Case Report

Primary Malignant Hepatic Pheochromocytoma with Negative Adrenal Scintigraphy

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A 60-year-old male patient with hypertension was referred to our hospital because of insufficient blood pressure control (190/98 mmHg) and to rule out secondary hypertension. A computed tomography scan revealed no adrenal tumor but a large liver mass (5 × 5 cm), and magnetic resonance imaging showed a high signal intensity lesion on the T_2 -weighted image. Twenty-four hour urinary excretion of catecholamine metabolites was markedly increased, although a ^{123}I -metaiodobenzyl guanidine (MIBG) scintigram failed to show accumulation in the hepatic mass, and no difference was noted between the catecholamine concentration in the tumor-drainage vein and that obtained from the vein draining from the non-tumor area. Liver biopsy did show features compatible with pheochromocytoma (*i.e.*, chromogranin A-positive cells). Transcatheter arterial embolization of the liver tumor was conducted and resulted in a marked (50%) decrease in the 24-h urine normetanephrine excretion. Several metastatic foci were noted in the spinal bone and transcatheter arterial embolization (TAE) was also conducted with successful results. Thus, we experienced a case of primary malignant hepatic pheochromocytoma with negative ^{123}I -MIBG scanning. (*Hypertens Res* 2006; 29: 551–554)

Key Words: pheochromocytoma, liver, metaiodobenzyl guanidine, metastasis, embolization

Introduction

Pheochromocytoma is a rare neoplasm, occurring in less than 0.6% of patients with hypertension (1, 2). Most of the cases with pheochromocytoma manifest marked hypertension and other symptoms associated with catecholamine excess (*e.g.*, palpitation), and the tumor can be discovered during imaging evaluation, including CT and MRI of the abdomen. Although pheochromocytoma primarily arises from the adrenal medulla, which serves as a part of the neuroendocrine system, approximately 10% of cases arise from Zuckerkandl tissues along the paravertebral sympathetic chains (3). Nevertheless, there have been very few case reports in which pheochromocytoma arose primarily from the liver (4–8). Furthermore, elevated production of catecholamines is usually associated with enhanced uptake of ^{123}I -metaiodobenzyl guanidine (MIBG), and a positive ^{123}I -MIBG scintigraphy scan strongly

supports the diagnosis of pheochromocytoma.

In this communication, we report a case in which marked hypertension and increased urinary catecholamine excretion developed, indicating the presence of pheochromocytoma. Notably, this patient possessed no adrenal tumor but suffered from a large hepatic mass. In concert with the results of a liver biopsy, these findings indicated that this patient had a primary hepatic pheochromocytoma.

Case Report

A 60-year-old male patient visited a local hospital with complaints of headache and palpitation in 1997. Marked hypertension (180/100 mmHg) was found and medication was started. Systolic blood pressure was reduced to between 140 and 160 mmHg by the combination treatment with amlodipine (5 mg/day) and valsartan (80 mg/day), whereby his headache disappeared. He experienced no complications

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Table 1. Time Course of Metanephrine, Normetanephrine and Vanillylmandelic Acid in 24-h Urine Collection

	On admission	Post hepatic TAE	Post spinal TAE	Post spinal operation
Metanephrine (mg/day)	0.11	0.16	0.14	0.13
Normetanephrine (mg/day)	16.00	7.40	5.40	4.00
VMA/creatinine (mg/g)	56.10	19.70	16.20	11.50

TAE, transcatheter arterial embolization; VMA, vanillylmandelic acid.

(A) MRI **(B) ¹²³I-MIBG**

Fig. 1. Abdominal MRI and ¹²³I-metaiodobenzyl guanidine (MIBG) scintigram of the hepatic lesion. A: A high signal intensity area at the dorsal segment of the liver on the T₂-weighted MRI image was observed. B: ¹²³I-MIBG scintigraphy failed to show the uptake in the hepatic lesion area (filled arrow). In contrast, spinal metastasis was clearly detected with ¹²³I-MIBG scintigraphy (open arrow).

other than paroxysmal hypertension until 2004. In June 2004, he again suffered from headache and general fatigue. Although the doses of both drugs were doubled, his blood pressure remained insufficiently controlled. Because of the body weight loss (–5 kg) and to rule out malignancies, an abdominal CT scan was performed, and revealed a large mass (5 × 5 cm) in the dorsal portion of the liver. He was referred to our hospital for further evaluation and blood pressure control.

