

Pheochromocytoma and Adrenocortical Adenoma in the Same Gland

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A right adrenal tumor was found incidentally during abdominal computed tomography exam in a 51-year-old female patient, who had had diabetes and hypertension for more than 10 years. The computed tomography scan was arranged for possible pancreatic lesion by a neurologist. Norepinephrine level was high in the plasma and urine. Vanillylmandelic acid level was elevated in the urine. Diurnal cortisol rhythm, plasma adrenocorticotropic hormone and urine free cortisol were all normal, but the plasma cortisol concentration could not be suppressed after a standard low-dose dexamethasone suppression test. Therefore, adrenal cortical adenoma with subclinical Cushing's syndrome was highly suspected; however, further imaging studies, including magnetic resonance image and ¹³¹I-6β-iodomethylnorcholesterol adrenal scintigraphy failed to discriminate an additional tumor. After right adrenalectomy, a small adrenal cortical adenoma and a large pheochromocytoma were noted. This is an extremely rare case of an adrenal incidentaloma consisting of both medullary and cortical tumors in the same gland. [*J Chin Med Assoc* 2007;70(7):289–293]

Key Words: cortical adenoma, pheochromocytoma, subclinical Cushing's syndrome

Introduction

Adrenal incidentalomas are encountered frequently as a result of the application of high-resolution anatomical imaging procedures. About 85% of incidentally found adrenal masses are nonfunctional masses, 9% are defined as subclinical Cushing's syndrome (SCS), 4% are pheochromocytomas, and only 1% of them are aldosteronomas.¹ Simultaneous occurrence of adrenocortical tumor and pheochromocytoma is rarely seen in the same gland. Herein, we report an extremely rare case of adrenal incidentaloma consisting of both medullary and cortical tumors in the same gland.

Case Report

A 51-year-old female patient had had diabetes and hypertension for more than 10 years. Her high blood

pressure was not paroxysmal type, and she had never experienced sudden episodes of headache, palpitation, profuse sweating or hot flushes. Her mean plasma glucose was around 300 mg/dL and blood pressure was 160/80 mmHg or so despite taking antidiabetic agents combined with insulin and antihypertension drugs regularly. This patient had gained about 11 kg body weight in the past 1 month. She had been followed up at the neurology clinic for diabetic neuropathy. Abdominal computed tomography (CT) for possible pancreatic lesion was arranged by the neurologist, and incidentally revealed a heterogeneous attenuation tumor with fat component, 4.2 × 3.4 × 3 cm in size, in the right adrenal gland (Figure 1A). Then, the patient was referred to the endocrine clinic for further evaluation. The urine free cortisol (UFC) was 79.8 μg/day (normal, < 100 μg/day), and morning plasma cortisol and adrenocorticotropic hormone (ACTH) concentrations were 20.43 μg/dL (normal, 5–25 μg/dL) and

