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CASE REPORT

Bilateral pheochromocytoma during the postpartum period

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Abstract
Background Pheochromocytoma manifesting during pregnancy is uncommon but it is responsible for a high maternal and fetal mortality rate, especially when unrecognized. Most cases of pheochromocytoma are sporadic but they can be part of hereditary autosomal dominant syndromes.
Case We describe a case of bilateral pheochromocytoma in a term-pregnant patient with a previous history of medullary thyroid carcinoma (MTC). Her genetic study revealed a heterozygous mutation, c.1900T>C, in the *RET* proto-oncogene which confirmed the diagnosis of multiple endocrine neoplasia type 2A (MEN2A). Unrecognized, the tumors caused a crisis with fatal outcome in the mother during the postpartum period. This event might have been prevented if the tumor had been detected previously.
Conclusion MEN2A affected pregnancy is an unusual condition. This syndrome should be suspected when a pregnant patient has a history of MTC. Early detection and appropriate management can prevent serious maternal and fetal complications. We also reviewed the literature of MEN2A-affected pregnancies.

Keywords MEN2A · *RET* gene · Bilateral pheochromocytoma · Pheochromocytoma crisis

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Introduction

Pheochromocytoma is a catecholamine-producing tumor arising from chromaffin cells of the adrenal medulla. It is a rare but treatable disorder with a prevalence of 0.1–0.6% in patients with hypertension [1]. Pheochromocytoma associated with pregnancy is exceedingly rare. Fewer than 300 cases have been reported. Less than 30 cases were bilateral [2]. Maternal and fetal mortality increases during pregnancy [3].

Pheochromocytoma can occur as a sporadic case or as a hereditary autosomal dominant syndrome; multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis (NF) type 1, von Hippel-Lindau (VHL) syndrome and familial non-syndromic pheochromocytoma/paraganglioma. The hereditary forms are usually diagnosed earlier and are extra-adrenal or present as multiple lesions [1].

MEN2A, caused by germline-activated mutations in the *RET* proto-oncogene, comprises medullary thyroid carcinoma (MTC) and a variable prevalence of pheochromocytoma (50% of patients) and primary hyperparathyroidism (20–30% of patients) [4]. It is uncommon to affect the pregnant. Early detection and appropriate management can lead to a lower mortality and morbidity. We present a clinically unrecognized bilateral pheochromocytoma in a term-pregnant patient which caused fatal cardiovascular collapse during the postpartum period. Genetic testing revealed a heterozygous mutation of the *RET* gene which confirmed the diagnosis of MEN2A.

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Case report

A 31-year-old Thai primigravida was admitted for elective cesarean section at 37 weeks' gestation. Her antenatal period was unremarkable. She had neither gestational diabetes nor arterial hypertension. By 34 weeks of gestation, her blood pressure reached 150/90 mmHg. It was controlled with hydralazine 100 mg/day. No classical symptoms suggesting pheochromocytoma such as headache, palpitation, or sweating were noted. Cesarean section under general anesthesia was performed with an uneventful outcome and a healthy male infant. After 1 day, she developed low grade fever and dyspnea. Her blood pressure fluctuated in the range from 90/50 to 220/120 mmHg. There was persistent tachycardia. She was initially treated as puerperal sepsis but cultures remained negative. Computerized tomography (CT) of the abdomen revealed bilateral adrenal masses (Fig. 1). The diagnosis of pheochromocytoma was confirmed by finding a markedly elevated 24-h urine vanilmandelic acid (VMA) (101 mg/24 h; normal 1.8–6.7 mg/24 h), urine metanephrine (34,672 µg/24 h; normal 52–341 µg/24 h) and urine normetanephrine (26,443 µg/24 h; normal 88–444 µg/24 h). Review of her past history revealed that she had undergone a total thyroidectomy for a thyroid nodule from another hospital with L-thyroxine replacement at the age of 29 years. The original histological diagnosis was follicular thyroid carcinoma. We revised the sections and found a mixed follicular pattern and spindle cells with positive calcitonin staining, compatible with MTC. This confirmed the diagnosis of MEN2A. Her mother died from an unknown type of thyroid carcinoma and her sister died at the age of 22 years from severe hypertension. Serum calcium, calcitonin and parathyroid hormone were normal. The patient was then started on an α-blocker, doxazosin mesylate 8 mg/day, and intravenous sodium nitroprusside. However, her clinical condition was complicated by a catheter-related infection and dilated cardiomyopathy. She died 2 weeks later from multisystem failure. Permission for necropsy was denied.

