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Case Report

Clinical Progression of a Paraganglioma Over Many Years in a Man With Congenital Heart Disease

Megan M. McConnell, MD [1,*], Maralee R. Kanin, MD [1], Martin S. Auerbach, MD [2], Run Yu, MD, PhD [1]

[1] *Division of Endocrinology, Diabetes & Metabolism, Department of Internal Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California*
[2] *Department of Nuclear Medicine and Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, California*

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ABSTRACT

Background: Documented symptomatic progression of a paraganglioma (PGL) over many years is unusual. Our objective is to report a young man with such an occurrence.
Case Report: A 27-year-old male presented with headache, sweating, and palpitation. He had a history of cyanotic congenital heart disease. Five years before presentation, he had 24-hour urine metanephrines 43 mcg/d (25-222), vanillylmandelic acid 3 mg/d (<6), and homovanillic acid 2.4 mg/d (1.6-7.5) levels and a 3.13 cm mass in the upper aortocaval space. Subsequent imaging showed slow growth of the mass. On admission, his blood pressure was 197/134 mm Hg, heart rate was 163 beats per minute, respiratory rate was 25 per minute, and oxygen saturation was 76% on room air. His 24-hour urine normetanephrine level was 2644 mcg/d (81-667) while metanephrine was 405 mcg/d (55-320). Plasma free metanephrine level was 0.92 nmol/L (0-0.49) and normetanephrine was 11.85 nmol/L (0-0.89). DOTATATE positron emission tomography–computed tomography revealed a 4.3 × 3.1 × 4.9 cm mass with activity in the right upper aortocaval space. He was treated with Prazosin. Two months later, he underwent resection of the mass. Pathology diagnosed a 4.9 cm PGL. He had improvement in metanephrine levels.
Discussion: PGL is diagnosed by documenting excess catecholamines and identifying a lesion on imaging. False negative laboratory testing is rare but can occur. Patients with cyanotic congenital heart disease have a greater risk of developing PGL.
Conclusion: It is crucial to evaluate a patient for PGL if clinical conditions suggest catecholamine excess, especially if a retroperitoneal tumor has grown or the patient has risk factors.

Introduction

Pheochromocytomas and paragangliomas (P-PGLs) are rare neuroendocrine tumors that arise from the chromaffin cells of the adrenal medulla and the ganglia, respectively. The catecholamines (dopamine, norepinephrine, and epinephrine) produced by P-PGLs can cause symptoms such as hypertension or hypertensive crisis characterized as a triad of headaches, sweating, and tachycardia/palpitations, and cardiovascular complications. The majority of patients with adrenal and extra-adrenal abdominal paragangliomas (PGLs) are functional in that they have increased plasma and urine concentration of catecholamines causing clinical features of excess catecholamines. However, approximately 8% to 9% of patients with sporadic PGL or 21% to 31% of those with hereditary PGL have normal plasma or urinary catecholamine levels.[1] Plasma and urinary concentrations of metanephrines may be normal in patients with very small tumors (<1 cm), in patients with PGLs that only produce dopamine, and in patients with mutations in the succinate dehydrogenase subunit B gene.[2]

Cyanotic congenital heart disease (CCHD) refers to a subset of congenital heart disease diagnoses that typically present after birth. As a result of impaired pulmonary flow and mixing of pulmonary and systemic venous blood, there is systemic hypoxemia and hypoxia.[3] There has been an increasing body of evidence linking hypoxia and hypoxia pathways with the progression of P-PGL.[4,5]

Abbreviations: CCHD, cyanotic congenital heart disease; CT, computed tomography; HVA, homovanillic acid; PET, positron emission tomography; PGL, paraganglioma; P-PGLs, pheochromocytomas and paragangliomas; VMA, vanillylmandelic acid.

* Address correspondence to Dr Megan McConnell, 10833 Le Conte Ave, CHS 57-145, Los Angeles, California 90095.
E-mail address: MMMcConnell@mednet.ucla.edu (M.M. McConnell).

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We present a patient with CCHD who was found to have catecholamine-induced cardiomyopathy due to a PGL that had progressed over at least a 5-year period.

