Sipple's Syndrome with Liver Tumors Examined by Iodine-131 MIBG and Technetium-99m(V)-DMSA

Hitoya Ohta, Keigo Endo, Toru Fujita, Mitsuru Koizumi, Junji Konishi, Atsuhiko Maki, Keiichirou Mori, Kazue Ozawa, Gen Inoue, and Yutaka Nakano

Department of Nuclear Medicine and Surgery, Kyoto University School of Medicine, Kyoto; and Shinkori Hospital, Osaka, Japan

This case report describes the localization and categorization of tumors using ^{99m}Tc(V)-dimercaptosuccinic acid and [^{131}I]metaiodobenzylguanidine scans in a very uncommon case of medullary thyroid carcinoma associated with pheochromocytoma (Sipple's syndrome) and hepatocellular carcinoma. Technetium-99m(V)-dimercaptosuccinic acid showed accumulation only in medullary thyroid carcinoma, but [^{131}I]metaiodobenzylguanidine scans were positive in both medullary thyroid carcinoma and pheochromocytoma. In advanced Sipple's syndrome, combined use of [^{99m}Tc(V)]dimercaptosuccinic acid and [^{131}I] metaiodobenzylguanidine may be useful for the categorization of tumor mass lesions and planning appropriate therapy.

J Nucl Med 29:1130–1135, 1988

Medullary thyroid carcinoma (MTC) is a unique cancer of the thyroid, accounting for 2% to 9% of all thyroid malignancies. It secretes calcitonin and CEA and is associated with pheochromocytoma also known as Sipple's syndrome.

Iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG), first reported as the imaging agent for the pheochromocytoma, has been found to be taken up in other neuroectodermally derived tumors, such as neuroblastoma, carcinoid tumors, and MTC (*1–5*). Technetium-99m(V)-dimercaptosuccinic acid ([Tc(V)] DMSA) specifically accumulates only in MTC among various thyroid cancers (*6,7*). However, uptake of both radiopharmaceuticals in MTC have been shown to be variable (*8,9*). Recently, we had the opportunity to examine a very uncommon case where recurrent Sipple's syndrome associated with hepatocellular carcinoma using [^{131}I]MIBG and [^{99m}Tc(V)]DMSA was present. The obtained images suggested that scintigraphic examinations are useful not only for the localization, but also for categorization of tumors.

Received Sept. 30, 1987; revision accepted Feb. 23, 1988.

For reprints contact: Hitoya Ohta, Dept. of Nuclear Medicine, Kyoto University Hospital, 54 Shogoin-Kawaharacho, Sakyoku Kyoto 606 Japan.

METHODS

[^{99m}Tc(V)]DMSA and [^{131}I]MIBG were prepared as previously reported (*1,6*). Purity of [^{99m}Tc(V)]DMSA was analyzed by thin layer chromatography (TLC) [Merck silica gel, developed with n-butanol/acetic acid/H_2O (3:2:3)], and no free pertechnetate or other ^{99m}Tc derivate was detected. [^{99m}Tc(V)] DMSA imaging was performed at 2 hr after 10 mCi i.v. injection, using a large field-of-view gamma camera with a low-energy, high resolution, parallel hole collimator. At 7 days following [^{99m}Tc(V)]DMSA scans, [^{131}I]MIBG imaging was obtained at 24 and 48 hr after 0.5 mCi i.v. injection, using a large field-of-view gamma camera with a high-energy, parallel hole collimator. Single photon emission computed tomography (SPECT) using [^{99m}Tc(V)]DMSA was performed with 64 different views over 360° and 15 sec, each view for a 5.6-degree rotation of the gamma camera with no attenuation correction. Computerized tomography (CT) was performed 2 wk before [^{99m}Tc(V)]DMSA scans.

