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Malignant Paragangliomas Associated with Mutations in the Succinate Dehydrogenase D Gene

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Introduction: Malignant paragangliomas have been well described in carriers of mutations of the succinate dehydrogenase B (SDHB) gene, but have rarely been associated with mutations in the succinate dehydrogenase D (SDHD) gene.

Aim: The aim of the study was to report the different clinical expression patterns of malignant paragangliomas in five patients with SDHD (D92Y) mutations observed in approximately 200 SDHD (D92Y) mutation carriers followed in our institution.

Results: Metastasis and/or local tumor invasion was documented 0 (n = 2), 1, 18, and 30 yr after the initial diagnosis of paraganglioma. Malignancy was proven by paraganglioma bone metastases (n = 2), intrathoracic paraganglioma with lymph node metastases, locally invasive head-and-neck paraganglioma with destruction of the petrosal bone, and locally invasive paraganglioma of the bladder with lymph node metastases. Four of the five patients developed catecholamine excess during follow-up due to intraadrenal paraganglioma (pheochromocytoma) (n = 1), extra adrenal paraganglioma (n = 2), and presumed subclinical disease (n = 1).

Conclusion: SDHD mutations (D92Y) are associated with malignant paragangliomas and catecholamine excess with remarkable interindividual variations despite the same mutation. We estimate that the prevalence of malignancy in carriers of D92Y mutations is at least 2.5%. **(*J Clin Endocrinol Metab* 92: 1245–1248, 2007)**

PARAGANGLIOMAS ARE TUMORS arising from neural crest cells associated with the autonomic nervous system. Some paragangliomas produce excessive amounts of catecholamines, especially if they are located in the adrenal glands (pheochromocytoma). Germline mutations in the genes encoding subunits B, C, and D of mitochondrial complex II succinate dehydrogenase (SDH) are associated with multiple paragangliomas (1–3). These SDH genes may behave as tumor suppressor genes (1, 4). Mutations in SDHD are the most prominent cause of head-and-neck paragangliomas (also referred to as glomus tumors), whereas mutations in SDHB are more frequently related to adrenal and extraadrenal pheochromocytoma and malignant disease (5–9). In contrast, malignant paragangliomas have only infrequently been associated with SDHD mutations (5, 10–12). We describe five patients with metastasized paragangliomas associated with SDHD (D92Y) mutations. These cases indicate that malignant conversion of paragangliomas may occur more frequently in patients with SDHD (D92Y) mutations than hitherto appreciated. Moreover, these cases illustrate the variability of the clinical behavior of malignant paraganglioma.

Patients and Methods

The Leiden University Medical Center is a referral center for paragangliomas. Patients are seen at least every 2 yr. Urine is collected over 24 h in duplicate under strict dietary regulations and after stopping medication for several weeks or changing antihypertensive medication to doxazosine. In the case of excessive catecholamine secretion, metaiodobenzylguanidine (MIBG) scanning and additional magnetic resonance imaging (MRI) of the adrenal glands are performed (13).

Epinephrine, norepinephrine, and dopamine in urine are quantified by reversed HPLC with an electrochemical detector. Interassay coefficients of variation for epinephrine were 4.3–9.0% ranging from high to low levels. For norepinephrine, these data are 2.7–3.6%, and for dopamine 3.1–4.8%. Vanillylic mandelic acid (VMA) in urine was measured using HPLC with fluorometric detection with coefficients of variation from 2.4 to 9.1%. Reference ranges were: norepinephrine, 0.06–0.47 μmol/24 h; epinephrine, less than 0.16 μmol/24 h; dopamine, 0.46–3.40 μmol/24 h; VMA, less than 30 μmol/24 h; and normetanephrine, 64–260 μmol per mol creatinine. Before germline mutation testing, informed consent was obtained from each patient. DNA was screened for the Dutch SDHD germ-line mutation D92Y by restriction digestion as described by Taschner *et al.* (14).

Case Reports

Patient 1

In 1972 a 28-yr-old female patient was evaluated for a left-side carotid body tumor. Family history revealed one sister with a glomus tumor. Resection of the tumor in 1972 was complicated by paresis of the left vocal cord.

In 1996 she was operated for a carotid body tumor on the right side. A glomus vagale on the left and a right-sided glomus jugulare tumor were left *in situ*. At that time variations in blood pressure (ranging from 230/160 to 130/70 mm Hg) were interpreted to result from loss of baroreceptor reflex mediated mechanisms because there was no excessive secretion of catecholamines in 24-h urine collections: norepinephrine, 0.17 and 0.22 μmol/24 h (see *Patients and Methods* for reference ranges); epinephrine, 0.02 μmol/24 h; and dopamine, 1.48 and 1.75 μmol/24 h.

