

# 46XX Testicular Disorder of Sex Development

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### ABSTRACT

In this case report, we present the case of a 31-year-old man who presented with primary infertility, azoospermia and occasional sexual dysfunction. History and general physical examination were unremarkable. Local examination showed bilateral low volume testes and remaining aspects of the male reproductive tract were unremarkable. Detailed investigation showed a hypergonadotropic hypogonadism suggestive of primary testicular failure. Genetic screening showed a 46XX karyotype and Y chromosome testing was positive for sex-determining region (SRY) gene. Ultrasound abdomen was normal renal system and adrenal glands. A diagnosis of 46XX testicular disorders of sex development (DSD) was made. The incidence of this disorder is estimated to be 1:20,000 males. Such syndromic male partners generally have normal external genitalia and discover this disorder only in adulthood because of infertility. Such men have small volume testes, azoospermia and hypergonadotropic hypogonadism. Genetic and endocrine consultations are necessary to manage hypergonadotropic hypogonadism. Testicular sperm extraction is not recommended as there are deletions in all regions of Y chromosome, and adoption or assisted reproduction technology with a sperm donor are fertility options.

**KEYWORDS:** *Abnormal karyotype, azoospermia, primary infertility, SRY positive*

## INTRODUCTION

Disorders of sex development (DSD) is a term used<sup>[1]</sup> for various rare conditions that are characterised by chromosomal, gonadal and genital sex development discrepancies. Considering XX male syndrome to be a part of DSD, it is also termed as 46XX testicular disorder of sex development. Such individuals present with normal external genitalia and discover this pathology only in adulthood because of primary infertility. The usual presenting features of this rare condition are 46XX karyotype, phenotype of a normal adult male, bilateral small volume testes, nonobstructive azoospermia and hypergonadotropic hypogonadism.<sup>[2]</sup> The disorder is rare and is estimated to be occurring in about 1:20,000 males.<sup>[2]</sup> The first case was described in 1964 by De la Chapelle;<sup>[3]</sup> and since then, 37 cases have been reported so far.<sup>[2]</sup> In this study, we present the case report of a 31-year-old man who presented with primary

infertility and azoospermia. Upon detailed investigations, a diagnosis of 46XX testicular DSD was done. This rare case report reaffirms the need for a detailed history and examination along with genetic screening in every individual presenting with azoospermia and primary testicular failure.

## CASE REPORT

A 31-year-old man came to our clinic with a history of azoospermia, primary infertility and occasional sexual dysfunction due to erectile dysfunction. There was no medical, surgical or family history of endocrine diseases, genetic syndromes infertility; additionally, no history of testicular trauma or cryptorchidism was reported. The patient is an engineer and his job does not expose him to radiation or cytotoxic agents. The frequency of sexual intercourse was very irregular and his libido was low,

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but in spite of erectile dysfunction couple managed to achieve penetrative sexual intercourse. Early morning erections were reported to be fine, and the patient manages to masturbate twice a week. Female partner, 27 years of age underwent a gynaecological consultation and no remarkable issues for infertility were noted.

The height and weight of the patient were 171 cm and 79 kg, respectively, with a body mass index of 27 kg/m<sup>2</sup>, and his blood pressure was 124/86 mmHg. General physical examination was normal with bilateral gynecomastia (grade II). Local genital examination showed stretched penis length of 6 cm, small testes (both 2 mL) and normal pubic hair (Tanner stage V). No clinical varicocele was elicited on palpation and valsalva manoeuvre. Digital rectal examination revealed a normal prostate gland. Standard abdominal ultrasonography showed normal kidneys and adrenals. Transrectal ultrasonography showed normal prostate gland and normal seminal vesicles, with no Müllerian derivatives.

Two semen analysis performed as per the World Health Organisation Laboratory manual for the Examination and Processing of Human Semen (5<sup>th</sup> edition), was performed after 3 to 5 days of abstinence showed azoospermia with low volume ejaculate (<1.5 ml). The sample was re-evaluated after centrifugation, and azoospermia was confirmed. Post-ejaculate urine examination was normal with no spermatozoa seen.

Hormone analysis revealed hypergonadotropic hypogonadism: Follicle-stimulating hormone and luteinising hormone were 30 mIU/mL (1–13 mIU/mL) and 15 mIU/mL (1–9 mIU/mL) respectively, whereas early morning total testosterone was 170 ng/dL (300–1200 ng/dL). Estradiol (E2) and prolactin (PRL) levels were 10 pg/mL (10–40 pg/mL) and 16 ng/mL (4–23 ng/mL) respectively; the laboratory parameters were confirmed by a second sample.

