

Ullrich-Turner Syndrome in an XY Female Fetus With Deletion of the Sex-Determining Portion of the Y Chromosome

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Here we describe a fetus in whom a cystic hygroma was detected by ultrasound during the second trimester. Autopsy demonstrated a female fetus with manifestations of Ullrich-Turner syndrome, including gonadal dysgenesis, generalized lymphedema, and preductal aortic coarctation. Surprisingly, the karyotype was 46,XY, with no evidence of mosaicism for a 45,X cell line. Y-DNA hybridization studies demonstrated a deletion of the sex-determining segment of the short arm of the Y chromosome. This is the first report, in a fetus, of XY Ullrich-Turner syndrome due to a Y chromosome deletion.

KEY WORDS: Y-chromosome deletion, sex-determining gene, cystic hygroma

INTRODUCTION

Increasing use of ultrasound during pregnancy for a variety of indications has led to the prenatal detection of unsuspected anomalies. These can present difficult diagnostic dilemmas. Cystic hygromas are most often associated with a 45, X chromosome constitution and Ullrich-Turner syndrome (UTS) phenotype, but can also be seen with other chromosome defects, as a recessively inherited disorder, or as an isolated malformation.

The evaluation of a fetus with a cystic hygroma should include a thorough anatomic survey, by ultrasound, and chromosome analysis. Most cases in which a cystic hygroma is associated with UTS are readily identified as 45,X by cytogenetic studies. A chromosome abnormality below the limits of cytogenetic detection is a possible explanation when the phenotypic and cytogenetic results

are discrepant. To our knowledge, the pregnancy we describe is the first report in which UTS and sex reversal in a 46,XY fetus are due to deletion of the male-determining portion of the Y chromosome.

CLINICAL REPORT

The mother, a 31-year-old white woman, requested amniocentesis at 16 weeks gestation to determine the possibility of Down syndrome. Ultrasound prior to amniocentesis demonstrated cystic masses in the area of the neck and chest and prompted referral for further evaluation.

Repeat ultrasound examination demonstrated a large septated cystic mass posterior and lateral to the fetal neck. There were bilateral pleural effusions, but no other fetal anomalies were seen. Persistent fetal bradycardia was noted. The cystic mass was thought to represent a cystic hygroma. The parents were counseled regarding cystic hygroma before the fetal karyotype was available. Following counseling, the patient elected to terminate the pregnancy, and labor was induced with prostaglandins at 18 weeks gestation. A 205 g stillborn girl with a large cervical cystic hygroma, lymphedema of all limbs, and female external genitalia was delivered (Fig. 1).

The autopsy confirmed the findings seen on external inspection. The pleural cavities contained fluid, and there were hypoplastic lungs that occupied less than 50% of the pleural cavity. Preductal coarctation of the aorta was noted. The gross examination of the urogenital system was normal. There were two kidneys with patent ureters. The uterus, fallopian tubes, and ovaries appeared normal. Histologic examination of the ovaries showed absence of follicular epithelium, an abnormal finding in an 18 week fetus. This finding is consistent with UTS.

CYTOGENETIC STUDIES

Karyotyping of the cultured amniotic cells showed a 46,XY chromosome constitution in all 30 cells examined. Chromosome analysis of cultured fetal skin fibroblasts confirmed this finding in 100 additional cells. No 45,X cells were seen. Parental lymphocyte chromosomes were normal. The fetal and paternal Y chromosomes were indistinguishable by metaphase-banding studies.

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TABLE I. Presence (+) or Absence (-) of Y-Specific Restriction Fragment

Probe/locus	pDP1007(ZFY)	pDP132	pDP61	50f2/A,B	pDP105A	pDP34	pDP97	50f2/D	12f	50f2/C,E	pDP105/B	pY431-HmfA
Enzyme	TaqI	TaqI	TaqI	EcoRI	TaqI	TaqI	EcoRI	TaqI	TaqI	EcoRI	TaqI	TaqI
Stringency ^a	M	H	H	M	M	H	H	M	M	M	M	H
Reference	c	d	d,*	f	d	g	d,h	f	i	f	d	j
Interval ^b	1	2	3	3	3	4A	4B	4B	5	6	6	7
Individual tested												
46,XY fetus	-	-	+	+	+	+	+	+	+	+	+	+
Father	+	+	+	+	+	+	+	+	+	+	+	+
Mother	-	-	-	-	-	-	-	-	-	-	-	-
Normal males	+	+	+	+	+	+	+	+	+	+	+	+
Normal females	-	-	-	-	-	-	-	-	-	-	-	-

^a H, high stringency (hybridization at 47°C, wash at 65°C); M, medium stringency (hybridization at 42°C, wash at 55°C).

^b Deletion intervals on the Y chromosome are as defined in Vergnaud et al. [1986] and Page [1986].

^c Page et al. [1987].

^d D.C.P. et al., in preparation.

