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*Case Report*

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# A phenotypical male with 46,XX karyotype: A rare case report

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## Abstract

The 46,XX testicular disorder of sex development (46,XX testicular DSD) is a rare phenotype. This disorder usually presents with varying degrees of clinical features, ranging from ambiguous to normal male genitalia. The usual presentation in adults is infertility. Here, we describe the clinical, biochemical, and cytological findings of a 28-year-old male patient with sex-determining region Y (SRY)-positive 46,XX testicular DSD presented with bilateral gynecomastia, erectile dysfunction, loss of libido, and infertility. Biochemical analysis revealed hyper gonadotrophic hypogonadism, and semen analysis showed azoospermia. Chromosomal analysis revealed 46,XX karyotype. Polymerase Chain Reaction (PCR) showed the SRY region translocated to the short arm of the X chromosome. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2025; 4 (1): 34-38]*

**Keywords:** 46,XX testicular DSD, SRY gene, Infertility, Gynecomastia

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## Introduction

46,XX Male Syndrome was first described by De la Chapelle et al. in 1964. It is a rare disorder with an incidence of 1/20,000 males.[1] Sex-determining region Y (SRY)-positive cases comprise about 80% of the cases; SRY-negative cases comprise the remaining. These individuals exhibit azoospermia, gynecomastia, hypogonadism, and infertility; typically, they are diagnosed after puberty.[2] Clinical, hormonal, and cytogenetic test results diagnose the disorder. Testosterone replacement therapy is the choice of treatment that is essential for the improvement of sexual characteristics and libido. In this study, we document a case who presented with bilateral gynecomastia, erectile dysfunction, and infertility.

## Case presentation

A 28-year-old male presented with bilateral gynecomastia, erectile dysfunction, decreased sexual activity, and small size of the testes. He was born of a non-consanguineous marriage at term after an uneventful pregnancy and was brought up as a male. His scholastic performance was good. He states that his secondary sexual characteristics (beard, mustache,

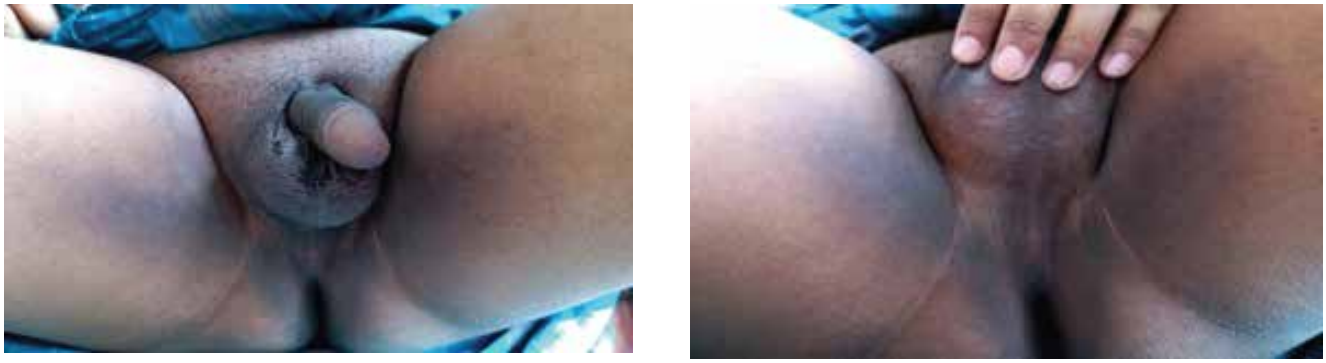

**Figure 1:** Normal male external genitalia; (a) normal appearance, (b) scrotum retracted forwards to show complete fusion of the scrotal folds

and pubic hair) appeared at the age of 16 years. He has been married for 4 years, and there was no significant complaint regarding his conjugal life during the initial year of his marriage. Thereafter, he developed erectile dysfunction and loss of libido. He complained of infertility and bilateral gynecomastia for 3 years, for which he consulted a urologist and was found to have azoospermia on semen analysis; then, he was referred to us for further evaluation. There was no significant family history or past medical history. Physical examination revealed his height 160 cm, weight 68 kg, body mass index (BMI) 26.56 kg/m$^2$, upper segment 73 cm, lower segment 87 cm, US: LS ratio 0.83, arm span 172 cm, sparse axillary hair, beard and mustache, bilateral gynecomastia. Tanner staging revealed P5, stretched penile length (SPL) was 10 cm, Testes were in the scrotum, and testicular volume on the right side was 6 ml and left 8 ml (Figure-1).

