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NOTE

A Case of Aldosterone-Producing Adrenocortical Adenoma Associated with Preclinical Cushing's Syndrome and Hypersecretion of Parathyroid Hormone

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Abstract. A rare case of aldosterone-producing adrenocortical adenoma with preclinical Cushing's syndrome and hypersecretion of parathyroid hormone (PTH) is described. A 64-year-old male patient had a history of hypertension for two decades and hypokalemia for 4 years. He suffered from left hemiparesis and aphasia due to cerebral hemorrhage, but his appearance was not Cushingoid. His plasma renin activity was below the normal range, while plasma aldosterone concentration was high. They did not respond to furosemide-upright test. His plasma cortisol level in the morning was at the upper limit of the normal range, but it did not show a diurnal rhythm nor was it suppressed by 1 mg and 8 mg of dexamethasone. Computed tomography showed a low density tumor in the right adrenal gland. An adrenal scintigram under dexamethasone treatment revealed an uptake of the tracer on the right side, and plasma aldosterone and cortisol concentrations in the adrenal vein were higher on the right side than on the opposite. The diagnosis of right aldosterone-producing adrenal adenoma with an autonomous production of cortisol was confirmed by right adrenalectomy. Histological findings showed an adenoma consisting mostly of clear cells, but that the nests of compact cells were scattered. Analysis of an extract from the adenoma revealed that the adenoma contained an excess amount of aldosterone and that the cortisol/corticosterone ratio was higher than that of aldosterone-producing adenoma. Both serum calcium and PTH levels remained high one year after adrenalectomy. Ultrasonography revealed the swelling of a parathyroid gland on the left side, indicating the coexistence of an autonomous hyperparathyroidism.

Key Words: Primary aldosteronism, Preclinical Cushing's syndrome, Hyperparathyroidism

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Primary aldosteronism (PA) has been established as an overproduction of aldosterone without hypersecretion of cortisol from adrenal gland(s) [1]. Although *in vitro* cortisol production from aldosterone-producing adenoma [2–4] or high plasma cortisol concentrations in the adrenal vein on the adenoma side of PA [5] has been demonstrated, few PA patients have shown evidence of *in vivo* autonomous cortisol secretion such as lack of dexamethasone suppressiveness [6].

A number of studies have revealed alterations of calcium metabolism and of parathyroid function in PA [7, 8]. PA patients thus show total serum and ionized calcium levels in the low-normal range due to high urinary calcium excretion and/or metabolic

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alkalosis, thereby leading to hypersecretion of PTH. Following adrenalectomy or spironolactone treatment, however, both serum ionized calcium and PTH levels were normalized in most cases, indicating the association of PA with secondary hyperparathyroidism. On the other hand, there have been reports of a few PA patients with autonomous (primary) hyperparathyroidism. One may speculate that chronic parathyroid stimulation in PA results in autonomous secretion of PTH, while some cases appear to fall within the multiple endocrine neoplasia type 1 [9].

We report here a case of aldosterone-producing adrenocortical adenoma associated with autonomous secretion of cortisol and PTH. Cortisol secretion did not cause manifestations of overt Cushing's syndrome, thus this case could be classified as preclinical Cushing's syndrome. High serum calcium level and hypersecretion of PTH persisted following adrenalectomy, while ultrasonographic study revealed the swelling of a parathyroid gland on the left side.

Case Report

In November 1998, a 64-year-old male Japanese patient was admitted to our hospital with a 7-month history of left hemiparesis and aphasia. His medical history revealed that he had been suffering from hypertension for 20 years. At age 60, he developed hypokalemia, which had not been improved by K supplementation. He developed a cerebral hemorrhage in April 1998. His family history showed that his mother had suffered from diabetes mellitus and hypertension.

