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Prophylactic Bilateral Gonadectomy for Ovotesticular Disorder of Sex Development in a Patient With Mosaic 45,X/46,X,idic(Y)q11.222 Karyotype

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ABSTRACT

Ovotesticular disorder of sex development is historically thought to confer a relatively low risk of germ cell malignancy relative to other disorders of sex development. This is likely due in part to the high prevalence of a normal 46,XX karyotype in these patients. However, disorders of sex development represent a broad phenotypic spectrum, and often patients cannot be neatly categorized with a single diagnosis. We report an atypical case of ovotesticular disorder of sex development in a child with ambiguous genitalia and 45,X/46,XY mosaic karyotype. Prophylactic bilateral gonadectomy was performed at age 14 months.
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Introduction

Disorders of sex development (DSD) comprise a diverse spectrum of genotypic and phenotypic presentations, with an overall incidence of approximately 1/4500 live births.[1] Ovotesticular disorder of sex development (OTDSD, formerly known as “true hermaphroditism”) accounts for less than 10% of all DSD, with an overall incidence of approximately 1/100,000 live births. While the distribution of karyotypes in OTDSD seems to vary by geographic region, mosaicism in this disorder is quite rare. We report the first case of the lateral subtype of OTDSD (ovary on one side and testis on the contralateral side, without the presence of an ovotestis) with 45,X/46,XY mosaic karyotype.

Case presentation

The patient was a 3090 g full term newborn with ambiguous genitalia, born to a 34-year-old G5P3013 mother after an uncomplicated pregnancy. Routine prenatal ultrasound at 18 weeks’ gestation had suggested female sex, and no prenatal genetic testing was performed. There was no known maternal exposure to exogenous androgens during the pregnancy and no remarkable prior obstetric history. On physical examination, the infant was active and alert, with stable hemodynamics and no signs or symptoms of salt-wasting congenital adrenal hyperplastic crisis. Genitourinary exam revealed Prader class 3 genitalia; nonpalpable gonads bilaterally, genital tubercle in the form of a clitorophallus measuring approximately 2.5 cm in length with severe chordee, and perineal hypospadias (Fig. 1). The anus was patent and normally positioned. No other dysmorphic features were noted.

After empiric coverage with corticosteroids, the patient underwent diagnostic testing to rule out congenital adrenal hyperplasia. Serum electrolytes and cortisol were within normal limits, and the child remained hemodynamically stable. Serum testosterone was 46 ng/dL, and 11-deoxycortisol, 17-hydroxypregnenolone, thyroxine, LH, and FSH were within normal ranges. A karyotype and fluorescence in situ hybridization analysis performed on peripheral blood cells demonstrated mosaicism, with 90% of cells having 45,X karyotype, and 10% of cells containing an isodicentric variant of the Y chromosome (46,X,idic[Y]) which showed two hybridization signals of the SRY probe. An array-based SNP analysis confirmed that the isodicentric Y chromosome comprised an inverted

Abbreviations: DSD, Disorder of sex development; OTDSD, Ovotesticular disorder of sex development; idic, isodicentric; GBY, Gonadoblastoma locus on the Y chromosome; TSPY1, Testis-specific protein, Y-linked 1.

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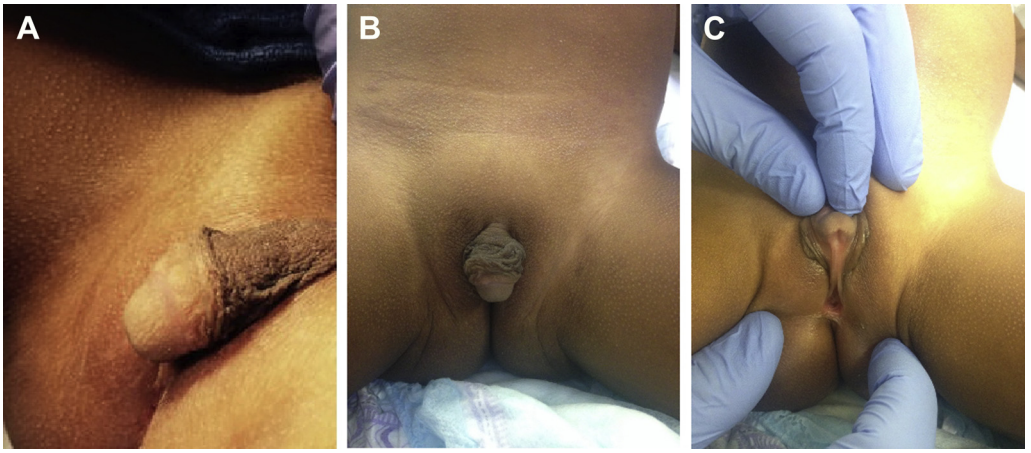

