

Ovarian Hyperthecosis in the Context of an Adrenal Incidentaloma in a Postmenopausal Woman

apresentação de caso

ABSTRACT

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Adrenal incidentaloma is not infrequent and can be found in hirsute women. We report a case of a 54-year-old woman with amenorrhea and hirsutism of abrupt onset and mild signs of virilization that had an adrenal incidentaloma coexisting with ovarian hyperthecosis. Basal total and free testosterone were 191 ng/dL and 179 pmol/L. Pelvic ultrasonography disclosed a right ovary with 10.3 cc and a left ovary with 9.8 cc without nodules or cysts, and computerized tomography of the abdomen disclosed a normal right adrenal gland. On the left adrenal gland a solid nodule with 0.8 cm was seen. After GnRH α administration, total testosterone was 23 ng/dL and free testosterone was 17 pmol/L. In view of a suppression of testosterone by GnRH α , the patient was submitted to a hysterectomy by laparoscopy. Symmetrically enlarged ovaries were seen. No tumor was apparent. Histology showed hyperthecosis, with foci of luteinized stromal cells. Only atretic follicles were detected. No hilar cell hyperplasia was seen. In conclusion, the presence of an adrenal mass in a hirsute woman can lead to a wrong diagnosis. In this case the suppression GnRH α test was fundamental to determine the origin of hyperandrogenemia. (**Arq Bras Endocrinol Metab 2008; 52/7:1184-1188**)

Keywords: Hirsutism; Ovarian hyperthecosis; Adrenal incidentaloma; Menopause

RESUMO

Coexistência de Incidentaloma Adrenal e Hipertecose de Ovário em Mulher Menopausada.

Os incidentalomas adrenais não são infreqüentes e podem ser encontrados em pacientes com hirsutismo. Nesse relato, apresentamos o caso de coexistência de um incidentaloma adrenal com hipertecose de ovário, em uma mulher com 54 anos de idade com amenorréia e hirsutismo de início abrupto e sinais leves de virilização. As testosteronas total e livre basal foram de 191 ng/dL e 179 pmol/L, respectivamente. O ultra-som pélvico demonstrou o ovário direito com 10,3 cc e ovário esquerdo com 9,8 cc, sem nódulos ou cistos e a tomografia computadorizada de abdome demonstrou adrenal direita adrenal e nódulo sólido de 0,8 cm na adrenal esquerda. Após a administração de análogo de GnRH, as testosteronas total e livre foram de 23 ng/dL e 17 pmol/L, respectivamente. Considerando a supressão da concentração de testosterona pelo análogo de GnRH, a paciente foi submetida a histero-ooforectomia por via laparoscópica. O diagnóstico histológico foi de hipertecose, com focos de células estromais luteinizadas. Somente folículos atréticos foram visualizados. Não se detectou hiperplasia de células hilares. Em conclusão, a presença de massa adrenal em uma paciente com hirsutismo pode levar ao diagnóstico errado. Neste caso, o teste de supressão com análogo de GnRH foi fundamental para se determinar a origem da hiperandrogenemia. (**Arq Bras Endocrinol Metab 2008; 52/7:1184-1188**)

Descritores: Hirsutismo; Hipertecose de ovário; Incidentaloma adrenal; Menopausa

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Hirsutism can be defined as excessive growth of androgen-dependent sexual hair. It is one of the manifestations of hyperandrogenic syndrome, a state of increase androgen production (1). It can be isolated or associated with other signs of increase in androgen level, as menstrual disturbances, acne, deepening of the voice, and increase in muscle mass, clitoromegaly, breast hypotrophy and frontoparietal balding.

The mainly causes of hirsutism in young women, polycystic ovary syndrome and idiopathic hirsutism, are not prevalent after the menopause. Apart from iatrogenia, hirsutism in menopause women can be arising out of nonclassical congenital adrenal hyperplasia, ovarian hyperthecosis or ovarian or adrenal tumors. This differential diagnosis is important, since adrenal and ovarian tumors can be life-threatening conditions and deserve surgical treatment. Hyperthecosis is characterized by hyperplasia and luteinization of the cortical stroma, and can occur in both premenopausal women, as a part of the HAIR-AN syndrome, and after menopause (2,3). While in the first, basic physiological mechanism is severe insulin resistance, in the second it is due to the continuous stimuli of high gonadotropins.

The following is a case report of a hyperandrogenic woman in menopause, where the finding of an adrenal adenoma could lead to a misleading treatment.

