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CASE REPORT

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Hyperandrogenism, oligomenorrhea, and erythrocytosis caused by an ovarian Leydig cell tumor: A case report

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Abstract

Leydig cell tumors are rare ovarian neoplasms. Affected individuals typically present with amenorrhea/oligomenorrhea and rapidly progressive features of virilization. Erythrocytosis can also occur as a result of high testosterone levels.

KEYWORDS

erythrocytosis, hyperandrogenism, Leydig cell tumor, oligomenorrhea

1 | INTRODUCTION

In this case report, we present the case of a 39-year-old woman with excessive testosterone production from a Leydig cell tumor of the left ovary resulting in oligomenorrhea, high erythrocyte count, and rapidly progressive virilization signs.

Leydig cell tumors (LCTs), a subtype of steroid cell tumors of the ovary, account for <0.1% of ovarian neoplasms.[1,2] LCTs are more common after menopause (average age of 58), being usually benign, unilateral, and small-sized solid tumors.[3,4] Approximately 75% of individuals with these tumors exhibit symptoms of hyperandrogenism due to excessive testosterone production.[5,6] Affected individuals typically present with amenorrhea/oligomenorrhea and rapidly progressive signs and symptoms of virilization (usually within months) with or without mass effect.[7] Those features include hirsutism, clitoromegaly, androgenic alopecia, acne, increased muscle mass, mammary atrophy, deep voice, or increased libido. Some of the differential diagnosis of these virilizing tumors include non-neoplastic causes of androgen excess such as polycystic ovary syndrome (PCOS), nonclassical congenital adrenal hyperplasia (or other adrenal enzymatic defects), or ovarian hyperthecosis. Another important diagnosis to consider is Cushing syndrome, that can sometimes be the result of an adrenocortical carcinoma cosecreting androgens and cortisol.[1]

Given the rarity of these tumors (that constitute only <0.2% of the cases of hyperandrogenism) and the multiplicity of possible alternative diagnosis,[7] it is essential to have a high index of suspicion. This is especially important before menopause and when no masses are detected on physical examination.[1] The authors report a case of a premenopausal

woman presenting with hirsutism, androgenic alopecia, and oligomenorrhea who was found to have a left ovarian LCT. An informed consent was obtained to use patient's medical data regarding the diagnosis and management of this Leydig cell tumor in our medical center (Centro Hospitalar e Universitário de S. João).

2 | CASE REPORT

A 39-year-old nulligravid Caucasian woman was referred to the Endocrinology Department with complains for the last 8 months regarding androgenic alopecia, facial acne, and hirsutism, more pronounced on the face, dorsum, and arms (score 12, *Ferriman-Gallwey* scale). Dorsocervical fat pad and axillary acanthosis nigricans were also found on physical examination. During the last 3 months, the patient noticed a weight gain of 6 Kg, mainly in the abdominal area, and sporadic ecchymosis with no recollection of trauma. She also reported menstrual irregularities with oligomenorrhea after stopping oral contraceptive 9 months before. She sustained she felt more depressed about the progressive changes on her body, mainly for esthetic concerns. No alterations in libido, muscular changes, or bone fractures were reported. She denied previous or recent consumption of alcohol or tobacco. She was diagnosed with primary hypothyroidism in 2011 (unknown cause, negative antithyroid antibodies), having class 1 obesity and arterial hypertension since 2008 (maximum tensional values of 150/94 mm Hg within the 12 months before endocrinology consultation, but usually with normotensive values under antihypertensive medication). Our patient was medicated with levothyroxine 100 μg once daily (q.d.), nebivolol 5 mg q.d., and an association of amlodipine 5 mg/valsartan 20 mg q.d. Regarding her family history, the patient reported that her mother had thyroid and breast cancer, hypertension, and type 2 diabetes, with the latter also

