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Asymptomatic Normotensive Primary Aldosteronism Case Report

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SUMMARY We report a case of primary aldosteronism in a 30-year-old woman without hypertension or any other characteristic symptoms. The condition was first suspected by hypokalemia (2.6 mEq/liter), which was incidentally found by routine checkup. There was evidence of suppressed plasma renin activity (PRA) and elevated plasma aldosterone levels. However, the blood pressure never reached a hypertensive level, and the circulating blood volume was within a normal range. A functioning right adrenal tumor was diagnosed by adrenal scintigraphy, computerized x-ray tomography, and adrenal venography. Adrenal venous catheterization suggested an aldosteronoma, which was confirmed by lateralized hypersecretion of aldosterone. After removal of the benign adenoma, the biochemical abnormalities were corrected, yet the blood pressure remained much the same. Hypertension is not necessarily a sign of primary aldosteronism. (*Hypertension* 5: 240-243, 1983)

KEY WORDS • aldosteronoma • blood pressure • aldosterone • renin •
hypokalemia • scintigraphy • computerized tomography • venogram

THE classic form of primary aldosteronism is characterized by hypertension and hypokalemia.¹ There have also been cases with normokalemia.² Although the hypertension is usually mild and may fluctuate, it is only recently that consistently normotensive cases of primary aldosteronism, due to adrenal adenoma³⁻⁵ and idiopathic adrenal hyperplasia,⁶ have been reported. All of the normotensive cases of aldosteronoma reported had been detected due to some symptoms related to hypokalemia. Herein, we report a case of aldosteronoma without hypertension which was first suspected because of persistent hypokalemia but revealed no symptoms characteristic of hypokalemia.

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Case Report

A 30-year-old single female factory worker was referred to the outpatient clinic of the Third Division of the Department of Internal Medicine, Kyoto University Hospital, on May 14, 1980, for a checkup of her gastrointestinal system, as she had had recurring abdominal discomfort since childhood, e.g., nausea and stomach ache. Her family physician had never recorded any abnormality in her blood pressure and no one in her family had hypertension except a grandfather who had died of stroke. She was 161.2 cm tall and weighed 62.0 kg. Examinations including x-ray showed no significant abnormality in the gastrointestinal system. Instead, the blood chemistry showed hypokalemia (2.6 mEq/liter), and repeated examinations of the serum potassium always showed low values (2.6-2.8 mEq/liter), despite some potassium supplementation (potassium aspartate 2.7 g/day, i.e., 16.2 mEq/day of potassium for 5 weeks). Thus, we suspected hyperaldosteronism, although the patient had no complaint at this time. Up to the end of 1980, however, her blood pressure was within normotensive range, varying from 128/84 to 138/88 except for occasional recordings of borderline levels, e.g., 146/95 or 154/94.

Laboratory data are summarized in table 1. The plasma renin activity (PRA) was low and did not respond to stimulation by intravenous furosemide (40 mg) and 30-minute ambulation. The peripheral venous plasma aldosterone level was elevated while the patient was on an unrestricted or constant sodium (136 mEq/day) diet. Plasma cortisol level, and urinary 17-hydroxycorticosteroids and 17-ketosteroids excretions were normal. The electrocardiogram showed slightly depressed T waves and manifest U waves. No significant cardiac hypertrophy was detected by echocardiography. Hemodynamic studies by radiocardiography⁷ indicated no significant increase in circulating blood volume or in cardiac output. Abnormalities in the chest roentgenogram and eye ground were nil. The urinary concentrating capacity was slightly impaired, but the other renal functions were normal.

Administration of spironolactone (50 mg daily) for 5 weeks restored the serum potassium level to 3.2 mEq/liter, with no significant effect on the blood pressure. However, the patient could not tolerate the continued ingestion of spironolactone because of abdominal discomfort.

