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BRIEF COMMUNICATION

Ovarian Stromal Hyperplasia: A Rare Cause of Postmenopausal Hyperandrogenism

Teresa Lozoya Araque[1], Isauro Rogelio Monfort Ortiz[2], José Enrique Martín González[1], Alenda Jiménez García[1], Inmaculada Navarro Hidalgo[3], Verónica Andrade Gamarra[4], Cecilia Parrell Soler[1], Fernando Gil Raga[1]

[1]Department of Obstetrics and Gynecology, Manises Hospital, Valencia, Spain, [2]Department of Obstetrics and Gynecology, La Fe University Hospital, Valencia, Spain, [3]Department of Endocrinology, Manises Hospital, Valencia, Spain, [4]Department of Anatomy, Manises Hospital, Valencia, Spain

Ovarian hyperthecosis and ovarian stromal hyperplasia (OSH) are two uncommon non-neoplastic causes of ovarian hyperandrogenism, whose etiology is still unknown. These conditions are characterized by obesity, hyperinsulinemia, acanthosis nigricans, and even virilization, mainly in postmenopausal women. Here we have reported the case of a 67-year-old patient with a diagnosis of OSH, which was resolved after bilateral laparoscopic oophorectomy. In this case report, we have discussed two different conditions posing a diagnostic challenge and requiring a high index of suspicion.

Key Words: Hyperandrogenism, Hyperplasia, Menopause, Virilization

INTRODUCTION

Ovarian hyperthecosis (OHT) and ovarian stromal hyperplasia (OSH) are two uncommon, non-neoplastic causes of ovarian hyperandrogenism (with an incidence of 1 in 300 to 1 in 1,000 cases of hirsutism) [1]. Their aethiology is not completely known, and some similarities with polycystic ovarian syndrome exist (as hyperandrogenism, obesity, hyperinsulinaemia, acanthosis nigricans, and metabolic syndrome, etc.) [2]. The main feature that differentiates OHT and OSH from polycystic ovarian syndrome is age of onset (typically, polycystic ovarian syndrome occurs in peripubertal women, while OHT and OSH are more common after the menopause, when follicle formation has ceased, and the ovaries appear more solid) [3,4].

They are characterised by the presence of nests of luteinized theca cells in the ovarian stroma due to differentiation of the ovarian interstitial cells into steroidogenically active luteinized stromal cells. Stromal hyperplasia is the nodular or diffuse proliferation of the ovarian stroma, whereas OHT is stromal proliferation accompanied by luteinised stromal cells [5].

They present with hyperandrogenism, obesity, hyperinsulinaemia, acanthosis nigricans, and even virilization, mainly in postmenopausal women [2].

CASE REPORT

Our patient was a 67-year-old woman with four previous pregnancies, who initially attended the endocrinology clinic due to hirsutism, alopecia and progressive deepening of her voice for approximately 10 years. She had high blood pressure and dyslipidaemia. In addition, she was hysterectomised due to a benign cause (with preservation of the ovaries) at the age of 42. At the time of presentation she was on treatment for her other pathologies with losartan, pantoprazole, tramadol and paracetamol.

On physical examination, she had obesity grade II

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Address for Correspondence: Teresa Lozoya Araque, Department of Obstetrics and Gynecology, Manises Hospital, 2nd floor, Av. de la Generalitat Valenciana, 50, 46940 Manises, Valencia, Spain
Tel: 34-961845000, **E-mail:** telozoar@gmail.com, **ORCID:** https://orcid.org/0000-0003-3388-7376

(body mass index [BMI] 35.4 kg/m^2), blood pressure 137/86 mmHg, hirsutism in her chin, breast, abdomen, lumbar area and upper back (corresponding to a Ferriman–Gallway scale of 18), as well as frontal alopecia.

A transvaginal ultrasound scan (TV scan) showed an atrophic, 18-mm-sized right ovary; the left ovary was not identified.

Blood tests showed glycaemia and HbA1c within normal levels, and an elevated total cholesterol, especially due to low density lipoprotein cholesterol. Table 1 shows the hormonal profile of our patient, in which we observe a high free androgen index (with a value of 10.68) as well as high levels of total testosterone (112.9 ng/dL) and free testosterone (2.4 pg/mL). Insuline resistance index was also elevated (with a score of 5.9).

Due to the presence of elevated androgens and a negative TV scan, an abdomino-pelvic magnetic resonance imaging (MRI) scan was performed, in order to exclude a possible adrenal androgen-producing tumour. The MRI scan showed normal findings, with no significant adnexal or adrenal lesions identified.

