Management of Postmenopausal Virilization

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Context: Mild clinical signs of hyperandrogenism such as hirsutism may appear during the menopausal transition as part of the normal aging process, but the development of frank virilization suggests a specific source of androgen excess, including androgen-secreting tumors.

Patient and Methods: A 68-yr-old postmenopausal woman was referred because of a history of progressive development of hirsutism and frontal balding for the previous 8 yr, together with moderate hyperandrogenemia. Initial imaging procedures depicted a 2-cm solid nodule in the right adrenal gland and normal appearance of both ovaries. To confirm the source of androgen excess, we conducted simultaneous selective venous sampling of adrenals and ovaries. Sampling was consistent with an ovarian source. After bilateral laparoscopic salpingo-oophorectomy, the patient was diagnosed with bilateral ovarian hyperthecosis. Three weeks after surgery, her androgen levels had decreased to the normal female range.

Conclusion: Diagnosis of hyperandrogenism in postmenopausal women is challenging. Postmenopausal virilization may be associated with adrenal or ovarian androgen-secreting tumors or with benign conditions. A detailed clinical history is critical to differentiate the progressive development of virilization that characterizes benign causes from the rapid progression that characterizes malignant tumors. Imaging techniques do not always reveal the cause of hyperandrogenism and may even be misleading. Although technically difficult, combined adrenal and ovarian venous sampling may be required to confirm the source of androgen excess before the best surgical approach is determined. **(*J Clin Endocrinol Metab* 97: 2584–2588, 2012)**

The postmenopausal ovary remains hormonally active, secreting significant amounts of androgens and estrogens, many years after menopause (1). Estrogen levels drop abruptly after menopause whereas androgen secretion gradually declines during the reproductive years. Subsequently, an imbalance among estrogens and androgens during menopause, amplified by a decrease in SHBG concentrations (2), may result in hyperandrogenic symptoms.

Androgen secretion in pre- and postmenopausal ovaries depends on LH stimulation. The very high gonadotropin levels of menopause could maintain ovarian androgen production (3, 4). As a result, menopause may be accompanied by the appearance of a few terminal hairs in the face and by a decrease in body and scalp hair that can be considered part of the normal menopausal process (5).

The development of true hirsutism (defined as the presence of excessive terminal hair in androgen-dependent areas), alopecia, or acne should not be considered normal in postmenopausal women. A detailed review of the causes of postmenopausal hyperandrogenism, including the aggravation of previously undiagnosed hyperandrogenic disorders by the physiological changes occurring during menopause, has been recently published (6).

Abbreviation: DHEAS, Dehydroepiandrosterone sulfate.

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When hirsutism is accompanied by signs of virilization such as severe balding, deepening of the voice, or clitoromegaly, an underlying androgen-secreting tumor that may be malignant must be ruled out. Postmenopausal virilization may result from adrenal tumors, including androgen-secreting carcinomas and adenomas; from ovarian tumors, including Sertoli-Leydig cell tumors (androblastoma, arrhenoblastoma), granulosa-theca cell tumors, and hilus-cell tumors; or from benign ovarian conditions such as ovarian stromal hyperplasia and hyperthecosis (7). Rarer causes, such as transfer of testosterone from a male partner using testosterone gels, have been described (8). The identification of the source of androgen excess in some cases of postmenopausal virilization may be a difficult challenge requiring a combination of clinical skills with appropriate laboratory and/or imaging techniques.

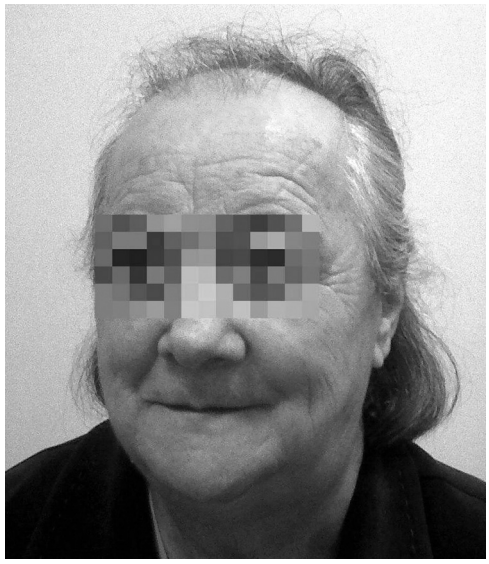

FIG. 1. Severe balding in a 68-yr-old woman presenting with an 8-yr progressive history of postmenopausal virilization.

