Case Report

From Ambiguity to Identity: A Case Report of XY Disorders of Sexual Development with Suspected Mayer-Rokitansky-Küster-Hauser and Androgen Insensitivity Syndrome

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ABSTRACT

Background: Disorders of Sex Development (DSD) encompass a range of congenital conditions involving discordance between chromosomal, gonadal, and phenotypic sex. One complex presentation involves phenotypically female individuals with a 46, XY karyotype, raising differential diagnoses such as Complete Androgen Insensitivity Syndrome (CAIS), Swyer syndrome, and Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome.

Case Presentation: A 22-year-old individual raised as female presented with primary amenorrhea. Physical examination showed Tanner stage 3 breast and pubic hair, absent vaginal introitus, and no palpable uterus. Pelvic MRI revealed agenesis of the uterus, cervix, and upper vagina, with bilateral intrapelvic gonads initially resembling ovaries. Hormonal tests showed elevated testosterone (88.67 nmol/L), high LH (30.8 mIU/mL), and low-normal estradiol (23.6 pg/mL). Karyotyping confirmed 46, XY. Despite initial imaging suggesting MRKH, the hormonal and chromosomal findings supported CAIS. Multidisciplinary assessments, including psychiatry and forensic medicine, affirmed a consistent female gender identity. The patient declined surgical intervention and was referred for long-term follow-up.

Conclusion: This case highlights the importance of integrating clinical, hormonal, radiologic, and genetic data to distinguish among 46, XY DSD etiologies. Accurate diagnosis is essential not only for guiding medical management but also for supporting gender identity and psychological well-being. In CAIS, gender-affirming, individualized care and long-term support are crucial for optimal health outcomes.

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Introduction

Disorders of Sex Development (DSD) are congenital conditions with atypical chromosomal, gonadal, or anatomical sex development, resulting in a mismatch between genetic and phenotypic sex [1]. They challenge binary sex classification and have significant clinical, psychological, ethical, and legal implications. Presentations range from ambiguous genitalia at birth to subtle findings in puberty or adulthood, such as primary amenorrhea or infertility. DSD encompasses over 60 categories caused by genetic mutations, hormonal imbalances, or receptor defects [2]. Among these, 46, XY disorders are particularly complex due to variations in androgen production and receptor sensitivity. Androgen Insensitivity Syndrome (AIS), resulting from androgen receptor (AR) gene mutations, leads to partial or complete androgen resistance despite normal or elevated testosterone. In Complete AIS (CAIS), individuals present with female external genitalia, absent Müllerian structures due to anti-Müllerian hormone, and lack masculinization [3]. In contrast, Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, typically in 46, XX individuals, involves agenesis or hypoplasia of the uterus and upper vagina with normal ovaries [4]. Overlapping features may cause diagnostic challenges when imaging or hormonal results are inconclusive.

Diagnosing DSD requires a stepwise approach, including detailed history, physical examination, pelvic ultrasound, MRI, hormonal assays (LH, FSH, testosterone, estradiol, AMH), and karyotyping, with gene sequencing or gonadal biopsy in selected cases.[3] Chromosomal data alone are insufficient, requiring integration with phenotypic and gonadal findings. For instance, a phenotypic female with a 46, XY karyotype and intra-abdominal gonads may have CAIS, gonadal dysgenesis, or rare ovotesticular DSD. Early, accurate diagnosis is crucial for management, malignancy risk assessment, and gender assignment [1].

This case report describes a 22-year-old with a 46, XY karyotype, primary amenorrhea, absent uterus and vagina, and female phenotypic features. The main diagnostic challenge is distinguishing AIS from atypical MRKH, especially when imaging shows follicular-like gonads and hormonal results are incongruent. This case illustrates the nuanced diagnostic process, the importance of affirming gender identity, and the value of multidisciplinary, patient-centered care. It also underscores the intersection of clinical, ethical, and psychosocial considerations in managing complex DSD in adulthood.

Materials and Methods

Study Design and Ethical Considerations

This retrospective clinical analysis is based on a single-patient observation, with data obtained from medical records at Dr. Soetomo General Hospital, Surabaya, Indonesia, between August 2023 and February 2024. The patient and family provided oral informed consent for evaluation, treatment, and anonymous publication.

