Primary Aldosteronism due to Unilateral Adrenal Microadenoma in an Elderly Patient: Efficacy of Selective Adrenal Venous Sampling

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Abstract

We encountered a case of drug-resistant hypertension and hypokalemia. Laboratory data suggested primary aldosteronism (PA). Computed tomography imaging appeared normal for a long duration with a left-sided nodule appearing far later; adrenal scintigraphy was first normal, and the second test showed right-sided uptake. However, a repeat selective adrenal venous sampling (SAVS) indicated a left-sided lateralization of the hypersecretion of aldosterone. Left adrenectomy was performed, and his clinical symptoms improved. The histopathological findings demonstrated the aldosterone-producing microadenoma with secondary micronodules. In conclusion, SAVS should be performed to determine the laterality of PA with obscure CT imaging.

Key words: primary aldosteronism, adrenal microadenoma, selective adrenal venous sampling (SAVS)

(DOI: 10.2169/internalmedicine.47.0333)

Introduction

The symptoms of primary aldosteronism (PA) frequently include hypertension, hypokalemia, and mild metabolic alkalosis. It has long been recognized as a rare disorder, but recently it is reported as a major cause of secondary hypertension (1). Omura et al reported the prevalence of secondary hypertension was 9.1% among 1,020 hypertensive patients, and PA accounted for about 65% of secondary hypertension and for about 6% of all cases of hypertension (2).

It has been clarified that patients with PA are vulnerable to progression of cardiovascular disease (3). Furthermore, recent reports have shown that aldosterone can directly damage various organs via non-epithelial mineral corticosteroid receptors, especially when patients are exposed to inappropriate high-salt diet (4). Therefore, diagnosis and appropriate treatment in the early stages of the disease are desirable. In addition, it is very important to determine whether the pathological lesion is bilateral or unilateral, as unilateral lesions are curable by surgical resection.

Here, we report a case of PA due to adrenal microadenoma, in which CT imaging was ineffective for detecting the tumor, and adrenal scintigraphy provided the only positive diagnosis, which, however, showed uptake on the contralateral side of the tumor. Selective adrenal venous sampling (SAVS) with stimulation by adrenocorticotropic hormone (ACTH) effectively identified the correct localization, which resulted in successful resection of the affected side of the adrenal gland.

Case Report

A 73-year-old man was admitted to our hospital because of hypertension and persistent hypokalemia in May 2004. He had been diagnosed with type 2 diabetes and hyperten-
On admission, physical examination revealed his height to be 159.4 cm, and his weight 58.1 kg with a BMI of 26.3 kg/m². His blood pressure was 138/72 mmHg with all the above antihypertensive drugs. He had a lump and pain in his breast, which was compatible with gynecomastia.

Laboratory data after cessation of spironolactone and candesartan are shown in Table 1. His renal function was slightly impaired. PAC was at the higher limit of normal (28.6 ng/dl), whereas PRA was suppressed to below the range of detection (<0.2 ng/ml/h), with an aldosterone/renin ratio (ARR) of over 143. Urine aldosterone excretion was elevated. Serum potassium levels dropped to 3.0 mEq/L. ACTH was elevated, but the cortisol level was normal and a one mg dexamethasone suppression test significantly decreased the serum cortisol level (10.7 to 0.7 μg/dl). Plasma levels of catecholamines were also normal. We further examined the furosemide plus upright test. It failed to stimulate plasma renin activity, which remained completely suppressed throughout the entire test. From these results, we diagnosed hyperaldosteronism. Because abdominal CT scan showed no obvious adrenal mass, we further obtained an 131I adosterol scintigram. However, no significant uptake was observed in either adrenal gland. We planned to test selective adrenal venous sampling (SAVS), but as the patient refused this test, we started conservative medical management. Because spironolactone had the adverse effect of gynecomastia, trilostane, a 3β-hydroxysteroid dehydrogenase inhibitor, was started, and the patient was discharged. Two months later, he underwent transurethral resection of the prostate due to nocturia. Pathology revealed adenocarcinoma, and bicalutamide, an antiandrogenic agent, was started.