Karyotyping was performed on peripheral blood lymphocytes and showed a 46XX karyotype. Considering karyotype showing a normal female karyotype; we repeated the blood investigation and noted the same findings. Fluorescent *in situ* hybridisation (FISH) was carried out using SRY probe revealing the sex-determining region Y (SRY) on the short (p) arm of the X chromosome. Genetic consultation confirmed the diagnosis of 46XX (SRY-positive) testicular DSD. Considering the Y chromosome microdeletions in Azoospermia Factor (AZF) A, B and C regions, limited role of testicular sperm aspiration (TESA) to obtain sperms was discussed. The patient agreed to defer TESA. Artificial insemination with sperm donation and

psychological support was offered to the couple as the next line of management.

## DISCUSSION

Male factor infertility is on the rise, and it is estimated to be around 30%–40%. 15% men presenting with infertility either have azoospermia or severe oligozoospermia.<sup>[4]</sup> Of these, 5.8% men seem to have cytogenetic abnormalities against 0.5% of the general population.<sup>[5]</sup> Hence, a structured approach with detailed history, thorough examination, two-three semen analysis, endocrine testing and genetic screening will help in optimal management and shorten the time to pregnancy. Endocrine tests and genetic screening help in prognosticating the management.

In this case report, the general physical examination and local examination findings are consistent with the previous reports published in literature.<sup>[6,7]</sup> Such men could present with normal external genitalia, small volume testes, cryptorchidism or hypospadias, azoospermia, hypergonadotropic hypogonadism, varying degrees of gynecomastia, poor facial hair growth, diminished libido and normal cognitive development.<sup>[2]</sup>

In this case, findings of normal male secondary sexual characters and a Tanner's stage correlating to stage 5 can be explained by the presence of SRY gene in spite of a 46XX karyotype report. If SRY gene is negative, then such men are born with ambiguous genitals,<sup>[8]</sup> and such pathologies are diagnosed in early childhood. SRY positive men with 46XX DSD present later in the life with infertility and is difficult to diagnose in adolescent age.

It has been shown that 80%–90% 46XX men have Y to X translocation during meiosis.<sup>[9]</sup> However, the exact pathogenesis of 46XX male DSD is still not clear. Following hypotheses have been proposed to support the translocation:<sup>[2]</sup>

- a. The hypothesis of target gene mutation<sup>[10]</sup>
- b. The hypothesis of SOX9 gene (SRY box-related gene 9) overexpression
- c. The hypothesis of Xp-Yp translocation.

Fertility consultants, urologists and andrologists should keep in mind the possible abnormalities linked to 46XX DSD and perform adequate screening, appropriate general physical and local examination with emphasis to detect cryptorchidism, hypospadias, gynecomastia.

Considering that most men with this disorder have low testosterone levels, an in-depth probing into sexual history and appropriate management has to be discussed.

Ultrasonography of the abdomen to exclude residual Müllerian structures will help in ruling out other genetic disorders. Endocrine consultations are to evaluate and manage low testosterone levels. Genetic consultations help to look for mutations of other genes involved in the sex determination cascade such as SOX9, SOX3, DAX1, WT1, FGF9 and SF1. Clinical Geneticist has an important role to play in the management of such individuals. After the confirmation of 46XX report in a male subject, it is important to understand whether the individual is SRY positive or negative. SRY-positive individuals need combined application of chromosomal analysis, AZF microdeletion evaluation, *SRY* detection and sequencing of key sex-determining genes. SRY negative individuals usually present with immature/ambiguous to normal genitalia, incomplete testicular development or ovotestis and varying degrees of masculinisation. A psychologist might also be needed to help the couple handle the situation optimally.

Nevertheless, such individual's fertility options are very limited. The role of surgical retrieval of sperms and assisted reproduction technology (ART) is very limited. These couples will need artificial insemination with donor sperm or adoption to complete their dream of parenthood. As a part of the counselling, the couple's acceptance for a donor-conceived child and the welfare of the child in the future needs to be assessed.

Overall, this case ideally demands a multi-disciplinary approach.

## CONCLUSION

46XX testicular DSD is rare and categorised by mismatch of genetic, gonadal and phenotypic appearance. FISH and PCR technology can quickly and accurately detect information about the SRY gene in patients so as to provide more valuable clinical information. A multidisciplinary management involving the endocrinologist, geneticist, psychologist and ART specialist is required for optimal management of such cases. For infertility management, TESA would not be beneficial and artificial insemination with donor sperm or adoption should be considered.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent. The patient has given consent for any images and other clinical information to be reported in the journal. The patient understands that no name or initials will be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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