Carotid Body Tumors and Adrenal Pheochromocytomas in Siblings of a Turkish Family

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Key Words

Familial pheochromocytoma · Carotid body tumor · Turkish family

Abstract

Objective: This is a report of 2 hypertensive siblings with a history of carotid body tumors and subsequent benign adrenal pheochromocytomas (pheos) in a family where the mother had died of possible adrenal carcinoma. **Clinical Presentation and Intervention:** The first case was a 35-year-old woman with paroxysmal hypertensive attacks and a right adrenal mass. She had earlier undergone surgery to remove bilateral carotid body tumors. Investigation revealed excessive excretion of catecholamines and their metabolites in the urine. Abdominal MRI and ¹³¹I-MIBG scintigraphy revealed a right adrenal tumor. Right adrenalectomy was performed. The second case, the 45-year-old brother of the first case, was found to have a left adrenal mass on abdominal MRI. Catecholamines and their metabolites in the urine were found to be increased. He had also had surgery to remove bilateral carotid body tumors of the neck. Left adrenalectomy was performed. Both siblings showed no evidence of other familial syndromes, such as multiple neoplasia type 2, von Hippel-Lindau disease or neurofibromatosis type 1.

Conclusion: Although the combination of familial carotid body tumors and pheo is rare, a patient who remains hypertensive after removal of a carotid body tumor deserves a careful evaluation to exclude pheo. Such tumors may be extra-adrenal or multifocal.

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Introduction

Pheochromocytomas (pheos) are catecholamine-producing, chromaffin tumors that arise in the adrenal medulla in 90% of cases and extra-adrenal sympathetic ganglia in the remaining 10% [1, 2]. Pheo is an important cause of secondary hypertension. Approximately 25% of pheo is hereditary, and it is a well-recognized feature of von-Hippel-Lindau (VHL) disease, of multiple-endocrine neoplasia type 2 and, rarely, of neurofibromatosis type 1 [2, 3]. It is now accepted that approximately 25% of pheos may be the result of germline mutations in genes known to be associated with disease, i.e. up to 25% may be familial [3]. It is also possible that a case of familial pheo may not be associated with any known syndrome and mutation has not been identified in any of the recognized genes associated with known familial syndromes.

Fig. 1. The family pedigree demonstrates the distribution of known and suspected pheos and carotid body tumors (CBTs) across 3 generations. Figures in circles or squares refer to the number of children.

However, familial cases with VHL germline mutations are by definition classified as having the VHL syndrome. Even in the case of a patient with an apparently sporadic pheo, the finding of a germline mutation in the *VHL* gene qualifies the patient as having VHL disease.

Multiple neoplasia type 2 is caused by *RET* oncogene mutations, while VHL disease is caused by mutations in the tumor suppressor *VHL* and neurofibromatosis type 1 by mutations in the *NF1* gene. In addition, it is now recognized that the newly identified pheo/paraganglioma syndromes may be caused by mutations in succinate dehydrogenase (SDH) subunits SDHD, SDHB and SDHC [1–3].

The hereditary paragangliomas belong to a group of dominantly inherited disorders characterized by the development of highly vascularized, nonchromaffin tumors arising in parasympathetic ganglia. Paragangliomas usually develop in the head and the neck, most commonly at the bifurcation of the carotid artery (i.e. in the carotid body). They are also known as chemodectomas or glomus tumors. Up to 50% of paragangliomas are familial.

The occurrence of pheo in some kindreds with hereditary paragangliomas as well as the occasional reports of familial and isolated cases of both pheo and carotid body tumors have suggested a possible etiological link [1, 4]. In the present paper, we report nonsyndromic familial adrenal and extra-adrenal (bilateral carotid body) tumors in 2 siblings.

