Bilateral Adrenocortical Adenomas Causing Cushing's Syndrome: Report of A Case Successfully Treated by Adrenal-Sparing Surgery

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ABSTRACT. A case of Cushing's syndrome in a 49-year old woman caused by bilateral adrenocortical adenomas was reported. Computed tomography (CT) disclosed bilateral adrenal tumors, and adrenal scintigraphy revealed positive accumulation of a radiopharmaceutical in these glands. Stronger accumulation was observed in the larger left tumor, but the cortisol concentration in the right adrenal vein was definitely higher than that on the left side. A right adrenalectomy and a left tumorectomy were performed, and hydrocortisone replacement was discontinued at 27 months postoperatively.

Key words: bilateral adrenocortical adenomas — Cushing's syndrome — adrenal-sparing surgery — steroid content of adenomas

In 80 percent of adult patients with adrenocorticotropic hormone (ACTH)-independent Cushing's syndrome, the cause is a single adrenocortical adenoma secreting excess amounts of cortisol.[1] The other important cause is adrenocortical carcinoma. Recently, several subtypes of this entity, including ACTH-independent macronodular adrenocortical hyperplasia (AIMAH),[2,3] primary pigmented nodular adrenocortical dysplasia (PPNAD)[3] and bilateral adrenocortical adenomas,[4-8] have been reported. Herein, we describe a patient with bilateral adrenocortical adenomas causing Cushing's syndrome who underwent adrenal-sparing surgery, and discuss the diagnosis and surgical treatment of bilateral adrenocortical adenomas.

CASE REPORT

A 49-year-old woman was admitted to our hospital with central obesity and edema of the lower extremities in November, 1993. Although she had received anti-hypertensive agents for five years, she had experienced a 6 kg weight gain, and Cushingnoid stigmata had developed during the last year even though her hypertension had been well controlled. Her blood pressure was 130/80 mmHg, and her height and weight were 149 cm and 54 kg, respectively. Routine laboratory tests, which consisted of a complete blood count, serum electrolytes and creatinine, a liver function test and a complete urinalysis, were

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within the normal ranges. Her fasting blood glucose level was normal, but an oral glucose tolerance test (75 g) showed an increase in her blood glucose level to the peak of 210 mg/dl at 120 minutes. Endocrine studies revealed suppressed plasma ACTH and high plasma cortisol with diminished circadian rhythms. Incomplete suppression of cortisol secretion by high-dose dexamethasone was also observed. Plasma ACTH and cortisol did not respond to corticotropin-releasing hormone (CRH), but the latter responded normally to ACTH loading. Her plasma concentration of dehydroepiandrosterone sulfate (691 ng/ml), plasma renin activity (0.86 ng/ml/h) and plasma aldosterone concentration (48 pg/ml) were within the normal ranges. There were no abnormalities in plasma concentrations of pituitary hormones other than ACTH (Table 1). An abdominal CT scan disclosed a single adrenal tumor in each adrenal gland. The left tumor was 3.5 × 3 cm in size, and larger than the right one (2 × 2 cm) (Fig 1a). Although adrenal scintigraphy with ^{131}I-6β-iodomethyl 19 nor-cholesterol (^{131}I-adosterol) revealed positive accumulation in both adrenal glands, the greater accumulation was in the left tumor (Fig 1b). In contrast, adrenal venous sampling showed the cortisol level in the right adrenal vein to be definitely higher (186 μg/dl) than that in the left adrenal vein (88.3 μg/dl). As the cortisol levels in both adrenal veins were definitely higher than those in the peripheral vein (27-31 μg/dl) or the vena cava (23.5-24.7 μg/dl), both tumors were considered to be secreting excessive amounts of cortisol. Neither a brain CT scan nor magnetic resonance imaging disclosed any abnormal findings. In view of the venous sampling data, a right adrenalectomy and a left tumorectomy were performed by the transabdominal approach in March, 1994. The removed right tumor was 1.8 × 1.8 × 1.5 cm in

