A Rare Case of Subclinical Primary Aldosteronism and Subclinical Cushing's Syndrome without Cardiovascular Complications

Natsumi KITAJIMA[*1], Toshiro SEKI[*1], Atsushi YASUDA[*1], Masayuki OKI[*2], Atsushi TAKAGI[*2], Kazuya HANAI[*3], Toshiro TERACHI[*3] and Masafumi FUKAGAWA[*1]

[*1] *Division of Nephrology, Endocrinology and Metabolism,*
[*2] *Division of General Internal Medicine, Department of Internal Medicine,*
[*3] *Department of Urology, Tokai University School of Medicine*

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We report a rare case of subclinical primary aldosteronism (PA) and subclinical Cushing's syndrome (CS). A 49-year-old woman was referred to our hospital for the evaluation of an adrenal incidentaloma. The patient had no previous medical history and no family history of notable illness. Her blood pressure was 103/60 mmHg. She had no Cushingoid features. Routine laboratory examinations were within the normal ranges including normokalemia. Based on the endocrinological results and imaging findings, we finally made a diagnosis of subclinical PA caused by both adrenal glands and subclinical CS caused by bilateral adrenal tumors. Interestingly, this patient had no risk factors for cardiovascular disease. In addition, the optimal management of patients with subclinical CS and subclinical PA has not been established. Therefore, we are observing her without medical therapy. Four years after diagnosis, no cardiovascular complications have been detected, including cerebral infarction, chronic kidney disease, cardiomegaly on echocardiography, and atherosclerosis on carotid ultrasonography. One important question is why the excessive hormone secretion did not affect the cardiovascular status of this patient. In this regard, we discuss several possible mechanisms including mineralocorticoid resistance and glucocorticoid sensitivity.

Key words: subclinical primary aldosteronism, subclinical Cushing's syndrome, adrenal incidentaloma, cardiovascular disease

INTRODUCTION

Subclinical Cushing's syndrome (CS) is characterized by a subclinical increase in cortisol secretion [1, 2]. In this condition, autonomous cortisol secretion exists, but the patients do not have the typical signs and symptoms of cortisol overproduction that are observed in the typical CS [1, 2]. Similarly, subclinical forms of primary aldosteronism (PA) are called subclinical PA [3]. This disease has been found in PA patients with mild hypertension and even in those with normotension [3]. Ito *et al*. noted that nearly 30 cases of subclinical PA had been reported in the English literature up to 2009 [3].

Recent improvements in and the widespread use of imaging studies have led to the detection of clinically silent adrenal masses, termed adrenal incidentalomas, in many examinations that are unrelated to adrenal disease [1–5]. When adrenal incidentalomas are encountered, it is necessary to assesse autonomous hormone production and rule out the possibility of malignancy. In this situation, approximately 5–20% of adrenal incidentalomas present subclinical CS [1, 2]. However, the prevalence of subclinical PA remains unknown [3].

Patients with subclinical CS lack specific symptoms of CS and present risk factors for cardiovascular disease, including diabetes mellitus, hypertension, or dyslipidemia related to the detrimental effects of chronic subtle cortisol excess [1, 2, 6]. Additionally, long-term exposure to an inappropriately elevated plasma aldosterone concentration (PAC) is well known to cause hypertension and target-organ dysfunction such as renal and cardiac dysfunction [7, 8].

We describe a case of subclinical PA and subclinical CS. This patient was referred to our hospital for the evaluation of an adrenal incidentaloma. She had no cardiovascular complications or risk factors for cardiovascular disease. In addition, the optimal management of patients with subclinical CS and subclinical PA has not been established [1–3, 6]. Thus, we observed her without medical therapy. We also discuss why excessive hormone secretion did not affect the cardiovascular status of this patient.

