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Case Report **OPEN ACCESS**

Challenges in diagnosing ovarian sertoli-leydig cell tumors: A Peruvian case series

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ABSTRACT

Introduction: The virilizing ovarian tumors represent less than 1% of ovarian tumors, with the most common being Sertoli-Leydig cell tumor (SLCT). This stufy is a case series.

Methods: We present the diagnosis, treatment, and evolution of 2 Peruvian women who developed virilization.

Results: Case 1 is a 27-year-old woman with a history of polycystic ovary syndrome (PCOS), whose usual treatment was combined oral contraceptives, which she discontinued in the last year; she presented with voice changes, increased muscular strength, and acne of 6 months duration. Physical examination revealed only clitoromegaly. Tests showed elevated total testosterone, normal dehydroepiandrosterone sulfate (DHEA-S), and transvaginal ultrasound with isoechoic image in frosted glass in the left ovary. Left salpingo-oophorectomy was performed, revealing SLCT. Case 2 is a 48-year-old woman with a history of PCOS since the age of 25, prediabetes, and dyslipidemia; she noticed progression of hirsutism, increased libido, deepened voice, alopecia, weight gain, and amenorrhea over the last 5 years. Physical examination revealed hirsutism, alopecia, and clitoromegaly. Tests showed markedly elevated total testosterone (1,080 ng/dl) and normal DHEA-S. Transvaginal ultrasound showed a larger right ovary, without tumor. Ovarian venous sampling showed lateralization towards the right ovary. Bilateral salpingo-oophorectomy plus hysterectomy was performed, revealing SLCT in the right ovary. In both post-surgery patients, there was normalization of androgens and clinical improvement.

Conclusions: SLCT s can occur at any age, with rapidly evolving hyperandrogenism and/or virilization symptoms, the cases described were of unusual presentation, which posed a diagnostic challenge.

Keywords: ovarian Sertoli-Leydig cell tumors, virilization, premenopausal, postmenopausal, ovarian neoplasms

INTRODUCTION

Virilizing ovarian tumors (VOT) are uncommon [1]. Most of these tumors derive from the sex cord or ovarian stroma cells and can affect both premenopausal and postmenopausal women, triggering rapidly progressive hyperandrogenism [2]. Sertoli-Leydig cell tumors (SLCT) or androblastomas are the most frequent and constitute approximately 0.5% of all ovarian tumors [3].

When evaluating a patient for hyperandrogenism, it is important to inquire about the severity of symptoms, but most importantly, it is essential to assess the onset and the dynamics of symptom progression [2]. Virilizing tumors typically present with oligomenorrhea or amenorrhea, followed by hirsutism, acne, male pattern baldness, deepened voice, increased muscle mass, increased libido, and clitoromegaly [4].

Most are tumors with low malignant potential, small, confined to the ovary, and detected early due to their clinical course, thus they have a good prognosis following surgical resection [4].

The objective of this manuscript is to present a series of cases of 2 women who developed virilization due to an ovarian SLCT, with an unusual clinical presentation.

METHODS

Study Design

This is a retrospective case series describing the clinical presentation, diagnosis, treatment, and progression of patjents with SLCT.

Table 1. Laboratory tests before and after surgery in patients 1 and 2

Biochemical tests	Before surgery		1 month post-surgery	
	Case 1	Case 2	Case 1	Case 2
Total testosterone (R.V.: < 62 ng/dL)	731	1,080	30	10
Free testosterone (R.V.: 0.1-6.4 pg/mL)	13.5	16.0	2.0	3.5
Androstendione (R.V.: 26-214 ng/dL)	191	200		
DHEA-S (R.V.: 35-430 µg/dL)	216	371		
17 OH progesterone (R.V.: 0.6-1.2 ng/mL)	1.7	1.4		
LH (R.V.: Follicular phase: 2.4-12.6 mUI/mL)	5.76	0.40		
FSH (R.V.: Follicular phase: 3.5-12.5 mUI/mL)	4.96	< 0.66		
Estradiol (R.V.: 12.5-166 pg/mL)	56.98	931.00		
Potasium (R.V.: 3.5-5.0 mmol/l)	4.1	3.7		
Sodium (R.V.: 135-145 mmol/l)	141	135		
Basal glucose (R.V.: 70-99 mg/dl)	98	90		
Prolactine (R.V.: < 25 ng/dl)	12.1	18.0		
TSH (R.V.: 0.4-5.5 mU/l)	1	3		
CA 125 (R.V.: <35 U/mL)	15.0	13.2		
CA 19–9 (R.V.: <37 U/mL)	10	12		
AFP (R.V.: <10 ng/mL)	2.0	3.2		
CEA (R.V. < 2.5 ng/mL)	1.0	0.9		

Note. TSH: Thyroid stimulating hormone; CEA: Carcinoembryonic antigen; & AFP: Alpha-fetoprotein

Participants

Two Peruvian women with SLCT.

