Two Rare Cases of Familial (Mother and Daughter) Adrenocorticotrophic Hormone-independent Cushing's Syndrome due to Adrenal Adenoma, as well as the Asynchronous Development of Another Contralateral Adrenal Adenoma in the Mother

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Abstract

We herein report two cases involving a mother and daughter who presented with clinical features of Cushing's syndrome (CS) at 50 and 29 years of age, respectively, and were both found to have adrenocorticotrophic hormone-independent adrenal adenoma. Furthermore, a new adenoma was detected in the contralateral adrenal gland in the mother 10 years after surgical treatment, when she presented with subclinical CS. The pathogenesis of this disorder, including the presence of unknown genetic abnormalities causing hereditary CS, is currently poorly understood. In this report, we describe our experience with and consider the pathophysiological implications of two rare and very interesting cases of familial CS.

Key words: familial, Cushing's syndrome, adrenal adenoma, asynchronous

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Introduction

Cushing's syndrome (CS) is characterized by pathologically by an elevated glucocorticoid level. Causes of CS in adults include Cushing's disease (pituitary-dependent bilateral adrenal hyperplasia), ectopic adrenocorticotrophic hormone (ACTH) (and corticotropin-releasing hormone) production and primary adrenal disorders (adenoma, adrenocarcinoma and nodular hyperplasia). Familial forms of CS are rare (1-3), and most reported cases have been associated with nodular adrenocortical dysplasia, which exhibits an autosomal dominant inheritance pattern. We herein report the cases of a mother and daughter who presented with clinical features of CS due to adrenal adenoma. Subsequently, an adrenal adenoma was detected in the contralateral adrenal gland in the mother 10 years after surgical treatment, when she presented with subclinical CS. To our

knowledge, this is the first report to describe this rare form of familial CS.

Case Reports

Case 1

A 29-year-old woman, the daughter of patient 2 described below, complained to her family physician of progressive weight gain, having reached 10 kg over the previous three years. She had also noted hypertension and a change in her facial appearance during the past year. She was concerned since the condition resembled her mother's former symptoms, and her family physician referred her to our hospital for a further evaluation. On a physical examination, the patient was 162 cm tall and weighed 68.2 kg. She exhibited several Cushingoid features, including a moon face, hirsutism, acne, buffalo hump and abdominal striae. Her blood

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Table. Endocrinological Data of the Patients (Mother and Daughter)

Case1 (Daughter)							Case2 (Mother at the 50yr)						Case2 (Mother at the 60yr)											
Circadian rhythm of Cortisol and Dexamethasone (Dex) Suppression Test																								
	9:00 AM	5:00 PM	9:00 PM	Dex 1mg	Dex 8mg		9:00 AM	5:00 PM	9:00 PM	Dex 1mg	Dex 8mg		9:00 AM	5:00 PM	9:00 PM	Dex 1mg	Dex 8mg							
Cortisol (μg/dL)	18.2	18.3	20.1	ND	27.0	Cortisol (μg/dL)	26.7	21.3	27.2	25.9	24.6	Cortisol (μg/dL)	13.9	7.6	8.3	ND	5.7							
CRH test																								
min	0	30	60	90	120	min	0	30	60	90	120	min	0	30	60	90	120							
ACTH (pg/mL)	<2.0	<2.0	<2.0	<2.0	<2.0	ACTH (pg/mL)	<5.0	<5.0	<5.0	<5.0	<5.0	ACTH (pg/mL)	15.7	31.4	38.4	31.3	24.7							
Cortisol (μg/dL)	18.3	16.2	16.1	15.8	14.5	Cortisol (μg/dL)	97.8	26.2	25.4	24.8	13.5	Cortisol (μg/dL)	12.9	17.0	17.0	15.9	14.4							
75g OGTT (at present)													75g OGTT (at present)											
min	0	30	60	90	120	180	min	0	30	60	90	120	180	min	0	30	60	90	120	180				
ACTH (pg/mL)	101	88.1	94.8	62.0	61.8	47.7	ACTH (pg/mL)	12.9	11.7	10.1	10.7	16.5	21.4	ACTH (pg/mL)	12.9	11.7	10.1	10.7	16.5	21.4				
Cortisol (μg/dL)	10.7	11.1	9.8	8.4	8.5	7.3	Cortisol (μg/dL)	13.9	12.2	10.3	13.0	16.4	19.8	Cortisol (μg/dL)	13.9	12.2	10.3	13.0	16.4	19.8				
IRI (μIU/mL)	0.65	55.9	80.4	67.4	33.0	22.5	IRI (μIU/mL)	2.86	39.1	37.5	62.4	113	53.8	IRI (μIU/mL)	2.86	39.1	37.5	62.4	113	53.8				
BS (mg/dL)	81	151	167	144	120	98	BS (mg/dL)	98	143	143	184	192	129	BS (mg/dL)	98	143	143	184	192	129				
11-OHCS (μg/dL)							19.5						22.9 (17-OHCS ; mg/day)						15.4					
17-KGS (mg/day)							24.0						9.8 (17-KS ; mg/day)						5.78					
U-cortisol(μg/day)							441						345						35.3					
DHEA-S(μg/dL)							170						219						27					
PRA(ng/mL/hr)							0.5						ND						0.4					
PAC(pg/mL)							76.1						ND						96.1					
metanephrine(mg/day)							0.10						ND						0.04					
normetanephrine(mg/day)							0.14						ND						0.22					
Adrenal tumor		left adrenal gland (30mm × 22 mm)					right adrenal gland (30 mm × 25 mm)					left adrenal gland (18 mm × 15 mm)												
Adrenal adosterol scintigraphy		positive uptake (left adrenal tumor) no uptake (right adrenal gland)					positive uptake (right adrenal tumor) no uptake (left adrenal gland)					ND												
Histology		Adrenocortical adenoma					Adrenocortical adenoma					(not removed at present)