Physical examination on admission showed the absence of any Cushingoid signs. His height was 165 cm and weight was 55 kg. Blood pressure was 132/80 mmHg when he had been taking anti-hypertensive agents (calcium antagonist, nicardipine hydrochloride, and an α-blocker, terazosin hydrochloride). Laboratory findings revealed a red blood cell count of $369 \times 10^4/mm^3$, hemoglobin at 12.5 g /dl, and hematocrit at 36.5%. The white blood cell count was $7700/mm^3$ with 70% neutrophils and 4% eosinophils, and his platelet count was $25.8 \times 10^4 /mm^3$. Serum electrolytes were the following: Na 144 mEq/l; K 2.7 mEq/l; Cl 100 mEq/l; Ca 10.8 mg /dl; P 3.3 mg/dl and Mg 2.4 mg/dl. Serum BUN was 18.6 mg/dl; creatinine, 1.1 mg/dl; and uric acid, 7.7 mg/dl. Total serum protein was 6.8 g/dl with 65.8% albumin; GOT, 19 IU/l; GPT, 23 IU/l; LDH, 455 IU/l; γ-GTP, 18 IU/l; and total cholesterol, 170 mg/dl. Fasting blood glucose was 94 mg/dl, and an oral challenge of 75 g of glucose showed normal glucose tolerance (Table 1). Arterial blood gas analysis revealed pH, 7.442; PaO_2, 69.0 mmHg; $PaCO_2$, 59.5 mmHg; HCO_3, 39.5 mEq/l and base excess of 12.6 mEq/l.

Endocrinological examinations

The following endocrinological examinations were undertaken under 7 g/day of NaCl diet with taking nicardipine hydrochloride and terazosin hydrochloride. Basal hormone levels are shown in Table 1. Plasma concentration of aldosterone (PAC) was high, whereas plasma renin activity (PRA) was below the normal range. Thus, his PAC (ng/dl)/PRA (ng/ml/h) ratio was approximately over 100, indicating a strong possibility of PA [10]. Plasma level of cortisol was at the upper limit of the normal range, and urinary excretion of free cortisol was slightly above the normal range. Urinary 17-OHCS and 17-KS were normal. Plasma level of dehydroepiandrosterone sulfate (DHEA-S) was low, whereas plasma ACTH level was within the normal range. Plasma intact PTH and HS (high sensitive) PTH levels were high despite high serum calcium, indicating the coexistence of primary hyperparathyroidism. Plasma cortisol did not exhibit a diurnal rhythm (plasma cortisol at 23 : 30 was 10.6 μg/dl, Fig. 1).

Intravenous administration of furosemide (40 mg) with the patient in an upright posture did not affect PRA and PAC (Fig. 2A). Plasma levels of aldosterone and cortisol showed good responses to the administration of synthetic ACTH (250 μg, iv) (Fig. 2B). The administration of dexamethasone, at 1 or 8 mg, failed to suppress plasma cortisol (Fig. 1). Both plasma cortisol and ACTH responded well to the administration of human CRH (hCRH; 100 μg, iv), while they did not respond to desmopressin (DDAVP; 4 μg, iv) (Fig. 3).

CT scanning showed a small nodule of approximately 1.5 cm in diameter in the right adrenal gland (Fig. 4A). Performance of an adrenocortical scintigram with ^{131}I-adosterol under dexamethasone treatment revealed a greater uptake of the tracer on the

Table 1. Results of hormonal examinations

Examination	Patient's value	Normal value
serum GH (ng/ml)	0.34	<0.42
serum PRL (ng/ml)	11.4	<10.0
serum LH (mIU/ml)	4.4	1.1–8.8
serum FSH (mIU/ml)	38.1	1.8–13.6
serum TSH (μIU/ml)	1.56	0.35–3.73
serum free T3 (pg/ml)	2.4	2.2–4.1
serum free T4 (ng/dl)	1.4	0.9–1.8
plasma renin activity (ng/ml/h)	<0.1	0.2–2.7
plasma aldosterone (pg/ml)	324.4	30–160
plasma ACTH (pg/ml)	25	9–52
plasma cortisol (μg/dl)	15.5	4.5–15.0
plasma DHEA-sulfate (ng/ml)	944	1300–5600
plasma epinephrine (ng/ml)	<0.03	<0.10
plasma norepinephrine (ng/ml)	0.15	0.05–0.40
plasma dopamine (ng/ml)	<0.02	<0.02
plasma intact PTH (pg/ml)	67	14–66
plasma HS PTH (pg/ml)	940	230–560
plasma calcitonine (pg/ml)	25	15–86
plasma gastrin (pg/ml)	72	5–200
plasma IRI (mU/ml)	1.9	3.0–15.0
serum glucagon (pg/ml)	80	23–197
urinary aldosterone (μg/day)	11.2	<10.0
urinary 17-OHCS (mg/day)	6.1	2.9–11.6
urinary 17-KS (mg/day)	6.5	4.6–13.0
urinary free cortisol (μg/day)	167	35–160
urinary epinephrine (μg/day)	12.3	1–23
urinary norepinephrine (μg/day)	249.4	29–120
urinary dopamine (μg/day)	1070.0	100–1000
urinary VMA (mg/day)	6.9	1.5–7.5
urinary HVA (mg/day)	3.0	1.0–7.0

