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Case Report

An Interesting Case of Hypogonadism: Workup in a Phenotypic Male Reveals XX Genotype

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Abstract

We present a patient case referred for evaluation of male hypogonadism with gynecomastia. On examination, he was noted to have microtestis, shorter than expected height, and bilateral gynecomastia. Further investigation revealed XX genotype and on fluorescence in situ hybridization analysis confirmed the SRY gene was present on the short arm of 1 X chromosome. This case highlights the importance of detailed history and examination and the indication for genetic counseling in selected cases.

Key Words: hypogonadism, gynecomastia, SRY gene, disorder of sexual development

Abbreviations: CT, computed tomography; DSD, disorder of sex development; FISH, fluorescence in situ hybridization.

Hypogonadism is commonly diagnosed and treated by primary care providers. It is important to diagnose the etiology before starting treatment. This case highlights the importance of thorough history and examination in a patient that led to his diagnosis of disorder of sexual development.

Case Presentation

A 26-year-old, previously healthy male presented to his primary care provider with gynecomastia. He complained of pain and tenderness around his right breast and discussed his desire to get surgery done for gynecomastia. The patient was evaluated by a surgeon for intervention. The workup revealed a low testosterone level, indicating hypogonadism. The patient was then referred to Endocrinology for management of hypogonadism.

Diagnostic Assessment

In the Endocrine clinic, a detailed review of the patient's history was conducted. The patient mentioned that he initially observed breast enlargement at the time of puberty (aged 14 years) with further enlargement around 2019 (aged 23 years). Recently, he noticed some pain and tenderness around his right breast, especially after working out in the gym. The patient denied a history of any serious head or groin injury and denied taking any hormone replacement or over-the-counter supplements, aside from protein supplements for muscle building. He mentioned that he lately had a decreased his sex drive and occasional episodes of erectile dysfunction. He noticed a decrease in intensity of erections during intercourse and morning erections. He was unsure if he has trouble with fertility because he had never tried to have a baby, although he had noticed low sex drive for the past few years.

The patient denied any personal history of mumps, HIV, or testicular torsion. He had never received radiation or chemotherapy and not on any chronic medications.

On examination, he was noted to have bilateral gynecomastia, with the right breast being slightly bigger and mildly tender to pressure. He also was noted to have very small testicles measuring about 1 cc and normal male pubic and axillary hair patterns.

The patient is 66.5 inches (166.5 cm) tall and significantly shorter than his father and both his brothers who are about 74 to 75 inches (187.5 cm) tall. His arm length of 68.5 inches (171.25 cm) exceeded his height by about 2 inches (5 cm). His weight was 146 lb (65.7 kg) and body mass index was 23.2.

Blood work showed decreased testosterone levels with elevated FSH and LH, consistent with primary hypogonadism (Table 1).

Ultrasound Doppler of the scrotum showed atrophic testicles bilaterally. The right testicle measured $1.40 \times 0.99 \times 1.0$ cubic cm (Fig. 1) and the left testicle measured $1.58 \times 1.06 \times 1.10$ cubic cm (Fig. 2). The testicles were atrophic and heterogeneous with microcalcifications bilaterally. The epididymides appeared relatively normal in size and echogenicity. No mass lesions or cysts were seen. No hydrocele, varicocele, or hernia was observed. There was normal vascular flow. Sperm analysis showed azoospermia.

Breast mammogram showed bilateral benign gynecomastia (Fig. 3), with the right breast larger than the left. There was moderate dendritic breast parenchyma seen in the right breast. On 2-dimensional and 3-dimensional mammograms, no suspicious mass, microcalcifications, or architectural distortions were seen. No suspicious abnormality was noted in either breast.

