Virilization caused by an ectopic adrenal tumor located behind the iliopsoas muscle

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Objective: Virilization due to androgen-secreting neoplasms in women is a result of androgen overproduction from benign or malignant tumors that are found in the ovaries or rarely in the adrenal glands. Virilizing tumors that arise from ectopic adrenal tissue are extremely rare. We describe a very rare case of an ectopic androgen-producing adrenal tumor.

Design: Case report study.

Setting: Endocrinology outpatient department of university-affiliated teaching hospital.

Patient(s): A 45-year-old woman with symptoms of virilization of abrupt onset and rapid progression, with high serum androgen hormone levels and normal glucocorticoid secretion.

Intervention(s): Basal hormonal levels, stimulation and suppression tests, imaging techniques, and selective venous sampling.

Main Outcome Measure(s): Localization and surgical removal of the source of androgen production.

Result(s): An ectopic mass was detected behind the left iliopsoas muscle. The patient was operated on and an oblong-shaped lesion, weighing 6 g, was removed. Histologically, the tissue was identified to be of adrenal origin. Postoperatively the androgen levels decreased to normal levels.

Conclusion(s): This case illustrates difficulties in detecting and localizing the rare contingency of an ectopic adrenocortical androgen-secreting tumor. (Fertil Steril 2007;87:1468.e13–6. ©2007 by American Society for Reproductive Medicine.)

Key Words: Ectopic adrenal tumor, hyperandrogenemia, virilization

In women, androgens are secreted by the ovaries and the adrenal glands, and virilizing tumors are expected to arise in one of those two organs. Ectopic tumors that are capable of androgen oversecretion are considered to be extremely rare (1).

The localization of an androgen-producing tumor is not always easy. Baseline androgen levels can be of limited help as they frequently overlap in women with non-neoplastic hirsutism and women with virilizing neoplasms (2, 3), although high serum testosterone (T) is indicative of the presence of a virilizing tumor (4, 5). The value of stimulation and suppression tests is debatable (4, 6–8). Imaging techniques including computerized tomography (CT), magnetic resonance imaging (MRI) and [131I]-iodomethylnorcholesterol scanning, although more specific (1, 6, 9), may fail to detect very small or ectopic masses. Selective venous sampling, an invasive and not widely available technique, has a significant morbidity and is far from infallible (1, 10–12).

Ectopic adrenocortical lesions are quite rare and usually produce cortisol. To our knowledge, only one case of an ectopic cortical adrenal mass in the thorax, producing strictly androgens, has been reported (1).

We present a 45-year-old woman with hyperandrogenism and virilization due to an ectopic androgen-producing adrenal tumor located behind the left iliopsoas muscle.

CASE REPORT

A 45-year-old white woman, mother of two healthy daughters, was referred to our Endocrine clinic for hirsutism. She had a prior history of polycystic ovary syndrome (PCOS) diagnosed at a young age although her menstrual periods were regular and she had no fertility problems. Her present problem started 2 years ago when she noticed rapidly progressing hirsutism despite treatment with a combination of oral contraceptives (OC) and antiandrogens in another institution.

On admission, the patient had intense hirsutism on all androgen-sensitive regions (face, chest, abdomen, and thighs), hoarseness of voice, male-type alopecia, and clitoridomegaly. However, her menstrual bleeding did not cease. Hormonal evaluation revealed increased levels of free T, Δ4-androstendione (Δ4-A), and 17α-hydroxyprogesterone (17-OHP), with DHEAS levels within normal range. Serum FSH was 9.4 mIU/mL, LH 4.6 mIU/mL, and E2 41 pg/mL (30–450 pg/mL) on the second day of her menstrual cycle. Tumor markers, including β-hCG, were negative.

A dexamethasone suppression test (DST: 0.5 mg, q.i.d. for 7 days) failed to suppress androgen levels, whereas ACTH...
and cortisol suppressed normally (Table 1). A tetracosactrin (Synacthen/Novartis 0.25 mg/mL, Institute of Pharmaceutical Research and Technology [IFET], Greece) stimulation test (250 μg IV) showed no response of serum free T and 17-OHP, whereas DHEAS increased by 44%, Δ4A by 17%, and serum cortisol rose to 610 nmol/L.

Computerized tomography scan and MRI of the adrenals and abdomen were reported as negative initially. The CT scans of the thorax and head were also unrevealing. An ultrasound of the ovaries revealed a 1.6-cm dense area in the left ovary. An [131I]-iodomethylnorcholesterol scan was unrevealing.