TABLE 1. Clinical Endocrine Data

Basal level of plasma		Normal range				
ACTH*	<4.0	4.4~48.0 pg/ml				
TSH	0.53	0.34~3.50 μIU/ml				
PRL	27.0	0.12~6.0 ng/ml				
GH	0.2	<5 ng/ml				
Urinary excretion of free cortisol	290	35~150 μg/day				
Diurnal rhythm of	8 a.m.	2 p.m.	8 p.m.	11 p.m.		
plasma cortisol (μg/dl)	31.3	29.9	25.5	27		
CRH* test (100 μg, iv)	0	15	30	60	120 min.	
ACTH (pg/ml)	<4.0	<4.0	<4.0	<4.0	<4.0	
cortisol (μg/dl)	26.9	26.1	26.6	24.8	24.6	
Rapid ACTH test (0.25 mg, iv)	0	30	60	120 min		
cortisol (μg/dl)	23.7	46.7	60	59.9		
Dexamethasone	1	2	3	4	5	6 day
suppression test		2 mg	2 mg	8 mg	8 mg	
U-17 OHCS* (mg/day)	23.5	25.2	15.8	13.8	16.3	18.6

Abbreviation: ACTH; adrenocorticotropic hormone, TSH; thyroid stimulating hormone, PRL; prolactin, GH; growth hormone, CRH; corticotropin-releasing hormone, U-17 OHCS; urinary excretion of 17-hydroxycorticosteroid

