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Reversal of Insulin-Requiring Diabetes after the Resection of a Large-Sized, Epinephrine-Dominant Pheochromocytoma, Following 9-Year Treatment of Diabetes without Hypertension

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Abstract **Case Report**

Hypertension (sustained or paroxysmal) is a cardinal feature of pheochromocytomas, which are rare catecholamine-producing tumors derived from chromaffin cell of the adrenal medulla. We presented a 62-year-old man with diabetes mellitus who was discovered to have a large-sized, epinephrine-dominant pheochromocytoma. The patient had been treated for diabetes without hypertension for 9 years. He was referred to our hospital due to the difficulty in glycemic control, and his computed tomography of the abdomen revealed a 5–cm left adrenal tumor. Plasma and urine levels of catecholamines were elevated and, especially, the epinephrine levels exceeded more than 10 times the upper limit of the reference range. The patient was diagnosed of pheochromocytoma and underwent the left adrenalectomy. Stimulation of α_2-adrenergic receptors decreases insulin secretion, which is the feature of epinephrine-associated hyperglycemia. The patient's insulin-required diabetes was reversed after the tumor resection, and the insulin secretion assessed by serum C-peptide was clearly increased. As demonstrated in this case, epinephrine-dominant pheochromocytomas may have unusual modes of presentation leading to misdiagnosis. Disturbed glucose and insulin metabolism in pheochromocytomas seem not to be well-recognized in general.

Keywords: Pheochromocytoma, hypertension, diabetes mellitus, catecholamine, epinephrine-dominant, insulin secretion.

INTRODUCTION

Hypertension (sustained or paroxysmal) is a cardinal feature of pheochromocytomas, which are rare catecholamine-producing tumors derived from chromaffin cell of the adrenal medulla [1]. A number of incidentally discovered pheochromocytomas are not associated with hypertension. Patients with such pheochromocytomas, compared with patients with hypertensive pheochromocytomas, had a similar tumor size and displayed reduced summed levels of urinary catecholamines, more specifically, reduced levels of epinephrine [2]. Here, we demonstrated a patient with diabetes mellitus who was discovered to have a large-sized, epinephrine-dominant pheochromocytoma, following 9-year treatment of diabetes without hypertension.

CASE REPORT

A 62-year-old man with diabetes mellitus was admitted to a hospital due to the difficulty in glycemic control under the use of metformin and sulfonylurea. The patient had been treated by his primary care physician with oral hypoglycemic agents for 9 years. During that period, his blood pressure remained normal without medication, and he had no symptoms of episodic headache, palpitations and sweating. At the age of 60 years, he started taking tamsulosin for benign prostatic hyperplasia. The patient had no family history of diabetes or endocrine disorders. He drank alcohol but did not smoke cigarettes.

On admission, the patient was 177 cm in height and 65 kg in weight. His blood pressure and heart rate were 114/75 mmHg and 70 beats per minute. No remarkable findings were noted on his physical examination. No diabetic retinopathy was detected. The patient's white blood cell count was 4,380/μl, hemoglobin was 14.9 g/dl, and platelet count was 158,000/μl. The levels of serum albumin, aspartate transaminase, alanine transaminase, γ-glutamyl transpeptidase, urea nitrogen, creatinine, sodium and

potassium were 4.4 g/dl, 22 U/l, 41 U/l, 105 U/l, 18 mg/dl, 0.8 mg/dl, 139 mEq/l, and 4.2 mEq/l, respectively. His HbA1c level was elevated at 10.1 %, and then oral hypoglycemic therapy was switched to insulin therapy. His fasting blood glucose and C-peptide levels 5 days after starting insulin therapy were 208 mg/dl and 0.67 ng/ml, when the insulin doses were 30 U a day. His blood pressure was twice recorded by a nurse as being high at 170/100 mmHg without symptoms during hospitalization.

While examining the difficulty in glycemic control, his computed tomography of the abdomen revealed a 5–cm left adrenal tumor (Figure 1). An iodine-123 metaiodobenzyl-guanidine (MIBG) whole-body scan detected increased accumulation in the region compatible with that of the left adrenal gland, suggesting pheochromocytoma (Figure 2). It was found that epinephrine, norepinephrine and dopamine levels were elevated at 1464 pg/ml (reference range, <100), 950 pg/ml (100 – 450) and 24 pg/ml (<20) in the plasma, and at 985.0 µg/day (3.4 – 26.9), 264.5 µg/day (48.6 – 168.4) and 565.9 µg/day (365.0 – 961.5) in the urine, respectively. Especially, the plasma or urine epinephrine level exceeded more than 10 times or 30 times the upper limit of the reference range. Other hormonal examination did not suggest multiple endocrine neoplasias, type 2. The patient was diagnosed of pheochromocytoma, and was transferred to the Department of Urology to undergo the left adrenalectomy.

