Case reports

Complete androgen insensitivity syndrome

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Síndrome de insensibilidad completa a andrógenos

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The authors declare there are no conflicts of interest.

Abstract
Presentation of the case. Phenotypically female patient, 18 years old, 46 XY karyotype, who was evaluated in a tertiary care center for pediatric medicine due to primary amenorrhea. Physical evaluation found adequate breast development, female external genitalia with slight hypoatrophy of the labia majora and minora, vaginal canal of 11 cm, ultrasound reports a linear rudimentary uterus and images suggestive of ovaries, magnetic resonance describes the presence of a bilobed tubular structure composed of two nodular images, which are located adjacent to the bladder wall in their aspect posterior, lateral and superior right 27,4 × 15,4× 11,0 mm, left inguinal canal two images, one solid nodular, ovoid, isointense 37 × 21 × 13,8 mm (nodular), cystic 22,7 × 14,0 mm, congenital absence of uterus. **Treatment.** In the laparoscopic examination, the presence of gonads in the inguinal and para-bladder canals was detected, and both gonads were resected. **Outcome.** She was managed with analgesia, antibiotics and was discharged three days after surgery. The biopsy reported cryptorchidism of the right and left testis.

Keywords
Androgen-insensitivity syndrome, testicular feminization, 46 XY gonadal dysgenesis, androgen effect, disorder of sex differentiation.

Resumen
Presentación del caso. Paciente fenotípicamente femenina de 18 años de edad, cariotipo 46 XY, que fue evaluada en centro de atención de tercer nivel de medicina pediátrica, por un cuadro de amenorrea primaria. En la evaluación física se encontró un adecuado desarrollo mamario, genitales externos femeninos con leve hipotrofia de labios mayores y menores, canal vaginal de 11 cm; ultrasonido reporta útero rudimentario lineal e imágenes sugestivas a ovarios. La resonancia magnética describe presencia de estructura de aspecto tubular bilobulada compuesta por dos imágenes nodulares, las cuales se ubican adyacentes a la pared vesical en su aspecto posterior, lateral y superior derecho de 27,4 × 15,4 × 11,0 mm. El conducto inguinal izquierdo presenta en dos imágenes: una nodular sólida, ovoide, isointensa de 37 × 21 × 13,8 mm (nodular), quística 22,7 × 14,0 mm, ausencia congénita de útero. **Intervención terapéutica.** En la exploración laparoscópica se detectó presencia de gónadas en canal inguinal y paravesical. Se procedió a la resección de ambas gónadas. **Evolución clínica.** Se manejó con analgesia, antibiótico y fue dada de alta a los tres días posteriores a la cirugía; la biopsia reportó criptorquidia de testículo derecho e izquierdo.

Palabras clave
Síndrome de insensibilidad a los andrógenos, feminización testicular, disgenesia gonadal 46 xy, efecto androgénico, trastornos de diferenciación sexual.

Introduction

Androgen insensitivity syndrome (AIS), also known as testicular feminization syndrome[1], includes a widely varied group of mutations that is related to androgen receptor dysfunction[2] and resistance of target tissues to the action of male hormones[3]. This is caused by localized genetic alterations in the coding sequence of androgen receptors linked to the chromosome Xq11 - 12[3], which is the gene encoding the androgen receptor, of a genetically male individual (46 XY)[3,4]. Mild, partial or complete clinical entities depend on the degree of androgen insensitivity[3].

Advances in genetic causes have allowed these congenital conditions of development of chromosomal, gonadal or atypical anatomical sex to be called disorders of sexual differentiation[5].

The main characteristic is the resistance of the target tissues to the action of male hormones[5,6]. The presence of the sexual differentiation protein Y promotes the formation of primordial testicles in the fetal abdomen. From the seventh week after conception, the fetal testicles begin to produce testosterone, whose activity is blocked by pathological processes that affect androgen receptors[7], which prevents the normal male development of the internal and external genitalia of genetically male individuals[6,8] and generates the differentiation of the external and female genitalia; Wolff duct derivatives which depend on androgenic action are not developed. The epididymis, deferent ducts and seminal vesicles[9], and the presence of anti-Müllerian hormone produced by the primordial testicles, suppresses the formation of the female genital organs. However, the lower part of the vagina is fully developed because it is not a derivative of the Müller duct. This is shorter than normal and has a blind end, lacks uterus and fallopian tubes[7], absent Müllerian or vestigial structures and testicles located on the lips, inguinal canal or abdomen[7].

