A Case with Primary Aldosteronism Due to Unilateral Multiple Adrenocortical Micronodules

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Abstract. A 46-year-old male with long-term treatment-resistant hypertension and past history of cerebral hemorrhage was found to have suppressed plasma renin activity (PRA) and normal plasma aldosterone concentration (PAC) with aldosterone/renin ratio of 25.3. Furosemide plus upright test did not stimulate PRA, but computed tomography scan of the abdomen revealed no abnormal lesions in either adrenal gland. Selective adrenal venous sampling (SAVS) showed that PAC in the left and the right adrenal vein were 1000 ng/dl and 230 ng/dl, respectively, which increased to 1500 ng/dl and 620 ng/dl, respectively, after ACTH stimulation. Diagnosis of primary aldosteronism due to hypersecretion of aldosterone from the left adrenal gland was made, and laparoscopic left adrenalectomy was performed. Pathological examination of the 'apparently normal' adrenal tissue resected revealed the presence of poorly encapsulated multiple adrenocortical micronodules which showed positive immunoreactivity for 3 β -hydroxysteroid dehydrogenase by immunohistochemical study, but negative immunoreactivity in the hyperplastic zona glomerulosa consistent with paradoxical hyperplasia associated with primary aldosteronism. Postoperatively, PRA was normalized and his high blood pressure was well controlled with lower doses of antihypertensive drugs than those used before surgery. The clinicopathological features of our case are consistent with the diagnosis of unilateral multiple adrenocortical micronodules (UMN), a new subset of primary aldosteronism, in which SAVS proved to be a useful diagnostic tool for its localization.

Key words: Primary aldosteronism, Unilateral multiple adrenocortical micronodules (UMN), Selective adrenal venous sampling, 3 β -Hydroxysteroid dehydrogenase

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RECENTLY, an increasing body of evidence suggests that aldosterone is an independent risk factor for cardiovascular disease based on many clinical and experimental studies [1–5]. Growing lines of evidence have consistently supported the view that secondary hypertension due to primary aldosteronism is much more frequent (8–20%) than previously suspected [6–10]. It is important to diagnose primary aldosteronism during

the early stage before the progression to end-organ damage because primary aldosteronism due to unilateral adrenal lesion, mostly aldosterone-producing adenoma, can be cured by surgery [11]. On the other hand, it is difficult to detect small adrenal lesions, such as microadenomas, micronodules and hyperplasia, by standard imaging tests, such as CT scan.

We herein describe a case with primary aldosteronism without adrenal mass or hyperplastic lesion on CT scan, who showed aldosterone hypersecretion in the left adrenal vein before and after stimulation with ACTH by selective adrenal venous sampling (SAVS), and was found to have unilateral multiple adrenocortical micronodules in the left adrenal gland after surgery.

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Case Report

A 46-year-old male was referred to Musashino Red Cross Hospital because of drug-resistant hypertension on October, 2002. He was pointed out high blood pressure in his twenties. He had putamen hemorrhage at the age of 41. Although he took multi-antihypertensive drugs (nifedipine 40 mg, betaxolol 20 mg, doxazosin 4 mg), his blood pressure remained uncontrolled (126–142/94–110 mmHg).

He was 167.5 cm tall, and weighed 79.2 kg. Blood pressure was 142/110 mmHg. Except for mildly low serum potassium level (3.6 mEq/l), biochemical parameters were otherwise all within the normal ranges. Echocardiography revealed borderline left ventricular hypertrophy and normal ejection fraction (68%). Fundoscopic examination showed mild hypertensive change. Urinalysis was normal and creatinine clearance was 85.5 ml/min. Endocrine data (Table 1) showed that PRA (0.3 ng/ml/hr) was suppressed, but PAC was normal (7.6 ng/dl) with aldosterone/renin ratio (ARR) of 25.3. Plasma levels of ACTH, cortisol and catecholamines were all within normal range. PRA remained suppressed (0.8 ng/ml/hr) and PAC was 14 ng/dl after stimulation with furosemide (40 mg) plus upright posture for 2 hours, suggesting the autonomous secretion of aldosterone. CT scan of the abdomen revealed no abnormal lesions in either adrenal gland (Fig. 1). The diagnosis of primary aldosteronism due to idiopathic hyperaldosteronism (IHA) was most likely based on clinical and endocrine data with negative adrenal lesions by CT scanning, which prompted us to perform selective adrenal venous sampling (SAVS).

