Case Report

Variant of Pre-Clinical Cushing's Syndrome: Hypertension and Hypokalemia Associated with Normoreninemic Normoaldosteronism

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The case of a 48-year-old woman with a left adrenocortical adenoma and showing hypokalemia, hypertension and normoreninemic normoaldosteronism is reported. Basal plasma adrenocorticotrophic hormone (ACTH) and cortisol levels were within the reference ranges. The patient's plasma cortisol level decreased insufficiently at night, and was insufficiently decreased by nighttime administration of dexamethasone. She showed no Cushingoid stigmata. Iodocholesterol scintigraphy revealed tumor-sided uptake alone. The plasma dehydroepiandrosterone-sulfate level was low-to-normal for her age. Metabolic alkalosis and increased potassium clearance after sodium thiosulfate loading were revealed. The plasma aldosterone level was within the normal range, but it was statistically higher than the range for patients with pre-clinical Cushing's syndrome. However, peripheral plasma renin activity (PRA) increased normally after the patient resumed an upright posture following furosemide administration. After adenomectomy the hypokalemia and hypertension were resolved, and the plasma ACTH, cortisol, and PRA remained within the reference ranges. The plasma aldosterone level decreased slightly, but also remained within the reference range after adenomectomy. Paradoxical hyperplasia in the non-neoplastic adrenal glomerulosa zone, which indicates primary aldosteronism, and slight atrophy of the non-neoplastic adrenal cortex, which indicates pre-clinical Cushing's syndrome, were demonstrated. These findings satisfied the criteria of pre-clinical Cushing's syndrome, but did not completely satisfy those of primary aldosteronism. However, the level of CYP11B2 mRNA in the tumor was in the lower-limit of the range for adenomas associated with primary aldosteronism and was higher than the ranges for adenomas associated with pre-clinical Cushing's syndrome and overt Cushing's syndrome. Based on these results, this case was suspected to constitute a variant of pre-clinical Cushing's syndrome with slight hypersecretion of aldosterone. (*Hypertens Res* 2002; 25: 623–630)

Key Words: aldosterone, primary aldosteronism, adrenal adenoma, mineralocorticoids

Introduction

It has been reported that aldosterone-producing adrenocortical tumors produce cortisol simultaneously (1–7). Recently, it was reported that so-called pre-clinical Cushing's syn-

drome (PC) is associated with primary aldosteronism, a condition known as primary aldosteronism associated with pre-clinical Cushing's syndrome (PAPC) (1, 3, 4, 8, 9). In patients with PAPC, cortisol is autonomously but not exaggeratedly secreted, aldosterone is autonomously and exaggeratedly secreted and plasma renin activity (PRA) is suppressed.

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Table 1. Endocrine Data of the Patients with Pre-clinical Cushing's Syndrome in Our Hospital

Case No.	Age and sex	Urinary excretion of free cortisol (nmol/day)	Diurnal rhythm of plasma cortisol level (mmol/l)				Plasma cortisol after Dex (nmol/l) [#]	Plasma ACTH level (pmol/l)	Plasma DHEA-S level (μmol/l)	Serum K level (mmol/l)	PRA (ng/l/s)	Plasma aldosterone level (pmol/l)	
			0600 h	0800 h	2000 h	2200 h							
1	48M	252	350	268	317	246	268 (317)	3.3	1.0	3.9	0.50	128	
2	36F	193	221	229	248	243	229 (257)	2.8	2.0	4.5	0.17	125	
3	64M	179	270	246	251	248	204 (251)	< 1.1	0.7	4.0	0.14	158	
4	58F	233	290	328	218	188	290 (201)	1.3	0.6	4.0	0.17	130	
5	61F	220	221	226	196	201	155 (86)	2.0	1.3	4.0	0.08	130	
6	64F	43	273	265	179	171	143 (138)	3.7	1.6	3.8	0.06	147	
7	63M	37	279	303	185	199	232 (193)	1.8	2.2	3.8	0.06	100	
8	68M	105	433	339	215	185	121 (108)	3.5	0.4	3.5	0.05	72	
9	61M	116	497	386	226	235	155 (188)	2.0	0.8	4.0	0.31	53	
10	63M	155	254	221	105	143	77 (91)	3.1	0.6	4.0	0.06	33	
11 *	48F	58	262	262	155	160	142 (144)	5.1	0.8	2.7	0.31	269	
Reference range		31–225	110–505		< 138		< 28 (< 83)		2.0–11.5		3.3–5.0	0.05–0.81	72–441