Figure 1. Abdominal CT scan shows of a hypodense, homogeneous nodular mass in the left adrenal gland measuring 30×22 mm, with well-defined margins.

pressure was 172/102 mmHg. The results of a routine laboratory examination included a serum potassium level of 4.2 mEq/L and a glucose level of 93 mg/dL. An endocrine evaluation revealed (Table) the plasma ACTH level to be low (09:00 h, <2.0 pg/mL). Meanwhile, the cortisol level was elevated without maintenance of the circadian rhythm (09:00 h, 18.2 μg/dL; 17:00 h, 16.2 μg/dL; 21:00 h, 20.1 μg/dL); the plasma cortisol level was not completely sup-

pressed by the overnight administration of 8 mg of dexamethasone (27.0 μg/dL). The urinary excretion of free cortisol (441 μg/day), urinary 11-hydroxycorticosteroid (11-OHCS: 19.5 μg/day) and 17-ketogenic steroids (17-KGS: 24.0 mg/day) was elevated. An abdominal computed tomography (CT) scan revealed a smooth, ovoid, well-defined nodular mass in the left adrenal gland measuring 30×22 mm in size with low attenuation (Fig. 1). Axial in-phase and out-of-phase adrenal magnetic resonance imaging (MRI) scans showed an oval-shaped tumor in the left adrenal gland with signal dropout, a finding suggestive of intracellular lipids, a characteristic feature of benign adenoma (Fig. 2). Adrenal scintigraphy using ¹³¹I-labeled adosterol revealed a positive uptake in the left adrenal tumor with no uptake in the right adrenal gland (Fig. 3). These findings indicated that the cortisol production in the adrenal tumor was not regulated by the hypothalamic-pituitary-adrenal axis.

The patient underwent left laparoscopic adrenalectomy, during which the surface of the tumor was found to be smooth and not adherent to the kidney. On the pathological examination, the maximal diameter of the left adrenal tumor was 30×25 mm. The lesion was well-demarcated, solid and yellowish-brown in color. The histological sections revealed the nodular proliferation of cells in the zona fasciculata of the adrenal cortex. Neither nuclear atypia nor mitotic figures were detected. The stroma consisted of sinusoidal vessels

Figure 2. Axial in-phase and out-of-phase adrenal MRI scans show an oval-shaped tumor of the left adrenal gland with signal drop-out, a characteristic feature of benign adenoma.

Figure 3. Adrenal scintigraphy using ^{131}I -labeled adosterol revealed positive uptake in the left adrenal tumor with no uptake in the right adrenal gland.

(Fig. 4). Immunohistochemistry staining was positive for CYP11B1, 17α -hydroxylase and 3β -hydroxysteroid dehydrogenase (HSD) (Fig. 5). An adrenal cortical adenoma producing cortisol was considered to be the most likely diagnosis.

The patient's clinical course was uneventful, and she was discharged on postoperative day 14. Hydrocortisone replacement therapy was continued for nine months after surgery. The administration of oral (75 g) glucose increased the patient's blood glucose and plasma insulin concentrations. In contrast, the oral administration of glucose induced no increases in the plasma cortisol level at that time (Table).

