Sympathetic Paraganglioma in a Patient with Unrepaired Tetralogy of Fallot: A Case Report and Review of the Literature

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Context: Paragangliomas are a type of neuroendocrine tumor that has been reported to be present in patients with cyanotic congenital heart disease. This report documents the first case of a patient with successful resection of a sympathetic paraganglioma in the setting of unrepaired tetralogy of Fallot, the most common cause of cyanotic heart disease, with pulmonary atresia.

Objective: We present a 33-yr-old woman with hypertensive crises from a paraganglioma who presented for surgical resection.

Patient and Methods: The patient’s preoperative workup was consistent with a functioning sympathetic paraganglioma. Preoperative transesophageal echocardiogram displayed normal ventricular function, moderate-severe right ventricular hypertrophy, severe right ventricular hypertension, an overriding aorta, bidirectional shunting, pulmonary atresia, and aortopulmonary collaterals.

Results: The patient underwent a successful laparoscopic resection of a functioning 7-cm paraganglioma after careful preoperative preparation and intraoperative monitoring. Pathology returned as a well-defined, partially hemorrhagic mass measuring 7.0 × 4.5 × 4.5 cm adjacent to and compressing the adrenal gland.

Conclusion: Surgical resection of paraganglioma tumors in rare patients such as this one is appropriate; however, surgery requires meticulous perioperative management with a multidisciplinary approach. Future studies are needed to determine whether there is a link between neuroendocrine tumors and cyanotic congenital heart disease. (J Clin Endocrinol Metab 98: 7–12, 2013)

Pheochromocytomas are rare neuroendocrine tumors that originate from neuroectodermal chromaffin cells of the adrenal medulla. When these tumors occur outside of the adrenal gland, they are termed sympathetic paragangliomas and can be found throughout the sympathetic nervous system. Typically, these are seen in the prevertebral and paravertebral sympathetic ganglia. Although pheochromocytomas and paragangliomas are similar in their presentation, morphological pathology, and genetic predisposition, paragangliomas are more likely to be malignant (5% in pheochromocytoma vs. 20% in paraganglioma) (1) and have a noradrenergic phenotype. Both tumor types require comprehensive preoperative and perioperative management due to their secretion of vasoactive hormones.

Pheochromocytomas and paragangliomas are members of the neuroendocrine tumor family. Over one third of patients with these tumors are associated with various genetic disorders including von Hippel-Lindau syndrome, von Recklinghausen’s fibromatosis, Carney’s syndrome, and multiple endocrine neoplasia type II (2). Additionally, they can be related to mutations in the succinate dehydro-

Abbreviations: CCB, Calcium-channel blocker; CT, computed tomography; MAPCA, major aortopulmonary collateral artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
Paraganglioma with Tetralogy of Fallot

Case Presentation

A 33-yr-old female presented to the emergency department complaining of paroxysmal palpitations, chills, diaphoresis, headaches, nausea, and anxiety in the setting of a known adrenal mass. These symptoms were occurring daily and lasting up to a few minutes per episode. The patient had three prior hospitalizations for these symptoms at an outside hospital and was treated with anxiolytics and opiates each time. On the final admission, a computed tomography (CT) scan was obtained, which showed a 6 × 6-cm left adrenal mass. There was a plan for biopsy; however, the patient decided to transfer to New York Presbyterian Hospital/Weill Cornell for further management.

At presentation, she was found to be comfortable, tachycardic to 120 beats per minute, mildly hypertensive to 148/78 mm Hg, tachypneic, with an oxygen saturation of 84% on room air. Her exam was notable for mucous membrane cyanosis, jugular venous distention, a right ventricular heave, a IV/VI harsh holosystolic murmur at the left scapula, a II/IV systolic ejection murmur at the left upper sternal border, a II/VI diastolic murmur at the left upper sternal border, and clubbing of her digits. Her hematocrit was 55.2%. She had a past medical history of unrepaired TOF with pulmonary atresia, a right-sided aortic arch, and resultant MAPCAs. Consequently, she had chronic hypoxemia (with oxygen supplementation requirements), polycythemia, pulmonary hypertension, and a history of endocarditis. She had previously had two MAPCA stents placed via catheterization. She also has a history of hypothyroidism. Her past surgical history included an uncomplicated, elective cesarean section under general anesthesia 4 yr before presentation. Her medications included aspirin, bisoprolol, sildenafil, levothyroxine, and alprazolam. She had no relevant family history.