oral challenge of 75 g of glucose

	0	30	60	120 (min)
plasma glucose (mg/dl)	79	110	128	105
plasma IRI (mU/ml)	1.9	10.1	28.9	9.7

right side (Fig. 4B). Adrenal venous sampling showed that plasma aldosterone and cortisol concentrations in the adrenal vein was higher on the right side (Table 2). Magnetic resonance imaging of the pituitary showed no abnormality.

Surgical and morphological findings

Right adrenalectomy was performed on February 24, 1999. The right adrenal gland was found to be enlarged with a single nodule (1.5 × 1.6 × 1.7 cm) with a yellowish cut surface (Fig. 5A). Light microscopic examination revealed that the nodule was composed mainly of clear cortical cells with scattered nests of compact cells (Fig. 5B). Immunohistochemical analysis revealed that tumor cells markedly expressed P-450scc, 3β-hydroxysteroid dehydrogenase (3β-HSD), P-450c21, P-450c17, and P-450c11 immunoreactivity. P-450c17 immunoreactivity was present mainly in the scattered foci of the compact cells (Fig. 6A). The adjacent non-neoplastic cortical cells demonstrated mild cortical atrophy with paradoxical

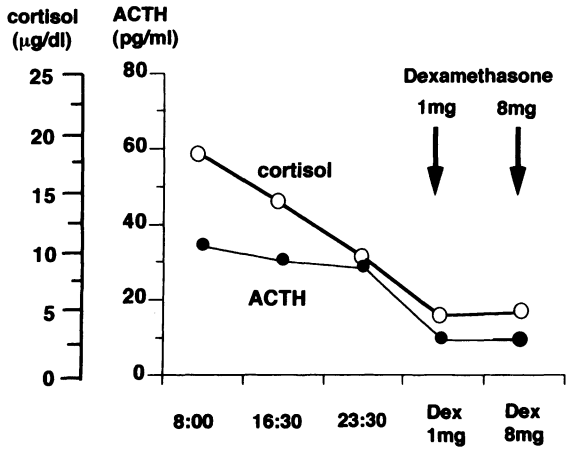

Fig. 1. Diurnal rhythm of plasma ACTH and cortisol, and plasma ACTH and cortisol responses to a low (1 mg) or high (8 mg) dexamethasone.

hyperplasia of zona glomerulosa. Immunoreactivity of dehydroepiandrosterone sulfotransferase (DHEA-ST) in the adjacent non-neoplastic cortical cells was detected without diminishment (Fig. 6B). There was no evidence of malignancy in the adrenocortical tumors according to the criteria of Weiss [11]. These findings were consistent with aldosterone-producing adrenocortical adenoma with autonomous secretion of cortisol.

Hormonal evaluation of the adenoma

Results of analysis of the corticosteroid concentration in the adenoma are shown in Table 3. High performance liquid chromatography (HPLC) revealed that the levels of 18-hydroxycorticosterone (18-OH B) and aldosterone were high compared with those in normal adrenal (normal level: 18-OH B, 0.13 ± 0.11; aldosterone, 0.09 ± 0.05 μg/g tissue) [4]. This result was consistent with aldosterone-producing adenoma. The level of cortisol (F) was low normal, but the F/B ratio (4.35) was between those of aldosterone-producing adenoma (1.92 ± 0.75) and Cushing's adenoma (15.43 ± 3.20), suggesting that this adenoma produced more cortisol than conventional aldosteronomas.

