Brief Communication

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 testis 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.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.119603

On examination height was 161 cm, arm spam = 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/m^2, stretch penile length (SPL) = 6 cm, testicular volume (TV) = 2 ml bilaterally, firm in consistency and with Tanner stage IV public 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 newborn

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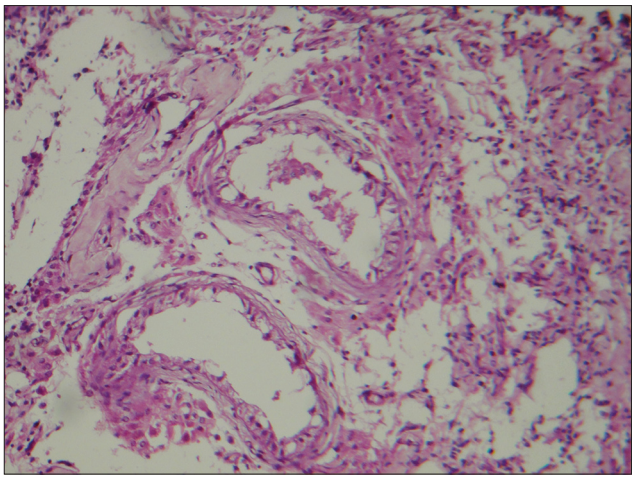

Figure 1: Seminiferous tubules without spermatogenic activity

Figure 2: Fluorescent *in situ* hybridization showing pair of X chromosome

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
Estradiole	26 pg/ml
Free triiodothyroxine	2.85 pg/ml
Free thyroxine	0.95 ng/dl
Thyroid stimulating hormone	1.42 μIU/ml
Ultrasonography abdominal and pelvic	Normal
Ultrasonography scrotum	LT-14×8×17 mm RT-15×7×20 mm
Semen analysis	2 ml, no spermatozoa
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

male.[2] According to Vorona *et al*., 100 cases have been reported between 1996 and 2006 worldwide.[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 Wolffian 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 Wolffian structure, and absence of Mullerian derivatives. Biochemical feature showed normal liver and renal function, hypergonadotrophic

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.

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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 Endocr Metab 2013;17:S271-3.

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