Combined Primary Aldosteronism and Cushing’s Syndrome Due to a Single Adrenocortical Adenoma Complicated by Hashimoto’s Thyroiditis

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Abstract

A 43-year-old Japanese woman presented hypertension, hypokalemia and typical Cushingoid signs. Autonomous secretion of both aldosterone and cortisol was shown. Abdominal computed tomography demonstrated a single tumor in the right adrenal gland, which established the diagnosis of combined primary aldosteronism and Cushing’s syndrome. The resected tumor was a golden yellow-colored adenoma (diameter 4.3 cm) which expressed P450aldo and P450npp, causing oversecretion of both hormones from this adenoma. After tumor resection, overproduction of both hormones disappeared and she developed adrenal insufficiency, suggesting the strong suppression of normal adrenal function. This case was complicated by Hashimoto’s thyroiditis.

Case Report

A 43-year-old Japanese woman was referred to our hospital for evaluation of hypertension. At age 39, hypertension and hypokalemia were noted at the former hospital. Therapy with antihypertensive agents and potassium chloride had been initiated, which resulted in only limited control. She complained of vertigo, headache, palpitation, fatigability, easy bruising and facial edema for 3 months, then she was transferred to our outpatient clinic. Her blood pressure was 190/114 mmHg despite taking antihypertensive agents (amlodipine besilate 5 mg/day, lisinopril 10 mg/day) and pulse rate was 90/min. Her height was 150 cm and weight was 53 kg. She had a temperature of 36.2°C. Her thyroid glands were diffusely enlarged, stony hard and non-tender with an irregular surface. Features of Cushing’s syndrome (truncal obesity with purple striae at the umbilical region) (Fig. 1) were noted. Fundoscopic examination revealed segmental narrowing of retinal arteries without exudate, hemorrhage and papilledema. Heart sounds were normal without murmurs. Lung sounds were clear to auscultation. Neurological examinations were normal. Chest X-ray film revealed no abnormalities. Electrocardiography revealed normal sinus rhythm at a rate of 87/min and left ventricular hypertrophy by voltage criteria.

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Introduction

Primary aldosteronism (PA) is generally caused by an overproduction of aldosterone from adrenocortical adenoma. Originally, PA has been defined as an overproduction of aldosterone from adrenal gland(s) without overproduction of cortisol (1). Therefore, oversecretion of cortisol should be excluded. However, since the report of Hogan et al (2), several papers have described an aldosterone-producing adenoma (APA) or adrenal carcinoma which autonomously secretes cortisol as well (3–8).

In most cases, the secretion of cortisol is kept under ACTH feedback control (9) and the amount of cortisol secreted from APA is too small to induce overt Cushingoid signs. Therefore, autonomous production of cortisol is rare and hypersecretion of cortisol, leading to typical clinical manifestations of Cushing’s syndrome, is extremely rare in aldosterone-producing tumor(s) (10–13).

Here we present a very rare case of combined PA and Cushing’s syndrome due to a single adrenocortical adenoma. This case was complicated by Hashimoto’s thyroiditis. Autonomous secretion of both hormones, aldosterone and cortisol, was confirmed by immunohistochemical findings and the clinical course following adrenalectomy.
Urine dipstick showed 1+ for protein. The white blood cell count was 8,400/μl; hemoglobin, 14.5 g/dl; and platelets, 22.4×10^4/μl. Hemocoagulation studies were normal. Evaluation of serum chemistry revealed hypokalemia (serum potassium, 2.9 mEq/l) despite potassium replacement therapy. Arterial blood gas analysis revealed pH, 7.488; PaO₂, 88.8 mmHg; PaCO₂, 39.5 mmHg; HCO₃⁻, 26.8 mEq/l. Her creatinine clearance was 45.8 ml/min. A cranial CT scan disclosed cerebral infarction. Holter electrocardiography and ultracardiology revealed no abnormalities, but plasma concentration of brain natriuretic peptide (BNP) was elevated (34.8 pg/ml, normal range <18 pg/ml).

Table 1 summarizes the basal hormonal data. Plasma aldosterone concentration (PAC) was elevated, whereas plasma renin activity (PRA) was at the lower limit of the normal range. Plasma cortisol was elevated, whereas plasma ACTH was below the detectable limit. The plasma level of dehydroepiandrosterone-sulfate (DHEA-S) was low. Plasma levels of epinephrine and norepinephrine were normal.

Intravenous administration of furosemide (40 mg) with the
Combined PA and Cushing’s Syndrome

Figure 2. Abdominal computed tomography. Before (upper) and after (lower) contrast enhancement. Adrenocortical tumor was slightly enhanced, indicating an adrenal adenoma.

The diurnal rhythm of plasma ACTH and cortisol was absent (Table 3), and plasma cortisol was not suppressed by overnight 8 mg dexamethasone administration (Table 4).

An abdominal CT scan demonstrated right adrenal adenoma, 4 cm in diameter (Fig. 2). The left adrenal gland was normal.

This case, hypertension, hypokalemia, high PAC and suppressed PRA were noted. Typical clinical signs of cortisol overproduction (truncal obesity, striae cutis and easy bruising) and autonomous secretion of cortisol were also observed, indicating Cushing’s syndrome. Based on these results, a preoperative diagnosis of combined PA and Cushing’s syndrome due to a single adrenocortical adenoma was made.

