

Case Report

Prenatal diagnosis of maternal uniparental disomy 5 by amniocentesis associated with confined placental mosaicism for trisomy 5 and fetal trisomy 21 in a pregnancy

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ABSTRACT

Objective: We present prenatal diagnosis of maternal uniparental disomy (UPD) 5 by amniocentesis associated with confined placental mosaicism (CPM) for trisomy 5 and fetal trisomy 21 in a pregnancy. **Case report:** A 45-year-old woman underwent chorionic villus sampling (CVS) at 11 weeks of gestation because of maternal advanced age and an increased nuchal translucency of 4.0 mm in the first-trimester screening. CVS revealed a karyotype of 47,XY,+21[98]/48,XY,+5,+21[25]. Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from chorionic villi revealed arr (5) × 3, arr (21) × 3 compatible with double trisomy 5 and trisomy 21. The woman underwent amniocenteses at 20 weeks and 22 weeks of gestation. Amniocenteses revealed a karyotype of 47,XY,+21. The parental karyotypes were normal. Quantitative fluorescent polymerase chain reaction (QF-PCR) on the DNA extracted from uncultured amniocytes showed trisomy 21 of maternal origin and maternal UPD 5. aCGH and interphase fluorescence *in situ* hybridization (FISH) on uncultured amniocytes confirmed trisomy 21. Prenatal ultrasound findings were unremarkable. The parents decided to continue the pregnancy, and a 2,198-g male baby was delivered at 38 weeks of gestation with characteristic phenotype of Down syndrome of hypertelorism, epicanthic folds and hypoplastic middle phalanx of the fifth fingers. Cytogenetic analysis of cord blood, umbilical cord and placenta revealed a karyotype of 47,XY,+21. QF-PCR analysis of the DNA extracted from placenta revealed double trisomy 5 and trisomy 21 with maternal gene dosage increase in chromosome 5 and chromosome 21.

Conclusion: Prenatal diagnosis of CPM for trisomy 5 at CVS can be associated with UPD 5 in the fetus, and UPD 5 causes no specific phenotype.

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Introduction

Chromosomal mosaicism caused by postzygotic mitotic non-disjunction in a diploid conceptus or by trisomy rescue of a mitotic loss of the supernumerary chromosome in a trisomic

conceptus can be detected in 1–2% of chorionic villi sampling (CVS) samples [1].

In a study of 52,673 CVS samples, Grati [2] found mosaic cases in 1.81% of the total cases and true fetal mosaicism in amniocytes in 12.8% of the mosaic cases. The frequency of uniparental disomy (UPD) involving chromosomes 2, 6, 7, 11, 14, 15, 16 and 20 in the study by Grati [2] was 0.01% in all CVS samples and was 2.5% in the investigated cases. In a study of 60,347 CVS samples, Malvestiti et al. [1] found mosaic cases in 2.18% of the total cases. Of the 1,001 mosaic cases with subsequent amniocentesis in their study, Malvestiti et al. [1] additionally found the overall risk of true fetal mosaicism was

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13%, and the UPD incidence was 2.1% in the investigated cases. Here, we present our experience of prenatal diagnosis of maternal UPD 5 by amniocentesis associated with confined placental mosaicism (CPM) for trisomy 5 and fetal trisomy 21 in a pregnancy.