PAC and plasma cortisol levels in adrenal venous effluents obtained by SAVS before and after ACTH stimulation are shown Fig. 2. Basal aldosterone levels in right and left adrenal vein were 230 ng/dl and 1000 ng/dl, respectively, which rose to 620 ng/dl and 1500 ng/dl, respectively, 30 min after stimulation with ACTH (Cortrosyn®: 250 µg). The data obtained from SAVS strongly suggested preferential aldosterone hypersecretion from the left adrenal gland. After obtaining informed consent for adrenal surgery, the left

Fig. 1. CT scan of the abdomen. Arrows indicate 'apparently normal' adrenal glands.

Table 1. Endocrine Data

Plasma ACTH (pg/ml)	23.9 (7.4–55.7)		
Plasma cortisol (µg/dl)	15.0 (4.0–18.3)		
PRA (ng/ml/hr)	0.3 (0.3–2.9)		
PAC (ng/dl)	7.6 (29.9–159)		
aldosterone/renin ratio (ARR)	25.3		
Plasma adrenalin (pg/ml)	46 (<100)		
Plasma noradrenalin (pg/ml)	402 (100–450)		
Plasma dopamine (pg/ml)	11 (<20)		
Furosemide plus upright test	0	120	(min)
PRA (ng/ml/hr)	0.4	0.8	
PAC (ng/dl)	9.3	14	

(numbers in parentheses: Reference values)

PAC (ng/dl)	F (µg/dl)	PAC/F
① 1000/1500	600/785	1.67/1.91
② 230/620	274/358	0.84/1.73
③ 12	20.5	0.59
④ 20	24.8	0.81

Fig. 2. Selective adrenal venous sampling. Plasma aldosterone concentration (PAC), cortisol (F), and the ratios of PAC/F in ① left adrenal vein, ② right adrenal vein, ③ inferior vena cava, ④ superior vena cava, are shown before and after stimulation with ACTH.

adrenal gland was surgically resected. Postoperative course was uneventful. PRA (1.7 ng/ml/hr) and serum K level (4.2 mEq/l) were normalized and PAC was 9.3 ng/dl with ARR of 5.5. The dose of antihypertensive drug was reduced (nifedipine 20 mg, betaxolol 10 mg), and blood pressure was well controlled (124/80 mmHg).

Pathological Examination

On gross examination, the left adrenal gland was 'apparently normal', 6.7×3.5×1.0 cm in size, weighing 8.6 g. However, multiple micronodules ranging up to

Fig. 3. Gross appearance of the resected left adrenal gland. Multiple small nodules were noted on the several cut surfaces of the adrenal tissue.

5 mm in greatest dimension were noted on the several cut surfaces of the resected adrenal tissue (Fig. 3).

Histological examination demonstrated the presence of poorly encapsulated multiple adrenocortical micronodules in the sections of the adrenal gland, composed of both compact and clear cells, the latter being predominant, and hyperplasia of the zona glomerulosa was detected in the non-nodular region (Fig. 4a). Immunohistochemical analysis of 3 β -hydroxysteroid dehydrogenase (3 β -HSD) [12] showed positive immunoreactivity for 3 β -HSD in cortical cells of the nodules (Fig. 4b), whereas negative for 3 β -HSD in hyperplastic zona glomerulosa cells, compatible with paradoxical hyperplasia associated with hyperaldosteronism [13]. These data are consistent with the notion that the cortical cells of micronodules actively synthesize aldosterone, but the hyperplastic zona glomerulosa cells do not.

Discussion

We present here a rare case of primary aldosteronism due to UMN as originally reported by Omura *et al.* [14]. The diagnosis of primary aldosteronism in the present case was most likely because of suppressed PRA with relatively high ARR [15, 16] and its failure to rise after stimulation with furosemide-upright position. Although his serum potassium level was low

Fig. 4. Microscopic examination of left adrenal gland. (a) adrenocortical micronodule (N) surrounded by hyperplastic zona glomerulosa (ZG) cells (HE, ×100), (b) immunohistochemistry; the cortical cells of the nodules (N) showed positive immunostaining for 3 β -HSD, but hyperplastic zona glomerulosa (ZG) cells were negative (×100).

normal, only a small population (9–37%) of primary aldosteronism from medical centers from five continents has recently been reported to be hypokalemic [17]. In fact, Omura *et al.* have also reported that hypokalemia (<3.3 mEq/l) was found in only one-quarter of the 61 patients with primary aldosteronism [10]. Our patient had been hypertensive since his twenties with past history of putamen hemorrhage, and his hypertension was poorly controlled with multi-antihypertensive drugs. However, he had no obvious adrenal lesions by adrenal CT scan. In order to localize the source of hypersecretion of aldosterone in patients with primary aldosteronism without obvious adrenal lesions by standard imaging tests, SAVS is highly recommended [14, 20].