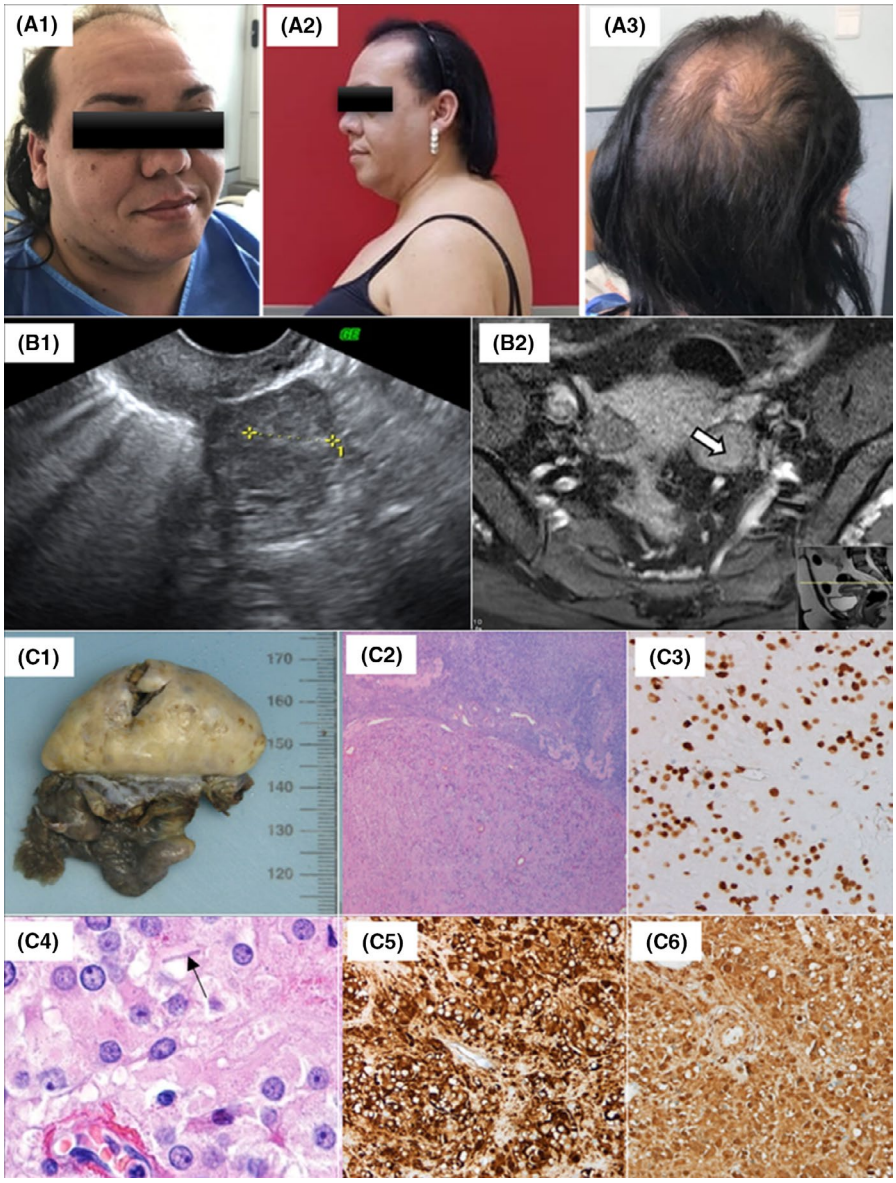

FIGURE 1 Clinical, imagiological, and pathological data regarding the presented clinical case. Physical examination findings of the patient before surgery (A1-3). Suprapubic ultrasound (B1) depicting a well-defined iso-mildly hyperechoic solid nodule in the central left ovarian stroma; pelvic MRI (B2) showing a moderately hyperintense nodule on axial fluid sensitive sequence; salpingoophorectomy specimen containing an ovary Leydig cell tumor (C1). The tumor (bottom) is well circumscribed. The tumor cells have uniform round nuclei and abundant eosinophilic to pale cytoplasm (C2). The eosinophilic fibrinoid changes in the walls of the blood vessels are a characteristic finding. Nuclear expression of androgen receptors (C3). Some cells contain Reinke crystals (arrow) (C4). Tumor cells are positive for inhibin (C5) and calretinin (C6)

present in other members of the family. Physical examination revealed an androgenic facies and alopecia, dorsocervical adiposity, axillary acanthosis nigricans, and clitoromegaly (Figure 1). No masses were detected on abdominal palpation. No breast atrophy, proximal myopathy, or violaceous striae were noted. Her body weight was 87.6 Kg on presentation, with a body mass index of 31.8 Kg/m^2 and blood pressure of 140/92 mm Hg.

