Pheochromocytoma Storm Presenting as Cardiovascular Collapse at Term Pregnancy

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Pheochromocytomas are neuroendocrine tumors that typically present with paroxysms of hypertension, but occasionally can lead to marked hemodynamic instability, left ventricular dysfunction, and cardiovascular collapse. Although pheochromocytoma in pregnancy is rare, factors specific to pregnancy can precipitate catecholamine crisis, making diagnosis and treatment challenging. We present a case of acute cardiovascular collapse with transient left ventricular dysfunction due to catecholamine crisis in a healthy young woman at term pregnancy. Further clinical and genetic investigation revealed pheochromocytoma as part of multiple endocrine neoplasia IIa (Sipple syndrome). A discussion of diagnosis and treatment strategies for pheochromocytoma in pregnancy and acute catecholamine crisis accompanies this report.
[Rev Cardiovasc Med. *2004;5(4):226-230*]

Key words: Pheochromocytoma • Pregnancy • Cardiomyopathy

A 24-year-old, healthy Hispanic female at term pregnancy (gravida 2, para 0), presented with acute onset shortness of breath and chest pain.

Examination, Initial Laboratory Data

Upon presentation to an outside emergency department, the patient was afebrile but dyspneic with a respiratory rate of 24 breaths/min, heart rate of 120 beats/min, blood pressure of 124/84 mm Hg, and oxygen saturation of 94%

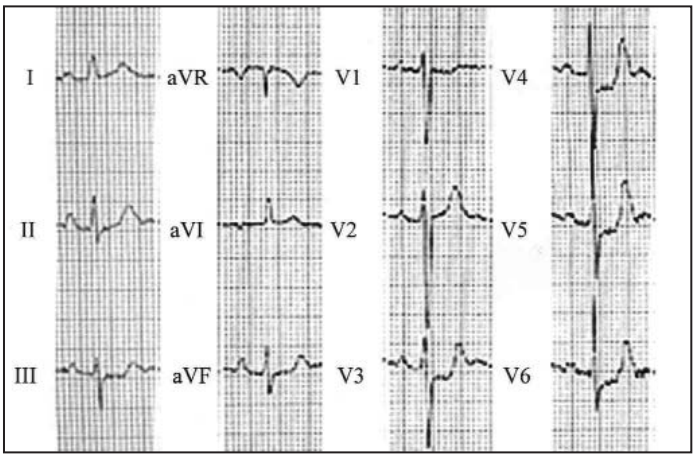


Figure 1. *Electrocardiogram obtained upon admission to the outside hospital revealed a heart rate of 120 beats/min and 2–mm ST segment depression in leads V3-V6.*

on room air. Inhaled albuterol, intravenous fluids, and supplementary oxygen were administered. Electrocardiogram revealed sinus tachycardia with 2-mm anterolateral ST segment depression (Figure 1). A chest X-ray revealed diffuse alveolar infiltrates consistent with pulmonary edema. Urinalysis showed marked glucosuria but was negative for protein and a toxicology screen was negative for illicit ingestions.

In the outside emergency department, the patient's oxygen saturation dropped precipitously to 67% and she was intubated. Obstetric evaluation revealed fetal bradycardia and an emergent cesarean section was performed. Intraoperatively, the patient continued to be hypoxemic and was noted to have wide swings in systolic blood pressure and persistent sinus tachycardia. Levophed and dopamine were administered without significant change in systolic blood pressure. A bedside transthoracic echocardiogram revealed severe global left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 15%. Cardiac enzymes were found to be elevated: creatinine kinase 350 U/L, myocardial band fraction 10.8, and troponins 0.97 ng/mL. The patient was taken emergently to the cardiac catheterization laboratory where angiography revealed normal coronary arteries. An intraaortic balloon pump was placed, milrinone and diuretics were administered, and the patient's oxygen saturation improved. The patient was then transferred to our hospital.

