CASE REPORT

Bilateral Aldosteronoma Associated with Secondary Aldosteronism in a Chronic Hemodialysis Subject

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Abstract

We demonstrated a rare case of bilateral aldosteronoma accompanied by secondary aldosteronism in a 37-year-old man with chronic renal failure on hemodialysis. He initially developed immunoglobulin A nephropathy at 11 years old, and had been treated with hemodialysis since the age of 17 years. His blood pressure was 110/68 mmHg, and no other abnormal findings were detected. Laboratory findings revealed that serum potassium was 3.9 mmol/L; plasma renin activity, 4.8 ng/ml/h and plasma aldosterone, 19,000 pg/mL. Abdominal computed tomography revealed bilateral adenocortical tumors, measuring 34 and 40 mm in diameter in right and left tumors, respectively. 131I-Adosterol scintigram showed bilateral accumulation. Left adrenalectomy was performed under laparoscopy. The tumor was encapsulated and well-circumscribed. The majority of the tumor was composed of a dark-brown portion admixed with sporadic foci of golden-yellow portions. Hyaline degeneration was detected in its central portion. The tumor was composed of clear cortical cells in viable portions. Tumor cells demonstrated immunoreactivity for the cholesterol side-chain cleavage enzyme, 3β-hydroxysteroid dehydrogenase (3β-HSD II) and 21-hydroxylase, but not 17α-hydroxylase. In the adjacent non-neoplastic adrenals, 3 β-HSD II was markedly present in the hyperplastic glomerulosar zone. These findings suggest that the presence of secondary aldosteronism, which is closely related to the conditions of chronic renal failure on hemodialysis, eventually promoted the development of bilateral aldosteronoma from the zona glomerulosar hyperplasia.

Key words: bilateral aldosteronoma, secondary aldosteronism

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Introduction

Edematous disorders including liver cirrhosis with ascites, congestive heart failure and nephrotic syndrome are often associated with secondary aldosteronism, which further exacerbates water and sodium retention (1-3). In such a state the renin-angiotensin-aldosterone system is activated, and there is high plasma renin activity and aldosterone concentration. In general, aldosterone-producing adenoma is not accompanied with secondary aldosteronism. However, it is not known whether aldosteronoma might develop from adrenal hyperplasia if secondary aldosteronism persists during an extremely long period.

Generally it is only one tumor in the unilateral adrenal gland that produces aldosterone. However, there is a rare disorder of bilateral adrenal tumors in primary aldosteronism (4-6). The tumor diameter usually ranges from less than 20 mm to about 30 mm. In contrast, the tumor grows primarily in non-functioning adrenal adenoma or metastatic tumors in adrenal gland.

Here, we report a man with bilateral aldosteronoma closely associated with secondary aldosteronism. We examined the immunohistochemistry of the steroidogenic enzymes to elucidate the steroidogenesis in adrenal tissues, and the relation of aldosteronoma with secondary aldosteronism.
Case Report

A 37-year-old man had been treated with chronic hemodialysis three times a week at a local dialysis clinic for 20 years. He was examined by abdominal CT and echogram, which revealed bilateral adrenal tumors of 34 and 40 mm in diameter, respectively. He was referred to Jichi Medical University Saitama Medical Center to further investigate adrenal tumors in October 2006. He initially had proteinuria at 11 years. Half a year later renal biopsy was carried out at Saitama Social Insurance Hospital, and he was diagnosed to have immunoglobulin A (IgA) nephropathy. His renal impairment gradually worsened, and finally hemodialysis was begun at 17 years. At 33 years he had secondary hyperparathyroidism, and three lobes of parathyroid glands were resected. He had had hypertension and had been treated with 10 mg olmesartan. However, oral administration of olmesartan was discontinued in September 2006 because his systolic blood pressure became less than 120 mmHg. Also, he received 2,250 U erythropoietin injection every week and 1 µg vitamin D₃ three times a week. He was in anuric state.

Physical findings at hospitalization showed that his height was 171.5 cm and body weight was 73.3 kg with a body mass index of 24.9. Blood pressure was 110/68 mmHg without postural change, and pulse rate, 84/min with regular rhythm. His consciousness was alert. Palpebral conjunctiva was anemic. There was an operation scar in his neck. No abnormal finding was found in his chest and abdomen. He had arterio-venous shunt in the right forearm. There was no edema in pretibia. Neurological findings showed diminished deep tendon reflexes and weakened vibration in the lower extremities.

