Catecholamine Secreting Glomus Tumor Detected by Iodine-123-MIBG Scintigraphy

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We report the case of a 41-yr-old woman who presented with arterial hypertension and tinnitus in the right ear synchronous with pulse. She had previously undergone surgery for suspected pheochromocytoma without positive therapeutic effect. CT and MRI revealed a homogenous tumor with contrast enhancement in the right hypotympanon and foramen jugulare, and [^{123}I]metaiodobenzylguanidine (MIBG) scintigraphy demonstrated strong tracer uptake in the same area. Selective venous sampling of catecholamines in the ipsilateral jugular vein confirmed the tumor to have originated from hormone production.

Key Words: iodine-123-MIGB; endocrine active glomus tumor; pheochromocytoma

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CASE REPORT

A 41-yr-old woman presented with tinnitus in the right ear (of 5 yr duration) synchronous with pulse, arterial hypertension and elevated urinary catecholamine excretion. These findings and the results of abdominal CT and [^{123}I]MIBG scintigraphy (multiplanar images of the trunk sparing the head) performed elsewhere, which were interpreted as being suggestive of pheochromocytoma, led to removal of the right adrenal gland at another hospital 6 mo prior to our evaluation. The medullary part of the adrenal exhibited an adenoma 3 mm in diameter, but histological and histochemical findings did not meet the criteria of pheochromocytoma. The normal aspect of the left adrenal gland in CT and MIBG scintigraphy was in agreement with intraoperative exploration. Because the arterial hypertension did not improve and urinary catecholamine excretion remained elevated, the patient was referred to our hospital.

RESULTS

Inspection of the right ear revealed a blue-reddish tumor behind the tympanic membrane. CT and MRI showed a homogenous tumor in the right hypotympanon and foramen jugulare with positive contrast enhancement. Measurement of urinary catecholamines revealed substantially elevated noradrenaline and slightly increased dopamine excretion rates on several occasions (Table 1).

TABLE 1
Urinary Catecholamines

Catecholamine	Sample no. 1	2	3
Noradrenaline [23–105 μg/24 hr]	683	701	690
Adrenaline [4–20 μg/24 hr]	2	1	4
Dopamine [190–450 μg/24 hr]	513	588	564

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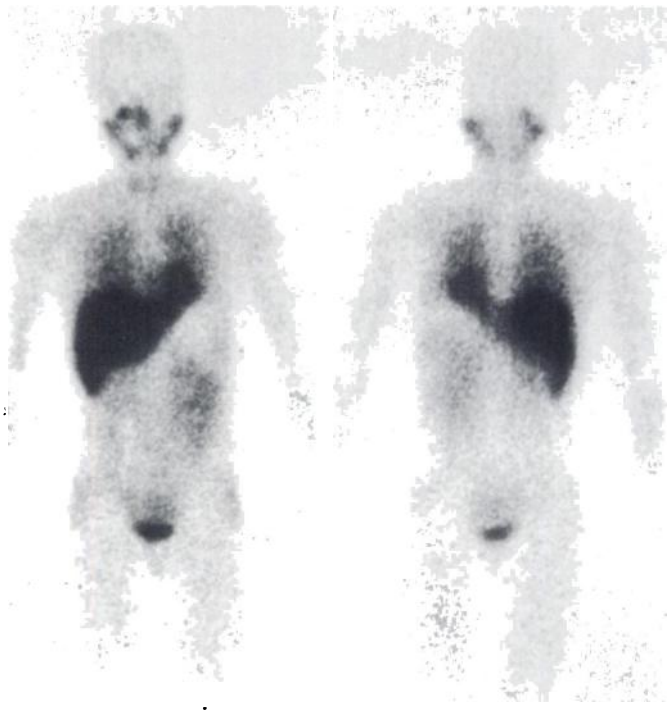

FIGURE 1. Whole-body image (3 hr p.i. [^{123}I]MIBG) shows increased MIBG uptake by a small focus next to the right parotic gland visible on the ventral and dorsal views, which is continued after 24 hr (not shown) and confirmed specific uptake of MIBG in the tumor.

