Quiz

Ovotesticular disorder of sex development presenting in adolescence with amenorrhea and clitoromegaly-what is your diagnosis?

An adolescent girl, aged 12 years presented to the gynecology out-patient department, with concerns of absent breast development and lack of menstruation. Her parents reported a gradual deepening of the voice and progressive enlargement of the clitoris over the past two years. There was no history of cyclic abdominal pain, galactorrhoea, visual disturbances, or chronic illness. There was no history of exogenous androgen exposure or anabolic steroid use. The patient's medical history was unremarkable. There was no history of neonatal ambiguity, salt-wasting crises, or similar conditions in family members. On general examination, the patient appeared tall and thin with an arm span exceeding height. She had poorly developed breasts (Tanner stage I) and minimal axillary and pubic hair (Tanner stage I) (Figure 1). No facial acne or hirsutism was noted. The external genitalia were of female phenotype. On local examination, the vaginal opening was not appreciable, and the uterus was not palpable, clinically. The urinary meatus was normal in position. The clitoris measured 2.5 cm in length and 1.3 cm in width, consistent with clitoromegaly (Figure 2). No dysmorphic features such as webbed neck, shield chest, or low hairline were evident. Systemic examination was otherwise normal. Baseline investigations, including complete blood count, liver, renal, and thyroid function tests, were within normal limits. Endocrine evaluation revealed elevated total serum testosterone of 468 ng/dL (normal: 15–70 ng/dL), low estradiol of 10 pg/mL (normal: 30–400 pg/mL), and reduced anti-Müllerian hormone of 0.60 ng/mL (normal: 1.0–10 ng/mL), suggesting impaired ovarian function and androgen excess. Gonadotropins were elevated, with luteinizing hormone (LH) 13.87 IU/L (normal: 1.9–12.5 IU/L) and follicle-stimulating hormone (FSH) 37.57 IU/L (normal: 2.5–10.2 IU/L), consistent with hypergonadotropic hypogonadism. Dehydroepiandrosterone (DHEA) was within normal limits at 5.60 μg/dL (normal: 1.7–7.0 μg/dL), and 17-hydroxyprogesterone (17-OHP) was low at 0.10 ng/mL (normal: 0.2–1.0 ng/mL), effectively excluding congenital adrenal hyperplasia (CAH). Peripheral blood karyotype demonstrated a 46,XY chromosomal pattern, supporting the diagnosis of ovo-testicular disorder with gonadal dysgenesis. Pelvic ultrasonography showed a small uterus with poorly visualized gonads. Magnetic resonance imaging (MRI) of the pelvis demonstrated a left ovary measuring 1.9×1.1 cm along with a uterine remnant, while the right ovary was not visualized. Two testicular structures were identified, with the right located in the peri vesical region measuring 1.0×1.2 cm and the left in the inguinal canal measuring 0.5×1.6 cm (Figure 3). Clitoromegaly with underlying cavernous tissue was noted, whereas the remainder of the pelvic organs appeared normal.

