Localization and Treatment of Familial Malignant Nonfunctional Paraganglioma with Iodine-131 MIBG: Report of Two Cases

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Two cases of familial, malignant, nonfunctional paraganglioma are reported. Uptake of iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG) by the tumors and metastases was demonstrated. In the first case, with multicentric and locally invasive disease, [^{131}I]MIBG correctly localized a right carotid body paraganglioma which had been missed arteriographically. In the second case, with widespread, symptomatic metastatic disease, a therapeutic dose of [^{131}I]MIBG produced palliation of bone pain after the failure of radio- and chemotherapy. Uptake of [^{131}I] MIBG by paragangliomas does not correlate with catecholamine secretory activity. Iodine-131 MIBG should be considered as a therapeutic option in unresectable, malignant paragangliomas which take up this radiopharmaceutical.

J Nucl Med 28:528–531, 1987

Paragangliomas are tumors arising from extra-adrenal paraganglion tissue, an extensive, multicentric system of histologically and ultrastructurally similar organs (paraganglia). Paraganglia can be shown to contain small amounts of catecholamine and are best classified according to their sites of origin; they are designated "functional" or "nonfunctional" according to whether or not they secrete catecholamines and produce the clinical syndrome of a pheochromocytoma (*1*). In this nomenclature, such confusing synonyms as "glomus tumor" and "chemodectoma" are discarded and the term "pheochromocytoma" is reserved for functional tumors of the adrenal medulla (*1*). Malignancy is defined by either local invasion, spread to regional lymph nodes, or metastasis to distant sites normally devoid of paraganglia, since there are no reliable histologic criteria which distinguish benign from malignant paragangliomas. Multicentric tumors occur in ~10% of cases (*2,3*).

Iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG) is a relatively new radiopharmaceutical which was first used to localize pheochromocytomas (*4,5*). It has now found a place in localization not only of pheochromocytomas but also of neuroblastomas (*6*), carcinoid tumors (*7*), and medullary carcinoma of the thyroid (*8*). It is also being used to treat malignant pheochromocytoma (*9*) and neuroblastoma (*6*). More recently, uptake of [^{131}I]MIBG has been reported in nonfunctional paragangliomas (*10,11*).

We report in this study two patients with multicentric, nonfunctional paragangliomas, both of whom had positive family histories of paraganglioma. In one patient, the tumor was locally invasive; in the other, widespread metastases developed. In both cases, the tumors took up [^{131}I]MIBG. In the second case, a therapeutic dose of [^{131}I]MIBG has been administered after external radiotherapy and combination chemotherapy failed to control or palliate the disease.

METHODS

Scintigraphy

Iodine-131 MIBG was obtained commercially.* It was administered intravenously as either a tracer or a therapeutic dose. At the time of injection, the preparation was shown by chromatography to contain <5% of free ^{131}I. Imaging was performed at 24, 48, and 72 hr after injection, using a computer-linked, large field-of-view gamma camera with a high-

Received Nov. 12, 1985; revision accepted Nov. 24, 1986.

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energy, parallel hole collimator. The patients' thyroids were blocked on each occasion with Lugol's solution and, in the case of the therapeutic dose, this was continued for 1 mo.

Dosimetry

The radiation dose delivered to the tumor by the [^{131}I] MIBG was estimated as follows.

1. The gamma camera/collimator sensitivity was determined by measuring the system's response to a source of known activity.
2. Correction factors for depth and loss of sensitivity due to increasing source-collimator distance were determined using the same source placed at increasing depths in a water bath.
3. Regions of interest and background regions were drawn around each tumor site. After background subtraction and correction for depth (calculated from lateral views with markers), the absolute activity at each tumor site was determined.
4. Using the deposits with the greatest uptake of [^{131}I] MIBG, the uptakes were back extrapolated to determine the effective half-life and the uptake at zero time.
5. Using the above data and a simple model of the total activity as being within a "thyroidlike" sample, the dose delivered to the total sample was estimated from the MIRD tables.

More precise estimation of delivered dose is not possible since the agent was taken up at multiple sites, each of unknown absolute size.