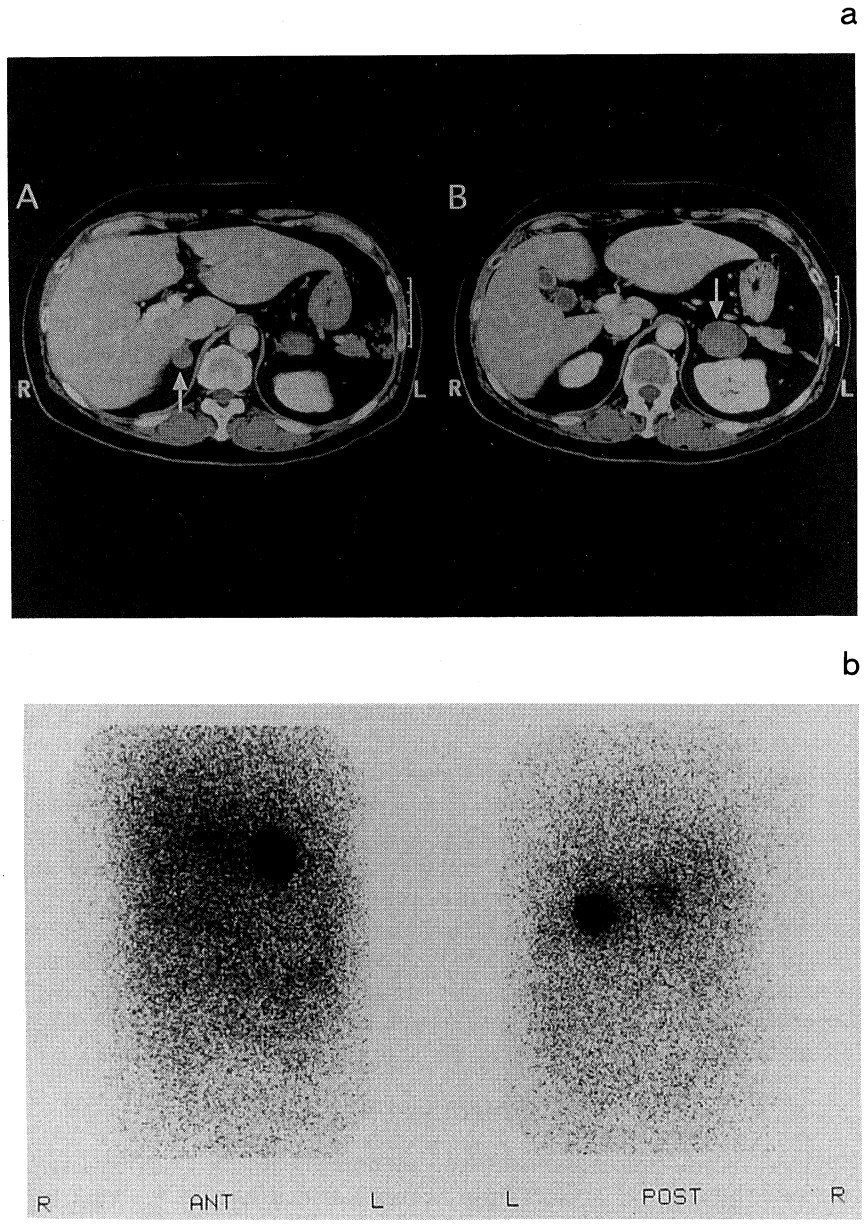

Fig 1. Imaging studies
a. Abdominal computed tomography (CT) Scan
A CT scan disclosed solitary low density masses in the right (2 × 2 cm, A) and left (3.5 × 3 cm, B) adrenal glands, respectively. Weak enhancement effects were observed in these bilateral tumors.
b. Adrenal scintigraphy
Adrenal scintigraphy with ^{131}I-6β-iodomethyl 19 nor-cholesterol revealed positive accumulation of radiolabeled material in the bilateral adrenal tumors, but the intensity of the accumulation was stronger in the left tumor with a larger volume. ANT: anterior view, POST: posterior view

size and weighed 7 g as a whole adrenal gland, while the left tumor was 3.5 × 3.0 × 2.5 cm in size and weighed 12 g. The cut surface of both tumors was yellowish-brown in color, and neither hemorrhage nor necrosis was seen (Fig 2a). Both tumors were encapsulated with thin fibrous tissue and were composed of alveolar or nest-like arrangements of dark compact cells and clear cells. Adrenocortical atrophy was observed in the non-tumorous area of the removed right adrenal gland. The pathological diagnosis was adrenocortical adenoma (Fig 2b, c). A postoperative supplement of hydrocortisone was started at 250 mg/day, and tapered to a maintenance dose of 25 mg/day (15 mg in the morning, 10 mg in the evening) at four weeks. Plasma ACTH levels became detectable, and the maintenance dose was reduced to 10 mg/day (given in the morning) at 12 months, and 5 mg/day at 16 months postoperatively. Although the patient suffered from mild steroid withdrawal syndrome at 20 months postoperatively, steroid replacement could be discontinued at 27 months postoperatively. Hypertension and glucose tolerance improved, and she has not had to take any anti-hypertensive agents. Nevertheless, even presently, 48 months postoperatively, recovery of her adrenal function is not yet considered sufficient, because plasma ACTH concentrations remain high and she sometimes complains of malaise and nausea when she has a common cold (Table 2).

ANALYSIS OF STEROID CONTENT OF ADENOMAS

The steroid content of the removed adenomas was measured by a method reported previously.[9] In the right adenoma, the cortisol concentration was much higher than that in normal adrenals and the left adenoma. In contrast, the corticosterone concentration in both adenomas was definitely lower than that in normal adrenals. The concentrations of other steroids were the same or somewhat lower than those in normal adrenals. These data suggest that the right adenoma was a typical cortisol-producing adenoma (CPA).[2,9] The cortisol concentration in the left adenoma, on the other hand, was not as high as that in a CPA, but a reduced corticosterone level and high cortisol/corticosterone ratio, which are not usually observed in patients with non-hyperfunctioning adenomas or normal adrenals,[10] were seen. Therefore, the left adenoma was considered to be a low-grade CPA (Table 3).