M, male; F, female; Dex, dexamethasone. [#]Plasma cortisol level following overnight suppression with 8 mg or 1 mg (in parenthesis) dexamethasone. * Present patient.

Hypertension and glucose intolerance are seen in many patients with PC (10, 11) and in some of these patients the pathological conditions improve after resection of the tumor (12). However, it is unknown whether the autonomous secretion of cortisol induces these pathological conditions. In this study we report the case of a woman with PC who showed hypokalemia, hypertension and normoreninemic normoaldosteronism, and whose blood pressure and serum potassium level normalized after resection of the adrenal tumor.

Materials and Methods

Clinical Examinations

All basal samplings were performed 1 h after bed rest following overnight fasting. A dexamethasone-suppression test, measurement of diurnal rhythm of plasma adrenocorticotrophic hormone (ACTH) and cortisol levels, and metoclopramide (PrimperanTM 10 mg; Fujisawa Yakuhin, Tokyo, Japan) loading test were conducted as reported elsewhere (13, 14). Potassium clearance was examined after the loading of sodium thiosulfate (DetoxolTM 8 g; Banyu Co., Tokyo, Japan) as reported by Abe (15); 80 ml of 10% sodium thiosulfate was administered i.v. for 10 min early in the morning. Fifteen minutes after the completion of the administration, potassium clearance was determined twice at a 30 min interval. The reference range was 13.1–23.9 ml/min. PRA and plasma aldosterone levels were measured before and 2 h after upright posture following i.v. administration of 40 mg furosemide. For the evaluation of aldosterone and cortisol levels in the adrenal veins, samples were taken from the bilateral adrenal and renal veins, and from the upper and lower portions of the renal veins in the vena cava through a soft

plastic catheter inserted from the right femoral vein by the Seldinger method without infusion of ACTH as reported by Weinberger *et al.* (16). PRA was measured in the bilateral renal veins and in the upper and lower portions of the renal veins in the vena cava. All examinations were performed after obtaining the informed consent of the patient according to the Declaration of Helsinki. To compare the basal plasma aldosterone level of the present patient with those of our previous PC patients, the endocrine data of 10 previous patients with PC are presented in Table 1.

Hormone Measurement

The levels of numerous hormones in plasma, serum, and urine were measured with commercially available kits. Plasma ACTH was measured with an immunoradiometric assay, ALLEGRO HS-ACTHTM (Nichols Inst., San Juan Capistrano, USA), with a reference range of 2.0–11.5 pmol/l. Plasma and urine cortisol levels were measured with a GAMMA-CORT CORTISOL KITTM (Incstar Co., Stillwater, USA) with reference ranges of 110–505 nmol/l and 31–225 nmol/day, respectively. PRA and plasma renin concentration (PRC) were measured with RENIN RIA BEADTM (Dainabot Co., Tokyo, Japan) and Renin IRMA DaiichiTM (Daiichi Isotope Co., Tokyo, Japan) kits with reference ranges of 0.05–0.81 ng/l/s and 2.49–21.4 pg/ml, respectively. Plasma aldosterone concentration and urinary excretion of aldosterone were measured with an ALDOSTERONE RIA KITTM (Shionogi Seiyaku, Osaka, Japan) with reference ranges of 72–441 pmol/l and less than 277 nmol/day, respectively. Plasma corticosterone and deoxycorticosterone levels were measured by radioimmunoassay as reported elsewhere (17, 18). The reference range of corticosterone was 1.10–24.3

