Case Report/Caso Clínico

Multiple endocrine neoplasia 2A syndrome and pregnancy

Síndrome de neoplasia endócrina múltipla 2A e gravidez

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Abstract

Pheochromocytoma during pregnancy is a rare but potentially dangerous condition. It has been historically associated with maternal mortality, especially when misdiagnosed. We report the case of a 36 year-old pregnant woman, diagnosed with a familial pheochromocytoma, as part of a multiple endocrine neoplasia 2A syndrome. Contrary to previous reports this case had normal maternal and fetal outcomes.

Keywords: multiple endocrine neoplasia 2A syndrome; pheochromocytoma; hypertension; pregnancy

INTRODUCTION

Pheochromocytoma complicating pregnancy is a rare event, even rarer when associated with medullary thyroid carcinoma and hyperparathyroidism, as part of Multiple Endocrine Neoplasia 2A (MEN 2A) syndrome. Due to the effects of catecholamines on blood pressure and on uteroplacental blood flow, pregnancy in a woman with pheochromocytoma is a high-risk pregnancy[1]. We report the case of a pregnant woman diagnosed with MEN 2A syndrome before pregnancy, with a pheochromocytoma, who had an unusual successful maternal-fetal outcome. A review of 41 cases reported in the literature, from 1988 to 1997, revealed that overall maternal mortality was 4% and fetal loss was 11%; antenatal diagnosis of pheochromocytoma reduced maternal mortality to 2%; however, fetal loss was 14%[2].

CASE REPORT

A 36 year-old, gravid 1, Caucasian woman, with the diagnosis of MEN 2A syndrome since 1995, presented at our Maternal-Fetal Unit with 21 weeks of gestation.

Her medical history was significant for paroxysmal hypertension, tachycardia and faintness. She was diagnosed a bilateral pheochromocytoma and submitted to right adrenalectomy in 1995 and left adrenalectomy in 1998. She was screened for RET proto-oncogene mutation which turned out positive, leading to the diagnosis of MEN 2A syndrome. Since this is an autossomal dominant condition, family members were investigated and her father was found to have a medullary thyroid carcinoma. Our patient

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was kept under thyroid sonographic surveillance, and in 2004 bilateral nodular lesions were detected and she was submitted to prophylactic total thyroidectomy. Pathohistological examination revealed a medullary carcinoma on the left lobe. Follow-up with calcitonin level assessment and cervical ultrasound scan showed no recurrence. In this case there was none hyperparathyroidism associated. Two years later she presented elevated levels of 24 hour urine normetanephrine and plasma adrenaline. A functional recurrent pheochromocytoma on the left adrenal gland was identified by computed tomography (CT) scan, and confirmed by ^{131}I-metaiodobenzylguanidine (MIBG) scan and magnetic resonance imaging (MRI). The patient refused surgical removal and was maintained on hormonal replacement therapy with L-thyroxine 0,2 mg/day, fludocortisone 0,1 mg/day and hydrocortisone 30 mg/day, which was kept unchanged during pregnancy.

Our patient was asymptomatic and her blood pressure remained within normal limits for the whole pregnancy. She refused amniocentesis for antenatal diagnosis after positive second trimester aneuploidy screening test. Fetal echocardiogram and ultrasonography, performed at 19 and 22 weeks of gestation, respectively, were normal. Urinary metanephrines and plasma catecholamines were intermittently elevated. Ultrasound for fetal evaluation was performed monthly from 22 weeks of gestation. Ultrasound scan at 31^{+5} weeks of gestation was unremarkable with fetal estimated weight of 1941g ($50/75^{th}$ percentile), biophysical profile 8/8 and normal umbilical artery fluxometry. Non-stress tests starting at 33 weeks of gestation were always reactive. Third trimester laboratorial screening, including thyroid and parathyroid function, was normal.

A multidisciplinary team (obstetrician, endocrinologist and anaesthesiologist) decided on patient admission in our Antenatal Care Unit at 36^{+5} weeks of gestation in order to monitor blood pressure and fetal well-being tighter. By this time she started treatment with an a-blocker (oral doxazosin 4 mg/day). Elective caesarean section under epidural anaesthesia was performed at 37^{+5} weeks of gestation. A normal male infant was delivered weighing 2810g, with Apgar score of 10/10 at 1^{st} and 5^{th} minute. Intravenous hidrocortisone 100mg was administered during anesthesia induction, surgery, and for the first hours after surgery in order to mimic its endogenous secretion during a stressful situation, and to avoid acute adrenal failure. Intravenous hidrocortisone 25mg 6/6 hours was administered during postpartum period, which was otherwise uneventful. The patient was discharged on day 4 with oral L-thyroxine 0,25mg/day, fludocortisone 0,1mg/day and hydrocortisone 30mg/day. Oral progestin (desogestrel 75µg/day) was prescribed for contraception.

Two months later she returned to our Maternal-Fetal Unit. She was asymptomatic and presented a blood pressure of 131/91mmHg. She maintained regular surveillance by the endocrinologist.