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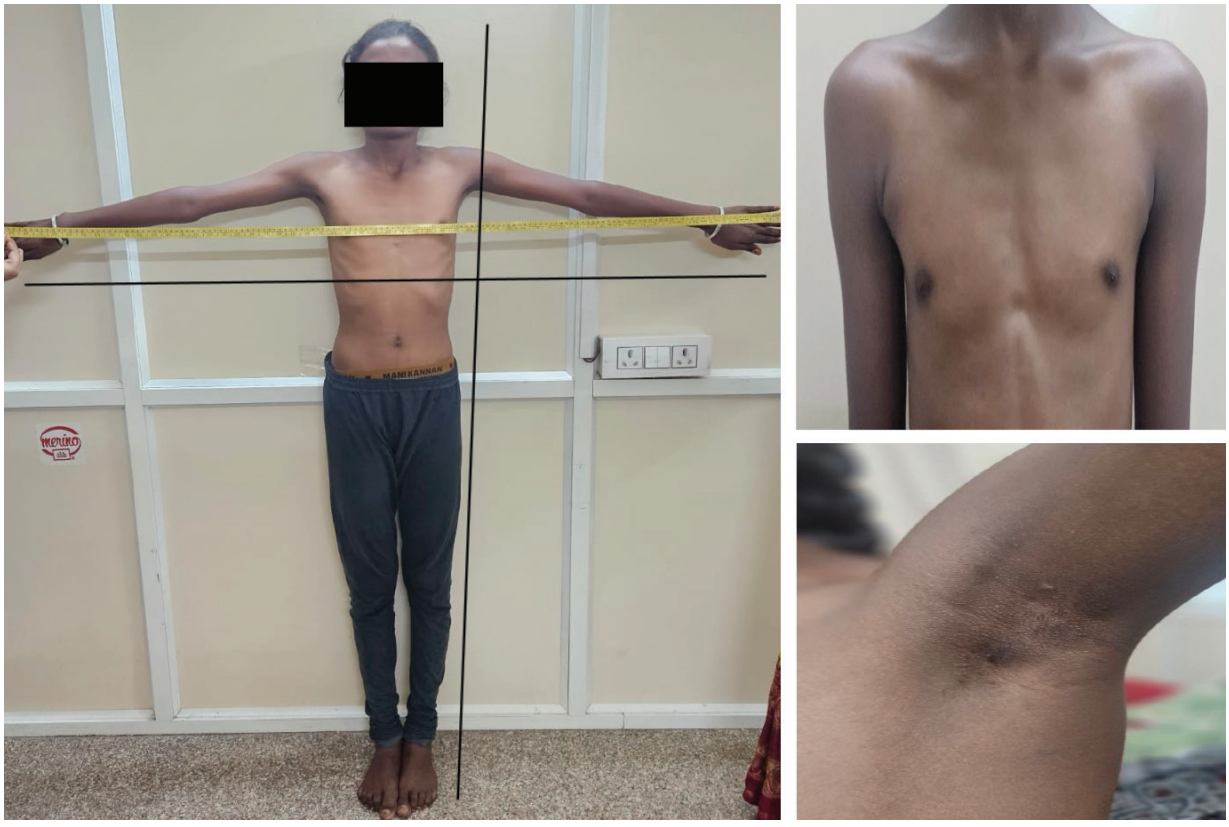

Figure 1. Clinical photograph showing delayed secondary sexual characteristics. The image demonstrates poorly developed breasts, minimal axillary hair, and an arm span greater than height

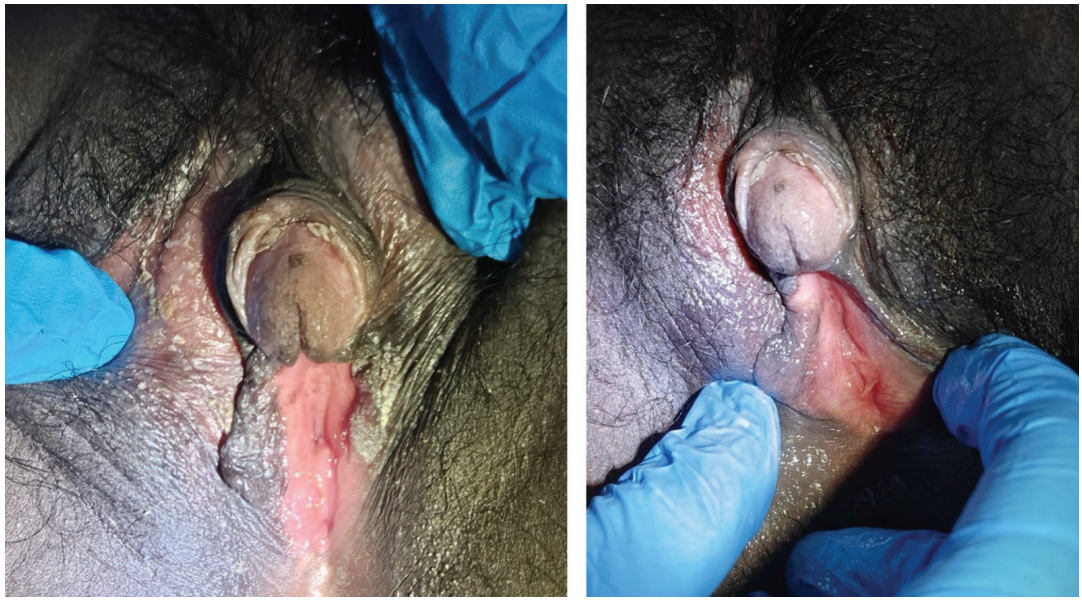

Figure 2. Clinical photograph illustrating clitoromegaly. The image shows enlargement of the clitoral body and glans beyond normal anatomical limits, consistent with clitoromegaly. Note the preservation of labia minora and majora morphology

