Disappearance of a virilizing adrenal tumor following therapy with cyproterone acetate

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Abstract

A 57-year-old woman presented with an apparently obvious diagnosis of iatrogenic virilization. At the age of 51, she began a 4-year treatment with prednisone or cyclosporine, which are known to promote hair growth, for Behçet disease. At the age of 56, osteoporosis was overtreated with the anabolic steroid nandrolone. Insignificant inhibition by dexamethasone of the extremely high serum concentrations of testosterone and less high concentrations of weak androgens prompted us to search for a virilizing tumor. Computed tomography showed a 2.3×1.5 cm nodule in the right adrenal gland. As the patient refused surgery, virilization was treated with the antiandrogen cyproterone acetate (CPA), but for only 4 months because clinical and hormone abnormalities reversed and the tumor was no longer visible. The patient remains symptom-free. This first report of a curative effect of CPA on a purely virilizing adrenal tumor opens new avenues in the management of such tumors.

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Introduction

Virilization is the combination of hirsutism plus signs of masculinization. Virilization is less common than hirsutism, but is more often associated with a potentially serious disorder, namely an ovarian or purely virilizing adrenal tumor (VAT), either tumor being very rare (Carr 1998). An additional cause of virilization is iatrogenic, such as use of anabolic steroids (androgens), and postmenopausal women are sensitive to even low doses of androgens (Speroff et al. 1999). The patient we report here is of interest because of the dual etiology of virilization: iatrogenic and neoplastic. We also report for the first time that the VAT literally vanished after a short-term treatment with cyproterone acetate (CPA).

Case report

A 57-year-old Caucasian woman was admitted in November 1999 because of virilization. Family history was negative for hirsutism, ambiguous genitalia or other endocrine problems. Menarche and menopause occurred at the age of 15 and 45 years respectively, and her menstrual cycles had been regular. She was mother of four children. At the age of 22, one cyst in the left mammary gland was surgically excised; another one in the same breast was excised 1 year later. At the age of 51, Behçet disease was diagnosed and treated with 5 to 25 mg daily po prednisone for the first 2 years, and po cyclosporin (50–100 mg daily) for the subsequent 2 years. Early in 1998, osteoporosis was diagnosed and treated with nandrolone decanoate (Decadurabolin, 50 mg, one i.m. injection every three weeks). However, because of the sense of well-being and vigor experienced after the initial injections, from May 1998 through June 1999 she increased the regimen to two vials every week. Nandrolone was discontinued June, 1999. Starting in September, 1998, the patient developed hirsutism, defluvium capillorum, deepening of the voice, increased libido and aggressiveness.
At admission, height was 160 cm, weight 60 kg, blood pressure 135/80 mmHg, and hirsutism severe (Ferriman–Gallway score = 30); hirsutism was accompanied by fronto-temporal balding, masculine body build and clitoromegaly (80 mm², sagittal x transverse diameters) and oily skin (Fig. 1). Cushingoid features, such as moon face, buffalo hump, striae rubrae, were absent. No abdominal or pelvic masses were palpated.

Results

Routine laboratory studies gave normal results (data not shown). Hormone measurements prior to and after dexamethasone suppression testing are reported in Table 1. Morning serum cortisol was normal and fell normally to <5 μg/dl after the 1 mg dexamethasone overnight test. Serum free testosterone, serum total testosterone, serum androstenedione, serum 17-hydroxyprogesterone and serum dehydroepiandrosterone sulfate (DHEAS) were elevated by 950, 575, 90, 80 and 50% respectively, than the corresponding upper normal limits. All these steroids were suppressed insignificantly by dexamethasone. Serum estradiol was slightly above normal, while serum gonadotropin concentrations were apro-
Figure 1 Top panel: clinical course throughout the 51 months of observation. Computed tomography of the adrenals at baseline (a) and at third month of treatment with cyproterone acetate (b). Note the disappearance of the 23x15 mm nodule in the right adrenal (b), as indicated by the arrow. Adrenal scintigraphy (posterior view) at 2 (c) and 7 (d) days after i.v. injection of $^{131}$I-norcholesterol + Technetium 99m labeled dimercaptosuccinic acid scintigraphy. Note the persistent focal radioactivity in the right adrenal, as indicated by the arrow. The patient was available to repeat adrenal scintigraphy after the cyproterone acetate treatment only in February, 2004 (e). No focal activity is evident.

