Meta-[I-131]Iodobenzylguanidine Uptake in a Nonsecreting Paraganglioma

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In a patient with a paraganglioma at the carotid bifurcation, intense uptake of meta-[I-131]iodobenzylguanidine (I-131 MIBG) in the tumor was found. There was no clinical or biochemical evidence for catecholamine secretion by the tumor, although analysis of the tissue revealed that catecholamine biosynthesis took place. We conclude that accumulation of I-131 MIBG may occur in a paraganglioma, but does not necessarily indicate endocrine activity of the tumor.

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Paragangliomas belong to the large group of tumors that share a number of specific histochemical and biochemical characteristics (*1*). The concept that apudomas are derived from the neural crest has been challenged lately and partly redefined, but is still considered valid for paraganglia (*2*). These organs, from which paragangliomas are derived, are found at many sites in the body. Paraganglion cells store catecholamines in electron-dense granules in the cytoplasm (*3*). If catecholamine secretion takes place, a paraganglioma is referred to as a pheochromocytoma, which is therefore not limited to the adrenal medulla.

Recently a scintigraphic technique has become available for the detection of pheochromocytomas, using meta-[^{131}I]iodobenzylguanidine (I-131 MIBG), a guanethidine analog with affinity for the adrenal medulla, as tracer (*4,5*). In this paper we present a case with intense accumulation of I-131 MIBG in a nonsecreting paraganglioma at the carotid bifurcation.

METHODS

Scintigraphy. I-131 MIBG was prepared as described by Wieland et al. (*6*). At the time of injection, 2% of free I-131 was present in the preparation. A dose of 486 μCi (18 MBq) I-131 MIBG was administered i.v., and 20, 48, and 72 hr later scintigraphy was performed with a LFOV gamma camera equipped with a high-energy, parallel-hole collimator. Lugol's solution was administered during 7 consecutive days starting on the day before injection. After the I-131 MIBG image, a flow of the neck was done using 2.7 mCi (100 MBq) Tc-99 HDP.

Determination of catecholamine metabolites. Urinary catecholamine metabolite levels were determined by gas chromatography and mass fragmentography (*7,8*). Tissue and plasma catecholamine concentrations were measured by high-performance liquid chromatography with electrochemical detection (*9*).

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CASE HISTORY

A 78-yr-old man was admitted because of congestive heart failure. Hypertension was known to exist for 30 yrs. Thirteen years previously, the patient presented elsewhere with a swelling of 7 × 5 cm in the left submandibular region. Microscopic examination of a biopsy showed medium-sized epitheloid cells with hazy cytoplasm and dark nucleus. The cells were arranged in nests that were surrounded by bands of highly vascular hyalin stroma. At carotid angiography the tumor was found to be adjacent to the bifurcation of the left carotid artery. A carotid paraganglioma was diagnosed. Because of inadequate collateral circulation in the circle of Willis, removal of the tumor was considered impossible. Eight years later, the patient had a myocardial infarction, and subsequently episodes of atrial flutter and congestive heart failure occurred. Urinary catecholamine metabolites, measured between such episodes, were not elevated. At admission, congestive heart failure was prominent.

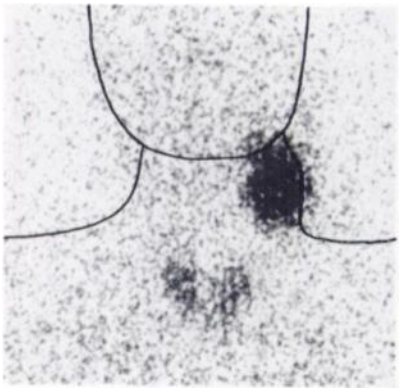

FIG. 1. Anterior I-131 MIBG scintiphoto of head and neck region, showing tracer uptake in left carotid paraganglioma. Thyroid gland is seen faintly. Scintigraphy performed 48 hr after injection. Images at 20 and 72 hr were similar.

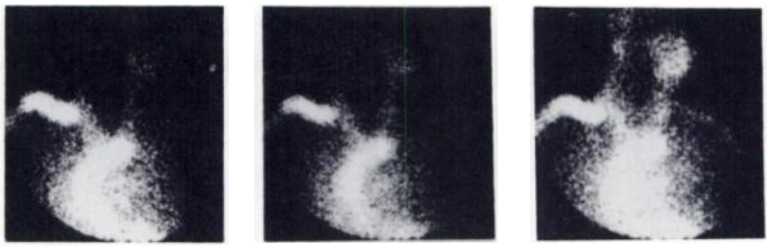

FIG. 2. Flow images of neck with Tc-99m HDP showing highly vascular nature of paraganglioma. Anterior view, 10-sec frames.

