A CURIOUS CASE OF A 46,XX MALE: AN UNUSUAL CAUSE OF PRIMARY HYPOGONADISM

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The authors have no conflicts of interest to disclose.

ABSTRACT:

Background: 46,XX testicular disorder of sexual development is a rare cause of primary hypogonadism, characterized by a male phenotype despite a female [i.e. 46,XX] karyotype. In the vast majority of cases, it is caused by a translocation of Y chromosomal material (containing the SRY gene) onto an X chromosome.

Case presentation: A 38 year-old male was referred to the endocrinology clinic for hypogonadism. His symptoms included decreased energy, diminished libido, weight gain and gynecomastia. There was no history of testicular torsion or trauma, cryptorchidism, orchitis, chemotherapy or radiation therapy. Despite 3 years of unprotected intercourse, his partner had not conceived. Physical examination was significant for bilateral gynecomastia, reduced androgen-dependent hair growth, and small, soft testes. Laboratory investigations revealed evidence of primary hypogonadism (low testosterone and elevated gonadotropins). Cytogenetic analysis revealed a 46,XX karyotype with an SRY translocation onto the short arm of the X chromosome.

Conclusion: We present a rare case of 46,XX testicular disorder of sexual development, a consequence of translocation of the SRY gene onto an X chromosome. We will review its epidemiology, pathogenesis, presentation, diagnosis and management.

INTRODUCTION:

Primary hypogonadism in males involves an intrinsic abnormality in the testes. It presents with low serum testosterone and elevated gonadotropins (follicle stimulating hormone (FSH) and luteinizing hormone (LH)). In contrast, central hypogonadism involves impaired pituitary (secondary hypogonadism) or hypothalamic function (tertiary hypogonadism), resulting in low serum testosterone and low or inappropriately normal gonadotropins. Consequences of hypogonadism depend on its age of onset, but may include ambiguous or female genitalia if established in the first trimester of gestation; absence or arrest of pubertal development if occurring at pubertal age; or loss of libido, erectile dysfunction, gynecomastia, decreased muscle and bone mass, fatigue and loss of body hair if established during adulthood.1 Common etiologies of primary hypogonadism include Klinefelter syndrome, bilateral torsion, orchitis, orchidectomy, and testicular trauma (induced by surgery, radiation or chemotherapy).2 We report a rare case of a 46,XX testicular disorder of sexual development (DSD); a phenotypic male with a female karyotype.
CASE PRESENTATION:

A 38-year-old Caucasian male was seen in the endocrinology clinic for hypogonadism. He presented with a 6 month history of decreased energy, diminished libido, 18 kg weight gain and gynecomastia. No changes in his voice or frequency of shaving were noted, although he mentioned that he only shaved once or twice weekly. He denied any history of mumps or other testicular infections, testicular trauma, torsion or cryptorchidism. He had never received chemotherapy or radiotherapy. His puberty was timely but incomplete: He exhibited scarce facial hair, as well as decreased hair growth on his arms, legs, axillae and abdomen. He had normal (i.e. Tanner Stage 5) public hair. His voice remained midpubertal in pitch. His muscle bulk did not increase with exercise. Despite 3 years of unprotected intercourse, his partner had not conceived. He had social difficulties during his youth and was never particularly athletic. In an effort to alleviate his hypogonadal symptoms, he had been started on oral testosterone undecanoate several weeks before his referral with limited effect.

His past medical history was significant for a motor vehicle collision resulting in a dashboard injury to his knees, a right scapholunate ligament repair, dyslipidemia and GERD. His medications included simvastatin, esomeprazole and testosterone undecanoate capsules. He was divorced, though newly engaged to a different partner, and worked as a carpenter. He quit smoking three years prior, consumed one to two alcoholic beverages per week, and denied illicit drug use. Family history was significant for type 2 diabetes and “heart problems” in his father.

On examination, he weighed 117 kg. His blood pressure was 126/92 mmHg and his heart rate was 76 bpm. Respiratory and cardiac examinations were within normal limits. He had Tanner stage III gynecomastia bilaterally with palpable glandular tissue. Abdominal examination was remarkable for a reduced amount of hair growth. His testicles were soft, measuring 6 mL on the right and 8 mL on the left (normal range 15-20 mL). No varicoceles were detected.

