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ORIGINAL ARTICLE

Concurrent bilateral pheochromocytoma and thoracic paraganglioma during pregnancy

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Abstract Although hypertension occurring during pregnancies is not uncommon and its prognosis is generally excellent, some of its unusual causes can lead to catastrophic consequences, especially in undiagnosed cases. Here, we report a pregnant woman who presented with hypertension in her early pregnancy. It was subsequently found to be caused by bilateral pheochromocytoma. After removal of both tumors, catecholamine levels unexpectedly and unexplainably remained elevated. At 23 weeks of gestation, the fetus was found dead in utero. After the fetal death, additional studies were performed and revealed a thoracic paraganglioma. To our knowledge, this is the first report of a case of three catecholamine-producing tumors occurring concurrently during a pregnancy. Genetic analysis helped identify this unprecedented condition; the patient harbored a heterozygous missense mutation c.482G>A in exon 3 of the *VHL* gene, indicating von Hippel-Lindau syndrome. Physicians who care for hypertensive pregnant patients should be aware of this condition as its diagnosis would probably lead to a better outcome.

Keywords *VHL* · Pregnancy · Bilateral pheochromocytoma · Paraganglioma

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Introduction

Pheochromocytoma and paraganglioma are catecholamine-producing tumors that are derived from the neural crest. Tumors that arise within the adrenal medulla are called pheochromocytoma while tumors that arise in sympathetic ganglia outside the adrenal gland are defined as extra-adrenal pheochromocytoma or paraganglioma [1]. The sympathetic or functioning paraganglioma are mainly located in abdomen and thorax. The term "paraganglioma" also include the tumors originated from parasympathetic ganglia, which are mainly in head and neck region and usually nonfunctioning [2]. Association of pheochromocytoma or paraganglioma with pregnancy are exceeding rare, with about 300 cases having been reported [3]. The simultaneous occurrence of both forms during pregnancy is even less common.

Pheochromocytoma or paraganglioma can occur as a sporadic case or as autosomal dominant inherited syndromes including von Hippel-Lindau (VHL) caused by germline mutations in the *VHL* gene; multiple endocrine neoplasia (MEN) type 2 caused by mutations in the *RET* gene; neurofibromatosis type 1 (NF-1) caused by mutations in the *NF1* gene; and the familial paraganglioma syndromes (PGL) caused by mutations in the *SDHB*, *SDHC,* or

SDHD genes [4, 5]. The hereditary forms are usually diagnosed earlier or present as paraganglioma or bilateral/multiple lesions.

The VHL syndrome can manifest as a variety of tumors, such as hemangioblastoma of the central nervous system and retina, clear cell renal carcinoma, pancreatic neuroendocrine tumor, and pheochromocytoma [6]. Predisposition to pheochromocytoma can be classified into type 1 (low risk) or type 2 (high risk) [7]. Onset of symptoms of VHL usually occurs between the second and fourth decades of life, which corresponds to the child-bearing period. It results in markedly increased maternal and fetal morbidity/mortality when the diagnosis is delayed. Herein, we report a bilateral pheochromocytoma combined with a paraganglioma during pregnancy. The patient carried the *VHL* mutation allele.

Case report

A 30-year-old woman, primigravida, 16 weeks' pregnant, was referred to our hospital due to an uncontrolled hypertension. The patient was symptom free prior to pregnancy. At the gestational age of 7 weeks, she complained of sweating, headache, and palpitation. Her blood pressure was 170/100 mmHg. Investigations revealed an elevated 24-h urine metanephrine of 1,094.72 μg/dl (normal range: 52–341 μg/dl) and normetanephrine of 5,721.60 μg/dl (normal range: 88–444 μg/dl). Magnetic resonance imaging (MRI) of her abdomen, without gadolinium enhancement, showed large bilateral adrenal masses (Fig. 1a), suggesting pheochromocytoma. With doxazosin mesylate 8 mg/day and amlodipine 20 mg/day, her blood pressure was well controlled. At 18 weeks' gestation, she underwent bilateral adrenalectomy with cortical sparing without peri-operative complications. Three weeks postoperative, her blood pressure returned to normal but the level of urine metanephrine/normetanephrine was still elevated (84.1 and 913.34 μg/dl, respectively). She experienced fetal death at 23 weeks with a fetal weight of 1,100 g. Autopsy of the fetal remains was denied.

She, then, underwent I-131 meta-iodobenzyl-guanidine (MIBG) scintigraphy and computerized tomography (CT) which demonstrated a paravertebral mass at the thoracic region (Fig. 1b). Histological findings confirmed paraganglioma. Follow-up 24 h urinary catecholamine metabolites 1 month later were normal. The 250-μg ACTH stimulation test at 4 months after adrenalectomy was 35 μg/dl, revealing normal adrenal reserve.

