Case Report

A Case of Primary Aldosteronism Associated with Renal Artery Stenosis and Preclinical Cushing's Syndrome

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We identified a left adrenal tumor, left renal atrophy, and left renal artery stenosis (RAS) in a 52-year-old man by MRI/magnetic resonance angiography (MRA) during evaluation of hypertension. Laboratory tests revealed hypokalemia, a high plasma aldosterone concentration (PAC), low plasma renin activity (PRA), and normal plasma cortisol. An excessive response of aldosterone and cortisol to adorenocorticotrophic hormone (ACTH) was found upon selective sampling of the left adrenal vein. Selective renal venous sampling showed a left/right renal venous PRA ratio of 1.7. A dexamethasone (8 mg) suppression test showed insufficient suppression of cortisol. We diagnosed this patient as having aldosterone-producing adrenal adenoma (APA) associated with renovascular hypertension (RVH) and preclinical Cushing's syndrome. As an initial treatment, percutaneous transluminal renal angioplasty was performed. Postoperatively, the patient's blood pressure decreased. One month later, the tumor was removed by complete laparoscopic left adrenalectomy. Postoperatively, blood pressure decreased further and both PAC and PRA were normalized. However, antihypertensive therapy could not be completely stopped. The renal dysfuntion that occurred prior to treatment seemed to prevent complete normalization of blood pressure. (*Hypertens Res* 2008; 31: 1669–1675)

***Key Words*: aldosterone-producing adenoma (APA), primary aldosteronism (PA), renal artery stenosis (RAS), renovascular hypertension (RVH), preclinical Cushing's syndrome**

Introduction

Aldosterone-producing adenoma (APA), a typical cause of primary aldosteronism (PA), and renovascular hypertension (RVH) due to renal artery stenosis (RAS) are two forms of secondary hypertension that can be cured completely. The renin profile of each disease demonstrates contrasting features, as PA is a typical example of low renin hypertension, whereas RVH caused by unilateral RAS is a typical form of high renin hypertension.

With recent developments in imaging and radioimmunoassay methods, diagnosis of both diseases has become easier. Recently, the frequency of RAS due to atherosclerosis has increased and this is one of the known causes of RVH (*1*). It is also clear that continuous hypertension caused by PA induces renal atherosclerosis at a high frequency (*2*). Therefore, the possibility exists that PA could be independently or secondarily associated with atherosclerotic RAS–cased RVH. However, there have been few case reports about PA associated with RVH or RAS. In fact, we have only found 18 studies published since 1960 (*3–20*) (Table 1). A few cases of APA associated with preclinical Cushing's syndrome have been reported recently (*21*, *22*). Here we report an interesting

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Table 1. Reported Cases of Concomitantly Occurring PA and RVH or RAS