Figure 1. Appearance of ambiguous genitalia at age 14 months. (A) Well-formed 2-3 cm clitorophallus, (B) severe chordee and minimal development of the genital folds, and (C) perineal hypospadias. Gonads were nonpalpable in the genital folds bilaterally.

duplication of the short arm, centromere, and the proximal part of the long arm to q11.222, with loss of the long arm distal to the q11.222 band (Fig. 2). Abdominal and pelvic ultrasound of the newborn was notable for the presence of a vagina, cervix, and uterus, as well as a right gonad located in the adnexa. The left gonad was not visualized. Echocardiogram performed at 7 days old showed a patent foramen ovale and no aortic coarctation or other abnormality.

The parents were counseled extensively about management options regarding gender assignment decisions and the risk of gonadal tumors in patients with a Y chromosome, intra-abdominal gonads, and disorders of sex development. The family made an initial gender assignment of female until patient preference could be elicited.

At 14 months of age, the child underwent a prophylactic laparoscopic bilateral gonadectomy to eliminate the risk of gonadoblastoma. Cystoscopic exam under anesthesia revealed a high urogenital sinus and normal-appearing bladder. Laparoscopically, a normal-appearing uterus was identified. Right and left gonads were identified in the juxtauterine adnexa. Grossly, the left gonad had a dysgenetic bilobular appearance; the right gonad appeared underdeveloped (Fig. 3A–C).

Pathologic examination of the left gonad revealed immature testicular and epididymal tissue (Fig. 3D and E). The right gonad showed benign immature ovarian tissue, benign fallopian tube, and benign immature epididymal tissue (Fig. 3F and G). Taken together, these findings are consistent with ovotesticular disorder of sex development. No evidence of germ cell tumors was noted within the excised tissue.

Discussion

Disorders of sex development carry an elevated risk of gonadal type II germ cell tumors. The absolute risk varies considerably depending on the specific diagnosis and other clinical features. However, a specific molecular diagnosis is determined in as few as 20% of all patients with DSD.[1] In general, the presence of Y chromosomal material (especially the GBY region containing the TSPY1 gene), dysgenetic or streak gonads, and intra-abdominal location of the gonads are thought to confer the highest risk.[1–3] Although OTDSD is thought to carry a relatively low (<5%) risk of germ cell tumors compared to other types of DSD, this determination is heavily skewed by the 70–90% of OTDSD patients who have a normal 46,XX karyotype. In fact, the current patient likely had a much higher absolute risk, based on her Turner mosaic karyotype.[4,5] Furthermore, her chances of future fertility were minimal based on historical data for OTDSD patients.

