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Taiwanese Journal of Obstetrics & Gynecology 50 (2011) 331–338

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Short Communication

Prenatal diagnosis of mosaic trisomy 8: Clinical report and literature review

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Accepted 26 April 2011

Abstract

Objective: To present prenatal diagnosis of mosaic trisomy 8 and to review the literature.
Materials, Methods, and Results: A 34-year-old woman underwent amniocentesis at 16 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+8[6]/46,XY[31]. Repeated amniocentesis at 21 weeks of gestation revealed a karyotype of 47,XY,+8[4]/46,XY[77]. Interphase fluorescence *in situ* hybridization analysis of uncultured amniocytes showed 25% (5/20) mosaicism for trisomy 8. Array comparative genomic hybridization (aCGH) and quantitative fluorescent polymerase chain reaction (QF-PCR) analyses of uncultured amniocytes revealed no genomic imbalance in chromosome 8. The result of QF-PCR excluded uniparental disomy 8. At 23 weeks of gestation, the woman underwent amniocentesis and cordocentesis at other hospitals. Amniocentesis revealed a karyotype of 47,XY,+8[6]/46,XY[10]. Cordocentesis revealed a karyotype of 47,XY,+8[1]/46,XY[29]. Level II ultrasound findings were unremarkable. The parents decided to continue the pregnancy. A 1373-g male baby was prematurely delivered at 29 weeks of gestation. The peripheral blood had a karyotype of 47,XY,+8[1]/46,XY[29]. The infant had normal growth and mental development at 4 months of age.
Conclusion: Fetuses with mosaic trisomy 8 are compatible with viability and can have a favorable outcome. QF-PCR and array comparative genomic hybridization have the limitation of detection of low-level mosaicism. We suggest that in instances of repeated amniocentesis for confirmation of mosaic trisomy 8, follow-up investigations should include interphase fluorescence *in situ* hybridization studies on uncultured amniocytes, uniparental disomy tests, and detailed ultrasound examinations.

Keywords: Mosaicism; Mosaic trisomy 8; Prenatal diagnosis; Trisomy 8

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1028-4559/$ - see front matter
doi:10.1016/j.tjog.2011.07.013

Introduction

Mosaic trisomy 8 has marked phenotypic and cytogenetic variability and an estimated frequency of 1:25,000−50,000 births [1,2]. Characteristic phenotypic features in mosaic trisomy 8 include limb and skeletal anomalies of deep palmar and longitudinal plantar furrows, absent or hypoplastic patellae, camptodactyly, spinal deformity and limitation of motion of joints, facial dysmorphisms of hypertelorism, full lips, a broad nasal root, a prominent forehead and a high arched palate, a long and slender trunk with narrow shoulders and pelvis, a short and webbed neck, corpus callosum agenesis, moderate mental retardation, congenital heart defects, facial clefts, and renal anomalies [1−3]. Prenatal diagnosis of mosaic trisomy 8 is uncommon. Herein, we present prenatal diagnosis and molecular genetic analyses of mosaic trisomy 8 in a pregnancy with a favorable fetal outcome and a review of the literature.

Materials, methods, and results

A 34-year-old, gravida 8 para 3, woman underwent amniocentesis at 16 weeks of gestation because of her advanced maternal age. In 6 of 37 separated cultured amniocyte colonies,

Fig. 1. A karyotype of 47,XY,+8.