Because of the ultrasound finding, the left ovary was removed by laparotomy and a radical wedged resection of the right ovary was performed without any effect on the serum androgen levels. The pathology of the ovary showed an old corpus luteum (CL) and lutenization of the theca externa. At this point, the patient was treated with four monthly injections of the GnRH analogue Triptorelin (3.75 mg in each dose) (IPSEN Limited, Slough, England) to determine whether a possible nonapparent ectopic ovarian or adrenal tissue (13). However, accessory adrenal tissue has been identified. The tumor was discovered by blunt dissection of the psoas muscle just in front of the left iliopsoas joint and was removed.

The weight of the surgical specimen was 6 g (6 by 1.5 by 0.5 cm). The tumor had histological features of either an ectopic normal adrenal tissue or ectopic adrenal adenoma, with eosinophilic cell clusters and normal round nuclei, positive for keratin AE3 and negative for vimentin, keratin AE1, and PAS.

Postoperatively the androgenic hormone levels decreased significantly: free T from 94 pmol/L preoperatively to 13.4 pmol/L (normal range 1–11 pmol/L), Δ4-A from 64.4 to 8.2 nmol/L (normal range 0.7–10.7 nmol/L), 17-OHP from 44.5 to 10.3 nmol/mL (normal range 0.3–3.6 nmol/mL), and DHEAS did not show any change (2.6–3.2 μmol/L (0.9–11.7 μmol/L). There was an amelioration of the original symptoms and signs.

**TABLE 1**

<table>
<thead>
<tr>
<th>Seven-day dexamethasone suppression test (DST)</th>
<th>Basal levels</th>
<th>Levels after DST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DST: 0.5 mg, q.i.d. for 7 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free T (0.6–2.7 pmol/L)</td>
<td>4.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Δ4-A (0.6–3.8 ng/mL)</td>
<td>4.6</td>
<td>6.5</td>
</tr>
<tr>
<td>17-OHP (0.1–1.5 ng/mL)</td>
<td>6</td>
<td>6.7</td>
</tr>
<tr>
<td>DHEAS (700–4,000 μg/dL)</td>
<td>2,650</td>
<td>2,200</td>
</tr>
<tr>
<td>Cortisol (50–250 nmol/l)</td>
<td>200</td>
<td>11</td>
</tr>
<tr>
<td>24-h Urinary cortisol (20–207 μg/24 h)</td>
<td>70</td>
<td>5</td>
</tr>
<tr>
<td>ACTH (0–50 pg/L)</td>
<td>11.7</td>
<td>3</td>
</tr>
</tbody>
</table>


**DISCUSSION**

Virilization is usually characterized by pronounced hirsutism, defeminizing, and masculinizing signs. A history of short duration or progressive worsening of hirsutism, the appearance in the third decade of life or later, as well as signs of virilization are suggestive of a possible virilizing tumor.

Virilizing neoplasms are rare and are usually derived from the ovaries. Androgen-producing adrenal tumors are even rarer. A few are adrenal adenomas but the majority are carcinomas.

Ectopic adrenocortical tumors have also been reported. Both the gonads and the adrenal glands originate from the mesoderm of the urogenital ridge and therefore adrenal remnants may be found in the gonads. The path of the adrenal cortical tissue descent (celiac plexus, broad ligament, spermatic cord) may also be a site of ectopic adrenocortical tissue (13). However, accessory adrenal tissue has been located in distant areas including the gallbladder, uterus, liver, mesentery of the small intestine, placenta, and central nervous system and this tissue usually produces cortisol (14).

The isolated oversecretion of androgens by ectopic adrenal tissue is extremely rare. Medeiros et al. (1) have described a case of intrathoracic ectopic androgen-producing adrenal tissue attached to the pericardium. What drives an ectopic adrenal cell to produce one over another steroid compound is not elucidated. The original pathways of steroid hormone biosynthesis, the microenvironmental influence of surrounding tissues (paracrine factors or loss of stimuli/inhibitors), or a secondary change of G-protein-mediated response could be involved. Aberrant or ectopic receptors and chromosomal mutations could result in cortisol, aldosterone, or gonadal steroid hypersecretion (14, 15).

Virilization occurs in approximately 20%–30% of patients with functional adrenal neoplasms as a result of excessive androgen production, mainly DHEA and DHEAS, Δ4-A,
and T (the latter being produced directly or indirectly through peripheral conversion) (16). Derksen et al. (4) suggested that the measurement of T and DHEAS are appropriate for initial evaluation, because women with values within the normal range are unlikely to have virilizing adrenal tumors. However, several investigators claim that elevated basal androgen values cannot discriminate non-neoplastic hirsutism from androgen-producing neoplasms (2, 3, 8).

