Vaginal delivery in a patient with pheochromocytoma, medullary thyroid cancer, and primary hyperparathyroidism (multiple endocrine neoplasia type 2A, Sipple's syndrome)

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ABSTRACT

Multiple endocrine neoplasia 2A (MEN 2A), or Sipple's syndrome is a rare inherited dominant syndrome, characterised by medullary thyroid carcinoma, adrenal pheochromocytoma and hyperparathyroidism, due to specific RET proto-oncogene mutations. The women with MEN 2A syndrome are at risk of complicated pregnancy because of unrecognised pheochromocytoma and transmission of RET mutation to the progeny. We report a case of a woman with MEN 2A diagnosed in early pregnancy. Alpha-blockade medical therapy was used effectively and time was given for fetal maturation. Uncomplicated vaginal delivery performed under epidural analgesia. Six weeks postpartum adrenalectomy, thyroidectomy and parathyroidectomy were performed uneventfully.

Key words: *Medullary thyroid cancer, multiple endocrine neoplasia 2A, pheocromocytoma, pregnancy*

INTRODUCTION

Multiple endocrine neoplasia type 2A (MEN 2A) or Sipple's syndrome, is a hereditary familial syndrome consisting of pheocromocytoma (PHEO) in 50% of cases, medullary thyroid carcinoma (MTC) in 90-100% and primary hyperparathyroidism (PHPT) in 20-30%.[1] The combination of Sipple's syndrome and pregnancy is very rare, with only a few cases reported in the literature. Whereas, MTC is the most aggressive tumor, PHEO raises great concern due to its life-threating manifestations. Unrecognized MEN 2A syndrome complicating pregnancy has been associated with severe life-threatening complications, including myocardial infarction, cardiovascular collapse at term, peripartum cardiomyopathy, intracranial haemorrhage and fatal adrenergic crisis.[2-5] We report a case of MEN 2A or Sipple's syndrome diagnosed in pregnancy, in which medical therapy allowed fetal maturation and vaginal delivery, followed by adrenalectomy, thyroidectomy, and parathyroidectomy.

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CASE REPORT

A 30-year-old woman (gravida 4, para 1) was initially assessed at 22 weeks gestation when presented complaining of having episodes of severe headache and noted to have hypertension (171/101 mmHg) and tachycardia (106 beats/min). She did not have appropriate and regular antenatal care. Previously, she had one uncomplicated pregnancy with term vaginal delivery and two mis-carriages. She mentioned that similar symptoms had occurred during her previous pregnancies and stated that preeclampsia was presented during all the previous pregnancies. A 24 h urine collection revealed increased levels of normetanephrine and metanephrine, which were 9.59 μmol/24 h (normal ≤ 2.13) and 4.64 μmol/24 h (normal ≤ 1.62), respectively, indicating PHEO. Biochemical investigations showed increased levels of parathormone (8.7 pmol/L with normal values 1.60-7.2) and calcitonin 325 pg/ml (normal up to 5), indicating hyperparathyroidism. Abdominal ultrasonography and magnetic resonance imaging (MRI) demonstrated a size 3.5 cm × 3.1 cm cystic mass located on the left adrenal gland. Thyroid MRI revealed thyroid nodules with bilateral

cervical lymph nodes, as well as multiple adenomatosis of parathyroid glands. Fine-needle aspiration of thyroid nodule revealed MTC. The final diagnosis was MEN 2A or Sipple's syndrome. Treatment for PHEO included oral phenoxybenzamine. For the MTC, she was advised to undergo as soon as possible total thyroidectomy. However, she denied against medical advice and since then lost her antenatal care.

At 39 weeks' gestation the woman (weight 92 kg, height 156 cm, body mass index 40.4 kg/m^2) presented for labor and delivery complaining of abdominal pain and back pain. She had contractions and 3 cm cervical dilatation. Blood pressure was 184/110 mmHg and heart rate 110/min. After discussion between the obstetricians, anesthetists and the patient, it was decided to proceed with epidural analgesia to achieve good pain relief and sympathetic blockade and then to go for vaginal delivery. Monitoring included invasive arterial blood pressure and other routine monitoring. A nitroprusside infusion was prepared as a rescue hypotensive agent. An epidural catheter was inserted uneventfully at L2-3. Test dose of 2 ml lidocaine 2% was given followed by a bolus of 8 ml ropivacaine 0.1% and an infusion of ropivacaine 0.1% with fentanyl 2 mcq/ml started at 15 ml/h. Within 20 min patient was comfortable without motor block. Blood pressure was 130/70 mmHg and heart rate 75/min. After 1 h, the patient had full cervical dilatation. A top up the dose of 5 ml ropivacaine 0.1% and fentanyl 50 mcq provided adequate sensory blockade up to T5. The labor progressed uneventfully. A healthy 3.4 kg boy was delivered assisted by forceps.