Author	Age/sex	Adrenal lesion	Renal lesion	Operation performed	Outcome
Hoet and Molineaux (*3*)	54/M	Lt. adenoma	Lt. atrophic kidney	None	Died from CH
Laidlaw *et al*. (*4*)	55/M	Blt. hyperplasia	Lt. renal occulison Lt. atrophic kidney	Blt. adrenalectomy	Died on the postoperative 8th day
Bloch (*5*)	54/F	Rt. adenoma	Blt. RAS Rt. atrophic kidney	Lt. renal bypass	Died from AMI immediately after surgery
Christenson *et al*. (*6*)	53/F	Rt. adenoma	Blt. RAS Rt. atrophic kidney	Rt. adrenalectomy	Poor postoperative BP control
Mills *et al*. (*7*)	41/F	Rt. adenoma	Blt. RAS	Rt. adrenalectomy →The extensive denervation of Rt. renal artery	Normotensive
Vircburger *et al*. (*8*)	35/M	Blt. adenoma	Rt. RAS	Rt. PTRA→Lt. adrenalectomy →Rt. nephrectomy/ Rt. adrenalectomy	Normotensive
Santangelo *et al*. (*9*)	64/F	Lt. adenoma	Lt. renal artery occlusion Rt. RAS	Rt. aortorenal bypass/ Lt. nephrectomy →partial Rt. adrenalectomy	Reduced dosage of drug
Takenaka *et al*. (*10*)	46/F	Lt. adenoma	Lt. renal artery occlusion	Lt. nephrectomy/ Lt. adrenalectomy	Normotensive
Ghilardi *et al*. (*11*)	45/F	Lt. adenoma	Lt. RAS	Grafting of Lt. renal artery/ Lt. adrenalectomy	Normotensive
Cheung *et al*. (*12*)	32/F	Rt. adenoma	Blt. RAS	Rt. adrenalectomy	Reduced dosage of drug
Stokes *et al*. (*13*)	51/M	Blt. hyperplasia	Lt. RAS	Lt. PTRA→Lt. adrenalectomy	Normalized blood pressure (reduced dosage of drug)
Chowdhury and Lasker (*14*)	22/F	Rt. adenoma	Lt. RAS	Rt. adrenalectomy→Lt. PTRA	BP155/72 (drug administration unknown)
Mattix *et al*. (*15*)	36/F	Rt. adenoma	Lt. RAS	Lt. PTRA→Rt. adrenalectomy	Normotensive
Mansoor *et al*. (*16*)	73/M	Blt. hyperplasia	Lt. RAS	Lt. PTRA/spironolactone	Normnotensive
	76/F	Blt. hyperplasia	Blt. RAS	Blt. iliac-renal bypass/ spironolactone	Normnotensive
Grodny *et al*. (*17*)	42/M	Lt. adenoma	Blt. RAS	Lt. PTRA→Lt. adrenarectomy →Rt. PTRA	Reduced dosage of drug
Karagiannis *et al*. (*18*)	58/F	Blt. hyperplasia	Blt. RAS	Blt. PTRA/stent in Rt. renal artery	Normotensive (spironolactone 25 mg only)
Tanemoto *et al*. (*20*)	64/F	Rt. adenoma	Lt. RAS	Stent in Lt. renal artery →Rt. adrenalectomy	Reduced dosage of drug
Present report	52/M	Lt. adenoma	Lt. RAS	Lt. PTRA→Lt. adrenarectomy	Reduced dosage of drug

Pizzolo *et al*. (*19*) reported 7 cases of PA (2 cases of APA) in 52 patients with post successful angioplasty of RAS in 2005, however they have not described in detail with respect to localization of APA and RAS, and selection for treatment methods in individual cases. M, male; F, female; PA, primary aldosteronism; RVH, renovascular hypertension; RAS, renal artery stenosis; Blt., bilateral; Rt., right; Lt., left; PTRA, percutaneous transluminal renal angioplast; CH, cerebral hemorrhage; AMI, acute myocardial infarction; BP, blood pressure.

case of APA associated with both RAS and preclinical Cushing's syndrome. Previous cases are also reviewed and compared with our patient.

Case Report

The patient was a 52-year-old man. On routine physical examination, hypertension and renal dysfunction were detected and he was referred to our hospital. He had been treated with antihypertensive agents (nifedipine 20 mg and atenolol 50 mg) for the past 5 years. No abnormalities were found on physical examination at the initial visit and his blood pressure was 122/79 mmHg when on medication. There was no cardiomegaly on the chest X-ray film, no left ventricular hypertrophy on the electrocardiogram, and no hypertensive changes of the ocular fundi.

General laboratory tests did not reveal any notable abnormalities, except for mild elevation of serum creatinine (sCre)

Table 2. Hormonal Examinations

Captopril 50 mg renin provocation test

	Pre	1 h	2 h
BP (mmHg)	134/85	134/83	134/85
PRA (ng/mL/h)	<0.1	<0.1	0.2
PAC (pg/mL)	150	130	170

Diurnal rhythm of ACTH and cortisol and dexamethasone suppression test

	6th hour	23rd hour	Dex 1 mg	Dex 8 mg
ACTH (pg/mL)	7.1–20.6	<5.0	<5.0	<5.0
Cortisol (μg/dL)	13.9–21.8	3.1	2.1	3.3

Urinary excretion of free cortisol 12.6 μg/d
Urinary excretion of 17OHCS 7.3 mg/d Urinary excretion of 17KS 5.7 mg/d
Plasma DHEAS 1,130 ng/mL