Blood pressure was 110/75 mmHg with a pulse of 90/min, regular on medication of digoxin, furosemide, isosorbidedinitrate, and coumarine. Prazosin and oxygen were added. The size of the carotid paraganglioma was unchanged. A period of atrial flutter occurred without change in blood pressure or other signs or symptoms of catecholamine release. One week after admission, while the patient was still in a state of overt congestive heart failure, determination of urinary catecholamine metabolite levels showed normal to moderately elevated values, with vanilmandelic acid excretion of 2.2 up to 4.6 mmol/mol creatinine (normal < 2.5). Urinary metanephrine excretion ranged from 39 to 122 μmol/mol creatinine (normal < 70), and normetanephrine 159 to 445 μmol/mol creatinine (normal < 260). Plasma catecholamine levels, in the seated position, did not show elevation of epinephrine, which was 0.19 nmol/L (normal supine 0.14 ± 0.03 s.d., standing 0.17 ± 0.03), or norepinephrine, 2.83 nmol/L (normal supine 1.54 ± 0.3 s.d., standing 3.48 ± 0.83).

An I-131 MIBG scintigram of the lumbar, thoracic, and neck regions was performed. The mass at the left side of the neck showed intense uptake of I-131 MIBG (Fig. 1). There was no increased uptake in the adrenal region. The flow study demonstrated the highly vascular nature of the mass (Fig. 2).

After temporary improvement, congestive heart failure worsened despite the addition of captopril, dopamine, and dobutamine, and the patient died. At autopsy the heart showed left-ventricular hypertrophy, aortic stenosis, and severe coronary artery sclerosis. A tumor with a diameter of 6 cm was attached to the left carotid bifurcation, without infiltration of surrounding tissues. The tumor revealed the same histologic features as described above. The Grimelius technique showed the cells to be argyrophilic. Ultrastructurally, electron-dense granules were present in the cytoplasm. The tissue was found to contain 2.3 μg of the norepinephrine per gram of tissue, and 0.15 μg of epinephrine per gram. This is far less than is found in the normal adrenal medulla or in pheochromocytoma (*10*). No metastases were found. The adrenals were normal.

DISCUSSION

Iodine-131 MIBG resembles norepinephrine in molecular structure, and probably enters adrenergic tissue by the same mechanism as that of the neurotransmitter or hormone (*4*). Consequently I-131 MIBG is concentrated in the adrenal catecholamine-storage vesicles. By virtue of this property, visualization of the adrenal medulla has been accomplished in dogs (*11*), monkeys (*12*), human pheochromocytoma (*4,5*), and adrenal medullary hyperplasia (*5*). Recently, in a study of 118 patients with suspicion of pheochromocytoma, the efficacy of the method was demonstrated (*13*).

Because of the structural resemblance between I-131 MIBG and norepinephrine, we can expect that scintigraphy with I-131 MIBG should visualize paragangliomas as well. Indeed, uptake of I-131 MIBG has been demonstrated in several cases of extraadrenal pheochromocytoma (*13,14*). In all cases, abnormally elevated secretion of catecholamines was present. In our patient intense uptake of I-131 MIBG in the tumor was found, more than can be explained by the large tumor size, so it must also have been due to active tracer uptake. Neither clinically nor biochemically could evidence be found for excessive catecholamine release by the paraganglioma. The modest elevation of urinary catecholamine metabolites, and the normal plasma catecholamine concentrations, point to an effect of cardiac failure rather than to excessive secretion by the tumor. The discrepancy between the intense uptake of I-131 MIBG and the absence of catecholamine hypersecretion in our patient indicates that I-131 MIBG uptake—which is believed to involve a norepinephrine "re-uptake" mechanism—does not necessarily parallel catecholamine synthesis and secretion (*14*).

