Adrenocorticotrophic Hormone-Secreting Pheochromocytoma

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A 41-year-old female had pheochromocytoma which secreted adrenocorticotrophic hormone (ACTH). She was admitted to our hospital because of weight loss and excessive sweating. Not only urinary metanephrine but also plasma ACTH was extremely high. An abdominal echogram showed a cystic tumor in the left adrenal gland. An abdominal magnetic resonance imaging scan showed a hyperintense T2-weighted abnormality inside the tumor. Left adrenalectomy was done. The tumor consisted of benign pheochromocytoma cells diffusely stained with anti-ACTH antibody. The present case did not show any typical Cushingoid symptoms which are common in ACTH-secreting pheochromocytomas. (Internal Medicine 37: 403–406, 1998)

Key words: adrenal gland neoplasm, ectopic adrenocorticotrophic hormone (ACTH) syndrome, Cushing's syndrome, adrenalectomy

Introduction

Pheochromocytomas are reported to secrete some hormones such as somatostatin (1), vasoactive intestinal peptide (2), calcitonin (2), parathyroid hormone (3) and adrenocorticotrophic hormone (ACTH) (4, 5). ACTH-secreting pheochromocytoma is a rare disease. Only twenty-four cases have ever been reported. Most of the cases showed typical Cushingoid symptoms. In this report, we present a case of ACTH-secreting pheochromocytoma without Cushingoid symptoms.

Case Report

A 41-year-old female was admitted to the hospital because of weight loss and excessive sweating. The patient had been well until three months earlier, when she felt a visual field defect in the center of the right eye. An ophthalmologist found that preretinal hemorrhage developed in the eye. In the week before admission, she had lost 5 kg over three days and began to complain of excessive sweating and weakness. Then she was admitted to the hospital.

The patient was a housewife. She had undergone right ovariectomy because of ectopic gestation eleven years before admission. She was treated for pneumonia at the age of 37. There is no family history of diabetes mellitus, thyroid diseases,

parathyroid dysfunction or pancreas tumors.

Her weight was 47 kg, and height 160 cm. The temperature was 36.1°C, and the pulse was 110 bpm. The blood pressure was 109/77 mmHg. Her skin showed acne vulgaris on the face and chest. The neck was normal. No lymphadenopathy was found. The lungs were clear, and the heart was normal. No mass lesions were palpable on abdominal examination. On neurological examination the patient was alert.

The urine was positive for glucose and protein. Table 1 shows the laboratory findings on admission. The values for serum lactate dehydrogenase and blood glucose were high. Not only plasma adrenaline and noradrenaline but urinary metanephrine and normetanephrine were extremely high. Plasma ACTH, cortisol, and urinary free cortisol were also high. Plasma corticotropin releasing hormone (CRH) was normal.

Abdominal ultrasonography showed a cystic lesion between the left kidney and the spleen. Computed tomography revealed a cystic mass of 6.5 cm in diameter in the left adrenal gland. An abdominal magnetic resonance imaging (MRI) scan showed a hyperintense T2-weighted abnormality inside the tumor (Fig. 1). These images revealed no evidence of right adrenal hypertrophy. ¹³¹I-metaiodobenzylguanidine (MIBG) scintigraphy showed an accumulation of the isotope on the left adrenal gland. No other ectopic accumulation was observed. A 24-hour monitoring of the blood pressure detected paroxysmal elevations of

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Table 1. Laboratory Data on Admission

Serum lactate dehydrogenase	1,100 IU/l	Plasma adrenaline	4,970 (<80) pg/ml
Serum sodium	134 mEq/l	Plasma noradrenaline	7,570 (90~420) pg/ml
Serum potassium	4.8 mEq/l	Plasma dopamine	51 (<30) pg/ml
Serum chloride	90.7 mEq/l	Urinary metanephrine	10.13 (0.05~0.23) mg/day
Serum calcium	5.2 mEq/l	Urinary normetanephrine	2.97 (0.07~0.26) mg/day
Plasma glucose	680 mg/dl	Plasma adrenocorticotrophic hormone	120 (9~52) pg/ml
Glycohemoglobin	7.5%	Plasma cortisol	66.5 (4.0~18.3) µg/dl
Urinary C-peptide	30 µg/day	Urinary free cortisol	3,580 (35~160) µg/day
Antibody to glutamic acid decarboxylase	<4.0 U/ml	Plasma corticotropin releasing hormone	24.8 pg/ml
Serum thyroid stimulating hormone	1.03 µU/ml	Serum aldosterone (supine)	59 (29.9~159) pg/ml
Serum free triiodothyronine	2.99 pg/ml	Urinary aldosterone (supine)	<4.8 (<10) µg/day
Serum calcitonin	35 (15~86) pg/ml	Plasma renin (supine)	3.6 (2.49~21.4) pg/ml

Figure 1. Abdominal MRI scans. A frontal T1-weighted MRI scan (left panel) and a horizontal T2-weighted scan (right panel). The tumor showed a bright T2 signal.

the systolic blood pressure in excess of 200 mmHg. The patient felt palpitation, headache and showed excessive sweating at the time of the attacks. Labetalol hydrochloride was effective. Serum potassium was normal at first and fell rapidly from 4.8 mEq/l to 2.1 mEq/l after admission.

