Extraadrenal pheochromocytoma and vagal paraganglioma

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Pheochromocytomas and catecholamine-secreting paragangliomas, also referred to as extraadrenal pheochromocytomas, are rare neuroendocrine tumors that arise from chromaffin cells of the adrenal medulla and sympathetic ganglia. These tumors are uncommon causes of hypertension, accounting for <0.2% of cases (1, 2). While pheochromocytomas are inherently catecholamine-secreting tumors, paragangliomas are less likely to be functional, especially when located in the head and neck. Paragangliomas are rare and widespread tumors, commonly found in the head and neck region. The most common location for head and neck tumors is at the carotid bifurcation, while abdominal tumors are most commonly found in the periaortic-pericaval region (3).

While most cases are sporadic, about one fourth of patients with pheochromocytomas are found to have genetic mutations associated with familial disorders, including multiple endocrine neoplasia type 2 syndrome associated with the *RET* protooncogene, von Hippel-Lindau syndrome associated with the *VHL* tumor suppressor gene, and mutations in succinate dehydrogenase subunits B and D. These patients typically present at a younger age and are more likely to have bilateral adrenal pheochromocytomas or paragangliomas (4). Paragangliomas are also associated with inherited syndromes caused by genetic mutations in succinate dehydrogenase subunits. Succinate dehydrogenase inactivation has been implicated with the activation of hypoxia-inducible genes involved with tumorigenesis and is an active area of cancer research (5).

Rates of malignancy for pheochromocytomas have been reported as 5% to 26%, while reports of malignant paragangliomas are more rare (6, 7). Malignant tumors lack histological and molecular markers that can reliably distinguish them from benign tumors (8). In addition, malignant tumors classified as benign may present at a later time with widely metastatic disease and associated decreased overall survival (9).

We present the case of a 51-year-old man with an extraadrenal pheochromocytoma and vagal paraganglioma diagnosed within several months of each other. The patient was successfully treated with surgical excision. While pheochromocytomas and paragangliomas are well documented, to our knowledge there are few if any case reports of an extraadrenal pheochromocytoma and a vagal paraganglioma in the same patient. Therefore, this case report should inform the practitioner of the possibility of

multiple primary tumors when treating patients with either condition.

CASE PRESENTATION

A 51-year-old Caucasian man was initially worked up at an outside institution for severe abdominal and back pain. A computed tomographic (CT) scan of the abdomen and pelvis demonstrated an approximately 4 cm retroperitoneal periaortic mass (*Figure 1*). The patient was then transferred to our institution for a higher level of care.

At presentation to our institution, the patient's blood pressure was 190/90 mm Hg, and his heart rate was 68 beats per minute with a regular rate and rhythm. The patient was a healthy appearing middle-aged male. No palpable masses were noted on the abdominal exam. Pertinent past medical history included the excision of an abdominal mass at 9 years of age.

Figure 1. Heterogeneously enhancing mass on the right side of the retroperitoneum within the aortocaval space. Subsequent excision revealed an extraadrenal pheochromocytoma.

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He was told that it was malignant but ceased follow-up for a number of years afterwards. In addition, the patient was recently diagnosed with hypertension that had been difficult to control pharmacologically. Otherwise, the patient had no significant medical history. He worked as an intensive care nurse and had no history of alcohol, tobacco, or substance abuse. Family history was negative for any similar familial tumors or hypertension.

The patient's 24-hour urine metanephrines were markedly elevated at 4057 mcg (reference range, 0–899), with normetanephrines of 4015 mcg (reference range, 0–599) and a metanephrine-to-creatinine ratio of 2352 (reference range, 0–599). Chromogranin A was also elevated at 1402 ng/mL (reference range, 0–15). Plasma-free normetanephrines were elevated at 9.74 (n < 0.9), and the plasma-free metanephrines were normal.

The patient was started on phenoxybenzamine, which normalized his blood pressure. He was subsequently started on atenolol once his blood pressure was appropriately blocked with the alpha-blockade. An excision of the retroperitoneal mass was performed with a multispecialty team, including surgical oncologists and vascular surgeons. The mass was identified at the aortic bifurcation at the organ of Zuckerkandl and was successfully excised, including resection of a portion of the aortic wall. No significant intraoperative blood pressure variations were noted. Postoperatively, the patient had labile blood pressure and initially required vasopressor support. After several days, the blood pressure stabilized and the patient was discharged home on postoperative day 6. Pathology confirmed the diagnosis of a 6.0 × 4.5 × 4.2 cm pheochromocytoma (Figure 2a), and the patient was followed as an outpatient.

Postoperatively his plasma-free metanephrines showed a normetanephrine still elevated at 295 (n < 148), and the metanephrine and chromogranin A were normal. A succinate dehydrogenase β genetic screen was negative.

While being followed as an outpatient, a metaiodobenzylguanidine (MIBG) scintiscan was obtained, which showed a mass in the left neck. A CT scan of the neck showed a mass that appeared to be at the carotid bifurcation, consistent with a carotid body tumor (Figure 3). The patient was referred to a vascular surgeon for excision. At that time, a palpable mass was present in the region of the carotid bifurcation in the left neck. Further questioning of the patient revealed that he had noticed

Figure 2. Histology for the two tumors. (a) The retroperitoneum tumor with chromogranin staining. (b) The cervical mass with hematoxylin and eosin staining.

Figure 3. Large vascular tumor seen (a) below and (b) extending above the left carotid bifurcation. Subsequent excision revealed a vagal paraganglioma.

this mass several months earlier but had not brought it to a physician's attention, and it had been missed on previous physical exams. Approximately 15 weeks after the first surgery, the patient returned for excision of this mass. Intraoperatively the mass was found to involve not the carotid body, as suspected, but the vagus nerve. It was successfully resected, and the patient had an uneventful postoperative hospital course. Pathology showed a 4.5 × 2.5 × 2.0 cm paraganglioma, consistent with a primary tumor based on location and histological findings (Figure 2b).

DISCUSSION

Given our patient's remote history of an abdominal tumor resection as a child, he likely had a recurrent pheochromocytoma with a concurrent vagal paraganglioma. The paraganglioma was diagnosed with CT scan and MIBG scan and presented as a palpable mass. This has been shown to be the most common presenting symptom of benign paragangliomas at 55%, with other presenting symptoms including tinnitus and cranial nerve palsies. The diagnosis of head and neck paragangliomas is made incidentally in up to 10% of cases when imaging is obtained for other reasons. Although head and neck paragangliomas are less likely to be functional, up to 4% have been shown to be functional, and therefore it is recommended that these patients are screened for catecholamine excess (3). Another study showed

that out of 175 patients with head and neck paragangliomas, 18.9% had multiple lesions and 6.3% were malignant. *SDH* mutation carriers had an even higher incidence of multiple tumors and malignancy, at 64.7% and 20.6%, respectively. The majority were again carotid body tumors, at 60% of head and neck paragangliomas in this particular series (10).

This case demonstrates that patients can present with multiple pheochromocytomas or paragangliomas either concurrently or with a significant time interval between diagnoses. In our case, the patient presented with two separate tumors in different anatomical locations approximately 42 years after surgical excision of his initial tumor. Although these cases are rare, clinicians treating patients with such conditions should maintain close follow-up even in the absence of clinical symptoms and with a history of benign pathology from previous excisions. Special attention should be paid to the head and neck exam, as these lesions can be easily overlooked. Finally, appropriate genetic screening should be considered in patients and families when hereditary syndromes are suspected.

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