Adrenal Scintigraphy and Computerized X-ray Tomography

The adrenal scintigram, done 7 days after intravenous 1 mCi ¹³¹I-6 β -indomethyl-19-norcholesterol, showed a predominant uptake by the right adrenal gland. Repeated scintigraphy after 7 days on dexamethasone (3 mg daily) revealed no suppression of the uptake by the right adrenal (fig. 1). Computerized x-ray tomogram showed a low density mass approximately 2 cm in diameter at the site of the right adrenal gland.

Adrenal Venous Catheterization

The patient was hospitalized, and both adrenal veins were catheterized. The right adrenal venogram showed abnormal vessels surrounding an abnormal space, which indicated a tumor mass, while the left adrenal venogram was normal. The plasma aldosterone levels from the right and left adrenal veins and the brachial artery were 552, 71, and 26 ng/dl, and the cortisol levels were 13.3, 9.3, and 5.8 μ g/dl respectively.

Salt Loading and Indomethacin Administration

To determine if low salt intake was preventing this patient from hypertension and hypervolemia, 230 mEq of sodium in the form of isotonic saline was infused daily in addition to 136 mEq sodium which was included in the diet. The blood pressure showed no significant change. Total blood volume before and after the 4-day salt loading was 2.91 liter/m² and 2.77 liter/m² of body surface respectively, showing no significant change. Peripheral plasma aldosterone levels before and after the salt loading were 24 and 45 ng/dl respectively.

Indomethacin, an inhibitor of prostaglandin synthesis, was given orally (300 mg/day for 3 days and 600 mg/day for another 3 days). Here again, no significant

TABLE 1. Laboratory Data before Surgery

Laboratory test	Value	Normal range
Plasma aldosterone concentration (ng/dl)	18-38	(4.4-12.4)
Plasma renin activity (ng/ml/hr)		
at rest	0-0.1	(0.5-2.1)
after 40 mg furosemide i.v. and 30-min ambulation	0.1	
Serum levels of electrolytes		
Na (mEq/liter)	142-147	(135-146)
K (mEq/liter)	2.6-2.8	(3.6-4.8)
Cl (mEq/liter)	103-107	(96-110)
Blood gas analysis		
pH	7.46	(7.35-7.45)
Carbon dioxide pressure (mm Hg)	36	(35-45)
Oxygen tension (mm Hg)	87	(85-95)
Bicarbonate (mEq/liter)	27	(21-29)
Oxygen saturation (%)	93	(92-96)
Hemodynamic study		
Total blood volume (ml/kg)	66.2	(55.2-84.8)
Total blood volume (liter/m ²)	2.45	(2.02-2.98)
Cardiac output (liter/min)	6.24	(4.13-7.49)
Cardiac index (liter/min/m ²)	3.80	(2.67-4.59)
Stroke index (ml/m ²)	52.8	(37.4-64.6)
Renal plasma flow (ml/min)	580	(435-700)
Glomerular filtration rate (ml/min)	114	(85-150)
Fishberg's concentration test		
1st urine (mOsm/kg)	541	(>850)
2nd urine (mOsm/kg)	531	
3rd urine (mOsm/kg)	489	

change occurred in the blood pressure, thereby indicating no appreciable involvement of the prostaglandin system in keeping the blood pressure within normal range.

Vascular Sensitivity Tests

Intravenous infusion rates of norepinephrine and angiotensin II required to elevate the diastolic blood pressure by 20 mm Hg were 88 ng/kg/min (normal range: 150 to 450 ng/kg/min) and 9.2 ng/kg/min (normal range: 3.5 to 14.5 ng/kg/min) respectively. Thus, the responsiveness to norepinephrine was enhanced but that to angiotensin II was normal.

Surgery

On April 28, 1981, the right adrenal, bearing a yellowish tumor (2.0 \times 2.4 \times 2.2 cm, weighing 14.0 g), was excised. Histologically, the tumor was a benign adenoma and mostly consisted of clear cells mixed with some degenerative eosinophilic cells.

