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REVIEW

Postmenopausal androgen-secreting ovarian tumors: challenging differential diagnosis in two cases

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ABSTRACT

Postmenopausal hyperandrogenism constitutes a very rare condition of tumoral or non-tumoral origin primarily residing either in the ovary or in the adrenal glands. We present herein two cases with this condition; one with abnormal postmenopausal genital bleeding and mild increase in facial hair, and the second with slow-developing hirsutism and virilization. Both cases shared a notorious increase in libido.

The laboratory tests showed high levels of testosterone (>100 ng/ml). A normal value of dehydroepiandrosterone sulfate and a normal cortisol level at 9 am after 1 mg of dexamethasone administered at midnight (Nugent test) made an adrenal etiology very unlikely. On the other hand, a high level of inhibine B oriented to an ovarian source. Transvaginal sonography failed to demonstrate an ovarian tumor, but an abdominal and pelvic computed tomography scan or magnetic resonance imaging detected an ovarian tumor and normal adrenal glands.

A laparoscopic oophorectomy was performed, and the histological study demonstrated a steroidal cell tumor in the first case and a Leydig cell tumor in the second.

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Introduction

Hyperandrogenism that starts in postmenopause constitutes a very rare condition of tumoral or non-tumoral origin primarily residing either in the ovary or the adrenal glands[1]. A rapid onset of hyperandrogenism associated with virilization suggests a subjacent malignant origin[1]. Consequently, sectional imaging along with most discriminatory biochemical tests should be prioritized. In the rest of the cases, adequate laboratory testing should precede imaging to detect the source of the androgen excess. In general, hyperandrogenism of adrenal origin is frequently associated with multiple hormone production, including cortisol and dehydroepiandrosterone sulfate (DHEAS), which makes it more easily diagnosed[2]. However, the ovarian origin is more difficult to specify, and the differential diagnosis is more complicated[1]. Occasionally, the ovarian origin is suspected only once the adrenal etiology has been ruled out.

In this article, we report two recent cases of androgen-secreting ovarian tumors (ASOT) that manifested as hyperandrogenism in the postmenopause whose clinical presentation varied significantly between them, demonstrating the wide spectrum of clinical manifestation of this condition. A short review of the differential diagnosis of hyperandrogenism in postmenopausal women is also included.

Case reports

Case 1

A 65-year-old woman without menopausal hormone therapy consulted because of abnormal uterine bleeding. She also complained of slow and progressive mild hirsutism on her face and exacerbated libido. Her past medical history was not relevant. The physical examination revealed a patient in overall good condition, body mass index 23.1, blood pressure 124/72 mmHg, and mild increase in facial hair. The rest of the physical examination was normal. Gynecological examination demonstrated only a bloody cervical discharge with a normal sized uterus, absence of clitoromegaly, and without any palpable adnexal mass. Laboratory evaluation showed high testosterone and estradiol levels with low gonadotropin levels for her menopausal status and normal DHEAS, androstenedione, and Nugent test (Table 1). The Homeostatic Model Assessment was normal. A grayscale transvaginal ultrasound showed an enlarged 21-mm homogeneous endometrium and asymmetry in ovary size (right 19 mm ×13 mm ×14 mm and left 27 mm ×16 mm ×10 mm), but no tumor was identified. Endometrial sampling demonstrated a simple hyperplasia without atypia. Abdomen and pelvic magnetic resonance imaging (MRI) revealed a 24-mm mass in the left ovary, with a normal right ovary and normal adrenal glands.

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Table 1. Laboratory tests in case 1.

