A Rare Case of Cushing's Syndrome Due to Bilateral Adrenocortical Adenomas

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We report a rare case of Cushing's syndrome caused by bilateral cortisol-secreting adenomas in a 63-year-old man. Our preoperative diagnosis was based on endocrinological results and imaging findings. Laparoscopic adrenalectomy has become a standard technique for adrenal tumors; however, bilateral adrenalectomy results in postoperative adrenal insufficiency, necessitating lifelong steroid replacement. To preserve adrenal function, the left adrenal gland was completely resected, whereas the right adrenal gland was partially resected laparoscopically. Hydrocortisone supplementation was initiated at a dose of 30 mg/day and was slowly tapered. However, symptoms of adrenal insufficiency developed, and adrenal steroid secretion did not respond to exogenous adrenocorticotropic hormone. Bilateral cortisol-secreting tumors rarely cause Cushing's syndrome. The present study comprised few patients, and the utilized surgical procedures (i.e., total/partial adrenalectomy or bilateral total adrenalectomy) were not uniform. Few cases of bilateral adrenal-preserving surgery have been reported. However, our patient developed adrenal insufficiency after the oral cortisone supplementation was tapered. This report demonstrates that partial adrenalectomy does not necessarily preserve normal adrenocortical function. Therefore, careful postoperative observation is necessary for patients undergoing a partial adrenalectomy.

Key words: bilateral adrenocortical adenoma, Cushing's syndrome, adrenal insufficiency, laparoscopic adrenalectomy

INTRODUCTION

Endogenous Cushing's syndrome can be divided into two general types: adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent. ACTH-dependent Cushing's syndrome is caused by excessive stimulation of the adrenal glands by ACTH, whereas ACTH-independent Cushing's syndrome is associated with autonomous adrenal cortisol production [1]. The majority of ACTH-independent Cushing's syndrome cases are caused by unilateral adrenocortical lesions. Occasionally, ACTH-independent Cushing's syndrome is caused by bilateral adrenocortical lesions [2, 3], including primary pigmented nodular adrenocortical disease (PPNAD), ACTH-independent bilateral macronodular adrenocortical hyperplasia (AIMAH) and bilateral adrenocortical tumors [4–6]. Primary bilateral adrenocortical tumors (i.e., bilateral adrenocortical adenomas [BAAs] or bilateral adrenocortical carcinomas) are extremely rare [7, 8]. It is problematic to diagnose and manage patients with ACTH-independent Cushing's syndrome and bilateral adrenal masses, particularly in cases of patient with bilateral adrenal adenomas [9, 10]. With the development of surgical modalities and increased experience, the number of laparoscopic adrenal surgeries has increased considerably. However, there is no consensus regarding the optimal management of bilateral adrenal disease. Such primary bilateral adrenal lesions are difficult to diagnose. In addition, treatments for Cushing's syndrome differ for these primary bilateral lesions, and clear diagnostic criteria and appropriate treatments are required. We present a patient with bilateral cortisol-producing adenomas (BiCPA) causing Cushing's syndrome. The patient underwent a laparoscopic adrenalectomy: a total left and a partial right adrenalectomy. A few cases of bilateral adrenal-preserving surgery have been reported. However, our report demonstrates that partial adrenalectomy does not necessarily preserve normal adrenocortical function.

CASE REPORT

A 63-year-old man was referred to our hospital for the evaluation of bilateral adrenal tumors. His past medical history included diagnoses of diabetes mellitus and hypertension 10 years prior. He had gained 3 kg over the last 2 years. There was no known family history of endocrine disease or malignant tumors.

The patient's height was 167 cm, and his body

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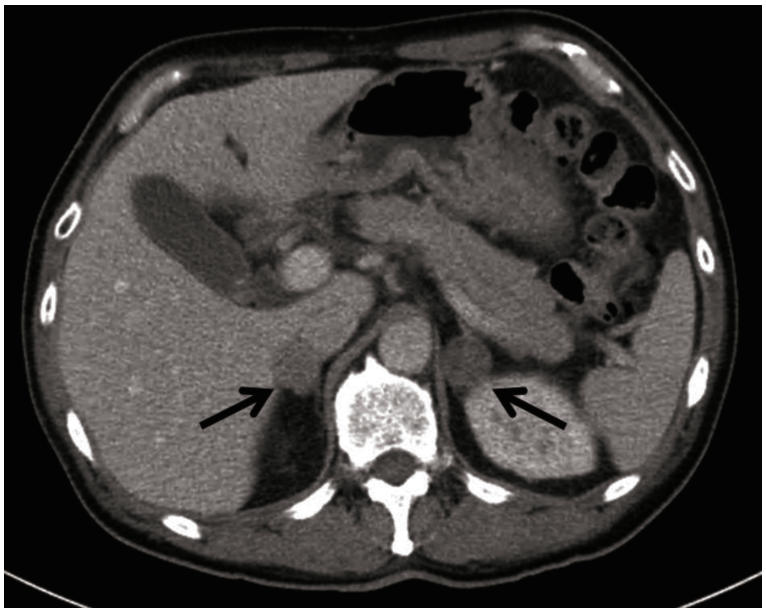