Despite the administration of trilostane, hypertension and hypokalemia were not well controlled, and the supplementary administration of slow release nifedipine, candesartan, bunazosin and KCl was still needed daily. PAC level was slightly decreased, but remained around 20 ng/dl, and occasionally over 30 ng/dl. PRA level also only slightly in-

### Table 1. Laboratory Data on First Admission

<table>
<thead>
<tr>
<th>CBC</th>
<th>PRA</th>
<th>PAC</th>
<th>Endocrine Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 5290 / mm³</td>
<td></td>
<td>&lt;0.2 ng/ml/h</td>
<td>&lt;0.2 ng/ml/h</td>
</tr>
<tr>
<td>RBC 361 x 10⁶ / mm³</td>
<td></td>
<td>28.6 ng/dl</td>
<td>28.6 ng/dl</td>
</tr>
<tr>
<td>Hb 12.0 g / dl</td>
<td>Plasma ACTH</td>
<td>84.9 pg/ml</td>
<td>84.9 pg/ml</td>
</tr>
<tr>
<td>Hct 35.4 %</td>
<td>Serum cortisol</td>
<td>10.7 μg / dl</td>
<td>10.7 μg / dl</td>
</tr>
<tr>
<td>Plt 20.7 x 10⁶ / mm³</td>
<td>Plasma adrenalin</td>
<td>&lt;10 pg/ml</td>
<td>&lt;10 pg/ml</td>
</tr>
<tr>
<td></td>
<td>Plasma noradrenalin</td>
<td>84 pg/ml</td>
<td>84 pg/ml</td>
</tr>
</tbody>
</table>

#### Blood Chemistry

| TP 6.1 g / dl | Urine Aldosterone | 13 μg / 24h |
| GGT 21 IU / l | Urine Cortisol | 10.9 μg / 24h |
| GPT 25 IU / l | Urine 17-OHCS | 5.7 mg / 24h |
| LDH 216 IU / l | Urine 17-KS | 5.7 mg / 24h |
| BUN 16 mg / dl | Urine Na | 166 mEq / 24h |
| Cre 1.3 mg / dl | Urine K | 44.8 mEq / 24h |
| Na 143 mEq / l |            |          |
| K 3.0 mEq / l |            |          |
| Cl 104 mEq / l | Min. | PRA(ng / ml/h) | Aldosterone (ng / dl) |
| HbA1c 6.6 % | 0 | <0.2 | 50.2 |
|            | 60 | <0.2 | 20.2 |
|            | 120 | <0.2 | 50.5 |

PRA; plasma renin activity, PAC; plasma aldosterone concentration, ACTH; adrenocorticotropic hormone, 17-OHCS; 17 α -hydroxycorticosteroids, 17-KS; 17-ketosteroids.
creased to about 0.8 ng/ml/h. During the ambulant follow-up, another \(^{131}\)I adosterol scintigram was obtained in May 2005, which showed radioiodine accumulation specifically higher in the right adrenal gland (Fig. 1). CT findings still remained normal. We persuaded the patient to undergo SAVS, and the first sampling test was held in February 2006. Aldosterone levels in the right and left adrenal veins 15 minutes after stimulation with 250 μg of ACTH were 566.2 ng/dl and 1,485 ng/dl, respectively, and the ratios of aldosterone/cortisol (PAC/F) were 0.54 and 5.4, respectively, from which the left/right ratio of PAC/F was calculated to be as high as 9.9 (Fig. 3A). However, because significant asymmetry in the cortisol level was observed in the first challenge, we performed another SAVS in August 2006. During this admission, the abdominal CT for the first time showed a nodule-like lesion, 1 cm in size and with a low density mass on the upper pole of the left adrenal gland (Fig. 2). The result of SAVS was reproducible, with ACTH-stimulated PAC in the left adrenal vein and the left/right ratio of PAC/F being 2,978.8 ng/dl and 14.5, respectively, a higher contrast than in the first challenge (Fig. 3B). The cortisol levels were comparable in each side. In both challenges, both aldosterone and cortisol levels were higher in the left inferior phrenic vein than in the left adrenal vein, which indicated considerable venous flow in that direction.

