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Detection of Trisomy 18 in a Fetal Tissue by Karyotyping and Chromosomal Microarray Analysis: A Case Report

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Abstract

We report the case of a 44-year-old woman who experienced a miscarriage. Fetal tissue obtained from the products of conception (POC) was analyzed to determine the genetic cause of pregnancy loss. Two complementary genetic testing methods were performed: conventional karyotyping and chromosomal microarray analysis (CMA). Karyotyping demonstrated an abnormal female karyotype, 47, XX +18, consistent with trisomy 18, while CMA identified a duplication of the entire chromosome 18, thereby confirming the presence of three copies of chromosome 18. The findings from both techniques were fully concordant and established trisomy 18 (Edward syndrome) as the cause of the miscarriage. This case highlights the value of combined cytogenetic and molecular genomics techniques to identify chromosomal anomalies and can be valuable for genetic counseling and for planning future pregnancies.

Keywords

Trisomy 18, Whole Chromosome, Chromosomal Microarray, Karyotyping, Pregnancies

1. Introduction

Trisomy 18, also known as Edwards syndrome, is a chromosomal disorder caused by the presence of an extra copy of chromosome 18. It is the second most common autosomal trisomy among live-born infants after Trisomy 21 and is associated with significant morbidity and mortality [1] [2]. The syndrome is characterized by multiple congenital anomalies, including cardiac defects, craniofacial abnormalities, musculoskeletal malformations, renal abnormalities, and severe neurodevelopmental impairment [1] [3]. Most affected pregnancies result in spontane-

ous miscarriage, stillbirth, or early neonatal death. The incidence of Trisomy 18 is estimated to be approximately 1 in 1,500 to 1 in 6,000 pregnancies, with advanced maternal age recognized as a major risk factor [1] [4]. In this case, Noninvasive prenatal testing (NIPT) was initially performed using Next generation sequencing and confirmed by cytogenetic or molecular genetic testing, such as karyotyping and chromosomal microarray analysis (CMA) [4] [5]. Analysis of products of conception (POC) following pregnancy loss plays a critical role in identifying chromosomal abnormalities and determining the underlying cause of miscarriage. Such investigations provide valuable information for genetic counseling and future reproductive planning [5] [6].

Here, we present a case of a first-trimester missed abortion in a 44-year-old woman in which chromosomal microarray and karyotype analysis of POC tissue revealed Trisomy 18, highlighting the importance of genetic evaluation in pregnancy loss associated with advanced maternal age.

2. Case Presentation

A 44-year-old pregnant woman presented for a routine first-trimester obstetric ultrasound examination at 8 weeks and 4 days of gestation. The patient was of advanced maternal age and had no significant clinical symptoms at the time of presentation. She reported no abdominal or pelvic pain, vaginal bleeding, fever, or other symptoms suggestive of pregnancy complications. Her medical history was unremarkable for malignancy, and there was no history of previous pelvic or uterine surgeries.

Following the guidelines from American College of Obstetricians and Gynecologists (ACOG). The patient was offered non-invasive prenatal testing (NIPT). Analysis of circulating cell-free fetal DNA obtained from maternal plasma was performed using next-generation sequencing to screen for common fetal aneuploidies involving chromosomes 13, 18, and 21. The NIPT results were positive for trisomy 18. Since NIPT is a screening test, to further evaluate and confirm this finding, using a diagnostic test, conventional karyotype analysis and chromosomal microarray analysis (CMA) were subsequently performed. No relevant family history of genetic disorders was available, and no additional genetic testing had been reported.

Ultrasonographic evaluation revealed findings consistent with a missed abortion, characterized by the absence of fetal cardiac activity despite the presence of an intrauterine gestational sac and fetal tissue corresponding to the gestational age. Following the diagnosis, products of conception (POC) were obtained and submitted to the laboratory for genetic evaluation to investigate a possible chromosomal etiology underlying the pregnancy loss.

