

HYPERANDROGENISM DUE TO A TESTOSTERONE-SECRETING SERTOLI-LEYDIG CELL TUMOR ASSOCIATED WITH A DEHYDROEPIANDROSTERONE SULFATE-SECRETING ADRENAL ADENOMA IN A POSTMENOPAUSAL WOMAN: CASE PRESENTATION AND REVIEW OF LITERATURE

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ABSTRACT

Objective: To report a case of hyperandrogenism attributable to the presence of an adrenal adenoma secreting dehydroepiandrosterone sulfate (DHEA-S) and an ovarian Sertoli-Leydig cell tumor secreting testosterone in a postmenopausal woman.

Methods: The laboratory, radiologic, and pathologic findings in our case are described. In addition, the pertinent literature is reviewed.

Results: A 56-year-old woman presented with a history of gradual increase in facial and body hair, scalp hair loss, male pattern baldness, and deepening of her voice, beginning a few years after spontaneous menopause at age 49 years. She had hypertension, obesity, and type 2 diabetes mellitus. Laboratory tests showed elevated levels of total testosterone (348 ng/dL) and DHEA-S (2,058 µg/dL), and a left adrenal tumor (3 by 4 cm) was detected on abdominal computed tomographic scan. Laparoscopic left adrenalectomy was performed, and the pathologic diagnosis was adrenal adenoma. The DHEA-S returned to normal levels, but the serum testosterone concentration remained elevated. Transvaginal ultrasonography disclosed an ovarian tumor. Bilateral oophorectomy was performed, and an ovarian Sertoli-Leydig cell tumor was diagnosed. The hormonal and clinical picture normalized after this surgical intervention.

Conclusion: After extensive review of the literature, we believe that this is the first reported case of a coincidental DHEA-S-secreting adrenal adenoma and a testosterone-secreting ovarian Leydig cell tumor causing signs of virilization. (*Endocr Pract.* 2009;15:149-152)

Abbreviations:

CT = computed tomographic; DHEA-S = dehydroepiandrosterone sulfate

INTRODUCTION

Virilization in postmenopausal women may be due to excessive androgen production by an adrenal or ovarian tumor, by ovarian hyperthecosis, or by the long-term administration of testosterone by injection, orally, or by skin absorption. In a study of 873 patients with hyperandrogenism, only 0.2% had virilizing tumors (1). Making the diagnosis and determining the cause of hirsutism or virilization are a challenge for the clinician; a careful medical history and physical examination, proper selection and interpretation of laboratory tests, and radiologic studies will enable the physician to make the correct diagnosis and select the appropriate therapy.

CASE PRESENTATION

A 56-year-old woman with a 3-year history of diabetes mellitus and hypertension presented to her physician for evaluation of an increase in facial and body hair. Two years after her spontaneous menopause at age 49 years, she noticed a gradual increase in facial and body hair, scalp hair loss, male pattern baldness (Fig. 1), and deepening of her voice. On questioning, she denied the use of any drugs known to produce hirsutism; she had never received hormone replacement therapy after menopause. She denied having any appreciable weight change, proximal muscle weakness, or symptoms of depression. There was no family history of hirsutism or virilization.

Physical examination revealed a blood pressure of 130/80 mm Hg, weight of 74 kg, and body mass index of 36.5 kg/m². Examination of her skin showed excessive hair on the upper lip, sideburns, chin, anterior aspect of the chest, lower abdominal area, and extremities (Ferriman-Gallwey score of 23). Temporal alopecia and clitoral enlargement were noticed. Abdominal palpation showed

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Fig. 1. Hirsutism and male pattern baldness in study patient.

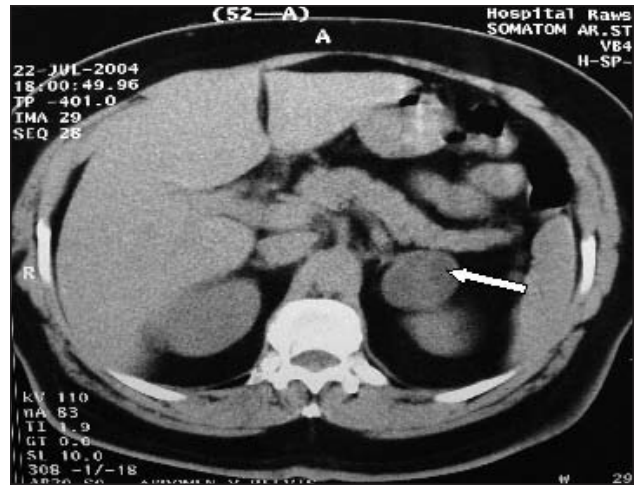


Fig. 2. Computed tomographic scan of the adrenal glands, disclosing a left adrenal tumor (arrow).

normal findings, with no evidence of organomegaly. There were no signs of hypercortisolism.

