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Case Report

Two Cases of Composite Pheochromocytoma-Ganglioneuromas With Plasma Metanephrine Levels in the Subclinical Range Pheochromocytoma-Ganglioneuroma

Mayssam El Najjar, MD [1], Elie Naous, MD [1], Caroline Blake [1], Aysegul Bulut, MD [2], Alexander Perepletchikov, MD [3], Ann T. Sweeney, MD [4, *]

[1] *Department of Medicine, St Elizabeth's Medical Center, Brighton, Massachusetts*
[2] *Department of Medicine, Division of Endocrinology, Boston Medical Center, Boston, Massachusetts*
[3] *Professional Pathology Services, Professional Corporation, Hilton Head Hospital, Hilton Head Island, South Carolina*
[4] *Department of Medicine, Division of Endocrinology, St Elizabeth's Medical Center, Brighton, Massachusetts*

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ABSTRACT

Background/Objective: In <10% of cases, pheochromocytomas coexist with other tumors, most commonly ganglioneuromas, and are termed composite pheochromocytoma-ganglioneuromas. We present 2 cases of composite pheochromocytoma-ganglioneuromas and review the diagnosis and management of these rare tumors.

Case Report: Patient 1 and patient 2 were 35-year-old and 45-year-old woman, respectively. Patient 1 presented with a history of controlled hypertension and symptoms of anxiety along with palpitations, diaphoresis, and flushing. Patient 2 complained of abdominal pain and underwent abdominal computed tomography (CT) imaging. Patient 1 and patient 2 had metanephrine levels of 76 pg/mL and 61 pg/mL (normal <57 pg/mL), respectively, and normetanephrine levels of 161 pg/mL and 116 pg/mL (normal < 148 pg/mL), respectively. CT scans depicted right adrenal masses in both cases: patient 1 had a 2.3 × 2.6 cm mass measuring 36 Hounsfield units on noncontrast CT imaging and patient 2 had a 4.5 × 3.5 cm right adrenal mass measuring 73 Hounsfield units on contrast CT imaging. Both patients underwent laparoscopic robotic adrenalectomies without complications. The pathologic analyses of both cases revealed composite pheochromocytoma-ganglioneuroma tumors. Surveillance at 1 year in both patients demonstrated no evidence of recurrence.

Discussion: The clinical and radiological presentation of composite pheochromocytoma-ganglioneuromas mirrors pheochromocytomas. The diagnosis relies on histopathological analysis. Treatment of pheochromocytoma-ganglioneuromas is complete surgical excision in a high-volume center with adrenal expertise and is associated with an overall excellent prognosis. The probability of recurrence is low, and distant metastases have rarely been reported.

Conclusion: Pheochromocytoma-ganglioneuromas may present with plasma metanephrine levels in the subclinical range. As with isolated pheochromocytomas, lifetime surveillance is critical for composite pheochromocytoma-ganglioneuromas.

Introduction

Pheochromocytomas are rare catecholamine-secreting tumors composed of the chromaffin cells of the adrenal medulla. In 1.5% to 9% of cases, pheochromocytomas may coexist with other developmentally related neurogenic tumors such as ganglioneuromas, neuroblastomas, ganglioneuroblastomas, or Schwannomas, and are termed composite pheochromocytomas.[1-4] Pheochromocytoma-ganglioneuroma is the most common composite pheochromocytoma.[3] There is limited information on these rare pheochromocytoma-ganglioneuroma tumors, and most of the available data originate from case reports, case series, and a few reviews.[3-10]

Abbreviations: CT, computed tomography; ULN, upper limit of normal.

* Address correspondence to Dr Ann T. Sweeney, Department of Medicine, Division of Endocrinology, St Elizabeth's Medical Center, 736 Cambridge Street, Brighton, MA 02135.
E-mail address: Ann.Sweeney@Steward.org (A.T. Sweeney).

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Herein we describe 2 cases of composite pheochromocytoma-ganglioneuroma and review the clinical presentation, diagnosis, and management of these unique tumors.

