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CASE REPORT

Complete Androgen Insensitivity Syndrome: Revisiting a Rarity—A Case Report

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Abstract

Complete androgen insensitivity syndrome is a rare disorder. Primary amenorrhea beyond 14 years of age without, and 16 years along with developed secondary sexual characters should raise suspicion of this entity as a cause. Inguinal examination may confirm presence of inguinal gonads. The absence of female internal genitalia on imaging, absence of pubic/axillary hair, and chromosomal analysis clinch the diagnosis. Surgical excision of gonads to prevent malignancy, estrogen supplementation, and vaginoplasty along with psychological counselling remain the mainstay of treatment.

Keywords Complete androgen insensitivity syndrome (CAIS) · Disorders of sexual development · Inguinal gonads · Primary Amenorrhea · Case report

Case Report

A 20-year-old lady, a firstborn of a non-consanguineous marriage presented first to our gynecologist 3 years ago with primary amenorrhea. There was no history of cyclical abdominal pain. She was of normal intelligence. She had a normal facial profile (Fig. 1A), normal breast development, and absent axillary and sparse pubic hair along with essentially normal female external genitalia. There was no clitoromegaly. A per-speculum examination showed a blind ending vagina. Anthropometrically, her body habitus was eunuchoid, with an arm span of 165 cm, a height of 160 cm, and with an upper to lower segment ratio of 0.93. USG Abdomen indicated normal kidneys with non-visualized uterus and ovaries. MRI pelvis confirmed findings of USG, but could no comment on the presence or absence of ectopic gonads. Her baseline hormonal values (Table 1) reported a normal LH, FSH, and Prolactin, and a low estradiol with very high testosterone in comparison to reference female range. A karyotype evaluation suggested a 46 XY male genotype (Fig. 1B). Upon re-evaluation of family history, she denied such a history of amenorrhea in maternal aunts or her sisters.

After her initial presentation for amenorrhea 3 years ago, she now presented with painful swellings in the inguinal region bilaterally since the last 1 year. Clinically palpable, these were reported on USG as bilateral iso- to hypo-echogenic, well-defined structures in relation to the superficial inguinal rings, suggestive of testes. The tentative diagnosis of complete androgen insensitivity syndrome (CAIS) was thus confirmed.

Bilateral gonadal excision via an inguinal approach was performed (Fig. 1C). Post -op period was uneventful. HPE confirmed benign testicular tissue and seminiferous tubules with maturation arrest of spermatogonia.

Presently patient has been started on estrogen replacement therapy. She has received psychological counselling and joined online CAIS support groups. Options for vaginal dilatation and vaginoplasty before marriage have been discussed. Results of genetic analysis for AR mutation are awaited.

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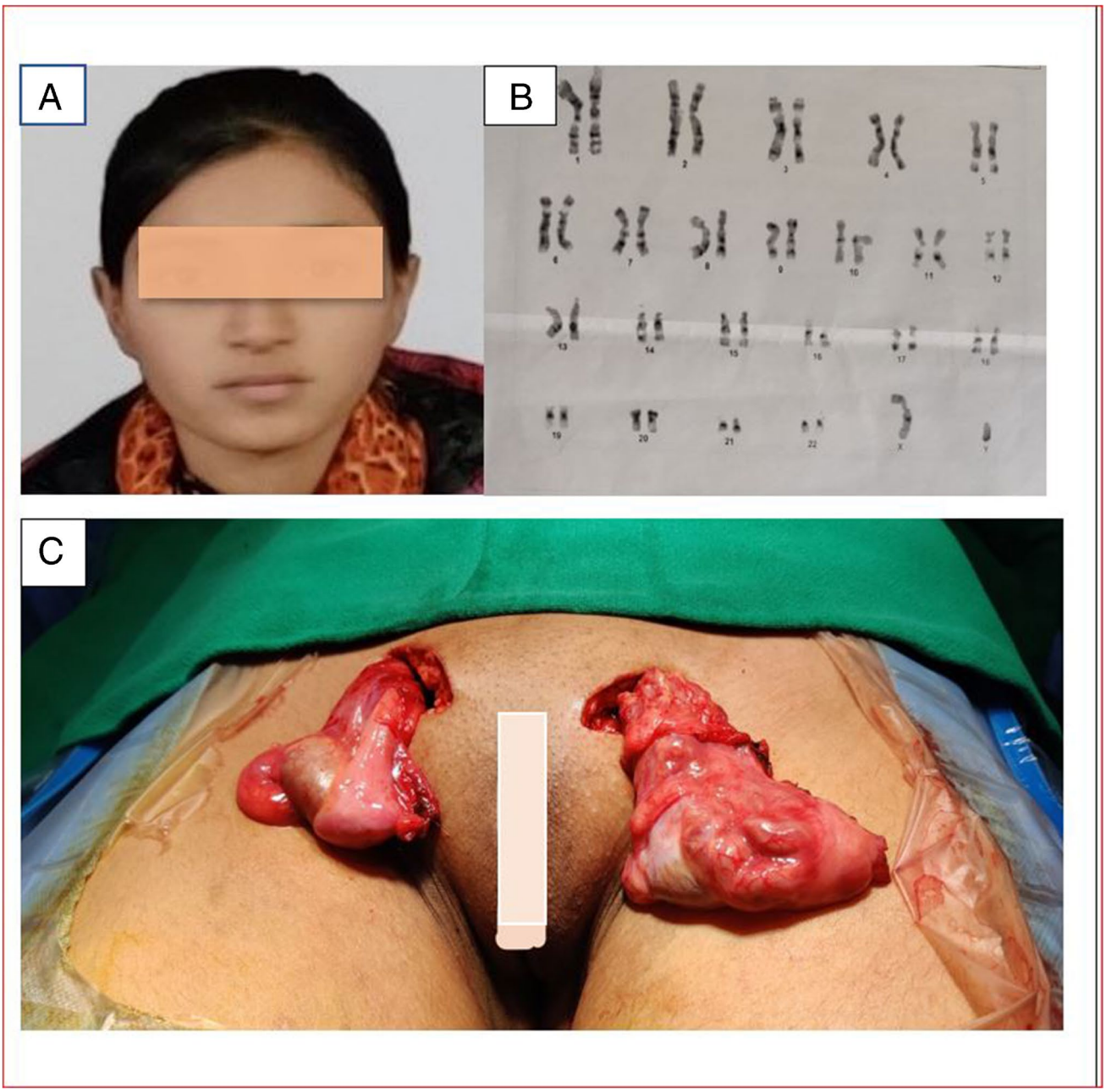

