Case report
UDC: 616-006:616-008.6:616.071

Pheochromocytoma in von Hippel-Lindau disease

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A 70-year old female was admitted to the hospital because of hypertension, increased sweating and weight loss. The hypertension was sustained. Five months before admission CT scan of the abdomen had revealed a well-defined right adrenal mass together with left kidney tumor. A magnetic resonance imaging of the abdomen confirmed the presence of the right adrenal and left kidney masses, but also showed another tumor in the pancreas between the body and the tail. Urinary 24-hour noradrenaline was grossly elevated and confirmed the diagnosis of pheochromocytoma. ^{131}I-metaiodobenzylgvanidine (MIBG) scintiscan showed increased MIBG uptake in the right adrenal gland. After pre-treatment with phenoxybenzamine 30 mg daily, the patient was operated, and the right adrenalectomy was done. Histopathological examination revealed encapsulated adrenal pheochromocytoma without infiltrative characteristics and lymph node metastasis. After the operation, hypertension was controlled easily with amlodipine. The patient was discharged for recovery. Ulteriorly, SSCP (single strand conformational polymorphism) method detected a point mutation in the third exon of the VHL (von Hippel-Linday) gene. It was decided to follow up the patient with the von Hippel-Lindau disease, while waiting for the results of the sequence analysis to confirm that the found mutation is not associated with renal cancer..

KEY WORDS: *Hippel-Lindau Disease; Germ-line Mutation; Pheochromocytoma*

INTRODUCTION

Pheochromocytomas are catecholamine-producing tumors of chromaffin cells that, although rare, must be considered in patients with hypertension, autonomic disturbances, panic attacks, adrenal events, or familial diseases featuring a predisposition to develop pheochromocytoma (1,2). They are one of the surgically curable causes of hypertension. Most pheochromocytomas are sporadic. Familial predisposition is seen mainly in patients with multiple endocrine neoplasia type II (MEN II), von Hippel-Lindau disease, neurofibromatosis type 1, and familial carotid body tumors (1,3). The exact molecular mechanisms by which the hereditary mutations lead to tumor development remain unknown. Specific genetic analysis enables the recognition of the genetic basis of pheochromocytomas (4-6), thus improving the clinical management of patients with hereditary tumors and making possible the screening of the patient's family members.

We present here a case of the von Hippel-Lindau disease complicated with pheochromocytoma.

CASE REPORT

A 70-year old female was admitted to the hospital because of hypertension, increased sweating, and weight loss. The patient had been well until five months earlier, when she was admitted to another hospital because of breathlessness during exertion. Routine ultrasonography of the abdomen incidentally discovered right adrenal mass together with the tumor of the left kidney. Computerized tomography confirmed these findings. The patient was transferred to another hospital for urologic investigation, but no indication for surgery was established. Endocrinological consultation for right adrenal mass was requested, and it was the first time that the possibility of the adrenal pheochromocytoma was assumed. Then, the patient was admitted to our hospital.

The patient had been loosing weight for the last 2 years (8 kg). She had increased sweating and rare palpitations while resting. The hypertension was sustained for the last 13 years, and at the

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The manuscript was received: 11. 09. 2003

Provisionally accepted: 16. 09. 2003

Accepted for publication: 17. 09. 2003

moment of admission she was taking metoprolol 100 mg and amlodipine 5 mg daily. No headaches were reported. She was also treated for diabetes mellitus for the last 7 years with sulfonylureas and diet. The patient had no offspring. Her mother had hypertension and died when she was 48 year old due to stroke.

Physical examination revealed blood pressure 155/80 mmHg and the pulse 80 beats per minute while she was supine, and 120/75 mmHg and the pulse 116 while she was standing. The temperature was 36.6˚C, the respirations were 14/min, and she appeared hypermetabolic with tremor of the fingers and sweaty cold skin. The lungs were clear. Heart sounds were normal. The abdomen was soft, and there was neither organomegaly nor palpable masses. No lymphadenopathy was found.