Postoperative Course

Serum potassium levels returned to normal (3.8 to 4.6 mEq/liter). On May 11, the peripheral plasma al-

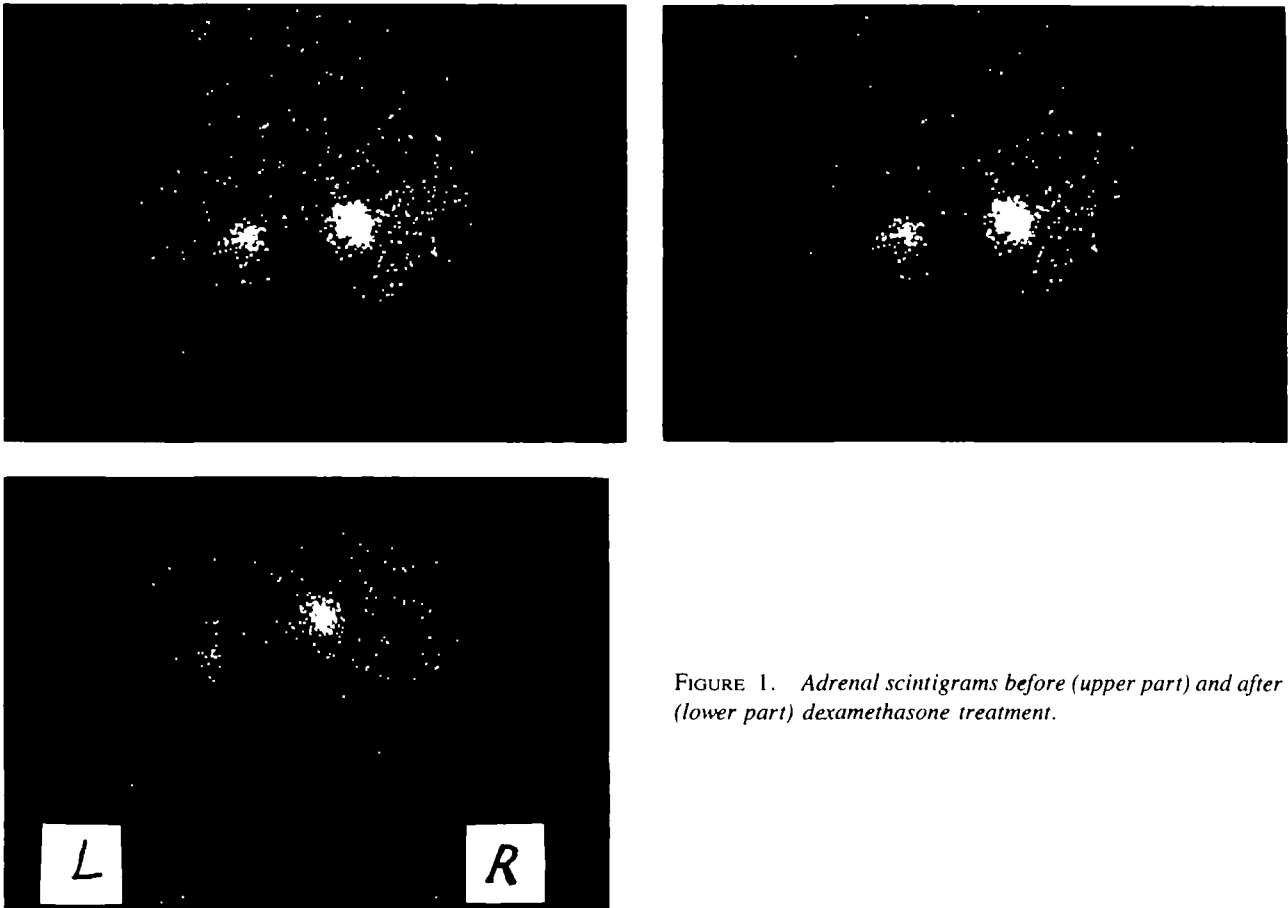


FIGURE 1. Adrenal scintigrams before (upper part) and after (lower part) dexamethasone treatment.

dosterone showed a normal value (12 ng/dl). The PRA was increased from 0.01 to 0.89 ng/ml/hr, responding to intravenous furosemide (40 mg) and 30 minutes of standing, and was elevated to 3.06 ng/ml/hr after a 3-day restriction of dietary sodium (2 g NaCl/day) and a 4-hour standing. The blood pressure varied from 126/84 to 134/92 mm Hg, showing no significant difference from the levels before the operation. This same level was recorded in December 1981. Radiocardiography done on December 23 revealed much the same findings as before the surgery.

