

A Case of Malignant Pheochromocytoma Presenting 7 Years After the Initial Surgery

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Background: Pheochromocytoma (PHEO) is a rare tumor of the adrenal medulla and sympathetic ganglion that produces the catecholamines norepinephrine and epinephrine. Traditionally, approximately 10% of PHEOs were thought to be malignant, but recent developments in PHEO research have noted that specific genetic mutations are associated with higher risk of metastatic spread.

Case Report: We report the case of a 71-year-old female who presented with abdominal pain in September 2009 when she was 64 years old. Evaluation at that time revealed cholelithiasis and bilateral adrenal masses. Workup showed elevated free normetanephrines, and positron emission tomography-computed tomography demonstrated bilateral adrenal hypermetabolic lesions concerning for malignancy. She underwent open bilateral adrenalectomies and cholecystectomy. The right adrenal mass was identified as a PHEO with nonaggressive features and negative margins, and the left adrenal mass was an adrenal cortical adenoma without dysplasia. In April 2016, the patient was referred by her endocrinologist for elevated blood pressure and 16-lb weight loss. The patient reported weakness, headaches, hot flashes, cold sweats, and fatigue. Laboratory workup revealed elevated plasma free normetanephrine, and imaging showed a recurrence of the PHEO in both the right adrenal bed and the head of the right humerus.

Conclusion: Current predictors of PHEO recurrence failed to identify the original tumor as aggressive or likely to return as a metastatic lesion. Because of the rarity of these tumors, few consistent laboratory or radiologic predictors of malignancy based on initial presentation have been identified; predictors of malignancy in PHEO warrant further investigation.

Keywords: 3-Iodobenzylguanidine, neuroendocrine tumors, pheochromocytoma

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INTRODUCTION

Pheochromocytoma (PHEO), a rare tumor of the adrenal medulla and sympathetic ganglion, arises from chromaffin cell lines and produces the catecholamines norepinephrine and epinephrine (incidence 1:300,000 per year).¹ Berdez is credited with its description in 1892,² and a report of the first successful resection of the tumor was published by Charles H. Mayo in 1927.³ One-fourth to one-third of PHEOs are associated with the genetic disorders multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, and neurofibromatosis type 1, but they can occur in isolation or as a part of other genetic mutations.⁴ The classic patient presentation involves hypertensive crisis in conjunction with palpitations, headache, and diaphoresis. Dyspnea, weakness, arrhythmias, visual disturbances, and metabolic effects such as weight loss have been repeatedly reported. Traditionally, approximately 10% of PHEOs were thought to be malignant, but recent developments in PHEO research have challenged this idea, noting that specific genetic mutations are associated

with higher risk of metastatic spread.⁴ Few reliable predictors for malignancy based on initial presentation have been confirmed. We report a case of a recurring PHEO.

CASE REPORT

A 71-year-old obese black female presented with abdominal pain in September 2009 when she was 64 years old. Evaluation revealed cholelithiasis and bilateral adrenal masses. Positron emission tomography-computed tomography demonstrated bilateral adrenal hypermetabolic lesions concerning for malignancy (Figure 1). The right adrenal mass measured 6 cm and the left measured 2.1 cm in their greatest dimension radiologically. The patient was noted to be hypertensive. Laboratory results showed that her initial urine normetanephrine and dopamine levels were both within normal ranges, but urine metanephrine was elevated at 368 µg/24 h (normal range, 30-350 µg/24 h). She did not have any known family history of an endocrine disorder. Given these findings, surgery was recommended.

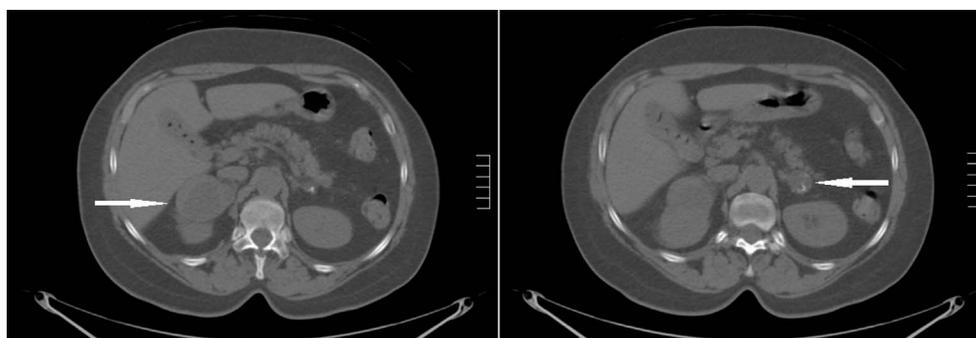


Figure 1. Positron emission tomography-computed tomography shows incidental bilateral adrenal masses (arrows).

