Case Report

A Case of Aldosterone-Producing Adrenocortical Adenoma Associated with a Probable Post-Operative Adrenal Crisis: Histopathological Analyses of the Adrenal Gland

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We describe a case of aldosterone-producing adrenocortical adenoma (APA) associated with a probable post-operative adrenal crisis possibly due to subtle autonomous cortisol secretion. The patient was a 46-year-old female who suffered from severe hypertension and hypokalemia. CT and MRI scans revealed a 2-cm diameter adrenal mass. The patient’s plasma aldosterone level was increased, and her plasma renin activity was suppressed, both of which findings were consistent with APA. Cushingoid appearance was not observed. Morning and midnight serum cortisol and plasma adrenocorticotropic hormone (ACTH) levels were all within the normal range. Her serum cortisol level was suppressed to 1.9 μg/dl as measured by an overnight 1-mg dexamethasone suppression test, but was incompletely suppressed (2.7 μg/dl) by an overnight 8-mg dexamethasone suppression test. In addition, adrenocortical scintigraphy showed a strong uptake at the tumor region and a complete suppression of the contra-lateral adrenal uptake. After unilateral adrenalectomy, she had an episode of adrenal crisis, and a transient glucocorticoid replacement improved the symptoms. Histopathological studies demonstrated that the tumor was basically compatible with APA. The clear cells in the tumor were admixed with small numbers of compact cells that expressed 17β-hydroxylase, suggesting that the tumor was able to produce and secrete cortisol. In addition, the adjacent non-neoplastic adrenal cortex showed cortical atrophy, and dehydroepiandrosterone sulfotransferase immunoreactivity in the zonae fasciculata and reticularis was markedly diminished, suggesting that the hypothalamo-pituitary-adrenal (HPA) axis of the patient was suppressed due to neoplastic production and secretion of cortisol. Together, these findings suggested that autonomous secretion of cortisol from the tumor suppressed the HPA axis of the patient, thereby triggering the probable post-operative adrenal crisis. Post-operative adrenocortical insufficiency should be considered in clinical management of patients with relatively large APA, even when physical signs of autonomous cortisol overproduction are not apparent. (Hypertens Res 2003; 26: 663–668)

Key Words: primary aldosteronism, aldosterone, cortisol, hypertension

Introduction

Primary aldosteronism (PA) is a syndrome characterized by hypertension, hypokalemia, suppressed plasma renin activity (PRA), and increased aldosterone secretion, and was first reported by Conn (1). As a result of technological advances in endocrinological and radiological examination techniques, it has recently been reported that the prevalence of PA is much larger than previously thought (2–4). Approximately two-
thirds of cases of PA are known to be caused by an aldosterone-producing adrenocortical adenoma (APA), while the remaining one-thirds being due to hyperplasia (5). Histopathologically, APA is usually composed of clear cells in the tumor and paradoxical hyperplasia in the zona glomerulosa of the adjacent adrenal tissue (6, 7). In contrast, adrenocortical adenoma demonstrating Cushing’s syndrome is usually composed of dominant compact tumor cells admixed with some clear cells, and is characterized by cortical atrophy of the adjacent adrenal tissue due to suppression of the hypothalamo-pituitary-adrenal (HPA) axis by neoplastic cortisol overproduction (8).

Recently, technological advances in CT and MRI scanning have resulted in an increased number of incidentally discovered adrenal tumors so called incidentalomas. Some of these cases have been reported to be associated with subtle autonomous cortisol secretion that is insufficient to cause clinically overt Cushing’s syndrome (9–11), and have been categorized as cases of preclinical (or subclinical) Cushing’s syndrome (12–16).

There have been a few reported cases of APA which were complicated with Cushing’s syndrome (17) or preclinical Cushing’s syndrome (18–21). In the present report, we describe the case of a patient with APA who suffered a probable transient post-operative adrenal crisis. In this case, suppression of the HPA axis was clearly indicated by histopathological analyses of resected adrenal specimens, including immunohistochemical analyses of steroidogenic enzymes.