Laboratory test	*Unit*	*Basal value*	*Postoperative value*	*Normal value*
Testosterone	ng/ml	128	6.4	2.9–40.8
SHBG	nmol/l	38.9	39.2	17.3–125
FAI		11.4	0.56	<4.5
Estradiol	ng/ml	124	ND	<5
FSH	mIU/ml	13.8	36.7	25.8–134.8
LH	mIU/ml	6.9	20.2	7.7–58.5
DHEAS	µg/ml	0.81	ND	0.35–4.3
Androstenedione	ng/ml	2.17	ND	0.4–2.7
Cortisol 9 am (Nugent test)[a]	µg/dl	0.8	ND	<1.8

DHEAS, dehydroepiandrosterone sulfate; FAI, Free Androgen Index; FSH, follicle stimulating hormone; LH, luteinizing hormone; ND, not done; SHBG, sex hormone binding globulin.
[a]Cortisol 9 am after 1 mg dexamethasone administered orally at midnight.

Table 2. Laboratory tests in case 2.

Laboratory test	*Unit*	*Basal value*	*Postoperative value*	*Normal value*
Testosterone	ng/ml	1500	7.9	2.9–40.8
SHBG	nmol/l	42.9	58	17.3–125
FAI		121.2	0.46	<4.5
Estradiol	ng/ml	42.7	<5	<5
FSH	mIU/ml	9.3	29.7	25.8–134.8
LH	mIU/ml	7.5	19.9	7.7–58.5
DHEAS	µg/ml	3.16	1.08	0.35–4.3
Cortisol 9 am (Nugent test)[a]	µg /dl	0.9	ND	<1.8
Inhibine B	pg/ml	9.4	ND	<4

DHEAS, dehydroepiandrosterone sulfate; FAI, Free Androgen Index; FSH, follicle stimulating hormone; LH, luteinizing hormone; ND, not done; SHBG, sex hormone binding globulin.
[a]Cortisol 9 am after 1 mg dexamethasone administered orally at midnight.

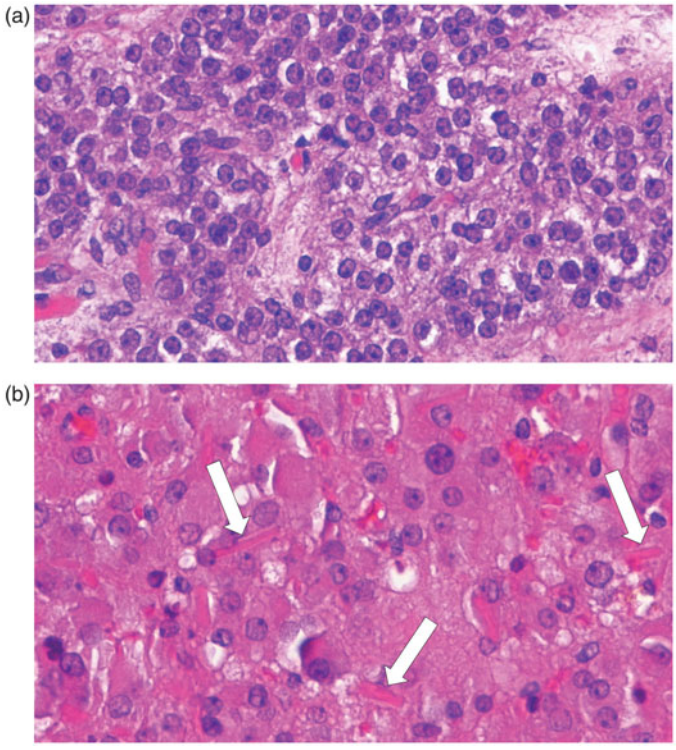

Figure 1. (a) Ovarian histology in case 1: the tumor consists of diffuse sheets or nests of steroid cells with foamy, lipid-rich cytoplasm without significant atypia and few, isolated mitotic figures (not shown) (hematoxylin and eosin [HE], 400×). (b) Ovarian histology in case 2: diffuse sheets of granular eosinophilic cytoplasm with abundant crystals of Reinke (white arrows). No mitotic activity or significant atypia was found (HE, 400×).