Whole-body scintigraphy (Fig. 1) and especially SPECT (Fig. 2A) of the head performed after injection of 185 MBq [^{123}I]MIBG showed an intense focus of uptake in the hypotympanic tumor; preoperative MRI revealed preoperative tumorous expansion in that area (Fig. 2B). No abnormal uptake was visible in the left adrenal gland, the lower abdomen or the mediastinum. Intraoperative blood samples taken from the right

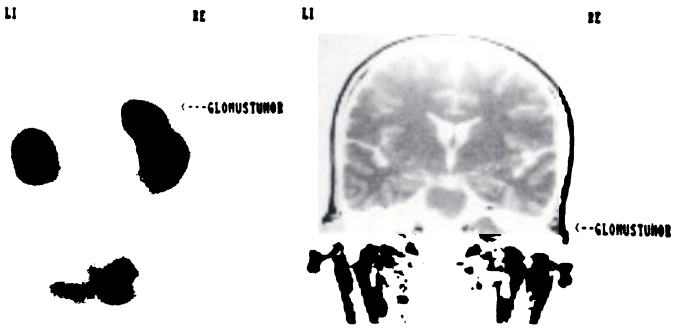

FIGURE 2. (Left) Coronal SPECT slices (3 hr p.i. [^{123}I]MIBG) show a circumscribed lesion medial and cranial to the right parotic gland and lying in the same plane. (Right) Coronal slice from MR image (T1-weighted) shows a tumor in the right hypotympanon and foramen jugulare. Signal intensity is comparable to that of the gray matter.

TABLE 2
Plasma Catecholamine Concentrations Obtained Intraoperatively

	Sample no.					
	Right internal jugular vein			Peripheral vein		
	1	2	3	1	2	3
Noradrenaline [10–60 ng/dl]	407	488	578	125	145	146
Adrenaline [1–8 ng/dl]	1	3	2	2	1	1
Dopamine [1–15 ng/dl]	11	14	16	2	5	3

internal jugular vein showed the noradrenaline and dopamine concentrations to be significantly elevated above those taken simultaneously from a peripheral vein (Table 2).

After removal of the glomus tumor, urinary excretion of noradrenaline and dopamine returned to normal (43 μg/24 hr resp., 284 μg/24 hr), and the blood pressure dropped from preoperative spikes of 240/120 mmHg into the normotensive range (110/75 mmHg).

DISCUSSION

Catecholamine secreting tumors are rare, accounting for only 0.1%–1% of all cases of hypertension. Some 90% of all tumors originate from within the adrenal medulla (pheochromocytoma), while the remainder consist of extra-adrenal neural crest derivatives. The diverse localization of such tumors is explained by the extensive distribution of neural crest derivatives and may occur at the skull base, pericardium, atria, para-aortic area, as well as the urinary bladder and the testicle (*1,2*). Paragangliomas, which include distinctive tumors of the carotid body, vagal body, glomus-jugulare complex, aortic and ciliary bodies, and tumors occuring as minute subpleural pulmonary nodules, have formerly been separated from other neural crest derivatives due to their nonchromaffin status and their probable origin from the chemoreceptor system. There is, however, considerable histochemical and ultrastructural evidence for the production of catecholamines in paragangliomas (*3*). Le Compte was the first to demonstrate that extracts from a carotid body tumor produced epinephrine-like elevations in the blood pressure of cats (*4*).

The earliest reports on documented catecholamine-secreting paragangliomas were by Cone (*5*) and Duke et al. (*6*). Zak and Lawson listed eight endocrine-active glomus jugulare, tympanicum and vagale tumors in their literature review (*7*). Schwaber et al. added three cases in 1984 and estimated that the incidence of functional activity of these tumors was 3% (*8*). Moll et al. (*9*) reported different MIBG-positive tumors other than neuroblastoma and pheochromocytoma with varying uptake of [^{131}I]MIBG in carotid body tumors. While the microscopic appearances of glomus jugulare tumors and carotid body tumors are the same, the glomus jugulare tumor arises from the glomus bodies located in the adventitia of the dome of the jugular bulb and belongs to the most frequent tumors of the middle ear.

The diagnosis of catecholamine-secreting tumors rests on the biochemical demonstration of elevated 24-hr urinary catecholamins or catecholamine metabolites (vanillyl mandelic acid and metanephrines) (*10*). The pattern of catecholamine hypersecretion varies with tumor localization: most tumors of adrenal origin secrete adrenaline in addition to noradrenaline, while extra-adrenal tumors mainly secrete noradrenaline (*2*). All but one of the tumors reported by Zak and Lawson (*7*) secreted noradrenaline only.

Once biochemical proof of catecholamine hypersecretion has been obtained, localization of the tumor is mandatory. Diagnostic methods include CT, MRI and [^{123}I] or [^{131}I]MIBG scintigraphy (*11–16*). The role of MIBG scintigraphy as a specific functional diagnostic tool for depicting endocrine tissue activity is well established by in vitro experiments, which show intracellular uptake by specific uptake mechanism and vesicular deposition, and in vivo studies in patients suffering from pheochromocytoma, neuroblastoma and heart disease (*17,18*).

