Case Report

Combined Primary Aldosteronism and Preclinical Cushing's Syndrome: an Unusual Case Presentation of Adrenal Adenoma

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A 55-year-old woman was referred to our institution for evaluation of elevated plasma creatine phosphokinase, hypokalemia and hypertension. Her chief complaints were muscle weakness and polyuria. A left adrenal mass, 4 cm in diameter, was noted on computed tomography. Hormonal assessment demonstrated markedly elevated plasma aldosterone concentration, markedly low plasma renin activity, an abnormal diurnal variation in serum cortisol levels, suppressed baseline plasma adrenocorticotrophic hormone, and non-suppression of serum cortisol by dexamethasone suppression test. She showed no symptoms or signs suggestive of Cushing's syndrome. Adrenal scintigraphy with ^{131}I -6- β -iodomethyl-norcholesterol showed uptake on the left adrenal and inhibition of the contralateral adrenal gland. She was diagnosed with combined primary aldosteronism and preclinical Cushing's syndrome. Cases of combined primary aldosteronism and preclinical Cushing's syndrome are extremely rare. In patients with large aldosterone-producing adenoma, contralateral adrenal insufficiency should be anticipated after the removal of the tumor. (*Hypertens Res* 2001; 24: 723–726)

Key Words: aldosteronism, adrenal tumor, Cushing's syndrome

Introduction

Increased left ventricular mass is a potent predictor of cardiovascular morbidity and mortality, independent of blood pressure or other risk factors (1). Although hypertension is present in about 80% of patients with Cushing's syndrome, left ventricular hypertrophy is reportedly less common than in patients with primary aldosteronism (2). The simultaneous presence in one patient of two uncommon syndromes, primary aldosteronism and cortisol hypersecretion (Cushing's syndrome), is extremely rare (3, 4). We here report the case of a patient with clinical and biochemical evidence of primary aldosteronism and preclinical Cushing's syndrome, caused by a single adrenal adenoma. The patient was referred to our institution for evaluation of elevated plasma creatine phospho-

kinase, hypokalemia and hypertension, and subsequently diagnosed with both primary aldosteronism and preclinical Cushing's syndrome. She underwent adrenalectomy and required a substitutive treatment with hydrocortisone after surgery.

Case Report

A 55-year-old woman was transferred to our department for the evaluation of elevated creatine phosphokinase. Antihypertensive therapy had been initiated at 44, when her blood pressure was 180/90 mmHg. At age 55, she originally presented with muscle weakness and nocturnal polyuria. Elevated creatine phosphokinase (5,660 IU/l) and hypokalemia (1.6 mEq/l) were noted and the patient was admitted to our hospital for evaluation. Her father had a history of cerebral in-

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Table 1. Laboratory Data When the Patient Was Transferred to Our Department

Hematocrit	35.0%	Sodium	144 mEq/l	ALP	128 IU/l
Red blood cell	$3.78 \times 10^4/\mu\text{l}$	Potassium	2.7 mEq/l	γ -GTP	4 IU/l
Platelet	$33.7 \times 10^4/\mu\text{l}$	Chloride	98 mEq/l	CPK	83 IU/l
Hemoglobin	11.8 g/dl	Calcium	9.0 mg/dl	ChE	3.7 IU/l
White blood cell	9,200/ μl	Phosphate	3.9 mg/dl	Amylase	389 IU/l
Total cholesterol	252 mg/dl	Total protein	7.1 g/dl	C-reactive protein	<0.1 mg/dl
Triglyceride	143 mg/dl	Albumin	4.5 g/dl		
Glucose	98 mg/dl	Total bilirubin	0.7 mg/dl	Urine protein	negative
Uric acid	4.7 mg/dl	AST	20 IU/l	Urine sugar	negative
Blood urea nitrogen	22 mg/dl	ALT	26 IU/l		
Creatinine	1.0 mg/dl	LDH	988 IU/l		

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ -GTP, γ -glutamyltranspeptidase; CPK, creatine phosphokinase; ChE, choline esterase.

Table 2. Hormonal Measurements of 24-Hour Urine Samples

		Normal range
Aldosterone ($\mu\text{g/day}$)	13	<10
Free cortisol (mg/day)	175	30–100
17-OHCS (mg/day)	10.5	2.2–7.3
17-Ketosteroid (mg/day)	1.8	2.4–11.0
Epinephrine ($\mu\text{g/day}$)	6.0	3.0–41.0
Norepinephrine ($\mu\text{g/day}$)	75.5	31.0–160.0
Dopamine ($\mu\text{g/day}$)	356.3	280.0–1,100.0
Vanillylmandelic acid ($\mu\text{g/day}$)	3.74	1.50–4.90
Homovanillic acid ($\mu\text{g/day}$)	2.21	2.40–6.00

17-OHCS, 17-hydroxycorticoid.

