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(CASE REPORT)

Sporadic metastatic pheochromocytoma: A case report highlighting diagnostic and clinical considerations and brief literature review

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Abstract

Sporadic metastatic pheochromocytoma is a rare, typically localized tumor, associated with catecholamine excess and have potential for metastatic spread, posing significant diagnostic and treatment challenges. We report the case of a 41-year-old woman who presented with a six-month history of episodic headaches, palpitations, diaphoresis, severe hypertension, weight loss, and worsening fatigue. She was initially treated with beta-blockade for presumed anxiety and hypertension, which led to worsening symptoms. Laboratory evaluation revealed markedly elevated plasma and urinary metanephrines. Imaging demonstrated an 11 cm heterogeneous left adrenal mass with areas of necrosis, retroperitoneal lymphadenopathy, and bilateral pulmonary nodules. Functional imaging with I-123 metaiodobenzylguanidine scintigraphy confirmed metastatic involvement of the lymph nodes and lungs.

After multidisciplinary discussion, the patient underwent preoperative alpha-adrenergic blockade with phenoxybenzamine and volume expansion, followed by open left adrenalectomy with regional lymph node dissection. Histopathology showed classic pheochromocytoma with Zellballen architecture, marked pleomorphism, lymphovascular invasion, and a Ki-67 index of 12%. Immunohistochemical (IHC) analysis was positive for chromogranin A, synaptophysin, GATA3, and S100, indicating the presence of S100-positive sustentacular cells.

Following surgery, the patient's blood pressure and biochemical markers normalized. At 28-month follow-up, she remained clinically stable with decreased pulmonary nodules and no evidence of disease progression. This case highlights the importance of early recognition, avoiding isolated beta-blockade, coordinated multidisciplinary care, and long-term surveillance in metastatic pheochromocytoma.

Keywords: Pheochromocytoma; Sporadic; Metastatic; Paraganglioma; Neuroendocrine Tumor; Zellballen

1. Introduction

Pheochromocytoma is a rare neuroendocrine tumor arising from chromaffin cells of the adrenal medulla and characterized by excess catecholamine secretion. [1] Although many tumors are localized at diagnosis, a subset demonstrates aggressive behavior with metastatic spread to lymph nodes, bone, liver, or lung. [2,3] Clinical presentation is variable and often includes episodic hypertension, headaches, palpitations, diaphoresis, anxiety, or weight loss, which may mimic more common cardiovascular or psychiatric disorders and delay recognition. [4]

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Histologic features alone do not reliably predict the metastatic potential of pheochromocytoma, underscoring the importance of clinical staging and long-term surveillance. [5] Advances in molecular testing have improved understanding of tumor biology, particularly alterations involving succinate dehydrogenase complex iron-sulfur subunit B (SDHB), which are associated with higher metastatic risk and less favorable outcomes. [6] Management requires a multidisciplinary approach that includes biochemical confirmation, targeted imaging, preoperative alpha-adrenergic blockade, surgical resection when feasible, and consideration of systemic or radionuclide therapy for advanced disease. [7,8,9]

Because metastatic pheochromocytoma is rare and clinically heterogeneous, well-documented cases offer valuable insight into diagnostic pitfalls, prognostic markers, and treatment strategies. We report this case to highlight the importance of recognizing apparently sporadic metastatic pheochromocytoma with somatic SDHB mutation and the need for integrated long-term management.

2. Case Presentation

2.1. Clinical Presentation, Physical Examination, History, Labs, Imaging, and Differential Diagnosis

A 41-year-old female initially presented with a six-month history of episodic headaches, palpitations, and profuse sweating, occurring two to three times per week and lasting 15 to 20 minutes each. Her primary care physician had managed her with a beta-blocker for presumed hypertension and anxiety, which paradoxically worsened her symptoms. She sought medical attention at the emergency department after a particularly severe episode accompanied by substernal chest pain and shortness of breath. She also reported unintentional weight loss of 10 kg over three months and progressive fatigue that limited her daily activities.

On physical examination, she appeared diaphoretic and anxious, with a blood pressure of 210/110 mmHg, heart rate of 120 beats per minute, and a respiratory rate of 22. Orthostatic hypotension was noted. Significant personal history was unremarkable, and she denied any family history of endocrine neoplasias or cardiac disorders. Laboratory work revealed elevated plasma-free metanephrines (normetanephrine 12.5 nmol/L) and urinary fractionated metanephrines three times the upper limit of normal. Computed tomography (CT) of the abdomen and pelvis showed an 11 cm heterogeneous left adrenal mass with central necrosis, multiple ipsilateral retroperitoneal lymph nodes measuring up to 2.5 cm, and several bilateral pulmonary nodules. I-123 metaiodobenzylguanidine (MIBG) scintigraphy demonstrated intense uptake in the primary tumor, lymph nodes, and lung nodules, confirming metastatic disease.