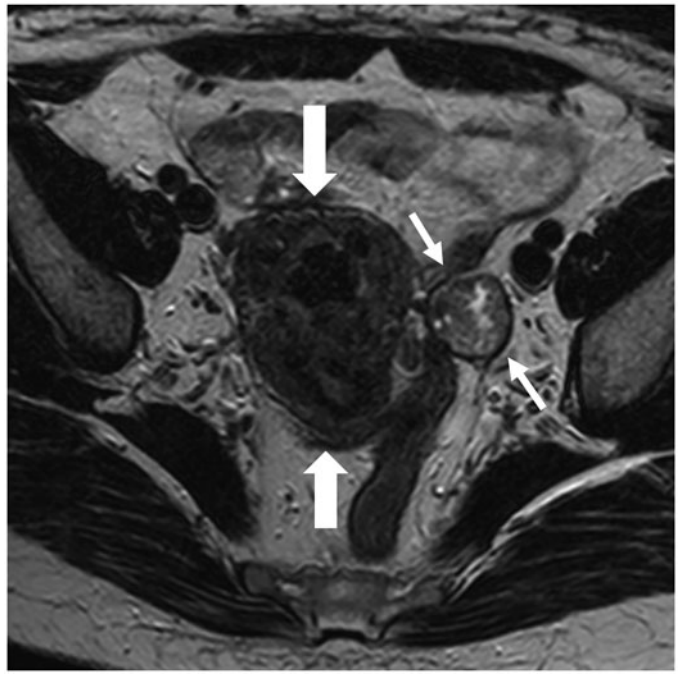

Figure 2. Pelvic magnetic resonance image in case 2 shows a myomatous uterus (thick arrows) and a solid left ovarian tumor with intermediate signal, relatively homogeneous in T2 (thin arrows).

A laparoscopic bilateral oophorectomy was performed, and the pathological report informed a left 15-mm ovoid tumor, yellow–orange; its histology revealed a steroidal cell tumor (ICD-O 8670/0, WHO 2013) (Figure 1(a)).

After surgery, the patient normalized their hormonal profile to the postmenopausal range (Table 1) and started complaining of moderate climacteric symptoms; therefore, it was necessary to start menopausal hormone therapy. She also described loss of libido and progressive disappearance of excess hair.

Case 2

A 50-year-old woman with hypothyroidism and prediabetes consulted because of the gradual appearance of bothersome hirsutism and acne evolving over 2 years that was exacerbated since the withdrawal of combined oral birth control pills 9 months before. She remained in amenorrhea, without climacteric symptoms and with an overexacerbated libido. The physical examination revealed an obese woman, body mass index 30.5, blood pressure 122/86 mmHg, hirsutism with a Ferriman–Galway score of 9, and alopecia grade 1 according to the Ludwig scale. She also had intense acanthosis nigricans in the neck and axilla. The rest of the examination was not relevant. The gynecological examination revealed clitoromegaly and enlarged uterus, without any palpable adnexal mass. Her laboratory workout 2 years before had shown very high testosterone levels (626.7 ng/dl) consistent with a tumoral origin, but no further investigation was done at that time. The patient's hormonal profile is presented in Table 2. Testosterone levels were extremely high with only mild elevation of estradiol and low gonadotropin levels for her age. Inhibin B was also elevated. DHEAS and the Nugent test were normal, making the adrenal

Table 3. Principal causes of postmenopausal hyperandrogenism[1].

Functional hyperandrogenism
Polycystic ovary syndrome
Congenital adrenal hyperplasia
Ovarian hyperthecosis
Cushing's syndrome
Acromegaly
Exposure to drugs (testosterone, dehydroepiandrosterone sulfate, danazol, phenytoin, minoxidil, cyclosporine)
Tumor-related hyperandrogenism
Androgen-secreting adrenal adenomas and carcinomas
Androgen-secreting ovarian tumors
Metastatic neuroendocrine tumor

