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Case Report

46,XX Testicular Disorder of Sex Development (DSD) Presenting With Male Hypogonadism

Run Ting Chin[1] **and Shao Feng Mok**[1]

[1]Division of Endocrinology, Department of Medicine, National University Hospital, Singapore

Correspondence: Run Ting Chin, MBBS, MMed (Int Med), MRCP, Division of Endocrinology, Division of Medicine, National University Hospital, Level 10, NUHS Tower Block, 1E Kent Ridge Rd, Singapore 119228, Singapore. Email: run_ting_chin@nuhs.edu.sg.

Abstract

Disorders of sex development are genetically complex, and phenotypes range from hypospadias to completely masculinized or feminized genitalia with a discordant karyotype. They arise as a result of alterations in gonad formation (sex determination stage) or function (sex differentiation stage). Reaching a specific diagnosis with the aid of molecular technologies is important for individualized management, genetic counseling, and prognostic prediction for fertility and risk of tumor development. This case report describes a young adult male who was referred initially with concern for Klinefelter syndrome based on a commercial genetic test. His laboratory investigations revealed hypergonadotropic hypogonadism, azoospermia, and a chromosomal karyotype of 46,XX. He was eventually diagnosed with 46,XX testicular disorder of sex development. He was initiated on testosterone replacement therapy and offered adoption and use of donor sperm for artificial reproduction techniques.

Key Words: disorder of sex development, male hypogonadism, infertility

Introduction

Male hypogonadism is a common presentation in endocrinology practice. Congenital or acquired disturbances at any level of the hypothalamic-pituitary-gonadal axis can lead to an impairment of reproduction function and the clinical syndrome of hypogonadism. Hypogonadism can be caused by a primary testicular pathology (hypergonadotropic hypogonadism) or hypothalamic and/or pituitary failures leading to secondary hypogonadism (hypogonadotropic hypogonadism). The signs and symptoms of hypogonadism vary, depending on age of onset, severity of testosterone deficiency, and androgen sensitivity.

Disorders of sex development (DSD) are congenital anomalies involving a discordance between chromosomal, genetic, gonadal, and/or genital sex. Most DSD affect the fetal endocrine and/or paracrine hormonal action, resulting in the wide spectrum of clinical and hormonal phenotypes. Currently only 13% to 20% of patients with DSD receive a specific molecular diagnosis. This diagnostic gap arises from inadequate knowledge of the pathogenesis of DSD, variation in assessment and in-depth phenotyping of these rare conditions, and limited awareness or availability of tools for molecular diagnosis. While challenging, reaching a specific diagnosis is important for individualized management, genetic counseling, and prognostic prediction for fertility and risk of tumor development. Optimal clinical management of individuals with DSD encompasses long-term management by an experienced multidisciplinary team.

Case Presentation

A 30-year-old Chinese man had requested for an endocrinology consult for concerns of possible Klinefelter syndrome. He had undergone a preconception genetic test via commercial direct-to-consumer nonclinical genetic testing of his salivary sample using a self-test kit. His health report indicated a "potential 47, XXY chromosomal state" and he was advised to seek further medical attention.

He was born at term and did not have issues with ambiguous genitalia. He underwent puberty around 13 years old when he experienced voice breaking and pubic hair growth. He shaved daily and had normal libido. He denied anosmia. He engaged in regular, unprotected sexual intercourse with his wife over the past 2 years and had never fathered a pregnancy. He denied asthenia or low mood. He had no history of prior fractures, testicular trauma, surgery, cryptorchidism, or exposure to radiation or gonadotoxic agents. He denied taking testosterone-containing supplements. There was no family history of endocrine diseases, genetic syndromes, or infertility. He was the shortest amongst his 2 older brothers, and their parents were nonconsanguineous.