Table 1 Plasma hormones at the initial evaluation of the patient, prior to and after dexamethasone suppression of the adrenal steroidogenesis

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference values*</th>
<th>Baseline*</th>
<th>1 mg overnight</th>
<th>2 mg per daily for two days</th>
<th>4 mg per daily for two days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (µg/dl)</td>
<td>6.8–26.3</td>
<td>20.1</td>
<td>3.1</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td>DHEAS (ng/ml)</td>
<td>100–800</td>
<td>1200</td>
<td>1100</td>
<td>1000</td>
<td>1200</td>
</tr>
<tr>
<td>Androstenedione  (ng/ml)</td>
<td>0.21–3.08</td>
<td>3.6</td>
<td>3.2</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>17OH-Pg (µg/L)</td>
<td>0.23–1.36</td>
<td>1.6</td>
<td>&lt;1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Testosterone (ng/ml)</td>
<td>0.4–0.7</td>
<td>4.1</td>
<td>3.1</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>0–3.6</td>
<td>34.2</td>
<td>20.1</td>
<td>21.0</td>
<td>22.0</td>
</tr>
</tbody>
</table>

DHEAS, dehydroepiandrosterone sulfate; 17OH-Pg, 17-hydroxyprogesterone.

* The normal values of DHEAS, 17OH-Pg and testosterone are for postmenopausal women.

* Other parameters measured at baseline were: serum FSH 20.3 mIU/L (normal values are 21.7–153), serum LH 15.8 mIU/L (normal values are 11.3–39.8), serum estradiol 44.9 pg/ml (normal values are <30), serum SHBG 35.2 nmol/L (normal values are 39–77), urinary cortisol 21.6 µg/24 h (normal values are 10–100). Conversion to S.I. Units. To convert cortisol, androstenedione, 17OH-Pg, testosterone and free testosterone in nmol/L multiply by 27.59, 3.492, 3.467 and 3.467, respectively. To convert serum DHEAS in µmol/L and estradiol in pmol/L multiply by 0.002714, and 3.671, respectively.
Figure 2 Changes in the profile of the indicated circulating hormones and total cholesterol. The gray area highlights the 4 months of oral administration of cyproterone acetate.
Cushingoid features, prompted us to search for an ovarian tumor or a purely virilizing adrenal tumor. Indeed, a 2.3-cm nodule in the right adrenal gland was demonstrated, which agrees with the right-sided preference of VAT (Derksen et al. 1994).

The disappearance of our patient’s tumor was the result not of surgical excision, but medical therapy with a short-term CPA course. However, based on the patient described below (Laszlo et al. 2000), not all antiandrogens seem as effective as CPA. This patient (Laszlo et al. 2000) matches our patient for gender, side and size of the purely VAT, same duration of the antiandrogen therapy (although with a different drug) and same duration of previous treatment with three drugs (although different from the three taken by our patient). This 55-year-old woman, who for the past 7 years had been treated with $β$-blockers, ACE inhibitors and diuretics for hypertension, was operated for a 3.0 × 2.6 cm purely VAT of the right gland. Unlike our patient, only serum testosterone was increased. Prior to surgical excision and for 4 months, the patient was treated with 50 mg daily flutamide. Steroid hormones either remained unchanged or even increased, indicating that no shrinkage of the mass had occurred.

Both flutamide and CPA inhibit the binding of DHT to the androgen receptor, but the former is a nonsteroidal drug while the latter is a potent progestative agent (Speroff et al. 1999). We have screened extensively the literature for possible antiproliferative effects of CPA. Other than the well-known effect, shared with the other antiandrogens, on androgen-dependent cancers (Griffin & Wilson 1998), an antiproliferative action has been reported only in meningiomas (Adams et al. 1990). In contrast, both flutamide and CPA (flutamide > CPA) inhibited the DHT-induced inhibition of proliferation on the adrenocortical carcinoma cell line NCI-H295 (Rossi et al. 1998). The effect of CPA was mimicked by another progestative agent, 11-α-hydroxyprogesterone, and by the dopamine agonist bromocriptine. Thus, these three drugs were proposed for the medical treatment of meningiomas (Adams et al. 1990).

The case reported here is the second patient with a purely VAT we have seen. Previously, one of us observed a 20-year-old woman with a 15-cm VAT of the right gland (Benvenga 1995). Citations of this case are pertinent because VATs overexpress cell-surface receptors LDL (Nakagawa et al. 1995), namely the receptors used by the LDL to provide 80% of the cholesterol needed for adrenal steroidogenesis (Orth & Kovacs 1998). Due to this overexpression, LDL are internalized at high rates, and circulating both LDL cholesterol and total cholesterol decrease; however, cholesterol concentration in blood increases once the tumor has been removed. In our patient, serum total cholesterol was relatively low, namely close to the fifth percentile for gender- and age-matched controls, prior to CPA therapy but it increased progressively during therapy. After disappearance of the tumor, cholesterol has remained stable but at levels that were approximately 35 mg/dl greater than prior to CPA therapy, reinforcing the concept that the step-wise increase in circulating cholesterol was not random, but due to the drug.

If the shrinkage of virilizing adrenal tumor caused by CPA will be confirmed (hopefully also in large tumors), then we have already available a drug to prepare patients for surgery and, when tumors are relatively small, even to avoid surgery.

References