We ordered karyotype testing considering the clinical findings in the setting of primary hypogonadism. As suspected, the karyotype result came back abnormal. However, to our

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Table 1. Laboratory results

Laboratory test	Reference range in conventional (and SI) units	July 2021
Testosterone	240-950 ng/dL (8.34-28.7 nmol/L)	139 ng/dL (4.81 nmol/L)
Free testosterone	5.05-19.8 ng/dL (0.17-0.68 nmol/L)	3.89 (0.13 nmol/L)
FSH	1.500-12.40 mIU/mL (1.5-2.4 IU/L)	58.5 mIU/mL (58.5 IU/L)
LH	1.5-9.3 mIU/mL (1.5-9.3 IU/L)	27.3 mIU/mL (27.3 IU/L)
Prolactin	4.79-23.30 ng/mL (99.6-503.2 mcg/L)	10.34 ng/mL (218.8 mcg/L)
HCG	≤5 mIU/mL (≤5 IU/L)	3.5 mIU/mL (3.5 IU/L)
Estradiol males	<11.80-39.8 pg/mL (<1.18-3.98 ng/dL)	14 pg/mL (1.4 ng/dL)
DHEA	<13 ng/mL (<35.2 nmol/L)	3.1 ng/mL (8.41 nmol/L)
PSA	0.040-4.000 ng/mL (40-4000 ng/L)	0.07 ng/mL (70 ng/L)

Abbreviations: DHEA, dehydroepiandrosterone; HCG, human chorionic gonadotropin; PSA, prostate-specific antigen.

greatest surprise, 46, XX karyotype was observed in this phenotypic male. One of the X chromosomes had an apparent deletion of Xp22.33 to Xpter and addition of chromatin material. Subsequently, fluorescence in situ hybridization (FISH) analysis was done. This demonstrated that the male sex-determining region of the Y chromosome, SRY, was present on the short arm of 1 X chromosome. This product of an X; Y interchange is typically associated with shorter than average stature, gynecomastia, small testes, and azoospermia.

The result of FISH analysis showed the following: 46,X, der(X)t(X;Y)(p22.33; p11.3).ish der(X)t(X;Y)(p11.3;XCEN) (SRY+, DXZ1+).

Next we ordered a computed tomography (CT) scan abdomen that showed normal prostate gland and absence of ovarian tissue. Testes were atrophic bilaterally. There was a small, fat-containing umbilical hernia and bilateral inguinal hernias. The rest of the CT scan was within normal limits.

Treatment and Follow-up

We had a detailed discussion with the patient about his long-term prognosis, including male infertility and inability to have biological children due to azoospermia reported on his sperm analysis. He decided to retain his sex identity as a male. He was started on biweekly intramuscular testosterone injections at 150 mg/mL to treat his hypogonadism. At his 6-week follow-up, he reported improvement in fatigue, libido, and erections. He mentioned that his semen is now thicker and stickier. We referred him for genetic counseling and urology to evaluate his risk of gonadoblastoma related to his microtestes with microcalcification. He will undergo breast surgery for management of gynecomastia.

Discussion

Male hypogonadism refers to a decrease in testosterone production. It can be primary (involving testes) with elevated FSH and LH or secondary (involving pituitary/hypothalamus) with low FSH and LH levels.

Gynecomastia is more common in primary disease because of a stimulatory effect of the supranormal FSH and LH concentrations on testicular aromatase activity. This results in increased conversion of testosterone to estradiol and enhanced testicular secretion of estradiol.

