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Case Report Open Access

Ovarian Steroid Cell Tumor Associated to Endometrial Hyperplasia and Presenting as Postmenopausal Vaginal Bleeding

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Abstract

Background: Ovarian Steroid cell tumor is a subtype of sex-cord stromal tumor which is very infrequent. It is usually benign and unilateral and causes hyperandrogenism and virilization.

Case report: A 57-year-old woman that presented with postmenopausal bleeding associated to atypical endometrial hyperplasia underwent total hysterectomy and bilateral oophorectomy and was diagnosed of Steroid Cell Tumor of the Ovary.

Discussion: Surgical treatment is mandatory and it ranges from unilateral oophorectomy to complete staging surgery. Adjuvant treatment is not usually required. Prognosis is good in most cases. Risk factors depend on histological examination of the tissue.

Conclusion: Steroid Cell Tumors of the ovary do not always present with hyperandrogenism and virilization. Atypical presentations as our patient´s must be taken into account for differential diagnosis of abnormal uterine bleeding in postmenopausal women.

Keywords: Steroid cell tumor; Ovary; Hormone-secreting tumor; Ovarian cancer; Virilization; Hyperandrogenism; Postmenopausal bleeding

Abbreviations:

CMI: Corporal Mass Index; SCT: Steroid Cell Tumor; SCT NOS: Steroid Cell Tumor Not Otherwise Specified; CT: Computerized tomography; MR: Magnetic Resonance; GnRH: Gonadotropin Releasing Hormone

Introduction

Hormone-secreting tumors of the ovary are very unusual. They account for 7% of all ovarian neoplasms. Sex-cord stromal tumors only represent 6% of them (less than 0.1% of all ovarian tumors) [1-3].

Young and Scully´s 1979 classification of ovarian tumors with endocrine manifestations (Figure 1) includes sex-cord stromal tumors, steroid-cell tumors and other ovarian disorders with endocrine function.

Clinical signs and symptoms of hormone-secreting tumors in women depend on the age of the patient, pre or post-menopausal state and the quantity of androgens and estrogens secreted by the tumor. The symptoms range from hirsutism and acne to heterosexual precocious puberty in prepuberal girls, virilization and amenorrhea in reproductive-age women and postmenopausal bleeding to endometrial hyperplasia or adenocarcinoma in postmenopausal women [2].

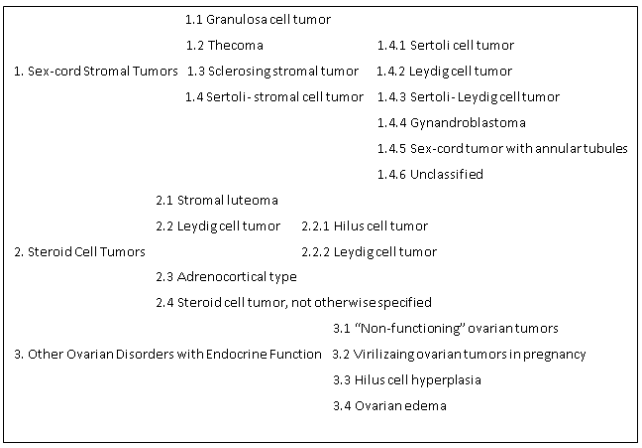

Figure 1: Young and Scully´s classification of ovarian tumors with endocrine manifestations.

The following is a case report of a postmenopausal woman who presented with postmenopausal bleeding and endometrial hyperplasia and was diagnosed of steroid cell tumor of the ovary. This clinical presentation differs from the usual clinical symptoms, which are virilization and signs of androgenism as hirsutism and change of body fat distribution. Knowing atypical presentation signs like these can help us make a prompt diagnosis which will benefit the patient.

Case Report

A 57-year-old woman attended gynecology office because of vaginal bleeding after ten years in menopausal state. She also felt breast engorgement despite having negative breast mammograms performed every two years. She did not develop any virilization signs.

Her clinical records included hiatus hernia, anxiety, a fracture of the left humerus and two vaginal deliveries. Physical and gynecological examination was normal (CMI 28).

Ultrasound identified a regular uterus with a heterogeneous endometrium of 11 mm (with no suspicion of invasion). Ovaries had normal sonographic appearance.