Case 2

A 50-year-old woman, the mother of patient 1 (the family pedigree is shown in Fig. 6), was hospitalized for a further evaluation of a right adrenal incidentaloma measuring 30×25 mm in 2002. The physical examination findings were notable for a Cushingoid appearance, including central obesity, moon face, hirsutism and buffalo hump. The initial laboratory results included a serum potassium level of 4.0 mEq/L

and a glucose level of 112 mg/dL. The serum cortisol level ranged from 21.3 to 27.2 $\mu\text{g/dL}$, without diurnal variation. The ACTH level was less than 2 pg/mL. A 24-hour urine collection specimen contained 345 $\mu\text{g/day}$ of free cortisol, 9.8 mg/day of 17-ketosteroids and 22.9 mg/day of 17-OHCS. Dynamic testing showed no suppression of free cortisol with high-dose dexamethasone (24.6 $\mu\text{g/dL}$) (Table). Abdominal CT scans showed a nodular mass in the right adrenal gland measuring 30×25 mm. The lesion was smooth, ovoid, well-defined, homogenous and exerted pressure on the inferior vena cava (Fig. 7). Adrenal scintigraphy using ^{131}I -labeled adosterol revealed a positive uptake in the right adrenal tumor with no uptake in the left adrenal gland (Fig. 8). Right adrenalectomy was performed.

The morphological findings indicated that the tumor was a demarcated round mass measuring 30×25 mm without capsule formation. Histological sections of the tumor demonstrated the proliferation of eosinophilic round tumor cells exhibiting a medullary growth pattern with mild lipofuscin deposition (Fig. 9). Immunohistochemistry demonstrated positive staining of CYP11B1, 17α -hydroxylase and 3β -

Figure 4. Macroscopic and microscopic appearances of the adrenal gland from the daughter. (A) Adrenal gland cross-sections. The tumor had a yellowish cut surface and was well-encapsulated without nodules in the surrounding tissue. Hematoxylin and Eosin staining of adrenal gland sections at low (B) and high-power (C) magnification ($\times 2$ and $\times 10$). Histological examination revealed that the sections showed nodular proliferation of cells in the zona fasciculata of the adrenal cortex. Adrenal cortical adenoma was considered to be the most likely diagnosis.

CYP11B1

17α -hydroxylase 3- β HSD

Figure 5. Immunohistochemistry showing a positive staining for, CYP11B1, 17α -hydroxylase and 3- β HSD in the left adrenal tumor.

β HSD in the tumor, whereas the adjacent atrophic adrenal gland showed no immunoreactivity (Fig. 10).

An adrenocortical adenoma producing cortisol, compact

cell type, was considered to be the most likely diagnosis. Hydrocortisone replacement therapy was continued for eight months after surgery, and the patient was subsequently fol-

Figure 6. Pedigree of the family. Affected patients are shown as full black symbols. Unaffected patients are depicted as white symbols. Numbers in parenthesis indicated the age at the time of death, the present age is indicated at the left upper side of the corresponding symbol. The number on the left lower side of the symbol is the age at the time of operation. The arrow identifies the index patients.

Figure 7. Abdominal CT shows a smooth, ovoid, well-defined, homogenous, nodular mass in the right adrenal gland measuring 30×25 mm, exerting pressure on the inferior vena cava.

Figure 8. Adrenal scintigraphy using ^{131}I -labeled adosterol revealed positive uptake in the right adrenal tumor with no uptake in the left adrenal gland.

lowed up by her family doctor.

After her daughter's surgery, i.e., 10 years after her adrenalectomy, a left adrenal incidentaloma measuring 18×15 mm was detected on abdominal CT performed for dyspepsia, and the patient again consulted our hospital. She had no clinical signs or symptoms of hypercortisolism. An endocrine evaluation revealed (Table) the basal levels of plasma ACTH and cortisol to be normal (13.5 pg/mL and 13.9 µg/dL, respectively). However, the nocturnal cortisol level was high (09:00 h, 13.9 µg/dL; 17:00 h, 7.6 µg/dL; 21:00 h, 8.3 µg/dL), and the plasma cortisol level was not completely suppressed by the overnight administration of 8 mg of dexamethasone (5.7 µg/dL). The urinary excretion of free cortisol (35.3 µg/day), urinary 11-OHCS (15.4 µg/day) and 17-KGS (5.78 mg/day) was normal. Other endocrine data were