The clinical differential diagnosis included metastatic paraganglioma, adrenocortical carcinoma, and, less likely, renal cell carcinoma or metastatic melanoma. Radiologic differential considerations included a large pheochromocytoma with metastases versus a primary adrenocortical malignancy.

2.2. Multidisciplinary Tumor Board Discussion and Management Decisions

The case was presented to the multidisciplinary tumor board, which included endocrinology, oncology, radiology, nuclear medicine, endocrine surgery, and pathology. The central discussion focused on the need for preoperative alpha-adrenergic blockades to prevent intraoperative hypertensive crisis, given the large tumor burden and metastatic disease. The team debated whether to pursue upfront surgical debulking of the primary tumor versus systemic therapy first. Consensus was reached that the patient's severe symptoms from catecholamine excess warranted preoperative medical optimization followed by resection of the primary adrenal tumor and involved lymph nodes to reduce hormonal burden, even if not curative.

Recommended next-step management included a 14-day preoperative titration of phenoxybenzamine, supported by a high-sodium diet and intravenous volume expansion to optimize hemodynamic stability. To evaluate the pulmonary nodules for metastatic disease while avoiding invasive procedures, functional imaging with 68Ga-DOTATATE PET/CT was performed. Percutaneous biopsy of the suspected pheochromocytoma was avoided because of the risk of catecholamine-mediated hypertensive crisis and other procedure-related complications. Following biochemical and radiographic evaluation, the patient was scheduled for open left adrenalectomy with concurrent regional lymph node dissection

2.3. Special Studies, Surgical Pathology, and Molecular Findings

Intraoperative findings confirmed a large, friable left adrenal tumor adherent to the renal vein and surrounding retroperitoneal lymph nodes. Gross pathology revealed an 11 cm tumor with extensive areas of hemorrhage and necrosis. Microscopic examination showed large, confluent nests of tumor cells and diffuse growth patterns. Thin

fibrovascular bands impart a "nested" appearance to the tumor (Zellballen). The tumor cells were large, polygonal, with extensively vacuolated granular cytoplasm. Marked nuclear pleomorphism, hyperchromasia, and focal cellular spindling were observed (Figure 1 A, B, C). IHC was strongly positive for chromogranin A, synaptophysin, and GATA3, with sustentacular cells showing S100 positivity, confirming the diagnosis of pheochromocytoma. The Ki-67 proliferative index was moderate at 12%. Two of the eleven resected lymph nodes confirm metastatic pheochromocytoma, corroborating the high-risk molecular profile. Pathologic differential diagnosis included composite pheochromocytoma or metastatic disease from another primary, both of which were excluded by negative cytokeratin and melanocytic markers. Periadrenal fat infiltration and lymphovascular invasion were noted.

Molecular testing detected a somatic SDHB p.Arg46Gln variant in the tumor. No germline variant was identified, so there was no evidence for an inherited SDHB mutation. This pattern was therefore consistent with a sporadic or apparently sporadic pheochromocytoma, although the tumor remains genetically driven.

2.4. Post-Operative Treatment, Outcome, and Follow-Up

Post-operatively, blood pressure normalized without antihypertensive medications. Life-long surveillance with periodic metanephrine testing and CT/MRI imaging was recommended. Follow-up at 12 months showed a partial response with a reduction of pulmonary nodules. At 28 months post-treatment, she remained clinically well, with stable residual lung nodules measuring less than 1 cm, no new metastases, and plasma metanephrine persistently within normal range. Annual surveillance imaging and metanephrine levels were recommended.