origin unlikely. A pelvic grayscale ultrasound informed miomatosis and normal-sized ovaries. An abdominal and pelvic computed tomography scan showed normal adrenal glands, a 30-mm leiomyoma in the uterine fundus, and identified a 14-mm cystic lesion in the left ovary and normal right ovary, but no tumor was identified. To clarify, a pelvic MRI scan was performed, identifying a 30-mm left solid ovarian mass (Figure 2). Then, according to the patient's desire, only laparoscopic left salpingo-oophorectomy and endometrial sampling were performed. Pathological analysis demonstrated a left ovary measuring 33 mm × 26 mm × 24 mm, with a 22-mm ovoid, orange–brown, partially cystic Leydig cell tumor (ICD-O 8650/0, WHO 2013) (in Figure 1(b)); the endometrial biopsy showed a fragment of squamous tissue. After surgery, testosterone normalized 3 weeks later (Table 2) and hyperandrogenism declined progressively as well as the exacerbated libido; only mild climacteric symptoms and emotional lability were referred by the patient, which did not require treatment.

Discussion

Herein, we present two cases of hyperandrogenism in postmenopausal age (testosterone >100 ng/dl) due to ASOT that show heterogeneity in the presentation of these disorders. Both cases manifested as the slow development of hirsutism, one with virilization, and the exacerbation of libido, symptoms that must be attributed to the increase in testosterone levels. If we analyze the possible causes of hyperandrogenism in postmenopause (Table 3)[1], we can state that the slow progression of the disease and the lack of cushingoid appearance made the existence of a malignant disease, such as adrenal carcinoma, very unlikely. Also, symptoms starting at a mature age allowed us to rule out a diagnosis of congenital adrenal hyperplasia or polycystic ovary syndrome, which give symptoms earlier on in life. Also, they did not mention the use of androgens and had no clinical elements of acromegaly. The diagnosis was circumscribed to an ovarian origin for the androgen excess with a very low possibility of a testosterone-only-secreting adrenal adenoma.

Although both patients have some similarities, the main reason for consultation differed in an important way: postmenopausal abnormal uterine bleeding in the first case and bothersome hirsutism with virilization in the second.

The initial evaluation of our patients included the measurement of several steroids to orient to the etiology of the disease. We measured plasma testosterone and sex hormone binding globulin to calculate the Free Androgen Index (testosterone [nmol/dl] × 100 / sex hormone binding globulin [nmol/dl]) and measured DHEAS oriented to the source of the hyperandrogenism; we also measured gonadotropins (follicle stimulating hormone and luteinizing hormone) and estradiol levels to detect the impact of the disorder on the gonadal axis. To rule out an autonomous glucocorticoid secretion, which is a frequent finding in adrenal carcinoma, it is also advisable to discard glucocorticoid hypersecretion by the measurement of plasma cortisol at 9 am after the administration of 1 mg of dexamethasone at midnight (Nugent test), as we did in both cases, or basal plasma adrenocortical stimulating hormone at 9 am.

Unlike ovarian tumors which secret testosterone as the main androgen, adrenal androgen-secreting tumors, mainly carcinomas, often cause elevation of cortisol and DHEAS to values over 700 μg/dl (Table 4)[2] and of androstenedione[3], which were normal in our cases. However, there are case reports of adrenal adenomas secreting exclusively testosterone which could complicate the differential diagnosis[4]. Severe testosterone excess is equally produced by adrenal carcinoma and ovarian pathologies such as ovarian hyperthecosis (OHT) or ASOT.

The magnitude of testosterone hypersecretion was very different in our cases. Case 1 had a moderate increase of testosterone associated with a relatively high level of estradiol which should have come from peripheral conversion of testosterone, since the ovarian hypersecretion of estradiol due to a granulosa cell tumor was ruled out. In this regard it has been demonstrated that aromatase activity increases with age[5]. The high estrogen level in this case was responsible for endometrial hyperplasia and abnormal uterine bleeding. We do not have an explanation for the modest increase of estradiol in case 2, considering the extremely high levels of its precursor testosterone and the fact that the patient was expected to have had high aromatase activity due to her obesity.

Isolated testosterone hypersecretion in both patients, with normal DHEAS and adequate suppression of cortisol in the Nugent test, made it possible to direct the imagological study to the ovaries.

