CASE REPORT

A Case of Myelolipoma with Bilateral Adrenal Hyperaldosteronism Cured after Unilateral Adrenalectomy

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Abstract

Myelolipomas are adrenal tumors composed of both adipose and hematopoietic tissues which are rarely associated with primary aldosteronism (PA). Here, we report a case of myelolipoma associated with PA. Aldosterone hypersecretion from bilateral adrenal glands had been confirmed by adrenal venous sampling and pathological analyses, but PA was clinically cured after surgical removal of the unilateral adrenal gland together with the myelolipoma that was not producing aldosterone. It is suggested that myelolipomas may release some factors which stimulate aldosterone production in adrenal glands, although further investigation is necessary. Obesity-related hyperaldosteronism might in part participate in generation of hypertension in the present case.

Key words: myelolipoma, primary aldosteronism, bilateral adrenal hyperplasia, aldosterone-releasing factor

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Introduction

Myelolipomas are uncommon, benign tumors, which are composed of mature adipose and hematopoietic tissues (1). They are usually non-functional, asymptomatic tumors which are occasionally detected incidentally on radiographic study. Most myelolipomas are situated in the adrenal glands and account for 3.6% of adrenal incidentalomas in Japan (2). Some of them are associated with other adrenal disorders, such as Cushing’s syndrome (3, 4), non-functional adenocortical adenomas (5), congenital adrenal hyperplasia (6-8), and primary aldosteronism (PA) (3). Almost all of the reported cases of myelolipomas associated with PA are concomitant occurrence with aldosterone-producing adenomas (APAs) (3). Here, we report a case of myelolipoma with bilateral adrenal hyperaldosteronism, in whom PA was clinically cured after surgical removal of the unilateral adrenal gland together with myelolipoma.

Case Report

A 46-year-old man who suffered from hypertension for several years visited a general practitioner’s office with eye redness and dizziness; his blood pressure was 190/115 mmHg. Oral administration of 8-mg candesartan cilexetil and 1-mg doxazosin mesilate was started and 2 weeks later he was referred to a hospital. At the first visit to the hospital, blood pressure was 160/100 mmHg and antihypertensive medicines were changed to 40-mg controlled-release

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nifedipine. Three weeks later, his body weight was 87.0 kg, blood pressure 138/80 mmHg, and the serum K⁺ concentration 4.2 mEq/L, and basal hormone levels were as follows: plasma aldosterone concentration (PAC) of 10.9 ng/dL (109 pg/mL), plasma renin activity (PRA) of 0.2 ng/mL/h, and aldosterone-renin ratio (ARR) of 54.5 ng/dL per mg/mL/h (545 pg/mL per mg/mL/h). Candesartan cilexetil (8 mg) was added due to blood pressure increase and 2 weeks later urinary aldosterone excretion was 9.0 μg/day upon urinary Na⁺ excretion of 353 mEq/day (Table 1). Five weeks later, candesartan cilexetil was discontinued and he was referred to our hospital. At the first visit to our hospital, his body weight was 80.0 kg, his blood pressure was 123/76 mmHg, and the dose of controlled-release nifedipine was reduced to 20 mg. Two weeks later he was hospitalized for further examinations.

Physical examination on admission showed the height of 163.9 cm, body weight of 80.9 kg, body mass index (BMI) of 30.1 kg/m², and blood pressure of 124/74 mmHg. Complete blood counts were normal. Blood chemistry revealed a serum K⁺ concentration of 4.0 mEq/L. Chest X-ray showed slight heart enlargement (cardiothoracic ratio of 53%) and electrocardiography indicated left ventricular hypertrophy (height of R wave of V5 was 2.62 mV). Basal hormone levels were PAC of 22.4 ng/dL, PRA of 0.6 ng/mL/h, and ARR of 37.3 ng/dL per mg/mL/h after 30-min rest in the supine position, and urinary aldosterone excretion was 10.9 μg/day (Table 1, at -14 months). A furosemide-upright test (FUP) and a captopril challenge test (CCT) were performed as described in the chapter of Secondary Hypertension in the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2009) (9). While FUP was negative (PRA increased to 2.5 ng/mL/h after an i.v. injection of 40-mg furosemide and subsequent 2-h standing), CCT was positive (PAC 11.0 ng/dL, PRA 0.2 ng/mL/h, ARR 55 ng/dL per mg/mL/h at 90 minutes after oral administration of 50-mg captopril, Table 2). These results confirmed the diagnosis of PA (9). On the other hand, basal plasma ACTH (26 pg/mL), serum cortisol (12.9 μg/dL), and plasma catecholamine concentrations (adrenalin 14 pg/mL, noradrenalin 110 pg/mL, dopamine<5 pg/mL) were within normal limits, and thyroid function was also normal (TSH 2.41 μU/mL, free T4 1.3 ng/dL). The diurnal change of serum cortisol concentration was not impaired (2.7 μg/dL at 23:00h) and the serum cortisol concentration was suppressed to 1.7 μg/dL by an overnight 1-mg dexamethasone suppression test, ruling out Cushing’s syndrome.