Plasma epinephrine 12 pg/mL Plasma norepinephrine 347 pg/mL
Urinary excretion of epinephrine 8.8 μg/d Urinary excretion of norepinephrine 223 μg/d

Captopril 50 mg loaded renal venous PRA (ng/mL/h)
Rigt renal vein (R) 0.3 Left renal vein (L) 0.5 Ratio (L/R) 1.7

ACTH 0.25 mg loaded adrenal venous PAC and cortisol

	IVC (upper)	IVC (lower)	Rigt adrenal vein	Left adrenal vein
PAC (pg/mL)	490	270	860	11,000
Cortisol (μg/dL)	30	19	43	427

BP, blood pressure; PRA, plasma renin activity; PAC, plasma aldosterone concentration; ACTH, adrenocorticotrophic hormone; Dex, dexamethasone.

to 1.07 mg/dL, a reduction of serum potassium to 3.6 mEq/L, and microalbuminuria (110 mg/d). The 24-h creatinine clearance (Ccr) was 67.3 mL/min. Captopril (50 mg)-loaded ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) renography/renoscintigraphy revealed a decrease of left renal function, with the estimated GFR of the left kidney being 23.6 mL/min *vs*. 60.5 mL/min for the right kidney.

Before the hormone studies, administration of atenorol was stopped. His blood pressure rose to over 160/100 mmHg, so the dosage of nifedipine was increased from 20 mg to 60 mg to maintain blood pressure below 140/90 mmHg. Table 2 shows the results of the hormone test. Plasma renin activity (PRA) was reduced to less than 0.1 ng/mL/h (normal range: 0.3 to 2.9 ng/mL/h) and the plasma aldosterone concentration (PAC) was 150 pg/mL (normal range: 30 to 120 pg/mL). In the captopril (50 mg) renin provocation test, PRA rose slightly from <0.1 ng/mL/h to 0.2 ng/mL/h, and PAC increased from 150 pg/mL to 170 pg/mL. The early morning plasma concentration of adrenocorticotrophic hormone (ACTH) was 7.1 to 20.6 pg/mol (normal range: 7.4 to 55.7 pg/mL), while plasma cortisol was 13.9 to 21.8 μg/dL (normal range: 4.0 to 18.3 μg/dL). At 23:00, the plasma ACTH level was less than 5.0 pg/mL and that of plasma cortisol was 3.1 μg/dL, indicating a normal diurnal rhythm for both. In the dexamethasone (1 mg and 8 mg) suppression test, ACTH was completely suppressed to less than 5.0 pg/mL, whereas cortisol levels declined to only 2.1 μg/dL and 3.3 μg/dL, respectively, suggesting insufficient suppression of cortisol secretion. Neither the corticotropin-releasing factor (CRF) test nor the ACTH test was performed. Urinary catecholamine, 17OHCS, 17KS, and free cortisol were all found to be within the normal range (Table 2).

Abdominal MRI showed a nodular lesion (18 mm) in the left adrenal gland and a small left kidney (87 mm) (Fig. 1). There were no morphological abnormalities of the right adrenal gland or the right kidney. Abdominal magnetic resonance angiography (MRA) showed severe stenosis at the central portion of the left renal main artery. Regarding the ^{131}I-6-β-iodomethyl-norcholesterol adrenal scintigraphy, no difference in defined aggregation was found between the left and right sides. Cranial MRI did not detect any abnormalities of the pituitary gland.

Abdominal aortography and selective renal arteriography showed severe stenosis of the main left renal artery (Fig. 2), while there were no abnormalities of the right renal artery. Prior to abdominal aortography, selective renal venous and adrenal venous sampling was performed. After captopril (50 mg) administration, the left/right renal venous PRA ratio was