CASE REPORT

A 66-yr-old male was admitted to the hospital because of paroxysmal hypertensive attack and right hypochondrial pain. His health was good until he was 43 yr old, when he underwent an operation for bilateral adrenal pheochromocytomas. At age 55 yr, total thyroidectomy was performed because of MTC. His son also had pheochromocytoma accompanied with MTC and diagnosed as familiar Sipple's syndrome. On this admission, physical examination revealed three hard masses of his

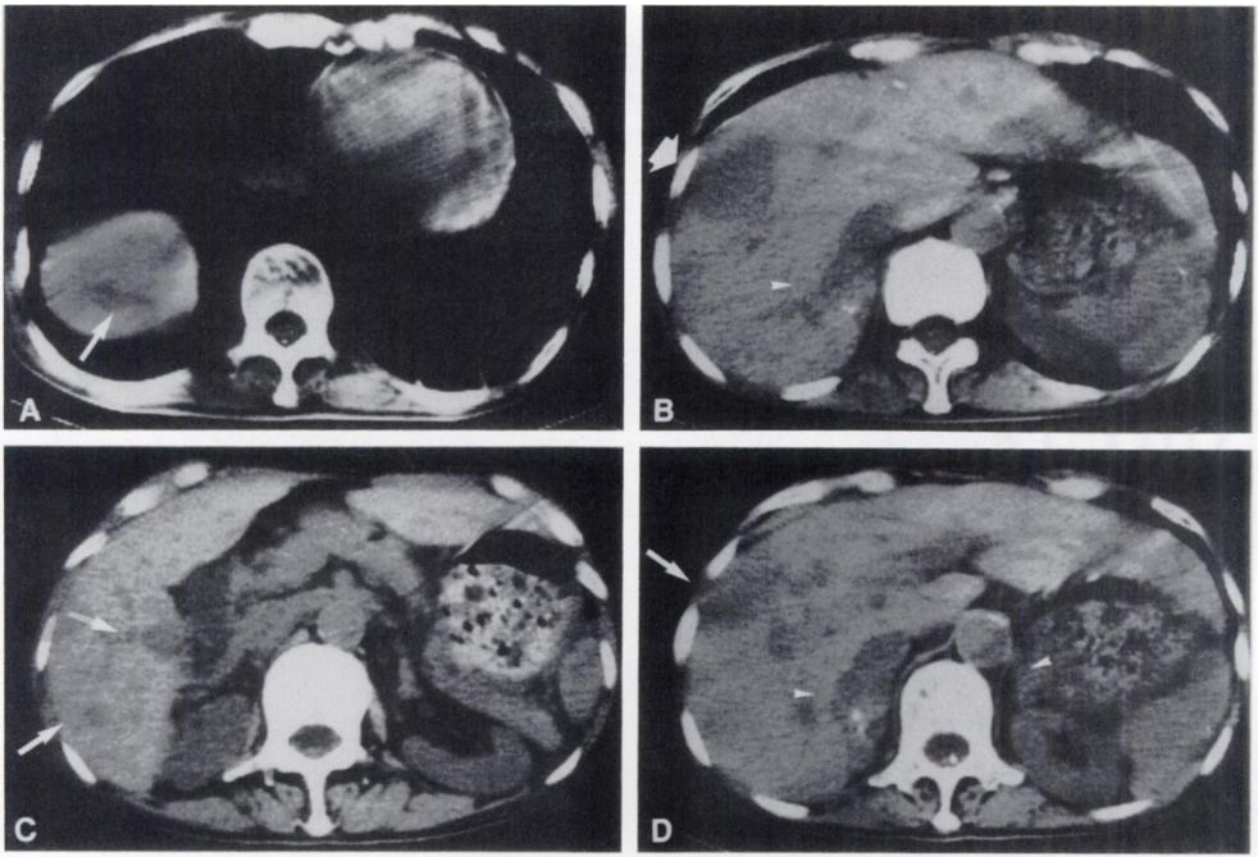

FIGURE 1
A, B, C, D: CT scans of abdomen. CT revealed multiple liver tumors (arrow) and bilateral adrenal tumors (arrowhead). Histology revealed that tumors in A and C were metastatic liver tumors from medullary thyroid carcinoma and tumor in B was hepatocellular carcinoma. Adrenal tumors were recurrences of pheochromocytoma.