Measurement of Urinary Catecholamines and Metabolites

Urinary levels of catecholamines and dopamine were measured by high performance liquid chromatography (*12*). Urinary vanillylmandelic acid (VMA) levels were measured by the method of Pisano (*13*), and homovanillic acid (HVA) levels were measured by gas liquid chromatography (*14*).

CASE REPORTS

Case 1

A 33-yr-old normotensive housewife was referred because of a slowly enlarging mass in the right side of her neck. On examination, there was also a smaller mass palpable in the region of the left carotid bifurcation, and paralysis of the right hypoglossal nerve. Three of her sisters had carotid body paragangliomas (bilateral in one).

Bilateral carotid angiography demonstrated a single, large, vascular tumor on the right side, invading the petrous temporal bone, with an appearance suggestive of an intravagal paraganglioma. The left-sided mass had the typical appearance of a carotid body paraganglioma. At operation, a 2-cm-diam mass was removed from the left carotid bifurcation; the histology was characteristic of a paraganglioma. However, during the fourth hour of an otherwise uneventful operation, while the tumor was being manipulated, the patient became hypertensive and tachycardic, both these abnormalities settling slowly without specific treatment. Because of the dramatic rise in the patient's heart rate and blood pressure during her first operation, it was considered essential to exclude a functional paraganglioma before resecting the larger, right-sided tumor. Urinary excretion of epinephrine, norepinephrine, dopamine and VMA were repeatedly normal; she was nevertheless treated with a small dose of phenoxybenzamine (10 mg twice daily) in the week before her second operation.

Prior to the second operation, an [^{131}I]MIBG scan was performed using 500 μCi (18.5 MBq). The uptake in the right side of the neck suggested either a bilobed tumor or two closely adjacent tumors (Fig. 1). Normal uptake of radiopharmaceutical was also seen in the left parotid, myocardium, liver, spleen, and left adrenal gland.

At re-operation, a large tumor, approximately 6 cm in diameter, was resected from paravagal tissue; the tumor extended from just below the right carotid bifurcation up into the base of the skull. In addition, a 1.5-cm-diam right carotid body paraganglioma was found and excised. Once again, both right-sided tumors were histologically typical of paragangliomas. As complete resection of the vagal paraganglioma was not possible, the patient is now being considered for either external irradiation or a therapeutic dose of [^{131}I]MIBG.

Case 2

A 35-yr-old businessman was admitted with a 6-mo history of lower thoracic back pain and 1 wk's history of progressive leg weakness and sensory loss. Physical examination revealed signs of a spastic paraparesis with a sensory deficit below the 9th thoracic dermatome, and tenderness over the seventh through tenth thoracic vertebrae. A 6-cm diam, pulsatile, nontender lesion was present on the vertex of his skull. The patient was normotensive.

In April 1982, while living elsewhere, he had undergone partial resection of a right stellate ganglion paraganglioma. Excessive bleeding had precluded complete removal of the tumor. One month later, an abdominal paraganglioma was removed. In 1971, the patient's mother had been treated for a jugular paraganglioma with external irradiation.

The radiological studies demonstrated a complete spinal block above T10, with destruction and replacement by soft tissue of the right neural arches, pedicles and transverse processes of T7, 8, and 9. Anterior to the body of T1, there was a prevertebral soft-tissue mass and there was also evidence of

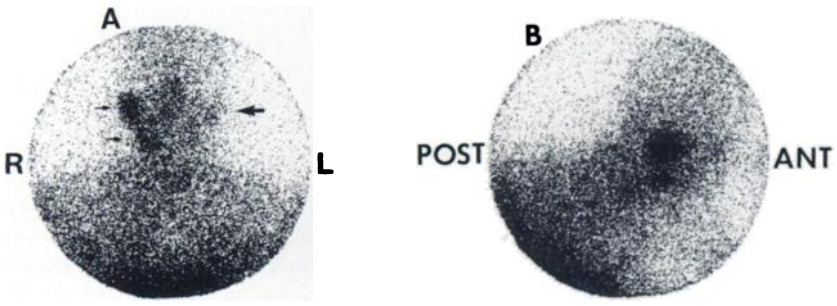

FIGURE 1
Anterior (A) and right lateral (B) views of the head and neck in Case 1, demonstrating two areas of abnormal [^{131}I]MIBG uptake in the right side of the neck (small arrows). Large arrow in A. indicates faint uptake of MIBG by left parotid.