Biochemical investigations revealed normal biochemistry, renal function, liver function, and thyroid function tests. Hormone analysis revealed hypergonadotropic hypogonadism (table-1). Ultrasonogram of the scrotum reflected both testicles in the scrotum, but both were smaller than normal (right testicle: 1.7x1.11 cm, left testicle: 1.1x0.6 cm), both epididymis were of normal size and structure with regular blood supply. Magnetic resonance imaging (MRI) of the pelvis revealed – underdeveloped testes at both sides, well-demarcated small scrotal sac, small size penis, and no evidence of uterus in the pelvic cavity. Testicular biopsy revealed-epididymal tissue, an area of fibrosis, and thick-walled blood vessels; no testicular tissue or ovarian tissue was seen, and no malignancy was seen. Azoospermia was seen on repeated semen analysis. A summary of laboratory investigations is given in Table I. Karyotype analysis of the patient confirmed a 46,XX karyotype (Figue-2). Real-time polymerase chain reaction (PCR) analysis revealed that the SRY gene was positive.

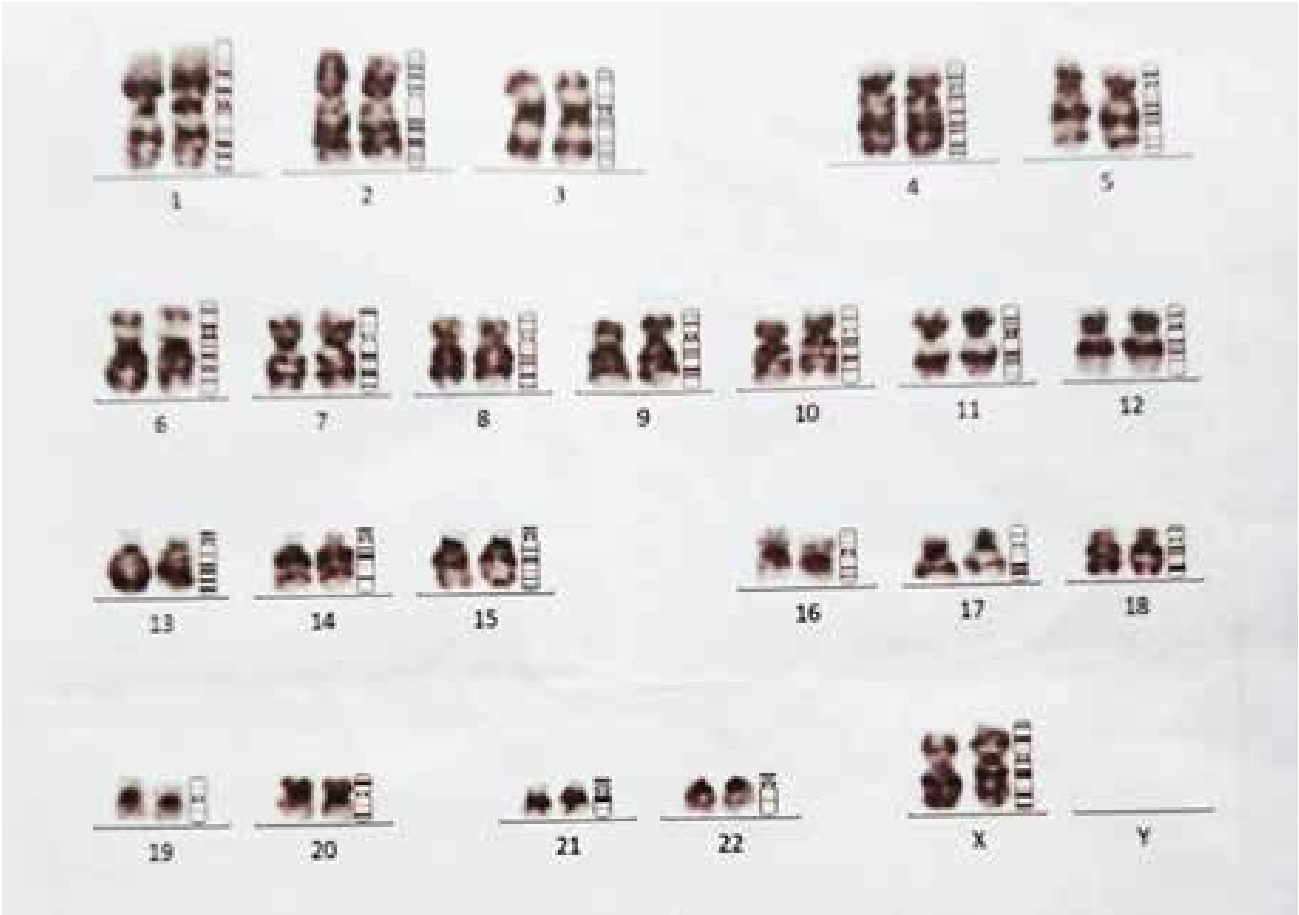


**Figure 2:** Figure-3: Karyotype confirms 46,XX

**Table-I:** Laboratory findings of the patient

| Investigations | Value | Reference value |
|---|---|---|
| Total testosterone (ng/dL) | 27.9 | 240 - 871 |
| FSH (IU/L) | 28.8 | 0.6 - 14.7 |
| LH (IU/L) | 18.2 | 0.7 - 7.9 |
| Estradiol (pg/mL) | <11.8 | ≤ 29 |
| Prolactin (ng/mL) | 7.2 | 2.1 - 17.7 |
| DHEAS (ug/dL) | 41.6 | 110 - 510 |
| TSH (mIU/L) | 2.67 | 0.45 - 4.12 |
| S. Creatinine (mg/dl) | 1.1 | 0.7 - 1.3 |
| SGPT (U/L) | 44 | 10 - 49 |
| Lipid profile (mg/dl) | | |
| Total cholesterol | 196 | 200 |
| Triglyceride | 174 | <150 |
| LDL-C | 120 | <100 |
| HDL-C | 41 | >60 |
| RPG (mmol/L) | 5.1 | |
| S. Electrolyte (mmol/L) | | |
| Na+ | 136 | 135-145 |
| K+ | 4.1 | 3.5-5.0 |
| Cl- | 101 | 97-105 |
| TCO2- | 27 | 23-29 |
| Semen analysis | Azoospermia | - |

FSH: follicle-stimulating hormone
LH: luteinizing hormone