Case Report

Case 1

A 35-year-old woman with a history of controlled hypertension presented with anxiety associated with palpitations and diaphoresis. Her physical examination was unremarkable. Her laboratory evaluation showed metanephrine level of 78 pg/mL (normal, <57 pg/mL) and normetanephrine level of 161 pg/mL (normal, <148 pg/mL). Aldosterone, renin, dehydroepiandrosterone sulfate, and cortisol levels were unremarkable. An abdominal computed tomography (CT) scan showed a right adrenal mass measuring 2.3 × 2.3 × 2.6 cm (Fig. 1) with smooth margins measuring 36 Hounsfield units on noncontrast CT imaging with 0% relative and absolute washout on delayed imaging after intravenous contrast. In preparation for surgery, she was treated with volume repletion, and preoperative α- and β-adrenoreceptor blockade was initiated 7 to 10 days before surgery. She underwent a laparoscopic right robotic adrenalectomy without complications. Pathologic analysis revealed a 25 g, 5.7 × 3.8 × 2.7 cm tumor consistent with a composite of pheochromocytoma with a ganglioneuroma component. The pheochromocytoma comprised 90% of the tumor (Fig. 2). One month after surgery, her plasma metanephrine levels returned to normal and her spells no longer occurred. She was offered genetic testing but declined.

Case 2

A 54-year-old woman with no pertinent history presented for evaluation of an incidentally discovered 4.5 × 3.5 cm right adrenal mass seen on abdominal CT scan with intravenous contrast measuring 73 Hounsfield units, and on subsequent abdominal magnetic resonance imaging scan (Fig. 3) the mass had heterogeneous signal intensity without drop of signal on out-of-phase imaging. Metabolic studies revealed metanephrine and normetanephrine levels at 61 pg/mL (normal, <57 pg/mL), and 116 pg/mL (normal, <148 pg/mL), respectively. Aldosterone, renin, dehydroepiandrosterone sulfate, and cortisol levels were unremarkable. She was prepared for surgery with volume repletion, and preoperative α- and β-adrenoreceptor blockade were initiated 7 to 10 days before surgery. She underwent a laparoscopic right robotic adrenalectomy without complications. Pathologic analysis revealed a 59 g, 7.5 × 5.5 × 3.3 cm tumor composed of predominantly large, polygonal cells with abundant cytoplasm arranged in nested (zellballen) and trabecular architectural patterns intimately intermixed with mature ganglion cells with filamentous processes entrapped in collagenized stroma consistent with composite pheochromocytoma-ganglioneuroma (Fig. 4). Chromogranin A and synaptophysin stains were immunoreactive in the pheochromocytoma and ganglioneuroma components. S100 stain highlighted sustentacular cells and focal ganglion cells. Ki-67 stain demonstrated very low proliferative labeling index (<1%). Subsequent genetic testing revealed no germline pathogenic variants in *RET*, *VHL*, *NF1*, *SDHx*, *TMEM127*, and *MAX* genes. Surveillance at 1 year demonstrated no signs of recurrence.

Discussion

We present 2 cases occurring in women of nonfamilial, benign composite pheochromocytoma-ganglioneuroma with mildly elevated metanephrine levels. The diagnosis of a composite pheochromocytoma requires the complete architectural and cytologic phenotype of the neuroblastic tumor to be present in addition to the pheochromocytoma. At least 10% of the tumor must be composed of each component to diagnose the tumor as a composite pheochromocytoma. Prominent areas of Schwann cells are the hallmark findings that identify these tumors as composite pheochromocytomas. The ganglion cells are typically located adjacent to the Schwann cells. Composite pheochromocytomas are rare, with only 110 cases have been reported in a recent review of the world literature.[4] However, a cohort study from the Mayo Clinic reported that close to half (44%) of their patients with adrenal ganglioneuromas had composite pheochromocytoma-ganglioneuromas. The authors concluded that the association of pheochromocytoma with ganglioneuroma is frequent and the diagnosis of an adrenal ganglioneuroma should include biochemical testing for pheochromocytoma.[9] The authors noted the larger proportion of composite tumors in their study compared with others may have been due to underreporting, exclusion of composite tumors from prior studies, underrecognition of this entity, or possibly referral bias.