DISCUSSION

Pheochromocytomas are chromaffin tumours that secrete catecholamines. They are an uncommon cause of hypertension with an estimated prevalence of 0,1%[1]. Most of the tumours are located in the adrenal medulla, but 10% are found in the sympathetic ganglia. They are known as the "10% tumours" since 10% are bilateral, 10% are extra-adrenal, and about 10% are malignant; the majority occurs sporadically but approximately 10% are familial, usually bilateral. When bilateral pheochromocytoma is found, specific syndromes should be searched. These include MEN 2A (Sipple syndrome), MEN 2B (Mucosal neuroma syndrome), neurofibromatosis, Von Hippel- -Lindau disease, familial pheochromocyotoma and familial paraganglioma. Manifestations of pheochromocytoma are usually paroxysmal and consist of hypertensive crisis, seizure activity, or anxiety attacks[1]. However, hypertension is sustained in 60% of patients. Other paroxysmal symptoms include headache, profuse sweating, and palpitations, as well as chest pain, tachycardia, nausea and vomiting, pallor and flushing. The paroxysmal hypertensive crisis during pregnancy poses a difficult differential diagnosis with preeclampsia.
Diagnosis of asymptomatic patients with a pheochromocytoma has become more common because of the widespread use of computer imaging, which can incidentally find an adrenal mass[3].

Pheochromocytoma during pregnancy is a rare but potentially dangerous condition[1]. It has been historically associated with maternal mortality especially when misdiagnosed. However, ante partum recognition of this condition has become more common, providing a unique opportunity for hypertension treatment, and thus reducing maternal mortality.

In our report pheochromocytoma was familial, as part of MEN 2A syndrome, an autossomal dominant condition that includes medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism[1]. Medullary thyroid cancer is usually the first manifestation of MEN 2A syndrome due to its earlier occurrence and higher penetration[4]. However, pheochromocytoma was the first manifestation

in our patient. Mutations of the RET proto-oncogene, found in MEN 2A syndrome, are gain-of-function mutations, causing activation of tyrosine kinase, responsible for hyperplasia of calcitonin-parafolicullar cells and adrenomedullary chromaffin cells, with subsequent neoplastic transformation[5]. The specific type of mutation correlates with the aggressiveness of medullary thyroid cancer, being important in order to stratify risk and to define the type of screening in carriers[4]. In our case, information regarding specific type of RET mutation was not available. However, the patient was kept under close surveillance for thyroid disease as well as for pheochromocytoma recurrence or metastic disease.

Quantification of catecholamine metabolites in a 24 hour urine specimen is the standard screening test for pheochromocytoma[1]. CT scan can be used to locate the tumour, but MRI stands out for higher accuracy, high quality images, and lack of ionizing radiation, an important feature in pregnancy[2]. Extra-adrenal tumours may also be detected by CT or MRI, but in some cases ^{131}I-MIBG scan is necessary for location [1].

The treatment of choice for pheochromocytoma is surgical resection[2]. Before pregnancy our patient was submitted to total right adrenalectomy and three years later to partial left adrenalectomy. When bilateral adrenalectomy is performed, life-long glucocorticoid and mineralocorticoid replacement therapy is prescribed[6]. Twenty-four hour urinary excretion of metanephrines and catecholamines or plasma metanephrines should be checked annually for life, searching for metastatic disease, tumour recurrence in the adrenal bed, or delayed appearance of multiple primary tumours. Recurrence rates are highest in patients with familial disease, as in our case, or with paraganglioma. In our patient the diagnosis of residual functional pheochromocytoma was confirmed by measurements of 24 hour urine normetanephrines and of plasma catecholamines. Location of the residual tumour was accomplished with CT scan, ^{131}I-MIBG scan and MRI. However, the patient refused surgical removal.

Adverse fetal outcomes in pregnancies complicated by pheochromocytoma have been described and include fetal growth restriction, secondary to reduced uteroplacental perfusion, fetal hypoxia and fetal death as a consequence of acute hypertensive crises, with or without placental abruption, maternal collapse and maternal death[1,2]. In our case, fetal development and growth were normal, and fetal well-being tests were always reassuring.

A multidisciplinary approach was the key for success. We planned to terminate pregnancy at 37 weeks of gestation and the patient was admitted in our Antenatal Care Unit approximately one week before, in order to initiate therapy with an a-blocker for preoperative blood pressure control[2]. Because the drug of choice, phenoxybenzamine, was not available, we chose doxazosin (4 mg/day), a selective short acting a-blocker. It is believed that mechanical pressure placed on adrenal tumour by the gravid uterus, uterine contractions or expulsive efforts may cause a sudden release of catecholamines, precipitating a potentially fatal hypertensive crisis[2]. Therefore vaginal delivery is considered contraindicated and elective cesarean section is recommended[2].

In conclusion, MEN 2A syndrome during pregnancy portents maternal and fetal risk, related to pheochromocytoma and secondary hypertension. Ante partum diagnosis, referral to a tertiary centre and a multidisciplinary approach are crucial to reduce morbidity and mortality. Our case is remarkable for the successful maternal, fetal and neonatal outcome.

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