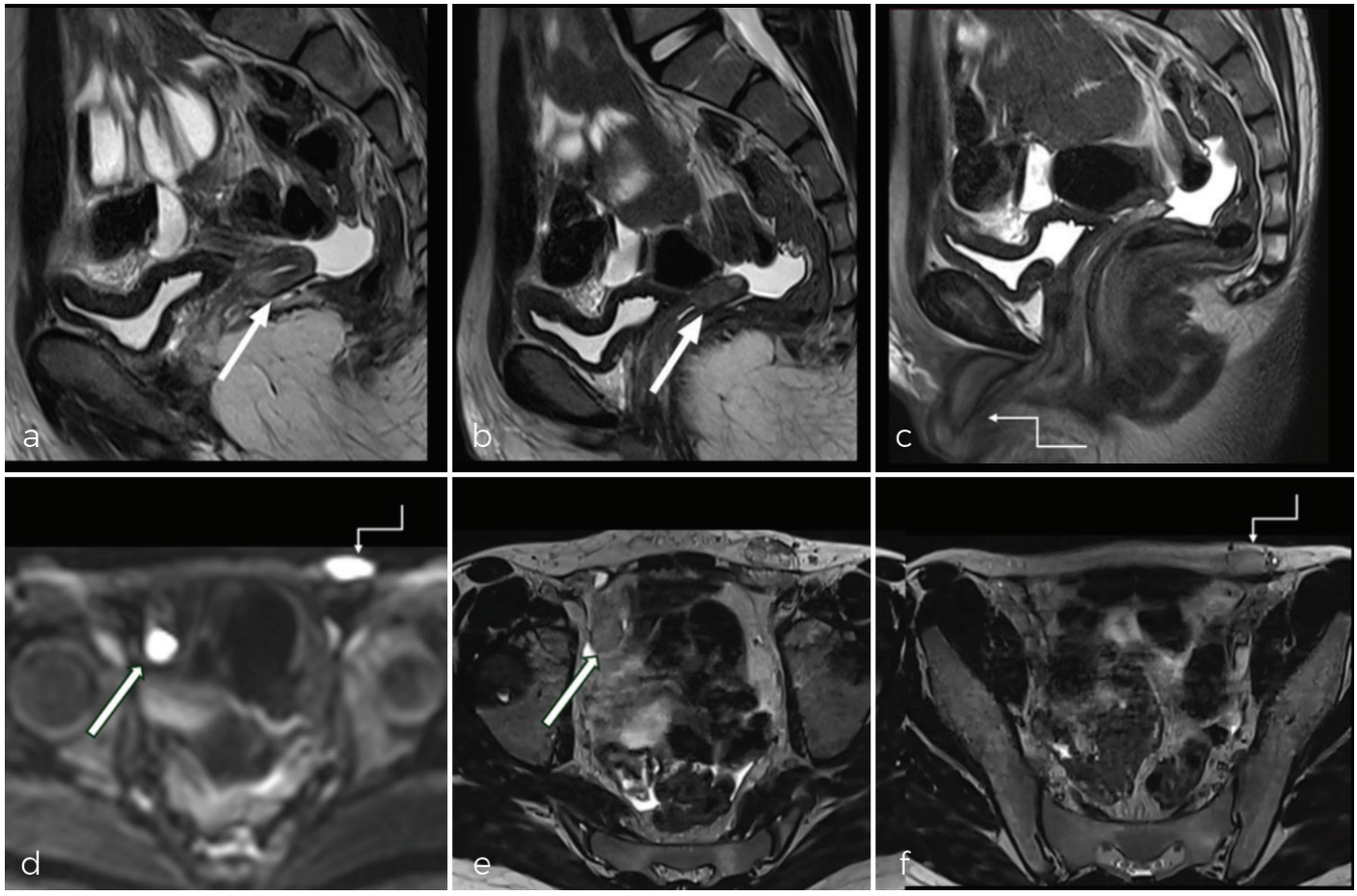

Figure 3. Axial (a) diffusion-weighted imaging and T2 space sequence (b, c) shows T2 homogeneously hyperintense gonads with diffusion restriction in the right side of the pelvis (arrow) and left inguinal region (bent arrow) with no follicles. Sagittal T2 images show a hypoplastic retroverted uterus (arrow in d, e) measuring app. 4 cm x 2.7 cm x 1.3 cm, showing endomyometrial differentiation. Sagittal T2 image (f) shows an enlarged clitoris (bent arrow)