Pheochromocytoma-ganglioneuroma is the most common composite pheochromocytoma reported in 65% to 75% of cases.[3,4,8] Notably, the clinical and radiological presentation of the pheochromocytoma-ganglioneuroma composite tumor closely mirrors that of an isolated pheochromocytoma. The definitive diagnosis though relies on the histopathological analysis.[10,11] Histologically the composite tumor is composed of 2 distinct patterns with the pheochromocytoma component showing angular cells with granular, basophilic cytoplasm, arranged in nests or alveoli, surrounded by sustentacular cells whereas the ganglioneuroma component displays ganglion cells in fibrous stroma. The pheochromocytoma component is usually the dominant component in pheochromocytoma-ganglioneuroma composite tumors.[11] Immunohistochemical staining also helps to differentiate the tumors as pheochromocytomas exhibit robust staining for chromogranin A and synaptophysin, whereas ganglioneuromas display an affinity for S-100 protein and neurofilament antibody.[3]

The majority of the cases of pheochromocytoma-ganglioneuroma described in the literature are diagnosed between age 40 and 60 years. The frequency of occurrence is slightly higher in women (57% vs 43%).[7] Most (75%) of the composite tumors reported have been functional and demonstrated increased levels of catecholamines—59.6% adrenergic, 15.7% noradrenergic, and 24.7%

Highlights

- The clinical presentation closely mirrors that of isolated pheochromocytomas
- Treatment is complete surgical excision in a high-volume center with adrenal expertise
- The probability of recurrence is low and distant metastases have rarely been reported
- Lifelong surveillance is imperative for composite pheochromocytoma-ganglioneuromas

Clinical Relevance

In <10% of cases, pheochromocytomas coexist with other tumors, most commonly ganglioneuromas, termed composite pheochromocytoma-ganglioneuromas. We present 2 cases of composite pheochromocytoma-ganglioneuromas and review the diagnosis and management of these rare tumors.

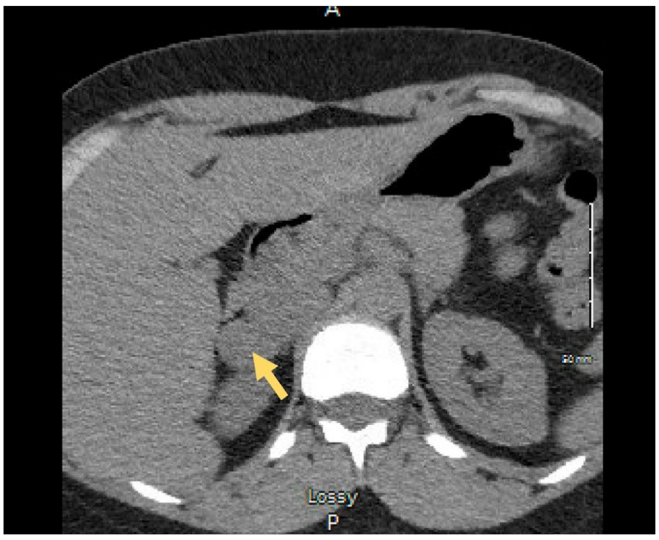

Fig. 1. Adrenal washout computed tomographic scan before administration of contrast medium, showing a right adrenal mass.

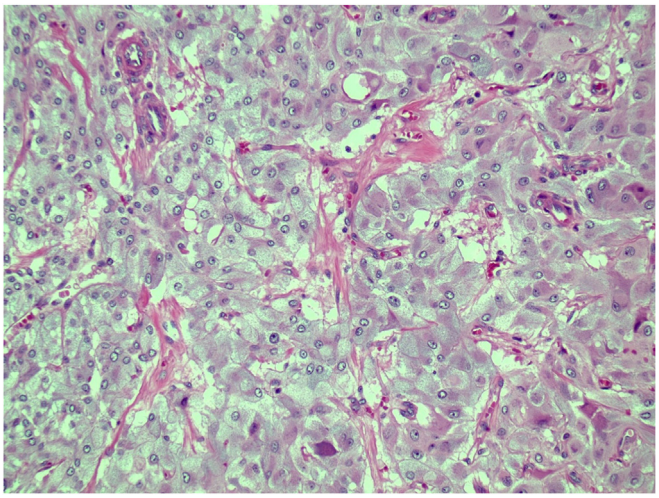

Fig. 2. Classic zellballen pattern of pheochromocytoma, H&E, x200. *H&E*, hematoxylin and eosin.

