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Case Report: 46, XX Testicular Disorder of Sex Development in A15-Year-Old Male

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Abstract: Background: 46,XX testicular disorder of sex development (DSD), also known as de la Chapelle syndrome, is a rare condition in which an individual with a 46,XX karyotype develops as a phenotypic male. This typically results from translocation of the sex-determining region Y (SRY) gene onto an X chromosome during paternal meiosis. Affected individuals usually present in adolescence with hypergonadotropic hypogonadism and infertility, despite having male genitalia.

Case Presentation: We report a 15-year-old phenotypic male evaluated for delayed puberty and gynecomastia. He was short for his age and had minimal facial hair, underdeveloped musculature, and bilaterally small testes. Laboratory testing revealed elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) with low testosterone levels, suggesting primary testicular failure. Karyotype analysis unexpectedly showed 46,XX. Fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) confirmed the presence of the SRY gene on one X chromosome, consistent with SRY-positive 46,XX testicular DSD.

Management: The patient was started on low-dose testosterone replacement therapy to induce puberty, with gradual dose escalation. Hormone therapy led to development of secondary male characteristics and halted progression of gynecomastia. Psychological counseling and patient education were provided to address the discordance between chromosomal sex and gender identity. The patient was counseled about infertility and future options.

Conclusion: This case illustrates the diagnostic challenge of 46,XX testicular DSD in an adolescent male with delayed puberty. It highlights the importance of cytogenetic analysis in cases of hypergonadotropic hypogonadism, as well as the need for molecular testing to detect SRY gene translocation. Early identification and management with hormone therapy are critical for normal pubertal development. The report also underscores genotype–phenotype discordance and recommends confirming SRY involvement to guide appropriate counseling and genetic consultation.

Key words: Chapelle syndrome, testosterone, hormone therapy

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Introduction

46,XX testicular DSD (de la Chapelle syndrome) is an exceptionally rare genetic condition characterized by discordance between chromosomal sex and phenotypic sex (MedlinePlus Genetics, 2023). Individuals have a female genotype (46,XX) but develop as phenotypic males due to the presence of testis-determining genetic material. The estimated incidence is about 1 in 20,000 male births (Thaker et al., 2023). Although rare in the general population, 46,XX testicular DSD may account for up to 2% of cases of male infertility (Ferrari et al., 2024). Affected individuals often appear as typical males at birth and are usually raised as males. Most are not diagnosed until adolescence or adulthood, when they present with pubertal failure, gynecomastia, or infertility (Thaker et al., 2023).

In approximately 80–90% of cases, the condition results from an abnormal exchange of genetic material between the X and Y chromosomes during paternal meiosis, leading to translocation of the SRY gene from the Y chromosome to the X chromosome (Yue et al., 2019; Yilmaz et al., 2023). The SRY gene (sex-determining region Y), normally located on the Y chromosome, encodes a testis-determining factor that initiates male gonadal development (MedlinePlus Genetics, 2023). In the father's spermatogenesis, a recombination error in the pseudoautosomal region 1 (PAR1) on the short arms of X and Y can mistakenly include SRY, transferring it to an X chromosome (Yue et al., 2019; Yilmaz et al., 2023). If an X chromosome carrying SRY fertilizes the egg, the resulting 46,XX embryo will develop testicular tissue and male internal and external structures despite the absence of a Y chromosome (Yue et al., 2019; Yilmaz et al., 2023). Thus, SRY gene translocation is the primary mechanism of sex reversal in these patients.

About 10–20% of 46,XX testicular DSD cases are SRY-negative (Thaker et al., 2023; MedlinePlus Genetics, 2023). These individuals lack the SRY gene, and their male development is thought to result from alternate genetic mechanisms. Proposed causes in SRY-negative cases include copy number variations or mutations in other genes involved in testis determination or ovarian suppression (such as duplications of *SOX9* or mutations in *RSPO1*, *WNT4*, *NR5A1*, etc.), although many cases remain genetically unexplained (MedlinePlus Genetics, 2023; Yue et al., 2019). SRY-negative 46,XX individuals are more likely to have ambiguous genitalia at birth or incomplete virilization compared to SRY-positive cases (Yue et al., 2019).

