Surgery 165 (2019) 228–231

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Multifocal pheochromocytoma-paraganglioma in a 29-year-old woman with cyanotic congenital heart disease ☆

Susan M. Wcislak, MD[a], William S. King, MD[b], Benjamin R. Waller III, MD[c], Natasha Goins, APRN[a], Paxton V. Dickson, MD[a,*]

[a] University of Tennessee Health Science Center, Department of Surgery, Division of Surgical Oncology, Memphis TN
[b] Memphis Surgical Associates, Memphis TN
[c] University of Tennessee Health Science Center, Department of Pediatrics, Division of Cardiology, Memphis TN

ARTICLE INFO

Article history:
Accepted 28 August 2018
Available online 16 October 2018

ABSTRACT

Background: Multifocal pheochromocytoma/paraganglioma presenting at an early age is commonly associated with a hereditary syndrome.
Case Report: A 29-year-old woman was referred for evaluation of multifocal pheochromocytoma/paraganglioma. Interestingly, her family history did not include pheochromocytoma/paraganglioma, and comprehensive genetic testing for the well-documented pheochromocytoma/paraganglioma susceptibility genes was negative. Of note, this patient had a history of a complex cardiac defect resulting in cyanotic congenital heart disease and had never undergone operative repair. Thus she lived in a chronic hypoxic state with a baseline oxygen saturation of about 80%. Laboratory evaluation found marked increases in plasma norepinephrine and normetanephrines with normal epinephrine and metanephrines. Imaging revealed 4 aortocaval masses and a right adrenal mass. After appropriate preoperative preparation she underwent successful resection of each of the neoplasms, with pathologic testing revealing multifocal pheochromocytoma/paraganglioma.
Discussion: This case highlights a growing recognition of the potential development of pheochromocytoma/paraganglioma in patients with cyanotic congenital heart disease. The underlying pathophysiology and phenotypic similarities between pheochromocytoma/paraganglioma in patients with cyanotic congenital heart disease and those with mutations that lead to cellular pseudohypoxia are reviewed.
© 2018 Elsevier Inc. All rights reserved.

Introduction

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are neuroendocrine neoplasms arising from chromaffin tissue of the adrenal medulla and extra-adrenal paraganglia. The clinical presentation of patients with PHEO/PGL may be indicative of a sporadic neoplasm or arising as part of an inherited syndrome with a known germline mutation.[1]

Cyanotic congenital heart disease (CHD) refers to a group of cardiac defects that result in hypoxia secondary to compromised pulmonary blood flow and mixing of pulmonary and systemic venous blood. Cyanotic CHD is reported to occur in approximately 0.1% of live births,[2] and the majority of patients born in the United States undergo repair during childhood to avoid chronic hypoxia.

Over the last several years there has been an increased understanding of the influence that hypoxia-induced cellular pathways have in PHEO/PGL tumorigenesis.[3-5] There is a small body of literature drawing a potential correlation of hypoxia from cyanotic CHD and the development of PHEO/PGL.[6-10] Herein we report a case of a young woman with cyanotic CHD presenting with multifocal PHEO/PGL. We further discuss similarities identified between these patients and PHEO/PGL in patients with gene mutations that cause pseudohypoxia, such as *VHL* and *SDHx*.

Case presentation

A 29-year-old woman was referred for surgical evaluation of intra-abdominal PGL. Prereferral computed tomography (CT) indicated 4 hypervascular, para-aortic masses and a similar appearing right adrenal mass (Fig 1, *A* and *B*). She had also undergone percutaneous biopsy of the largest lesion, with pathologic testing

☆ Presented at the 39th Annual Meeting of the American Association of Endocrine Surgeons, Macy 6–8, 2018, Durham, NC.

* Corresponding author: Department of Surgery, Division of Surgical Oncology, University of Tennessee Health Science Center, 910 Madison Ave., Suite 301, Memphis, TN 38163. Tel.: (901) 448-2919; fax: (901) 448-1498.
E-mail address: pdickso1@uthsc.edu (P.V. Dickson).

https://doi.org/10.1016/j.surg.2018.08.033
0039-6060/© 2018 Elsevier Inc. All rights reserved.

