Case Report

Small Extra-Adrenal Pheochromocytoma Causing Severe Hypertension in an Elderly Patient

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We report the case of a 67-year-old woman with severe hypertension caused by an extra-adrenal pheochromocytoma. The tumor was detected by ^{131}I metaiodobenzylguanidine scintigraphy and it was found to be small (2 cm ø) by enhanced CT. After the extirpation of the tumor, the blood pressure of the patient immediately normalized. It should be taken into account that a small extra-adrenal pheochromocytoma can be one of the causes of secondary hypertension in elderly patients. Since small extra-adrenal pheochromocytomas are difficult to detect, it is also important to perform suitable examinations to establish the diagnosis. Furthermore, we emphasize the importance of an accurate diagnosis in elderly patients with pheochromocytoma, for they often have less symptomatology and more severe cardiovascular complications due to refractory hypertension than younger patients. (*Hypertens Res* 2006; 29: 635–638)

***Key Words*: pheochromocytoma, extra-adrenal, hypertension, diagnosis**

Introduction

Pheochromocytoma is one of the major causes of secondary hypertension, drug-resistant hypertension, and malignant hypertension (*1–3*), but the rate of occurrence of the tumor has been reported as only 0.6% in Japanese patients with secondary hypertension (*4*). The presence of pheochromocytoma can often lead to a fatal outcome because of cardiovascular or cerebrovascular events (*5*, *6*).

Although hypertension, hypermetabolism, hyperglycemia, headache, and hyperhidrosis (the 5 H's) are usually the dominant clinical manifestations of pheochromocytoma, approximately 30% of these patients do not present these signs (*7*). Since most of their clinical signs and symptoms are derived from the actions of catecholamines secreted from the adrenal glands, adrenal pheochromocytoma induces more severe clinical signs than those observed in extra-adrenal pheochromocytoma (*7*). Furthermore, in elderly patients it is likely that pheochromocytoma will not cause the classical symptoms, such as headache, sweat and palpitation, because these patients have lower cardiovascular reactivity in response to catecholamines than younger patients (*7*). Therefore, it is important to choose the appropriate imaging techniques to diagnose extra-adrenal pheochromocytoma, especially in elderly patients.

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Table 1. The Serum Catecholamines and Urine Metabolites of the Patient

	Patients	Normal range
Serum adrenaline (ng/ml)	0.025	0.01–0.18
Serum noradrenaline (ng/ml)	3.689	0.06–0.45
Serum dopamine (ng/ml)	0.023	0.00–0.09
Urine metanephrine (mg/day)	0.08	0.05–0.23
Urine normetanephrine (mg/day)	1.27	0.07–0.26
Urine vanillylmanderic acid (VMA) (mg/day)	4.9	1.3–5.1
Urine homovanillic acid (HVA) (mg/day)	2.7	1.5–6.6

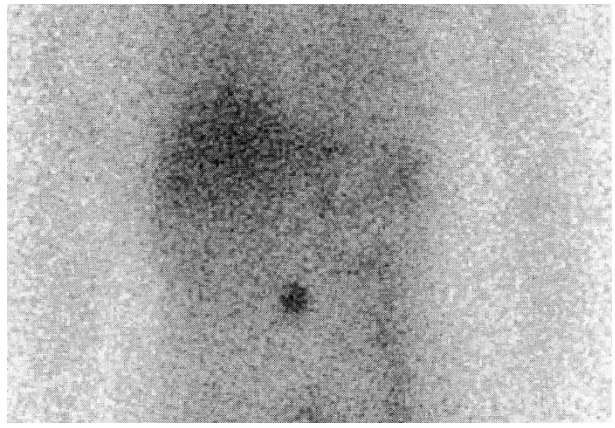

Fig. 1. *^{131}I-MIBG scintigraphy revealed positive uptake in the umbilical region.*

In this report, we present a very rare case of secondary hypertension in an elderly woman who was found to have a small (2 cm ø) extra-adrenal pheochromocytoma. We also discuss the clinical features of the disease in elderly patients and the appropriate imaging techniques for diagnosis.

Case Report

A 67-year-old woman who had severe hypertension was admitted to our hospital in April, 2005. Three years previously, the patient had her first visit to a hospital due to epistaxis; her systolic blood pressure was found to be above 250 mmHg. However, she refused to accept treatment for her severe hypertension until January 2006. At this time, she complained of a sudden onset of dizziness, nausea, headache, and sensory deficit in her left arm and thigh; she was diagnosed as having had a cerebral infarction and was hospitalized in another hospital. Three months later, she was transferred to our hospital for further evaluation and medical treatment for severe hypertension. The patient had already been treated with several antihypertensive agents, including β-blockers, α-blockers, angiotensin receptor antagonists, and calcium blockers. Her familial history was negative for hypertension, diabetes mellitus, renal diseases, cardiovascular diseases and stroke.