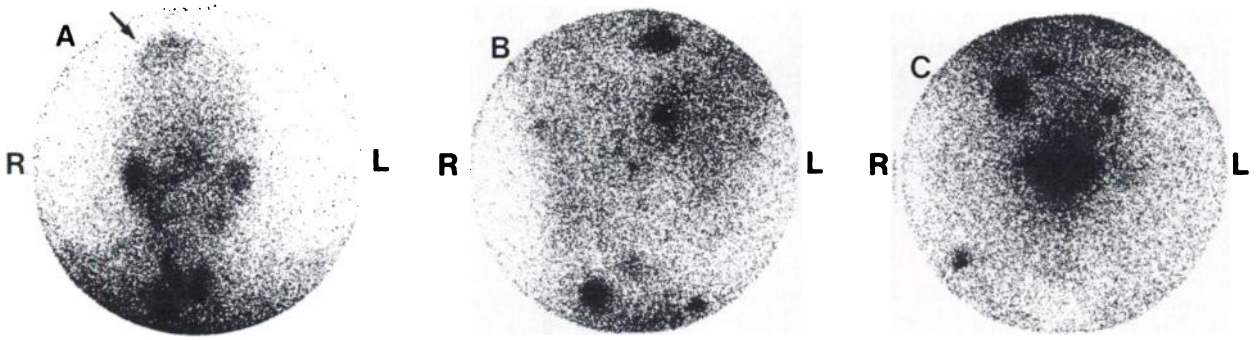

FIGURE 2
Camera views of head and neck (A), abdomen (B), and pelvis and proximal femora (C) of Case 2 following the tracer dose of [^{131}I]MIBG, demonstrating multiple areas of abnormal uptake. Arrow in A. indicates uptake by the clinically palpable mass near the skull vertex. Large central area of activity in C. represents tracer in the bladder.

metastatic disease in C4, C7, T11, and T12. Fulminating paraplegia rapidly followed myelography.

Decompression laminectomy of T7 and T9 with Harrington instrumentation was performed urgently; histologically, the highly vascular tumor was typical of a paraganglioma with local infiltration. Induction of anesthesia and surgery were uneventful, and neurological function of the lower limbs improved postoperatively.

Urinary VMA and HVA levels were normal on two occasions. As the disease was widely disseminated, an attempt was made to treat him with combination chemotherapy, but this regimen was abandoned after two cycles because of intolerable toxicity and lack of subjective or objective benefit. The patient then received 40 Gy in 20 fractions to his skull and thoracic spine which produced slight shrinkage and healing sclerosis of the calvarial deposit.

He was subsequently readmitted because of pain in his right hip associated with lytic lesions in his right femur and acetabulum. He underwent a Jewett's nail fixation, excision and bone graft of his femoral deposit, and excision and bone graft of the pelvic metastases. A [^{131}I]MIBG scan with 1.5 mCi (55.5 MBq) demonstrated multiple areas of uptake (13 in all) and quantification revealed a total tumor uptake in the region of 1.4% of the total administered dose (Fig. 2). It was thus decided that, due to the deterioration in the patient's condition, a therapeutic dose of [^{131}I]MIBG should be given, and a total of 104 mCi (3,850 MBq) was administered. Twenty-five areas of abnormal uptake were now clearly seen (Fig. 3). Quantitation of the total tumor uptake yielded a value of 1.6% of the administered dose, the total radiation dose to the whole tumor being ~43.6 Gy.

After this dose, he experienced relief of his bone pain, and his requirement for opiate analgesia fell. No adverse effects have been noted in 6 mo of follow-up. A repeat [^{131}I]MIBG scan has not been performed; however, using the calvarial deposit as an index lesion, there has been no reduction (or increase) in tumor size. He is being considered for a second dose.

