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CASE REPORT

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A case of normotensive incidentally discovered adrenal pheochromocytoma

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Key Clinical Message

Pheochromocytomas are catecholamine-producing neuroendocrine tumors that arise from the adrenal medulla. The clinical presentation includes headache, palpitation, and hypertension, but pheochromocytomas are sometimes clinically silent. The present case highlights the importance of biochemical testing for pheochromocytoma in patients with adrenal incidentaloma, even if they are completely normotensive and asymptomatic.

KEYWORDS

adrenal incidentaloma, doxazosin, immunohistochemistry, metaiodobenzylguanidine scintigraphy, normotensive, pheochromocytoma

1 | INTRODUCTION

Adrenal incidentaloma is an asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease.[1] In most cases, adrenal incidentalomas are nonfunctioning adrenocortical adenomas, but they may also represent conditions requiring therapeutic intervention, including hormone-producing adenoma, adrenocortical carcinoma, metastasis, and pheochromocytoma (PC).

Pheochromocytomas are rare catecholamine-producing neuroendocrine tumors that arise from chromaffin cells of the adrenal medulla.[2] The typical clinical presentation of PC, which is attributed to the hemodynamic and metabolic actions of the excessive catecholamines secreted by the tumors, includes episodic headache, palpitation, sweating, anxiety, hyperglycemia, and sustained or paroxysmal hypertension. However, some PC patients, especially those with an adrenal incidentaloma, are asymptomatic and have consistently

normal blood pressure (BP).[3-9] The frequency of incidentally discovered normotensive PC is increasing owing to the better availability and accessibility of imaging procedures.[3,6]

Studies have suggested some differences in the clinical, hormonal, and molecular characteristics between normotensive and hypertensive patients with PC.[8,9] Although the elevated urinary excretion of catecholamines and their metabolites (metanephrines) is a useful biochemical diagnostic tool for typical hypertensive PC,[2] it is less sensitive in normotensive patients with PC, regardless of tumor size,[8,9] and normotensive PC often poses a diagnostic challenge.

Here, we report a case of a patient with normotensive, incidentally discovered adrenal PC.

2 | CASE PRESENTATION

A 32-year-old Japanese male was admitted to our hospital in February 2013 for detailed examination for adrenal incidentaloma. He had a family history of paternal type 2 diabetes mellitus, essential hypertension, cerebral infarction, and maternal essential hypertension. The patient had never drank alcohol or smoked cigarettes. His medical history was unremarkable, aside from mild mental retardation. He was considered to have abnormal lung shadow on chest X-ray at a routine medical checkup in autumn 2012 and visited a local hospital in November of the same year. His BP and pulse rate measured in the seated position were 128/68 mm Hg and 60 beats per minute, respectively. Chest and abdominal computed tomography (CT) showed no abnormalities in the lungs, heart, liver, spleen, pancreas, or kidneys, but it incidentally detected a 6-cm left adrenal tumor that showed a Hounsfield unit value of 30 and heterogeneous contrast enhancement with an iodine contrast media (Figure 1A,B). Differential diagnosis for his adrenal incidentaloma included lipid-rich adrenocortical adenoma, malignant tumors, and PC.[1] The patient was referred to our hospital for further endocrinological examination of his adrenal incidentaloma.

Upon admission, the patient had no episodic palpitations, headache, sweating, anxiety, or body weight loss. A physical examination showed that his height, body weight, and body temperature were 172 cm, 77 kg, and 36.0°C, respectively. His BP and pulse rate measured in the supine position and after standing for 3 minutes were 131/79 mm Hg and 59 beats per minute, and 127/72 mm Hg and 77 beats per minute, respectively. Twenty-four-hour ambulatory BP monitoring showed that his mean BP levels during the day and night were 128/80 mm Hg and 104/68 mm Hg, respectively, without paroxysmal hypertension or hypotension. No thyroid struma, chest rales, heart murmurs, abdominal tenderness or mass, or peripheral edema were detected. There were no rashes, tumors, or fibromas on the skin or mucosa. He had no signs of Cushing's syndrome, such as rounded face, thin skin, easy bruising, or purple striae.