Outside hospital records were obtained, which included a prior transthoracic echocardiogram that revealed normal ventricular function, a membranous VSD with left to right shunting, a thickened right ventricular wall, and an overriding aorta. A CT angiogram of the chest demonstrated a right-sided aortic arch with pulmonary arteries fed by the thoracic aorta and soft tissue attenuation within the left adrenal gland. A ventilation/perfusion scan demonstrated 15% perfusion to the right lung. A cardiac catheterization displayed normal biventricular function, but pulmonary hypertension with a proximal left pulmonary artery pressure of 114/62 mm Hg and a right upper lobe pulmonary artery pressure of 188/93 mm Hg.

A CT of her abdomen was performed on admission, which showed an enhancing mass in the left adrenal bed measuring 6.0 × 4.6 × 4.8 cm (Fig. 1). Laboratory values for the workup of this mass are listed in Table 1. Results were consistent with a pheochromocytoma. A metaiodobenzylguanidine scan was performed, which did not show any extraadrenal disease. Surgical resection of this mass was deemed necessary. A transesophageal echocardiogram was obtained, which again demonstrated normal ventricular function, moderate-severe right ventricular hypertrophy, severe right ventricular hypertension, an overriding aorta, bidirectional shunting, pulmonary atresia, and aortopulmonary collaterals (Fig. 2).
The patient had numerous crises in the first few days of hospitalization, with blood pressures as high as 205/106 mm Hg, warranting transfer to the cardiac care unit for close monitoring. Cardiology, endocrinology, pulmonology, endocrine surgery, hypertension, and specialized anesthesiology physicians were all consulted in the management of this patient. α-Blockade was not initially used because there was a concern for extreme vasodilation leading to a decrease or total reversal of the left to right shunt and further hypoxemia. A low-dose calcium-channel blocker (CCB) was therefore started for blood pressure control; however, the patient became hypoxic after administration of this medication. Inhaled iloprost and her home dosage of sildenafil were started for pulmonary vasodilatation, with the hope of decreasing pulmonary vascular resistance and improving left to right shunting. α-Methyl-L-tyrosine, a catecholamine synthesis inhibitor, was started to reduce catecholamine levels (Table 1). α-Blockade with phentolamine, chosen for its rapid onset and offset of action, was initiated 7 d before surgery at a low dose, was slowly titrated, and was tolerated well. β-Blockade with an esmolol drip was started that same day, and the patient continued to have stable hemodynamics.

On hospital d 14, the patient was taken to the operating room for a laparoscopic left adrenalectomy. Induction of general anesthesia was well tolerated. The patient was monitored intraoperatively with an arterial line, a central venous catheter, and intraoperative transesophageal echocardiogram. The patient was placed in a right lateral decubitus position and pneumoperitoneum was achieved, both of which did not alter hemodynamics. The spleen was mobilized from its posterolateral attachments and was reflected anteriorly and medially. The tail of the pancreas was adherent to the mass and was dissected anteriorly. The tumor was initially mobilized from its posterior attachments, and then from the renal vein and artery. A large adrenal vein was then dissected free and clipped. At first there was a decrease in blood pressure; however, the patient became hypertensive shortly thereafter. A significantly dilated (~1-cm diameter) inferior phrenic vein was then identified. This was clipped, and the patient’s mean arterial pressures significantly decreased. Intravenous drips were changed at this point from blocking agents to vasopressor support. The tumor was removed, and the procedure was completed without complication. The patient was extubated and taken to the cardiothoracic intensive care unit on vasopressor support with norepinephrine and vasopressin.

The patient’s postoperative course was uncomplicated. Vasopressor support was weaned off by postoperative d 1.

