Genetics Corner: A Newborn with a Disorder of Sex Development Caused by 45,X/46,X,idic(Y) Mosaicism

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Summary:

An infant with ambiguous genitalia was born at 37 weeks 6 days gestation by repeat C-section to a 37-year old G4P4 mother with well-controlled gestational diabetes (class A2). The mother had a cell-free fetal DNA screening test that was positive for an increased risk for Monosomy X. An offer of amniocentesis was declined. The parents were expecting a female infant based on genital anatomy on fetal ultrasound (US) examinations. Family history was noncontributory. Apgar scores were 8¹ and 8⁵. Birth weight was 2.51 kg (3rd %ile, Z=-1.87), birth length was 46 cm (2.01%ile, Z=-2.05), head circumference was 32 cm (2.63 %, i.e., Z=-1.94). Placental weight was 286.9 grams, smaller than expected for the gestational age: (<3rd %ile for males at 37 weeks gestation). (1)

“The mother had a cell-free fetal DNA screening test that was positive for an increased risk for Monosomy X. An offer of amniocentesis was declined. The parents were expecting a female infant based on genital anatomy on fetal ultrasound (US) examinations.”

Physical exam revealed a small nondysmorphic infant with ambiguous incompletely virilized external genitalia. A phallic structure with prepuce, measured >1.5 cm in

length, was present with proximal hypospadias. Gonads were palpable bilaterally in a well-rugated, deeply pigmented bifid scrotum. There was no pedal or hand edema or neck webbing.

The pelvic US showed a normal-appearing bladder and no unusual masses or other structures that suggested a uterus, ovary, or testis within the pelvis. The US of the kidneys was normal. The US of the groin revealed “a probable right testicle within the right inguinal canal/scrotum and an ill-defined, heterogeneous ovoid structure in the left inguinal/scrotal region with a questionable peripheral follicle that may represent an ovotestis or dysplastic ovary or testis.” Endocrine studies ruled out the salt-wasting type of congenital adrenal hyperplasia. Testosterone, luteinizing hormone, and 17-hydroxypregnenolone were normal.

Chromosome analysis in 30 metaphase cells showed a 45,X chromosome complement, and parents were informed that their child had a likely diagnosis of 45,X/46,XY mosaicism, and male sex assignment was recommended. They understood that further studies were in progress to identify Y-bearing cells. Chromosome microarray was consistent with monosomy X: arr(X)x1. Fluorescence in situ hybridization (FISH) studies with probes for X and SRY (Yp11.3) were ordered, but results did not return until after the child was discharged. FISH studies revealed an isodicentric Y chromosome in 2 of 20 metaphases: ish dic(Y)(SRY++)[2/20]. “The isodicentric Y chromosome hybridized with two copies of SRY on each of the attached Y short arms. Thus each isochromosome had two copies of the SRY gene. In 18 of 20 selected metaphases, there was a single X chromosome.” Parents were informed of these results by phone.

The child returned at a month of age with his family for outpatient counseling regarding his diagnosis. His parents had accepted a male sex assignment for him. Although his weight had improved slightly (4th %ile, Z=-1.77), his height had not (<1st %ile, Z=-2.88). Repeat chromosome analysis from genital skin and testicular biopsy of both gonads was recommended in conjunction with his hypospadias repair, which is planned when he reaches an appropriate weight. He was referred for an endocrinology evaluation for short stature. An echocardiogram was ordered.

Discussion:

This child has a disorder of sex development (DSD) caused by sex chromosome mosaicism, which is categorized as a sex chromosome DSD (2). Sex chromosome

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DSDs include Turner syndrome, Klinefelter syndrome, and 45,X/46,XY gonadal dysgenesis. Our patient is mosaic for 2 cell lines: 45,X in the majority of lymphocytes and a small percentage of cells with a structurally abnormal isodicentric Y chromosome (idicY), consisting of 2 copies of the Y short arm separated by two centromeres, and, presumably, a small amount of the Y long arm between them. An isodicentric chromosome can be unstable during cell division if both centromeres are active during cell division. When two centromeres are pulled toward opposite poles of the dividing cell, an idicY can be pulled apart, resulting in monosomy X in the surviving daughter cell. This is the likely mechanism for the monosomy X cell line in this patient. A structurally abnormal Y chromosome is not infrequent in children with 45,X/46,XY mosaicism. The percent of 45,X cells in lymphocytes does not correlate with the genital/gonadal phenotype, and indeed the percentage of 45,X, and 46,X,idicY cells varies with the tissue type.

