A Rare Case of Adrenal Cysts Associated With Bilateral Incidentalomas and Diffuse Hyperplasia of the Zona Glomerulosa

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Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CT, computed tomography; CYP11β2, 18-hydroxylase; DHEA-ST, dehydroepiandrosterone-sulfotransferase; HPA, hypothalamus-pituitary-adrenal; HSD3β, 3β-hydroxysteroid dehydrogenase; H, Hounsfield unit; MRI, magnetic resonance imaging; PET, positron emission tomography; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose co-transport protein-2.

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Abstract

Characterization of adrenocortical disorders is challenging because of varying origins, laterality, the presence or absence of hormone production, and unclarity about the benign or malignant nature of the lesion. Histopathological examination in conjunction with immunohistochemistry is generally considered mandatory in this characterization. We report a rare case of bilateral adrenocortical adenomas associated with unilateral adrenal endothelial cysts in a 65-year-old woman whose condition was not diagnosed before surgery. Detailed histological examination of the resected adrenal glands revealed hyperplasia in the zona glomerulosa. Despite hyperplasia, the patient had normal serum aldosterone levels and renin activity without clinical evidence of hypertension. The patient was treated with a sodium-glucose cotransporter protein 2 (SGLT2) inhibitor. This may have stimulated the renin-angiotensin-aldosterone system. To the best of our knowledge, this is the first case in which both relatively large bilateral adrenocortical adenomas and unilateral adrenal endothelial cysts were detected. This case also highlights the complexity and difficulty of preoperative diagnosis. Furthermore, this case reports the first detailed histopathological examination of adrenal lesions with SGLT2 treatment and the possibility of SGLT2 inhibitor treatment resulting in histological hyperplasia in the zona glomerulosa; however, it is difficult to prove a causative relationship between
SGLT2 inhibitors and hyperplasia of the zona glomerulosa based on the data of this case. It can be confirmed only under limited conditions; therefore, further studies on adrenal gland histology employing SGLT2 inhibition are warranted.

**Key Words:** adrenal incidentaloma, aldosterone, diffuse adrenocortical hyperplasia, endothelial cyst, renin, SGLT2 inhibitor

Adrenal cysts are rare cystic masses that are detected incidentally during autopsy in 0.06% of the population [1]. Approximately 6% of tumors detected as adrenal incidentalomas are adrenal cysts, as observed from the data of surgical series [2, 3]; however, a recent prospective study clarified that the incidence is much lower (<1%) [4]. Adrenal cysts are classified as vascular or endothelial, epithelial, or parasitic [1, 5]. Pseudocysts are the most common type of adrenal cysts [6, 7]. Endothelial cysts associated with adrenal neoplasms are rare, with only a few reported cases [6, 8]. In addition, the cases of unilateral endothelial cysts and bilateral adrenal neoplasms have not been reported, to the best of our knowledge.

Primary aldosteronism is caused by the autonomous secretion of aldosterone owing to aldosterone-producing adenoma, multiple adrenocortical micronodules, and diffuse adrenocortical hyperplasia of the zona glomerulosa [9]. These conditions are known to be associated with high serum aldosterone and low renin levels, resulting in hypertension. However, we recently experienced a case of diffuse hyperplasia of the zona glomerulosa, positive for 18-hydroxylase: aldosterone synthase (CYP11B2), in which the patient had normal serum aldosterone levels, renin activity, and blood pressure.

Here, we report a rare case of bilateral adrenal adenomas with unilateral adrenal endothelial cysts. The possibility of sodium-glucose cotransporter protein 2 (SGLT2) inhibitor causing bilateral hyperplasia of the zona glomerulosa of the adrenal gland will also be discussed.

