Prenatal Diagnosis of mos45,X/46,X,+mar in a Fetus With Normal Male External Genitalia and a Literature Review

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SUMMARY

Objective: Prenatal diagnosis of mos45,X/46,X,+mar is difficult in genetic counseling. Patients with the presence of a Y-derived marker may manifest male or female external genitalia. Here, we report a fetus with phenotypically male external genitalia of mos45,X/46,X,+mar. In addition, the cases with prenatally detected mos45,X/46,X,del(Y)(q11.2) and normal male external genitalia are reviewed.

Case Report: A 30-year-old, primigravid woman was referred for amniocentesis because of an abnormal Down syndrome screening result at 20 weeks' gestation. Cytogenetic analysis showed mos45,X/46,X,+mar without a normal Y chromosome. Prenatal ultrasound detected symmetric intrauterine growth restriction and normal male external genitalia. After termination of the pregnancy, a phenotypically normal male fetus was delivered smoothly without apparent structural defects. Based on conventional G-banded analysis, the marker chromosome appeared as a Y chromosome that originated with a deleted Yq, designated as del(Y)(q11.2).

Conclusion: Based on a literature review, the addition of fluorescence *in situ* hybridization and molecular analysis to the conventional cytogenetic techniques can provide more accurate identification of a Y chromosome aberration in the prenatal detection of mos45,X/46,X,+mar, thus allowing more appropriate genetic counseling for the family. [*Taiwan J Obstet Gynecol* 2009;48(3):292–295]

Key Words: chromosome aberrations, mos45,X/46,X,+mar, prenatal diagnosis, sex differentiation

Introduction

Mosaic chromosome aberrations can be detected prenatally, and sex chromosome mosaicism is the most frequently seen [1]. In sex chromosome mosaicism, structural abnormalities (10.5%) are less common than numerical abnormalities (89.5%) [1]. Among the reported postnatal cases of mos45,X/46,X,+mar, the marker chromosome was often derived from either a normal or abnormal X or Y chromosome. Clinically, the phenotypes of such cases were determined not only by the characterization of the aberrant Y chromosomes but also by the ratio and the distribution of 45,X cells [2]. It is supposed that a case with a 45,X cell line has an increased risk of being a phenotypic female or to have ambiguous external genitalia regardless of the presence of Yp, Yq, both Yp and Yq, or even a normal Y chromosome in another cell line [2]. However, it has also been proposed that some genes present on the Y chromosome can avoid features of Turner syndrome and aid in male gonadal maturation and normal spermatogenesis [3]. Cases of mos45,X/46,X,Y-derived

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marker chromosomes have been reported to manifest in a wide spectrum including female genitalia, ambiguous genitalia, male external genitalia with gynecomastia, short stature, and azoospermia, or even normal male development [2,4,5]. Therefore, prenatal diagnosis of mos45,X/46,X,+mar is difficult in the interpretation of the results and in genetic counseling.

Here, we describe a fetus with phenotypically male external genitalia with a karyotype of mos45,X/46,X,+mar detected incidentally after a positive result of maternal serum multiple-marker screening and intrauterine growth restriction (IUGR). The marker chromosome was designated as del(Y)(q11.2) based on conventional G-banded analysis. In addition, the cases with prenatally detected mos45,X/46,X,del(Y)(q11.2) and normal male external genitalia are reviewed.

Case Report

A 30-year-old primigravid woman was referred to our hospital for amniocentesis at 20 weeks' gestation because of a positive result on maternal serum multiple-marker screening (1/146). At the same time, level II ultrasound showed symmetric IUGR with a biparietal diameter of 3.77 cm (16 weeks), a femur length of 1.8 cm (< 15 weeks), and normal male external genitalia. No associated structural malformations were detected. She denied exposure to teratogenic materials or medications during early pregnancy. Her husband was 34 years old. The couple were healthy and nonconsanguineous. In addition, the family history was unremarkable.

