Case Report
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LARGE PHEOCHROMOCYTOMA IN THE THIRD TRIMESTER OF GESTATION. CASE REPORT

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Abstract

Introduction. Pheochromocytoma is a rare clinical finding during pregnancy. Due to the variable clinical presentation it may be mistaken for preeclampsia or primary hypertension. The early antenatal diagnosis is crucial, because it reduces possible maternal and fetal complications. Pheochromocytomas are usually benign, but may also present as or develop into a malignancy. Malignancy requires evidence of metastases at non-chromaffin sites distant from that of the primary tumor. Large tumor size and malignant disease are not necessarily associated.

Case. The patient, a 39 years old multipara presented at 30 weeks of gestation with labile hypertension, headache and palpitations. She had a 6 years history of chronic hypertension controlled during the pregnancy with methyldopa. Using this treatment blood pressure was maintained at 140/100 mmHg. Further biochemical and radiological investigations confirmed the diagnosis of pheochromocytoma. The patient was invasively monitored and treated with alpha-adrenoblockers. Childbirth was performed by elective cesarean section at 34 weeks with simultaneous right-sided adrenalectomy. Postoperative period was uneventful. Histological examination of 12 cm encapsulated tumor revealed trabecular type pheochromocytma with focal capsular invasion. Although the usual criteria for malignancy, such as mitotic activity, nuclear pleomorphism, are not suitable to discern benign from malignant pheochromocytomas, we considered this large tumor presumably malignant in order to provide systematic long-term follow-up. Postoperative biochemical and imagistic screening was planned to detect and treat local recurrence or metastatic tumors.

Conclusions. A multidisciplinary team to diagnose and treat pheochromocytoma during pregnancy is mandatory. Careful postoperative monitoring of recurrent disease is necessary indefinitely.

Key words: large pheochromocytoma, pregnancy.

INTRODUCTION

Pheochromocytoma is a rare tumor originating from the chromaffin cells in the adrenal medulla, and with less frequency, from the chromaffin cells at the extra-adrenal sites in the body (paragangliomas). The incidence of pheochromocytoma is 2 to 8 per

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million persons per year (1). Only 10-20% of these cases have extra-adrenal localization (2). The peak incidence occurs in the third to fifth decades of life. The incidence is equal between males and females (3).

According to their biological behavior, pheochromocytomas are mostly benign tumors, with a distinctive clinical manifestation of paroxysmal hypertension crises, due to the excessive production of a different quantity of adrenaline and noradrenaline from the chromaffin cells. More rarely, these symptoms occur owing to hyperproduction of dopamine or other bioactive peptides secreted by APUD (Amine Precursor Uptake and Decarboxylation) cells (4).

There is no correlation between the size of pheochromocytoma and levels of circulating catecholamines, as well as there is no correlation between catecholamines levels and hypertension. The spectrum of clinical manifestations is so wide that a pheochromocytoma may mimic a variety of common disorders. Clinical manifestation of hypertension varies; it may be sustained or paroxysmal. The classical triade consists of headache, excessive sweating, and palpitations. Among patients with hypertension pheochromocytoma is diagnosed only in 0.1–1% (5). However, this probably accounts for only 50% of persons harboring pheochromocytoma, because it is considered that about half the patients with pheochromocytoma have only paroxysmal hypertension or are normotensive. Sometimes pheochromocytomas achieve a considerable size without any clinical manifestations (6). Pheochromocytoma is confirmed morphologically in approximately 5% of patients with adrenal incidentalomas (7). In less than 5% of the cases the biological behavior of the tumor is malignant (8). The only valid criterion that leads to such diagnosis is the existence of metastatic tumors on sites where chromaffin cells are not usually present (9).

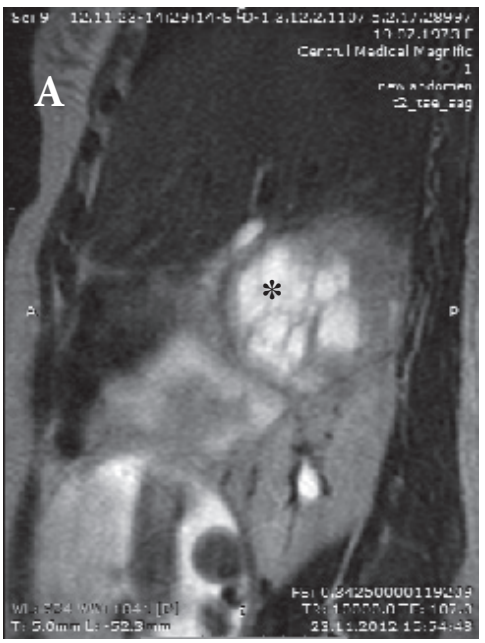
It is estimated that approximately ten to twenty-five percent of pheochromocytoma cases are genetically determined (10). There are a number of these genetic types of conditions, including Multiple Endocrine Neoplasia Syndromes (MEN), Von Hippel-Lindau, Von Recklinghausen's Neurofibromatosis, Succinic Dehydrogenase Mutation. Novel mutations that cause hereditary pheochromocytoma have been identified in the MYC-associated factor X (MAX) gene. This mutation is correlated with metastatic potential (11).

