

CASE STUDIES

Bilateral Sertoli-Leydig cell tumor in a patient with complete androgen insensitivity syndrome: a case report and brief review of the literature

Tumori bilaterale cu celule Sertoli-Leydig la o pacientă cu sindrom de insensibilitate completă la androgen: un studiu de caz și o scurtă revizuire a literaturii de specialitate

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Abstract

Introduction. Complete androgen insensitivity syndrome (46XY) with female phenotype is characterized by: well developed breasts, absent uterus and ovaries, short vagina, intra-abdominal testicles and also absent pubic and axillary hair. The cause is a mutation of the androgen receptor gene, located on the proximal long arm of the X chromosome (Xq11-120), which prevents the receptors and their ligands, including testosterone, to function properly.

Case. We report the case of a 40-year-old woman with primary amenorrhea and infertility problems who presented to the doctor after discovering two pelvic tumors. The diagnosis was complete androgen insensitivity syndrome with bilateral Sertoli-Leydig cell tumor and was based on the clinical features, histology exams and genetic result.

Conclusions. Intra-abdominal testes have a great risk of malignant transformation. Sertoli-Leydig cell tumors represent a rare entity, but being associated with the androgen insensitivity syndrome, they can appear in up to 80% of the cases. Genetic tests are of particular importance in sports selection and athletic performances in female athletes.

Keywords: androgen insensitivity syndrome, Sertoli-Leydig cells, infertility.

Rezumat

Introducere. Sindromul de insensibilitate completă la androgeni (46XY) se caracterizează prin: sâni bine dezvoltati, uter și ovare absente, vaginul scurt, testiculele intraabdominale prezente și părul pubian și axial absent. Cauza este o mutație a genei receptorilor de androgeni, localizată pe brațul lung proximal al cromozomului X-Xq11-12, care blochează receptorii la acțiunea hormonilor androgeni.

Cazul. Prezentăm cazul unei femei de 40 de ani cu amenoree primară și sterilitate, care se prezintă la medic pentru descoperirea unor formațiuni tumorale pelvine. Explorările clinice, histologice și rezultatele genetice au pus diagnosticul de tumoră bilaterală cu celule Sertoli-Leydig asociată sindromului de insensibilitate completă la androgeni.

Concluzii. Testiculele intraabdominale prezintă un risc crescut de malignizare. Tumorile cu celule Sertoli-Leydig reprezintă o entitate rară care, în asociere cu sindromul de insensibilitate completă la androgeni, se întâlnesc în până la 80% din cazuri. Testele genetice prezintă o importanță deosebită în selecția sportivă și în evaluarea performanțelor sportive în cazul sportivelor.

Cuvinte cheie: sindrom de insensibilitate completă la androgeni, celule Sertoli-Leydig, infertilitate.

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Introduction

Androgen insensitivity syndrome (AIS) or testicular feminization, named after the American gynecologist John Morris, is an X-linked recessive genetic condition. AIS leads to 46, XY, with the presence of a female phenotype: well developed breasts, absent uterus and ovaries, short vagina, bilateral undescended testes and also absent pubic and axillary hair (Sharma et al., 2012; Pizzo et al., 2013; Hughes et al., 2012). This can be caused by a mutation of the androgen receptor gene, located on the proximal long arm of the X chromosome - Xq11-12- which prevents the receptors and their ligands, including testosterone, to function properly (Ozülker et al., 2010).

AIS has 3 subcategories: complete (CAIS), mild (MAIS) and partial (PAIS) insensitivity; this classification describes the different levels of virilization (Farhud et al., 2016). The prevalence of AIS has been estimated to be one case in every 20,000 to 64,000 newborns for CAIS and it is unknown in the case of PAIS (Mendoza & Motos, 2013).

Diagnosis is made at puberty as primary amenorrhea must be present. AIS includes normal testicular development and an increased risk of malignant germ cell tumors, therefore early gonadectomy is recommended (Bel Hadj Youssef et al., 2008). Sertoli and Leydig cell tumors represent 1% of germ tumors and they are frequently associated with the testicular feminization syndrome (Fagouri et al., 2014).

We present a rare case of the association of bilateral Sertoli-Leydig cell tumors in a patient with CAIS.

Hypothesis

We present the case of a 40-year-old woman with AIS and bilateral Sertoli-Leydig cell tumor as a model for postoperative management of treatment.

