46 XY Female with Bilateral Gonadoblastoma

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Informed consent was obtained from the patient.

Abstract

We report the case of a 17 years old girl, investigated for primary amenorrhea and lack of pubertal development. She had normal height and Tanner stages - P1 B1. The hormonal investigations revealed hypergonadotropic hypogonadism. The CT examination showed a small uterus but no internal gonads. The karyotype was 46 XY and she was diagnosed with Swyer syndrome with streak gonads. Gonadectomy was performed. The histological and immunohistochemical examination showed bilateral gonadoblastomas. Under estro-progestative therapy the evolution was favorable, with regular menses and the development of secondary sexual characteristics.

Keywords: *46 XY female, SRY, gonadoblastoma*

Rezumat

Prezentăm o pacientă de 17 ani, investigată pentru amenoree primară. Pacienta prezintă statură nomală, cu stadiile Tanner P1 B1. Paraclinic s-a demonstrat hipogonadism hipergonadotrop. Examinarea CT a arătat un uter hipolazic, fără gonade interne. Cariotipul a fost 46 XY şi a fost diagnosticată cu sindrom Swyer. S-a practicat gonadectomie bilaterală. Examenul histopatologic şi imunohistologic au arătat gonadoblastoame bilaterale. Sub terapie estro-progestativă, a prezentat evoluție favorabila, cu menstre ritmice şi dezvoltarea caracterelor sexuale secundare.

Cuvinte-cheie: *46 XY sex feminin, SRY, gonadoblastom*

Introduction

Disorders of sexual development are characterized by disruption of typical sexual development, resulting in a discrepancy in the chromosomial, gonadal and phenotypical sex. Gonadobalstomas (GB) are rare benign tumors, developing in about 30% of patients with intersex disorders that have intraabdominaly located gonads and a complete or incomplete Y chromosome. These sex disorders include: male pseudohermafroditism and complete androgen resistance (karyotype: 46 XY); mixed gonadal dysgenesis (karyotype: 45 X/46XY) and some Turner patients (karyotype: 45 XO, SRY +). Because of the risk for malignant degeneration of GB into a malignant germinoma, prophylactic gonadectomy is recommended.

Case report

We present the case of a 17 years old girl admitted for primary amenorrhea and lack of pubertal development. The personal and familial histories were unremarkable.

The clinical examination showed a normal weight patient (BMI - 19 kg/m^2), with a normal height, corresponding with the mid-parental height (169 cm tall, +0.9 SD). The external genitalia were normal but infantile, and her Tanner stages were B1P1.

The biochemical and hematological panel were normal.

The hormonal investigations revealed hypergonadotropic hypogonadism: low levels of estradiol and testosterone (E2-3.19 pg/mL; TST-0.6 ng/mL, normal values lower than 0.72) and high levels of gonadotrophs LH-43.41 mUI/mL; FSH-160.44 mUI/mL. The levels of Prolactin were normal (Prl-24.38 ng/mL, normal values <28 ng/mL) and also the thyroidian function (TSH-1.68 mUI/L, normal range 0.5-4.5 mUI/L)

The computed tomography of the abdomen and pelvis showed only a small uterus, of 1.08 cm by 2.16 cm, but no visible internal gonads (figure 1).

The karyotype was 46 XY with a negative Barr test. She was diagnosed with XY gonadal dysgenesis with streak gonads and gonadectomy was

