Pentavalent Technetium-99m (V)-DMSA Uptake in a Pheochromocytoma in a Patient with Sipple's Syndrome

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This case report describes ^{99m}Tc(V)-dimercaptosuccinic acid (DMSA) accumulation in a pheochromocytoma in a patient with Sipple's syndrome. Scintigraphy with ^{99m}Tc(V)-DMSA demonstrated uptake in medullary carcinoma of the thyroid gland (MCT). Iodine-131 metaiodobenzylguanidine (MIBG) scintigraphy showed the bilateral pheochromocytomas but did not demonstrate uptake in the MCT.

J Nucl Med 1990; 31:106–108

Pheochromocytoma and medullary carcinoma of the thyroid together constitute Sipple's syndrome or multiple endocrine neoplasia, type IIA. The pheochromocytoma is frequently bilateral. In approximately one-half the patients parathyroid hyperplasia is also present. Since both the parafollicular (or C) cells of the thyroid and the adrenal medulla originate in the neural crest, Sipple's syndrome is directly related to abnormal neural crest development. The disorder is familial and kindreds should therefore be regularly screened for biochemical evidence of both conditions.

Technetium-99m dimercaptosuccinic acid (DMSA) scintigraphy has been used for the diagnosis of medullary carcinoma of the thyroid gland (MCT) as well as for the localization of metastatic sites and residual tumor (*1–5*). Ohta et al. (*4*) have also shown ^{99m}Tc(V)-DMSA uptake in a variety of benign and malignant soft-tissue and bone tumors. We report the scintigraphic findings in a patient with the rare disorder of Sipple's syndrome in which ^{99m}Tc(V)-DMSA uptake is visualized in both the MCT and the larger of bilateral pheochromocytomas.

MATERIALS AND METHODS

Technetium-99m (V)-DMSA was prepared by a method similar to that of Westera et al. (*6*). To a commercial kit of [Tc] DMSA kidney agent, [Amerscan Technetium (DMSA) Agent N. 107, Amersham International plc, Amersham, UK] containing 1.0 mg DMSA, 0.42 mg $SnCl_2 \cdot 2H_2O$, 0.70 mg ascorbic acid, 2.90 mg NaCl and 50.0 mg inositol, 0.1 ml of sterile, pyrogen-free solution of 7% $NaHCO_3$ was added. Immediately after shaking the vial 11 mCi of [^{99m}Tc]pertechnetate in 3.0 ml of physiological saline was added. The vial was then gently reshaken and incubated for 30 min at room temperature. The commercial kit used here was virtually identical to the one used by Westera et al. (*6*). The only difference is that the $SnCl_2$ in the kit used by Westera et al. (*6*) was in the anhydrous form whereas the kit used in this study contained the dihydrate. The same quantity of $SnCl_2$ (0.35 mg) is present in both kits. Jeghers et al. (*7*) compared the ^{99m}Tc(V)-DMSA supplied by Daiichi (Daiichi Radioisotopes, Tokyo, Japan) with that produced by Westera et al. and found no significant difference between the two either in clinical studies or in biodistribution in rats.

Radiochemical purity of the agent was checked by thin layer chromatography (TLC) on silica gel 60 (Merck) eluting with n-butanol/acetic acid/H_2O (3:2:3) freshly made up to preclude esterification. Technetium-99m(V)-DMSA activity in the main peak (Rf 0.66) exceeded 90%. This corresponds closely with the experimentally maximized yield reported by Yokoyama et al. (*8*).

The patient received 10 mCi of ^{99m}Tc(V)-DMSA intravenously, and whole-body and localized images were taken 2 hr postinjection using a large field-of-view gamma camera. A low-energy, diverging parallel-hole collimator was used for the whole-body imaging and a low-energy, high resolution parallel-hole collimator was used in taking localized images.