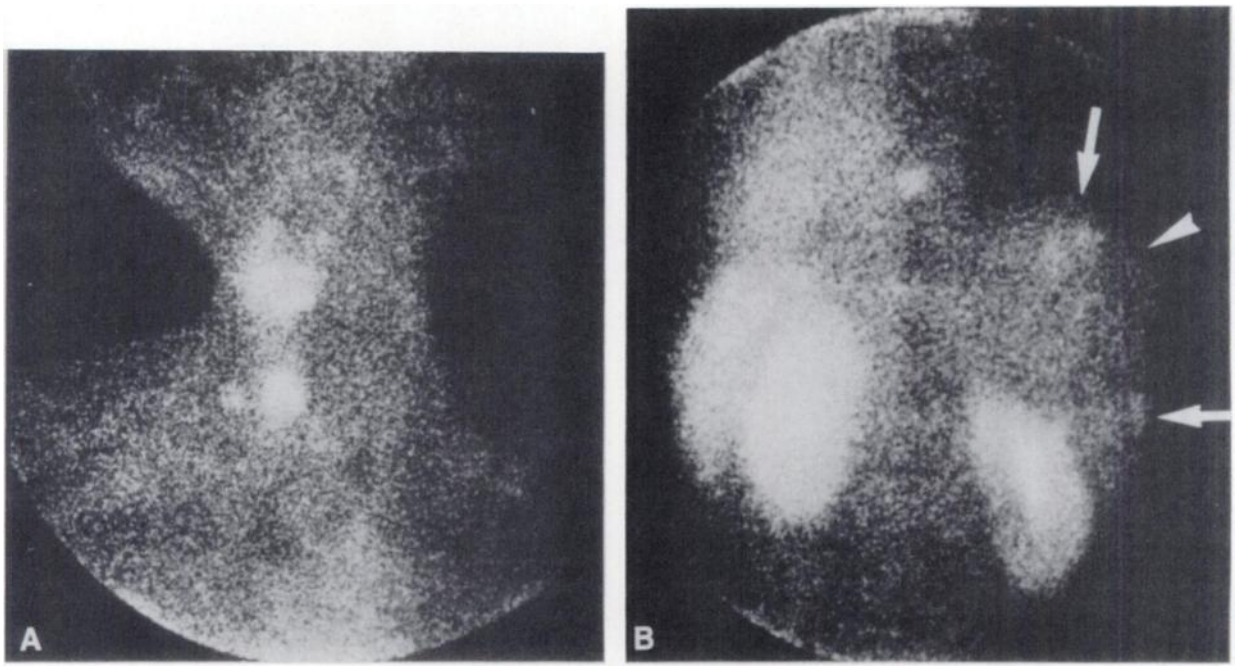

FIGURE 2
A, B: Scintigrams made 2 hr after i.v. administration of 10 mCi [^{99m}Tc(V)]DMSA, showing strong accumulation to the neck lymph nodes (A, right anterior oblique view) and multiple focal accumulations to the liver (B, posterior view).