As shown in Figure 3, the cut surface of the removed adrenal tumor (6.5 x 5 x 4 cm) showed that the encapsulated, well-circumscribed tumor had fibrous necrotic tissue in the center, with the atrophic adrenal cortex residing at the margin of the tumor. The tumor tissue was immunohistochemically positive for chromogranin A, where the cytoplasm of chromaffin cells was stained, and positive for S100 protein, where the cytoplasm and nuclei of sustentacular cells surrounding chromaffin cells were stained. As in Table 1, after surgery, the epinephrine and norepinephrine levels in the plasma and the urine were normalized. The blood glucose levels were improved by diet alone, and insulin secretion assessed by serum C-peptide levels measured 2 weeks after the tumor resection were apparently increased (Table 2). His glycemic levels were remained within a normal range (HbA1c, 5.6 – 5.9 %) without the recurrence of pheochromocytoma for more than 10 years after surgery, and he was returned to his primary care physician.

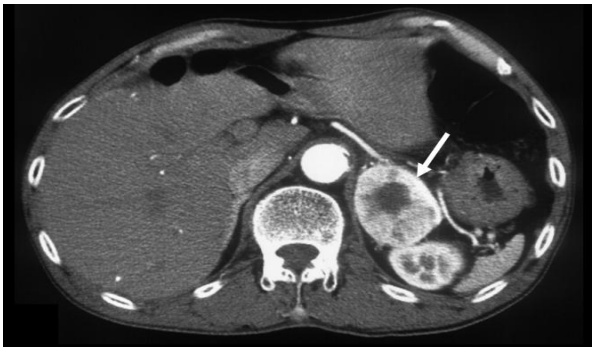

Fig-1: Contrast-enhanced computed tomography of the abdomen shows a 5-cm left adrenal tumor (arrow) with inhomogeneous enhancement

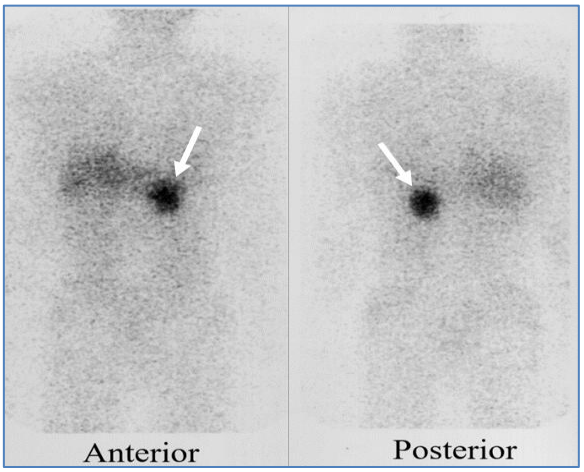

Fig-2: ^{123}I-MIBG whole-body scan shows increased accumulation (arrow) in the region compatible with that of the left adrenal gland

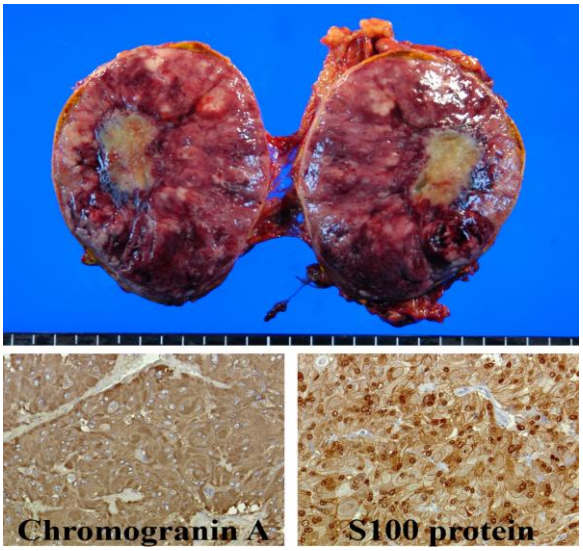

Fig-3: Gross and histopathological findings of the resected left adrenal tumor (6.5 x 5 x 4 cm). The cut surface of the gross specimen shows that the encapsulated, well-circumscribed tumor has fibrous necrotic tissue in the center, with the atrophic adrenal cortex residing at the margin of the tumor (upper). The tumor tissue is immunohistochemically positive for chromogranin A (lower left) and positive for S100 protein (lower right)

