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Case Report

Prenatal diagnosis of low-level mosaicism for trisomy 13 at amniocentesis associated with a favorable outcome

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ABSTRACT

Objective: We present prenatal diagnosis of low-level mosaicism for trisomy 13 at amniocentesis associated with a favorable outcome.

Case report: A 35-year-old woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+13[5]/46,XY[20]. Oligonucleotide array comparative genomic hybridization (aCGH) analysis on uncultured amniocytes revealed arr [GRCh37] (13)×3 [0.10], (X,Y)×1 compatible with trisomy 13 mosaicism. Prenatal ultrasound was unremarkable. Repeat amniocentesis was performed at 21 weeks of gestation. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes revealed a mosaic trisomy 13 level of 10% (10/100 cells). aCGH analysis on uncultured amniocytes revealed a result of arr 13q12.11q34 (20,407,323–115,092,619)×2.1 with a $\log_2$ ratio of 0.06 compatible with a 10% level of mosaicism. Polymorphic DNA marker analysis excluded uniparental disomy 13. The parental karyotypes were normal. Conventional cytogenetic analysis using cultured amniocytes at repeat amniocentesis revealed a karyotype of 46,XY in 23/23 colonies. The pregnancy was carried to 37 weeks of gestation, and a 3600-g phenotypically normal male baby was delivered. When examined at 8 months of age, the infant was doing well and was normal in psychomotor and growth development. The peripheral blood had a karyotype of 46,XY, and interphase FISH analysis on uncultured urinary cells revealed a mosaic trisomy 13 level of 4.4% (2/45 cells).

Conclusion: Low-level true mosaicism for trisomy 13 at amniocentesis without ultrasound abnormalities can be associated with a favorable fetal outcome.

Introduction

Trisomy 13 occurs in 0.5–1 per 10,000 births, and trisomy 13 mosaicism occurs in only 5% of all cases with trisomy 13 [1]. Patients with complete trisomy 13 usually manifest early death, severe mental retardation, and structural abnormalities of holoprosencephaly, Dandy–Walker complex, congenital heart defects, facial cleft, nuchal edema, cystic hygroma, scalp defects, omphalocele, urinary tract abnormalities and polydactyly [2,3]. However, patients with mosaic trisomy 13 have phenotypic variability ranging from grossly normal to the abnormal phenotype of trisomy 13 [4–7]. Prenatal diagnosis of mosaic common trisomies by amniocentesis without ultrasound abnormalities remains a challenge to obstetricians and genetic counselors. We previously reported prenatal diagnosis of low-level mosaic trisomy 21 and mosaic trisomy 18 in two cases respectively with a favorable fetal outcome [8,9]. Here, we present a case of mosaic trisomy 13 at amniocentesis with a favorable outcome.

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Case report

A 35-year-old, gravida 3, para 2, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Her husband was 35 years old, and there was no history of congenital malformations. Amniocentesis revealed a karyotype of 47,XY,+13[5]/46,XY[20]. Among 25 colonies of cultured amniocytes, five colonies had the karyotype of 47,XY,+13, while the other 20 colonies had the karyotype of 46,XY. Simultaneous oligonucleotide array comparative genomic hybridization (aCGH) analysis on uncultured amniocytes revealed arr [GRCh37] (13)×3 [0.10], (X,Y) ×1 compatible with trisomy 13 mosaicism. Prenatal ultrasound was unremarkable. Repeat amniocentesis was performed at 21 weeks of gestation. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes revealed a mosaic trisomy 13 level of 10% (10/100 cells) (Fig. 1), compared with 0.12% (1/83 cells) in the normal control. aCGH analysis on uncultured amniocytes revealed a result of arr 13q12.11q34 (20,407,323–115,092,619)×2.1 with a $\log_2$ ratio of 0.06 compatible with a 10% level of mosaicism.