Procedures and Assessments

Comprehensive clinical evaluation was conducted, including detailed medical history and thorough physical examination. Laboratory tests were performed to measure hormonal levels, including gonadotropins, total testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), and tumor markers. Imaging studies such as transvaginal ultrasound and contrast-enhanced computed tomography (CT) were utilized to assess tumor location and characteristics. Ovarian venous sampling was performed in the second case to precisely locate the tumor before surgical intervention.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Helsinki Declaration. Written informed consent was obtained from all patients prior to their participation and for the publication of these clinical cases.

RESULTS

Case 1

A 27-year-old nulliparous Peruvian woman with no relevant medical or family history. She reached thelarche and pubarche at age 10 and menarche at age 14, since then she had oligomenorrhea. At age 18, she was diagnosed with polycystic ovary syndrome (PCOS) and was prescribed combined oral contraceptives (COCs), which regularized her menstruations (catamenial regimen 5/28-30). She was referred to the endocrinology outpatient clinic for presenting acne on her face and back, a change in voice tone, increased muscle strength, and weight gain over the past 6 months; there were no changes in the catamenial regimen. She denied the use of oral contraceptives for the past 8 months or androgens.

On physical examination, she was afebrile, had a heart rate of 70 beats per minute, blood pressure of 110/60 mmHg, and a body mass index (BMI) of 27.5 kg/m^2. Her skin and appendages showed acne on her face, chest, and back, without hirsutism (Ferriman-Gallwey scale: 4 points) or androgenic alopecia (Ludwig scale: 0 points). Breast development and pubic hair were Tanner stage 5. Pelvic examination revealed clitoromegaly (clitoral length 25 mm and width 15 mm). The rest of the physical examination was normal.

Laboratory tests revealed elevated levels of total testosterone (731 ng/dl) and free testosterone (13.5 pg/ml), but 17 OH-progesterone (1.7 ng/ml), DHEA-sulfate (216 ug/dl), and androstenedione (191 ng/dl) were within normal ranges. The 1 mg dexamethasone suppression test suppressed (serum cortisol level < 1.8 µg/dl), and the rest of the tests were within normal limits (**Table 1**). Transvaginal ultrasound revealed an isoechoic 3.6 × 2.9 × 3.15 cm, ground-glass image in the left ovary. Abdominal CT with contrast reported adrenals of normal appearance and no ascites or para-aortic lymphadenopathy.

Given the suspicion of an androgen-producing ovarian tumor, the patient was referred to the gynecology department for surgical treatment. A laparoscopic left salpingo-oophorectomy was performed without postoperative complications. Histopathological analysis revealed a moderately differentiated SLCT. Immunohistochemistry showed that Sertoli and Leydig cells were positive for α-inhibin and Leydig cells were positive for calretinin (**Figure 1**).

One month after surgery, testosterone levels normalized and signs of virilization improved. The patient continues to be followed up by the specialty.

Case 2

A 48-year-old multiparous Peruvian woman with a medical history of prediabetes under treatment with metformin 850 mg/day and hypertriglyceridemia under treatment with gemfibrozil 600 mg BID. She reached menarche at age 11, had oligomenorrhea, hirsutism, and acne since age 25, for which she required COCs for 2 years, and was diagnosed with PCOS. She attended the endocrinology outpatient clinic due to progression of hirsutism that required facial shaving, increased libido, deep voice, alopecia, weight gain, and secondary amenorrhea for the past 5 years, receiving spironolactone 100 mg/day for 6 months without clinical improvement. The patient denies the use of anabolic androgenic steroids and progestogens. She was referred to our hospital to the

