

## HYPERANDROGENISM PRODUCED BY OVARIAN TUMORS IN WOMEN AT DIFFERENT LIFE STAGES.

*HIPERANDROGENISMO TUMORAL OVARICO EN DIFERENTES ETAPAS DE LA VIDA.*

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### Abstract

Objective: to evaluate the different presentations of hyperandrogenism produced by ovarian tumors in women at different life stages

Design: case report

Setting: academic institutions

Patient(s): 3 patients at different life stages, with increased androgen levels

Intervention(s): review of hospital records

Main Outcome Measure(s): clinical and biochemical features, treatment and follow-up

Result(s): a 10 year-old girl with Leydig cell tumor presented with hyperandrogenemia, virilization and changes in social behavior. Another patient, at reproductive age, with a tumor >10 cm, presented with signs of virilization and abdominal mass, whose pathologic analysis disclosed a carcinoid tumor of the ovary associated with stromal hyperplasia. The third patient was a postmenopausal woman with severe alopecia, who presented a steroid cell tumor, rare at that age.

Conclusion(s): the evaluation of women with signs and symptoms of virilization should include a detailed clinical record, thorough physical examination and an appropriate hormonal dosage, especially when images are inconclusive.

**Key words:** virilization, ovarian tumors

### Resumen

Objetivo: evaluar las diferentes manifestaciones del hiperandrogenismo tumoral de origen ovárico en distintos grupos etarios.

Diseño: reporte de casos.

Lugar de trabajo: centros académicos.

Pacientes: son reportadas tres pacientes con exceso de andrógenos.

Resultados: describimos una paciente de 10 años con hiperandrogenemia y signos de masculinización secundarios a un tumor de células de Leydig; otra paciente, en edad fértil, con un tumor carcinoide de ovario asociado a hiperplasia estromal que se manifestó con signos de masa abdominal y de virilización. El tercer caso una mujer, en etapa postmenopáusica con alopecia severa, tenía un tumor de células esteroideas, raro en este grupo etario.

Conclusión: la evaluación de una mujer con signos y síntomas de virilización debe incluir una detallada historia clínica, examen físico y apropiados dosajes hormonales, especialmente si existe dificultad en establecer su origen cuando los estudios imagenológicos son normales.

**Palabras claves:** virilización, tumores de ovario

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## Background

Androgen-secreting tumors are rare, representing approximately 0.2% of the causes of hyperandrogenism and more than a half of them are malignant<sup>(1, 2)</sup>. These tumors have different clinical presentations and are located at the ovaries or adrenal glands. The ovarian origin is the most frequent<sup>(3)</sup>. The clinical signs and symptoms depend on the patient's age, the amount of testosterone secreted, the production of other androgens, the amount of estrogens secreted or produced from the extraglandular aromatization and the time of evolution from onset of the disease until diagnosis<sup>(4, 5)</sup>. Herein, we describe the characteristics of three patients at different life stages, which presented tumoral hyperandrogenism of ovarian origin.

**Case 1- A** 10-year old girl was referred due to changes in her voice tone, which had become deeper and signs of progressive hyperandrogenism for the last year. Her parents had noted lost of interest in female games and preference for physical activities. The girl complained of vulvar pruritus and leukorrhea. One year before the consult, she had noted increased amount of facial hair, acne and deepening of her voice tone. The patient did not have family history of endocrine disorders. At physical examination, her height was 142 cm, weight 37 kg she had severe acne, hirsutism and muscular hypertrophy in upper and lower extremities. She had an important amount of pubic hair distributed as inverted triangle (Stage V of Tanner), breast enlargement (Tanner II) and clitoral hypertrophy (1.5 x 2.0 cm). The patient's blood pressure was 100/60 mm/Hg. During the regular pelvic exam, no tumors were noted. The laboratory analysis demonstrated: total testosterone: 332 ng/dl (nv: 0-0.60 ng/dl), androstenedione >10 ng/ml (nv: 0.4-2.7 ng/ml) and 17-hydroxiprogesterone: 10 ng/ml (0.07-1.58 ng/ml) and post ACTH: 7.5 ng/ml; DHEA-S: 55.7 µg/dl (34-129 µg/dl). X-ray exams of her left hand and wrist revealed bone age of 13 years old. The abdominal and pelvic ultrasound revealed a left ovary with prominent stroma, with a heterogeneous nodular image of 26 mm and increased peripheral vascularization. We performed a laparoscopic exploration and left -oophorectomy. The histological examination evidenced a well-differentiated Leydig cell tumor. One week after the surgery, the level of testosterone had decreased to 93 ng/dl reaching normal values at the first monthly control (<0.20 ng/dl). Two months after the surgery, the patient had her menarche and the clinical signs of hyperandrogenism progressively disappeared. Five years later, her menstrual cycles are regular, she is asymptomatic and healthy. From the social point of view, she is integrated with her partners according to age and sex.