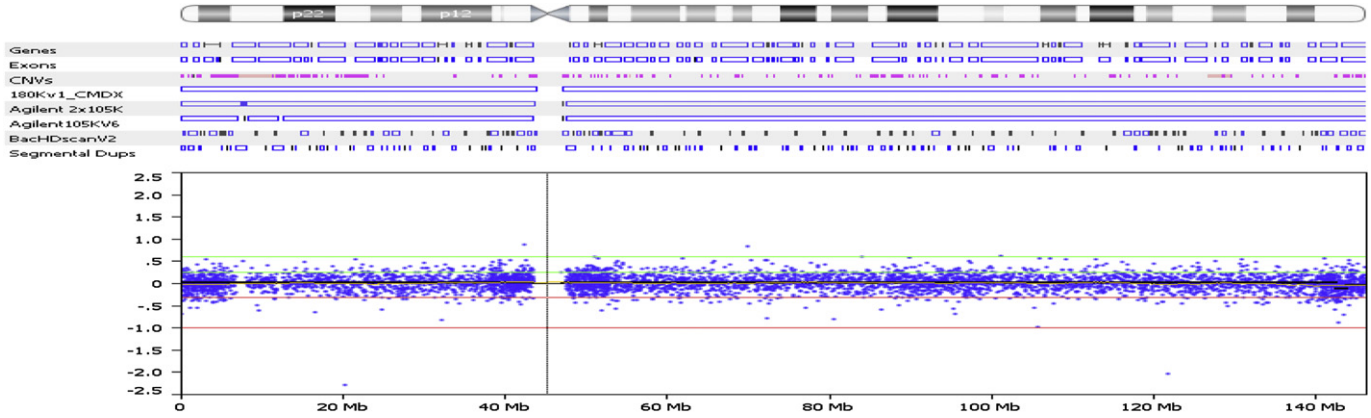

Fig. 2. Oligonucleotide-based array comparative genomic hybridization analysis of uncultured amniocytes using Oligo HD Scan (CMDX, Irvine, CA, USA) shows no genomic imbalance in chromosome 8.

an abnormal karyotype of 47,XY,+8 was found (Fig. 1), whereas the other 31 colonies had a karyotype of 46,XY. The cytogenetic result of amniocentesis was 47,XY,+8[6]/46,XY[31]. The parental karyotypes were normal. Prenatal ultrasound findings were unremarkable. At 21 weeks of gestation, repeated amniocentesis was performed. Array comparative genomic hybridization (aCGH) analyses by CMDX BAC aCGH 3000 Chips and Oligo HD Scan (CMDX, Irvine, CA, USA) (Fig. 2) and quantitative fluorescent polymerase chain reaction (QF-PCR) analysis (Fig. 3) of uncultured amniocytes did not manifest any genomic imbalance in chromosome 8. The result of QF-PCR excluded uniparental disomy (UPD) 8 (Table 1). Interphase fluorescence *in situ* hybridization (FISH) analysis of uncultured amniocytes showed three signals of chromosome 8p11.1-specific probe (RP11-65O11) (spectrum green) in 5 of 20 uncultured amniocytes and two signals in the remaining 15 uncultured amniocytes, indicating 25% (5/20) mosaicism for trisomy 8 (Fig. 4). Cytogenetic analysis of cultured amniocytes revealed a karyotype of 47,XY,+8[4]/46,XY[77]. At 23 weeks of gestation, she consulted another hospital and underwent repeated amniocentesis, which revealed a karyotype of 47,XY,+8[6]/46,XY[10] in cultured amniocytes. At 24 weeks of gestation, she consulted the third hospital and underwent cord blood sampling. Cordocentesis revealed a karyotype of 47,XY,+8[1]/46,XY[29]. FISH analysis of cultured interphase lymphocytes showed 5% (5/100) mosaicism for trisomy 8 (D8Z3×3). The parents decided to continue the pregnancy. At 29 weeks of gestation, preterm rupture of the membranes occurred and a 1373-g male baby was delivered with Apgar scores of 8 and 9 at 1 minutes and 5 minutes, respectively by cesarean section because of malpresentation. Cytogenetic analysis of the peripheral blood revealed a karyotype of 47,XY,+8[1]/46,XY[29]. The infant was grossly normal at birth. The brain and heart ultrasound findings were unremarkable. At a routine pediatric follow-up examination at 4 months of age, the infant showed normal growth and mental development.

