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CASE REPORT

SRY-negative 45,X/46,XY adult male with complete masculinization and infertility: A case report and review of literature

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Abstract

BACKGROUND

45,X/46,XY mosaicism is a rare chromosomal abnormality with a wide range of phenotypes in both males and females, from normal individuals with different degrees of genital ambiguity to those who show signs of Turner's syndrome. More rarely, cases of 45,X/46,XY mosaicism with a normal-appearing male phenotype are not found until a chromosome test is performed to investigate the cause of male infertility.

CASE SUMMARY

In this study, a 29-year-old male patient with complete azoospermia is reported. Chromosomal analyses of his lymphocytes revealed the karyotype 45,X[93%]/46,X,+mar(Y)[7%]. In addition, Y chromosome-specific markers, such as *SRY*, *ZFY*, *AZF*a, *AZF*b and *AZF*c, were not observed in his blood DNA according to multiplex polymerase chain reaction test. A literature review identified several 45,X/46,XY cases with a normal-appearing male phenotype, most of whom were diagnosed during infertility investigation. However, the present case is the first *SRY*-negative 45,X/46,XY male case diagnosed during a premarital medical examination.

CONCLUSION

This finding further suggests that sex determination is a complex process regulated by multiple genetic and environmental factors.

Key Words: Azoospermia; Sex chromosome; Mosaicism; Y chromosomal microdeletions; *SRY*-negative; Case report

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Core Tip: A rare chromosomal abnormality is 45,X/46,XY mosaicism. Here, we describe the diagnosis of a rare case of a 45,X/46,XY *SRY*-negative man with complete virilization and infertility as the main anomaly.

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INTRODUCTION

As a rare complement, the chromosomal abnormality of 45,X/46,XY mosaicism is found in 1.7 cases among 10000 newborns[1]. The spectrum of observed phenotypes ranges continuously from normal individuals with varying degrees of genital ambiguity to Turner's syndrome[2]. Most normal-appearing male phenotype cases are diagnosed during the prenatal period, and cases with genital/gonadal anomalies are usually diagnosed after birth[3]. More rarely, cases of 45,X/46,XY mosaicism with a normal-appearing male phenotype are not found until a chromosome test is performed to investigate the cause of male infertility.

Because the Y chromosome carries testis-determining factor, which is a genetically predominant locus, under normal circumstances, the bipotent gonadal primordium can be triggered and testes formation can be processed, which makes the Y chromosome a key factor in human sex determination. The *SRY* gene located in Yp11.2 was found to be cytogenetic and confirmed to play a critical role in the complex and tightly regulated processes of testis development[4] and sex differentiation[5]. However, more and more *SRY*-negative male cases with various karyotypes have been reported. In addition, increasing studies have shown that other factors, including both genetic and environmental factors, may regulate gender determination and differentiation through a multi-target approach.

Key genetic factors are known to regulate spermatogenesis on Yq, namely azoospermia factors (*AZFs*), including *AZF*a, *AZF*b and *AZF*c. Spermatogenetic failure caused by *AZF* microdeletions is a common cause of male infertility. Studies have shown that *AZF* microdeletions can be detected in approximately 10%-15% of azoospermia patients in China[6].

In the present report, we describe the diagnosis of a rare *SRY*-negative male case with 45,X/46,XY mosaicism. In addition, we review the 45,X/46,XY male phenotype cases reported in the literature to date to provide a more comprehensive description of the genetic and pathological features of this subgroup.

CASE PRESENTATION

Chief complaints

A 29-year-old man visited our urology clinic for a premarital medical examination, with complaints of occasional scrotal pain.

History of present illness

For the previous month, the patient had experienced occasional minor pain in the testicles.

History of past illness

The patient had no notable previous medical history.

Personal and family history

He denied any family history and had no specific past history.