Fig. 1 A preoperative abdominal CT scan. Bilateral adrenal tumors (arrows) and atrophied glands were observed. Both tumors were well-circumambulated masses, without apparent irregularity on the surface or inside.

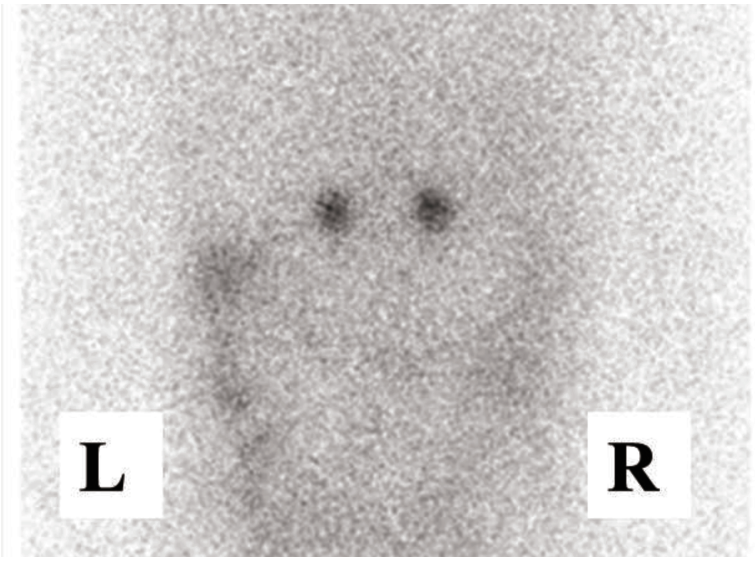

Fig. 2 Preoperative adrenal scintigraphy. Adrenal scintigraphy using ^{131}I-adosterol showed bilateral uptake of the tracer.

weight was 65 kg. His blood pressure was 169/101 mmHg, with a pulse of 95 beats per minute, although he was taking 5 mg/day of amlodipine and 40 mg/day of telmisartan. He had central obesity, moon face, thin skin, easy bruising, striae cutis, buffalo hump and pitting edema of the lower extremities. Osteoporosis was not present, as evidenced by a normal lumbar dual energy X-ray absorptiometry (DXA) examination. Before evaluating the adrenal tumors and hypertension, telmisartan was discontinued, and 5 mg/day of amlodipine was added for blood pressure control. We intentionally limited the use of anti-hypertensive agents to calcium channel blockers to minimize any effects on the renin-angiotensin-aldosterone system during the diagnostic process [11].

The initial laboratory data were as follows. The complete blood cell count and electrolyte analysis showed a mildly elevated neutrophil count of 75.1% and a decreased eosinophil count of 0.3%, without leukocytosis. Serum electrolytes (i.e., Na 144 mEq/L, K 4.5 mEq/L, Cl 104 mEq/L) were within the normal ranges.

The hormonal examination revealed high levels of urinary free cortisol (90.0 μg/day; normal range, 11.2–80.3 μg/day). There was no circadian variation in the serum cortisol levels (19.9 μg/dL at 8 am and 14.6 μg/dL at 11 pm; normal range, 4.0–18.3 μg/dL at 8 am), and the plasma ACTH levels were repeatedly undetectable (< 2.0 pg/mL; normal range, 7.2–63.3 pg/mL). The plasma cortisol levels were not suppressed after the low and high dose overnight dexamethasone suppression tests (13.7 μg/dL after 1 mg of dexamethasone and 20.0 μg/dL after 8 mg; normal range, < 5 μg/dL). Computed tomography (CT) scans of the abdomen showed bilateral adrenal tumors (Fig. 1). Iodocholesterol scintigraphy revealed bilateral adrenal activity (Fig. 2). Adrenal venous sampling (AVS) was performed to determine the laterality of the excessive cortisol secretion. The cortisol levels before and after the ACTH stimulation (an iv bolus injection of 0.25 mg ACTH) were 238.3

Table 1 Results of preoperative AVS.

