphism, and pre-axial polydactyly. The fetal cardiac findings including monoventricle physiology, ventricular septal defect, abnormal outflow tracts, and pulmonary artery hypoplasia are consistent with severe laterality disorder.

Genetic etiologies have been implicated in heterotaxy syndrome, particularly genes involved in ciliary function and embryonic left-right patterning (3–5). The DNAH9 gene identified in this case is associated with primary ciliary dyskinesia, a disorder known to affect laterality determination during embryogenesis (3,5). Although the identified variants were classified as variants of uncertain significance, their potential contribution to the phenotype cannot be excluded.

The TRIO gene variant identified on WES has previously been associated with intellectual developmental disorders and microcephaly; however, its significance in the present phenotype remains uncertain.

The normal couple karyotype and negative thrombophilia workup reduced the likelihood of common chromosomal rearrangements or maternal thrombophilic causes. Increased sperm DNA fragmentation observed in the husband may have contributed to recurrent pregnancy loss.

This case highlights the importance of combining prenatal imaging, fetal autopsy, and advanced genomic investigations in evaluating recurrent pregnancy loss associated with congenital anomalies. Comprehensive evaluation is essential for appropriate counselling and future reproductive planning.

VII. CONCLUSION

This case highlights the significance of detailed prenatal evaluation and advanced genetic testing in couples with recurrent pregnancy loss and fetal structural anomalies. Comprehensive assessment including fetal autopsy, chromosomal microarray analysis, and whole exome sequencing may aid in identifying possible underlying etiologies and assist in recurrence risk counselling and future reproductive planning.

ETHICAL APPROVAL

Ethical approval was not required for this case report.

CONSENT

Written informed consent was obtained from the patient for publication of this case report.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Figure

Fig. 1: Pedigree Chart