1. **Case Presentation**

A 65-year-old Japanese woman was referred to our hospital for characterization of the bilateral adrenal incidentaloma. At age 63, the patient was diagnosed with type 2 diabetes, which had been treated with diet and exercise therapy, and a gallstone identified by abdominal ultrasonography at a nearby clinic. Other than the diabetes and gallstone, she did not have any past medical history that needs specific mention. At age 64, the patient was administered an SGLT2 inhibitor, empagliflozin (10 mg/day), without any other medications and underwent abdominal ultrasonography for follow-up of the gallstone; however, adrenal masses were not identified at this point. At age 65, adrenal masses were incidentally identified during the abdominal ultrasonography during the follow-up examination of the gallstone. Consequently, subsequent plain abdominal computed tomography (CT) was performed, which revealed bilateral masses measuring 6.2 × 2.5 cm on the right side and 4.6 × 4.1 cm on the left side (Fig. 1A). The right-sided mass was flat, with a small high-density spot, and heterogeneous, with a high-density (30-50 Hounsfield units [H]) and a low-density area (10-20 H). The left-sided mass was almost round with a relatively heterogeneous density (10-40 H).

The patient was admitted to our hospital for detailed examination. On admission, the patient did not present any signs or symptoms associated with excess adrenal cortical hormone levels or its deficiency. She had been taking an antidiabetic drug (empagliflozin, 10 mg/day) for approximately 1 year, and her diabetes was well controlled (fasting blood glucose: 116 mg/dL, glycated hemoglobin [hemoglobin A1c]: 6.9%). Between the third and first month prior to her introduction to our hospital, the patient used an ointment containing betamethasone butyrate propionate (exogenous glucocorticoid) for dermatitis. Physical examination revealed no significant findings. Clinical parameters were as follows: body height, 145.9 cm; body weight, 55.9 kg; blood pressure, 122/60 mm Hg; and heart rate, 60 beats/min. The laboratory data are presented in Table 1. The complete blood count and blood biochemistry tests were almost within the normal range.

Endocrinological data are also presented in Table 1. Blood and 24-hour urine catecholamines were within the normal range. Plasma aldosterone concentration of 149 pg/mL, plasma renin activity of 2.3 ng/mL/h, and aldosterone/renin ratio of 65 were within the normal range. Urine aldosterone level (11 µg/day) was slightly elevated. Cortisol and adrenocorticotropic hormone (ACTH) levels early in the morning were 5.3 µg/dL and 15.8 µg/mL (at an outpatient clinic) and 7.0 µg/dL and 32.0 µg/mL (after hospitalization), respectively (cortisol and ACTH levels were measured by Eclusys Cortisol II and Eclusys ACTH; reference values were 6.2-19.4 µg/dL and 7.2-63.3 µg/mL, respectively [Roche Diagnostics Inc]). In addition, the cortisol levels at 12:00, 18:00, and 23:00 h were 4.4, 3.4, and 3.4 µg/dL, respectively. Although adrenal insufficiency could be caused by prior exogenous corticosteroid use, load test with adrenocorticotropic hormone (ACTH: tetracosactide acetate
250 μg) was performed and the ACTH-stimulated cortisol response was low (cortisol less than 18 μg/dL as a basis for adrenal insufficiency). Load test with corticotropin-releasing hormone (CRH:corticorelin 100 μg) was also performed and the CRH-stimulated ACTH response was intact, but the cortisol response was low. These results indicated secondary adrenocortical hypofunction, probably due to the ointment containing glucocorticoid.

In addition to a plain CT, contrast-enhanced CT was also performed (Fig. 1B). The bilateral tumor showed a clear margin. Cystic regions were clearly detected in the right adrenal region. Magnetic resonance imaging (MRI) revealed some encapsulated fluid lesions in the right-sided mass with high signal intensity on T2-weighted images (Fig. 1C and 1D), suggesting the possibility of cysts or hemangiomas. The left-sided mass showed higher signal intensity than the liver on T2-weighted images. On chemical shift MRI (Fig. 1E and 1F) of the adrenal glands, the loss of signal intensity was not detected in out-of-phase imaging when compared with that of the spleen, suggesting the possibility of malignancy rather than adenoma [10]. However, on 18F-fluorodeoxyglucose positron emission tomography (PET), no suspicious malignant lesion was detected.

The patient underwent laparoscopic right adrenalectomy because the possibility of malignancy could not be excluded. The resected right adrenal gland weighed 45 g, and the tumor measured 45 × 40 × 32 mm. Representative histological findings are illustrated in Fig. 2A and 2B. The tumor was composed of compact cells with eosinophilic cytoplasm and scattered foci of clear cells. Based on the Weiss criteria, the tumor was diagnosed as an adrenocortical adenoma, and the cysts were detected adjacent to the tumor. Most of the right adrenal glands remained intact.