Case report

A 54-year-old woman had a 4-year history of excessive hair growth, hair loss and acne. She had had normal menstrual cycle since menarche and became amenorrheic with hot flushes and increase in libido 4 years ago. She denied any changes in her voice and muscle mass. She had two normal pregnancies previously. A thyroidectomy was performed for papillary thyroid carcinoma at the 'Hospital Nipo-Brasileiro', in 2002. Her family history was unremarkable. At presentation she was under treatment with *l*-thyroxine sodium.

Physical examination revealed a grade I obese woman (body mass index of 30.4 kg/m²), with male pattern baldness, acne in her face, parietal temporal baldness and marked hirsutism with terminal hair on face, chest, abdomen and extremities (grade 15 of the Ferriman & Gallwey score, normal < 9) (4). Her voice was feminine and her muscle mass was slightly enlarged. Blood pressure was 150 × 98 mmHg and heart rate was 80/min. There were no striae or bruises. No acanthosis nigricans was noted. Breasts were atrophic,

without masses or galactorrhea. Abdomen was normal. Pelvic examination revealed clitoromegaly. No anexial mass was palpable.

The initial laboratory investigation revealed normal blood count and liver and renal function were within normal range.

Measurements of circulating hormone levels under basal and dynamic condition are shown in Table 1. All studies were conducted between 7:30 and 8:30 a.m. after 8 hours of fasting. For the ACTH stimulation test, blood was collected for cortisol and 17-hydroxyprogesterone (17-OHP) determination 60 minutes after the administration of 0.25 mg of ACTH-(1-24) (Cortrosyn™, Organon, USA) by IV route over 60 seconds. The GnRHa suppression test was performed through the administration of 3.75 mg of leuprolide acetate (lupron® depot) by IM route every 30 days, for 2 months, and blood collect after 30 days of each administration for determination of gonadotropins (LH and FSH), estradiol, cortisol, DHEAS and total and free testosterone.

Pelvic ultrasonography disclosed a right ovary with 10.3 cc and a left ovary with 9.8 cc, without nodules or cysts. Computerized tomography of the abdomen disclosed a normal right adrenal gland. On the left adrenal gland, a solid nodule with 0.8 cm was seen.

Cushing syndrome was ruled out by an overnight dexamethasone suppression test (1 mg – cortisol < 1.0 µg/dL), primary hyperaldosteronism by the measurement of serum potassium (4.1 mEq/L), aldosterone (3.1 ng/dL) and plasma renin activity (1.1 ng/mL/h) and pheochromocytoma by the measurements of urinary catecholamines (norepinephrine = 31 µg/24 h, epinephrine = 3 µg/24 h and dopamine = 185 µg/24 h) and metanephrine (0.22 metanephrine µg/mL of creatinine).

Patient was submitted to a hysterectomy by laparoscopy. Symmetrically enlarged ovaries, with 3.0 cm and 10.0 g (right ovary) and 2.5 cm and 8.0 g (left ovary), with dense capsules were seen. No tumor was apparent. Histology showed hyperthecosis with foci of luteinized stromal cells. Only atretic follicles were detected. No hilar cell hyperplasia was seen.

Patient was submitted to blood collection 45 days after surgery and reexamined 60 days after the surgical procedure. Total and free testosterone decrease to normal range. She had hot flushes, reduced libido and acne.

Table 1. Hormone levels under basal and dynamic condition and after surgery.

	Basal hormone levels	ACTH-stimulate hormone levels ¹	30 days after 1 st GnRHa administration ²	30 days after 2 nd GnRHa administration ²	45 days after surgery
LH (IU/L)	84.2	-	1.1	< 0.6	30.2
FSH (IU/L)	54.0	-	8.6	6.7	53.0
Estradiol (pg/mL)	24.0	-	20.0	< 13.0	16.0
Progesterone (ng/mL)	0.3	-	< 0.3	< 0.3	< 0.3
Total Testosterone (ng/dL)	191.0	-	21.0	23.0	36.0
Free Testosterone (pM/L)	179.0	-	15.0	17.0	25.0
Andro (ng/mL)	3.3	-	1.0	1.3	4.2
DHEAS (ng/mL)	1,340	-	1,310	1,110	1,410
Cortisol (µg/dL)	7.1	22.7	8.7	8.2	11.5
17-OHP (ng/mL)	0.7	4.3	0.7	0.7	0.8

60 minutes after the administration of 0.25 mg of ACTH-(1-24) by IV route; 30 days after the administration of 3.75 mg of leuprolide acetate by IM route; LH: luteinizing hormone; FSH: follicle stimulating hormone; Total and Free Testosterone: total and free testosterone; Andro: androstenedione; DHEAS: dehydroepiandrosterone sulphate; 17-OHP: 17-hydroxyprogesterone.

On the other hand, male pattern baldness and hirsutism were not reduced.