^e Derived from plasmid 115 [Geldwerth et al., 1985].

^f Guellaen et al. [1984].

^g Page et al. [1984].

^h Derived from cosmid Y97 [Wolfe et al., 1985].

ⁱ Bishop et al. [1984].

^j K. Smith, unpublished.



Fig. 1. Affected fetus.

DNA EXTRACTION AND GEL-TRANSFER HYBRIDIZATION

Human genomic DNAs prepared from parental lymphoblastoid cell lines and fetal fibroblasts were digested with restriction endonucleases, electrophoresed on 0.7% agarose gels, transferred to nylon membranes, and hybridized with ³²P-labeled DNA probes as described elsewhere [Page et al., 1987]. DNA hybridization probes detecting Y-specific restriction fragments are listed in Table I.

An 8 interval deletion map of the human Y chromosome has previously been constructed on the basis of Y-DNA hybridization studies [Page, 1986; Vergnaud et al., 1986]. The presence or absence of each of these 8 deletion intervals was tested by using a set of previously characterized hybridization probes detecting Y-specific restriction fragments. The results of these Y-DNA hybridization studies are summarized in Table I. In the fetus, we detected the presence of most if not all of the long arm (deletion intervals 4B-7), the centromere (interval 4B), and the proximal short arm (intervals 3 and 4A) of the Y. The distal short arm (intervals 1 and 2), including *ZFY*, the putative sex-determining gene [Page et al., 1987; Page, 1988], was absent (Fig. 2). No Y-specific DNA sequences were found in the mother, demonstrating that the fetus inherited this Y-chromosome material from the father.

DISCUSSION

Monosomy X is the single most common aneuploidy in human conceptions, occurring in approximately 1:17,500 live births [Hook and Warburton, 1983], but

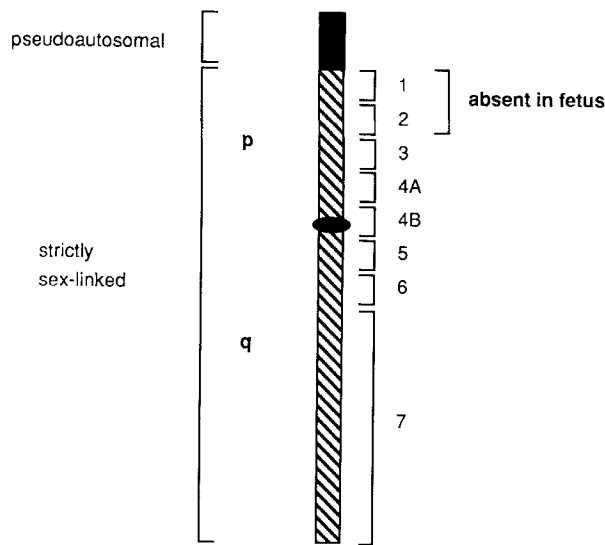


Fig. 2. Y-chromosome deletion map.

may be difficult to recognize in the newborn. Manifestations that may lead to neonatal diagnosis include edema of the dorsal hands and feet, webbed neck, and low birth weight. Patients often come to medical attention during adolescence because of short stature and delayed puberty. Approximately 50% of first trimester abortuses have chromosome abnormalities, and of these, 20% are reported to have a 45,X chromosome constitution [Warburton et al., 1981]. Indeed, it is estimated that 99% of 45,X embryos abort spontaneously [Hook and Warburton, 1983]. The increased use of ultrasound and amniocentesis has led to recognition of 45,X fetuses that survive the first trimester. These fetuses have large cystic neck masses. Commonly, generalized edema and hydrops fetalis are followed by intrauterine fetal death [Chervenak et al., 1983].

The marked variability in the phenotypic manifestations and clinical course of pregnancies with X monosomy is not understood. It has been postulated that more often mildly affected live-born infants are the product of cryptic mosaicism [Hook and Warburton, 1983]. Although a large proportion of women with UTS have the 45,X chromosome constitution, the same phenotypic manifestations may be seen with mosaicism (45X/46,XX or 45X/46,XY) or structural abnormalities of the X chromosome, resulting in deletion of a critical segment of the short arm [Simpson et al., 1982].

Several cases of 46,XY females who have a deletion of a segment of the Y chromosome have been described. In 1979, Rosenfeld et al. reported a 46,XYp- female with stigmata of UTS. At birth, the patient was noted to have marked lymphedema of limbs and nuchal skinfolds. Cubitus valgus and a broad chest were noted on later evaluation. A laparotomy at age 3 months demonstrated a normal uterus, but the gonads were small and undifferentiated [Rosenfeld et al., 1979]. In 1984, Magenis et al. described a female infant with a 46,XY chromosome constitution and manifestations of UTS, including pedal

edema and redundant neck skin folds. Surgical exploration at 30 months confirmed the presence of a uterus and fallopian tubes and bilateral gonadoblastomas in dysgenetic gonads. This child had a cytogenetically detectable deletion of the terminal band of Yp. It was proposed that the male-determining gene was located in this area and was deleted in this patient [Magenis et al., 1984].