Computed tomography (CT) revealed a homogenous, low-density mass with a diameter of 3 cm in the left adrenal gland (Fig. 1A). Magnetic resonance imaging showed that opposed-phase T1-weighted signal intensity of the adrenal
mass was suppressed as compared with in-phase T1-weighted signal intensity, suggesting that the mass was an adrenocortical adenoma (Fig. 1B-C). Dexamethasone-suppression $^{131}$I-6β-iodomethyl-19-norcholesterol adrenal scintigraphy showed uptake in neither bilateral adrenal glands nor the tumor. An adrenal venous sampling (AVS) was performed with ACTH stimulation as described previously (10). Judging from serum cortisol concentrations in adrenal veins, catheterization to bilateral adrenal veins was successful before and after the ACTH loading (Table 3). PAC in both adrenal veins was above 250 ng/dL and 1,400 ng/dL before and after the ACTH loading, respectively, and lateralization ratios of PAC/cortisol ratios were less than 2.6 before and after the ACTH loading (Table 3), indicating that aldosterone hypersecretion was present in bilateral adrenal glands (11,12). We tentatively diagnosed this case with idiopathic hyperaldosteronism (IHA) accompanied by a non-functioning adrenocortical adenoma, and chose medical treatment with spironolactone of 50 mg.

Six months after the first admission, his blood pressure rose and the dose of spironolactone was increased to 75 mg. Four months later, a follow-up CT showed that the tumor grew from 3 to 4 cm in the largest diameter and some fat-density areas appeared in the tumor. One month later, a further increase of the spironolactone dose to 100 mg was needed to control blood pressure, but skin rash appeared and the dose of spironolactone was reduced to 50 mg with the addition of 5-mg amlodipine (at -3 months in Table 1). One month later (2 months before the surgery), a follow-up CT revealed that the tumor grew to 4.9 cm in the largest diameter and heterogeneous appearance became more pronounced (Fig. 1D). The emergence of obvious fat-density areas in the tumor suggested a myelolipoma but the possibility of malignancy was clinically postulated by the rapid increment of tumor size. Therefore, laparoscopic left adrenalectomy was performed. Grossly, the tumor was present in the left adrenal gland, and there were no other tumorous lesions in the left adrenal gland. On light microscopic examinations, a well circumscribed and partially encapsulated tumor composed of mature adipocytes and hematopoietic cells (Fig. 2A, B) was detected; this lesion was subsequently diagnosed as a myelolipoma. Both 3β-hydroxysteroid dehydrogenase (HSD) and 17α-hydroxylase (c17) (Fig. 2B-D) were not expressed in the tumor cells of myelolipoma. The non-neoplastic adrenal cortex was discernible without fatty metamorphosis of adrenocortical cells adjacent to the myelolipoma (Fig. 2A, B). Scattered foci of hyperplastic glomerulosa cells, which expressed 3β-HSD but not c17, were detected in the attached adrenal cortex (Fig. 2B-G). The immunoreactivity of 3β-HSD was at least not diminished in the hyperplastic zona glomerulosa cells (Fig. 2C, F). Therefore, the hyperplasia of zona glomerulosa cells is not considered as paradoxical hyperplasia of the zona glomerulosa, which is reported in the adrenal cortex attached to an APA.
These findings of the zona glomerulosa were at least not inconsistent with those of IHA, although diffuse hyperplasia of zona glomerulosa with marked 3β-HSD expression, a typical feature of IHA, was not detected in this case. Cortical microadenomas, hyperplasia of zona fasciculata or zona reticularis of the cortex, or tumors or hyperplasia of the medulla were not found in the left adrenal gland.

