Adrenogenital Syndrome Caused by an Androgen-Producing Adrenocortical Tumor

Toshiko Sakuma, Toru Yamaguchi, Hiromi Abe, Fumio Kanda, Keisuke Hanioka*, Katsuya Hisano**, Hiroshi Ito***, Masayoshi Okada** and Kazuo Chihara

We describe here a typical case of virilizing adrenocortical tumor. A 23-year-old Japanese woman had her male-like musculature, hirsutism, the absence of breast development and marked clitoromegaly. Adrenal androgens were remarkably elevated, with plasma dehydroepiandrosterone sulfate 2,752 μg/dl, plasma testosterone 250 ng/dl and urinary 17-ketosteroids 203.4 mg/day. A well-encapsulated tumor approximately 7 cm in diameter was detected in the left adrenal gland by computed tomography, magnetic resonance imaging and arteriography. The tumor was surgically resected and histologically diagnosed as a benign adrenocortical adenoma. The elevated adrenal androgens returned to normal postoperatively with amelioration of her masculinized clinical features. (Internal Medicine 33: 790-794, 1994)

Key words: virilization, hirsutism, adrenal gland, dehydroepiandrosterone, testosterone

Introduction

The vast majority of cases of female pseudohermaphroditism reported in Japan are caused by congenital adrenal hyperplasia, but a small percentage (3.6%) are caused by an androgen-producing adrenal tumor (1). Seventy-five percent of such tumors are malignant (2), and thus a benign virilizing adrenal tumor is rather unusual. We describe here a typical case of virilizing adrenocortical tumor without apparent histological evidence of malignancy.

Case Report

A 23-year-old Japanese woman was admitted to our hospital in April 1993, with the complaint of the absence of breast development. The patient’s menstrual cycle had been irregular since menarche at age 11. She began to notice the appearance of a deep voice and the presence of excess body hair at age 12, as well as the growing of a sparse beard at age 14. The beard gradually became heavy and necessitated shaving every day at age 20.

On physical examination the patient showed male-like musculature with undeveloped breasts (Fig. 1A). Her blood pressure was 106/60 mmHg. A fist-sized elastic soft mass was palpable in the left subcostal region of the abdomen. A gynecological examination revealed marked enlargement of the clitoris (Fig. 1B), ovarium of normal size and slightly atrophic uterus. The peripheral blood count and blood chemistry were all normal. The patient had a normal 46, XX karyotype.

Endocrinological studies revealed that adrenal androgens were remarkably elevated, with plasma dehydroepiandrosterone (DHEA) 17,000 ng/dl (normal range 212-803 ng/dl), plasma dehydroepiandrosterone sulfate (DHEA-S) 2,752 μg/dl (normal range 72-325 μg/dl), plasma androstenedione 6.72 ng/ml (normal range 0.14-1.03 ng/ml), plasma testosterone 250 ng/dl (normal range 10-90 ng/ml) and urinary 17-ketosteroids (17-KS) 203.4 mg/day (normal range 2.4-11.3 mg/day). In contrast, glucocorticoid levels were all normal, with plasma 11-deoxycortisol 0.18 ng/ml (normal range 0.04-1.16 ng/ml), plasma cortisol 10.7 μg/dl (normal range 6.4-18.5 μg/dl) and urinary 17-hydroxycorticoids (17-OHCS) 6.7 mg/day (normal range 1.6-8.8 mg/day). Concerning levels of the mineralocorticoids, plasma deoxycorticosterone (0.17 ng/ml; normal range 0.08-0.28 ng/ml) and cortisol (6.38 ng/ml/h; normal range 3.8-8.42 ng/ml/h) were normal, Plasma renin activity (4.6 ng/ml/h; normal range 0.3-2.9 ng/ml/h) and plasma aldosterone (273 pg/ml; normal range 56.9-150.3 pg/ml) were moderately elevated. Both values were elevated to 18 ng/ml/h.