Routine hematology and biochemical laboratory values were normal except for the finding of the moderate persistent neutrophilic leukocytosis (white cell count per mm^3 12.600 with 80% of neutrophils), fasting hyperglycemia (mean blood glucose level 8.9 mmol/l), and elevated erythrocyte sedimentation rate (40/h). Serum total calcium was normal. Neurone-specific enolase (NSE) and CA 19-9 in the blood were elevated (30.87 ηg/l, normal up to 15.2, and 88.2 IU/l normal up to 37, respectively). Hormonal analysis (Table 1) revealed grossly elevated urinary 24h noradrenaline.

Table 1. Hormonal analysis

Analysis	Value			Normal values
CORTISOL 08h (nmol/l)	428			180-670
TOTAL THYROXIN (nmol/l)	131.9			55-160
TSH (mIU/l)	0.26			0-9
Ultrasensitive TSH (mIU/l)	0.356			0.35-5.5
FT4-free thyroxin (pmol/l)	14.8			11.5-22.7
NORADRENALIN-urine (μg/24h)	217.6	236.5	217.8	10-25
ADRENALIN-urine (μg/24h)	6.4	8.6	6.9	1-6
DOPAMINE-urine (μg/24h)	128.9	131.1	129.5	100-300

An electrocardiogram showed left ventricular hypertrophy and the strain. Radiographs of the chest and scull were normal. Endoscopic ultrasonography of the pancreas revealed the tumor of the body and tail of the pancreas. A magnetic resonance imaging (MRI) of the abdomen revealed well-demarcated right adrenal mass, 36 by 36 mm, with signs of focal necrosis and bleeding (Figure 1), with left kidney mass, 29 by 25 mm, homogeneously enhanced after paramagnetic contrast, bulging the lateral margin of the kidney, without extrarenal propagation (Figure 2). Also another tumor was discovered in the pancreas between the body and the tail, 30 mm by 20 mm, with heterogeneous enhancement after contrast material and without signs of infiltration of the surrounding structures (Figure 3). Pancreatic duct was moderately dilated. Funduscopic examination revealed no pathologic finding.

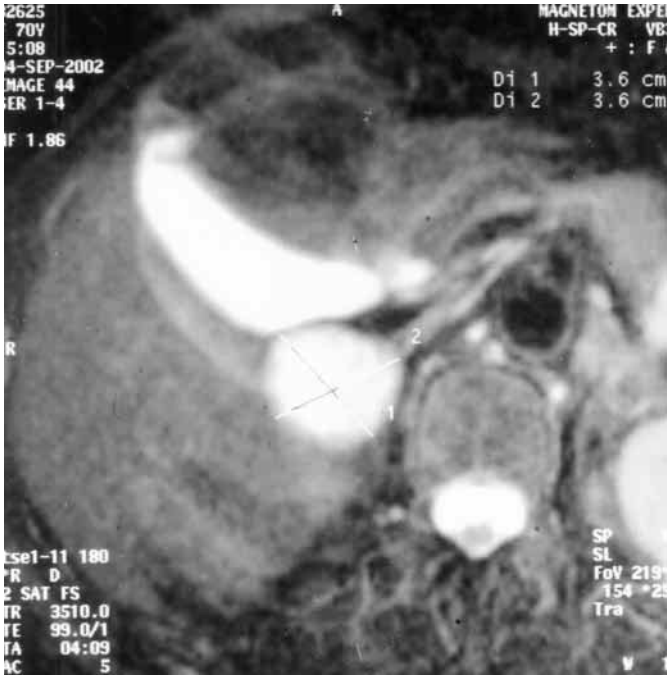

Figure 1. T1-weighted MRI scan of the abdomen after the administration of contrast material, showing a right(sided adrenal mass (cross lines)

