A Case of a Clinically "Silent" Pheochromocytoma

Kazuhiko YOSHIDA, Manabu SASAGURI, Akio KINOSHITA, Munehito IDEISHI, Masaharu IKEDA and Kikuo ARAKAWA

A case of a clinically “silent” pheochromocytoma is presented. The adrenal mass was incidentally discovered by abdominal ultrasonography and computed tomography. In the course of hospitalization, the patient was normotensive and asymptomatic. Plasma catecholamine levels were nearly normal, whereas urinary levels of catecholamine metabolites were slightly elevated. A glucagon provocative test and ¹³¹I-metaiodobenzylguanidine scintigram were useful for diagnosing such an atypical pheochromocytoma. A discussion of clinically-unsuspected pheochromocytoma is also presented.

Key words: Pheochromocytoma, Glucagon provocative test, [¹³¹I]MIBG-scan, Adrenal mass

Most patients with pheochromocytoma have sustained or paroxysmal arterial hypertension, with frequent complaints of headache, sweating, palpitation, pallor, and nausea. In a recent study, a scoring system based on these symptoms has been shown to provide a 96% sensitivity and a 64% specificity for the diagnosis (1). The symptoms are sometimes paroxysmal in nature, resulting from an episodically-elevated plasma catecholamine level. In spite of the secretion of catecholamines, some patients are reportedly asymptomatic (2–5). It is rare for the tumor not to secrete catecholamine so that the patient is asymptomatic for varying intervals as reported here.

METHODS

To measure catecholamines, blood was drawn into a syringe containing EDTA-2Na and centrifuged at 4°C for the recovery of plasma. Urine was collected into a chilled glass containing 10 ml of 6N hydrochloric acid for a 24 hours specimen. Plasma catecholamines (norepinephrine and epinephrine) were quantitated by HPLC (6). HPLC was performed on a Catecholamine Analyser instrument (Eicom Corp. Kyoto, Japan) equipped with a 4.6×250-mm Eicompack MA-ODS column, using a reversed-phase system. Catecholamines were eluted with 0.1 M monochloroacetate containing 0.02 mM EDTA, pH3.0 and the effluent was monitored by Electrochemical Detector. Urinary catecholamine and metabolites (metanephrine, normetanephrine and vanillylmandelic acid) were also measured by HPLC (6–8). A tissue specimen was obtained and part of it was homogenized in a chilled glass containing 10 ml of 6 N hydrochloric acid, and assayed for catecholamine by HPLC.

The blood pressure and heart rate of the patient were indirectly monitored for 24 hours using a portable blood pressure recorder (ABPM-630, Nihon-korin Company, Japan).

CASE REPORT

A 49-year-old truck driver (male) was admitted to our hospital following identification of an adrenal mass. The symptoms were said to date four months earlier from an episode of abdominal pain and hematemesis. Fluoroscopic and endoscopic examination of the stomach revealed evidence of gastric...
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Fig. 1. CT scan. A cystic adrenal mass on the right was detected.

ulcer. During abdominal ultrasonography, an adrenal mass was incidentally identified and the patient was subsequently referred to our hospital. Past medical history included an appendectomy 20 years before and a left partial nephrectomy due to a renal stone 3 years before. There was no history of hypertension in the subject or his family.

On admission, physical examination was carried out. His blood pressure was 130/70 mmHg and was maintained throughout the course of hospitalization. The pulse rate was regular at 80 per minute. Ocular fundi were normal. There was no goiter. Lungs were clear. A grade 2 systolic murmur was heard at the apex. There was no hepatomegaly. The extremities were normal, and neurological examination was negative.

Further, the chest X-ray showed clear lungs and a normal heart. Likewise, both electrocardiograph and echocardiograph (M-mode and two-dimensional) studies were normal. However, CT-scan revealed a right adrenal mass (Fig. 1).

Blood analyses, including of blood urea nitrogen, creatinine, serum potassium, calcium, and phosphorus were normal, as well as urine analyses. Adrenal cortical examinations were normal as evaluated by diurnal plasma cortisol levels, baseline urinary 17-hydroxysteroids and 17-ketosteroids. The data for urine and plasma catecholamines are listed in Table 1. Repeat examination showed that values of plasma and urinary epinephrine, urinary norepinephrine, metanephrine and norepinephrine were slightly elevated, although plasma noradrenaline was stabilized.

Blood pressure monitored for 24 hours showed no episodes of hypertension or tachycardia. Initially, the clinical impression of pheochromocytoma was suspected, in spite of the normal blood pressure. The glucagon provocative test was performed. Blood

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* Range of three samples taken and measured as described in the methods section.
** Upper normal values
*** Normal values reported by Taubman et al (3)
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Fig. 2. Glucagon provocative test. A 1.0 mg dose of glucagon was given as an i.v. bolus. Plasma catecholamine levels increased 1–3 minutes following drug administration. Simultaneously, both blood pressure and pulse rate were increased.