Case Report

A 68-yr-old woman presented with an 8-yr history of progressive hirsutism, accompanied by development of alopecia during the past 4 yr. She had regular menstrual cycles from menarche at age 12 yr to menopause at age 50 yr. She had no prior history of infertility or of symptoms of polycystic ovary syndrome during her reproductive years. She denied deepening of voice, enlarged muscle mass, or increased libido. She had impaired fasting glucose, poorly controlled hypertension, and postsurgical hypothyroidism. She was not taking any drug with androgenic effects, and her family history was unremarkable.

On physical examination, her body mass index was 32 kg/m^2. Acanthosis nigricans, acne, and signs of hypercortisolism were absent. Hirsutism was confirmed by a modified Ferriman-Gallwey score (9) of 14 (nine body areas are scored from 0, meaning absence of terminal hair, to 4, equaling the quantity of terminal hair of a well-virilized adult man). She had frontotemporal alopecia (Fig. 1), clitoromegaly, and mild enlargement of labia minora.

The initial diagnostic tests conducted by the endocrinologist referring the patient showed moderately increased testosterone levels (120 ng/dl), normal basal 17-hydroxyprogesterone levels (0.76 ng/ml), and gonadotropin and estradiol concentrations in the menopausal range (LH, 16 mU/ml; FSH, 24 mU/ml; and estradiol, 26 pg/ml). Circulating dehydroepiandrosterone sulfate (DHEAS) concentrations were not measured during initial evaluation, yet Cushing's syndrome had been reliably ruled out by the finding of normal free urinary cortisol levels (36 μg/d; normal range, $<$140 μg/d) and suppression of 0900 h plasma cortisol concentrations below 2 μg/dl after 1 mg of dexamethasone was administered the previous night. Initial transabdominal ultrasound examination of the ovaries and the adrenal showed no lesions.

We confirmed hyperandrogenemia by a second testosterone determination of 129 ng/dl with a SHBG level of 32 μg/dl. Serum DHEAS levels were 1220 ng/ml (normal, $<$ 3500 ng/ml). An adrenal computed tomography scan showed a 21-mm mass in the right adrenal gland suggestive of adrenal adenoma. Transvaginal ultrasound examination showed normal small ovaries (right ovary, 2.3 ml; left ovary, 1.5 ml) without any lesions, and a 6.9-mm endometrial thickness that is higher than expected in a postmenopausal woman.

We considered the postmenopausal onset of the symptoms and their slow progression as suggestive of ovarian hyperandrogenism, rather than probably being related to the small adrenal tumor. Therefore, before submitting the patient to adrenal surgery because of the finding of an adrenal mass, we decided to conduct combined adrenal and ovarian venous sampling to determine the actual source of androgen excess.

After careful catheterization and radiological confirmation of the correct placement of all the catheters by injection of small boluses of iodinated contrast, we obtained blood samples simultaneously from right adrenal and ovarian veins, left adrenal and ovarian veins, and right brachial vein. We assayed these samples for serum concentrations of total testosterone, androstenedione, DHEAS, and cortisol. Total testosterone and androstenedione concentrations were much higher in both ovarian veins compared with the concentrations found in both adrenal veins and in the brachial vein (Table 1).

The patient underwent laparoscopic bilateral salpingo-oophorectomy, and pathology of both ovaries revealed

TABLE 1. Results of the combined adrenal and ovarian adrenal sampling

	Total testosterone (ng/dl)	Androstenedione (ng/ml)	DHEAS (ng/ml)
Left ovary	857	7.4	667
Right ovary	2170	>10	761
Left adrenal	81	1.8	907
Right adrenal	95	2.3	853
Brachial vein	84	1.2	793

Catheters were placed in the venous effluents of both adrenals and ovaries and in a brachial vein, and samples were obtained simultaneously for the measurement of serum androgen concentrations.

stromal hyperplasia with small nests of luteinized theca cells diagnostic of bilateral ovarian hyperthecosis (Fig. 2) (10). Twenty days after surgery, her total testosterone concentrations normalized (31 ng/dl), and the patient is currently under follow-up with periodic ultrasound measurements of the endometrial thickness because chronic exposure to increased estrogen levels derived from peripheral conversion of androgens might result in endometrial hyperplasia, and her endometrial thickness was mildly increased before oophorectomy (10). Informed consent from the patient and Institutional Review Board exemption were obtained.

Discussion

The present clinical case exemplifies the diagnostic challenges of severe postmenopausal hyperandrogenism. A detailed clinical history and physical examination are the essential tools for a correct diagnosis—a rule that also applies when hyperandrogenism develops before menopause.