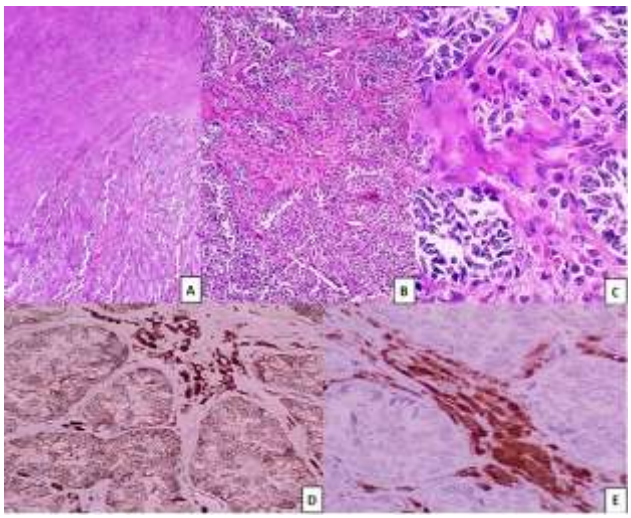

Figure 1. Microphotographs from the histopathological study of the surgical specimen in case 1 using hematoxylin-eosin stain: (A) low-power view of moderately differentiated Sertoli-Leydig cell tumour, shows Sertoli cells arranged in cords or clusters without open lumen formation and open sertoliform tubules are also seen; (B) Sertoli-Leydig cell tumour, with open and closed sertoliform tubules; (C) The sertoliform tubules are separated by Leydig-cells with eosinophilic cytoplasm; (D) Sertoli-Leydig cell tumors are inhibine positive; & (E) Calretinine immunohistochemistry showing staining in Leydig cells (reprinted with permission of patients)

Figure 2. Signs of virilization in case 2: (A) Androgenic alopecia & (B) Clitoromegaly (reprinted with permission of patients)

endocrinology department and was hospitalized to complete studies.

On physical examination, she was afebrile, had a heart rate of 75 beats per minute, blood pressure of 110/70 mmHg, and a BMI of 27.6 kg/m^2. Her skin and appendages showed hirsutism (Ferriman-Gallwey scale: 14 points) and androgenic alopecia (Ludwig scale: 3 points). Breast development and pubic hair were Tanner stage 5. Pelvic examination revealed clitoromegaly (clitoral length 15 mm and width 12 mm) (**Figure 2**).

Laboratory tests revealed very elevated levels of total testosterone (1,080 ng/dl), but 17 OH-progesterone (1.4 ng/ml), DHEA-S (343 ug/dl), and androstenedione (200 ng/dl) were within normal ranges. Estradiol was elevated, and gonadotropin levels were decreased. The 1 mg dexamethasone suppression test suppressed. Transvaginal ultrasound revealed a difference in adnexal volumes, with the right ovary measuring 15x21 mm and the left ovary 11 × 7 mm, with no other significant findings. Abdominal CT with contrast reported adrenals of normal appearance.

Given the imaging study results, ovarian venous sampling with total testosterone measurement was decided. The total testosterone level in the right ovarian vein was 2,160 ng/dl, left ovarian vein was 845 ng/dl, and peripheral vein was 741 ng/dl, showing laterality towards the right ovary, considering a VOT of the right ovary, with ovarian hyperthecosis (OH) being less likely.

Given these results, the patient was evaluated by the gynecology department for surgical treatment, deciding on a bilateral salpingo-oophorectomy plus laparoscopic hysterectomy. Histopathological study revealed a well-differentiated SLCT in the right ovary, with immunohistochemistry positive for calretinin, CD 99, and inhibin. The patient remained in follow-up after surgery, with normalization of serum testosterone and clinical improvement.

DISCUSSION

VOTs are uncommon, mainly affecting premenopausal patients [5]. SLCTs represent <0.5% of all ovarian tumors [3], belonging to the subgroup of mixed sex cord-stromal tumors, generally being benign and unilateral [4, 6]. The peak incidence of women diagnosed with SLCTs occurs in the second and third decade of life, but it can occur in all age groups [3-5], with 25% occurring after menopause [7]. In the present case series, the first patient was 27 years old, which is consistent with the literature; however, the second patient was 48 years old. In postmenopausal women with hyperandrogenism, the prevalence of VOT is 2.7% [7].

Women with SLCTs develop signs of androgen excess in 40-50% of cases [4]. VOTs usually present with rapid progression of hyperandrogenism and/or virilization symptoms, often within months, especially along with high testosterone levels, above 5 nmol/L (144.2 ng/dl) [7, 8]. A premenopausal woman will develop oligomenorrhea or amenorrhea [7, 8]. Virilization may present with severe hirsutism, acne, frontal hair thinning, male pattern baldness, deepened voice, increased muscle mass, breast atrophy, increased libido, and clitoromegaly, the latter defined as a clitoral length >10 mm [6-10].

The rapid onset of hirsutism is suspicious for an androgen-producing tumor compared to PCOS, 12 months versus 42 months in one study [8]. In case 2, hirsutism had a slow onset over 5 years, similar to another reported case [10], which necessitated differential diagnosis with OH, a relatively rare disorder presenting with a slow progression of severe hyperandrogenism symptoms [7, 9], more common in postmenopausal women, with a prevalence of 9.3% in women evaluated for hyperandrogenism [9].

The described VOT cases posed diagnostic challenges. Case 1 involved a patient without hirsutism and with a regular menstrual cycle, which is notable as both hirsutism and menstrual irregularity are predominant and early findings in most VOT cases [3-5]. Similarly, case 2 was unusual because, in addition to a slowly progressive disease course, she was postmenopausal.