Physical examination on arrival revealed the patient to be intubated and sedated. She was afebrile with a heart rate of 122 beats/min and a blood pressure of 92/56 mm Hg. There was a 4-cm horizontal scar on the anterior lower neck. Lung exam revealed coarse rhonchi throughout the lung fields. Heart examination revealed a nondisplaced PMI and a normal carotid upstroke, and auscultation revealed no murmurs. A third heart sound was noted. There was a large horizontal incision on the lower abdomen that was healing well. Bowel sounds were present but decreased. There was a balloon pump catheter in the right iliac artery. There was no peripheral edema. Laboratory studies on presentation to this hospital and on subsequent days are listed in Table 1.

History

The patient's medical history was significant for medullary carcinoma of the thyroid post resection 3 years earlier, with subsequent hypothyroidism. The current pregnancy had been complicated only by mild intrahepatic cholestasis. She had 1 previous pregnancy, which ended with a first trimester miscarriage. Her

Table 1
Laboratory Values

Substance*	Day 1	Day 2	Day 4	Day 7
Troponin (< 0.10 ng/mL)	1.08	0.8		
CK (9-185 U/L)	1150	1258		
MB-RI%	1.9	1.5		
Urine Epi (0-20 μg/24 h)	72		40	21
Urine NE (15-80 μg/24 h)	103		54	30
Urine DA (65-400 μg/24 h)	69		92	95
Urine Met (30-180 μg/24 h)	3978		1775	1696
Urine NM (103-390 μg/24 h)	2002		967	773
Serum Calcium (8.4-10.2 mg/dL)	6.6		6.4	8
Thyrotropin (TSH, 0.3-3.8 mIU/mL)	18		45	
Thyroxine (5.0-11.6 μg/dL)	5.2		5.6	
Creatinine (0.5-1.4 mg/dL)	1.1	0.8	0.5	0.6

CK, creatinine kinase; DA, dopamine; Epi, epinephrine; MB-RI %, MB relative index; Met, metanephrine; NE, norepinephrine; NM, normetanephrine.
*Reference range is given in parentheses.

preadmission medications were levothyroxine and cholestyramine. Her family history was significant only for the unexpected death of her mother during her third pregnancy with no clear diagnosis determined. The patient's obstetrician reported a normal pregnancy without hypertension, proteinuria, or edema.

Hospital Course

A management plan was initiated with the presumptive diagnosis of peripartum cardiomyopathy. Captopril, furosemide, and spironolactone were initiated, calcium was repleted, and the levothyroxine dose was increased. Given the history of medullary thyroid cancer and the wide swings in systolic blood pressure on presentation, 24-hour urine collection for urinary catecholamines and metabolites was also initiated. The intraaortic balloon pump was removed and milrinone was discontinued by the second hospital day, and the patient was extubated on the third hospital day. Due to a marked elevation in urinary metanephrine and normetanephrine, an abdominal ultrasound was obtained and revealed a 3-cm left suprarenal mass. Phenoxybenzamine was then started with a new presumptive diagnosis of pheochromocytoma. An I131 metaiodobenzylguanidine (MBIG) scan and a magnetic resonance scan of the abdomen and thorax were obtained and confirmed an isolated left adrenal tumor consistent with a pheochromocytoma (Figure 2).

A repeat transthoracic echocardiogram performed on hospital day 6 was normal; complete resolution of the left ventricular dysfunction had occurred. Genetic testing revealed a mutation in the RET protooncogene consistent with multiple endocrine neoplasia (MEN) IIa (Sipple syndrome). The patient was discharged on day 13. She returned for elective laparotomy and resection of the mass 2 weeks later. Pathology confirmed it to be a benign pheochromocytoma (Figure 3). The patient and her child are currently doing well.

