A GONADOTROPHIN-RESPONSIVE VIRILIZING ADRENAL TUMOUR IDENTIFIED AS A MIXED GANGLIONEUROMA AND ADRENO-CORTICAL ADENOMA

By

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ABSTRACT

A 38-year-old gravida 2, para 1 woman, who had suffered from virilization and amenorrhoea for 8 years was examined. She had peripheral serum testosterone (T) levels of 3.9–8.7 ng/ml (normal level: 0.32 ± 0.09 ng/ml) with normal serum levels of dehydroepiandrosterone (DHA), aldosterone and cortisol (F) and normal urinary 17-ketosteroids (17-KS). Dexamethasone (DXM 2 mg/day for 5 days) suppressed the serum F level adequately, but reduced the high T levels only slightly. The administration of commercial hCG 6000 IU for 3 days increased both the serum T levels (5.68 to 9.83 ng/ml) and the serum DHA levels (4.9 to 9.8 ng/ml, normal range 4–6 ng/ml), but synthetic ACTH-Z (Cortrosyn-Z®, 1 mg, Organon) did not affect the serum T level. The basal serum LH level was abnormally low, and constant infusion of synthetic LH-RH (200 µg/5 h) resulted in good responses of serum LH and FSH and increase in the serum T level from 5.2 to 9.1 ng/ml.

Computerized tomography, ultrasonography and pneumo-retroperitoneum-roentgenography showed the presence of a large tumour in the right adrenal. The tumour was a circumscribed irregularly lobulate mass, measuring 16 x 8 x 8 cm and weighing 500 g. Histologically, it was identified as a ganglioneuroma containing numerous scattered groups of large polyhydral cells similar to adrenocortical cells, forming islets in some places. After removal of the tumour from the right adrenal, the high serum T level decreased to the normal female level in 24 h.
Adrenal tumours producing androgen, controlled by gonadotrophin, appear to be extremely rare, since there have been only four previous detailed reports on tumours of this kind, all of which were adrenocortical adenomas (Werk et al. 1973; Givens et al. 1974; Blichter-Toft et al. 1975; Larson et al. 1976). We have recently seen a case of virilizing adrenal tumour in which urinary excretion of 17-ketosteroids (17-KS) was not greatly increased, and the secretion of testosterone (T) by the tumour was enhanced by the injections of hCG and LH-RH, but not by administration of synthetic ACTH. This tumour was identified as a mixed tumour consisting of ganglion cells and cells resembling adrenocortical cells.

It is thus important to recognize that the effects of gonadotrophin on androgen production do not necessarily indicate the ovarian origin of hyperandrogenaemia, and that total oophorectomy is often erroneously performed because of a misleading response to gonadotrophin (Givens et al. 1974; Larson et al. 1976).

**MATERIALS AND METHODS**

**Case history**

A 38-year-old woman was referred to our clinic in April, 1975, because of virilization. She had given birth to a daughter at the age of 21 without complications. Her menstruation had stopped at the age of 29, but had become regular again at the age of 36, in the spring of 1973. She had gradually developed hirsutism, acne and hypertrophy of the clitoris from the age of 30. Physical examination revealed BP 118/60 mmHg, height 152 cm and weight 55 kg. Her breasts and subcutaneous fat tissue were poorly developed. She had acne on the face and a masculine habitus, including prominent musculature, the male pattern of pubic hair distribution, hirsutism of the legs, and a mustache requiring daily shaving. On pelvic examination her uterus was rather atrophic and her ovaries were not palpable. Routine laboratory studies gave normal results, including those for urine protein and sugar, blood analysis, liver function and serum electrolytes.

**Assays**

Serum LH and FSH concentrations were measured with double-antibody immunoassay (RIA) kits (Daiichi Radioisotope Laboratories, Tokyo, Japan) with the 2nd IRP-hMG as a reference standard, and expressed in µg of LER-907 per 100 ml of serum. Serum steroids were measured by the modification of the RIA reported by Furuyama & Nugent (1971), using Sephadex LH-20 microcolumns instead of Al₂O₃ microcolumns. Antisera for serum steroid assay were obtained from the Research Laboratories, Teikoku Hormone Mfg. Co., Ltd., Japan. Serum T and cortisol (F), respectively, were measured by RIA using T-3-oxime-BSA and F-21-hemisuccinate-BSA antisera after separation by microcolumn chromatography. The microcolumn consisted of 2 ml of Sephadex LH-20 in a 2 ml tuberculin syringe (9 cm x 7 mm i.d.) and the T and F fractions were eluted with hexane:benzene:methanol (80:10:10, v/v) and benzene:methanol (85:15, v/v), respectively. Serum dehydroepiandrosterone (DHA) and androstenedione (A), respectively, were measured by RIA using DHA-3-succinatc-BSA and A-3-oxime-BSA antisera without column chromatography. Serum aldosterone was determined by RIA using antiserum of aldosterone-3-oxime (Dinabot Laboratory Kit, Japan)
without chromatographic purification. Urinary 17-KS and 17-hydroxycorticosteroids (17-OHCS) were determined by colorimetry (Dreker 1947; Silber & Porter 1954). Blood samples were obtained from the antecubital vein or by venous catheterization using the Seldinger approach (Kirschner & Jacobs 1971; Stahl et al. 1973). Serum was collected after centrifugation and stored at -20°C until analyzed.

