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Case Report

46, XX Ovotestis with Negative Sry, Exceptional Variant of Disorders of Sexual Differentiation: About a Case

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Abstract

Disorders of sexual differentiation (DSD) encompass a range of clinical conditions that diverge from the traditional definitions of male or female at birth. The development of sexual characteristics can be influenced by genetic, gonadal, or phenotypic factors, or a combination thereof. The incidence of DSD is approximately 1 in 400 births. The classification of these disorders, understanding the genetic and hormonal anomalies, and formulating a comprehensive management plan represent significant challenges for clinicians. Some DSDs are extremely rare, with limited data available on their impact on fertility and the potential for genomic interventions. This article aims to elucidate the complexities of the diagnostic process, underscore the rarity of certain DSD cases, and highlight the challenges involved in their management.

Keywords: *DSD; SRY; 46 Ovotestis*

Introduction

Disorders of Sexual Differentiation (DSD) are clinical conditions that deviate from the conventional definitions of male or female at birth. These anomalies can be attributed to genetic, gonadal, or phenotypic factors. The prevalence of DSD is approximately 1 in 400 births. The process of understanding, classifying, and managing DSD presents significant challenges. There is a paucity of data regarding fertility and genomic approaches in these conditions. This study examines a case of 46, XX ovotestis lacking the SRY gene, encompassing clinical, laboratory, and fertility findings. Early intervention is crucial to preserving ovarian function.

Observation

A 55-day-old infant presented with an anomaly of sexual differentiation. The family history revealed a non-consanguineous marriage, with no similar cases reported. The pregnancy was uneventful, and the infant adapted well to extra-uterine life. Born at 38 weeks of gestation, the infant had a birth weight of 3600 grams. Upon admission, clinical examination indicated a tonic and reactive infant in good general condition. Vital signs were as follows: temperature at 37.5°C, heart rate at 110 beats/min, respiratory rate at 41/min, arterial oxygen saturation at 98% in ambient air, capillary refill time (CRT) less than 3 seconds, weight at 5 kilograms (+1 standard deviation), and height at 63 centimeters (+1 standard deviation). Examination of the external genitalia revealed an indeterminate phenotype, characterized by a median genital bud measuring 25 mm at its base, with a single orifice of a narrow urogenital sinus. The partially fused genital

pads exhibited a transverse stripe pattern, suggesting a scrotal appearance without palpable gonads. The findings were consistent with Prader stage IV (Figure 1).

Figure 1: *Picture showing anomalies of sexual differentiation Prader IV.*

The remainder of the clinical examination revealed no remarkable findings, and the patient's morphotype appeared normal. Abdominal ultrasound indicated the presence of bilateral cryptorchidism in the inguinal region, with no visible uterine cavity. Genitography identified a male-type urethra. An abdomino-pelvic MRI demonstrated a male-type genital bud with a penis containing a cavernous body and bilateral cryptorchidism in the inguinal region, with no detectable ovarian or uterine structures.

Laboratory findings

The biological screening revealed the following: cortisolemia at 1.7 ng/mL; 11-deoxycortisol at 1.3 ng/mL; 11-deoxycortisone at < 10 ng/mL; testosterone (T) at 2.77 nmol/L; anti-Müllerian hormone (AMH) at 19.1 ng/ml; dehydroepiandrosterone (DHEA-S) at 0.1 µg/dL; progesterone at 0.56 µg/L; 17α-hydroxyprogesterone (17OHP) at 1.4 ng/mL; δ4-androstenedione (δ4AS) at 1.15 ng/mL; follicle-stimulating hormone (FSH) at 3.53 mIU/mL; and luteinizing hormone (LH) at 5.99 mIU/L.

The constitutional karyotype was determined to be 46, XY, with a negative result for the SRY locus. Exome sequencing is currently in progress. Histological examination of gonadal biopsies indicated an ovotestis on the right side and a testis on the left side (Figure 2-4).

Discussion

Disorders of sexual differentiation (DSD) lead to incongruities between gonadal and phenotypic sex. These conditions can be categorized based on anomalies related to X chromosomes, genetic determination, and the development of ducts and genitalia. Such anomalies may manifest as conditions like androgen insensitivity syndrome, Mayer-Rokitansky-Küster-Hauser syndrome, and true hermaphroditism [1].