The occurrence of a pheochromocytoma during pregnancy is very rare with frequency of 0.002% (12). Review of the scientific literature identifies approximately 200 cases of such association. For such country as Moldova with about 40.000 live births per year, it means only one diagnosed case in several years. Timely recognition of this condition during pregnancy is very important, since untreated tumor constitutes a very high risk for both mother and fetus. Nowadays, in such situations fetal and maternal mortality rates remain at 17 per cent and 8 per cent respectively, even with proper treatment (13).

The main causes of maternal morbidity and mortality are cardiovascular complications (arrhythmias, acute coronary syndrome and myocardial infarction,

cardiomyopathy, stroke, pulmonary edema, etc.), which occur mostly during the peripartum period. The fetal risks are determined by the vasoconstrictive effects of catecholamines on the placental circulation and include placental abruption and intrauterine hypoxia.

We describe a case of pheochromocytoma during pregnancy, which is distinct because of a large size of the tumor and unclear clinical presentation resulted in late diagnosis and operation in the third trimester of the gestation.



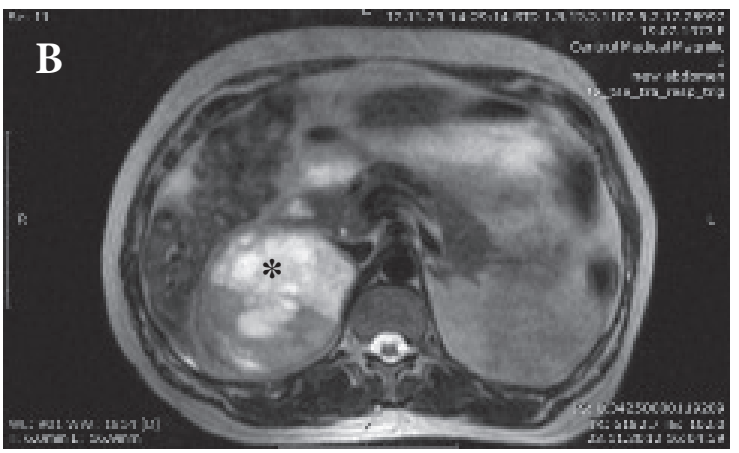


Figure 1 A, B. MRI images of the large right adrenal tumor* which compresses inferior vena cava. Note the internal septa on the sagittal view.

CASE PRESENTATION

A 39 year old woman, para 4, presented during gestation week 30 with hypertension-associated headache, palpitations and fatigue. She was diagnosed with hypertension in 2006 during the third pregnancy when, at 30-34 weeks, an elevation of blood pressure values up to 160-180/100 mmHg was observed. This state was treated as preeclampsia and the pregnancy finalized with a vaginal delivery of a full-term, healthy infant. During the fourth pregnancy in 2012 her blood pressure readings varied between highs of 140-180/100 mmHg and normal values. Treatment with Methyldopa (250 mg twice a day, 29 weeks) and acetylsalicylic acid was initiated with maintaining of blood pressure at 140/100 mmHg. Routine abdominal ultrasound revealed a large, 120 x 85 mm, heterogeneous, hyperechoic mass at the upper pole of the right kidney.

This finding was confirmed by MRI scan, which showed a retroperitoneal right adrenal tumor of 115 x 90 x 85 mm, with mixed structure (having

both cystic and solid components). This mass had well-defined contours and a hypointense capsule on both T1- and T2-weighted images. The right adrenal gland was not visualized. The tumor compressed and displaced inferior vena cava, but without signs of thrombosis or extracapsular invasion (Figure 1).