A blood analysis showed a normal complete blood count, a normal balance of serum electrolytes, slightly elevated triglyceride levels, and normal fasting plasma glucose and glycated hemoglobin values (Table 1). Blood basal levels of cortisol, aldosterone, dehydroepiandrosterone sulfate, and catecholamines were normal. A 1-mg overnight dexamethasone suppression test did not detect autonomous cortisol secretion. The mean values of three measurements of 24-h urinary excretion of noradrenaline (199 μg/d, reference range: 31.0-160 μg/d) using high-performance liquid chromatography (Tosoh Corporation, Tokyo, Japan) and that of normetanephrine (0.33 mg/d reference range: 0.10-0.28 mg/d) using liquid chromatography-tandem mass spectrometry (Bio Medical Laboratories, Tokyo, Japan) were both slightly elevated (Table 2A). A glucagon stimulation test showed no abnormal elevation in plasma catecholamines (Table 2B). A clonidine suppression test showed a normal decrease in plasma catecholamines (Table 2C). An iodine-123 metaiodobenzylguanidine (MIBG) whole-body scan detected increased accumulation in the region of the left adrenal tumor, with no pathological accumulation seen in any other region. These findings indicated a diagnosis of left adrenal PC without high BP. To rule out hereditary disorders, such as multiple endocrine neoplasm type 2 or Von-Hippel Lindau disease, brain, and spinal cord MRI and neck ultrasound were performed, but revealed no abnormalities in the central nervous system, thyroid, or parathyroid glands.

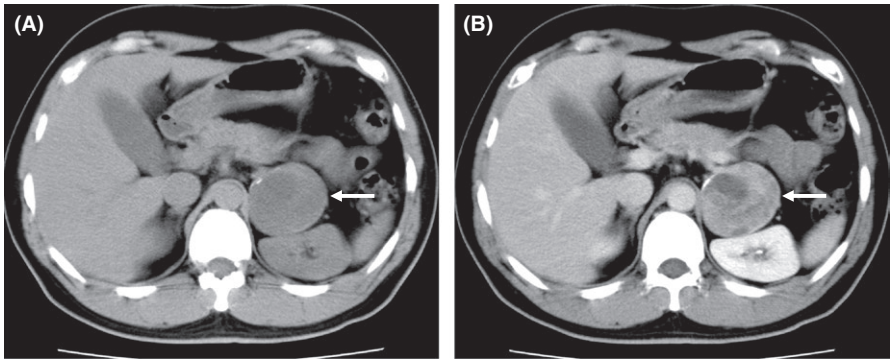

FIGURE 1 Computed tomography (December 2012). A, Plain computed tomography (CT) scan showing a 6-cm left adrenal tumor with calcification at the margin (arrow). B, Contrast-enhanced CT scan showing inhomogeneous enhancement in the tumor (arrow)

TABLE 1 Laboratory findings at the time of admission (February 2013)

Hematology	
Red blood cells	500×10^4/μL (427-571)
Hemoglobin	15.5 g/dL (12.4-17.2)
Hematocrit	44.7% (38.7-50.3)
White blood cells	4800/μL (4000-9000)
Platelets	17.4×10^4/μL (12.0-30.0)
Blood chemistry	
Urea nitrogen	9.5 mg/dL (8.0-20.0)
Creatinine	0.80 mg/dL (0.60-1.10)
Sodium	142 mmol/L (137-147)
Potassium	3.6 mmol/L (3.5-4.7)
Chloride	106 mmol/L (98-108)
Total cholesterol	176 mg/dL (130-220)
Triglycerides	218 mg/dL (50-130)
Fasting plasma glucose	90 mg/dL (70-109)
Glycated hemoglobin	5.3% (4.6-6.2)
Thyroid-stimulating hormone	1.57 μIU/mL (0.30-4.30)
Free triiodothyronine	3.04 pg/mL (2.00-4.90)
Free thyroxine	1.10 ng/dL (0.70-1.80)
Adrenocorticotropic hormone	43.6 pg/mL (4.4-48.0)
Cortisol	15.4 μg/dL (10.0-25.0)
Dehydroepiandrosterone sulfate	1187 ng/mL(1060-4640)
Aldosterone	12.9 ng/dL (3.0-15.9)
Plasma renin activity	1.8 ng/mL/h (0.1-2.0)
Noradrenaline	0.08 ng/mL (0.06-0.46)
Adrenaline	0.01 ng/mL (0-0.07)
Dopamine	0.01 ng/mL (0-0.14)

Blood samples were taken in the morning (8 AM) with the patient in the supine position. The reference range for each parameter is shown in parentheses.

In preparation for adrenal surgery, an oral α1-adrenergic blocker, doxazosin, was begun, with increases in water and salt intake, and the patient was discharged on day 15 after admission. The dose of doxazosin was titrated to 12 mg/d.