Initial Clinical Evaluation

The patient presented to the urogynecology outpatient clinic with lifelong amenorrhea. Initial evaluation included a detailed gynecological history (menarche status, sexual development, family history) and physical examination, assessing secondary sexual characteristics (Tanner staging), external genitalia (Prader scale), breast development, pubic hair distribution, and presence of Adam's apple.

Radiological Investigations

Internal genital structures were evaluated using transabdominal ultrasound (August 1, 2023) to assess the uterus and ovaries, and abdominal–pelvic MRI (October 4, 2023) with T1- and T2-weighted axial and coronal sequences to examine Müllerian structures and localize gonads.

Hormonal and Genetic Assessment

Endocrine evaluation was carried out using standard immunoassay techniques. Blood samples were taken to assess serum levels of Luteinizing Hormone (LH), Estradiol (E2), and Testosterone (TST).

Results

Patient History and Presenting Complaint

A 22-year-old individual, assigned and raised female, presented to the Urogynecology Clinic of Dr. Soetomo General Hospital in August 2023 with primary amenorrhea. Menstruation had never occurred, and initial treatment at age 16 by a local midwife with oral medications for two months was unsuccessful. From 2018 to 2021, the patient intermittently used "menstruation-inducing drugs" from midwives and pharmacies without effect, then discontinued care until May 2023. In June 2023, ahead of a planned marriage in April 2024, an evaluation at RS Prima Husada suggested vaginal agenesis, prompting referral to Dr. Soetomo Hospital for further assessment.

Table 1. Hormonal Profile – December 12, 2023

Hormone	Value	Normal Range (Female)	Interpretation
Luteinizing Hormone (LH)	30.8 mIU/mL	1.9 – 12.5 mIU/mL	Elevated (androgen resistance)
Estradiol	23.6 pg/mL	15 – 350 pg/mL	Normal range
Testosterone	88.67 nmol/L	0.4 – 2.4 nmol/L	Highly elevated

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Physical Examination

Initial examination showed Tanner stage 3 breast and pubic hair development (female-pattern distribution), normal labia majora/minora, mild clitoral hypertrophy, absent vaginal introitus, Prader score 3/5, and no palpable uterus or cervix. No virilization signs were noted. Anthropometric data (February 2024): height 170 cm, weight 82 kg, BMI 28.3 kg/m².

Radiological Findings

1. **Ultrasound (August 1, 2023):** No uterus or cervix visualized; both intrapelvic gonads resembled ovaries with multiple cysts.

2. **MRI Abdomen & Pelvis (October 4, 2023):** Absence of uterus, cervix, and upper vagina; midline triangular soft tissue suggestive of residual Müllerian or fibrous tissue. Right gonad measured 1.88 × 1.02 × 0.63 cm, left gonad 1.37 × 1.60 × 0.75 cm, both containing multiple follicular-like cysts.

3. **Interpretation:** Findings favored Müllerian agenesis (MRKH Type A), though cystic morphology suggested possible functional ovarian tissue.

Hormonal findings attached on Table 1—elevated testosterone (88.67 nmol/L) and LH (30.8 mIU/mL) with low-normal estradiol (23.6 pg/mL)—strongly indicate Complete Androgen Insensitivity Syndrome (CAIS). The female phenotype, despite high androgens, suggests defective androgen receptors, with elevated LH reflecting failed negative feedback. Estradiol, likely from peripheral aromatization of testosterone, supports partial breast development. This profile differentiates CAIS from other 46, XY DSDs, including gonadal dysgenesis and partial AIS.

Karyotyping Test

Chromosomal analysis on October 23, 2023, revealed a 46, XY karyotype, confirming genetic male sex and excluding conditions such as MRKH syndrome, typically seen in 46, XX individuals with normal ovarian function. In a phenotypic female, 46, XY narrows the differential to CAIS, Swyer syndrome, 5-alpha reductase deficiency, and related disorders. Combined with normal breast development, absent virilization, and elevated testosterone, this finding strongly supports CAIS. Karyotyping thus shifted the impression from a Müllerian anomaly to an androgen function disorder, highlighting its key role in diagnosis and long-term management.