Both of these problems, the structurally abnormal Y chromosome and the 45,X cell line, contributed to this child's phenotype in different ways. Mosaicism causes tissue-specific differences in the chromosome complement. The presence of 45,X cells in the gonadal ridge in early embryonic development seems to have diluted the effect of the idic Y cells that express the testis determining factor, SRY. SRY (Sex determining Region on the Y chromosome), a gene on the distal short arm of the Y chromosome (Figure 1), is a key factor that initiates early differentiation of the bipotential gonad by directing support cells to become Sertoli cells in a testis rather than granulosa cells in an ovary. In this patient, the idicY has two copies of SRY, but this cell type, it seems, may not have been in the majority in the gonadal ridge.

We expected that our patient might be infertile as an adult. Azoospermia factor regions a, b, and c (AZFa, AZFb, AZFc), located on the Y q arm, are required for normal sperm production and are often deleted in men with 45,X/46,XY mosaicism who present with infertility. An idicY, with two copies of the p arm and loss of the Y q arm material, increases the chance of azoospermia later in life. Indeed, idicY is a common finding among azoospermic men. (3)

There is a well-described ascertainment bias in reports of 45,X/46,XY mosaicism. Over ninety percent of prenatally diagnosed cases have a normal male phenotype, (4) whereas postnatally diagnosed cases are highly variable and present with a wide spectrum of genital/gonadal phenotypes. This is also the case for individuals with 45,X/46,X,idic(Y). In their review of 32 prenatally diag-

nosed patients with an isodicentric Y chromosome, Yang and Hao (5) report six prenatally diagnosed patients with mosaic 45,X/46,idic(Y) and review the literature to describe 27 others. In their series, most individuals (84%) were phenotypically normal males (27/32), 10% were phenotypic females (3/32), and the rest had ambiguous genitalia (2/32). The breakpoint on the Y chromosome did not correlate with the genital phenotype. Although most prenatally detected isodicentric Y chromosomes had similar breakpoints (Yq11.2 or Yp11.3), the breakpoints had no direct correlation with the phenotype at birth.

“Males with 45,X/46,XY mosaicism should not be referred to as having “male Turner’s syndrome” since Turner syndrome is generally regarded as a disorder described in females. Nevertheless, they can share similar features with females who have Turner syndrome. In their review, because of the range of problems present, Debo and colleagues advocate for multidisciplinary and specialized care for males with 45,X/46,XY mosaicism. (6) ”

Males with 45,X/46,XY mosaicism should not be referred to as having “male Turner’s syndrome” since Turner syndrome is generally regarded as a disorder described in females. Nevertheless, they can share similar features with females who have Turner syndrome. In their review, because of the range of problems present, Debo and colleagues advocate for multidisciplinary and specialized care for males with 45,X/46,XY mosaicism. (6) Short stature is a common finding, which justifies chromosome analysis in all boys with short stature, the recommended diagnostic test for all short girls. Small size at birth is not universal, and some children do not exhibit short stature until after age 2. Short stature has a similar cause in girls with Turner syndrome and in males with 45,X/46,XY mosaicism. Both have a heterozygous loss of SHOX (Short stature HOmeoboX) in the 45,X cell line. This gene, which participates in chondrocyte proliferation and differentiation, is located in the PAR1 region

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of both the X and Y chromosome short arms, and two functioning copies are required for normal growth in both males and females. Growth hormone treatment may be beneficial for short stature in this group, especially when treatment is initiated early with appropriate dosing. (7) Cardiac anomalies, primarily left-sided lesions such as bicuspid aortic valve or coarctation of the aorta, are found in about 1/3 of patients and are equally common in males with 45,X/46,XY mosaicism, and in females with Turner syndrome. Similar rates of renal anomalies are also seen in both groups. Importantly, there is a risk for gonadoblastoma in phenotypic males and females with mosaicism for a Y-bearing cell line. The risk for gonadoblastoma is higher in individuals with intraabdominal streak gonads and ambiguous genitalia. Because of the potential benefits of endogenous testosterone production and preservation of fertility, scrotal gonads are often preserved when possible and monitored for neoplastic changes with ultrasound and testicular biopsy.