Pressure increased from 120/80 to 168/90 mmHg and simultaneous measurement of plasma catecholamine also showed an increase in levels from 655 to 1588 pg/ml (epinephrine plus norepinephrine), 1–3 minutes following i.v. bolus administration of 1.0 mg glucagon (Fig. 2).

The patient underwent a $[\text{I}^{131}]$-meta-iodobenzylguanidine ($[\text{I}^{131}]$-MIBG) scan, which revealed an area of increased uptake above the right kidney, compatible with a right adrenal pheochromocytoma (Fig. 3).

Considering the positive glucagon provocative test, the positive $[\text{I}^{131}]$-MIBG scan and the possibility of malignancy of this tumor, surgical removal of the pheochromocytoma was recommended. Throughout the operational procedure, blood pressure did not elevate. A cystic tumor, (4.5 by 3.8 by 3.5 cm, weighing 18 g) attached to the right adrenal gland, was isolated. Histological examination identified this tumor as a pheochromocytoma. The tissue was homogenized with 6 N HCl to measure tissue catecholamine levels. Tissue catecholamine, especially norepinephrine, were markedly elevated (Table 1). Following the operation, the patient recovered and resumed normal activity.

**DISCUSSION**

Patients with pheochromocytoma are typically symptomatic and sometimes the symptoms are dramatic. The incidence of unsuspected pheochromocytoma in the absence of classical symptoms has been reported to be about 30% (9). The majority of the cases of unsuspected pheochromocytoma was found at autopsy (15%), by abdominal CT scan, or during surgical exploration for other indications (9, 10). Rarely, however, has there been a report in which the tumor is not associated with hypertension, especially in patients with familial tumors (5). Biochemical confirmation of excessive catecholamine production is required for definitive diagnosis. In 24 patients with pheochromocytoma, Bravo et al (2) reported that two patients were completely normotensive throughout the course of hospitalization. Louis et al (4) reported that two of 11 patients remained normotensive despite persistent high norepinephrine production. Both Taubman et al (3) and Ho et al (5) described individual patients who were essentially asymptomatic despite the presence of predominantly norepinephrine-secreting pheochromocytoma.

The asymptomatic nature of our patient could be explained by the near normal plasma levels of catecholamine. However, urinary normetanephrine and metanephrine were slightly, but distinctly elevated in contrast to an almost normal plasma catecholamine level. This dissociation of plasma and urinary values might be due to brief secretory paroxysm in any 24-hour period in our patient. When the glucagon provocative test was performed, blood pressure was elevated and tachycardia ensued coupled with an elevation in plasma catecholamine.
levels. It is reasonable to assume that the pheochromocytoma in this case is functional. Tissue levels of catecholamines were undoubtedly high although plasma levels were low. It is not known why large amounts of catecholamines were not secreted from the tumor to the circulation under basal conditions although the tumor contained high levels of catecholamines. It is rare for patients with pheochromocytoma to have near normal plasma catecholamine values. Bravo et al (2) reported that among 23 patients with pheochromocytoma, only one had normal plasma catecholamine levels. Krane (9) described one patient with pheochromocytoma who was normotensive and showed normal urinary catecholamine metabolite levels.

Plasma catecholamine assay is reportedly useful for diagnosing pheochromocytoma (2), although urinary catecholamine is considered more practical (11). In this case, measurement of urinary catecholamine metabolites was more reliable than plasma catecholamine assay.

In such an atypical case, the glucagon provocative test is also very useful even with the side effect taken into account. Glucagon was shown to have a direct adrenomedullotropic effect. It is proposed that in patients with pheochromocytoma, glucagon evokes a release of excessive quantities of catecholamines, resulting in a hypertensive paroxysm (12). The glucagon provocative test has been proven to be of value in diagnosing patients with paroxysmally-functioning pheochromocytomas. The specificity of this test is increased by the use of plasma catecholamine assays (13).

Recently, a new approach to the localization of pheochromocytoma has been facilitated by the use of [131I]-metaiodobenzylguanidine (MIBG), an adrenergic tissue-localizing tracer (14). The [131I]-MIBG scan is useful for the diagnosis and localization of pheochromocytoma whereby [131I]-MIBG is considered as the initial procedure (15). Even in the present atypical case, the tumor selectively took up [131I]-MIBG.

Additionally, with the wide and increasing application of ultrasonography and CT scans (16), the incidental discovery of adrenal mass has become more common. Van Heerden and his associates reported that the abdominal CT scan is a highly accurate and non-invasive tool for the localization of pheochromocytoma (17). Recently, the incidence of clinically-unsuspected pheochromocytoma has decreased from 53% to 18% with the aid of abdominal CT scan and biochemical screening techniques (10). Furthermore, the combination of the glucagon provocative test and [131I]-MIBG scan can be considered to be very useful for the diagnosis of a clinically "silent" pheochromocytoma in a patient with nearly normal plasma catecholamine levels.

REFERENCES

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