Genomic DNA was extracted from peripheral blood leukocytes by the phenol–chloroform method. The coding sequence of exon 8–15 of the *RET* gene was amplified by PCR using primers and conditions as previously described [5]. The PCR products were treated with ExoSAP-IT (USP Corporation, Cleveland, USA) according to the protocols supplied by the manufacturer, and sent for direct sequencing to the Macrogen Inc., Seoul, South Korea. This study was approved by the local Ethics Committee; written informed consent was obtained from each person included in this study. Sequencing analysis revealed that the patient was heterozygous for a transition c.1900T>C in exon 11 of the *RET* gene (Fig. 2), expected to result in substitution of cysteine to arginine at codon 634 (C634R). Her son was also found to carry this mutation. This most common mutation site is usually related to the aggressiveness and earlier onset of MTC. Therefore, we strongly recommend that her

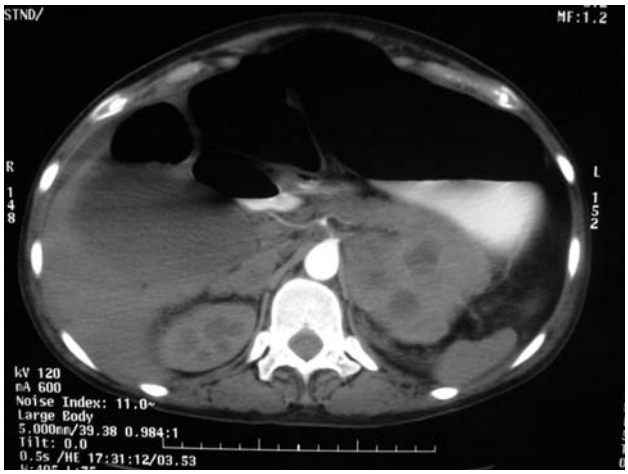

Fig. 1 CT abdomen revealed heterogeneous enhancing bilateral lobulated adrenal masses, 2.0 × 2.7 × 3.3 cm on the right side and 6.2 × 6.4 × 8.0 cm on the left side

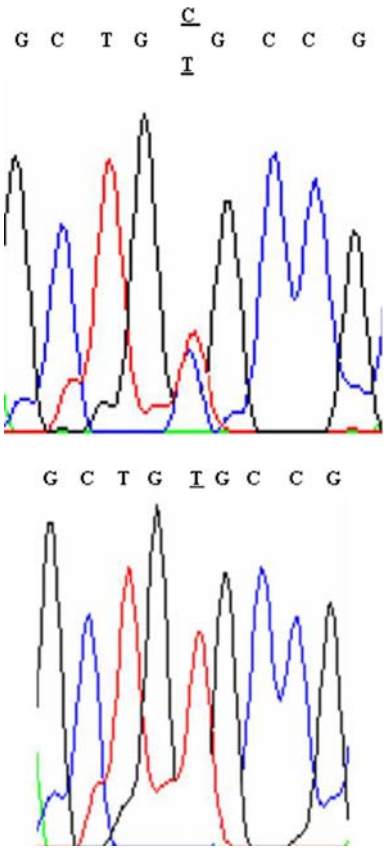

Fig. 2 The sense sequence of exon 11 of the *RET* gene of the patient showing a heterozygous mutation at c.1900T>C (*upper panel*), compared to that of a control (*lower panel*)