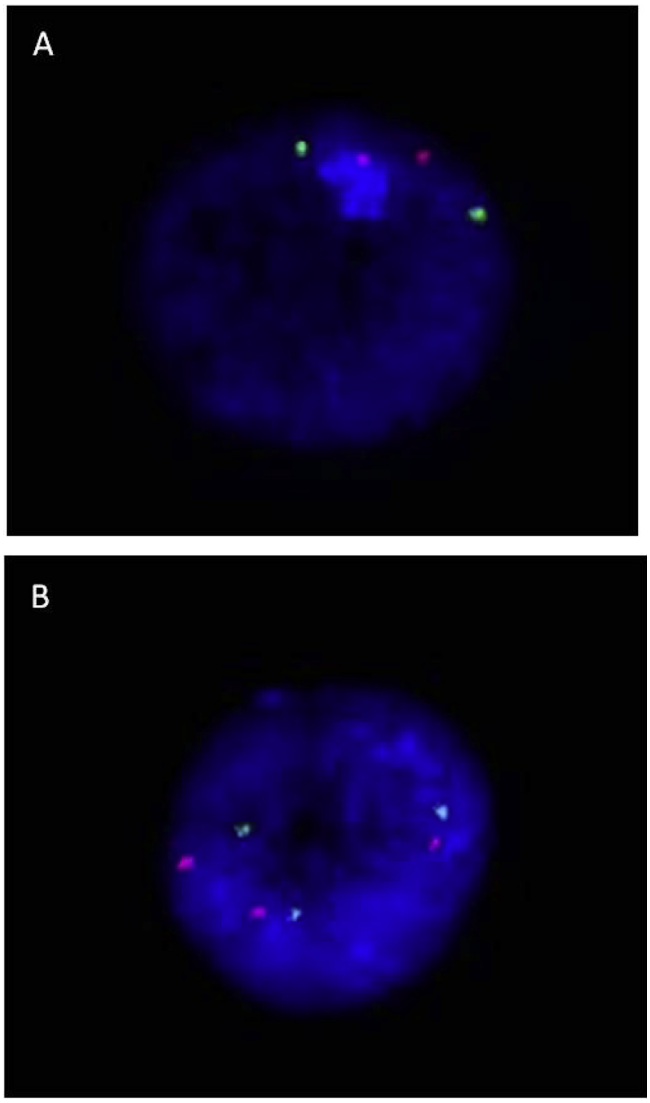

Fig. 1. Interphase fluorescence *in situ* hybridization analysis on uncultured amniocytes using the 13q12.11-specific probe of RP11-937D19 [fluorescein isothiocyanate (FITC), spectrum green] and the 13q33.3-specific probe of RP11-925F2 (Texas Red, spectrum red) shows (A) a normal disomy 13 cell with two green signals and two red signals and (B) a trisomy 13 cell with three green signals and three red signals.

Polymorphic DNA marker analysis excluded uniparental disomy 13. The parental karyotypes were normal. Conventional cytogenetic analysis using cultured amniocytes at repeat amniocentesis revealed a karyotype of 46,XY in 23/23 colonies. The pregnancy was carried to 37 weeks of gestation, and a 3600-g phenotypically normal male baby was delivered. When examined at 8 months of age, the infant was doing well and was normal in psychomotor and growth development. The peripheral blood had a karyotype of 46,XY in 40/40 lymphocytes. Interphase FISH analysis on uncultured urinary cells revealed a mosaic trisomy 13 level of 4.4% (2/45 cells) compared with 0% (0/40 cells) in the normal control.

Discussion

The present case had 20% (5/25 colonies) true chromosome mosaicism for trisomy 13 at first amniocentesis. Wilson et al. [10] found level III mosaicism in 0.2% of 6000 amniocentesis samples. Hsu et al. [11] found true chromosome mosaicism in 0.27% (50/22,000 cases) of the amniocentesis samples, and among 50 cases of true chromosome mosaicism, only two cases were mosaic trisomy 13. Hsu et al. [12] additionally found true chromosome mosaicism in 0.3% (555/179,663 cases) of the amniocentesis samples. The present case also manifested cytogenetic discrepancy between uncultured and cultured amniocytes at repeat amniocentesis. Interphase FISH analysis on uncultured amniocytes revealed 10% (10/100 cells) mosaicism for trisomy 13, while conventional cytogenetic analysis on cultured amniocytes revealed a normal karyotype in all 23 colonies. The present case shows that aCGH and interphase FISH analyses on uncultured amniocytes are useful for rapid confirmation of low-level true mosaicism for trisomy 13 at repeat amniocentesis.