Physical examination

His height was 167 cm, and his weight was 57.9 kg. After physical examination, we found that he had no dysmorphisms and had a normal distribution of pubic hair and body hair. His external urethral meatus was in a normal position, and his penis had a normal appearance and size (5.7 cm, non-erectile).

Laboratory examinations

The results of the patient's serum test revealed that the luteinizing hormone (LH) concentration was elevated at 15.73 IU/L (normal range: 1.7-8.6 IU/L), and the follicle-stimulating hormone (FSH) concentration was elevated at 14.13 IU/L (normal range: 1.5-12.4 IU/L). However, the serum testosterone hormone concentration was 3.22 μg/L, which was in the normal range for adult males of 2.49-8.36 μg/L. Azoospermia was determined after repeated seminal analysis. Chromosomal analysis was performed twice on samples collected at different times, and 100 metaphases were analyzed in each analysis. Two different cell lines with the karyotype 45,X[93%] /46,X,+mar(Y)[7%] were observed by GTG banding. Fluorescence *in situ* hybridization analysis with screening of metaphase and interphase lymphocytes was carried out to confirm the result of the karyotype analysis. Two cell lines, one with one green signal for Xcen (182/200) and the other with one green signal and one red signal for Xcen and Ycen (18/200), respectively, were observed according to fluorescence *in situ* hybridization (Figure 1A and B). All the metaphase and interphase lymphocytes showed one signal for Xcen but no *SRY* signal, except for cell lines containing *SRY* (Figure 1C). Polymerase chain reaction amplification of 16 *Y-STS* gene loci (*SRY*, *ZFY*, *sY86*, *sY84*, *CDY2*, *SMCY*, *sY127*, *sY134*, *sY1161*, *sY1191*, *sY254*, *sY255*, *DAZ*, *sY157*, *CDY1*, *ZFX*, *SMCX*, *DAZL*) using a Y-chromosome microdeletion detection kit (Microread Gene; Beijing, China) demonstrated the presence of Y chromosome-derived sequences. The *SRY* and *ZFY* genes were not amplified in the *AZF* region (Figure 1D). The negative amplification of *SRY* further confirmed the partial absence of the Y-chromosome sequence.

Imaging examinations

Ultrasound scanning of the scrotum showed that both testicles were located in the scrotum, but the volumes (6.6 mL and 6.8 mL, respectively) were significantly smaller than the normal adult male testicle size (range: 15-23 mL). In addition, a normal-sized prostate and seminal vesicles were observed by internal genitalia ultrasound analysis.

FINAL DIAGNOSIS

Azoospermia.

TREATMENT

The recommended treatments were hormone replacement therapy, including oral testosterone undecanoate to maintain sexual function, and sperm donation and assisted reproductive technology to solve fertility problems.

OUTCOME AND FOLLOW-UP

Follow-up found that the patient had a normal penile erection. He was married 1 year later, and the couple decided to adopt a child after marriage.

DISCUSSION

Stability of the number and structure of chromosomes is the basic requirement for maintaining the normal sex differentiation process. Two decades ago, Telvi *et al*[3] found that 45,X/46,XY mosaicism can manifest as a normal male phenotype and can also cause some abnormal clinical phenotypes, including Turner's syndrome, pseudohermaphroditism, and mixed gonad dysplasia. The subgroup of 45,X/46,XY mosaicism with normal adult male phenotype is usually diagnosed during infertility