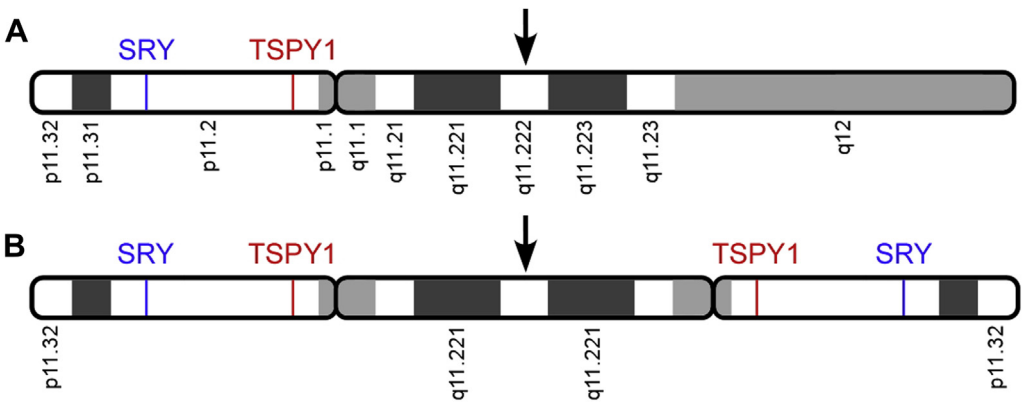

Figure 2. Schematic representation of genetic anomaly. (A) Ideogram of normal Y chromosome. (B) Ideogram of isodicentric Y chromosome variant idic(Y)q11.222. The breakpoint (arrow) was located at the q11.222 band of the long arm, with duplication of all short arm and proximal long arm material, and loss of all distal long arm material. SRY and TSPY1 loci are shown.

