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Androgen Insensitivity Syndrome: Case Report With Review of the Literature

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ABSTRACT

Androgen insensitivity syndrome (AIS), also known as testicular feminization, encompasses a wide range of phenotypes that are caused by numerous different mutations in the androgen receptor gene. AIS is an X-linked recessive disorder that is classified as complete, partial, or mild based on the phenotypic presentation. The clinical findings include a female type of external genitalia, 46-XY karyotype, absence of Müllerian structures, presence of Wolffian structures to various degree, and normal to high testosterone and gonadotropin levels. The syndrome is illustrated by a 24-year-old phenotypic female who presented with an inability to conceive, normal-appearing external genitalia, an absent uterus and ovaries, and bilateral testes at the level of the internal inguinal ring. Management includes counseling, gonadectomy to prevent primary malignancy in undescended gonad, and hormone replacement. The karyotyping of family members is advocated because of known familial tendencies.

KEYWORDS: Androgen insensitivity syndrome; Androgen receptor gene; Testicular feminization syndrome; Gonadectomy

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Abbreviations and Acronyms

AIS, androgen insensitivity syndrome (CAIS, complete; MAIS, mild; PAIS, partial)
AR, androgen receptor
LH, luteinizing hormone

INTRODUCTION

Androgen insensitivity syndrome (AIS), which is also known as testicular feminization, encompasses a wide range of phenotypes that are caused by numerous different mutations in the androgen receptor gene. The name *testicular feminization syndrome* was coined by John McLean Morris of Yale University in 1953. The first description of this syndrome dates back to 1817, as quoted by Morris [1]. It is the third most common cause of primary amenorrhea after gonadal dysgenesis and Müllerian agenesis [2]. The syndrome is usually detected on evaluation of a phenotypic female with primary amenorrhea who presents for treatment of infertility. We report one such case.

CASE REPORT

A 24-year-old phenotypic female presented to the outpatient section of the obstetrics and gynecology department with complaints of amenorrhea. She was married and complained of an inability to conceive for the last 4 years. Her marital life was normal and she reported no difficulty in having sex until about the last month, when she began to experience dyspareunia.

The patient's built was normal and she had well-developed breasts (Figure 1; Figure 2). Pubic and axillary hair were sparse. The labia were poorly developed (Figure 3). The vagina was 3

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Figure 1. Clinical photograph of the patient with androgen insensitivity syndrome.
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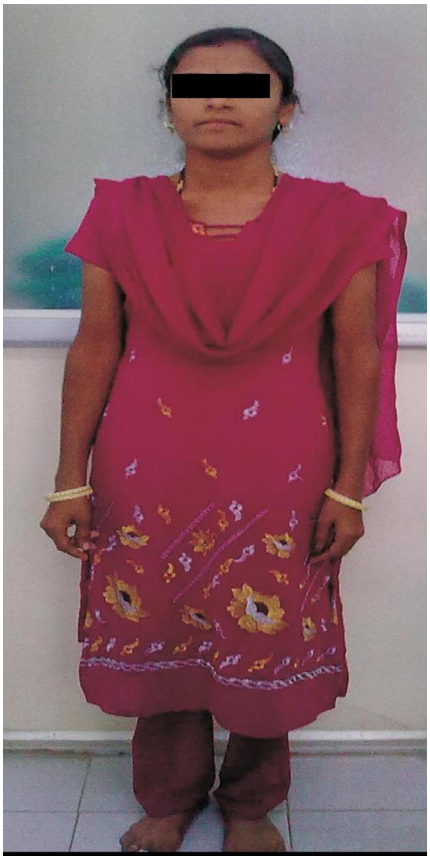

inches in length and appeared otherwise normal. However, the cervix could not be visualized on speculum examination (Figure 4).

