Possibly Simultaneous Primary Aldosteronism and Preclinical Cushing’s Syndrome in a Patient with Double Adenomas of Right Adrenal Gland

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Abstract. We reported a rare case of simultaneous primary aldosteronism and preclinical Cushing’s syndrome due to unilateral double adrenocortical adenomas in a 57 year-old woman who had had hypertension for the last 10 years. Abdominal computed tomography showed double tumors in her right adrenal gland. Physical findings revealed simple obesity and hypertension, but no other abnormal findings were detected. Laboratory findings demonstrated that serum potassium was 3.8 mmol/l; plasma renin activity, 0.3 ng/ml/h; plasma aldosterone, 100 pg/ml, and aldosterone renin ratio (ARR), 33. Serum cortisol was 15.7 µg/dl. There was no circadian rhythm of serum cortisol, and no suppression of serum cortisol in response to exogenous dexamethasone administration. Right adrenalectomy was performed under laparoscopy. Two well-circumscribed tumors, whose sizes were 21 and 19 mm in greatest diameter, were detected. They were macroscopically composed of a golden-yellow portion admixed with a brown portion, which corresponded to clear cells and compact cells, respectively. Immunohistochemical staining for steroidogenic enzymes demonstrated the presence of all the enzymes involved in corticosteroidogenesis in these two adenomas, indicating that the two adenomas produced both cortisol and mineralocorticoid. Specifically, one adenoma mainly caused excessive production of cortisol as compared to the other one. These findings indicate that overproduction of both cortisol and mineralocorticoid was evident in the two adenomas of the right adrenal gland in immunohistochemical study for steroidogenic enzymes, whereas there was less clinical manifestation of primary aldosteronism and Cushing’s syndrome in the present patient.

Key words: Unilateral double adrenocortical adenomas, Aldosterone renin ratio (ARR), Immunohistochemical staining, Adrenocortical steroidogenic enzymes

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AUTONOMOUS production of both aldosterone and cortisol is found in adrenal adenoma, and there are approximately 20 cases that have been reported in the literature written in English [1–11]. The adenomas cause both primary aldosteronism and preclinical Cushing’s syndrome. Plasma renin activity (PRA) is suppressed, but serum potassium (K) levels are variable, ranging from hypokalemia to normokalemia [12]. Also, clinical manifestation of preclinical Cushing’s syndrome seems to be less evident, and impaired glucose tolerance is found in most of the patients [13, 14]. Generally there is only a tumor in the unilateral adrenal gland, which produces both aldosterone and cortisol inappropriately [1–4, 6–11]. A few of the variant cases have more than two tumors in uni- or bilateral adrenal glands, which autonomously produce both two hormones [5, 15, 16]. There are only two cases with concurrent primary aldosteronism and Cushing’s syndrome that had double adenomas in the unilateral adrenal gland [5, 17]. In the case of multiple tumors...
it is hard to determine whether each tumor produces exaggerated levels of both aldosterone and cortisol, if we use conventional diagnostic methods including ultrasound sonography, computed tomography and adrenal venous sampling as well as routine endocrinological examination.

In the present study we report a woman with primary aldosteronism and preclinical Cushing’s syndrome who had double adenomas in the right adrenal gland. We also examined immunolocalization of the steroidogenic enzymes to elucidate the steroidogenesis in adrenal adenomas.

**Case Report**

A 57 year-old woman visited her local doctor because of back pain in September 2004. She took medication, but her back pain remained unchanged. She was referred to Jichi Medical University Omiya Medical Center to have further examination in December 2004. Abdominal computed tomography (CT) scan showed double tumors in the right adrenal gland, whose sizes were 21 mm and 19 mm in diameter. She was admitted to elucidate adrenal tumors in February 2005. She had had hypertension for the last 10 years, and has been treated with 5 mg amiodipine besilate, 2 mg trichloromethiazide and 40 mg valsartan. After the admission, 1 mg doxazosin mesilate was administered instead of valsartan. Her body weight was 58 kg at 54 years, and she had gradually gained weight.

Physical findings at hospitalization were height 145 cm and body weight 63 kg, with a body mass index of 29.9. Blood pressure was 150/60 mmHg without postural change, and pulse rate, 67/min with regular rhythm. She had simple obesity, but not truncal one because her waist circumference was 88 cm. There were no Cushingoid stigmata, that is, she did not have moon face, thin and fragile skin, red striae, hirsutism or petechiae. In addition, there was hypertensive change of Scheie grade II in ocular fundi [18].

