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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of low-level mosaicism for tetrasomy 18p at amniocentesis in a pregnancy with a favorable outcome

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ABSTRACT

Objective: We present prenatal diagnosis of low-level mosaicism for tetrasomy 18p at amniocentesis in a pregnancy with a favorable outcome.

Case Report: A 40-year-old woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a *de novo* supernumerary isochromosome 18p in eight of 39 colonies of cultured amniocytes. The karyotype was 47,XX,+i(18)(p10)[8]/46,XX[31]. Array comparative genomic hybridization (aCGH) analysis using uncultured amniocytes revealed arr 18p11.32p11.21 [hg 19] (148,963–14,081,887) × 2–3. Repeat amniocentesis was performed at 20 weeks of gestation. Interphase fluorescence *in situ* hybridization (FISH) analysis showed four 18p11.22-specific probe (RP11-918F20) signals in 11.7% (12/103 cells) of uncultured amniocytes. aCGH analysis on uncultured amniocytes did not detect genomic imbalance in chromosome 18. The parental karyotypes were normal. Polymorphic DNA marker analysis excluded uniparental disomy 18. Cytogenetic analysis of cultured amniocytes at repeat amniocentesis revealed a karyotype of 47,XX,+i(18)(p10)[2]/46,XX[12]. Prenatal ultrasound was unremarkable. The pregnancy was carried to 38 weeks of gestation, and a 2742-g phenotypically normal female baby was delivered with a cord blood karyotype of 46,XX. When examined at 8 months of age, the infant was normal in growth and psychomotor development. Interphase FISH analysis on 21 uncultured urinary cells revealed normal signals in all cells and no mosaic tetrasomy 18p.

Conclusion: Low-level mosaic tetrasomy 18p at amniocentesis without ultrasound abnormalities can be associated with a favorable outcome.

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Introduction

Tetrasomy 18p [Online Mendelian Inheritance in Man (OMIM) 614290] or isochromosome 18p syndrome is characterized by low-set malformed ears, small pinched nose, small mouth, high-arched palate, micrognathia, prognathism, developmental delay, cognitive impairment, feeding problems, growth retardation, microcephaly, strabismus, abnormal muscle tone, scoliosis/kyphosis, common findings of neonatal jaundice, respiratory distress, recurrent otitis media, hearing loss, seizures, refractive errors, constipation, gastroesophageal reflux, cryptorchidism, congenital heart defects and foot anomalies; and occasional findings of hernias, myelomeningocele, kidney defects, short stature and failure to respond to growth hormone stimulation [1,2].

However, mosaic tetrasomy 18p have been associated with phenotypic variability ranging from an apparently normal phenotype to multiple abnormalities [3–11].

Prenatal diagnosis of mosaic tetrasomy 18p is uncommon, and remains a challenge to obstetricians and genetic counselors. To our knowledge, only 10 cases of prenatally detected mosaic tetrasomy 18p have been reported [3–10,12]. We previously reported two cases of prenatally detected low-level mosaicism for tetrasomy 18p with a favorable fetal outcome [Chen et al., 2012, 2014]. Here, we present an additional case. Our reports provide evidence that low-level mosaicism for tetrasomy 18p at amniocentesis without abnormal ultrasound findings can be associated with a favorable outcome.

Case report

A 40-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Her husband was 37 years old, and there was no history of congenital malformations. Cytogenetic analysis of cultured amniocytes revealed mosaic supernumerary isochromosome 18p. In eight of 39 separated colonies of cultured amniocytes, an abnormal karyotype of 47,XX,+i(18)(p10) was noted, while the other 31 colonies had a karyotype of 46,XX. The karyotype of amniocentesis was 47,XX,+i(18)(p10)[8]/46,XX[31]. Array comparative genomic hybridization (aCGH) analysis by ISCA oligonucleotide array using uncultured amniocytes revealed arr 18p11.32p11.21 [hg 19] (148,963–14,081,887) × 2–3. Level II ultrasound findings were unremarkable. Repeat amniocentesis was performed at 20 weeks of gestation. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes showed four 18p11.22-specific probe (RP11-918F20) signals in 11.7% (12/103) of the cells (Fig. 1). The normal control did not have such abnormal signals. aCGH analysis on uncultured amniocytes using CytoChip ISCA (Illumina, San Diego, CA, USA) did not detect genomic imbalance in chromosome 18. The parental karyotypes were normal. Polymorphic DNA marker analysis excluded uniparental disomy 18. Cytogenetic analysis of cultured amniocytes at repeat amniocentesis revealed a karyotype of 47,XX,+i(18)(p10)[2]/46,XX[12]. Among 14 colonies of cultured amniocytes, two colonies had tetrasomy 18p, while the rest 12 colonies had a normal karyotype (Fig. 2). Metaphase FISH analysis on cultured amniocytes using 18p11.22-specific probe of RP11-918F20, 18q12.1-specific probe of RP11-467D2 and 18p11.31-specific probe of RP11-945C19 confirmed mosaic tetrasomy 18p, and the supernumerary marker chromosome as derived from two 18p (Fig. 3). After genetic counseling of low-level mosaicism for tetrasomy 18p, the parents decided to continue the pregnancy. At 38 weeks of gestation, a 2742-g phenotypically normal female baby was delivered. The cord blood had a karyotype of 46, XX in 40/40 lymphocytes. The infant was doing well. When examined at 8 months of age, she was phenotypically normal and had normal growth and psychomotor development. Interphase FISH analysis on uncultured urinary cells revealed normal signals in 21/21 cells.