A pelvic ultrasound, which is advised as the first image in these cases, does not always reveal the etiology of the disease[6], as was our experience in both patients, showing only ovarian asymmetry but not an ovarian tumor. This failure does not rule out the existence of a tumor, since it may be small[7]. It must be emphasized that color Doppler ultrasonography could had been a more precise method for the initial approach than the grayscale pelvic ultrasound we utilized[8].

Table 4. Some strategies to differentiate the adrenal or ovarian origin of postmenopausal hyperandrogenism.

Test	*Suggest ovarian origin*	*Suggest adrenal origin*
Plasma DHEAS	Normal	High
Plasma 9 am ACTH	Normal	Low (if there is concomitant adrenal hypersecretion of cortisol)
Plasma inhibine A and B	High	Normal
GnRH analog suppression test	Testosterone suppresses >50%	Testosterone suppresses <50%
Adrenal and ovarian vein catheterization (in the case of adrenal and ovarian suspicious images)	Secretion lateralizes to the compromised ovary	Secretion lateralizes to the compromised adrenal
Radiological images	MRI	MRI or CT scan with adrenal protocol

ACTH, adrenocortical stimulating hormone; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; GnRH, gonadotropin-releasing hormone; MRI, magnetic resonance imaging.

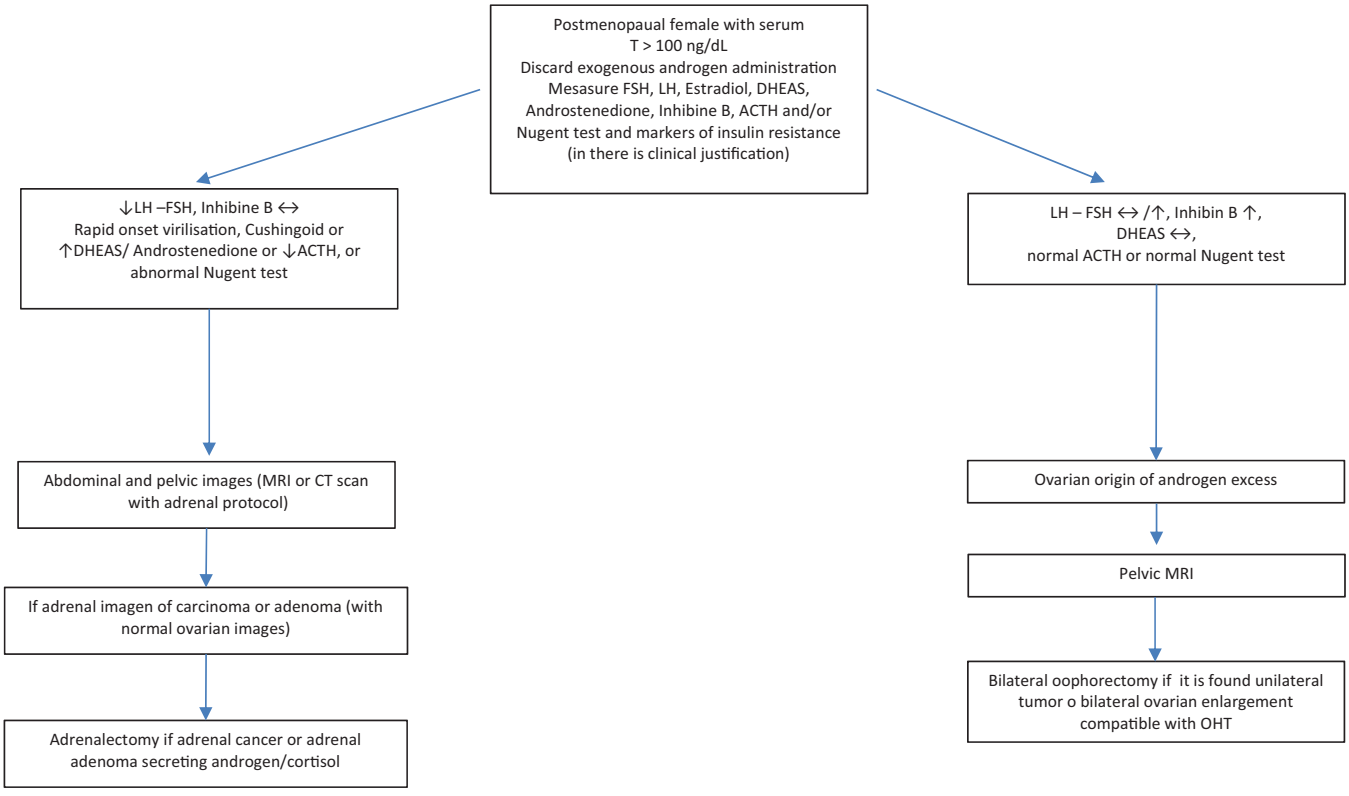

Figure 3. Diagnostic approach in postmenopausal-onset hyperandrogenism and high testosterone levels. ACTH, adrenocortical stimulating hormone; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; FSH, folicle stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging; OHT, ovarian hyperthecosis; T, testosterone.

The best method to detect ovarian tumors is pelvic MRI, which can demonstrate even small ovarian masses[9,10], especially in Leydig cell tumors which usually have a high lipid content, and the signal intensity on T2-weighted MRI reflects the content of the stroma[11]. It is important to highlight that the pelvic computed tomography scan failed to demonstrate the ovarian tumor in case 2.

The reason for starting the study with the hormonal profile before taking images is to avoid misdiagnosis in the case of an adrenal incidentaloma[12]. The only exceptions are those cases of rapid-onset virilization, where abdominal and pelvic MRI should be requested early.