While the characteristics of the left adrenal lesion could not be determined, the left adrenal gland had a different shape from the right adrenal mass, and the possibility of malignancy could not be completely excluded. Therefore, the patient subsequently underwent laparoscopic left adrenalectomy. The resected left adrenal gland weighed 54 g, and the tumor measured 65 × 50 × 30 mm. Representative histological findings are illustrated in Fig. 2C and 2D. The histological features of the tumor in the left adrenal gland were similar to those in the right adrenal gland. The tumor on the left side was also diagnosed as an adrenocortical adenoma. No cysts were discernible in the left resected specimen, and most of the left adrenal glands remained intact.

In addition to the hematoxylin-eosin stain, we immunolocalized steroidogenic enzymes in both the resected adrenal glands (Figs. 3-5). In both tumors, immunoreactivity of 3β-hydroxysteroid dehydrogenase (HSD3β), 17α-hydroxylase, and 11β-hydroxylase (Fig. 3A and 3D) was diffusely detected but that of CYP11B2 [9, 11] was not (Fig. 3B and 3E). These results demonstrate...
Table 1. Laboratory findings of the patient

| Peripheral blood | Endocrinological data | Load test |
|------------------|-----------------------|-----------|
| **WBC** | 6060/mm$^3$ (3300-8600) | (Plasma) | (CRH load) |
| **RBC** | $462 \times 10^6$/mm$^3$ (386-492) | Epinephrine | 24 pg/mL (0-100) | ACTH 0 min 23.1 pg/mL |
| **Hb** | 15.0 g/dL (11.6-14.8) | Norepinephrine | 304 pg/mL (100-450) | 30 min 185.9 pg/mL |
| **Ht** | 44.3% (35.1-44.4) | Dopamine | 10 pg/mL (0-20) | 60 min 155.2 pg/mL |
| **Plt** | $17.8 \times 10^4$/mm$^3$ (15.8-34.8) | Renin | 2.3 ng/mL/h (0.3-5.4) | 90 min 65.6 pg/mL |
| **Biochemical data** | | Aldosterone | 149 pg/mL (29.9-159) | 120 min 37.3 pg/mL |
| **TP** | 7.2 g/dL (6.6-8.1) | ACTH (06:00) | 32.0 pg/mL (7.2-63.3) | 30 min 4.8 μg/dL |
| **Albumin** | 4.2 g/dL (4.1-5.1) | (12:00) | 10.4 pg/mL | 60 min 5.5 μg/dL |
| **TBil** | 0.6 mg/dL (0.4-1.5) | (18:00) | 12.5 pg/mL | 90 min 5.7 μg/dL |
| **AST** | 25 U/L (13-30) | (23:00) | 13.6 pg/mL | 120 min 5.5 μg/dL |
| **ALT** | 29 U/L (7-23) | Cortisol (06:00) | 7.0 μg/dL (6.2-19.4) | |
| **LDH** | 248 U/L (124-222) | (12:00) | 4.4 μg/dL | (ACTH load) |
| **ALP** | 156 U/L (106-322) | (18:00) | 3.4 μg/dL | Cortisol 0 min 4.3 μg/dL |
| **rGTP** | 28 U/L (9-32) | (23:00) | 3.4 μg/dL | 30 min 4.5 μg/dL |
| **BUN** | 13 mg/dL (8-20) | DHEA-S | 96 μg/dL (12-133) | 60 min 5.2 μg/dL |
| **CREA** | 0.68 mg/dL (0.46-0.79) | | | 90 min 5.7 μg/dL |
| **Na** | 138 mEq/L (138-145) | (Urine) | | 120 min 6.0 μg/dL |
| **K** | 4.2 mEq/L (3.6-4.8) | Epinephrine | 8.2 μg/d (3.4-26.9) | |
| **Cl** | 105 mEq/L (101-108) | Norepinephrine | 133.3 μg/d (48.6-168.4) | |
| **Glucose** | 116 mg/dL (73-109) | Dopamine | 800.2 μg/d (365-961.5) | |
| **Tchol** | 177 mg/dL (142-220) | Aldosterone | 11 μg/d (0-10) | |
| **HbA$_1c$** | 6.9% (4.9-6.2) | Cortisol | 75.3 μg/d (11.2-80.3) | |
| **sIL-2R** | 325 U/mL (121-613) | | | |

Reference ranges are in parentheses.