After we obtained informed consent from the patient and her family members, genomic DNA was extracted from their peripheral blood leukocytes by the phenol–chloroform method. Each of the exons of the *VHL* gene was amplified by PCR using primers and conditions as previous described [8]. PCR products were treated with ExoSAP-IT (USP Corp., Cleveland, OH), according to the manufacturer's recommendations, and sent for direct sequencing at the Macrogen Inc., Seoul, Korea.

Only the patient was found to be heterozygous for a c.482G>A tranversion in exon 3 of the *VHL* gene (Fig. 2) resulting in substitution of arginine to glutamine (R161Q) [9]. Further analyses revealed no abnormalities in other organ-associated VHL syndromes.

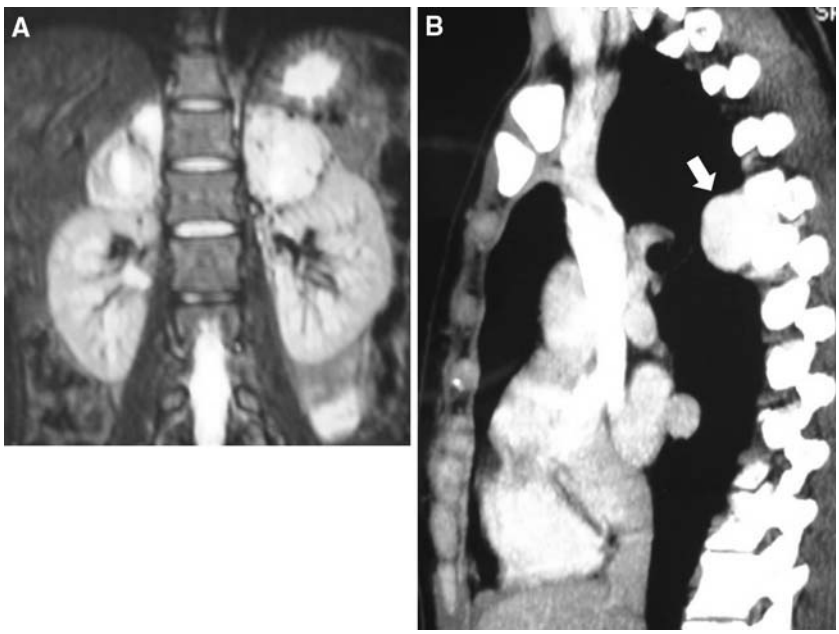

Fig. 1 **a** An axial T_2-weighted MRI of the upper abdomen showing inhomogeneous hyperintensity masses of the right and left adrenal glands, size about 3.5 × 4.2 × 5.3 cm and 4.2 × 4.5 × 5.4 cm, respectively. **b** A sagittal view of CT scan of the chest, showing a 4-cm mass involving posterior mediastinum and paraspinal region at T_4 level

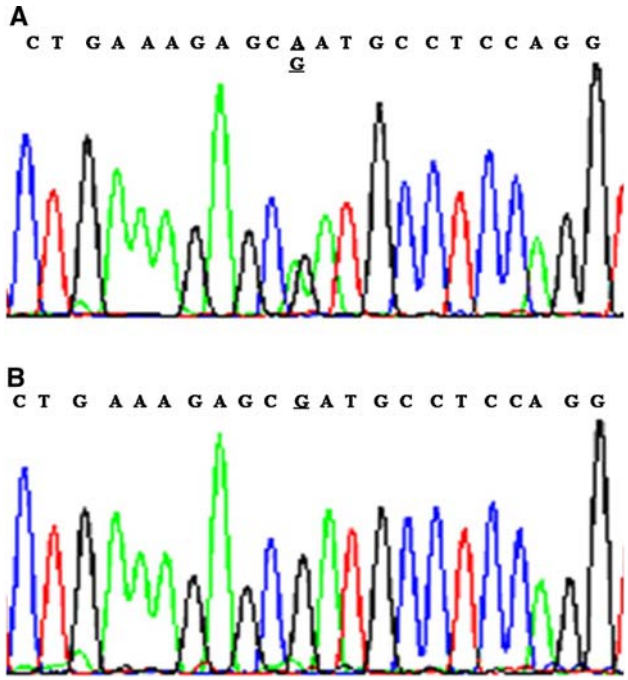

Fig. 2 The sense sequencing of *VHL* gene of our patient (**a**) showing a heterozygous missense mutation, c.482G>A, and of the wild type (**b**)

Discussion

We report a pregnant Thai patient with bilateral pheochromocytoma and an unrecognized thoracic paraganglioma leading to a dismal fetal outcome. To the best of our knowledge, this is the first report of co-existence of these tumors during pregnancy. Her genetic study revealed a *VHL* gene mutation which confirms the hypothesis that this is a genetic defect causing bilateral or extra-adrenal pheochromocytoma [5–7].