AIS is one of the common causes of disorders of sexual development that give rise to varied phenotypes[4]. A prevalence of two to five cases per 100 000 males genetically born has been estimated with an estimated incidence of one case per 20 000 to 90 000 males genetically born[5,10].

The phenotypic spectrum of individuals depends on the residual activity of the androgen receptor and ranges from individuals with a completely female phenotype, with testicles in the absence of derivatives of the Wolff and Müller ducts and absence of sexual hair to a male phenotype with infertility and devirilization[2,3,12]. These variations define the classification in complete and partial AIS[2].

The complete AIS was described by Morris in 1953. This is characterized by presenting in a person of female appearance, with normal breast development, little body hair, primary amenorrhea and undescended testicles located instead of the ovaries[1]; it is part of the most frequent disorders of sexual differentiation.

Case presentation

This is a phenotypically female patient, 16 years of age, who consulted in a child care hospital for amenorrhea with normal breast and external genital development. With the surgical history of bilateral inguinal hernioplasty at three years of age, in which they reported as an incidental finding the presence of ovaries in hernial sacs, so they introduced again to the abdominal cavity. He had not initiated sexual activity; telarquia at 12 years, pubic hair appearance at 13 years, no axillary hair appearance and heterosexual sexual preference. She had no other pathological medical history.

Studies were indicated for the suspicion of primary amenorrhea. Laboratory tests reported hormonal alterations related to anovulation with a slight elevation of follicle-stimulating hormones and luteinizing hormones with low testosterone levels (Table 1). Pelvic ultrasonography reported that the uterus was sparsely visible, child-sized, with no evidence of endometrium; the right ovary of 5 cm^3 and the left one of 3,9 cm^3; no follicles were evident. The karyotype was performed, which reported 46 XY. She was evaluated by pediatric urology, where a diagnostic laparoscopic video was indicated. In this procedure, a sample of the apparent right gonad was taken for biopsy. The histopathological study reported a tissue consisting of multiple foci of hypoplastic seminiferous tubules scattered in ovarian stroma with granulosa cells, histopathological diagnosis ovotestis.

When she turned 18 years old, she was referred to the endocrinology outpatient clinic from another national hospital, with a diagnosis of sexual development disorder XY, with complete androgen insensitivity syndrome suspicion.

In the reference hospital, laboratory studies were started again, which reported maintaining the slight elevation of follicle stimulating hormones, luteinizing and low testosterone levels (Table 1). Moreover, pelvic ultrasonography described the rudimentary linear uterus 3,7 cm with suggestive images of ovaries. It was requested to repeat the revision of the sheets of the previous biopsy and a testicular tissue consisting of underdeveloped seminiferous tubules was reported, some with sclerosis and fibrosis of the tubular basement membrane arranged in their fibrous stroma, no spermatogenesis, no presence of ovarian tissue, diagnosis of testicular hypoplasia.

Abdomino-pelvic magnetic resonance described the presence of a bilobed tubular structure, composed of two nodular images, which were located adjacent to the bladder wall in its posterior, lateral and upper right aspect of 27,4 × 15,4 × 11,0 mm (Figure 1). The left inguinal duct reflected two nodular

images as a solid, ovoid, isointense of 37 × 21 × 13,8 mm (nodular) and another of cystic characteristics of 22,7 × 14,0 mm (Figure 2) and congenital absence of uterus.

She was evaluated by the gynecology unit, where she was instructed to start hormone replacement therapy, after surgical treatment. Also, he referred to the psychological care area where a session was held with the patient's mother to evaluate her response to diagnosis and treatment. It concluded that gender reinforcement was not necessary.