This case highlights that careful clinical examination is essential when evaluating a patient. The pulse synchronous tinnitus and a visible mass behind the tympanic membrane pointed to the presence of an extra-adrenal problem which may be related to hypertension and catecholamine hypersecretion. Second, the pattern of catecholamine levels was more typical for an extra-adrenal tumor. Third, MIBG scintigraphy must cover the whole body, with special attention to the adrenals, mediastinum, urinary bladder and skull base. Fourth, MIBG scintigraphy excels in screening the entire patient for second primary and occult metastatic disease even when an anatomical imaging modality has already located one lesion. This is all the more important since the occurence of glomus tumors in association with multiple pheochromocytoma has been described in literature (*19,20*). The rare association of multiple paragangliomas with neurofibromatosis should also be noted (*21*).

Although planar imaging was adequate for evaluating a MIBG-positive lesion in this patient's head, SPECT allowed diagnosis of a lesion in the skull base in accordance with MRI. SPECT is particularly useful for discriminating MIBG-positive glomus tumors and overlying or adjacent salivary glands (*22*).

CONCLUSION

Selective blood sampling from a vein draining the tumor and normalization of blood pressure after surgery confirmed the diagnosis and functional nature of the tumor in our patient. Correct preoperative diagnosis and location of functional paragangliomas is important, however, as intraoperative manipulation of the tumor may lead to potentially life-threatening complications, such as hypertensive crisis and arrhythmias, which can be potentially lethal (*8,23*). Therefore, the surgical approach includes preoperative embolization for reduction of blood flow (*24*), an infratemporal approach to the tumor (*25*) which reveals a maximum of tumor and allows optimal reduction of blood supply by ligature of the main vessels and en bloc removal of the tumor (*26,27*).

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Transient Cranial Neuropathy in Prostatic Cancer with Bone Metastases after Rhenium-186-HEDP Treatment

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Rhenium-186 (tin) hydroxyethylidene diphosphonate (^{186}Re-HEDP), a bone-seeking radiopharmaceutical, has been successfully used in the treatment of patients with painful bone metastases. Toxicity is usually limited to reversible thrombocytopenia. An infrequent but clinically significant side effect is the occurrence of transient cranial neuropathy. We report on two prostatic cancer patients with metastatic bone cancer. Both patients developed transient cranial neuropathy shortly after treatment with ^{186}Re-HEDP. Transient neuropathy of cranial nerves needs to be distinguished from neurological abnormalities caused by disease progression.

Key Words: rhenium-186-HEDP; bone metastases; cranial neuropathy

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Up to 80% of patients with prostate cancer develop painful bone metastases, including metastases to vertebral bodies (*1*). The majority of these patients will require single or multiple courses of external beam radiotherapy to palliate the pain and/or treat or prevent epidural compression caused by local tumor progression. Alternatively, bone-seeking radiopharmaceuticals have recently been used successfully in the treatment of painful bone metastases (*2–4*). Rhenium-186 (tin) hydroxyethylidene diphosphonate (^{186}Re-HEDP) is one of the radiopharmaceuticals currently under investigation for this indication. Pain relief has been reported in up to 80% of the patients (*5–7*) and toxicity is limited to transient bone marrow suppression, typically presenting as thrombocytopenia (*8*). Metastases to the base of the skull are the most common causes of cranial neuropathy in patients with systemic malignancies, especially in those patients suffering from prostate and breast cancer (*9,10*). To date, at our institution, 154 treatments of ^{186}Re-HEDP were given to patients with metastatic bone pain originating from prostatic cancer.

This report describes two patients with metastatic prostate cancer who developed transient cranial neuropathy shortly after a therapeutic dose of ^{186}Re-HEDP. The low frequency of these adverse events and the transient character are important in distinguishing from much more frequently occurring neurological dysfunction caused by progressive growth of the metastatic tumor.

CASE REPORT

Patient 1

A 64-yr-old man was referred to our department because of increasing bone pain due to hormone-resistant metastatic prostate cancer. Six months after the presentation of the primary tumor, bone metastases were detected and systemic therapy with luteinizing hormone releasing hormone (LHRH) analogues was started. Later on, cyproterone acetate was added. Stabilization of the disease lasted about 1 yr. He then received a therapeutic dose of 1295 MBq ^{186}Re-HEDP. The day after ^{186}Re-HEDP administration the patient noted increasing difficulty in swallowing solid foods and liquids. This was reported by the patient at the first follow-up visit after 1 wk. At that time, he already noted some improvement of these complaints. On neurological examination, paresis of the right pharyngeal musculature and a deviation of tongue motility towards the right side was diagnosed, indicating dysfunction of the

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