CASE REPORT

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Late diagnosis of androgen insensitivity syndrome in an adult female phenotype patient with a hemiczygous variant c.2391G>A p.(Trp797Ter)

Diagnóstico tardío del síndrome de insensibilidad a los andrógenos en una paciente adulta con fenotipo femenino y variante hemicigota c.2391G>A p.(Trp797Ter)

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ABSTRACT

Disorders of Sex Development (DSD) are congenital conditions that affect chromosomal, gonadal, or phenotypic sexual development. One of the most common DSDs is Androgen Insensitivity Syndrome (AIS), with a prevalence of 1:60,000 live births. It is characterized by female-appearing external genitalia, absence of the uterus and ovaries, and the presence of intra-abdominal testes in individuals with a 46,XY karyotype. We present the case of a 29-year-old woman with an initial diagnosis of Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, which was later confirmed as AIS by genetic sequencing. Prophylactic gonadectomy was performed to prevent malignancy. This case highlights the importance of timely diagnosis to prevent complications such as gonadal tumors and psychological problems related to gender identity. Early intervention and proper management are essential for the physical, sexual, and emotional well-being of patients with AIS.

Keywords: Androgen Insensitivity syndrome, Disorders of sex development, Genetic diagnosis, Gonadal dysgenesis, Rare disease.

RESUMEN

Los Trastornos del Desarrollo Sexual (DSD) son condiciones congénitas que afectan el desarrollo sexual cromosómico, gonadal o fenotípico. Uno de los DSD más comunes es el Síndrome de Insensibilidad a los Andrógenos (SIA), con una prevalencia de 1:60,000 nacimientos vivos. Se caracteriza por genitales externos de apariencia femenina, ausencia de útero y ovarios, y presencia de testículos intraabdominales en individuos con cariotipo 46,XY. Presentamos el caso de una mujer de 29 años con un diagnóstico inicial de síndrome de Rokitansky, que posteriormente fue confirmado como SIA mediante secuenciación genética, se realizó gonadectomía profiláctica para prevenir la malignidad. Este caso resalta la importancia de un diagnóstico oportuno para prevenir complicaciones como tumores gonadales y problemas psicológicos relacionados con la identidad de género. La intervención temprana y el manejo adecuado son fundamentales para el bienestar físico, sexual y emocional de las pacientes con SIA.

Palabras clave: Síndrome de Insensibilidad a los Andrógenos, Trastornos del Desarrollo Sexual, Diagnóstico Genético, Disgenesia Gonadal, Enfermedad Rara

Introducción

Disorders of Sex Development (DSD) are congenital conditions involving chromosomal, gonadal, or phenotypic abnormalities in sexual development, characterized by atypical presentations of the genitals and other sexual characteristics[1]. One of the most representative presentations of DSD is androgen insensitivity syndrome (AIS), which is the most common form of Y-chromosome-related DSD, with an estimated prevalence of 1:60,000 live births. It manifests with female-appearing external genitalia, female breast development, an unaltered vagina, absence of a uterus and ovaries, and intra-abdominal testes, in the presence of a 46,XY karyotype[1,2].

Phenotypic similarities and a variety of etiologies make accurate diagnosis and timely, appropriate management difficult. These delays or inadequate management can be associated with complications in adulthood, such as cancer, infertility, and mental disorders, among others[2,3]. The objective of this manuscript is to present the case of a patient with a late diagnosis of AIS and to review the literature on the importance and implications of timely diagnosis.

Clinical case

A 29-year-old patient who, at the age of 15, consulted for primary amenorrhea, underwent a pelvic MRI with contrast, which documented agenesis of the uterus and ovaries. No hormonal profile or karyotype was reported. An initial diagnosis of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome was made, and hormone replacement therapy (HRT) with oral conjugated estrogens was administered. Subsequently, she developed breasts and pubic hair, but treatment was suspended due to severe pelvic pain, with no subsequent follow-up by gynecology.

Fourteen years later, the patient presented with chronic pelvic pain, vaginal dryness, and dyspareunia, accompanied by reduced genital lubrication and vasomotor symptoms, including hot flashes. She did not report sexual dysfunction and identified as a cisgender heterosexual woman, that is, a woman whose gender identity matches the sex assigned at birth and whose sexual orientation is characterized by attraction to men.. Physical examination revealed a macroscopically normal vulva, sparse pubic hair, no evident vaginal abnormalities, and absence of a palpable uterus or abdominal masses. Transvaginal ultrasonography demonstrated uterine agenesis and bilateral ovarian replacement by cystic structures, classified as O-RADS 2.