The patient underwent laparoscopic left adrenalectomy in April 2013. There was no hemodynamic instability during surgery. The histopathological features of the tumor (Figure 2) were consistent with those of intra-adrenal paraganglioma.[10] The tumor cells were immunohistochemically negative for steroidogenic factor 1 but positive for chromogranin A, synaptophysin, tyrosine hydroxylase, and succinate dehydrogenase subunit B (SDHB). The Pheochromocytoma of the Adrenal gland Scaled Score (PASS)[11] was 0 (maximum score = 20).

The patient discontinued oral doxazosin just after surgery and then his supine BP levels (around 120/70 mm Hg) were normal, without episodic hypertension or hypotension. The patient's 24-h urinary excretion of noradrenaline (106 μg/d) and normetanephrine (0.19 mg/d) were also normal (Table 2A).

His postoperative course during close follow-up for >5 years has been uneventful, without local or distant recurrence of PC.

3 | DISCUSSION

A patient with a high density 6-cm adrenal incidentaloma according to CT had neither sustained nor paroxysmal hypertension and had no PC symptoms, such as headache, palpitation, sweating, or body weight loss during the entire clinical course. However, he showed a slight elevation of 24-hours urinary excretion of noradrenaline and normetanephrine and a positive iodine-123 MIBG scan result. He underwent adrenalectomy, and histopathological analysis of the resected adrenal tumor revealed PC.

Measurement of urinary fractionated metanephrines is a useful biochemical test for PC, but it is less sensitive for diagnosing normotensive PC than hypertensive PC.[8,9] There are several reports on other biochemical findings in normotensive and asymptomatic patients with PC. A case of normotensive bilateral PC associated with Von-Hippel Lindau disease showed an increase in plasma catecholamine levels, with no changes in BP, following administration of catecholamine secretagogues, metoclopramide, and glucagon.[12] In addition, a study of patients with incidentaloma, including three patients with normotensive PC, reported high plasma catecholamine levels before and after glucagon administration in two patients, and normal plasma catecholamine levels before and after glucagon administration in the other patient.[13] In the present case, the patient showed normal levels of plasma catecholamines before and after glucagon administration. Additionally, he showed a normal reduction in plasma catecholamine levels in response to administration of clonidine, a centrally acting α2-agonist. These findings suggest that the slight elevation in 24-h urinary excretion of noradrenaline and normetanephrine sensitively reflected the mild catecholamine hypersecretion from PC in our normotensive, asymptomatic patient.

Preoperative management of hypertensive PC with α1-adrenoceptor blockade is useful in preventing catecholamine-induced complications during the perioperative period, such as hypertensive crisis, arrhythmias, and pulmonary edema.[2] However, the efficacy and necessity of preoperative management with α-adrenoceptor blockade in normotensive PC patients is controversial.[14-16] In the present case, the patient received the α1-adrenoceptor blocker doxazosin before surgery and experienced no hemodynamic instability or complications during the perioperative period; thus, the effectiveness of α1-adrenoceptor blockade could not be determined in our case.

TABLE 2 Endocrinological investigation. (A) Urinary excretion of catecholamines and metanephrines before and after adrenal surgery. (B) Glucagon stimulation test (February 2013). (C) Clonidine suppression test (February 2013)

(A)

	Reference range	Before (Feb 2013)	After (April 2013)
Adrenaline (μg/day)	3.0-41.0	10.0	17.5
Noradrenaline (μg/day)	31.0-160	199	106
Metanephrine (mg/day)	0.04-0.18	0.14	0.13
Normetanephrine (mg/day)	0.10-0.28	0.33	0.19

(B)

		Time (min)				
	Reference range	0	2	4	6	10
Plasma adrenaline (ng/mL)	0-0.07	0.02	0.06	0.04	0.03	0.02
Plasma noradrenaline (ng/mL)	0.06-0.46	0.10	0.12	0.12	0.14	0.16
Plasma dopamine (ng/mL)	0-0.14	< 0.01	< 0.01	< 0.01	0.02	0.02
Systolic BP (mmHg)	100-139	115	120	121	117	122
Diastolic BP (mmHg)	60-89	55	51	49	45	46
Pulse rate (beats/min)	60-100	60	69	69	65	63

(C)

		Time (h)			
	Reference range	0	1	2	3
Plasma adrenaline (ng/mL)	0-0.07	< 0.01	<0.01	<0.01	<0.01
Plasma noradrenaline (ng/mL)	0.06-0.46	0.10	0.04	0.04	0.03
Plasma dopamine (ng/mL)	0-0.14	0.02	0.02	0.03	0.02
Systolic BP (mmHg)	100-139	112	95	102	98
Diastolic BP (mmHg)	60-89	56	46	45	48
Pulse rate (beats/min)	60-100	53	45	44	43

(A) Twenty-four-hour urine samples were collected three times for three consecutive days before and after adrenal surgery. Values for each parameter represent the means of the three samples. The means of collected urine volumes before and after adrenal surgery were 1820 mL/day and 1630 mL/day, respectively.
(B) Glucagon (1 mg) was administered intravenously in the morning (8 AM). The patient was maintained in the supine position throughout the test.
(C) Clonidine (0.3 mg) was administered orally in the morning (8 AM). The patient was maintained in the supine position throughout the test. BP, blood pressure.