Pheochromocytoma or paraganglioma during pregnancy, if undiagnosed, leads to catastrophic consequence. Early diagnosis and proper management can prevent complications. A recent review article shows that antenatal diagnosis, made in 83% of cases, resulted in reduction of maternal mortality from 50% to only 2%, and in fetal mortality from approximately 50 to 10% [10]. Our patient presented as uncontrolled hypertension without proteinuria during the early phase of pregnancy (before 20 weeks gestation) and with the triad symptoms of sweating, palpitation, and headache. These should raise the suspicion of pheochromocytoma. Other clinical features that should alert physicians include hypertension with postural hypotension worsening in the supine position or with a positive history of hereditary pheochromocytoma syndrome [4, 10]. Demonstration of an increased catecholamine and its metabolites on 24 h uine or from a plasma collection is required to confirm the diagnosis of pheochromocytoma. These are not normally affected by pregnancy or by pregnancy-induced hypertension (PIH) [10]. MRI can produce high quality images and causes no exposure to ionized radiation. Functional imaging with I-131 MIBG may be helpful in detecting paraganglioma, but it is contraindicated in pregnancy.

Treatment of pheochromocytoma requires aggressive medical control of blood pressure and surgical removal of the tumor. α-blockade (phenoxybenzamine, prazosin, or doxazosin) was used as first line medical treatment to control blood pressure and restore vascular volume [1]. Other antihypertensive drugs such as calcium channel blockers or magnesium sulfate ($MgSO_4$) also have efficacy in this setting. β-blockers may be used to control tachyarrhythmia. Best timing for surgery is the major problem of pheochromocytoma in pregnancy. In early pregnancy, tumor removal by laparotomy, without interfering with the gravid uterus, is the optimal choice but the risk of abortion is increased. After 24 weeks' gestation, an enlargement of the uterus may make abdominal exploration for tumor removal difficult. Most groups have recommended elective cesarean section once fetal maturity is attained [10, 11]. Adrenalectomy can be performed at the time of delivery or at a suitable interval following recovery from childbirth. In patients with bilateral lesions, some authors recommend considerations of cortical sparing adrenalectomy [10]. Unfortunately, our case resulted in fetal death, although fetal growth had been regular and maternal blood pressure was well controlled. Death may not have been due to the direct effects of the catecholamine on the fetus, because the placenta possesses high levels of catechol-O-methyltransferase (COMT) and monoamine oxidase that protect the fetus from catecholamine excess. Nevertheless, the high catecholamine levels may cause vasoconstriction of the uteroplacental circulation leading to intrauterine fetal retardation, fetal hypoxia, spontaneous abortion, or intrauterine fetal death [12].

Pheochromocytoma is present in 10–20% of patients with the VHL syndrome [6, 7]. It can be present alone (VHL type 2C) or be associated with other VHL-associated tumors (VHL type 2A or B). Genotype–phenotype correlation has been identified where VHL type 2 patients usually carried missense mutations [13]. VHL-associated pheochromocytoma tends to present at younger age and bilateral or as multiple lesions. However, paraganglioma or malignant lesions are also noted [2, 6]. Biochemically, pheochromocytoma in VHL syndrome is less likely to express the enzyme phenylethanolamine-N-methyltransferase (PNMT) that converts norepinephrine to epinephrine, resulting in a higher level of normetanephrine in VHL patients compared with others [6]. This finding may also be found in paraganglioma due to its lack of immediate proximity to the adrenal cortex, which ordinarily

provides the high concentrations of cortisol needed for induction of the PNMT enzyme [1, 3].

The management of paraganglioma during pregnancy depends on whether the tumor is functioning or non-functioning. In case of functioning tumors, the management is urgent and in the same line as that of pheochromocytoma [10]. On the contrary, removal of non-functioning paraganglioma can be delayed until after delivery [11]. In addition, awareness of the possibility of multiple lesions along the sympathetic/parasympathetic chains and malignant prone is of importance [2].

Genetic testing is another important part of the management. Approximately one-third of all pheochromocytoma or paraganglioma patients carrying a mutation in one of these six susceptible genes: *VHL*, *RET*, *SDHB*, *SDHC, SDHD* and *NF1* [5]. In case any syndromic features are present in either affected patients or their familial members, this will point to which susceptibility gene to analyze for mutation. However, in non-syndromic or apparently sporadic patients, whether mutation analysis of which genes should be performed is less obvious. Recent studies suggested that some clinical parameters, especially age of onset, tumor site, bilateral or multiple lesions, and malignancy, are useful to determine the gene analysis algorithm [5, 14–16]. In our case, according to the guideline, the presence of bilateral lesions and paraganglioma warrants mutation analyses of *VHL,* followed by *SDHB* and *SDHD*.

In conclusion, we report a patient with concurrent bilateral pheochromocytoma and thoracic paraganglioma presenting during pregnancy. Physicians who care for hypertensive pregnant patients should be aware of this condition. This study also substantiates the value of genetic analysis in patients with apparently sporadic pheochromocytoma.

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