DISCUSSION

Iodine-131 MIBG is a radioiodinated aralkylguanidine which combines the benzyl portion of bretylium with the guanidino group of guanethidine, making it resistant to catabolism by catechol-*o*-methyltransferase and monoamine oxidase, respectively. It is taken up into catecholamine storage vesicles through the sodium-dependent "norepinephrine re-uptake" mechanism (*15*). Studies in patients with malignant pheochromocytoma (*16*), neuroblastoma (*6*), and paraganglioma (*10,11*) have failed to find a correlation between [^{131}I] MIBG uptake and endocrine activity by these tumors. Our findings in these two patients confirm this dissociation.

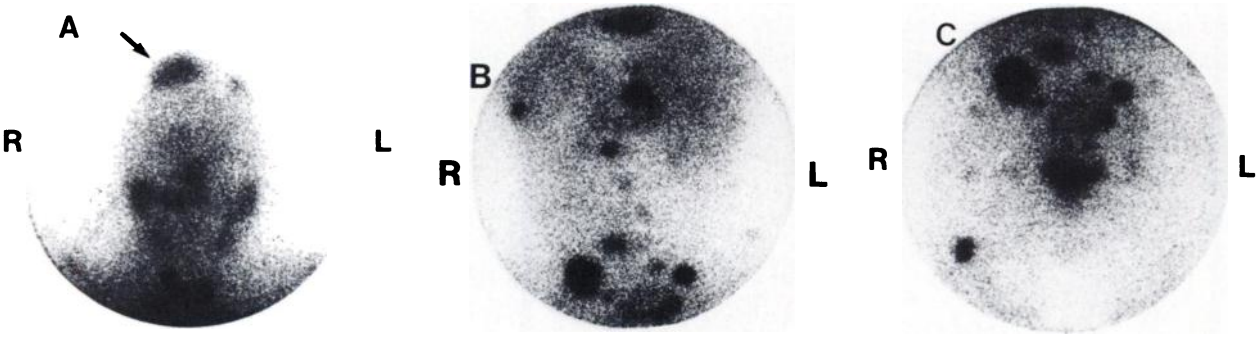

FIGURE 3
Case 2. Camera views following the administration of 104 mCi of [^{131}I]MIBG, demonstrating a number of additional foci of uptake by tumor: head and neck (A), abdomen (B), pelvis and proximal femora (C).

The familial occurrence of paragangliomas is well described (*17,18*). In Grufferman's review (*18*), 2.5% of familial carotid body tumors were malignant, as opposed to 12% of sporadic cases; while 6–7% of patients in both categories had primary tumors other than carotid body paragangliomas, in familial cases they were invariably other paragangliomas or pheochromocytomas but in sporadic cases only 52% were of this type. Both our patients had positive family histories of paraganglioma. Our first case had a locally invasive intravagal tumor associated with bilateral carotid body paragangliomas. Our second case had widely disseminated disease, presumably arising from his stellate ganglion paraganglioma, and an associated abdominal paraganglioma.

We are aware of only one other case of nonfunctional, malignant paraganglioma localized with [^{131}I]MIBG (*11*). To our knowledge, there have been no reports of the therapeutic use of [^{131}I]MIBG in this disease. Iodine-131 MIBG allowed us to accurately define the extent of disease in our cases; certainly, in Case 1, it clearly demonstrated the right carotid body paraganglioma which had not been suspected radiographically. In addition, it offered us a further therapeutic option in our second patient, and provided worthwhile palliation of bone pain after the failure of radiotherapy and chemotherapy to do so. Judging from the experience of others in dealing with malignant pheochromocytoma (*9*), repeated treatments with [^{131}I]MIBG may be necessary, and this option is currently being considered for the second patient.

NOTE

* Amersham Australia Pty Ltd., Surry Hills, NSW.

ACKNOWLEDGMENTS

The authors acknowledge the secretarial assistance of Mrs Janet Wickham and Miss Linda Cichocki; the technical assistance of Miss Heather McGeary, Department of Chemical Pathology, for the assays of catecholamines and metabolites; and the Central Medical Illustration Department, Royal Brisbane Hospital.

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