DISCUSSION

The MEN 2A syndrome is characterized by a strong genotype-phenotype correlation and a specific RET mutation may be responsible for a particular phenotype and a more or less aggressive clinical course.[1,6] In our case, family history was positive for three MEN 2A cases. Fertile women with MEN 2A syndrome are at risk of complicated pregnancy because of unrecognized PHEO and transmission of RET mutation to the progeny. From this point of view, MEN 2A except from being a medical challenge, in addition represents a significant ethical issue. MTC is the only malignant tumor and the most severe disease of the syndrome so that in the majority of cases the prognosis of the disease is mainly related with the prognosis of the MTC.[7] Up to 70% of MTC patients have already cervical lymph node metastases at diagnosis and this is an unfavorable prognostic factor for the cure of the disease with a median survival of 5-10 years.[7] This was also a finding in our case.

Pheocromocytoma and PHPT are benign diseases, but when present, they can severely affect the patient. PHPT in MEN 2A syndrome is usually mild and manifests as only a slight elevation of serum calcium.[1,6] However, an undiagnosed PHEO can be catastrophic in pregnancy with maternal and fetal mortalities approaching 50%.[8] With antepartum diagnosis, maternal mortality may be reduced to nearly 0% and fetal loss to 15%.[9] Unrecognized PHEO in pregnancy can result in potentially fatal hypertensive crises precipitated by general anesthesia, vaginal delivery or the mechanical effects of an enlarging uterus, uterine contractions or fetal movements.[9]

The traditional dictum that vaginal delivery is a contraindication in the presence of PHEO is based largely on high mortality outcomes resulting from labor in the setting of a previously undiagnosed PHEO. Effective alpha-blockade has been shown to allow a safe vaginal delivery.[10] However, most authors agree that a caesarean section is a more controlled process for delivery and is therefore advocated. In our case, it was decided to proceed with epidural analgesia. This allowed the option of vaginal delivery or "topping up" in case of emergency cesarean section. The adrenal gland is innervated by sympathetic nerves from T5 to T12. Consequently, the epidural sympathetic blockade across these levels would obtund the possible mechanical or neurogenic stimulation of the adrenal tumor. Five weeks postpartum, the patient underwent uneventful laparoscopic left adrenalectomy and 2 weeks later underwent an uncomplicated total thyroidectomy and total parathyroidectomy with central neck lymph nodes dissection. She was advised to perform a complete RET genetic screening to the baby and family relatives, in order to exclude the possibility that they are bearing the same mutation of RET proto-oncogene.

REFERENCES

1. Moline J, Eng C. Multiple endocrine neoplasia type 2: An overview. Genet Med 2011;13:755-64.
2. Langerman A, Schneider JA, Ward RP. Pheochromocytoma storm presenting as cardiovascular collapse at term pregnancy. Rev Cardiovasc Med 2004;5:226-30.
3. Kim J, Reutrakul S, Davis DB, Kaplan EL, Refetoff S. Multiple endocrine neoplasia 2A syndrome presenting as peripartum cardiomyopathy due to catecholamine excess. Eur J Endocrinol 2004;151:771-7.
4. Moraca-Kvapilová L, Op de Coul AA, Merkus JM. Cerebral haemorrhage in a pregnant woman with a multiple endocrine neoplasia syndrome (type 2A or Sipple's syndrome). Eur J Obstet Gynecol Reprod Biol 1985;20:257-63.
5. Wattanachanya L, Bunworasate U, Plengpanich W, Houngngam N, Buranasupkajorn P, Sunthornyothin S, *et al*. Bilateral pheochromocytoma during the postpartum period. Arch Gynecol Obstet 2009;280:1055-8.
6. Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, *et al*. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple

endocrine neoplasia type 2. International RET mutation consortium analysis. JAMA 1996;276:1575-9.
7. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, *et al*. Medullary thyroid cancer: Management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.
8. Biggar MA, Lennard TW. Systematic review of phaeochromocytoma in pregnancy. Br J Surg 2013;100: 182-90.
9. Harper MA, Murnaghan GA, Kennedy L, Hadden DR, Atkinson AB. Phaeochromocytoma in pregnancy. Five cases and a review of the literature. Br J Obstet Gynaecol 1989;96:594-606.
10. Junglee N, Harries SE, Davies N, Scott-Coombes D, Scanlon MF, Rees DA. Pheochromocytoma in pregnancy: When is operative intervention indicated? J Womens Health (Larchmt) 2007;16:1362-5.

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