Seven days after the initial injection a dose of 0.5 mCi of [^{131}]MIBG was administered intravenously to the patient. Imaging was performed at 24 and 48 hr using a large field-of-view gamma camera equipped with a medium-energy, parallel-hole collimator. Images of 50,000 counts were obtained. Lugol's solution (30 mg daily) was administered 24 hr before the MIBG injection, and continued for 5 days after. Five millicuries of ^{99m}Tc diethylenetriaminepentaacetic acid (DTPA) was administered for kidney localization.

CASE REPORT

A 57-yr-old man was admitted to hospital with a 4-yr history of left upper quadrant pain which had become worse

Received July 7, 1989.
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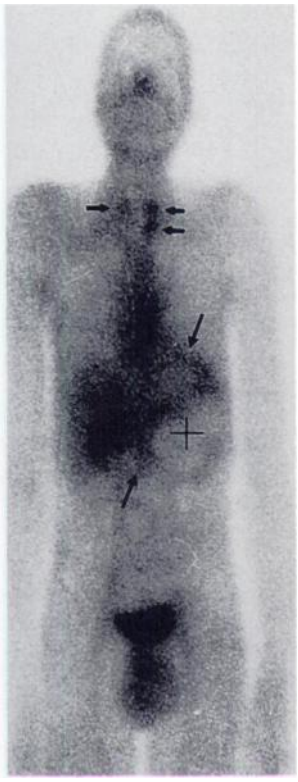

FIGURE 1
Anterior whole-body ^{99m}Tc-(V)DMSA scintigram demonstrating accumulation in the medullary carcinoma of the thyroid (small arrows) and in the large pheochromocytoma (large arrows). The necrotic center is evident (cross).

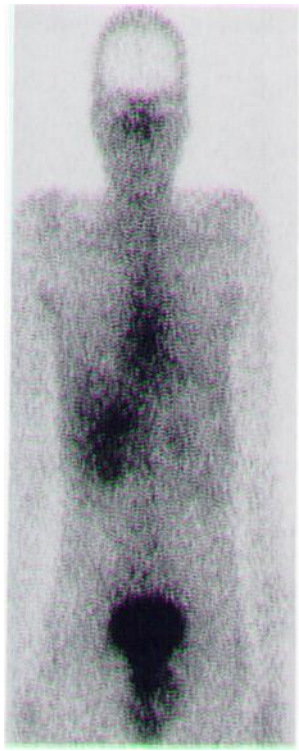

FIGURE 2
Anterior whole-body ^{99m}Tc-(V)DMSA scintigram after surgical removal of the pheochromocytoma showing the absence of the previously visualized activity in the left upper abdomen. Note also the absence of thyroid activity.

6 mo prior to admission. This was associated with constipation, loss of appetite, loss of weight and generalized weakness. Physical examination revealed bilateral firm thyroid nodules and bilateral cervical lymphadenopathy. He was normotensive at examination and a 24-hr halter blood pressure recording failed to demonstrate hypertensive episodes. Cardiovascular examination proved normal. Examination of the abdomen revealed a large, firm mass in the left upper quadrant.

Chest radiographs showed an elevated left hemidiaphragm. Computerized tomography (CT) images demonstrated a 14 cm by 12 cm mass in the left upper quadrant, the origin of which was uncertain. The mass had a large necrotic center. Intravenous urography showed that the mass was compressing the left kidney. Biochemical investigations revealed elevated serum calcitonin levels in excess of 200 pmol/l (normal range: 0–9.9 pmol/l) and urinary normetadrenaline levels of 75–118 μmol/24 hr (normal range 0–5 μmol/24 hr). Parathormone levels were within the normal range. Biopsy of a cervical lymph node demonstrated metastases from an MCT.