Clinical course

Following right adrenalectomy, the patient received hydrocortisone, but it could be terminated after only a month. After cessation of hydrocortisone replacement, basal plasma cortisol and ACTH and their responses to hCRH were normal (basal cortisol, 9.4–10.5 μg/dl; ACTH, 14–35 pg/ml). Plasma cortisol and ACTH were suppressed normally by 1 mg dexamethasone. Serum K, PRA, PAC, and urinary excretion of free cortisol and aldosterone were also normalized (K, 3.7–4.5 mEq/l; PRA, 1.0–2.0 ng/ml/hr; PAC, 68.1–83.5 pg/ml; urinary free cortisol, 75–82 μg/day; urinary aldosterone, 1.5–

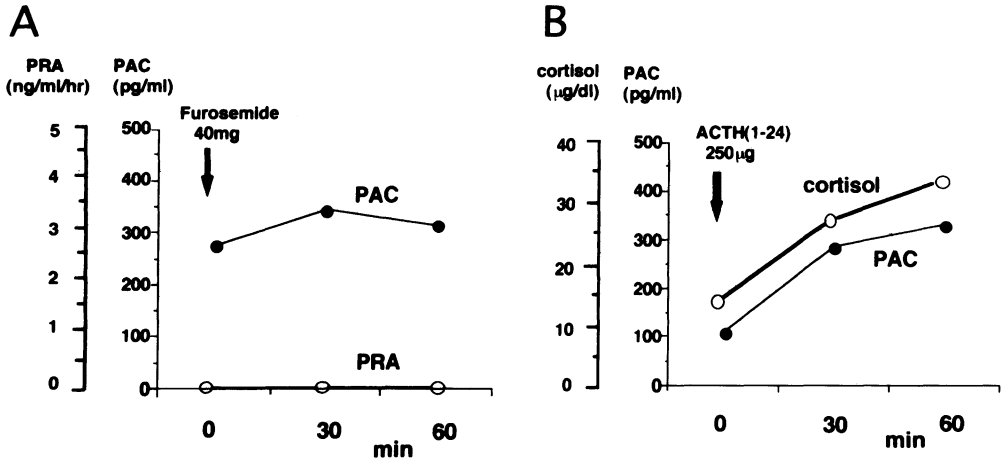

Fig. 2. Plasma aldosterone (PAC) and plasma renin activity (PRA) responses to intravenous administration of furosemide (40 mg) with upright posture (A) and plasma cortisol and PAC responses to 1–24 ACTH (250 μg) (B).

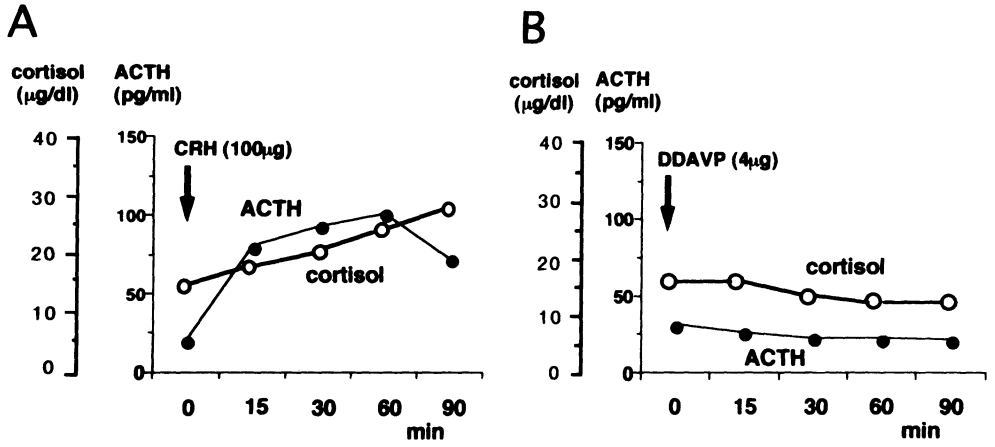

Fig. 3. Results of provocation testing of pituitary-adrenocortical function. Human CRH (100 μg) (A) or desmopressin (DDAVP, 4 μg) (B) was given iv.