The laboratory received fetal tissue derived from the POC specimen for cytogenetic and molecular analysis. Two complementary genetic testing methods were performed: conventional karyotype analysis and chromosomal microarray analysis (CMA). Karyotyping was utilized to evaluate the fetal chromosomal comple-

ment and detect numerical or large structural chromosomal abnormalities, while CMA was performed to provide a high-resolution genome-wide assessment for chromosomal copy number changes. These analyses were undertaken to identify potential genetic abnormalities associated with the miscarriage and to provide information relevant to genetic counseling and future reproductive planning.

The results of both karyotype and chromosomal microarray analyses demonstrated the presence of an extra copy of chromosome 18, consistent with Trisomy 18 (Edwards syndrome) (**Figure 1**). Maternal cell contamination was excluded based on cytogenetic findings and specimen processing procedures. This finding established a chromosomal cause for the pregnancy loss and was concordant with the increased risk of fetal aneuploidy associated with advanced maternal age.

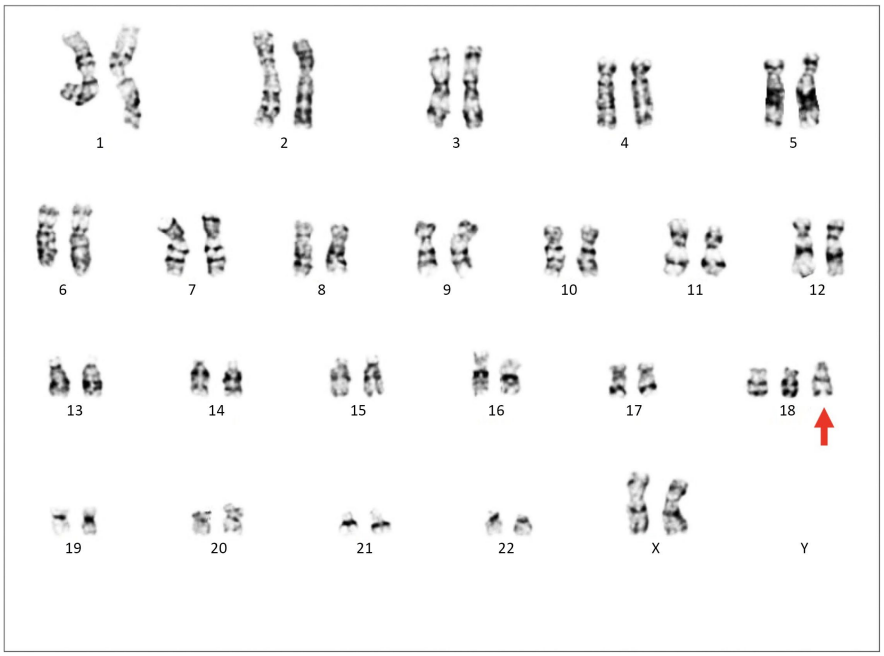

Figure 1. Karyotype analysis demonstrating trisomy 18 in the product of conception (POC).

Karyotype analysis of fetal tissue obtained from products of conception (POC) revealed an additional copy of chromosome 18, resulting in a karyotype consistent with trisomy 18 (Edwards syndrome) (Red Arrow). The sex chromosome complement was 46, XX, indicating a female fetus. The findings confirm the presence of a chromosomal aneuploidy associated with pregnancy loss.

3. Technology

In Clinical Diagnostics, Karyotype has been the gold standard for visualizing chromosomes. The technology involved for Karyotyping is much simpler. The main instrument used for analysis is a Brightfield microscope in order to scan and count the 20 metaphase cells. In more advanced labs, there are automated scanners that scan each harvested slide for any metaphases present, which can make it easier for

the technologists and analysis. The resolution of detecting genomic changes is low often limited to be up to 5 MB.

Whereas a chromosomal microarray analysis can detect duplications and deletions, low-level mosaicisms in the genomic material (DNA) at a higher resolution than a routine karyotype.

