CASE REPORT

Reproductive consequences of genome-wide paternal uniparental disomy mosaicism: description of two cases with different mechanisms of origin and pregnancy outcomes

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Objective: To describe the molecular and cytogenetic characterization of two different prenatal cases of androgenetic/biparental mosaicism and review the different possible mechanisms of origin in each case.
Design: Case study and literature review.
Setting: Tertiary medical center (prenatal diagnosis unit).
Patient(s): A 26-year-old pregnant woman referred for suspected partial mole placenta and a 33-year-old pregnant woman referred for polyhydramnios and fetal malformations.
Intervention(s): Ultrasound examination, prenatal invasive procedures, molecular and cytogenetic analysis, physical and pathologic evaluation, and genetic counseling.
Main Outcome Measure(s): Cytogenetic analysis, fluorescent in situ hybridization, and quantitative fluorescence polymerase chain reaction (QF-PCR) analysis.
Result(s): The finding of a normal karyotype together with a triploidy-like QF-PCR profile led to the diagnosis of two cases of androgenetic (genome-wide paternal uniparental disomy)/biparental mosaicism. The first case showed placental mesenchymal dysplasia and a normal fetus, and the second one presented a fetus showing Beckwith-Wiedemann syndrome features and an apparently normal placenta.
Conclusion(s): These cases highlight the wide range of possible clinical presentations of androgenetic/biparental mosaicism, the variety of mechanisms of their origin, and the importance of the combination of molecular and cytogenetic analysis to achieve an accurate diagnosis and provide reproductive counseling. (Fertil Steril® 2009;92:393.e5–e9. ©2009 by American Society for Reproductive Medicine.)

Key Words: Androgenetic, mosaicism, genome-wide paternal UPD, placental mesenchymal dysplasia, Beckwith-Wiedemann syndrome, QF-PCR

Quantitative fluorescence polymerase chain reaction (QF-PCR) has been developed as a rapid method to detect common autosomal and sex chromosome aneuploidies in prenatal diagnosis (1, 2). Triploidy is one of the abnormalities which can be detected by QF-PCR in prenatal samples and occurs in 3% of human pregnancies, although most of them are aborted spontaneously between 7 and 17 weeks of gestation (3). However, a similar whole-genome triallelic QF-PCR profile could be obtained from a mixed population of normal and androgenetic (complete genome-wide paternal uniparental disomy) cells, which has been previously associated with placental mesenchymal dysplasia (PMD) (4–6). Although PMD has recognizable clinicopathologic features, it is often mistaken as partial hydatidiform mole (PHM). Placental mesenchymal dysplasia can be associated with normal fetuses and pregnancies often extending into the third trimester. However, the fetuses are at risk of intrauterine growth restriction (IUGR) and fetal/neonatal death, and about 20% of them have Beckwith-Wiedemann syndrome (BWS), which is characterized by macrosomia, visceromegaly, hemihyperplasia, macroglossia, omphalocele, cytomegaly of adrenal glands, and polyhydramnios (7, 8). Beckwith-Wiedemann syndrome

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presents a complex mode of inheritance, including abnormal expression of imprinted genes located at chromosome 11p15.5 as a consequence of defective/absent maternal gene copy or duplicated paternal gene copy.

In the present report, we describe two different prenatal cases in which the finding of a normal karyotype together with a triploidy-like QF-PCR profile led to the detection of an androgenetic cell line in addition to the normal one and to explain the resulting phenotypes.

MATERIALS AND METHODS

This study was reviewed and approved by the Research Ethics Committee of the Hospital Clinic, and informed patient consents were obtained.

Clinical Case 1

A 26-year-old woman was referred for chorionic villi sampling (CVS) at 13.4 weeks' gestation owing to the sonographic suspicion of partial mole placenta. Discrepancies between the results obtained by QF-PCR and full karyotyping led to the performance of an amniocentesis at 15 weeks' gestation. The QF-PCR studies were also carried out in amniotic fluid and parents' blood. The results showed a normal male karyotype, and the couple decided to continue the pregnancy.