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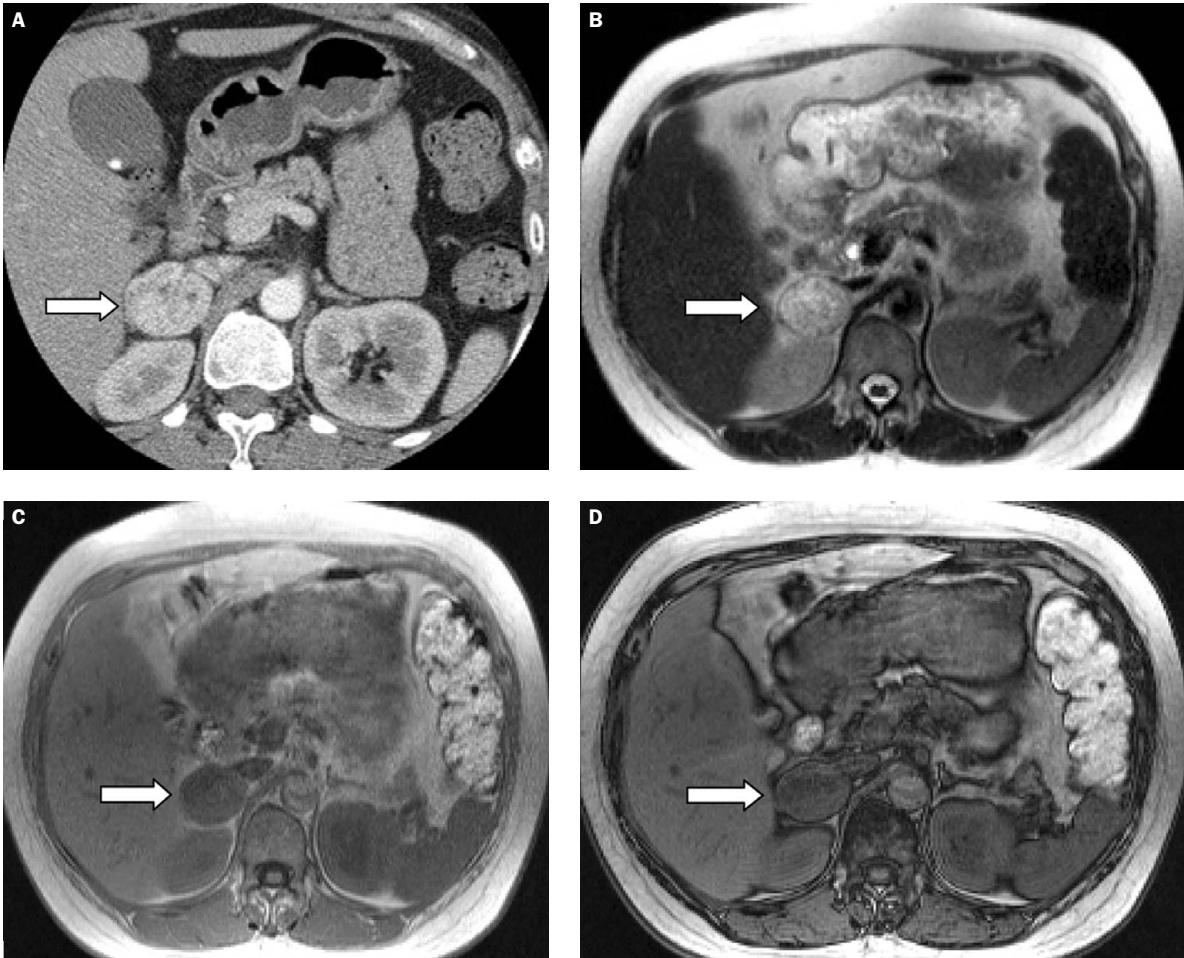


Figure 1. (A) Contrast-enhanced computed tomography reveals a heterogeneous mass (arrow) in the right adrenal gland. (B) Magnetic resonance imaging shows the high signal intensity of the mass on T2-weighted imaging. (C) Chemical shift in-phase and (D) opposed-phase disclose no obvious signal intensity decrease of the tumor.

20.5 pg/mL (normal, 9–52 pg/mL), respectively. However, urine norepinephrine level was markedly elevated to 431 µg/day (normal, 10–80 µg/day). Therefore, the patient was admitted to our hospital for further examination and treatment.

On admission, physical examination revealed a generalized obese woman, 168 cm in height and 90 kg in weight. There were no classic signs of Cushing's syndrome such as purple striae, facial plethora, buffalo hump, and ecchymoses. Blood pressure was 160/80 mmHg, and pulse rate was 80/min. Laboratory examinations revealed her condition as follows: fasting plasma glucose 410 mg/dL, glycated hemoglobin 12.1%; serum sodium 132 mmol/L (normal, 135–147 mmol/L), potassium 4.6 mmol/L (normal, 3.4–4.7 mmol/L); total cholesterol 470 mg/dL (normal, 125–240 mg/dL), triglycerides 1,624 mg/dL (normal, 20–200 mg/dL), and recumbent plasma aldosterone 105 pg/mL (normal, 10–160 pg/mL). Urinary

Table 1. Endocrinologic studies for pheochromocytoma

	In this patient	Reference range
Plasma		
Epinephrine (pg/mL)	26	10–67
Norepinephrine (pg/mL)	>2,000	950–446
Urine		
Epinephrine (µg/d)	8	0–24
Norepinephrine (µg/d)	226	10–80
Dopamine (µg/d)	116	138–540
Vanillylmandelic acid (mg/d)	11.3	1.0–7.0

excretion of vanillylmandelic acid and both plasma and urine norepinephrine concentrations were high (Table 1). A 24-hour UFC excretion and circadian rhythms of plasma cortisol and ACTH were normal. The plasma cortisol levels could only be suppressed