Material and methods

The study was carried out according to current deontological laws, with the approval of the Ethics Committee of the Clinical Emergency Hospital Cluj-Napoca, after the patient gave her written informed consent.

Research protocol

a) Period and place

In September 2017, the patient presented to the “Domic Stanca” Clinic of Obstetrics and Gynecology Cluj-Napoca after discovering a large pelvic tumor.

b) Subjects

Patient D.D., aged 40 years, first medical examination was 5 years before for primary amenorrhea, infertility problems and discovery of a large pelvic tumor. The patient described the absence of menarche, however she observed the first signs of puberty at the age of 11.

c) Tests applied

Clinical examination revealed female phenotype, with adequate development of sexual characteristics: normal breasts (Tanner IV), height 174 cm and weight 86 kg. The gynecological exam showed normal external genital organs and the absence of pubic hair (Tanner III), normal labia and clitoris, without hypertrophy, short blind vaginal pouch, absent cervix. At bimanual vaginal examination, a right sided mobile tumor, with a diameter of 10 cm, firm consistency, mildly sensitive, was palpable. The uterus and

ovaries were not palpable.

Ultrasound showed an irregular, large pelvic tumor of 10.5/7.7 cm, with parenchymal consistency; the uterus and ovaries were not visualized. For a better view, MRI was suggested.

MRI exam identified two pelvic tumors, a right latero-uterine mass of 10/10/9.9 cm (AP/CC/LL); in the left iliac region, a mass of 1.9/5.7/2.3 cm (AP, CC, LL); no signs of uterus and ovaries (Fig. 1).

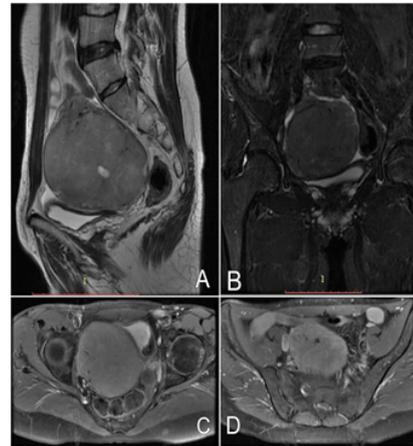


Fig. 1 – A and B - Sagittal and coronal T2W MRI scan of the abdomen and pelvis shows a tumor mass with a hypointense zone that corresponds to fibrous tissue; in the upper region there is a liquid capsule rich in flow voids that appear to be blood vessels. C and D - Axial T2W MRI scan shows a high uptake mass in the left iliac region, posterior to the psoas muscle.

During exploratory laparotomy, a midline fibrous tissue was seen at the insertion of the bilateral uterosacral ligaments. The uterus, bilateral fallopian tubes and cervix were absent. In the right iliac region, a 10/8 cm well-defined fibrous mass was found, in contact with the round ligament. Contralateral to this mass, an ovary-like connective tissue was present, without any specific structure.

The mass was extracted and sent to histology exam, which revealed either ovarian dysgerminoma with Sertoli and Leydig cell proliferation, or atrophic testes (pT2NxMxL1v0) (Fig. 2).

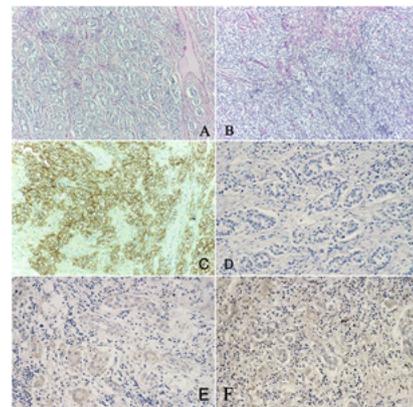


Fig. 2 – A - Hematoxylin-eosin (H & E) stain: the tubular pattern component of the tumor. B - H&E stain: nests of tumor cells separated by fibrous stroma with lymphocytes and giant cells. C - CD117 (c-Kit): strong membrane expression. D - CK7: negative. E - Alpha-fetoprotein (AFP): negative. F - CD30: negative - original magnifications X200 (A, B, C) and X400 (D, E, F).

During endovaginal *ultrasonographic exams*, a tumor in the left iliac region was found, which increased in size during a year, from 39/24 mm to 62/45 mm, and showed no signs of vascularization. As the patient had a history of Sertoli-Leydig cell tumor, another surgical intervention was advised. Laparotomy revealed an irregular mass 5x3 cm in size, with firm consistency, located in the left iliac region (Fig. 3).