CASE REPORT

A 49-year-old woman was referred to our hospital for the evaluation of an adrenal tumor, which was found in medical checkup by chance (adrenal incidentaloma). She had no symptoms, including muscle weakness. This patient had no previous medical history and no family history of notable illness. The patient's height was 152.5 cm, and her body weight was 58.0 kg. Her blood pressure was 103/60 mmHg, with a pulse of 72 beats per minute. She had no Cushingoid features (i.e., moon face, buffalo hump, central obesity,

Toshiro SEKI, Division of Nephrology, Endocrinology and Metabolism, Department of Internal Medicine, Tokai University School of Medicine, 143 Shimokasuya, Iseharashi, Kanagawa 259-1193, Japan Tel: +81-463-93-1121 Fax: +81-463-91-3350 E-mail: tsekimdpdd@tokai-u.jp

Table 1 Routine laboratory examinations.

Urinalysis		Blood chemistry	
color	yellow	CRP	< 0.09 mg/dL [< 0.3]
pH	7.0	TP	6.9 g/dL [6.5–8.0]
protein	(−)	Alb	3.9 g/dL [3.9–4.8]
occult blood	(−)	AST	12 IU/L [< 30]
glucose	(−)	ALT	9 IU/L [< 35]
ketone body	(−)	LDH	136 IU/L [110–219]
		ALP	135 IU/L [100–310]
Hematological examination		γ-GTP	12 IU/L [< 35]
WBC	7500/μL [400–8000]	Na	141 mEq/L [136–145]
Neu	61.1% [40–70]	K	4.0 mEq/L [3.5–4.8]
Lym	29.7% [20–40]	Cl	108 mEq/L [98–108]
Mo	3.6% [3–8]	Ca	8.8 mg/dL [8.6–10.0]
Eo	4.9% [1–4]	P	3.2 mg/dL [2.5–4.5]
Ba	0.7% [0–1]	BUN	10 mg/dL [8–20]
RBC	409×10^4/μL [380–480]	Cr	0.53 mg/dL [0.5–0.8]
Hb	12.6 g/dL [11.5–15.5]	UA	3.7 mg/dL [3.0–6.0]
Ht	38.8% [34.0–42.0]	TG	51 mg/dL [50–150]
Plts	25.0×10^4/μL [14.0–40.0]	T-cho	157 mg/dL [140–220]
		HDL-cho	51 mg/dL [40–100]
		LDL-cho	97 mg/dL [< 120]
		Glucose	87 mg/dL [70–110]
		HbA1c	4.9% [4.3–5.8]

Abbreviations: [ ], reference range.

Table 2 Results of the circadian variation and overnight dexamethasone suppression tests for serum cortisol levels.

The circadian variation		
Time	8 am	11 pm
Cortisol (μg/dL)	11.7	3.3
ACTH (pg/mL)	< 2.0	11.3

The overnight dexamethasone suppression test		
Dexamethasone	1 mg	8 mg
Cortisol (μg/dL)	1.8	1.7
ACTH (pg/mL)	< 2.0	< 2.0

Abbreviations: ACTH, adrenocorticotropic hormone.

purple abdominal striae). Osteoporosis was not present, as evidenced by a normal lumbar dual energy X-ray absorptiometry (DXA) examination.