Table 2. Endocrinologic studies for Cushing's syndrome

	Day 1	Day 2	Reference range
Baseline			
8 AM serum cortisol ($\mu\text{g/dL}$)	12.12	21.14	5–25
10 PM serum cortisol ($\mu\text{g/dL}$)	2.70	6.66	<5
8 AM plasma ACTH (pg/mL)	10.0	10.0	9–52
10 PM plasma ACTH (pg/mL)	4.0	5.0	9–52
UFC ($\mu\text{g/d}$)	7.9	2.9	<100
LDDST			
8 AM serum cortisol ($\mu\text{g/dL}$)	5.58		<1.85
HDDST			
8 AM serum cortisol ($\mu\text{g/dL}$)	0.55		

ACTH = adrenocorticotropic hormone; UFC = urine free cortisol; LDDST = low-dose dexamethasone suppression test; HDDST = high-dose dexamethasone suppression test.

by a standard high-dose dexamethasone suppression test with dexamethasone 2.0 mg po q6h for 2 days rather than by a standard low-dose dexamethasone suppression test with 0.5 mg dexamethasone po q6h for 2 days (Table 2).

The ^{131}I -6 β -iodomethylnorcholesterol (NP-59) adrenal scintigraphy, after giving dexamethasone suppression (8 mg/day), failed to show any adrenal uptake within 5 days. Abdominal magnetic resonance image (MRI) revealed high signal intensity on a T2-weighted image and no obvious chemical shift of the right adrenal mass (Figures 1B–D).

Right adrenalectomy was performed, and 2 tumors were found in the same gland. The sizes of the tumors were 6.0 \times 4.0 \times 1.5 cm and 1.5 \times 1.0 \times 1.0 cm, respectively (Figure 2A). Histologically, the small tumor, yellowish, encapsulated and composed of lipid-laden clear cells, was diagnosed an adrenal cortical adenoma (Figures 2B, 2C). The large brownish tumor was a pheochromocytoma composed of large cells with abundant basophilic granular cytoplasm and mildly nuclear pleomorphism (Figure 2D).

The results of endocrinologic tests, including ACTH stimulation test, were all normal after the operation. However, glycemic control remained poor and the patient's weight remained the same 1 year later.

Discussion

The simultaneous occurrence of pheochromocytoma and adrenal cortical adenoma is extremely rare, especially in the same adrenal gland. There have only been 13 pheochromocytomas either with functioning or non-functioning adrenal cortical adenoma reported, more than half of which were found in Japan.^{2–13} The

coexistence was believed to be coincidental in most reports. Catecholamines have an effect on steroidogenesis of adjacent cortical cells by a paracrine manner.¹⁴ Human pheochromocytoma may also synthesize and secrete several regulatory peptides, such as adrenomedullin, somatostatin, neuropeptide Y, and galanin, which are able to influence adrenocortical steroid production.¹⁴ In addition, adrenal medulla may serve as an extrapituitary source of ACTH production. Long-term secretion of ACTH, catecholamines and several other peptides might result in adrenal cortical adenoma formation. However, it is still difficult to explain why most patients with pheochromocytoma do not develop cortical hyperplasia or adenomas.

In the present case, although there were no typical symptoms and signs, a large pheochromocytoma was diagnosed without difficulty according to the biochemical data and imaging studies. Larger pheochromocytomas may outgrow the corticomedullary blood supply, thus losing the exposure to high local concentrations of glucocorticoids that regulate the activity of phenylethanolamine-N-methyltransferase (PNMT), which is an essential enzyme to convert norepinephrine into epinephrine in the adrenal gland.¹⁵ This may explain the disproportionately high plasma and urine concentration of norepinephrine to epinephrine in this case.

The patient had a normal 24-hour UFC level and normal circadian rhythms of plasma cortisol and ACTH. However, abnormal low-dose dexamethasone suppression test made SCS a reasonable suspicion, although the abdominal MRI and NP-59 adrenal scintigraphy failed to discriminate an adrenal cortical tumor. Corticotropin-releasing hormone stimulation test may provide more information in this case,¹⁶ however, it was not taken at that time.