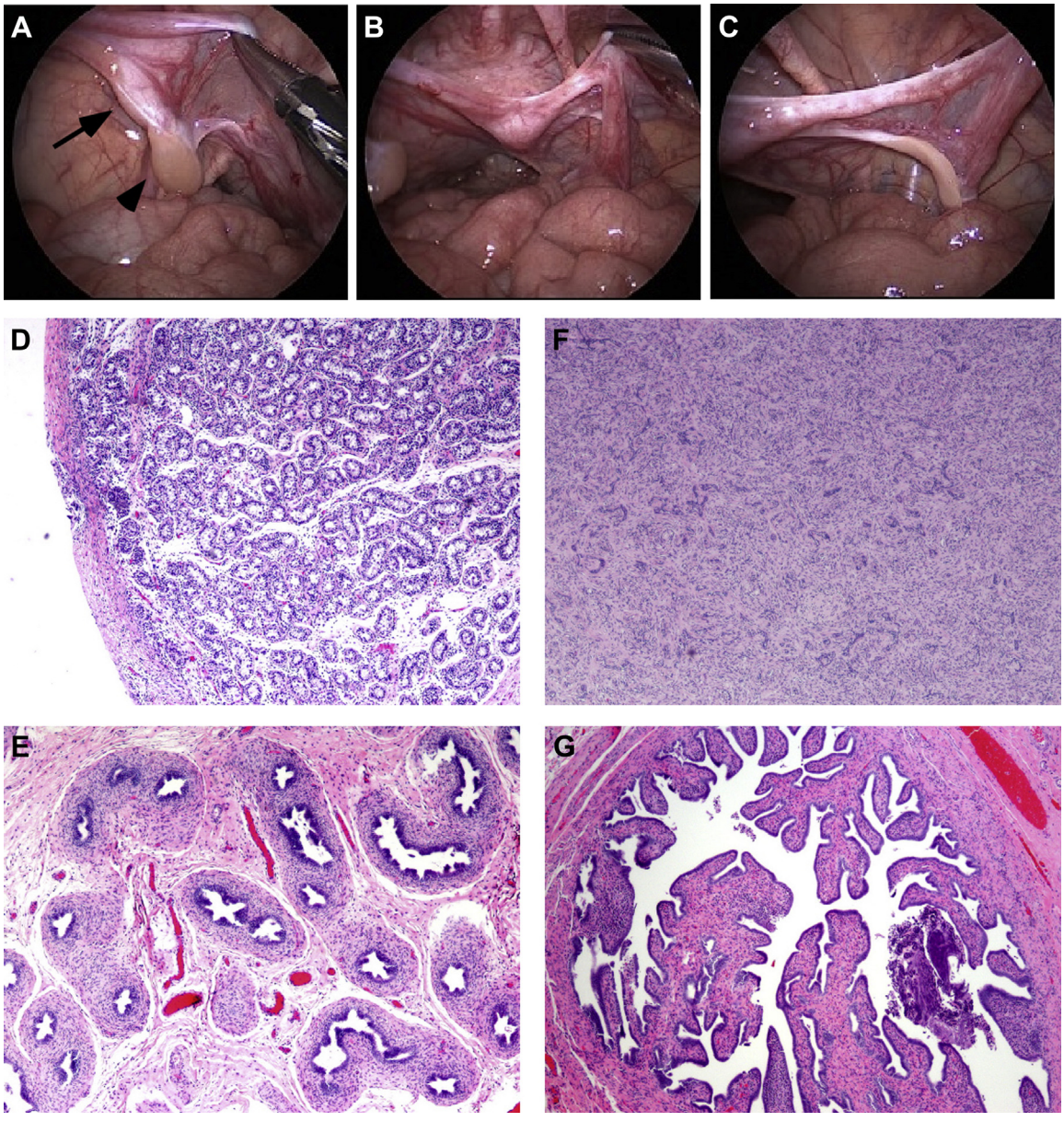

Figure 3. Intraoperative appearance and histopathologic findings. (A) Bilobular-appearing left gonad, with grossly testicular-appearing superior pole (arrow) and adipose/ovarian lower pole (arrowhead). (B) Well-formed Müllerian remnant consistent with a uterus. (C) Streak-appearing right gonad. All gonadal tissue was excised and sent for pathologic examination. Left gonad: (D) benign immature testicular tissue and (E) epididymal tissue. Right gonad: (F) benign immature ovarian tissue and (G) fallopian tube.

Table 1
Previously reported cases of 45,X/46,XY mosaic karyotype with OTDSD

	Karyotype	Presentation	Age at diagnosis	Sex assignment	Age at gonadectomy	Right gonad	Left gonad	Tumor	Age at first-stage genitoplasty
Sloan et al. 1984	45,X/46,X,idic(Y)p11	Primary amenorrhea & virilization	24 years	Female	24 years	A; ovotestis	A; streak	NR	NR
Shimoda et al. 1998	45,X/46,X,idic(Y)q11.2	Ambiguous genitalia	29 years[a]	Female	29 years	A; ovotestis	A; streak	(Right) seminoma	NR
Gole et al. 2008	45,X/46,X,idic(Y)q11.2	Clitoromegaly & short stature	32 months	Female	32 months	A; ovotestis	A; streak	NR	32 months
Pascual et al. 2009	45,X/46,X,idic(Y)q12	Ambiguous genitalia	Newborn	Male	2 months	S; ovotestis	I; ovotestis	(Right) juvenile granulosa cell tumor?	NR
Tran et al. 2011	45,X/46,X,idic(Y)q11.23	Ambiguous genitalia	Newborn	Male	19 months	A; testis & streak	A; ovotestis	none	19 months
Current report	45,X/46,X,idic(Y)q11.222	Ambiguous genitalia	Newborn	Female	14 months	A; ovary	A; testis	none	deferred

A: intra-abdominal, I: inguinal, S: scrotal, NR: not reported, idic: isodicentric (break point shown).
[a] Prior workup at 5 years and 19 years of age provided inconclusive and/or false diagnosis.

To our knowledge, only five reports of OTDSD in patients with the mosaic karyotype 45,X/46,XY have been published to date, all of which displayed an isodicentric Y chromosomal variant with breakpoints similar to the currently reported case (Table 1). It is noteworthy that these isodicentric variants almost certainly contain duplicated copies of TSPY1, the overexpression of which is thought to play a major causative role in the development of germ cell tumors in DSD patients.[2] All reported cases underwent prophylactic bilateral gonadectomy soon after diagnosis, and two of five patients had germ cell tumors found on pathologic examination of the excised tissue: a seminoma in the ovotestis removed from a 29-year-old, and likely juvenile granulosa cell tumor in the ovotestis of a 2-month-old.

Conclusion

This patient exemplifies several important principles in the management of DSD patients: 1) Clinical presentation is highly variable and often requires individualized management by an experienced multidisciplinary team, 2) Accurate diagnosis often requires an extensive multimodal diagnostic evaluation, and 3) Management decisions must take into account not only gender assignment and psychological considerations, but also the risk of germ cell tumors and the potential for future fertility. Due to the rarity of these disorders, the majority of the literature on DSD is based on small retrospective clinical series and case reports. Further studies are needed to guide clinicians in the classification, risk-stratification, and appropriate management of these patients.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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