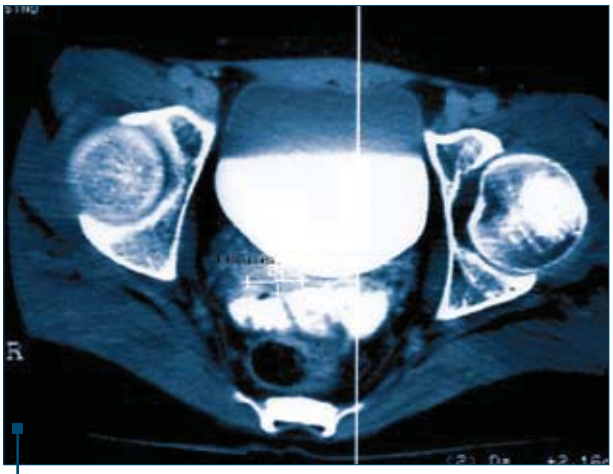

Figure 1. CT exam of the pelvis showing a small uterus, but no internal gonads

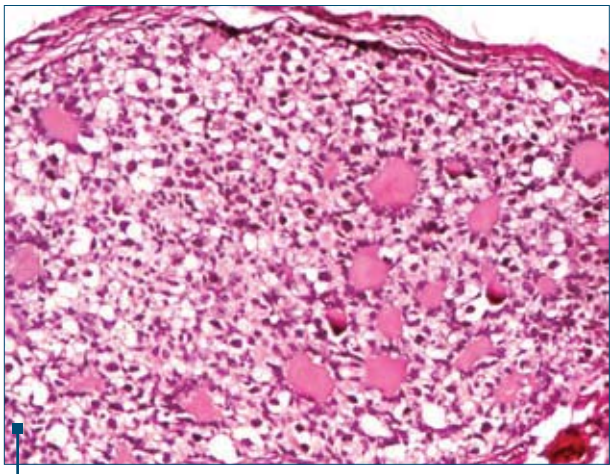

Figure 2. Histological aspect: Haematoxilin-eosin, 10X

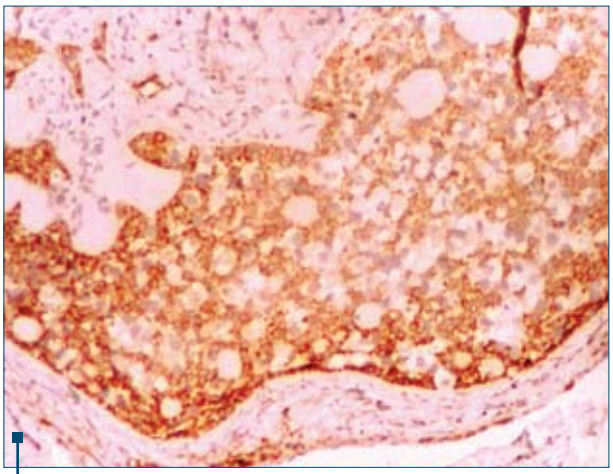

Figure 3. Imunohistochemical aspect: INHIBINA positive, 20X

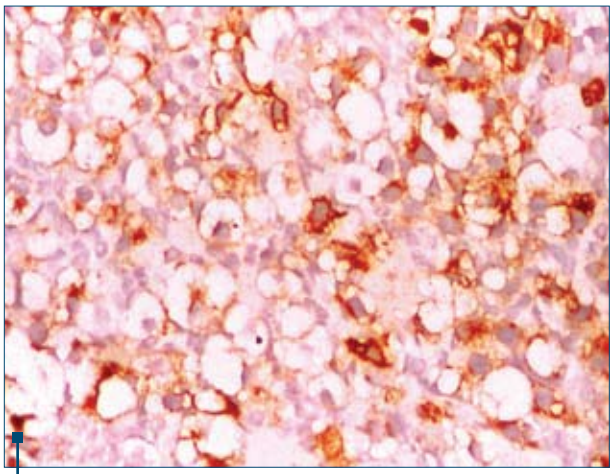

Figure 4. Imunohistochemical aspect: PLAP positive, 20X

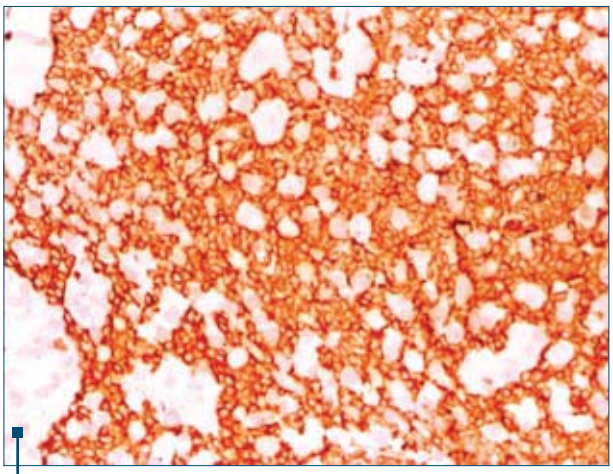

Figure 5. Imunohistochemical aspect: VIM positive, 10X

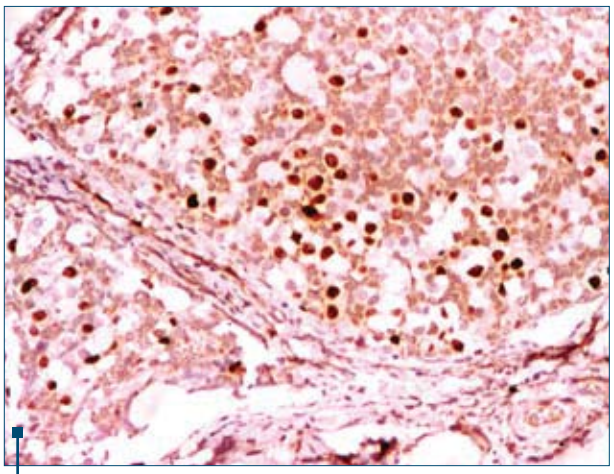

Figure 6. Imunohistochemical aspect: Ki 67-10% positive, 10X

decided. The surgical exploration of the pelvis revealed small, atrophic gonads (of 1 by 0.5 cm) at the lateral extremities of the Fallopian tubes. The uterus and the Fallopian tubes were atrophic. Bilateral gonadectomy was performed, leaving the uterus in place. The histological examination revealed the aspect of ovotestis, with tumoral proliferation of the cells from sexual cords, suggesting a gonadoblastoma (figure 2).

The immunohistochemical examination confirmed the diagnosis of gonadoblastoma: with Inhibin, ViM, Melan A and PLAP positive in the majority of the tumoral cells and Calret and EMA positive in a minority of tumoral cells. MNF116 was negative and Act was positive in the blood vessels and the stroma. The proliferative index Ki67 was 10% (figures 3-6).

After the surgical scar healed, substitution therapy with estrogens and progesterone was started. The secondary sexual characteristics developed normally and after 12 month she had regular menses and her Tanner stages were B4P3.

Discussions

Disorders of sexual development are conditions in witch there is atypical sexual development of the embryo resulting in discordance between chromosomial, gonadal and phenotypical sex[1]. Swyer syndrome is a distinct type of pure gonadal dysgenesis characterized by a 46 XY karyotype in female phenotypic patients. The estimated prevalence is about 1 in 80,000[2], out of a total prevalence of disorders of sex development of 1 in 20,000[3]. Such cases, like the one we presented, are usually diagnosed later in life, patients usually presenting with primary amenorrhea and delayed puberty.