Cytogenetic analysis of cultured amniocytes revealed mos45,X[23]/46,X,+mar[20] in different culture dishes from *in situ* cultures (Figure). By conventional G-banded analysis, the marker chromosome appeared as a Y chromosome with Yq deletion, designated as del(Y)(q11.2). After genetic counseling for the parents, they opted to terminate the pregnancy at 24 weeks' gestation because of the possibility of fertility problems from the deleted Yq segment and the possible associated abnormalities caused by the presence of 45,X cells. The pregnancy was terminated using intravaginal prostaglandin E_1. A phenotypically normal male fetus was delivered smoothly with a body weight of 342 g and no apparent structural defects were detected. The placenta appeared normal and weighed 180 g. Postnatal cytogenetic analysis of the placenta showed mos45,X[2]/46,X,del(Y)(q11.2)[2] and of cord blood showed mos46,X,del(Y)(q11.2)[42]/45,X[8]. The parental karyotypes were unavailable.

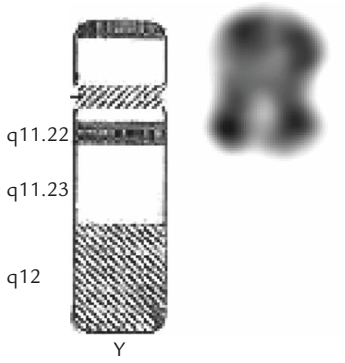

Figure. Partial karyotype of the proband shows the abnormal Y chromosome with a Yq11.2–qter deletion.

Discussion

An aberrant Y chromosome leading to its instability results in mosaic 45,X with partial or complete loss of the Y chromosome [6]. Cases with the karyotype of mos45,X/46,X,Y-derived marker can have variable manifestations. Three females of 45,X/46,X,del(Y)(q12) karyotype have been reported to have sexual infantilism, short stature, and somatic Turner stigmata [4]. The authors also reviewed cases of mos45,X/46,X,del(Yq) whose sexual development was classified into three categories: (1) female individuals with infantile sex and Turner syndrome features, (2) individuals with ambiguous genitalia, and (3) male individuals with azoospermia [4]. Hsu [2] reported 38 postnatal cases of mos45,X/46,X,del(Y)(q11) manifesting as phenotypic males in 13 cases (34.2%), intersex in 18 cases (47.4%), and phenotypic females in seven cases (18.4%). Among the 13 phenotypic males, the associated anomalies included short stature in eight cases and genital anomalies such as small or abnormal testes in seven cases, hypospadia in four cases, small penis in three cases, and gonadoblastoma in one case. It seemed that a case with mosaic 45,X had an increased risk of having ambiguous external genitalia or of being a phenotypic female. In addition, the presence of the Y-derived marker may be associated with abnormalities of the external genitalia at birth, lack of secondary sexual characteristics at puberty, and/or development of gonadal tumors. Therefore, it is difficult to interpret the chromosomal karyotype and provide genetic counseling when prenatal diagnosis of a mos45,X/46,X,del(Yq) karyotype is made.

Only a few postnatal cases of the karyotype of mos45,X/46,X,del(Y)(q11.2) have been reported to have normal male external genitalia [7–9]. There are even fewer cases which were diagnosed prenatally. Here, we have summarized the prenatally detected cases of mos45,X/46,X,del(Y)(q11.2) characterized by normal male external genitalia in the Table [9,10]. Because of

Table. Prenatally detected cases of mos45,X/46,X,del(Y)(q11.2) with normal external male genitalia

	Case 1 [9]	Case 2 [10]	Current case
Maternal age (yr)	29	32	30
Paternal age (yr)	NA	36	34
G, P and A	G2P0A1	G3P1	G1P0
Indications	PPROM	AMA	MSS and IUGR
Gestational age (wk)	18	18	20
Diagnosis			
G-banded	(+)	(+)	(+)
FISH	(+)	(+)	(−)
Microsatellite	(+)	(+)	(−)
Multiplex PCR	(+)	(+)	(−)
Parental karyotype	Normal	Normal	NA
External genitalia	Normal male	Normal male	Normal male
Final karyotype	46,X,del(Y)(q11.23)/45,X	46,X,del(Y)(q11.2)/45,X	46,X,del(Y)(q11.2)/45,X
Mosaic ratio (46,X,+mar/45,X)			
Amniocytes	65/110 (37.1%)	52/19 (73.2%), 12/12 (50.0%)*	20/23 (46.5%)
Cord blood	81/21 (79.4%)	(−)	42/8 (84.0%)
Villi	4/5 (44.4%)	17/5 (77.3%)	2/2 (50.0%)
Skin	90/10 (90.0%)	(−)	(−)
Gonads	(−)	14/7 (66.7%)	(−)
Spleen	(−)	14/7 (66.7%)	(−)
Outcome	Alive and normal development at 5 years old	Terminated	Terminated