Fig. 3 – Gross image of the removed left gonad

Histology of the mass describes a well differentiated Sertoli-Leydig cell tumor (Meyer type I) (Fig. 4).

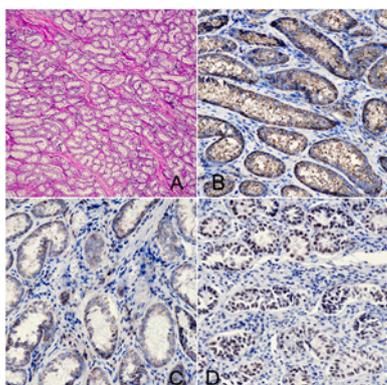


Fig 4 – **A** - Hematoxylin-eosin stain shows a tubular pattern of cubic and cylindrical cells, with round, basal oriented nuclei and clear cytoplasm (Sertoli cells), intermingled with small nests of tumor cells with eosinophilic cytoplasm (Leydig cells). **B** - Inhibin stain highlights cytoplasmic positivity in both tumor cell populations (Sertoli cells and Leydig cells). **C** - Melan - A expression. **D** - WT-1 stain shows nuclear positivity in Sertoli cells - original magnifications X100 (A) and X400 (B, C, D).

A detailed clinical inspection and histology exams were followed by genetic testing which resulted in 46, XY.

Our diagnosis of complete androgen insensitivity syndrome with bilateral Sertoli-Leydig cell tumor was based on the clinical features, histology exams and genetic result.

Discussion

Sexual differentiation is a complex mechanism and is compound of the following major elements: chromosomes

and genes, gonads, hormonal profile, anatomy and psyche. Chromosomal and genetic sex is determined in the first seconds of life, and is essential for the development of the next levels. At the time of fertilization, two *haploid* chromosomal sets fuse, each of them containing 22 autosomal chromosomes and 1 heterosomal chromosome, and form a *diploid* cell, either 46, XY (male), or 46, XX (female). The Y chromosome has a sex determining region (SRY - sex determining region of Y), which plays a major role in testicular formation and differentiation. In the absence of this gene, the presence of testes is improbable and feminine gonads appear. By the 9th week of male development, Leydig cells are formed and start to produce testosterone, responsible for male phenotype and characteristics; Sertoli cells secrete anti-Mullerian factor which prevents the development of Mullerian ducts into female genital organs: uterus, fallopian tubes and upper part of the vagina (Sadler, 2010).

In the absence of testosterone, the male phenotype is compromised; however, the presence of the anti-Mullerian factor inhibits the internal female genital organs to form, causing testicular feminization. Altered testosterone action can appear in different situations. On the proximal long arm of X chromosome (locus Xq11-Xq12), there is a gene responsible for specific nuclear androgen receptor, which is essential for the hormone's intracellular action. Mutation or absence of this gene causes malfunction of androgen receptors and prevents testosterone to act on peripheral cells. In 1989, Lubahn et al. (Lubahn et al., 1989) isolated the 8 exons of the AR (autosomal recessive) gene, located on the X chromosome, and also its mutation resulting in testicular feminization. This condition was first reported by John Morris (1853) (Galani et al., 2008).

In sports competitions, the presence of pseudohermaphrodites violates the principles of biological equality. Intersexuals benefit from androgen hormones, which are responsible for more developed muscle mass and mental balance. Here we include women with pure dysgeusia, such as AIS, and women with hypoplastic ovaries, normal karyotype and primary amenorrhea. These, despite having no additional sources of androgens, are taller and have longer legs (Drăgan et al., 1982).

In 1966, tests for female eligibility were introduced. These tests were based solely on physical examination. Since the 2000 Summer Olympics, questioned sex and gender has been evaluated on a case-by-case basis by a team of specialists in endocrinology, genetics, gynecology and psychology (Ballantyne et al., 2012).

Endogenous androgenic hormones in the circulation of elite female athletes with disorders of sex development give them a competitive advantage. In the case of CAIS, a high testosterone level would be of no significance. The genetic component in the case of sex segregation in sports seems largely provided by the Y chromosome. Tallness, whether determined by genes on the Y or any chromosome, offers an example of an acceptable variable that contributes to athletic success in elite female athletes, including those with 46 XY (Ferguson-Smith & Bavington, 2014).