Fig. 1. Computed axial tomography of the left adrenal tumor (arrow). The tumor was 2 cm in diameter and showed two regions of different density.

nmol/l and that of plasma deoxycorticosterone was 0.24–0.85 nmol/l. Plasma dehydroepiandrosterone (DHEA) and DHEA-sulfate (S) were measured with DHEA RIA Mitsubishi™ (Tokyo Mitsubishi Pharm. Co., Ltd., Tokyo, Japan) and Coat-A-Count DHEA-SO₄™ (Diagnostic Product Corp. Tokyo, Japan) kits with reference ranges of 6.8–15.9 nmol/l and 679–5,292 nmol/l for females in the fifth decade, respectively. Plasma human atrial natriuretic peptide (hANP) was measured by immunoradiometric assay using SHIONORIA ANP™ (Shionogi Seiyaku) with a reference range of less than 12.8 pmol/l.

Measurement of Aldosterone Synthase (CYP11B2) Transcript in the Tumor

Quantitation of *CYP11B2* transcript in the adrenal tumor of the present patient was done as previously described (19). Briefly, total RNA prepared from frozen tissues was reverse transcribed, and the quantitative competitive RT-PCR method was employed to measure the mRNA levels of *CYP11B2* and glyceraldehydes 3-phosphate dehydrogenase (GAPDH), a housekeeping gene. The mRNA levels of *CYP11B2* were presented as ratios relative to GAPDH mRNA levels to control for inefficiency in the reverse transcription steps. The results were compared with those for previous patients with adrenal adenomas who showed primary aldosteronism ($n = 25$), PC ($n = 3$) and overt Cushing's syndrome ($n = 5$).

Case Report

In 1999, a 46-year-old woman consulted her doctor with a complaint of headache. Upon initial consultation her height and weight were 156 cm and 57 kg, and she showed simple but not truncal obesity. She had high blood pressure of

180/110 mmHg, and a low serum potassium level of 3.2 mmol/l. She was treated with 2.5 mg bisoprolol fumarate a β_1 receptor antagonist and 50 mg spironolactone. Five months later, her blood pressure had decreased to 110–120/80–90 mmHg and her serum potassium had increased to 4.1 mmol/l. Nonetheless, she suddenly stopped her treatment. In 2001, more than 1 year later, she again experienced headaches and consulted her doctor. Her blood pressure was 190/120 mmHg, and her serum potassium level was 2.8 mmol/l. Secondary hypertension was suspected, and she was referred to the Endocrine Division of Matsunami General Hospital. As part of her outpatient treatment, an abdominal computed axial tomography was performed and a round tumor 2 cm in diameter showing two parts with different densities was revealed in the left adrenal gland (Fig. 1).

On admission, her serum biochemical data were unremarkable, with the exceptions of a serum potassium level of 2.7 mmol/l and serum sodium level of 147 mmol/l. Other parameters were as follows: serum total cholesterol, 5.56 mmol/l; triglyceride, 0.91 mmol/l; urea nitrogen, 3.93 mmol/l; creatinine, 70.7 μ mol/l; fasting plasma glucose, 5.6 mmol/l; and glycohemoglobin, 5.8%. Her creatinine clearance was normal (1.89 ml/s), no proteinuria was detected, and other urinalysis results were unremarkable. Urinary secretion of β_2 -microglobulin was 68 μ g/l, within the reference range of less than 230 μ g/l. Initially, primary aldosteronism was suspected because of the hypertension associated with adrenal tumor and hypokalemia without cushingoid stigmata. Potassium clearance after sodium thiosulfate injection was 26.2 ml/min. The arterial blood gas analysis revealed metabolic alkalosis: pH 7.432, PaCO₂ 47.5 mmHg, PaO₂ 80.6 mmHg, HCO₃ 31.6, base excess 7.0 mmol/l, and O₂ Sat 96.1%. However, the PRA was 0.31 ng/l/s, within the reference range, and increased normally to 0.56 ng/l/s 2 h after the upright posture following furosemide administration. The basal plasma aldosterone concentration, 269 pmol/l, was within the reference range. The PRA was also within the reference range at the two additional samplings (0.3 and 0.31 nmol/l/s). PRC was also within the reference range at the two additional samplings, 15.1 and 14.3 pg/ml. Urinary excretion of aldosterone was also within the normal range (102, 90 and 100 nmol/day at the three samplings). During metoclopramide stimulation, plasma aldosterone showed a slight increase from 250 to 277 pmol/l. And the plasma hANP level was slightly increased to 24.3 pmol/l.