This ability to detect submicroscopic genomic abnormalities has revolutionized the clinical diagnostic approach to individuals with genetic conditions. Over the past decade, many pivotal advances have emerged from SNP array analysis. Microarray technology in prenatal diagnosis is emerging and promises higher sensitivity for detecting genomic abnormalities in fetuses with ultrasound abnormalities and other indications.

Here we use the Applied Biosystems CytoScan HD assay, which provides a genome-wide approach that enables high-resolution DNA copy number analysis to detect gains, losses, loss of heterozygosity (LOH), regions identical by descent, and uniparental disomy (UPD) on a single array.

4. Methods

DNA extraction from the fetal tissue sample was performed using the DNeasy Blood & Tissue Kit (Cat. No. ID69504) from QIAGEN. According to the CytoScan HD Assay protocol, 500 ng of input DNA at a concentration of 75 ng/μL was used. The DNA was subsequently digested, ligated, labeled, fragmented, and hybridized to the CytoScan HD microarray, which contains approximately 2.69 million markers distributed across the entire genome, including both copy number and single-nucleotide polymorphism (SNP) probes. These markers enable the detection of chromosomal copy number changes, allelic imbalances, and regions of loss of heterozygosity/absence of heterozygosity (LOH/AOH).

The CytoScan HD array was developed by the International Standard Cytogenomic Array Consortium (ISCA) for the detection of clinically significant genomic copy number abnormalities. During interpretation, detected copy number gains and losses were cross-referenced with publicly available genomic databases, including the International Standards for Cytogenomic Arrays (ISCA) database, the Database of Genomic Variants (DGV), and the Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources (DECIPHER), to assess their clinical significance. Data analysis was performed using Chromosome Analysis Suite (ChAS) software. Primary analysis was conducted by scientists certified by the American Society for Clinical Pathology (ASCP), and final interpretation was provided by a laboratory director certified by the American Board of Medical Genetics and Genomics (ABMGG).

The assay is designed to detect genomic deletions and duplications represented on the array; however, not all genomic variants can be identified. Point mutations, balanced chromosomal rearrangements (including reciprocal and Robertsonian translocations), uniparental disomy, and low-level mosaicism may not be detected by this methodology. In addition, the clinical interpretation of copy number var-

iants is based on currently available genomic knowledge and may be subject to future re-evaluation as additional evidence becomes available.

For conventional cytogenetic analysis, products of conception (POC) tissue were processed and cultured on the day of specimen receipt. Cells were distributed into multiple culture vessels and maintained in culture media to promote cellular growth. Cultures were monitored until adequate cellular proliferation was achieved, after which metaphase chromosomes were harvested for analysis. G-banded chromosome analysis was performed using GTG banding at an approximate resolution of 450 bands per haploid set. A minimum of 20 metaphase cells were evaluated according to standard cytogenetic laboratory guidelines to assess for numerical and structural chromosomal abnormalities.

5. Results and Discussion

Conventional cytogenetic analysis demonstrated an abnormal female karyotype, 47, XX, +18, consistent with complete trisomy 18 (Figure 1). Twenty metaphase cells were analyzed, and all cells demonstrated the presence of an additional chromosome 18. Chromosomal microarray analysis (CMA) confirmed a whole-chromosome gain involving chromosome 18, consistent with complete trisomy 18 (Figure 2). No additional clinically significant copy number abnormalities were identified. The findings obtained by both methodologies were fully concordant and established trisomy 18 as the genetic etiology of the pregnancy loss.