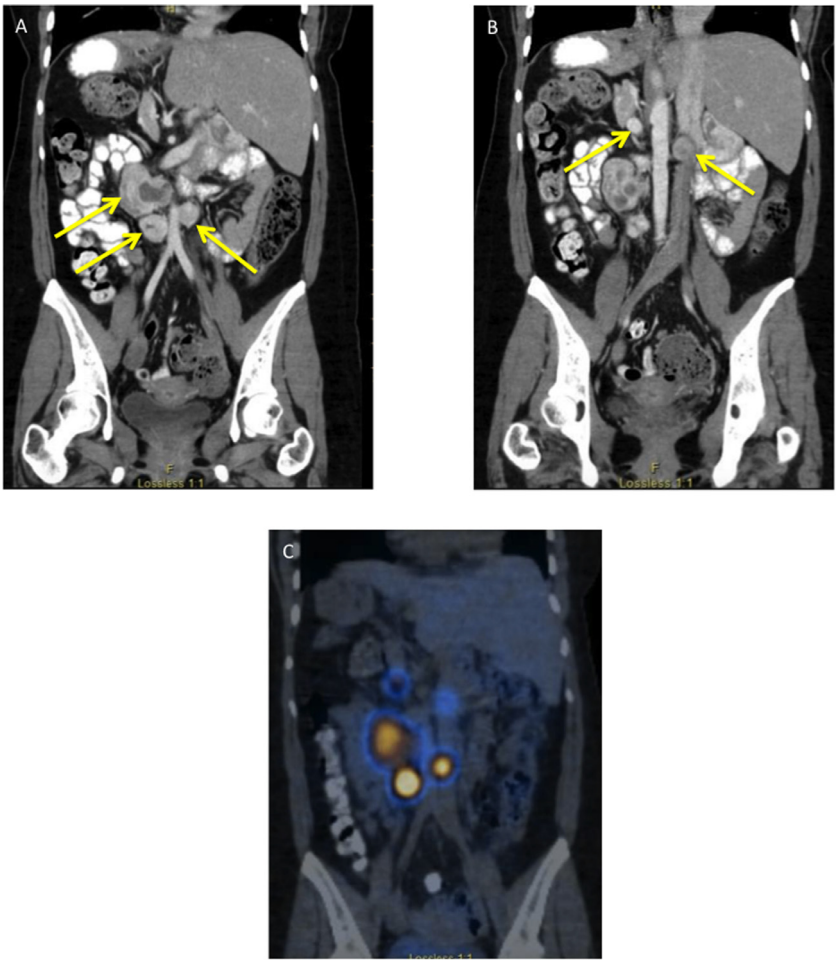

Fig 1. (*A* and *B*) Computed tomography (CT) showing 4 aortocaval hypervascular masses, a right adrenal mass, and situs inversus anatomy. (*C*) Metaiodobenzylguanidine imaging indicated activity in each of the lesions seen on CT but no further sites of disease.

revealing "cellular changes consistent with paraganglioma" with positive immunostaining for chromogranin A and S100.

At presentation, her only complaints were mild abdominal discomfort and intermittent diaphoresis; she denied palpitations, severe headaches, and hypertension. Of note, her medical history was pertinent for complex cyanotic CHD. She was born with situs inversus with congenitally corrected transposition of the great vessels, a large ventricular septal defect, and severe pulmonary valvular stenosis. The family had opted not to have the defect corrected, and thus she had lived with chronic cyanosis with a baseline oxygen saturation of about 80%. Interestingly, 4 years before referral, she had undergone thoracotomy with resection of a mediastinal paraganglioma at an outside institution; no abdominal imaging was obtained at that time. The patient and her mother denied any family history of PHEO/PGL or other endocrinopathies. On physical examination she was healthy appearing, with a pulse of 85, blood pressure of 113/75, and O_2 saturation of 79%. Her neck was supple with no cervical masses. Cardiac examination revealed a prominent systolic ejection murmur. She had peripheral cyanosis with mild clubbing and no extremity edema. Her lungs were clear, and the abdomen was soft and benign with no palpable masses.