**Case 2- A** 37-year old female, pregnancies 4, deliveries 1, miscarriages 3, was admitted at the Department of Endocrinology for evaluation of secondary amenorrhea and hyperandrogenism. Since her menarche, she has had oligomenorrheic menstrual cycles and hirsutism, which progressively worsened. One year before the consult, the patient had noted absence of menstruation, increased growth-speed of the facial hair and appearance of terminal hair between her breasts, associated with abdominal distension. The patient did not present toxic habits or history of medicine intake. She had family history of obesity, diabetes and early cardiovascular diseases. At the physical exam, she presented severe hirsutism (Ferriman and Gallwey score 27) and seborrhea with mild alopecia with frontal and temporal distribution, in addition to muscular and clitoris hypertrophy. Her blood pressure was 140/90 mm Hg. She had centripetal obesity (BMI: 34.2 kg/m<sup>2</sup>, waist circumference: 109 cm). She did not present moon face, plethora or buffalo hump. Intense acanthosis nigricans was noted on the back of the neck, armpit and inner thighs. On pelvic examination a firm mass was palpable. Breasts were normal without galactorrhea. Laboratory findings showed: total testosterone: 220 ng/dl (nv: 0-80 ng/dl), androstendione 3.9 ng/ml (nv: 0.4-2.7 ng/ml), DHEA-S: 315 µg/dl (nv: 16- 304 µg/dl), 17-hydroxiprogesterone: 1 ng/ml (nv: 0.1-1.5 ng/ml), prolactin: 14.4 ng/dl (nv: 0- 25 ng/ml), LH: 2.1 mUI/ml (nv: 1.7-14mUI/ml) , FSH: 6.02 mUI/ml (nv: 3.9-10 mUI/ml), estradiol: 43 pg/ml (nv: 30-150 pg/ml), TSH: 1.71 µU/ml (nv: 0.25-4 µU/ml). Free urine cortisol was normal (37 ug/ 24 h, nv: 10-95), as also was Nugent's test. An oral glucose - tolerance test was performed: basal glycemia was 99 mg/dl and after 120' was 150 mg/dl, insulinemia 55.6 uU/ml, total cholesterol 242 mg/dl, HDL-cholesterol 32 mg/dl and triglycerides 317 mg/dl. Later on, the transvaginal ultrasound revealed a tumor on the left ovary. Tumoral markers (Ca-125, alpha fetoprotein, beta-hCG) were normal. Treatment consisted in unilateral salpingo-oophorectomy. The tumor measured 11.5 x 11 x 9 cm and the pathologist exam revealed insular carcinoid of the ovary with stromal hyperplasia (Figure 1). The immunohistochemistry results were negative for inhibin and positive for chromogranin. One week after the surgery, the serum level of testosterone decreased to 17 ng/dl and one month later the patient had her menstrual cycle spontaneously. The patient did not present symptoms compatible with carcinoid syndrome and the urinary level of 5-hydroxyindole acetic acid (5-HIAA) after the pathological diagnosis was normal (2.6 mg /24 hours, nv: 2-8 mg/24 hours). Four years later, the patient developed type 2 diabetes controlled with nutritional plan, physical

activity and metformin. The hirsutism improved, she had monthly menstruations and no evidences of tumor recurrence.