The patient was 148 cm tall and weighed 46.9 kg (body mass index: 21.4 kg/m^2), with no history of either constipation or weight loss. Her blood pressure was 191/97 mmHg and her pulse rate was 68/min on admission. She did not have orthostatic hypotension but did have paroxysmal hypertension. Even during quiet bed rest, her systolic and diastolic blood pressure ranged from 133 to 219 mmHg and from 82 to 114 mmHg, respectively. Her average 24-h blood pressure was 188/98 mmHg by ambulatory blood pressure monitoring (ABPM), and her nocturnal blood pressure rose significantly to 213/101 mmHg. Her left ventricle enlargement (interventricular septum: 14 mm, left ventricular posterior wall: 15 mm) as assessed by echocardiograph was acceptable. Laboratory data revealed no abnormalities such as hypermetabolism, hyperhidrosis, or diabetes associated with undersecretion of insulin, except for high levels of serum noradrenaline and urinary metanephrine. Her serum noradrenaline level was 3.689 ng/ml (normal range: 0.06–0.45 ng/ml) and her urinary normetanephrine level was 1.27 mg/day (normal range: 0.07–0.26 mg/day). Other hormonal data are shown in Table 1. There was no hyperglycemia. We then examined her by abdominal ultrasonography, plain CT, and ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy. The scintigraphy showed positive uptake in the umbilical region (Fig. 1), although no abnormality could be detected by abdominal ultrasonography and plain CT. We therefore performed an enhanced CT, which revealed an enhanced para-aortic tumor (about 2 cm ø) in the lower duodenum (Figs. 2, 3) that had not been clear on the plain CT image. There was no evidence of multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, or neurofibromatosis type 1.

We diagnosed her as having a solitary extra-adrenal pheochromocytoma. Since no distant metastases were detected by various examinations, the patient was immediately subjected to total tumorectomy. The tumor was about 2 cm × 2 cm × 2 cm, and histopathological findings of the resected tumor corresponded to those of pheochromocytoma without any signs of malignancy. After the operation, her systolic blood pressure was 120–140 mmHg without antihypertensive drugs, and her serum noradrenaline level decreased to within the normal range. She was discharged on the 20th postoperative day.

Discussion

According to former case reports, most adrenal or extra-adrenal pheochromocytomas have been detected before the age of 60 years (*1*, *7*, *8*). On the other hand, a report questioning whether pheochromocytoma was an under-diagnosed disease in elderly patients had already been presented in 1986 (*9*). Anderson *et al*. (*10*) carefully evaluated 1,915 hypertensive

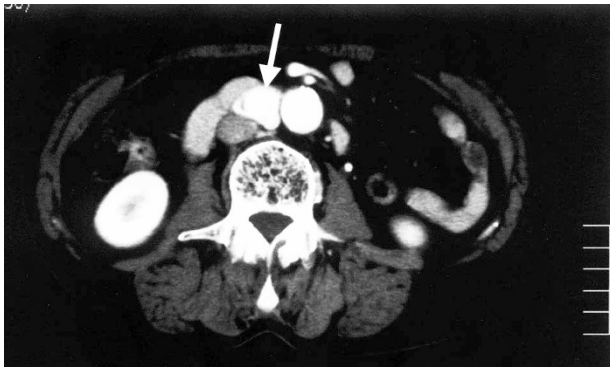

Fig. 2. *Enhanced CT revealed a slightly enhanced paraaortic tumor in the lower duodenum.*

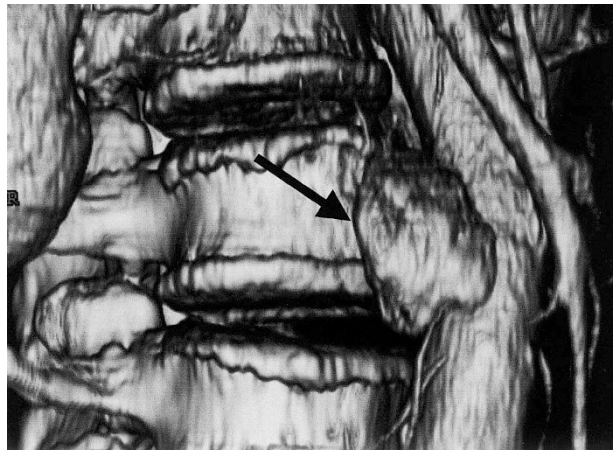

Fig. 3. *Three-dimensional CT showing the solitary paraaortic tumor (about 2 cm ø). The location of this tumor corresponded to the positive uptake detected by ^{131}I-MIBG scintigraphy.*