The long-term prognosis of patients after resection of normotensive PC remains uncertain. In general, PCs are malignant in approximately 10% of patients; recurrence or malignant behavior of PCs occurs more often in patients with large adrenal tumors (>5 cm), extra-adrenal disease, a familial (hereditary) form, or SDHB gene mutations than in those with small adrenal tumors or a sporadic form.[1] Histological differentiation between benign and malignant tumors is difficult; the latter is diagnosed by the presence of metastatic disease or recurrence, whereas a high PASS, as a postoperative histological evaluation, may be predictive of recurrence[11,17]. In the present case, histopathological analysis of the resected 6-cm adrenal tumor showed a PASS of 0 points. Genetic testing was not performed in our patient for financial reasons, and the possibility of a hereditary disorder has not been completely ruled out. He experienced no recurrence or metastasis during postoperative follow-up for >5 years. Continued follow-up is needed during the patient's lifetime.

In conclusion, we report a case of normotensive, incidentally discovered adrenal PC. A combination of CT findings of a high-density 6-cm adrenal tumor, slightly elevated urinary noradrenaline and normetanephrine levels, and a positive iodine-123 MIBG scan result led to a preoperative diagnosis of PC in our patient. The present case reiterates and emphasizes the importance of biochemical testing for PC in patients with incidentaloma, even when they are completely asymptomatic and normotensive.

CONSENT

Written informed consent was obtained from the patient for publication of this case report.

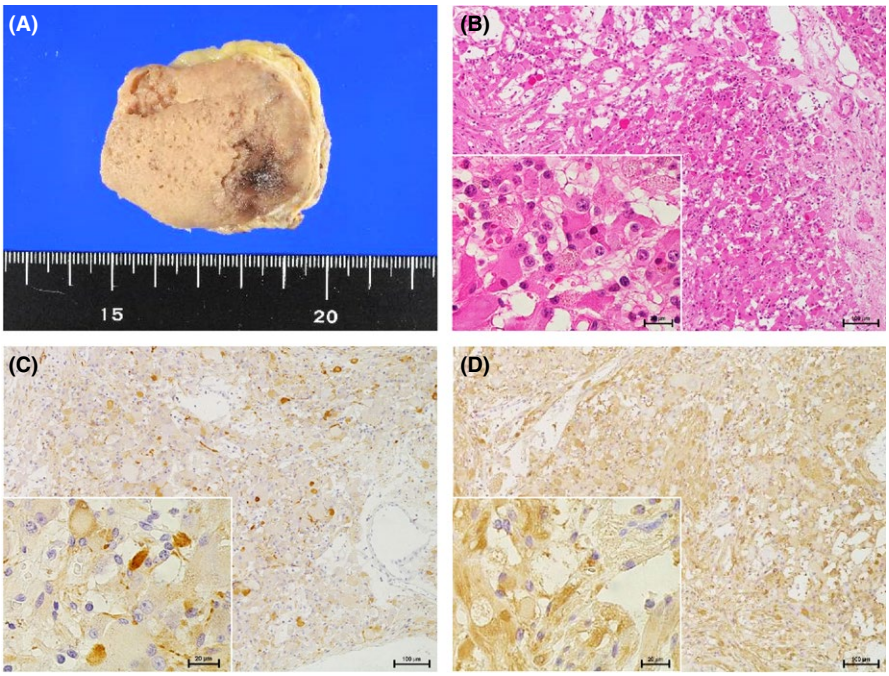

FIGURE 2 Histopathological findings of the resected left adrenal gland (April 2013). A, Gross appearance of the cut surface of a left adrenal tumor. B-D, Microscopic examination of the left adrenal tumor. The tumor cells display eosinophilic cytoplasm, with no evident cellular or nuclear atypia (B: hematoxylin and eosin staining). The tumor cells are immunohistochemically positive for chromogranin A (C) and tyrosine hydroxylase (D)

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AUTHORS' CONTRIBUTIONS

NO, MK, YY, HI, FI, RM, KS, TK, and KK: contributed to patient management. HU, YY, and HS: conducted histopathological investigations. NO: was a major contributor to the writing of the manuscript. KK: critically reviewed the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

None declared.

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