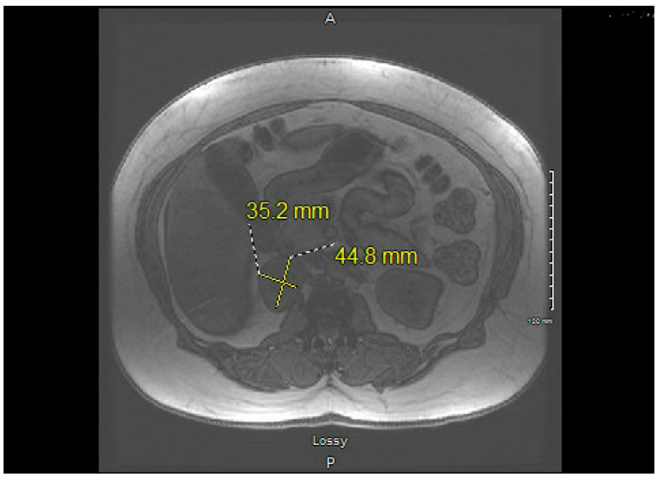

Fig. 3. Adrenal magnetic resonance imaging showing the 4.5 × 3.5 cm right adrenal mass.

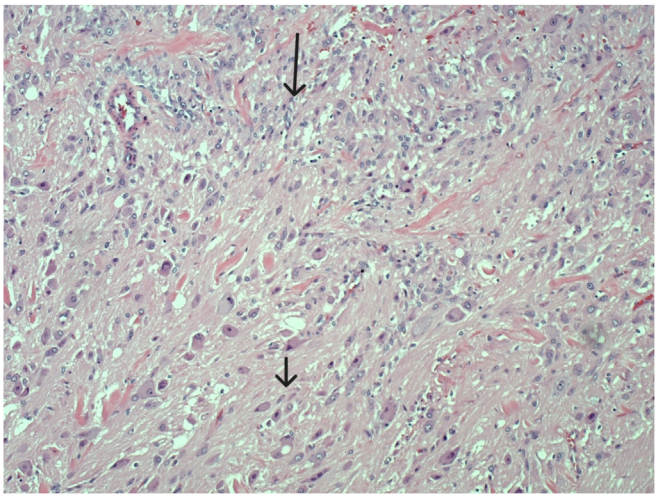

Fig. 4. Pheochromocytoma (upper image/long arrow) intimately intermixed with ganglion cells within fibrotic stroma (midinferior image/short arrow), H&E, x100. *H&E*, hematoxylin and eosin.

nonfunctional.[4] To our knowledge, levels of catecholamines and metanephrines in pheochromocytoma-ganglioneuroma have not been systematically compared with those of isolated pheochromocytomas, but our 2 pheochromocytoma-ganglioneuroma cases had an adrenergic phenotype with mildly elevated plasma metanephrine levels—symptomatic patient 1 had metanephrine levels that were 1.36 times the upper limit of normal (ULN) and normetanephrine levels 1.08 times the ULN, whereas asymptomatic patient 2, with an incidentally discovered composite tumor, had metanephrine levels that were 1.07 times the ULN with normal normetanephrine levels. In retrospective analyses, symptomatic and incidental pheochromocytomas have metanephrine levels that are 13.8 and 6.4 times the ULN, respectively.[12] According to Endocrine Society clinical guidelines, plasma metanephrine levels that are twice the ULN are considered a positive screen for pheochromocytoma.[13,14] The mildly elevated metanephrine levels in our patients are consistent with levels seen in patients with subclinical pheochromocytoma though both tumors were larger (and without hemorrhagic or necrotic areas) than those typically seen in patients with subclinical or silent pheochromocytoma and one of our patients was clinically symptomatic. We found only one other case report of a composite pheochromocytoma-ganglioneuroma that was described as a subclinical pheochromocytoma, though many of the case series and reports do not detail metanephrine levels but merely categorize them as functional or nonfunctional.[10] Subclinical pheochromocytomas are most often asymptomatic, detected incidentally, and the metanephrine levels are less than twice the ULN.[15] Factors that are associated with subclinical pheochromocytomas include false negative screening, small (<3 cm) tumor size, large tumor size with extensive necrosis, cystic change, and hemorrhage as well as a deficiency of requisite enzymes for catecholamine synthesis or metabolism such as tyrosine hydroxylase and dopamine B-hydroxylase respectively.[15,16] The tumor size of case 1 was small consistent with a subclinical pheochromocytoma. No special stains were performed to ascertain whether a deficiency in catecholamine metabolic enzymes could possibly explain the lower levels of metanephrines.