	Cortisol (μg/dL)		Aldosterone (pg/mL)	
	RAV	LAV	RAV	LAV
Baseline	238.3	298.1	1340	441
After ACTH 250 μg	485.9	1523	4910	3930

Abbreviations: ACTH, adrenocorticotropic hormone; AVS, adrenal venous sampling; RAV, right adrenal vein; LAV, left adrenal vein.

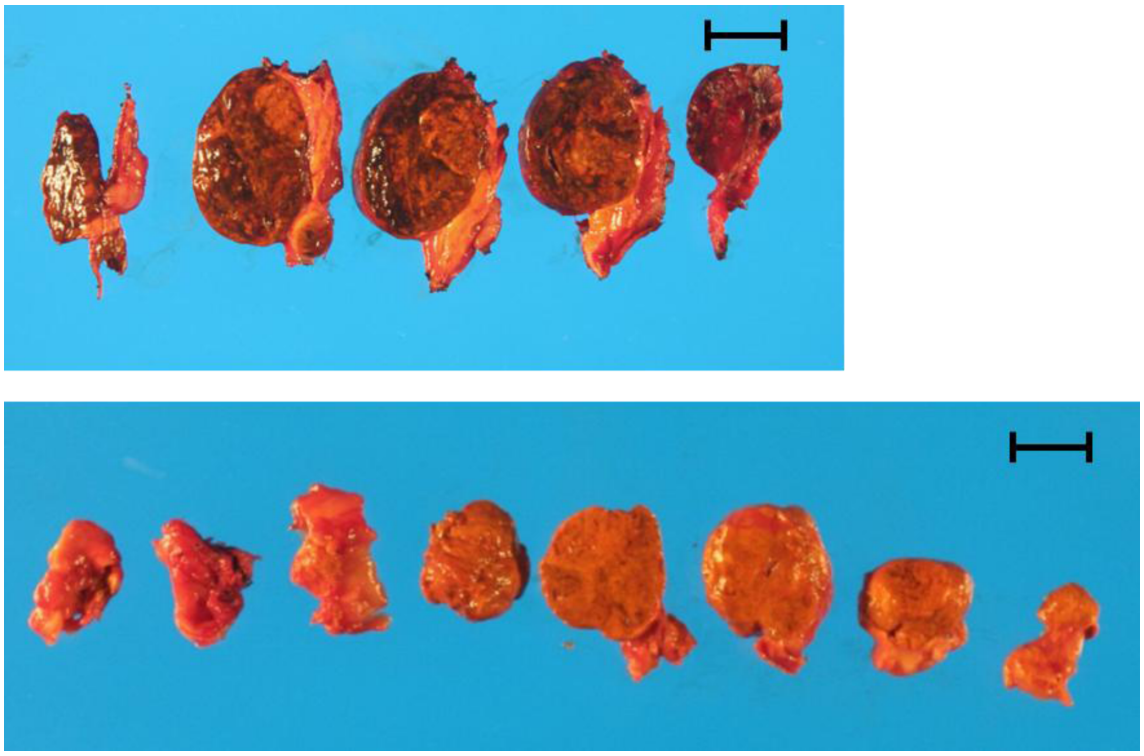

Fig. 3 Gross appearance of the surgically resected adrenal glands. The partially resected right gland (upper column) and the completely resected left gland (lower column) are shown. The bars represent 1 cm.

μg/dL (normal range, > 40 μg/dL) and 485.9 μg/dL (normal range, > 400 μg/dL), respectively, from the right adrenal vein and 298.1 μg/dL (normal range, > 40 μg/dL) and 1523 μg/dL (normal range, > 400 μg/dL), respectively, from the left adrenal vein (Table 1). The respective aldosterone levels obtained from the right and left adrenal veins were 1340 and 441 pg/mL, respectively, at baseline and 4910 and 3930 pg/mL, respectively, after the ACTH stimulation (Table 1). The results indicated non-lateralization, which confirmed that both adenomas were secreting cortisol. Excess aldosterone was not present by the standard diagnostic criteria in Japan [12]. Based on these findings, we made a preoperative diagnosis of bilateral adrenal tumors causing Cushing's syndrome.

