Pheochromocytoma in pregnancy: a case report


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Abstract. – BACKGROUND: Pheochromocytoma (PHEO) in pregnancy is a rare disease, and the management of this situation is not well established. The misdiagnosis of the disease often leads to adverse outcomes for both mothers and infants.

CASE REPORT: Here, we describe a case of a pregnant woman at 25 weeks' gestation presenting with headache, chest tightness, and shortness of breath, which was found to have a left adrenal mass and hypertensive urgency and diagnosed pregnancy with PHEO in our hospital. The timely diagnosis and proper treatment came with an optimal maternal and fetal outcome.

CONCLUSIONS: The case of pheochromocytoma in pregnancy we report demonstrated that early diagnosis and a multidisciplinary approach ensured a favorable prognosis for both maternal and fetal, and we also addressed the importance of individual basis evaluation during the whole journey.

Key Words: Pheochromocytoma, Pregnancy, Hypertension.

Introduction

Pheochromocytoma (PHEO) is a rare tumor that develops from the chromaffin cells of the adrenal medulla or the sympathetic/parasympathetic ganglia, which secrete a large amount of catecholamine (CA). PHEO is much rare in pregnancy and causes malignant hypertension. The reported prevalence rate in the literature is only 0.007%. It is commonly misdiagnosed, and this can lead to adverse outcomes for both maternal and fetal. According to previous reports, the maternal and fetal mortality rate reaches 58% when failing in timely diagnosis and treatment, while early recognition decreases the maternal mortality rate to less than 5% and the fetal death rate to less than 15%. Therefore, for such patients, early recognition of PHEO before or during pregnancy is crucial to a good prognosis. However, not many cases of pregnancy complicated with PHEO have been reported. This paper illustrates the case of a pregnant woman, diagnosed with PHEO, and successfully treated in the Second Affiliated Hospital of Guangxi Medical University. This case report was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University.

Case Presentation

A 35-year-old woman at 25 weeks gestation was admitted to the hospital on August 6, 2020, complaining of dizziness, and headache for 5 days. The patient had a history of paroxysmal hypertension episodes for the past 2 years, and has suffered from dizziness, headache, chest tightness, shortness of breath, general fatigue, and other discomforts since 2018, with a maximum history of blood pressure of 200/120 mmHg (1 mmHg = 0.133 kPa), but she did not follow doctors’ advice and failed to get regularly monitored and treated. On July 2, 2020 (16th week of pregnancy), the blood pressure measured in the Outpatient Department was 188/112 mmHg, for personal reasons, she refused the recommendation of hospitalization after being fully informed by the doctor. On August 1 (24th week of pregnancy), the patient suffered from dizziness again with systolic blood pressure at 120/200 mmHg and diastolic blood pressure at 62/94 mmHg. The local hospital diagnosed her with severe preeclampsia then she was admitted. A routine urine examination showed negative urine protein. After treatment with magnesium sulfate, labetalol, and nifedipine, the blood pressure was poorly controlled, then she was referred to our hospital.
Patient history: a healthy baby girl was delivered via cesarean section full-term in 2014. In 2016, the patient was diagnosed with thyroid papillary adenocarcinoma and received surgery and postoperative radiotherapy.

After being admitted to our hospital, the patient still complained of dizziness, headache, dyspnea, convulsions, and no vomiting, with maximum values of systolic blood pressure at 108/210 mmHg and diastolic blood pressure at 76/147 mmHg. No edema in both lower limbs, the abdominal bulge was consistent with the gestational week without any signs of uterine contraction, and the fetal heart rate was around 150 bpm. Urinary protein collection over 24 hours was 375.1 mg.

OGTT result: 4.14-10.95-10.14 mmol/l. No abnormality was found in platelet, liver, and kidney function. Electrocardiogram (ECG) showed sinus tachycardia. The ultrasound of the fetus, thyroid ultrasound, and cardiac ultrasound were all normal during the workup.

The abdominal ultrasound revealed a 3.0 × 2.7 cm hypoechoic mass over the left kidney, which was considered an adenoma.

In the left adrenal area, magnetic resonance imaging (MRI) revealed a well-defined, round mass with a maximum diameter of 3.3 cm. In T2-weighted images, the mass was highly intense (described as light bulb bright) in some areas, which is a typical characteristic of PHEOs. Neither the extra-adrenal location nor lymph node metastasis was spotted (Figure 1).

Urinary vanillylmandelic acid (VMA) levels over 24 hours were high (Table I).