Case Report

Case 1

A 35-year-old woman presented with a 9-month history of paroxysmal hypertensive attacks (180/120 mm Hg) associated with severe throbbing headaches, palpitations, nervousness and sweating. She had undergone 2 resections of bilateral carotid body tumors 20 and 6 months earlier, respectively. Histology confirmed bilateral paragangliomas. The second operation was complicated by an attack of hypertension. The patient continued to be hypertensive postoperatively. The patient's mother had died of possible adrenal carcinoma. This finding was obtained from abdominal computed tomography and ultrasonography reports in the mother's file in another hospital in our city (invasive adrenal mass measuring 60 × 50 mm, with splenic multiple metastases and neoplasms consisting of atypical epithelial cells on adrenal fine-needle aspiration biopsy). Other characteristics of the family pedigree are demonstrated in figure 1. Physical examination revealed arterial tension of 200/140 mm Hg, and a rhythmic arterial pulse of 124/min. She had postural hypotension. Laboratory values were as follows: hemoglobin, 10.6 g/dl; hematocrit, 30%; fasting blood glucose, 116 mg/dl; impaired glucose tolerance, 185 mg/dl at 2 h. ECG revealed sinus tachycardia. Urine catecholamines and metabolites were as follows: urine norepinephrine, 2,062 µg/24 h (normal = 12.1–85.5); epinephrine, 16.1 µg/24 h (0.5–22.4); normetanephrine, 3,499 µg/24 h (88–444); metanephrine, 81.3 µg/24 h (52–341); vanillylmandelic acid, 12.5 mg/24 h (1.8–9.8); dopamine, 662 µg/24 h (65–563); homovanillic acid, 4.3 mg/24 h (2–7.4). The levels of serum calcitonin, intact PTH, carcinoembryonic antigen and α-fetoprotein were within normal ranges. Abdominal magnetic resonance imaging (MRI) demonstrated a well-demarcated hyperintense mass measuring 38 × 22 mm, located in the right adrenal gland (fig. 2a). An iodine-131-metaiodobenzylguanidine (¹³¹I-MIBG) scan revealed uptake within the mass in the right adrenal gland (fig. 2b). Normotension was reached after adequate α-receptor blockade with phenoxybenzamine, a β-adrenoceptor blocker (propranolol), had been added to the therapy. Right adrenalectomy was performed by the transabdominal route. Gross pathological examination revealed an encapsulated mass (3.5 × 3.2 cm) weighing 20 g; the cut surface was pinkish brown without evidence of hemorrhage or necrosis. Histology showed tumor cells characteristically arranged in well-defined nests ('Zellballen') surrounded by a delicate fibrovascular stroma. The cells have a finely granular cytoplasm. The nuclei are round or oval with prominent nucleoli. The cells were strongly positive for chromogranin A and synaptophysin on immunohistochemical study. The patient has remained normotensive 15 months postoperatively.

Case 2

A 45-year-old man, the brother of the first case, presented 3 months later with a 5-year history of headaches, palpitations and sweating associated with paroxysmal hypertensive attacks (200/130 mm Hg). Selective carotid angiography had revealed features consistent with carotid body tumor (fig. 3). He had undergone 2 resections of bilateral carotid body tumors 8 and 6 months before his sister presented to us. These were confirmed histologically as paragangliomas. The patient continued to be hypertensive postoperatively. On physical examination, arterial tension was found to be 210/130 mm Hg, with a rhythmic arterial

Fig. 2. a Axial T₂-weighted MR image demonstrates high-intensity pheo in the right adrenal gland (arrow). **b** ¹³¹I-MIBG scan demonstrates faint uptake within pheo in the right adrenal gland (arrow).

pulse of 72/min. He had postural hypotension. Urine catecholamines and metabolites were as follows: norepinephrine, 299 µg/24 h (normal = 12.1–85.5); epinephrine, 6.5 µg/24 h (0.5–22.4); normetanephrine, 1,843 µg/24 h (88–444); metanephrine, 364 µg/24 h (52–341); vanillylmandelic acid, 22.9 mg/24 h (1.8–9.8); dopamine, 356 µg/24 h (65–400); homovanillic acid, 6.8 mg/24 h (1.4–8.8). The levels of serum calcitonin, intact PTH, carcinoembryonic antigen and α-fetoprotein were within normal ranges. Abdominal MRI demonstrated a well-demarcated hyperintense mass measuring 21 × 15 mm located in the left adrenal gland. A ¹³¹I-MIBG scan revealed uptake within the left adrenal mass. Normotension was reached after adequate α-receptor blockade with phenoxybenzamine, a β-adrenoceptor blocker (propranolol), had been added to the therapy. Left adrenalectomy was performed by the transabdominal route. Gross pathology showed an encapsulated mass, 20 × 15 mm, and on sectioning revealed a reddish brown surface with areas of hemorrhage. Histological examination confirmed pheo. Immunohistochemical study showed diffuse chromogranin A and synaptophysin positivity. Residual nonparoxysmal hypertension continued in this patient. Urine catecholamines and their metabolites returned to

Fig. 3. Preoperative angiographic (intravenous digital subtraction angiography) appearance of the carotid body tumor fed by branches of the external carotid artery (characteristic hypervascular mass arising at the bifurcation of the common carotid artery).

the normal range, except for normetanephrine and vanillylmandelic acid at 6 months postoperatively. However, the levels of urine normetanephrine and vanillylmandelic acid decreased (780 µg/24 h and 15 mg/24 h, respectively). Adrenal MRI and ¹³¹I-MIBG scan were normal.

Discussion

Pheos are neural-crest-derived tumors that usually occur sporadically but may also be part of inherited syndromes. In 15–20% of the cases, pheo localizes in extra-adrenal sites (paragangliomas) and in about 15% of cases it is multiple. Pheo can cause endocrine hypertension due to oversecretion of catecholamines. Such hypertension can be sustained or paroxysmal and may lead to death from cardiovascular or cerebrovascular disease [2].