fraction. Computed tomography (CT) of the abdomen revealed a retroperitoneal mass. Hypertension, hypokalemia, high plasma aldosterone levels (2,100 pg/ml), and suppressed plasma renin activity (<0.1 ng/ml/h) were also noted. Antihypertensive therapy using long-acting nifedipine (40 mg/day), amlodipine besilate (5 mg/day), spironolactone (50 mg/day) and potassium aspartate (2,700 mg/day) was started. She was referred to our department for the evaluation of primary aldosteronism due to adrenal adenoma. On the day of admission, she had a temperature of 37.2°C, pulse rate of 96 beats/min, and blood pressure of 160/90 mmHg, and her height and weight were 1.57 m and 46.5 kg. Her blood pressure did not differ significantly between the upper and lower extremities. Physical examination showed no abnormality. Heart sounds were normal, with no murmurs. The lungs were clear to auscultation. On abdominal examination, bowel sounds were normal. No masses or areas of tenderness were noted, and the liver, kidneys, and spleen were not palpable. No abdominal bruits were audible. Neurologic examination was normal. Signs of Cushing's syndrome, virilization and other abnormalities were not noted on physical examination. Fundoscopic examination showed segmental narrowing of the retinal arteries without exudate, hemorrhage, papilledema or light reflex changes in the arterial walls. Rou-

tine blood tests showed hypokalemia (Table 1).

Table 2 summarizes the hormonal data, which showed slightly elevated basal urinary free cortisol and 17-hydroxycorticoid. A 24-h urine collection revealed a normal adrenomedullary function (Table 2). Table 3 summarizes the circadian changes in serum cortisol, plasma adrenocorticotrophic hormone (ACTH), plasma renin activity and plasma aldosterone concentration. The patient's serum cortisol levels were slightly elevated, accompanied by a loss of diurnal rhythm. Plasma ACTH was either low or undetectable throughout the day. Serum cortisol after 1 mg dexamethasone administration exceeded half of the value before dexamethasone, indicating a lack of suppression of cortisol by dexamethasone.

An electrocardiogram showed normal sinus rhythm at a rate of 79/min and left ventricular hypertrophy (depression of ST segment, T inversion and high voltage ($\text{SV}_1 + \text{RV}_5 = 6.5 \text{ mV}$)). Cardiomegaly (cardiothoracic ratio 53.5%) was noted on chest radiographs. Computed tomography of the abdomen demonstrated left adrenal adenoma, 4 cm in diameter and hydronephrosis in the left kidney (Fig. 1). Magnetic resonance-urography showed left hydronephrosis (Fig. 1). Magnetic resonance imaging showed stenosis due to a small mass in the left ureter. Scintigraphy using ^{131}I -MIBG disclosed no abnormal accumulations. Adrenal scintigraphy with ^{131}I -6- β -iodomethyl-norcholesterol showed significant uptake on the left adrenal and inhibition of the contralateral adrenal gland (Fig. 1).

Bilateral adrenal venous catheterization demonstrated that the cortisol concentration in the adrenal venous blood from the side of the mass lesion (70.4 $\mu\text{g/dl}$) was greater than in the contralateral side (15.7 $\mu\text{g/dl}$). The plasma aldosterone concentration in the adrenal venous blood from the side of the mass lesion (18,000 pg/ml) was also higher than in the contralateral side (1,000 pg/ml). Plasma epinephrine concentrations in blood from the left and right adrenal veins were 2.73 pg/ml and 0.13 pg/ml, respectively. The plasma renin activities in the adrenal venous blood from the side of the mass lesion and from the contralateral side were markedly

Table 3. Circadian Changes in Plasma Adrenocorticotrophic Hormone (ACTH), Serum Cortisol, Plasma Renin Activity, Plasma Aldosterone, Plasma Corticosterone and Plasma Deoxycorticosterone

	Time of day						
	Before dexamethasone					Dexamethasone	
	8:00	12:00	16:00	20:00	24:00	8:00	12:00
ACTH (pg/ml)	7	<5	6	5	6	<5	<5
Cortisol (μ g/dl)	15.1	11.3	10.0	8.0	10.3	10.5	7.7
Renin (ng/ml/h)	0.2	0.2	0.3	0.3	0.2	0.2	0.2
Aldosterone (pg/ml)	530	400	350	250	420	330	280
Corticosterone (ng/ml)	11.4	7.89	6.59	4.12	8.96	6.26	3.74
Deoxycorticosterone (ng/ml)	0.700	0.830	0.990	0.740	0.840	0.960	0.530

Dexamethasone was administered orally at a dose of 1.0 mg at 24:00. Normal ranges of each hormone are as follows: plasma ACTH, 9–52 pg/ml; serum cortisol, less than 25 μ g/dl; plasma renin activity: 0.3–2.9 ng/ml/h; plasma aldosterone, 30–150 pg/ml; plasma corticosterone: 0.21–8.48 ng/ml; plasma deoxycorticosterone: 0.03–0.33 ng/ml.