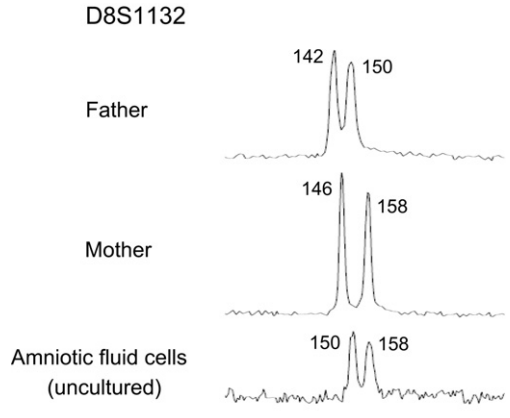

Fig. 3. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction. The marker D8S1132 shows two peaks (150 basepairs and 158 basepairs; paternal and maternal, respectively) of equal fluorescent activity from two different parental alleles in uncultured amniocytes with a dosage ratio of 1:1 (paternal:maternal).

Table 1
Genotypic information of the father, mother and amniotic fluid uncultured cells at short tandem repeat markers specific for chromosome 8 obtained by quantitative fluorescent polymerase chain reaction assays[a]

Markers	Locus	Father	Mother	Amniotic fluid (uncultured cells)
D8S1042	8p23.2	185, 185	185, 185	185, 185
D8S1106	8p22	141, 145	141, 149	141, 149
D8S500	8p21.2	182, 182	178, 178	178, 182
D8S1104	8p11.21	141, 141	129, 137	137, 141
D8S587	8q11.22	183, 187	157, 183	157, 187
D8S593	8q11.23	202, 202	202, 202	202, 202
D8S591	8q11.23	154, 162	158, 166	154, 166
D8S1134	8q21.11	148, 156	148, 148	148, 156
D8S1127	8q22.1	156, 176	164, 176	164, 176
D8S1132	8q23.1	142, 150	146, 158	150, 158

[a] Alleles (basepair sizes) are listed below each individual.

Discussion

The present case provides evidence that the use of interphase FISH in uncultured amniocytes is practical for confirmation of low-level mosaicism for trisomy 8 at amniocentesis. The interphase FISH has been shown to be an efficient method for confirmation of the status of mosaicism in the amniocytes before culture [4]. In this study, both QF-PCR and aCGH were not able to detect the low-level mosaicism for mosaic trisomy 8 in the uncultured amniocytes. QF-PCR has been reported to detect mosaicism when the abnormal cell line comprises at least 15% of the whole sample [5]. aCGH has been reported to detect low-level mosaicism as low as 20% in peripheral blood cells [6,7]. Recently, using a 50K SNP microarray (Affymetrix 50K *Xba* SNP microarray) to evaluate detection of mosaicism for trisomy by mixing measured amounts of fibroblasts containing trisomy 8 from a male with aliquots of cells with a normal female karyotype, Cross et al [8] reported to detect mosaicism at the lower limit for detection level of 10%.

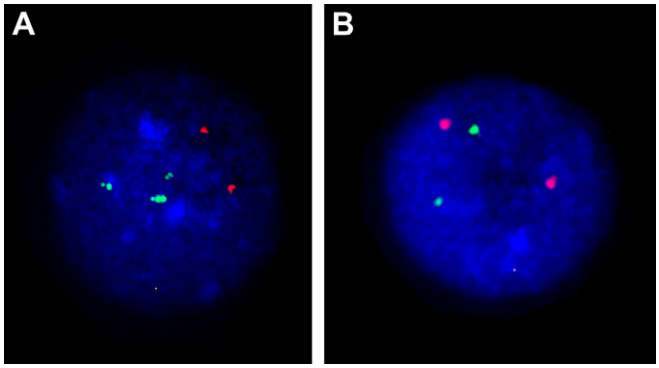

Fig. 4. Fluorescence *in situ* hybridization analysis of uncultured interphase amniocytes using a bacterial artificial chromosome (BAC) probe RP11-65O11 (8p11.1; physical map: 43,787,386–43,922,621; spectrum green), and a BAC probe RP11-448N11 (6q11.1-q11.2; physical map: 63,207,561–63,411,061; spectrum red) as internal control shows (A) three green signals in a cell with trisomy 8 and (B) two green signals in a cell with disomy 8. The physical map is according UCSC genome browser on human March 2006 (NCBI 36/hg 18) assembly.