To preserve adrenal function, the left adrenal gland was totally resected, whereas the right adrenal gland was partially resected laparoscopically. The right adenoma was 2.4 × 2.0 cm, and the left adenoma was 2.5 × 2.1 cm (Fig 3). Hematoxylin-eosin staining revealed that both tumors were partially encapsulated and consisted of clear, compact cells (Fig 4). Microscopic examination confirmed that the bilateral tumors were benign adrenocortical adenomas. Immunohistochemical analyses of certain steroidogenic enzymes [i.e., 3β-hydroxysteroid dehydrogenase (3β-HSD), 17 α-hydroxylase (P450c17) and dehydroepiandrosterone-sulfotransferase (DHEA-ST)] were performed, according to previously described methods [13]. Immunohistochemistry of the adrenocortical tumors revealed strong positive staining for 3β-HSD and P450c17 (Fig. 5). The surrounding cortical cells in both adrenal glands were atrophic (Fig. 6). DHEA-ST expression was low. The analysis of both adenomas was consistent with their abilities to secrete cortisol, which contributed to the clinical and biochemical manifestations of Cushing's syndrome in this patient.

After adrenalectomy, our patient continued to take maintenance doses of hydrocortisone (15–30 mg/day). He became normotensive in the postoperative period, and the antihypertensive drugs were gradually tapered. The Cushingoid features disappeared. Six months after surgery, the patient was easily fatigued and perspired and had a finger tremor, as well as hyperthyroidism; his serum free thyroxine [FT4] and free triiodothyronine [FT3] were abnormally high, and his thyroid-stimulating hormone [TSH] levels

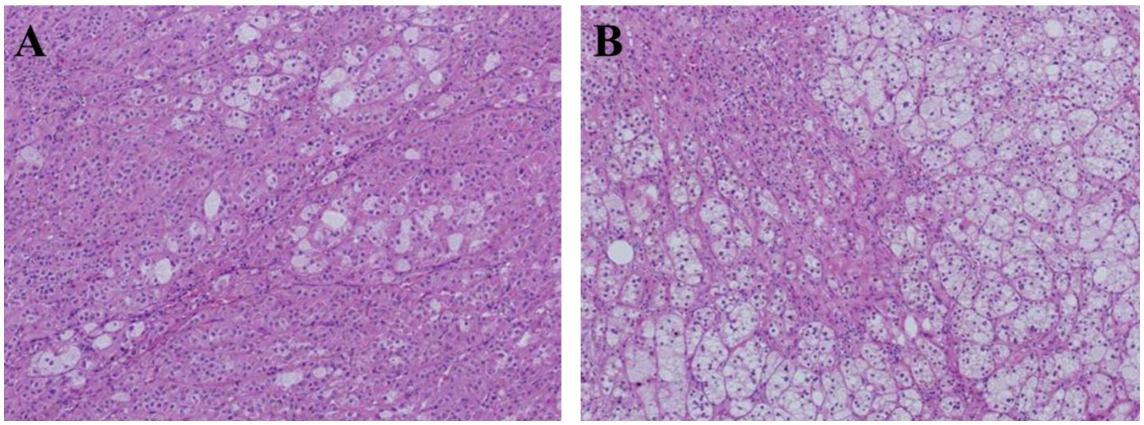

Fig. 4 Histological characteristics of the adenomas. The right (A) and left (B) adenomas comprised both clear cells and compact cells (Hematoxylin-eosin stain, × 100). Both adenomas were partially encapsulated.