Fig. 1. CT of adrenal tumor (left upper panel), magnetic resonance-urography (left lower panel), preoperative posterior adrenal scintigraphy with ^{131}I -6- β -iodomethyl-norcholesterol (middle lower panel) and with ^{131}I -MIBG (right lower panel), and gross appearance of resected adrenal tumor (right upper panel). Abdominal CT showed a round, well-circumscribed mass of 4-cm diameter in the left adrenal gland. Magnetic resonance-urography showed left hydronephrosis. Posterior adrenal scintigraphy with ^{131}I -6- β -iodomethyl-norcholesterol showed uptake on the left adrenal and inhibition of the contralateral adrenal gland. No abnormal uptake was observed with ^{131}I -MIBG. The excised adrenal tumor was a well capsulated and poorly vascularized yellow nodular mass.

low (0.3 ng/ml/h).

During surgery, an adrenal adenoma of $2.4 \times 2.3 \times 3.8$ cm was removed (Fig. 1). The cut surface of the adenoma from the patient was golden yellow, which is typical of aldosterone-producing adenoma. However, atrophy of the adjacent normal tissues was evident histologically. Postsurgical substitutive treatment with oral hydrocortisone 30 mg daily was started.

Discussion

The adrenal cortex is divided into three functionally distinct zones: the outer zona glomerulosa, the intermediate zona fasciculata, and the inner zona reticularis. The principal steroids

produced in these zones are aldosterone, cortisol and sex steroids, respectively. Major differences in the enzymatic arsenal between these zones are responsible for the direction of the biosynthetic pathways towards the production of their typical steroid hormones (4, 5). The zona glomerulosa contains the enzyme corticosterone methyl oxidase type II (CMO, 18-dehydrogenase), which is able to convert corticosterone, via 18-hydroxycorticosterone, into aldosterone. Hormone production by this zone is under the control of the renin-angiotensin system. The zona fasciculata contains the enzyme 17 α -hydroxylase, which is responsible for the conversion of progesterone into 17 α -hydroxyprogesterone, a precursor of cortisol and androgens; 18-hydroxylation, which causes formation of 18-hydroxycortisol, also occurs in

this 17-hydroxysteroid pathway. However, oxidation of the 18-hydroxylated compounds to synthesize aldosterone does not occur, since the zona fasciculata lacks the CMO enzymes (4, 5). ACTH is the regulator of steroidogenesis in this zone, as well as its growth factor.

In primates, the fetal adrenal gland is comprised of three functional zones: the inner fetal zone (FZ), which has the enzymes necessary for dehydroepiandrosterone sulfate production beginning early in gestation; the transitional zone (TZ), which possesses enzymes necessary for cortisol production; and the outer, definitive zone (DZ), which appears to function as a reservoir of progenitor cells that move centripetally to populate the remainder of the gland and does not acquire a steroidogenic phenotype with the capacity to produce mineralocorticoids until the near term (5). Late in gestation, when the cells in definitive zone have adopted a steroidogenic phenotype, mineralocorticoid (aldosterone) production is initiated (5). From the points of view of embryological development, it is of interest to observe the adrenal adenoma of our patient, which has the capacity to produce aldosterone but does not lose the capacity to produce cortisol.

Since the advent of sensitive noninvasive methods to image the abdomen, such as CT scanning, the discovery of incidental adrenal masses has become fairly common. In some of these patients, slight or marked overproduction of glucocorticoids without physical signs or symptoms of Cushing's syndrome has recently been described (6, 7), and has been termed "preclinical Cushing's syndrome" (6, 7). It is important to clarify whether the adrenal tumors incidentally discovered are functionally active, even when symptoms and physical signs are absent, because unilateral adrenalectomy in these patients poses a potential risk of Addisonian crisis (6, 7). Our case, which showed autonomous cortisol production that was not suppressed by low dose dexamethasone, but no other signs of Cushing's syndrome, was originally diagnosed as a case of aldosterone-producing adenoma. The clinical and laboratory features of the present case fulfill the recently reported diagnostic criteria of preclinical Cushing's syndrome (8). This case demonstrates that the condition of preclinical Cushing's syndrome also exists in aldosterone-producing adenoma.

Adrenal scintigraphy with radioactive cholesterol has been well demonstrated to provide a reliable measure of adrenocortical function in addition to being a localizing technique (9, 10). In order to estimate the potential risk of Addisonian crisis after adrenalectomy, it is very important to determine the degree of suppression on the contralateral adrenal gland by means of scintigraphic scanning analysis. In the present patient, adrenal scintigraphy with ^{131}I -6- β -iodomethyl-norcholesterol showed uptake on the left adrenal and inhibition of the contralateral adrenal gland. There have been several reports describing the risks of adrenocortical insufficiency after adrenalectomy in patients with preclinical Cushing's syndrome (6, 7, 11–13). Although in the present case of pri-

mary aldosteronism the tumor appeared to be clinically non-functional, it was subsequently revealed that the tumor was autonomously producing cortisol and suppressing the contralateral adrenal gland.

In summary, we treated a patient with clinical and biochemical evidence of primary aldosteronism and preclinical Cushing's syndrome. It is extremely rare to see both these conditions caused by a single adrenal adenoma. In patients with a large aldosterone-producing adenoma, adrenal insufficiency should be anticipated after the removal of the tumor.

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