Our patient had a very high 17-OHP level, not suppressed by dexamethasone, and not reduced after ovariectomy, indicative of an enzymatic block in the steroidogenesis in a nonovarian and non-ACTH-dependant tissue. The DHEAS is mainly secreted by the adrenals. Some investigators suggest that androgen-producing adrenocortical neoplasms are never encountered with DHEAS levels <8 μg/mL (9), although others have reported virilizing tumors with low DHEAS levels, sometimes because of the inability of the tumor for sulfation of DHEA (17, 18). Lack of suppression by dexamethasone in our patient was suggestive that its origin was other than the normal adrenal glands.

The high Δ4-A along with high T was also consistent with a tumor (9), and although the latter is not secreted by the normal adrenal gland, it appears to be the main androgen produced in virilizing tumors. There have been reports of adenomas of adrenocortical origin that were producing only T (19). In a series of 190 adrenal tumors, 10 (5.3%) were virilizing, two of them producing only T (20). A serum T level 2.5–3 times above the upper limit of normal is strongly suggestive of the presence of an androgen-producing tumor (2, 9). However, high serum T levels cannot discriminate between tumors of ovarian or adrenal origin (7).

Failure of suppression of androgen secretion by dexamethasone is considered to be characteristic of hyperandrogenism of neoplastic origin (4, 8). Virilizing adrenal tumors may not respond to dexamethasone suppression or ACTH stimulation because of lack of ACTH receptors or postreceptor anomalies (21, 22). Some investigators suggest that dynamic tests of androgen production are not very helpful and can occasionally be misleading (20), as in our case.

Imaging techniques for virilizing tumors include intravaginal ultrasound, which is considered very sensitive for ovarian tumors, CT scan, MRI, and scintigraphy. Unfortunately, the ultrasound finding in the left ovary of our patient as well as the hormonal profile misled us to the possibility of an ovarian tumor.

Localization of ectopic adrenal tissue is quite difficult. The CT scan or alternatively MRI provide the most appropriate method and should always precede functional scintigraphic imaging. The CT scan densitometry of a lesion is also of use in differential diagnosis (23). However, these methods are not always helpful for the investigation of ectopic adrenal masses, because ectopic adrenal tissue can be found in unpredictable regions, as in our case. Thus, the complementary use of investigational techniques like radio-nuclide scintigraphy and venous sampling is useful, especially in small tumors (24).

The [131I]-iodomethylnorcholesterol scanning is an established method for imaging steroid-secreting adrenocortical tumor tissue (6). Specificity tends to be 100%, but with a sensitivity of about 70%, not all adrenocortical tissue tumors can be identified (11). In our case the use of this method failed to reveal uptake of the nuclide by the tumor.

Selective venous sampling is considered to be a gold standard examination when there is a problem in localizing the source of androgen production. However, technical difficulties as well as morbidity discourage its use (1). In a series of patients, there was a success rate of 80%–85% and a morbidity rate of 5% (11). Kaltas et al. (10) suggest that vein catheterization needs to be reserved for when all other imaging techniques fail and uncertainty remains as to the presence of an androgen-producing tumor. In our case the result of the selective venous catheterization was inconclusive and this provided an indication that veins of the tumor were not related to the catheterized veins.

In conclusion, we present a woman with virilization due to an ectopic adrenocortical mass located behind the left iliopsoas muscle, detected by CT scan and MRI when it had reached a size large enough to be identified, although signs of hyperandrogenemia were present years before the diagnosis. Apparently the tumor produced T, Δ4-A, and 17-OH-P. The patient had serum E2 levels in the premenopausal range and this probably explains her menstrual breakthrough bleeding. The dynamic tests and selective venous sampling performed were not conclusive. It has been suggested that in postmenopausal women with hyperandrogenemia and a negative CT scan of the adrenals, a bilateral salpingo-oophorectomy is appropriate for a presumed ovarian tumor, as CT is reliable in detecting even small adrenal tumors in situ (17). These hormonal profiles in combination with the absence of any lesion in the adrenals, the existence of an ovarian abnormality by the ultrasound, and the patient’s consent led to an unnecessary oophorectomy. The case is presented because of the unexpected and unique region where the mass was found. This is, to our knowledge, the second reported case of an adrenocortical ectopic mass secreting only androgens, and this may explain the diagnostic difficulties.

REFERENCES