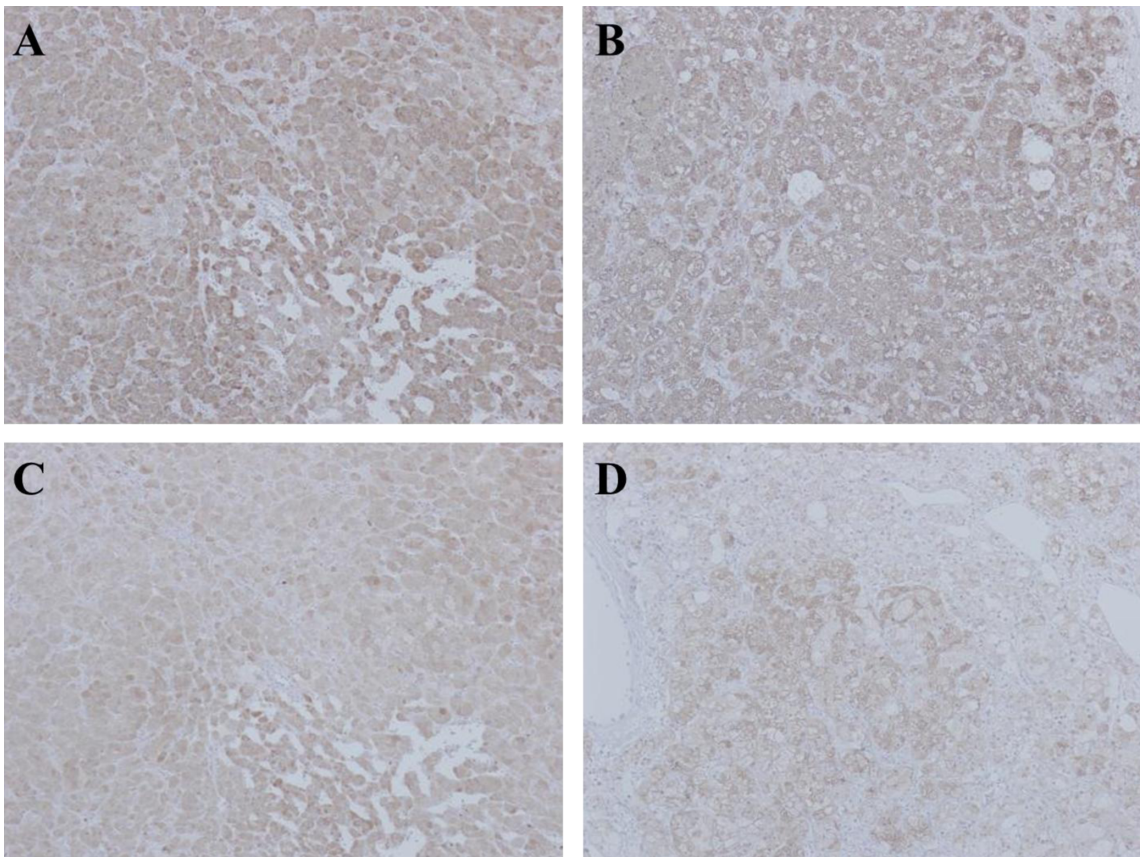

Fig. 5 Immunohistochemistry and enzyme histochemistry of the adrenal adenomas (× 100). The right and left adenomas were strongly positive for 3β-HSD (A and B) and P450c17 (C and D).

had decreased. Tests for antimicrosomal and antithyroglobulin antibodies were positive, but a test for the TSH-receptor antibody was negative. His thyroid gland had become barely palpable. The patient had transient hyperthyroidism due to thyroiditis and had developed adrenal insufficiency after tapering the oral cortisone supplementation (Fig. 7). His symptoms improved after an increased dose of hydrocortisone was administered, and his serum FT3 and FT4 levels gradually returned to normal. We performed an abdominal CT scan (Fig. 8A) and an ACTH stimulation test to confirm sufficient adrenocortical function (Table 2). However, functional recovery of the remaining adrenal tissue was not detected. We attempted to taper the dose of hydrocortisone. At the 15-month follow-up, the patient's cortisol levels remained low, but the ACTH levels were high and the electrolyte levels were normal. The CT scan revealed an atrophic right adrenal gland (Fig. 8B), and an ACTH stimulation test indicated a low adrenal reserve (Table 2). The patient was maintained on a daily dose of hydrocortisone (15 mg). He is being followed by the Nephrology, Endocrinology and Metabolism outpatient division. Currently, 15 mg/