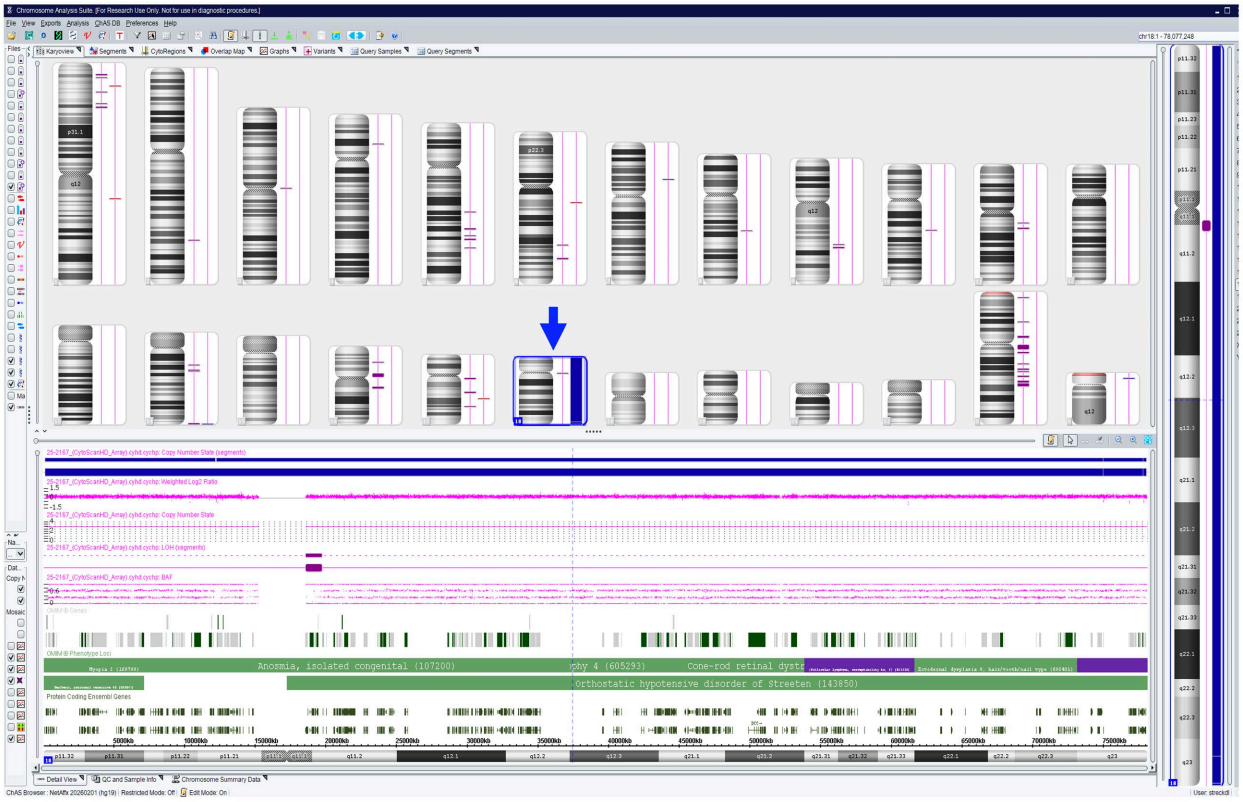

Figure 2. Chromosomal microarray analysis demonstrating complete trisomy 18.

Chromosomal microarray analysis (CMA) of products of conception demonstrated a whole-chromosome gain of chromosome 18 (Blue arrow), reported as arr [GRCh37] 18p11.32q23 (184254_78012829) x 3. The finding indicates three copies of chromosome 18 across the entire chromosome, consistent with complete trisomy 18 (Edwards syndrome). The CMA result was concordant with the conventional karyotype findings and confirmed the chromosomal basis of the pregnancy loss.

Trisomy 18, also known as Edwards syndrome, is one of the most common autosomal chromosomal abnormalities observed in human pregnancies and is associated with high rates of spontaneous miscarriage, stillbirth, and neonatal mortality [1]. The disorder results from the presence of an extra copy of chromosome 18, most commonly arising from meiotic nondisjunction. Advanced maternal age is a well-recognized risk factor for chromosomal nondisjunction events, and the maternal age of 44 years in this case likely contributed to the increased risk of fetal aneuploidy. The identification of trisomy 18 in the products of conception provides a definitive genetic explanation for the pregnancy loss and offers valuable information for patient counseling regarding recurrence risk and future reproductive planning. Because complete trisomy 18 in products of conception most commonly arises from sporadic meiotic nondisjunction, the recurrence risk in subsequent pregnancies is generally low and is primarily related to maternal age, unless a parental chromosomal rearrangement or other inherited predisposition is identified.