### Table 1. Adrenal mass workup

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Value</th>
<th>Normal range</th>
<th>Value after α-methyl-L-tyrosine</th>
<th>Value after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>137 mmol/liter</td>
<td>136–144 mmol/liter</td>
<td></td>
<td></td>
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<tr>
<td>Potassium</td>
<td>3.9 mmol/liter</td>
<td>3.2–5.2 mmol/liter</td>
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<tr>
<td>Urine VMA</td>
<td>68 mg/g</td>
<td>0–6 mg/g</td>
<td></td>
<td></td>
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<tr>
<td>Urine dopamine/creatinine</td>
<td>257 μg/g CR</td>
<td>0–250 μg/g CR</td>
<td>947 μg/g CR</td>
<td>18 μg/g CR</td>
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<tr>
<td>Urine epinephrine/creatinine</td>
<td>8 μg/g CR</td>
<td>0–20 μg/g CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine norepinephrine</td>
<td>2862 μg/g CR</td>
<td>0–45 μg/g CR</td>
<td>502 μg/g CR</td>
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<tr>
<td>Plasma normetanephrine</td>
<td>44.70 nmol/liter</td>
<td>0.00–0.89 nmol/liter</td>
<td>0.64 nmol/liter</td>
<td>&lt;0.1 nmol/liter</td>
</tr>
<tr>
<td>Plasma metanephrine</td>
<td>0.24 nmol/liter</td>
<td>0.00–0.49 nmol/liter</td>
<td></td>
<td></td>
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<tr>
<td>Serum aldosterone</td>
<td>&lt;1.6 ng/dl</td>
<td>≤31.0 ng/dl</td>
<td></td>
<td></td>
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<td>Renin activity, plasma</td>
<td>1.15 ng/ml/h</td>
<td>0.25–5.82 ng/ml/h</td>
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<tr>
<td>ACTH</td>
<td>15 pg/ml</td>
<td>6–58 pg/ml</td>
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<tr>
<td>Testosterone</td>
<td>16 ng/dl</td>
<td>10–75 ng/dl</td>
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<tr>
<td>DHEA</td>
<td>91 ng/dl</td>
<td>31–701 ng/dl</td>
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<tr>
<td>Androstenedione</td>
<td>0.520 ng/ml</td>
<td>0.260–2.140 ng/ml</td>
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<tr>
<td>24-h Urine cortisol</td>
<td>7.96 μg/g CR</td>
<td>&lt;45 μg/g CR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory values for the patient’s adrenal mass workup are shown, in addition to her catecholamine excretion levels after α-methyl-L-tyrosine. Bold represents abnormal values. VMA, Vanillylmandelic acid; DHEA, dehydroepiandrosterone; CR, creatinine.
Her diet was advanced, her pain was adequately controlled, and she was discharged on postoperative d 5. Her plasma metanephrines normalized (Table 1). The pathology report revealed that the tumor was an extraadrenal mass measuring 7.0 × 4.5 × 4.5 cm. It was described as a well-defined, partially hemorrhagic nodule adjacent to and compressing the adrenal gland. Focal lymphovascular invasion was identified. The surgical resection margin was free of tumor, and there were two benign lymph nodes. The attached adrenal gland was normal (Fig. 3). The patient received genetic counseling postoperatively; however, she refused any genetic testing. At 1-yr follow-up, she remains well, with normal plasma metanephrines, and no longer requires antihypertensive medications.

Discussion

Surgical resection of paragangliomas is the standard of care, but it requires preoperative blockade of the effects of catecholamine secretion, careful intraoperative monitoring of hemodynamic fluctuations, and judicious postoperative blood pressure support. α-Adrenergic blockade should be initiated in the preoperative setting to protect against hemodynamic instability, and this is a recommendation from the First International Symposium on Pheochromocytoma (10). Preoperative α-blockade has been reported to decrease intraoperative hemodynamic complications to approximately 3 vs. 69% in patients who did not receive preoperative α-blockade (11). The use of β-blockade is administered only after sufficient α-blockade is attained (10). Our patient had been taking β-blockade before presentation at our institution and was living with unopposed catecholamine-induced vasoconstriction, likely contributing to the extreme elevations in blood pressure upon presentation.