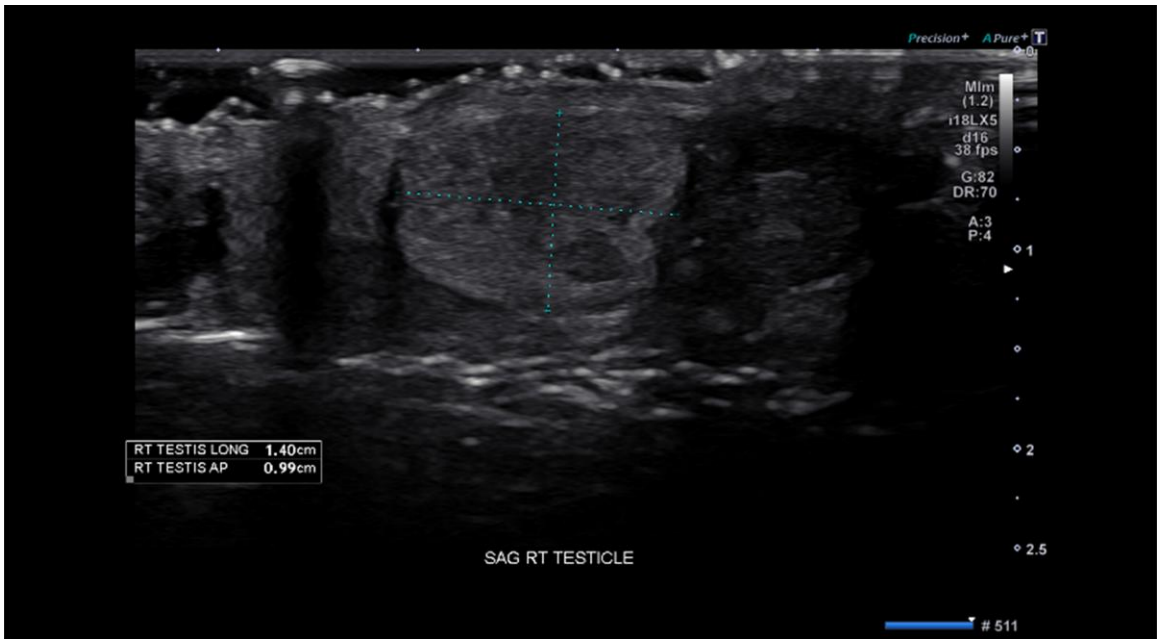

Figure 1. The right testicle measured 1.4 × 0.99 × 1.0 cubic cm.

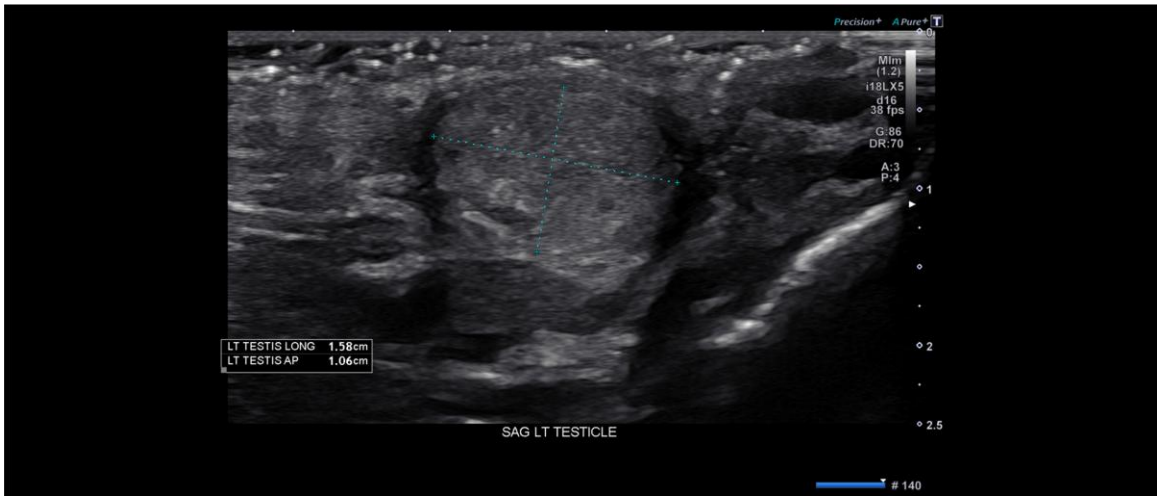

Figure 2. The left testicle measured 1.58 × 1.06 × 1.1 cubic cm. The testicles were atrophic and heterogeneous with microcalcifications bilaterally. The epididymides appeared relatively normal in size and echogenicity. No mass lesions or cysts were seen. No hydrocele, varicocele, or hernia was observed. There was normal vascular flow.