The phenotype is female, with an above normal height and normal Mullerian internal structures, unlike patients with androgen resistance syndrome, which they otherwise resemble[2,4]. The external genitalia can be normal or they can present clitoromegaly, depending on the degree of testicular differentiation and secretion of testosterone. Hirsutism is not usually present, although in cases with androgen secretion from the ovarian tumor, it can be present. As all patient with hipogonadism, they can present low bone mineral density as evaluated by dual X ray absorbtion, and one study found osteopenia in 60% of subjects[2].

Paraclinical investigations reveal hypergonadotrophic hypogonadism, with high values of FHS and LH during infancy and after puberty and low levels of estradiol. Androgens are within normal range for females, but low for males. Stimulation with hCG analogues does not increase the level of testosterone, but such test is not compulsory for diagnosis.

Patients with disorders of sexual development present the risk of GB development, with a cumulative risk about 30% by the age of 40[2]. GB are considered benign tumors, and do not metastasize, but can progress to a seminomatous or non-seminomatous invasive cancer so prophylactic bilateral gonadectomy is recommended(5). If it can not be performed, annual abdominal sonograms are necessary for surveillance.

Sometimes, as with our patient, gonadoblastomas are too small to be visible imagisticaly. If large enough, they appear as solid tumors in the lower abdomen. Cases with bloody ascites have been reported[6].

GB can be hormonally active, and a study on 6 patients with Swyer syndrome and GB or dysgerminoma, 2 secreted estrogens and one androgens[7].