At 33.5 weeks' gestation there was premature rupture of membranes and induced delivery at 34.2 weeks. A phenotypically normal boy was born, with a birth weight of 2,190 g (42nd percentile). Postnatal development was normal. Pathologic and histologic examination of the placenta gave no signs of molar degeneration but showed features of PMD (cystic structures, dilated villus vessels, multiple thrombi, and no evidence of trophoblastic hyperplasia). Samples were taken from five different placental locations to perform QF-PCR and fluorescence in situ hybridization (FISH) analysis.

Clinical Case 2

A 33-year-old woman was referred at 30 weeks' gestation owing to polyhydramnios and fetal malformations (hepatomegaly, hyperplasia of the left kidney, and paravesical cyst) detected at ultrasound examination. An amniocentesis had previously been performed at 26 weeks in another center, with discrepant results between QF-PCR and full karyotyping. Amnioreduction was performed, and cytogenetic and QF-PCR analyses of the new amniotic fluid sample were done. Spontaneous fetal death took place 1 day after amniodrainage. Labor was induced and a female fetus was delivered at 30.2 weeks gestation, with a birth weight of 1,740 g (90th percentile). Pathologic findings included hypertrophy of the right lung, right kidney and liver, peritoneal cyst adjacent to liver, and hamartoma in right pancreas. The fetus exhibited features consistent with BWS, including polyhydramnios, overgrowth, embryonic tumors, and visceromegaly. The placenta weighed 312 g and its macroscopic appearance was normal, and the umbilical cord showed hypoplasia of one of its three vessels. Unfortunately, no placental samples were collected to perform neither histologic nor genetic analysis. A blood sample was obtained from the fetal heart, and new QF-PCR studies were carried out, as well as with the parents' blood.

Cytogenetic Studies

Karyotype from CVS was obtained after short-term culture (overnight incubation) and long-term culture (10–15 days' incubation) using standard methods (case 1). Twenty-two and 16, respectively, G-banded Wright-stained metaphases were analyzed. Chromosome analysis was also performed on cultured amniocytes (cases 1 and 2); 20 G-banded Wright-stained metaphases from two independent cultures were analyzed.

The FISH analysis was performed on deparaffinized sections of placenta samples (case 1) using cenX/cenY probe (Vysis, Downers Grove, IL). Paraffin-embedded samples were deparaffinized using standard protocols, and FISH was performed following the manufacturer's instructions. Fifty nuclei from each sample were scored.

Molecular Studies

Genomic DNA was obtained from part of the CVS (case 1), amniotic fluid (cases 1 and 2), five different fresh placenta samples (case 1), fetal blood (case 2), and peripheral blood of both parents by standard methods (cases 1 and 2). The QF-PCR was performed using 18 microsatellite markers from chromosomes 13, 18, 21, X, and Y. To determine the origin of the extra allelic dose, 17 more microsatellite markers from chromosomes 1, 3, and 4 were tested in case 1 and 15 microsatellites from chromosomes 7, 11, and 15 were tested in case 2. The PCR amplification was performed under standard conditions using fluorescently labeled primers. The PCR products were run on an ABI3100 Genetic Analyzer (ABI, Foster City, CA), and results were analyzed with GeneMapper 3.5 software (ABI).

RESULTS

Case 1

Both CVS short- and long-term cultures showed a normal male karyotype, whereas QF-PCR showed a triploid (triallelic) profile (69,XXY), which was an expected result because the indication for the prenatal diagnosis was a suspicion of PHM. A confirmatory amniocentesis was performed, giving normal cytogenetic and QF-PCR results (46,XY). Molecular studies showed that the extra chromosome set found in the CV sample was of paternal origin. Microsatellite markers test revealed two different paternal alleles, so there were two distinct haploid paternal contributions (Table 1). After delivery, pathologic examination of the placenta led to the diagnosis of PMD. Because this condition has been reported to be associated with the presence of