An ultrasound of the abdomen and pelvis revealed an absent uterus and ovaries. Karyotyping revealed a 46, XY pattern. Follicle stimulating hormone (FSH) was elevated with a value of 90 mIU/mL (reference range for normal adult male: 1-12 mIU/mL) [3]. Luteinizing hormone (LH) was also elevated with a value of 20 mIU/mL (reference range for normal adult male: 2 to 12 mIU/mL) [3]. However, serum testosterone level was normal with a value of 300 ng/dL (reference range for normal adult male: 300 to 1000 ng/dL) [4].

Diagnostic laparoscopy revealed bilateral testes approximately 2 cm x 1.5 cm x 1 cm in size, located at the level of the internal inguinal ring (Figure 5). They were excised and the histopathology revealed Sertoli cell hyperplasia with absent lumen in the seminiferous tubules and an absence of spermatogonia. Histopathology did not reveal any evidence of malignancy. Genital reconstruction was not done because the patient had normal-appearing female external genitals. The patient was put on estradiol oral replacement therapy after counseling.

DISCUSSION

Androgen insensitivity syndrome is typically characterized by evidence of feminization (ie, undermasculinization) of the external genitalia at birth, abnormal secondary sexual development in puberty, and infertility in individuals with a 46,

Figure 2. Well-developed breasts of the patient with androgen insensitivity syndrome.
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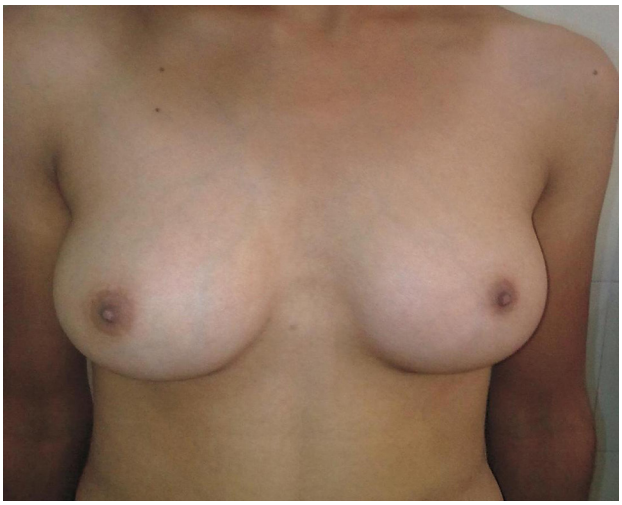

Figure 3. External genitalia of the patient with androgen insensitivity syndrome.
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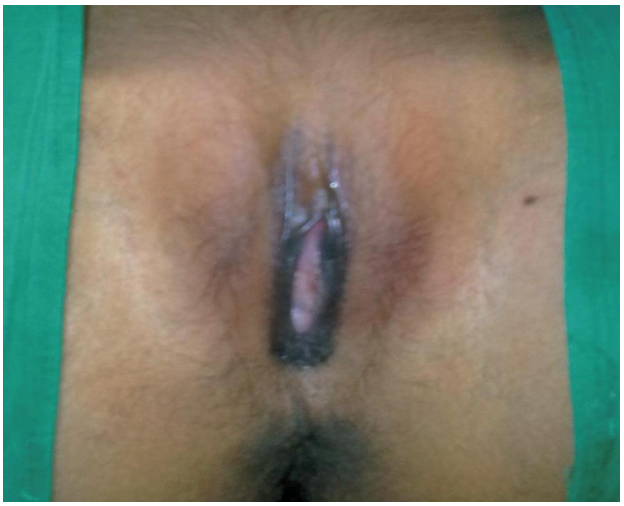

