Pheochromocytoma with Negative Urinalysis in Pregnancy

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We present a rare case of adrenal pheochromocytoma in pregnancy, with serial 24-h urine specimen collections showing normal concentrations of catecholamine metabolites. The diagnosis was based on clinical presentation, abdominal ultrasound, and magnetic resonance imaging, and was confirmed on post-operative pathohistological examination. Clinical suspicion of pheochromocytoma in pregnancy should be sufficient to implement adequate therapeutic measures, regardless of urine catecholamine concentrations.

Key words: diagnosis, differential; metanephrine; pheochromocytoma; pregnancy outcome; urinalysis; vanilmandelic acid

Case Report

A 37-year old woman, gravida 3, para 3, was referred to the Department of Internal Medicine of the Zagreb University Hospital Center by her primary care gynecologist at the 23rd week of gestation. Her two previous pregnancies were uneventful and she had no significant family history. She had a 10-month history of intermittent weakness attacks associated with paroxysmal arterial blood pressure elevations ranging from 110/60 to 170/90 mmHg, palpitations and pallor, followed by facial flushing. Several weeks prior to admission she had had episodic uterine tenderness and contractions, with nausea and vomiting. Her appetite was good and she had gained 5 kg during pregnancy. She had not been taking any medication during the pregnancy. On admission, her blood pressure was 115/70 mmHg, pulse rate 96/min, and clinical examination revealed no abnormalities. Her full blood count, blood glucose level, blood electrolyte levels, and urinalysis were normal. Twenty-four-hour urine specimens were collected on 5 occasions and showed normal concentrations of norepinephrine, epinephrine, or one of their metabolites. Once the biochemical diagnosis is made, the presence and exact localization of the tumor should be confirmed by computed tomography or magnetic resonance imaging (6). However, not all usual symptoms are necessarily present and the obstetrician has to suspect the presence of tumor early enough to protect the lives of the mother and fetus (1-6). We described a case of pheochromocytoma in pregnancy associated with persistently normal urine catecholamine metabolites.

Pheochromocytoma is a rare medical complication in pregnancy, with only several hundreds of cases reported in the medical literature (1-4). Arterial hypertension is the leading symptom of the disease, often indistinguishable from pregnancy-induced hypertension or pre-eclampsia, a mistake that can be fatal for both the mother and the fetus (2). Maternal mortality rate from undiagnosed disease is around 50%, decreasing significantly if the diagnosis is made antepartum and followed by surgical treatment and careful perioperative management (3,4). Unfortunately, fetal loss rate remains high (15-50%), even when the diagnosis is made antenatally (4,5).

If pheochromocytoma is present, 24-h urine specimens should reveal increased concentrations of norepinephrine, epinephrine, or one of their metabolites. Once the biochemical diagnosis is made, the presence and exact localization of the tumor should be confirmed by computed tomography or magnetic resonance imaging (6). However, not all usual symptoms are necessarily present and the obstetrician has to suspect the presence of tumor early enough to protect the lives of the mother and fetus (1-6). We described a case of pheochromocytoma in pregnancy associated with persistently normal urine catecholamine metabolites.
nostic work-up and surgical removal of the adrenal tumor was postponed until after delivery. The patient was released and advised to check her blood pressure every day and take labetalol if her blood pressure rises again.

Five weeks later, at the 28th week of gestation, she was admitted to the same Department, following several episodes of sudden rise in blood pressure (up to 180/100 mmHg), combined with strong, pulsating headaches, palpitations, nausea, and vomiting. The daily labetalol dose was increased up to 800 mg/day, without any significant effect on blood pressure level. On admission, her blood pressure was again normal, 100/55 mmHg, pulse rate was 88/min., as were other laboratory tests. Twenty-four-hour urine specimens were collected 10 times, but the quantities of norepinephrine, epinephrine, and VMA remained normal in all collections. A therapy with an α-blocker, phenoxybenzamine (10 mg 2 times daily, increasing to 20 mg 2 times daily) was introduced.

During the first day of such therapy, the patient's blood pressure decreased to 80/50 mmHg, and 0.9% saline infusion had to be given to correct the vasodilating effect of exaggerated α-blockade. All symptoms gradually disappeared. Fetal growth and well being were checked regularly. At 32 completed weeks of pregnancy, dexamethasone was administered to reduce the risk of fetal lung immaturity. The patient was transferred to the urology unit for preoperative assessment. At 32±3 weeks of gestation, cesarean section was performed, immediately followed by the right adrenalectomy. A slightly growth-restricted male child was delivered, weighing 1,860 grams, 42 cm long, with Apgar scores 5 at 1 minute and 8 at 5 minutes. The post-operative period was uneventful for both the mother and the neonate, and both were discharged after 10 days. Pathohistological examination of the removed adrenal gland confirmed the diagnosis of pheochromocytoma. Seven months after the surgery, the woman has remained healthy. Her blood pressure has been stable at 120/80 mmHg without any other complaints.