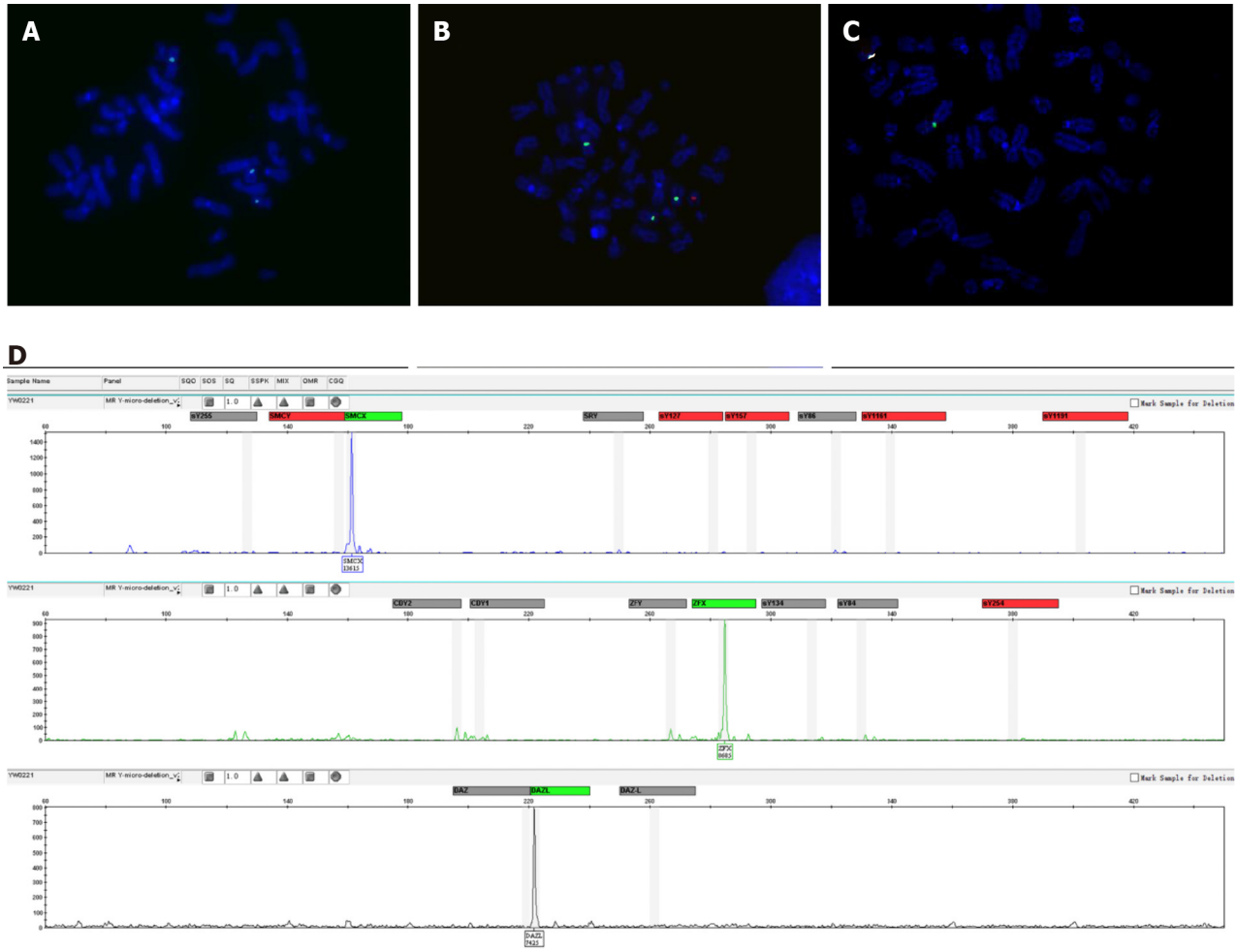

Figure 1 Fluorescence *in situ* hybridization analysis of metaphase chromosomes. A-C: Fluorescence *in situ* hybridization analysis showed the presence of two cell lines, one with one green signal for Xcen (A) and the other with one green signal and one red signal for Xcen and Ycen, respectively (B), as well as the absence of the *SRY* gene, with only green signal of the X chromosome (C); D: Polymerase chain reaction amplification of *16 Y-STS* gene loci.

investigation. Lashkari *et al*[7] reported that the occurrence rate of 45,X/46,XY mosaicism in azoospermic and oligozoospermic patients was 0.78%. Among the 49 infertile adult male patients with the 45,X/46,XY mosaicism karyotype that they evaluated, 21 showed azoospermia, 24 had sperm abnormalities, and four displayed a normal spermogram.