To determine the best treatment plan, the multidisciplinary team, including experts of obstetricians, urologists, endocrinologists, and cardiovascular physicians, had a thorough discussion. The diagnosis of PHEO in pregnancy was confirmed. Alpha- and beta-blockers (prazosin and labetalol) combined with nifedipine were used to treat hypertension. Blood pressure was monitored continuously over 24 hours, recording a minimum of 70/51 mmHg and a maximum measurement of 235/136 mmHg, the blood pressure increased significantly in the early morning. Thus the medication was adjusted according to her situation: labetalol 100 mg (8:00, 16:00, 23:00), nifedipine 20 mg (11:00, 23:00), prazosin 1 mg (20:00), prazosin 4 mg (1:00), and prazosin 2 mg (4:00). the blood pressure was under control after the adjustment, and the heart rate was less than 100 bpm.

Afterward, the pregnancy journey was closely supervised. On September 28, 2020, at 33 weeks gestation, due to blood pressure fluctuations, an uncomplicated elective C-section was performed to terminate the pregnancy under epidural anesthesia combined with general anes-

<table>
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<th>Table I. Patient’s adrenal hormone levels.</th>
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<td><strong>Value</strong></td>
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<tr>
<td>24-h urine VMA</td>
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<tr>
<td>24-h urine CA</td>
</tr>
<tr>
<td>Epinephrine</td>
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<td>Norepinephrine</td>
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<td>Dopamine</td>
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<td>3-methoxytyramine</td>
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A healthy girl infant weighing 1,990 g was delivered. As to tumor management, due to the emergency of unstable blood pressure, there was not much time left for the urologist to perform the routine preoperative preparation, besides, dilatation at that time could bring extra risks for the patient, therefore, the urologist recommended that the adrenalectomy should be delayed for 2-4 weeks. On September 29, 2020, the patient was admitted to the Urology Department, and the adrenal CT was rescheduled to confirm the left adrenal space occupation (about 3.0 cm × 3.5 cm × 3.3 cm in size), considering PHEO (Figure 2). The medications were adjusted based on the patient’s blood pressure: prazosin 5 mg q 6 h, labetalol 150 mg (8:00, 16:00, 23:00), and nifedipine 30 mg qd, the blood pressure was well-controlled. On October 14, 2020, laparoscopically left adrenalectomy was performed under general anesthesia, without remarkable blood pressure fluctuations (Figure 3). The pathologist confirmed the suspected diagnosis of PHEO (Figure 4). Because the patient’s mother and her brother also had a history of thyroid cancer, we recommended the family a genetic test to rule out the multiple endocrine neoplasia (MEN), but they refused due to financial concerns. During the follow-up visits, the blood pressure was normal, and the blood catecholamine (CA), metanephrine and normetanephrine (MNs), and urinary VMA returned to normal.

**Figure 2.** Coronal CT view of the left adrenal gland.

**Figure 3.** Left adrenal mass.

**Figure 4.** Pathological section of the left adrenal mass (HE staining, magnification × 200).
Discussion

PHEO is most common in the adrenal medulla (about 85%)2, which is a neuroendocrine tumor, and 87% of patients with PHEO during pregnancy have hypertension3, putting the patients at risk for cardiovascular and cerebrovascular accidents, PHEO crisis, placental abruption, fetal hypoxia, and intrauterine fetal death, all of which pose a serious threat to the life of mothers and infants4,8. According to recent research2,10, the maternal mortality rate of pregnancy complicated with PHEO is 8%, and the fetal and neonatal mortality rate is 17%. The maternal and infant mortality rates can be significantly reduced if there is an early diagnosis. The main symptom of PHEO is hypertension, which can be misdiagnosed as preeclampsia. Therefore, for pregnant women with hypertension, we must be aware of the likelihood of PHEO and differentiated from preeclampsia, early diagnosis is crucial.

Preeclampsia causes persistent hypertension, which is usually accompanied by a positive urine protein test or other organ function damage, and it often occurs after 20 weeks of pregnancy. Hypertension caused by PHEO can develop before or during pregnancy, with characteristics of paroxysmal hypertension. Supine hypertension can be seen due to the tumor compression by the enlarged uterus while standing upright leads to hypotension2,11. Furthermore, other symptoms such as palpitation, headache, and sweating are the classic triad of PHEO, but hyperglycemia helps with differential diagnosis12.