At 0800 h both the basal plasma cortisol (262 nmol/l) and ACTH (5.1 pmol/l) levels were normal, but at 2300 h the plasma cortisol level was slightly elevated to 155 nmol/l. After overnight administration of 1 mg and 8 mg dexamethasone, plasma cortisol was insufficiently suppressed to 144 and 142 nmol/l, respectively. Urinary excretion of free cortisol (43 to 77 nmol/day) was within the normal range. ¹³¹I-iodocholesterol (¹³¹I-Adosterol™) scintigraphy without dexamethasone treatment revealed left sided-uptake alone. The plasma DHEA-S level was 0.8 μ mol/l, or low-to-normal for

aldosterone (pmol/l), cortisol (nmol/l), PRA (nmol/l·s))

Fig. 2. The results of adrenal venous sampling. The values are given in the following order: plasma aldosterone levels, plasma cortisol levels, and plasma renin activity.

a patient of her age.

The basal plasma corticosterone level was slightly increased to 43 nmol/l, and the plasma deoxycorticosterone level, 0.4 nmol/l, was within the normal range. Urinary excretions of epinephrine (48 nmol/day; reference range, 16.4–81.9), norepinephrine (585 nmol/l; 154–810), dopamine (298 μ g/day; 190–740), vaniryl mandelic acid (22 μ mol/day; 6.6–25.7), homo-vaniryl mandelic acid (35 μ mol/day; 8.2–36.4), metanephrine (0.7 μ g/day; 0.27–1.26) and normetanephrine (2.0 μ mol/day; 0.41–2.53) were all within the reference ranges.

As shown in Fig. 2, the plasma aldosterone and cortisol levels in the left adrenal vein were high, while the corresponding levels in the right adrenal vein were rather low as compared with those in the renal veins, vena cava and peripheral vein. Similar PRA values were obtained for both renal veins and the upper and lower levels of the renal veins in the vena cava. According to the diagnostic criteria of adrenal PC recommended by the Research Committee of the Japanese Ministry of Health and Welfare for Disorders of Adrenal Hormones in 1995 (20), these results (no Cushingoid stigmata, insufficient decrease of plasma cortisol in the night and after the suppression with dexamethasone, and unilateral adrenal uptake in iodocholesterol scintigraphy) were consistent with adrenal PC. However, the present finding of normoreninemic normoaldosteronism was inconsistent with previously reported cases of PAPC (1, 3, 4, 8, 9), despite the fact that our patient had the usual findings of hypertension and hypokalemia with metabolic alkalosis and high potassium clearance after sodium thiosulfate loading.