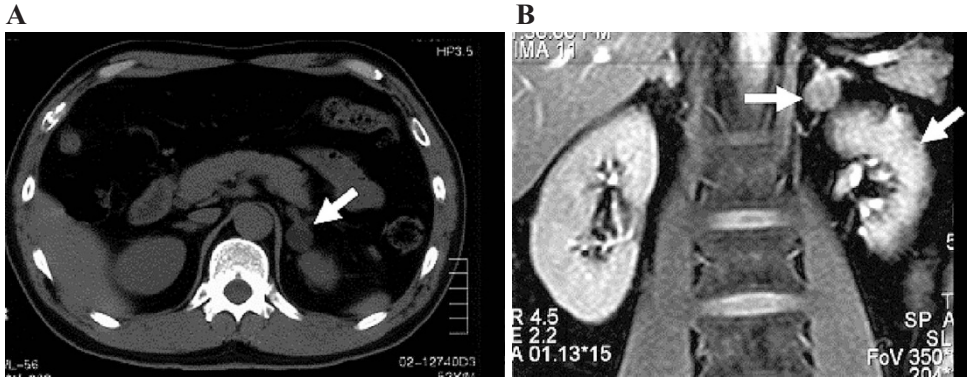

Fig. 1. *Abdominal MRI transvers section (A) and coronary section (B) show a left adrenal tumor (18 mm) and small left kidney (87 mm).*

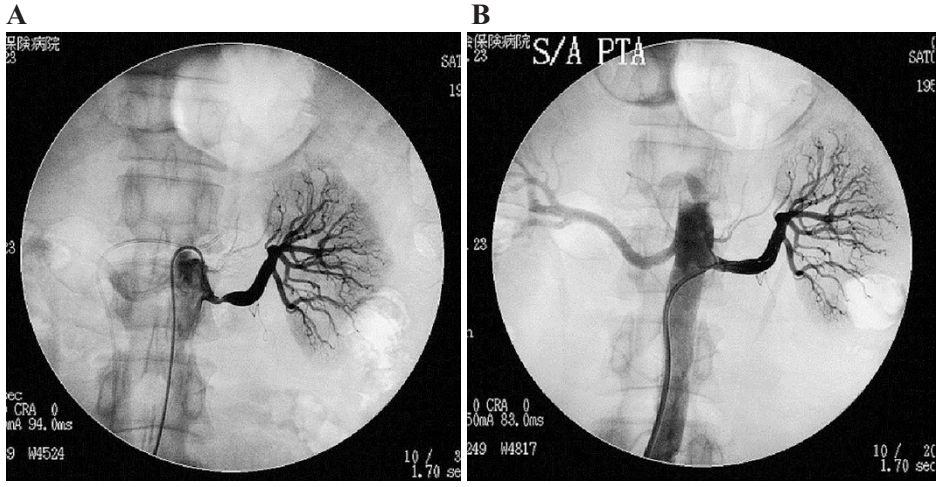

Fig. 2. *Selective renal arteriography of the left renal artery prior (A) and following (B) angioplasty. A high degree of stenosis of the main left renal artery, narrowing of renal peripheral arteries and thinning of the renal cortex are seen. Collateral arteries are not seen.*

1.7 (left kidney: 0.5 ng/mL/h *vs*. right kidney: 0.3 ng/mL/h), suggesting that renin secretion was greater on the left side. At 15 min after intravenous injection of 0.25 mg of tetracosactide acetate, the left adrenal venous PAC level was 11,000 pg/mL and the cortisol level was 427 μg/dL, while the right adrenal venous PAC level was 860 pg/mL and cortisol level was 43 μg/dL (Table 2). These findings suggested excessive secretion of aldosterone and cortisol from the left adrenal gland. Based on the above results, this patient was diagnosed as having APA and preclinical Cushing's syndrome due to a left adrenal adenoma associated with RVH caused by left RAS.

Treatment was conducted in two stages. Initially, left RAS was dilated by percutaneous transluminal renal angioplasty (PTRA) (Fig. 2). After PTRA, blood pressure decreased rapidly from 130 to 110 mmHg (systolic) and from 90 to 70 mmHg (diastolic). Nifedipine (60 mg/d) was stopped on the 6th postoperative day and cilnidipine (10 mg/d) was started. Since blood pressure was maintained in the range 102 to 122 mmHg (systolic) and 59 to 75 mmHg (diastolic) during the following 7 d, cilnidipine was temporarily stopped. However, blood pressure then rose to a range of 130 to 145 mmHg (systolic) and 78 to 89 mmHg (diastolic) from the 2nd day after stopping cilnidipine, so cilnidipine was restarted at 10 mg/d to maintain blood pressure at 110 to 130 mmHg (systolic) and 70 to 80 mmHg (diastolic). One month later, complete laparoscopic left adrenalectomy was performed. Since blood pressure decreased postoperatively, cilnidipine was stopped as of the 3rd day. However, blood pressure tended to rise again, so cilnidipine (10 mg/d) was restarted beginning with the 8th postoperative day.