When the differential diagnosis between ovarian and adrenal origin of hyperandrogenism is difficult, as it could be in the case of the coexistence of adrenal and ovarian masses, using the different methods summarized in Table 4 has been suggested. The simplest method is to measure DHEAS, which was normal in both cases, or adrenocortical stimulating hormone, which is expected to be suppressed if there is autonomous adrenal cortisol secretion. It is also useful to measure plasma levels of inhibin A and B that should be high if the ovary is the cause and normal if the adrenal gland is the cause[13]; the high level of inhibin B in case 2 oriented also to an ovarian etiology. Another method is the gonadotropin-releasing hormone analog (GnRHa) suppression test, which suppresses androgens >50% if the cause is ovarian and <50% if it is adrenal, because the secretion of androgens in the latter does not respond to luteinizing hormone[14]. A final method is ovarian and adrenal vein sampling[15]. However, this method is a technically challenging procedure with potentially false positive results and needs a very experienced radiologist, not available everywhere.

In our cases, it was unnecessary to perform the GnRHa suppression test or the differential vein catheterization

because the adrenal origin of the disease was ruled out with biochemical testing and the normal adrenal images. Hence, our differential diagnosis was confined to an ovarian source of hyperandrogenism, mainly ASOT or OHT. Although the ASOT group showed higher testosterone and estradiol and lower gonadotropin levels than the OHT group, a great overlap occurred among the hormone levels[16]. In case 2, the presence of prediabetes was compatible with OHT since pathophysiology of this disease considers that the combination of insulin resistance, characteristic of this state, plus high postmenopausal luteinizing hormone levels is pathogenic for this condition. Pelvic MRI provides an accurate differentiation of these two conditions[16], demonstrating an ovarian nodule in ASOT, as was the case in our two patients, and solid bilateral enlargement of both ovaries in OHT due to stromal hyperplasia.

According to the current practice, bilateral salpingo-oophorectomy is advised to cure these cases[17], a procedure that was offered to our patients.

Considering that cases such as ours are infrequent, physicians should follow a strict flow chart to guide their studies like the one we used (outlined in Figure 3), emphasizing that clinical and hormonal parameters must precede the realization of images, avoiding erroneous diagnosis in the case of adrenal incidentalomas.

In conclusion, we report two rare cases of ASOT presenting as hyperandrogenism in postmenopausal women, although with different clinical presentations. We emphasize the importance of following a strict protocol to avoid misdiagnosis or erroneous decisions. A revision of the differential diagnosis in these cases is also included.

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