After obtaining the patient's informed consent, a laparoscopic left adrenalectomy was performed. After the operation, prednisolone was administered daily. Five days after the operation, the prednisolone was withdrawn without inducing any withdrawal symptoms. Immediately after the op-

Fig. 3. Macroscopic findings of the resected tumor. The cut surface of the tumor showed an admixture of two different neoplastic components; a brown inner portion and a golden-yellow outer portion. The former was demarcated with the latter.

eration, the blood pressure was still high (160/88 mmHg) and the serum potassium level was low (2.3 mmol/l), but at 10 days after the operation these values had normalized to 142/70 and 4.0 mmol/l. Sixteen days after the operation, the basal PRA was 0.4 nmol/l/s and the plasma aldosterone was 89 pmol/l without antihypertensive agents. In the outpatient clinic after discharge, her blood pressure fluctuated at around 140–160/80–90 mmHg. Thereafter she was treated with a calcium channel blocker, amlodipine besilate, at 5 mg/day, and her blood pressure became well controlled at around 120/70 mmHg. Here serum potassium level was 4.1 to 4.3 mmol/l, and her PRA and plasma aldosterone levels were 0.22 nmol/l/s and 50 pmol/l, respectively, under the treatment with amlodipine.

Pathological Findings

Macroscopic Findings

The resected round tumor was 27 × 17 × 18 mm in size and weighed 11.0 g. The macroscopic findings of the cut surface of the tumor showed an admixture of two different neoplastic components: a brown inner portion and a golden-yellow outer portion. The former was demarcated with the latter (Fig. 3).

Microscopic Findings

The brown inner region was predominantly composed of compact cells, some of which had lipofuscin granules in eosinophilic cytoplasm. The golden-yellow outer region was predominantly composed of tumor cells with clear cytoplasm (Fig. 4). The tumor was encapsulated and well-circumscribed. Cortical atrophy was detected in the non-neoplastic adrenal tissue attached to the tumor, and paradoxical hyperplasia was detected in the zona glomerulosa of the non-

Fig. 4. Light microscopic features of the adenoma. The portion with compact cells and that with clear cells were distinctively demarcated.

Fig. 5. Light microscopic features of the non-neoplastic adrenal gland. Hyperplasia of the zona glomerulosa consistent with paradoxical hyperplasia as well as mild degree of cortical atrophy in the zona fasciculata and reticularis were detected.

neoplastic adrenal gland (Fig. 5).

Immunohistochemical Staining for Adrenocortical Steroidogenic Enzymes

All tumor cells showed immunoreactivity for the cholesterol side-chain cleavage enzyme (CYP11A1), 3β -hydroxysteroids dehydrogenase (3β -HSDII), 21-hydroxylase (CYP21A2), 11 β -hydroxylase (CYP11B1), 17 α -hydroxylase (CYP17) and DHEA sulfotransferase (DHEA-ST). 3β -HSDII was more abundant in the cells of the outer parts of the tumor (clear cells) than in cells in the inner parts (compact cells). CYP17 immunoactivity was detected in both portions of the tumor. 3β -HSDII was not detected in the hyperplastic glomerulosa zone of the adrenal tissue attached to the tumor (Fig. 6). Immunoreactivity for DHEA-ST was diminished in the zona fasciculata and reticularis of the non-neoplastic adrenal gland (Fig. 7).

Electron Microscopic Findings

Mitochondria having tubulolamellar cristae and smooth-surfaced endoplasmic reticula were well developed in the cells of the outer part of the tumor (clear cells). In the inner part of the tumor (compact cells), however, these organelles were

Fig. 6. Immunohistochemistry of 3β -hydroxysteroid dehydrogenase type II in the non-neoplastic adrenal gland. Immunoreactivity was detected in the zona fasciculata-reticularis but not in the zona glomerulosa, which is consistent with paradoxical hyperplasia.

Fig. 7. Immunohistochemistry of dehydroepiandrosterone sulfotransferase in the non-neoplastic adrenal gland. Immunoreactivity was focal and weak.