We concluded that overproduction of aldosterone in this patient occurred exclusively in the left adrenal gland, even though this was inconsistent with the results of scintigraphy, and thus a left adrenectomy was performed in October 2006. On gross pathological examination, the left adrenal gland measured 50×28×18 mm in size and weighed 15 gram. Cross-cut sections of the specimen revealed the presence of multiple yellowish microcortical nodules with diameters ranging up to 3.5 mm in the adrenal cortex (Fig. 4A). Histological examination revealed a well-encapsuled, 2 mm-in-size cell proliferation with clear cells predominating outside the micronodules (Figs. 4A, 4B). Immunohistochemical analysis of \(3\beta\)-dehydrogenase (\(3\beta\)-HSD) and \(17\alpha\)-hydroxylase (P450c17) demonstrated positive immunoreactivity in these small cluster of cells, the former predominantly in clear cells and the latter primarily in compact cells (Figs. 4C, 4D). The zona glomerulosa was morphologically hyperplastic but it was totally devoid of \(3\beta\)-HSD immunoreactivity. Therefore, this lesion was diagnosed as adrenocortical microadenoma (2 mm in diameter) consistent with aldosteronoma in conjunction with paradoxical hyperplasia of the zona glomerulosa and secondary adrenocortical nodules. The so-called “aldactone body” was not found in the resected tissues.

After surgery, the patient’s symptoms improved without trilostane. Both PAC (5.9 ng/dl) and PRA (1.13 ng/ml/h) normalized. The serum cortisol level (10.0 μg/dl) did not decrease and ACTH level (66.7 pg/ml) did not increase compared to the levels of preoperatively. The serum potassium level recovered to normal without replacement of KCl, and the systolic blood pressure level was successfully controlled at around 120 mmHg with low doses of slow release nifedipine (20 mg daily) and candesartan (8 mg daily), although complete cessation of antihypertensive drugs was not achieved.
Figure 3. Results of the first (A) and second (B) selective adrenal venous sampling (SAVS) tests. Plasma aldosterone (PAC, ng/dl) and cortisol (F, μg/dl) concentrations were measured at each point before and after ACTH stimulation. Numbers in parentheses indicate PAC/F ratios, and numbers in the bold line boxes indicate the left/right ratios of PAC/F.

Discussion

The etiology of primary aldosteronism (PA) is widely varied. Aldosterone-producing adenoma (APA), which is narrowly-defined PA, and idiopathic hyperaldosteronism (IHA) are the most common and account for over 90% of all cases. Other minor categories include unilateral adrenal hyperplasia (UAH), adrenal cancer, glucocorticoidremediable aldosteronism, and unilateral adrenocortical micronodules (UMN). Recently, Oda et al reported that expression of angiotensin II receptor (AT2R) may partially contribute to the overproduction of aldosterone in angiotensin II-resistant APA (5). However, the pathophysiological mechanism of overproduction of aldosterone in PA remains grossly unclear. Clinically, it is very important to determine whether the pathological lesion is bilateral or unilateral because the strategies of treatment are completely different; if unilateral, surgery is the first-line therapy. However, it is often very difficult to detect UAH or UMN by imaging test. Moreover, recent reports have shown there are many cases of small size APA (microadenomas), which are also undetectable by classical imaging tests. Nishikawa et al reported that 47% of aldosterone-producing adenomas are less than 5 mm in diameter, and are thus not detectable by the highest resolution CT (1). These cases (UAH, UMN, and microadenoma) with apparently normal CT imaging are frequently diagnosed as IHA, and are treated only with conservative medication. In the present case, likewise, CT imaging did not demonstrate masses in either adrenal gland for more than 2 years. However, even if good control can be achieved, patients are forced into a life-long administration of drugs. Thus, if unilateral localization can be confirmed, surgical resection is the most reliable treatment. Actually, in our case, the patient was successfully weaned from KCl supplementation and the amount of antihypertensive drugs was reduced after surgery. The reason that all medications could not be stopped was that he had a long history of hy-
Figure 4. Histopathological features of the left adrenal gland. A: Gross appearance of sections of the left adrenal gland. Multiple small nodules are found in the cortex. The thick arrow indicates the microadenoma, and the thin arrows indicate micronodules. B-D; Microscopic findings of microadenoma of the left adrenal gland. B; Hematoxylin and Eosin staining. C; Immunostaining with 3\(\beta\)-HSD. D; Immunostaining with P450c17.

pertension, diabetes mellitus and slight insufficiency in his renal function, which led to irreversible vascular damage, although Omura et al reported that the rate of cure of hypertension is much higher in patients with microadenoma than in patients with macroadenoma (6).