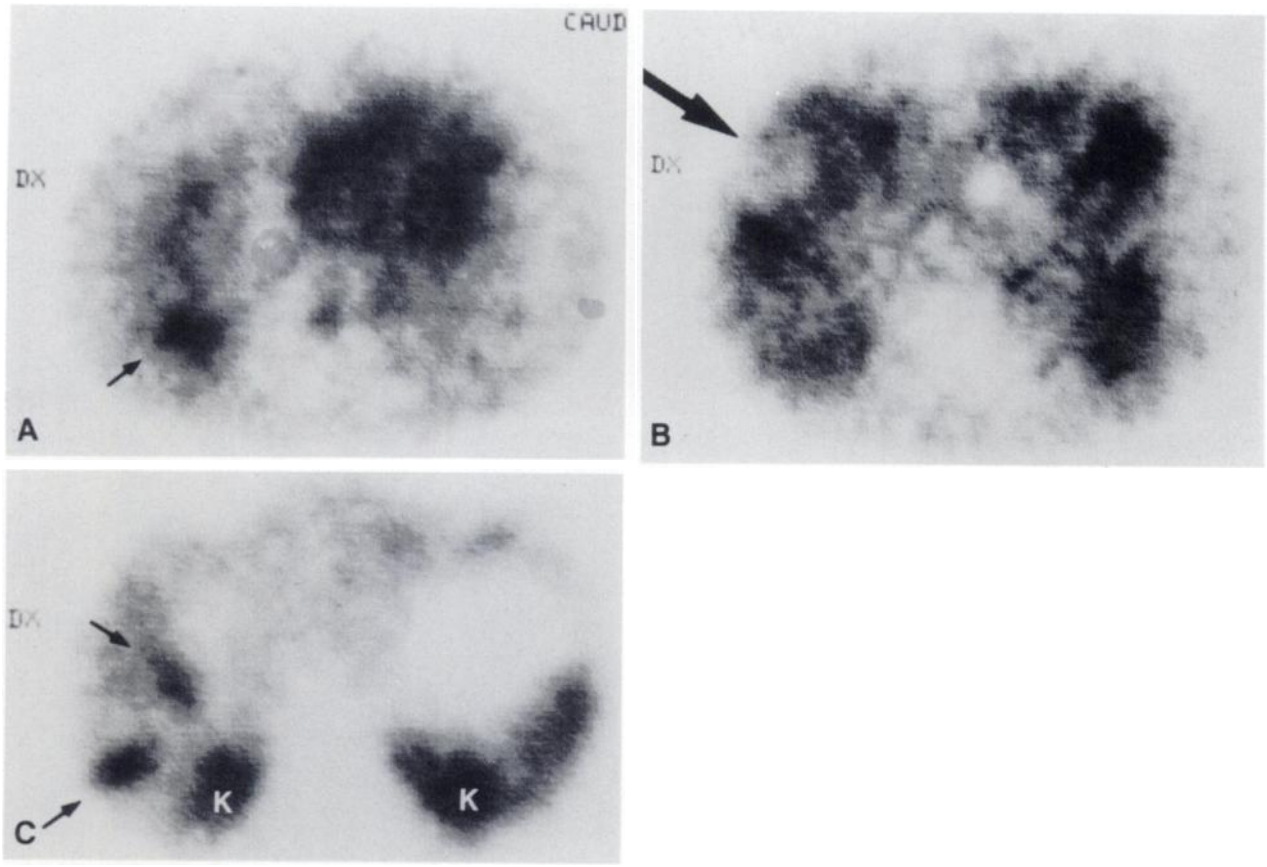

FIGURE 3
A, B, C: SPECT images of [^{99m}Tc(V)]DMSA at the almost same level with CT. [^{99m}Tc(V)]DMSA positive tumors were metastases from medullary thyroid carcinoma (A, C), (K: Kidney) whereas [^{99m}Tc(V)]DMSA negative tumor was found to be hepatocellular carcinoma (B).