Laboratory findings showed that white blood cells were 5,430/cmm; red blood cells, 316×10⁴/cmm; hemoglobin, 10.8 g/dL; hematocrit, 31.5%; and platelets, 14.0×10⁴/cmm. Serum sodium (Na) was 136 mmol/L; potassium (K), 3.9 mmol/L; chloride, 103 mmol/L; calcium, 10.7 mg/dL; and phosphate, 3.9 mg/dL. Blood urea nitrogen was 44 mg/dL; serum creatinine, 10.48 mg/dL; and uric acid, 5.7 mg/dL. Fasting plasma glucose was 104 mg/dL; total cholesterol, 140 mg/dL; and triglyceride, 225 mg/dL. Endocrinological data are summarized in Table 1. Plasma renin activity was 4.8 ng/mL/hr and plasma aldosterone concentration was 19,000 pg/mL. Serum cortisol was 6.7 µg/dL; serum dehydroepiandrosterone sulfate (DHEA-S), 101 ng/mL; and plasma ACTH, 28.0 pg/mL. Urinary excretion of catecholamine was not determined. There was no change in daily profiles of plasma renin activity and plasma aldosterone level (data not shown). Electrocardiogram showed sinus rhythm without any ischemic change. Abdominal CT depicted bilateral adrenal tumors. Right adrenal tumor was 34 mm in diameter, and located in the S7 region of the liver which seemed likely to be a solitary tumor in the liver (Fig. 1A). The density was homogeneous. There was no enhancement in the right adrenal tumor. Successive slices on CT indicated that the tumor was derived from an adrenal gland, but not an intrahepatic one. The left adrenal tumor was 40 mm in diameter. The density was homogeneous (Fig. 1B), and there was no enhancement. ¹³¹I-Adosterone scintigram was performed 7 days after the administration of 2 mg dexamethasone, and showed isotope accumulation bilaterally at equivalent levels (Fig. 2).

Clinical course

These findings indicated that extreme overproduction of aldosterone was profoundly linked to bilateral adrenal tumors. Because he had had chronic renal failure on hemodialysis for 20 years, the laboratory data showed secondary aldosteronism. He did not have severe hypertension or hypokalemia, and so we wondered whether his aldosterone is

| Table 1. Laboratory Findings on Admission |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| TSH             | 3.002 μU/mL     | LH              | 8.39 mIU/mL     | FSH             | 6.15 mIU/mL     |
| ACTH            | 28 pg/mL        | Cortisol        | 6.7 μg/dL       | Aldosterone     | 19000 pg/mL     |
| Cortisol        | 6.7 μg/dL       | PRA             | 4.8 ng/mL/Hr    | DHEA-S          | 101 ng/mL       |
| Aldosterone     | 19000 pg/mL     | DHEA-S          | 101 ng/mL       | Plasma corti   | 6.7 μg/dL       |

| Figure 1. Abdominal computed tomography revealed bilateral low density tumors in the adrenal regions. |
biologically active. Since the tumor size was 40 mm in diameter and malignant tumor could not be ruled out, left adrenalectomy was initially carried out in April 2007. The resected adrenal tissue was examined by immunocytochemistry to determine the production of aldosterone, as noted below. After the operation, he continued to be treated with hemodialysis. His blood pressure was 120/68 mmHg. Plasma renin activity and plasma aldosterone concentration were decreased to 2.6 ng/mL/hr and 974 pg/mL 2 weeks after the operation. However, a year and half later plasma renin activity and plasma aldosterone levels were again elevated to 4.7 ng/mL/hr and 15,100 pg/mL, respectively.

**Pathological findings**

**Macroscopic findings**

There was a relatively well-circumscribed adrenocortical tumor detected in his left adrenal gland. Its size at the cut surface was 40 mm in greatest dimension. The tumor was encapsulated and well circumscribed. The cut surface of the tumor was mostly dark brown, with sporadic foci colored golden yellow (Fig. 3). Non-neoplastic adrenal tissue was identified.

**Microscopic findings**

The tumor was considered an adrenocortical adenoma according to the criteria of Weiss (7-9). Hyaline degeneration was detected in the center of the lesion, in which cortical parenchymal cells demonstrated histologically pseudoglandular formation (Fig. 4A). The tumor was predominantly composed of clear cortical cells (Fig. 4B). Tumor cells demonstrated immunoreactivity for the cholesterol side-chain cleavage enzyme, 3β-hydroxysteroid dehydrogenase (3β-HSD II) and 21-hydroxylase (Fig. 5A, B, C). However, 17α-hydroxylase immunoreactivity, which is essential for cortisol synthesis but not aldosterone synthesis, was absent in the tumor cells (Fig. 5D).