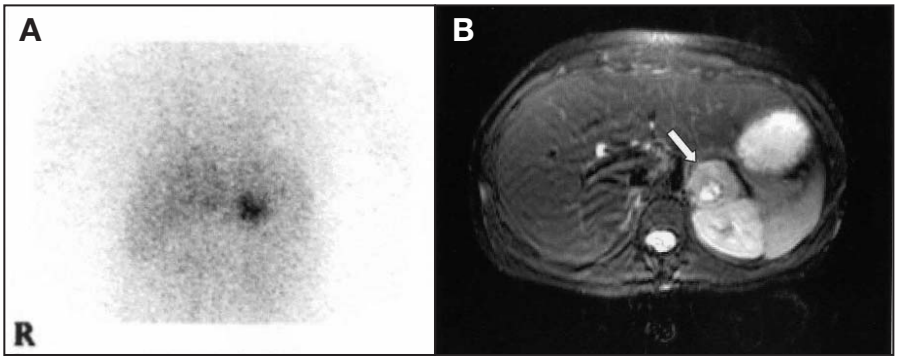


Figure 2. (A) *I-131 metaiodobenzylguanidine scan demonstrates increased left suprarenal tracer uptake.* **(B)** *T2-weighted axial fat saturated magnetic resonance imaging demonstrates a 3.7-cm T2 signal mass in the expected region of the left adrenal gland, consistent with pheochromocytoma.*

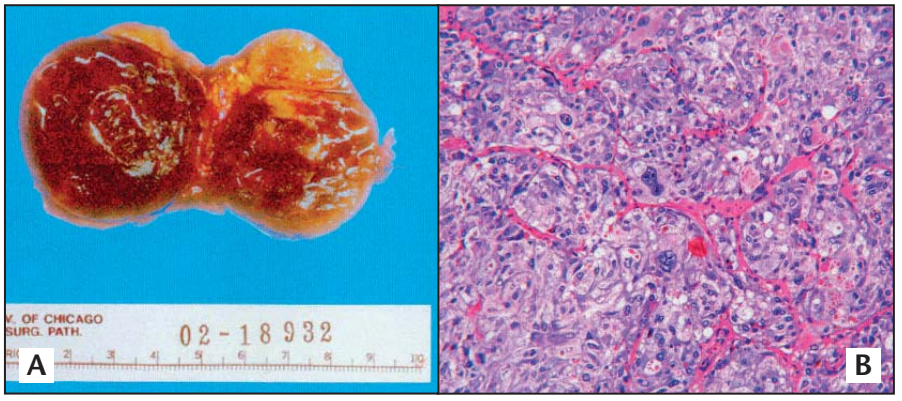
Discussion

Pheochromocytomas are tumors of the adrenal medulla that commonly produce hormones such as epinephrine, norepinephrine, and dopamine, and occasionally produce other vasoactive peptides including somatostatin, vasoactive intestinal peptide, and adrenocorticotropic hormone.

Pheochromocytoma in pregnancy is rare, with an estimated prevalence of 1 in 50,000 to 54,000 full-term pregnancies.[1,2] Pheochromocytoma typically presents with paroxysmal severe hypertension associated with the triad of headache, tachycardia, and diaphoresis,[3] though this triad is less common in the pregnant patient.[4] Pheochromocytoma in the obstetric patient can often mimic preeclampsia, though the complex hormonal milieu can lead to a variety of signs and symptoms ranging from palpitations and fever to nonspecific complaints of weakness, dizziness, or anxiety.[3]

In the setting of a pheochromocytoma crisis, massive amounts of vasoactive hormones are released from the tumor, causing marked

Figure 3. (A) *Gross examination of the surgical specimen revealed a 26.7-gram mass measuring 6.5 cm in largest diameter within the left adrenal gland.* **(B)** *Histopathologic examination revealed a highly vascular tumor with blood vessels surrounding nests of cells arranged in a classic Zellballen pattern. Cells are polygonal with granular amphiphilic to basophilic cytoplasm (hematoxylin-eosin, × 200).*



hemodynamic alterations.[5] During pregnancy, pheochromocytoma crises can be precipitated by mechanical compression by the gravid uterus, vigorous fetal movement, uterine contractions, the stress of active labor or cesarean section, and the induction of anesthesia.[4] Pregnant patients experiencing a catecholamine crisis rarely have other complications seen in pregnancy-induced hypertension, such as proteinuria, hyperuricemia, and liver or platelet abnormalities.[4,6,7]