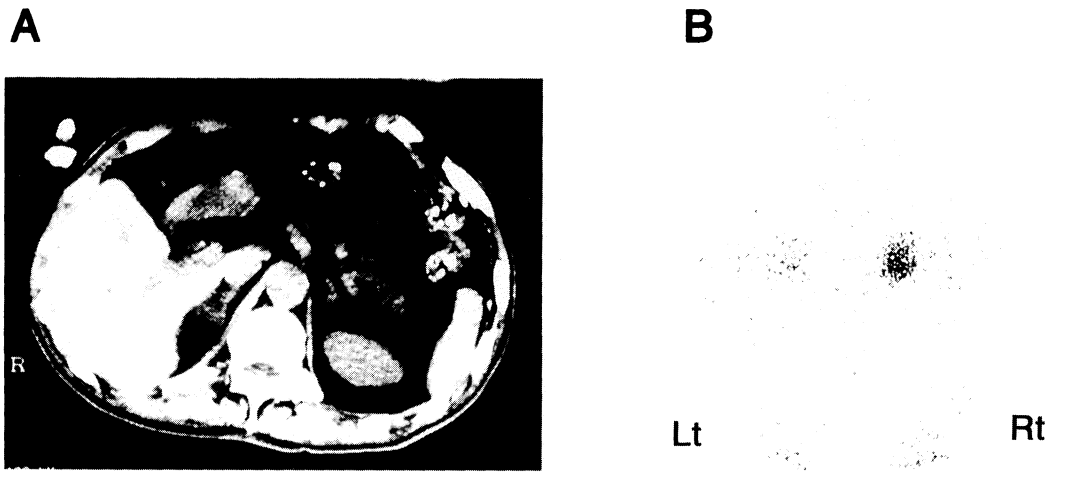

Fig. 4. Computed tomography of adrenal glands revealed a low density nodule in the right gland (A) and adrenocortical scintigram with ^{131}I-adosterol under dexamethasone treatment showed an uptake of tracer on the right side (B).

Table 2. Adrenal-vein plasma aldosterone and cortisol concentrations

vein	aldosterone (pg/ml)	cortisol (μg/dl)
right adrenal	14760	40.0
left adrenal	129.6	10.9
right renal	150.6	11.7
left renal	153.9	9.6
upper IVC	170.2	14.6
lower IVC	214.9	14.2

IVC: inferior vena cava

3.2 μg/day). His blood pressure also was gradually normalized over one year, and anti-hypertensive agents were no longer required. The variables related to calcium metabolism prior to and one year after adrenalectomy are shown in Table 4. As mentioned above, prior to surgery, intact PTH and HS PTH were inappropriately high despite the patient's high serum Ca level, indicating autonomous PTH secretion. Urinary calcium excretion, calcium/creatinine ratio, nephrogenous cyclic AMP [12], and % tubular phosphorus reabsorption (%TRP) were all consistent with primary hyperparathyroidism. One year after surgery, these variables remained abnormal. Ultrasonography revealed the swelling of a parathyroid

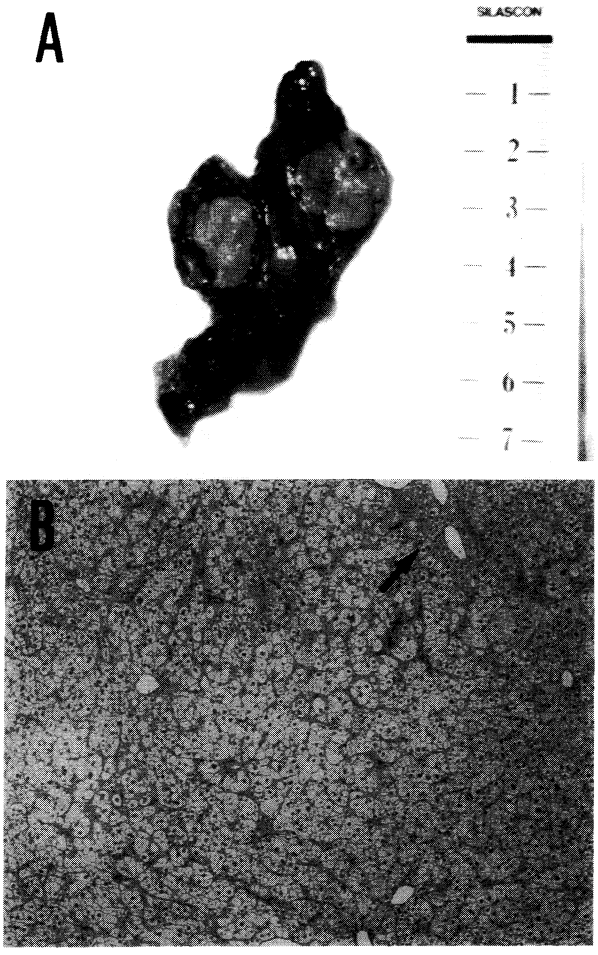

Fig. 5. Right adrenalectomy confirmed the presence of a single nodule with a yellowish cut surface (A). Microscopic findings revealed that the nodule was composed mainly of clear cells with scattered nests of compact cells (B). Arrow indicates a nest of compact cells.