DISCUSSION

Bilateral or multiple adrenocortical adenomas causing Cushing's syndrome are very rare, but several articles have been published lately.[4–8] Aiba *et al*, in a review of the literature, reported 14 cases with bilateral or multiple adrenocortical adenomas causing Cushing's syndrome.[4] According to their report, 13 cases were female with an average age of 42.5 years, and the size of the adenomas was somewhat smaller than that of a single adenoma. Regarding the diagnosis of bilateral or multiple adrenocortical tumors, subtypes of nodular hyperplasia such as AIMAH and PPNAD should be excluded. AIMAH is usually observed in old men, and huge adrenal masses have been identified by imaging methods.[1–4] In contast, PPNAD is usually discovered in younger patients, and macronodular adrenals have not been identified.[1,3,4] Adrenal scintigraphy is useful in evaluating the endocrine function of

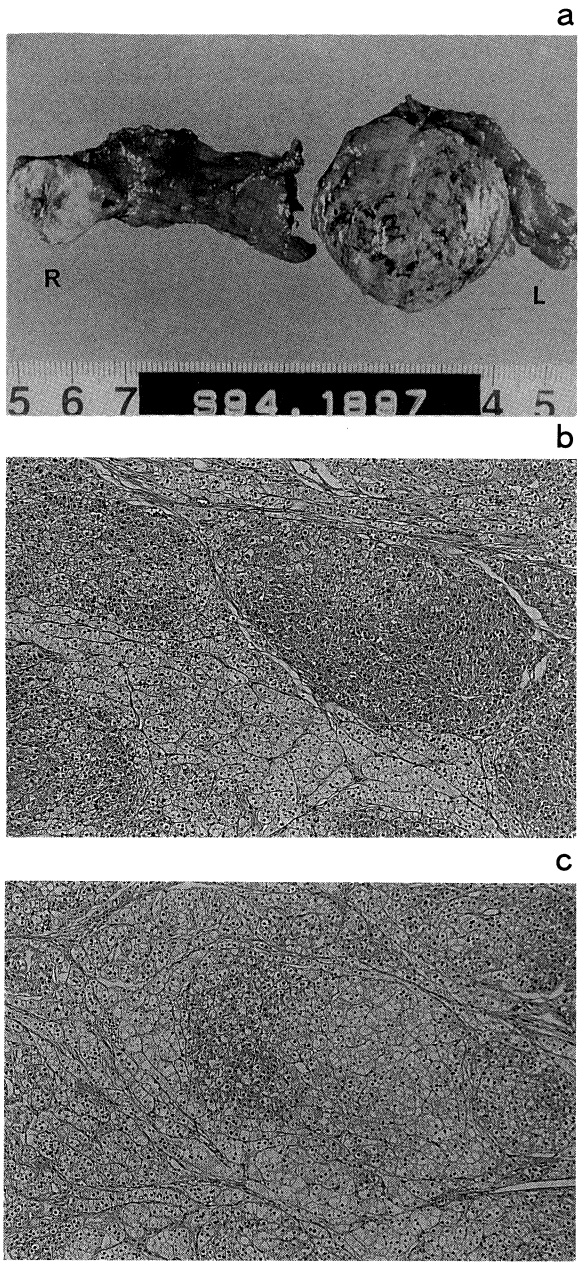

Fig 2. Macroscopic and microscopic appearance of removed tumors
a. Gross appearance
Solitary adrenal tumors were seen in bilateral adrenal glands. The cut surface of both tumors was yellowish-brown in color, and neither necrosis nor hemorrhage was observed.
b, c. Histopathological findings of the removed tumors (H & E stain, reduced from 200 ×). b : right adenoma, c : left adenoma
Both tumors were composed of alveolar arrangements of dark compact cells and clear cells. Neither mitotic figures nor nuclear atypism was observed, and these tumors were diagnosed as an adrenocortical adenoma. Dark compact cells were more frequently seen in the right tumor (b) than the left one (c).