Laboratory findings showed white blood cells were 7830/cmm (neutrophilic leukocyte, 71.9%; eosinophilic leukocyte, 1.1%; basophilic leukocyte, 0.7%; monocyte, 5.6%; and lymphocyte, 19.1%); red blood cells, 446 × 10⁶/cmm; hemoglobin, 14.0 g/dl; hematocrit, 40.5%; and platelets, 30.2 × 10⁹/cmm. Serum sodium (Na) was 148 mmol/l; potassium (K), 3.8 mmol/l; and chloride, 108 mmol/l. Blood urea nitrogen was 14 mg/dl; serum creatinine, 0.57 mg/dl; and uric acid, 5.2 mg/dl. Fasting plasma glucose was 103 mg/dl; hemoglobin A1c, 5.9%, total cholesterol, 190 mg/dl; triglyceride, 185 mg/dl. Creatinine clearance was 129 ml/min. Blood gas analysis showed no metabolic alkalosis. HOMA-R was 3.24. 75 g glucose tolerance test showed impaired glucose tolerance (Table 1). Serum γ-globulin was in normal range. Urinalysis showed no proteinuria. Urinary Na and K excretions were 90 and 38 mmol/day, respectively. Endocrinological data are shown in Table 1. Plasma renin activity (PRA) was 0.3 ng/ml/h and plasma aldosterone concentration was 100 pg/ml. The ratio of aldosterone (ng/dl) to PRA (ng/ml/h) was 33. PRA increased from 0.2 to 1.1 ng/ml/h 2 hours after the upright posture following 40 mg furosemide administration. There was no circadian rhythm of serum cortisol with total suppression of plasma ACTH less than 5 pg/ml, as serum cortisol was 15.7 µg/dl (normal value; 4.0–18.5) at 0600 h and 21.4 µg/dl at 2300 h, respectively. Overnight administration of 1 and 8 mg dexamethasone did not suppress serum cortisol levels at all. Urinary excretion of free cortisol was 80.7 µg/day. Plasma dehydroepiandros-

<table>
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<th>Table 1. Endocrinological data</th>
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<tr>
<td>1) 75 g Oral glucose tolerance test</td>
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<tr>
<td>Time (min) &amp; 0 &amp; 30 &amp; 60 &amp; 120</td>
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<tr>
<td>Plasma glucose (mg/dl) &amp; 106 &amp; 203 &amp; 233 &amp; 98</td>
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<tr>
<td>IRI (µU/ml) &amp; 12.4 &amp; 43.2 &amp; 63.9 &amp; 16.9</td>
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<td>2) Circadian rhythm</td>
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<tr>
<td>Time (h) &amp; 6:00 &amp; 23:00</td>
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<tr>
<td>Cortisol (µg/dl) &amp; 15.7 &amp; 21.4</td>
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<tr>
<td>ACTH (pg/ml) &amp; &lt;5.0 &amp; &lt;5.0</td>
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<td>3) Rapid dexamethasone suppression test</td>
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<tr>
<td>Time (min) &amp; 0 &amp; 1mg &amp; 8mg</td>
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<tr>
<td>Cortisol (µg/dl) &amp; 15.7 &amp; 17.7 &amp; 17.4</td>
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<tr>
<td>ACTH (pg/ml) &amp; &lt;5.0 &amp; &lt;5.0 &amp; &lt;5.0</td>
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<tr>
<td>4) Rapid ACTH test</td>
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<tr>
<td>Time (min) &amp; 0 &amp; 30 &amp; 60</td>
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<tr>
<td>Cortisol (µg/dl) &amp; 18.5 &amp; 31.3 &amp; 29.1</td>
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<tr>
<td>Aldosterone (pg/ml) &amp; 73 &amp; 170 &amp; 200</td>
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<tr>
<td>5) Furosemide and upright posture test</td>
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<td>Time (min) &amp; 0 &amp; 120</td>
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<tr>
<td>Plasma renin activity (PRA) (ng/ml/h) &amp; 0.2 &amp; 1.1</td>
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<tr>
<td>Aldosterone (pg/ml) &amp; 110 &amp; 270</td>
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<td>6) CRH test</td>
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<tr>
<td>Time (min) &amp; 0 &amp; 30 &amp; 60 &amp; 90</td>
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<tr>
<td>Cortisol (µg/dl) &amp; 15.0 &amp; 17.4 &amp; 16.8 &amp; 15.6</td>
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<tr>
<td>ACTH (pg/ml) &amp; &lt;5.0 &amp; &lt;5.0 &amp; &lt;5.0 &amp; &lt;5.0</td>
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terone sulfate (DHEA-S) was 261 ng/ml (normal value, 110–1160). Electrocardiogram showed neither left ventricular hypertrophy nor ischemic change. Abdominal CT depicted two isolated tumors in right adrenal gland, in which the density was not equivalent with the sizes of 21 (tumor #1) and 19 mm (tumor #2) in diameter (Fig. 1). The density was not homogenous in tumor #1, but it was homogenous in tumor #2. Left adrenal gland seemed to be atrophic. There was no enhancement in the two adrenal tumors, but a little enhancement was found in the normal parts of the adrenal glands. $^{131}$I-adosterol scintigram showed isotope accumulation only in the right adrenal gland, but no accumulation in the left gland (Fig. 2). Her bone mineral density was as low as 78.4% compared with the age-matched control, thus indicating osteopenia.