Discussion

Current diagnostic methods and management of pheochromocytoma in pregnancy have dramatically improved maternal and even fetal survival. Most case reports published to date undoubtedly stress the importance of early diagnosis and immediate operative treatment of the disease (1,5-7). Our patient suffered from intermittent hypertension, palpitations, pallor, and nausea before the onset the pregnancy, but the diagnosis of pheochromocytoma was not even suspected. During early pregnancy, the symptoms continued and worsened as the pregnancy progressed. Differential diagnosis included malignant hypertension, congestive heart failure, hypertension, early onset pre-eclampsia, and hypertensive crisis caused by other diseases, including pheochromocytoma. It was important to make the diagnosis quickly, since cardiac output markedly falls even during mild paroxysmal hypertension, adversely affecting both the mother and the fetus (8). The absence of proteinuria, edema, and hyperuricemia, and the fact that hypertension crises predated pregnancy, strongly pointed towards causes of arterial hypertension other than preeclampsia. In our patient, the correct diagnosis was not made initially because her 24-hours urine specimens, collected 15 times, repeatedly showed normal quantities of catecholamine metabolites. It was felt that, since plasma catecholamine testing was insensitive and technically difficult to perform (6), the diagnosis of pheochromocytoma needed to be confirmed by elevated quantities of VMA, fractionated metanephrines and catecholamines in 24-hours urine specimens. The sensitivity of urinary VMA and metanephrine for diagnosing a pheochromocytoma is 98% and 90%, respectively (9). However, the difficulty of “catching” rare episodic hormonal secretion of the tumor in the hospital setting has been observed in several previously reported cases (2,7-12). Stimulation tests, used in such situations, had to be avoided in pregnant women because of high risk of fetal loss (3). The first important clues to the diagnosis in our case were ultrasound and magnetic resonance scans, which revealed tumor mass in the suprarenal gland. Primary tumors other than pheochromocytoma, as well as metastatic lesions, were also considered, since magnetic resonance imaging is not decisive for definite diagnosis. Another important clue was successful therapy with an α-blocker, phenoxybenzamine. We had no opportunity to analyze plasma levels of recently discovered markers of neuroendocrine differentiation or vasoactive substances produced in adrenal medulla, such as chromogranin, pancreastatin (13) or plasma neuropeptide Y (14), which could explain intermittent hypertensive episodes. However, the combination of patient’s clinical presentation, imaging, and therapeutic effect of α-blockers strongly suggested the possibility of adrenal pheochromocytoma.

The timing of surgical excision of pheochromocytoma in pregnancy depends largely on the gestational age (5,11). Laparoscopic removal of the tumor has been recently reported as an alternative to surgical resection in early pregnancy (11). Our management plan was to monitor the patient’s response to medical therapy and plan the timing of delivery accordingly. The woman remained asymptomatic, the fetus appeared to be thriving, and we decided to prolong the pregnancy until 32 weeks and then perform a cesarean section and a right adrenalectomy at the same time. This is in accordance with the recommendations from the literature (3,10,15). It was mandatory to achieve normal blood pressure levels at least 1-2 weeks before surgery to avoid significant intraoperative complication (15). This was successfully accomplished with α-blocking agents, allowing the re-expansion of maternal vasculature. The only transitory complication of the therapy was arterial hypotension, corrected with saline infusions. There were no episodes of cardiac arrhythmia or tachyphylaxis, and there was no need for urgent pharmacological or surgical intervention during the antenatal period. Although there are several reports on severe hypertensive complications during and after the surgery, probably due to catecholamine release (3,15), cesarean section and removal of the tumor were uncomplicated, as was the post-operative course.

This case shows that pheochromocytoma in pregnancy can exist without clear biochemical confirmation of the disease. The opposite is also true, i.e., catecholamine levels can be elevated without tumor be-
ing found at surgery (2,12). Therefore, if clinical suspicion is strong, all available diagnostic methods should be used, including imaging, followed by pharmacological therapy, with close multidisciplinary monitoring. Repeatedly negative biochemical findings do not exclude the presence of pheochromocytoma, and there should be no difference in the management of biochemically evident and suspected cases of pheochromocytoma in pregnancy.

References


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