The clinical evaluation of the urology specialty reported that breast development with Tanner V stage was adecuate. Bilateral umbilical and parainguinal scars were evident without other abdominal or inguinal canal abnormalities. He also described the female external genitalia with the presence of sparse fine pubic hair, distribution of genital pubic hair in stage V in the Tanner scale, mild hypotrophy of the labia majora and minora, the hymen of annular shape, when performing the vaginal touch, the wide and functional vaginal canal was identified that only allowed the introduction of a finger, the measurement of the vaginal canal resulted in 11 cm in length. Visualization of the urethral meatus was difficult.

Treatment

Surgical intervention was scheduled seven days after evaluation. The patient was admitted to the endocrinology service three days before her surgery to complete the pre-surgical evaluations. Prophylaxis with cefazolin of one gram intravenously was indicated, 30 minutes before the start of surgery.

The surgical procedure consisted of laparoscopic removal of the gonads by a closed technique. A periumbilical incision a 10 mm trocar was placed through a periumbilical incision ; the pneumoperitoneum of 12 mmHg and an initial flow of 5 L/min were formed. A 5 mm trocar was placed on the lower left and right flanks. The presence of gonads at the level of the bilobed left inguinal canal (Figure 3), the bilobed right paravesical gonad (Figure 3) and the uterus of linear appearance was evidenced. Finally, the bilateral gonadectomy was performed and sent for histological study.

Outcome

In the immediate postoperative period, the patient was treated with ketorolac and ceftriaxone intravenously and started

Table 1. Laboratory test results

Laboratory test	Pediatric hospital results	Result of the reference hospital	Reference value
Follicle stimulating hormone	15,4 mIU/mL	13,19 mIU/mL	2 – 9 mIU/mL
Luteinizing hormone	47,6 mIU/mL	55,51 mIU/mL	1 – 12 mIU/mL
Thyrotropin	0,6 µUI/mL	0,347 µUI/mL	0,3 – 5,6 µUI/mL
Triiodothyronine	2,8 pg/mL	3,64 pg/mL	2,5 – 3,9 pg/mL
Thyroxine	5,2 µg/dL	0,85 ng/dL	0,61 – 1,12 ng/L
Testosterone	1407 ng/mL	12,67 ng/mL	1,75 – 7,81 ng/mL
Estradiol	36,46 pg/mL	-	30 – 400 pg/mL
Cortisol AM	-	3,45 ug/dL	6 – 23 ug/dL
Prolactin	-	16,06 ng/mL	1 – 23 ng/mL

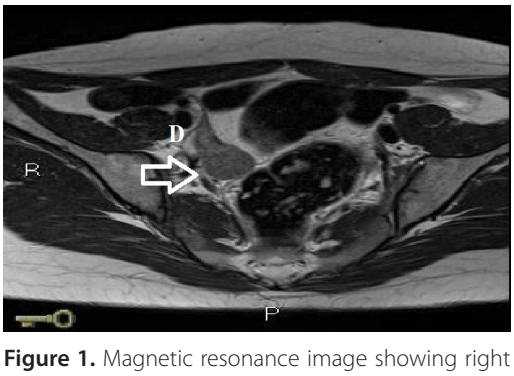

Figure 1. Magnetic resonance image showing right gonad

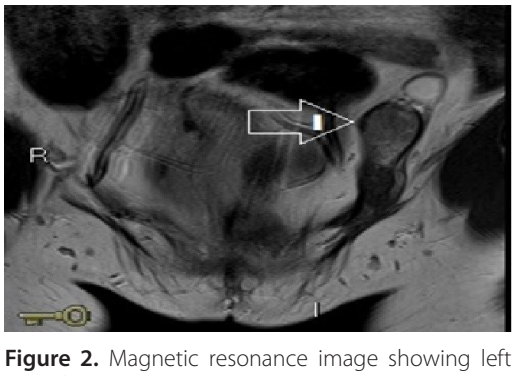

Figure 2. Magnetic resonance image showing left gonad

feeding six hours after surgery. Hospital discharge was indicated on the third post-operative day. After four days, follow-up was given for post-surgical evaluation and for the report of the biopsy that showed vascularized fibromuscular stroma with testicular tissue. He presented lumenless seminiferous tubules composed solely of Sertoli cells; the interstitium presented Leydig cell hyperplasia (Figure 4), without the presence of epididymis, vas deferens or malignancy. Also, there are small tubules lined by columnar epithelium that probably corresponded to paramesonephric remnants.

