Dangerous Pitfall: Peripartum Pheochromocytoma Mimicking Severe Preeclampsia

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Hypertension is a common peripartum problem. Preeclampsia is defined as hypertension that develops 20 weeks after gestation in association with proteinuria or pitting edema. Most physicians control hypertension under the provisional diagnosis of preeclampsia without further investigation. Although uncommon, pheochromocytoma misdiagnosed as preeclampsia may put both the mother and fetus in danger and, if not identified early and treated promptly, lead to a disastrous outcome. Herein, we report a 35-year-old, gravida 2, para 1 woman with an unremarkable medical history who presented with hypertension after 20 weeks of gestation. We diagnosed her condition as preeclampsia; but when the hypertension persisted after delivery, the diagnosis was changed to pheochromocytoma and confirmed by a series of examinations. Fortunately, both the mother and baby are healthy and without complications. Nevertheless we made an incorrect diagnosis, which could have had serious consequences. A high index of clinical suspicion must be kept and all those at risk must be investigated to achieve an early diagnosis of pheochromocytoma in pregnancy and improved maternal and fetal outcomes.

Key Words: Catecholamine • Peripartum • Pheochromocytoma • Preeclampsia • Pregnancy

INTRODUCTION

Peripartum pheochromocytoma, although rare, can be elicited after 20 weeks of gestation and mimic the clinical presentation of preeclampsia. Unless the physician is vigilant, it may be misdiagnosed, leading to catastrophic consequences. Here, we present the case of a pregnant woman with a delayed diagnosis of pheochromocytoma but, fortunately, good clinical outcomes. Anti-hypertensive medications are always prescribed for pregnant women under the provisional diagnosis of preeclampsia whenever hypertension is associated with excessive urine protein or pitting edema. However, peripartum pheochromocytoma is an unexpected and dangerous pitfall that we overlooked. Diagnosing peripartum pheochromocytoma is challenging and extremely important. Early identification followed by specifically modified medical treatment, anesthesia, and delivery methods will reduce maternal and fetal mortality and improve outcomes.

CASE REPORT

A 35-year-old, gravida 2, para 1 woman with an unremarkable medical history presented at a routine prenatal clinic visit during the 24th week of gestation with blood pressure of 150/100 mmHg. The next day, her blood pressure remained high (up to 180/100 mmHg); and medical treatment with hydralazine 200 mg daily, divided into four doses, and labetalol 400 mg daily,
divided into two doses, was initiated. The subsequent ultrasound findings were normal for the gestational age of the fetus. Three months later, the patient’s blood pressure remained in the range of 180/110 mmHg despite incremental increases of labetalol to 400 mg twice daily. The patient was thought to have preeclampsia and was admitted to our hospital.

The patient did not smoke, drink alcohol, or use illicit drugs. Her mother, 64 years of age, had hypertension, which had been discovered when she was in her 50s; her siblings and other relatives were well. She had had no difficulty conceiving with either this pregnancy or a previous one 3 years earlier, when she had experienced mild, diet-controlled gestational diabetes. The patient gained 6.8 kg in weight during this pregnancy. She did not have proximal muscle weakness, bruising, abdominal pain, or changes in vision.

On physical examination after admission, her weight was 80 kg and height was 170 cm, and she had a body mass index of 28. Her blood pressure was 180/100 mmHg and pulse was 88 beats per minute. Her face was slightly round in appearance. Extraocular movements and visual fields were intact, and the thyroid was normal in size, without palpable nodules. The abdomen was ovoid, with mild striae over the lower abdomen. No tenderness or rebounding pain was noted. Proximal muscle strength and reflexes were normal, and the lower limbs revealed mild pitting edema. Urinary analysis showed daily protein loss of 231 mg/day. Extended-release nifedipine 30 mg daily was additionally prescribed for optimal control of blood pressure. The patient was discharged after 5 days of hospitalization in stable condition. Two weeks later, she experienced labor pains and then delivered by cesarean section at the 38th week of gestation.