While the biochemical evaluation of patients with suspected pheo has been well described, radiological diagnosis continues to evolve [2]. Either computed tomography or MRI scanning can detect tumors as small as 0.5 cm in diameter. An advantage of MRI is that the pheo appears as a bright mass on a T₂-weighted image [5]. Doppmann et al. [5] reported that a signal intensity ratio or adrenal mass to liver on T₂-weighted images of 3 or greater was characteristic of pheos. Other lesions, lower in relative signal intensity ratio, were less likely to be consistent with this diagnosis. Occasionally, despite a biochemical diagnosis, imaging techniques do not reveal a pheo. In such cases, scanning with ¹³¹I-MIBG may be useful, since it is concentrated in pheos. ¹³¹I-MIBG has been reported to be able to locate primary, ectopic and metastatic lesions. However, tumors secreting predominantly norepinephrine may be difficult to visualize by this technique [6].

The definitive treatment for pheo is surgical excision of the tumor. Surgery for pheo entails several considerations. Induction of anesthesia before surgery, manipulation of the tumor or other stimulation can cause massive outpouring of catecholamines from the tumor, resulting in hypertensive crisis, arrhythmias or myocardial infarction [2]. To prevent these problems, patients with pheo must undergo pharmacological blockade of catecholamine synthesis or its effects before surgery [7].

Before the introduction of adrenergic blockade, surgical mortality rates in pheo ranged from 24 to 50% [7, 8]. Routine preoperative pharmacological blockade with phenoxybenzamine, an α-adrenergic receptor antagonist, opposes catecholamine-induced vasoconstriction. A β-adrenoceptor blocker is added to prevent the reflex

tachycardia often associated with α-blockade, as was done in these 2 cases. This leads to patient survival rates of 97.7–100%. Sometimes residual nonparoxysmal hypertension is found in 27–38% of patients after tumor removal [9]. Residual nonparoxysmal hypertension was observed in case 2.

Pathologically, carotid body tumors and pheos consist of a nest of cells in a Zellballen arrangement separated by thin fibrovascular trabeculae. The malignant potential of paragangliomas cannot be predicted reliably by histological criteria and, therefore, patients with a history of either of these tumors require a careful follow-up. Although the combination of familial carotid body tumors and pheo is rare, a patient who remains hypertensive after removal of a carotid body tumor should be evaluated carefully to exclude pheo. This fact is exemplified by the 2 siblings in this study. Such tumors may be extra-adrenal or multifocal and can be distributed throughout the sympathetic chain [1, 4, 6]. MRI can be useful to evaluate suspected tumors, particularly small masses in the retroperitoneum.

Germline mutations in 3 subunits of mitochondrial complex II (succinate dehydrogenase subunits SDHB, SDHC and SDHD) cause susceptibility to pheo and/or head and neck paraganglioma [10, 11]. Recently it has been revealed that *SDHB* mutations are most commonly associated with pheo susceptibility and *SDHD* with the development of head and neck paraganglioma [11]. Moreover, although paraganglioma has been clinically recognized for more than 40 years, it is only in the last 5 years that it has been classified on the basis of molecular genetics: *SDHD* mutations predispose to the susceptibility gene for paraganglioma syndrome type 1 (PGL-1); mutations in an unidentified gene on chromosome 11 predispose to *PGL-2*, *SDHC* mutations to *PGL-3* and *SDHB* mutations to *PGL-4* [12]. In addition, recent studies suggest that germline *SDHD* and *SDHB* mutations are an important cause of familial and isolated pheo. The mechanism by which *SDH* subunit mutations predispose to pheos has not been defined in detail, but dysregulation of hypoxia-responsive genes and impairment of mitochondria-mediated apoptosis have both been suggested [9]. Although diagnoses of carotid body tumors and adrenal pheos in our cases have been made by clinical and laboratory findings, genetic screening should be performed for a definitive diagnosis [3, 9].

In this family, there was no clinical and laboratory evidence, including hypercalcemia, increased PTH level, increased serum calcitonin level, a marfanoid habitus, multiple mucosal neuromas, retinal and cerebellar hem-

angioblastomas, and renal cell carcinoma, renal and pancreatic cysts, a variety of skin manifestations, including café-au-lait spots, subcutaneous multiple neurofibromas, and axillary and inguinal freckles as well as neural gliomas (e.g. optic nerve) and hamartomas of the iris (Lisch nodules), to suggest other familial syndromes, e.g. multiple neoplasia type 2, VHL disease and neurofibromatosis type 1.

Conclusion

Although the combination of familial carotid body tumors and pheo is rare, a patient who remains hypertensive after removal of a carotid body tumor should be carefully evaluated to exclude pheo, as such tumors may be extra-adrenal and multifocal.

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