Laboratory investigations revealed a total testosterone level of 2.0 nmol/L (normal range 7.6-31.4 nmol/L), LH 29 IU/L (normal range 2-9 IU/L) and FSH 45 IU/L (normal range 2-12 IU/L). Prolactin and iron studies were normal.

A karyotype was requested to assess the possibility of Klinefelter syndrome. The chromosomal analysis using G-banding (550 bands of resolution) revealed a 46,XX karyotype (Figure 1). Polymerase chain reaction (PCR) analysis showed amplification of the SRY locus, a gene on the Y-chromosome (p11.31). Fluorescence in situ hybridization (FISH) analysis confirmed translocation of the implicated SRY gene to the short arm of the X chromosome (Figure 2). A follow-up appointment was arranged with the genetic counseling service.

DISCUSSION

Our patient had 46,XX testicular DSD, which is a rare cause of primary hypogonadism. The differential diagnosis for primary hypogonadism is quite broad, and is listed in Table 1.
Table 1. Causes of primary hypogonadism in males.

FETAL ONSET

1. Whole gonadal dysfunction

Gonadal dysgenesis:
- Chromosome defects: Deletions of Yp, 9p, XX/XY, XY/X, other mosaicisms
- Gene mutations: SRY, CRX2, MAMLD1, SF1, WT1, SOX9, DHH, XH2, DHC, TSPYL1, etc.

Vanishing testes

Klinefelter syndrome
46,XX disorder of sexual development
- Ovotesticular DSD
- XX males

2. Dissociated gonadal dysfunction

Leydig cells
- Hypoplasia/aplasia: LH/CG-R mutation
- Steroidogenic defects: CYP11A1, CYP17A1, HSD3B2, POR, CYB5A, or HSD17B3 mutation
- INSL3 mutations

Sertoli cells
- FSH receptor mutation
- AMH mutation

POST-NATAL ONSET

1. Whole gonadal dysfunction

- Prader-Willi syndrome*
- X-linked adrenal hypoplasia congenita*
- Cranial radiotherapy and chemotherapy*
- Lead intoxication*
- Marijuana consumption*
- Total body irradiation*
- Orchitis
- Testicular torsion or trauma
- Down syndrome
- Varicocele
- Chronic illnesses: e.g. granulomatous diseases, amyloidosis, cystic fibrosis, chronic pulmonary disease, renal failure, neurologic disorders
- Late-onset hypogonadism

2. Dissociated gonadal dysfunction

- Y chromosome deletions and microdeletions: AZF
- Gene mutations: CILD1, USP9Y, etc.
- Chemotherapy
- Abdominopelvic radiotherapy
- Pharmacological treatments: spironolactone, ketoconazole

* indicates combined central and primary hypogonadism

Adapted from [1] with permission.

EPIDEMIOLOGY

46,XX testicular DSD, formerly known as “XX male syndrome”, was initially described by Albert de la Chapelle and colleagues in 1964.5 It is a rare disorder with an incidence of 1 in 20,000-25,000 male newborns.4,6 80-90% of cases are SRY (sex-determining region Y)-positive; 10-20% are SRY-negative.4,6

PATHOGENESIS

During paternal meiosis, “crossing over”, or genetic recombination of chromosomal material, takes place between the X and Y chromosomes at homologous sequences of nucleotides known as pseudoautosomal regions.4 Certain regions of the Y chromosome – known as sex-determining regions – do not normally participate in recombination.9 One such region includes the SRY gene (located on Yp11.3), which plays a pivotal role in the development of the embryonic testes, and hence male sex determination.5,10 As a consequence of erroneous recombination involving the SRY gene, patients with 46,XX DSD ultimately have a male phenotype despite possessing a female (i.e. 46,XX) karyotype. Translocation of the SRY gene to the X chromosome is almost always a de novo translocation, although rarely it may be inherited.11 Other rare possibilities include a de novo or inherited translocation of SRY to an autosome.11 Consistent with their male phenotype, these patients exhibit male psychosexual identification.11 Infertility is caused by the absence of the spermatogenesis locus on the long arm of the Y chromosome, which contains three AZF (azoospermia factor) regions.5,9