Whole-body ^{99m}Tc(V)-DMSA scintigraphy was performed, which showed accumulations in the two thyroid nodules and a further focus inferior to these (Fig. 1). In addition, uptake was noted in the region of the mass in the abdomen. Uptake was visualized mainly in the upper third of the tumor and as a peripheral rim of activity surrounding a central lobulated area of reduced activity (Fig. 1). The radioactivity noted in the great vessels, heart, kidneys, bladder and liver at 2 hr after injection was similar to the uptake found by Ohta et al. (*4*). Postoperative ^{99m}Tc(V)-DMSA scintigraphy failed to reveal the previously visualized abdominal activity (Fig. 2).

Seven days after the initial ^{99m}Tc(V)-DMSA study iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG) imaging demonstrated a large accumulation of uptake in the left upper abdomen and a small focus of activity in the region of the right adrenal. The larger lesion had a central area of reduced activity and showed maximal uptake in its superior third and inferior pole (Fig. 3A and B). The [^{131}I]MIBG failed to localize in the thyroid masses. Both abdominal masses, the thyroid and the cervical lymph nodes were surgically removed. Histology of the abdominal tumors showed typical features of pheochromocytoma. The tumor did not reveal any calcitonin immunoreactivity on immunohistochemistry. The large pheochromocytoma on the left was found to have multiple cyst-like spaces filled with necrotic tumor. The thyroid tumors had the histologic features of MCT.

DISCUSSION

This case describes accumulation of ^{99m}Tc(V)-DMSA in both the MCT and pheochromocytoma in a patient with Sipple's syndrome. Recent studies have suggested that MCT was more frequently detected by MIBG in patients with Sipple's syndrome (*9*). In this patient ^{131}I-MIBG was taken up by the pheochromocytomas, but not by the MCT. This finding is not unusual in light of studies that have shown that the sensitivity of ^{131}MIBG for the detection of MCT primary and metastatic disease is low (*3*).

The fact that ^{99m}Tc(V)-DMSA accumulation was localized mainly in the periphery of the large pheochro-

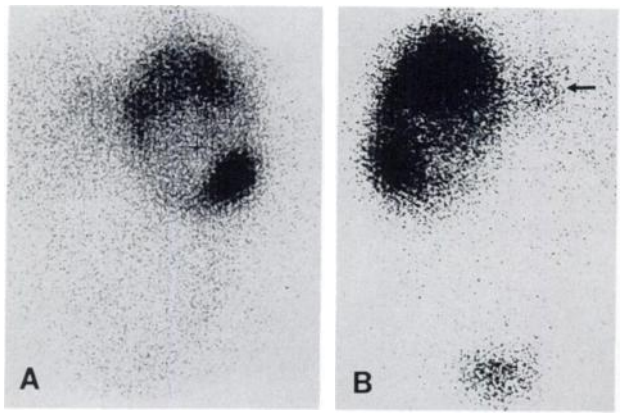

FIGURE 3
A: Iodine-131 MIBG anterior scintigram of the abdomen demonstrating accumulation in the large pheochromocytoma. The necrotic center is visualized (cross). B: Iodine-131 MIBG posterior scintigram of the abdomen showing the large pheochromocytoma on the left and a second lesion on the right (arrow).

mocytoma was probably due to the extensive central necrosis of the tumor. The mechanism of uptake remains unknown. The fact that both MCT and pheochromocytomas are APUDomas suggests a common mechanism of accumulation. As [^{131}I]MIBG accumulation is known to occur in both of these tumors a related mechanism of uptake based upon the embryologic relationship of the APUD cell series is suggested. This argument is strengthened by a recent case report which showed [^{131}I]MIBG uptake in a parathyroid adenoma (*10*). Immunohistochemical studies performed on the large pheochromocytoma revealed no evidence of calcitonin-like immunoreactivity in the tumor, thus ruling out the presence of calcitonin producing tissue as a possible mechanism of ^{99m}Tc(V)-DMSA uptake (*11*). However, Ohta's claims (*2*) that it may be possible to categorize and diagnose tumors in Sipple's syndrome upon the basis of scintigraphy may be complicated by the ^{99m}Tc(V)-DMSA uptake by pheochromocytomas.

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