Table-1: Plasma and urine levels of catecholamines before and after surgery

	Before surgery	After surgery	Reference range
Plasma epinephrine (pg/ml)	1464	24	< 100
Plasma norepinephrine (pg/ml)	950	161	100 – 450
Plasma dopamine (pg/ml)	24	7	< 20
Plasma vanillylmandelic acid (ng/ml)	37.6	8.0	3.3 – 8.6
Urine epinephrine (μg/day)	985.0	12.2	3.4 – 26.9
Urine norepinephrine (μg/day)	264.5	95.1	48.6 – 168.4
Urine dopamine (μg/day)	565.9	1013.1	365.0 – 961.5
Urine vanillylmandelic acid (mg/day)	13.5	4.1	1.5 – 4.3

Table-2: Blood glucose and C-peptide levels before and after surgery

Before surgery (insulin therapy)	Fasting	2 hours after breakfast
Blood glucose levels (mg/dl)	208	383
Serum C-peptide levels (ng/ml)	0.67	2.47
After surgery (diet alone)	**Fasting**	**2 hours after breakfast**
Blood glucose levels (mg/dl)	88	78
Serum C-peptide levels (ng/ml)	1.73	3.95

DISCUSSION

The most common sign of pheochromocytoma is hypertension that was found in approximately 95% of patients with catecholamine excess [1]. The present patient with a large-sized, epinephrine-dominant pheochromocytoma had been treated for diabetes without hypertension for 9 years. The patient's insulin-required diabetes was reversed by the surgical resection. From the view of his clinical course and symptoms, the patient was not thought to have paroxysmal hypertension, at least until he was admitted to the hospital. In a retrospective study including 96 consecutive patients with sporadic unilateral pheochromocytomas recruited from 2001 to 2011 in France, 21 patients were normotensive and 3 patients of them had diabetes [2]. Apart from this, out of 43 patients with pheochromocytoma who underwent the surgical resection from 1981 to 1989 in a Japanese university hospital, 7 patients were incidentally discovered to have pheochromocytoma after 3-month to 13-year (mean, 3.5-year) treatment of diabetes [3].

Simply, norepinephrine acts through α_1- and β_1-adrenergic receptors, while epinephrine acts through β_1- and β_2-adrenergic receptors. Stimulation of α_1-adrenergic receptors induces vasoconstriction; stimulation of β_1-adrenergic receptors induces positive inotropic effects in cardiomyocytes; and stimulation of β_2-adrenergic receptors induces vasodilation [1]. Accordingly, in the norepinephrine-dominant type, peripheral vascular resistance is mainly increased, resulting in sustained hypertension. In the epinephrine-dominant type, cardiac output is mainly increased and episodic symptoms with increased systolic blood pressure are more common [4]. On the other hand, pheochromocytoma is one of the endocrine disorders with the highest prevalence of diabetes mellitus at 33 %. Stimulation of β_2-adrenergic receptors (affinity, epinephrine > norepinephrine) increases glucagon secretion inducing gluconeogenesis and glycogenolysis in the liver. Stimulation of α_2-adrenergic receptors (affinity, epinephrine > norepinephrine) decreases insulin secretion, which is the feature of epinephrine-associated hyperglycemia. Norepinephrine mainly increases insulin resistance by stimulation of α_1-adrenergic receptors (affinity, norepinephrine > epinephrine) inducing an increase in glucagon secretion and lipolysis [5]. In the present patient with epinephrine-dominant pheochromocytoma, insulin-requiring diabetes following 9-year treatment of diabetes without hypertension was reversed after the surgical resection, and the insulin secretion assessed by serum C-peptide was clearly increased. These changes are considered to be associated with epinephrine-dominant actions described above.

Pheochromocytomas are rare adrenal tumors and may have unusual modes of presentation leading to misdiagnosis, where disturbed glucose and insulin metabolism seems not to be well-recognized [6]. The increasing prevalence of incidentally discovered normotensive pheochromocytoma is attributable to the widespread availability of imaging procedures [2, 7]. A case report of incidentally discovered pheochromocytoma [7] described that the patient was normotensive and asymptomatic but had a 6-cm left adrenal tumor, similar to our patient. However, their patient showed a slight increase in urinary excretion of catecholamines, and therefore the fasting glucose level was normal.

CONCLUSION

The present patient was discovered to have a large-sized, epinephrine-dominant pheochromocytoma after 9-year treatment of diabetes without hypertension. The patient's insulin-requiring diabetes was reversed after the surgical resection, and the insulin secretion assessed by serum C-peptide was clearly increased. These changes were considered to be associated with epinephrine-dominant actions. As demonstrated in this

case, pheochromocytomas may have unusual modes of presentation leading to misdiagnosis. Disturbed glucose and insulin metabolism in pheochromocytoma seems not to be well-recognized in general.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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