The SRY gene is responsible for the development of testicular embryonic tissue and male physical characteristics. Mutations in the SRY gene can result in disorders of sexual development. In the 46, XX ovotestis phenotype, an excess of SRY genes can lead to differentiation anomalies and the manifestation of some male phenotypic characteristics. However, the absence of a Y chromosome along with anti-

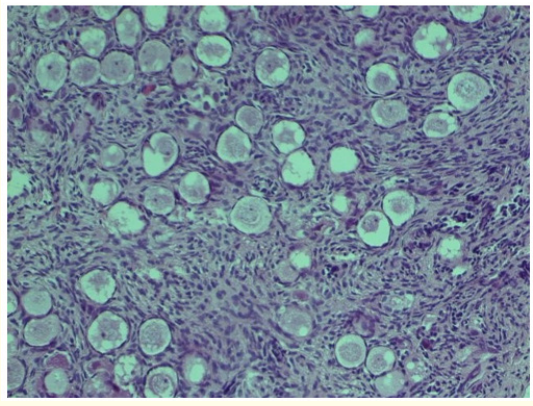

Figure 2: *Biopsy on the right gonad shows ovarian tissue containing several primordial ovarian follicles.*

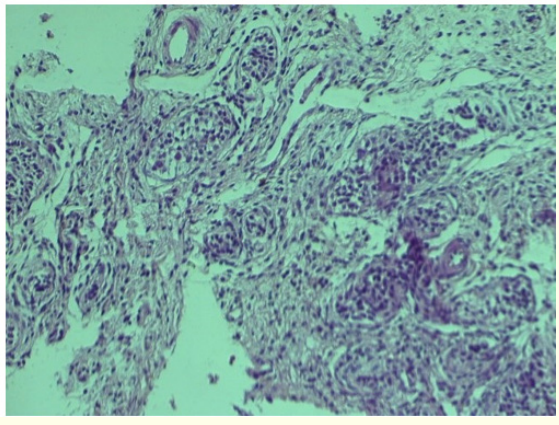

Figure 3: *Biopsy of the right gonad shows testicular tissue, breech of seminiferous tubules edged by Sertoli cells.*

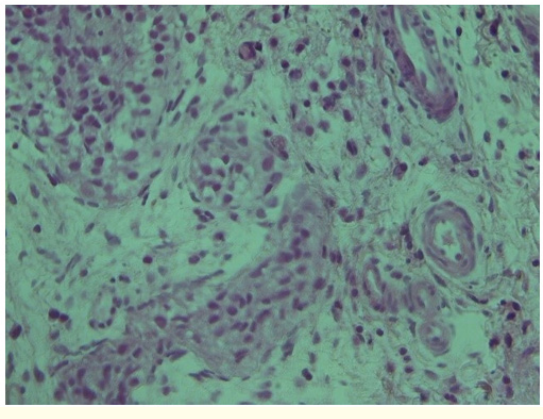

Figure 4: *Biopsy performed on the left gonad showing testicular tissue made of atrophic seminiferous tubules, absence of Leydig cells. There was no stool loss syndrome or adrenal insufficiency.*

Müllerian hormone results in a female phenotype. Some individuals with a 46, XX karyotype may develop secondary sexual characteristics similar to those observed in androgen insensitivity syndrome. Genetic studies suggest that certain SRY proteins may compensate for functional deletions [2].

Anomalies of sexual differentiation can present in various phenotypes, such as 46, XX ovotestis without SRY. This can result in diverse clinical presentations, including ovotesticular disorder, pure gonadal dysgenesis, or a typical male or female phenotype. Physical examination of individuals raised as females often reveals hypergonadotropic hypogonadism. Diagnosis is challenging due to overlapping signs and symptoms. Sex differences are determined by chromosomes, gonads, and hormones, leading to anatomical and physiological variations. The condition of the uterus and fallopian tubes may indicate underlying issues. Patients with a Y chromosome exhibit variable physical presentations and fertility. Ovotesticular DSD patients exhibit slow progression. Thorough evaluation and examination are necessary due to physical variations. Gender assignment should be made after counseling. There is limited data on patient management outcomes, and surgical findings do not always correlate with karyotype [2].