She had follicle-stimulating hormone (FSH) levels of 10.48 IU/L, luteinizing hormone (LH) levels of 20.25 IU/L, and estradiol levels of 40 pg/ml, as well as a karyotype of 46,XY. Given the suspicion of AIS, a genetic study of the AR gene was performed, which revealed hemicigosity for a pathogenic variant: c.2391G>A p.(Trp797Ter), confirming the diagnostic hypothesis.

The pelvic MRI showed absence of the uterus, with the right ovary replaced by a bilobulated cystic structure measuring 1.9 x 1.6 cm and the left ovary replaced by a trilobulated structure measuring 4.3 x 3.2 cm (Figure 1). Given the suspicion of the presence of gonads and with the aim of reducing the risk of malignancy, laparoscopic gonadectomy was performed without complications (Figure 2), revealing atrophic testicles with spermatoceles (Figure 3). Histopathological examination ruled out malignancy. HRT was continued with marked improvement in the symptoms described. After six months of follow-up, no complications were reported.

Discussion

Androgen insensitivity syndrome AIS (OMIM: #300068) was described by Morris in 1953 as testicular feminization syndrome in a series of patients with a female phenotype, female external genitalia, undescended testes, and absence

Figure 1: Axial T1 image (A) and coronal T1 image (B) showing bilateral cystic testes (white arrows), bladder (white dot), and vaginal cavity without uterus (black arrows).

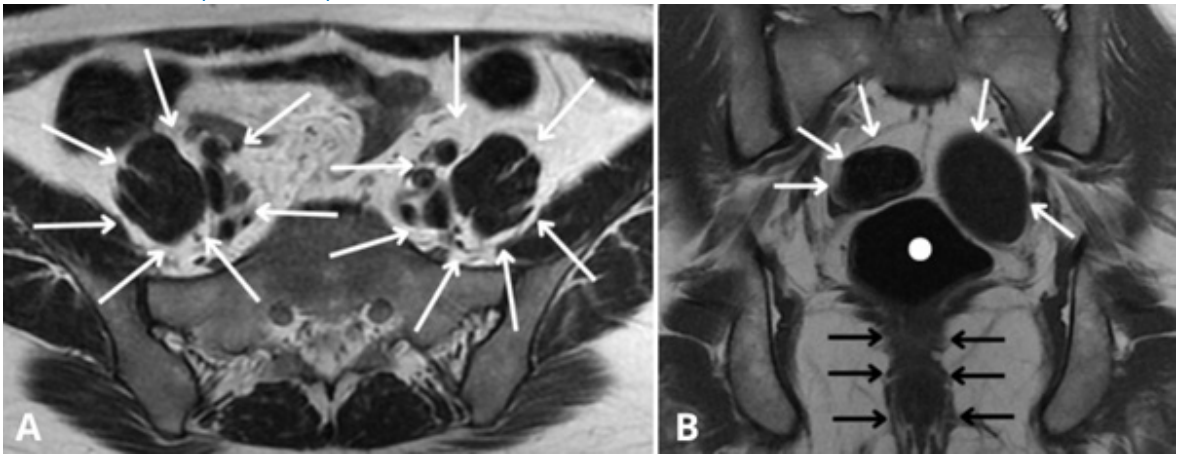


Figure 2: Intraoperative laparoscopic image showing spermatocele resection (white arrows) in an atrophic gonad, with identification of adjacent structures: peritoneum (white dot) and intestine (red arrows).

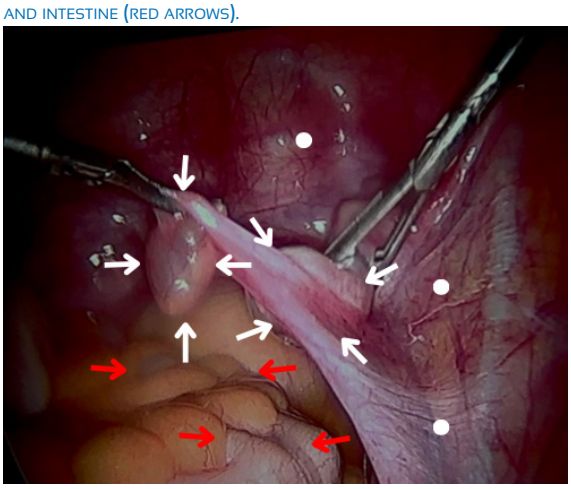
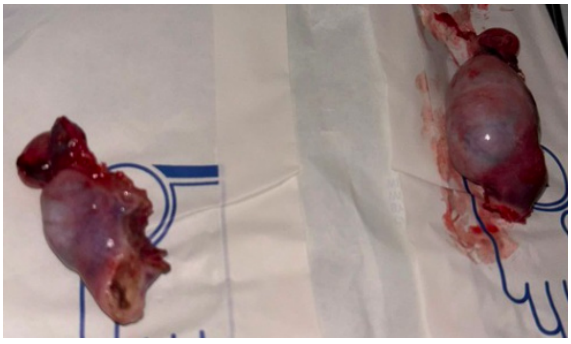