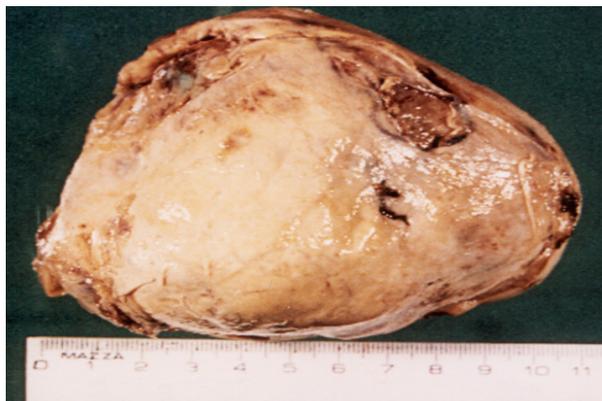


Fig.1 Macroscopic appearance of resected specimen

**Case 3-** A 62-year old female was referred for evaluation of her thyroid function. At physical exam, she presented severe androgenic alopecia. Her medical records revealed growth of body hair in androgen-dependent areas, along with temporal hair loss of one-year evolution. She did not present history of gynecological diseases. At physical exam, we noted mild hirsutism (Ferriman and Gallwey score: 12), voice deepening, marked temporal alopecia, BMI: 26 kg/m<sup>2</sup>, blood pressure: 120/80 mm/Hg, diffuse goite and absence of palpable abdominal masses. The laboratory tests showed: serum total testosterone: 150 ng/dl (nv: 0-80 ng/dl); free testosterone: 16 pmol/l (nv: 2.8-11); DHEA-S: 68 ug/dl (nv: 12-142 ug/dl); androstenedione: 3.7 ng/ml (nv: 0.4-2.7 ng/ml); TSH: 1 uU/ml (nv: 0.25-4 uU/ml); ATPO: 6 UI/ml (nv: <34 UI/ml). As abdominal and transvaginal ultrasounds were normal we decided to perform a laparoscopy with bilateral oophorectomy. Pathological examination showed a solid tumor of 10 mm on the left ovary, identified as steroid cell tumor not otherwise specified (Figure 2). One month after the surgery, serum total testosterone decreased to 12 ng/dl. Follow up at seventh month, hirsutism improved mildly and alopecia did not worsen. Four years later alopecia disappeared.

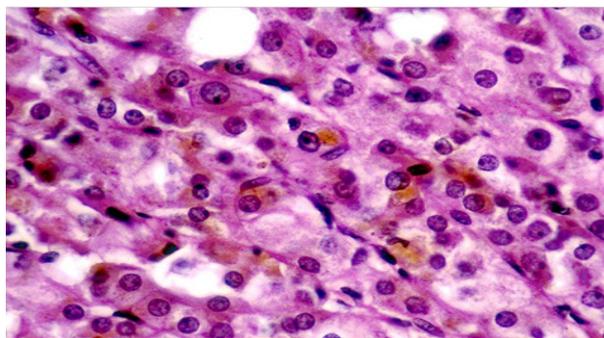


Fig. 2 Tumor cells are polygonal in shape, with granular abundant and vacuolated cytoplasm

## Discussions

In prepubertal girls, virilizing tumors produce hirsutism and other signs of hyperandrogenism, like seborrhea and acne, or as in our first case, voice deepening due to laryngeal hypertrophy and clitoris enlargement; the later ones being real signs of virilization. Other findings could be early pubarche or growth acceleration associated with signs of virilization or even a precocious puberty<sup>(2,3)</sup>. All these signs and symptoms were present in our patient, but pre-puberty hyperandrogenism can also be observed in non-classical congenital adrenal hyperplasia and in polycystic ovary syndrome (PCOS)<sup>(6,7)</sup>. In women the diagnosis is usually made at birth because of sexual ambiguity. In less severe forms hyperandrogenism begins at puberty. Overall, 21-hydroxylase non-classical congenital adrenal hyperplasia is one of the most common autosomal recessive disorders of woman, affecting between 1% and 10% of hyperandrogenic women<sup>(6,8,9)</sup>. This disorder is recognized by the exaggerated secretion of the immediate  $\Delta 4$  precursor 17-hydroxiprogesterone (17-HP), either basal or more commonly after ACTH stimulation<sup>(6)</sup>. In our patient an ACTH test was performed yielding a normal 17-HP response excluding 21-hydroxylase deficiency. The basal 17-HP level was elevated, probably because of gonadal secretion of this steroid. PCOS, the most frequent cause of hyperandrogenism, has specific diagnostic criteria and other disorders associated with androgen excess and/or menstrual irregularities should be excluded. As it is characterized by peri-menarche beginning, PCOS do not usually presents with so high androgen levels and frank virilization, both suggestive of a malignant process<sup>(12)</sup>. During the data recording, drugs like valproic acid or surreptitious intake of anabolic steroids must be excluded<sup>(2,11)</sup>. Due to the high clinical suspicion and markedly high androgen levels we request an ultrasound that confirmed the origin of the process.

