CASE REPORT

The malignant potential of a succinate dehydrogenase subunit B germline mutation

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ABSTRACT. Familial catecholamine secreting tumors have been associated with multiple endocrine neoplasia type 2, Von Hippel-Lindau disease and neurofibromatosis type 1. In the last years, mutations of genes encoding subunits B, C and D of the succinate dehydrogenase have been discovered as other causes of pheochromocytomas and paragangliomas. We diagnosed a malignant retroperitoneal paraganglioma in a 64-yr-old man with bone metastasis in 2001. Two years later a retroperitoneal benign paraganglioma was found and resected in his 32-yr-old daughter. Thus we diagnosed in this family a paraganglioma syndrome. We performed molecular genetic analyses of the genes SDHB, SDHC, and SDHD. We detected in the SDHB gene the mutation SDHB c. 558-3 C>G affecting the splice site of exon 5. In a second daughter the mutation was also detected, thorough clinical investigation revealed normal results. We conclude that the SDHB mutation predisposes to abdominal extra-adrenal and potential malignant pheochromocytoma with incomplete penetrance.

INTRODUCTION

The catecholamine secreting tumors, pheochromocytoma and paraganglioma, are one of the treatable causes of hypertension. Most pheochromocytomas (90%) are benign and sporadic. For a long time it has not been frequent to find malignant pheochromocytomas in a familiar syndrome. The most common pheochromocytoma/paraganglioma associated familial syndromes are multiple endocrine neoplasia type 2 and Von Hippel-Lindau disease. Recently mutations of genes encoding subunits of the succinate dehydrogenase (SDHB, SDHC, SDHD) have been connected with familial pheochromocytomas and paragangliomas (1-4).

The mitochondrial respiratory chain consists of five protein complexes. The complex II of the mitochondrial chain contains four proteins, SDHA, SDHB, SDHC, and SDHD (5). Mutations in these genes encoding the corresponding proteins lead to inactivity of complex II in the mitochondrial respiratory chain and activate the hypoxia pathway (6).

The prevalence of SDHB and SDHD gene mutations is similar, 4 to 6%. Typical lesions of the PGL1 syndrome, caused by mutations of the SDHD gene, are multifocal adrenal pheochromocytomas and paragangliomas of the head and skull base. In contrast, the PGL4 syndrome, caused by mutations of the SDHB gene, is characterized by a high proportion of extra-adrenal, malignant pheochromocytomas (4, 7). Mutations of the SDHC gene are rare and only detected in patients with paragangliomas of the head and skull base. We report two cases of a familial paraganglioma associated with a SDHB gene mutation.

PATIENTS AND METHODS

Case 1

A 64-yr-old man was admitted in the Hospital of Navarra in July 2001. He had arterial hypertension and was diabetic since 1980. He was under medication of antidiabetics with an excellent glycemic control. Since September 1999 he had palpitations and profuse sweating. One year later the episodes became more frequent and were accompanied with worsening of the hypertension. While he was in hospital, the episodes occurred, whenever he was sitting or
in an abdominal flexion position. In the last 2 yr, both hypertension
the glycemic control have been more resistant to treatment.
We collected 24 h urine for total metanephrines and catecholamines.
He had increased normetanephrines of 8911 μg/24 h (normal: up to
400), norepinephrine of 230 μg/24 h (up to 80), and vanillylmandelic
acid of 25 mg/24 h (up to 7). The computed tomography (CT) scan of
the abdomen with contrast showed a paraaortic mass just above of the
celiac trunk measuring 4x2 cm (Fig. 1). The adrenal glands were nor-
mal. By $^{131}$I-metaiodobenzylguanidine scintigraphy we found
an area of increased uptake that corresponded to the mass seen on
abdominal CT. In addition, the scintigraphy showed an uptake in the
11th and 12th left rib. He required insulin, while he was in hospital.
The patient was diagnosed with a malignant catecholamine
secreting abdominal paraganglioma and was treated with pheno-
oxymetrazoline before surgery. The abdominal paraganglioma
and rib metastases were resected in one operation. Afterwards he
became asymptomatic. The 24 h urinary excretion control of cate-
cholamines and total metanephrines, however, did not normalize
post-operatively and revealed normetanephrines of 895 μg/24 h
and metanephrines of 15 μg/24 h (normal: up to 320). A new scan-
ning with $^{131}$I-metaiodobenzylguanidine did not indicate
new lesions, nor the [111 In] octreotide scintigraphy could identify
any remnants of a catecholamine secreting tumor. In contrast, a
FDG PET discovered a metastasis in the left femoral neck.

Case 2
In October 2002, the patient’s first 32 yr old daughter was admitted
with a blood pressure of 160/130 mmHg. For 18 months she had pal-
pitations, sweating, headaches and trembling, when she layed down.
These episodes declined spontaneously. Because of her family history
we performed a 24 h urine test which revealed elevated normetane-
phrines of 8796 μg/24 h, norepinephrine of 2460 μg/24 h, dopamine
of 775 μg/24 h (normal: up to 400), and vanillylmandelic acid of 27 mg/
24 h (normal: up to 7). An ultrasonography and a CT scan showed a
7x7 cm mass just under the liver, that arose along the abdominal aorta.
Both adrenal glands were not involved. Magnetic resonance imaging
(MRI) confirmed a right paraaortic tumor which appeared as a bright
mass on a T2 weighted image (Fig. 2). The $^{131}$I-metaiodine-MIBG revealed
an isolated abdominal uptake on the right side.
The patient presented in the first 2 days hyperadrenergic crises
with blood pressure up to 220/110 mmHg and headaches. Treat-
ment with phenoxybenzamine normalized the situation. The
paraganglioma was resected by laparotomy. Post-operatively the
24 h urine catecholamines were normal.

Molecular genetic testing
Peripheral blood samples were analyzed by PCR, SSCP and direct
sequencing in the Department of Nephrology and Hypertension of
Freiburg in order to search for mutations of the SDHB, SDHC,
and SDHD genes. The patients provided written informed consent.
No mutations were found in SDHC and SDHD. In contrast, both pa-
tients were carriers of the mutation SDHB c. 558-3 C>G. This mutation
affects the splice site of exon 5 and results in the loss of exon 5. We have
performed the SSCP also for 100 healthy controls. We did not find a
similar pathological band pattern as seen in the patients of this family.
Surprisingly, the second daughter, age 33 yr, who is totally asym-
omatic, was found to carry also the mutation. Subsequently she
underwent an extended screening program including CT scan of

Anterior view  Posterior view
Fig. 1 - Case 1: $^{131}$I-metaiodobenzylguanidine scintigraphy.

Fig. 2 - Case 2: Abdominal magnetic resonance imaging (MRI)
showing extra-adrenal of paraganglioma.