Figure 1 (adapted from Figure 1, Signore et al. 2019) (8)

The Y chromosome consists of a short arm, Yp, and a long arm Yq, separated by a centromere. The dark areas represent bands that appear after Giemsa staining. Two pseudoautosomal regions, PAR1 and PAR2, located at distal Yp and Yq respectively, bind to counterparts on the distal ends of the X chromosome. Unlike other sex-linked genes that are subject to X-inactivation, PAR1 and PAR2 are expressed from both the X and the Y chromosomes. SRY (Sex-determining Region on Y) at Yp11.31 is a key factor in developing the testis from the primordial gonad early in embryonic life. Azoospermia factors a, b, and c (AZFa, AZFb, AZFc) are located in the long arm of the Y.

“Because of the potential benefits of endogenous testosterone production and preservation of fertility, scrotal gonads are often preserved when possible and monitored for neoplastic changes with ultrasound and testicular biopsy.”

Practical applications:

1. Recognize that a child with a 45,X chromosome complement with ambiguous genitalia is likely to have a Y-bearing cell line. Utilize fluorescence in situ

hybridization (FISH) with probes for X and Y chromosome regions, esp SRY, to establish the presence of a Y chromosome that contains SRY. Note that the chromosome microarray in this child did not detect the idicY because it was present at a low level of mosaicism.

2. Do not refer to males with 45,X/46,XY mosaicism as having “male Turner syndrome” since that diagnosis is understood to refer to females.
3. Anticipate that males with 45,X/46,XY mosaicism may have short stature and benefit from early growth hormone treatment.
4. Recognize that individuals with 45,X/46,XY mosaicism are at risk for gonadoblastoma, left-sided cardiac defects, renal anomalies, and other features that can be seen in Turner syndrome. Refer to a multidisciplinary center for specialized care if possible.
5. Recognize that there is an increased risk for infertility in adulthood posed by deletion of the long arm of the Y chromosome.

References:

1. Almog B, Shehata F, Aljabri S, Levin I, Shalom-Paz E, Shrim A. Placenta weight percentile curves for singleton and twins deliveries. *Placenta*. 2011 Jan;32(1):58-62. doi: 10.1016/j.placenta.2010.10.008. Epub 2010 Oct 30. PMID: 21036395.
2. Witchel SF. Disorders of sex development. *Best Pract Res Clin Obstet Gynaecol*. 2018 Apr;48:90-102. doi: 10.1016/j.bpobgyn.2017.11.005. Epub 2017 Nov 22. PMID: 29503125; PMCID: PMC5866176.
3. Li L, Zhang H, Yang Y, Zhang H, Wang R, Jiang Y, Liu R. High frequency of Y chromosome microdeletions in male infertility patients with 45,X/46,XY mosaicism. *Braz J Med Biol Res*. 2020 Feb 14;53(3):e8980. doi: 10.1590/1414-431X20198980. PMID: 32077464; PMCID: PMC7025455.
4. Chang HJ, Clark RD, Bachman H. The phenotype of 45,X/46,XY mosaicism: an analysis of 92 prenatally diagnosed cases. *Am J Hum Genet*. 1990 Jan;46(1):156-67. PMID: 2294747; PMCID: PMC1683543.
5. Yang Y, Hao W. Clinical, cytogenetic, and molecular findings of isodicentric Y chromosomes. *Mol Cytogenet*. 2019 Dec 27;12:55. doi: 10.1186/s13039-019-0465-x. PMID: 31890035; PMCID: PMC6935080.
6. Debo B, Van Looke M, De Groote K, De Leenheer E, Cools M. Multidisciplinary Approach to the Child with Sex Chromosomal Mosaicism Including a Y-Containing Cell Line. *Int J Environ Res Public Health*. 2021 Jan 21;18(3):917. doi: 10.3390/ijerph18030917. PMID: 33494433; PMCID: PMC7908257
7. Bertelloni S, Baroncelli GI, Massart F, Toschi B. Growth in Boys with 45,X/46,XY Mosaicism: Effect of Growth Hormone Treatment on Statural Growth.

Sex Dev. 2015;9(4):183-9. doi: 10.1159/000441342. Epub 2015 Nov 4. PMID: 26529521.

8. Signore F, Gulia C, Votino R, De Leo V, Zaami S, et al. The Role of Number of Copies, Structure, Behavior and Copy Number Variations (CNV) of the Y Chromosome in Male Infertility. *Genes (Basel)*. 2019 Dec 29;11(1):40. doi: 10.3390/genes11010040. PMID: 31905733; PMCID: PMC7016774.

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