He was 1.67 m tall and weighed 65.2 kg with a body mass index of 23.7 kg/m^2. His mid-parental height was 1.67 m (father's height of 1.66 m and mother's height of 1.55 m). His arm span was 1.63 m. He had normal skeletal proportions. He did not have dysmorphic, cushingoid, or acromegalic features. He had a deep voice with normal male pattern hair distribution and presence of axillary hair. There was no

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gynecomastia. Examination of the genitalia showed a well-developed adult male phallus without hypospadias. The testes, however, were atrophied (volume 6 mL bilaterally) and soft in consistency. Pubic hair was of Tanner stage 5. On digital rectal examination, the prostate measured 2.5 finger-breadths in width. Overall, he was clinically well-virilized but had small testes size concerning for hypogonadism. The presence of normal skeletal proportions, penile length, voice, and prostate size with normal skeletal proportions suggested a postpubertal onset of hypogonadism.

Diagnostic Assessment

Initial investigations (Table 1) showed low normal serum testosterone with elevated LH and FSH, suggesting underlying primary hypogonadism (hypergonadotropic hypogonadism). Full blood count, renal function, liver function, and thyroid function were normal. Semen analysis revealed azoospermia. These findings accounted for the greater elevation in FSH compared to LH and suggested more significant dysfunction within Sertoli germ cells compared to the testosterone-producing Leydig cells. His results and clinical history were consistent with the initially suspected diagnosis of Klinefelter syndrome, with a differential diagnosis of Y chromosome microdeletion.

Klinefelter syndrome is the most common genetic cause of hypogonadism with variable clinical manifestations. Patients have small, firm testes and are generally infertile. Despite being a congenital cause of primary hypogonadism, some men with mosaicism have normal testicular size and spermatogenesis at puberty, with progressive loss of germ cells over time. Hence, this remains a possible diagnosis despite clinical findings that are suggestive of a postpubertal onset of male hypogonadism. Diagnosis of Klinefelter syndrome is confirmed by karyotyping.

Acquired causes of primary hypogonadism would include testicular trauma or torsion, radiation or chemotherapy, medications such as glucocorticoids, ketoconazole, infiltrative disease such as haemochromatosis, cirrhosis, or excessive alcohol intake—all of which were absent in our patient.

Our patient's chromosomal karyotype returned a surprising result of 46,XX (Fig. 1). The discordance between phenotypic and chromosomal sex was unexpected. Within the 46,XX DSD classification, differentials would include disorders of gonadal development (ovotesticular DSD, testicular DSD, and gonadal dysgenesis), androgen excess or other causes, for example, vaginal atresia. The latter 2 were unlikely given a completely masculinized external genitalia. The most likely diagnosis is 46,XX testicular disorder of sex development.