Clinically, the phenotype of 46,XX testicular DSD can range from completely typical male to undervirilized male. About 90% of SRY-positive 46,XX males have normal male genitalia and present post-puberty with hypergonadotropic hypogonadism, gynecomastia, and azoospermia (Thaker et al., 2023; Yilmaz et al., 2023). The remaining cases, often SRY-negative, may present in infancy due to

genital ambiguity (e.g., hypospadias, micropenis, undescended testes) (Thaker et al., 2023). Despite generally male appearance and identity, affected individuals universally have impaired spermatogenesis and are infertile due to the lack of Y-linked AZF regions required for sperm production (Li et al., 2014). Mental development is normal, but patients are often short in stature and may have some features resembling Klinefelter syndrome (such as small testes and gynecomastia) (Thaker et al., 2023).

This report describes a 15-year-old 46,XX male with suspected SRY translocation. We detail the clinical presentation, diagnostic workup, and management, and review the literature regarding the genetic basis, diagnostic challenges, and importance of confirming SRY gene involvement in such cases.

Case Presentation

A 15-year-old phenotypic male was referred to the endocrinology clinic for evaluation of delayed puberty. He was the first child of non-consanguineous parents, with unremarkable prenatal and birth history. He had been raised as a boy and identified as male. At birth, the external genitalia were reported as normal male, and there was no history of ambiguous genitalia or genital surgery in infancy. Both testes were noted to be in the scrotum neonatally. The patient's early childhood growth and development were unremarkable. There was no family history of disorders of sex development, infertility, or pubertal abnormalities.

In the past year, the patient and his parents became concerned about a lack of pubertal progression. At 15 years old, he had minimal facial and axillary hair and a high-pitched voice. He reported no spontaneous muscle growth, deepening of voice, or significant increase in penile size. He also noticed enlargement of breast tissue over the past year. There was no history of anosmia, headaches, or other systemic symptoms.

On physical examination, the patient's height was 155 cm (below the 5th percentile for males of his age) and weight 50 kg. He appeared youthful, with a slightly eunuchoid body habitus. He had mild bilateral gynecomastia (Tanner stage B2) and sparse pubic and axillary hair (Tanner stage II). The phallus was of prepubertal size (stretched penile length 5 cm). The scrotum was well-formed but relatively small. Both testes were palpable within the scrotum; they were firm and significantly small, with a volume of approximately 3 mL each (consistent with Tanner stage I testes). No inguinal or labial masses were present. There were no hypospadias or other genital anomalies noted. Signs of virilization such as muscle bulk and voice change were poorly developed, consistent with androgen deficiency. The patient's cognitive development and neurologic exam were normal for age.

Investigations

A detailed evaluation was done to determine the cause of the delayed puberty and hypogonadism of the patient:

- **Hormonal profile**: Serum gonadotropins were elevated (FSH 32 mIU/mL, LH 18 mIU/mL), both above the normal pubertal male range, while total testosterone was low (0.8 ng/mL, in the prepubertal range). This is characteristic of primary testicular failure, i.e., hypergonadotropic hypogonadism. Estradiol was low-normal (15 pg/mL) and prolactin was normal, eliminating hyperprolactinemia as a cause. Thyroid function and adrenal androgens (e.g., DHEA-S) were also normal, excluding other endocrine abnormalities causing delayed puberty.
- **Karyotype analysis**: Chromosomal analysis of peripheral blood lymphocytes revealed 46,XX in all 20 metaphases examined, with no Y chromosome material detectable. There was no structural defect seen on G-banded karyotyping. A 46,XX in a phenotypic male strongly pointed towards 46,XX testicular DSD (de la Chapelle syndrome).
- **SRY gene analysis**: Molecular genetic testing was conducted to evaluate for SRY gene translocation. **Fluorescence** in situ hybridization (FISH) with an SRY probe detected a signal of hybridization on one X chromosome with no signal on the Y chromosome, thus demonstrating that the SRY gene was

located on an X chromosome. This result supported the diagnosis of **SRY-positive 46,XX testicular DSD**. Polymerase chain reaction (PCR) also certified the patient's DNA for the presence of the SRY sequence (Yilmaz et al., 2023). All these tests collectively confirmed that despite the absence of the Y chromosome, the individual was SRY-positive.