Case Report

A 27-year-old male was admitted to the hospital with tachycardia, hypertension, and hypoxia. He reported worsening episodes of headaches, sweating, palpitations, nausea, emesis, anxiety, and hypertension for the past several months. His medical history included CCHD due to pulmonary atresia, hypoplastic right ventricle, and sinusoidal right ventricular to coronary artery connections requiring multiple surgeries including the Fontan procedure at age 5. He developed hypertension at age 20 and suffered a brainstem stroke at age 26. His medications included apixaban 5 mg twice daily and labetalol 200 mg twice daily although he reported that he took labetalol intermittently.

His prior outpatient laboratory tests 5 years before had been notable for 24-hour urine metanephrines 43 mcg/d (25-222), vanillylmandelic acid 3 mg/d (<6), and homovanillic acid 2.4 mg/d (1.6-7.5) levels. He had complained of episodes of tachycardia, hypertension, sweating, and palpitations around that time. Later that year, cardiac magnetic resonance imaging identified a 3.13 cm mass in the upper aortocaval space. Magnetic resonance enterography from 3 years before had showed a 3.3 × 1.6 × 2.5 cm nodule in the upper aortocaval space that had been present and largely stable. Review of subsequent imaging showed gradual growth of this mass (Fig. 1 and 2).

Physical examination revealed that his blood pressure was 197/134 mm Hg, heart rate 163 beats per minute, respiratory rate 25 per minute, oxygen saturation 76% on room air, and body mass index 20.8. He was ill appearing, diaphoretic, tachycardiac, tearful, anxious, and in moderate respiratory distress. Sinus tachycardia was treated with multiple boluses of intravenous adenosine and an amiodarone infusion without significant response in heart rate. He was administered labetalol 200 mg intravenous and started on a nicardipine infusion. He developed worsening hypoxic respiratory failure requiring intubation. Cardiac ultrasound revealed newly depressed left ventricular systolic function with ejection fraction <20% and he was initiated on extracorporeal membrane oxygenation.

Laboratory evaluation revealed 24-hour urine metanephrine at 405 mcg/d (55-320) while normetanephrine was 2644 mcg/d (81-667). Plasma free metanephrine was 0.92 nmol/L (0-0.49) and normetanephrine was 11.85 nmol/L (0-0.89). Computed tomography (CT) of the abdomen/pelvis without contrast showed normal adrenal glands and noted the aortocaval nodule previously seen on imaging was now 4.9 cm in size. DOTATATE positron emission tomography (PET)/CT revealed a soft tissue mass measuring 4.3 × 3.1 × 4.9 cm with intense DOTATATE activity located in the right paravertebral space between the aorta and cava at the level of the second lumbar spine, suspicious for PGL (Fig. 3). There was no evidence of multifocal or metastatic disease.

The patient was diagnosed with catecholamine-induced cardiomyopathy due to a PGL. Treatment was started with alpha-blockade. Prazosin was increased to 4 mg twice daily. In addition, he was started on metoprolol tartrate which was increased to 100 mg thrice daily. His ejection fraction improved to 50%, and he was discharged to a rehabilitation unit. Two months later, the patient underwent open resection of the PGL. Pathologic diagnosis was a 4.9 cm encapsulated PGL with single microscopic (<0.1 cm) focus in adjacent brown adipose tissue without evidence of cytologic atypia, elevated mitotic index, necrosis, lymphatic invasion, or vascular invasion. Three months after surgery, plasma free metanephrine was 0.30 nmol/L (0-0.49) and normetanephrine was 3.82 nmol/L (0-0.89). Normetanephrine levels remain slightly increased. Blood pressure and heart rate were under control. He was referred to genetics but has not scheduled the consultation yet.

Highlights

- Pheochromocytomas and paragangliomas (P-PGLs) are rare neuroendocrine tumors
- Coexistence of paragangliomas (PGLs) and cyanotic congenital heart disease has been reported
- Diagnosis of PGL relies on biochemical and imaging documentation
- False negative laboratory testing for PGL is rare but can occur
- Repeat evaluation for PGLs is necessary when there is a clinical change

Clinical Relevance

We report a patient with cyanotic congenital heart disease who had documented symptomatic progression of a paraganglioma (PGL) associated with significant tumor growth resulting in catecholamine-induced cardiomyopathy. Untreated PGLs have high mortality.

