

8. Seregni E, Ferrari L, Bajetta E, Martinetti A, Bombardieri E. Clinical significance of blood chromogranin A measurement in neuroendocrine tumors. *Ann Oncol.* 2001;12 Suppl. 2:S69–72.
9. Korse CM, Muller M, Taal BG. Discontinuation of proton pump inhibitors during assessment of chromogranin A levels in patients with neuroendocrine tumours. *Br J Cancer.* 2011;105:1173–5.

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A hidden cause of virilization in postmenopausal women[☆]



Una causa oculta de virilización en mujeres postmenopáusicas

Virilizing ovarian tumors are very infrequent, representing less than 0.2% of all cases of hyperandrogenism and less than 1% of ovarian tumors.¹ Two women with severe hyperandrogenism who turned out to have a Leydig cell tumor are reported.

Our first patient was a 50-year-old woman with a 5-year history of weight gain of 20 kg, secondary amenorrhea, acne, hirsutism and progressive virilization (male-pattern alopecia, clitoromegaly and deepening of the voice). On physical examination, she revealed moon facies, buffalo hump, thin and wrinkled skin and abdominal purple red striae. Ferriman–Gallwey hirsutism score was 18. Plasma ACTH and cortisol, and urinary free cortisol were increased. Hormonal assessment is summarized in Table 1. Very high testosterone, slightly high androstenedione (4.59 ng/mL, normal 0.3–3.5) but normal dehydroepiandrosterone sulfate (DHEAS) levels (1.25 mcg/mL, normal 0.35–4.3) were detected. FSH and LH levels were 27.4 and 13.4 U/L respectively (normal range for postmenopause 20–100 IU/L). Dexamethasone suppression tests (1 and 8 mg) were diagnostic of Cushing's disease; magnetic resonance imaging (MRI) revealed a 7 mm microadenoma in the right lateral margin of the pituitary gland, which was resected by transsphenoidal surgery. One month after surgery, she complained of no improvement of her symptoms. Remarkably high testosterone levels, slightly elevated androstenedione (3.89 ng/mL) but normal DHEA-S (2.15 mcg/mL) were found (Table 1). These findings could indicate either an ovarian origin of hyperandrogenism or persistence of Cushing's disease. Although other diagnoses, such as ovarian hyperthecosis, could not be excluded, the rapid onset and very high levels of androgens suggested an ovarian tumor. Pituitary MRI could match with either tumor persistence or postsurgical changes; neck, thorax and abdominal CT scan and pelvic transvaginal ultrasound failed to find any mass. Bilateral laparoscopic oophorectomy was

performed. A pure Leydig cell tumor of 12 mm was found on histological examination of the left ovary. Alpha-inhibin immunohistochemical staining was found to be positive. Total and free testosterone levels returned to the normal range (Table 1), and the patient referred improvement in her voice, hair loss, acne and hirsutism, together with development of hot flushes. As hormonal findings suggested persistent Cushing's disease, MRI was performed showing a focal area of low intensity signal on non-contrast T1 suggesting a remaining microadenoma. Some months later the patient finally agreed to a new transsphenoidal pituitary surgery; unfortunately, the adenoma was not found and hypercortisolism persisted (Table 1). A new MRI revealed a 3 mm microadenoma in the posterolateral right area of the pituitary; Gamma Knife radiosurgery was then delivered, with a maximum irradiation dose of 33.33 Gy. Along the following months the patient lost 10 kg, her general condition improved and hormonal levels finally normalized (Table 1).

The second patient was a 60-year-old woman referred to the Endocrinology clinic due to 5-year complaints of male pattern alopecia, hirsutism and deepened voice. Hormonal evaluation showed increased total (8.58 and 4.86 ng/mL) and free testosterone levels (16 and 13.7 pg/mL); gonadotropin levels were low for postmenopausal state (luteinizing hormone 2.5 IU/L, follicle-stimulating hormone 3.84 IU/L). Other androgens remained within the normal range: androstenedione 2.92 ng/mL, DHEAS 0.81 mcg/mL. A CT scan and transvaginal ultrasound revealed no enlargement or mass in abdomen or pelvis. Considering the differential diagnosis of ovarian hyperthecosis vs ovarian tumor both ovaries were removed. A Leydig cell tumor of 15 mm was found in the right ovary, with positive staining for alpha-inhibin. After surgery, free and total testosterone levels fell to 0.7 pg/mL and 0.22 ng/mL. The physical changes gradually reversed and she suffered hot flushes.

Virilizing ovarian tumors are an unusual cause of hyperandrogenism; however, rapidly worsening signs of virilization in a postmenopausal woman should prompt an urgent diagnostic work-up for an androgen-secreting tumor. Peripheral total testosterone higher than 2 ng/mL (>7 nmol/L), or 3–4 times higher than the upper limit of normal range may be a cut-off level for ovarian neoplasm suspicion.² One study has shown that testosterone level >8.67 nmol/L (2.5 ng/mL) had 100% sensitivity for ovarian neoplasm, together with 98% specificity.³ Our initial differential diagnosis also considered

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Table 1 Hormonal levels in Patient 1 along evolution.