Answer

The diagnosis of 46,XY ovotesticular disorders of sex development (DSD) was made based on a combination of clinical, hormonal, and cytogenetic findings. The patient presented with virilization (clitoromegaly, hoarse voice), delayed puberty, and absent secondary sexual characteristics. Hormonal evaluation showed elevated testosterone with low estradiol and hypergonadotropic hypogonadism. Cytogenetic analysis confirmed a 46,XY karyotype, and imaging suggested the presence of both ovarian and testicular tissue, consistent with ovotesticular DSD with gonadal dysgenesis. The patient was managed with a multidisciplinary approach involving endocrinology, gynecology, and psychiatry. Given her age and ongoing pubertal development, hormone replacement therapy (estrogen) was initiated to induce secondary sexual characteristics, promote bone mineralization, and support psychosocial development. Psychosocial support and genetic counselling were provided, and long-term follow-up was planned to monitor pubertal progression and optimize reproductive health. Definitive gonadal evaluation via laparoscopy and biopsy is planned at 18 years to confirm the presence of ovotesticular tissue and assess malignancy risk, allowing for individualized surgical management. Bone health was supported with calcium and vitamin D supplementation and monitored via DEXA scans. Genital reconstruction (clitoroplasty ± vaginoplasty) is planned after pubertal induction and in consultation with the patient. The patient and family were counselled regarding the nature of the disorder, potential fertility implications, and the importance of long-term follow-up, including monitoring for gonadal tumors and optimizing hormonal therapy. The patient was enrolled in regular follow-up for monitoring of pubertal development and psychological well-being.

46,XY ovotesticular DSD, is among the rarest forms of sexual developmental disorders (1-3). Unlike the more common

46,XX ovotesticular DSD, which often results from *SRY* translocation, the 46,XY form usually reflects partial testicular dysgenesis or mutations affecting testis-determining genes, such as *SOX9*, *WT1*, or *SF1* (4). The coexistence of ovarian and testicular tissue in the same individual represents incomplete differentiation of bipotential gonads (5). In 46,XY individuals, defective expression of testis-determining genes leads to partial or asymmetric gonadal differentiation, producing an ovotestis on one side and a dysgenetic gonad on the other. The resulting endocrine imbalance causes ambiguous genitalia or, as in this case, delayed puberty and virilization. Residual Leydig cells produce androgens, explaining the hoarse voice and clitoromegaly, while insufficient estrogen production results in absent breast development and delayed skeletal maturation (6). In the present case, reduced AMH indicated impaired Sertoli cell function. Normal DHEA and low 17-OHP excluded CAH.

The patient demonstrated hypergonadotropic hypogonadism, with high LH/FSH and low estradiol, indicating gonadal failure. Testosterone was elevated but insufficient for full virilization, explaining the coexistence of partial androgen effects (clitoromegaly, hoarse voice) and hypogonadal features (poor breast development, sparse axillary hair, increased arm span). MRI showed discordant gonadal anatomy: a left ovary with a uterine remnant, an absent right ovary, and bilateral dysgenetic testes. The risk of gonadal malignancy is higher in patients with Y chromosome material, underscoring the need for biopsy or gonadectomy. Molecular studies (*SRY*, *SOX9*, *NR5A1*, *WT1*, *DMRT1*) are recommended to clarify the etiology.

Patients with 46,XY ovotesticular DSD are at increased risk of gonadal malignancy, particularly gonadoblastoma and dysgerminoma, due to the presence of Y chromosome material and dysgenetic gonads (7). Therefore, prophylactic gonadectomy is generally recommended on the side of dysgenetic or testicular tissue. However, in this patient histopathological evaluation was deferred until late adolescence. This approach is clinically acceptable, as early invasive procedures can interfere with natural pubertal development, especially if hormone replacement therapy is initiated to induce secondary sexual characteristics. Planned laparoscopy and targeted biopsy at 18 years allow for a more mature and accurate assessment of gonadal tissue, aiding individualized surgical planning, including malignancy risk stratification and potential fertility preservation. Close clinical monitoring, imaging, and hormonal follow-up in the interim ensure patient safety, consistent with current recommendations from the Chicago Consensus and ESPE guidelines for DSD management (8).