### Methods and Results

#### Case Report

A 46-year-old female who had experienced nocturia, edema, and weight gain since 1997 was admitted to a local hospital in February 1998 due to sudden muscle weakness of the extremities. Severe hypertension and hypokalemia were confirmed, and she was referred to the Department of Medicine of Tohoku University Hospital, Sendai, Japan in April 1998. Her blood pressure was 174/104 mmHg. She had slight muscle weakness, nocturia, and hypertensive/arteriosclerotic retinopathy (Scheie II). Abdominal vascular murmur was not audible. No clinical symptoms of Cushing’s syndrome — i.e., central obesity, moon face, striae cutis, acne, and etc. — were present. Laboratory data demonstrated a low serum potassium level (2.3 mEq/l), increased urine potassium secretion (38.5 mEq/day), mild metabolic alkalosis (pH 7.449, base excess 3.5 mEq/l), and moderately decreased glomerular filtration rate (58 ml/min). Proteinuria and hematuria were not observed, and urinary sediment was not prominent. As shown in Table 1, her plasma aldosterone level was extremely high (83.2 ng/dl; normal range, 2–12 ng/dl), and her plasma renin activity was suppressed (5.2 ng/ml/6 h; normal range, 5–30 ng/ml/6 h). Neither of these symptoms was affected by oral administration of 50 mg captopril (data not shown). Morning and midnight serum cortisol and plasma adrenocorticotropic hormone (ACTH) levels were all within the normal range (Table 1). Although the plasma cortisol level was suppressed to 1.9 µg/dl as measured by an overnight 1-mg dexamethasone suppression test (normal range <3 µg/dl), cortisol suppression was incomplete when measured by an overnight 8-mg dexamethasone suppression test (2.7 µg/dl; normal range <1 µg/dl) (Table 1). The urinary excretions of both free cortisol (108.6 µg/day) and 17-hydroxycorticosteroids (5.2 mg/day) were approximately within the normal range, while urinary 17-ketosteroids excretion was decreased (2.0 mg/day). As shown in Fig. 1, a CT scan demonstrated a low-density 2-cm diameter tumor in the right adrenal gland (A, indicated by an arrow) that was heterogeneously enhanced by contrast imaging (B, indicated by an arrow). Slight, but not significant, cortical atrophy of the left adrenal gland was observed in the CT scan (Fig. 1A, B). Moreover, an out-of-phase image of the MRI scan demonstrated heterogeneous suppression of the fat-containing area of the tumor (Fig. 1C, indicated by an arrow). Adrenocortical scintigraphy using 131I-6-β-iodomethyl-norcholesterol demonstrated a strong uptake at the tumor and a complete suppression of the contra-lateral adrenal uptake (Fig. 1D).

#### Table 1. Endocrinological Examinations

<table>
<thead>
<tr>
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<th>Preoperative</th>
<th>Postoperative</th>
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<tr>
<td></td>
<td>Circadian rhythm</td>
<td>Dexamethasone suppression</td>
</tr>
<tr>
<td></td>
<td>2300 h 0800 h</td>
<td>1 mg 8 mg</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>83.2</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/6 h)</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Serum cortisol (µg/dl)</td>
<td>2.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Plasma ACTH (pg/ml)</td>
<td>6.3</td>
<td>27.0</td>
</tr>
<tr>
<td>Urinary free cortisol (µg/day)</td>
<td>108.6</td>
<td>54.1</td>
</tr>
<tr>
<td>Urinary 17-hydroxycorticosteroids (mg/day)</td>
<td>5.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Urinary 17-ketosteroids (mg/day)</td>
<td>2.0</td>
<td>1.8</td>
</tr>
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</table>

ACTH, adrenocorticotropic hormone.
Based on these findings, a diagnosis of PA due to right APA with mild autonomous cortisol secretion was made. Her blood pressure and serum potassium levels were controlled by oral administration of several anti-hypertensive drugs (nifedipine, lisinopril, amosulalol, and spironolactone) and potassium chloride. She was then referred to the Department of Urology of Tohoku University Hospital, and a right adrenalectomy was performed in July 1998. The size of the tumor was $2.2 \times 2.2$ cm, and it appeared golden yellow on the cut surface (Fig. 2A). There was no evidence of adrenocortical malignancy based on the criteria of Weiss (22). The tumor was mainly composed of clear cells (Fig. 2B) admixed with foci of compact cells (Fig. 2C, indicated by arrows). In the non-neoplastic adrenal glands, paradoxical hyperplasia, which is frequently detected in non-neoplastic adrenals of patients with APA, was observed in the zona glomerulosa (Fig. 2D, indicated by arrows), along with cortical atrophy in the zonae fasciculata and reticularis. Intravenous hydrocortisone was administrated post-operatively on the day of the operation. Several days after the operation, she experienced severe general fatigue, dizziness, appetite loss, abdominal pain, nausea, vomiting, shortness of breath, a slight fever ($\sim 37^\circ$C), and a lowering ($\sim 20$ mmHg) of blood pressure. Since her chest X-ray and CRP were almost normal, and her relative ratio of eosinophil was increased (4–5%) compared with the pre-operative range (0–1%), her symptoms were considered to represent a probable post-operative adrenal crisis. From post-operative day 5 to 12, she received oral administration of a steroid replacement (dexamethasone 1 mg/day). Her symptoms of adrenal crisis improved, and the steroid replacement was tapered. Her blood pressure was controlled by benidipine alone, and her serum potassium levels returned to normal without potassium supplementation. Both her plasma aldosterone level and plasma renin activity were normalized after the operation (Table 1). Although the serum cortisol and plasma ACTH levels were also within the normal range post-operatively, the post-operative urinary excretions of free cortisol and 17-hydroxycorticosteroids were significantly decreased (Table 1), indicating that her HPA axis was suppressed by neoplastic cortisol overproduction. Moreover, the fasting plasma glucose level was decreased post-operatively (from 105 to 82 mg/dl), also indicating that neoplastic cortisol affected her glucose metabolism.