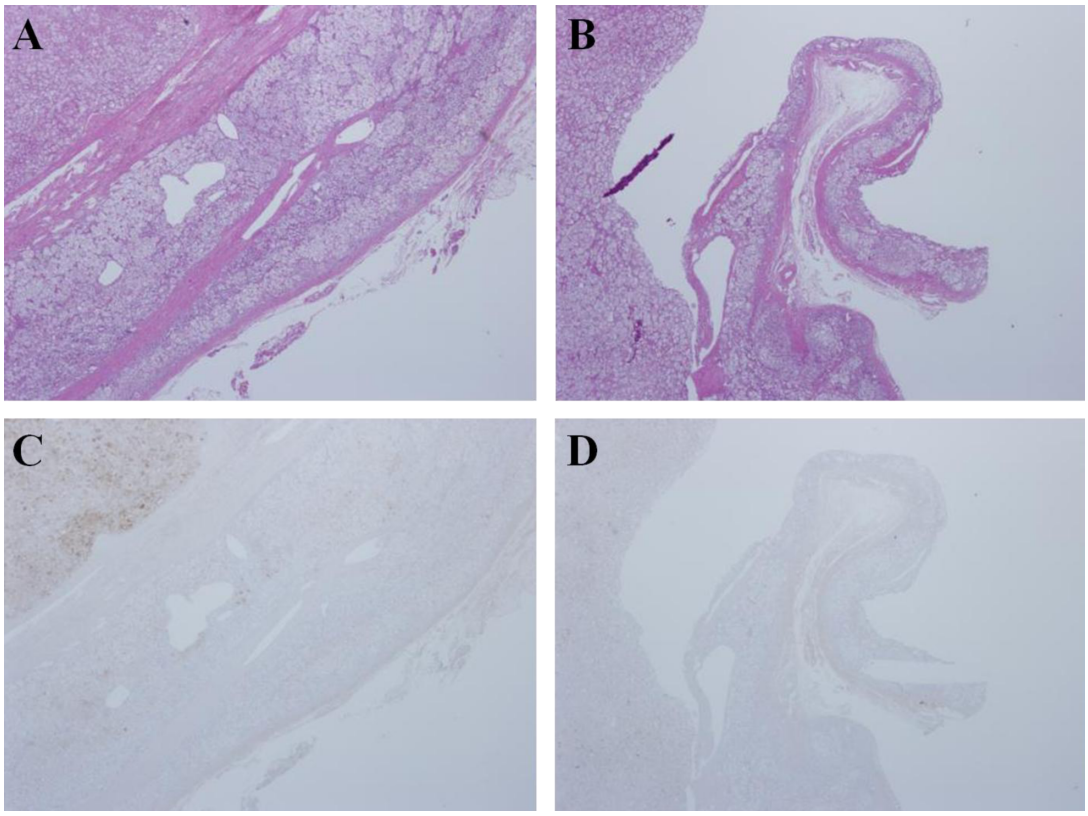

Fig. 6 The surrounding cortex. Cortical cells adjacent to the adenoma showed marked atrophy in the right and left glands (A and B: Hematoxylin-eosin stain, × 20), and dehydroepiandrosterone-sulfotransferase (DHEA-ST) expression was low (C and D, × 20).