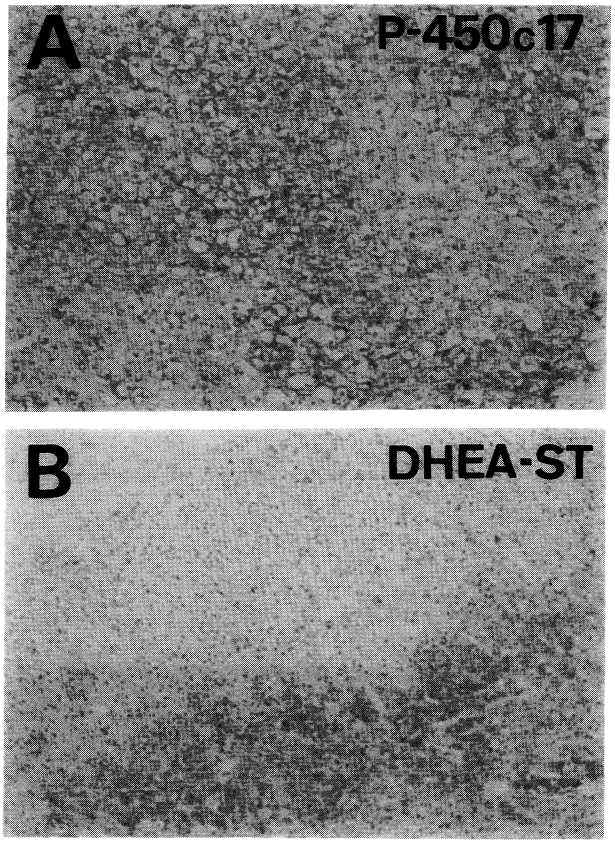

Fig. 6. Representative immunohistochemical findings in the right adrenal gland. In the adenoma, compact cells show intense expression of P-450c17, suggesting compact cells as the main source of cortisol production (A). Atrophy of the surrounding cortical cells was mild and the expression of dehydroepiandrosterone sulfotransferase (DHEA-ST) was not suppressed (B).

gland on the left side, indicating the coexistence of an autonomous hyperparathyroidism.

Discussion

Several *in vitro* studies have demonstrated that aldosterone-producing adenomas are capable of producing cortisol [2–4]. Among these studies, Stowasser *et al.* examined *in vivo* cortisol secretion in PA, but all five cases they presented were dexamethasone suppressive [3]. Nomura *et al.* reported patients with higher adrenal-vein plasma cortisol concentration on the adenoma side, supporting the

Table 3. Concentration of corticosteroids in the adenoma

18-OH corticosterone (18-OH B)	1.02
aldosterone	0.49
cortisol (F)	3.95
corticosterone (B)	0.91
11-deoxycortisol (S)	0.57
11-OH androstendione	0.35
11-deoxycorticosterone (DOC)	0.19
androstendione	n.d.
17-OH progesterone	0.21
progesterone	n.d.
	(μg/g tissue)
F/B ratio	4.35

u.d.: undetectable

Table 4. Variables related to calcium metabolism

	Prior to ADX	After ADX	Normal range
Plasma			
intact PTH (pg/ml)	67	63	10–60
HS PTH (pg/ml)	940	790	230–560
1,25-$(OH)_2$D (pg/ml)	11.1	32.9	20–60
serum Ca (mg/dl)	10.8	11.1	8.4–10.4
serum P (mg/dl)	3.3	3.1	2.5–4.5
serum Ca^{2+} (mEq/l)	2.64	2.62	2.41–2.72
urinary Ca (mg/day)	170–200	180–190	PHP>200
urinary Ca/creatinine	0.28	0.27	PHP>0.2
nephrogenic cAMP (nmol/dlGF)	3.32	2.90	0.34–2.70
%TRP	80	82	86–95

PHP: primary hyperparathyroidism

notion that aldosterone-producing adenomas secrete cortisol *in vivo*, although all of their cases showed normal glucocorticoid feedback (i.e., normal responsiveness of cortisol and ACTH to metyrapone) [5]. Tunny *et al.* demonstrated that 2 of 17 PA cases showed autonomous secretion of cortisol as well as of aldosterone *in vivo* as indicated by lack of dexamethasone suppressiveness [6]. Thus, PA with autonomous secretion of cortisol is rare in the literature.