SRY-negative 46,XX DSD includes patients with ovotesticular-DSD (true hermaphrodites having both testicular and ovarian tissue in the gonads) and testicular-DSD (both gonads are testes with no evidence of ovarian tissue).6 Their phenotype may result from excessive or absent actions of other important genetic factors within the sexual differentiation cascade, including SOX9, DAX-1, Ad4BP/SF-1, WT1 and GATA4.5,10 Unlike their SRY-positive counterparts, SRY-negative 46,XX DSD patients often present with ambiguous genitalia at birth with a high incidence of penoscrotal hypospadias and cryptorchidism, and almost invariably develop gynecomastia around the time of puberty.5,11 True hermaphrodites may have a uterus or hemi-uterus, as well as female-range estrogen levels.11

CLINICAL PRESENTATION

Patients present with primary hypogonadism manifesting as small testes (microorchidism), gynecomastia, non-obstructive azoospermia and infertility.5,8 Penile size is normal, and Müllerian structures are absent.11 Testes are generally soft, but may become firmer with age.11 Furthermore, these patients may display poor facial hair growth and female pubic hair distribution.6,8 One notable difference between 46,XX testicular DSD and Klinefelter syndrome is that shorter-than-average stature is often seen in the former, which may be related to the absence of specific growth-related genes on the Y chromosome.5,9 In addition, there is no association between learning disorders or behavioural issues and 46,XX testicular DSD.13 Although not
warranted for diagnosis, testicular biopsy generally demonstrates a decrease in size and number of seminiferous tubules, peritubular fibrosis, absence of germ cells, and Leydig cell hyperplasia.\textsuperscript{11}

In 46,XX testicular DSD, testosterone levels are normal during puberty but they begin to decline during adulthood leading to primary hypogonadism.\textsuperscript{4} Diagnosis in adulthood during investigations for infertility is a classic occurrence.\textsuperscript{4,6} 46,XX karyotypic abnormalities have been reported with an incidence of 0.9% in azoospermic males.\textsuperscript{14}

**DIAGNOSIS**

Diagnosis of 46,XX testicular DSD requires cytogenetic analysis, which reveals a normal female (46,XX) karyotype. Next, FISH of an SRY probe to metaphase chromosomes should be undertaken, in order to determine the nature of the rearrangement.\textsuperscript{11} This may involve SRY translocated on an X chromosome (most common scenario), or rarely, SRY translocated on an autosome.\textsuperscript{11} It is important to determine the nature of the rearrangement, as the modes of inheritance and implications for genetic counseling are different.\textsuperscript{11} Although PCR for SRY is more sensitive than FISH, it cannot establish the nature of the chromosomal rearrangement, and hence the inheritance pattern.\textsuperscript{11}

**MANAGEMENT**

With respect to management of 46,XX testicular DSD, patients may benefit from psychological support, particularly after disclosing their diagnosis.\textsuperscript{11} They require lifelong endocrinology follow-up with regular bone mineral density (BMD) measurements and treatment of osteopenia, as well as testosterone supplementation.\textsuperscript{5} The latter is generally initiated after age 14 at low doses, and gradually increased to reach adult levels.\textsuperscript{11} Our patient had a suboptimal response to oral testosterone undecanoate, conceivably because the latter is known to have unreliable oral bioavailability, fluctuating serum levels and a short half-life, necessitating multiple daily dosing.\textsuperscript{15} For these reasons, intramuscular and transdermal testosterone preparations are preferable. Gynecomastia, if still a concern following testosterone replacement therapy, can be treated by reduction mammoplasty.\textsuperscript{11} Genetic counseling would also be beneficial in order to educate patients on the nature, inheritance and implications of their condition.\textsuperscript{11}

**CONCLUSION**

We report a rare case of 46, XX testicular DSD with an SRY translocation on the short arm of an X chromosome. Cytogenetic analysis is a crucial investigative tool for this particular condition. These patients benefit from genetic counseling and lifelong endocrinology follow-up.

**Abbreviations**

FISH: follicle-stimulating hormone; LH: luteinizing hormone; G-banding: Giemsa banding; PCR: polymerase chain reaction; SRY: sex determining region Y; FISH: fluorescence in situ hybridization; DSD: disorder of sexual development; AZF: azoospermia factor.

**References**