**Immunohistochemical Studies**

Characteristics of the tumor were further examined by immunohistochemical studies. We examined the immunolocal-
The results of the immunohistochemical studies are summarized in Table 2. P450scc, 3β-HSD (Fig. 3A), P450c21, and P450c11 immunoreactivity was all apparent in the tumor cells, while DHEA-ST immunoreactivity was not (Table 2). 3β-HSD immunoreactivity was not detected in those zona glomerulosa cells of the adjacent adrenal tissue that demonstrated paradoxical hyperplasia (Fig. 3B, indicated by arrows). P450c17 immunoreactivity was focally present in the compact tumor cells admixed with the clear cells (Fig. 3C, indicated by arrows). DHEA-ST immunoreactivity was markedly diminished in the zona fasciculata and reticularis of the adjacent non-neoplastic adrenal tissue (Fig. 3D).

**Discussion**

We here reported the case of a female patient with APA who suffered a probable post-operative adrenal crisis. Her laboratory data, including overnight dexamethasone suppression tests, demonstrated that the tumor autonomously secreted small amounts of cortisol in addition to large amounts of aldosterone, although the overnight 1-mg dexamethasone suppression test is known to be affected by several factors (23). Histopathological data were consistent with APA, since the tumor was mainly composed of clear cells with paradoxical hyperplasia in the zona glomerulosa of the adjacent adrenal tissue, where 3β-HSD was not present (6). As usually observed in APA, DHEA-ST was not expressed in the tumor cells (7). Relatively small numbers of compact tumor cells and predominant clear tumor cells in the neoplasm expressed P450c17 immunoreactivity, indicating that the compact cells could produce and secrete cortisol. Cortical atrophy and reduced expression of DHEA-ST were detected in the cortex of the adjacent non-neoplastic adrenal gland, indicating that the HPA axis of the patient was suppressed (24, 25). The cortical atrophy and reduced expression of DHEA-ST of the patient were not prominent compared with those of patients with Cushing’s syndrome, but were consistent with the mild
pre-operative hormonal abnormality and rapid recovery from a probable post-operative adrenal insufficiency. Therefore, the results of these histopathological studies clearly demonstrated the suppression of HPA, which may have caused her probable post-operative adrenal crisis.

There have been a few reported cases of APA which were complicated with Cushing’s syndrome (17) or preclinical Cushing’s syndrome (18–21). Although two of the APA cases associated with preclinical Cushing’s syndrome received a transient steroid replacement therapy, no symptoms of post-operative adrenal crisis were detected (18, 21). The adenomas in these cases were large (greater than 3 cm), and an overnight 1-mg dexamethasone suppression test had no effect on their cortisol levels (18, 21). There has also been a recent report of a patient with APA who suffered a transient post-operative adrenal crisis (19). The adenoma was also large (greater than 3 cm) in this case, and the clear tumor cells were admixed with large numbers of compact cells (19). The APAs of these cases may therefore have been characterized by a strong autonomy of neoplastic cortisol secretion. The present case was distinct from the above-described cases in that the probable post-surgical adrenal crisis may have occurred through HPA axis suppression due to small amounts of autonomous cortisol secretion, as indicated by both endocrinological evaluation and histopathological examinations of resected adrenal specimens. These results suggest that the occurrence of post-operative adenocortical insufficiency should be included in the differential diagnosis of patients with large APA, even when no physical signs of autonomous cortisol overproduction are suggested. Careful pre-operative endocrinological examinations should also be required to predict the risk of crisis due to the post-operative adrenal insufficiency, and intensive histopathological examinations, especially those in non-neoplastic adjacent adrenal tissue, are very useful to confirm the cortical atrophy.

### Table 2. Summary of Immunohistochemistry of Steroidogenic Enzymes

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Rt. adrenal adenoma</th>
<th>Rt. attached adrenal</th>
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<tbody>
<tr>
<td>P450scC11</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3β-HSD</td>
<td>+</td>
<td>- (zona glomerulosa)</td>
</tr>
<tr>
<td>P450c21</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>P450c17</td>
<td>f +</td>
<td></td>
</tr>
<tr>
<td>P450c11</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>DHEA-ST</td>
<td>-</td>
<td>w +</td>
</tr>
</tbody>
</table>

-, negative; +, positive; f+, focally positive; w+, weakly positive. Rt., right; P450scC11, cholesterol side chain cleavage; 3β-HSD, 3β-hydroxysteroid dehydrogenase; P450c21, 21-hydroxylase; P450c17, 17α-hydroxylase; P450c11, 11β-hydroxylase; DHEA-ST, dehydroepiandrosterone sulfotransferase.

### References

17. Baert D, Nobels F, Van Crombrugge P: Combined Conn’s and Cushing’s syndrome: an unusual presentation of ade-