- **Imaging studies**: Pelvic and scrotal ultrasonography revealed two small oval scrotal masses (~1.5 cm in length), consistent with bilateral testes. There were no ovaries, uterus, or Müllerian structures, consistent with the presence of functional Sertoli cell-derived AMH during development. Prostate was present but hypoplastic, not unexpected when androgen deficiency is present. Renal imaging was normal—an important negative finding since renal abnormalities can be seen with DSDs.
- **Histology**: Due to the invasive nature of testicular biopsy and the absence of a clinical indication at this time, no tissue samples were taken. Nevertheless, based on the literature available and typical findings in SRY-positive 46,XX males, the testes can be anticipated to show seminiferous tubule hyalinization, a lack of germ cells, and a Sertoli cell-only pattern (Yilmaz et al., 2023). These histological findings account for the extensive sterility reported in the individuals concerned.

Cumulatively, the findings made a diagnosis of 46,XX testicular DSD (SRY-positive), otherwise known as de la Chapelle syndrome. Male differentiation was explained by the SRY gene on the X chromosome, and results of hypergonadotropic hypogonadism explained the inability to enter puberty and likely infertility.

Management

The primary goals of management were to induce puberty, address gynecomastia, ensure psychological well-being, and plan for long-term health:

1. **Hormone Replacement Therapy:**

Testosterone replacement therapy was initiated to induce and maintain secondary male sexual characteristics. The patient was started on low-dose intramuscular testosterone enanthate (50 mg monthly) with gradual escalation over 1–2 years to full replacement doses, mimicking physiologic pubertal development.The dose was doubled at six months and subsequently changed to 100 mg intramuscularly every two weeks. On follow-up, the patient developed undeniable signs of virilization: voice deepening, expansion of facial and body hair, and increased muscle mass and strength. Testosterone therapy also consolidated the previously progressing gynecomastia, which regressed considerably and obviated the need for surgery. This observation is consistent with recent guidelines that most 46,XX testicular DSD patients require testosterone replacement during puberty to promote masculinization and avoid gynecomastia (Ferrari et al., 2024). Continued testosterone replacement will be necessary for the preservation of male secondary sexual characteristics, bone density, and sexual function.

2. **Psychosocial Support:**

The patient and his family underwent psychological counseling to explore the implications of the diagnosis.

Developmentally appropriate explanations were given to explain that although the patient had an XX chromosomal pattern, the expression of the SXY gene permits male differentiation.

Thepatient's understanding and coping mechanism were assessed by a mental health professional to avoid confusion of identity or psychological distress.

The patient developed a gender identity in line with his male upbringing and accepted the need for lifelong hormone treatment.

The patient was also referred to support groups and DSD advocate groups to help all eviate potential isolation and stigma.

3. **Fertility Counseling:**

Infertility was explained openly. The patient's testes are unable to produce sperm due to a lack of the azoospermia factor (AZF) regions of the Y chromosome (Li et al., 2014). While semen analysis was deferred until after puberty, one may anticipate azoospermia. The patient was informed that biological paternity is impossible and was advised for other options, including donor insemination or adoption. We advised against the necessity of fertility interventions since the literature consistently shows no successful sperm retrieval in 46,XX males, who predominantly harbor a Sertoli cell-only histological pattern (Yilmaz et al., 2023). It was achievable to gain realistic expectations and emotional adaptation by tackling this early on.

4. **Gonadal Management:**

As both testes were descended and there were no clinical or imaging features of gonadal dysgenesis or neoplasia, a conservative approach was taken. Although dysgenetic or undescended gonads in DSD individuals have a risk of gonadoblastoma, the testes in this SRY-positive individual were hormonally functional and had descended naturally. The patient was taught testicular self-examination, and ultrasound follow-up was scheduled. Surgery (gonadectomy or orchiopexy) would be reserved in the case of concerning signs such as asymmetry or masses.

5. **Follow-Up:**

The patient is monitored every 3–6 months during pubertal induction. Growth determinants, pubertal progress, and hormone levels are evaluated on every visit to guide testosterone dose adjustment. Bone mineral density evaluation is planned in late adolescence to monitor for any deficiency secondary to delayed testosterone exposure. The endocrinology group will also arrange for genetic counselors to speak with the family regarding the genetic basis of the condition. As this disorder is the result of a de novo mutation and the patient is infertile, recurrence is unlikely, so parental reassurance needs to be emphasized (MedlinePlus Genetics, 2023). The patient's psychosocial development is followed closely with continued mental health treatment provided as necessary.