DHEAS: Dehydroepiandrosterone sulfate
TSH- thyroid stimulating hormone
SGPT: Serum glutamic pyruvic transaminase
LDL-C: Low density lipoprotein cholesterol
HDL-C: High desnity lipoprotein cholesterol
RPG: Random plasma glucose

The patient was diagnosed as a 46,XX testicular DSD. Counseling was done, and testosterone replacement therapy at three-week intervals in the intramuscular route was initiated. After taking three doses of testosterone replacement, his general health condition was improved, and biochemical investigations revealed a normal serum testosterone level (Table II).

**Table-I:** Investigations on follow-up after 3 months of treatment

| Investigations | Value | Reference value |
|---|---|---|
| Total testosterone (ng/dL) | 747 | 240 - 871 |
| Complete blood count | | |
| Haemoglobin (g/dL) | 13.3 | 13-17 |
| Hematocrit (%) | 43.8 | 40-54 |
| SGPT (U/L) | 47 | 10-49 |
| SGOT (U/L) | 60 | <34 |

SGPT: serum glutamic pyruvic transaminase
SGOT- serum glutamic oxaloacetic transaminase

## Discussion

Primary hypergonadotropic hypogonadism due to genetic causes may be seen in adults. 46,XX male DSD is usually sporadic; however, there have also been reports of familial cases.[3,4] Our patient had no family history and was regarded as sporadic. The exact etiology is yet unknown. Three possible mechanisms account for the development of 46, XX male DSD: (i) X-linked mutation/overexpression in the genes that cause testis differentiation or mutation/overexpression in autosomal genes [e.g., SRY box-related gene 9 (SOX9)] in SRY negative XX males; (ii) translocation of the Y chromosome, including the SRY gene, on the X chromosome or on autosomal chromosomes, which occurs due to recombination during paternal meiosis; and (iii) secret Y mosaicism found only in the gonads.[2] In our case, PCR evidence of the SRY locus translocated on the short arm of the X chromosome supports the idea that SRY plays a significant role in male differentiation.