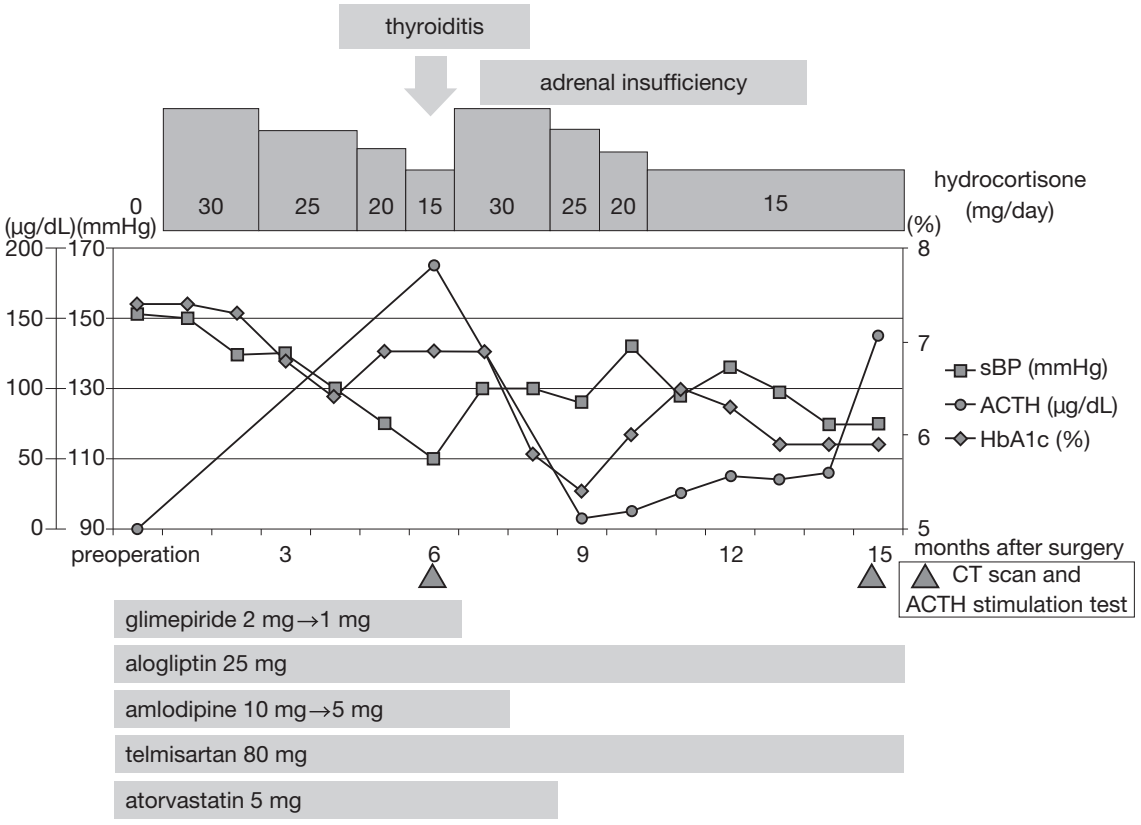

Fig. 7 The postoperative clinical course. Our patient became normotensive in the postoperative period, and antihypertensive drugs were gradually tapered. Six months after surgery, the patient had transient hyperthyroidism due to thyroiditis and had developed adrenal insufficiency. His symptoms improved after cortisone supplementation. However, a functional recovery of the remaining adrenal tissue was not detected. The patient was maintained on a daily dose of hydrocortisone (15 mg).

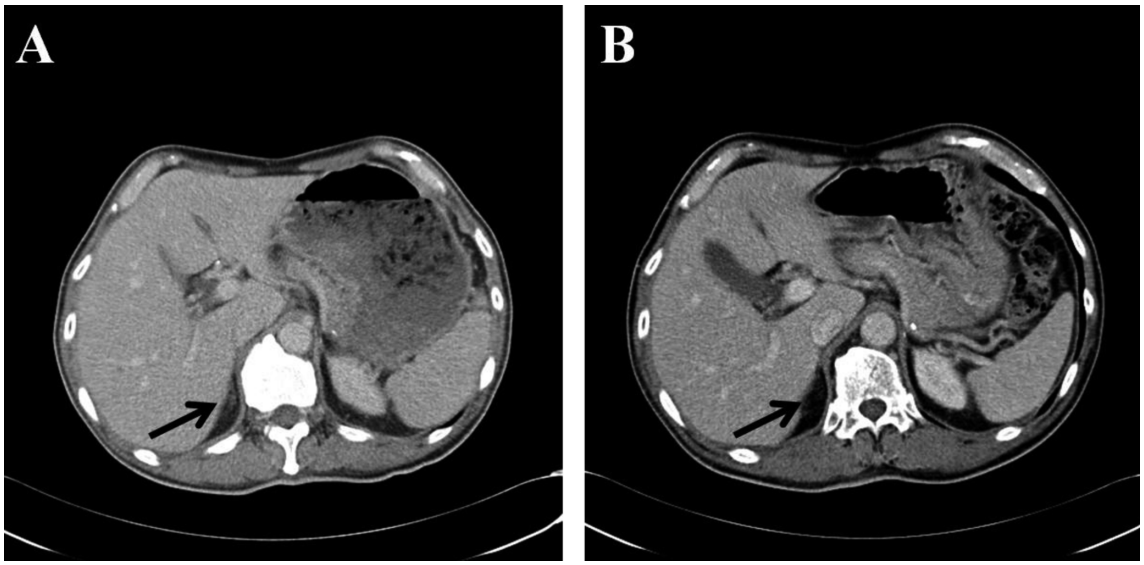

Fig. 8 Postoperative CT scans of the abdomen at 6 (A) and 15 months (B). The CT scan still showed an atrophic right adrenal gland (arrows).

Table 2 Results of rapid ACTH test at 6 and 15 months after surgery.

	6 months			15 months		
min	0	30	60	0	30	60
ACTH (pg/mL)	188			142		
Cortisol (μg/dL) [peak level > 18]	1.6	1.2	1.9	2.5	2.8	2.8

Abbreviations: ACTH, adrenocorticotropic hormone; [ ], normal range.

day of hydrocortisone is being administered.