Treatment

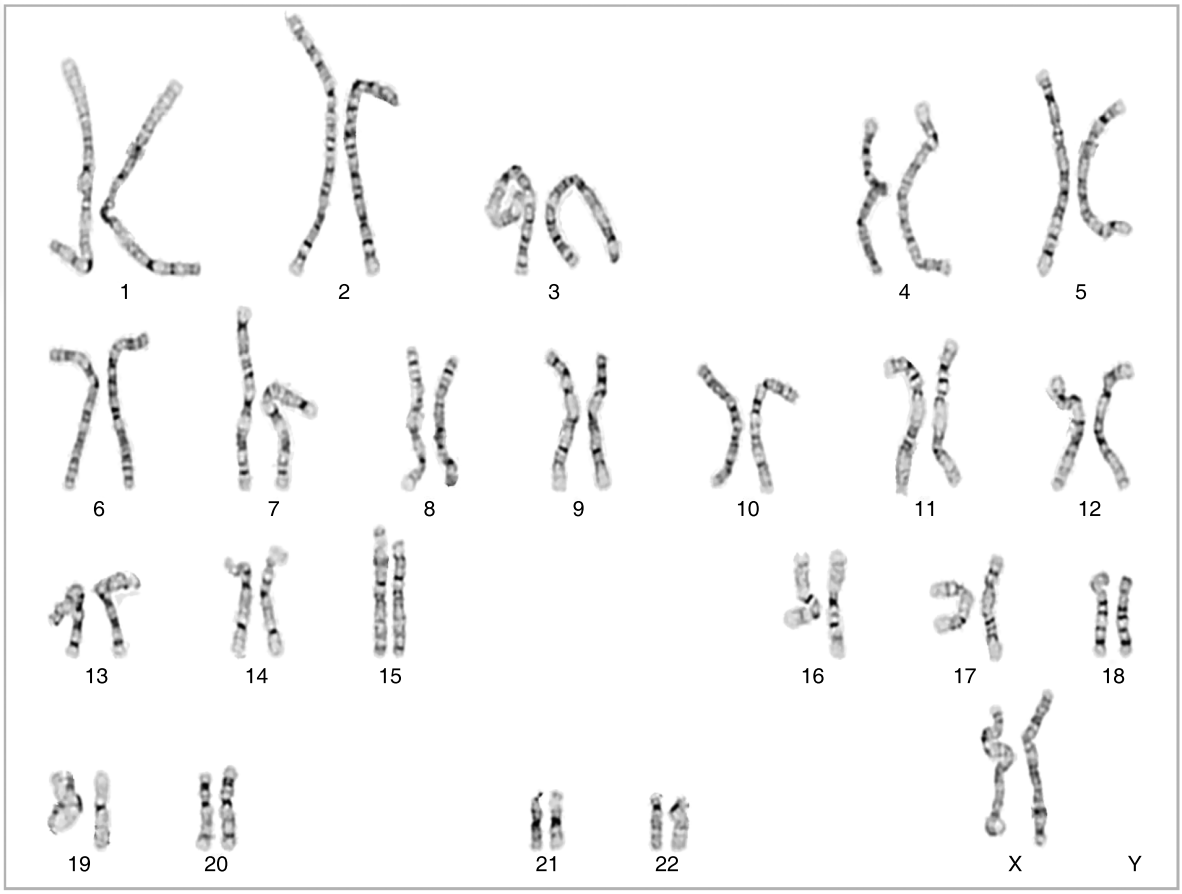
Our patient underwent formal genetic counseling by a clinical geneticist with reassurance that his gender identity remains male despite the discordant chromosomal sex. The most likely pathology was a translocation of the sex-determining region Y protein (SRY) gene to the X chromosome (SRY positivity found in 80% of patients with 46,XX DSD), and the SRY gene could be detected via fluorescence in situ hybridization or chromosomal microarray. He was not keen to pursue further molecular genetic testing as it would not alter his overall management and prognosis.

Our patient was counseled regarding testosterone replacement therapy where the goal of treatment is to maintain secondary sexual characteristics, sexual function, bone health,

Table 1. Summary of initial investigations in our patient

Investigation	Result (reference range)	
	Conventional units	**Système international (SI) units**
Male hormone profile		
Estradiol	25.0 pg/mL (<31.5 pg/mL)	92 pmol/L (<116 pmol/L)
LH	**19.4** mIU/mL (0.8-6.1 mIU/mL)	**19.4** IU/L (0.8-6.1 IU/L)
FSH	**47.7** mIU/mL (1.5-12.4 mIU/mL)	**47.7** IU/L (1.5-12.4 IU/L)
Prolactin	278 mIU/L (72-320 mIU/L)	13.1 µg/L (3.38-15.0 µg/L)
Testosterone (Chemiluminescent microparticle immunoassay, Abbott platform)	288 ng/dL (240-869 ng/dL)	9.99 nmol/L (8.33-30.19 nmol/L)
SHBG	25 nmol/L (11-52 nmol/L)	25 nmol/L (11-52 nmol/L)
Free Androgen Index	39.96% (15.50-102.00%)	
Semen analysis		
Investigation	**Result**	**Reference range**
Appearance	Normal	Gray-opalescent
Liquefaction	Normal	<60 minutes (R.T.)
Consistency	Normal	Low viscosity
Volume	2.0 mL	1.5 mL (lower limit)
pH	8.5	≥7.2
Concentration	**0.00** × 10^6/mL	15 × 10^6/mL
Total sperm number	**0.00** × 10^6/ejaculate	39 × 10^6/ejaculate
Comment	**No sperm seen in concentrated specimen**	

Abnormal values are shown in bold font.