The analytical diagnostic workout demonstrated a marked increase of total testosterone levels and normal levels of DHEA and estradiol, with suppression of FSH and LH. Normal prolactin and thyroid function as well as normal 24-hours urinary free cortisol level and 1mg dexamethasone suppression test were documented. The hemogram of the patient evidenced erythrocytosis and increased level of plasmatic hemoglobin (Table 1). Gynecological imaging assessment through suprapubic and transvaginal ultrasound revealed a well-defined solid lesion in the left ovary, measuring 15 × 15 × 16 mm, slightly heterogeneous, but with no clear suspicious findings. No abnormal endometrial thickening was detected. Pelvic magnetic resonance imaging (MRI) findings were consistent with ultrasound, revealing a solid left adnexal lesion, with smooth margins and moderate hyperintensity on T2 sequences, with no evidence of aggressive features. There were also no ascites or abnormal lymph nodes, and the adrenal glands were unremarkable at computed tomography imaging (CT).

Considering these findings, our patient was referred to the Gynecology Department. She presented no relevant findings on gynecological examination beyond clitoromegaly. After evaluating all the presented data, the gynecological team decided to perform a laparoscopic left salpingoophorectomy (that proceeded without complications). A microscopic analysis of the surgical specimen revealed a Leydig cell ovarian tumor. This mass presented expansive limits and contained cells with uniform round nucleus and abundant cytoplasm that stained positive for inhibin α, calretinin, and androgen receptors. Crystals of *Reinke* were also detected on microscopy as well as rare mitotic figures.

In the postsurgery follow-up medical consultations at 1 and 4 months, there was a marked improvement of the clinical hyperandrogenism (hirsutism, androgenic alopecia), with regularization of the menstrual cycles and normalization of the serum total testosterone and erythrocyte count. The patient underwent fertility treatments with ovulation inductors (human chorionic gonadotropin and clomiphene citrate), being actually pregnant with twins.

TABLE 1 Analytical parameters determined before (initial consultation) and 6 mo after surgery

	Before	After	Reference values
Hemoglobin (g/dL)	18.2	14.7	12.0-16.0
Erythrocyte count (×10^{12}/L)	5.84	4.81	4.0-5.0
Total testosterone (ng/dL)	1052	38	6-82
Androstenedione (ng/mL)	5.13	1.47	0.3-3.3
DHEAS (μg/dL)	246.6	186.3	60.9-337
FSH (mUI/mL)	0.87	5.98	2.1-12.6
LH (mUI/mL)	0.61	13.11	2.4-12.6
Free T4 (ng/dL)	1.28	1.08	0.70-1.48
TSH (μUI/mL)	1.98	2.54	0.35-4.94
Estradiol (pg/mL)	41.8		1.3-266
Prolactin (ng/mL)	32.7		4.8-23.3
24-h urinary free cortisol (μg/day)	15.6		36.0-137.0
1 mg overnight dexamethasone suppression test (μg/dL)	0.8		0-1.8

3 | DISCUSSION

In this case, we present a woman with excessive testosterone production from a Leydig cell tumor of the left ovary resulting in oligomenorrhea and rapidly progressive virilization signs. In patients with this clinical presentation, a careful history and thorough physical examination remain good predictors of neoplasm related hyperandrogenism.[5,7] The time of signs and symptoms onset may be an important clue to diagnosis. This relates to the fact that the usual nontumoral causes of hirsutism and menstrual cycle abnormalities, such as PCOS and nonclassical congenital adrenal hyperplasia, commonly need years or decades to develop those symptoms, whereas those with virilizing neoplasms only take a few months (as in the presented case report).[7] In the particular case of adrenal tumors, these signs of hyperandrogenism can be associated with cushingoid features due to the concomitant production of androgens and cortisol by some tumors. Regarding physical examination, attention should be paid to presence of clitoromegaly or adnexal masses during gynecological examination. Another important diagnostic keystone is serum androgen measurement, such as total testosterone and dehydroepiandrosterone sulfate (DHEAS). Most physicians start to look for a tumor when the serum total testosterone concentration is higher than 150-200 ng/dL (5.2-6.9 nmol/L) or, in the case of an adrenal source of androgens, when the DHEAS is higher than 700 μg/dL (18.9 micromole/L).[8] Our patient presented high total testosterone levels (pointing to a neoplastic source of virilization) and a normal serum DHEAS concentration with absence of adrenal CT abnormalities, which all together raised the concern for an ovarian tumor. It is important to stress that although concomitant Cushing