DISCUSSION

Cases of Cushing's syndrome associated with adrenocortical adenoma are secondary to unilateral adrenocortical adenoma in approximately 90% of cases [14]. In contrast, bilateral cortisol-secreting tumors are a rare cause of Cushing's syndrome [9]. Bilateral adrenocortical adenomas (BAAs) are rare in general [9]. To the best of our knowledge, only 36 BAA cases have been published. Our patient was diagnosed with ACTH-independent Cushing's syndrome based on biochemical testing, and an abdominal CT scan detected bilateral adrenal tumors. Three possibilities can explain these findings: (a) bilateral cortisol hyper-functioning tumors, (b) bilateral macronodular adrenal hyperplasia, or (c) a unilateral cortisol-secreting tumor and a contralateral nonfunctioning tumor or functioning tumor, such as an aldosteronoma, pheochromocytoma, or virilizing tumor [15]. To adequately distinguish these conditions, adrenal scintigraphy, confirmatory tests for primary aldosteronism and AVS were performed. AVS provides important information concerning the laterality of excessive aldosterone secretion. Adrenal scintigraphy has also been used to differentiate between unilateral and bilateral causes of Cushing's syndrome and primary aldosteronism but has reduced sensitivity and specificity compared with the more commonly used CT and AVS techniques. Additionally, it is not possible to establish a differential diagnosis using scintigraphy in the case of (c). Confirmatory tests should be highly sensitive to avoid missing primary aldosteronism; otherwise, there will be a false-positive result. Based on these findings, AVS was necessary to obtain a definitive diagnosis in our case. However, the use of AVS in patients with Cushing's syndrome and bilateral adrenal adenomas has rarely been reported. Thus, we present this case to emphasize that AVS is useful for obtaining differential diagnoses in these cases. By reviewing cases similar to ours, new diagnostic criteria, such as primary aldosteronism, may be obtained for Cushing's syndrome caused by bilateral cortisol-secreting adenomas.

When bilateral adrenal tumors are encountered, a unilateral or bilateral partial adrenalectomy is a better choice if functional adrenal tissue can be preserved because a bilateral total adrenalectomy causes acute adrenal insufficiency, necessitating lifelong steroid replacement. Certain pheochromocytomas are hereditary and are usually bilateral. Partial adrenalectomies for bilateral pheochromocytomas have been successful [16–19]. Conversely, partial adrenalectomies for bilateral adrenal cortical functioning tumors causing Cushing's syndrome or primary aldosteronism are extremely rare, and only two cases of bilateral adrenal-preserving surgery for Cushing's syndrome have been reported [15, 20]. In

addition, little is known about how much residual adrenal tissue is required for adequate adrenal function. Brauckhoff *et al.* estimated that preserving approximately one-third of the entire adrenal gland would allow sufficient function [21]. Several authors have advocated preserving the adrenal vein because adequate venous drainage seems to be important for maintaining the functionality of the remnant tissue [22, 23]. In our case, at least a third of the adrenal gland remained, and the adrenal vein was preserved. However, functional recovery of the remaining adrenal tissue was not detected. Few studies have demonstrated the feasibility of a partial adrenalectomy for bilateral Cushing's adenoma [15]. In most cases, impairmed adrenocortical function is likely caused by atrophy of the normal adrenal tissue as a result of chronic suppression by the low ACTH levels in the hypercortisolism state. It is expected that recovering adrenal function is difficult after a partial adrenalectomy for bilateral Cushing's adenoma, and our case is valuable in supporting this hypothesis.

There are several medications for Cushing's syndrome, including a glucocorticoid receptor antagonist (mifepristone) and adrenal steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane, and etomidate) [24–26]. As expected with glucocorticoid receptor antagonism, the hypothalamic-pituitary-adrenal (HPA) axis is rapidly activated, with ACTH levels rising appropriately [27]. The adrenal steroidogenesis inhibitors are similarly effective, and ACTH stimulates the remaining adrenal tissue to grow [24]. After a unilateral adrenalectomy, it would be useful if ACTH was secreted in response to the above-mentioned medications such that ACTH could stimulate the atrophic adrenal tissue before performing surgery on the other side. Accordingly, the remaining adrenal tissue may easily develop after surgery. If these medicines were administered before surgery, adrenal function might have been restored in our case. The functional recovery of the remaining adrenal tissue likely requires more than several months, and the tapered discontinuation of the replacement therapy is necessarily slow. Long-term data are needed to further define the role of additional medications in the treatment of Cushing's syndrome due to bilateral adrenocortical adenomas.

In summary, we report a case of BiCPA, which caused Cushing's syndrome in a patient who underwent laparoscopic adrenalectomy: a total left and a partial right adrenalectomy. There is no consensus regarding the optimal diagnostic criteria and appropriate treatment in such cases. Few cases of bilateral adrenal-preserving surgery have been reported. However, our patient developed adrenal insufficiency after the oral cortisone supplementation. This report demonstrates that partial adrenalectomy does not necessarily preserve normal adrenocortical function. In addition, AVS has rarely been reported in patients with Cushing's syndrome and bilateral adrenal adenomas. Our case emphasizes that AVS is useful for obtaining differential diagnoses in such cases.

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