On the 22nd hospital day, the left adrenal gland was removed. The resected specimen was a cystic tumor of about 6 cm in diameter encapsulated by thin gland tissues, and contained bloody fluid inside (Fig. 2). After discharge of the inner fluid, the tumor weighed 54 g. The cut surface of solid portion was dark red in color (Fig. 3).

The histological examination of the tumor revealed medullary and alveolar growth of large polyhedral tumor cells with a vesicular, round nucleus and a rather prominent nucleolus. The histological feature was that of a typical benign pheochromocytoma.

Mitosis or capsular invasion was not seen. Nerve fiber-like and ganglion cell-like differentiations were observed. An NSE (neuron-specific-enolase)-stained specimen was focally positive. The tumor was diffusely stained with anti-ACTH antibody (Fig. 4). It was also positive part of the nerve fiber-like differentiation. The tumor compressed the left adrenal cortex. This cortex showed cellular hypertrophy but not hyperplasia. The values for ACTH (991 pg/ml), cortisol (229 µg/dl), adrenaline (285,509 pg/ml) and noradrenaline (503,287 pg/ml) were extremely high in the inner fluid of the tumor.

After the removal of the tumor, the values of plasma ACTH and urinary metanephrine decreased to the normal range. The urinary free cortisol was also normalized after the surgery (Table 2). Clinical symptoms such as excessive sweating and palpitation completely disappeared. Paroxysmal hypertension

Figure 2. External appearance of the resected tumor. The size was approximately 6 cm in diameter.

Figure 4. A microscopic examination shows it was diffusely positive for ACTH stain (x50).

Figure 3. A section of the tumor. The amount of the inner fluid was 50 ml.

was not seen. The values for blood glucose, urinary C-peptide and serum potassium were normalized after the surgery.

Discussion

Pheochromocytoma which ectopically secretes ACTH is

not a common disease, and only twenty-four cases were reported before (6–9). The present case showed some symptoms derived from adrenocortical excess such as hyperglycemia, weakness, hypokalemia, and acne vulgaris. The etiology of ACTH excess in pheochromocytoma is as follows: (i) direct secretion from the tumor, (ii) combined adrenocortical adenoma and adrenomedullary hyperplasia (10), (iii) corticotropin-releasing hormone (CRH)-secreting pheochromocytoma (11), (iv) pheochromocytoma with pituitary tumor and/or ectopic ACTH syndrome such as small cell carcinoma. The level of CRH was normal in this case. Ectopic ACTH syndrome such as small cell lung cancer, thymic carcinoid tumors, pancreatic islet cell tumors, bronchial carcinoid tumors, and medullary thyroid cancer may cause Cushing's syndrome (11). These candidates were ruled out in the present case.

Most of the cases of ACTH-secreting pheochromocytoma presented Cushing's syndrome (6–8, 12–17). The present case did not show any typical Cushingoid symptoms such as central obesity, rounded facie, skin fragility and increased pigmentation in spite of high levels of plasma cortisol. This finding is the most characteristic feature of the present case. We thought that the absence of Cushingoid symptoms was due to the rapid

Table 2. Changes in Plasma ACTH and Adrenal Hormones Following Adrenalectomy

Case No.	Plasma ACTH (pg/ml)		Urinary free cortisol (μg/day)		Urinary metanephrine (mg/day)	
	before	after	before	after	before	after
1*	62.6	14.6	997	8	2.2	0.3
2*	310	15.2	12,341	17	2.7	0.1
3*	503	9.4	4,226	21	3.6	0.8
4*	292	7.2	3,559	86	4.5	0.7
5**	120	7.6	3,580	17.8	10.13	0.03

*The series of cases reported by Chen et al (6). **The present case.

increase of the ectopic secretion of ACTH from the tumor. Rapid worsening of hypokalemia after admission, and a loss of hypertrophy of another side of the adrenal cortex support this hypothesis. In addition, hypersecretion of catecholamines and severe hyperglycemia might be responsible for the absence of typical Cushingoid symptoms.

The tumor cells positive for ACTH-stain do not always secrete ACTH. A report described that ACTH was found or stained on specimens of some types of pheochromocytomas which did not secrete ACTH themselves (18). In the present case, ACTH was really secreted ectopically from the left adrenal tumor.

Chen et al proposed the following criteria for ACTH-secreting pheochromocytomas: (i) clinical and laboratory evidence of hypercortisolism, (ii) elevated plasma ACTH level, (iii) evidence of a pheochromocytoma by urinary catecholamines, metanephrines, or vanillylmandelic acid, or MRI evidence of an adrenal mass with a bright T2 signal, (iv) resolution of symptoms – signs of adrenocorticoid and catecholamine excess after unilateral adrenalectomy, and (v) rapid normalization of plasma ACTH levels after adrenalectomy (6). The present case completely fulfilled these criteria.

All previously reported cases of ACTH-secreting pheochromocytomas except for one were benign (6–9). Many other tumors associated with ectopic ACTH secretion such as small cell lung cancer, carcinoid, or medullary thyroid cancer tend to be unresectable or metastatic. However, most ACTH-secreting pheochromocytomas need only unilateral adrenalectomy. The patient is well fourteen months after the surgery with no evidence of recurrence of the disease.

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