In the present case, plasma cortisol and urinary excretion of free cortisol were slightly above or in the upper limit of the normal range. Adrenal venous sampling showed that adrenal-vein plasma cortisol concentration was higher on the adenoma side. It should be noted, however, that low cortisol concentration in the left adrenal vein might be caused by our sampling failure rather than by suppression of cortisol secretion from the left adrenal vein, because plasma ACTH was not suppressed in this patient. Nevertheless, plasma cortisol was not suppressed by either 1 or 8 mg of dexamethasone, indicating that cortisol secretion was autonomous. Mild increases, however, in plasma cortisol and urinary free cortisol suggest that this patient was in the preclinical stage of Cushing's syndrome [13–18]. Normal plasma ACTH concentration and normal response of plasma ACTH to hCRH also indicate that the plasma cortisol level in this patient was not high enough to suppress plasma ACTH. Lack of Cushingoid signs in this patient may also be attributable to a mild increase in plasma cortisol. According to magnetic resonance imaging of the pituitary and DDAVP administration [19–21], the possibility of a coexisting ACTH-producing pituitary adenoma was excluded. In this context, low DHEA-S concentration in plasma may be associated with aging [22–24] rather than with suppression of ACTH.

Analysis of the corticoid content in the adenoma revealed that the patient's F/B ratio was between that of aldosterone-producing adenoma and Cushing's adenoma [4]. This result is further evidence that the cortisol production in this case is at a higher level than in cases of aldosterone-producing adenoma, but is less than that of overt Cushing's syndrome, namely, that of preclinical Cushing's syndrome. Immunohistochemical findings revealed that compact cells scattered in the clear cells showed an intense expression of P-450c17, suggesting that cortisol was produced mainly by compact cells. Moreover, only mild cortical atrophy without suppression of DHEA-ST expression in the adjacent cortical cells also correlates with the normal plasma ACTH level in this patient.

Several investigators have focused on calcium metabolism and parathyroid function in PA. Resnick and Laragh [7] reported that PA patients showed low-normal serum calcium and ionized calcium levels due to sodium volume expansion and increased urinary calcium excretion induced by aldosterone excess, thereby leading to the dramatic elevation of PTH. They also found no appropriate increase of 1,25-$(OH)_2$-vitamin D and decrease of an inhibitory effect of vitamin D on PTH secretion in

PA [25]. Rossi *et al.* [8] demonstrated that low serum ionized calcium and high serum intact PTH levels in PA were normalized by spironolactone treatment or successful adrenalectomy. Thus, secondary hyperparathyroidism is a common feature of PA. However, Resnick and Laragh presented 2 of 10 PA patients with high serum ionized calcium levels, and suggested that chronic parathyroid stimulation secondary to low serum calcium levels might even progress to autonomous hyperparathyroidism [7]. This concept was extended by Yamasaki *et al.* who presented four Japanese women with both PA and primary hyperparathyroidism [26].

In the present case, high serum calcium and high-normal ionized calcium levels were associated with high intact PTH level, and these abnormalities were not normalized after successful adrenalectomy. Moreover, ultrasonography revealed the swelling of the left lower parathyroid gland. Although parathyroid adenoma has not been confirmed by surgery, it is highly likely that this patient showed a combination of PA and primary hyperparathyroidism. Interestingly, his plasma 1,25-$(OH)_2$-vitamin D level was low and was restored to the normal range following adrenalectomy. This is consistent with a previous report showing the lack of an appropriate increase of 1,25-$(OH)_2$-vitamin D under mineralcorticoid excess [25].

A number of cases with a combination of PA and primary hyperparathyroidism have been described [9, 26–30]. As noted above, chronic parathyroid stimulation in PA may develop into autonomous hyperparathyroidism. Alternatively, this combination has been described as part of multiple endocrine neoplasia type I (MEN I) in that the incidence of hyperparathyroidism is $>90\%$ while that of adrenocortical tumors is 40% [31]. Since most adrenocortical tumors are asymptomatic, the combination of PA and hyperparathyroidism is extremely uncommon. Genetic analysis of the aldosterone-producing adenoma showed loss of heterozygosity for polymorphic chromosome 11 DNA markers including the MEN locus [9]. Although no family history of endocrine disorders is evident in this patient, the possibility of genetic abnormality awaits examination.

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