Discussion

PGLs are exceedingly rare neuroendocrine tumors. Diagnosis is difficult to obtain as clinical and biochemical presentation is diverse. The diagnosis of PGL is made by documenting excess production of catecholamines on laboratory testing and locating the tumor on medical imaging.[6] Five years before hospitalization, the patient's workup revealed 24-hour urine metanephrines, vanillylmandelic acid, and homovanillic acid levels that were within the reference range. The patient's PGL was incidentally found on imaging several months after the normal urinary test results for PGL were obtained. According to the most recent Endocrine Society Guidelines, the initial screening test for P-PGLs should be the measurement of fractionated urinary or plasma free metanephrines.[7] According to Perry et al,[8] the measurement of 24-hour urinary fractionated metanephrines by tandem mass spectrometry assay provides an excellent sensitivity of 97% and a specificity of 91% for diagnosis of P-PGLs. Given that the patient had clinical symptoms of P-PGL at initial presentation, it may have been reasonable to also check plasma free metanephrine because it offers a slightly higher sensitivity of 99% (95% CI, 96%-100%) compared to urinary fractionated metanephrines at 97% (95% CI, 92%-99%).[1]

The patient was thought to have a nonfunctional PGL at initial presentation given that the urinary metenephrine levels were within the normal range. However, it is possible that the patient's initial negative urinary metanephrine test was a false negative test. False-negatives are quite rare; normal values, because normal values can occur between pulsatile bursts of catecholamine and may not be picked up on assay. The patient's initial negative urinary metanephrines may have reflected the smaller size of the PGL at the time of diagnosis or a change over time of the hormone producing cells in the setting of chronic hypoxemia. The PGL should have been present at the time of laboratory testing because PGLs generally grow slowly,[9] and the tumor was already quite sizable upon discovery. We hypothesize that alterations in gene expression during significant tumor growth may be responsible for the clinical progression of the PGL. Nowell et al[10] postulated that the original tumor clone can acquire genetic variability and produce different subpopulations of cells with varying phenotypic characteristics.

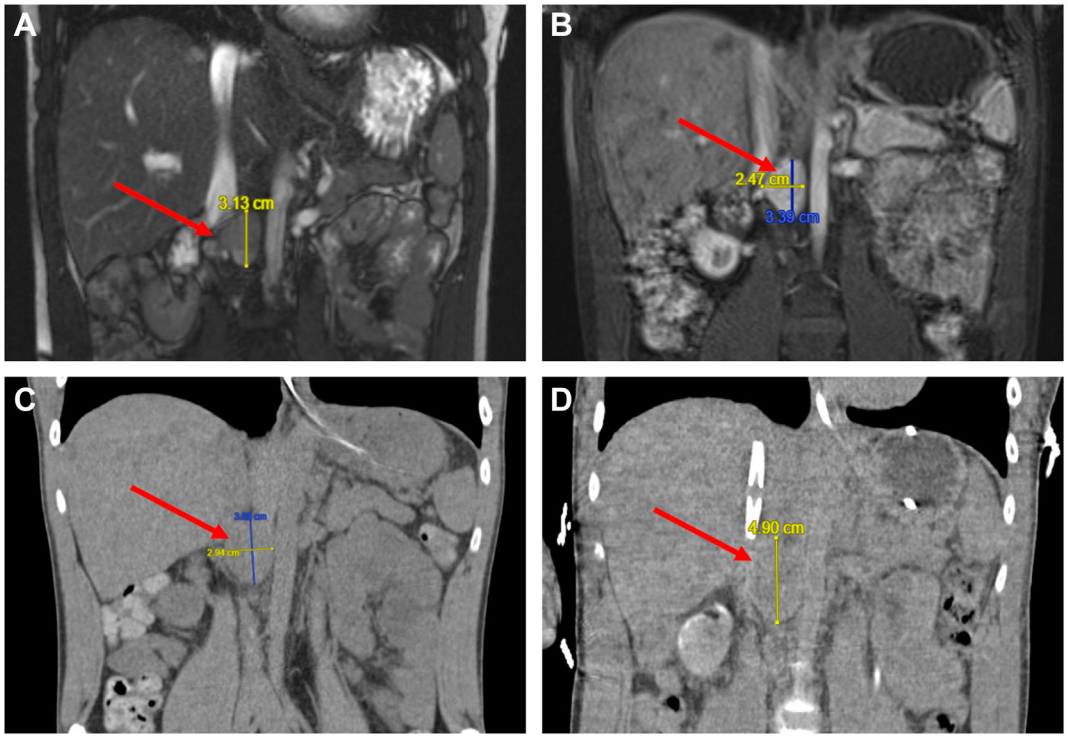

Fig. 1. *A*, Cardiac magnetic resonance imaging 12/2017 – 3.13 cm mass; *B*, Magnetic resonance enterography 01/2019 – 3.39 cm mass; *C*, CT without contrast 08/2021 – 3.88 cm mass; and *D*, CT without contrast 04/2022 – 4.90 cm mass.