The resected left adrenal gland contained numerous tumors of varying sizes (Fig. 3). Small nodules were found outside the capsule. The attached adrenal cortex did not show atro-

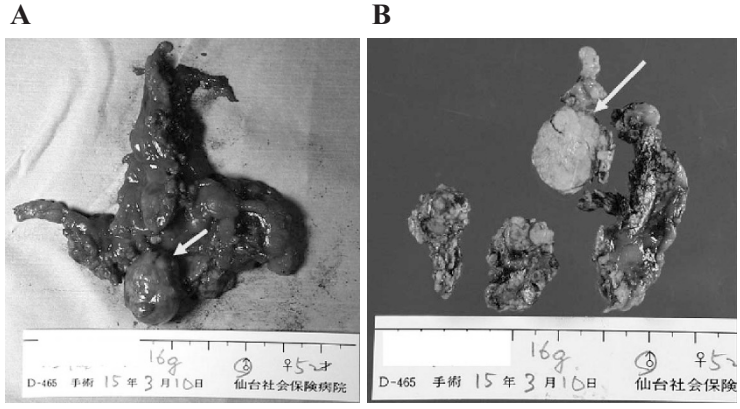

Fig. 3. *Gross appearance of a resected adrenal tumor (A: a surface, B: a cut section). Resected left adrenal tumor weighing 16 g. Multiple nodules (maximum 18 mm, minimum 5 mm in diameter) are seen.*

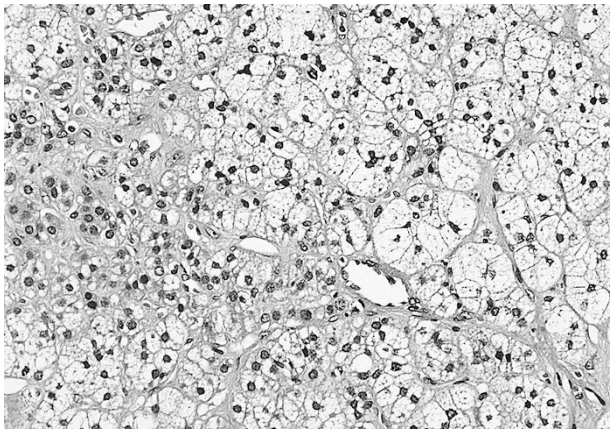

Fig. 4. *Microscopic appearance of resected adrenal tumor. The tumor consisted predominantly of large and clear cells. Also, compact cells containing granular materials are partially seen.*

phy. Histopathological examination was performed in only the largest tumor (18 mm). It was found to be an adrenal cortical adenoma that consisted predominantly of large and clear cortical cells, with compact cortical cells containing granular material in some parts. These were arranged in a cord-like or bushy-like state. A relatively small nucleus was found in dominant and a large nucleus in part (Fig. 4). Staining of the tumor for aldosterone- or cortisol-synthesizing enzymes was not performed.

After surgery, PAC was normalized rapidly to 86 pg/mL within 3 d and PRA was normalized slowly to 0.4 ng/mL/h by the 3rd postoperative month. Unfortunately, the dexamethasone suppression test was not performed after surgery.

Discussion

The prevalence of RVH among hypertensive patients is assumed to be approximately 1–5% (*23*, *24*), while the prevalence of PA is approximately 1–2% (*25*, *26*). Since these are independent diseases, the possibility of them coexisting in the same hypertensive patient is statistically 1–10 out of 10,000 patients. As mentioned in the Introduction, PA induces renal atherosclerosis, which is a cause of RAS, at a high frequency (*2*). In fact, Beevers *et al*. detected atherosclerotic RAS as a cause of RVH in 10 (7.4%) out of 136 cases of APA (*27*), while Ghilardi *et al*. reported RVH in one (5.8%) out of 17 cases of APA (*11*). Therefore, the possibility always exists that PA could be independently or secondarily associated with RVH caused by atherosclerotic RAS. In addition, although the frequency may be low, the simultaneous occurrence of both diseases should be considered as a cause of refractory hypertension. That is, if hypertension persists even after removal of an APA, latent RVH should be suspected. Conversely, if hypertension is still detected after successful dilation of RAS, latent PA should be suspected (*17*, *19*).