Discussion

This patient did not have hypertension, an important sign of primary aldosteronism. However, the diagnosis was established from other characteristic features, i.e., benign adrenal adenoma, elevated plasma aldosterone level, suppressed plasma renin activity, and hypokalemia. The reason for the absence of hypertension has not been revealed in any of the cases of normotensive primary aldosteronism reported so far.³⁻⁶ It is also obscure in the present case. Lack of hypervolemia in this patient does not explain the lack of hypertension, since many patients with full-blown primary

aldosteronism have been shown to have normal circulating blood volumes. One possibility is that the condition was too mild to develop hypertension as well as potassium depletion severe enough to show characteristic symptoms. However, we have treated some cases of hypertensive primary aldosteronism that had a similar degree of hypokalemia without characteristic symptoms. The presence of some degenerative changes in the tumor may suggest that the condition might once have been more severe. In spite of careful questioning, however, she denied any history of hypertension or symptoms indicating hypokalemia. The negative findings in the salt loading test eliminated the possibility that a low salt intake may have prevented the development of hypertension. From the negative response to indomethacin, it is not likely that the prostaglandin system participated in maintaining the blood pressure within a normal range.

Production of excessive quantities of corticosterone and other mineralocorticoids has been found in many cases of primary aldosteronism, and the contribution of these steroids to the full development of the clinical features of primary aldosteronism was suggested as there was difficulty in reproducing this state by the administration of aldosterone alone.^{8,9} Lack of overproduction of these steroids other than aldosterone

cannot be ruled out in our patient, since the levels of these hormones were not measured. However, the physiologic potency of these other hormones is relatively weak compared to aldosterone, and hypertension can be induced in humans and laboratory animals by administering aldosterone alone.^{10, 11} In the studies of aldosterone administration, changes in electrolyte metabolism seem to precede the development of overt hypertension.¹⁰⁻¹³ Therefore, it is possible that our patient may have been in an early stage of primary aldosteronism before the development of hypertension. The occasional recordings of borderline levels of blood pressure suggest the possibility that her blood pressure may have been higher than her own normal level, although it mostly remained within normal range.

One peculiarity in our patient was the normal response to angiotensin II despite suppressed plasma renin activity, since it is a general rule that the responsiveness is inversely related to the blood level of angiotensin II and is exaggerated in low renin states such as primary aldosteronism.^{14, 15} The lack of the hyperresponsiveness in our patient does not explain the lack of hypertension, since there is no evidence that the renin-angiotensin system participates in the maintenance of blood pressure in low renin states. The hyperresponse to norepinephrine rules out a general reduction of vascular reactivity to pressor agents. Also unexplained was why the plasma renin remained suppressed despite a lack of hypertension or a detectable hypervolemia.

In the heretofore reported cases of normotensive primary aldosteronism due to adrenal adenoma, all were detected because of complaints associated with hypokalemia, such as muscle weakness, paralytic attack, or polyuria.³⁻⁵ One case of hyperaldosteronism due to adrenal hyperplasia was associated with depression.⁶ The present report is yet another case of aldosteronoma in the absence of hypertension. The lack of no specific complaint is unique and such patients may well be misdiagnosed unless careful examinations are done. It cannot be answered whether this patient would develop manifest hypertension when left untreated. Our patient already showed a slight impairment of urinary concentrating capacity, which indicated kaliopenic nephropathy. The early diagnosis may thus have prevented development of hypertension and renal impairment. Although primary aldosteronism had origi-

nally been classified as a hypertensive disease of endocrine origin, hypertension should no longer be considered an essential sign for the diagnosis of primary aldosteronism.

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