Laboratory evaluation revealed increases in plasma norepinephrine of 2021 pg/mL (normal 80–520 pg/mL) and normetanephrine of 21.85 mmol/L (0–0.89 mmol/L), normal plasma epinephrine and metanephrines, and an increased chromogranin A of 451 units (normal 0–95 units). CT examination of the neck and chest did not indicate any cervical or thoracic lesions. Metaiodobenzylguanidine (MIBG) scan revealed activity in the aortocaval and adrenal masses seen on abdominal CT but identified no additional lesions (Fig 1, *C*). Given the presentation of a young patient with multifocal PHEO/PGL, we were concerned for a potential germline mutation. Comprehensive genetic testing for *VHL, SDHB, SDHD, SDHA, SDHC, NF1, RET, MEN1, FH, MAX*, and *TMEM127* was negative.

In preparation for operating, the patient was initiated on selective $\alpha 1$ blockade with subsequent β blockade and received preoperative volume expansion executed in close coordination with her cardiologist. She then underwent exploration with performance of a cortical-sparing right adrenalectomy and resection of the aortocaval masses. At operation, these lesions were well encapsulated and did not demonstrate any substantial peritumoral desmoplasia or extension into surrounding soft tissue. On histopathologic examination the tumors consisted of compact, organized epithelioid cells that stained positive for chromogranin A, neuron-specific enolase, and synaptophysin. Aggressive histologic features, such as nuclear polymorphism, obvious vascular invasion, or internal necrosis, were not identified. Her postoperative course was uneventful, and at 1 year after resection, biochemical evaluation and cross-sectional imaging revealed no evidence of recurrent disease. Just before the drafting of this manuscript, the patient underwent a left bidirectional cavopulmonary anastomosis from which she has recovered well. At her first postoperative visit after this operation, her resting oxygen saturation was 87%.

Discussion

PHEO/PGL are rare neuroendocrine neoplasms that arise from the adrenal medulla and extra-adrenal autonomic paraganglia, respectively. Although the majority of PHEO/PGL are sporadic, up to 40% may be associated with a hereditary syndrome.[11] For patients presenting at a young age or with multifocal tumors, a thorough family history, genetic counseling, and consideration of an analysis of germline mutations should be pursued owing to the implications to other family members.[1] Although the association of pheochromocytoma with Von Hippel–Lindau syndrome (VHL), multiple endocrine neoplasia type 2, and neurofibromatosis type 1 (NF1) has been known for some time, a number of additional PHEO/PGL susceptibility genes have been defined over the last 2 decades. Most notably, mutations in genes coding for subunits of the enzyme mitochondrial succinate dehydrogenase (SDH) have led to characterization of specific hereditary PGL syndromes with well-defined genotype-phenotype correlations.[12] Furthermore, recent genomic expression profiling has led to classification of PHEO/PGL into the following 4 subtypes based on driver mutations: a pseudohypoxia cluster including *VHL, SDHx*, and *HIF2A*; a kinase signaling cluster including *RET, NF1, TMEM127, MAX*, and *HRAS*; a Wnt-altered group including *WNT4, DVL3*, and *CHGA*; and a cortical admixture subtype.[13]

With our patient's history of a mediastinal PGL and the hypervascular appearance of the adrenal and para-aortic tumors on contrast-enhanced CT, the plasma or urinary biochemical evaluation would have been sufficient to make a diagnosis. Our patient had actually undergone prereferral biopsy. This is an important point to discuss because of the risk of inciting a hypertensive crisis during needle biopsy of PHEO/PGL; it is important that patients with a hypervascular adrenal or retroperitoneal mass be evaluated with plasma or 24-hour urinary fractionated metanephrines and catecholamines before or in lieu of a biopsy. Biopsy should be reserved for cases in which there is no clinical or biochemical evidence of catecholamine secretion and only when a tissue diagnosis will alter the treatment.

