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【 CASE REPORT 】

Bilateral Adrenocortical Adenomas along with Virilization and Cushing's Syndrome

Toshihiro Kobayashi[1], Hitomi Imachi[1], Seisuke Sato[1], Tomohiro Ibata[1], Kensaku Fukunaga[1], Takuo Yoshimoto[1], Fumi Kikuchi[1], Kazuko Yonezaki[1], Nao Yamaji[1], Jingya Lyu[1], Tao Dong[1], Hiromi Nagata[1], Kyuichi Kadota[2], Yoshio Kushida[2], Reiji Haba[2] and Koji Murao[1]

Abstract:
We herein present the case of a 27-year-old woman with clinical and biochemical features of virilism. Imaging studies revealed the presence of a bilateral adrenal tumor. Although the secretion of androgens was remarkable, the autonomous production of cortisol was also evident because of a loss of circadian rhythm and the absence of cortisol suppression by dexamethasone. The surgical excision of both adrenal tumors was performed, and the histological examination showed no malignancy. We also report the successful pregnancy and delivery of the patient who showed evolving adrenocortical insufficiency along with virilization and Cushing's syndrome and who continued to receive glucocorticoid replacement therapy during pregnancy.

Key words: adrenocortical adenoma, bilateral, Cushing's syndrome

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Introduction

Cases of bilateral adrenal tumor along with virilism are extremely rare and can have several clinical manifestations (1). Adrenal virilism is a syndrome in which the excessive production of adrenal androgens causes virilization. A clinical diagnosis is confirmed based on elevated androgen levels. The symptoms include excess facial and body hair, deepening of the voice, baldness, acne, and increased muscularity and sex drive (2). To the best of our knowledge, there have only been two reported cases of bilateral adrenal tumors along with virilization (3, 4). We herein report a case of bilateral virilizing tumors along with Cushing's syndrome, and describe the successful pregnancy and delivery of the patient who showed evolving adrenocortical insufficiency due to bilateral adrenalectomy.

Case Report

A 27-year-old woman was admitted to our hospital due to progressive hirsutism and amenorrhea. Menarche occurred at 13 years of age. Her menstrual cycle had been regular until 22 years of age. She had visited a gynecologist at 25 years of age due to amenorrhea. At the time, hormone therapy was administered with estradiol and progesterone to treat the symptoms of amenorrhea. However, these symptoms did not improve. Upon admission to our hospital, a physical examination revealed a masculine appearance along with hirsutism and systemic pigmentation. She also had several clinical sings of Cushing's syndrome, including moon face, buffalo hump and skin striae.

Her laboratory data are shown in Table. The results of routine laboratory evaluations were normal. Her thyroid function and the levels of other pituitary hormones were normal. Her serum aldosterone and plasma renin activity were within the normal ranges. Her serum levels of testosterone, free testosterone, dehydroepiandrosterone sulfate, estrogen and 17-ketosteroid were markedly increased (Table). Her cortisol level was elevated (23.5 μg/dL), and her corticotrophin concentration was lower than detectable levels. The daily secretion pattern of cortisol did not exhibit a nor-

[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kagawa University, Japan and [2]Departments of Diagnostic Pathology, Faculty of Medicine, Kagawa University, Japan
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Correspondence to Dr. Toshihiro Kobayashi, koba1987@med.kagawa-u.ac.jp

Table. The Summary of Laboratory Data.

Endocrine		Reference	*Catecholamine (Plasma)*		Reference
Cortisol(μg/dL)	23.5	4.5-21.1	Adrenaline(pg/mL)	5.0	≤100
U-17-OHCS(mg/day)	7.9	2.2-7.3	Dopamine(pg/mL)	5.0	≤30
U-17-KS(mg/day)	491.8	2.4-11.0			
Testosterone(ng/mL)	5.3	0.06-0.80	*Catecholamine (Urine)*		
Free testosterone(pg/mL)	40.7	0.4-2.3	Noradrenaline(μg/day)	37.0	31.0-160.0
DHEA-S(ng/mL)	33,500	180-3,910	Dopamine(μg/day)	464.1	280.0-1,100.0
17α-OHP(ng/mL)	6.2	0.2-4.5	VMA(mg/day)	3.10	1.50-4.90
U-estrogen(mg/day)	226	0.005-0.02			
Pregnanediol(mg/day)	9.70	0.28-6.83	DEX 1mg suppression test		
Pregnanetriol(mg/day)	7.79	0.13-1.90	Cortisol(μg/dL)	21.9	
Aldosterone(pg/mL)	316.0	29.9-158.8	Testosterone(ng/mL)	4.6	
Plasma renin activity(ng/mL/h)	2.0	0.2-2.3	U-17-KS(mg/day)	60.4	
			DEX 8mg suppression test		
			Cortisol(μg/dL)	20.9	
			Testosterone(ng/mL)	3.6	
			U-17-KS(mg/day)	472.0	
			U-17-OHCS(mg/day)	14.9	