Primary hypogonadism is more often associated with a decrease in sperm production than in testosterone production. In secondary hypogonadism, there is a proportionate reduction in testosterone and sperm production. Acquired causes of primary hypogonadism include: infection (mumps orchitis, HIV); radiation and chemotherapy; trauma; testicular torsion; chronic, systemic diseases; environmental toxins; suramin; ketoconazole; glucocorticoids; and autoimmune damage. If there is a clear history of any of these conditions, genetic workup is not necessary.

Congenital abnormalities include: Klinefelter syndrome (the most common congenital cause), FSH and LH receptor mutations, cryptorchidism, disorders of androgen biosynthesis, and myotonic dystrophy.

Our patient presented with gynecomastia despite a normal body mass index, and workup revealed primary hypogonadism. Acquired causes were ruled out on clinical evaluation. Moreover, he has atrophic testes with microcalcification, azoospermia, shorter than expected height, and gynecomastia, which promoted further workup for genetic causes. In general, genetic testing is not required for management of hypogonadism; however, because of the phenotypic abnormalities mentioned, we ordered karyotype analysis.

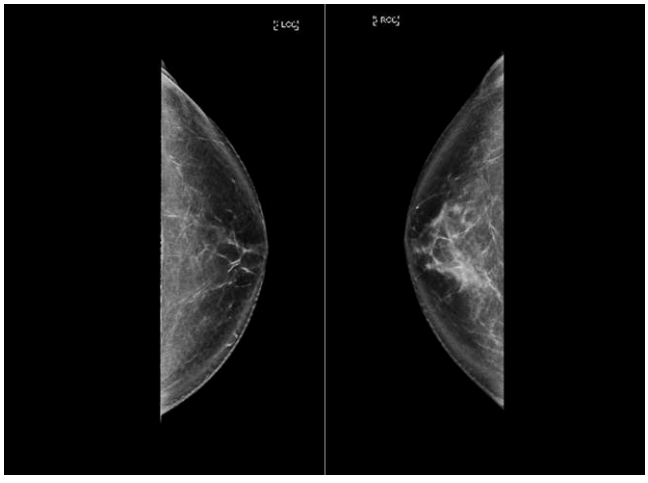

Figure 3. Breast mammogram showed bilateral benign gynecomastia, with the right breast larger than the left. There was moderate dendritic breast parenchyma seen in the right breast. No suspicious mass, microcalcifications, or architectural distortion were seen bilaterally.

Our patient's karyotype result showed 46,XX karyotype. One of the X chromosomes was structurally abnormal with an apparent deletion of Xp22.33 to Xpter and addition of chromatin material.

Infants born with genitals that do not appear typically male or female or that have an appearance discordant with the chromosomal sex are classified as having a difference or disorder of sex development (DSD).

In XX testicular DSD, the gonads develop along the testicular rather than the ovarian pathway (1). As a result, the gonad may be either a normal or a dysgenetic testis. The phenotype that the patient develops depends on the degree of production of testosterone and antimüllerian hormone (also known as müllerian-inhibiting substance and müllerian regression factor) (2).

Many causes of XX testicular DSD can also cause XX ovotesticular DSD in which both ovarian follicular and testicular tubular tissue are present. Hormonal evaluation, imaging, and histology help in making the final diagnosis.

XX testicular or ovotesticular DSD is suggested by detection of higher-than-expected levels of testosterone, antimüllerian hormone/müllerian-inhibiting substance in an XX individual. XX testicular DSD is associated with infertility because subjects lack an intact Y chromosome that is required for spermatogenesis. If there is intact ovarian tissue, fertility may be possible in some cases of XX ovotesticular DSD. Our patient has azoospermia and no ovarian tissue on CT scan.