**Dexamethasone suppression and hCG stimulation tests**

Dexamethasone (DXM), 0.5 mg every 6 h, was administered for 8 days to suppress ACTH secretion. hCG (hCG Mochida®, 6000 IU, Mochida Pharm. Co., Ltd., Japan) was injected intramuscularly for 3 days in June, 1975, under DXM suppression. Blood samples were obtained in the morning.

**Synthetic LH-RH infusion, synthetic ACTH-Z administration**

Synthetic LH-RH (LH-RH Tanabe®, 200 μg, Tanabe Pharm. Co., Ltd., Japan), at 40 μg/h in 500 ml of 5% glucose, was infused for 5 h (10.00–15.00) in July, 1975, and samples for serum steroid and gonadotrophin assays were taken at 30 min interval for 5 h. In October, 1975, after intramuscular injection of synthetic ACTH-Z (Cortrosyn-Z®, 1 mg, Organon), the patient was kept in the supine position for 5 h (14.30–19.30), and samples were taken every 30 min for assays of serum F, A and T.

**RESULTS**

**DXM suppression and hCG stimulation tests**

The control serum T levels of the patient were about 10–20 times those in normal women. These high T levels varied from 3.9 to 8.7 ng/ml in samples taken between April, 1975, and May, 1976. Serum A levels were slightly above the normal range. Serum DHA, F and urinary 17-KS were consistently within the normal ranges. Administration of DXM at a dose of 2 mg per day for 5 days suppressed the serum F and urinary 17-OHCS adequately. Serum T was 5.7 ng/ml, and though it was suppressed slightly by DXM treatment, it was increased to 10.7 ng/ml by 6000 IU hCG per day for two days. Injection of hCG also increased the serum DHA level from 4.9 to 8.6 ng/ml, but did not affect serum A. Urinary 17-KS secretion was slightly suppressed by DXM treatment, but returned to the level before treatment on hCG stimulation (Table 1). Urinary excretion of 17-OHCS was low, although the serum F level was within the normal range.

**Synthetic LH-RH infusion, synthetic ACTH-Z administration**

The high T levels were also responsive to pituitary gonadotrophin. During infusion of LH-RH, 200 μg over 5 h, the serum LH, FSH and T levels increased synchronously, reaching maxima 90 min after the beginning of infusion and then remaining high during the remainder of the infusion period (Fig. 1). ACTH-Z, given as a single intramuscular injection of 1 mg, increased the serum F and A levels, but did not affect the serum T levels within 5 h (Fig. 2).
Table 1.
Urinary 17-ketosteroids (17-KS), 17-hydroxycorticosteroids (17-OHCS), and serum cortisol (F), dehydroepiandrosterone (DHA), testosterone (T) and androstenedione (A) and their responses to dexamethasone (DXM) and human chorionic gonadotrophin (hCG).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Urinary 17-KS (mg/day)</th>
<th>Urinary 17-OHCS (mg/day)</th>
<th>Serum F (μg/100 ml)</th>
<th>Serum DHA (ng/ml)</th>
<th>Serum T (ng/ml)</th>
<th>Serum A (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>7.9</td>
<td>0.7</td>
<td>8.7</td>
<td>4.9</td>
<td>5.68</td>
<td>4.4</td>
</tr>
<tr>
<td>DXM 2 mg × 5</td>
<td>5.1</td>
<td>0.2</td>
<td>0.5</td>
<td>4.0</td>
<td>4.68</td>
<td>1.4</td>
</tr>
<tr>
<td>DXM 2 mg × 6 + hCG 6000 IU × 1</td>
<td>0.1</td>
<td>trace</td>
<td>8.96</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXM 2 mg × 7 + hCG 6000 IU × 2</td>
<td>1.8</td>
<td>6.9</td>
<td>10.73</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXM 2 mg × 8 + hCG 6000 IU × 3</td>
<td>7.8</td>
<td>trace</td>
<td>8.6</td>
<td>9.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal range&lt;sup&gt;a&lt;/sup&gt; (adult female)</td>
<td>5–15</td>
<td>2.2–6.6</td>
<td>3–18</td>
<td>4–6</td>
<td>0.23–0.41</td>
<td>1.5–3.4</td>
</tr>
</tbody>
</table>

Dexamethasone, 0.5 mg every 6 h, was administered for 8 days. In addition 6000 IU of hCG was injected daily for 3 days starting from the 6th day of adrenal suppression; <sup>a</sup>: normal range in our laboratory.
Fig. 1.
Serum LH (▲), FSH (▲) and testosterone (●) responses in 5 h (10.00–15.00) on infusion of synthetic LH-RH at 40 μg/h in 500 ml of 5% glucose.