Talking about equality, in events where androgenization provides a powerful advantage, women competing against women with a degree of hyperandrogenism that gives

them a male physiology are likely to be at a disadvantage tantamount to competing in the male category. For this reason, women with AIS and hyperandrogenism have two options of treatment to stop virilization: hormonal suppression of androgens (estrogen-containing oral contraceptives) or surgical removal of the source of androgens.

The policies about eligibility of females with hyperandrogenism have been criticized by some. For eligibility purposes, no female athlete is forced to undergo gonadectomy.

Particular attention should be paid to how assessments are initiated to protect athletes from stigma. Informed consent, privacy and psychological support all along the process and during the first years of treatment are of critical importance (Bermon et al., 2015).

AIS can be classified into 3 subgroups, each of them describing a different level of virilization: CAIS (complete AIS); PAIS (partial AIS); MAIS (mild AIS). According to Qigley et al. (1995), CAIS represents a normal female phenotype with the absence of pubic and axillary hair; PAIS is a combination of female and male characteristics, and MAIS can be described as a normal male phenotype, with infertility due to azoospermia and reduced virilization.

Our patient showed clinical features characteristic of CAIS, with the absence of pubic and axillary hair, well represented feminine adipose tissue and breasts. Female external genital organs were present but the labia majora was underdeveloped. Internal female genital organs were absent, with total absence of the uterus and presence of two tumor masses in the pelvis. As total absence of the uterus was first discovered by imaging techniques (US/MRI) and later by exploratory laparoscopy, hormonal assessment of primary amenorrhea was not performed. The first diagnosis was Mayer-Rokitansky-Kuster-Hauser syndrome; however, MRI showed an irregular tumor with unusual structure in the right side of the pelvis, with increased dimensions compared to a normal ovary. Clinical examination showed sensitivity in the lower abdomen, therefore extraction and histological examination of the right lateral mass was recommended. Histological findings showed either an ovarian dysgerminoma with the proliferation of Sertoli and Leydig cells, or atrophic testes. Ovarian Sertoli-Leydig cell tumors are considered rare conditions which appear in women aged 20-30 years and represent less than 0.5% of all ovarian neoplasms (Melero Cortés et al., 2017). CAIS patients have a 5-10% higher risk of developing germ cell tumors, neoplasms being uncommon. Sertoli-Leydig cell tumors are usually benign in this category of patients. Also, well differentiated Sertoli-Leydig cell tumors are associated with CAIS in 10% of the cases. In CAIS, malignant evolution of remnant testes is imminent and has a 5-10% risk in the first 25 years, which can increase up to 33% at the age of 50 (Fagouri et al., 2014). According to these findings and histological results, the left sided tumor mass was also extracted and analyzed, to prevent its possible malignant transformation. The second histopathological diagnosis showed a well differentiated Sertoli-Leydig cell tumor. The association of the Mayer-Rokitansky-Kuster-Hauser syndrome with the rare Sertoli-Leydig cell tumors was highly improbable, therefore

chromosomal testing for CAIS was recommended, which showed 46, XY. Chromosomal testing along with imaging, histological and clinical findings confirmed the diagnosis of CAIS. Mutation analysis of our patient's and her family's genome could provide the final diagnosis of the AIS type, but we should consider some psychological and social aspects before revealing our results to the patient. She is now a 40-year-old woman, married, who wants children and has difficulties accepting the fact that without uterus this is impossible, and this information could also affect her interpersonal relationship with her husband. We also analyzed the family history, which evidenced no signs of infertility or intersexuality problems, but this cannot exclude the presence of the recessive mutation in the genome of other female relatives. This ethical dilemma implies multidisciplinary cooperation.

Conclusions

1. AIS is a rare condition, caused by the resistance of peripheral tissues to androgens.
2. Female athletes with hyperandrogenism do not possess any physical attribute relevant to athletic performance that is neither attainable, nor present in other women.
3. Sertoli-Leydig cell tumors represent a rare entity, but being associated with testicular feminization, they can appear in up to 80% of the cases. Treatment is composed of prophylactic bilateral gonadectomy and hormonal substitution for the proper development of secondary genital characteristics.
4. Genetic tests are of particular importance in sports selection and athletic performances in female athletes.

Conflicts of interests

Nothing to declare.

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