Case report

A 45-year-old, gravida 3, para 0, woman underwent CVS at 11 weeks of gestation because of maternal advanced age and an increased nuchal translucency of 4.0 mm in the first-trimester screening. Her husband was 37 years old, and there was no family history of congenital malformations. CVS revealed a karyotype of 47,XY,+21[98]/48,XY,+5,+21[25]. Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from chorionic villi revealed $\text{arr}(5) \times 3$, $\text{arr}(21) \times 3$ compatible with double trisomy 5 and trisomy 21. The woman underwent amniocentesis at 20 weeks and 22 weeks of gestation. Amniocentesis revealed a karyotype of 47,XY,+21. The parental karyotypes were normal. Quantitative fluorescent polymerase chain reaction (QF-PCR) on the DNA extracted from uncultured amniocytes showed trisomy 21 of maternal origin and maternal UPD 5 (Fig. 1). aCGH and interphase fluorescence *in situ* hybridization (FISH) on uncultured amniocytes confirmed trisomy 21. Prenatal ultrasound findings were unremarkable. The parents decided to continue the pregnancy, and a 2,198-g male baby was delivered at 38 weeks of gestation with characteristic phenotype of Down syndrome of hypertelorism, epicanthic folds and hypoplastic middle phalanx of the fifth fingers. Cytogenetic analysis of cord blood, umbilical cord and placenta revealed a karyotype of 47,XY,+21. QF-PCR analysis of the DNA extracted from placenta revealed double trisomy 5 and trisomy 21 with maternal gene dosage increase in chromosome 5 and chromosome 21 (Fig. 1).

Discussion

We have presented a very rare case of UPD 5 at amniocentesis associated with CPM for trisomy 5 at CVS. The occurrence of UPD in

all CVS samples is about 0.01% and is about 2.5% in the investigated cases [2]. The present case provides evidence that mosaic trisomy 5 at CVS can be associated with UPD 5 in the fetus, and UPD 5 causes no specific phenotype. Daniel et al. [3] previously reported a case of trisomy 5 at CVS, and maternal UPD 5 and normal karyotype at amniocentesis. In that case, CVS showed trisomy 5 of maternal origin of a 42-year-old mother, and the infant was normal at term and developed normally. Prenatal diagnosis of trisomy mosaicism at CVS should alert the possibility of UPD formation after the rescue of a trisomic zygote. UPD for chromosomes 6, 7, 11, 14, 15, 16 and 20 have been reported to be associated with abnormal phenotype such as paternal UPD 6 with transient neonatal diabetes mellitus (TNDM) [Online Mendelian Inheritance in Man (OMIM) 601410], maternal UPD 7 with Silver-Russell syndrome 2 (OMIM 618905), maternal UPD 11 with Silver-Russell syndrome 1 (OMIM 180860), paternal UPD 11 with Beckwith-Wiedemann syndrome (OMIM 130650), maternal UPD 14 with Temple syndrome (OMIM 616222), paternal UPD 14 with Kagami-Ogata syndrome (OMIM 608149), maternal UPD 15 with Prader-Willi syndrome (OMIM 176270), paternal UPD 15 with Angelman syndrome (OMIM 105830), maternal UPD 20 with growth failure and hyperactivity (OMIM 139320) and paternal UPD 20 with pseudohypoparathyroidism 1B (OMIM 603233), and maternal UPD 16 syndrome.

The present case was associated with CPM for trisomy 5 but no mosaic trisomy 5 at amniocentesis. It is estimated that about 13% of the mosaic cases at CVS have true fetal mosaicism at amniocentesis [1,2]. Mosaic trisomy 5 at amniocentesis can be associated with fetal abnormalities. In a review of seven cases with mosaic trisomy 5 at amniocentesis, Chen et al. [4] found 4/7 had clinically normal outcome, 3/7 had structural defect, mainly ventricular septal defect, 6/6 had normal karyotype in the blood, and 2/3 had mosaic trisomy 5 in the fetal tissues other than blood. Mosaic trisomy 5 at amniocentesis can also be associated with UPD 5. Reitinger et al. [5] reported prenatal diagnosis of 33% (5/15 cells) mosaic trisomy 5 by amniocentesis associated with UPD 5 and multiple anomalies of facial dysmorphism, bilateral bifid thumbs, hypospadias, a perineal fistula, unilateral multicystic kidney and complex congenital heart disease with ventricular and atrial septal defects and polyvalvular defects. The peripheral blood had a normal karyotype. Hwang et al. [6] reported a case of VACTERL phenotype with mosaic trisomy 5 and UPD 5. Prenatal ultrasound showed a ventricular septal defect and agenesis of the corpus callosum, aCGH analysis on amniotic fluid revealed 14% mosaic trisomy 5 and UPD 5. Cultured skin fibroblasts revealed trisomy 5. However, isolated UPD 5 without mosaic trisomy 5 at amniocentesis causes no abnormal phenotype. Kunwar et al. [7] recently reported prenatal diagnosis of isolated paternal UPD 5 due to intrauterine growth restriction in a pregnancy with phenotypically normal child.