Given the age, distribution of tumors, and biochemical profile of our patient, we had a high level of suspicion for PGL-4 syndrome (*SDHB* mutation). Comprehensive genetic testing, however, did not reveal a mutation of any SDH subunit gene or other gene mutations known to be associated with PHEO/PGL. Admittedly, we did not consider chronic hypoxia as the pathogenesis of her tumors until performing a literature search for PHEO/PGL in patients with cyanotic CHD.

A potential association of PHEO/PGL with cyanotic CHD was first described in 1964 in a case series of 5 patients from the Johns Hopkins Hospital.[14] Although the cellular physiology that might lead to development of PHEO/PGL in cyanotic patients had not been elucidated at that time, the authors postulated that chronic hypoxia might lead to adrenal medullary hyperplasia. Subsequent case reports of PHEO/PGL in patients with cyanotic CHD[6-10] have led to a growing recognition that their co-occurrence is more than coincidence. The link between cyanotic CHD and development of PHEO/PGL is probably best highlighted by Opotowsky et al.[10] In a population-based analysis, they found that hospitalized patients with cyanotic CHD had an increased likelihood of PHEO/PGL (odds ratio 6.0, 95% confidence interval 2.6–13.7, $P < .0001$) compared with those without CHD and that noncyanotic CHD patients had no greater risk (odds ratio 0.9, 95% confidence interval 0.7–1.2, $P = .48$). On review of the current literature, there does not appear to be one particular form of cyanotic CHD that is more closely associated with development of PHEO/PGL than others. Moreover, PHEO/PGL has been reported in patients with complex congenital heart defects as well as ventricular or atrial septal defects (simple defects) resulting in Eisenmenger syndrome.[6-10] That chronic hypoxia may predispose to the development of PHEO/PGL has also been recognized in reports of carotid body tumors among patients living at high altitudes.[15]

Although the mechanisms driving tumorigenesis in patients with chronic hypoxia are not fully elucidated, the presentation is phenotypically similar to those within the pseudohypoxia PHEO/PGL subtype.[13] In the report by Opotowsky et al,[10] patients with cyanotic CHD associated with PHEO/PGL presented at a young age (median 31.5 years), often had multifocal tumors, and a noradrenergic biochemical profile. This presentation is analogous to that found in our patient as well as other case reports of cyanotic CHD and PHEO/PGL.[6-9] That these clinical features mirror those often found in patients with *VHL* or *SDHx* mutations indicates they likely have related molecular pathogenesis. It is well described that development of PHEO/PGL in patients with *VHL* or *SDHx* mutations results from alterations of intracellular oxygen metabolism that cause "pseudohypoxia" and subsequent increased stability and cellular levels of hypoxia-induced factor 2α (HIF2α).[3-5] HIFs are involved in upregulation of several processes that result in tumor development, such as angiogenesis, cell migration, and degradation of the extracellular matrix.[5] It is postulated that HIF2α may influence certain chromaffin cell types at different locations or sympathoadrenal progenitor cells in a way that makes these cells more susceptible to mutations causing cellular hypoxia and affects tumor location and the specific catecholamines synthesized.[4] This concept is reflected in patterns of tumor location and secretion of norepinephrine (and dopamine) in patients with *VHL* and *SDHx* mutations. In a case reported by Zhao et al[9] of a 30-year-old patient with cyanotic CHD and multifocal PHEO/PGL, tissue from the resected neoplasm had marked HIF2α immunostaining. The role of HIF2α in PHEO/PGL tumorigenesis has been further confirmed by the recent identification of somatic *HIF2A* gene mutations resulting in multifocal PHEO/PGL, somatostatinomas, and polycythemia (Pacak-Zhuang syndrome).[16,17] Based on the similarities in clinical presentation, it seems reasonable to extrapolate that the mechanisms driving PHEO/PGL in patients with chronic hypoxia from cyanotic CHD parallel those found with *VHL, SDHx*, and *HIF2A* mutations.