Fig. 8. The CYP11B2 transcript levels in the tumor. APA, aldosterone producing adenoma (n = 25); pt, the presented patient's tumor; closed square, the inner part of the tumor (compact cells); open square, the outer part of the tumor (clear cells); PC, adenoma of pre-clinical Cushing's syndrome (n = 3); OC, adenoma of overt Cushing's syndrome (n = 5).

not very well developed and lysosomes containing lipofuscin were abundant.

mRNA Level of CYP11B2 in the Resected Adrenal Tumor (Fig. 8)

The *CYP11B2* transcript levels, presented as a ratio against that of *GAPDH*, were 12×10^{-3} in the inner part of the tumor and 0.94×10^{-3} in the outer part. As shown in Fig. 8, the *CYP11B2* transcript levels in the adenomas of patients with primary aldosteronism ranged from 12×10^{-3} to 510×10^{-3} ($(170 \pm 31) \times 10^{-3}$, mean $\pm$ SE), those in the adenomas of patients with PC ranged from 0.15×10^{-3} to 0.49×10^{-3} , and those in the adenomas of patients with Cushing's syndrome ranged from less than 0.10×10^{-3} to 0.59×10^{-3} .

Discussion

The physical and endocrine results of the present patient were consistent with PC. To our knowledge, hypokalemia has not been reported in a patient with PC, although hypertension and glucose intolerance are frequently seen (10, 20). The suppression of iodocholesterol uptake in the contralateral adrenal gland to the tumor has frequently been observed in cases of PC, even in patients with normal plasma ACTH (20) like the present patient. It has been reported that 50% of the adrenal uptake of iodocholesterol is induced by ACTH, 10% is induced by angiotensin, and the remaining 40% of the uptake is induced by several other factors, such as tumor size, HDL-cholesterol receptors in the adrenal cortex, and serum cholesterol level (21). In cases of PC, the effect of an imbalance of these factors on the adrenal iodocholesterol uptake may be responsible for the suppression of contralateral adrenal uptake to the tumor.

In the present case, the peripheral plasma aldosterone concentration and urinary secretion of aldosterone were within the normal ranges. However, when the data on the present patient were combined with those for our previous 10 cases of PC, the mean basal plasma aldosterone concentration was 122 ± 63 (SD) pmol/l (Table 1). In this group, only the value of the present patient (269 pmol/l) was statistically (Grubbs-Smirnov test) high ($p < 0.05$); that is, the basal plasma aldosterone concentration of the present patient was statistically excluded from the group of our patients with PC. Low or no response of plasma aldosterone to the administration of metoclopramide is frequently seen in Japanese patients with primary aldosteronism (13), as it was in the present patient, although one study has also reported a high response of plasma aldosterone to this drug (22). Pathologically, the adrenocortical adenoma of the present patient was consistent with PAPC. The detection of paradoxical hyperplasia in the non-neoplastic glomerulosa zone, as well as the mild degrees of adrenocortical atrophy of the zonae fasciculata and reticularis and the absence of 3β -HSDII in these paradoxical hyperplastic glomerulosa cells, suggested the presence of primary hyperaldosteronism and PC (8). A hyperplastic glomerulosa zone is seen also in idiopathic hyper-

aldosteronism, although this condition is also characterized by the clear presence of 3β -HSDII in the glomerulosa zone. No hyperplasia of the non-neoplastic glomerulosa zone is seen in PC alone. The potassium clearance under sodium thiosulfate loading is a useful indicator of mineralocorticoid excess (15, 23). And its value in the present patient was in the lower-limit of the range observed in patients with primary aldosteronism, 49.7 ± 2.9 ml/min ($n = 28$) (range, 26.3–82.4) (23) and was higher than the reference range described before. These results indicate a slight excess of mineralocorticoids, particularly aldosterone, in the present patient. The *CYP11B2* mRNA level in the inner part of the tumor (compact cells) was in the lower-limit of the range of that of the adenomas of primary aldosteronism and was higher than those of the adenomas of PC and overt Cushing's syndrome. This result indicated that the aldosterone production from the inner part of the tumor was compatible with that from the aldosteronoma, although it was not particularly high. Since the *CYP11B2* mRNA level in the outer part of the tumor was low and compatible with those in cases of PC or overt Cushing's syndrome, the aldosterone was considered to have been produced mainly from the inner part of the tumor, and not from the outer part.