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Figure 4. Blind-ending vagina with the absence of cervix on speculum examination.
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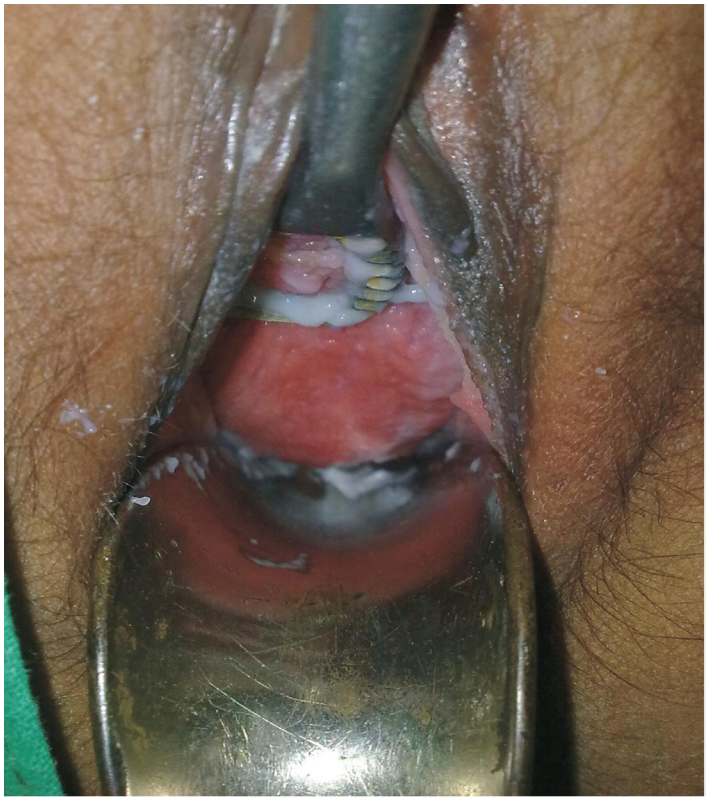

Figure 5. Testis at internal inguinal ring as seen in laparoscopy.
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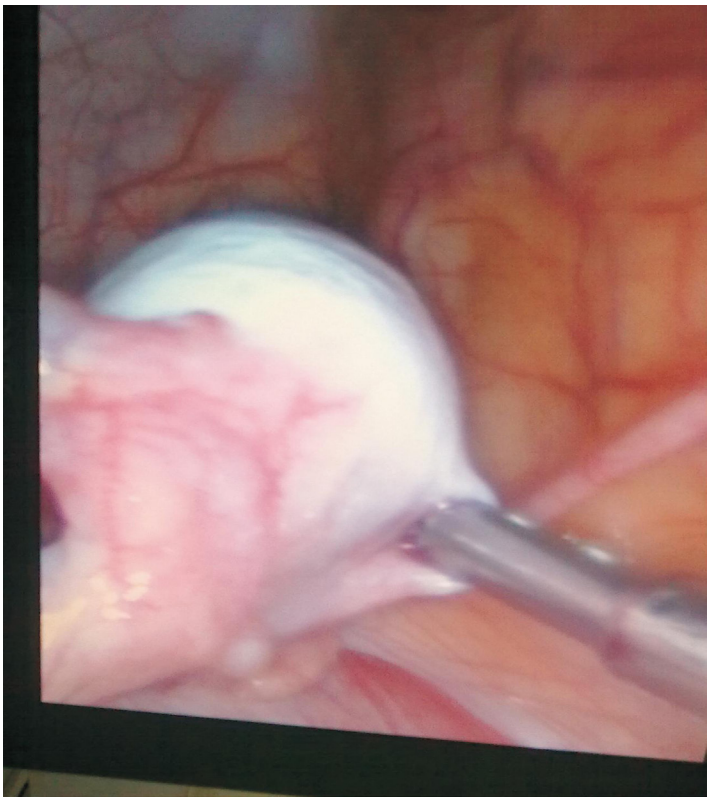

XY karyotype. It represents a spectrum of defects in androgen action and can be subdivided into 3 broad phenotypes: (1) complete androgen insensitivity syndrome (CAIS) with typical female genitalia; (2) partial androgen insensitivity syndrome (PAIS) with predominantly female, predominantly male, or ambiguous genitalia; and (3) mild androgen insensitivity syndrome (MAIS) with typical male genitalia [5]. The incidence of androgen insensitivity syndrome is estimated to be 1:20,000-64,000 male births [6].

