Malignant and Metastatic Pheochromocytoma: Case Report and Review of the Literature

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ABSTRACT
Pheochromocytomas are rare neuroendocrine tumors. Although predominantly occurring in the adrenal glands, these tumors can present anywhere along the sympathetic chain. Indeed, classical teaching states that 10% of pheochromocytomas are extra-adrenal and 10% are malignant. We report a case of a 61-year-old female who underwent presumptive cytoreductive nephrectomy and adrenalectomy for renal carcinoma but was instead found to have malignant pheochromocytoma. Proper identification, surgical extirpation, and follow-up are imperative for treatment. We review the classic and current literature regarding management of this uncommon tumor.

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Introduction
Pheochromocytomas are rare neuroendocrine tumors of the chromaffin system. Although most chromaffin cells degenerate after fetal life, residual cells reside within the adrenal medulla. However, persistent extra-adrenal chromaffin tissue can exist anywhere along the sympathetic chain. Classically, these catecholamine-secreting tumors have been termed the “10% tumor,” in which 10% are malignant, 10% are bilateral, 10% are familial, and 10% are extra-adrenal. Familial causes include multiple endocrine neoplasia type IIA, multiple endocrine neoplasia type IIb, von Hippel-Lindau disease, and neurofibromatosis type 1. Extra-adrenal pheochromocytomas are also described as paragangliomas.

Malignancy in pheochromocytoma is difficult to diagnose microscopically. Therefore, malignant pheochromocytomas are diagnosed by the presence of local invasion or metastatic disease. When metastatic, the most frequent locations are bone, lymph nodes, liver, lung, and brain.

Case presentation
A 61-year-old female presented to her physician with episodic abdominal pain. Her medical history was notable for hypertension and a history of well-differentiated papillary breast adenocarcinoma status 12 years after lumpectomy. An ultrasonogram was obtained, which revealed pancreatic and adrenal masses. Computed tomography (CT) scan showed a 4.1-cm right adrenal mass, an 8.6 × 6 cm enhancing left renal mass, and a 2-cm solid right pulmonary mass (Fig. 1). Follow-up positron emission tomography and CT showed fluodeoxyglucose uptake in all of these lesions. The presumptive diagnosis of metastatic renal cell carcinoma (RCC) was made, and she was taken to surgery for cytoreductive nephrectomy and contralateral adrenalectomy. She had an uncomplicated surgery and recovery. Final pathologic analysis revealed pheochromocytoma in both the kidneys and the adrenal gland. Grossly, there was a 7.4 × 6.8 × 6.5 cm white renal mass with multifocal hemorrhage and necrosis. The adrenal mass measured 5.5 × 4.5 × 3.8 cm. Histologically, the tumor was comprised of neuroendocrine cells with a focally spindled appearance arranged in small nests (Fig. 2). Lymphovascular invasion was identified. Immunohistochemical stains were performed and revealed the tumor cells to be synaptophysin positive and chromogranin negative. An S-100 immunostain highlighted sustentacular cells.

Postoperative metaiodobenzylguanidine (MIBG) scan was obtained 6 weeks postoperatively. There was expected I-123 MIBG activity in the salivary glands, myocardium, liver, and urinary bladder (Fig. 3). The left adrenal gland demonstrated mild uptake of I-123 MIBG thought to be hypervirility. Images of the right lower lobe pulmonary nodule showed no I-123 MIBG activity but revealed an increase in size. A subsequent resection of the pulmonary nodule was diagnosed as metastatic breast cancer.

Discussion
Pheochromocytomas are rare neuroendocrine tumors, with a peak incidence between the third and fifth decades of life.
Classically, patients report headache, palpitations, diaphoresis, and are found to be hypertensive. Approximately 0.02%-0.5% of patients are diagnosed with pheochromocytoma on hypertensive workup, whereas 10% of pheochromocytomas are found incidentally.¹

Malignant or metastatic pheochromocytoma is based on the invasion of adjacent structures or the presence of multifocal disease. In a review of 550 nephrectomy specimens, 80 specimens had concomitant adrenal lesions, of which 3 contained pheochromocytomas.² One renal specimen contained RCC, suggesting von Hippel-Lindau disease as the etiology. The other 2 patients had pheochromocytoma invading the kidney and oncocytoma. There were no reports of multifocal pheochromocytoma.

The diagnosis of pheochromocytoma is often made by testing urine catecholamines or plasma-free metanephrines. Plasma-free metanephrines have a 96% diagnostic sensitivity and 85% diagnostic sensitivity for pheochromocytoma.³ If not already performed, imaging is used for localization. Ninety-eight percent of pheochromocytomas are located in the abdomen, and 90% are found within the adrenal medulla. Magnetic resonance imaging (MRI) has been the imaging modality of choice, providing accurate localization with contrast enhancement and without the use of ionizing radiation. MIBG and CT imaging have historically provided lower sensitivity for pheochromocytomas but still play a role in staging and following these masses.

Histologically, pheochromocytomas are usually well-circumscribed masses. Nests of polygonal or rounded cells, eponymously named Zellballen, are characteristic. Features suggestive of aggressive tumor growth include spindle morphology, increased mitotic rate, and invasion of the organ’s capsule.

Radiographically, these tumors have characteristic high signal intensity on T2-weighted MRI. Our patient did not receive this initial MRI because the patient’s presentation and CT suggested metastatic RCC. MIBG imaging is also used to identify and confirm metabolically active lesions. In patients receiving chemotherapy for pheochromocytoma, MIBG shows utility in tracking response to chemotherapy.⁴ A recent study of imaging findings in histologically confirmed pheochromocytomas showed that these tumors can deviate from the classic presentation and appear heterogeneous or have low signal intensity on T2 imaging. As a result, the authors present another “10%” rule for negative activity on MIBG imaging.

Based on data from the Mayo clinic, 5-year survival for malignant pheochromocytoma is 44%, compared with 96% for benign tumors.⁵ Survival is further decreased with the presence of pulmonary metastases. Surveillance should include plasma-free or
urinary metanephrines every 3 months for 12 months. Meta-
nephrines should be checked annually thereafter. Lifelong sur-
veillance is recommended. Most recurrences occur within 5 years,
but recurrences have been reported as long as 40 years from
original resection. Nonsurgical treatment includes high-dose
MIBG or chemotherapy comprising vincristine, dacarbazine, and
cyclophosphamide. Unfortunately, there have been no complete
responses reported and only 57% of cases experience a partial
response.

Conclusion

Malignant and metastatic pheochromocytoma is a rare neuro-
endocrine tumor. Although they have the same radiographic and
histologic characteristics of their benign counterpart, malignant
pheochromocytomas are diagnosed by the presence of multiple
tumors and offer a poorer prognosis. Treatment is typically
extirpative surgery, although MIBG and chemotherapy have been
offered in nonsurgical cases.

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