LABORATORY EVALUATION

A laboratory evaluation revealed the following: serum luteinizing hormone 1.85 mIU/mL, follicle-stimulating hormone 5.27 mIU/mL, serum testosterone 348 ng/dL, dehydroepiandrosterone sulfate (DHEA-S) 2,058 μ g/dL, androstenedione 3.23 ng/mL, morning serum cortisol 23.9 μ g/dL, and urinary cortisol 70 μ g/24 h (reference range, <100).

An abdominal and pelvic computed tomographic (CT) scan showed a lesion (3 by 4 cm) of the left adrenal gland; it was round, was circumscribed, and had well-defined margins (Fig. 2). The ovaries appeared to be normal.

A laparoscopic left adrenalectomy was performed. The pathologic diagnosis confirmed the presence of an adrenal adenoma (Fig. 3).

Postoperatively, there were no changes in the clinical characteristics of the patient's hirsutism. At 1-month follow-up, her total serum testosterone level was 440 ng/dL, androstenedione was 6.9 ng/mL, and DHEA-S was 299 μ g/dL (Table 1).

Transvaginal ultrasonography demonstrated a 4.7-cm lesion in the right ovary. With the patient's consent, a total hysterectomy and bilateral oophorectomy were performed; the pathologic diagnosis was a well-differentiated Sertoli-Leydig cell tumor (Fig. 4). A month after this surgical intervention, total testosterone and androstenedione levels returned to normal (Table 1).

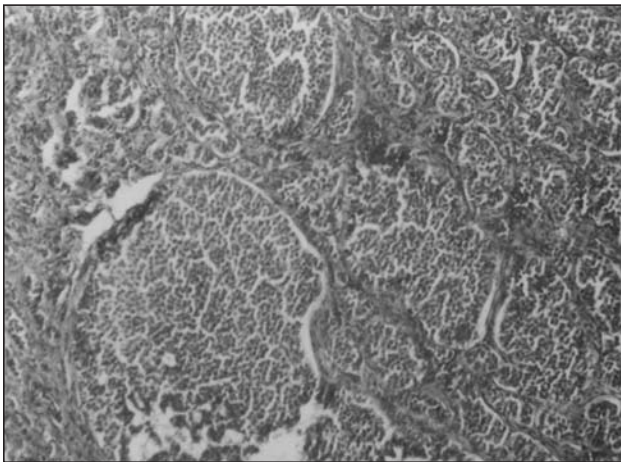


Fig. 3. Histologic appearance of adrenal glandular tissue composed of large cells, generally uniform, with large granular cytoplasm, showing no mitosis or atypia. There are no signs of malignant involvement. (Hematoxylin-eosin stain; original magnification $\times 10$.)

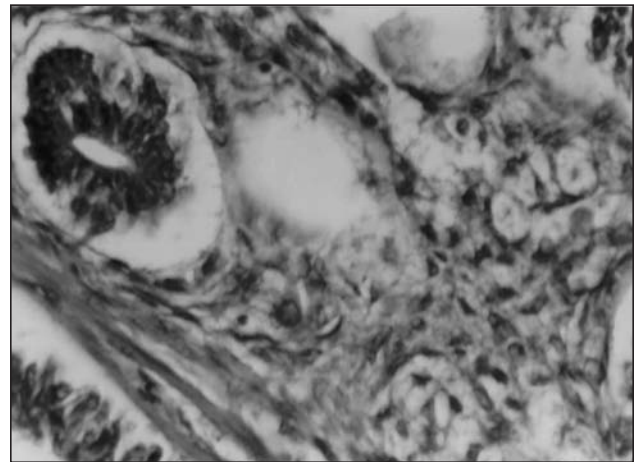


Fig. 4. Histologic appearance of the right ovary, demonstrating replacement of the architecture by numerous tubular structures covered by cylindrical cells with slightly hyperchromatic, round nuclei, separated by abundant clusters of Leydig cells with wide pale cytoplasm, consistent with Sertoli-Leydig cell tumor. (Hematoxylin-eosin stain; original magnification $\times 10$.)