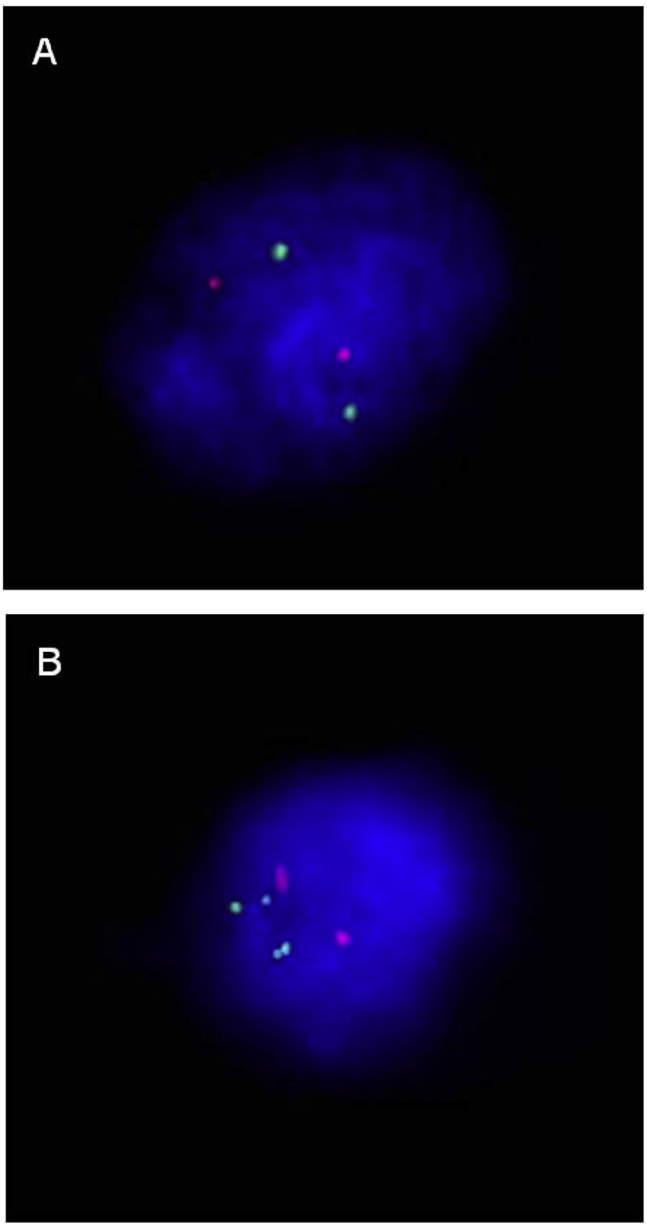

Fig. 1. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes using the 18p11.22-specific probe of RP11-918F20 [fluorescein isothiocyanate (FITC), spectrum green] and the 18q12.1-specific probe of RP11-467D2 (Texas Red, spectrum red) shows (A) two green signals and two red signals in an amniocyte with disomy 18 and (B) four green signals and two red signals in an amniocyte with tetrasomy 18p.

Discussion

Low-level mosaicism for tetrasomy 18p at amniocentesis has been reported to be associated with normal or near-normal phenotype at birth. Hsu et al. [6] reported 33.3% (total 27 cells)