Abbreviations: ACTH, adrenocorticotropin; ALP, alkaline phosphatase; ALT, alanine transferase; ARR, aldosterone/renin ratio; AST, aspartate transaminase; BUN, blood urea nitrogen; Cl, chlorine; Crea, creatinine; DHEA-S, dehydroepiandrosterone-sulfate; Hb, hemoglobin; HbA$_1c$, glycated hemoglobin; Ht, hematocrit; K, potassium; LDH, lactate dehydrogenase; Na, natrium; Plt, platelets; RBC, red blood cells; rGTP, γ-glutamyl transferase; sIL-2R, soluble interleukin-2 receptor; TBil, total bilirubin; Tchol, total cholesterol; TP, total protein; WBC, white blood cells.
that the tumor cells could produce cortisol but not aldosterone. Immunoreactivity of dehydroepiandrosterone-sulfotransferase (DHEA-ST) in the zona reticularis of the attached nonneoplastic adrenal cortex, which reflects the long-term dynamics of the hypothalamus-pituitary-adrenal (HPA) axis, was within normal limits (Fig. 3C and 3F). Therefore, cortisol produced by these tumors did not affect the HPA axis in the patient. Ki-67 labeling indices were 2.5%
in the right adrenal tumor and less than 1% in the left adrenal tumor. The right-sided cysts were diagnosed as endothelial cysts because the monolayer lining cells were positive for CD31 immunoreactivity (Fig. 4). The nonneoplastic adrenal glands adjacent to the tumors on both sides had similar pathological features: morphologically hyperplastic in the zona glomerulosa (immunohistochemically positive for HSD3β and CYP11β2 [Fig. 3B and 3E and Fig. 5]) [9]. The final diagnosis of the resected adrenal glands following detailed analyses of steroidogenesis was that of a bilateral nonfunctional adrenocortical adenoma with cortisol-producing ability, with endothelial cyst formation and bilateral diffuse hyperplasia of the zona glomerulosa in the adjacent nonneoplastic adrenal glands.

The postoperative course of the patient was uneventful. Hydrocortisone replacement was continued. Fludrocortisone was not administered according to a clinical practice guideline on primary adrenal insufficiency by the Japan Endocrine Society [12]. However, the clinical practice guideline of the Endocrine Society recommends mineral corticoid replacement with fludrocortisone and no restriction on salt intake [13]. Her blood pressure was 102 to 120/56 to 80 mm Hg. The patient’s blood biochemistry data were almost within the normal range. Fasting blood glucose and hemoglobin A1c levels were improved, reaching 100 mg/dL and 6.5%, respectively, without the administration of SGLT2 inhibitor or other diabetic medications (empagliflozin was stopped before the first surgery). This remission of diabetes might be caused by the reduction of body weight and cessation of the exogenous glucocorticoid.

2. Discussion

In our case, the adrenal glands showed relatively large bilateral adrenal incidentalomas (measuring 6.2 × 2.5 cm on the right side and 4.6 × 4.1 cm on the left side) and unilateral cysts on the right side. In addition, these tumor masses showed a density of 30 to 50 H on the right side and 10 to 40 H on the left side on CT. To date, 24% of adrenal incidentalomas measuring more than 4 cm in diameter have been reported as being malignant lesions, with 90% of adrenal carcinomas having been reported to be larger than 4 cm in diameter [14]. The lipid content of the adrenal mass
Adrenal endothelial cysts are rare diseases, and cases complicated with adrenal neoplasms are known to be extremely rare [6, 8], with a female predominance and a right-sided prevalence [7], as observed in our case. The pathogenesis of an endothelial cyst with an adrenocortical adenoma has been speculated by a previous study: local circulatory failure by repeated cycles of thrombus formation and recanalization and blood flow communication to a preexisting hemangiomia [6].