Fig. 1 **A**. Facial Profile, **B**. Chromosomal Analysis 46XY, **C**. Intraoperative photograph showing the bilateral dissected inguinal gonads, prior to excision

Table 1 Hormonal values and reference range

Values	LH (IU/ml)	FSH (IU/L)	Prolactin (ng/ml)	Testosterone (ng/dl)	Estradiol (pg/ml)
Patient	12.9	6.4	5.4	1293	51
Ref female	Less than 17	5–21	Less than 27	6–82	85–500
Ref males	0.5–10	1.5–10	Less than 27	300–1000	10–40

Discussion

Post-pubertal females presenting to the gynecologist with primary amenorrhea are only unconventionally referred to the urologists, for management of palpable inguinal gonads, after establishing a rare diagnosis of CAIS.

CAIS is a rare disorder, occurring with a frequency of 1:20,000 to 1:90,000 genetic males [1]. It is the third most

Table 2 Differentiating features of causes of primary amenorrhea

	CAIS	Mullerian agenesis	Swyer syndrome
Phenotype	Female	Female	Female
Pubic and axillar hair	Absent	Present	Absent
Breast development	Normal	Normal	Absent/partially developed
Mullerian structures on imaging	Absent	Absent/rudimentary	Rudimentary but present
Gonads	Testes	Ovaries	Streak
Chromosomal analysis	46XY	46XX	46XY
Gonadotropins	Mildly elevated	Normal	Highly elevated
Testosterone	Elevated (in male range)	Low(in female range)	Minimal
Chromosomal studies	Androgen receptor gene mutation	May be associated with Turner's syndrome (45 XO)	SRY gene mutation

common cause of primary amenorrhea, after Müllerian agenesis [2] and gonadal dysgenesis, also referred to as Swyer syndrome (SS) [3]. CAIS can result from X-linked recessive mutations on the androgen receptor gene (Xq12) [1].

An understanding of the prenatal development of the reproductive system clarifies the cause-and-effect relationship in CAIS. In utero, the developing testes produce both testosterone and anti-Mullerian hormone (AMH). The androgen receptor defect with insensitivity to androgens does not permit the development of Wolffian duct structures, i.e., the epididymis, the vas deferens, and seminal vesicles bilaterally. The AMH on the other hand suppresses Müllerian duct development; therefore, the uterus and the fallopian tubes are also absent. Due to AMH mediating descent, the testes may be found anywhere along the path of descent. The histology of the excised gonad exhibits maturation arrest of spermatogenesis [4].

Due to the absent androgenic action, the external genitalia are feminine phenotypically. The vagina, derived only from the urogenital sinus, is short, ending blindly. The cervix and uterus too are absent. Patients with complete AIS appear normal at birth. Growth and development during childhood also are generally normal, overall height usually is above average, and the body habitus somewhat eunuchoid (long arms, large hands, and feet) [1]. At puberty, the breasts develop, driven by peripheral aromatization of high circulating testosterone levels to estrogen. Axillary hair do not develop, due to the absence of androgen stimulation, and pubic hair are sparse. The condition may also be recognized at birth or in childhood when a female child presents with an inguinal hernia, which may contain a gonad. A karyotype (46, XY) establishes the diagnosis. The location of the testes usually can be detected by USG or MR. A table differentiating the features of the three most common etiologies of primary amenorrhea is given. (Table 2).

The treatment of CAIS addresses functional, sexual, and psychological issues such as disclosure, gonadectomy, and creation of functional vagina, hormone replacement, and genetic advice. Gonadectomy is often delayed in patients with CAIS, to permit a smooth pubertal transition, via endogenous mechanism, rather than the use of exogenous supplementation. Excision of streak gonads, on the contrary, in Swyer's syndrome should be done early to prevent a malignant change. Also, the gonadal tumors develop less often in patients with CAIS and rarely before puberty [5]. Psychological support should be directed towards reinforcement of their female gender identity and include truthful education for both patient and parents.

Conclusion

CAIS forms an important differential diagnosis in patients of post-pubertal primary amenorrhea. Diagnosis can be clinched with a combination of clinical, imaging, and chromosomal analysis.

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Declarations

Ethics Approval and Consent to Participate Not applicable.

Conflict of Interest The authors declare no competing interests.

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