We reviewed additional literature regarding 45,X/46,XY adult male cases (Table 1)[8-18]. Among the 34 cases reviewed, 96.5% (28/29) showed azoospermia or oligozoospermia. The 45,X/46,XY mosaicism rates ranged from 6/93.3 to 94/6.7. There was no relationship between the mosaicism rate in peripheral blood lymphocyte and the phenotype, which was consistent with previous results[19,20]. The mosaicism ratio in different tissues may explain the variety of phenotypes in mixed gonadal dysgenesis[21]. Moreover, these individuals showed short or normal stature, with height ranged from 148-181 cm (data from 24 cases). Most of the patients had small testicles (92%, 23/25), elevated LH concentration (65.2%, 15/23), elevated FSH concentration (80.9%, 17/21), and normal testosterone concentration (95.2%, 20/21). All patients had the *SRY* gene, while 62.1% (18/29) had the *AZF* microdeletion. The most common *AZF* microdeletions were *AZF*(b+c) (66.7%, 12/18) followed by *AZF*c (22.2%, 4/12), *AZF*b (5.5%, 1/18), and *AZF*(a+b+c) (5.5%, 1/18). In our study, the man with the 45,X/46,XY mosaic karyotype also showed complete masculinization and azoospermia, with short stature, small testicles, elevated LH and FSH concentrations, and a normal T concentration. However, the *SRY* gene, *ZFY* gene, and *AZF*(a+b+c) regions of blood DNA were missing in this case, and this is the first male with the *SRY* -negative 45,X/46,XY mosaic karyotype according to our literature search results.

The process of sexual differentiation begins in the early stages of human embryo development. After a series of complex and orderly procedures, bipotential gonads eventually develop into testes or ovaries. The *SRY* gene plays a critical role in the cascade of events of sexual differentiation. The histogenesis of testis is initiated by the