The routine laboratory examinations were within the normal ranges, including serum electrolytes and potassium (Table 1). An examination of hormone levels revealed normal circadian variation in serum cortisol levels (11.7 μg/dL at 8 am and 3.3 μg/dL at 11 pm; normal range, < 5 μg/dL at 11 pm, Table 2), and the plasma adrenocorticotropic hormone (ACTH) level was undetectable (< 2.0 pg/mL; normal range, 7.2-63.3 pg/mL). The plasma cortisol level was suppressed following the low-dose overnight dexamethasone suppression test for subclinical CS (1.8 μg/dL after 1 mg of dexamethasone; normal range, < 3 μg/dL, Table 2) but was not suppressed following the high-dose test (1.7 μg/dL after 8 mg of dexamethasone; normal range, < 1 μg/dL, Table 2). The PAC was normal (110 pg/mL, normal range, 30–159 pg/mL), and the plasma renin activity (PRA) was suppressed (0.1 ng/mL/hr, normal range, 0.3–5.4 ng/mL/hr). The aldosterone renin ratio (ARR) was greater than 200. Computed tomography (CT) scans of the abdomen showed bilateral adrenal tumors (Fig. 1 A-1, A-2). Adrenal scintigraphy revealed bilateral adrenal activity (Fig. 2). We performed confirmatory tests for PA. The captopril test and furosemide-upright test were positive, whereas the saline-loading test was negative (Table 3). To determine the laterality of the excessive cortisol or aldosterone secretion, we performed adrenal venous sampling. As shown in Table 4, the cortisol levels obtained from the right and left adrenal veins were 20.8 and 25.8 μg/dL, respectively, at baseline and 1,102 and 894.0 μg/dL, respectively, after ACTH stimulation (an IV bolus injection of 0.25 mg of ACTH). The respective aldosterone levels obtained from the right and left adrenal veins were 3,550 and 1,570 pg/mL (normal range, < 2,000 pg/mL, [9]), respectively, at baseline and 27,600 and 28,600 pg/mL (normal range, < 14,000 pg/mL, [9]), respectively, after ACTH stimulation (Table 4).

The patient has attended our hospital for four years. We have performed CT scans of the abdomen every