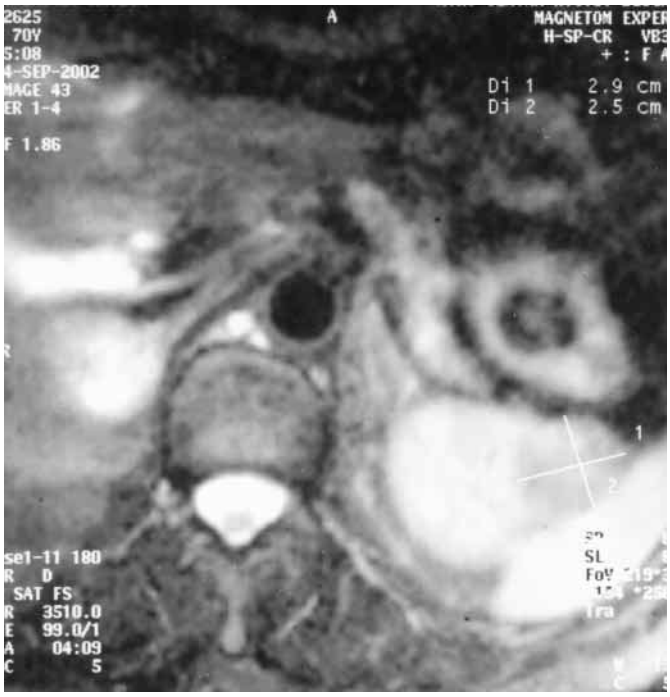

Figure 2. T1-weighted MRI scan of the abdomen after the administration of contrast material, showing a left kidney mass (cross lines)

After proper pretreatment with phenoxybenzamine (60 mg daily), a nonspecific α-adrenergic-receptor antagonist, surgical excision of the adrenal tumor was performed through a transabdominal incision. Residual nonparoxysmal hypertension was easily controlled with amlodipine 10 mg daily. The patient was discharged for recovery. Macroscopically, the resected pathological specimen consisted of a soft, lobulated brown adrenal tumor 35x30x30 mm in diameter, with signs of focal hemorrhage.

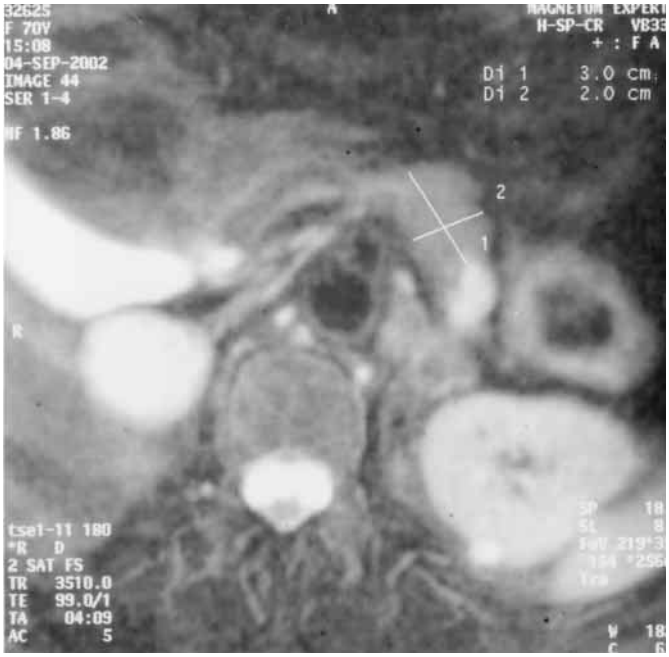

Figure 3. T1-weighted MRI scan of the abdomen after the administration of contrast material, showing a pancreatic tumor (cross lines)

Microscopic examination showed an encapsulated tumor composed largely of polygonal cells with uniform nuclei and eosinophilic cytoplasm. Although rare cells had atypical nuclei, mitotic activity and necrosis were absent. Sustentacular cells were scattered mostly in the periphery of the tumor. There were no clear signs of the invasion of tumor capsule. Adrenal cortex was compressed by the tumor.

Ulteriorly, SSCP (single strand conformational polymorphism) method detected a point mutation in the third exon of the VHL (von Hippel-Linday) gene. Definitive diagnosis was revised to von Hippel-Lindau disease. It was decided to follow up the patient with the von Hippel-Lindau disease, while waiting the results of the sequence analysis to confirm that the found mutation is not associated with renal cancer.

DISCUSSION

A case of a 70-year old patient with von Hippel-Lindau (VHL) disease (syndrome) consisting of three components, namely pheochromocytoma, kidney and pancreatic tumor, was described. Upon surgical removal of the pheochromocytoma, dilemma persisted concerning further treatment of the patients other tumors.