**Repeat amniocentesis results. NA = not available; G = gravidity; P = parity; A = abortion; PPROM = preterm premature rupture of membranes; AMA = advanced maternal age; MSS = an elevated result of maternal serum screening; IUGR = intrauterine growth restriction; (+) = done; (−) = not done; FISH = fluorescence in situ hybridization; PCR = polymerase chain reaction.*

the lack of significant fetal structural defects prenatally, this mosaic sex chromosomal abnormality is usually incidentally detected with different obstetric indications. In the Table, all of the subjects were characterized with normal male external genitalia, which may be associated with the increased ratio of the 46,X,del(Y)(q11) cell line in the fetal cord blood, skin, gonads and spleen (> 50%). In addition, we noted that the presence of 45,X cell line in amniocytes is not only from extra-embryonic placentas but also from the embryonic tissues. Therefore, Turner syndrome stigmata may occur in the fetus such as in IUGR seen in our case. However, the correlation between the 45,X cell line and IUGR still remains controversial, because the ratio of 45,X was not higher than that of the other two cases which had normal fetal growth. More accurate identification of the ratio and the distribution of 45,X cells in different tissues by genetic dosage analyses might be required to explain the possible correlation.

The human Y chromosome is widely considered to be a morphologic variation and contains only a few genes known to be important for normal male development, such as the sex-determining region of the Y chromosome (*SRY* gene). Some genes on the deleted Yq11 segment are critical for normal germ cell development, such as the azoospermia factor (AZF) gene on Yq11.2. The gene is separated into four sub-regions including AZFa on Yq11.21, AZFb on Yq11.22, AZFd, and AZFc on Yq11.23 [11]. AZFd is located between AZFb and AZFc. Complete or partial deletions of these sub-regions may be related to abnormal gonadal development, including a complete absence of germ cells (also called Sertoli-cell-only syndrome; AZFa), a meiotic maturation arrest of spermatogenesis (AZFb), and the presence of variable testicular pathology (AZFc) [12]. Despite the fact that the exact correlation between genotypes and phenotypes remains to be elucidated, more severe phenotypes associated with abnormal spermatogenesis will occur with the presence of more deletions on Yq11.2 [13,14]. The distal Yq (Yq12) contains constitutive heterochromatin; it is genetically inactive, and cases with only deleted Yq12 regions can expect

no phenotypic effects unless the euchromatic Yq is also deleted. In the Table, both the reported cases were analyzed using fluorescence *in situ* hybridization initially, and the marker chromosome was identified to be of Y chromosome origin. Subsequently, molecular diagnostic tools using microsatellite markers or multiplex polymerase chain reaction characterized the detailed Yq deletion. These tools are helpful in identifying the nature and origin of unknown markers and rearrangements which have important implications in sexual differentiation. Case 1 had a deleted segment of Yq11.23–Yqter involving the AZFc sub-region only, and normal male development was documented at 5 years of age. Case 2 had the breakpoint at Yq11.21 (AZFa)–Yq11.22 (AZFb), which might be associated with future infertility of the proband. In this case, we proposed that the marker chromosome was of Y chromosome origin because of the presence of male external genitalia but the absence of a normal Y chromosome, and then the breakpoint, designated as del(Y)(q11.2), was determined using a G-banding ideogram. However, we could not exactly determine the deleted region without the introduction of any molecular analyses. Mezei et al [15] reported that the major determinant of parental decision making toward termination of a pregnancy with sex chromosome aneuploidy was the possibility of abnormal sexual development or infertility in the child [15]. Therefore, prenatal application of a reliable molecular method for detailed analysis of this Y-derived marker chromosome, such as the AZF region on Yq11.2, is clinically important to provide appropriate genetic counseling to the family.

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