mal circadian rhythm. Both low-dose (1 mg) and high-dose (8 mg) dexamethasone overnight suppression tests revealed non-suppressed serum cortisol levels. The clinical diagnosis was Cushing's syndrome with virilism.

Abdominal computed tomography (CT) showed bilateral homogeneous adrenal masses of 7 cm in diameter on the right side and 5 cm in diameter on the left side without calcification (Fig. 1a). These masses were homogeneously enhanced on contrast CT. The characteristics of the adrenal glands on CT was not consistent with autonomous, macronodular adrenal hyperplasia. This result was confirmed via magnetic resonance imaging (MRI) (Fig. 1b). MRI showed bilateral adrenal masses with low signal intensity on the T1-weighted imaging and high signal intensity on T2-weighted imaging. Moreover, out-of-phase MRI scan showed the homogeneous suppression of the fat-containing area of the tumor. No evidence of locoregional invasion or metastasis was observed. ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) and ^{131}I-iodocholesterol scintigraphy, but not iodinated metaiodobenzylguanidine (^{131}I-MIBG), revealed a significant uptake of radiotracer in the bilateral adrenal tumors (Fig. 1c, d). Thus, a clinical diagnosis of bilateral adrenocortical tumor was made, and malignancy was also suspected.

The patient underwent bilateral adrenalectomy. The right and left adrenal tumors were 7 cm and 5 cm in diameter, respectively. Both tumors were well circumscribed and soft with a brown cut surface, and were sharply demarcated from the normal gland (Fig. 2). A gross examination revealed that the right adrenal tumor was 7.0 cm in diameter, which was considered to be the largest tumor measurement; the left tumor was 4.7 cm in diameter. Upon serial sectioning, both tumors were well circumscribed. Microscopically, the tumor cells of both tumors showed alveolar nest and trabecular architecture with eosinophilic and partially clear cytoplasm. Some of the tumor cells had nuclear atypia. However, we did not identify high mitotic activity, atypical mitotic figures, tumor necrosis, venous invasion, sinusoid invasion, or capsular invasion. An atrophic adrenal cortex was observed at the periphery of the tumors. Based on the Weiss criteria, these tumors were considered to represent adrenal cortical adenoma (Fig. 1e, f).

The clinical data showed the over-secretion of cortisol and adrenal androgens from the tumors. Since 17α-hydroxylase (P450c17) is reported to be only be present in zona fasciculate and reticularis, leading to the production of cortisol and adrenal androgens, respectively (5), P450c17 was immunohistochemically analyzed. The tumors were mainly composed of compact cells with a pronounced P450c17 immunoreactivity, indicating the ability to synthesize glucocorticoids and androgens (Fig. 3).

After the operation, the patient's serum ACTH (12 pg/mL), cortisol (20.9 μg/dL) and DHEA-S (135 ng/mL) levels (during glucocorticoid replacement therapy) were within normal ranges. The post-operative course of the patient was unremarkable, since she was on daily hormone replacement therapy (20 mg of hydrocortisone). The clinical signs of virilism progressively decreased. She subsequently achieved pregnancy at 33 years of age. Hydrocortisone replacement was continued during the pre-gestational period after increasing the dose by 1.5 times. She remained normotensive, and neither proteinuria nor glycosuria was observed during her pregnancy. At 38 weeks of gestation, she was given a stress dose of intravenous hydrocortisone (100 mg) before caesarean section, and hydrocortisone weaning was scheduled for infant delivery. No fetal or maternal complications were observed. The latest follow-up examination showed that the patient and her 6-year-old child were both mentally and physically healthy.