**Clinical course**

These findings indicated that overproduction of both aldosterone and cortisol was closely associated with adrenal tumors, but clinical manifestation of primary aldosteronism and Cushing’s syndrome was not overt. Her hypercorticoioidism was in concert with the criteria of preclinical Cushing’s syndrome [19]. After the patient gave informed consent, right adrenalectomy was carried out under laparoscopy on March 2005. We also obtained informed consent from the patient to study immunohistochemical findings. The resected adrenal tissue was examined by immunohistochemistry to determine the production of aldosterone and cortisol, as noted below. After the operation, hydrocortisone 20 mg was administered, which was later withdrawn after 2 months. The anti-hypertensive drugs were withdrawn, but her blood pressure normalized to 120–130/70 mmHg, and serum K levels ranged from 4.1 to 4.3 mmol/l. PRA and plasma aldosterone concentra-
tion were 0.4 ng/ml/h and 38 pg/ml, respectively. Serum cortisol was 9.6 µg/dl and it was totally suppressed by 1 mg dexamethasone administration.

Pathological findings

Macroscopic findings

There were two oval shaped adrenocortical tumors in her right adrenal gland (Fig. 3). Their sizes at the cut-surface were 21 (tumor #1) and 19 mm (tumor #2) in greatest diameter. Both of these tumors were encapsulated and well-circumscribed. The cut surface of the tumors demonstrated an admixture of two different neoplastic components, that is, a brown portion and a golden-yellow portion. In both tumors, the golden-yellow portions were predominant, and the small brown portions were distributed in an islet-like appearance.

Microscopic findings and immunohistochemical staining for steroidogenic enzymes

Tumor #1: The tumor was considered to be an adrenocortical adenoma according to the criteria of Weiss [20]. It was predominantly composed of compact cells with relatively abundant eosinophilic cytoplasm admixed with foci of clear cortical cells (Fig. 4A). There were also foci of myelolipomatous degenerative changes in the tumor. Tumor cells demonstrated immunoreactivity for the cholesterol side-chain cleavage enzyme (scc), 3β-hydroxysteroid dehydrogenase (3β-HSD II), 21-hydroxylase (CYP21), 11β-hydroxylase (CYP11B1), and 17α-hydroxylase (CYP17) [21]. The immunoreactivity of CYP17, which is essential for cortisol synthesis, but not aldosterone synthesis, was detected abundantly in the compact cells (Fig. 5A) and weakly in the clear cells. Some of the tumor cells with eosinophilic cytoplasm were associated with the expression of DHEA-ST.

Tumor #2: This tumor was also considered to be an adrenocortical adenoma according to the criteria of Weiss [20]. The tumor was predominantly composed of clear cortical cells admixed with foci of clear cortical cells. The immunoreactivity of scc, 3β-HSD II, CYP21, CYP11B1 and CYP17 was obtained in the tumor cells. However, the number of tumor cells with

![Fig. 3. Macroscopic findings of the cut surface of the right adrenal tumors. A golden yellow portion was admixed with islet-like distributed brown portion. Both tumors were well circumscribed and encapsulated.](image)

![Fig. 4. Light microscopic finding. (A) The adenoma shows both compact and clear tumor cells. Haematoxylin-eosin stain. ×400. (B) Cortical atrophy and paradoxical hyperplasia in the zona glomerulosa in the non-neoplastic adrenal gland adjacent to the tumor. ×400.](image)
the immunoreactivity of CYP17 was markedly small as compared to that in tumor #1 (Fig. 5B).