Re-evaluation studies were performed 2 weeks after the surgery. His body weight was reduced to 73.0 kg (BMI: 27.2 kg/m²), and his blood pressure was normal (116/82 mmHg) without antihypertensive treatment (Table 1). Basal PAC, PRA, and ARR were 9.9 ng/dL, 2.7 ng/mL/h, and 3.7 ng/dL per ng/mL/h, respectively (Table 1). Both CCT and FUP were negative after the surgery; ARR was 0.42 ng/dL per ng/mL/h at 90 minutes after oral administration of 50-mg captopril (Table 2), and PRA was 13.5 ng/mL/h after an i.v. injection of 40-mg furosemide and subsequent 2-h standing. A saline infusion test, performed as previously described (9), was also negative after the surgery; PAC was 4.6 ng/dL after an i.v. drip infusion of 2-L saline over 4 hours. These results indicate that hyperaldosteronism independent from the renin-angiotensin system (RAS), which had been observed before the surgery, was absent after the surgical removal of the left adrenal gland with the myelolipoma. Six months after the surgery, blood pressure (133/78 mmHg) and the serum K⁺ concentration (4.9 mEq/L) were maintained within the normal range without medication, while his body weight slightly increased to 76.0 kg (Table 1). Basal PAC, PRA, and ARR were 16.4 ng/dL, 2.3 ng/mL/h, and 7.1 ng/dL per ng/mL/h, respectively (Table 1). Urinary aldosterone excretion was 7.7 μg/day (Table 1). Eleven months after the surgery, 5-mg amlodipine was required to maintain blood pressure at 122/75 mmHg as body weight increased to 80.0 kg. ARR remained at 8.0 ng/dL per ng/mL/h, but PAC increased to 19.2 ng/dL (Table 1). Nineteen months after the surgery, 0.5-mg doxazosin mesilate was required in addition to 5-mg amlodipine to maintain blood pressure at 115/66 mmHg, but PAC and ARR decreased to 7.1 ng/dL and 2.3 ng/dL per ng/mL/h, respectively, as body weight decreased to 76.0 kg (Table 1). At 4 years after the surgery, body weight rebounded to a similar level but urinary aldosterone excretion was reduced by about 70%, as compared with those at 15 months before the surgery (Table 1).

### Table 3. Adrenal Venous Sampling

<table>
<thead>
<tr>
<th>Sampling point</th>
<th>PAC (ng/dL)</th>
<th>Cortisol (µg/dL)</th>
<th>PAC/cortisol ratio</th>
<th>Lateralization ratio</th>
<th>Contralateral ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ACTH loading</td>
<td>IVC</td>
<td>6.5</td>
<td>10.8</td>
<td>0.60×10⁻³</td>
<td>3.93</td>
</tr>
<tr>
<td></td>
<td>Left adrenal vein</td>
<td>261.0</td>
<td>110.4</td>
<td>2.36×10⁻³</td>
<td>2.17</td>
</tr>
<tr>
<td></td>
<td>Right adrenal vein</td>
<td>252.0</td>
<td>49.3</td>
<td>5.11×10⁻³</td>
<td>2.20</td>
</tr>
<tr>
<td>During ACTH loading</td>
<td>IVC</td>
<td>14.5</td>
<td>17.1</td>
<td>0.85×10⁻³</td>
<td>2.52</td>
</tr>
<tr>
<td></td>
<td>Left adrenal vein</td>
<td>2320</td>
<td>492.3</td>
<td>4.71×10⁻³</td>
<td>2.20</td>
</tr>
<tr>
<td></td>
<td>Right adrenal vein</td>
<td>2360</td>
<td>1102</td>
<td>2.14×10⁻³</td>
<td>2.52</td>
</tr>
</tbody>
</table>

Adrenal venous sampling was performed as described previously (Ref 10). PAC, plasma aldosterone concentration; IVC, the inferior vena cava peripheral to the confluence of renal veins; Lateralization ratio, the dominant side to recessive side ratio of PAC/cortisol ratios; Contralateral ratio, the recessive side to IVC ratio of PAC/cortisol ratios.

### Discussion

We diagnosed the present case with PA following JSH 2009 (9) and the Guidelines for the Diagnosis and Treatment of Primary Aldosteronism—Japan Endocrine Society 2009 (13). The present case showed grade III hypertension and ARR of greater than 30 ng/dL per ng/mL/h with PAC of greater than 15 ng/dL (Table 1). The CCT was also positive following the Endocrine Society’s guidelines (14); PAC did not decrease by greater than 30% with PRA being suppressed 1 and 2 hours after oral administration of 50-mg captopril (Table 2). There is no worldwide consensus on the cut-off adrenal venous PAC values determining aldosterone hypersecretion, but Japan Endocrine Society’s guidelines recommend using absolute values of adrenal venous PAC to determine aldosterone hypersecretion as described above (11-13). Based on the Endocrine Society’s guidelines, with ACTH administration, the definition of unilateral aldosterone hypersecretion is that the lateralization ratio is greater than 4, otherwise the disease is determined to be bilateral (14). The disease of the present case was bilateral also based on this definition (Table 3). If ectopic aldosterone production existed in the present case, hyperaldosteronism would not have been improved by the adrenalectomy. Therefore, we concluded that aldosterone hypersecretion was present in bilateral adrenal glands before the surgery in the present case.