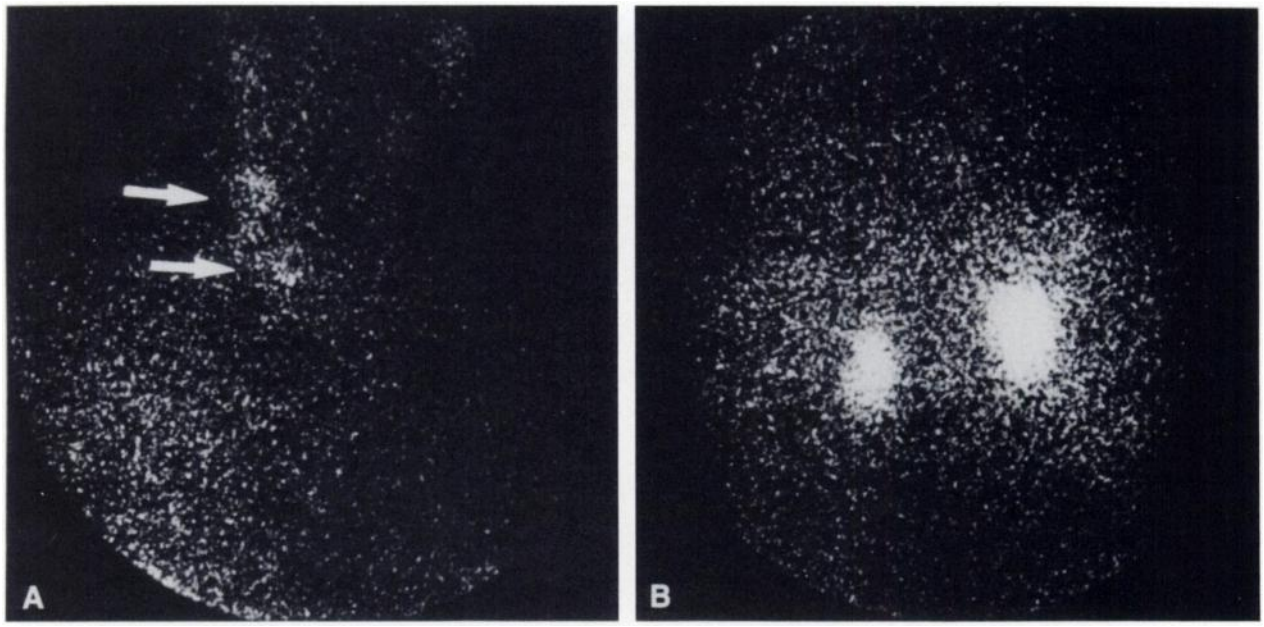

FIGURE 4
A, B: Scintigrams made 48 hr after i.v. administration of 0.5 mCi [^{131}I]MIBG. Faint uptake to the neck metastases of medullary thyroid carcinoma (A) and strong accumulations to bilateral adrenal pheochromocytomas (B) (posterior view) were recognized.

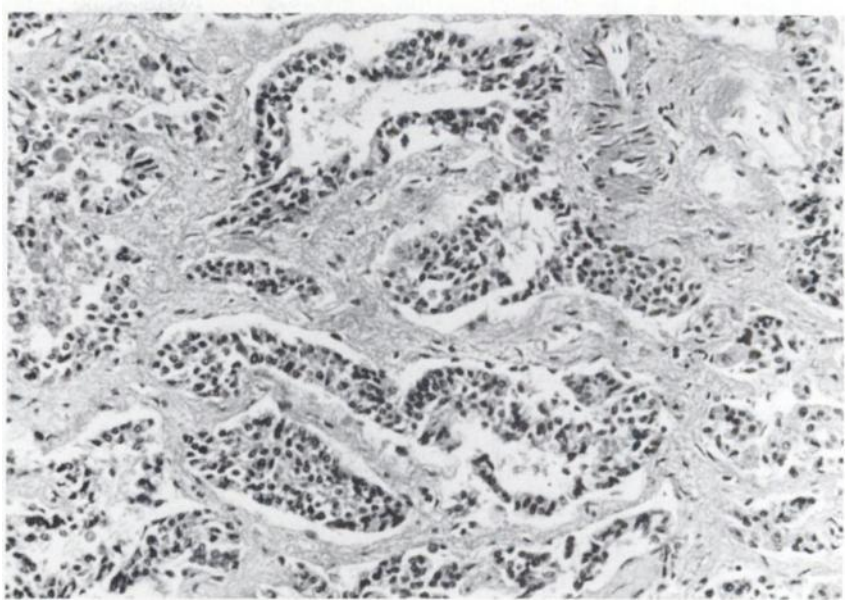

FIGURE 5
Histopathology revealed metastases from medullary thyroid carcinoma to liver (H · E stain × 100).

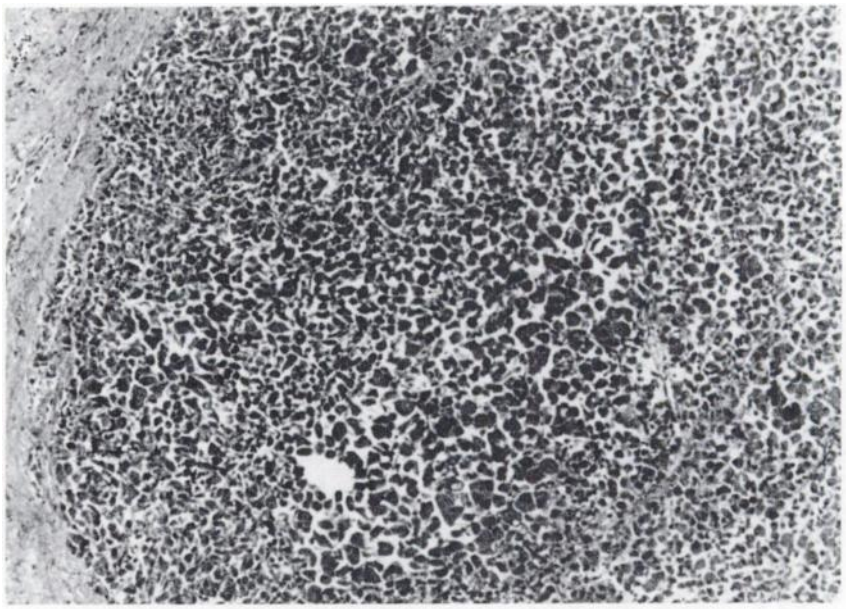

FIGURE 6
Histopathology revealed well capsulated hepatocellular carcinoma (H · E stain × 40).