On the day of hospitalization, he manifested marked hypertension (supine: 190/98 mmHg; upright: 140/88 mmHg; with pulse rates of 100 and 100 beats/min, respectively). He was experiencing headache and excessive perspiration, but appeared to be in good general condition, and the findings of his physical examination were otherwise unremarkable. His eye grounds showed signs of mild hypertensive vascular changes. Laboratory examination showed normal red blood cell ($4.5 \times 10^6/\text{mm}^3$) and white blood cell counts ($7,900/\text{mm}^3$), and his serum creatinine (1.0 mg/dl), hepatic enzymes (aspartate aminotransferase: 35 IU/l; alanine aminotransferase: 22 IU/l; alkaline phosphatase: 343 IU/l; γ -glutamyl transpeptidase: 73 IU/l), lipids (triglyceride: 113 mg/dl; total cholesterol: 219 mg/dl), blood glucose (111 mg/dl) and urinalysis

were within normal ranges. Electrocardiography showed left ventricular hypertrophy. Twenty-four hour urinary excretions of noradrenaline, normetanephrine and vanillylmandelic acid were markedly increased (Table 1), whereas the excretions of adrenaline and metanephrine were not elevated. These physical (blood pressure) and biochemical results led us to suspect pheochromocytoma or a related disease (*e.g.*, paraganglioma). The patient was treated with an α -adrenergic blocking agent (doxazosin, 8 mg/day), and subsequently a β -adrenergic blocking agent (metoprolol, 120 mg/day) was added for the treatment of tachycardia. He has no family history of pheochromocytoma or related endocrinopathies, such as von Hippel-Lindau syndrome or multiple endocrine dysplasia (MEN)-2. No other endocrinological abnormality was noted, including plasma parathyroid hormone, insulin, acetylcholine (ACTH) and urinary 5-hydroxyindoleacetic acid (HIAA) excretion.

MRI of the abdomen revealed a high signal intensity area at the dorsal segment of the liver on the T₂-weighted image (Fig. 1A). No tumor in the adrenal gland or paraganglia was found with CT/MRI of the abdomen and mediastinum. The spinal MRI, however, showed the presence of several lesions at the thoracic vertebra suggestive of metastasis. ¹²³I-MIBG scintig-

Fig. 2. Histological appearance of the liver tumor. A: Proliferation of tumor cells with round nuclei was observed adjacent to the normal liver tissue (hematoxylin-eosin stain). Tumor cells were positive for chromogranin A (inset). B: Similar histological findings were observed in the spinal tumor (hematoxylin-eosin stain), which showed positive chromogranin A staining (inset).

raphy showed radioactivity in the spinal tumors but no activity in the hepatic tumor (Fig. 1B). Positron emission tomography (PET) scanning using ^{18}F -deoxyglucose revealed a high signal intensity area in both the liver and spine. Other examinations, including gastroduodenal fiberoscopy and barium enema of the colon, did not show significant findings.

Because of these apparently discrepant observations, we conducted selective hepatic venous sampling to examine whether the hepatic mass produced catecholamines. The noradrenaline concentration in the blood from the tumor-drainage vein (95 ng/ml) was nearly identical with that from other veins draining from the non-tumor area (93 ng/ml), although it was slightly higher than that from the peripheral vein (76 ng/ml). We therefore performed an ultrasonography-guided liver biopsy, and found that the tumor tissue contained chromogranin A-positive cells (Fig. 2A).

After obtaining informed consent from the patient, transcatheter arterial embolization (TAE) was performed to reduce the size of the hepatic tumor, and resulted in a marked decrease in 24-h urinary excretion of catecholamines and their metabolites (Table 1). In addition, we conducted TAE for the vertebral tumor, after which the spinal bone lesions were removed. The histopathologic findings were compatible with those of pheochromocytoma, *i.e.*, chromogranin A-positive cells (Fig. 2B). Further decreases in 24-h urinary excretion of catecholamines and their metabolites were obtained (Table 1). After the above procedures, combination treatment with amlodipine (5 mg/day) and doxazosin (4 mg/day) was initiated, and the blood pressure decreased to below 130/85 mmHg. The patient was discharged from our hospital for further follow-up at the outpatient clinic.