The catecholamine secretory profile of PHEO/PGL is related to both tumor location and genotype. Whereas PHEOs secrete both normetanephrine and metanephrine, PGLs predominantly secrete normetanephrine. The enzyme phenylethanolamine N-methyltransferase, which converts norepinephrine to epinephrine, requires cortisol as a cofactor, explaining the noradrenergic secretion found in sympathetic extra-adrenal PGLs.[18] It is important, however, to appreciate that unlike sporadic, multiple endocrine neoplasia type 2 and NF1-associated PHEOs, VHL-associated PHEOs have a predominantly noradrenergic secrotype. This is, in part, because of decreased expression of phenylethanolamine N-methyltransferase in VHL-associated PHEOs.[19] Of note, our patient did have one intra-adrenal lesion but had normal plasma epinephrine and metanephrines levels. Moreover, 7 of the 20 patients in the series by Opotowsky et al[10] had an isolated PHEO and in each case had only noradrenergic secretion. These observations further illustrate that the phenotypic similarities identified between PHEO/PGL in patients with chronic hypoxia and those with *VHL* and *SDHx* mutations are likely related to similar alterations at a molecular level.

Another clinical point worth noting is that the preferred imaging for patients with PHEO/PGL has evolved over the last decade. Although the MIBG scan correlated with the CT and intraoperative findings in our patient, the functional imaging modality of choice for a patient like ours or in the setting of an *SDHx* mutation is currently (^{68}Ga)-DOTATATE positron emission tomography/CT.[20,21] If this study is not readily available, an 18F-fluordeoxyglucose positron emission tomography/CT would be preferred over MIBG.[20]

That hypoxia appears to be the driving mechanism in the development of PHEO/PGL in patients with cyanotic CHD raises certain questions. For instance, if hypoxia is reversed by correction of the cardiac anomaly, are patients protected from the future development of chromaffin cell neoplasms? Furthermore, if hypoxia is corrected, will established neoplasms regress spontaneously? Based on previous reports, PHEO/PGL may be diagnosed several years after the operative correction of the cardiac defect and after long periods without cyanosis,[7,10] but it is unclear if there is a critical duration or severity of hypoxia that results in the physiologic insult leading to persistent tumorigenesis. It is also unknown if there are certain patients with cyanotic CHD who have other factors predisposing them to the development of PHEO/PGL. Interestingly, there is at least 1 case of regression of bilateral carotid body tumors identified in a patient with hypoxemic pulmonary disease after treatment and improved oxygenation.[22] Based on the relatively limited reporting of PHEO/PGL in association with cyanotic CHD and chronic hypoxia, these mechanistic questions remain unanswered. Continued understanding of the molecular pathogenesis of PHEO/PGL, particularly in patients with *VHL*, *SDHx*, and *HIF2A* mutations, may uncover these and other unknowns in this relatively unique clinical scenario.

The present case adds to accumulating evidence suggesting that patients with cyanotic CHD have an increased risk for developing PHEO/PGL. Certainly, without screening a large population of such patients, it is impossible to understand the true incidence of PHEO/PGL within this group of individuals. We are not aware of any reported procedure-related or intraoperative adverse hemodynamic occurrences in patient with cyanotic CHD with an undiagnosed PHEO/PGL, but it seems prudent to evaluate for PHEO/PGL before invasive procedures or operations in patients with cyanotic CHD, similar to that performed in patients with a new diagnosis of medullary thyroid cancer. Our patient has recently undergone left bidirectional cavopulmonary anastomosis with a resultant improvement in her baseline oxygen saturation, although she remains mildly hypoxic. Whether improvement of hypoxia at such a late stage will prevent development of further PHEO/PGL is unclear. For now, our plan for this patient is to continue annual biochemical and radiographic surveillance.