Table 2
Reported cases of mosaic trisomy 8 detected or not detected by amniocentesis, chorionic villus sampling, cordocentesis, or fetal tissue sampling

Authors	Cases	Indication	Prenatal diagnosis	Confirmatory studies	Outcome and phenotype
Swisshelm et al [16]	47,XY,+8/46,XY	AMA	Amniocentesis: T8 = 28%	Skin (right arm): T8 = 32% (33/103 cells) Skin (left leg): T8 = 39.7% (56/141 cells) Liver, testis, cord, placenta, brain, kidney, lung, and amnion: T8 = 0%	TOP, abortus with no abnormalities
Vekemans et al [17]	47,XY,+8/46,XY	AMA	Amniocentesis (1st): T8 = 4% (100 cells) Fetoscopy (2nd) amniotic fluid: T8 = 0% (100 cells) Cord blood: T8 = 0% (50 cells)	Cord blood: T8 = 0% (50 cells, at birth)	Normal liveborn
Camurri et al [18] Camurri and Chiesi [19]	47,XX,+8/46,XX	Previous malformed child	Amniocentesis: T8 = 4.3% (1/23 cells) Cordocentesis: T8 = 0.3% (1000 cells)	Blood: T8 = 0.7% (1000 cells) Skin: T8 = 0% (401 cells)	Normal liveborn, normal at 3 years
Welborn and Lewis [20]	47,XY,+8/46,XY	NA	Amniocentesis: T8 = 7.5% (40 cells)	—	Normal liveborn
Ledbetter et al [21]					
Case 6-AGG063	Mosaic T8	NA	CVS (direct): T8 = 0% (20 cells) CVS (culture): T8 = 66.7% (20/30 cells) Amniocentesis: T8 = 0% (49 cells)	Fetal tissue: T8 = 24% (12/50 cells) Chorionic villus: T8 = 28.3% (17/60 cells)	TOP, NA
Klein et al [11]	47,XY,+8/46,XY	AMA	CVS (culture): T8 = 81% (43 cells) Amniocentesis: T8 = 0% (20 colonies)	Placenta: T8 = 60% (30 cells) Blood: T8 = 4% (100 cells) (at age 2 months) Blood: T8 = 1% (100 cells) (at age 7 months) Skin: T8 = 0% (100 cells) (at age 7 months)	Normal liveborn, normal at age 30 months
Schneider et al [12]	47,XY,+8/46,XY	Elevated MSAFP	Amniocentesis: 46,XY (7 colonies) Recheck: T8 = 0% (additional 40 metaphases)	Blood: T8 = 25% (120 cells)	Abnormal liveborn, low-birth weight, asymmetrical cranium, small lids, deep palmar and plantar grooves, hypospadias, dermoidal sinus, corpus callosum agenesis, and seizures
Guichet et al [22]	47,XY,+8/46,XY	Abnormal ultrasound: cystic hygroma, pyelectasis	CVS (direct): 46,XY CVS (culture 1): T8 = 50% CVS (culture 2): T8 = 82%	Amniotic fluid: T8 = 7% (3/44 cells) Fetal blood: T8 = 24% (12/50 cells) Placenta: T8 = 82% (41/50 cells)	TOP, abnormal abortus, facial dysmorphism, hypertelorism, brachycephaly, thick neck skin, arthrogryposis, syndactyly and camptodactyly of the hands, dilated pelvis
Hanna et al [13]					
Case 1	47,XY,+8/46,XY	AMA, elevated MSAFP, abnormal ultrasound: lemon and banana sign	Amniocentesis: 46,XY (15 colonies) Recheck: T8 = 4.3% (2/47 colonies)	Blood: T8 = 50%	Abnormal liveborn, oligohydramnios, ventriculomegaly, ASD, VSD, PDA, lumbosacral meningomyelocele, bilateral inguinal hernias, umbilical hernia
Case 2	47,XY,+8/46,XY	AMA	Amniocentesis (1st): T8 = 6.7% (1/15 colonies) Amniocentesis (2nd): 46,XY (26 colonies)	Blood: T8 = 54.5% (22 cells)	Abnormal liveborn, corpus callosum agenesis
Hsu et al [23]					
Antley, Case VIII-1	47,XX,+8/46,XX	NA	Amniocentesis: T8 = 77% (27 cells)	—	TOP, abnormal abortus

