Small Pheochromocytoma in an Elderly Woman with Hypertension

Minamoto M¹, Fukuoka T¹*, Umakoshi H¹ and Murakami K²

¹Department of Internal Medicine, Matsuyama Red Cross Hospital, Japan
²Department of Health care and Preventive Medicine, Matsuyama Red Cross Hospital, Japan

Abstract

A 77-year-old woman who had controlled hypertension was referred to our hospital due to recent paroxysmal elevation in blood pressure. Computed tomography showed a 17-mm nodule in right adrenal gland, whereas hormonal markers were normal levels except plasma norepinephrine and urinary normetanephrine were modestly high (≥ 2.0-fold the upper limit of normal range). Even though the slight elevation in biochemical markers, ¹²³I metaiodobenzylguanidine scintigraphy confirmed the abnormal uptake in the right adrenal gland, the patient was submitted to laparoscopic adrenalectomy. Surgical pathology was diagnostic of pheochromocytoma. Postoperatively, plasma catecholamines were all in normal range and paroxysmal hypertension disappeared.

Introduction

Pheochromocytomas are rare but clinically important tumors, whose failure to diagnose can result in sudden and lethal complications [1,2]. Pheochromocytomas are usually suggested by paroxysmal symptoms such as headache, sweating, palpitation and hypertension [3]. Although sporadic pheochromocytomas are most common, there is a growing incidence of genetically driven cases possibly secondary to widespread availability of genetic testing in some parts of the world [4]. Traditionally, sporadic forms of Pheochromocytomas occur in individuals aged 40-50 years and tumors size are large [5,6]. Using improved biochemical tests and imaging modalities, they have become to be diagnosed at earlier stage, so that the size of diagnosed tumors is decreasing [6]. Here we report a case of 17-mm in the largest dimension pheochromocytoma detected by ¹²³I -metaiodobenzylguanidine scintigraphy without significant excessive production of catecholamines. Postoperatively, her blood pressure was well controlled with half the number of antihypertensives and paroxysmal hypertension disappeared.

Case Presentation

A 77-year-old woman who had controlled hypertension was referred to a local hospital for investigation of sudden and striking blood pressure elevations. She had 17-year history of hypertension well controlled with several antihypertensive agents, but she became to have recent symptom of paroxysmal hypertension. On first visit, a screening abdominal computed tomography (CT) with 1-mm thin slices revealed a 17 × 9 mm sized homogeneous mass with soft tissue density (approximately 30-40 Hounsfield units) in right adrenal gland (Figure 1). Biochemical tests revealed that plasma norepinephrine concentration was slightly elevated (824 pg/ml), however, the levels were not within the threshold range suggested for the diagnosis of pheochromocytoma (Table 1) [7]. Plasma renin activity, plasma aldosterone concentration and adrenocorticotrophic hormone were all in normal range (Table 1). Additionally, plasma cortisol was under 1.00 μg/dL after low dose (1 mg) dexamethasone overnight suppression test. Six months later, a follow-up anatomic test coupled with biochemical measurements (plasma catecholamines and urine fractionated metanephrines) were performed. An abdominal CT demonstrated that the tumor size was no change. Biochemical tests showed that plasma norepinephrine concentration (976 pg/ml) and urinary normetanephrine excretion (713 μg/gCr) were modestly high (Table 1). Although the elevation of biochemical markers for pheochromocytoma was slight, the patient still had the symptom of paroxysmal hypertension, a functional imaging was performed. The ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) planar image showed abnormal uptake in the right adrenal gland indicating that the tumor was a potential pheochromosyotma. Then, she was admitted to our hospital for further evaluation for possible pheochromosyotma. During testing at hospitalization, she had the paroxysmal hypertension. Plasma catecholamine levels were within normal limits, whereas 24-hour urinary excretion rates
of norepinephrine, VMA and normetanephrine were higher than upper limits of normal range, especially the urinary norepinephrine excretion elevated to more than three times the normal value (Table 1). On the basis of the symptom, the positive ¹²³I-MIBG scintigraphy and the significant elevation of biochemical markers, the patient was subjected to laparoscopic right adrenalectomy. Postoperative pathologic findings confirmed pheochromocytoma (Figure 2). Histologically, well demarcated area was detected within the adrenal medulla. The region was composed of adrenal medullar cells with clear/cosinophilic cytoplasm arranged in zellballen pattern (Figure 2 A and B). Immunohistochemically, the tumor cells stained positive for Chromogranin A (Figure 2C). The tumor cells exhibited a low Ki-67 index (Figure 2D). Postoperatively, her plasma catecholamine levels were all in normal range. She remained free from symptom of paroxysmal hypertension even though she still needed antihypertensive agents to control her hypertension.