The role for α-blockade in this patient with unrepaired TOF with pulmonary atresia and MAPCAs was not straightforward. Specifically, her pulmonary blood flow solely depends upon her MAPCAs and is therefore determined by her systemic blood pressure and left to right shunt; her shunt fraction is largely determined by her afterload and pulmonary vascular resistance. Our concern was that the α-agonism and resultant systemic vasoconstriction provided by the paraganglioma was important in increasing her left to right shunt, and thereby her oxygenation. In the setting of α-blockade and resultant systemic afterload reduction, pulmonary blood flow could potentially decrease and worsen arterial blood oxygenation. Because of this, she was initially started on a CCB. This medication inhibits norepinephrine-mediated calcium entry into the smooth muscle of cardiac vasculature, minimizing hypertension and tachycardia. CCBs are recommended in the place of α-blockade to prevent the sustained hypotension occasionally seen in those with intermittent hypertension (12); however, our patient did not tolerate this medication. When α-blockade was started in this patient, it was initiated at a low dose in a closely monitored setting, and the dosage was gradually titrated. In addition, she was started on phentolamine, a rapidly reversible, rapidly titratable nonselective α-adrenergic antagonist rather than phenoxybenzamine (an irreversible α-blocker and typically the initial α-blocker of choice) or a competitive, longer acting α-blocker such as doxazosin or terazosin. Furthermore, she was receiving pulmonary vasodila-
tors, which enhanced oxygenation by decreasing her pulmonary vascular resistance, thus increasing her left to right shunt without significantly dropping her systolic blood pressure (to avoid a right to left shunt).

This patient underwent a laparoscopic adrenalectomy. The use of open adrenalectomy was considered because intraoperative positioning and intraabdominal insufflation (and resulting increased pulmonary hypertension) associated with laparoscopic surgery was an initial concern. For the laparoscopic approach, the patient would be in a right lateral decubitus position. This would in fact aid in this patient’s oxygenation because perfusion to the lower lung has been shown to be increased in the lateral decubitus position (13). This patient would benefit from enhanced perfusion to her already compromised right lung with previously documented 15% perfusion. Moreover, the increase in intraabdominal pressure associated with laparoscopic surgery increases afterload, which would increase her left to right shunt and thereby also increase pulmonary blood flow. Additionally, it was felt that this patient would considerably benefit from the decreased blood loss, decreased incidence of postoperative ileus, decreased narcotic usage, and more rapid recovery reported with laparoscopic adrenalectomy compared with open adrenalectomy (14). Finally, given the fact that this mass was 6 cm on preoperative imaging, open resection was considered; however, laparoscopy was ultimately decided on because large size (>10 cm) is not a contraindication to the laparoscopic approach for pheochromocytoma (15). There are few case reports of patients with pheochromocytoma and TOF. Kita et al. (9) describes two patients with this rare combination. The first was a 45-yr-old female with corrected TOF and a pheochromocytoma who received preoperative α-blockade and had a successful left adrenalectomy. The second patient, a 41-yr-old female, refused surgical resection and was treated solely with α- and β-blockade (9). Filgueiras-Rama et al. (16) discuss a patient with complex cyanotic congenital heart disease and Eisenmenger’s syndrome, pheochromocytoma, and paraganglioma in the neck. The adrenal tumor was successfully resected using a laparoscopic approach, and the paraganglioma was conservatively managed because the patient was not symptomatic from this mass. De la Monte et al. (6) reported 15 patients with congenital heart disease and peripheral neuroendocrine tumors. Four of these patients had TOF; three developed pheochromocytomas, and one developed a neuroblastoma. The incidence of congenital heart disease in patients found to have neuroendocrine tumors was more than two times the incidence of congenital heart disease in the remaining subjects (P < 0.001). The authors reported that all peripheral neuroblastoma tumors associated with congenital heart disease were benign, and the most common cardiac abnormalities associated with peripheral neuroendocrine tumors are those leading to cyanosis (87% of subjects in this study) (6). These reports have fueled the hypothesis that chronic hypoxic states and cyanosis are linked to the development of peripheral neuroendocrine tumors. This theory is consistent with results showing the role of hypoxia inducible factor expression in the development of certain pheochromocytomas and paragangliomas (17). Another possible link may be related to the disruption of embryological neural crest cells because these cells are involved in the septation of the cardiac outflow tract, and paraganglioma and pheochromocytoma are well-known neural crest-associated tumors. However, further studies must be done to substantiate this relationship.

In conclusion, we have reported the first case of the management of a functioning paraganglioma in a patient with unrepaired TOF with pulmonary atresia. We recommend surgical resection of these tumors in this setting, although with careful preoperative, intraoperative, and postoperative management by a multidisciplinary team with members experienced in the management of patients with pheochromocytoma and cyanotic congenital heart disease. Further studies are warranted to establish whether an association between congenital heart disease and paragangliomas exists.

Acknowledgments
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Disclosure Summary: The authors have nothing to disclose.

References


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