The von Hippel-Lindau (VHL) disease is a rare autosomal dominant condition characterized by the development of specific benign and malignant tumors (1,3). Patients with von Hippel-Lindau disease have a germline mutation of the von Hippel-Lindau gene on human chromosome 3p25 (5,6). Penetrance is known to be relatively high (approximately 70% by the age of 70) (4). The VHL gene is a tumor suppressor gene and is involved in blood vessel formation by regulation of the activity of hypoxia-inducible factor (HIF)-1α (3). Affected persons can develop early-onset bilateral kidney tumors and cysts, pheochromocytomas, cerebellar and spinal hemangioblastomas, retinal angiomas, pancreatic cysts and tumors, epididymal cystadenomas, and tumors in the endolymphatic sac canal of the inner ear (1). Renal cell carcinoma occurs in about 40%-70% of patients and is the leading cause of mortality (7). As many as 50% of patients in VHL families may show only one manifestation of the syndrome (7). On the basis of its clinical expression, VHL syndrome has been divided into two main subtypes: VHL type 1 and VHL type 2, with a central role for pheochromocytoma (6,8). Carriers of VHL type 2 mutations are at risk to develop pheochromocytoma, whereas carriers of type 1 mutations are not. VHL type 2 has further been subdivided into mutation carriers with a low (VHL type 2A) or high risk (VHL type 2B) to develop renal cell carcinoma. A third group is characterized by the pheochromocytoma only phenotype (9).

The VHL gene consists of three exons and encodes a 213 aminoacids protein, which is necessary for the target cells ability to orchestrate the expression of a diverse set of genes involved in some signal transduction pathways, cellular response to hypoxia, and regulation of the microenvironment in tumors (6). It is necessary to have both copies of the VHL gene mutated in order to have loss of the tumor-suppressor activity and the expression of the syndrome.

It is becoming increasingly apparent that tumors of a single histological type are heterogeneous in their natural history, molecular differences, prognosis, and response to treatment. It is a widespread assumption that most pheochromocytomas are sporadic and only about 10 percent is hereditary (1). When hereditary, pheochromocytoma can be a component of multiple endocrine neoplasia type 2 (MEN 2), caused by mutations of the *RET* gene; von Hippel-Lindau disease, caused by mutation of the *VHL* gene; and, rarely, neurofibromatosis type 1 (1,3,5). Recently, mutations of the gene for succinate dehydrogenase subunit D (*SDHD*) were identified for another related neuroendocrine disease, familial paragangliomas of the neck, or glomus tumors (10). *SDHD* and *SDHB* encode mitochondrial enzymes involved in oxidative phosphorylation. Nevertheless, genetic evaluation of 271 unrelated patients who presented with nonsyndromic pheochromocytoma revealed that 66 (24%) had hereditary disease, i.e. newly discovered mutations in the VHL, RET, SDHD or SDHB gene (4). Therefore, so called sporadic pheochromocytomas without a family history of the disease, might in fact represent a case of spontaneous mutations in one of the susceptibility genes, and consequently one of hereditary syndromes. Genetic testing can be a powerful aid to the identification of a syndrome in such case (4), and obviously in every case of presumably spo-

radic pheochromocytoma genetic analysis should be done. This is very important, because the identification of a new case of hereditary pheochromocytoma should prompt genetic testing of all first-degree relatives of the carrier to determine the presence or absence of the family-specific mutation. Since disease is likely to develop in virtually all patients with a famil-(specific mutation, it seems reasonable to subject such patients to lifelong surveillance, prophylactic surgery, or both, depending on the precise genetic diagnosis.

In the case presented in this paper, adrenal pheochromocytoma was associated with other tumors raising the possibility of von Hippel-Lindau disease, which was ulteriorly confirmed. Our patient had no offspring or close relatives, so genetic testing of family members was not feasible. In order to confirm that the found *VHL* gene mutation is not associated with the development of renal cancer, sequence analysis should be done to determine the type of mutation.

In conclusion, in each case of nonsyndromic pheochromocytoma genetic testing should be considered to investigate the possibility of hereditary cancer syndrome.

Acknowledgment:

MRI scans have been obtained in the MRI Center of the Clinical Center of Serbia in Belgrade.

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