syndrome strongly indicates an adrenal cancer, rare steroid cell tumors of the ovary may also coproduce androgens and cortisol.[9] In our case, despite the presence of some features such as central obesity, dorsocervical fat pad, ecchymosis, or axillary acanthosis, the possibility of associated Cushing syndrome was ruled out by two normal screening tests (24-hours urinary free cortisol and overnight 1 mg dexamethasone test). This clinical case is particularly interesting for two reasons: One is the atypical presentation of a LCT in a premenopausal woman and the other is the presence of erythrocytosis related to testosterone excess, that has normalized after tumor removal. At least three cases of erythrocytosis secondary to ovarian LCT are described in the literature, one of them describing a woman with hyperandrogenism and recurrent pulmonary embolism.[3]

Hyperandrogenism can be the result of a variety of tumors, some of them of gynecological origin, such as choriocarcinoma, hydatidiform mole, or adnexal androgen-producing tumors. Among the latter, there are several groups such as the sex cord-stromal tumors (that include the Sertoli-Leydig neoplasms), tumors of the ovary with functioning stroma, or the steroid cell tumors (which incorporate the presented LCT of our patient).[10] LCTs are masses of steroid cells usually with abundant eosinophilic cytoplasm, very few mitosis, and round nuclei.[11] The presence of crystals of Reinke (rod-shaped structures within the cytoplasm) is a very characteristic feature that supports the diagnosis of LCT.[12] Among the multiplicity of immunohistochemical markers, the ones frequently studied are inhibin and calretinin because they are expressed by many steroid cell tumors like LCT.[1]

These neoplasms are frequently so small (<3 cm) that in many cases they are not even able to be found, posing a diagnostic challenge even after careful gynecological and radiological investigation.[12] Fortunately, that was not the case of our patient, who had her LCT detected on transvaginal ultrasound (TVU). This examination is often the initial imagiological examination due to its good sensitivity, high availability, and low cost.[7] However, its accuracy relies on the operator performing the examination. MRI is the second-line imaging modality for evaluating adnexal masses due to the high soft tissue resolution. It can sometimes find masses not otherwise diagnosed at the TVU (78% positive and 100% negative predictive value, as revealed by the results of a large study).[13,14] When TVU and MRI are inconclusive or fail to detect any neoplasm but there is still a strong clinical suspicion, bilateral ovarian vein catheterization may be an option to confirm the source of androgen excess. This method has some setbacks: It may pose risks for the patient (such as ovarian vein thrombosis or intracorporeal hemorrhage), and it is performed only in a few centers worldwide and does not provide satisfactory sensitivity. For these reasons, the option that is usually preferred in these difficult diagnostic cases is ^{18}F-fluorodeoxyglucose PET imaging (^{18}F_FDG-PET), that uses pathologic glucose uptake by neoplastic cells as a mean to visualize the tumor.[11]

Surgery is the preferred therapeutic approach for androgen-secreting tumors, usually leading to permanent cure (most of these tumors are benign).[7] The option to perform a unilateral or bilateral salpingoophorectomy depends on the ability to find the tumor and on the woman menopausal status. In postmenopausal women (the main group affected by LCT), bilateral salpingoophorectomy with or without total hysterectomy is the favored approach (considering the concomitant risk of endometrial carcinoma in some cases).[14] Regarding our case of a premenopausal woman, after evaluation of the results of TVU and MRI, a laparoscopic left salpingoophorectomy was performed. This option was taken to preserve fertility. This issue was a major concern to our patient because she had no offspring to date and wanted to conceive.

After surgery, the aim is to normalize the levels of androgens, that should be assessed during follow-up to diagnose a possible recurrence. Our patient had a significant improvement of both clinical and analytical hyperandrogenism, as a successful surgical result.

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Published with written consent of the patient.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

FM: primary author of the final manuscript. SS: co-authored manuscript. DM: contributed with endocrinological expertise and images of the patient. RP and ARC: contributed with pathological expertise and images and revised the manuscript. IP: contributed with her radiological knowledge and images and revised the manuscript. ASF, VF, ST, and JB: followed the patient and advised FM in gynecological issues related with this case report. DC: advised and oversaw manuscript drafting and publishing.

ETHICAL APPROVAL

An informed consent was obtained. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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