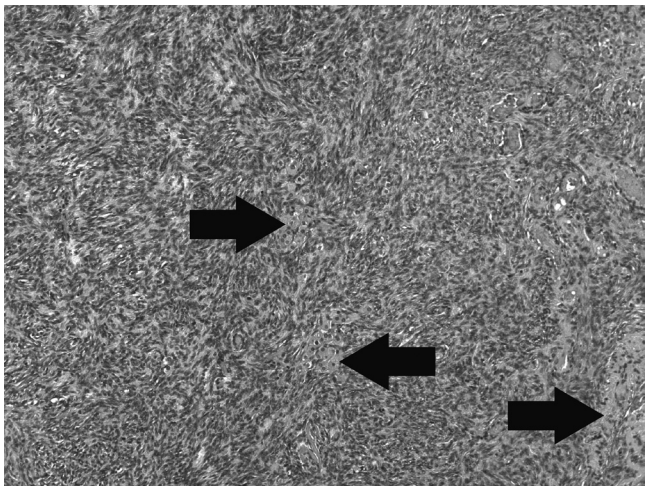

FIG. 2. Histological examination of the ovaries showing the nests of luteinized theca cells (*black arrows*) scattered throughout a hyperplastic ovarian stroma characteristic of ovarian hyperthecosis.

The onset, progression, and severity of hyperandrogenic signs must be established (11). Manifestations of functional causes of hyperandrogenism such as polycystic ovary syndrome or nonclassic congenital adrenal hyperplasia appear around puberty and progress slowly. Of note, the clinical consequences of these functional hyperandrogenic disorders do not end with menopause (12), and symptoms such as hirsutism and alopecia may even get worse because of the imbalance among estrogens and androgens described earlier. Hence, a detailed interrogation about the presence of hyperandrogenic symptoms, menstrual disturbances, or infertility during the reproductive years is crucial. Quite the opposite, more severe causes of hyperandrogenism, including tumors, rarely present around puberty, may progress rapidly, and usually associate signs of virilization or defeminization (loss of female secondary sexual characters; *i.e.* decreased breast size) (13).

Clinical history and physical examination were essential for the correct management of our patient. The premenopausal absence of hyperandrogenic symptoms and their onset a full decade after menopause made highly unlikely the aggravation of a previously undiagnosed functional form of hyperandrogenism. Moreover, clitoromegaly and enlarged labia minora suggested a specific hyperandrogenic disorder, prompting the search for androgen-secreting neoplasms, even when the progression of the symptoms was relatively slow.

Of note, the moderate increase in serum androgen levels found in our patient further indicates that the search for the source of androgen excess in cases of virilization should not be oriented by the severity of hyperandrogenemia. Very high serum androgen levels (total testosterone above 150–200 ng/ml and/or DHEAS level above 6000 ng/ml) may suggest an androgen-secreting neoplasm. However, measurement of basal androgen levels is of limited predictive value because as many as 50% of such tumors do not have levels of total testosterone or DHEAS above these cutoff values (14). In women with severe hyperandrogenemia, the low-dose dexamethasone suppression test has been proposed to distinguish androgenic ovarian and adrenal tumors from non-neoplastic causes of hyperandrogenism (15, 16) because both adrenal and ovarian tumors would fail to suppress androgen levels after glucocorticoid administration (16). Similarly, suppression of hyperandrogenemia in response to long-acting GnRH agonists in postmenopausal women would be suggestive of ovarian hyperandrogenism (17). However, utilization of adrenal and gonadal stimulation and suppression are considered unreliable for determining a source of

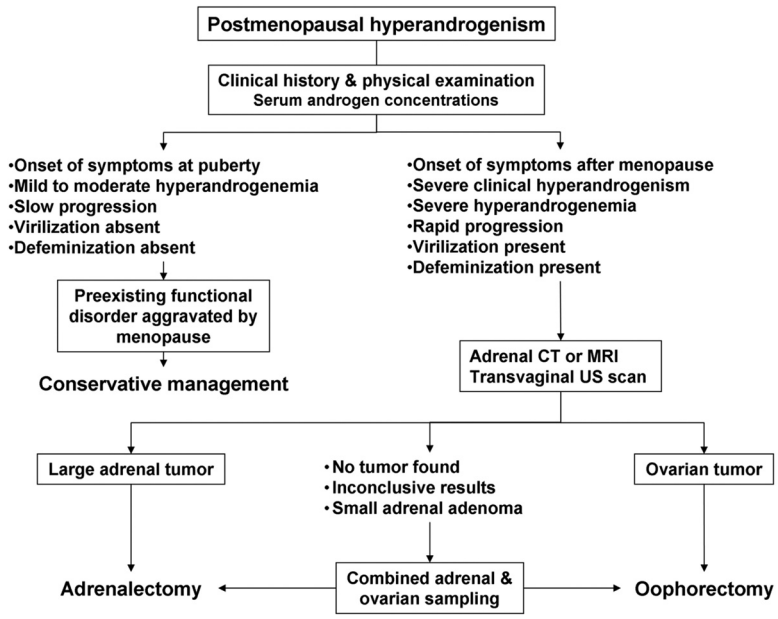

FIG. 3. Algorithm for the diagnosis and management of postmenopausal hyperandrogenism. CT, Computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

androgens (14), and long-term follow-up of most women presenting with androgen levels greater than the above-mentioned cutoff values fails to reveal any androgen-secreting tumor (18).