Myelolipomas are sometimes associated with abnormalities of adrenocortical hormones, and Cushing’s syndrome is the most frequent one among them (3). Some studies referred to the possibility that stimulation by cortisol mediates transformation of adrenocortical cells to myeloid cells and fatty replacement (4), whereas others proposed that necrosis of the adrenal tissue caused by peripheral circulatory disturbance results in myelolipomatous degeneration (15). Myelolipomas associated with PA were far less frequently reported than those with Cushing’s syndrome, and almost all of them showed concomitant occurrence with APA in an adjacent adrenal gland (3). Only one case of a myelolipoma associated with bilateral adrenal hyperplasia and PA simulating IHA, in whom PA was not cured by surgical removal of the myelolipoma, was reported in the literature, although detailed endocrine workups such as endocrine pathological
correlation were not performed in this case (16). In the present case, endocrine-pathological evaluation demonstrated that aldosterone hypersecretion was from bilateral adrenal glands with the hyperplasia of 3β-HSD-positive zona glomerulosa cells that actively synthesized aldosterone (Fig. 2B-G). Lack of expression of 3β-HSD and c17 in the myelolipoma also indicated that the tumor was not producing cortical steroids (Fig. 2B-D). The present case is unique because bilateral adrenal hyperaldosteronism was cured or clinically ameliorated by the surgical removal of the unilateral myelolipoma without aldosterone production.

Where aldosterone hypersecretion from each adrenal gland is insufficient but the sum of that from both adrenal glands is enough to generate signs and symptoms of PA, PA
at least appears to have been cured following unilateral adrenalec-ty but the signs and symptoms may appear again as the hypersecretion from the remaining adrenal gland increases in the patient. The fact that RAS-independent hyperaldosteronism was kept cured until at least 4 years after the unilateral adrenalec-tomy suggests that this possibility is low.

A sub-analysis of the Primary Aldosteronism Prevalence in Hypertension (PAPY) Study showed that BMI could predict PAC independently from PRA, sodium intake, age, and sex in patients with essential hypertension (17). It was also reported that PACs were significantly decreased by body weight reduction (18). The adipose tissue appears to secrete some mineralocorticoid-releasing factors, because conditioned media from primary cultures of human mammary gland and subcutaneous adipocytes reportedly stimulated aldosterone secretion from human adrenocortical cells (19, 20). In the present case, body weight reduction from 80.9 kg to 73.0 kg itself might improve RAS-independent aldosterone hypersecretion. Although the basal ARR did not reach a level indicating reappearance of PA, it gradually increased from 3.7 ng/dL per ng/mL/h at 2 weeks after the surgery to 8.0 ng/dL per ng/mL/h at 11 months after the surgery and hypertension appeared again, as body weight rebounded to 80.0 kg (Table 1). This observation might indicate the time course of obesity-related hyper-aldosteronism.

At 4 years after the surgery, body weight rebounded to a similar level and sodium intake was smaller, as compared with those at 15 months before the surgery (Table 1). The inhibition of aldosterone secretion by 10-mg telmisartan that was used at 4 years after the surgery is expected to be weaker than that by 8-mg candesartan cilexetil that was used at 15 months before the surgery, because it was reported that doses required for 50% blockade of the type 1 angiotensin II receptor were 6 mg for candesartan cilexetil and 54 mg for telmisartan in humans (21). If aldosterone secretion depended mainly on the RAS activity and body weight, the urinary aldosterone excretion at 4 years after the surgery would be expected to be greater than that at 15 months before the surgery. However, the former was smaller by about 70% than the latter (Table 1). This suggests that the myelo-lipoma or attached adrenal tissue removed by the surgery was releasing some factors that stimulate aldosterone secre-tion from adrenal glands in the present case.

Diffuse hyperplasia and tumors, which could be lesions that secrete aldosterone-releasing factors, were not detected in the removed left adrenal gland, except for the myelolipoma. An admixture of adipose and hematopoietic ele-ments of myelolipoma results in imaging features indistin-guishable from those of adrenocortical adenomas both in CT and magnetic resonance imaging (22). In the present case, hyperaldosteronism worsened as the tumor grew in an adi-pose tissue element dominant manner, which resulted in the appearance change of the tumor. It is possible that the adipose tissue element of the myelolipoma was secreting mineralocorticoid-releasing factors. The hematopoietic ele-ment may release renin-like enzyme activities, because leu-kemia cells released renin-like enzyme activities and re-sulted in hyperaldosteronism with diffuse hyperplasia of the zona glomerulosa of the adrenal cortex in a patient with acute myeloid leukemia (23). In the present case, it is un-likely that the tumor was releasing renin-like enzyme activi-ties, because PRA, as all enzyme activities generating an-giotensin I, was low. In conclusion, the present case sug-gests that myelolipomas may release some aldosterone-releasing factors. Obesity-related hyperaldosteronism might also exist in the present case. Further analyses will be needed to establish a theory.

The authors state that they have no Conflict of Interest (COI).

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