Thyroid function test revealed serum levels of free T₃ 6.6 pg/ml (normal range 3.7–5.5 pg/ml), free T₄ 1.63 ng/dl (normal range 0.85–1.65 ng/dl), TSH <0.05 μU/ml (normal range 0.40–4.45 μU/ml), showing hyperthyroidism. Anti-thyroglobulin, thyroid peroxidase, and thyroid microsomal antibody were all positive. The titers of these three antibodies were extremely high. On the other hand, TSH receptor antibody and thyroid stimulating antibody were negative. Ultrasonography of the thyroid gland showed diffuse enlargement of the glands without any masses. Echo level of the thyroid glands was very low, consistent with Hashimoto’s thyroiditis. Two months later, the TSH level rose to 109.00 μU/ml and she developed persistent hypothyroidism.

We speculated that her hyperthyroidism was painless thyroiditis. At present, she needs 150 μg per day of levothyroxine in order to maintain normal thyroid function.

Right adrenalectomy was performed on April 12, 2000 and an adrenal adenoma of 4.3x3.1x2.8 cm was removed (Fig. 3). The adenoma was circular and encapsulated. Its cut surface was golden yellow. Light microscopic examination showed that the adenoma was composed of large clear cortical cells laden with lipid (Fig. 4). The adjacent normal adrenocortical tissues were atrophic. Immunohistochemical examination revealed that adenoma cells expressed immunoreactivity of 3β-hydroxysteroid dehydrogenase (3β-HSD), aldosterone synthase cytochrome P450 (P450₆p₆₈) (Fig. 5A) and cytochrome P450₁₁β.
Figure 5. Immunohistochemical staining of adrenal adenoma positive for P450aldo (A) and P450lrp (B) (×10).

Discussion

In this paper, we described a very rare case of combined PA and Cushing’s syndrome. Concurrent oversecretion of aldosterone and cortisol from a single adrenocortical adenoma was strongly suggested by the clinical course after adrenalectomy. Soon after the operation, her PAC and serum potassium concentration were normalized. Her blood pressure was decreased significantly. During the tapering of hydrocortisone, she developed adrenal insufficiency. These observations indicate the loss of autonomous secretion of these two hormones after surgery.

The resected adenoma was composed of lipid-rich clear cells and its cut surface was golden yellow-colored, which were typical characteristics of APA. There was no evidence of malignancy in the adrenocortical tumor according to the criteria of Weiss (14). Immunohistochemical examination revealed the expression of P450aldo as well as P450iar, confirming the ability of cortisol secretion. The precise mechanism of simultaneous expression of both enzymes in a single tumor was not clear. One possibility is that APA might be differentiated from transitional cells, which are located between the zona glomerulosa and zona fasciculata bearing characteristics of both glomerulosa and fasciculata cells (15). In normal conditions, this transitional zone exists only during the embryological development period (16). In some pathological conditions, such as glucocorticoid-suppressible aldosteronism, transitional cells have been identified (17). Another possibility is that APA is composed of both aldosterone-producing cells and cortisol-producing cells. The reports describing the APA containing zona glomerulosa, zona fasciculata and their hybrid cells (9, 18, 19) support this possibility. In our case, the latter possibility is more likely considering the result of immunohistochemical studies.

In the present case, evident clinical Cushingoid signs were present. The basal level of plasma cortisol was above the normal range and overnight suppression of cortisol secretion after the administration of 8 mg dexamethasone was absent. These observations are the evidence of autonomous secretion of cortisol.

The most interesting finding in this case was that the removed adenoma was as big as 4.3 cm in diameter. The mechanism underlying autonomous cortisol secretion is not clear. It is intriguing to speculate that the number of the cells expressing P450iar in this adenoma was increased excessively, and it may be that the net activity of P450iar became excessive, resulting in escape from the feedback regulation of ACTH.

After the adrenalectomy, this patient developed adrenal insufficiency. Histological examinations demonstrated the atrophy of adjacent adrenocortical tissue. Considering this postoperative event, function of the contralateral adrenal gland must have been suppressed, although abdominal CT revealed no abnormality in the left adrenal gland. The low DHEA-S level might reflect suppressed adrenal function. This adrenal insufficiency might be influenced by severe hypothyroidism, which needed 150 μg of levothyroxine to be controlled. It seems that severe hypothyroidism might be responsible for the delay of cortisol metabolism, leading to the strong pharmacological glucocorticoid effect, and suppressed normal adrenal function.

In our case, adrenal venous sampling was not performed. The content of aldosterone in the resected adenoma was not measured. The enzymatic activity of P450aro was not measured,
either. Therefore, we do not have any direct evidence that this adenoma produced an excessive amount of aldosterone. Consequently, the possibility of idiopathic hyperaldosteronism (IHA) cannot be excluded. In the case of IHA, it is known that aldosterone concentration is normalized after unilateral adrenalectomy. Thus, it is necessary to be on the alert for a subsequent increase in aldosterone concentration and blood pressure.

In this patient, cranial CT revealed cerebral infarction, although no clinical signs were present. Plasma BNP levels were elevated and hypertension was persistent even after the tumor resection. Proteinuria was present and creatinine clearance was reduced, suggesting the renal insufficiency. Aldosterone excess has been shown to be closely related to the congestive heart failure (20, 21), renal dysfunction (22), or cerebral infarction (23). On the other hand, hypercortisolemia is known to cause cardiovascular disease such as hypertension (24). Therefore, the multiple organ damage in this patient tempted us to speculate the possibility of additive pathophysiological effects of aldosterone and cortisol on vital cardiovascular organs, such as kidneys, heart, brain and blood vessels.

References


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