Crandall, Case VIII-3	47,XY,+8/46,XY	NA	Amniocentesis: T8 = 8.6% (46 cells)	Fetal tissue: mosaic T8	TOP, normal abortus
Disteche, Case VIII-4	47,XY,+8/46,XY	AMA	Amniocentesis: T8 = 27.2%	Kidney: T8 = 0% (50 cells) Brain: T8 = 0% (50 cells)	TOP, normal abortus
Martin, Case VIII-5	47,XY,+8/46,XY	NA	Amniocentesis: T8 = 40% (77 cells)	Skin: T8 = 30% Placenta: T8 = 50%	TOP, normal abortus
Menuntti, Case VIII-6	47,XX,+8/46,XX	NA	Amniocentesis: T8 = 13% (53 cells)	Fetal tissue: mosaic T8	TOP, normal abortus
Neu, Case VIII-7	47,XY,+8/46,XY	AMA	Amniocentesis: T8 = 11.8%	Cord blood: T8 = 0% (50 cells)	Normal liveborn
Case VIII-8	47,XY,+8/46,XY	AMA	Amniocentesis: T8 = 3.4% (58 cells)	Skin: T8 = 80% (20 cells)	TOP, normal abortus
Case VIII-9	47,XX,+8/46,XX	AMA	Amniocentesis: T8 = 8.4% (59 cells)	—	TOP, normal abortus
Case VIII-10	47,XX,+8/46,XX	AMA, elevated MSAFP	Amniocentesis: T8 = 3.8% (52 cells)	Blood: T8 = 0% (50 cells)	Normal liveborn
Case VIII-14	47,XY,+8/46,XY	AMA	Amniocentesis: T8 = 37.5%	Blood: T8 = 50% (10 cells)	TOP, normal abortus
Miller et al [24]					
Case 3	Mosaic T8	AMA	CVS (culture): T8 = 61.6% (16/26 clones) Amniocentesis: T8 = 0% (48 colonies)	Blood: T8 = 5% (124 cells, at birth) Blood: T8 = 0.7% (2/279 cells, at age 5 months) Amnion: T8 = 0% (101 cells, (1st) Amnion: T8 = 80% (72/90 cells, 2nd) Placenta: T8 = 0% (45 cells, 1st) Placenta: T8 = 0% (58 cells, 2nd) Placenta: T8 = 100% (17 cells, 3rd)	Normal liveborn, deep palmar and plantar furrows, normal at age two-and-half years
Southgate et al [14]	47,XX,+8/46,XX	Elevated MSAFP, abnormal ultrasound: hemivertebra, ventriculomegaly, nuchal fold thickening	Amniocentesis: 46,XX (20 colonies)	Blood: T8 = 35% (20 cells) Skin: T8 = 75% (20 cells)	Abnormal liveborn, facial asymmetry, clinodactyly, corpus callosum agenesis, colpocephaly, hemivertebra, hypotonia
Webb et al [25]	47,XY,+8/46,XY	Abnormal ultrasound: oligohydramnios, megacystis, hydronephrosis	CVS (direct): 46,XY (10 cells) CVS (culture): T8 = 100% (50 cells) Fetal urine aspiration: T8 = 4.8% (3/63 cells)	Blood: T8 = 0% (100 cells) Skin: T8 = 13.3% (4/30 cells) Muscle: T8 = 2% (4/50 cells) Kidney: T8 = 10.6% (10/94 cells, FISH)	TOP, abnormal abortus, hydronephrosis, megacystis, flexion deformities of the joints
Campbell et al [26]	47,XY,+8/46,XY	Abnormal ultrasound: reversed end-diastolic ductus venosus flow	CVS (direct): 46,XY CVS (culture): mosaic T8	Liver, spleen, skin, lung, muscle: mosaic T8 (FISH) Skin: T8 = 6.7% (2/30 cells, FISH) Muscle: T8 = 6.7% (2/30 cells, FISH)	TOP, abnormal abortus, absence of the flap valve of the foramen ovale
van Haelst et al [15]					
Case 7	47,XY,+8/46,XY	AMA	CVS (STC villi): 46,XY (50 cells)	Blood: T8 = 24% (50 cells) Skin: T8 = 6% (50 cells)	Abnormal liveborn, congenital heart disease, hydronephrosis, clubfeet, syndactyly of feet
Case 10	47,XY,+8/46,XY	Abnormal ultrasound: microcephaly, hypertelorism, radius aplasia	Cordocentesis: T8 = 6.2% (4/65 cells)	Amniotic fluid: T8 = 0% (cultured cells, FISH)	TOP, abnormal abortus
Hulley et al [27]	47,XY,+8/46,XY	Abnormal maternal serum screen	Amniocentesis: T8 = 32% (8/25 colonies)	Blood: T8 = 54% (200 cells) Cord: T8 = 57% (100 cells) Amnion: T8 = 43% (100 cells) Chorion: T8 = 8% (100 cells) Villi: T8 = 9% (66 cells)	Abnormal liveborn, bitemporal narrowing, large ears, hypoplastic nails, deep palmar and plantar furrows, hypospadias, cardiomegaly, pulmonary hypertension, death at age 8 weeks