Table 1 Characteristics of 34 reported 45,X/46,XY adult male cases

Ref.	No.	Age in yr	Karyotype[%]	Reason for examination	Semen analysis	Height in cm	Genital/gonads	LH in U/L	FSH in U/L	T in ng/mL	E2 in pg/mL	*AZF*	*SRY*
Wu *et al*[8], 2017	1	22	45,X[93.3]/46,XY[6.7]	Primary sterility	AZO	148	Male/left and right TV: 4.4 mL, 1.6 mL dysplasia of epididymis	17.07	52.78	3.94	13.58	No missing	+
	2	23	45,X[36.7]/46,X,del(Y)(q11.223)[63.3]	Primary sterility	AZO	159	Male/left and right TV: 8.7 mL, 8.7 mL	9.98	16.22	4.32	37.38	*AZF*(b+c)	+
	3	23	45,X[65]/46,XY[35]	Primary sterility	AZO	173	Male/left and right TV: 4 mL, 5.4 mL	9.10	15.33	2.52	< 5.00	*AZF*(b+c)	+
	4	26	45,X[6]/46,XY[94]	Primary sterility	AZO	170	Male/left and right TV: 3.8 mL, 4.5 mL	9.32	17.04	4.06	47.79	*AZF*(b+c)	+
	5	26	45,X[83.3]/46,X,Yqh–[16.7]	Primary sterility	AZO	165	Male/left and right TV: 6 mL, 6 mL	10.44	28.20	7.12	33.26	*AZF*(b+c)	+
	6	29	45,X[45]/46,X,Yqh–[55]	Primary sterility	AZO	160	Male/left and right TV: 5.4 mL, 6.2 mL	13.58	22.00	3.49	40.95	*AZF*(b+c)	+
	7	29	45,X[28.3]/46,XY[71.7]	Primary sterility	AZO	165	Male/left and right TV: 6 mL, 3.2 mL	14.26	31.31	3.26	20.64	*AZF*(b+c)	+
Akinsal *et al*[9], 2018	8	24	45,X[66]/46,XY[34]	Primary sterility	AZO	158	Male/left and right TV: 18 mL, 12 mL	19.7	15.15	3.83		*AZF*c	+
	9	26	45,X[70]/46,XY[30]	Primary sterility	AZO	178	Male/left and right TV: 9 mL, 9 mL	7.5	9.8	6.74	16.14	No missing	+
	10	29	45,X[40]/46,XY[60]	Primary sterility	AZO	156	Male/left and right TV: 7 mL, 7 mL	7.97	20.4	7.44	48.6	*AZF*c	+
	11	40	45,X[30]/46,XY[70]	Primary sterility	AZO	165	Male/left and right TV:14 mL, 14 mL	9.96	22.29	3.78		No missing	+
	12	26	45,X[55]/46,XY[45]	Primary sterility	AZO	165	Male/left and right TV: 12 mL, 14 mL	7.96	6.91	3.96	19.01	No missing	+
	13	29	45,X[66]/46,XY[34]	Primary sterility	AZO	164	Male/left and right TV: 8 mL, 10 mL	13.2	28	4.00	40.8	*AZF*(b+c)	+
	14	33	45,X[73]/46,XY[27]	Primary sterility	AZO	160	Male/left and right TV: 18 mL, 18 mL	3.8	11.12	2.52	18.63	No missing	+
	15	41	45,X[45]/46,XY[55]	Primary sterility	AZO	155	male/left and right TV: 8 mL, 7 mL	19.25	25.16	1.68	72.06	No missing	+
Lindhardt *et al*[10], 2012	16	20	45,X[63]/46,Xdel(Y)(q12)[37]	Delayed puberty			Male/left and right TV:12 mL, 15 mL					*AZF*(b+c)	+
	17	28	45,X[20]/46,XY[80]	Infertility			Male/left and right TV: 2 mL, 0 mL					No missing	+
	18	33	45,X[55.6]/46,XY[44.4]	Infertility			Male/left and right TV: 12 mL, 6 mL					*AZF*(b+c)	+
	19	49	45,X[33.3]/46,Xidic(Y)(p)[66.7]	Infertility			Male/left and right TV: 4 mL, 4 mL					*AZF* (a+b+c)	+

Ren *et al*[11], 2015	20	27	45,X[50]/46,XY[50]	Primary infertility				N	14 IU/L	N	N	No missing	+
Rosa *et al*[12], 2014	21	24	45,X[33]/46,XY[67]	Primary infertility	AZO		EMS 12	N					
Ketheeswaran *et al*[13], 2019	22	39	45,X[6]/46,XY[94], peripheral blood; 46,XY, buccal mucosal cells	Primary infertility	N	181	Male/left and right TV: 20 mL, 18 mL	1.8 IU/L	1.3 IU/L	10.2 nmol/L	0.06 nmol/L		
Reddy *et al*[14], 1998	23	37	45,X[47]/46,XY[53], peripheral blood; 45,X[43]/46,XY[57], testis	Infertility	AZO		Male/atrophic testis						
Gassó-Matoses *et al*[15], 1992	24	33	45,X[85]/46,XY[15], testis	Infertility	AZO	157	Bilateral small testis	10	17.2	430 ng/dL			
Li *et al*[16], 2013	25	23	45,X[19]/46,XY[81]	Primary infertility	AZO	162	N					*AZF*c	+
	26	25	45,X[15]/46,XY,Yqh-[85]	Primary infertility	OLIGO	158	N					No missing	+
	27	30	45,X[15]/46,XY[85]	Primary infertility	AZO	163	N					*AZF*(b+c)	+
	28	24	45,X[56]/46,X,dic(Y)[44]	Primary infertility	AZO	157	N					*AZF*c	+
	29	36	45,X[55]/46,XY,Yp+[45]	Primary infertility	AZO	155	N					No missing	+
	30	26	45,X[22]/46,X,dic(Y)[78]	Primary infertility	AZO	168	N					No missing	+
Kilic *et al*[17], 2010	31	28	45,X[5]/46,XY[95]	Infertility	AZO		Testicular diameters: 3 cm × 3.5 cm	16	21	2.21		*AZF*b	+
	32	25	45,X[20]/46,XY[80]	Primary infertility	OLIGO		Testicular diameters: 3.2 cm × 2.5 cm	18	26	2.8			
	33	32	45,X[45]/46,XY[55]	Primary infertility	AZO		Testicular diameters: 4.0 cm × 2.8 cm	17	23	2.77		*AZF*(b+c)	+
Valetto *et al*[18], 2004	34	41	45,X[71]/46,X,idic(Yp)[26]/46,XY[3]	Infertility	AZO	155		N				*AZF*(b+c)	+