In 1986, Disteche et al. reported two cases of XY females with some manifestations of UTS. The first patient had lymphedema at birth, particularly of the feet. She was found to have streak gonads with dense ovarian stroma at age 17 months. The second patient had a short neck, wide-spaced nipples, and congenital lymphedema. Bilateral gonadoblastomas were identified at age 15 years. Both patients had terminal Yp deletions demonstrated on high-resolution banding. Y-DNA hybridization studies demonstrated that both had deletions of the sex-determining region of Yp [Disteche et al., 1986a]. To date, ten live-born 46,XY females, most, if not all, with manifestations of UTS, have been shown to have such deletions by Y-DNA hybridization [Disteche et al., 1986b; Muller et al., 1986; Magenis et al., 1987; Page et al., unpublished results].

The patient reported here presented a diagnostic dilemma. The clinical findings were most consistent with UTS; however, the amniotic fluid and fetal skin fibroblast cultures demonstrated a 46,XY chromosome constitution. In order to resolve this apparent discrepancy, we investigated whether this fetus was mosaic for a 45,X cell line. The cytogenetic studies of fetal skin failed to show mosaicism. In addition, we were unable to find cytogenetic evidence of a deletion in the fetal Y chromosome. We were unable to distinguish morphologically the fetal Y from the paternal Y chromosome.

However, Y-DNA hybridization studies detected a deletion of intervals 1 and 2, the distal short arm of Y chromosome. The absence of interval 1, to which the sex-determining factor has been mapped [Vergnaud et al., 1986; Page et al., 1987], accounts for the female phenotype. We note, in particular, the absence of *ZFY*, the putative sex-determining gene [Page et al., 1987; Page, 1988]. These results support the observation of a deletion below the current limit of cytogenetic detection.

The abnormal development in this patient is consistent with UTS. Molecular studies of the two patients reported by Disteche et al. [1986b] showed deletions of intervals 1, 2, and 3, and 1, 2, and 4A. These patients had some manifestations of UTS, notably lymphedema at birth. They did not have the severe lymphatic and cardiovascular abnormalities seen in our patient, in which the deletions were limited to intervals 1 and 2. Thus, a deletion of intervals 1 and 2 is sufficient to result in UTS phenotype. The variation in phenotype is consistent with that observed when the disorder is due to a 45,X chromosome constitution.

Interestingly, in the previously reported cases, the XY females with UTS due to Yp deletion all had normal stature. It is possible that this reflects activity of the Y chromosome in these individuals.

In a review of fetal cystic hygromas by Chervenak et al. [1983], one of the fetuses was 46,XY with female

genitalia. A presumptive diagnosis of XY gonadal dysgenesis was made. We suspect that this fetus may have also had a deletion of the male-determining region of the Y chromosome, similar to our patient.

We believe that our patient illustrates several important points regarding prenatal diagnosis of unsuspected cystic hygromas. The information available at the time of counseling the patient was probably adequate in terms of predicting the outcome for this pregnancy. Regardless of the cause, a large cystic hygroma identified in the second trimester is likely to result in fetal demise or perinatal loss. Two series noted a high rate of intrauterine death or bradycardia prior to elective termination [Chervenak et al., 1983; Garden et al., 1986].

Chromosome analysis is an important part of the evaluation of these patients. Most patients with cystic hygromas are 45,X [Chervenak et al., 1983; Garden et al., 1986]. However, cystic hygromas have been seen with a variety of chromosome abnormalities including trisomy 21, 18, and 13. Cystic hygroma has also been reported in a 47,XXY male. Other chromosome abnormalities that have been associated with this finding include 13q-, 18p-, partial 11q/22q trisomy, and mosaic trisomy 22 [Greenberg et al., 1983; Garden et al., 1986; Hahm et al., 1986].

In addition to chromosome studies, the ultrasonic fetal survey and autopsy are important. Cystic hygromas may be observed as an occasional manifestation in certain syndromes. These include Roberts syndrome [Garden et al., 1986], familial lethal multiple pterygium syndrome [Martin et al., 1986], and distichiasis-lymphedema [Chervenak et al., 1983]. Sibs with cystic hygroma have also been reported [Morgan et al., 1976; Bieber et al., 1979; Cowchock et al., 1982; Dallapiccola et al., 1984]. In these patients, the cystic hygroma is presumed to be a manifestation of an autosomal recessive condition.

This XY fetus had UTS. It is important to recognize this entity so that appropriate counseling can be given. This XY fetus was the result of a crossover event in spermatogenesis, with a recurrence risk of less than 1% for future pregnancies. The molecular data were valuable in understanding the findings in this case. Further analysis of such XY females with Yp deletions should lead to better understanding of the genetic basis of the UTS phenotype.

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