(*continued on next page*)

Table 2 (*continued*)

Authors	Cases	Indication	Prenatal diagnosis	Confirmatory studies	Outcome and phenotype
Present case	47,XY,+8/46,XY	AMA	Amniocentesis (1st): T8 = 16.2% (6/37 colonies) Amniocentesis (2nd): T8 = 4.9% (4/81 colonies) T8 = 25% (5/20 uncultured cells, FISH) Amniocentesis (3rd): T8 = 37.5% (6/16 colonies) Cordocentesis (4th): T8 = 3.3% (1/30 cells) T8 = 5% (5/100 interphase nuclei, FISH)	Blood: T8 = 3.3% (1/30 cells, at birth)	Normal liveborn, normal at age 4 months

— = no information; AMA = advanced maternal age; ASD = atrial septal defect; CVS = chorionic villus sampling; FISH = Fluorescence *in situ* hybridization (abnormal/total); MSAFP = maternal serum α-fetoprotein; NA = not available; PDA = patent ductus arteriosus; T8 = trisomy 8; TOP = termination of pregnancy; VSD = ventricular septal defect.

The present case was not associated with UPD 8. Prenatal diagnosis of low-level mosaic trisomy should alert UPD. Although there is no evidence for an imprinting locus on chromosome 8, UPD 8 can be associated with major clinical consequences when a recessive mutation is reduced to homozygosity [9,10]. Benlian et al [9] reported lipoprotein lipase deficiency associated with paternal isodisomy of chromosome 8 because of a homozygous *LDL* mutation. In that case, the father of the proband was a heterozygous carrier of the mutation. Varon et al [10] reported Nijmegen breakage syndrome associated with maternal isodisomy of chromosome 8 because of a homozygous *NBN* mutation. In that case, the mother of the proband was a heterozygous carrier of the mutation.