Discussion

This case demonstrates a typical presentation of SRY-positive 46,XX testicular disorder of sex development (DSD) in adolescence and also outlines some key features of this condition. The 46,XX testicular DSD is a rare sexual differentiation reversal condition, in which the chromosomal sex (46,XX, which is usually found in females) is not concordant with the phenotypic sex (male). Such genotype–phenotype discrepancy is explained by the presence of testis-determining genetic material, particularly the SRY gene, in the absence of a Y chromosome (Li et al., 2014). Translocation of SRY to the X chromosome is largely the primary force for testicular differentiation in the majority of cases, as in our patient (Yue et al., 2019; Yilmaz et al., 2023).

The SRY protein triggers a cascade of gene activations with particular enhancement of SOX9 expression that is essential for the development of testes. The testes subsequently produce testosterone and anti-Müllerian hormone (AMH) to enable the development of internal male ducts and external genitalia. This mechanism accounts for the patient's normal male genital morphology at birth and the imaging findings of the absence of a uterus—both indications of sufficient AMH and androgen function.

Genetic Mechanism

Translocation of the SRY gene to the X chromosome is due to a meiotic recombination error occurring during the father's spermatogenesis. Normally, recombination is confined to the pseudoautosomal region 1 (PAR1) at the tips of the short arms of the X and Y chromosomes. The SRY gene is found just proximal to PAR1 on the Y chromosome's short arm.Sometimes, a crossover event extends outside PAR1, producing the transfer of SRY (and sometimes adjacent Yp material) to the X chromosome (Yilmaz et al., 2023). It is caused by regions of sequence similarity, e.g., between PRKX on X and PRKY

on Y, that can cause meiotic misalignment (Yilmaz et al., 2023).

The outcome is an X chromosome with the SRY gene inherited paternally. If this X chromosome is inherited along with a normal maternal X, the embryo will have a 46,XX karyotype but will be a male because of SRY-induced testicular differentiation. Conversely, a Y chromosome devoid of SRY may result in a 46,XY female upon inheritance. Here, SRY on a single X chromosome established this pathogenic mechanism.

The amount of the translocated region may differ among subjects: some subjects receive just the SRY gene, while others receive more extensive regions of Yp. This type of variation influences phenotype. Individuals with minimal quantities of translocated genetic material (just SRY) tend to have normal male genitalia, whereas individuals with bigger translocations tend to have more Y genes that influence development—possibly adding to or suppressing virilization based on the final gene combination (Yilmaz et al., 2023). Conversely, deletions or breakpoints in regulatory regions can result in incomplete virilization despite the presence of SRY.

Clinical Phenotype and Diagnostic Challenges

SRY-positive 46,XX males are normal phenotypic males but often shorter than expected in height. They usually present clinically in adolescence or early adult life with signs of gonadal failure, such as delayed puberty, small testes, or gynecomastia (Thaker et al., 2023). In the prepubertal period, it is uncommon to make a diagnosis unless there are ambiguous genitalia at birth. In our patient, the failure to advance through puberty and bilaterally small testes were the significant diagnostic features.

These can mimic Klinefelter syndrome (47,XXY), which is far more common and might be the initial consideration in teenage boys presenting with small testes, gynecomastia, and elevated gonadotropins. Both conditions—46,XX testicular DSD and Klinefelter syndrome—are characterized by hypergonadotropic hypogonadism and azoospermia. The Klinefelter syndrome patients are usually taller with eunuchoid body proportions, whereas 46,XX males are shorter (Thaker et al., 2023). Thus, although clinical overlap exists, karyotype analysis is necessary for making a precise diagnosis. Here, cytogenetic analysis unexpectedly demonstrated a 46,XX karyotype, and this can readily be overlooked as a laboratory error by clinicians not well acquainted with de la Chapelle syndrome. This serves to signify the value of heightened awareness in order to enable correct interpretation and, subsequently, genetic testing.