In our case, in addition to bilateral adrenocortical adenoma with endothelial cysts, morphologically and immunohistochemically confirmed diffuse adrenal hyperplasia of the zona glomerulosa was detected. Although serum aldosterone levels, serum renin activity, and blood pressure were all within the normal range, detailed examination of the resected adrenal gland revealed diffuse hyperplasia of the zona glomerulosa, which was diffusely positive for CYP11B2. High sodium intake in the modern lifestyle has been reported to diminish the area of zona glomerulosa with aging [20, 21] as the renin-angiotensin-aldosterone system (RAAS) is relatively suppressed [20]. Consequently, elderly people usually have a smaller area of zona glomerulosa. Hyperplasia of the zona glomerulosa was detected during excessive activation of the RAAS, which further results in secondary aldosteronism [20]. The patient in our study did not have diseases causing secondary aldosteronism, but one possibility for the activated RAAS was the use of empagliflozin, an SGLT2 inhibitor, which led to diffuse hyperplasia of the zona glomerulosa. Serum renin and aldosterone levels have been reported to increase significantly with SGLT2 inhibitor use within 1 month, which is associated with a decrease in extracellular fluid [22, 23]. Inconsistent results have been reported for the changes in RAAS in long-term treatments with SGLT2 inhibitors [24]. Although renin activity and aldosterone levels both were reported to normalize after 6 months of SGLT2 inhibitor treatment in some studies [22], increased RAAS activation after 24 weeks of SGLT2 inhibitor treatment was reported in another study [25]. Dehydration is one of the most frequent adverse events of SGLT2 inhibitor use [26, 27] due to the excretion of abundant urinary glucose. In our case, although serum renin and aldosterone levels were within the normal range, urine aldosterone level was above normal, and serum aldosterone level was close to the upper limit of the normal range. In addition, our patient had increased blood hemoglobin and hematocrit levels (15.0-15.7g/dL and 43.5%-46.4%, respectively), which suggest dehydration associated with SGLT2 inhibitor treatment before the operation, which returned to normal levels (13.9-14.5g/dL and 40.5%-42.6%, respectively) after discontinuation of the SGLT2 inhibitor post operation. In our study, surgical resection of the bilateral adrenal glands for the treatment of an adrenocortical adenoma with endothelial cysts enabled us, for the first time, to examine the morphology and histology of adrenal glands under SGLT2 inhibitor use.
treatment, leading to unexpected findings of diffuse bilateral hyperplasia of the zona glomerulosa, with no functional changes in renin and aldosterone levels, and no increase in blood pressure. These results suggest the possibility of SGLT2 inhibitors having some effect on the zona glomerulosa of the adrenal gland; for instance, the latent loss of plasma volume caused by the SGLT2 inhibitor stimulating the zona glomerulosa chronically, leading to hyperplasia.

3. Conclusion

To the best of our knowledge, this is the first case in which both relatively large bilateral adrenocortical adenomas and unilateral adrenal endothelial cysts coexisted, demonstrating the complexity and difficulty of preoperative diagnosis of bilateral adrenal incidentaloma. The adrenal mass in our case was not malignant, but a large tumor with cysts should be considered for resection because potential malignancy is ruled out by detailed histopathological evaluation of the lesions. In addition, surgical resection of bilateral adrenal glands for the treatment of adrenocortical adenoma with endothelial cysts enabled us, for the first time, to examine in detail the morphology and histology of the adrenal glands under SGLT2 inhibitor treatment, leading to an unexpected finding of diffuse bilateral hyperplasia of the zona glomerulosa in nonneoplastic adrenal glands, without clinically demonstrating primary aldosteronism. Therefore, we advocate a new hypothesis that SGLT2 inhibitors affect the zona glomerulosa of the adrenal gland; however, it is difficult to prove a causative relationship between SGLT2 inhibitors and hyperplasia of zona glomerulosa based on the data in this singular case. Because this can be confirmed only under limited conditions, additional case reports or animal model studies on adrenal gland histology under SGLT2 inhibition are warranted.

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Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Additional Information

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