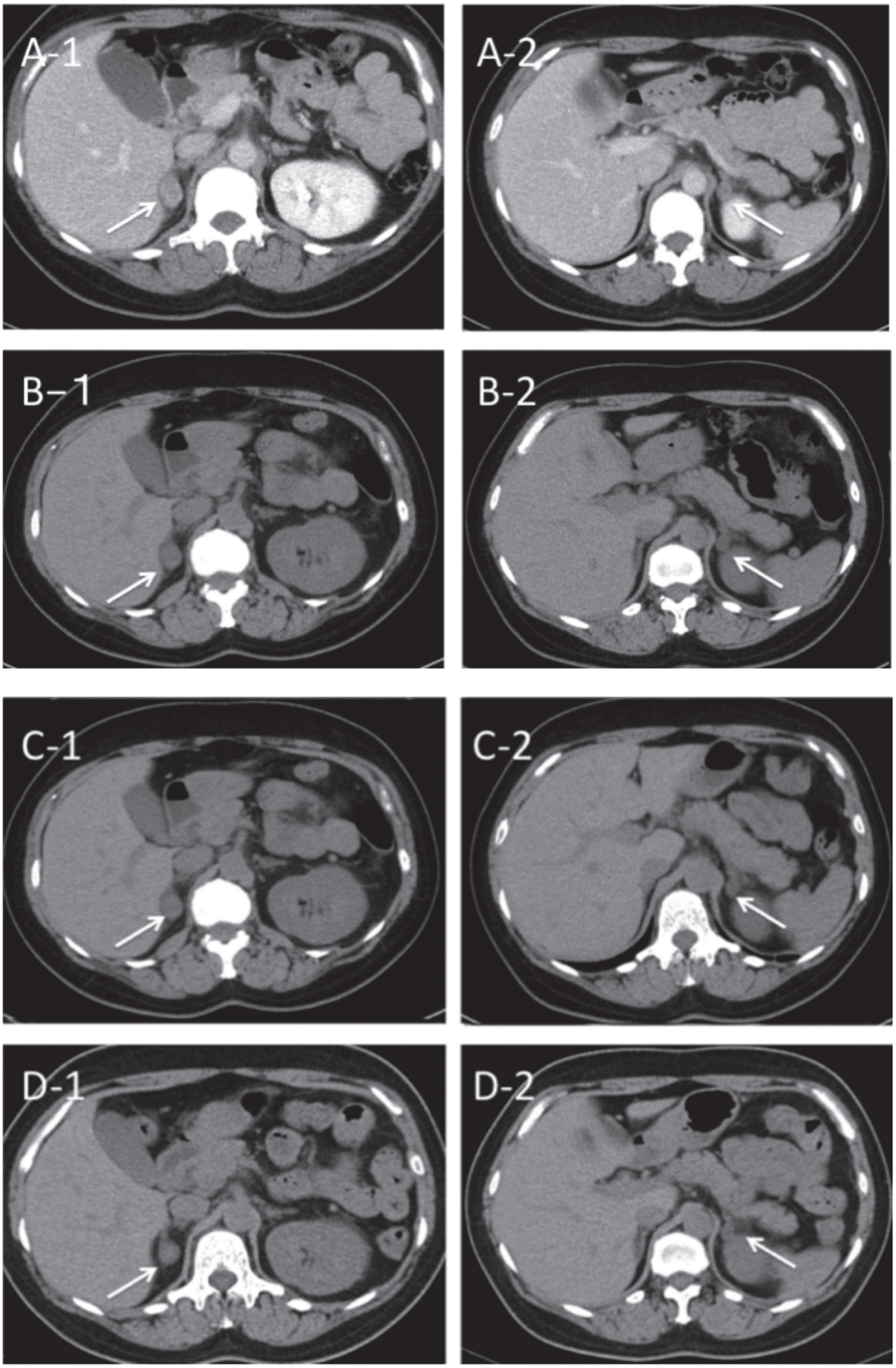

Fig. 1 Computed tomography (CT) scans of the abdomen. We performed CT scans of the abdomen every year (A-1 and A-2: first year, B-1 and B-2: second year, C-1 and C-2: third year, D-1 and D-2: fourth year). Bilateral adrenal tumors (arrows) and atrophied glands were observed. Both tumors were composed of well-circumambulated masses, without apparent irregularity on the surface or inside. The sizes of the bilateral adrenal tumors did not change, and there were no changes in the low-density area that indicates fat tissue inside either tumor during the four-year period.

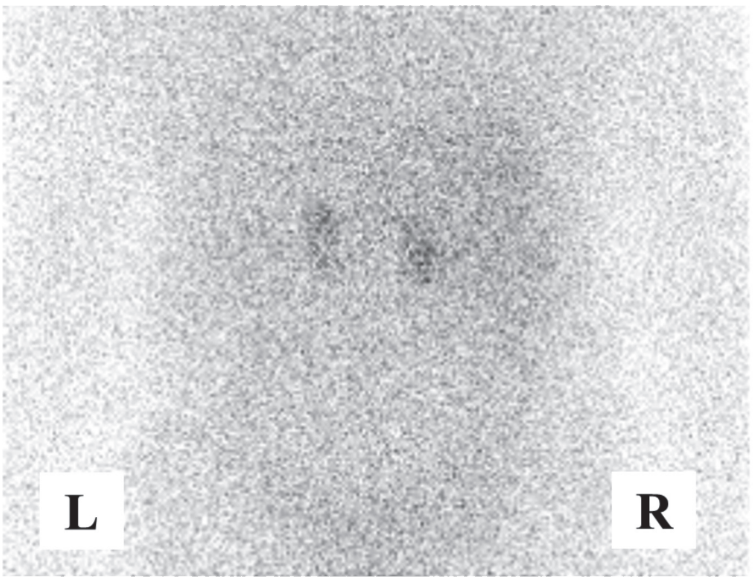

Fig. 2 Adrenal scintigraphy of the bilateral adrenal tumors. Adrenal scintigraphy using ^{131}I-adosterol showed bilateral uptake of the tracer.

Table 3 Results of the confirmatory tests for primary aldosteronism.