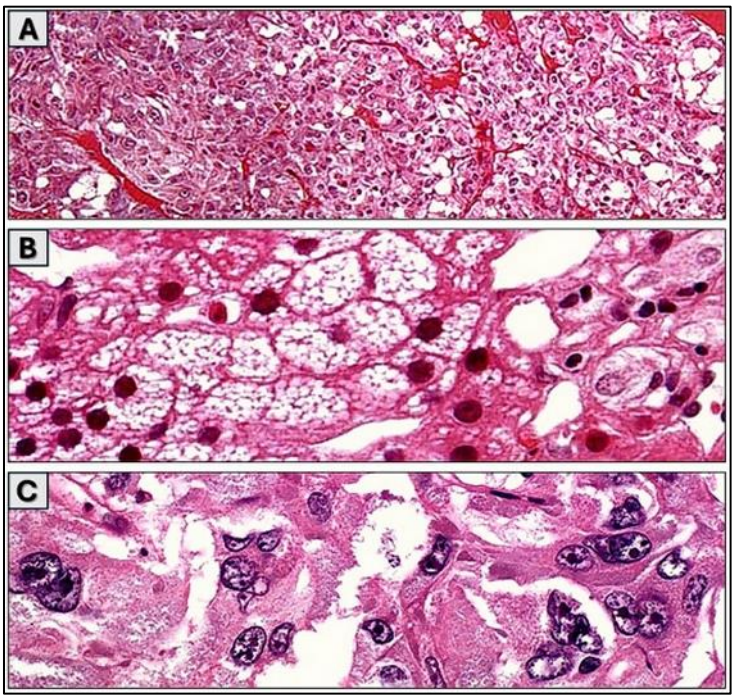

Figure 1 Microscopic findings of the excised pheochromocytoma

- 1A: Low-power view showing large, confluent nests of tumor cells and a diffuse growth pattern. Thin fibrovascular bands impart a "nested" appearance to the tumor (Zellballen). (H&E stain X20).
- 1B: Intermediate power view showing large polygonal cells with extensive granular vacuolation (H&E stain X40).
- 1C: High power view showing marked nuclear pleomorphism, hyperchromasia, and focal cellular spindling (H&E stain X60).

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

The name "pheochromocytoma" was introduced by Ludwig Pick in 1912, after he observed that tumor tissue turned dark brown when exposed to chromium salts. This coloration indicated catecholamine oxidation within chromaffin cells and acted as an early diagnostic sign. [5,10] Patients with pheochromocytoma commonly experience episodes characterized by heightened sympathetic nervous system activity, leading to sudden increases in blood pressure along with intense headaches, excessive sweating, heart palpitations, and pallor. While the majority of pheochromocytomas arise in the adrenal glands, tumors found outside this region are referred to as paragangliomas. [10]

The medical community has generally shifted away from using the terms "benign" and "malignant" to describe pheochromocytoma. Because no histological grading, including pheochromocytoma of the adrenal gland scaled score (PASS), is 100% reliable, official guidelines from bodies like the Endocrine Society classify all pheochromocytomas as having some metastatic potential. This necessitates lifelong biochemical and clinical follow-up for all patients. [3] The World Health Organization's (WHO) latest classification of endocrine tumors recognizes pheochromocytomas and paragangliomas associated tumors with varying metastatic potential rather than strictly classifying them as benign or malignant. This approach highlights risk stratification based on genetic influences, tumor location, and clinical features. [5]

The estimated annual incidence is 2-8 cases per million people, with an increasing prevalence attributed to advancements in abdominal imaging techniques and enhanced biochemical screening practices. [4,5] Pheochromocytomas are typically diagnosed in individuals during their third to fifth decades of life but can occur at any age. The average diagnostic age is about 24.9 years for hereditary cases and 43.9 years for sporadic occurrences. There is no significant difference in incidence by gender. [2]

Environmental or occupational risk factors remain poorly understood. About 10-20% of pheochromocytomas demonstrate metastatic potential; however, most are localized, unilateral tumors that primarily secrete catecholamines and infrequently produce other hormones, such as erythropoietin (EPO). [11] Pheochromocytomas generally exhibit a predominant catecholamine pattern; about half primarily secrete epinephrine, with varying levels of norepinephrine. Other types, such as sympathetic paragangliomas, mainly produce norepinephrine, with dopamine as a by-product.

Around 90% of pheochromocytomas and paragangliomas (PPGLs) originate from the adrenal medulla, physiologically stimulated by acetylcholine, while approximately 10% extra-adrenally within sympathetic ganglia or at multiple sites. [12] Roughly two-thirds of pheochromocytomas develop spontaneously without a known family history; nonetheless, genetic factors could still influence these cases.