Pheochromocytoma-ganglioneuromas have been reported to also secrete vasoactive intestinal peptide and cause the watery

diarrhea, hypokalemia, and achlorhydria syndrome more commonly than pheochromocytomas.[3,17] The majority of pheochromocytoma-ganglioneuroma composite tumors occur sporadically, but a genetic syndrome is associated with them in 16.9% of cases.[4] Neurofibromatosis type 1 is the most common associated genetic syndrome occurring in 10.8% of cases, followed by multiple endocrine neoplasia type 2A and von Hippel-Lindau disease each occurring in 2.4% of cases, and multiple endocrine neoplasia type 2B occurring in 1.2% of cases.[4] Both of our patients were female, with the first case exhibiting classic pheochromocytoma symptoms, whereas the second case presented with an incidentally detected adrenal mass. The vast majority of pheochromocytoma-ganglioneuromas occur unilaterally and a recent comprehensive review reported only 3.6% occur bilaterally.[4]

The definitive treatment for pheochromocytoma-ganglioneuromas is complete surgical excision of the tumor which is associated with an overall excellent prognosis. Like pheochromocytomas, patients need to be treated with volume repletion and a high salt intake before surgery and then appropriately treated with α- and β-adrenoreceptor blockade 7 to 10 days before surgery. A multidisciplinary team should follow the patient in a high-volume center with adrenal expertise and have a highly experienced surgeon and anesthesia team.[13] The probability for recurrence is extremely low though distant metastases have rarely been reported.[4] In the largest published study, 83.9% of patients diagnosed with pheochromocytoma-ganglioneuroma remained free from disease, 9.7% died due to the disease itself, an additional 5.8% died of unrelated causes, and 1% were alive with disease. Nine patients (8.2%) had metastases.[4] Therefore, lifetime surveillance is critical in these patients and they should be followed yearly with plasma metanephrines.[13,14] All patients with pheochromocytoma should also receive genetic counseling and genetic testing.[13]

Conclusion

Composite pheochromocytoma-ganglioneuromas resemble isolated pheochromocytomas clinically and radiologically. Biochemically the pheochromocytoma-ganglioneuromas we report had mildly elevated plasma metanephrine levels consistent with those typically seen in subclinical pheochromocytomas. Further studies are needed to explore plasma metanephrine levels in composite pheochromocytoma-ganglioneuromas. The definitive treatment for pheochromocytoma-ganglioneuromas is complete surgical excision and is associated with an overall excellent prognosis. The probability of recurrence is low, and distant metastases have rarely been reported. As with isolated pheochromocytomas, lifetime surveillance is critical for composite pheochromocytoma-ganglioneuromas.

Patient Consent

Patient consent was obtained.

Disclosure

A.T.S. is on the Editorial Board of *AACE Clinical Case Reports* and is currently a guest editor. The other authors have no conflicts of interest to disclose.