Excessive of CAs (epinephrine, norepinephrine, and dopamine) or their O-methylated metabolites (metanephrine, normetanephrine, and 3- methoxytyramine, respectively) in plasma or urine is essential in establishing the diagnosis of PHEO, with the sensitivity and specificity of plasma MNs being 99% and 89% respectively, and of urinary MNs being 97% and 93% respectively13. B-ultrasound and magnetic resonance imaging (MRI) are recommended for examination during pregnancy. MRI is the best choice during pregnancy because of no radiation, high sensitivity, and accurate positioning2,13. The patient, in this case, showed elevated blood pressure before pregnancy, which was accompanied by dizziness and headache, and her blood glucose increased during pregnancy. In a local hospital, it was treated as preeclampsia, and the blood pressure was poorly controlled. Ultrasound and MRI showed mass in the left adrenal space. The levels of urine VMA, CA, and MNs over 24 hours were significantly increased. PHEO was confirmed after a multidisciplinary team (MDT) discussion, and the diagnosis was verified by the postoperative histopathological examination. The fetus showed no abnormalities when the patient was evaluated for the first time. Obstetricians should be vigilant about pheochromocytomas and paragangliomas (PPGL)/multiple endocrine neoplasia (MEN) and be very cautious with patients with extremely abnormal hypertension history. If a patient is diagnosed with a tumor before or in the early stages of pregnancy, there is a possibility of undergoing surgical treatment to remove it.

In the past, PHEO was considered sporadic, but with the advancement of sequencing technology, it was shown that 30-40% of patients with PHEO had a close relationship to hereditary autosomal dominant syndrome6,14, and 20-30% of patients had gene mutation. There are several familial syndromic disorders associated with adrenal PHEO: von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NFI), neurofibroma protein, transmembrane protein 127, H-RAS HRAS proto-oncogene, etc15. Multiple endocrine neoplasia type 2A (MEN2A) is characterized by medullary thyroid cancer (MTC) in all patients, PHEO in 50%, primary hyperparathyroidism in 20%, and cutaneous lichen amyloidosis in 5%. The patient herself, in this case, with her mother and her brother, shared the same history of thyroid cancer. We recommended them to take the test to rule out the MEN syndromes, unfortunately, they refused further genetic testing due to financial concerns.

Surgery is the most effective for PHEO. Fully preoperative preparation is the key to ensuring the safety of both maternal and fetal, as well as the effectiveness, by means of controlling blood pressure, correcting arrhythmia, and expanding blood volume. At present, α-blockers (such as phenoxybenzamine, etc.) are commonly used before the operation, which can antagonize the effects of CA and improve the prognosis, but it also comes with effects such as maternal tachycardia, neonatal hypotension, and decreased placental circulation8, so it requires liquid volume expansion and β-blockers that correct the tachycardia. This is the reason why tumor resection was performed 2 weeks after C-section for this patient. Doxazosin and prazosin, which are selective α-1 receptor blockers, have no such adverse effects, and they are more recommended16. However, α-1 receptor blockers are less effective in managing blood pressure when the control is not ideal, so calcium channel
Blockers (such as nifedipine) are usually added\(^\text{17}\). It should be noted that β-blockers should not be given without prior appropriate alpha blockade, or it will cause hyperadrenergic states in patients with PHEO. Labetalol is a combined beta-adrenergic and alpha-adrenergic blocker that can effectively lower blood pressure and slow down heart rate. As a first-line antihypertensive drug for the treatment of gestational hypertension\(^\text{18}\), it is safer than other receptor blockers compared with metoprolol, propranolol, and other β-blockers. Pregnancy could be continued to term or not depending on whether blood pressure is controlled with medicine. If blood pressure cannot be controlled, the fetal survival chance shall be assessed carefully, and the delivery should be performed after fetal pulmonary maturation therapy\(^\text{19}\).

Laparoscopic tumor resection is the first choice for PHEO\(^\text{20}\), and the timing of tumor resection should be comprehensively considered with gestational age. Due to the high risk of abortion in early pregnancy and the limited operating space in late pregnancy, the operation in the second trimester of pregnancy is preferred. If PHEO is diagnosed before 24 weeks gestation, tumor resection can be performed after adequate preoperative preparation. Medication treatment could be used until delivery or after delivery if patients are diagnosed after 24 weeks of pregnancy\(^\text{20-22}\). To evaluate the surgical removal of the tumor, the CA level in plasma or urine was measured 2-6 weeks after surgery.

PHEO crisis can be caused by tumor compression and pain stimulation during vaginal delivery. Previous studies\(^\text{5}\) showed a higher maternal mortality rate in vaginal delivery than in C-sections, considering a better control of blood pressure during cesarean section. C-section is generally considered as the preferred mode of delivery.

### Conclusions

PHEO in pregnancy is a rare disease that seriously endangers the life of maternal and fetal, and it is easy to confuse with preeclampsia. Clinicians should be aware of the presence of PHEO in hypertensive pregnant women and get an earlier diagnosis. MDT discussion is essential to develop individualized treatment according to the patient’s gestational age, PHEO functional status, and treatment effect. Furthermore, the screening for susceptibility genes in suspected groups of patients is of great significance for the prevention, diagnosis, and treatment of PHEO in the future.

### References

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