The present case is a complete androgen insensitivity syndrome because the phenotype is female with genetic male and minimal Wolffian structures. However, the definition of CAIS itself is controversial, with different authors expressing different views. Griffin et al [7] define CAIS as completely female external genitalia, paucity of axillary and pubic hair, and absent Wolffian duct derivatives. Quigley [8] defines CAIS as completely female external genitalia without pubic hair, but states that remnants of Wolffian duct derivatives may be found. The presence of any amount of pubic hair is held as evidence of some degree of androgen responsiveness and thus classified as PAIS [9]. In the classification of Sinnecker et al [10], CAIS is a female phenotype with scant pubic and axillary hair (type a) or a female phenotype with absence of any androgen-dependent structures such as pubic and/or axillary hair (type b). No comment is made on the development of Wolffian duct derivatives.

AIS is an X-linked recessive disorder [11]. The androgen receptor (AR) gene is located on the X-chromosome at Xq11--12 and codes for a protein with a molecular mass of approximately 110 kDa. The androgen receptor belongs to the family of steroid-thyroid hormone-retinoid nuclear receptors. It contains 3 major domains: a hormone-binding region, a DNA-binding region, and an amino-terminal region. In the AR gene, 4 different types of mutations have been detected in DNA from individuals with AIS: (1) single point mutations resulting in amino acid substitutions or premature stop codons; (2) nucleotide insertions or deletions most often leading to a frame shift and premature termination; (3) complete or partial gene deletions; and (4) intronic mutations in either splice donor or acceptor sites, which affect the splicing of AR ribonucleic acid [12,13].

The diagnosis of AIS in individuals with a 46,XY karyotype is based on the following clinical findings: undermasculinization of the external genitalia, impaired spermatogenesis with otherwise normal testes, absent or rudimentary Müllerian structures, evidence of normal or increased synthesis of testosterone and its normal conversion to dihydrotestosterone, normal or increased LH production by the pituitary gland, and deficient or defective androgen-binding activity of genital skin fibroblasts. Molecular genetic testing of the AR gene (the only gene known to be associated with AIS) detects mutations in more than 95% of probands with complete androgen insensitivity and is available clinically. Its yield in individuals with partial or mild forms of AIS is unknown [5]. In the present case, the diagnosis was established by undermusculinized external genitalia, intraabdominal testis without any spermatogenesis, normal testosterone levels, and raised gonadotropin levels.

To prevent testicular malignancy, treatment of CAIS includes either removal of the testes after puberty when feminization is complete or prepubertal gonadectomy accompanied by estrogen replacement therapy. The laparoscopy can be used to locate as well as remove the gonads [14]. Additional treatment for CAIS may include vaginal dilatation to avoid dyspareunia. Treatment of PAIS in individuals with predominantly female genitalia is similar to treatment of CAIS, but is more likely to include prepubertal gonadectomy to help avoid clitoromegaly at the time of puberty.

Individuals with PAIS who are living as males may undergo surgery such as orchiopexy and hypospadias repair. Individuals with PAIS who are living as females and undergo gonadectomy after puberty may need combined estrogen and androgen replacement therapy. Males with MAIS may require mammoplasty for gynecomastia. A trial of androgen pharmacotherapy may help improve virilization in infancy. Surveillance includes periodic reevaluation for gynecomastia during puberty in individuals living as males [5,15,16]. We managed the present case with laparoscopic bilateral orchiectomy and estrogen supplementation.

AIS is associated with numerous psychosexual issues. Therefore, systematic disclosure of the diagnosis of AIS should be done in an empathic environment, with both professional and family support [5,17].

As demonstrated by the present case, the 46-XY phenotypic female is almost always infertile. However, carrier females have a 50% chance of transmitting the mutated AR gene in each pregnancy [5]. Carrier testing is advocated within the family because the disease has known familial tendencies [18]. The present patient was the only case in her family and no carrier testing has been done in other family members.

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