She received perioperative alpha blockade with phenoxybenzamine and underwent open bilateral adrenalectomies and cholecystectomy.

The right adrenal gland contained a 65-g, 7.5 × 4.5-cm PHEO. No atypical mitotic figures, tumor capsular invasion, nuclear pleomorphism, or hyperchromasia were observed to suggest aggressive physiology. The left adrenal gland contained a 2.4 × 2.0-cm adrenal cortical adenoma with no suggestion of a medullary tumor or dysplasia. The patient's postoperative course was uneventful.

Metaiodobenzylguanidine (MIBG) scan 1 year later showed no evidence of any MIBG-avid malignancy in the neck, thorax, abdomen, or pelvis. Annual computed tomography (CT) scans were performed for 5 years to monitor for recurrence and showed only normal postoperative changes. The patient also underwent annual monitoring of serum metanephrines and normetanephrines. Based on the pathologic features of the original tumor and known predictors of metastatic recurrence, this tumor was deemed unlikely to recur.

In April 2016 when the patient was 71 years old, her endocrinologist referred her because of elevated blood pressure (229/103 mmHg) for 2 weeks and a 16-lb weight loss. The patient reported weakness, lightheadedness, headaches, hot flashes, cold sweats, fatigue, and dyspnea on exertion. She also reported chronic back pain and knee pain but did not report any new bone pain. Laboratory workup showed elevated free plasma normetanephrine (3,274 pg/mL). Urine catecholamines were not collected. Chromogranin A level was elevated at 59 ng/mL. Her endocrinologist had been following these laboratory values and had noted a steady increase in normetanephrine since 2011 (Table). MIBG scan revealed residual activity in the right adrenal bed and the right humeral head (Figure 2), and

CT showed PHEO recurrence in the right adrenal bed (Figure 3).

CT-guided biopsy of the right humeral head demonstrated rare clusters of epitheloid cells and marrow fibrosis. Immunostains showed synaptophysin, chromogranin, and cytokeratin AE1/AE3 and were weakly positive for S-100 and negative for epithelial membrane antigen. These results were consistent with metastatic PHEO.

The patient was treated with 200 mCi I-131-labeled MIBG. Her thyroid was blocked with potassium iodide. She is taking losartan 50 mg/d and nifedipine 60 mg/d for hypertension. We anticipate that she will have 2 additional cycles of approximately 200 mCi I-131 during the next 6-8 months. She will be followed with tumor markers and radiographic images to assess her tumor response.

DISCUSSION

It is generally accepted that the only way to establish the diagnosis of a malignant PHEO after resection is to note recurrence months or years later. Medeiros et al conducted a clinicopathologic review of 60 cases to evaluate the utility of histopathologic evaluation in predicting the prognosis for these tumors.⁵ They concluded that malignant tumors were usually larger (mean benign mass, 156 g; mean malignant mass, 759 g), had extensive areas of necrosis, and were composed of small cells. They noted that morphologic criteria such as nuclear atypia, capsular and vascular invasion, and mitotic activity were of little value in predicting the behavior of adrenal PHEOs. They also concluded that sex was not a good predictor of malignancy.

Linnoila et al conducted a clinicopathologic study of 120 cases to identify predictors of malignant behavior.⁶ Logistic regression analysis of 16 nonhistologic and histologic parameters showed 4 of them to be most predictive of

Table. Serial Plasma Metanephrine, Normetanephrine, and Chromogranin A Values

	Reference Range	9/29/2011	4/4/2012	7/15/2013	11/26/2013	2/25/2015	8/25/2015	3/8/2016
Free metanephrine, pg/mL	≤57	<25	<25	<25	<25	<25	<25	<25
Free normetanephrine, pg/mL	≤148	172	174	185	235	511	1,151	3,274
Chromogranin A, ng/mL	<15					31		59

