A Case of Glucocorticoid-Suppressible Hyperaldosteronism with Aldosterone Producing Adenoma

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Abstract

A 34-yr-old woman with hypertension (142/102 mmHg), hypokalemia, high plasma and urinary aldosterone and low plasma renin activity was studied. A left adrenal tumor and enlarged right adrenal gland were demonstrated by adrenal venography. During administration of dexamethasone (2 mg daily, for 3 weeks), urinary aldosterone excretion decreased abruptly from 22.5 to 9-11 μg/day, serum potassium increased and blood pressure fell to 120-130/80-90 mmHg. After left adrenalectomy, all manifestations improved with no medication. The resected adrenal gland revealed clear cell adenoma and micronodular adrenocortical hyperplasia. The patient was considered to be a rare case of glucocorticoid-suppressible hyperaldosteronism with an aldosterone-producing adenoma.

Glucocorticoid-suppressible hyperaldosteronism (GSH) is a rare form of hyperaldosteronism, first described by Sutherland et al. (1966). The features of this disorder are hypertension, hypokalemia, suppressed plasma renin activity (PRA) and high aldosterone production as primary aldosteronism. It is, however, clearly distinguished from other forms of primary aldosteronism by complete amelioration of manifestations and biochemical abnormalities during treatment with small doses of glucocorticoid (Sutherland et al., 1966; Miura et al., 1968; Giebink et al., 1973; New et al., 1973; Ganguly 1982). No adrenal adenoma has been found in such patients. On the other hand, in patients with primary aldosteronism due to an aldosterone-producing adenoma (APA) or idiopathic adrenal hyperplasia, glucocorticoid administration decreases aldosterone production only partially and transiently, and has no effect on their hypertension and hypokalemia (Salton et al., 1969; Ganguly et al., 1977).

We reported here a case of 34-yr-old woman with APA and micronodular adrenocortical hyperplasia. For this patient, the administration of dexamethasone (Dexa) was associated with a sustained suppression of hypertension and hyperaldosteronism.
Materials and Methods

Case report

A 34-yr-old Japanese housewife had hypertension (140/90 mmHg) at the age of 27 during pregnancy but was not treated. From age 30, she was treated with hydrochlorothiazide. At the age of 31, she had episodes of muscle weakness of the extremities. The serum potassium (K⁺) was 2.1 mEq/l and the plasma aldosterone concentration (PAC) was 35 ng/dl. A diagnosis of hypokalemic periodic paralysis with primary aldosteronism was made and she was sent to our hospital. Her grandmother had hypertension but details were unknown. The patient has three siblings but none are apparently hypertensive.

On admission, the blood pressure was 142/102 mmHg. There was no other abnormal finding on physical examination except for a grade I change in the optic fundi. Following cessation of medication, serum sodium (Na⁺) and K⁺ were 143 and 3.3 mEq/l, respectively. Endocrine data are shown in Table 1. The daily urinary excretion of 17-hydroxycorticosteroid and serum cortisol at 0800 h were slightly elevated but the serum cortisol concentration showed a diurnal rhythm and was suppressed to 3.0 µg/dl with the administration of Dexe (1 mg). The urinary 17-ketosteroid and catecholamines were normal. PRA and PAC at 0800 h in a supine position were 0.2-0.4 ng/ml/h and 42-48 ng/dl, respectively. After the intravenous injection of furosemide (40 mg) and being upright for 2 h, the PRA did not increase. PAC showed a distinct circadian pattern, a suppression with Dexe (1 mg), and a marked rise with a rapid ACTH test, in parallel with the serum cortisol. Urinary aldosterone was increased to 22.5 µg/day. Serum levels of other steroids were all in the normal range, plasma ACTH was low normal and plasma β-lipotropin was low.

Table 1. Endocrine studies

1) Basal hormone levels

<table>
<thead>
<tr>
<th>Hormone level (normal range)</th>
</tr>
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<tbody>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>progesterone</td>
</tr>
<tr>
<td>11-deoxycorticosterone</td>
</tr>
<tr>
<td>corticosterone</td>
</tr>
<tr>
<td>aldosterone</td>
</tr>
<tr>
<td>17α-hydroxyprogesterone</td>
</tr>
<tr>
<td>cortisol</td>
</tr>
<tr>
<td>dehydroepiandrosterone</td>
</tr>
<tr>
<td>dehydroepiandrosterone sulfate</td>
</tr>
<tr>
<td>ACTH</td>
</tr>
<tr>
<td>β-lipotropin</td>
</tr>
<tr>
<td>Plasma renin activity</td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td>17-ketosteroid</td>
</tr>
<tr>
<td>17-hydroxycorticosterone</td>
</tr>
<tr>
<td>aldosterone</td>
</tr>
</tbody>
</table>

2) Circadian rhythm, Dexe suppression test and ACTH test

<table>
<thead>
<tr>
<th>Dexe (1 mg, p.o.)</th>
<th>β₁-24ACTH (250 µg, i.v.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>0900 1700 2100 0900 0930 1000</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>(ng/dl) 42 21 17 11 50 38</td>
</tr>
<tr>
<td>Cortisol</td>
<td>(µg/dl) 24.5 16.5 1.1 3.0 14.3 25.3</td>
</tr>
</tbody>
</table>
Fig. 1.