References

1. Linnoila RI, Keiser HR, Steinberg SM, Lack EE. Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. *Hum Pathol*. 1990;21(11):1168–1180. https://doi.org/10.1016/0046-8177(90)90155-x
2. Lam AK. Update on adrenal tumours in 2017 World Health Organization (WHO) of endocrine tumours. *Endocr Pathol*. 2017;28(3):213–227. https://doi.org/10.1007/s12022-017-9484-5
3. Khan AN, Solomon SS, Childress RD. Composite pheochromocytoma-ganglioneuroma: a rare experiment of nature. *Endocr Pract*. 2010;16(2):291–299. https://doi.org/10.4158/EP09205.RA
4. Costa J, Jácome M, Souteiro P, Santos C, Cunha AL. Composite pheochromocytoma of the adrenal gland-a review of published cases. *Virchows Arch*. 2023;483(2):267–275. https://doi.org/10.1007/s00428-023-03492-y
5. Mahajan H, Lee D, Sharma R, et al. Composite phaeochromocytoma-ganglioneuroma, an uncommon entity: report of two cases. *Pathology*. 2010;42(3):295–298. https://doi.org/10.3109/00313021003636451
6. Kikuchi Y, Wada R, Sakihara S, Suda T, Yagihashi S. Pheochromocytoma with histologic transformation to composite type, complicated by watery diarrhea, hypokalemia, and achlorhydria syndrome. *Endocr Pract*. 2012;18(4):e91–e96. https://doi.org/10.4158/EP11370.CR
7. Araujo PB, Carvallo MS, Vidal AP, et al. Case report: composite pheochromocytoma with ganglioneuroma component: a report of three cases. *Front Endocrinol (Lausanne)*. 2022;13(13):903085. https://doi.org/10.3389/fendo.2022.903085
8. Dhanasekar K, Visakan V, Tahir F, Balasubramanian SP. Composite phaeochromocytomas-a systematic review of published literature. *Langenbecks Arch Surg*. 2022;407(2):517–527. https://doi.org/10.1007/s00423-021-02129-5
9. Dages KN, Kohlenberg JD, Young Jr WF, et al. Presentation and outcomes of adrenal ganglioneuromas: a cohort study and a systematic review of literature. *Clin Endocrinol (Oxf)*. 2021;95(1):47–57. https://doi.org/10.1111/cen.14460
10. Chee YJ, Teo CHY, Au RTM, Kon YC. Subclinical phaeochromocytoma: a diagnostic and management challenge. *BMJ Case Rep*. 2022;15(4):e248571. https://doi.org/10.1136/bcr-2021-248571
11. Shawa H, Elsayes KM, Javadi S, Sircar K, Jimenez C, Habra MA. Clinical and radiologic features of pheochromocytoma/ganglioneuroma composite tumors: a case series with comparative analysis. *Endocr Pract*. 2014;20(9):864–869. https://doi.org/10.4158/EP14010. OR
12. Gruber LM, Hartman RP, Thompson GB, et al. Pheochromocytoma characteristics and behavior differ depending on method of discovery. *J Clin Endocrinol Metab*. 2019;104(5):1386–1393. https://doi.org/10.1210/jc.2018-01707
13. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(6):1915–1942. https://doi.org/10.1210/jc.2014-1498
14. Nölting S, Bechmann N, Taieb D, et al. Personalized management of pheochromocytoma and paraganglioma. *Endocr Rev*. 2022;43(2):199–239. https://doi.org/10.1210/endrev/bnab019
15. Mannelli M, Lenders JW, Pacak K, Parenti G, Eisenhofer G. Subclinical phaeochromocytoma. *Best Pract Res Clin Endocrinol Metab*. 2012;26(4):507–515. https://doi.org/10.1016/j.beem.2011.10.008
16. Kumar S, Wu K, Rodrigo N, Glover A. Massive biochemically silent pheochromocytoma masquerading as nonfunctioning adrenocortical cancer. *JCEM Case Rep*. 2023;1(3):luad061. https://doi.org/10.1210/jcemcr/luad061
17. Yee SK, Meyer JH, Wong LL. Vasoactive intestinal peptide-secreting pheochromocytoma: a case report and review of literature. *AACE Clin Case Rep*. 2022;8(4):158–162. https://doi.org/10.1016/j.aace.2022.03.003