Following SRY gene analysis, 46,XX male patients are classified as SRY positive and SRY negative clinical groups. About 80% of these people have the SRY gene, with the remaining 20% having the SRY gene negatively. SRY-positive people are typically diagnosed in adulthood with infertility, and they have tiny testes, azoospermia, and normal male genitalia.[5,6] Gynaecomastia may affect about one-third of affected individuals. The external genitalia in this instance were completely male; the pubic hair and penile size were normal, but the testicles were small. Due to inadequate development of the external genital organs, 46,XX SRY-negative males can be diagnosed shortly after birth; however, the typical male appearance of the external genitalia can also be observed.[4,7]

In addition to the SRY gene, SOX9 is involved in the differentiation of the testes, and its duplication may result in the generation of SRY-negative 46,XX males. There have been reports recently of SOX9 triplication, duplication of SOX3 gene, and SOX9 duplication resulting in 46,XX SRY-negative men.[8] An uncommon clinical condition where palmoplantar hyperkeratosis and SRY-negative XX male are combined with a propensity to squamous cell carcinoma of the skin caused by mutations in the

gene encoding R-spondin1 (RSPO1).[5] Since our case tested positive for SRY, no additional testing for Y mosaicism or the SOX9, SOX3, or RSPO1 genes was done.

Klinefelter syndrome, mixed gonadal dysgenesis (46,XX/46,XY and 46,X/46,XY) and congenital adrenal hyperplasia (CAH) are common differential diagnoses for 46,XX testicular DSD. Tall stature, tiny testes, eunuchoid body habitus, and aberrant sexual development during puberty are the typical symptoms of Klinefelter syndrome. Testicular failure-related infertility, low testosterone levels, erectile dysfunction, low bone mineral density, learning and behavioral abnormalities, and delayed speech are also seen in this syndrome.[9] True hermaphrodites with 46,XX/46,XY chimerism phenotypically may present from normal male to normal female. Short stature in males with 45,X/46,XY karyotype is evident based on the 45,X cell percentage. It cannot be differentiated from 46,XX testicular disease by clinical examination. In this case, chromosomal findings are diagnostic.[10]

CAH is another differential diagnosis. It comprises a set of autosomal recessive hereditary disorders caused by defects in one of the adrenal cortex's steroidogenesis pathway's enzymes. 21-hydroxylase (21-OH) enzyme deficiency is the most prevalent form of CAH. Adolescents with the non-classical form of CAH caused by a 21-OH deficit typically present with features of androgen excess.[11] Completely normal male-looking genitalia are present in 46,XY CAH patients and virilizing type ambiguous genitalia are also occasionally observed.[12]

The diagnosis of primary testicular failure was made in our case based on a combination of features, including infertility, bilateral gynecomastia, erectile dysfunction, loss of libido, absence of intra-abdominal Mullerian organs, normal male phenotypic, and hormone tests indicating primary hypogonadism. Small testes and other characteristics were similar to Klinefelter syndrome. Through karyotype analysis, this syndrome and other sex chromosomal abnormalities were ruled out. 46,XX CAH is ruled out by the testicles, tiny penis, and lack of the uterus and ovary.

Patients with 46,XX male should be treated with a multidisciplinary approach. An endocrinologist should monitor these individuals' gonads, take their bone mineral density, and perform hormone testing regularly for the rest of their lives. The most prominent treatment modality for 46,XX males is testosterone replacement therapy, which is required to develop secondary sexual characteristics, sexual desire, muscle strength, and bone health maintenance. Psychological support is an essential component of the comprehensive approach. All 46,XX males are infertile due to azoospermia, as the absence of the AZF region, which is essential for spermatogenesis.[13] The AZF region is located on the long arm of the Y chromosome (Yq11) and contains the three AZF regions (AZFa, AZFb, and AZFc).[13] Consequently, the desire for fatherhood in 46,XX males could be fulfilled through artificial insemination or in vitro fertilization using donor sperm or child adoption.