A: Right adrenal venography reveals an enlarged adrenal gland (arrow, 7.0 cm in length) and a fan-shaped spread of small adrenal veins.

B: Left adrenal venography shows an adrenal mass (arrow).
Table 2. Plasma aldosterone and cortisol concentrations in adrenal veins, inferior vena cava and peripheral vein

<table>
<thead>
<tr>
<th></th>
<th>Aldosterone (ng/dl)</th>
<th>Cortisol (µg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal vein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>2400</td>
<td>465</td>
</tr>
<tr>
<td>right</td>
<td>175</td>
<td>538</td>
</tr>
<tr>
<td>Inferior vena cava</td>
<td>30</td>
<td>6.0</td>
</tr>
<tr>
<td>Peripheral vein</td>
<td>26</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Adrenal venography (Fig. 1) demonstrated a left adrenal mass and an enlarged right adrenal gland with a fan-shaped spread of small veins. Blood samples were collected from the bilateral adrenal veins. Blood from the left adrenal vein had an aldosterone concentration 13.7 times greater than that from the right adrenal vein (Table 2). Abdominal computerized transaxial tomography (CT) also showed a left adrenal mass.

These findings confirmed that the patient had a left APA. She underwent left adrenalectomy.

**Studies of Dexe treatment**

Studies were performed during admission two weeks after all medication had been stopped and the patient was given a constant diet containing 154 mEq Na⁺ and approximately 75 mEq K⁺ daily. 0.5 mg of Dexe was administered orally every 6 hours. First, it was given for 6 days. Because her blood pressure fell to within the normal range during the Dexe treatment, another Dexe treatment was performed for 3 weeks. Blood samples at 0800 h and aliquots of 24 h urine were collected and serum Na⁺ and K⁺, PAC, PRA, and urinary Na⁺, K⁺, and aldosterone excretion were determined serially. Blood pressure was taken twice daily (1000 h, 1600 h) and the mean was found.

**Results**

**Response to treatment with Dexe**

Fig. 2 shows the response of blood pressure, serum K⁺, PRA, PAC and urinary aldosterone, K⁺ and Na⁺ excretion to long term administration of 2 mg of Dexe daily.

Fig. 2. Response to treatment with dexamethasone (Dexe) in blood pressure, serum potassium (K⁺), plasma renin activity (PRA), plasma aldosterone concentration (PAC), urinary aldosterone, urinary K⁺, and urinary sodium (Na⁺).
During the first trial with Dexa, the blood pressure fell and became normal after 5 days. Serum K$^+$ rose from 3.3 to 3.7 mEq/l. After the Dexa was discontinued, the blood pressure was elevated to pretreatment levels and the serum K$^+$ decreased to 2.7 mEq/l. For confirmation, a second trial of Dexa was started. The blood pressure fell to 120–130/80–90 mmHg after 7 days on Dexa. The high urinary aldosterone excretion decreased to normal, 9–11 µg/day, within 2 days of the treatment, while the PAC fell from 40 to 17 ng/dl. The decrease in aldosterone was associated with an increase in urinary Na$^+$, a decrease in urinary K$^+$ excretion, a rise in serum K$^+$ from 2.7 to 3.2 mEq/l, and an increase in PRA from 0.2 to 5.0 ng/ml/h.

These results indicate that the hyperaldosteronism in this patient was continuously suppressed by treatment with Dexa, similarly to GSH.

**Pathological studies**

The left adrenal gland weighed 7 g and had a 12 mm in diameter tumor. On the cut surface, the tumor was glistening, golden yellow and enclosed by a capsule (Fig. 3). The cortex of the surrounding adrenal gland was 1 mm thick. Microscopic examinations revealed that the adrenal tumor was a clear cell adenoma, whose cells were large, vacuolated and arranged in nests, as commonly seen in APAs (Fig. 4). In the adrenal cortex adjacent to the adenoma, the zona glomerulosa was prominent and wide. However, it was noted that in the zona fasiculata, especially in the outer zone, multiple micronodular lesions were evident and some of them swelled to a capsule of the adrenal gland. These nodular lesions were composed of large clear cells containing spongy cytoplasm, as seen in the adenoma cells (Fig. 5A, 5B).
Post-operative studies
After left adrenalectomy, all manifestations were abruptly normalized as follows: blood pressure 116-128/64-88 mmHg, serum K+ 4.1 mEq/l, PAC 6-8 ng/dl, PRA 1.0-2.2 ng/ml/h, urinary aldosterone 1.4 µg/day. PRA and PAC were increased by loading with furosemide (40 mg, iv) and standing for 2 h from 2.2 to 12.1 ng/ml/h and from 13 to 25 ng/dl, respectively. PAC showed neither a circadian rhythm nor an increasing response to ACTH.