Discussion

Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells in the adrenal medulla. They are rare but clinically important tumors, whose failure to diagnose can result in sudden and lethal complications [1,2]. Based on autopsy studies, however, many cases are probably missed than are diagnosed. At the Mayo clinic in the 50-year period (1928-1977), 40,078 autopsies were performed and pheochromocytomas were present in 54 patients. Among these patients, 13 patients were diagnosed during life, and 41 patients were unsuspected autopsy findings [8]. On the other hand, even among patients suspected to have a pheochromocytoma, the diagnosis is rarely confirmed [9]. Because pheochromocytomas can have a highly variable presentation and an overlooked clinical entity, the diagnosis of pheochromocytomas is difficult, especially when a tumor size is small. In the present case, there are several practical points related to the diagnosis and management of small pheochromocytomas. First, small pheochromocytomas did not always have excessive catecholamine production. Marlon et al showed a direct correlation between tumor size and hormone level that was independent of the clinical presentation [5]. Run Yu et al. [6] showed that most of the patient with small pheochromocytomas exhibits modestly elevated or normal biochemical marker levels, resulting in underdiagnosis. Other study showed that small tumors have slower turnover rates and release free catecholamines into the circulation that lead to hyperadrenergic symptoms [10]. In our case, repeated biochemical measurements of plasma catecholamines and urinary catecholamines or fractionated metanephrines yield false-negative results. Plasma norepinephrine level (976 pg/ml) and urinary excretion of fractionated metanephrines (713 μg/gCr) were modestly high (plasma fractionated metanephrines are not available in Japan), however, the levels were not within the diagnostic threshold for pheochromocytoma. Therefore, referred to the recommended testing algorithms, pheochromocytoma should have been excluded in the present case [7]. Currently, there exist several guidelines based on which biochemical tests should be used to confirm or exclude a suspected pheochromocytoma, but no guideline address the importance of tumor size in the diagnosis of pheochromocytomas [11,12]. Our case suggests that it is essential to pay sufficient attention to the influence of tumor size on biochemical measurements because small pheochromocytoma often exhibits modestly elevated or normal biochemical marker levels, resulting in underdiagnosis.

Secondly, small pheochromocytoma exhibits same suspicious

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<tr>
<th>Blood tests</th>
<th>First Testing</th>
<th>Second Testing</th>
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<td>Catecholamines (HPLC)</td>
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<td>unmeasured</td>
<td>7.55 (mg/24h)</td>
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On the first visit (first testing), plasma norepinephrine concentration (824 pg/ml) was elevated but did not reach a cutoff of inclusion criteria of pheochromocytoma. Six months later (second testing), plasma norepinephrine concentration (976 pg/ml) and urinary normetanephrine excretion (713 μg/gCr) were modestly high. On admission, the plasma catecholamine levels were within normal limits. 24-hour urinary excretion rates of norepinephrine (576 μg/24h), VMA (7.55 μg/24h) and normetanephrine (300 μg/24h) were higher than upper limit of normal range.
features on imaging as larger tumor, regardless of low biochemical marker levels [6,13]. In the present case, abdominal CT identifies 17-mm mass of which appearance of homogeneity with soft-tissue density (approximately 40-50 HU) is suggestive of a pheochromocytoma. Moreover, 123I-MIBG scintigraphy clearly showed a focus of radioactivity in the mass. The current 123I-MIBG scintigraphy has a high sensitivity at 83%-100% for a specificity of 95%-100% [14]. Owing to high sensitivity and specificity, Ioannis et al. [14], say that the presence of pheochromocytomas should always be ruled out or confirmed with I-MIBG scintigraphy. Run Yu et al. [6], also recommends to incorporate imaging characteristics of the tumor into the interpretation of biochemical test results. CT with contrast wash-out studies are alternative imaging modalities which may help characterize suspicious adrenal lesions or pheochromocytomas.

Finally, in our patient, small pheochromocytoma did not contribute to hypertension. Her hypertension didn’t extremely improve after the operation. This may be come from her long duration of hypertension and progression of arteriosclerosis. A prior study demonstrated that only a quarter of the patients with small pheochromocytomas can expect improvement of preoperative hypertension after tumor removal [6]. Regardless of a poor improvement of hypertension, resection of small pheochromocytoma is necessary, because most of tumors, if untreated, cardiovascular morbidity and mortality are high [15].

Conclusions

A diagnosis of probable pheochromocytoma should still be pursued in patients with modestly elevated catecholamine profiles, especially if clinical history or imaging findings are suggestive. The presence of typical adrenergic symptoms, oscillating blood pressures, known genetic predisposition or characteristic radiological findings would increase the pre-test probability of diagnosing a catecholamine producing tumor. Consideration should be given to functional imaging modalities in such cases.

References