patients over 49 years old for secondary hypertension, to emphasize that pheochromocytoma, while an uncommon disease in the elderly, could be found across all age groups. However, pheochromocytoma is often masked by arteriosclerosis in elderly patients, and for this reason is more likely to result in a fatal outcome in elderly than in younger patients. In fact, Sutton *et al*. (*11*) examined 40,000 autopsies over a 50-year period and found that only 24% of autopsy-proven pheochromocytomas were correctly diagnosed during the patient's lifetime, indicating that many pheochromocytomas might go undiagnosed and be directly related to the cause of death.

The present patient had severe paroxysmal and drug-resistant hypertension concomitant with stroke and significant cardiac hypertrophy. In fact, according to ABPM, an excessive circadian blood pressure amplitude was recorded and the average 24-h systolic blood pressure was 180 mmHg despite aggressive antihypertensive therapy. As for laboratory data, both the plasma concentration and urinary excretion of norepinephrine were more than 10 times the normal value. Phenylethanolamine-*N*-transferase, the enzyme that converts norepinephrine to epinephrine, has been shown to be abundantly expressed in adrenal tissue (*12*), and extra-adrenal pheochromocytomas have been demonstrated to predominantly secrete norepinephrine, which is consistent with the findings in the present case.

Our patient was 67 years old and did not present the typical features of the disease; namely, overhydration, constipation, hyperglycemia, *etc*. In the autopsy cases of extra-adrenal pheochromocytoma reported by Sutton *et al*. (*11*), not all of the individuals diagnosed at autopsy were older patients, but those who were elderly tended to have a less florid symptomatology than the younger patients. In the elderly, pheochromocytoma was characterized by cardiomegaly and left ventricular hypertrophy, as in our case, rather than the series of classical symptoms (*11*). Alternatively, there could be decreased cardiovascular responsiveness to catecholamines with age, so that the classical symptoms are less evident in the elderly, as in the present patient (*13*).

For sometime, the prevalence of extra-adrenal pheochromocytoma (paragangloma) has been considered to be approximately 10%; however, recent advances have begun to improve both the detection and diagnosis of this disease. Thus, in recent reports, approximately 15–20% of pheochromocytomas were found to originate from extra-adrenal chromaffin tissue (*7*, *14*). The majority of extra-adrenal pheochromocytomas occur in the intra-abdominal or retroperitoneal regions and originate from the organ of Zuckerkandl, paraspinal ganglia and bladder. About 2% of extra-adrenal tumors are extra-abdominal, often occurring in the neck and thorax, even the myocardium (*15*), and therefore patients require a detailed evaluation.

Indeed, in the 1980s and early 1990s, very few cases of pheochromocytoma were correctly diagnosed when the tumor was less than 4 cm in diameter (*16*, *17*). According to a recent report by Kohane *et al*. (*18*), the smaller tumors tended to be diagnosed more frequently in patients with a shorter duration of hypertension than in the past. In our patient, the tumor was 2 cm in diameter, which can be categorized as small in comparison with recent reports (*18*, *19*). Thus, it is suggested that the imaging techniques described above are suitable to diagnose these tumors, especially in elder patients with refractory hypertension, even if the patients have fewer symptoms.

It has been reported that ^{131}I-MIBG scintigraphy is more useful in the diagnosis of extra-adrenal pheochromocytoma than CT (*20*). CT has good sensitivity for detecting adrenal pheochromocytoma (93–100%), but its sensitivity decreases to about 90% for extra-adrenal pheochromocytoma (*21*). On the other hand, ^{131}I-MIBG scintigraphy offers superior specificity for extra-adrenal pheochromocytoma (95–100%) (*22*, *23*). In addition, it has been reported that ^{123}I-MIBG scintigraphy has several potential advantages over ^{131}I-MIBG scintigraphy (*24*, *25*), although ^{123}I-MIBG scintigraphy is less

commonly used than ^{131}I-MIBG scintigraphy in Japan. In the present case, ^{131}I-MIBG scintigraphy combined with CT was effective for the diagnosis.

In conclusion, we have reported the case of an elderly patient with a small extra-adrenal pheochromocytoma. Because her hypertension could have led to fatal cardiovascular or cerebrovascular events, we considered that it was very important to provide the most effective treatment for extra-adrenal pheochromocytoma (*26*). Furthermore, we emphasize the importance of an accurate and prompt diagnosis in elderly patients with pheochromocytoma, who often present a less florid symptomatology and have more severe cardiovascular complications in their late years than younger patients.

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