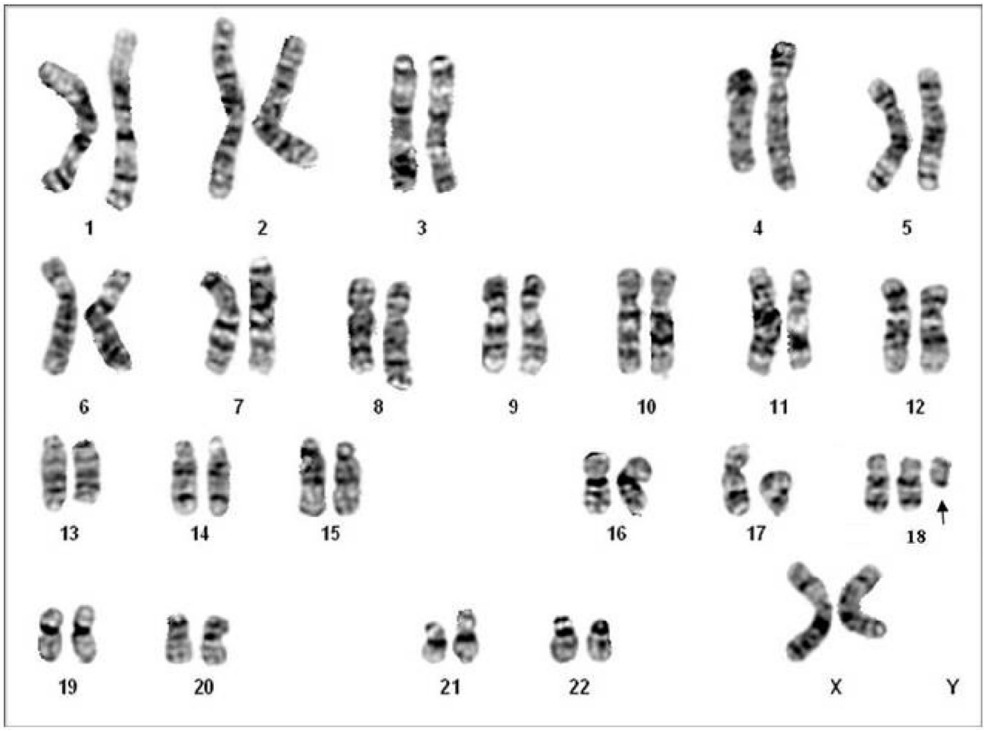

Fig. 2. A karyotype of 47,XX,+i(18)(p10). The arrow indicates a supernumerary isochromosome 18p.

mosaicism for tetrasomy 18p at amniocentesis in cultured amniocytes in a case. The cord blood had a normal karyotype. The male liveborn was normal. Kim et al. [8] reported 35% (29/83 colonies) mosaicism for tetrasomy 18p at amniocentesis in cultured amniocytes in a case. Cord blood sampling revealed a normal karyotype. Uncultured amniocytes revealed an unusual skewed allele ratio at a single locus for 18p. Prenatal ultrasound showed normal findings except an absent cavum septum pellucidum. A normal male baby was delivered. The infant was healthy at 4 weeks of age. Postnatal ultrasound was normal except an absent cavum septum pellucidum. In 2012, we reported low-level mosaicism for tetrasomy 18p at amniocentesis in cultured amniocytes in a case [9]. Conventional cytogenetic analyses on cultured amniocytes at two amniocenteses revealed mosaic tetrasomy 18p levels of 14.2% (2/14 colonies) and 11.5% (3/26 colonies), respectively. Prenatal ultrasound was normal. Interphase FISH on uncultured amniocytes revealed a mosaic tetrasomy 18p level of 5.7% (3/53 cells). aCGH analysis on uncultured amniocytes revealed no genomic imbalance in chromosome 18. The cord blood had a normal karyotype. A normal male baby was delivered. The infant was healthy at 2 months of age. Interphase FISH on uncultured urinary cells revealed a mosaic tetrasomy 18p level of 9.4% (3/32 cells). The infant is now 5 years old at this writing. He is healthy and is phenotypically normal in growth and psychomotor development at postnatal follow-up. Lau et al. [12] reported prenatal diagnosis of 18p duplication by non-invasive prenatal testing (NIPT). Amniocentesis at 16 weeks of gestation revealed 14-Mb partial trisomy 18p by aCGH and mosaic tetrasomy 18p with a mosaicism level of 23.3% (7/30 cells) by conventional cytogenetics. Prenatal ultrasound did not show any structural abnormalities. The pregnancy was subsequently terminated. Postmortem examination showed no structural abnormalities. In 2014, we additionally reported low-level mosaicism for tetrasomy 18p at amniocentesis in cultured amniocytes in another case [10]. Conventional cytogenetic analyses on cultured amniocytes at three amniocenteses revealed mosaic tetrasomy 18p levels of 12.1% (4/33 colonies), 17.4% (8/46 colonies) and 33.3% (9/27 colonies), respectively. Interphase FISH on uncultured amniocytes revealed a mosaic tetrasomy 18p level of 7.1% (6/84 cells). aCGH analysis on uncultured amniocytes revealed genomic increase in 18p with a $\log_2$ ratio of 0.019. Prenatal ultrasound was normal. A normal male baby was delivered. The cord blood had a normal karyotype. The infant was healthy at 1 months of age. Interphase FISH on uncultured urinary cells revealed a mosaic tetrasomy 18p level of 5.2% (5/97 cells). The infant is now 3 years old at this writing. He is phenotypically normal and is healthy in growth and psychomotor development at postnatal follow-up. The present case had low-level mosaicism for tetrasomy 18p at amniocentesis. Conventional cytogenetic analyses on cultured amniocytes at two amniocenteses revealed mosaic tetrasomy 18p levels of 20.5% (8/39 colonies) and 14.2% (2/14 colonies), respectively. Interphase FISH on uncultured amniocytes revealed a mosaic tetrasomy 18p level of 11.7% (12/103 cells). aCGH analysis on uncultured amniocytes at repeat amniocentesis revealed no genomic imbalance in chromosome 18. Prenatal ultrasound was normal. The infant was healthy and normal at age 8 months. The cord blood and urinary cells did not present mosaic tetrasomy 18p by conventional or molecular cytogenetic analysis.