Our patient showed hypersecretion of aldosterone from the left adrenal gland because of the greater lateralized ratio of PAC (left /right: 4.3) and the greater PAC (1500 ng/dl) in the left adrenal vein after ACTH stimulation. The diagnosis of IHA could be excluded because PAC was comparable in both adrenal veins. The laterality of PAC, as demonstrated in our case, strongly suggests that the left adrenal gland was responsible for the abnormal aldosterone hypersecretion. Although the resected left adrenal gland was 'apparently normal', histopathologic and immunohistochemical analysis established the diagnosis of UMN as originally reported by Omura *et al.* [14]. The left adrenal gland contained small, poorly encapsulated multiple cortical nodules, distinct from well-encapsulated adenoma. Furthermore, immunohistochemical study revealed positive immunoreactivity for 3β -HSD in cortical cells of these micronodules, but negative immunoreactivity in the hyperplastic zona glomerulosa. These histopathological and immunohistochemical features were all compatible with those of UMN [14].

The diagnosis of primary aldosteronism due to unilateral adrenal pathology, including unilateral adrenal hyperplasia (UAH), UMN, and microadenoma (less than 6 mm in size), is clinically important but difficult to localize with the diagnostic imaging tests, such as CT scan. Therefore, patients with UMN may be misdiagnosed as either low-renin essential hypertension or IHA, and treated with antihypertensive drugs for long-term periods as in the present case. Distinct from IHA, hypertension caused by UMN apparently responds to unilateral adrenalectomy [14]. His preoperative treatment-resistant hypertension was well controlled

by reduced doses of antihypertensive drugs after removal of the affected left adrenal gland. Since he had a long history (more than 20 years) of hypertension and the recent history of putamen hemorrhage, the failure of complete normalization of blood pressure after surgery could be accounted for by aldosterone-induced and/or hypertension-induced end-organ damage [18, 19].

SAVS should be performed in those patients with primary aldosteronism with 'apparently normal' adrenal glands on CT scan to determine whether hypersecretion of aldosterone is from unilateral or bilateral source [20, 21]. If it is bilateral, the diagnosis of IHA is made with first line of medical treatment using aldosterone receptor antagonists in combination with or without other antihypertensive drugs. If it is unilateral, the diagnosis of unilateral adrenal pathology including UMN, UAH and microadenoma, is most likely, and surgical treatment (unilateral adrenalectomy) is recommended.

The significance of ACTH stimulation in the correct lateralization of unilateral adrenal pathology remains open to question. Previous reports have recommended ACTH stimulation during SAVS to minimize the pulsatile variation in aldosterone release [22, 23]. Contrary to these reports, Magill *et al.* have reported that ACTH stimulation did not significantly improve the diagnostic accuracy during SAVS [24]. ACTH stimulation in our case did not increase the lateralized ratios (dominant to nondominant PAC and normalized PAC). Our data are consistent with those of Tanabe *et al.* who reported that the lateralized ratios were unchanged or even decreased after ACTH stimulation during SAVS in most patients with primary aldosteronism [25]. In contrast, the absolute value of PAC (1500 ng/dl) in the left adrenal vein after ACTH stimulation in our case is consistent with the diagnosis of aldosterone hypersecretion (more than 1400 ng/dl) as proposed by Omura *et al.* [10]. Thus, further studies are needed to establish the significance of ACTH stimulation during SAVS for the improvement of diagnostic accuracy in localization of primary aldosteronism.

In conclusion, our male patient is the fifth case of primary aldosteronism due to UMN thus far reported, in which SAVS proved to be a useful diagnostic tool for its localization. However, a long-term follow-up is needed to observe whether or not aldosterone hypersecretion may recur from the 'apparently normal' adrenal gland left intact.

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