Discussion
We presented a patient with APA in the left adrenal gland, whose manifestations of hyperaldosteronism were corrected with the administration of Dexta. Our patient had hyperaldosteronism with hypertension, hypokalemia and suppressed PRA. Abdominal CT and adrenal venography demonstrated a left adrenal mass. After removal of the adrenal gland including the tumor, all clinical findings were normalized. These observations are consistent with primary
Fig. 5 A
Photomicrograph of the adrenal cortex adjacent to the adenoma. The zona glomerulosa is hypertrophic. The outer zona fasciculata has microadenomas. Silver stain, original magnification ×196.

Fig. 5 B
Histology of the adrenal gland, original magnification ×136.

A: Silver stain, original magnification ×196. B: Hematoxylin and eosin stain, original magnification ×136.
aldosteronism due to APA (Conn and Conn 1961; George et al., 1970). The treatment with Dexa caused an abrupt and sustained decrease in urinary aldosterone to the normal level and was associated with Na⁺ loss, K⁺ retention, increased PRA and a gradual fall in blood pressure to within the normal range. Although Dexa treatment produces a decrease in PAC in patients with APA, it is only partial, lasts 1 or 2 days and is not associated with a fall in blood pressure (Salton et al., 1969; Ganguly et al., 1977). On the other hand, GSH is distinguished from other forms of primary aldosteronism by its sustained responsiveness to glucocorticoid treatment with a complete reversal of all features of hyperaldosteronism (Sutherland et al., 1966; Giebink et al., 1973; New et al., 1973; Grim and Weinberger 1980; Oberfield et al., 1981; Gill and Bartter 1981). Our patient had almost all of characteristic features of patients with GSH, except for clear evidence of familial occurrence. However, urinary aldosterone decreased only to the high normal range, PAC decreased but not to the normal range and serum K⁺ increased but not to the normal level during the second period of Dexa treatment. Dexa might be able to suppress the aldosterone secretion from APA sufficiently to normalize the elevated blood pressure, but did not do so completely, in our patient.

Pathological studies of the left adrenal gland showed that the tumor was a clear cell adenoma and that the remainder of the tissue had hyperplastic zona glomerulosa, as usually observed in an adrenal gland with APA (George et al., 1970). However, in the zona fasiculata, especially in its outer zone, there were multiple micronodular lesions composed of cells similar to the adenoma cells. On the adrenal pathology in patients with GSH, Sutherland et al. (1966) and Miura et al. (1968) reported that the excised adrenal gland revealed a cortical hyperplasia. Matsuo et al. (1985) reported that the outer zona fasiculata was centrifugally arranged in small alveoli associated with hypertrophic zona glomerulosa. They also noted electronmicroscopical evidence of hyperfunctioning cells in outer zona fasiculata. These observations resemble the pathological findings on the adrenal cortex in our patient. From our pathologic findings, it is conceivable that adenoma cells were derived from the same origin as hyperplastic cells in this case. If so, the APA cells might be suppressed by Dexa similarly to the hyperplastic cells.

It is unclear whether the enlarged right adrenal gland in this case was hyperplastic or not. The venography showed a enlarged right adrenal gland with a fan-shaped spread of small veins, which is usually observed in hyperplasia. However, the APC in the right adrenal vein was lower than in the left one. Dufau et al. (1968) reported that aldosterone production in adjacent adrenal tissue of the APA was markedly suppressed. If so, the right adrenal gland in our patient may be hyperplastic but suppressed by the coexistent APA.

The pathogenesis of sustained suppression of aldosterone secretion by Dexa in our patient is of considerable interest. In GSH, several possible pathogenetic abnormalities have been suggested at the pituitary or adrenal level. At the pituitary level, preopiomelanocortin-derived peptides were felt to play a role in this disorder (Murlow 1981). In our case plasma ACTH and β-lipotropin were low normal and low, respectively. Gullner et al. (1983) reported similar findings. At the adrenal level, the greater response to ACTH (Grim and Weinberger 1980; Ganguly et al., 1984), excessive secretion of unknown mineralocorticoid (Speiser et al., 1985) and maturational abnormality from glomerular to fasicular cells in the adrenal cortex (Oberfield et al., 1981; Gomez-Sanchez et al., 1984; Connell et al., 1986) were suggested as pathogenetic factors in GSH. We found
the micronodular hyperplasia in the outer zona fasciculata and this suggests there was some abnormality in the adrenal cells between the zona glomerulosa and fasciculata in our patient.

There is the possibility of a recurrence of the hyperaldosteronism as a result of changes in the remaining enlarged adrenal gland. The patient is being closely followed-up.

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References