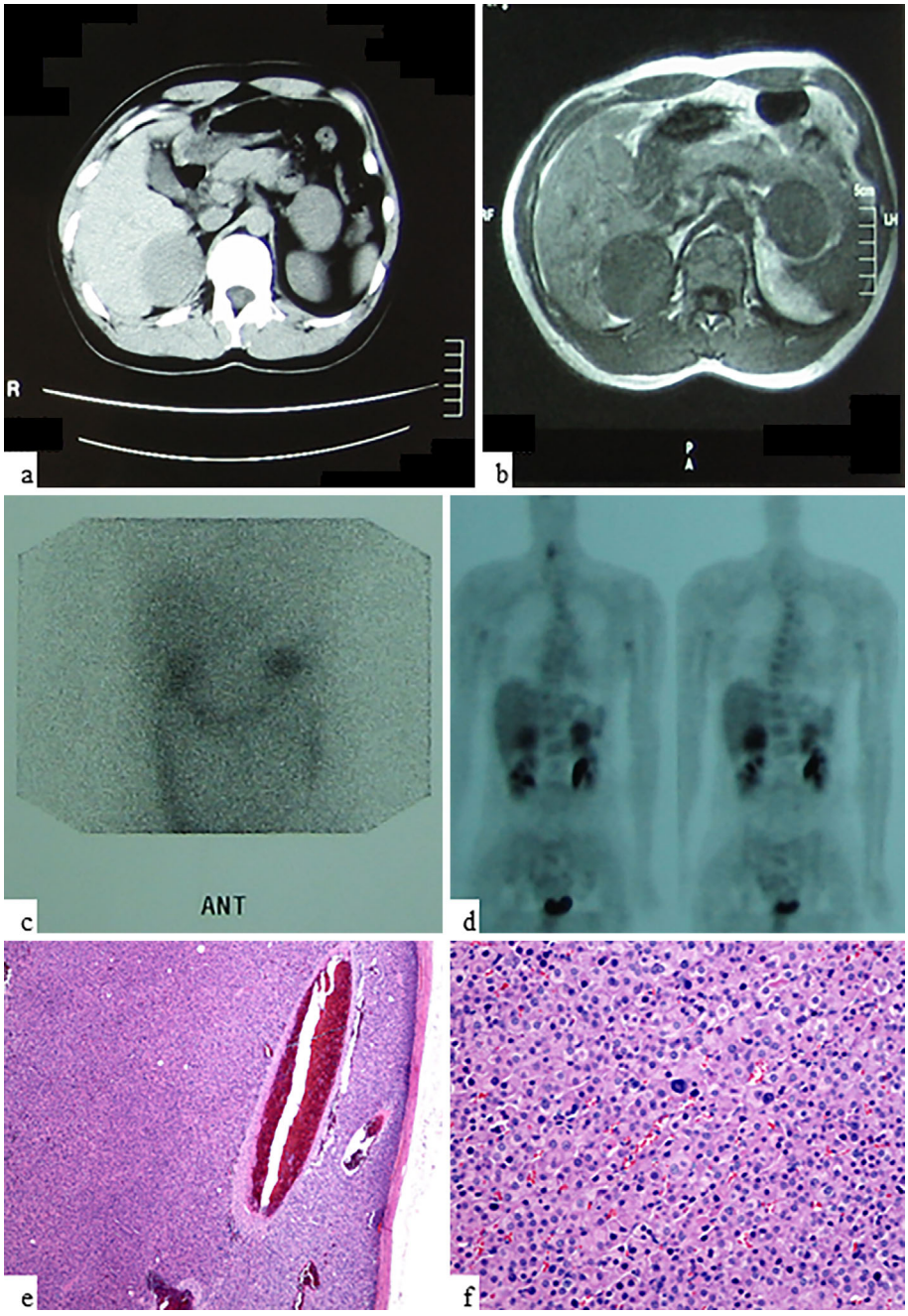

Figure 1. **Abdominal CT (a) and MRI (b) showing bilateral adrenal tumors, ^{131}I-iodocholesterol scintigraphy (c) and FDG-PET (d) revealing bilateral abdominal accumulation. (e) The right adrenal tumor: The tumor was a well-circumscribed mass, and showed alveolar nests and trabecular architecture. (f) The right adrenal tumor: Tumor cells had an eosinophilic and partially clear cytoplasm; some of them showed nuclear atypia.**

Discussion

Adrenal virilism is the development or premature development of male secondary sexual characteristics caused by the excessive production of androgens by the adrenal gland. In children and infants, adrenal virilism is usually the result of adrenal gland enlargement at birth (referred to as congenital adrenal hyperplasia), which is associated with a disease-causing gene that promotes severe enzyme deficiency. In rare cases, adrenal virilism is caused by an adrenal gland tumor. The tumor can be benign (adrenal adenoma) or malignant (adrenal carcinoma) (6).