3.2. Pathogenesis, Pathophysiology

A pheochromocytoma arising from adrenal medullary chromaffin cells, producing catecholamines autonomously, explains the patient's episodic headaches, diaphoresis, palpitations, severe hypertension, orthostasis, weight loss, and perioperative hemodynamic risk. Malignant behavior in pheochromocytoma is defined not by cytologic atypia alone but by metastasis to sites lacking normal chromaffin tissue, including lymph nodes and lungs, as occurred in this case. [4,13] The tumor showed several biologic features associated with aggressive behavior: large size, necrosis, lymphovascular and periadrenal fat invasion, moderately elevated Ki-67 index, and nodal metastasis. [13]

The somatic SDHB p. Arg46Gln variant provided a plausible molecular driver despite negative germline testing. Loss or impairment of succinate dehydrogenase complex activity promotes succinate accumulation, inhibits α-ketoglutarate-dependent dioxygenases, stabilizes hypoxia-inducible pathways, and dysregulates epigenetics, angiogenesis, invasion, and metastatic potential. [7] Clinically, this biology correlated with a predominantly noradrenergic phenotype, large tumor burden, and pulmonary dissemination. Thus, the case illustrated how an apparently sporadic pheochromocytoma could still behave as a genetically driven, pseudohypoxic, metastatic neuroendocrine malignancy.

3.3. Comparative Analysis of Our Case with Existing Literature

This case shared several features with reported cohorts of metastatic pheochromocytoma/paraganglioma. In the National Institutes of Health series of 132 metastatic cases, approximately 10–20% of PPGLs were metastatic, 45% were apparently sporadic, and most primary metastatic tumors were larger than 4.5 cm; common metastatic sites included lymph nodes, bone, lung, and liver. [13] Our patient's 11 cm adrenal primary, nodal involvement, and pulmonary metastases therefore aligned closely with established high-risk patterns. The presentation also paralleled consensus

descriptions of SDHB-driven disease, in which succinate accumulation and pseudohypoxia promote recurrence, invasion, and metastasis. [7]

However, unlike many SDHB-associated reports, this patient had no germline pathogenic variant, making the tumor apparently sporadic while still harboring a somatic SDHB alteration. This distinction is clinically important because metastatic adult PPGLs may be divided between hereditary SDHB-associated disease and apparently sporadic tumors, with better survival reported in the latter group. [13]

Compared with recent reports of pulmonary metastatic PPGL, our case was less fulminant. Charles et al. described adolescents with extensive lung metastases, hypoxemia, and treatment challenges related to catecholamine excess and hypoxia-driven tumor biology. [8] Zhang et al. reported a 40-year-old patient with SDHB-mutated metastatic paraganglioma and diffuse lung metastases who required systemic cyclophosphamide, vincristine, and dacarbazine (CVD) chemotherapy and achieved a durable partial response. [14] In contrast, our patient improved biochemically after surgical debulking and remained clinically stable with small residual pulmonary nodules, reinforcing the value of individualized, multidisciplinary management and careful surveillance. [9]

4. What Have We Learned from This Case?

This case highlighted several practical lessons. First, the classic triad of episodic headache, palpitations, and diaphoresis, especially when accompanied by paroxysmal or resistant hypertension, should promptly raise suspicion for PPGL and trigger biochemical testing. Symptoms that worsen after beta-blockade further strengthen this concern. Current guidelines recommend plasma-free or urinary fractionated metanephrines as the initial tests and adrenergic blockade before surgery for functional tumors. [4]

Second, a large adrenal mass with necrosis, markedly elevated normetanephrine, pulmonary nodules, lymphadenopathy, and orthostatic hypotension should be treated as a catecholamine-secreting tumor until proven otherwise; percutaneous biopsy should generally be avoided unless PPGL has been biochemically excluded or the patient is appropriately prepared. [4]

Third, the absence of a germline mutation did not eliminate metastatic potential. Somatic SDHB alteration, high Ki-67, lymphovascular invasion, and nodal disease supported lifelong surveillance with metanephrines and cross-sectional or functional imaging. Finally, the favorable symptom control after resection demonstrated that cytoreductive surgery could provide meaningful clinical benefit by reducing catecholamine burden even when distant metastases made a cure unlikely. [9]

Abbreviations: Succinate dehydrogenase complex iron-sulfur subunit B (SDHB), Metaiodobenzylguanidine (MIBG); Immunohistochemistry (IHC); Pheochromocytoma of the adrenal gland scaled score (PASS); Pheochromocytomas and paragangliomas (PPGLs)

5. Conclusion

We report this case as it demonstrates that metastatic pheochromocytoma could present as an apparently sporadic adrenal tumor while retaining molecular features associated with aggressive SDHB-related biology. The patient's course highlighted the diagnostic danger of misattributing catecholamine spells to anxiety or essential hypertension, the importance of alpha-blockade and multidisciplinary planning, and the clinical value of tumor debulking for symptom control. For the medical community, this case serves as a practical reminder that metastatic potential should be integrated with clinicopathologic risk, not based on family history alone. Lifelong biochemical and radiologic surveillance remained essential, even after biochemical remission and radiographic stability.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations

Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.

Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

The present research work does not include any studies on animal or human subjects conducted by any of the authors. This study was conducted as a retrospective review of archival pathology material collected during routine clinical care. All data were fully de-identified prior to analysis.

Statement of informed consent

The patient was lost to follow-up, and all attempts to reach the patient were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

References

[1] Lehman KA, Zynger DL. Pheochromocytoma. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/adrenalpheochromocytoma.html. Accessed May 26th, 2026.

[2] National Cancer Institute. Pheochromocytoma and Paraganglioma Treatment (PDQ®)–Health ProfessionalVersion. https://www.cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq#link/_64_toc Updated: July 9, 2015. Accessed: February 12, 2017.

[3] Puneet K. Gupta; Bharat Marwaha. Pheochromocytoma. Treasure Island (FL): StatPearls Publishing; 2026 Jan. https://www.ncbi.nlm.nih.gov/books/NBK589700/

[4] Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young Jr WF. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2014 Jun 1;99(6):1915-42.

[5] Mete O, Asa SL, Gill AJ, Kimura N, de Krijger RR, Tischler A. Overview of the 2022 WHO classification of paragangliomas and pheochromocytomas. Endocr Pathol. 2022;33(1):90-114.

[6] Sarkadi B, Saskoi E, Butz H, Patocs A. Genetics of Pheochromocytomas and Paragangliomas Determine the Therapeutical Approach. Int J Mol Sci. 2022 Jan 27;23(3)

[7] Taïeb D, Nölting S, Perrier ND, Fassnacht M, Carrasquillo JA, Grossman AB, Clifton-Bligh R, Wanna GB, Schwam ZG, Amar L, Bourdeau I. Management of phaeochromocytoma and paraganglioma in patients with germline SDHB pathogenic variants: an international expert consensus statement. Nature Reviews Endocrinology. 2024 Mar;20(3):168-84.

[8] Charles KM, Nazari MA, Jha A, Talvacchio S, Kuo MJ, Patel M, Ling A, Alzahrani AS, Prodanov T, Derkyi A, Chen A. A case series of three patients with extensive lung metastatic pheochromocytoma/paraganglioma: evaluation, treatment challenges, and outcomes. Exploration of Endocrine and Metabolic Diseases. 2024 Nov 15;1(5):218-33.

[9] Fishbein L, Del Rivero J, Else T, Howe JR, Asa SL, Cohen DL, Dahia PL, Fraker DL, Goodman KA, Hope TA, Kunz PL. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and management of metastatic and/or unresectable pheochromocytoma and paraganglioma. Pancreas. 2021 Apr 1;50(4):469-93.

[10] Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. WHO Classification of Tumors of Endocrine Organs. 4th ed. Lyon: IARC Press; 2017.

[11] Ishizaki F, Taguchi T, Murata M, Hoshino S, Toba T, Takeda K, Tasaki M, Yamana K, Kasahara T, Hoshii T, Obara K. Long-term outcomes and prognostic factors of metastatic or recurrent pheochromocytoma and paraganglioma: a 20-year review in a single institution. Scientific Reports. 2024 Nov 2;14(1):26456.

[12] Kasper DL, Fauci AS, Hauser SL, et al. Harrison's Principles of Internal Medicine. New York, NY: McGraw-Hill Education; 2015

[13] Turkova H, Prodanov T, Maly M, Martucci V, Adams K, Widimsky Jr J, Chen CC, Ling A, Kebebew E, Stratakis CA, Fojo T. Characteristics and outcomes of metastatic SDHB and sporadic pheochromocytoma/paraganglioma: a National Institutes of Health study. Endocrine practice. 2016 Mar 1;22(3):302-14.

[14] Zhang C, Wei Y, Cheng K, Cao D. Durable and deep response to CVD chemotherapy in SDHB-mutated metastatic paraganglioma: case report. Frontiers in Endocrinology. 2024 Dec 18;15:1483516.