Captopril test					
min	0	60	90		
PAC (pg/mL)	90.7	76.1	84.7		
PRA (ng/mL/hr)	2.5	0.4	0.2		
ARR	36.3	190.3	423.5		
Furosemide-upright test					
min	0			120	
PAC (pg/mL)	61.6			166	
PRA (ng/mL/hr)	< 0.1			0.3	
Saline-loading test					
min	0				240
PAC (pg/mL)	44.4				35.3
PRA (ng/mL/hr)	0.5				0.3

Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, PAC/PRA ratio.

Table 4 Results of adrenal venous sampling.

	Cortisol (μg/dL)		Aldosterone (pg/mL)	
	RAV	LAV	RAV	LAV
Baseline	20.8	25.8	3550	1570
After ACTH 250 μg	1102	894.0	27600	28600

Abbreviations: RAV, right adrenal vein; LAV, left adrenal vein; ACTH, adrenocorticotropic hormone.

year. In the first year, the right adrenal tumor had a diameter of 18 mm, and the left had a diameter of 13 mm. On the annual CT scans, the sizes of the bilateral adrenal tumors have remained unchanged, and there has been no change in the low-density area that indicates fat tissue inside either tumor (Fig. 1). There has been no change in the serum levels of ACTH or cortisol or in the PAC or PRA (Fig. 3). In addition, the serum the potassium level has remained within the normal range (Fig. 4), and Cushingoid features have not been observed. These findings indicate that her hormonal condition has remained unchanged over the four-year period.

Furthermore, she has maintained office blood pressure readings in the normal range. Her systolic blood pressure has been in the range of 90–110 mmHg, and her diastolic blood pressure has been in the range of 60–70 mmHg with no medication (Fig. 4). She has maintained normal home blood pressure values (data not shown). Her body weight has remained unchanged, at approximately 58 kg. The fasting plasma glucose levels have been in the range of 90–100 mg/dL, and the HbA1c level has been normal, at 4.9–5.6%; thus, glucose intolerance has not been observed (Fig. 4). Low-density lipoprotein (LDL) cholesterol and triglycerides have remained within normal ranges, and dyslipidemia therefore not occurred (Fig. 4). Albuminuria has remained in the normal range, and elevation in plasma

