A Rare Case of 46, XX (SRY+) With Normal Male Stature and Unilateral Absence of the Vas Deferens

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Abstract

Objective: This study aimed to investigate the cause of primary infertility in a rare case with unilateral absence of vas deferens.

Case report: A 35-year-old man was presented to the Infertility Clinic at the National Center of Maternal and Child Health (NCMCH) with an eight-year history of primary infertility. Clinical examination showed a normal intelligence with a coarse facial appearance and small testicles. Hormonal tests detected elevated levels of prolactin (PRL), follicle stimulating hormone (FSH), and luteinizing hormone (LH), and low levels of testosterone. Chromosomal analysis with fluorescence in situ hybridization (FISH) revealed a 46XX with SRY (sex-determining region Y) positive karyotype with translocation of the SRY gene (46XX der(X)t(X:Y)(p11.1:p11.3)(SRY+)). Magnetic resonance imaging (MRI) revealed bilateral seminal vesicles atrophy and agenesis of the vas deferens on the right side, which is rarely found in 46, XX male syndrome.

Conclusion: Although 46XX testicular disorder of sexual development (DSD) cases are rare, multiple aspects of the clinical examinations are important to make an accurate diagnosis and to provide proper genetic counseling and guidance to patients in their long-term management.

Keywords: Chromosomal Aberrations; Male Infertility; Magnetic Resonance Imaging; Sexual Development; 46, XX Testicular Disorders of Sex Development

Introduction

The term ‘disorders of sexual development’ (DSD) refers to three major groups of congenital conditions associated with abnormal development of internal and external genital organs. The first group includes abnormal sex chromosome disorders consisting of Turner and Klinefelter syndrome or translocation conditions with 46, XX/46, XY karyotype. The second group is characterized by XY DSD, consisting of disorders of testicular development or disorders of androgen synthesis or action. The third group consists of XX DSD, which comprises disorders of ovarian development or disorders of androgen excess (1). The 46, XX, testicular DSD, is a part of the first group and occurs in about 1 in 20,000 newborn males. The

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46, XX karyotype has three different phenotypes: phenotypically healthy men, men with genital ambiguities, and true hermaphrodites (2). Cases with genital ambiguities and true hermaphrodites have a higher risk of developing cancers because of extra Y chromosomal material, whereas 46, XX men might have an ovarian cancer predisposition (3).

The sexual differentiation of the embryos is determined by the presence of the Y chromosome initiating the expression of the SRY gene. Approximately 80% of 46, XX, testicular DSD cases are SRY positive as a result of translocation from the Y chromosome to the X chromosome (4). Most patients with SRY positive 46, XX DSD have a male phenotype with small testes and may have cryptorchidism or hypospadias, azoospermia resulting in primary infertility, and gynecomastia with normal cognitive development (5). On the contrary, SRY negative patients could be easily diagnosed because of genital abnormalities shortly after birth; some patients even show genital ambiguity (4, 6).

Here we report the first case of a male diagnosed with 46, XX, testicular DSD in Mongolia, who presented with a normal male phenotype, small testis, gynecomastia, hypergonadotrophic hypogonadism, azoospermia, bilateral seminal vesicles atrophy, and vas deferens agenesis on the right side. Molecular cytogenetic studies confirmed SRY translocation as the cause of 46, XX, testicular DSD.

**Case report**

A 35-year-old man was presented to the Infertility Clinic at the National Center of Maternal and Child Health (NCMCH), Mongolia, with an eight-year history of primary infertility in October 2017. The patient had an unremarkable medical history and reported reduced libido and sexual function. His wife had no significant medical history; her biochemical and hormonal investigations were within the normal range. Physical examination revealed a height of 171 cm, a weight of 82 kg, a body mass index (BMI) of 28.0 kg/m², a horizontal abdominal diameter of 32 cm, and a sagittal pelvic diameter of 34 cm. His waist and hip circumferences were 129 cm and 114 cm, respectively. On the national reference data for men of his age range (35-44 years), these values were 85.2±0.05 cm and 94.9±0.03 cm (mean±SD), respectively (7). He presented coarse body hair and bilateral gynecomastia (grade II), which started at the age of 19 years. Genital examination revealed normal symmetrical male genitals with small testicles and sparse pubic hair corresponding to stage III on the Tanner scale. The testicles were palpable and small for his age, approximately 2-2.5 ml as measured by a Prader orchidometer.

Semen analysis was done after five days of sexual abstinence according to the World Health Organization (WHO) guideline and showed a normal ejaculate volume of 1.5 ml (1.5-5 ml) and azoospermia. A hormonal analysis revealed high levels of both gonadotropins, with an FSH level of 45.3 IU/L (normal value 1.5-12.4 IU/L) and an LH level of 39.1 IU/L (normal value 1.24-7.8 IU/L). The early morning total testosterone and calculated free testosterone were 0.97 ng/ml (2.8-11 ng/ml) and 0.3 pg/dl (9-30 pg/ml), respectively. These results were consistent with hypergonadotrophic hypogonadism.

Klinefelter syndrome (47, XXY) was first suspected in this patient based on the presence of gynecomastia, hypogonadism, and azoospermia. To test the possibility, we performed chromosomal testing on peripheral blood leukocytes using Giemsa staining, which revealed a 46, XX phenotype (Figure 1A).