The diagnosis of pheochromocytoma begins with a 24-hour urine collection to screen for the hormones and their metabolites. Due to the heterogeneous nature of the hormones produced, a good strategy for screening is to test for all of the most likely products: metanephrines, normetanephrines, vanillylmandelic acid, dopamine, epinephrine, and norepinephrine.[3] Plasma levels of metanephrines have been shown to have a high sensitivity but poor specificity and thus are useful only as a screening test in metabolically stable patients.[2] Localization of the tumor can initially be done by ultrasound, magnetic resonance image (MRI), or computed tomography. MRI is generally the diagnostic modality of choice because a bright mass on a T2-weighted imaging often allows a pheochromocytoma to be distinguished from incidental adrenal adenomas.[8] This may be particularly important in the immediate postpartum period of patients in catecholamine crises where MRI may provide a diagnosis prior to biochemical diagnosis.[8] MBIG scanning allows specific localization in adrenal tissues with an accuracy of 86%-94%.[3] MRI and MBIG scanning are also useful in localizing or excluding extra adrenal disease.[9]

Treatment in the acute setting consists of phentolamine or nitroprusside to reduce hypertension.

Caution must be exercised with ß-blockade, which can precipitate further hypertensive crisis due to unopposed α-adrenergic stimulation, unless α-blockade is first carried out with phenoxybenzamine or selective α1 antagonists such as prazosin or terazosin. Definitive treatment is surgery, ideally carried out when the patient is fully recovered from catecholamine crisis.[3] However, even in patients with a benign pheochromocytoma at initial surgical resection, recurrence may occur. Tumor-free cure rates at 5 and 10 years have been reported to be 92% and 80%, respectively.[10]

Pheochromocytoma in the obstetric patient can often mimic preeclampsia, though the complex hormonal milieu can lead to a variety of signs and symptoms ranging from palpitations and fever to nonspecific complaints of weakness, dizziness, or anxiety.

Our patient had severe left ventricular dysfunction with an initial LVEF of 15%, which spontaneously recovered by hospital day 6. Congestive heart failure and left ventricular dysfunction that resolves with resolution of catecholamine crisis is known to occur.[11-13] Pheochromocytoma-associated cardiomyopathy is likely due to adrenergic receptor stimulation by high concentrations of catecholamines.[13] The resulting coronary and peripheral vasoconstriction can lead to increased wall stress and focal or diffuse myocardial ischemia or necrosis. Catecholamines also appear to have direct myocyte cellular toxicity.[5] The initial biochemical and cellular changes are commonly reversible with the withdrawal of catecholamines; however, long-term damage can occur.[5,12,13]

Our patient also was found to have MEN IIa, a syndrome caused by a gain-of-function mutation in the RET protooncogene. The syndrome consists of a nearly 100% lifetime risk of medullary thyroid cancer as well as pheochromocytomas and parathyroid hyperplasia.[14] Pheochromocytomas develop in approximately 30%-50% of patients with MEN IIa, but are rarely the presenting complaint of the syndrome.[15] A recent study found that approximately 5% of pheochromocytomas are associated with the RET protooncogene (MEN II), though as many as 24% are associated with any familial genetic syndrome.[16]

Conclusion

Pheochromocytomas are neuroendocrine tumors that generally present as a secondary cause of hypertension but occasionally present with catecholamine crisis with marked hemodynamic alterations and even cardiovascular collapse. Athough pheochromocytomas are rare in pregnancy, obstetric patients encounter stressors that make them more susceptible to catecholamine crisis from pheochromocytoma. As our case demonstrates, early recognition of presenting features is critical to the effective management of these patients. ■

The authors would like to thank Brian A. Herman, MD, and Zeba Singh, MD, for their assistance with the preparation of the figures in this manuscript.

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