There have been a number of reports in which SAVS could accurately identify the laterality. In fact, many cases of PA due to unilateral microadenoma (7) or micronodules (8, 9) have been diagnosed only by SAVS, with normal results by CT imaging. In all these cases, unilateral adrenalectomy led to a good clinical response. On the contrary, there may be cases in which IHA is accompanied by a nonfunctional unilateral adrenal tumor. In those cases, surgical resection is contraindicated even if an obvious tumor is identified in either adrenal gland. From this point of view, SAVS is the gold standard method in all PA cases for determining laterality.

What is the diagnostic accuracy of adrenal scintigraphy? In the present case, it first gave bilateral negative findings, and the second time it showed positive uptake on the side opposite the microadenoma. It has been shown that scintigraphy has a higher sensitivity and a greater positive predictive value than CT, and that higher diagnostic accuracy can be achieved by combining these two methods (10). However, Glodny et al have shown a considerably high error rate associated with \(^{131}\)I radiocholesterol scanning. They reported that scintigraphy yielded accurate localizations in only 19 cases of 29 cases of APA, while there were no errors by SAVS (11). In fact, there has been a reported case of UAH in which the results of laterality diagnosed by scintigraphy were incorrect and opposite to those obtained by SAVS, just like our case (12). These reports indicate that the results of adrenal scintigraphy should not relied upon exclusively.

Although SAVS is a highly recommended diagnostic technique for PA patients, there has been controversy in its interpretation. In a report by Omura et al, the diagnosis of aldosterone hypersecretion was made when aldosterone concentrations in each adrenal vein were greater than 1,400 ng/dl after ACTH stimulation, which resulted in 98 percent of patients being correctly diagnosed as a unilateral lesion and all of them cured or improved after surgery (13). Both of our two challenges met the diagnostic criteria.

There is another diagnostic category, however, in which the aldosterone concentration of each adrenal vein is divided by the concentration of cortisol, to correct for any asymmetric dilutional effect. These “cortisol-corrected” aldosterone levels were compared, and if the ratio of dominant to non-dominant cortisol-corrected aldosterone is over some threshold level following ACTH stimulation, for example, 4 in the reports by Magill et al (14) and Young et al (15), it is recognized that there is a unilateral source of aldosterone. Our case also fulfills these criteria, although the left/right ratio of PAC/F was rather decreased after ACTH stimulation, whereas, in general, it is known to be elevated.

We repeated SAVS because a significant asymmetry in the cortisol level was observed in the first challenge. Theo-
rtically, a cortisol-overproducing tumor in the contralateral side may exist when the cortisol level after ACTH stimulation is very low. However, this was not the case here, because no obvious tumor was found in the right adrenal gland, and 1 mg dexamethasone completely suppressed the serum cortisol level. The cortisol level in the left renal vein turned out to be sufficiently high in the second challenge. Nevertheless, as there has been no agreement on the higher limit of cortisol, extreme asymmetry in cortisol levels may affect the PAC/F ratio. Moreover, because some IHA cases might be misdiagnosed as unilateral, careful interpretation is needed when this ratio is used as an indicator of laterality.

In the present case, macroscopic examination of the resected adrenal glands at first suggested UMN, because multiple adrenocortical micronodules were identified in the sections, as had been seen in the last CT imaging. However, there was a small but clearly demarcated or well circumscribed cluster of clear cortical cells outside the micronodules, which demonstrated relatively abundant immunoreactivity for both 3β-HSD and p450c17. Therefore, we diagnosed the latter lesion of this adrenal as microadenoma and the main aldosterone hypersecreting lesion, and the former as secondary adrenocortical nodules due to hypertensive changes. The so-called ‘paradoxical’ hyperplasia of the zona glomerulosa is occasionally associated with APA or UMN but its precise etiology remains unknown.

In conclusion, we encountered a case of primary aldosteronism in an elderly patient due to unilateral microadenoma, in which the results of laterality were discrepant between scintigraphy and SAVS. In a significant proportion of cases of unilateral adrenal hyperplasia or microadenoma, CT imaging may not be effective, and the interpretation of the scintigram should be made carefully due to its poor specificity. SAVS is the most useful and reliable tool for identifying the correct localization of aldosterone-overproducing tissues, which are obscure in CT imaging.

Acknowledgement
We would like to thank Dr. Masao Omura for his advice in interpreting the results of SAVS.

References