Endocrine evaluation can be useful to distinguish between tumor and non-tumor causes of virilization [8]. The biochemical characteristics of VOTs usually include clearly

elevated total testosterone levels (> 5 nmol/L), often in the male range (8-29 nmol/L) [4, 6, 7], with a concomitant increase in androstenedione, while levels of 17-hydroxyprogesterone (17-OHP), DHEA-S, and cortisol are generally normal [11]. In both presented cases, hormonal evaluation indicated an androgen-producing tumor of ovarian origin.

Additionally, an elevated testosterone/androstenedione (T/A) ratio (greater than 1.5) should raise suspicion for an androgen-secreting ovarian tumor or hyperthecosis, unlike in women with PCOS (T/A less than 1.5) [12]. In the presented case series, the T/A ratio was greater than 1.5. A cutoff value of testosterone to differentiate between a VOT and OH has not been proposed [13], which was challenging to rule out prior to ovarian venous sampling in the second patient. Measuring DHEA-S can be useful for assessing adrenal hyperandrogenism, although it can be elevated in both PCOS and adrenal tumors. However, if DHEA-S is >700 µg/dl, an adrenal tumor should be ruled out [7, 8]. In the case series, DHEA-S levels were within the normal range in both women, with no adrenal mass evidence on tomography. Gonadotropin levels decrease in association with a virilizing effect [7, 8], as observed in both patients, correlating with testosterone levels and the degree of virilization [11].

VOTs are usually small in size, particularly SLCTs, which may be less than 3 cm in volume. The first-line study is transvaginal or pelvic ultrasound with color Doppler, where SLCTs are mostly unilateral, solid masses, isoechoic or hypoechoic with increased vascularization [5]. If the ultrasound is negative, the next step is to perform an MRI [7, 8]. Ovarian asymmetry can suggest a tumor; however, the absence of an ovarian tumor on imaging does not rule out a VOT [5, 7, 8]. In case 1, the tumor location in the left ovary was documented by transvaginal ultrasound, guiding surgery. In case 2, the ultrasound did not identify a tumor; however, there was asymmetry with a larger volume in the right ovary, where the VOT was eventually located.

It is noteworthy that OH can be described on ultrasound as a bilateral increase in ovarian stroma without hypervascularization, a single ovarian nodule, or it may also appear normal [5, 13], the latter being possible in case 2. 18FDG-PET is generally reserved for selected cases when traditional imaging is negative or inconclusive [7, 8].

Only in selected cases when pelvic and adrenal imaging is negative is it necessary to perform ovarian and adrenal venous sampling by a highly experienced interventional radiologist [8]. First, in premenopausal women where fertility preservation is desired and the localization of an ovary for resection is required [8], which was not necessary in case 1 since the tumor was found by transvaginal ultrasound; and second, in postmenopausal women with a small adrenal nodule but in whom an ovarian source is suspected [8]. Although the patient in case 2 did not meet any of the criteria, ovarian venous sampling was decided upon, indicating that the lesion was in the right ovary, which was confirmed after surgery.

The treatment of SLCT is surgical. The choice of surgical method should be based on the patient's age, desire for fertility, tumor size, surgical staging, and degree of differentiation [4, 14, 15]. For premenopausal women with unilateral and benign tumors desiring fertility, unilateral resection is recommended [4, 14, 15], as in case 1. In women with unilateral and benign tumors who have completed childbearing or are postmenopausal, bilateral laparoscopic salpingo-oophorectomy with or without hysterectomy is recommended, as was the outcome in case 2. However, malignant VOTs and/or metastatic disease recommend cytoreductive surgery that preserves lymph nodes and adjuvant chemotherapy. High-risk factors for SLCT include advanced clinical stage, low differentiation, large tumor size, and the presence of a reticular growth pattern and/or heterogeneous component [14, 15].

According to the International Federation of Gynecology and Obstetrics [16], the pathological findings indicated that both patients were diagnosed with stage 1 SLCT, whose outcomes in both cases were favorable with symptom resolution. The limited experience of the interventional radiology department at the hospital in performing ovarian venous catheterization, which, however, was successfully carried out without complications, revealed the location of the lesion in case 2.

CONCLUSIONS

In conclusion, SLCTs can vary in their presentation, emphasizing the need for thorough evaluation in cases where suspicion is high. Additionally, ovarian venous sampling gains importance when imaging is inconclusive. Moving forward, a multidisciplinary approach involving endocrinologists, gynecologists, and radiologists could enhance diagnostic accuracy and facilitate timely intervention.

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Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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