Table 1
Hormonal Results in Study Patient Before and After Adrenalectomy
and After Total Hysterectomy and Bilateral Oophorectomy

Laboratory study	Reference range	At presentation	After adrenalectomy	After total hysterectomy
Total testosterone (ng/dL)	4-74	348	440	1.02
Androstenedione (ng/mL)	<1.0	3.23	6.9	<0.3
Dehydroepiandrosterone sulfate (μg/dL)	110-660	2,058	299	67
Morning serum cortisol (μg/dL)	5-25	23.9	7.94	...
Urinary cortisol (μg/24 h)	25-100	70

DISCUSSION

In the presence of recent onset of hirsutism in a postmenopausal woman, with or without virilization, the possibility of an adrenal or ovarian tumor should be entertained. Hirsutism due to an adrenal tumor may manifest with an elevated level of serum DHEA-S, serum testosterone, or both (2-6). In women beyond age 40 years, virilizing testosterone-secreting adrenal tumors are, in the majority of cases, carcinomas; such lesions may also produce other androgens, such as DHEA-S and androstenedione, as well as cortisol and occasionally aldosterone (2). The tumor may be large enough to be easily palpable, and the associated long-term prognosis is poor.

In cases of virilizing ovarian tumors, serum testosterone levels are usually more than 200 ng/dL; however, serum DHEA-S levels are normal or low. Although high-resolution imaging for tumor localization is very helpful in the detection of adrenal tumors, it is not always informative in patients with small ovarian tumors (5). In such cases, even vaginal ultrasonography may be unable to detect ovarian lesions because of their small size.

In a review of 350 women with hyperandrogenism, a Leydig cell tumor and an adrenal carcinoma were detected in 1 patient (7). In another study of 478 women with hirsutism, a single case of an ovarian tumor producing hyperandrogenism was found (8).

Of 107 patients with an adrenal mass, 84 had "incidentalomas," diagnosed by abdominal CT scans done for unrelated reasons (3). None of these patients presented with elevated serum DHEA-S levels.

Among ovarian tumors, only 5% are virilizing; they are derived from sex cord-stromal cells and include Sertoli-Leydig cell tumors, hilar cell tumors, lipoid cell tumors, and adrenal rest tumors, of which fewer than 20% display malignant behavior (9). Ovarian hyperthecosis, another cause of hirsutism with or without virilization, occurs in both premenopausal and postmenopausal

women. In this condition, serum testosterone values are as high as those seen in virilizing adrenal or ovarian tumors, and serum DHEA-S levels are normal. Pelvic or vaginal ultrasonography may show an increase in ovarian stroma, although the sensitivity and specificity of the test are not well established. Most women affected by ovarian hyperthecosis are obese and have clinical manifestations of insulin resistance, including acanthosis nigricans. The syndrome is more common than virilizing tumors. It is due to the presence of nests of luteinized theca cells in the ovarian stroma, which produce testosterone; the actual cause is unknown. There is an increased incidence of endometrial hyperplasia and carcinoma in such patients (10).

The association of testosterone-producing ovarian tumors and adrenal pathologic conditions is extremely rare; only a few cases have been described in the medical literature (5,7,11-13). To our knowledge, this is the first reported case of hyperandrogenism due to the presence of 2 functional tumors—an adrenal adenoma secreting DHEA-S and an ovarian Sertoli-Leydig cell tumor secreting testosterone. Young and Scully (11) reported 3 cases of ovarian tumors associated with Cushing syndrome. Regnier et al (5) described a case of a 41-year-old premenopausal woman with a 3-year history of hirsutism, high serum testosterone concentrations, and normal DHEA-S serum levels. In their case, a benign-appearing adrenal mass (13 by 6 mm) was detected by CT scan. Transvaginal ultrasound examinations failed to detect any ovarian abnormality, and selective adrenal vein catheterization showed normal findings. A 1.5-cm Leydig cell tumor of hilar type was found at surgical intervention. Gorgojo et al (12) described a 46-year-old woman with a functioning adrenal tumor producing cortisol and a hilar steroid cell tumor of the ovary secreting testosterone. Diab et al (13) reported a similar case, a virilizing ovarian Leydig cell tumor associated with an adrenal mass, with low levels of DHEA-S and subclinical Cushing syndrome.

CONCLUSION

The patient described herein presented with a clinical picture of virilization a few years after menopause, in conjunction with high serum levels of testosterone, androstenedione, and DHEA-S. A 4-cm left adrenal tumor was diagnosed by CT scan, but no ovarian abnormalities were detectable by pelvic CT scan. In view of the adrenal lesion and the elevated levels of serum androgens, including DHEA-S, a diagnosis of functional adrenal virilizing tumor was made, which suggested a possible malignant lesion. After removal of the adrenal mass, however, the serum DHEA-S value returned to normal, but testosterone levels remained elevated. Transvaginal ultrasonography demonstrated an ovarian tumor. After surgical extirpation of the lesion, serum androgen levels returned to normal, together with resolution of the clinical picture. To our knowledge, this is the first case described in the English literature of a coincidental benign adrenal adenoma secreting DHEA-S and a testosterone-secreting ovarian tumor.

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DISCLOSURE

The authors have no conflicts of interest to disclose.

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