Scintigraphy with I-131 MIBG has been proven to be a reliable method for visualizing functioning pheochromocytomas. This report adds nonsecreting paraganglioma to the list of I-131 MIBG-accumulating lesions. The case described above emphasizes that the imaging of adrenergic tissue with I-131 MIBG cannot always be interpreted to mean endocrine activity in terms of release of catecholamines, but rather that the tissue possesses Type I catecholamine uptake and storage capacity.

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Visualization of Hepatic Adenoma with Tc-99m di-Isopropyl IDA

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A case of hepatic adenoma is reported, presenting as a defect on sulfur colloid liver image and visualized on a biliary scintigram. Although biliary imaging in the evaluation of sulfur colloid defects may be of value in selected patients, combination imaging in this case could not distinguish a benign from a malignant process.

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The Tc-99m IDA biliary imaging agents are processed by the parenchymal cells of the liver, whereas Tc-99m sulfur colloid is concentrated by the Kupffer cells. A case of hepatic adenoma is presented, visualized on a biliary image but appearing as a focal defect with sulfur colloid. Combination imaging suggested hepatocyte function but none in the retriculoendothelial system (RES). It could not distinguish benign from malignant disease.

Sulfur colloid scintigraphy continues to play an important role in the evaluation of the liver. However, its nonspecificity with respect to focal defects has contributed to the increased use of ultrasound and transmission computerized tomography (TCT). Combination imaging with gallium-67 citrate (*1,2*), Tc-99m-labeled red blood cells (*3*), Tc-99m-labeled hepatobiliary agents (*4*), and In-111-labeled leukocytes (*5*) has been advocated to improve specificity. Lamki recently discussed dichotomous hepatic uptake of Tc-99m IDA and Tc-99m sulfur colloid (TcSC) (*6*).

This report describes the use of Tc-99m diisopropyl IDA to assist TcSC imaging. The tumor presented as a large focal defect on liver-spleen scintigram; it was solid by ultrasound. Tc-99m IDA imaging revealed hypervascularity as well as radionuclide concentration within the lesion. Gamma imaging therefore suggested hepatocyte function but no RES function.

CASE REPORT

A 77-yr-old male presented with a history of right upper quadrant fullness. He admitted consumption of 250 cc of alcohol per day, and was taking only digoxin and a diuretic for arteriosclerotic heart disease.

On physical examination he was found to have hepatomegaly but no other abnormalities.

Laboratory tests indicated normal liver function. A TcSC image showed a large photopenic area in the right lobe (Fig. 1, left). Ultrasound disclosed a 9.5-cm mass with multiple internal echoes (Fig. 1, right). A Tc-99m DISIDA series showed increased vascularity in the area of the sulfur colloid defect, and complete filling in of the defect on the hepatic-phase images (Fig. 2). Percutaneous liver biopsy was typical of hepatic adenoma (Fig. 3) as described by Kerlin et al. (*8*).

DISCUSSION

A focal defect identified on liver image is often a nonspecific finding. Kupffer cells phagocytize sulfur colloid, and absence of radionuclide activity implies failure of these cells. Many modalities are available to improve specificity, including TCT, ultrasound, angiography, and various radiotracer approaches. Utz first reported visualization of a hepatoma with the biliary agent Tc-99m pyridoxylidene glutamate (*7*). Subsequently, many causes for discordant hepatic uptake of Tc-99m sulfur colloid and hepatobiliary agents have been identified (*6,9*).

Our case provides an example of discordant imaging in a benign liver tumor. Histologically, hepatic adenomas are characterized by hepatocyte proliferation devoid of bile ducts and Kupffer cells. Lamki lists hepatic adenoma as a common cause of a photopenic defect on the colloid image, but intense or normal uptake with IDA (*6*). In this case the value to the clinician is unclear. Firstly, dichotomous uptake of Tc-99m IDA and TcSC could not separate benign from malignant disease. Secondly, it is unlikely that the constellation of scintigraphic and ultrasound findings would obviate the need for biopsy. Thirdly, after reviewing the literature, we consider the incidence of discordant images to be too low to justify routine use of Tc-99m IDA to evaluate colloid defects.

In selected cases, however, the information can be quite valuable. A good example is the evaluation of a solitary defect in or near the inferior margin of the liver. Usually a Tc-99m IDA image can establish the presence or absence of the gallbladder in this location (*10*).

Our patient presented clinically in an atypical way for hepatic adenoma. According to Kerlin et al. (*8*), these patients are gen-

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