AZO: Azoospermia; E2: Estrogen; EMS: External masculinization score; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; N: Normal; OLIGO: Oligozoospermia; T: Testosterone; TV: Testicular volume.

SRY gene, beginning at about 6 wk post-implantation[21,22]. On the other hand, a deletion mutant of the *SRY* gene can affect masculinization and may cause 46,XY female sex reversal[23]. Even though the *SRY* gene is critical in the initiation of testis determination, some of the *SRY*-negative phenotype may show the typical male phenotype, as seen in the present patient. Our findings further suggest that testicular formation and development occurs *via* a comprehensive process jointly regulated by other key genetic factors or environmental factors in addition to the *SRY* gene. Several hypotheses have attempted to explain rationally the formation of testicles in *SRY*-negative males, such as the possible predominance of the 46,XY cell line in the gonads[20], hidden mosaicism for a Y-derivative material, or mutation of an autosomal or X-chromosomal gene downstream from *SRY*. In addition, studies have shown that

overexpression of the *SOX9* gene can initiate testis differentiation when the *SRY* gene is silenced. This result indicates that the *SOX9* gene, as downstream factor of *SRY*, plays an important role in the sex determination process[24-26]. In the present study, the patient refused to undergo genetic analysis of genital skin and gonadal fibroblasts as well as further examinations, and thus, the exact mechanism of his gender development could not be explained.

The *AZF* gene is located on the long arm of the Y chromosome, and its locus contains protein-coding genes essential for spermatogenesis[27]. Y chromosome microdeletion, which might result from Y-chromosome instability and lead to 45,X karyotype, is one of the key causes of severe male infertility. Clinical statistics indicate that 10%-15% of azoospermic patients and 5%-10% of severe oligospermia patients have Y chromosome microdeletion[6,28]. Studies have reported that deletion of large and submicroscopic Y chromosome may lead to an increased proportion of 45,X abnormal karyotype cells among sperm cells and lymphocytes[29]. In the present case, the patient had deletions of *AZF*(a+b+c) regions in addition to 45,X/46, XY mosaicism, which may explain the high percentage of 45,X cells and azoospermia.

From the perspective of oncology, gonadal germ cell tumors are detected at an elevated frequency among patients with a 45,X/46,XY karyotype and malformations of the external genitalia[30]. The risk for malignant transformation is reportedly about 10% and increases with age in patients with 45,X/46,XY gonadal dysgenesis[31,32]. It is worth noting that the prognoses of 45,X/46,XY patients with an apparently normal male phenotype until adulthood and patients who are born with severe genital anomalies show no statistical difference[33]. Therefore, adult patients with the 45,X/46,XY mosaic karyotype must be followed up for life, with particular focus on testicular function and testicular tumor screening.

CONCLUSION

In conclusion, we have described the clinical and genetic findings for a male with complete virilization in *SRY*-negative 45,X/46,XY mosaicism. We believe that a perfect karyotype analysis and Y-microdeletion analysis could not only reveal the cause of male infertility, in order to facilitate reproductive counseling, but also provide prognostic information for patients with specific karyotypes.

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