Clinical history	Male infertility
Sample	Peripheral blood
Karyotype	46,XX
Interpretation	Female karyotype. No major chromosome abnormality detected.
Comments	Please note that the phenotypic sex is male. Further molecular testing and genetic counselling is recommended.
Results	20 GTL-banded metaphases have been counted, of which a minimum of 4 have been analyzed and karyotyped. Submicroscopic or cryptic chromosomal rearrangements cannot be excluded using this test. Average bands per haploid set: 600.

Figure 1. Results of chromosomal karyotype, taken from peripheral blood sample, returned as 46,XX.

body composition, and quality of life. He was initiated on intramuscular (IM) testosterone cypionate 50 mg every 2 weeks, and the aim was to achieve a testosterone concentration in mid-normal range (14-24 nmol/L). He was started at a lower dose as his testosterone deficiency was mild and he was relatively asymptomatic. The patient was informed that he would be unable to father a biological child and was offered options of either adoption or in vivo fertilization with donor sperm.

The presence of the Y chromosome in DSD patients increases the risk for a gonadal tumor. A gonadal tumor in 46,XX testicular DSD without the Y chromosome is extremely rare [1] and is limited to isolated case reports of germ cell tumor [2] and Leydig cell tumor [3]. Testicular ultrasound in our patient revealed a 0.2-cm hypoechoic focus within the right testis, which subsequently reduced in size on repeat scan.

Outcome and Follow-up

Our patient will be continued on lifelong testosterone replacement with routine monitoring of clinical symptoms, hematocrit, lipid profile, bone health, and prostate size. Three years since diagnosis, he is currently maintained on IM testosterone cypionate 150 mg twice weekly, with serum testosterone levels fluctuating between 8.0 and 26.0 nmol/L. He has declined a switch to IM testosterone undecanoate, which would provide more stable testosterone levels. He will also require urology follow up and surveillance for gonadal germ cell

tumor. Our patient and his wife have gradually accepted the diagnosis and the implications of not having their own biological children.

Discussion

The diagnosis of male hypogonadism is based on assessment of signs and symptoms and on low serum testosterone concentrations on a reliable assay. Klinefelter syndrome is the most common genetic cause of hypogonadism, and hence the most likely initial differential diagnosis. In contrast to 46, XX testicular DSD, Klinefelter syndrome is often characterized by tall stature, speech delay, learning disorders, and behavioral problems.

DSD is an umbrella term for rare conditions characterized by an incongruence of chromosomal, gonadal, and genital sex development [4]. Discrete genetic conditions that underlie DSD are rarely identified [5]. This diagnostic gap arises from inadequate knowledge of the pathogenesis of DSD, variation in assessment and phenotyping of these rare conditions and limited awareness or availability of tools for molecular diagnosis. While the traditional diagnostic approach is stepwise from clinical phenotyping, biochemical analysis, karyotyping to genetic analysis, the recommended multidisciplinary approach integrates the above information in parallel [6].

46,XX testicular DSD occurs in about 1 in 20 000 males. Eighty percent of individuals with nonsyndromic 46,XX testicular DSD are SRY-positive [7]. The proximity of SRY to pseudoautosomal region 1 makes it susceptible to translocation to the X chromosome during paternal sperm meiosis and results in X-type sperm containing the SRY gene. This leads to 46,XX offspring when combined with eggs, which then results in 46,XX testicular DSD. Rearrangements in or around SOX9 and SOX3 have been reported in a few cases.

While the clinical symptoms are heterogenous, the development of genitalia is usually normal and masculinity signs are obvious in SRY-positive patients [8], as exemplified by our patient. Eighty-five percent of patients with 46,XX DSD present after puberty with normal pubic hair and normal penile size. Small testes, gynecomastia, and sterility from azoospermia are common features [9]. SRY-positive patients are often incidentally found by chromosome evaluation for infertility or poor testicle development. On the contrary, SRY-negative patients are easily discriminated after birth because of abnormal genitalia.

