CLINICAL CASE

Complete androgen insensitivity syndrome: a case report and surgical management illustration

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Abstract The term “disorders of sexual differentiation” (DSD) encompasses a group of abnormalities in the development of the genitourinary tract. Atypical development occurs at one or more chromosomal, gonadal, or anatomic levels. 46 XY genetic males may present with external genitals that are phenotypically female or ambiguous. Androgen insensitivity syndrome could be considered a disease caused by resistance to androgenic action due to the Xq11-12 mutation that affects the androgenic receptors. Clinical presentation depends on the degree of insensitivity: mild (infertile male), partial, or complete, as with our patient. Psychologic and psychiatric follow-up is required for both the patient and family members so there can be adequate psychosexual development before and after definitive surgical treatment.

The aim of this article was to conduct a systematic review of published reports in the MEDLINE database to identify the epidemiology and incidence of complete androgen insensitivity syndrome and to examine the approach, treatment, and follow-up of these cases.

We present herein a 23-year-old patient, with an unremarkable pathologic history, who began to be studied by the Gynecology Service at 17 years of age due to amenorrhea and lack of secondary sexual development. Imaging studies failed to show Müllerian structures. Diagnostic laparoscopy was performed on 2 occasions in which female sexual organs or vestiges of testes were unable to be identified. Hormonal study revealed obviously low levels of estrogens and testosterone, and follicle-stimulating hormone (FSH), luteinizing hormone (LH), and gonadotropin-releasing hormone were within normal parameters; 46XY karyotype was reported. Psychiatric support was then offered. It was decided that the patient would continue to be raised and treated as a female and therefore she was given breast implants. Our service was subsequently consulted for performing vaginoplasty using an intestinal segment as the vaginal canal.
Introduction

The recently coined term “disorders of sexual differentiation” (DSD), previously known as “intersex condition, hermaphroditism, and pseudohermaphroditism”, has now been adopted, since experts worldwide prefer this nomenclature; it is a class of abnormalities in the development of the genitourinary tract, in which there is atypical development at one or more levels: chromosomal, gonadal, or anatomic. Genetic males with DSD (46XY) can present with genitalia externally phenotypically feminine or ambiguous. The syndrome of insensitivity to androgens could be considered an entity caused by the resistance to the action of androgens, caused by the mutation Xq11-12, which affects the androgen receptors; the clinical presentation will depend on the degree of insensitivity, male (infertile), moderate or complete as in our case. Requires follow-up by psychologist and psychiatrist for family and patient, for a psychological-adolescent development, before and after the definitive surgical treatment.

Case presentation

A 23-year-old patient, single, with no past history of remarkable hereditary, familial, or personal pathologies related to this case, began to be studied at 17 years of age by the Gynecology Service for presenting with amenorrhea and lack of development of secondary sexual characteristics. Imaging studies revealed no evidence of Müllerian structures or renal alterations and so the patient underwent diagnostic laparoscopy on 2 occasions in which internal sexual organs were looked for. No female sexual organs or remnants of testes were found and an immediate hormone study showed a total estrogen level of 15 pg/dl. These studies were repeated various times with no significant differences; follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were within normal low parameters and testosterone was always very low (the last value was 1.07 ng/dl). The genetics team was called in and they carried out the karyotype study that reported 46XY (fig. 1).

The case was presented to the Hospital Ethics Committee and with the consent of the patient and her family she underwent breast implantation at the Plastic Surgery.
Service. Finally, we were consulted to perform a vaginoplasty using intestinal segment for the vaginal canal.

Initially, patient preparation was a liquid diet one day before surgery and enemas. With the patient under general anesthesia and in the lithotomy position, a midline infraumbilical incision was made. Dissection up to the abdominal cavity was done by layers, and detailed exploration revealed the absence of Müllerian structures and testicular remnants, a normal capacity bladder, and no bimanually palpable prostate. The opening of the dome in the urogenital diaphragm was begun (figs. 2 and 3).

Twelve centimeters of the sigmoid colon were then selected, due to its extensive vasculature and redundant mesentery. An end-to-end anastomosis was performed. The resected segment was taken to the new vaginal canal and anastomosed and closed in 2 layers (figs. 4-6).

Because the patient progressed adequately, she was promptly released from the hospital. Follow-up included 20-minute dilations with a Hegar dilator at home, 3 times a week, with a gradual increase in measurements from 8 to 22 mm at the end of 10 months. At the 6-month follow-up, the patient presented with a mild discharge of mucus twice a week, due to the colon segment. She continues to undergo both psychologic and psychiatric treatment and has a satisfactory sex life with her current partner, as well as a normal work life.