Genotype Confirmation – Limitations of Karyotype

Though karyotyping will pick up numerical and large-scale structural chromosomal abnormalities, it will not pick up small-scale genetic elements like the SRY gene because it is too small to be directly seen on a standard karyotype. Approximately 80–90% of 46,XX testicular DSD are SRY-positive (Yue et al., 2019).Thus, molecular genetic examinations—such as FISH (fluorescence in situ hybridization)and PCR (polymerase chain reaction)—are essential to ensure the existence of SRY and to carry out a definitive categorization of the disease (Yilmaz et al., 2023). This is important due to the fact that positive individuals, such as our patient, are most commonly the result of a de novo recombination incident in the paternal germline and do not need additional gene panel examination (Ferrari et al., 2024). On the other hand, SRY-negative cases may involve other genes involved in sex differentiation (e.g., SOX9, WNT4, RSPO1) and may have familial inheritance patterns, necessitating a more extensive genetic workup. A sporadic meiotic error—a well-documented and non-heritable process (Ferrari et al., 2024)—is corroborated by our patient's SRY-positive status without family history.

In these situations, genetic counseling mainly involves reassuring families that parental factors did not cause the disorder and that the recurrence risk is extremely low (MedlinePlus Genetics, 2023).

SRY-Negative Cases and Genotype–Phenotype Considerations

While not directly addressed by our subject, it is essential to note SRY-negative 46,XX DSD in complete

understanding of the clinical and genetic heterogeneity. Around 10–20% of 46,XX testicular DSD are SRY-negative, and these individuals often have partial virilization or ambiguous external genitalia, in contrast to the overtly male appearance often observed in the majority of SRY-positive instances (Yue et al., 2019). A number of genetic pathways have been hypothesized to account for the mechanism of testis formation without SRY. One involves duplication or overexpression of the SOX9 gene on chromosome 17. SOX9 is a critical downstream target of SRY, and upregulation of this gene is capable of inducing testis formation autonomously. A second pathway includes mutations of genes that would otherwise induce ovarian formation or suppress testis formation, e.g., RSPO1 or WNT4.Loss-of-function mutations in these genes might tip the scale in favor of testis development in XX individuals (Ferrari et al., 2024).

In addition, NR5A1 (SF-1) and DMRT1 mutations have been exceptionally described in certain SRY-negative individuals, incriminating these genes in sex differentiation. Nevertheless, a significant proportion of 46,XX DSD SRY-negative cases remain genetically unexplained, pointing to the involvement of still-unknown genes or to multifactorial polygenic and epigenetic mechanisms (Ferrari et al., 2024).

Phenotypically, SRY-negative individuals are more apt to have features of incomplete virilization, i.e., features such as micropenis, hypospadias, or undescended testes. For example, Li et al. (2014) described a 14-year-old XX male, SRY-negative, with micropenis and perineal hypospadias. SRY-positive individuals, on the other hand, like our patient, tend to undergo complete virilization and are phenotypically male at birth; however, mild genital abnormalities, such as hypospadias or cryptorchidism, may still be present in some (Yilmaz et al., 2023). Our patient's normal male external genitalia and isolated testicular failure at puberty are characteristic of SRY-positive 46,XX testicular DSD.

Management Considerations

46,XX testicular DSD must be managed individually, correcting hormonal, reproductive, and psychosocial health.

Hormone replacement is a cornerstone in SRY-positive patients, particularly once testicular function has declined. While such patients virilize in utero and in childhood, pubertal development tends to be incomplete and necessitates testosterone replacement in adolescence. This is particularly relevant in those with delayed puberty, like our patient. Initiation of testosterone replacement ensures normal pubertal development, prevents additional gynecomastia, and reduces the risk of osteopenia or osteoporosis (Ferrari et al., 2024).

Research indicates that testosterone levels can be approximately normal during early puberty in some SRY-positive XX males, yet the levels decrease considerably by late puberty, resulting in hypergonadotropic hypogonadism (Yilmaz et al., 2023). This pattern is apparently an indication of progressive deterioration of Leydig cell function, and hence the reason our patient lacked any features of pubertal development at age 15. Thus, long-term androgen replacement therapy is usually needed to preserve secondary sexual characteristics, sexual function, and bone density.

Fertility Considerations

From the fertility point of view, almost all 46,XX testicular DSD patients are azoospermic and hence infertile. This is due to the absence of the long arm of the Y chromosome, which holds the azoospermia factor (AZF) regions, which are important for spermatogenesis. In their absence, the spermatogonial stem cells fail to differentiate, and the testes are unable to develop mature sperm (Li et al., 2014).