Fig. 2.
Serum testosterone (●), androstenedione (▼) and cortisol (▼) responses in 5 h (14.30–19.30) after intramuscular injection of synthetic ACTH-Z, 1 mg.
Procedures for location of the lesion

When serum T levels are stimulated by gonadotrophin, an ovarian tumour or the polycystic ovary syndrome is usually suspected, so we performed ovarian wedge resection after laparoscopy in April, 1976, but no abnormalities other than a few obstructed follicles and cortical fibrosis could be observed. After this operation, the serum T levels remained high.

To locate the source of T, venous catheterization was carried out from the right femoral vein in May, 1976. However, this failed to reveal elevated T levels in samples from the right adrenal vein, because the tip of the catheter could not be inserted into the right adrenal vein. In the left adrenal vein, the serum T, F and aldosterone levels were 9.3 ng/ml, 155 μg/100 ml and more than 2000 pg/ml, respectively. In the peripheral vein, inferior vena cava and right renal vein, the serum T, F and aldosterone levels were 8.7–9.3 ng/ml, 12–14 μg/100 ml and 95–120 pg/ml (normal range in our laboratory: 50–125 pg/ml), respectively. Though this examination failed to clarify the source of serum T, it showed that the left adrenal had normal function and was not the source of hypertestosteronaemia.

Ultrasonography (Picker Model-102) and computerized tomography (ACTA-scanner) showed a right adrenal tumour of about twice the size of the kidney in the upper part of the right kidney. The size of the tumour was estimated to be 12.2 × 6.6 × 6.6 cm.

Pathological investigation

In June, 1976, the tumour located in the right adrenal area was removed without any adhesive tissue. It was a solid elastic tumour weighing 500 g and measuring 16 × 8 × 8 cm. The cut surface showed that the right adrenal gland had been completely replaced by homogeneous hard elastic pale-yellow tissue. Microscopically the tumour was composed of uniform spindle cells separated by densely packed nerve fibers, ganglion cells with abundant cytoplasm and round or oval nuclei, and nests of large polyhedral cells containing eosinophilic and slightly granular cytoplasm. The nuclei of these polyhedral cells were generally round or oval with a moderate amount of chromatin (Fig. 3). Crystalloids of Reinke were not observed. The cell masses in these nests may have been derived from the adrenal cortex. The tumour seemed to be a mixed ganglioneuroma and adrenocortical adenoma.

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Fig. 3.
Photomicrograph of the mixed adrenocortical adenoma and ganglioneuroma. The mixed tumour was composed of islets of adenoma cells, ganglion cells with abundant cytoplasm and round or oval nuclei, and spindle cells with nerve fibers. (Haematoxylin and eosin. Original magnification, ×100).
Changes after surgery

After removal of the tumour from the right adrenal, the serum T level decreased to the normal female level in 24 h. No changes were recognized on hCG stimulation. Hirsutism, acne and enlargement of the clitoris disappeared within 6 months.

DISCUSSION

The tumour described in this report had several unique features. First, there was excessive testosterone production of adrenal origin, yet urinary 17-KS was within the normal range. A second unusual feature of this case was the increase of serum T and DHA on administration of hCG or LH-RH. The basal testosterone level varied in the range of 3.9-8.7 ng/ml. This variation was probably due to fluctuation in endogenous gonadotrophin secretion, because this patient had shown ovulatory cycles and occasionally anovulatory cycles in the basal body temperature since March, 1975. Four cases of gonadotrophin-responsive, androgen-secreting adrenal adenoma have been reported. In the cases reported by Werk et al. (1973) and Givens et al. (1974), the urinary 17-KS levels were within the normal range, and the plasma T levels were high (8.5-9.1 ng/ml). In the case reported by Blichert-Toft et al. (1975), the serum T level was slightly elevated, and the urinary excretions of DHA, androsterone, aetiocholanolone, and 11-oxy-17-KS were remarkably increased. Androgen production in these reported cases was suppressed by administration of ACTH, but it was not suppressed in the present case.

Another unusual feature of this case is the histological characteristics of the tumour, which contained ganglion cells and groups of large polyhedral cells resembling adrenocortical cells. The islets containing large polyhedral cells may have been formed by hyperplasia, or by tumour cells showing autonomic multiplication. We consider that the tumour was a mixed ganglioneuroma and adrenocortical adenoma that secreted testosterone. No previous case of a virilizing adrenal tumour with a histological picture similar to that of the present case has been reported.

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REFERENCES


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