Two months after delivery, persistent hypertension with systolic blood pressure around 160 mmHg was noted. However, delivery of the infant is considered the definitive treatment of preeclampsia; also, it is unusual for preeclampsia to persist for more than 6 weeks in the postpartum period. Owing to the possibility of underlying causes of secondary hypertension, the patient was referred to our cardiologist for further investigations, including urinary analysis, serum potassium level, renin/aldosterone ratio, cortisol level, 24-hour collection for vanillylmandelic acid (VMA), color Doppler ultrasound of the renal arteries, and abdominal sonography. Elevated levels of VMA in the 24-hour urine sample amounting to 35.5 mg/24 hr (normal range: 1-7.5 mg/24 hr) were noted, and the abdominal sonography revealed a massive lesion over the right supra-renal area suggestive of pheochromocytoma. In order to localize and characterize the tumor, magnetic resonance imaging (MRI) was arranged because of its multiplanar capability and high sensitivity with contrast enhancement in the diagnosis of pheochromocytoma. The result showed a heterogeneous mass about 13.5 × 9.3 × 9 cm over the right supra-renal area and high signal intensity on T2-weighted imaging, which is typical of pheochromocytoma (Figure 1). The patient underwent uneventful surgical removal of the tumor, and the histopathologic findings confirmed the diagnosis of pheochromocytoma (Figure 2). After surgery, the patient was normotensive and did not require any antihypertensive medication.

**DISCUSSION**

Hypertension during pregnancy is a common prob-
lem that causes significant maternal and fetal morbidity and mortality. By far, preeclampsia is the most common cause, affecting 5-10% of primigravid women.1 Although rarely seen, pheochromocytoma can be elicited after 20 weeks of gestation and mimic the presentation of preeclampsia. Pheochromocytoma is a rare catecholamine-producing tumor of chromaffin cells of the adrenal medulla or paraganglion, and its prevalence in hypertensive patients is about 0.2-0.4%. However, in full-term pregnancies, the estimated prevalence is only 1 in 50,000 to 54,000.2 Several mechanisms might explain why pheochromocytoma could become clinically overt only during pregnancy. It has been hypothesized that increased intra-abdominal pressure, fetal movement, uterine contraction, abdominal palpation, the process of delivery, and general anesthesia can induce a surge of catecholamines and activate the pheochromocytoma.3 If managed inadequately, disastrous outcomes may develop, such as fatal arrhythmia, stroke, heart failure, or even death.4

Before 1970, the diagnosis was made during pregnancy in only 25% of cases of peripartum pheochromocytoma, resulting in maternal and fetal mortality close to 50%. In a more recent review, antenatal diagnosis was made in up to 83% of cases and this resulted in reduction of maternal mortality to 2% and fetal mortality to approximately 10%. Even with the advances in diagnosis, however, up to 20% of cases remain unrecognized and present cardiologists, obstetricians, and anesthetists with a major challenge.

The diagnosis of pheochromocytoma depends crucially on demonstration of excessive production of catecholamines. The commonly used biochemical tests for pheochromocytoma include measurements of plasma and urinary catecholamines, urinary fractionated metanephrines, urinary total metanephrines, 24-hour urinary VMA, and a more promising test for plasma free metanephrines. Among these, Lenders et al concluded that testing for plasma free metanephrines has the highest sensitivity (97-99%) and specificity (82-96%).5 Because of its high sensitivity, the assessment of plasma free metanephrines is a powerful method to rule out pheochromocytoma in highly suggestive cases. After biochemical testing reveals pheochromocytoma, imaging is necessary to establish tumor location and identify functional status. Although computed tomography with con-
Contrast can yield a sensitivity of 98% and a specificity of 92% for detecting pheochromocytoma, it is not indicated for pregnant women because of the inherent exposure to radiation. On the other hand, MRI provides superior contrasting effects in soft tissues and, therefore, allows better assessment of the relationship of the tumor to its environment. Furthermore, Kamari et al recommended MRI as the only choice of imaging for localizing pheochromocytoma during pregnancy because it does not involve any radiation exposure and provides good anatomical description. On MRI, pheochromocytoma shows high signal intensity on T2-weighted imaging, best appreciated with the use of fat suppression. The tumors are typically heterogeneous and may be described as having a salt-and-pepper appearance.