	Initial levels (June 2005)	1 month after first transsphenoidal surgery (February 2006)	After ooforectomy (January 2007)	1 month after second transsphenoidal surgery (March 2009)	12 months after radiosurgery (March 2013)	Normal range
ACTH (pg/mL)	57.7 and 75 ^a	52.3 and 48.2 ^a	83.2	123 and 80.2	52.1	2–50
Plasma cortisol (μg/dL)	17.6 and 32.5 ^a	7.6 and 15.6 ^a	20.2	16.1	8.61	5–25
Morning plasma cortisol after DXM 1 mg 11 p.m. (μg/dL)	7.31 and 9.13 ^a	10.8 and 9.8 ^a	9.64	6.45	1.0	Serum corti- sol < 1.8 mcg/dL (<50 nmol/L)
Morning plasma cortisol after DXM 2 mg/6 h or 8 mg 11 p.m. (μg/dL)	1.25 and 1.18 ^a	–	1.44	1.17	–	Serum cortisol decrease >50%
Urinary free cortisol (μg/24 h)	122.6 and 345 ^a	135.6	335.6	215	31.2	35–120
Total testosterone (ng/mL)	5.35 and 3.99 ^a	5.2 and 6.12 ^a	0.31	–	0.221	Women 0.2–0.9
Free testosterone (pg/mL)	22.5 and 18 ^a	20 and 28 ^a	1.7	1.26	1.88	0.06–2.6

DXM, dexamethasone.

^a Two samples were obtained in different days to confirm these results.

stromal hyperthecosis. Pure Leydig cell tumors typically occur in postmenopausal women, with hirsutism or virilization in 75% of cases. These tumors are typically small at presentation,¹ so imaging studies are often not useful for the diagnosis,⁶ as happened in our cases. Less than 150 cases have been reported to date.^{4,5}

In our first case, differential diagnosis of hyperandrogenism was particularly challenging, as our patient also suffered from Cushing's disease with an awkward evolution. However, as adrenal glands produce up to 95% of DHEA-S, its normal levels ruled out an adrenal origin of hyperandrogenism, while high testosterone levels indicated a virilizing ovarian tumor. Coexistent adrenal and ovarian hyperandrogenism has been reported in other unusual settings.⁷ Rare steroid cell ovarian tumors of adrenocortical type have also been reported to result in cortisol co-secretion.⁸ Ovarian tumors may also be associated with Cushing's syndrome due to ectopic secretion of ACTH or corticotropin-releasing factor (CRF).^{9,10} Our patient showed an ACTH-dependent Cushing's syndrome, which ruled out the possibility of cortisol co-secretion. Besides, hyperandrogenism disappeared after tumor removal, while Cushing's disease persisted; therefore, an ectopic source of ACTH secretion could also be ruled out.

In conclusion, screening for virilizing ovarian tumors is mandatory in rapidly progressive virilization, with elevated testosterone levels, after ruling out other more frequent causes. In the unusual situation of coexisting hypercortisolism, DHEA-S can be useful for differential diagnosis, as normal levels are found when the androgen source is ovarian. Normal imaging does not rule out virilizing ovarian tumors.

References

1. Faria AM, Perez RV, Marcondes JA, Freire DS, Blasbalg R, Soares J, Simões Jr K. A premenopausal woman with virilization secondary to an ovarian Leydig cell tumor. *Nat Rev Endocrinol*. 2011;7:240–5.
2. Meldrum DR, Abraham GE. Peripheral and ovarian venous concentrations of various steroid hormones in virilizing ovarian tumors. *Obstet Gynecol*. 1979;53:36–43.
3. Waggoner W, Boots LR, Azziz R. Total testosterone and DHEAS levels as predictors of androgen-secreting neoplasms: a populational study. *Gynecol Endocrinol*. 1999;13:394–400.
4. Rothman MS, Wierman ME. How should postmenopausal androgen excess be evaluated? *Clin Endocrinol (Oxf)*. 2011;75:160–4.
5. Kozan P, Chalasani S, Handelsman DJ, Pike AH, Crawford BA. A Leydig cell tumor of the ovary resulting in extreme hyperandrogenism, erythrocytosis, and recurrent pulmonary embolism. *J Clin Endocrinol Metab*. 2014;99:12–7.
6. Hofland M, Cosyns S, De Sutter P, Bourgain C, Velkeniers B. Leydig cell hyperplasia and Leydig cell tumour in postmenopausal women: report of two cases. *Gynecol Endocrinol*. 2013;29:213–5.
7. Regnier C, Bennet A, Malet D, Guez T, Plantavid M, Rochaix P, et al. Intraoperative testosterone assay for virilizing ovarian tumor topographic assessment: report of a Leydig cell tumor of the ovary in a premenopausal woman with an adrenal incidentaloma. *J Clin Endocrinol Metab*. 2002;87:3074–7.
8. Young RH, Scully RE. Ovarian steroid cell tumors associated with Cushing's syndrome: a report of three cases. *Int J Gynecol Pathol*. 1987;6:40–8.
9. Parsons V, Rigby B. Cushing's Syndrome associated with adenocarcinoma of the ovary. *Lancet*. 1958;272:992–4.