Hirsutism concomitant with amenorrhea in females at reproductive age is a typical presentation of virilizing tumors. These patients usually have history of regular menstrual cycles that suddenly discontinued, along with signs of rapid-progressing hyperandrogenism<sup>(3)</sup>. Testosterone concentration, usually greater than 200 ng/dl points to a tumoral origin; even though lower values do not exclude it. On the other hand, concentrations higher than 200 ng/dl can occur in some non-tumoral disorders, like ovarian hyperthecosis<sup>(2,12)</sup>. In the second case, oral glucose tolerance test showed intolerance to carbohydrates and hyperinsulinemia, along with atherogenic lipid profile and hypertension. Virilizing tumors, as well as PCOS or hyperthecosis, could present with this clinical presentation<sup>(13)</sup>. Due to the

high levels of testosterone we intended to discard the tumoral origin. Tumors of adrenal co-secretant, usually androgens and cortisol, causing Cushing's syndrome. Adrenal adenomas that produce pure androgens rarely occur, being in these cases the DHEA-S levels usually greater than  $> 600 \text{ ug/dl}$  <sup>(12, 14)</sup>. Even though the prevalence of Cushing's syndrome in hyperandrogenic women appears to be well below 1%, so we should suspect them at the appearance of rapid weight gain, oligo-amenorrhea, signs of hyperandrogenism, impaired glucose tolerance and hypertension. If this clinical picture presents in association with thinned skin, easy bruisability, moon-faces and myopathy, a diagnosis of cortisol excess should be considered <sup>(15)</sup>. In our patient, Cushing's syndrome was discarded with appropriate biochemical tests. The ultrasound showed a tumor on the left ovary and histology revealed an insular carcinoid. Primary ovarian carcinoids are very rare tumors that account for less than 5% of all carcinoids and 0.1% of all ovarian malignancies. The carcinoid syndrome is observed in almost the fourth part of the patients and the level of 5-HIAA and the presence of tumoral markers contribute to diagnosis <sup>(16)</sup>. In our patient, all these factors were negative, being the histology an incidental finding. Robby S et al, have reported a series of eighteen cases of primary trabecular carcinoid tumors, of which only one patient had virilizing manifestations. In this case, along with ours, the androgen production can be explained by the histological finding of luteinized stromal cells with stromal hyperplasia in the periphery of the carcinoid tumor <sup>(17)</sup>. When the androgen elevation is marked, luteinized cells are usually found within the ovarian stroma in greater quantities than in the typical PCOS and this condition is called hyperthecosis. The later is typically associated with more profound virilization that overlaps both clinically and pathologically with PCOS. Ovary hyperthecosis is considered a severe form of PCOS, having a direct correlation between its severity and the level of insulin resistance <sup>(10, 12)</sup>. Our patient developed diabetes as expected for patients with PCOS or hyperthecosis with insulin resistance <sup>(12)</sup>.

During menopause, the ovarian secretion of androgens continues, but not enough to produce signs of virilization. Differently than women in reproductive age, signs of hyperandrogenism manifest with lower levels of testosterone. When signs of virilization appear, even subtly in this stage of life, an androgen-secreting tumor must be suspected<sup>(3)</sup>. Due to the difficulties to establish the origin of hyperandrogenism, and with the imaging studies and pelvic examination normal, our patient underwent bilateral oophorectomy, with favorable evolution. Ovary tumors, according to Young and Scully clas-

sification, which are able to present endocrine manifestations, include the ones derived from gonadal stroma, sexual cords and steroid cells tumors. The later one is very infrequent comprising only the 0.1 % of every ovary neoplasms. In this group are included the tumors that our patients of case 1 and 3 had. Leydig cells tumor is the most frequent in postmenopausal and steroid cell tumor not otherwise specified is the most frequent in younger women <sup>(3)</sup>. Our cases do not follow this age pattern. Ovarian tumors present a great variety of morphological and functional manifestations, which should interest, not only to gynecologists, pathologists and oncologists, but also to endocrinologists and dermatologists. The better predictors of tumoral hyperandrogenism are clinical findings.

The author(s) declare that they have no competing interests.

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