## Conclusions

A karyotype study should be carried out in patients with hypergonadotropic hypogonadism who present with clinical symptoms such as infertility, small testes, azoospermia, and gynecomastia, to establish this rare syndrome and to rule out other diagnoses, such as Klinefelter's syndrome.

**Conflict of interest**

The authors have no conflicts of interest to disclose.

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**Financial Disclosure**

We are grateful to the study participant for giving the consent to report the case..

**Data Availability**

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author upon reasonable request.

**Ethical Approval and Consent to Participate**

Written informed consent was taken from the patient.



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## References


1. De La Chapelle A, Hortling H, Niemi M, Wennstroem J. XX sex chromosomes in a human male. Acta Med Scand 1964;175: Suppl 412:25-28. DOI: 10.1111/j.0954-6820.1964.tb04630.x.
2. Zenteno-Ruiz JC, Kofman-Alfaro S, Mendez JP. 46,XX sex reversal. Arch Med Res 2001;32:559-66. DOI: 10.1016/s0188-4409(01)00322-8.
3. Fechner PY, Marcantonio SM, Jaswaney V, Stetten G, Goodfellow PN, Migeon CJ, et al. The role of the sex-determining region Y gene in the etiology of 46,XX maleness. J Clin Endocrinol Metab 1993;76:690-95. DOI: 10.1210/jcem.76.3.8383144.
4. Zenteno JC, Lopez M, Vera C, Mendez JP, Kofman-Alfaro S. Two SRY-negative XX male brothers without genital ambiguity. Hum Genet 1997;100:606-10. DOI: 10.1007/s004390050561.
5. Parma P, Radi O, Vidal V, Chaboissier MC, Dellambra E, Valentini S, et al. R-spondin1 is essential in sex determination, skin differentiation and malignancy. Nat Genet 2006;38:1304-09. DOI: 10.1038/ng1907.
6. Ryan NA, Akbar S. A case report of an incidental finding of a 46,XX, SRY-negative male with masculine phenotype during standard fertility workup with review of the literature and proposed immediate and long-term management guidance. Fertil Steril 2013;99(5):1273-76.DOI: 10.1016/j.fertnstert.2012.11.040.
7. Ergun-Longmire B, Vinci G, Alonso L, Matthew S, Tansil S, Lin-Su K, et al. Clinical, hormonal and cytogenetic evaluation of 46,XX males and review of the literature. J Pediatr Endocrinol Metab 2005;18:739-48. DOI: 10.1515/jpem.2005.18.8.739.
8. Cox JJ, Willatt L, Homfray T, Woods CG. A SOX9 duplication and familial 46,XX developmental testicular disorder. N Engl J Med 2011;364:91-93. DOI: 10.1056/NEJMc1010311.
9. Aksglaede L, Link K, Giwercman A, Jørgensen N, Skakkebaek NE, Juul A. 47,XXY Klinefelter syndrome: Clinical characteristics and age-specific recommendations for medical management. Am J Med Genet C Semin Med Genet 2013;163:55-63. DOI: 10.1002/ajmg.c.31349.
10. Berta P, Hawkins JR, Sinclair AH, Taylor A, Griffiths BL, Goodfellow PN. Genetic evidence equating SRY and the testis-determining factor. Nature 1990;348:448-50. DOI: 10.1038/348448A0.
11. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocr Rev 2000;21:245-91. DOI: 10.1210/edrv.21.3.0398.
12. Woelfle J, Hoepffner W, Sippell WG, Brämswig JH, Heidemann P, Deiss D, et al. Complete virilization in congenital adrenal hyperplasia: clinical course, medical management and disease-related complications. Clin Endocrinol (Oxf). 2002;56:231-38. DOI: 10.1046/j.0300-0664.2001.01463.x.
13. Vogt PH, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, Kiesewetter F, et al. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. Hum Mol Genet 1996;5:933-43. DOI: 10.1093/hmg/5.7.933.