In summary, we present prenatal diagnosis of low-level mosaic tetrasomy 18p at amniocentesis associated with a favorable outcome. Our presentation shows that interphase FISH on uncultured amniocytes at repeat amniocentesis in very useful for confirmation of the mosaic level in cases of mosaic tetrasomy 18p,

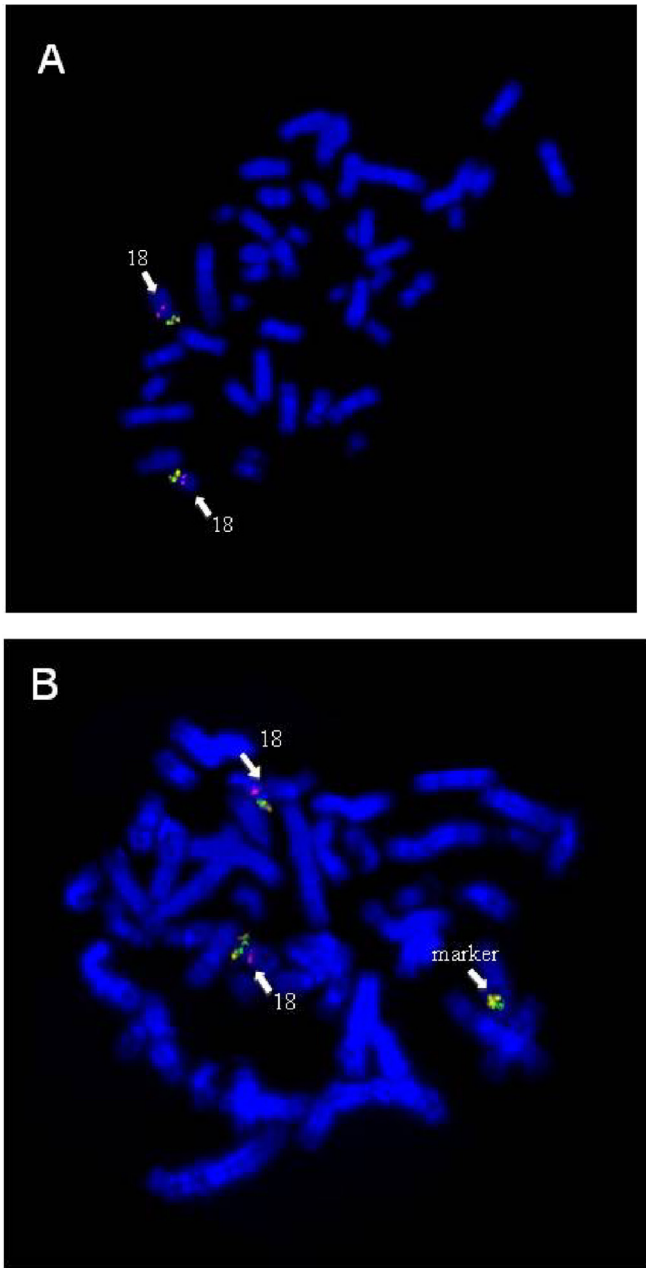

Fig. 3. Metaphase FISH analysis on cultured amniocytes using the 18p11.22-specific probe of RP11-918F20 (FITC, spectrum green), the 18q12.1-specific probe of RP11-467D2 (Texas Red, spectrum red) and the 18p11.31-specific probe of RP11-945C19 (Cyanine 5, spectrum yellow) shows that the supernumerary marker chromosome is derived from two chromosomes 18p. (A) A normal amniocyte and (B) an abnormal amniocyte with a supernumerary marker chromosome.

and low-level mosaic tetrasomy 18p at amniocentesis without ultrasound abnormalities can be associated with a favorable outcome.

Conflicts of interest

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

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