The adjacent non-neoplastic adrenal tissues demonstrated a moderate degree of hyperplasia of zona glomerulosa [MBS1] and zona reticularis. 3β-HSD II immunoreactivity was markedly detected in the hyperplastic glomerulosa cells (Fig. 6). These findings are consistent with secondary aldosteronism due to chronic renal failure.

**Discussion**

There was a marked increment in plasma aldosterone concentration concomitant with high plasma renin activity in the patient with end-stage kidney disease on hemodialysis. The pathogenesis is clinically consistent with secondary aldosteronism. The plasma aldosterone levels are typically high in patients with end-stage kidney disease as compared with those with normal renal function, in part because of impaired urinary excretion as well as accumulation of inactive metabolites (10). An atypical finding is an extremely high level of plasma aldosterone, which is 19,000 pg/mL. As noted earlier, adrenal gland had bilateral large aldosteronomas accompanied with hyperplasia in the non-neoplastic adrenal tissues. Plasma aldosterone, in general, might not reach such a high concentration in either primary or secondary aldosteronism. We assume that two large aldosteronomas augmented the autonomous synthesis of aldosterone. Also, both aldosteronomas and hyperplasia of non-neoplastic adrenal tissues could respond to the enhanced renin-angiotensin system to excessively produce aldosterone. However, it may not be simply that the plasma aldosterone concentration is associated with the tumor size of aldosteronoma. The present patient’s blood pressure was not so high although anti-hypertensive agents had been withdrawn one month before admission. Also, the serum potassium level was within normal range under the condition of end-stage kidney disease. These physical and laboratory findings suggested a diminished biological activity of aldosterone in the present subject. However, the subject had been treated with chronic hemodialysis for 20 years, and he was in anuric state. Under such a pathological state aldosterone could not effectively act on renal tubules to cause hypertension or hypokalemia. Hypertension is much more dependent on the circulatory blood volume in hemodialysis patients. The absence of aldosterone-dependent hypertension
Figure 4. Light microscopic finding. (A) The adenoma showed hyaline degeneration in a major part of the central portion, accompanied with some clear tumor cells. The change allowed for pseudoglandular formation. (B) Paradoxical hyperplasia in the zona glomerulosa in the non-neoplastic adrenal tissue. Hematoxylin and Eosin staining. ×400.

Figure 5. Immunohistochemical findings of (A) cholesterol side-chain cleavage enzyme, (B) 3β-hydroxysteroid dehydrogenase (3β-HSD II), (C) 21-hydroxylase and (D) 17α-hydroxylase in the left adrenal tumor.

and hypokalemia might not be the major issue to deny the aldosterone activity in the subject. Further study will be necessary to elucidate the exact mechanism for the remarkably high level of plasma aldosterone.

He had bilateral adrenal tumors, and the left adrenal tumor was resected. Histological study clearly demonstrated aldosteronoma associated with hyperplasia of non-neoplastic adrenal tissues. In particular, the immunoreactivity of 3β-HSD II was positive in the non-neoplastic tissues, which is in general not detected in primary aldosteronism (11, 12). Thus, the present aldosteronoma is quite a unique tumor regarding the following several points: First, there were bilateral large adrenal tumors, which were greater than 30 mm in diameter. The left adrenal tumor was histologically confirmed as aldosteronoma. Though the right adrenal tumor was not examined, it also could be aldosteronoma. The size of greater than 30 mm is very uncommon as aldosteronoma. Because hyaline degeneration occupied a considerable central portion of aldosteronoma, the tumor had developed gradually for the long time to the present size. Second, aldosterone was not only synthesized in the aldosteronoma, but also in the non-neoplastic adrenal tissues because of the positive immunostaining of 3β-HSD II. The subject had had secondary aldosteronism for the long time since he had been treated with hemodialysis for 20 years. Basically adrenal hyperplasia persisted, and we cannot rule out the possibility
that aldosteronoma had developed from adrenal hyperplasia of bilateral adrenal glands. Such an aldosteronoma has been reported in the literature (13-16). This could be a rare histological observation that adrenal hyperplasia converts to adrenal aldosteronoma during the long duration of secondary aldosteronism.

In summary, the present study demonstrated bilateral large aldosteronomas closely associated with secondary aldosteronism in a subject with end-stage kidney disease on hemodialysis. This was subsequently confirmed by immunohistochemical study. He had a remarkably high level of plasma aldosterone, but clinical features of hypertension and hypokalemia were not manifested. The present findings indicate that secondary aldosteronism, which had persisted for more than 20 years, may eventually develop bilateral aldosteronomas based on adrenal hyperplasia.

References