Figure 3: Surgical specimen after laparoscopic gonadectomy: bilateral atrophic testes with spermatoceles.



of female internal genitalia[2,4,5]. It is caused by a genetic mutation in the androgen receptor (AR) gene (OMIM: *313700), located in the Xq12 region. Its dysfunction causes a defect in proper hormonal signaling, altering embryonic development. This occurs because the SRY region of the Y chromosome triggers the development of primordial testes, which produce testosterone, promoting the formation of the epididymis, vas deferens, and seminal vesicles from the Wolffian ducts. Dihydrotestosterone allows the development of the prostate, penis, and scrotum, while anti-Müllerian hormone (AMH) prevents the formation of female internal organs by inducing the regression of the Müllerian ducts[5–7].

The present case corresponds to a patient with complete androgen insensitivity syndrome, characterized by female external genitalia, absence of female internal reproductive organs, and the presence of intra-abdominal testicles[7,8]. During puberty, breast development and a typically female pattern of adipose tissue distribution occur as a result of peripheral aromatization of androgens to estrogens. Pubic and axillary hair are usually sparse or absent, and the vaginal length is generally sufficient to permit sexual intercourse, such that it is not commonly a presenting complaint. Primary amenorrhea remains one of the most frequent reasons for medical consultation, as observed in the present case[7,8].

The AIS shows elevated levels of LH and testosterone compared to female ranges, while FSH is usually within normal values, probably due to the inhibition exerted by gonadal inhibin. Estradiol levels are low or borderline compared to female values[8,9]. In our patient, the hormonal profile showed significantly elevated LH levels and estradiol levels close to the lower limit, which led to a reevaluation of the initial diagnosis of Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome and allowed the correct diagnosis to be established.

The diagnosis of AIS is based on clinical presentation, laboratory tests, imaging studies, and a 46,XY karyotype, and is confirmed by AR gene analysis[1,4,6]. Early prenatal diagnosis is possible by detecting discordance between phenotypic and chromosomal sex using fetal DNA obtained from maternal cells. However, this finding is usually incidental during studies for aneuploidy[2,3]. In the case of our patient, the diagnosis was confirmed by the presence of a mutated variant that causes loss of AR gene function, which has been previously described and is registered in genetic variant databases[6].

Historically, early gonadectomy was recommended to prevent germ cell tumors, followed by HRT similar to that used in postmenopausal women[9]. However, concerns about the actual incidence of malignancy, ethical considerations regarding hormone deprivation, autonomy in sexual decisions, and the impact on mental health have changed the current therapeutic paradigm[10]. Currently, a conservative approach is suggested, postponing gonadectomy until spontaneous puberty, induced by the aromatization of testosterone into estrogens[11]. In our patient, due to the delay in diagnosis and previous exposure to hormone treatment, a high risk of malignancy was considered, and gonadectomy was chosen.

The differential diagnosis should consider other etiologies that can alter the development of male genitalia in individuals with a 46,XY karyotype, due to genetic variants, alterations in hormone secretion, or peripheral insensitivity to androgens[9]. These include mutations in the SRY gene, 5-alpha-reductase deficiency, Swyer syndrome, 17-alpha-hydroxylase deficiency, or Smith-Lemli-Opitz syndrome[2,5,9]. CAH is often underdiagnosed or confused with MRKH until adulthood, especially when karyotyping is omitted or the image is interpreted incorrectly, as was the case in our patient, providing evidence to suggest the systematic inclusion of karyotyping and molecular testing.

Timely diagnosis enables appropriate clinical management, thereby reducing the risk of physical complications, metabolic disorders, and neoplastic transformation, as well as mitigating potential emotional or psychiatric sequelae related to gender identity or sexual orientation[12]. In the present case, however, none of these complications were observed despite the delayed diagnosis, a finding that is consistent with recent evidence discouraging routine prepubertal gonadectomy. This recommendation is based on the low risk of malignancy prior to puberty and the benefit of permitting spontaneous pubertal development through peripheral aromatization of androgens[13]. Accordingly, a comprehensive multidisciplinary approach is advised, encompassing genetic counseling regarding inheritance patterns, identification of familial cases presenting with a female phenotype, and individualized management of disease-specific risks.

Conclusion

Androgen Insensitivity Syndrome is a rare disorder of sexual development that occurs in individuals with a 46,XY karyotype who exhibit a female phenotype. Early diagnosis is crucial to prevent both organic and psychological complications, including the potential development of gonadal tumors. In the present case, the patient underwent surgical management, received hormone replacement therapy (HRT), and was provided with psychiatric support, measures that enabled appropriate follow-up and resulted in marked clinical improvement.

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