The patient required emergent dilation and curettage because of anemizing vaginal bleeding (Hemoglobin 8.2 g/dL). Histological examination showed endometrial hyperplasia without atypia. Laparoscopy with total hysterectomy and bilateral oophorectomy was performed, using a 10 mm umbilical trocar and three 5 mm accessory trocars. No intra-operative or post-operative complications took place. She had a favorable post-operative evolution.

Diagnosis by histological examination was the following

1. Steroid cell tumor of the right ovary, not otherwise specified, with no superficial affection, moderate cellular atypia (grade 2) and 12 mitosis per 10 high-power field.
2. Proliferative endometrium.
3. Right fallopian tube and left ovary without alterations.

Testosterone, S-human-β-globulin and α-inhibin blood tests were performed after surgery, but results were negative.

She has received no adjuvant treatment and has been followed up for 8 months up to date, without complications or recurrence.

Discussion

Steroid cell tumors (SCT) are composed of steroid- secreting cells (lutein cells, Leydig cells and adrenal-cortical cells). They have also been called lipoid or lipid- cell tumors [2]. Young and Scully [1], established four subclasses of SCT: stromal luteoma, Leydig cell tumor, steroid cell tumor of adrenal type and steroid cell tumor not otherwise specified (SCT NOS). SCT NOS is the most common subtype of SCT, accounting for approximately 60% of cases [4].

Knowing the pathophyisiology of these tumors is important for understanding the disease. Tumor cells of stromal tumors, such as granulose cells or theca cells, may produce estrogens, androgens and related hormones [5,6] in response to a disturbing environment as the presence of cysts, other tumors or proinflammatory conditions. Damage to the ovarian stroma during normal cycles can also contribute to activate the non-neoplastic counterpart of these hormone- producing cells [5]. In menopause, high levels of gonadotropin (FSH, LH) can stimulate hormone- secreting cells of the ovary to produce androgens or estrogens [7].

Ovarian SCT may occur at any age. The mean age of diagnosis is 58 years for stromal luteomas and Leydig cell tumors [2], and usually affects younger women for adrenal cortical SCT [2,8-10] and SCT NOS [2,11]. Adrenal-cortical and SCT NOS can present prior to puberty [2,3,8,11], and have even been described in fetuses [12]. In prepuberal girls it can cause isosexual precocity [13,14], with hirsutism, acne, growth- acceleration, clitoral enlargement and pubic hair. Laryngeal hypertrophy and deepening of the voice has also been described [2].

During reproductive age, the typical presentation is virilization (hirsutism, hair loss, amenorrhea or oligomenorrhea), although 10 to 25% of SCT NOS do not produce any hormones or symptoms [3,15,16]. Hirsutism and abrupt cessation of cyclic menses usually appear at the same time. Androgenic changes are proportional to the amount of testosterone secreted by these tumors [2]. Secretion of other hormones as estrogen (6-23%), cortisol (6-10%), prolactin or prorenin has also been reported, but is less common [15-17]. Excessive estrogen production can produce menorrhagia and even endometrial hyperplasia (such as the case of our patient) or endometrial adenocarcinoma at any age [2,3,15].

In postmenopausal women virilization signs can even be seen with small increases of testosterone. Hyperestrogenism is also common, and can be related with presenting symptoms as postmenopausal bleeding and breast pain and tenderness (like the case of our patient), vaginal rugae and cervical mucus [2].

A high level of testosterone (>200 ng/dL) is the threshold for differential diagnosis between androgen- secreting tumors and non-neoplastic lesions [3], such as polycystic ovary syndrome, stromal hyperthecosis or incidental functional cysts. Other hormones (serum DHEA, LH, FSH and 17-OH progesterone) must be included in the lab tests for hyperandrogenism.

Ovarian tumor markers (CA125, CEA, Ca 19.9 and AFP) must also be analyzed to rule out ovarian adenocarcinoma [17]. They are usually negative in SCT [16].

Complete work-out for women with virilization includes bimanual exam, serum hormones and tumor markers, abdominal and endovaginal ultrasound and CT or MR of the adrenals and ovaries [17-19]. Endometrial sampling is mandatory in patients with postmenopausal bleeding or abnormal menses.

On CT and ultrasound most tumors appear to be solid or mostly solid. The amount of solid tissue varies with the tumor type. According to Outwater et al. the ovarian masses are isoechogenic (82%) or hypoechogenic (18%) and ascites is an infrequent finding (23%). Only a minority of SCT (14%) are calcified on image studies. Many are small (< 5 cm) and are difficult to recognize morphologically as a mass [18]. On Doppler studies they have a high diastolic flow. On contrast- enhanced CT the masses are isoattenuating to the uterus (80%). On T1-weighted spin echo MR images, the tumors are isointense and on T2-weighted images hyperintense. The majority of cases are stage I tumors at presentation [18].