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Abbreviations: CT, Computed tomography; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; SDH, succinate dehydrogenase; VMA, vanillylic mandelic acid.

In 2002 an MRI of the pelvis was performed because of progressive pain, which revealed a lytic lesion in the left iliac crest with destruction and invasion into the adjacent muscles. MIBG scanning showed increased activity only in this specific locus. With the exception of the already known head-and-neck paragangliomas, no other locations of the disease were found at that time during extensive imaging studies. A biopsy of the pelvic lesion revealed a metastasis of a paraganglioma. This pelvic lesion was treated by local radiotherapy.

In 2003 she was admitted with persistent fever, without signs of catecholamine excess. At physical examination she appeared to have an enlarged lymph node in the left groin. There was no excessive secretion of catecholamines in the urine: norepinephrine, 0.15 and 0.34 μmol/24 h; epinephrine, 0.00 μmol/24 h; dopamine, 0.53 and 2.25 μmol/24 h; and VMA, 16 and 23 μmol/24 h. No infectious agents could be identified. Histological examination of the lymph node revealed a metastasis of the paraganglioma. A computed tomography (CT) scan of the abdomen revealed two new lytic lesions in the ischium and three enlarged parailiacal and paraaortic lymph nodes. Because there was no uptake on an I-131 MIBG scan, there was no possibility for I-131 targeted therapy. Octreotide scintigraphy revealed multiple lesions throughout the abdomen, in addition to the already known lesions in the pelvis. On an empirical basis, she was unsuccessfully treated with octreotide in an attempt to reduce her (para)neoplastic symptoms. In 2004 she died of metastatic disease, 32 yr after the initial diagnosis and 2 yr after the discovery of malignant disease. Genetic analysis revealed that she was carrier of a SDHD D92Y mutation.

Patient 2

In 1975 a 36-yr-old female patient was operated for bilateral carotid body tumors. Her family history was positive for glomus tumors. In 1986 she presented with a recurrent carotid body tumor on the right side and was found to have additional vagal and jugular tumors on that side. The attending physicians decided for a wait-and-scan policy because of the multiple lesions and because of the likelihood that surgical removal carried a serious risk of damage to adjacent nerves. Although she had hypertension (148/104 mm Hg), 24-h urine samples did not reveal excessive catecholamine secretion: norepinephrine, 0.23 and 0.27 μmol/24 h; epinephrine, 0.00 and 0.03 μmol/24 h; dopamine, 1.89 and 2.09 μmol/24 h; and VMA, 17 and 18 μmol/24 h. An abdominal CT scan did not show adrenal or extraadrenal paragangliomas.

In 1993 she was evaluated for anemia and an increased erythrocyte sedimentation rate in the absence of any specific complaints. Additional investigations revealed multiple pulmonary nodules and a nodular lesion with a diameter of 12 mm in the left adrenal gland. Bone scintigraphy showed hot spots in the 10th thoracic vertebra and in the left iliac crest. Histological evaluation of a biopsy of this last lesion revealed paraganglioma cells. Because there were no options for curation and because of the extremely slow progression of the disease, the wait-and-scan policy was continued. In 2002, 24-h urine collections showed a persistent increase in norepinephrine excretion (0.87 and 0.88 μmol/24 h) and VMA (31 μmol/24 h) without excessive excretion of other catecholamines (epinephrine, 0.06 μmol/24 h; dopamine, 2.04 μmol/24 h). An MIBG scan showed intense activity in the area of the left adrenal gland, the known tumors in the head-and-neck area, and in the left iliac crest. Bone scintigraphy revealed multiple new lesions in vertebrae 4 and 9 and irregular uptake in several ribs. MRI documented a nodular lesion with a diameter of 2 cm of the left adrenal gland. After appropriate preoperative treatment with doxazosine, a left-side adrenalectomy was performed. Pathological examination confirmed a pheochromocytoma with a diameter of 2 cm. Postoperatively, the excretion of catecholamines in 24-h urine collections was within normal ranges.

In 2006 she is doing well without any complaints, 31 yr after the initial diagnosis and 13 yr after diagnosis of metastatic disease. The initial glomus tumor is asymptomatic and 10 cm in diameter in the submandibular region. Genetic analysis revealed a SDHD D92Y mutation.

Patient 3

In 2005 a 66-yr-old female patient was operated for an orbital meningioma for which decompressive surgery was performed. Because a tumor in the anterior mediastinum was found on a routine chest x-ray, she was referred to the pulmonology department in our hospital. Because of a suspected thymoma, a thymectomy was performed. Histopathological investigation of the resected tissue showed a paraganglioma with a diameter of 4.4 cm. Two of the five resected lymph nodes were positive for paraganglioma cells. Therefore, the diagnosis was malignant paraganglioma. She was referred to our department. The family history of this patient was positive for glomus tumors: her father, grandfather, and a nephew had been operated for this diagnosis.