as follows: plasma aldosterone, 96.1 pg/mL; plasma renin activity (PRA), 0.4 ng/mL/h; plasma epinephrine, 9 pg/mL; plasma norepinephrine, 238 pg/mL; plasma dopamine, <5 pg/mL; urinary epinephrine, 3.7 µg/day; urinary norepinephrine, 183.5 µg/day; urinary metanephrine, 0.04 mg/day; urinary normetanephrine, 0.22 mg/day; urinary vanillylmandelic acid, 3.1 mg/day; and urinary homovanillic acid, 3.4 mg/day. The administration of oral (75 g) glucose induced increases in the blood glucose and plasma insulin levels; however, the plasma cortisol level did not increase significantly following the administration of glucose. Abdominal CT scans revealed a nodular mass in the left adrenal gland measuring 18×15 mm (Fig. 11). The lesion was hypodense, homogenous and exhibited rapid enhancement following the injection of intravenous contrast medium. Axial in-phase and

Figure 9. Microscopic appearances of the adrenal gland from the mother. Hematoxylin and Eosin staining of adrenal glands at low (A) and high-power (B) magnification (×2 and 10). Sections show proliferation of eosinophilic round tumor cells forming a medullary growth pattern. Mild lipofuscin deposition is present in the tumor. Adrenal cortical adenoma, compact cell type, was considered to be the most likely diagnosis.

CYP11B1

17 α -hydroxylase 3- β HSD

Figure 10. At the immunohistochemical investigation, the adrenal tumor cells were diffusely positive for CYP11B1, 17 α -hydroxylase and 3- β HSD. Conversely, no immunoactivity was found in the adjacent adrenal gland.

Figure 11. Abdominal CT scan shows a nodular mass in the left adrenal gland measuring 18×15 mm. The mass was hypodense, homogenous, and showed rapid enhancement after intravenous contrast medium injection.

Figure 12. Axial in-phase and out-of-phase adrenal MR images show the left adrenal gland mass with classic signal drop-out, a characteristic feature of benign adenoma.

out-of-phase MR images showed the mass to display classic signal dropout (Fig. 12). These findings indicated that the tumor was an adenoma associated with subtle abnormalities of the hypothalamic-pituitary-adrenal axis. Since the patient had only one adrenal gland and there were no remarkable signs or symptoms of CS, she was closely followed without intervention.

Discussion

The initial step in the differential diagnosis of CS is to distinguish ACTH-dependent from ACTH-independent forms of hypercortisolism. ACTH dependency accounts for 80% of cases of CS. Of these cases, 85% involve ACTH-secreting pituitary adenomas, while 15% involve ectopic ACTH-secreting tumors (4). ACTH-independent hypercortisolism is always of adrenocortical origin. By far the most common cause (>95% of cases) is adrenocortical adenoma or carcinoma. Most remaining patients have primary pigmented nodular adrenal dysplasia (PPNAD), a syndrome characterized by the presence of multiple small bilateral pigmented adrenocortical nodules, often in association with the Carney complex (5, 6). The Carney complex presents in adolescence or young adulthood in patients with unusual conditions, such as myxomas with spotty skin pigmentation, endocrine overactivity or schwannomas. The adrenal glands in patients with this disorder are often small or normal in size with multiple black and brown nodules associated with intranodular cortical atrophy. An even rarer form of ACTH-independent primary adrenal hypercortisolism consists of multiple bilateral adrenocortical macronodules inducing the striking enlargement of the adrenal glands, called ACTH-independent macronodular adrenocortical hyperplasia (AIMAH) (7-11). The histological features of adrenal glands with AIMAH include multiple large nodules with interspersed markedly hyperplastic adrenal tissue between the nodules; there is no pigmentation.

The present patients, a mother and daughter, had ACTH-independent forms of hypercortisolism with single adrenal tumors on CT or MRI in addition to unilateral uptake on ad-

renal scintigraphy. Histologically, the excised adrenal tumors were very similar, and both were adrenal adenomas. The tumor features in the mother and daughter included a compact cell type and demarcated round masses without capsule formation. Immunohistochemistry demonstrated that both adenomas produced cortisol.