Adrenal tumors are very common, accounting for 3-10% of the human population; most tumors are small benign non-functional adrenocortical adenoma (ACA). Adrenocortical cancer (ACC) is an extremely rare disease (1). In our case, CT of the abdomen revealed bilateral homogenous adrenal masses with of 7 cm and 5 cm in diameter on the right and left sides, respectively. Upon clinical presentation, ACC tu-

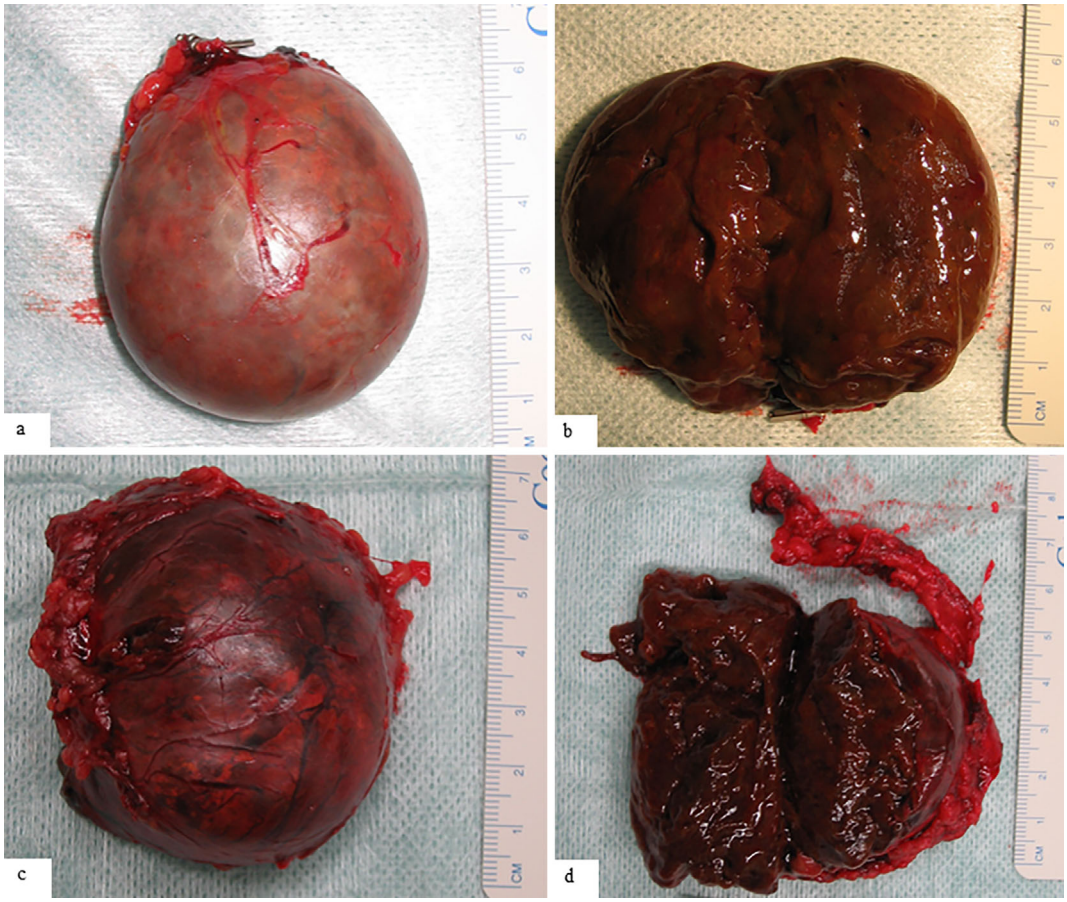

Figure 2. **The macroscopic appearance of the left adrenal tumor (a) (b) and the right adrenal tumor (c) (d).**