Diagnosis of 46,XX DSD depends on a combination of clinical findings, endocrine testing (hypergonadotropic hypogonadism), and cytogenetic testing (46,XX karyotype). Although our patient did not undergo confirmatory SRY gene testing, his clinical phenotype suggests that he likely harbors an SRY translocation. Other differential diagnoses for 46,XX testicular DSD are less likely. 46,XX ovotesticular DSD are defined as presence of both testicular and ovarian tissue and most commonly present with ambiguous genitalia. 46,XX ovotesticular DSD may be associated with presence of a uterus while Mullerian structures are absent in 46,XX testicular DSD.

Prior commercial genetic testing, which had claimed to utilize whole exome sequencing (WES), had shown a "potential 47XXY chromosomal state" and brought the patient to evaluation initially. The patient's formal chromosomal karyotyping, however, returned a discordant finding of 46,XX. WES is a genomic technique for sequencing of all protein-coding regions of genes and can potentially identify mutations or variants that might be associated with genetic disorders. In 46,XX testicular DSD, WES would be able to identify mutations or structural variants in SRY. The identification of Y chromosome in the commercial genetic test is dependent on the choice of probes for Y chromosome, which is possibly the SRY gene in this case. Consequently, the 47XXY chromosomal state reported by the patient's commercial test kit was likely due to the detection of a translocated SRY gene. In contrast, karyotyping is useful for detecting large chromosomal abnormalities and confirm the absence of the Y chromosome in our patient. Another possibility for the difference in the results of his direct-to-consumer genetic testing and the karyotype may also be false positivity resulting from assay issues in the former.

Azoospermia is seen on semen analysis since all Y chromosome azoospermia factors are absent. A review of 55 patients with 46,XX testicular DSD revealed testicular atrophy in all [10]. Testis biopsy showed absence of spermatogenesis. Hence, patients with classical 46,XX testicular DSD seeking fertility should be discouraged from undergoing testicular sperm extraction because of complete absence of spermatogenic cells [11]. Adoption or donor sperm usage in in vivo fertilization are the only fertility options.

The management of 46,XX testicular DSD [7], summarized in Table 2, requires a holistic and patient-centered model of care that is sensitive to the physical, psychological, and emotional aspects of DSD. The involvement of the clinical geneticist in reaching a specific genetic diagnosis for our patient has helped to provide closure, guide treatment, and prognosticate

Table 2. Summary of management of 46,XX testicular DSD

Establish extent of disease	**Treat manifestations**
• Assess mood, libido, energy, erectile function, acne, breast tenderness and size • BMD • Consultation with clinical geneticist	• >14 years old, low-dose testosterone therapy is initiated and gradually increased to reach adult levels • Gynecomastia—may regress with testosterone therapy; consider reduction mammoplasty • Osteopenia—calcium, vitamin D, bisphosphonates • Psychological support
Surveillance	**Management of infertility**
• Testosterone effects including prostate size and prostate-specific antigen in adults, hematocrit, lipid profile, BMD • Surveillance for germ cell tumor	• Artificial insemination of female partner with donor sperm • Adoption

Abbreviations: BMD, bone mineral density; DSD, disorders of sex development.

for fertility. The role of the endocrinologist is essential in the initial evaluation of a young male presenting with hypogonadism, treatment of clinical manifestations with consideration for testosterone therapy, and longitudinal surveillance for complications of hypogonadism and its treatment. The urologist may need to be involved in the surveillance for germ cell tumors as well as management of infertility.

Learning Points

- 46,XX male DSD, characterized by mismatch of genetic, gonadal, and phenotypic sex is rare. DSD are genetically heterogeneous and careful assessment by multidisciplinary teams is essential to accurately diagnose them.
- Although chromosomal abnormalities are rarely present in patients with apparently normal external genitalia, they should be considered particularly in the investigation of gynecomastia or infertility.
- Molecular technologies can help to clarify the etiology and facilitate the diagnosis of DSD eg, fluorescence in situ hybridization can quickly and accurately detect information about the SRY gene in patients.
- Holistic treatment of DSD require multidisciplinary care by teams of relevant subspecialists working in close collaboration.

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Informed Patient Consent for Publication

Signed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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