The present case provides evidence that low-level true mosaicism for trisomy 13 at amniocentesis can be associated with a favorable fetal outcome. Hsu et al. [11] reported that 45% (5/11 cases) of the cases with mosaic trisomy 13 at amniocentesis had abnormal phenotype. Wallerstein et al. [13] reported that 40% (10/25 cases) of the cases with mosaic trisomy 13 at amniocentesis had abnormal outcomes including five cases with multiple congenital anomalies, two cases with intrauterine growth restriction and three cases with intrauterine death. Wallerstein et al. [13] found that in 15 cases of mosaic trisomy 13 at amniocentesis with mosaic trisomy 13 levels less than 50%, there was a 26.7% (4/15) risk of abnormalities, while in 10 cases with mosaic trisomy 13 levels more than 50%, there was a 60% (6/10) risk of abnormalities. Wallerstein et al. [13] additionally found that in cases of mosaic trisomy 13 at amniocentesis with an abnormal outcome, the mean mosaic trisomy 13 level was 58% (range: 6–94%), while in cases with a normal liveborn, the mean mosaic trisomy 13 level was 9.3% (range: 5–13%).

Mosaic trisomy 13 at amniocentesis has been reported to be associated with normal or near-normal liveborns. Delatycki and Gardner [4] reported two cases of mosaic trisomy 13 at amniocentesis with a favorable outcome. One case with level II mosaic trisomy 13 was normal at age 3 years and 6 months, and the other case with level II mosaic trisomy 13 was normal at age 17 months. Di Giacomo et al. [14] reported a case of mosaic trisomy 13 at amniocentesis with a favorable outcome. The child was normal with no dysmorphic features at age two years. In that case, amniocentesis revealed 70.6% (24/34 colonies) mosaic trisomy 13, cord blood sampling revealed 10% (10/100 cells) mosaic trisomy 13, neonatal blood had 10.3% (11/107 cells) mosaic trisomy 13, peripheral blood at age 2 years had 15.8% (18/114 cells) mosaic trisomy 13, and FISH analysis on buccal mucosal cells, skin fibroblasts and urinary tract cells revealed mosaic trisomy levels of 0% (0/103 cells), 5% (29/575 cells) and 23% (13/56 cells), respectively. Etoubleau et al. [15] reported a case of true prenatal mosaic trisomy 13 at amniocentesis with a normal phenotype at age 6 years. In that

case, two amniocenteses revealed mosaic trisomy levels of 14.3% (3/21 cells) and 0% (0/14 cells), respectively, interphase FISH analysis at repeat amniocentesis revealed 6% (14/235 cells) mosaic trisomy 13, cord blood sampling revealed a normal karyotype, and the buccal smears of the child had less than 1% (2/203 cells) mosaic trisomy 13. Chen et al. [6] reported a case of high-level mosaic trisomy 13 at amniocentesis with a relatively mild phenotype of low-set ears, absence of the 12th rib and a ventricular septal defect, but normal development at the age 8 months. In that case, two amniocenteses revealed mosaic trisomy 13 levels of 77.4% (24/31 colonies) and 78.3% (36/46 colonies), respectively. Cord blood sampling revealed a mosaic trisomy 13 level of 14% (14/100 cells). Cytogenetic analysis of skin, cardiac tissue and blood at age 6 months revealed a normal karyotype.

In conclusion, low-level true mosaicism for trisomy 13 at amniocentesis without ultrasound abnormalities can be associated with a favorable fetal outcome, and interphase FISH and aCGH analyses on uncultured amniocytes are useful for rapid confirmation of low-level true mosaicism for trisomy 13 at repeat amniocentesis.

Conflicts of interest

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

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