10. Nichols J, Warren JC, Mantz FA. ACTH-like excretion from carcinoma of the ovary: the clinical effect of m,p'-DDD. *J Am Med Assoc.* 1962;182:713–8.

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Sexual differentiation anomalies. XX male syndrome[☆]



Anomalías de la diferenciación sexual. Síndrome del varón XX

The XX male syndrome was first described in 1964 by De la Chapelle, who called it "sex inversion in women". This author reported patients with male phenotype and psychosexual identification in whom the gonad was of the testicular type and who had no microscopic or gross evidence of ovarian tissue and karyotype 46,XX.¹

Frequency of this syndrome is very low (1/20,000 live newborns). It is called the XX male syndrome, and is currently classified within sex differentiation abnormalities, a group of conditions where a defect occurs in normal fetal development of genetic sex, gonadal sex and/or external genitalia.²

The XX male syndrome consists of a discordance between a male phenotype and a female karyotype. During sex differentiation occurring between the fifth and seventh weeks of embryonic development, anti-müllerian hormone (AMH) is sufficient in these patients to inhibit development of müllerian structures, with complete differentiation of wolffian derivatives and adequate masculinization of external genitalia. Spermatogenesis is highly deficient or absent, and patients are therefore infertile. However, Leydig cells have a variable development, and produce sufficient androgens to ensure marked post-pubertal virilization.³

Most patients have normal male phenotype, but hypospadias, cryptorchidism, and ambiguous genitalia have been reported in 10–15% of cases. Diagnosis is made at pubertal age, when the most common clinical and laboratory signs occur: gynecomastia, hypogonadism, shorter penile length, and infertility due to oligospermia or azoospermia. Height is usually normal, and well as psychomotor development and intellectual capacity.⁴

As regards management after diagnosis, regular monitoring, closer in puberty, is done, and repair surgery and psychological support is offered.

We report the case of a one month-old infant who was referred for balanic hypospadias, a supernumerary first

finger, and agenesis of the second finger in both hands. Physical examination was otherwise normal. As was genital examination, which revealed a well developed scrotum containing testes 2 mL in volume and a 2.9 cm long penis (P50 for age) of normal thickness and with erectile capacity. The infant had no remarkable family and personal history. Because of the described physical abnormalities, karyotype was requested and was reported to be 46, XX, with no detection of the SRY gene by FISH (46, XX; SRY(–)). Hormone tests performed included AMH, testosterone precursors (5-DHT; 17-OH progesterone; 17-OH pregnenolone), LH, and FSH; basal serum levels were normal for males. Ultrasonography and abdominal and pelvic MRI were also normal for a male. Abnormal sex differentiation consisting of a XX male syndrome with no SRY detection was diagnosed. Genetic study should be elaborated on at this point.

The XX male syndrome is a very uncommon condition (1–9 cases per 1,000,000 males) difficult to diagnose before puberty or adult age due to the scarcity or absence of physical manifestations. It may be suspected in a newborn with perineal hypospadias and cryptorchidism. Our case was diagnosed by chance when karyotyping was requested due to abnormalities seen in both fingers, plus hypospadias.

Clinical suspicion is based on physical examination and is supported by hormone testing. Diagnosis of certainty is genetic, based on the finding of the karyotype 46, XX.

During sex differentiation, genetic sex determines gonadal sex from the sixth month of pregnancy. The undifferentiated gonad spontaneously tends to female sex. Masculinization starts by the action of the testicular development factor (TDF), encoded by the SRY gene, which will lead to differentiation of the seminiferous cord that contains pre-Sertoli cells (secreting AMH) and spermatogonia. AMH causes disappearance of müllerian ducts (and the resultant absence of Fallopian ducts, uterus, and vagina), while androgens secreted by Leydig cells will determine differentiation of Wolffian ducts into epididymis, deferent ducts, and seminal vesicles. Decreased testicular testosterone production in cases with hypogonadism causes in some patients abnormalities in the external genitalia.

AMH production by Sertoli cells in testes remains high during infancy, but decreases to low levels during puberty and adult life. In recent years, AMH measurement is widely used to assess testicular presence and function in boys with hermaphroditic conditions or ambiguous genitalia.⁵

The sex-determining region Y (SRY) gene, critical for male sex differentiation, is located in the short arm of

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