At least 90% of sexual anomalies are identified through physical examination. A comprehensive examination is essential to detect subtle variations and establish a differential diagnosis. Careful analysis and comparison of patient records are crucial to avoid diagnostic errors. The external appearance of females with 46, XX gonadal dysgenesis does not provide useful diagnostic information. Diagnosing 46, XX ovotestis is typically performed clinically for subjects over one year old, while younger subjects may be missed due to the underdevelopment of typical sex phenotypes. Diagnosis involves clinical assessment and laboratory tests. Phenotypic evaluation is complex due to overlapping patterns with other conditions [3].

Early and accurate diagnosis is critical in managing DSD patients, as it improves sex assignment decisions, avoids inappropriate assignments, and prevents sex identity issues. The diagnostic process should involve a multidisciplinary team, including pediatric endocrinologists, surgeons, radiologists, and adult DSD specialists. These consultations are essential, particularly for late diagnoses. Laboratory work-up is important for identifying anomalies of sexual differentiation, aiding in diagnosis, and predicting outcomes. Some tests guide further investigation, while others support clinical evaluation. Genetic evaluation is necessary in all cases, with blood samples collected pre- and postnatally to test for endocrinological and genetic markers [4].

A prenatal amniotic fluid karyotype is necessary for investigating fetal ultrasound anomalies. Ambiguous cases require a genital examination and leukocyte karyotype. Hormonal profiles, biomarkers, and 500+ metaphase spreads should be considered. Immunohistochemistry, skin biopsies, and genetic testing may be required. Krüppel-like factor proteins are potential biomarkers. FISH can test for chromosomal abnormalities in amniocytes. Further genetic testing is necessary in the absence of SRY positivity in 46, XX sex reversal cases [5].

Ultrasound is preferred for evaluating gonads in patients with sexual differentiation issues. Factors complicating detection include patient age, remission, and abnormalities. MRI provides better contrast and multiplanar imaging for assessing structures. Both ultrasound and MRI confirm gonadal presence and determine anatomy. Monitoring at birth, 3 months, and 6 months, followed by pelvic ultrasound and MRI, is recommended [6].

A reliable diagnosis of ambiguous genitalia cannot be made by visual inspection and clinical examination alone. Additional imaging procedures are required to view the gonadal pathway and internal genital anatomy. Ultrasound is the primary diagnostic tool for identifying these structures. The aim of ultrasound and MRI is to identify various anatomical structures, as the hormonal function of the gonads plays a determining role in the phenotype and degree of genital virilization.

An interdisciplinary approach is required for managing sexual differentiation anomalies, involving endocrinology, clinical genetics, gynecology, and pediatric endocrine surgery. Treatment should be tailored to individual needs, including psychological support. Success is measured by overall well-being, rather than cosmetic or fertility outcomes. Follow-up with a doctor or psychologist is recommended [7].

Possible interventions: For male patients, non-treatment may be considered; however, surgical removal of anomalous gonads, genital surgery, and gonadal surgery with fertility preservation are potential interventions. Biopsies may be warranted for non-malignant conditions during puberty and potential malignancies. For cases of indeterminacy, discussions with family members and ethical authorities are imperative. Detecting neoplasia is crucial, and interventions should align with the patient's preferences. Gonadal removal is strongly recommended, while continuous biopsies are unnecessary. Normal biopsy results suggest a reduced risk of malignancy, while abnormal biopsies indicate localized malignancy. Repeated biopsies have minimal consequences and should be discussed with patients [8]. Surgical intervention is essential for specific sexual differentiation anomalies. Decisions should prioritize patient harm and the necessity of intervention. The timing and type of surgery vary based on the specific abnormality. Pediatric surgeries typically focus on the external genitalia, and potential complications should be discussed with the family beforehand. Some surgeries may involve dilation of the neovagina for sexual intercourse or pregnancy [9].

Conclusion

Anomalies of sexual differentiation are generally rare; however, their incidence increases in postnatal hematological analyses. Genetic abnormalities and developmental processes that do not correspond complicate the management of sexual differentiation disorders. The correlation between genotypes and phenotypic appearance is complex in these conditions.

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