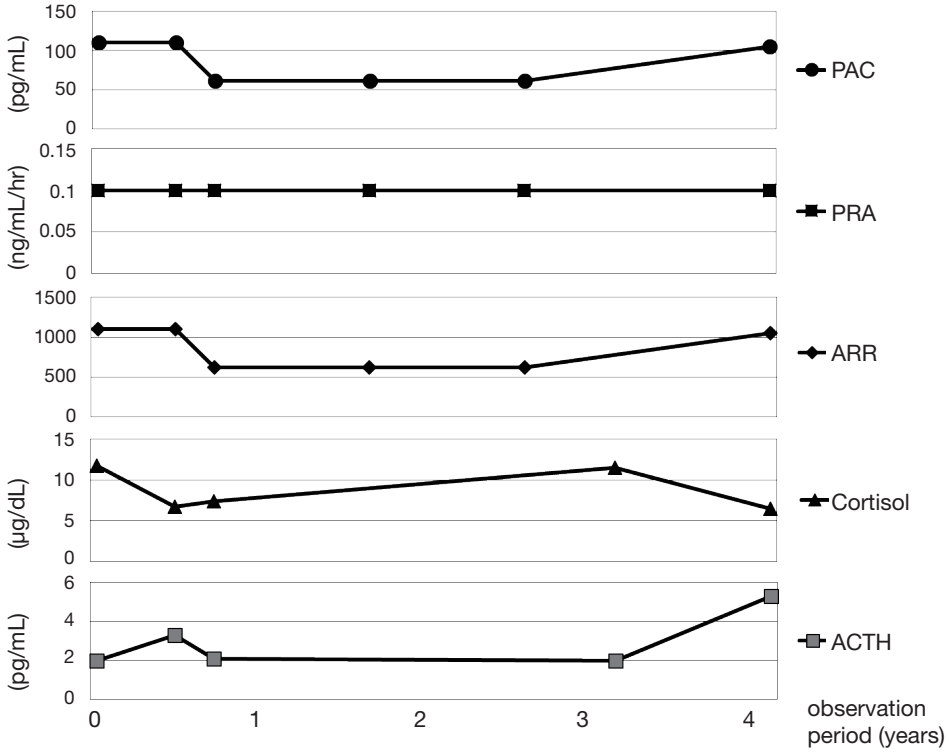

Fig. 3 Course of endocrinological examinations. The plasma aldosterone concentration (PAC) remained in the normal range, and the plasma renin activity (PRA) was suppressed. Furthermore, the aldosterone renin ratio (ARR) was always greater than 200. The plasma cortisol levels were in the normal range, and the plasma adrenocorticotropic hormone (ACTH) levels were repeatedly suppressed.

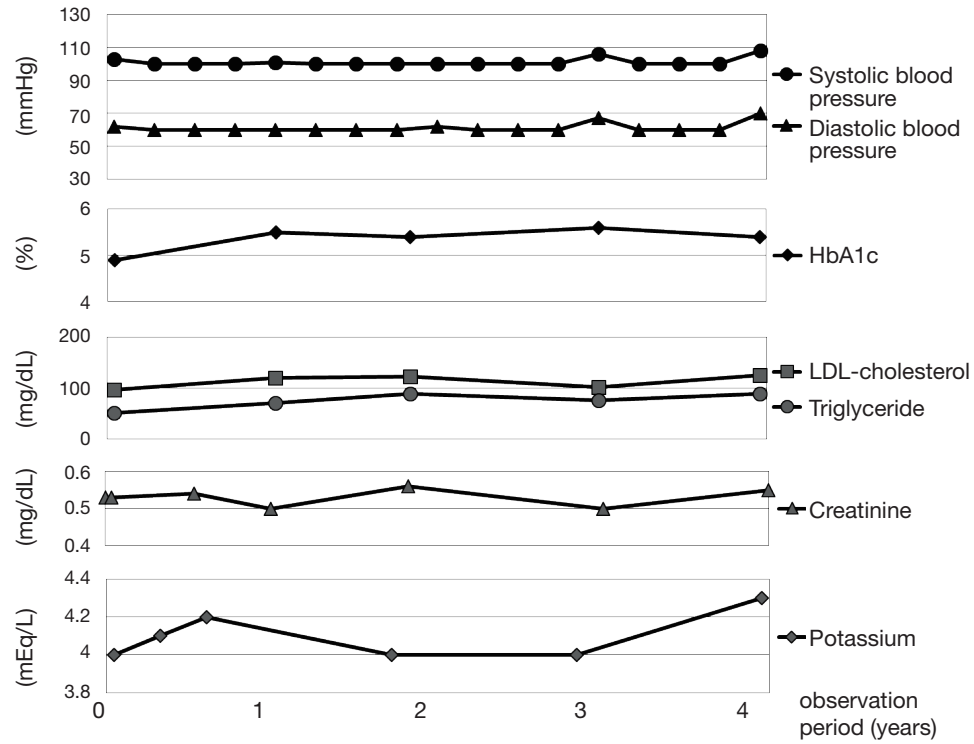

Fig. 4 Course of findings for cardiovascular complications. The patient maintained office blood pressure readings in the normal range. HbA1c levels were normal. Low-density lipoprotein (LDL) cholesterol and triglycerides were in the normal ranges. Elevation in plasma creatinine and hypokalemia were not observed during the four-year period.

creatinine associated with chronic kidney disease (CKD) has not occurred (Fig. 4). We also performed echocardiography on the patient annually, and the observed wall motion has been normal, with a 70–80% left ventricular ejection fraction. Additionally, cardiomegaly has not appeared on echocardiography, and ischemic heart disease has not been observed during the clinical course. On carotid ultrasonography, plaques have not been observed on either side of the carotid artery, and vascular stenosis has not been observed. As shown by the above clinical course, she has not presented with risk factors for cardiovascular disease or with cardiovascular complications during the four years of observation. She is being followed by the Nephrology, Endocrinology and Metabolism Outpatient Division.