Treatment of pheochromocytoma requires aggressive medical control of blood pressure and definitive surgical removal of the tumor. Before surgical intervention, the traditional initial approach is 10 mg phenoxybenzamine, a non-selective α-blocker, twice daily for normotension and prevention of hypertensive crisis in a 24-hour blood pressure protocol. Beta-blockers should only be used after sufficient α-blockage because they might provoke vasoconstriction with marked blood pressure increments. Hypertensive crises are controlled with nitroprusside, nitroglycerin, and phentolamine by intravenous infusion. These drugs also appear to be safe during pregnancy, although no formal large studies have been undertaken. Bullough et al also suggested intravenous infusion with magnesium sulfate provided additional benefit as a main anti-adrenergic agent as well as part of the epidural anesthetic management of pheochromocytoma.

Surgical removal is the definitive treatment of pheochromocytoma once the diagnosis is confirmed. However, the timing of surgery during pregnancy is controversial and challenging. It may depend on the gestational age, the clinical response to medical treatment, the accessibility of the tumor, and the presence or absence of fetal stress. Kalra et al. have concluded that earlier surgical intervention before 24 weeks of gestation obtains better outcomes for the fetus and mother. After 24 weeks of pregnancy, uterine size makes abdominal exploration and assessment of the tumor difficult. Optimizing medical therapy is preferred until fetal maturity is attained. Then surgical intervention for pheochromocytoma is indicated after elective cesarean delivery.

Moreover, once the diagnosis of pheochromocytoma has been established, careful pedigree evaluation is essential to consider possible two pheochromocytoma-associated inherited cancer syndromes, multiple endocrine neoplasia type 2 (MEN-2) (with medullary thyroid carcinoma and hyperparathyroidism) and von-Hippel-Lindau disease (with retinal angioma, hemangioblastoma of the central nervous system, renal cell carcinoma, pancreatic cyst, and epididymal cystadenoma). Jimenez et al. recommended that sporadic pheochromocytoma had a higher hereditary tendency in patients at a young age, during pregnancy, or multifocal tumors suggestive of inherited syndrome. It is important to identify the two autosomal dominant inherited disorders, because the risk of other tumor involves not only the index patient but also the whole family. Hence, all pregnant women with definite pheochromocytoma should be considered to evaluate for these associated syndromes and offer genetic screening.

Physicians are more likely to consider possible underlying pheochromocytoma in a pregnant woman when hypertension occurs before 20 weeks of gestation. However, pheochromocytoma can also mimic preeclampsia after 20 weeks gestation, just as in our case. In this situation, it is easily missed and can cause maternal and fetal mortality. In a recent review article, Oliva et al suggested when there is persistence of symptoms, classic signs and symptoms of pheochromocytoma (headache, sweating, palpitation, and proxysmal change in pulse and blood pressure) and a failure to lower blood pressure despite multidrug maximal therapy in pregnancy, a high index of clinical suspicion and careful history taking must be obtained. All those at risk should be investigated to achieve an early diagnosis of pheochromocytoma in pregnancy and prevent unexpected catastrophic outcomes. Early diagnosis and prompt treatment of peripartum pheochromocytoma require the collaboration of cardiologists, obstetricians, experienced anesthesiologists, and general surgeons to insure the best outcomes for both mother and baby. Finally, despite the good maternal and fetal outcomes in our case, an undiagnosed peripartum pheochromocytoma does not always have such favorable results. We must be vigilant and carefully deal with gestational hypertension to escape from such a dangerous pitfall.
REFERENCES