DISCUSSION

The patient under discussion is a 54-year-old woman with a history of hyperandrogenic symptoms of a 4 year duration, coincident with the menopause. Relevant positive physical findings included hirsutism, acne, frontoparietal baldness and clitoromegaly. According to these signals, the patient was classified as a hyperandrogenic virilized woman. As expected, total and free testosterone were markedly elevated at 191 ng/dL (normal value < 98 ng/dL) and 179 pmol/L (normal value < 45 pmol/L), respectively.

Considering the virilizing syndrome, the main hypothesis for this patient was adrenal or ovary virilizing tumor or hyperthecosis of the ovary. Although a small number of patients with polycystic ovary syndrome could have signals and symptoms of virilization, these, as well as idiopathic hirsutism, are diseases of premenopausal women. On the other hand, although the non-classical form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency was rarely report in patients in menopause, this diagnosis was discarded through the appropriate test (ACTH stimulated 17-OHP < 17 ng/mL) (5).

Computerized tomography of the abdomen disclosed a solid nodule with 0.8 cm on the left adrenal gland, compatible with an adrenal tumor. These, mostly benign adenomas, are frequently in the general population and nowadays more often found incidentally (6), while adrenocortical cancer is rare, with an estimated prevalence between 0.6 to 2 cases per million in the normal population (7). Adrenal tumors can be hormonally silent or hormone-secreting. Most of the adrenal tumors are benign and hormonally silent. Virilization secondary to hypersecretion of adrenal androgens occurs in less than 20% of adults with functional adrenal neoplasms in our institution (8). The others syndrome associated with adrenal tumors, as Cushing's syndrome, primary hyperaldosteronism and pheochromocytoma were discharged in this patient by the clinical pictures and the appropriate laboratory tests.

On the other hand, pelvic ultrasonography in this patient disclosed bilateral enlarged ovaries, without nodules or cysts. Although bilateral virilizing ovarian tumors have been described (9), the most common pathology associated with this finding is hyperthecosis of the ovary (10), a nonmalignant ovarian disorder characterized by increased production of testosterone by luteinized theca cells in the stroma, due to the differentiation of the ovarian interstitial cells into steroidogenically active luteinized

stromal cells (11), leading to increased serum testosterone concentrations.

Hyperthecosis can occur during the reproductive years, usually associated with acanthosis nigricans and in the postmenopausal period, with different pathophysiological mechanism. In some patients with polycystic ovary syndrome, luteinized theca cells can be found confined to areas around cystic follicles and it is still unclear if hyperthecosis is a distinct disorder or is part of the spectrum of the polycystic ovary syndrome. While in young women the precipitating abnormality is thought to be insulin resistance (2), with a secondary increase in insulin levels and subsequent overproduction of androgens by the ovaries, in postmenopausal patients it is a gonadotropin dependent hyperandrogenic syndrome not related to insulin resistance, possibly due to continuous stimuli of luteinizing hormone (11). The hallmark of this syndrome is an increase in bilateral ovarian volume, although unilateral increase in ovarian volume has been described (12). Although specificity of the ultrasound has not been determined, the ovaries appear more solid with very few or no cysts.

In view of the above finding, we considered that this patient had a nonfunctional adrenal adenoma coexisting with an ovary producing androgen pathology, most possibly ovarian hyperthecosis. We choose to submit this patient to a gonadotropin analogue (GnRH α) suppression test, with the purpose to separate a gonadotropin-dependent from a gonadotropin independent hyperandrogenemia. Usually, we administer GnRH α until complete LH suppression (< 0.6 IU/mL), up to 3 doses. Although there are anecdotal reports of gonadotropin dependent adrenal tumors (13), the suppression of testosterone level by GnRH α could point to ovarian-secreting testosterone pathology, although we cannot separate ovarian hyperthecosis from virilizing ovarian tumor, as some are gonadotropin-dependent (14). Only a few women with hyperthecosis have been treated with a GnRH agonist, but all had a substantial decrease in serum androgen concentrations (15-18). These results indicate that the ovarian hyperandrogenism in these women is at least partly gonadotropin-dependent.

In view of the finding of a suppressed testosterone after GnRH α administration we indicated bilateral oophorectomy, considering the menopausal status of the patient. Another approach could be a bilateral and si-

multaneous catheterism of the adrenal and ovary, but this is an invasive procedure with sometime misleading results (19). The histopathological diagnosis was compatible with ovarian hyperthecosis.

This case illustrated the difficulty related to differential diagnosis in virilizing hyperandrogenic syndromes due to the high prevalence of nonfunctional adrenal adenoma in the population. The suppression GnRH α test was fundamental to determine the cause of hyperandrogenemia.

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

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