In contrast, autonomous secretion of aldosterone was not revealed in the present patient. The non-suppressed basal PRA and normally increased PRA after upright-posture were inconsistent with primary aldosteronism. Recently, the ratio of PRA (ng/ml/h) to plasma aldosterone concentration (ng/dl) was reported to be useful for the screening of primary aldosteronism, with a ratio greater than 20 (24) or 25 (25) suggestive of primary aldosteronism. In our patient, the ratio was only 7.0 to 10.0.

In adrenal venous sampling in cases of complete catheterization of adrenal glands, a dominant to nondominant aldosterone ratio of 4 (26) or 5 (27, 28) or greater defines the presence of primary aldosteronism due to aldosteronoma. In the present patients, the ratio was 38.8. However, a markedly lower aldosterone level in the adrenal vein contralateral to the tumor was inconsistent with non-suppressed PRA. According to previous results of an adrenal venous sampling without ACTH infusion in patients with essential hypertension (29), the plasma aldosterone level in the adrenal vein ranges from about 600 to 33,000 pmol/l. In primary aldosteronism in this report, the plasma aldosterone level in the tumor-sided adrenal vein ranged from about 13,000 to 66,000 pmol/l. Plasma aldosterone in the tumor-sided adrenal vein in the present patient was not so high; rather, it was within the former range. Furthermore, the finding that the cortisol level in the adrenal vein contralateral to the tumor was lower than that in the peripheral vein was also inconsistent with PC (30). It seems likely that the sampling from the right adrenal vein was insufficient. Thus no conclusive information was obtained from the aldosterone and cortisol levels of the adrenal veins in this study.

Plasma deoxycorticosterone, which has weak mineralo-

corticoid activity (31), was within the reference range in the present patient, although plasma corticosterone, which shows little mineralocorticoid activity, was slightly increased. Probably these steroids were independently secreted from both the tumor and the non-neoplastic adrenal cortex. In patients with overt Cushing's syndrome due to adrenocortical adenoma, hypertension and hypokalemia are commonly seen (31), but PRA is not suppressed. We cannot completely rule out the possibility that one or more of the factors previously suggested to affect hypertension and hypokalemia in cases of Cushing's syndrome (32–34) may have also played a role in the present case. A few cases of primary aldosteronism associated with overt Cushing's syndrome (PAOC) (35–37) have been reported. In one of them (37), the macroscopic and microscopic findings of the adrenocortical adenoma were very similar to those of the present patient: that is, the macroscopic findings revealed two distinct color regions, a golden-yellow region microscopically composed of clear cells occupying two-thirds of the tumor and a dark brown region composed of compact cells occupying the remaining one-third. The details of the progression of the pathophysiology of primary aldosteronism have not been clarified yet. However, we hypothesize that overproduction of aldosterone may initially induce the acceleration of sodium absorption and potassium excretion in the distal tubules, resulting in hypokalemia and volume expansion. Then, in the following stage, the volume expansion and hypertension induce the suppression of PRA (38). The initial stage of primary aldosteronism may show only hypertension, and not hypokalemia or hyporeninemia. Normotensive primary aldosteronism (25) and especially normokalemic primary aldosteronism (24, 25) are frequently seen. However, even in these patients, the ratio of plasma aldosterone concentration to PRA is reported to be high (24, 25). Two cases of normoreninemic primary aldosteronism (35, 39) have been reported, to our knowledge. In these cases, the pathogenesis of normoreninemia was unknown. One of them (35) was diagnosed with PAOC. In the present case, the pathophysiological anomaly due to aldosterone hypersecretion might not have been particularly advanced. Accordingly, PRA might not yet have been suppressed. The present case was likely accompanied by PC with slight overproduction of aldosterone and thus demonstrated normoreninemia and normoaldosteronemia in spite of the presence of hypokalemia and hypertension. In the future, this condition might be designated as pre-primary aldosteronism.

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