Although chromosome 5 does not contain imprinting genes, UPD 5 may be associated with some autosomal recessive disorders if there is homozygosity for a recessive mutation resulting from UPD. Nomata et al. [8] reported a 10-year-old Japanese girl with Netherton syndrome (OMIM 256500), an autosomal recessive syndrome type of ichthyosis, due to maternal isodisomy of chromosome 5 with a pathogenic mutation in *SPINK5*. García et al. [9] reported prenatal diagnosis of homozygous mutation of *SLC26A2* associated with autosomal recessive multiple epiphyseal dysplasia by amniocentesis in a pregnancy with polyhydramnios and fetal skeletal dysplasia. The father was a carrier of the mutation, and postnatal polymorphic DNA marker analysis confirmed paternal isodisomy of chromosome 5 in the proband. Park et al. [10] reported a 22-year-old female with an autosomal recessive disorder of hereditary sensory and autonomic neuropathy 2B caused by a homozygous *RETREG1* mutation inherited from a carrier father and paternal isodisomy of chromosome 5.

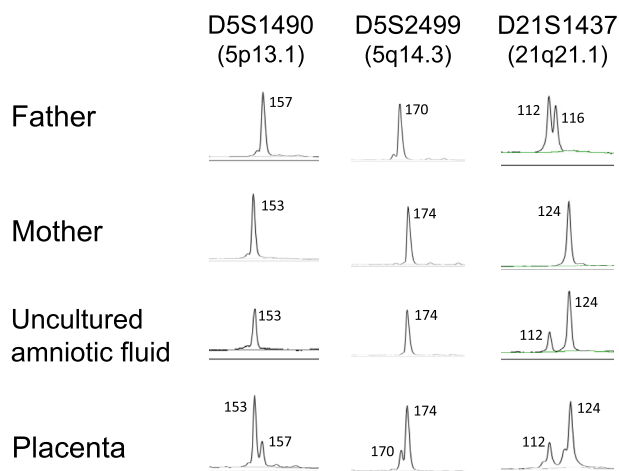


Fig. 1. Quantitative fluorescent polymerase chain reaction assays on the DNAs extracted from parental bloods, uncultured amniocytes and placental tissues using the informative markers of D21S1437, D5S1490 and D5S2499 shows a maternal origin of trisomy 21 and maternal uniparental disomy (UPD) for chromosome 5 in the uncultured amniocytes, and double trisomy 5 and trisomy 21 in the placental tissues. In the markers of D5S1490 and D5S2499, the uncultured amniocytes inherit only the maternal allele, consistent with the diagnosis of UPD 5, and the placental tissues inherit a maternal gene dosage increase with a maternal allele: paternal allele ratio of 2:1, consistent with the diagnosis of trisomy 5. In the marker of D21S1437, both uncultured amniocytes and placental tissues inherit a maternal gene dosage increase with a maternal allele: paternal allele ratio of 2:1, consistent with the diagnosis of trisomy 21.

In summary, we present prenatal diagnosis of maternal uniparental disomy (UPD) 5 by amniocentesis associated with CPM for trisomy 5 and fetal trisomy 21 in a pregnancy. Prenatal diagnosis of CPM for trisomy 5 at CVS can be associated with UPD 5 in the fetus, and UPD 5 causes no specific phenotype.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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