DISCUSSION

As shown in the case report section, the results of adrenal venous sampling indicated that both adrenal glands produced excessive aldosterone and that laterality of the cortisol secretion was not present, as discussed in our previous reports [10, 11]. Based on the above findings, we made a diagnosis of subclinical PA caused by both adrenal glands and subclinical CS caused by the bilateral adrenal tumors. Interestingly, this patient had no risk factors for cardiovascular disease. In addition, the optimal management of patients with subclinical CS and subclinical PA has not been established [1–3, 6]. Thus, we decided to observe her without medical therapy.

Patients with subclinical CS lack specific symptoms of CS but chronic exposure to subtle cortisol excess may be associated with risk factors for cardiovascular disease including diabetes mellitus, hypertension, or dyslipidemia [1, 2, 6]. In fact, the cause of death is mostly related to cardiovascular events in patients with subclinical CS [12, 13]. However, it remains unknown whether the mortality rate is higher than that of the general population [12, 13]. In addition, there is no evidence to suggest a relationship between subclinical cortisol overproduction and morbidities associated with risk factors for cardiovascular disease [1, 2, 14]. Recently, Zografos *et al*. described the difficulty in assessing a cause and effect relationship between subclinical cortisol overproduction and potentially related morbidities [2]. They suggested that three possibilities could underlie this difficulty: (a) the variability of clinical symptoms depending on the degree and duration of cortisol overproduction, (b) interindividual sensitivity to cortisol excess, and (c) the intermittent cortisol overproduction [2]. In our patient, no risk factors for cardiovascular disease or cardiovascular complications have been detected at four years after diagnosis. Factor (b) may apply to our case because the patient's hormonal condition (ACTH and cortisol) has remained unchanged over the four years of observation. However, the long-term observation of this patient may be still required to resolve the above difficulties.

It is well known that long-term exposure to an inappropriately elevated PAC can induce hypertension and target-organ dysfunction [7, 8]. However, in our patient, hypertension and cardiovascular complications such as cerebral infarction, chronic kidney disease, cardiomegaly on echocardiography, or atherosclerosis on carotid ultrasonography have not been detected at four years after diagnosis. Therefore, the critical issue is why excessive aldosterone secretion did not affect the cardiovascular status of this patient. In this regard, Ito *et al*. recently reviewed several possible mechanisms of normotensive PA (termed subclinical PA) [3]. They demonstrated that five possibilities could explain the causes of this normotensive form of PA: (a) an early state of the disease, (b) a mild form of the disease, (c) a low spontaneous baseline blood pressure level, (d) low sodium intake and/or high consumption of green tea, or (e) a low body mass index (BMI) [3].

Factors (a) and (b) do not apply to our case because the patient's hormonal condition (PAC and PRA) and blood pressure level have remained unchanged during the observation period. However, the long-term observation of our patient is still required to resolve this issue, as shown in a previous report [15]. Factors (d) and (e) are unlikely to be the mechanisms underlying the normotension in our patient based on her medical history and physical findings (salt intake: approximately 11 g/day and BMI: approximately 24.9). Factor (c) indicates that excessive aldosterone secretion induces relative hypertension, but the blood pressure may remain in the normal range because of very low spontaneous baseline blood pressure levels [3]. In fact, many previous reports have demonstrated that some environmental factors or genetic diseases that cause vasodilation and/or sodium wasting can mask the effect of excessive aldosterone secretion and lower blood pressure [16–18]. Additionally, mineralocorticoid resistance can mask the blood pressure-raising effect of aldosterone overproduction [18–21]. It is likely that factor (c) may apply to our case. However, many detailed examinations of environmental or genetic factors are required to confirm this mechanism.

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