Discussion

The androgen insensitivity syndrome can be considered a disease caused by resistance to androgen action that influences 2 things: the morphogenesis and differentiation of body structures and systems that these hormones have an effect on. It depends on an X mutation in the androgen receptor gene in which a variety of phenotypes can be expressed; from infertile males to normal external female genitals.\(^1\) John Morris\(^2\) was the first to describe this syndrome, but it was not until 1989 that the exact location of the androgen receptor gene was discovered to be on Xq11-12, where it was demonstrated that the mutation can present and the disease develop.\(^3\) The androgen receptors are expressed from gestation week 8, and the testes of the male embryo begin to secrete testosterone at week 9, with 2 peaks at weeks 11 and 18. The epididymis, vas deferens, and seminal vesicles simultaneously differentiate from the Wolffian ducts. A more potent androgen, dihydrotestosterone, originates from testosterone through the action of type 2 5-alpha-reductase and stimulates the differentiation of the male genital primordium.\(^9\)

The clinical phenotypes of androgen insensitivity syndrome may vary depending on the severity of resistance and they are classified into 3 grades: complete, partial, and mild.\(^10\) Complete resistance, in particular, is characterized by a short vagina ending in a blind sac, absence of the Wolffian products such as the epididymis, vas deferens, seminal vesicles, or prostate. Clinical presentation from birth is a totally female phenotype, making its early diagnosis difficult.\(^11\) An important pattern helping establish clinical suspicion is that in puberty there is generally slow or small mammary growth in relation to chronologic age, with very little or no axillary and pubic hair.\(^12\) Other clinical characteristics that can be found are mono or bilateral inguinal hernia, even though the differences with apparently female patients are minimal, making an earlier diagnosis difficult to suspect. This syndrome is the cause of 10% of all cases of primary amenorrhea.\(^5\)

With respect to endocrine presentation in these patients, we can find: normal or increased LH and testosterone slightly above normal in the first month of life. After that, LH and testosterone levels are normal until puberty\(^13\), due
androgen insensitivity and the lack of negative feedback of the sex hormones in the hypothalamus and hypophysis. Testosterone is aromatized and converted into estrogens at a later time through enzyme action. This is why patients with complete insensitivity have higher estrogen levels than normal males and develop mammary growth. In addition, they can have normal anti-Müllerian hormone levels, explaining the absence of internal female sexual characteristics.

Differential diagnoses in 46XY patients

Among the other diagnoses that should be contemplated when evaluating an individual with DSD are: Swyer syndrome, in which the lack of testicular development in the early stages of the embryonic period leads to the formation of female sexual characteristics such as the uterus and Fallopian tubes; paramesonephric duct participation and the lack of testosterone and anti-Müllerian hormone sent by the testes results in rudimentary female sexual development with no ovaries. Among other differential syndromes are: testicular feminization that consists of well differentiated female sexual characteristics, with a short undeveloped vagina, and bilateral cryptorchidism, but with no uterus, and ovotestes, also known as “true hermaphrodite” syndrome, which presents with ovaries with seminiferous tubes, as listed in table 1.

Follow-up

It is currently recommended to raise the awareness of the patient’s relatives in regard to the surgical management, emphasizing its risks, benefits, and potential outcomes so that they can participate more actively in the care of their child. Psychosocial management is the basis of promoting a positive adaptation. These patients require professional follow-up to help them manage the sexual dysfunction and gender dysmorphia as they become present. Group therapy is also recommended because support is necessary up to the adult age so these patients can develop a healthy psychosexual life.

The risk for acquiring malignant disease in this type of patient exists, especially for presenting germ cell tumors such as gonadoblastoma, dygerminoma, or seminoma,
given that they all belong to the same type of cancer and arise from undifferentiated gonadal tissue. Therefore they should be intentionally looked for and dysmorphic gonads should be extracted at an early age.

Today an international database, called i-DSD, is accessible that includes cases recognized by researchers from specialized centers, as well as isolated case reports from private medical practices. This information is available to patients, their families, and doctors so they can know where to find the specialized research centers and information on the disease, treatment, and follow-up.

**Conclusions**

Complete androgen insensitivity is included in the term DSD, and can include patients ranging from infertile men to those individuals presenting with complete female phenotype with no internal sexual organs, as was the case with our patient.

It is a rare entity that has a psychologic impact on family members, as well as a psychosexual impact on the patient. Thus, counseling is required from the time of diagnosis, so that doubts can be cleared up and there can be support during the sexual adaptation. These patients require lifetime maintenance from their psychotherapist, as well as their urologist, who will monitor lower urinary symptoms and carry out periodic hormone function tests. A database is currently at the disposition of patients, relatives, and attending physicians where they can become familiar with the clinical characteristics of the disease and connect with support groups.

During surgical treatment it is important to provide extensive counseling on the expectations of both the patient and family members in relation to the procedure, clearly explaining its likely complications. The surgeon should also intentionally look for hypofunctioning dysmorphic gonads and remove them, in order to prevent the aforementioned probability of malignant transformation.

**Table 1** Differential diagnoses in the medical conditions of disorders of sex differentiation.

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Clinical characteristics</th>
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<tr>
<td>Swyer syndrome</td>
<td>Presence of a uterus and rudimentary tubes</td>
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<tr>
<td>Testicular feminization</td>
<td>Female secondary sexual characteristics, but bilateral cryptorchidism</td>
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<tr>
<td>Ovotestis</td>
<td>Presence of seminiferous tubes in ovaries</td>
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**Conflict of interest**

The authors declare that there is no conflict of interest.

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**References**