A dexamethasone suppression test with 1 mg of dexamethasone was then performed, and cortisol decreased from 20.4 to 0.6 μg/dL. This excluded a possible Cushing's syndrome which could be responsible for functional hyperandrogenism in our patient. Total testosterone levels also drecreased from 129.1 to 116.4 ng/dL after the test.

A conservative management was then proposed with cyproterone acetate for approximately 2 months, with only a slight improvement of her symptoms.

Given the findings of long-term postmenopausal hyperandrogenism, elevated androgenic hormone profile and normal imaging tests, OHT or OSH were suspected. A laparoscopic bilateral oophorectomy was proposed in order to reach a definitive diagnosis and treatment. She underwent an uneventful procedure.

The pathology report confirmed an OSH, showing a significant increase in the cortico-medullar relationship, with a densely cellular cortical stroma and a discrete pseudonodular pattern without atypia with scant intercellular collagen. Stromal oedema was identified in relation to groups of cells that showed a large cytoplasm, a small rounded nucleus without atypia, albicans bodies and foci of endosalpingiosis (Fig. 1).

3 months following surgery, our patient reported an improvement in her hirsutism and frontal alopecia. Her BMI was down to 34 kg/m^2.

Testosterone levels were normalised, but biochemical markers of insulin-resistance did not improve after oophorectomy (glycaemia, triglyceridaemia and total cholesterol were paradoxically increased). This could be explained because lifestyle related factors, such as daily physical activity or dietary intake can directly influence these parametres. Blood presure after surgery remained unchanged, without any modifications in antihypertensive drugs (135/88 mmHg).

DISCUSSION

New-onset hyperandrogenism in postmenopausal women is a very infrequent pathology whose aethi-

Table 1. Patient's hormonal profile

Hormone	Value	Reference value (according to age)
Follicle stimulating hormone (mIU/mL)	45.5	23–116
Luteinizing Hormone (mIU/mL)	24.7	15.9–54.0
Oestradiol (pg/mL)	33.8	Non detectable–32
Free androgen index	10.68[a]	0.54–9.63
Total testosterone (ng/dL)	112.9[a]	14–76
Free testosterone (pg/mL)	2.4[a]	0.13–1.8
Dehydroepiandrosterone sulphate (μg/dL)	34	35–430
Sex hormone binding globulin (nmol/L)	35.1	18–144
Androstendione (ng/mL)	1.7	0.4–4.1
17-hydroxy-progesterone (ng/mL)	0.3	0.11–18.86
Thyrotropin hormone (mU/L)	3.2	0.55–4.780
Prolactin (ng/mL)	6.2	< 25

[a]Increased values compared to the reference population.

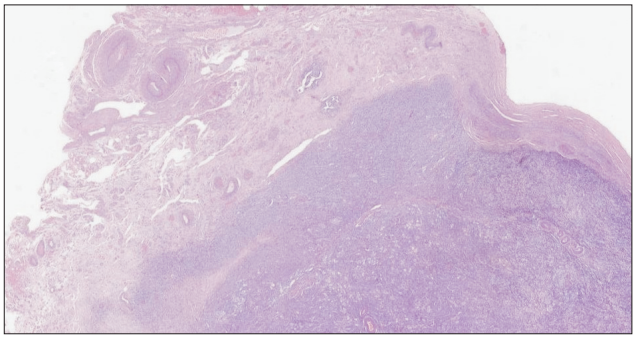

Fig. 1. Patology image with H&E stain and magnification ×1 that shows an increment in the cortico-medullar relationship, with a densely cellular cortical stroma and pseudonodular pattern without atypia with scant.

ological diagnosis can sometimes be challenging [3,6].

Initial management of hyperandrogenism would be to rule out iatrogenic factors such as cosmetic products or drugs used to increase libido [7]. In our case, none of these products had been used.

Other possible causes of hyperandrogenism like adrenal tumurs or Cushing's syndrome were excluded with our investigations.

Ovarian virilizing tumurs and hyperthecosis of the ovarian stroma are the most common causes of virilization in postmenopausal patients. However, differential diagnosis between these two entities is not easy.

Clinical assessment, determination of levels of testosterone and gonadotrophins as well as the presence or absence of an ovarian tumur on MRI scan are the main distinguishing features. However, the histopathology report is the gold standard for diagnosis [8].

OHT and OSH are characterised, as discussed before, by severe hyperandrogenism and insulin-resistance, mainly in postmenopausal women, with deepening voice, acne, hirsutism, frontal alopecia, clitoromegaly, as well as acanthosis nigricans, acrochordons, central obesity, increased risk of vaginal bleeding, endometrial hyperplasia and carcinoma, cardiovascular pathology and diabetes mellitus [2,9].