Non-neoplastic adrenal tissue: The adjacent non-neoplastic adrenal glands demonstrated marked cortical atrophy of the zonae fascicularis and reticularis (Fig. 4B) in which little immunoreactivity of DHEA-ST was detected (Fig. 6A). The zona glomerulosa morphologically demonstrated hyperplasia (Fig. 4B), but the immunoreactivity of 3β-HSD II was not detected in the hyperplastic glomerulosa zone of the adjacent adrenal tissue attached to the tumor.

**Discussion**

The patient had had hypertension for the last 10 years, and was treated with antihypertensive agents as essential hypertension. Except for hypertension, there were no typical features of primary aldosteronism and Cushing’s syndrome. Right adrenal tumors were found incidentally, when abdominal CT scan was performed for the survey of back pain. Diagnostic criteria for primary aldosteronism have changed from classical manifestation to subtle changes in PRA and aldosterone concentration. Many investigator groups have emphasized that if aldosterone renin ratio (ARR) is more than 12, 20 or 25 [22–24], further examination is necessary to exactly diagnose primary aldosteronism. Omura et al. [12] commented that classical primary aldosteronism accounted for only 20% of the total number of primary aldosteronism cases. Similarly, non-suppressible release of cortisol was associated with preclinical Cushing’s syndrome. Diagnostic criteria
for preclinical Cushing’s syndrome was defined by the Research Committee of the Japanese Ministry of Health and Welfare for Disorders of Adrenal Hormones [19]. There were no Cushingoid stigmata, no circadian rhythm of serum cortisol, no alteration in serum cortisol after dexamethasone administration, and unilateral accumulation in adrenal scintigram. The present findings were compatible with the above diagnostic criteria, except for incomplete suppression of PRA in response to the furosemide and upright posture test. It is known that such a finding is also reported in cases with concurrent primary aldosteronism and Cushing’s syndrome [25]. In addition, the patient had impaired glucose tolerance, insulin resistance and osteopenia. There was little clinical manifestation of primary aldosteronism and preclinical Cushing’s syndrome in this patient, though hypersecretion of aldosterone and cortisol was evident. Latent preclinical Cushing’s syndrome could be obtained in pathological states of metabolic syndrome.

There were two adenomas in the right adrenal gland in the present patient. As normal tissue resided between the two adenomas, they grew independently of one another. Immunohistochemical study demonstrated the presence of immunoreactivity for all enzymes of scc, 3\(\beta\)-HSDII, CYP21, CYP11B1 and CYP17 involved in cortisol synthesis in the two adenomas [26, 27], but there was difference in the immunoreactivity of CYP17 between the two adenomas. Tumor #1 was considered to be profoundly involved in excessive cortisol production and secretion because of its CYP17 expression and its histopathological features including tumor cells with eosinophilic cytoplasm and myelolipomatous degeneration [26]. Tumor #2 was considered to be less involved in overproduction of cortisol because of its relative paucity of CYP17 expression and its histopathological features including tumor cells with relatively clear cytoplasm [26]. Glomerulosa zone of the adjacent adrenal tissue was histologically hyperplastic in this case, but there was no immunoreactivity for 3\(\beta\)-HSD. This finding indicates no synthesis of aldosterone in this hyperplastic zona glomerulosa of the adjacent non-neoplastic adrenal tissue, consistent with paradoxical hyperplasia closely associated with primary aldosteronism [27]. In the present patient we could not totally exclude the possibility of deoxycorticosterone-producing tumor. As ARR was 33, which was decreased to 9.5 after the adrenalectomy, the excessively produced mineralocorticoid hormone could probably be aldosterone. Furthermore, the atrophy of the zona fascicularis and reticularis was less manifested than that in overt Cushing’s syndrome [27], although DHEA-ST immunoreactivity was diminished compared to normal adrenal gland [28]. These histological findings therefore indicate that these two adrenal adenomas cause excessive production and secretion of cortisol and aldosterone autonomously in the right adrenal gland.

In conclusion, the present study demonstrated combined primary aldosteronism and preclinical Cushing’s syndrome in a 57 year-old woman. She had two adenomas in the right adrenal gland. Because she had little clinical manifestation, the adenomas were only incidentally discovered. As the right adrenal gland had double functioning adenomas, this clearly indicated adrenalectomy for the therapeutic approach. The present study strongly indicates that overproduction of both aldosterone and cortisol was evident in the two adenomas of the right adrenal gland in immunohistochemical study for steroidogenic enzymes, whereas there was less clinical manifestation of primary aldosteronism and Cushing’s syndrome in the present patient.

References

the left adrenal gland of a patient with Cushing’s syndrome. *Clin Endocrinol (Oxf)* 46: 227–234.