Clinical diagnosis

Clinical imaging and histological evaluations allowed to define the diagnosis of complete insensitivity syndrome to androgens or Morris syndrome.

Discussion

In complete AIS, there is no response to androgens, which prevents the development of any male characteristic and normal female external genital development occurs[12]. That is why they are educated as women and their identity and sexual inclination are not affected. In addition, its gonads are azoospermic testicles of variable localization, they are most often found in the inguinal ducts, with the presence or not of epididymis[6].

It is unlikely to be diagnosed during childhood. The detection of an inguinal hernia or signs of edema in the labia majora in preschool age should make this syndrome suspect[13]. The association among inguinal hernia in prepubertal girls has been known for more than 60 years. Doctors who treat inguinal hernias in childhood may have the first chance to diagnose it[6]. In these cases, the diagnosis is made by the pathologist after analyzing the surgical piece[13]. It is usual to diagnose it during puberty, for primary amenorrhea, and even later, when consulting an endocrinologist or gynecologist for sterility.

Puberty occurs without virilization and the risk of developing a testicular germ cell tumor[13,14] is 0,02 % in children under 30 years of age; above that age, the risk increases to 22 %[5,7]. Therefore, prophylactic gonadectomy has been recommended after puberty, when the feminization of the affected person has completed, since it is produced in part by testicular estrogen production and by the peripheral conversion of androgens to estrogens. Only in cases where the testicles are palpated in the groin

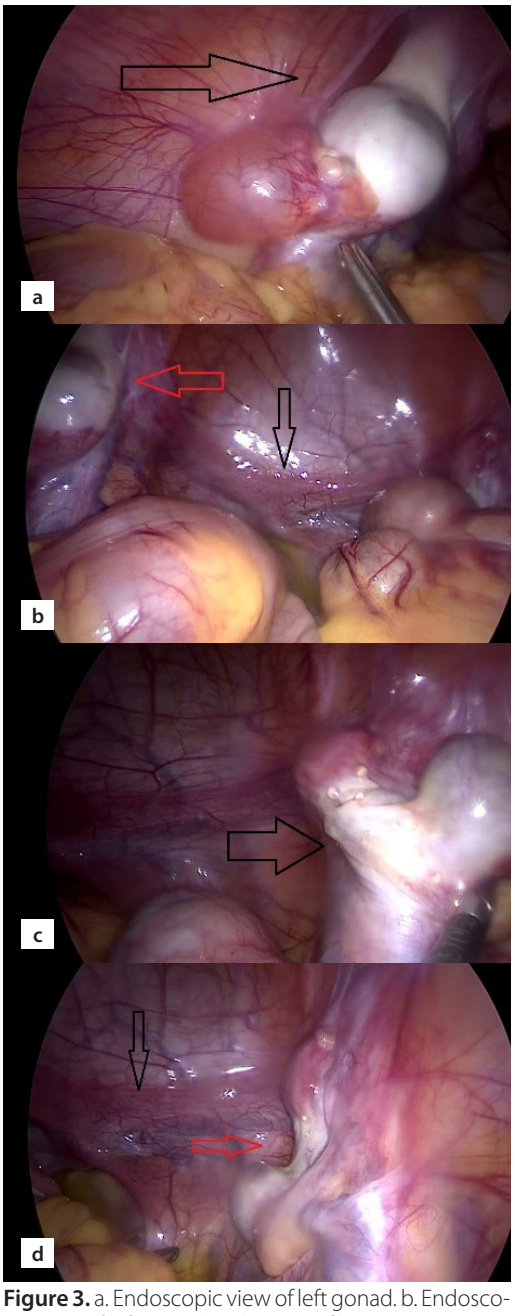

Figure 3. a. Endoscopic view of left gonad. b. Endoscopic view of left gonad and uterus of linear appearance. c. Endoscopic view of right gonad. d. Endoscopic view of right gonad and uterus of linear appearance