From the Third Division, Department of Medicine, *the Department of Pathology, **the Second Department of Surgery and ***the First Department of Pathology, Kobe University School of Medicine, Kobe

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Reprint requests should be addressed to Dr. Toru Yamaguchi, the Third Division, Department of Medicine, Kobe University School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650
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Table 1. Effect of Dexamethasone Ingestion on Plasma Cortisol, DHEA-S and Urinary 17-KS Levels (Dexamethasone Suppression Test)

<table>
<thead>
<tr>
<th>Dexamethasone dose*</th>
<th>Plasma cortisol (µg/dl)</th>
<th>Plasma DHEA-S (µg/dl)</th>
<th>Urinary 17-KS (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>11.1</td>
<td>2,329</td>
<td>261.5</td>
</tr>
<tr>
<td>2 mg/day</td>
<td>1.1</td>
<td>1,918</td>
<td>203.6</td>
</tr>
<tr>
<td>8 mg/day</td>
<td>1.0</td>
<td>1,476</td>
<td>225.4</td>
</tr>
</tbody>
</table>

*Oral administration of dexamethasone at 2 mg/day or 8 mg/day caused a significant suppression of plasma cortisol, but did not significantly suppress plasma DHEA-S or urinary KS.

Table 2. Circadian Rhythm of Plasma ACTH and Cortisol Levels

<table>
<thead>
<tr>
<th>Time</th>
<th>Cortisol (µg/dl)</th>
<th>ACTH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00</td>
<td>6.1</td>
<td>16.5</td>
</tr>
<tr>
<td>16:00</td>
<td>5.9</td>
<td>14.1</td>
</tr>
<tr>
<td>23:00</td>
<td>1.4</td>
<td>7.1</td>
</tr>
</tbody>
</table>

The circadian rhythms of plasma ACTH and cortisol levels were normal, showing declines during a nocturnal period.

Discussion

Adrenal tumors are usually categorized as either benign or malignant or as either functional or nonfunctional. An adrenal mass has been discovered incidentally in at least 2% of patients, through the recent expansion of the application of CT in upper abdominal examinations (3). A recent, large-scale survey of 210 cases of incidental adrenal tumors conducted in Japan (4) revealed that the most common diagnosis was
nonfunctioning cortical adenoma (69 cases), followed by pheochromocytoma (49 cases). A total of 14 malignant tumors (6.7%) and 16 functioning benign cortical lesions were also found. However, no virilizing adrenal tumor was found in this survey, indicating its rare incidence. Another literature search by Shimazaki et al. (5) found that 374 cases of adrenocortical tumors were reported in Japan through 1993, and that 68 of the tumors (18%) resulted in virilization. Virilizing adrenal tumors predominantly occur in childhood, as 51 of the above cases (75%) occurred at age 10 or less.

The present case is thought to have the typical clinical features of a virilizing adrenocortical tumor, in terms of the physical, hormonal and radiological findings. The hormonal study showed that neither plasma DHEA-S nor urinary 17-KS were suppressed by dexamethasone, suggesting autonomous secretions of adrenal androgens from the tumor. The pathological findings of the resected specimen confirmed the adrenal origin of the tumor, and plasma adrenal androgens and their metabolites in the urine returned to normal after surgery, indicating that the tumor itself clearly secreted adrenal androgens to the circulating blood, thereby causing virilization in this patient.