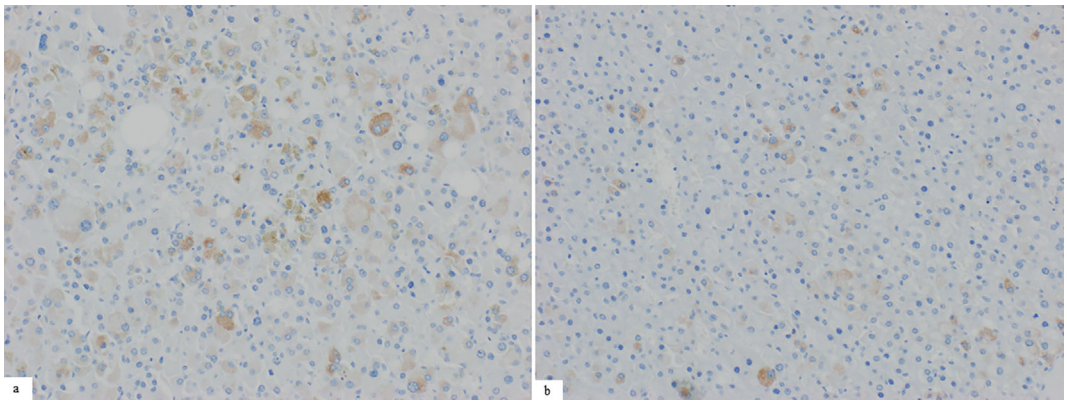

Figure 3. **The expression of P450c17 in the left adrenal tumor tissue (a) and right adrenal tumor tissue (b).**

mors are typically large, often measuring >6 cm in diameter (7). Moreover, the tumors in ACC tend to vary in appearance with frequent heterogeneous enhancement (e.g., internal hemorrhage, calcification, and necrosis. In our case and common ACC, CT and MRI showed the homogenous appearance of the tumors with/without enhancement. Based on PET imaging, ACC patients typically present with a large mass with an intense FDG uptake that is greater than the liver background. Groussin et al. reported that ^{18}F-FDG-PET showed 100% sensitivity and 88% specificity in distinguishing benign lesions from malignant lesions in a study of 77 patients with a clinically proven diagnosis of ACA or ACC (8). In our case, the significant accumulation of [^{18}F] FDG-PET was observed. Arlt et al. pointed out significant differences in the steroid hormone precursor and metabolite profiles of the urine of ACC patients in comparison to patients with benign adrenal tumors (9). However most of these metabolites are not routinely measured. In our case, the patient exhibited large bilateral adrenal tumors along with virilism and Cushing's syndrome, and malignancy of

the adrenal tumor was also suspected. However, the results of the pathological examination revealed adrenocortical adenoma, not carcinoma. To the best of our knowledge, there are only two other reported cases of bilateral ACC.

Adrenal adenomas generally only secrete glucocorticoids. In contrast, androgen excess usually occurs in women with adrenal cancer or ACTH-stimulated hyperandrogenism (10). In our patient, however, the serum DHEAS levels (33500 ng/mL) were very high before surgery and below the normal range (135 ng/mL) after adrenalectomy. Adrenal cancer was ruled out using the Weiss score. An immunohistochemical analysis of the resected adrenal adenomas revealed the pronounced expression of P450c17. These enzymes are implicated in glucocorticoid and androgen production in the normal zona fasciculate and reticularis, suggesting the overproduction of glucocorticoids and androgens in bilateral adenomas. a finding consistent with the clinical endocrine data. As for ruling out ACTH-independent macronodular adrenocortical hyperplasia, the cut surface of the adenomas appeared reddish brown in color without multiple yellowish nodules; thus, the findings may not be compatible with a diagnosis of AIMAH.

The hypothalamic-pituitary-adrenal axis, which controls fertility, arterial blood pressure, hydroelectrolyte balance, and delivery, plays an important role during pregnancy. Untreated adrenocortical hypofunction increases maternal and fetal morbidity and mortality (11). In our case, the patient was normotensive and did not develop electrolyte imbalance at any stage in her pregnancy while under glucocorticoid therapy without mineralocorticoid therapy. Despite the absence of lethargy in our case, the hydrocortisone dose was increased by 1.5 times in the third trimester to catch up with the normally increasing serum cortisol levels as pregnancy progressed. We reported that pregnancy and delivery were successful in a patient with evolving adrenocortical insufficiency due to the treatment of bilateral adrenocortical adenomas along with virilization and Cushing's syndrome, who continued glucocorticoid replacement therapy during pregnancy. This study may be helpful for patients with adrenal insufficiency who wish to have a successful pregnancy and delivery-although the optimal management of adrenal insufficiency during pregnancy and delivery has not been determined.

In conclusion, we herein described a unique case of bilateral adrenal adenomas along with virilization and Cushing's syndrome.

The authors state that they have no Conflict of Interest (COI).

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