Further investigations were consistent with pheochromocytoma. Plasma free metanephrines were markedly elevated: metanephrine – 1621.5 pg/mL (normal: <90), normetanephrine: 5358.7 pg/mL (normal: < 180). Urinary fractionated metanephrines measured: metanephrine fraction – 9219 μg / 24 hours (normal: < 375), normetanephrine fraction – 10982 μg / 24 hours (normal: < 550), 3-methoxytyramine - 832 μg/ 24 hours (normal: < 460). Serum cortisol was within normal range – 166 nmol/L. Thyroid-stimulating hormone and thyroglobulin were both within normal limits: 1.2 mIU/L and 11 ng/mL respectively. Comparative data regarding essential hormonal values before and after the intervention (at 1 month follow-up visit) are reflected in Table 1. The treatment was changed to phenoxybenzamine 10 mg twice daily, 10 days for preoperative alpha-blockade. After 5 days of phenoxybenzamine administration atenolol (25 mg once a day) was added. Patient maintained acceptable blood pressures until gestational week 34, when she underwent elective cesarean section. The newborn's 1 minute and 5 minute Apgar score was 8 and 9 respectively, birth weight was 3200 g and birth length 51 cm. After delivery of a healthy neonate, excision of the pheochromocytoma was performed. Postoperatively she became normotensive and antihypertensives were discontinued. The mother and infant had uneventful postoperative courses and were discharged 1 week later. Six month postoperatively, the patient was normotensive with 24 hour urinary catecholamine metabolites within reference range. Gross pathology demonstrated a large tumor, 12x9x7 cm of the right adrenal gland with multiple cystic cavities and smooth fibrous capsule envelope (Figure 2). Microscopic examination revealed tumor cells arranged in trabecular pattern and interrupted by fibrous septa with focal necrosis (Figure 3A). Tumor cells are polygonal with finely granular and eosinophilic cytoplasm. Several foci of capsular invasion

Table 1. Essential hormonal values before and after the intervention

Parameter	Value before the intervention	Value at 1 month after the intervention	Reference range
Metanephrine, urine (mcg/24h)	9219.0	215	< 377
Normetanephrine, urine (mcg/24h)	10982.0	834	< 550
3-methoxytyramine, urine (mcg/24h)	832.0	267	<460
Metanephrine, plasma(pg/mL)	1621.5	8.4	<90
Normetanephrine, plasma (pg/mL)	5358.7	31.3	<180
VMA urine(mg/24h)	3.74	---	1-11
Cortisol, plasma 8.00(nmol/L)	166	174	147-720
TSH,plasma(mlu/L)	1.2	---	0.17-4.05
Thyroglobulin, plasma(ng/mL)	11	---	<78

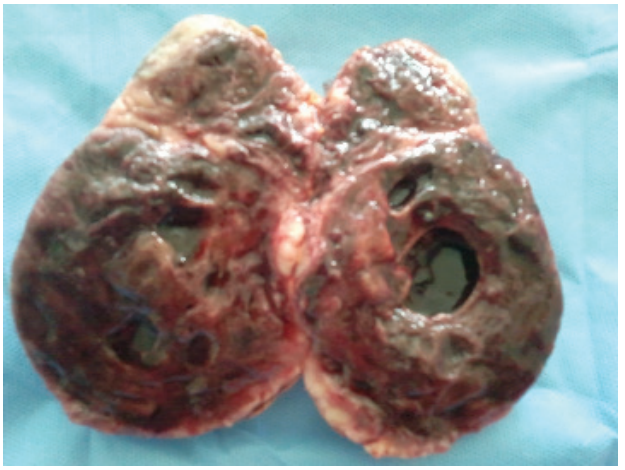


Figure 2. Macroscopic view of encapsulated adrenal tumor, 12 x 9 x 7 cm. The tumor is mixed solid and cystic pheochromocytoma with zones of necrosis.

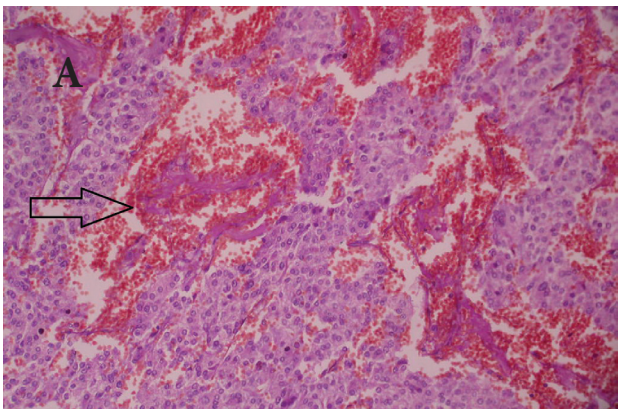


Figure 3 A. Pheochromocytoma showing trabecular pattern with zones of haemorrhage (arrow).