Table 1 Reported cases of MEN2A affected pregnancy

Reference, year	Patient characteristics		MEN2A manifestations			Pheochromocytoma crisis	Outcome	
	Age (yr)	Parity	MTC	Pheochromocytoma	HPT		Maternal	Fetal
Chodankar [9]	24	G_4P_3	+	Bilateral	–	+ (32nd week)	Died	N/A
Moraca-Kvopiola [10]	25	G_3P_1	+	Bilateral	–	+ (35th week)	Alive	Alive
van der Vaart [11]	25	G_1	+	Bilateral	–	–	Alive	Alive
Wax [12]	30	G_1	+[a]	–	–	–	Alive	Alive
Huang [13]	35	G_3P_1	+[a]	–	–	–	Alive	Alive
Joseph [14]	21	G_1	+	Bilateral	–	–	Alive	Alive
Tewari [15]	22	G_1	–	Bilateral	+[b]	–	Alive	Alive
Martinez-Brocca [16]	34	G_1	+[a]	Unilateral	–	–	Alive	Alive
Ahn [17]	N/A	G_1	+[a]	Unilateral	–	+ (38th week)	Alive	Alive
Martinelli [18]	31	G_1	+[a]	Unilateral[a]	–	–	Alive	Alive
Langermann [19]	24	G_2P_0	+[a]	Unilateral	–	+ (at term)	Alive	Alive
Kim [7]	24	G_3P_1	+[a]	Unilateral	–	+ (38th week)	Alive	Alive
Frayssinet [20]	22	G_1	+[a]	Unilateral	–	–	Alive	Alive
Present case	31	G_1	+[a]	Bilateral	–	+ (Postpartum)	Died	Alive

N/A not available, *MTC* medullary thyroid carcinoma, *HPT* hyperparathyroidism

[a] Developed before

[b] Developed after

son should have an early prophylactic total thyroidectomy before the age 5 years [4, 6].

Discussion

We report an unrecognized bilateral pheochromocytoma presenting as hypertensive crisis at term pregnancy, resulting in a fatal outcome of the mother. Her past history of MTC found to carry a *RET* gene mutation that confirmed the diagnosis of MEN2A.

Hypertension during pregnancy is common and of multiple causes. However, certain clinical manifestations should alert the physicians to the possibility of pheochromocytoma. These include hypertensive episodes with triad symptoms (palpitation, sweating and headache) occurring before the first 20 weeks of pregnancy, postural hypotension, worsening in the supine position or a positive history of hereditary pheochromocytoma syndrome [3, 7]. Pheochromocytoma can be confirmed by detecting increased catecholamine and metabolites on 24-h urine or a plasma collection. This is unaffected by pregnancy or pregnancy-induced hypertension (PIH) [3]. Magnetic resonance imaging (MRI) has the advantages of producing high-quality images and detects extra-adrenal lesions without exposure to ionized radiation to the fetus. Treatment of pheochromocytoma during pregnancy requires aggressive medical control of blood pressure and surgical removal of the tumors.

Pheochromocytoma crisis is a rare life-threatening emergency that may present spontaneously or as a result of precipitating factors such as trauma, surgery, anesthesia and medications such as β-blockers [8]. The crisis during pregnancy can be triggered by mechanical pressure on the adrenal gland from a growing uterus, uterine contractions, fetal movement, the process of delivery and general anesthesia [7]. Manifestations are variable, ranging from severe hypertension to circulatory failure and shock. Myocardial ischemia or cardiomyopathy, pulmonary edema, encephalopathy and multiorgan failure have all been reported [7, 9, 10]. This dismal event was delayed in diagnosis in our patient leading to a fatal outcome during the postpartum period. Death might have been prevented if pheochromocytoma had been detected antenatally by her previous history of MTC and a suspected family history of MEN2A.

Up to now, only 13 cases of pregnancy complicated by MEN2A have been reported (Table 1). All but one had MTC. Concordant with the previous data, pheochromocytoma usually follows manifestation of MTC and tends to occur bilaterally (50–80%) [4, 21]. Crisis has been reported in five cases. Most were diagnosed during the third trimester or postpartum period and resulted in a poor maternal–fetal outcome. Due to its earlier presentation, a history of MTC should raise the possibility of this syndrome [13, 18]. Hormonal screening for pheochromocytoma before or early in pregnancy should be performed in all females who have a history of MTC or carried the *RET* mutation.

In conclusion, MEN2A should be considered in pregnant patients who have a history of MTC. The present study also demonstrates the importance of careful history taking and physical examination in preventing such serious maternal and fetal complications.

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Conflict of interest statement The authors declare that we have no conflict of interest.

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