Most often Cushing's disease occurs as a sporadic, isolated condition. Rarely, it can appear as a component of genetic syndromes, such as multiple endocrine neoplasia type 1 (*MEN1*), Carney complex (CNC) and micronodular adrenal disease. *MEN1* is a familial disorder that exhibits autosomal-dominant transmission due to an inactivating mutation in the *MEN1* gene located in chromosome 11q13. Most adrenal tumors in patients with *MEN1* are nonfunctional; however, a few cortisol-producing tumors have been reported (12). In the present cases, neither the daughter nor her mother had *MEN1*-related endocrine disorders, including hyperparathyroidism, the most frequently observed endocrine disorder in *MEN1* patients. CNC is another genetic disorder that can cause Cushing's syndrome. Inactivating germline mutations in the gene coding for *PRKARIA*, a regulatory subunit of PKA, have been found (13, 14). The gene coding for *PRKARIA* is located on chromosome 17q22-23. All described mutations (small or large deletions, base substitutions, etc.) usually result in premature stop codons. It has been noted that such mutations can also induce the expression of abnormal proteins, thus demonstrating that alteration of the *PRKARIA* function augments the PKA activity, thereby leading to tumorigenesis in tissues affected by CNC. More than 60% of CNC patients harbor pathogenic *PRKARIA* mutations. Other loci located on chromosome 2 (2p16, 2q31.2 regions) have been implicated in the tumorigenesis of CNC. Inactivating mutations in the *phosphodiesterase11A* (*PDE11A*) gene, located on chromosome 2q31.2, have been described in patients with PPNAD negative for *PRKARIA* mutations (15). Inactivating mutations in *PDE11A* result in the disruption of the ability to hydrolyze cAMP and cGMP. For example, a mutation in the gene coding for *PDE8B* (locus 5q13) resulting in a disrupted ability to hydrolyze cAMP has been described (16). The gross and

histological appearance of PPNAD is characteristic. The pathological findings of the present cases did not involve PPNAD characteristics, and we did not detect any other CNC-related disorders, such as skin pigmentation or cardiac myxoma. Based on these clinical and pathological observations, we concluded that genetic alterations of these known genes were unlikely to be present in these cases. Therefore, we did not perform any genetic testing.

Other genetic mutations responsible for several primary cortical disorders have been identified (17). A somatic mutation of TP53, a tumor suppressor gene (18), and a germline mutation of the adenomatous polyposis coli (APC) gene that result in the activation of the Wnt/ β -catenin signaling pathway also play important roles in cell proliferation and have been demonstrated in patients with adrenocortical tumors (19). Recently, aldosterone-producing adenoma (APA) was shown to possess somatic mutations (G151R and L168R) in KCNJ5 that cause alterations in channel selectivity leading to nonselective Na entry and chronic depolarization (20).

In addition, several hypotheses have been proposed in the literature (17, 21, 22), including the presence of unknown non-ACTH adrenal growth factors or the expression of ectopic receptors for such substances, such as increased responsiveness to gastric inhibitory polypeptide receptors (food-dependent hypercortisolism), vasopressin receptors or β -adrenergic receptors and so on, that do not usually control the adrenal growth or function. Even if the plasma cortisol concentration did not increase significantly following the administration of oral glucose in either the mother or daughter, the examinations conducted after the removal of the adrenal adenomas detected overt Cushing's syndrome. The possibility that these pathological mechanisms may have played a role in the present cases cannot be completely excluded. As far as we were able to investigate, there were no endocrine disorders in relatives or consanguineous marriage, although the existence of an asymptomatic endocrine disease also cannot be completely excluded (Fig. 1). Therefore, the pathogenesis underlying these familial cases remains unclear, although the presence of unknown genetic abnormalities causing hereditary CS is suggested. Further genetic analyses of such familial cases are required.

In the literature, reported bilateral adrenocortical adenomas have usually been found simultaneously. However, in the present case 2, the right and left adrenocortical adenomas inducing the excess production of cortisol developed 10 years apart. Tung et al. (23) also reported bilateral adrenocortical adenomas causing ACTH-independent CS diagnosed nine years apart. Imai et al. (24) reported the results of long-term follow-up studies after adrenalectomy in 122 patients with CS. Of 70 patients with adrenocortical adenoma, CS recurred in two (2.9%) cases due to the development of contralateral adrenocortical adenomas 20 years after the first adrenalectomy. These findings highlight the importance of providing regular follow-up in patients treated with unilateral adrenalectomy for adrenocortical adenoma.

To our knowledge, the present cases are the first reported familial cases of CS caused by adrenal adenoma. Furthermore, a second adrenocortical adenoma producing excess cortisol developed 10 years after the first lesion in the mother. Although the pathogenesis underlying these cases is currently poorly understood, further study is warranted, and close follow-up of both patients is required, focusing particularly on the possibility of tumor development in the other adrenal gland in the daughter and the presence of the clinical features of CS in the mother.

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

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