To date, at least 22 cases of prenatally detected mosaic trisomy 8 and 5 cases [11−15] of prenatally undetected mosaic trisomy 8 have been reported (Table 2) [11−27]. Of the 27 cases, at least 11 cases (40.7%) were associated with phenotypic abnormalities, suggesting that the malformation risk should be concerned in prenatal diagnosis of mosaic trisomy 8. Among normal fetuses, the sex ratio is 1.07 (males/females). Table 2 shows that the sex ratio for fetal mosaic trisomy 8 is 3.33 (20 males/6 females), indicating a male preponderance in fetal mosaic trisomy 8 and a natural selection against mosaic trisomy 8 female conceptuses. In a study of 26 cases of mosaic trisomy 8, Karadima et al [28] found a skewed sex ratio of 2.71 (19 males/7 females) and a ratio of 3 (15 males/5 females) in the postzygotic mitotic group. In a review of about 120 cases of mosaic trisomy 8, Schinzel [3] found that more than three of four of the patients were male. Table 2 also shows that mosaic trisomy 8 can prenatally be associated with elevated maternal serum α-fetoprotein (MSAFP), abnormal maternal serum screening, and abnormal ultrasound findings. Miller et al [29] reported an extremely elevated MSAFP level (13.89 MoM, multiples of median) and a mild elevated maternal serum human chorionic gonadotropin level (3.57 MoM) in a pregnancy with mosaic trisomy 8, bilateral pyelectasis, and a prominent third ventricle. Schneider et al [12] reported high MSAFP levels, 2.8 MoM and 4.5 MoM, respectively, in two maternal serum screens in a pregnancy with mosaic trisomy 8 and corpus callosum agenesis. In that case, the levels of amniotic fluid AFP were normal. Hanna et al [13] reported a high MSAFP level of 9.7 MoM and a high amniotic fluid AFP level of 3.58 MoM in a pregnancy with fetal mosaic trisomy 8. The fetus prenatally manifested a lemon and banana sign on ultrasound. Southgate et al [14] reported an elevated MSAFP level in a pregnancy with mosaic trisomy 8 and fetal ventriculomegaly. The reported abnormal ultrasound findings associated with mosaic trisomy 8 include nuchal thickening, cystic hygroma, megacystis, pyelectasis, microcephaly, ventriculomegaly, hemivertebra, limb defects, and reverse end-diastolic ductus venosus flow. Prenatal diagnosis of corpus callosum agenesis and ventriculomegaly should alert mosaic trisomy 8. Markov et al [30] reported corpus callosum agenesis in a fetus with mosaic trisomy 8 at 30 weeks of gestation. In a study of 35 cases of prenatally detected corpus callosum agenesis, Pilu et al [31] found that 8.6% (3/35) were mosaic trisomy 8. Table 2 shows that among the 28 cases with mosaic

trisomy 8, three have corpus callosum agenesis, one has ventriculomegaly and meningomyelocele, and one has colpocephaly.

Mosaic trisomy 8 may be missed at amniocentesis. Klein et al [11], Schneider et al [12], Hanna et al [13], Southgate et al [14] and van Haelst et al [15] reported on clinical cases with mosaic trisomy 8 missed at amniocentesis. It has been suggested that when mosaic trisomy 8 is encountered at chorionic villus sampling, cordocentesis rather than repeated amniocentesis is preferably recommended [13,15]. Hulley et al [27] observed selective growth advantage of normal cells and growth disadvantage of trisomy 8 cells in mosaic trisomy 8. In those reported cases with mosaic trisomy 8 missed at amniocentesis, the disappearance of trisomy 8 amniocytes was likely caused by selective growth disadvantage of the abnormal trisomy 8 cell line following the culture procedure. As presented in this case, in instances of repeated amniocentesis for confirmation of mosaic trisomy 8, the interphase FISH study on uncultured amniocytes is practical and should be included in the follow-up investigations.

Genetic counseling of mosaic trisomy 8 at prenatal diagnosis remains difficult because of marked phenotypic and cytogenetic variability. The percentage of trisomy 8 metaphase cells in blood or skin has been noted to have no correlation with the severity of clinical manifestation, the incidence of malformations and the degree of mental retardation, and the amount of the aneuploid cell line can decrease with age [3]. Because fetuses with mosaic trisomy 8 are compatible with viability and can have a favorable outcome, prenatal diagnosis of mosaic trisomy 8 should include thorough investigations of structural abnormalities and UPD 8. Early diagnosis of associated anomalies and UPD 8 may provide more information for genetic counseling and lessen the dilemma for genetic counselors.

Acknowledgments

This work was supported by research grants NSC-97-2314-B-195-006-MY3 and NSC-99-2628-B-195-001-MY3 from the National Science Council and MMH-E-100-04 from Mackay Memorial Hospital, Taipei, Taiwan.

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