Virilizing adrenal tumors are known to be associated with high levels of both plasma DHEA and DHEA-S in almost all cases, whereas plasma glucocorticoids and their urinary metabolite, 17-OHCS, are not always elevated but are fre-
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Fig. 3. A) Cut surface of the adrenal tumor containing areas of necrosis and hemorrhage. B, C) Microscopic appearance of the adrenal tumor (HE stain, x40 and x120, respectively).

quently normal (5). This is because virilizing adrenal tumors tend to have normal or diminished activities of the enzymes 3β-hydroxysteroid dehydrogenase-isomerase, 21-hydroxylase and 11-hydroxylase (6-8). All of these enzymes are indispensable for the syntheses of glucocorticoids, but not for the syntheses of DHEA or DHEA-S in the adrenal gland. Therefore, only approximately one-fourth of virilizing adrenocortical tumors have been reported to secrete sufficient levels of glucocorticoids into the circulating blood to induce Cushing’s syndrome (5). Contrary to the typical elevation of plasma levels of both DHEA and DHEA-S in the present patient, neither clinical features nor hormonal abnormalities characteristic of glucocorticoid excess were found: both basal levels and circadian rhythms of plasma ACTH and cortisol were normal, and plasma cortisol levels were suppressed by a small dose of dexamethasone, indicating a normal ACTH-glucocorticoid axis.

In the present case, the plasma aldosterone level was moderately elevated. Since neither plasma deoxycorticosterone nor corticosterone, both aldosterone precursors, increased, it is unlikely that the high aldosterone level was due to excess production by the tumor itself. Elevated plasma renin activity (PRA) was probably responsible for this high aldosterone level in the patient, since a dependency of aldosterone secretion on PRA was demonstrated by the test of compulsive intravascular
dehydration.

Seventy-five percent of virilizing adrenocortical tumors reported in Japan were malignant according to a literature search from 1968 to 1986 by Nakagawa et al (2). Preoperative evaluation of the nature of the adrenal mass is important, since the prognosis of malignant adrenocortical tumors is poor, with overall median and five-year survival rates of 14 months and 24%, respectively (9). In general, early and complete demonstration of tumor involvement by imaging modalities, such as CT, MRI and arteriography, allows accurate assessment of tumor extension and subsequent complete surgical removal (10, 11). When a tumor is apparently confined to the adrenal gland without any dissemination to other organs, the criterion of a mass larger than 6 cm is considered to be the most positive predictor of malignancy (3). Copeland (8) reported that adenomas larger than 6 cm in diameter were rare (3 in 12,000 autopsies), whereas most adrenocortical carcinomas (105 of 114) were over 6 cm in diameter. However, the size of an adrenal mass as an indicator of malignancy or benign status is still the subject of controversy (12, 13). Fishman et al (14) have recently reported that the size of adrenocortical carcinomas tended to be smaller than 6 cm in diameter on CT, contrary to the established concepts. The presence of calcification and low density areas within the mass also have been proposed as characteristics of adrenocortical carcinomas on CT (15), but these characteristics can be observed in both benign and malignant tumors, and thus are of little help in the discriminating process (13, 14). A biochemical marker of adrenocortical carcinomas was reported by Bertagna and Orth (16). They found that a daily 17-KS excretion of greater than 20 mg was strongly suggestive of carcinoma. In addition, Aupetit et al (17) recently reported that hypoaldosteronism with normal or somewhat elevated levels of some aldosterone precursors may occur in adrenocortical tumors, but never in benign tumors. The latter biochemical criteria were not applicable to the present patient, since she exhibited no hypoaldosteronism. Although the large tumor size (>6 cm) and the extraordinarily high level of urinary 17-KS in this patient might be suggestive of malignancy, the clinical history of the patient revealed that her virilization started at 12 years of age, approximately 10 years before admission, suggesting slow tumor growth and hence its possible benign nature. In fact, the surgical and histological findings showed no evidence of malignancy, with neither microscopically visible extension beyond the adrenal capsule nor apparent dissemination into the surrounding tissue. The uneventful clinical course after surgery also seems to support the tumor's benign character. In general, however, the diagnosis of endocrinological tumors as definitely benign is occasionally difficult, even when tissue is available for pathological examination. There is a recent case report of an unusual adrenocortical carcinoma that recurred 16 years after an apparently curative surgical excision (18). This demonstrates the importance of a life-long follow-up of the present patient as well.

References