Malignancy risk in dysgenetic gonads is heterogeneous and depends on the specific DSD diagnosis, presence of Y-chromosome material, and degree of gonadal dysgenesis. Individuals with Y-bearing dysgenetic gonads are at substantially increased risk for gonadoblastoma and other germ cell tumors compared with 46,XX ovotesticular DSD, but reported risk estimates vary between studies. Contemporary reviews place the overall tumor risk in dysgenetic gonads broadly from low single-digit percentages in some ovotesticular series to much higher rates reported in cohorts of 46,XY gonadal dysgenesis or mixed gonadal dysgenesis (range quoted across series ~3% up to 25% or more), reflecting heterogeneity of case mix and diagnostic criteria (9,10). Guidance from multidisciplinary DSD consensus documents and contemporary cohort studies supports individualized timing of gonadectomy. For high-risk diagnoses with frank dysgenetic testicular tissue and Y-material (for example, classic 46,XY complete gonadal dysgenesis), early prophylactic gonadectomy is generally recommended because of the higher malignancy risk. For conditions with lower and more uncertain risk, such as some ovotesticular presentations, delaying gonadectomy until late adolescence (commonly around age 16–18 years) may be reasonable if there is careful clinical and imaging surveillance, because delay permits pubertal induction, assessment of pubertal progression, and time for shared decision-making about gender, fertility preservation and psychosocial support. This approach is supported by cohort data and expert consensus placing the optimal timing for prophylactic gonadectomy in many Y-bearing phenotypic females at around 16–18 years, with earlier surgery when imaging or clinical features are suspicious.

Psychosocial counselling forms a cornerstone of management, addressing gender identity, fertility expectations, and body image. Hormonal therapy should be individualized, balancing feminizing and metabolic needs while ensuring adequate bone mineralization. Table 1 presents the close differential diagnoses, highlighting conditions with overlapping clinical, hormonal, and imaging features that should be considered to guide accurate evaluation and management. With timely diagnosis and appropriate management, patients can achieve satisfactory secondary sexual development and psychosocial adjustment. Lifelong follow-up is essential to monitor for neoplastic transformation, bone health, and hormonal balance (11,12).

46,XY ovotesticular DSD with gonadal dysgenesis is an exceedingly rare but clinically significant cause of delayed puberty and virilization in phenotypic females. A combination of detailed clinical evaluation, hormonal profiling, imaging, and histopathological confirmation is essential for accurate diagnosis. Early gonadectomy of dysgenetic tissue, hormone replacement therapy, and psychological support form the cornerstone of management. Early recognition and

Table 1. Close differentials of 46,XY ovo testicular DSD (2,5,8,11)

Disorder	Karyotype	Gonads	Internal structures	External genitalia	Hormone profile	Key differentiating features
Ovotesticular DSD	46,XY (rare)	Ovotestis ± ovary/testis	Uterine remnant ± Wolffian derivatives	Ambiguous; clitoromegaly/ undervirilized male	Variable T/E2; ↑LH/FSH	Both ovarian and testicular tissue (histology)
Mixed gonadal dysgenesis	45,X/46,XY mosaic	Dysgenetic testis + streak gonad	Oftena hemi-uterus, Müllerian remnants	Ambiguous, asymmetric	↑FSH/LH, low sex steroids	Asymmetric gonads; mosaicism
46,XY complete gonadal dysgenesis (Swyer)	46,XY	Bilateral streak gonads	Normal uterus and tubes	Normal female	Very low T/E2; ↑↑FSH/LH	No testicular tissue; pure streak gonads
Partial androgen insensitivity syndrome	46,XY	Testes (inguinal/ abdominal)	Absent uterus (AMH active)	Under virilized male/ambiguous	High T; normal/↑LH	Testes only, uterus absent

DSD: Disorders of sex development, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, AMH: Anti-Müllerian hormone

multidisciplinary management are crucial for guiding gender assignment, monitoring malignancy risk, and ensuring psychosocial support.

Ethics

Informed Consent: *Written informed consent for publication, including images and clinical details, was obtained from the patient and her legal guardians.*

Footnotes

Conflict of Interest: *No conflict of interest is declared by the authors.*

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