right neck. Hematologic examination, liver, kidney, and lung function tests, and serum electrolytes were normal. But serum calcitonin level was higher than 50,000 pg/ml (normal range <170 pg/ml). Serum noradrenalin was 0.71 ng/ml (0.04 ~ 0.35 ng/ml), and adrenalin was 0.31 ng/ml (<0.12 ng/ml). Urinary noradrenalin was 1043 μg/day (25–120) and adrenalin was 1,152 μg/ml (2–30). Serum AFP was 4.4 ng/ml and CEA was 300 ng/ml. Hypertensive attacks were difficult to control by medication.

Computed tomographic (CT) scans of abdomen revealed multiple low density areas in the liver and bilateral adrenal tumors (Fig. 1A,B,C,D). For the categorization of these tumors, [^{99m}Tc(V)]DMSA and [^{131}I]MIBG scans were performed. [^{99m}Tc(V)]DMSA scans showed clear accumulations in the neck tumors (Fig. 2A), and focal accumulations were also seen in the liver (Fig. 2B). Single photon emission computed tomography of the abdomen demonstrated [^{99m}Tc(V)] DMSA accumulation in regions concordant with low density

areas revealed by CT (Fig. 3A,C), except one (Fig. 3B). Adrenal tumors were negative with [^{99m}Tc(V)]DMSA (Fig. 2B). [^{131}I] MIBG also showed accumulations in the neck tumors (Fig. 4A) and bilateral adrenal tumors (Fig. 4B). These findings indicated that liver tumors were unlikely to be metastases from pheochromocytoma, since primary and metastatic tumors of pheochromocytomas are generally positive with [^{131}I] MIBG but negative with [^{99m}Tc(V)]DMSA scans. About the [^{99m}Tc(V)]DMSA defect (Fig. 3B), we interpreted the possibility of tumor necrosis, because the possibility of metastasis from pheochromocytoma was low because of the lack of [^{131}I] MIBG accumulation. In order to control hypertensive attacks, bilateral adrenal tumors were successfully resected, and histology revealed the recurrence of pheochromocytoma. After operation, serum and urinary catecholamine levels fell to normal and hypertensive attacks were well controlled without medication. Biopsy of liver and neck tumors revealed multiple metastases of MTC to neck lymph nodes and liver (Fig. 5), and primary hepatocellular carcinoma (HCC) were also found in the liver (Fig. 6).

DISCUSSION

This case report describes [^{99m}Tc(V)]DMSA and [^{131}I] MIBG scans involving a very rare case of MTC associated with pheochromocytoma and HCC, and presented for two reasons. First, both [^{99m}Tc(V)]DMSA and [^{131}I] MIBG were accumulated in MTC. Second, combined use of both reagents provided a good clinical information about the localization and categorization of tumors in patients with advanced Sipple's syndrome.

Recent development of endocrinological imaging is remarkable by using organ or tumor specific radiopharmaceuticals. Localization of [^{131}I]MIBG and [^{99m}Tc(V)] DMSA in primary and metastatic MTC has been reported (*3–10*). On the other hand, false negative cases with [^{99m}Tc(V)]DMSA and [^{131}I]MIBG scans in the imaging of MTC are also reported (*11*). Miyauchi et al. have examined scintigraphic imaging and biodistribution of [^{99m}Tc(V)]DMSA in patient with thyroid cancers (*7*). Specific accumulations on scintigraphic images with high tumor-to-normal thyroid uptake ratio has been only seen in MTCs among thyroid malignancies. As Jeghers reported (*12*), tissue distribution of ^{99m}Tc compounds is greatly affected by the technetium valency and quality control of [^{99m}Tc(V)]DMSA will be indispensable for successful imaging of MTC.

