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.

Endocrine-Related Cancer (2005) 12 939–944

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 inappropriate low for a postmenopausal woman.

Transvaginal ultrasonography revealed a single uterine myoma of 56 x 56 mm and no masses in the two ovaries. Computed tomography (CT) showed a 23 x 15 mm nodule in the right adrenal gland, while the left one was normal by size and morphology (Fig. 1). Adrenal scintigraphy showed, in the scans taken 2 and 7 days after injection of 131I-labeled cholesterol, a focal area of tracer accumulation below the liver and above the kidney, a position consistent with the right adrenal gland (Fig. 1).

As the above results clearly supported the diagnosis of a VAT and because the tumor could have been a virilizing carcinoma, based on its overwhelming preference for the right gland and occurrence at a median age (53 years) comparable to our patient's age (Dерksen et al. 1994), we recommended prompt surgical excision of the mass. However, the patient repeatedly postponed admission to the Department of Surgery. Eventually she refused explicitly the intervention, preferring to be treated medically for the hirsutism. Thus, in April 2000, we started treating her with CPA (Androcur) at a dose of 50 mg daily. This treatment was followed by the reversal of the clinical symptoms (Fig. 1, top) and normalization of the steroid hormone levels (Fig. 2). This normalization, in turn, was secondary to the CT-documented disappearance of the adrenal mass (Fig. 1, middle). At the end of July 2000, CPA was withdrawn.

Periodic routine clinical chemistry showed an unequivocal progressive increase in serum total cholesterol (+14% at the end of CPA therapy) (Fig. 2). No recurrence in the clinical (Fig. 1, top) or hormone (Fig. 2) abnormalities had occurred as of February 2004, the latest control visit. Adrenal scintigraphy performed in February 2004 demonstrated no focal activity in the right adrenal gland (Fig. 1, bottom). Her husband confirmed that libido had returned normal, and the whole family confirmed that she was no longer aggressive.

Discussion

Although more modern drugs are available, nandrolone decanoate continues to be sporadically used for treating osteoporosis, sometimes without realizing the irresponsible consequences such as causing changes in singers’ voices (Baker 1999). Other drugs that can cause hirsutism or hypertrichosis are danazol, certain progestagens contained in oral contraceptives, glucocorticoids, metyrapone, phenytoin, diazoxide, minoxidil and cyclosporin (Karpas 1987, Speroff et al. 1999). Glucocorticoids cause hypertrichosis by promoting the passage from the telogen to the anagen phase of the hair follicle cycle (Karpas 1987). Cyclosporin causes hypertrichosis and/or hirsutism by increasing the peripheral conversion of testosterone to the more potent 5α-dihydrotestosterone (DHT) through activation of the 5α reductase activity (Boudou et al. 1990). Appearance of tumors has been reported in association with cyclosporine therapy (Ptachinski et al. 1985), but we are aware of only one case of adrenal adenoma (Fahmi et al. 1998). This was a left adrenal adenoma oversecreting aldosterone which appeared in a 58-yr-old man who had received a cadaveric renal transplant and had been treated with cyclosporine as an immunosuppressant (Fahmi et al. 1998).

Concerning our patient, considering that cyclosporine was not the only drug taken and that it had been discontinued 3 years before the appearance of the hyperandrogenic symptoms, we tend to exclude its role in the formation of the VAT.

Careful pharmacological history is an essential part of the diagnostic work-up of hirsutism/virilization. Since history of our patient had disclosed prolonged therapies with three of the drugs mentioned above, we could have stopped any further investigation. However, the progression of the symptoms 5 months after withdrawal of nandrolone and the absence of...
Observation

<table>
<thead>
<tr>
<th></th>
<th>Cyproterone 50 mg/d</th>
</tr>
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<tbody>
<tr>
<td>Libido</td>
<td>3 + 3 + 3 + 2 + 1 + 1 + ––</td>
</tr>
<tr>
<td>Balding</td>
<td>3 + 3 + 3 + 3 + 2 + 2 + 1 + 1 + 1 + 1 + ––</td>
</tr>
<tr>
<td>Deepening of the voice</td>
<td>3 + 3 + 2 + 2 + 2 + 1 + ––</td>
</tr>
<tr>
<td>Clitoromegaly</td>
<td>2 + 2 + 2 + 1 + 1 + 1 + 1 + ––</td>
</tr>
<tr>
<td>Ferriman-Gallway score</td>
<td>30 32 33 32 26 24 21 20 18 16 14 12 8</td>
</tr>
</tbody>
</table>

| Nov. '99 | Dec. '99 | Jan. '00 | Feb. '00 | Mar. '00 | Apr. '00 | May '00 | Jun. '00 | Jul. '00 | Aug. '00 | Sep. '00 | Oct. '00 | Nov. '00 | Dec. '00 | Jan. '01 | Feb. '01 | Mar. '01 | Apr. '01 | May '01 | Jun. '01 | Jul. '01 | Aug. '01 | Oct. '01 | Nov. '01 | Feb. '02 |
|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|

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 23×15 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 131I-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 valuesa</th>
<th>Baselineb</th>
<th>1 mg overnight</th>
<th>2 mg per day for two days</th>
<th>4 mg per day for two days</th>
</tr>
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<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>1200</td>
<td></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.
a The normal values of DHEAS, 17OH-Pg and testosterone are for postmenopausal women.
b 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, 3.026, 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 (Benvenega 1995). Citation of this case is 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