Discussion

We herein reported the case of a patient with a large hepatic mass and marked hypertension. The biochemical data observed in this case are compatible with clinical features of pheochromocytoma. We further revealed that the biopsy specimen from the liver tumor contained chromogranin A-positive cells, and the catecholamine excretion was markedly decreased after the TAE of the liver (from 16.00 to 7.40 mg/day). In contrast, no adrenal mass or paraganglionic tumor was found. Accordingly, we concluded that the liver tumor was a primary focus of pheochromocytoma. Of note, the spinal bone lesions also contained chromogranin A-positive cells, and actually secreted catecholamines, based on the changes in urinary catecholamine excretion following the surgical intervention to the thoracic vertebrae. Nevertheless, the vertebrae have not been reported as a primary site of pheochromocytoma, although they are one of the tissues most frequently affected by metastasis of this neoplasm (9).

It is generally agreed that most catecholamine-secreting tumors arise from the retroperitoneum. Among them, 85–90% are adrenal in origin, and 5–10% are extra-adrenal (10, 11), with the paraganglion being the primary location for the latter. In the present case, the pheochromocytoma arose from the liver. Primary hepatic pheochromocytoma is very rare, with only a few cases having been reported to date (4–8). Both the case reported by Jaeck *et al.* (4) and that reported by Reif *et al.* (5) manifested as isolated hepatic pheochromocytoma without metastatic lesions, and did not show recurrence during the 37-month and 14-month follow-up period, respectively. In the current case, however, vertebral bone metastases indicated malignant pheochromocytoma. The diagnosis of

malignancy requires the evidence of metastasis at non-chromaffin sites distant from the primary tumor, since there are no reliable histopathological methods for distinguishing benign from malignant pheochromocytoma. Although the prevalence of malignancy is commonly cited as approximately 10%, other estimates suggest the rate ranges over 5–26% depending on how malignancy is defined, with lower or even higher values in certain patient groups depending on the underlying mutation (12–14).

Surprisingly, the present case showed negative results of ^{123}I -MIBG scintigraphy for the hepatic space-occupying lesion. It has been well established that this test has high specificity for pheochromocytoma. Recently, in a large European multicenter study, the sensitivity of ^{131}I -MIBG scintigraphy for detecting pheochromocytoma was reported to be 81% (15). Labeling MIBG with ^{123}I instead of ^{131}I may yield superior imaging quality (16–18), and may reduce false negative results. Nevertheless, approximately 13% of the cases with pheochromocytoma remained undetected after MIBG scintigraphy with ^{123}I in the largest published series to date (19). As reported by Reif *et al.* (5), the high background activity of the liver could mask the neoplastic activity. Alternatively, the structural and functional differences between pheochromocytomas and other tumors may be responsible for the lower ^{123}I -MIBG uptake in the former.

The results of the hepatic venous sampling, which was performed to confirm the endocrine activity of the tumor, also merit comment. The levels of catecholamines and their metabolites in the tumor-drainage vein were similar to those in the vein from the non-tumor area in this case, and the results proved inconclusive for determination of the localization of catecholamine production. Although the reason for this finding is unclear, hormone-producing sites other than the liver (*i.e.*, thoracic vertebrae) may have affected the plasma level in the peripheral vein. Alternatively, markedly elevated plasma catecholamine levels may have masked the difference in the concentration between tumor drainage and non-drainage veins.

In conclusion, we have experienced an extremely rare case of primary malignant hepatic pheochromocytoma. Furthermore, ^{123}I -MIBG scanning was negative in the liver of this patient, but catecholamines were actively released based on the measurement of catecholamine excretion following the TAE of the liver. Thus, the features of this case may provide clues toward a diagnostic and therapeutic strategy for hepatic pheochromocytoma in the absence of negative results by MIBG scan.

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