TABLE 2. Postoperative Endocrine Data and Hydrocortisone Replacement

Postoperative Period (Months)	Plasma ACTH (pg/ml)	Plasma cortisol (μg/dl)	Dosage of hydrocortisone replacement (mg/day)
3	4.2	6.2	25
6	5.5	14.9	25
9	4.4	11.4	15
12	7.1	10.2	10
16	33.8	15.0	5
18	ND*	5.2	5 every 2 days
20	ND	5.2	10**
25	138	8.9	5 every 2 days
27	138	6.8	0
33	130	9.6	0
39	138	9.9	0
48	108	10.4	0

ND* : not determined
10** : (replacement dosage was increased to 10 mg/day because of mild withdrawal syndrome)
Plasma hormone levels were measured in the morning before taking medicines.

TABLE 3. Steroid Content in Removed Adenomas

Steroid	right adenoma	left adenoma	CPA	Normal adrenal
F*	23.8	9.64	19.91±5.52	12.36±2.80
B	0.41	0.81	1.14±0.32	4.05±1.63
S	1.53	0.97	2.14±1.12	1.92±0.47
A	0.41	0.38	0.74±0.74	0.59±0.24
17OHP	0.42	0.74	1.65±1.74	1.39±0.37
P	0.13	0.13	0.47±0.36	0.41±0.21
F/B	58.0	11.9	17.37±1.69	3.24±0.66

Steroid content was expressed as μg/g tissue. The data of cortisol-producing adenomas (CPA) and normal adrenal glands were expressed as the mean ± standard deviation of five and eight cases, respectively.
Abbreviations of steroids ; F : cortisol, B : corticosterone, S : 11-deoxycortisol, A : androstenedione, 17OHP : 17-hydroxyprogesterone, P : progesterone, F/B : cortisol/corticosterone ratio

adrenocortical tumors, and radioisotope accumulation has usually been observed bilaterally in patients with bilateral adrenocortical adenomas. However, in the present case, stronger accumulation was observed in the larger left tumor with lower cortisol secretion. The results suggest that the intensity of radioisotope accumulation was not necessarily related to the endocrine function of the tumors.[5] Therefore, the functional superiority should be determined by measurement of the cortisol levels in each adrenal vein. Histologically, the non-tumorous adrenal cortex is usually atrophic in cases of adrenocortical adenomas. The active production of cortisol in removed adenomas should be verified by biochemical or immunohistochemical methods, because not all adenomas necessarily produce excessive amounts of cortisol.[4–6,8] In the present study, only one of the two adenomas was a typical CPA,[2,9]

while the other adenoma had the ability to produce some, but not an excessive amount of cortisol. Therefore, we described this adenoma as a low-grade CPA, which is sometimes observed in patients with preclinical Cushing's syndrome.[9,10] Concerning the mechanism of occurrence of bilateral or multiple adrenocortical adenomas, there are two theories. The first one argues that long-standing ACTH-dependent bilateral adrenal hyperplasia may develop into ACTH-independent adrenal nodular diseases. The other insists on the incidental occurrence of bilateral or multiple adenomas. The former theory has been derived from several reports describing the coexistence of adrenocortical adenomas and ACTH-dependent bilateral nodular diseases.[11-13] As to the latter argument, Aiba *et al*[4] examined the distribution of the steroidogenic enzymes and morphological characteristics of multiple adrenocortical adenomas, and reported that no difference was seen between single and multiple adrenocortical adenomas. In the present study, both adenomas produced excessive amounts of cortisol, and the non-tumorous adrenal cortex showed signs of cortical atrophy, suggesting the incidental occurrence of bilateral adenomas.

The surgical treatment for bilateral adrenocortical adenomas consists of a total bilateral adrenalectomy and adrenal-sparing surgery (tumorectomy). In the present case, the left adrenal gland could be preserved, and the patient no longer required steroid supplement at 27 months postoperatively. From the point of view of the quality of life, adrenal-sparing surgery should be considered unless there are technical problems.[4] On the other hand, if a definite difference in endocrine function is observed between bilateral tumors, a unilateral adrenalectomy for the hyperfunctioning tumor should be performed first, and the surgical indication for the contralateral tumor should be examined again in the follow-up period by means of re-evaluation of its endocrine function.[8]

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