Average age at which it usually appears is 55 years (with an age range from 51 to 64 years) [10]. In our patient, the clinical signs that we observed were deep voice, hirsutism and alopecia, as well as obesity, dyslipidemia and arterial hypertension. Alopecia and hirsutism are the most common symptoms in postmenopausal hyperandrogenism [11], and they were the main symptoms with which our patient presented.

On the other hand, due to peripheral conversion of androgens to oestrogen, postmenopausal vaginal bleeding can occur, with an increased risk of endometrial hyperplasia and carcinoma [11]. Our patient had undergone a hysterectomy due to benign causes at 42-year-old, so these risks were not present.

OHT is characterized usually by elevated testosterone levels, normal or suppressed follicle-stimulating hormone and luteinizing hormone levels, normal dehydroepiandrosterone (DHEA), DHEA-S, 17-OH-progesterone and prolactin levels, as well as hyperinsulinaemia which can increase the production of ovarian androgens [9,12]. Nevertheless, total testosterone levels higher than 200 ng/dL in postmenopausal women also should make us suspect the presence of an androgen-producing tumor [13].

In our patient, we found raised levels of total and free testosterone and normal levels of DHEA-S, androstenedione, 17-OH progesterone and sex hormone binding globulin. Imaging tests are of limited value. Occasionally, enlarged ovaries without areas of hypervascularisation can be a useful diagnostic feature but they are not always present [10]. In fact, in our patient, the ovaries were found to be atrophic both on TV scan and MRI scan.

OHT is observed mainly after the menopause due to the loss of aromatisation of androgens into oestradiol by the granulosa cells. If it occurs in premenopausal women, it can be differentiated from polycystic ovarian syndrome because both hirsutism and insulin resistance are much more severe.

In Cushing's syndrome we observe elevated testosterone levels, normal or suppressed DHEA-S, and suppression of the adrenocorticotropin hormone (ACTH). The suppression test with dexamethasone would show, in Cushing's syndrome, a serum cortisol not suppressed when low doses of dexamethasone are administered [3]. In women with hyperandrogenism, a reduction more than 40% in testosterone levels after a suppression test with low doses of dexamethasone (0.5 mg every 6 hours for 2 days) has a sensitivity of 100% and a specificity of 88% to differentiate hyperandrogenisms of tumural origin from other causes of hyperandrogenism [11].

In our patient, testosterone levels and bioavailable testosterone were determined after the administration of 1 mg of dexamethasone at night, with a reduction of 10% to 12%. If we extrapolate these results from other studies performed with higher doses of dexamethasone [11], our patient would have suppressed testosterone levels between 40% and 48%, had it been done with the same

dose administered in those studies, which allowed us to rule out an androgen-producing ovarian tumor (in which testosterone levels remain high). On the other hand, in cases of congenital adrenal hyperplasia, the serum cortisol values decrease when performing a suppression of ACTH secretion with dexamethasone, since its production is dependent on ACTH [11]. In our patient, after a dexamethasone suppression test, cortisol levels decreased, which allowed us to rule out an ACTH-dependent hyperandrogenism.

Additionally, the increased risk of non-alcoholic steatohepatitis (NASH) in patients with elevated androgens has been described in the literature [14]. More specifically, NASH has been related to the underlying hyperandrogenism in OSH [1]. This would be due to the insulin-resistance caused by hyperandrogenism of ovarian origin, and initially it presents with hepatomegaly and elevated transaminases in asymptomatic patients. However, in the various analytical controls performed on our patient, liver function remained preserved with liver profile values within normal parametres.

Finally, as for hyperthecosis management, laparoscopic bilateral salpingo-oophorectomy is the treatment of choice, since it serves both diagnostic and therapeutic purposes.

In women with high surgical risk, the use of antiandrogens or gonadotropin-releasing hormone analogues is a valid option [15].

In addition, hyperinsulinism produces theca cells hyperplasia and an increased production of ovarian androgens that it is not possible to convert to oestradiol in a postmenopausal ovary, and this is why drugs that increase insulin sensitivity and changes in lifestyle can be useful in the management of this pathology [3].

In our patient, antiandrogens (ciproterone acetate) only marginally improved her symptons, so a decision was made to offer her a more effective and definitive treatment in the form of surgery. After surgery, previously altered hormonal values were normalised, and her symptoms disappeared.

OHT and OSH are infrequent, benign causes of hyperandrogenism, which are difficult to diagnose.

Usual imaging techniques (TV scan or MRI scan) are not conclusive, and therefore a high index of suspicion is required.

Promptly and correct management of these conditions is of vital importance, given the long-term consequences (metabolic and with regards to the patient's quality of life) they can produce.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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