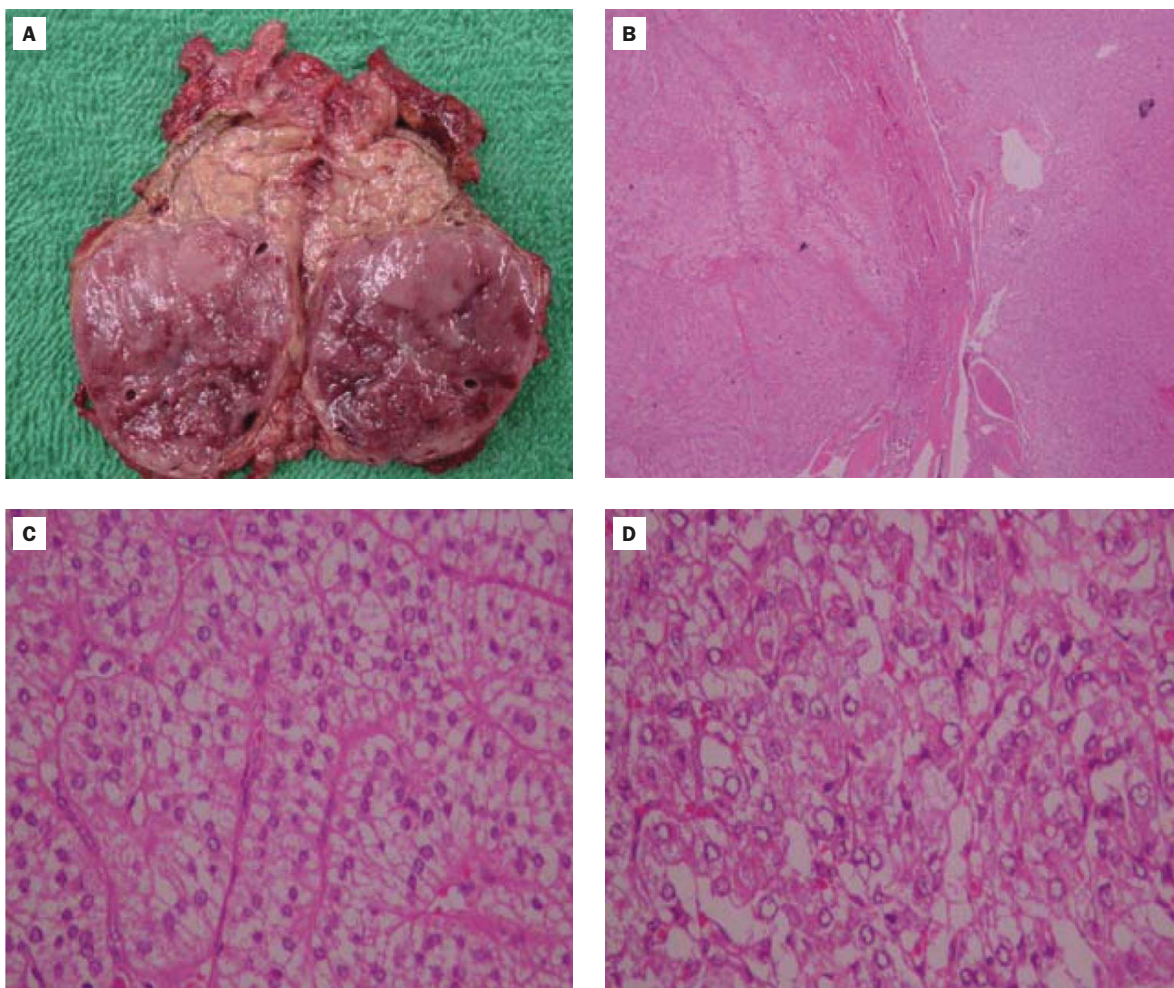


Figure 2. (A) Gross picture of the adrenal tumor shows 2 tumor components: a large dark brownish tumor and an encapsulated yellowish tumor. (B) Low-power magnification view of the specimen: an encapsulated adrenal cortical adenoma on the left side in contact with a pheochromocytoma on the right side of the picture (hematoxylin & eosin [H&E]). (C) High-power magnification view of the adenoma: lipid-laden clear cells arranged in acini (H&E). (D) High-power magnification view of the pheochromocytoma: large cells with abundant pink granular cytoplasm (H&E).

NP-59 scintigraphy is a sensitive functional adrenal imaging study, but it still failed to detect the adrenocortical adenoma in this case. There might be 3 possibilities for why. One is the hypercholesterolemia of the patient, which would disturb uptake of NP-59, leading to non-visualization of the adrenal glands. The others are that the cortical adenoma might have been too small to be detected and the tumor may have had low autonomous function which could be suppressed by high-dose dexamethasone during NP-59 scintigraphy.

In conclusion, adrenal incidentaloma usually exists as a nonfunctional or a single hormone-producing tumor. But there is a possibility that both adrenal medulla and cortical tumors might occur in the same gland. Thus, complete adrenal functional studies in adrenal incidentalomas are strongly suggested before surgical

intervention to prevent intraoperative hypertensive crisis or postoperative adrenal insufficiency.

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