Ovarian SCTs are usually smaller than 5 cm, unilateral and rarely malignant [2,3,18]. They are confined to the stroma and appear as circumscribed yellow or tan lesions. Cells are typically polygonal and contain abundant granular eosinophilic or vacuolated cytoplasm and grow in diffuse pattern or occasionally in nests and trabeculae [15]. The classification of SCT subtypes is done by histological examination and depends on the location and the presence of Reinke crystals, according to Young and Scully. Stromal luteoma is confined within the ovarian stroma and does not contain Reinke crystals. Leydig cell tumor contains these crystals in its cells and is predominantly located in the ovarian hilus. Those SCT that do not meet the criteria for the previous subtypes (50%) are classified as SCT NOS [20].

Inmunohistochemistry can also be useful for diagnosis of SCT. α inhibin is very helpful for differential diagnosis because most SCT

express this marker, although it is not expressed by all SCTs [21-23]. Some authors find calretinin more useful; in Deavers et al.'s study it was positive in 60 to more than 90% of tumor cells, whereas inhibin reactivity ranged from <5% to >90%. However, calretinin is less specific than inhibin in the diagnosis of sex cord- stromal tumors and is less reliable in the differential diagnosis of sex cord- stromal tumors and endometrioid carcinoma because it is also frequently expressed in epithelial ovarian tumors [24]. Other markers such as CD99 or A103 (a melanoma marker that reacts with steroid producing cells) are less sensitive and less specific than inhibin and calretinin and should never be used in isolation for diagnosis of sex-cord stromal tumors [24].

Prognosis is good for most SCT of the ovary, although malignancy has been reported in as high as 28.6- 43 % of cases [3,25]. Hayes and Scully [15] identified the pathological features most associated with malignancy: more than two mitoses per 10 high-power field, presence of necrosis, ≥7 cm, hemorrhage and nuclear atypia ≥ grade 2.

The patient of our case report had a tumor of 3.3 cm, with grade 2 atypia, 12 mitoses per 10 high-power field and absence of necrosis and hemorrhage.

Treatment depends on the age of the patient. Surgical removal of the tumor must be performed to confirm diagnosis. Unilateral oophorectomy is usually adequate for young patients with child-bearing wishes. If genesic wishes are complete, hysterectomy, bilateral oophorectomy and complete surgical staging is recommended. Monitoring of hormone levels must be included in postoperative follow-up [3,19].

The paper of radiotherapy or chemotherapy is not well established. Chemotherapy should be based on malignant factors in histology examination and stage of the tumor. Few studies are available, but BEP (bleomycin, etoposide and cisplatin) appears to be an active first-line chemotherapy regimen for malignant stromal tumors [19,25].

Some authors suggest that GnRH can be used as postoperative adjuvant therapy or an alternative to surgery in inoperable cases [26-28]. This is based on the hypothesis that some androgen- secreting tumors depend on continuous gonadotropin stimulation in postmenopausal women, as we have mentioned before. Chung et al. used Gonadotropin Releasing Hormone Agonist after tumor-rupture during surgery, with no recurrence of SCT [29].

Conclusion

Steroid cell tumors of the ovary form a rare entity that can cause symptoms of virilization, isosexual precocity, oligomenorrhea or amenorrhea and postmenopausal bleeding. It is associated to high levels of testosterone (>200 ng/dL) and other hormones in a lower percentage.

Differential diagnosis with other entities causing these symptoms - such as polycystic ovary syndrome, stromal hyperthecosis or incidental functional cysts- is difficult, but early diagnosis is important as a small percentage of these tumors can be malignant.

SCTs are usually unilateral, circumscribed to the ovary, smaller than 5 cm and benign. Unilateral oophorectomy is the treatment of choice for young women with child- bearing wishes, but complete staging with hysterectomy and bilateral oophorectomy is preferred in postmenopausal women or patients with fulfilled genesic wishes. Chemotherapy is reserved for malignant tumors. GnRH agonists can be used as adjuvant treatment or in inoperable cases. Prognosis is usually good, with very low recurrence rates. Recurrence is associated with malignant histological risk factors.

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