Establishing the cause of hyperandrogenism in women with virilization actually requires the proper use of imaging techniques with the aim of localizing the rare possibility of an androgen-secreting tumor (one in every 300-1000 patients presenting with hyperandrogenic signs) (14). Computed tomography or magnetic resonance scans are the most effective techniques for visualizing the adrenals, and transvaginal ultrasound examination is the technique of choice for the imaging of the ovaries (19). These techniques detect most adrenal and ovarian androgen-secreting tumors (14), yet some ovarian androgen-secreting tumors are very small and may be missed even by transvaginal ultrasound.

Positive imaging findings must always be interpreted carefully while taking into account the clinical context of the patient, and the finding of a small adrenal mass in our patient serves as an example. Among androgen-secreting neoplasms, ovarian tumors are much more frequent compared with adrenal tumors. After menopause, ovarian causes of hirsutism and virilization are more frequent compared with adrenal disorders and include androgen-secreting neoplasms and benign disorders such as ovarian stromal hyperplasia and hyperthecosis (7, 10). Adrenal androgen-secreting neoplasms are usually large and aggressive carcinomas that present also with Cushing's syndrome and have a very rapid progression and almost invariably a fatal outcome (14). These carcinomas are more frequent in young children and adults 40 to 50 yr old (20). Adrenal adenomas that secrete testosterone and/or other androgens or steroids are extremely rare and are usually large adrenal masses at diagnosis (21); the differentiation between adrenal adenomas and carcinomas depends not on histology but on the benign or malignant clinical outcome after successful surgery (21). Moreover, adrenal tumors frequently present with increased DHEAS levels, which were normal in our patient.

For these reasons, and considering that the probability of finding an unsuspected adrenal mass in patients over 70 yr of age reaches 7% (22, 23), we were unconvinced that the small right adrenal mass was responsible of the patient's hyperandrogenic symptoms. Of note, incidentally discovered adrenal masses have been recently reported in women with virilization of ovarian origin (24, 25).

The results of combined adrenal and ovarian venous sampling suggested the ovaries as the more likely source of androgen excess in our patient. Bilateral laparoscopic salpingo-oophorectomy and histological examination confirmed bilateral ovarian hyperthecosis, and the patient was spared an unnecessary adrenalectomy. Her increased androgen concentrations rapidly returned to the normal range, further confirming the diagnosis.

Finally, Fig. 3 provides an algorithm for the correct diagnostic and therapeutic approach to postmenopausal hyperandrogenism in which an accurate clinical history and a detailed physical examination play a central role. In women with a chronic history of mild or moderate hyperandrogenic symptoms before menopause, in the absence of virilization and defeminization and especially if accompanied by menstrual disturbances and infertility, aggravation of a preexisting condition such as polycystic ovary syndrome or nonclassic congenital adrenal hyperplasia must be suspected, and conservative management is warranted. In contrast, when symptoms clearly develop after menopause, hyperandrogenism is severe, progression is rapid, and virilization or defeminization are present, adrenal and ovarian imaging must be conducted immediately. The presence of a large or irregular adrenal mass in computed tomography or magnetic resonance scans, especially if there is evidence of hypercortisolism, is highly suggestive of an adrenal carcinoma, and adrenalectomy must be performed to confirm the diagnosis. If transvaginal ultrasound examination shows an ovarian tumor, oophorectomy must be conducted. Combined adrenal and ovarian venous sampling may also prove useful

to determine the most likely source of androgen excess, but simultaneous catheterization of all adrenal and ovarian veins is difficult, with success rates as low as 26–45% (26). Hence, this procedure must be conducted in experienced hands and reserved for patients in whom uncertainty remains because imaging techniques show no tumor, imaging findings are inconclusive, or a small adrenal tumor suggestive of an adenoma is found.

In summary, diagnosis of hyperandrogenism in postmenopausal women is a difficult challenge. Postmenopausal virilization may be associated with adrenal or ovarian androgen-secreting tumors or with benign conditions. A detailed clinical history is critical to differentiate the progressive development of virilization that characterizes benign causes from the rapid progression that characterizes malignant tumors. Imaging techniques do not always reveal the source of androgen excess and may even be misleading. Although technically difficult, combined adrenal and ovarian venous sampling may be required to confirm the source of androgen excess before the most appropriate surgical approach is decided.

Acknowledgments

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