All males do not have 46 xy karyotype: A rare case report

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ABSTRACT

The sex of an embryo is determined by genetic sex due to presence or absence of Y chromosome, but it may not be true in all. We hereby report an interesting case of a phenotypic male carrying a female karyotype (46 XX). A 26-year-old male presented with bilateral gynecomastia, poor development of secondary sexual characters and azospermia. On evaluation patient had hypergonadotrophic hypogonadism and chromosomal analysis revealed 46 XX karyotype. The ultrasound revealed no Mullerian structures. Fluorescent in situ hybridization (FISH) showed sex determining region of Y chromosome (SRY) gene locus on X chromosome.

Key words: 46 XX testicular disorder of sex development, hypergonadotrophic hypogonadism, SRY translocation

INTRODUCTION

In mammals Y chromosome is responsible for the development of testis and termed testis determining factor (TDF). However, because of abnormal X/Y terminal exchange during male meiosis, some patient develop testes in the absence of Y chromosome with development of genital tract and present with infertility, short stature, and rarely as ambiguous genitalia. These groups of patients are treated with testosterone replacement similar to other causes of testosterone deficiency.

CASE REPORT

A 26-year-old male presented with bilateral gynecomastia for last 6 years with poor development of secondary sexual characters. He was fourth of the siblings and born out of nonconsanguineous marriage with male external genitalia.

On examination height was 161 cm, arm span = 164 cm, upper segment/lower segment (US/LS) ratio = 1.06, weight = 60 kg, midparental height (MPH) =172 cm with a body mass index (BMI) of 23.14 kg/m², stretch penile length (SPL) = 6 cm, testicular volume (TV) = 2 ml bilaterally, firm in consistency and with Tanner stage IV pubic hairs, sparse axillary, facial hairs, and gynecomastia.

On investigation liver and renal function test were within normal limits. Gonadotrophins (luteinizing hormone (LH) and follicle stimulating hormone (FSH)) value were elevated with low serum testosterone, normal estradiol and thyroid hormones, and ultrasonography (USG) did not reveal any Mullerian derivatives but had small size testis. Semen analysis showed azoospermia and testicular biopsy revealed seminiferous tubules without spermatogenic activity [Figure 1]. Chromosomal analysis of peripheral blood using 72 h stimulated culture with GTG banding revealed 46 XX pattern. Fluorescent in situ hybridization (FISH) by multicolor DNA probe kit (CEP X/Y) showed presence of sex determining region of Y chromosome (SRY) gene locus on X chromosome [Figure 2 and Table 1].

DISCUSSION

46 XX sex reversal was first reported by de la Chapelle et al., in 1964[1] and incidence was one in 20,000-25,000 newborns.

Access this article online

Quick Response Code:
Website: www.ijem.in
DOI: 10.4103/2230-8210.119603

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According to Vorona et al., 100 cases have been reported between 1996 and 2006 worldwide.\[^{2,3}\]

On the basis of SRY gene, this condition is divided into two groups: (1) SRY positive (most common 90%) and (2) SRY negative in 10% of cases.\[^{2,3}\] In SRY positive patient, there is translocation of the gene to short arm of X chromosome as found in the present case and it involves a mistake in the crossover between pseudoautosomal region of sexual chromosome during paternal meiosis.\[^{4,5}\]

In the absence of SRY gene, male phenotype in 46 XX have been considered due to upregulation of SRY related high mobility group (HMG) box (SOX) family or absence of Respondin 1 (RSPOI) or wingless-type mouse mammary tumor virus (MMTV) integration family member 4 (Wnt4).

46 XX male presents phenotypically with normal external and internal genitalia or ambiguous genitalia or true hermaphrodite.\[^{2,3}\] All present with male infertility because of absence of azoospermia factor gene (AZF gene) found on the long arm of Y chromosome and it has gene complex necessary for the development and differentiation of germ cell.\[^{6}\] In classical form, 46 XX male is present with normal penile length, microorchidism (either with normal scrotal position/undescended testis), infertility, gynecomastia, presence of Wolfian structure with absence of Mullerian structures, and short stature which may be due to absence of testosterone dependent pubertal growth spurt or loss of Y gene related growth.\[^{5}\]

Management of 46 XX testicular disorder of sex development (DSD) is same as other causes of testosterone deficiency. After 14 year of age, low dose testosterone can be initiated (inj. testosterone enanthate given intramuscularly (IM) every 3-4 weeks, starting at 100 mg increasing by 50 mg every 6 months to 200-400 mg). If patients need growth hormone therapy, testosterone should be delayed or given at a lower dose to maximize the growth potential. Gynecomastia needs reduction mammoplasty. Psychological support is important to minimize psychological distress.\[^{7}\]