References

1. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99:1915–1942.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39:1890–1900.
3. Vicha A, Taieb D, Pacak K. Current views on cell metabolism in SDHx-related pheochromocytoma and paraganglioma. *Endocr Relat Cancer*. 2014;21:R261–R277.
4. Richter S, Qin N, Pacak K, Eisenhofer G. Role of hypoxia and HIF2alpha in development of the sympathoadrenal cell lineage and chromaffin cell tumors with distinct catecholamine phenotypic features. *Adv Pharmacol*. 2013;68:285–317.
5. Jochmanova I, Yang C, Zhuang Z, Pacak K. Hypoxia-inducible factor signaling in pheochromocytoma: turning the rudder in the right direction. *J Natl Cancer Inst*. 2013;105:1270–1283.
6. Singh GD, Anuradha S, Sethi P, Singla S, Saran RK, Dewan R. Pheochromocytoma and tetralogy of Fallot: coincidence or a rare association? *Asian Cardiovasc Thorac Ann*. 2016;24:75–77.
7. Kita T, Imamura T, Date H, Kitamura K, Moriguchi S, Sato Y, et al. Two cases of pheochromocytoma associated with tetralogy of Fallot. *Hypertens Res*. 2003;26:433–437.
8. Kasaliwal R, Sarathi V, Pandit R, Budyal SR, Bukan A, Kakade H, et al. Pheochromocytoma and tetralogy of Fallot: a rare but potentially dangerous combination. *Endocr Pract*. 2014;20:e80–e85.
9. Zhao B, Zhou Y, Zhao Y, Zhao Y, Wu X, Bi Y, et al. Co-occurrence of pheochromocytoma-paraganglioma and cyanotic congenital heart disease: a case report and literature review. *Front Endocrinol (Lausanne)*. 2018;9:165.
10. Opotowsky AR, Moko LE, Ginns J, Rosenbaum M, Greutmann M, Aboulhosn J, et al. Pheochromocytoma and paraganglioma in cyanotic congenital heart disease. *J Clin Endocrinol Metab*. 2015;100:1325–1334.
11. Rana HQ, Rainville IR, Vaidya A. Genetic testing in the clinical care of patients with pheochromocytoma and paraganglioma. *Curr Opin Endocrinol Diabetes Obes*. 2014;21:166–176.
12. Mannelli M, Rapizzi E, Fucci R, Canu L, Ercolino T, Luconi M, et al. 15 Years of paraganglioma: metabolism and pheochromocytoma/paraganglioma. *Endocr Relat Cancer*. 2015;22:T83–T90.
13. Fishbein L, Leshchiner I, Walter V, Danilova L, Robertson AG, Johnson AR, et al. Comprehensive molecular characterization of pheochromocytoma and paraganglioma. Cancer Cell 217;31:181-93.
14. Folger Jr GM, WC Roberts, Mehrizi A, Shah KD, Glancy DL, Carpenter CC, et al. Cyanotic malformations of the heart with pheochromocytoma: a report of five cases. *Circulation*. 1964;29:750–757.
15. Rodriguez-Cuevas S, Lopez-Garza J, Labastida-Almendaro S. Carotid body tumors in inhabitants of altitudes higher than 2000 meters above sea level. *Head Neck*. 1998;20:374–378.
16. Zhuang Z, Yang C, Lorenzo F, et al. Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. *N Engl J Med*. 2012;367:922–930.
17. Jochmanova I, Lazurova I. A new twist in neuroendocrine tumor research: Pacak-Zhuang syndrome, HIF-2alpha as the major player in its pathogenesis and future therapeutic options. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2014;158:175–180.
18. Fliedner SMJ, Brabant G, Lehnert H. Pheochromocytoma and paraganglioma: genotype versus anatomic location as determinants of tumor phenotype. *Cell Tissue Res*. 2018;372:347–365.
19. Eisenhofer G, Walther MM, Huynh TT, Li ST, Bornstein SR, Vortmeyer A, et al. Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. *J Clin Endocrinol Metab*. 2001;86:1999–2008.
20. Castinetti F, Kroiss A, Kumar R, Pacak K, Taieb D. 15 Years of paraganglioma: imaging and imaging-based treatment of pheochromocytoma and paraganglioma. *Endocr Relat Cancer*. 2015;22:T135–T145.
21. Janssen I, Blanchet EM, Adams K, Chen CC, Millo CM, Herscovitch P, et al. Superiority of [68Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. *Clin Cancer Res*. 2015;21:3888–3895.
22. Gruber H, Metson R. Carotid body paraganglioma regression with relief of hypoxemia. *Ann Intern Med*. 1980;92:800–802.