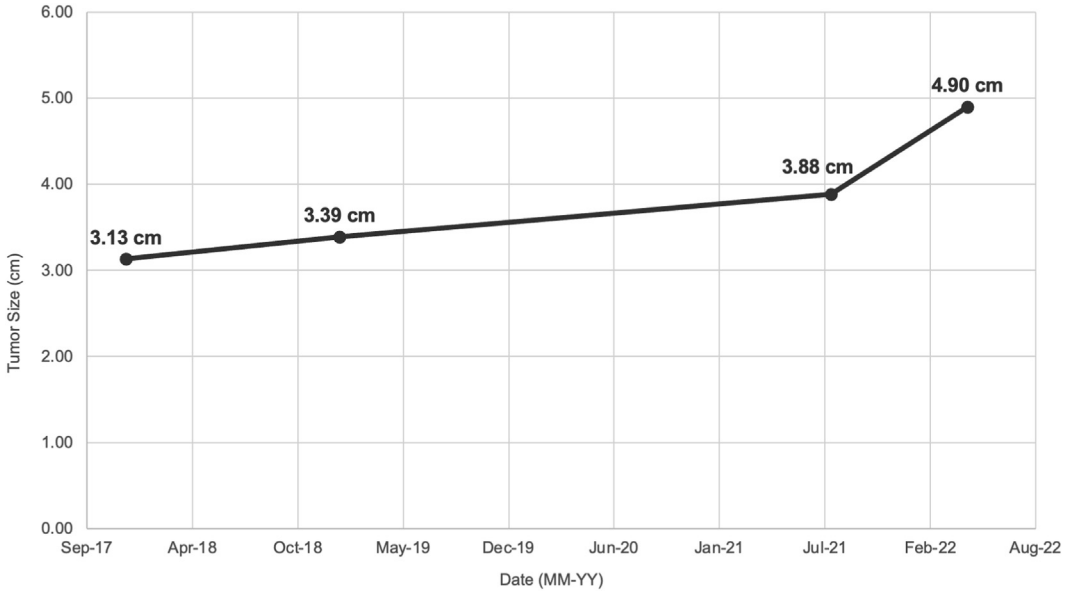

Fig. 2. Linear growth speed of the paraganglioma.

Thus, one possible hypothesis is that the patient's tumor had phenotypic heterogeneity and cells that produced catecholamines increased in number from initial to secondary presentation.

The coexistence of CCHD and P-PGL has been reported.[11] Opotowsky et al[3] showed that patients with CCHD have a greater risk of developing P-PGL (adjusted odds ratio 6.0) compared to individuals without CCHD. It is suspected that the cardiovascular alterations from chronic hypoxemia favor abnormal development of chromaffin cells.[12] A dominant noradrenergic biochemical phenotype is observed among patients with CCHD and P-PGL,[3] which was the case in the patient.

Symptoms of progressive CCHD overlap with those seen in P-PGL. Thus, it is essential to identify patients early on because undiagnosed P-PGL can lead to progression of heart failure as well as increased morbidity and mortality. At present, there are no guidelines that recommend P-PGL testing if there is an unexplained clinical decline in a patient with CCHD. Furthermore, there is no data to guide interpretation of serum and urine catecholamine levels in patients with CCHD who are expected to have higher baseline catecholamine levels.[3,13] Additional guidance on appropriate approach to care is needed in this patient population.