Final Diagnosis

Following evaluation with history, examination, imaging, hormonal assays, karyotyping, and multidisciplinary review, the patient was diagnosed with 46, XY DSD, most consistent with Complete Androgen Insensitivity Syndrome (CAIS). The diagnosis was supported by a female phenotype, absent uterus and vagina, elevated testosterone and LH, 46, XY karyotype, and affirmed female gender identity. Initial suspicion of MRKH Type A was excluded due to male karyotype and hyperandrogenaemia. The absence of virilization despite high androgens further confirmed CAIS. The patient and family chose to maintain female gender, declined surgery, and were referred for long-term multidisciplinary follow-up, including psychological support, gonadal surveillance, and reproductive counselling.

Discussion

Disorders of Sex Development (DSD) comprise congenital conditions with discordance between chromosomal, gonadal, and phenotypic sex. This case represents a 46, XY DSD in which a genetically male individual exhibited a female phenotype with breast development, absent virilization, and no internal female reproductive organs. Differential diagnoses included Complete Androgen Insensitivity Syndrome (CAIS), Swyer syndrome, and—less likely—Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, which

typically occurs in 46, XX individuals [7].

CAIS is characterized by a 46, XY karyotype, normal-to-elevated testosterone, elevated luteinizing hormone (LH), and a female external phenotype due to androgen receptor (AR) insensitivity. The AR gene, located on the X chromosome, regulates male differentiation; mutations lead to variable androgen resistance [8]. In CAIS, complete androgen unresponsiveness causes feminization despite high testosterone, as in our case (88.67 nmol/L), with elevated LH reflecting absent negative feedback at the hypothalamic-pituitary level [9].

An early diagnostic challenge arose from MRI findings suggestive of MRKH type A, classically seen in 46, XX females with Müllerian agenesis and normal ovarian function [10]. MRKH does not account for a 46, XY karyotype or high testosterone. The "ovarian-like" gonads with follicular cysts likely represented undescended testes with cystic degeneration or dysgenetic gonads mimicking ovarian morphology [[10], 11]. Accurate classification required integrating radiology, hormonal assays, karyotyping, and phenotype assessment.

The absence of Müllerian structures aligns with anti-Müllerian hormone (AMH) secretion by Sertoli cells, which inhibits female tract development. In CAIS, AR defects also prevent Wolffian structure formation, producing a female phenotype [13]. Intra-abdominal gonads may remain undescended and carry a low but increasing risk of germ cell tumors post-puberty [14]. Gonadectomy is generally delayed until after puberty to allow spontaneous breast development via aromatization of testosterone; malignancy risk is estimated at 1.5–5%, warranting individualized decisions and ongoing surveillance [15]. In this case, surgery was deferred in favour of regular monitoring and patient autonomy.

Psychological impact is substantial in DSD, though CAIS patients raised female with consistent gender identity often have good adjustment when supported [16]. Psychiatric evaluation confirmed a stable female identity without dysphoria, consistent with phenotype and family support. Gender-affirming care, including psychological support and legal documentation, is essential for well-being [17].

From a medicolegal perspective, accurate sex verification is vital for legal identity, marriage eligibility, and access to gender-specific services. In Indonesia, recognition may require expert certification or judicial approval [18]. Forensic medicine input ensured gender designation matched the patient's affirmed identity and clinical evidence. This case underscores the value of interdisciplinary collaboration—psychiatry, radiology, gynecology, endocrinology, and forensic medicine—in delivering ethically grounded, patient-centered care.

Conclusion

This case illustrates the diagnostic and ethical challenges of managing 46, XY DSD, particularly CAIS, highlighting the need for a multidisciplinary approach that integrates genetic, hormonal, radiologic, psychological, and cultural factors. Management should prioritize accurate diagnosis, respect for patient autonomy, and long-term holistic care addressing both physical and psychosocial well-being.

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Conflicts of Interest

The authors report there are no competing interests to declare.

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