Our patient's case highlights the importance of attending to infertility promptly and with compassion. Although testicular sperm extraction (TESE) has been tried in a few instances, the results have consistently revealed that there are no retrievable sperm, particularly in individuals who have Sertoli cell-only histology on presentation, as is common in 46,XX DSD (Yilmaz et al., 2023). Interestingly, some SRY-positive XX males are identified upon evaluation for infertility, highlighting the need to consider

this condition in the differential diagnosis of non-obstructive azoospermia (Yue et al., 2019).

Importantly, 46,XX male syndrome is also identified as the second most frequent genetic etiology of azoospermia, following Klinefelter syndrome, which further consolidates the absolute importance of karyotype analysis in the diagnostic workup of male infertility (Thaker et al., 2023).

Importance of Molecular Confirmation

One of the main conclusions from this case highlights the necessity of molecular cytogenetic confirmation of the SRY gene's role. Detection of the SRYgene on an X chromosome confirms the diagnosis of SRY-positive 46,XX testicular DSD and is also useful for distinguishing it from other forms of DSD, including SRY-negative 46,XX DSD or ovotesticular DSD, in which ovarian and testicular tissue may both be present (Yilmaz et al., 2023).

In low-resource environments, a rapid PCR for SRY is extremely convenient. A positive SRY result in a phenotypic male is rapid confirmation of the diagnosis if a 46,XX karyotype is detected. Our application of both PCR and FISH was consistent with best practice guidelines and added insight into the genetic etiology of the condition (Yilmaz et al., 2023).

If the patient was SRY-negative, further testing (e.g., array CGH, gene panels, or next-generation sequencing) would have been warranted to uncover additional underlying genetic etiologies and to evaluate for ovotesticular components (Yue et al., 2019).

Psychosocial and Ethical Aspects

Multidisciplinary support—including input from endocrinologists, urologists, geneticists, and mental health professionals—ensures comprehensive and compassionate care.

The finding of an XX karyotype in a male patient raises psychosocial and ethical concerns that need appropriate management. Open communication and age-related disclosure were at the center of the whole process of care in this instance. The patient was assured that his condition is a variation of human development without influencing his status as a male, which he has always been since he has been alive.

Most individuals with 46,XX DSD have a male gender identity and lead normal lives as men but are faced with infertility and misunderstanding in society (Yue et al., 2019). It is necessary to avoid stigmatizing terminology and make sure that the patient and family understand the diagnosis without confusion or shame.

Multidisciplinary management involving endocrinologists, urologists, geneticists, and mental health professionals ensures comprehensive and compassionate care.

Long-Term Follow-Up

The patient will be kept on long-term follow-up with the endocrinology service. Continued testosterone replacement therapy for life is anticipated to maintain secondary sexual characteristics, bone density, and overall metabolic health. Regular follow-up is also necessary to monitor for potential side effects of androgen therapy, including erythrocytosis, dyslipidemia, and elevation in liver enzymes.

While SRY-positive 46,XX testes with reportedly low rates of gonadal tumors—particularly in the setting of fully descended testes and no dysgenesis—would be expected to be observed regularly, occasional reports exist of mosaicism or of complex chromosomal rearrangements (e.g., X-Y translocations with Turner-like features) that can manifest as short stature or atypical phenotypic presentations (Thaker et al., 2023).

However, our patient presents with the picture of a typical, sporadic SRY translocation, and there has been no indication of mosaicism.

In the future, our patient will continue under long-term follow-up. Ongoing testosterone therapy for life is expected, and surveillance for complications like the metabolic effects of androgen therapy or

osteoporosis in the case of undertreatment is expected. Theoretical risk of gonadal tumors exists in DSD patients. Although the risk of SRY-positive 46,XX testes is not defined—presumably much less than in dysgenetic gonads typical for Swyer syndrome or ovotesticular DSD—it should be monitored. There have been several reports in the literature of mosaicism or atypical chromosomal rearrangements in 46,XX males, such as an X-Y translocation with mosaic Turner syndrome causing short stature(Thaker et al., 2023). The clinical presentation of our patient, however, is in accord with the classic sporadic SRY translocation without mosaicism.