In the present case, whether or not RVH was caused by left RAS remains questionable. However, the patient's blood pressure decreased rapidly after dilation of the left RAS and the dosage of antihypertensive drugs could be reduced, which strongly suggests the presence of RVH due to left RAS. In general, patients with unilateral RVH have a high PRA, which was not found in our current case. However, PRA is not always high in RVH. For example, in the presence of ischemic renal dysfunction due to advanced unilateral RAS or bilateral RAS, volume-dependent hypertension occurs and PRA falls to a low level (*28*, *29*). In addition, β-blockers such as atenolol inhibit renin secretion. In the present patient, volume-dependent hypertension induced by hyperaldosteronism and renal dysfunction, as well as long-term administration of atenolol, were assumed to have modified the PRA. PRA had

been measured in 15 previous cases and two patients showed levels of less than 0.1 ng/mL/h (*12*, *20*). This suggests that PRA is not always high in this complex physiological state.

It would be interesting to determine whether the onset of APA or RVH was earlier in the present case. The hypothesis of "tertiary aldosteronism" has been proposed (*30*). This states that angiotensin II being elevated continuously by RAS overstimulates aldosterone synthesis in the adrenal gland, so that the adrenal escapes from feedback regulation of aldosterone synthesis, but there is no direct evidence to support such a hypothesis at this time (*31*). Therefore, it seems reasonable to consider that the two conditions occurred independently in our patient, as reported previously. In the current case, hypokalemia was mild and the aldosterone concentration was not so high, so APA was assumed to be of recent onset. On the other hand, the diameter of the left kidney was less than 9 cm, indicating that atrophy was advanced, so left RAS may have been present for a long period. Thus, we assumed that RAS occurred first and RVH second, with the onset of APA following later.

We prioritized the treatment of RAS by PTRA over laparoscopic adrenalectomy because we thought that the less invasive treatment should be done first. Whether intervention for RAS or adrenalectomy was performed first depended on the circumstances in past reports (Table 1). Although very few patients could stop antihypertensive therapy after surgery, hypertension could be controlled more easily compared with the preoperative state. In the present case, blood pressure fell both after dilation of RAS and removal of the APA, so that antihypertensive therapy was successfully reduced (but not completely stopped). According to our long-term surveillance of patients after APA surgery, if renal dysfunction exists prior to the operation (24 h Ccr $<$ 70 mL/min), it is difficult to completely stop drugs for hypertension after surgery (*32*). Another study including investigation by renal biopsy has shown that if pathological hypertensive renal dysfunction is present, it is difficult to normalize blood pressure after APA resection (*2*). Thus, the renal dysfunction that occurred prior to treatment in our patient seemed to prevent the complete normalization of blood pressure.

Our patient was assumed to have APA associated with preclinical Cushing's syndrome, and similar cases have been reported recently (*21*, *22*). The mechanism by which APA may acquire autonomous production of cortisol was reported in detail elsewhere (*21*), so it will not be discussed here.

Suzuki *et al*. previously reported that most of small adrenocortical tumors have the capacity to produce biologically active adrenal hormones, which was revealed by immunolocalization of steroidogenic enzymes (*33*). Also, Watanabe *et al*. reported bilateral APA in two patients diagnosed by immunohistochemical analysis of steroidogenic enzymes (*34*). Thus, we speculate that numerous tumors of varying sizes observed in the left adrenal gland were hormonally functional to some degree.

Conclusion

A rare case of APA associated with RAS and preclinical Cushing's syndrome was reported. With the development of better diagnostic methods, diagnosis of PA and RAS has become easier. Also, the occurrence of RVH due to atherosclerotic RAS has increased along with the increase in the population of elderly patients. Thus, the chance of encountering patients with simultaneous occurrence of PA and RVH seems to be increasing.

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