In the present case we found gynecomastia, short stature, microorchidism with Wolfian structure, and absence of Mullerian derivatives. Biochemical feature showed normal liver and renal function, hypergonadotropic

### Table 1: Clinical and biochemical profile of the patient

| Age            | 26 year |
|----------------|---------|
| Height         | 161 cm  |
| Weight         | 60 kg   |
| Body mass index| 23.14 kg/m\(^2\) |
| Stretch penile length | 6 cm   |
| B/L testicular volume | 2 cm3 |
| Pubic hairs    | Tanner stage 4 |
| B/L breast bud | 5 cm    |
| Liver function test | S. Bilirubin-(T/D): 1/0.3, AST: 43, ALT: 34 |
| Renal function test | S. Urea/Creatinine: 22/0.8 |
| Follicle stimulating hormone | 33.11 mIU/ml (normal: 1.2-5 mIU/ml) |
| Luteinizing hormone | 16.75 mIU/ml (normal: 2-9.8 mIU/ml) |
| S. testosterone | 182.6 ng/dl |
| Estradiol      | 26 pg/ml |
| Free triiodothyroxine | 2.85 pg/ml |
| Free thyroxine | 0.95 ng/dl |
| Thyroid stimulating hormone | 1.42 μU/ml |
| Ultrasonography abdominal and pelvic | Normal |
| Ultrasonography scrotum | LT-14×8×17 mm, RT-15×7×20 mm |
| Semen analysis | 2 ml, no spermatozoon |
| Testicular biopsy | Seminiferous tubules without spermatogenic activity |
| Karyotype      | 46XX |
| Fluorescent in situ hybridization | SRY gene locus on chromosome X |

S: Serum, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LT: Left, RT: Right, SRY: Sex determining region of Y chromosome

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\[^{2}\] Agrawala, et al.: All males do not have 46 xy karyotype

\[^{3}\] According to Vorona et al., 100 cases have been reported between 1996 and 2006 worldwide.

\[^{4}\] In the absence of SRY gene, male phenotype in 46 XX have been considered due to upregulation of SRY related high mobility group (HMG) box (SOX) family or absence of Respondin 1 (RSPOI) or wingless-type mouse mammary tumor virus (MMTV) integration family member 4 (Wnt4).

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Figure 1: Seminiferous tubules without spermatogenic activity

Figure 2: Fluorescent in situ hybridization showing pair of X chromosome
hypogonadism, azoospermia, 46 XX karyotype and SRY translocation to X chromosome which represents the classic form of 46 XX testicular disorder; a rare variety of overall causes of DSD.

REFERENCES

1. Delahapelle A, Hortling H, Niemi M, Wennstroem J. XX sex chromosomes in a human male. First case. Acta Med Scand 1964;175(Suppl 412):25-8.
2. Ergun-Longmire B, Vinci G, Alonso L, Matthew S, Tansil S, Lin-Su K, et al. Clinical, hormonal and cytogenetic evaluation of 46, XX male and review of the literature. J Pediatr Endocrinol Metab 2005;18:739-48.
3. Vorona E, Zitzmann M, Gromoll J, Schüring AN, Nieschlag E. Clinical, endocrinological, and epigenetic features of the 46, XX male syndrome, compared with 47, XXY klinefelter patients. J Clin Endocrinol Metab 2007;92:3458-65.
4. Dauwerse JG, Hansson KB, Brouwers AA, Peters DJ, Breuning MH. An XX male with the sex-determining region Y gene inserted in the long arm of chromosome 16. Fertil Steril 2006;86:463.e1-5.
5. Kojima Y, Hayashi Y, Mizuno K, Sasaki S, Fukui Y, Koopman P, et al. Up-regulation of SOX9 in human sex-determining region on the Y chromosome (SRY)-negative XX males. Clin Endocrinol 2008;68:791-9.
6. Ahmad A, Siddiqui MA, Goyal A, Wangnoo SK. Is 46 XX karyotype always a female? BMJ Case Rep 2012;2012.
7. Vilain EJ. 46, XX Testicular disorder of sex development, synonyms: 46, XX testicular DSD; XX male syndrome. Includes: SRY-Negative 46, XX Testicular disorder of sex development; SRY-Positive 46, XX Testicular disorder of sex development: Bookshelf ID: NBK1416.

Cite this article as: Agrawala RK, Choudhury AK, Mohanty BK, Baliarsinha AK. All males do not have 46 xy karyotype: A rare case report. Indian J Endocrin Metab 2013;17:S271-3.

Source of Support: Nil, Conflict of Interest: None declared.