Recent study of [^{131}I]MIBG scans of MTC patients in Europe has indicated that scans could be useful not only for detecting associated pheochromocytoma but also in patient with familial MTC or multiple endocrine adenomatosis (*13*). However, it should be noted that uptake of both reagents are not seen in every MTC, an indication of MTC cells heterogeneity or other factors such as tumor size and location site (*8*).

Most patients with pheochromocytoma are positive with [^{131}I]MIBG but negative with [^{99m}Tc(V)]DMSA as was seen in this case. Liver tumors, detected by CT, were positive with [^{99m}Tc(V)]DMSA but negative with [^{131}I]MIBG, indicating that liver tumors were unlikely to be metastases from pheochromocytoma.

Following surgical resection of bilateral pheochromocytoma, hypertensive attacks were well controlled without medication. These results indicated that tumor-specific radiopharmaceuticals could be clinically useful not only for the localization, but also for the categorization or pathologic diagnosis of tumors.

ACKNOWLEDGMENTS

The authors thank Daiich Radioisotope Laboratories (Tokyo, Japan), Atsuko Ohta, Rie Ohta, and Bungo Onoue for their valuable assistance.

REFERENCES

1. Wieland DM, Wu JL, Brown LE, et al. Radiolabeled adrenergic neuron blocking agents: adrenal medulla imaging with ^{131}I-iodobenzylguanidine. *J. Nucl Med* 1980; 21:349–353.
2. Shapiro B, Copp JE, Sisson JC, et al. ^{131}I-metaiodobenzylguanidine for the locating of suspected pheochromocytoma; experience in 400 cases (441 studies). *J Nucl Med* 1985; 26:576–585.
3. Endo K, Shiomi K, Kasagi K, et al. Imaging of medullary carcinoma of the thyroid with ^{131}I-MIBG. *Lancet* 1984; ii:233.
4. Moll LV, McEwan AJ, Shapiro B, et al. Iodine-131 MIBG scintigraphy of neuroendocrine tumors other than pheochromocytoma and neuroblastoma. *J Nucl Med* 1987; 23:979–988.
5. Koizumi M, Endo K, Sakahara H, et al. Computed tomography and ^{131}I-MIBG scintigraphy in the diagnosis of pheochromocytoma. *Acta Radiol* 1986; 27:305–309.
6. Ohta H, Yamamoto K, Endo K, et al. A new imaging agent for medullary carcinoma of the thyroid. *J Nucl Med* 1984; 25:323–325.
7. Miyauchi A, Endo K, Ohta H, et al. 99m-Tc(V)-dimercaptosuccinic acid scintigraphy for medullary thyroid carcinoma. *World J Surg* 1986; 10:640–645.
8. Endo K, Ohta H, Torizuka K, et al. Technetium-99m(V)-DMSA in the imaging of medullary thyroid carcinoma. *J Nucl Med* 1987; 28:252–253.
9. Clarke SEM, Lazarus CR, Edwards S, et al. Scintigraphy and treatment of medullary carcinoma of the thyroid with iodine-131 metaiodobenzylguanidine. *J Nucl Med* 1987; 28:1820–1825.
10. Clarke SEM. Lazarus CR, Wraight P, et al. Pentavalent [^{99m}Tc]DMSA, [^{131}I]MIBG, and [^{99m}Tc]MDP-an evaluation of three imaging techniques in patients with medullary carcinoma of the thyroid. *J Nucl Med* 1988; 29:33–38.
11. Hilditch TE, Connell JMC, Elliott AT, et al. Poor results with technetium-99m(V)DMSA and iodine-131MIBG in the imaging of medullary thyroid carci-

noma. *J Nucl Med* 1986; 27:1150–1153.
12. Jeghers D, Puttemans N, Urbain D, et al. Technetium-99m DMSA uptake by metastatic carcinoma of the prostate. *J Nucl Med* 1986; 27:1223–1224.
13. Baulieu JL, Guilloteau D, Delisle MJ, et al. Radioiodinated metaiodobenzylguanidine uptake in medullary thyroid cancer; a French cooperative study. *Cancer* 1987; 60:2189–2194.