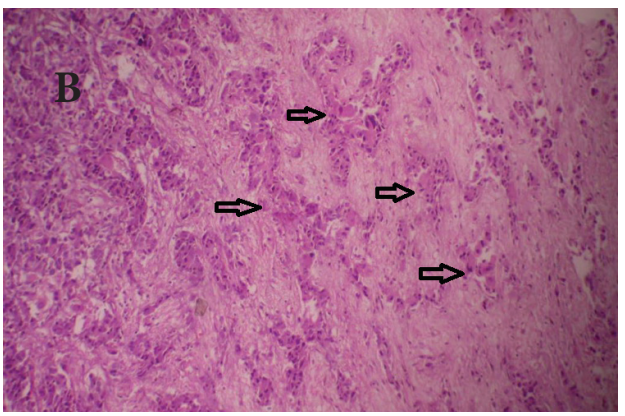


Figure 3 B. Islets of tumor cells interspersed between fibrous bands at the spot of capsula invasion (arrows).

were observed (Figure 3B).

This tumor was considered presumably malignant and the patient scheduled for long-term monitoring, with repeat catecholamine testing and MRI or positron emission tomography/magnetic resonance (PET/MR) every 12 months, for signs of local tumor recurrence or metastasis.

DISCUSSION

Typical symptoms of pheochromocytoma such as headache and sustained hypertension are not uncommon during pregnancy. In spite of rarity of this condition during gestation, a high index of suspicion is necessary to establish an early diagnosis and to improve the overall outcome. Recently published systematic review demonstrated that higher survival rate (both mother and fetuses) was achieved when the diagnosis of pheochromocytoma was made in the antenatal period than when it was made during labour or immediately postpartum (14). In our case the presence of adrenal tumor could be thought of much earlier: during the third pregnancy, when the elevated blood pressure was observed

for the first time. Clinical suspicion of pheochromocytoma in pregnant patient must be verified by measurement of urinary metanephrines and abdominal echographic examination. The next diagnostic step is use of T2-weighted MRI, which is the imaging procedure of first choice since CT scanning involves radiation exposure.

The main goal of preoperative management of a pregnant pheochromocytoma patient is to normalize blood pressure and heart rate for at least 2 weeks prior to surgery. In this period the function of other organs and of placenta is improved, thus risk to the fetus is minimized. The secondary objective is prevention of postoperative catecholamine release and its consequences on the cardiovascular system. The optimal time for surgery is either early in pregnancy or after delivery by cesarean section (in the same session or at a later date) (15). It is preferable to remove the tumor in the second trimester of the gestation before the age of fetal viability (24 weeks of gestation), because the risk of spontaneous abortion is higher in the first trimester. In our case the diagnosis was established late, in the third trimester, the intervention was postponed 4 weeks, giving the chance for better fetal maturation.

Long-term follow-up of patients who underwent removal of pheochromocytoma demonstrated that a certain number of them have persistent benign hypertension which may require treatment and some patients develop malignant pheochromocytoma many years after the operation.

Malignant pheochromocytomas are histologically and biochemically the same as benign ones. Vascular invasion, cellular atypia, and even local recurrence do not definitively identify a pheochromocytoma as malignant. Thus, the only clue to the presence of a malignant pheochromocytoma are distant metastases, which may occur as long as 15 years after resection (15, 16). Larger tumors and extra-adrenal tumors are more likely to exhibit malignant behavior (17). The 5 year survival rate for malignant disease is estimated to be between 34% and 60%, depending on the location of metastasis (18). We prefer to consider presented case to be a presumable malignant pheochromocytoma, due to large tumor size, macroscopic zones of necrosis and microscopic capsular invasion. Thus, careful monitoring for other sites of recurrent disease will be necessary indefinitely.

Existing diagnostic tools often do not allow early detection of pheochromocytoma recurrence. Reported false-negative rate of MIBG scintigraphy is 10% (19). A recent publication from Germany shows possibility of excellent PET/magnetic resonance imaging and tumor dosimetry based on high spatial resolution using metaiodobenzylguanidine (mIBG) labeled with 124-iodine (20).

The improved management of pregnant patients with pheochromocytoma is the result of awareness raising of clinicians about this pathological association, high sensitivity of available biochemical and imaging tests, improved preoperative, surgical and postoperative care.

The crucial factor for better prognosis is earlier recognition of the potential presence of a

pheochromocytoma in a pregnant patient with hypertension. Additional benefit can be expected if these patients are treated by a multidisciplinary team with high-level expertise in this specific field. We emphasize on the importance of long-term postoperative follow-up even in the apparently benign cases.

Conflict of interest

We declare that there is no conflict of interest.

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