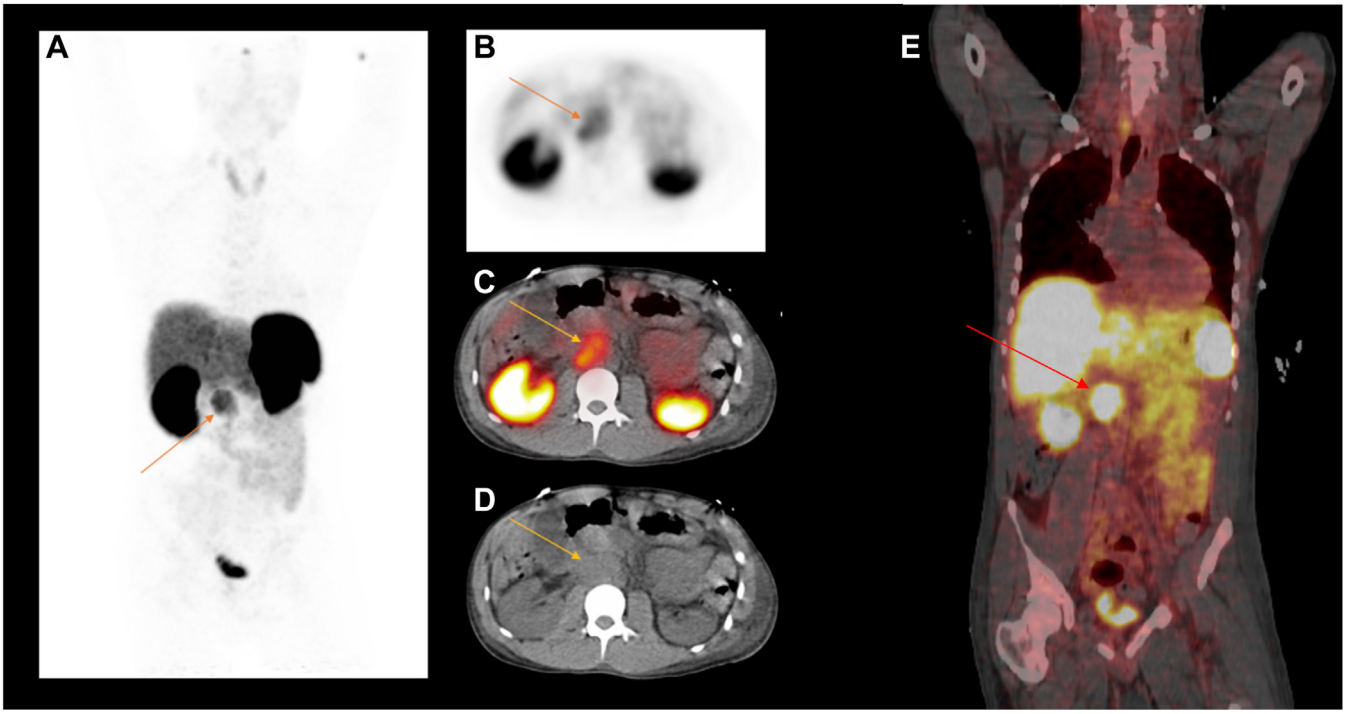

Fig. 3. *A*, Maximal intensity projection of DOTATATE PET showing a single positive uptake corresponding to the aortocaval space mass; *B*, Axial view of DOTATATE PET at the level of the mass; *C*, Merged axial view of DOTATATE PET and CT; *D*, Axial view of CT at the level of the mass; and *E*, Coronal view of DOTATATE PET. Arrows: paraganglioma.

In general, for patients with and without CCHD and functional PGL, surgery is definitive management. These tumors are resected based on biochemical and imaging documentation.[6] Biopsy is not typically recommended because accidental seeding of the PGL may cause acute symptoms.[7,14] Combined alpha- and beta-adrenergic blockade treatment is required before surgery to control blood pressure and prevent intraoperative hypertensive crisis.[6] Nonfunctional PGL may also be treated with surgery due to potential malignant transformation.[15] Following the patient's treatment with Prazosin and Metoprolol, he underwent resection of his PGL. The patient's postoperative normetanephrine levels remain slightly elevated, which is likely consistent with hemodynamic changes from Fontan circulation.[13]

Conclusion

Clinical courses suspicious for catecholamine excess should prompt evaluation for a PGL, even if initial catecholamine testing was within the normal range. Given that CCHD is a risk factor for PGLs, physicians must have high clinical suspicion for PGLs in patients with suspicious symptoms or radiographic findings.

Disclosure

The authors have no multiplicity of interest to disclose.

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Patient Consent

The patient gave his consent for the information to appear in a journal article.

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