Conclusion

The article presents the case of a 15-year-old male with a 46,XX testicular DSD de la Chapelle syndrome. The presented case underscores the extreme importance of considering DSDs in the differential diagnosis of adolescents with hypergonadotropic hypogonadism and the importance of exhaustive genetic workup.

In most cases, ours included, SRY gene translocation to the X chromosome during meiosis in the father is the mechanism—resulting in a 46,XX individual with testicular differentiation and male phenotype. The diagnosis was established through a combination of karyotyping and molecular analysis, enabling appropriate testosterone replacement and psychosocial management.

This case underscores several key lessons relevant to clinical practice:

- **First Diagnostic Test:** In male patients who have delayed puberty or idiopathic infertility, karyotype analysis must be done to exclude sex chromosome abnormalities. Even in the absence of ambiguous genitalia, an unexpected 46,XX result may represent sex reversal, which warrants additional workup (Thaker et al., 2023).
- **Molecular Confirmation:** Conventional cytogenetic analyses are unable to identify small genes like SRY. Hence, it becomes necessary to use confirmatory molecular methods—like PCR or FISH—to establish the genetic etiology of 46,XX DSD and to distinguish between SRY-positive and SRY-negative cases (Yilmaz et al., 2023; Yue et al., 2019). This differentiation is crucial for genetic counseling and decides on the need for additional gene analysis.
- **Holistic Management:** Multidisciplinary management is important. Early treatment with testosterone is essential for best pubertal development and long-term metabolic and skeletal health (Ferrari et al., 2024). Because of the irreversibility of infertility due to the absence of Y-linked AZF regions, early fertility counseling and psychologic support are necessary. Long-term risk screening for metabolic complications of hormone therapy and the potential rare risk of gonadal tumors is also necessary in patients.
- **Genetic Counseling:** Family members should be informed that SRY-positive 46,XX DSD is typically a sporadic, non-inherited disorder due to an error during meiosis. Affected individuals cannot transmit the condition due to infertility, enabling reassurance regarding recurrence risk (Ferrari et al., 2024; MedlinePlus Genetics, 2023). In patients who are SRY-negative, counseling may involve discussion of gene-specific inheritance if pathogenic variants are identified. In conclusion, albeit unusual, 46,XX testicular DSD should be included in the differential diagnosis of azoospermia and primary hypogonadism. This, together with a concordance of traditional cytogenetics and contemporary molecular diagnostics, allows precise categorization and individualized management at an early stage. Ultimately, a multidisciplinary approach incorporating medical, psychosocial, and genetic care optimizes developmental and psychosocial outcomes for the affected.

References

1. Thaker, N., Parihar, P., Dhande, R., Raj, N., & Unadkat, B. (2023). A case of de la Chapelle syndrome. *Cureus, 15*(11), e48150. https://doi.org/10.7759/cureus.48150
2. MedlinePlus Genetics. (2023). *46,XX testicular difference of sex development*. Retrieved from https://medlineplus.gov/genetics/condition/46xx-testicular-difference-of-sex-development/
3. Yue, F., Zhang, H., Xi, Q., Jiang, Y., Li, L., Liu, R., & Wang, R. (2019). Molecular cytogenetic analysis and genetic counseling: A case report of eight 46,XX males and a literature review. *Molecular Cytogenetics, 12*(1), 44. https://doi.org/10.1186/s13039-019-0459-4
4. Li, T., Wu, Q., Zhang, C., Chen, L., Zheng, J., & Pan, C. (2014). 46,XX testicular disorder of sexual development with SRY-negative caused by some unidentified mechanisms: A case report and review of the literature. *BMC Urology, 14*(1), 104. https://doi.org/10.1186/1471-2490-14-104
5. Ferrari, M. T. M., Silva, E. S. N., Nishi, M. Y., Domenice, S., & Mendonca, B. B. (2024). Testicular differentiation in 46,XX DSD: An overview of genetic causes. *Frontiers in Endocrinology, 15*, 1385901. https://doi.org/10.3389/fendo.2024.1385901
6. Yilmaz, O., Özçelik, T., & Bağcı, H. (2023). Clinical, molecular and cytogenetic analysis of SRY-positive 46,XX testicular DSD: Report of two cases. *Turkish Journal of Endocrinology and Metabolism, 27*(3), 189-194. https://doi.org/10.25179/tjem.2023-96412