Treatment with estrogens and progestatives is necessary in order to increase BMD and to induce the development of secondary sexual characteristics. Pregnancy can be achieved with hormonal preparation and donated ovules[2].

Gonadal biopsy or the post operatory examination can reveal gonads with reduced size and number of seminiferous tubules, without germ cells, with peritubular fibrosis, and hyperplasia of Leydig cells, or in cases of complete gonadal dysgenesia, undeveloped streak gonads. GBs appear as an intimate mixture of germ cells and elements resembling immature granulosa or Sertoli cells. In a study performed on 5 cases of Swyer syndrome, two patients presented streak gonads, two had GB and one had dysgerminoma[4].

A study on 60 specimens obtained from patients with gonadal disgenesys identified GB in 20, imunohistochemicaly, all were positive for octamer binding transcription factor (OCT) 3/4. In 50% of cases, the tumor was surrounded by areas of undifferentiated gonadal tissue, with similar imunohistochemical staining, suggesting that these cells are the origin of GB[8].

For the development of GB, the presence of a complete or partial fragment of the Y chromosome, containing the GBY region is mandatory. The gene considered responsible is the TSPY gene, which in normal males is involved in stem cell proliferation. Studies on mice reveal that abnormally increased TSPY expression increases cell proliferation and the development of tumors by interacting with the type B cyclins and promoting G(2)/M transition in the cell cycle[9].

Because the difficulty of differentiating between (pre)malignant germ cells such as GB and normal germ cells showing delayed maturation, in order to prevent excessive gonadectomy OCT ¾ and TSPY have been proposed as tracers[10].

Genetics

There are several genes involved in the appearance of Swyer syndrome, but 5 of them are more frequent: SRY, (affected by deletion or sequence va-

riant), NR5A1 (sequence variant), DHH (sequence variant), NR0B1 (duplication), or WNT4 (duplication).

Mutations or deletions in the SRY gene have been identified in 15-20% of individuals with Swyer syndrome, implying complete loss of gene function. In about 1% of patients with disorders of sexual development, mutations with partial loss of function have been identified. Cases are mostly sporadic, but one third are familial some inherited from a father with a Y chromosome mosaicism. The rest of the familial cases are probably determined by the presence of other genes that alter the expression of SRY or its DNA binding capability[11].

Mutations in NR5A1 (also known as SF1) have been initially found in patients with congenital adrenal hypoplasia and primary adrenal insufficiency. In these cases, the patients were homozygous for mutations witch decreased the binding ability of SR1 to the nuclear receptor. Heterozygous relatives were normal, suggesting a dose dependant mechanism. But recently patients having only gonadal hypogenesia with various degrees of undervirilisation without adrenal insufficiency have been identified. In a study on 30 patients with 46, XY disorders of sex development, heterozygous missense mutations in NR5A1 were found in four individuals (13%). No one had adrenal insufficiency. In two cases the mutations were de novo, in the rest, inherited in a sex-limited autosomal dominant manner from a heterozygous mother[12].

The Desert hedgehog (DHH) gene is involved in regulating morphogenesis and the expression of SRY. In a study on 6 patient of Mexican descent with 46 XY complete gonadal disgenesis, 3 were homozygous for mutations in the DHH gene, with an autosomal recessive pattern of inheritance[13] and up to 20% of patients with partial disorders of sexual differentiation present heterozygous mutations of HDD. A case in witch 46 XY gonadal disgenesis was associated with minifascicular neuropathy has been described[14].

Duplications of NR0B1, (also known as DAX-1) are less frequently involved in complete sex reversal. In a study on thirty-three 46, XY sex-reversed Brasilian patients, none had anomalies at this level[15]. Depending on dimensions of the duplicated fragment, male to female sex reversal can be the only manifestation, or it cam be accompanied by facial anomalies and mental retardation[16]. Some mutations are inheritable[11].

Duplications of WNT4 also cause complete male sex reversal, but there incidence appears to be low[15]. In female patients, mutations in WNT4 can cause Rokitansky-Kuster-Hauser syndrome or SERKAL syndrome.

Conclusions

Swyer syndrome is a rare pathology, and its study can bring new insights into normal sexual development. ■

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