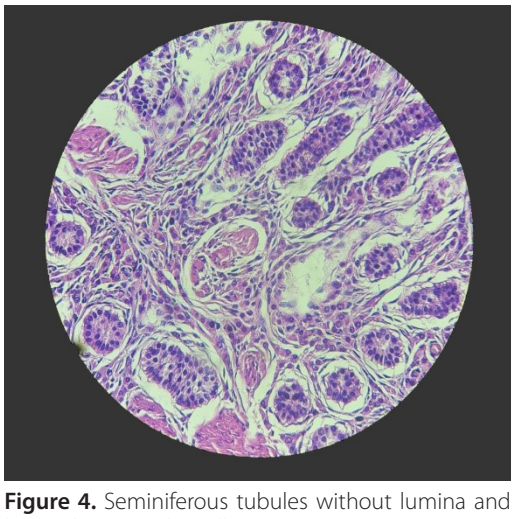

Figure 4. Seminiferous tubules without lumina and hyperplastic Leydig cells

area and cause discomfort or for aesthetic reasons, it will be necessary to remove them before puberty, with hormone replacement therapy to initiate puberty until the desired breast and genital development is reached[10].

Subsequently, estrogens should be started at sufficient doses to allow vaginal lubrication and bone gain[5,10]. For short vaginas, dilation techniques or surgery can be used to allow sexual intercourse and avoid dyspareunia. Periodic monitoring should be maintained in the areas of endocrinology, gynecology, psychology and urology[9,10,15]. Morris describes that after castration there are hot flashes, vaginal dryness and breast atrophy, so it was not advisable to perform this procedure[1].

Women who do not accept gonadectomy should maintain an annual follow-up, due to the risk of malignant degeneration, with pelvic ultrasound and abdomino-pelvic magnetic resonance imaging to evaluate the size and location of the gonads in addition to the verification of tumor markers such as alpha fetal protein, human chorionic gonadotropin beta fraction and lactate dehydrogena[16].

It has been described in women with normal breast development and high height, female hair and without baldness, who less frequently present some masculinization of external genitalia, such as clitoromegaly or fusion of the lips. In some of the revisions, it has even been possible to find remains of Müller's ducts (fallopian tubes) in up to a third of those affected[10].

Testosterone levels rise in the period of puberty at the same time that follicle stimulating hormone levels increase with decreased luteinizing hormone levels, which suggests that there is androgenic resistance in the pituitary hypothalamic level[17]. The increase in gonadotrophins, as a result of insensitivity, produces an increase in the production of testosterone and estradiol by Leydig cells[5,17]. Similarly, because aromatase activity (an enzyme that transforms testosterone into estradiol) is preserved, it increases the synthesis of estrogens, which are responsible for breast development during puberty in these individuals[5].

The recommended imaging studies to confirm the diagnosis of absence of Müllerian structures and location of the gonads are pelvic ultrasonography and magnetic resonance imaging[13,18]. The testicles are bilaterally retained in the abdomen between 50 and 70 % of cases; in the inguinal region, in 20 %; located one in the inguinal region and one in the abdomen, between 10 and 30 % of cases. Other rare locations occur in the labioscrotal region[8].

The differential diagnoses to be taken into account correspond to the deficiency of the enzyme 5α-reductase, the Mayer-Rokintansky-Küster-Hauser syndrome, the Kallmann syndrome, the pure gonadal dysgenesis 46 XX, 46 XY, the agenesis of Leydig cells due to abnormality in the receptor for luteinizing hormone and the enzymatic deficit that are expressed as sexual ambiguity at birth[18].

In the complete AIS, personal characteristics and external genitalia correspond to those of a woman. In general, these women do not differ from others with respect to patterns of marriage or other types of relationships, so it is not often that sex assignment dilemmas arise, although some of them may present conflicts of sexual identity[19]. Hence the importance of multidisciplinary care, and including the collaboration of a psychologist or psychiatrist in treatment considerations, to assess the patient's need to reinforce sexual identity; to the family, to prepare them for the sequences of diagnoses and treatments that await them during their lifetime[9].

Ethical aspects

For the publication of this case, the informed consent of the patient and the person in charge was obtained, both for the hospital care in which the physical examination was carried out and for the publication of this article with the commitment to maintain the privacy of the patient, as established in the Declaration of Helsinki.

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