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**Figure 1:** (A) Constitutional karyotype, 46, XX. Mitotic metaphase spreads were prepared from cells, which showed a 46, XX phenotype. A red asterisk shows the derivative X chromosome in the patient. (B) Fluorescence in situ hybridization images of the case, consistent with a karyotype of 46XX der (X) t(X:Y) (p11.1:p11.3) (SRY+). Representative FISH images of interphase and metaphase cells. SRY (red arrow) and DXZ1 in the X centromere (blue arrow) were observed, while DYZ1 in Yq12 of the Y chromosome (green) could not be detected.
To identify any structural rearrangement of the SRY gene to cause a 46, XX male phenotype, we performed FISH analysis using the Cytocell SRY probe (Yp11.31), which can detect a centromere region of chromosome X (DXZ1) and a telomere region of the Y chromosome (DYZ1). All the 300 cells and 15 metaphase cells revealed the presence of SRY region on one of the X chromosomes with DXZ1 without DYZ1, which is consistent with a karyotype of 46, XX and der (X)t(X:Y) (p11.1:p11.3) (DXZ1x2, SRY+) (Figure 1B).

Furthermore, we performed imaging exams to exclude a risk of malignancy due to the presence of the female internal organs. Magnetic resonance imaging (MRI) of the pelvic region revealed the seminal vesicles (SV) with a size of 1.1x0.7x3.7 cm³ in the right and 1.5x0.8x3.7 cm³ on the left side (normal range 1.5x1.5x3 cm³). Axial and coronal T2-weighted intra-abdominal MRI demonstrated a low T2 signal with a very small number of glandular cells in the SV, where the grape-like features of SV were lost, suggesting dysgenesis and atrophic residues (Figure 2A). Moreover, the vas deferens were absent on the right side (Figure 2B, C). The presence of both testicles was confirmed inside the scrotum (right 1.8x2.2 ml, left 2x2.3 ml), both of which were smaller than the normal range 13.67±3.49 ml (mean±SD) (8).

Based on FISH findings and MRI images, this case was confirmed to be a 46, XX, testicular DSD syndrome due to chromosomal rearrangement between the sex chromosomes. During genetic counseling, multiple aspects of the disease were provided to the patient and his spouse to help comprehend the disease prognosis. They were offered options such as artificial insemination with sperm donation, child adoption, and psychological support, and the patient was on clinical follow-up at the time of writing this report.

![Figure 2](image_url): Atrophic seminal vesicles and absence of vas deferens on the right. (A) Axial T2-TSE weighted MRI images show abnormal SVs with low T2 signal intensity. The SVs (red arrow) were diffusely atrophied with low T2 signal, consistent with radiation atrophy or dysgenesis. (B) Axial T2-Blade weighted MRI images show the absence of the right-side vas deferens at the intra-abdominal portion. The left side vas deferens is pointed with a red arrow; (C) it could be seen through different MRI slices.
Discussion

To the best of our knowledge, this was the first case of a male diagnosed with 46, XX, testicular DSD in Mongolia, who presented with infertility and small testicles, hypergonadotrophic hypogonadism, azoospermia, and dysgenesis of male internal genital organs. His FISH analysis showed that the SRY locus had been translocated to the short (p) arm of the X chromosome. DSD results from atypical testicular tissue differentiation in XX fetuses, a condition called 46, XX, testicular DSD. These may also arise from the coexistence of an ovary and testis, a condition known as 46, XX, an ovotesticular (6). With MRI images, we were able to diagnose this case a 46, XX, testicular DSD. A recent study recruiting 144 males with a 46, XX karyotype confirmed that gonadotropin elevations are the main hallmarks of the condition regardless of SRY presence (5). So far, SRY is identified to be the main gene leading to the formation of a testis from the indifferent gonadal ridge (4). In the present case, we observed gynecomastia, a small testis, azoospermia, hypergonadotrophic hypogonadism, and SRY translocation, which are typical symptoms of 46, XX, testicular DSD.

Most patients with 46, XX, testicular DSD have a normal male phenotype during childhood and usually discover the pathology in their adulthood (33.14±11.4 years) because of gynecomastia or infertility (4). A systematic review describing 64 DSD adults out of 37 selected studies reported a mean (SD) weight of 70.3 (10.2) kg and a mean (SD) height of 165.3 (7.2) cm. These patients had small testes or gynecomastia, in 22/39 cases. We compared the anthropometric values of our patient with the mean values of weight and height of Mongolian men aged 35-45 years (7). He was taller and overweight compared to the reference population. The length of the legs, bi-iliac diameter, and circumferences of the bust line, waist, and hip were all increased, while the bi-acromial width and bi-testicular volume were reduced. It has been reported that 46, XX males are usually shorter than healthy men or men with Klinefelter syndrome (9). However, we observed a contrary phenomenon in our case. This could be explained by the amount of the translocated Y chromosomal region, which might contain other genes, such as a growth-control gene critical region located in the Y chromosome. Individuals with Klinefelter syndrome are taller than average men and 46XX males, which is explained by the extra copy number of the genes located in the X chromosomes (9). We also assume that this could be influenced by other genes of autosomal chromosomes running in the family (10).

MRI findings of the internal genital organs of 46, XX male cases are usually normal (8). However, it is necessary to confirm the absence of ambiguous genitals because they might develop into tumors later in life and will have to be removed by surgery. We did not find any residues of female internal genitalia in our case, but he demonstrated poorly differentiated SV and undeveloped vas deferens on the right side (Figure 2C), which are rarely found in 46, XX males, highlighting a clinical diversity in our case. His testicles were underdeveloped and unable to produce sperms, and if they did produce sperms, they could not be transported fully through the vas deferens to become a part of semen because of the unilateral absence of the vas deferens. As a result, this patient was unable to father children (infertile) unless the couple used assisted reproductive technologies.

Conclusion

In conclusion, multiple aspects of the clinical and laboratory examinations are needed in these patients to provide more valuable clinical follow-up. Sperm donation or adopting a child was suggested as the fertility option for the family. They are currently in the process of adopting a baby girl.

Conflict of Interests

Authors have no conflict of interests.

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