One of the causes of XX testicular or ovotesticular DSD include presence of SRY (3, 4). This is because of a translocation of SRY (sex-determining region on the Y chromosome) to the X chromosome or an autosome and accounts for roughly one-half of cases of XX testicular DSD. The presence of SRY results in activation of testicular pathways in the developing gonad, as seen in our patient.

In our patient, FISH analysis demonstrated that the male sex-determining region of the Y chromosome, SRY, is present on the short arm of 1 X chromosome. This product of an X;Y

interchange is typically associated with shorter than average stature, gynecomastia, small testes, and azoospermia (5).

It has been noted that inaccurate or absent SRY expression or a disturbed expression of other male-determining genes prohibits sex cord formation and differentiation. Surviving germ cells residing in undifferentiated gonadal tissue (including immature sex cord) contain a high risk for the development of gonadoblastoma (6).

The prevalence of germ cell tumors in patients with gonadal dysgenesis is about 30% (7).

It is important to schedule genetic counseling for such patients to discuss and understand their prognosis for fertility, as well as increased risk of malignancies and other physical and mental health issues related to their diagnosis.

Learning Points

- The first step in managing men with confirmed hypogonadism is to differentiate between primary vs secondary (8) causes based on clinical presentation and blood work.
- Karyotype analysis and genetic workup is not necessary if it is clear that there is an acquired cause of primary hypogonadism. These include infection (mumps orchitis, HIV); radiation/chemotherapy; trauma; testicular torsion; chronic, systemic diseases; environmental toxins; suramin; ketoconazole; glucocorticoids; and autoimmune damage.
- Key symptoms and signs that prompt genetic tests are primary hypogonadism with microtestes, gynecomastia, azoospermia, and abnormal phenotype such as genitals that do not appear typically male or female.
- Genetic counseling is important for patients with an abnormal karyotype to discuss their prognosis for fertility, as well as any increased risk of malignancies and other physical and mental health issues related to the diagnosis.

Contributors

Both the authors contributed individually to authorship. A.M. and T.S. were involved in the diagnosis and management of this patient and in manuscript submission. Both the authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

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Data Availability Statement

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References

1. Simpson JL. Male pseudohermaphroditism: genetics and clinical delineation. *Hum Genet*. 1978;44(1):1-9.
2. Hughes IA, Nihoul-Fékété C, Thomas B, Cohen-Kettenis PT. Consequences of the ESPE/LWPES guidelines for diagnosis and treatment of disorders of sex development. *Best Pract Res Clin Endocrinol Metab*. 2007;21(3):351.
3. Ürel Demir G, Doğan ÖA, Şimşek Kiper PÖ, *et al*. Coexistence of trisomy 13 and SRY (-) XX ovotesticular disorder of sex development. *Fetal Pediatr Pathol*. 2017;36(6):445-451.
4. Stoppa-Vaucher S, Ayabe T, Paquette J, *et al*. 46, XY gonadal dysgenesis: new SRY point mutation in two siblings with paternal germline mosaicism. *Clin Genet*. 2012;82(6):505-513.
5. Délot EC, Vilain EJ. Nonsyndromic 46, XX testicular disorders/differences of sex development. In: Adam MP, Mirzaa GM, Pagon RA, *et al*., eds. *GeneReviews®*. University of Washington; 1993-2022. pp. 6–7.
6. Cools M, Drop SLS, Wolffenbuttel KP, Wolter Oosterhuis J, Looijenga LHJ. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. *Endocr Rev*. 2006;27(5):468-484.
7. Verp MS, Simpson JL. Abnormal sexual differentiation and neoplasia. *Cancer Genet Cytogenet*. 1987;25(2):191-218.
8. Bhasin S, Brito JP, Cunningham GR, *et al*. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744.