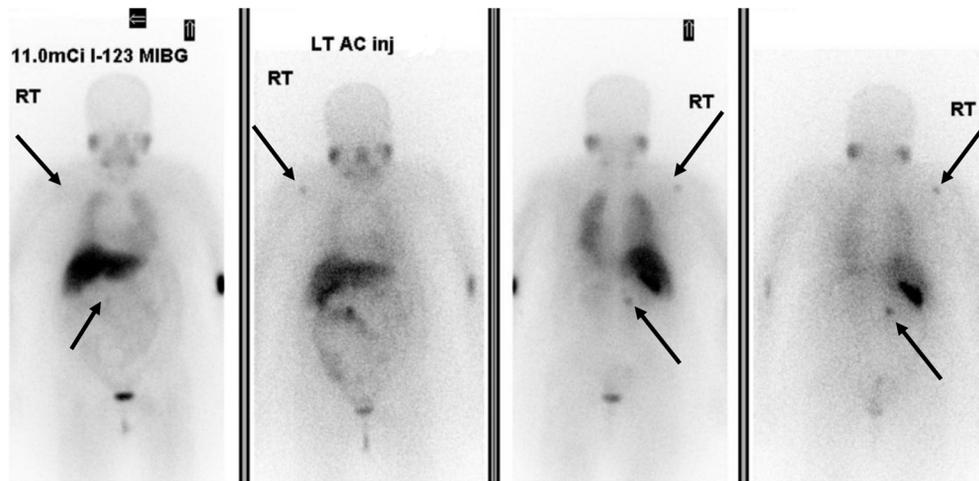


Figure 2. Metaiodobenzylguanidine (MIBG) scan demonstrates metastatic pheochromocytoma in the right adrenal bed and right humerus (arrows). RT, right; LT AC Inj, left antecubital injection.

malignancy: extraadrenal location, coarse nodularity of the primary tumor, confluent tumor necrosis, and absence of hyaline globules. Features noted more frequently in malignant tumors included male predominance, greater tumor weight, and the presence of vascular invasion and/or extensive local invasion.

John et al published a case series of 86 patients with 85 benign and 10 malignant PHEOs during 35 years to look for clinical and pathologic predictors for malignancy.⁷ They concluded that high preoperative 24-hour urinary dopamine levels, extraadrenal tumor location, large tumor mass (>80 g), elevated tumor dopamine concentration, and postoperative persistent arterial hypertension are factors that increase the likelihood of malignant PHEO. They also concluded, contrary to Linnoila et al,⁶ that sex did not predict malignancy. Our patient's tumor size was 65 g, smaller than this case series' cutoff for predicted malignancy.

In 2002, Thompson proposed the Pheochromocytoma of the Adrenal Gland Scaled Score (PASS), a system of scoring 12 histologic attributes that may predict the likelihood of PHEO recurrence.⁸ A PASS score ≥ 4 is considered biologically aggressive compared to a PASS

score < 4 that is indicative of tumors that behave in a benign fashion. However, assessments of the PASS system have been inconclusive, with 1 review of 51 tumors strongly endorsing the system,⁹ 1 review of 130 tumors suggesting it might work with some improvements,¹⁰ but at least 2 reviews with a combined 190 tumors failing to confirm the predictive value of the system.^{11,12}

Various molecular, immunohistochemical, and genetic markers have been explored as predictors for malignancy: MIB-1,¹³ c-erbB-2,¹⁴ p53,¹⁵ BCL-2,¹⁵ E-cadherin,¹⁶ HER-2/neu,¹⁶ retinoblastoma gene,¹⁶ hTERT,¹⁷ and Ki-67.¹⁷ MIB-1, c-erbB-2, retinoblastoma gene, hTERT, and Ki-67 have all been found to be associated with malignancy, whereas p53, E-cadherin, and HER-2/neu do not seem to have diagnostic utility in the prediction of biologic behavior in PHEOs. None of these markers was investigated in our patient.

Malignant PHEO has a poor prognosis, with an overall 5-year survival rate reported to be 30%-60%.¹⁸ The 10-year survival rate was zero in at least one case series.⁷ The principal goal of surgical treatment is removal of the primary tumor and, when possible, the resection of local and distant metastases. Some patients receive I-131-labeled MIBG as well as pharmacologic treatment for hypertension and symptom control. However, not all PHEOs respond to I-131-labeled MIBG.¹⁹ Following the presentation of this case at a multidisciplinary endocrine conference, it was felt that this patient would benefit from systemic MIBG, given the high risk of future distant recurrences. We decided that radiation would be an option for symptomatic bone pain. In other patients, another option for treating malignant, nonresectable PHEO is sunitinib, a molecular-targeted therapy that inhibits vascular endothelial growth factor.²⁰ However, because of the rarity of these tumors, evidence of sunitinib's efficacy is limited.

CONCLUSION

Current predictors of PHEO recurrence failed to identify our patient's original tumor as aggressive or likely to return as a metastatic lesion. Because of the rarity of these tumors, few consistent laboratory or radiologic predictors of malignancy have been identified; predictors of malignancy in PHEO warrant further investigation.



Figure 3. Computed tomography demonstrates pheochromocytoma recurrence in the right adrenal bed (arrow).

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