Chromosomal abnormalities account for approximately 50% - 60% of first-trimester pregnancy losses, with autosomal trisomies representing the most frequently identified genetic abnormalities in products of conception [7]. Although trisomy 16 is the most commonly observed autosomal trisomy associated with miscarriage, trisomy 18 remains a significant contributor to early fetal loss. The diagnosis of trisomy 18 in this case is consistent with the known natural history of the disorder, as many affected pregnancies result in spontaneous miscarriage before fetal viability.

This case also highlights the complementary roles of conventional karyotyping and chromosomal microarray analysis in the evaluation of pregnancy loss. Conventional karyotyping remains the gold standard for detecting numerical chromosomal abnormalities and large structural rearrangements, while CMA provides a higher-resolution genome-wide assessment capable of identifying submicroscopic copy number variants that may not be detectable by routine chromosome analysis. In the present case, both methodologies produced concordant results, demonstrating complete trisomy 18 and confirming the chromosomal basis of the miscarriage. The agreement between these independent testing platforms increases diagnostic confidence and supports the accuracy of the findings.

The use of CMA has expanded considerably in reproductive genetics because it does not require successful cell culture and can detect genomic imbalances at a much higher resolution than conventional cytogenetic techniques [8]. This advantage is particularly relevant in products of conception specimens, where culture failure can limit the success of karyotype analysis. Nevertheless, conventional

chromosome analysis continues to provide important information regarding chromosomal structure and balanced rearrangements that cannot be fully characterized by microarray alone. Therefore, the combined application of both technologies offers a comprehensive approach to identifying chromosomal abnormalities associated with pregnancy loss.

Overall, this case demonstrates the value of genetic evaluation following miscarriage, particularly in pregnancies occurring at advanced maternal age. The concordant identification of complete trisomy 18 by both karyotype and chromosomal microarray analysis established a clear genetic cause for the pregnancy loss and provided clinically meaningful information for genetic counseling and future reproductive decision-making.

6. Limitation

This report describes a single case and therefore its findings cannot be generalized to all pregnancy losses or cases of trisomy 18. In addition, parental cytogenetic studies were not performed, and the evaluation did not include determination of the parental origin or specific meiotic mechanism responsible for the extra chromosome 18. Consequently, the underlying nondisjunction event could not be further characterized. Despite these limitations, the concordant results obtained by conventional karyotyping and chromosomal microarray analysis established trisomy 18 as the genetic cause of the pregnancy loss.

7. Conclusion

This case demonstrates the utility of both conventional karyotyping and chromosomal microarray analysis in the evaluation of products of conception following pregnancy loss. Concordant findings from both methodologies confirmed complete trisomy 18 as the underlying genetic cause of the miscarriage. While karyotyping remains valuable for the detection of numerical and structural chromosomal abnormalities, chromosomal microarray analysis provides higher-resolution genomic assessment and serves as an important complementary tool in reproductive genetics. Accurate identification of chromosomal abnormalities is essential for patient counseling, recurrence risk assessment, and future reproductive planning. Complete Trisomy 18 in POC usually reflects sporadic meiotic nondisjunction with future risk driven mainly by advanced maternal age unless there is parental rearrangement suspected.

Ethics Statement

Consent for this publication was obtained for this case report. Institutional review was waived off.

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Conflicts of Interest

We hereby confirm that there are no known conflicts of interest related to this publication and that no significant financial support was received that could have influenced the results or conclusions of this work. We further confirm that all listed authors have reviewed and approved the manuscript, and that no individual meeting the criteria for authorship has been omitted. Additionally, all authors have agreed to the order in which their names appear in the manuscript.

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