On clinical examination she had hypertension (180/100 mm Hg). No paragangliomas were identified by palpation or MRI scan of head and neck. A CT scan revealed a borderline enlarged mediastinal lymph node, but no other lesions suspect for paraganglioma in the thorax or abdomen. In 24-h urine collections, elevated levels of norepinephrine (0.62 and 0.57 μmol/24 h) and normetanephrine (393 μmol per mol creatinine) were found. Excretion of epinephrine (0.02 μmol/24 h) and dopamine (1.40 μmol/24 h) were within reference values. An MIBG scan revealed a very discrete level of activity on the right between the thyroid and parotid gland, which could not be identified on subsequent MRI. Octreotide scintigraphy did only show increased activity in the remnants of the known orbita-meningioma. Patient 3 is currently treated with 8 mg doxazosine, and her blood pressure ranges between 144/79 and 119/61 mm Hg. Genetic analysis revealed a SDHD D92Y mutation.

Patient 4

In 1993 a 52-yr-old male patient presented with hearing loss due to a left-side jugulotympanic tumor. Family history revealed glomus tumors in the family of his father. MRI showed a jugulotympanic glomus tumor on the left, for which a wait-and-scan policy was chosen. In 1998 he developed nervousness, palpitations, and excessive sweating and

was referred to the Department of Endocrinology. On physical examination, blood pressure was 170/92 mm Hg, and pulse rate was 88 regular beats per minute. Twenty-four-hour urine collections showed elevated levels of norepinephrine (0.65 and 0.50 μmol/24 h), whereas other catecholamines (epinephrine, 0.07 μmol/24 h; dopamine, 1.89 μmol/24 h) were within reference values. A CT scan revealed irregular destruction of the petrosal bone and the temporomandibular joint. No further investigations for other paragangliomas or pheochromocytoma were performed at that time. A subtotal extirpation of the glomus tumor was performed under labetalol treatment. Paraganglioma cells were found in both the primary lesion and the marrow of bone fragments resected during operation. Lymph nodes were reported to be free of paraganglioma cells. Postoperatively, 24-h urinary catecholamine secretion was normal.

In 2005, the patient was again found to have hypertension (170/100 mm Hg). Biochemical evaluation revealed elevated excretion of norepinephrine (0.51 μmol/24 h), whereas the increase in VMA excretion was borderline (30 μmol/24 h). Both epinephrine (0.02 μmol/24 h) and dopamine excretion (2.28 μmol/24 h) were within the normal range. An MIBG scan revealed increased uptake in the right side of the neck, suspect for paraganglioma, and intense uptake in the area of the right adrenal and the liver, suspect for a pheochromocytoma and/or liver metastases. On MRI, the adrenals appeared to be completely normal, whereas a large round mass ($4.0 \times 4.4 \times 3.3$ cm) was seen lateral of the inferior vena cava. In the liver, three small cysts were seen with a maximal diameter of 6 mm, which did not correlate with uptake on the MIBG scan. Doxazosine therapy was started, and the tumor was surgically removed. The liver lesions were not biopsied. On pathological examination, paraganglioma was diagnosed. Postoperatively, 24-h urine catecholamine secretion returned to normal. The patient was found positive for the SDHD D92Y mutation.

Patient 5

In 2005 a 42-yr-old female patient was referred to our hospital for analysis of a possible pheochromocytoma. Her medical history showed hypertension since 1981, and in 2002 Graves' disease was diagnosed, for which she was treated with thionamides. She had persistent hypertension (160/112 mm Hg) despite treatment with a combination of hydrochlorothiazide, losartan, propranolol, and doxazosine. Twenty-four-hour urine samples showed elevated levels of norepinephrine (10.70 μmol/24 h) and dopamine (4.13 μmol/24 h). An abdominal ultrasound and CT scan demonstrated a tumor with a diameter of 8 cm in direct relation with the bladder but no adrenal abnormalities. An MIBG scan showed symmetrical physiological activity. The diagnosis was an extraadrenal pheochromocytoma (paraganglioma), for which she was referred to our hospital. After preoperative treatment with 16 mg of doxazosine, a partial cystectomy with extirpation of two parailiacal lymph nodes was performed. Pathological investigation revealed invasive growth into both the smooth muscle of the bladder and the peritoneum. Lymph nodes were positive for paraganglioma cells. Postoperative urine samples showed a reduction in catecholamine secretion, but no normalization (norepinephrine, 0.82 μmol/24 h; dopamine, 1.53 μmol/24 h). Octreotide scintigraphy showed hot spots in the region where the original tumor had been located and intense activity in the left parotid region. MRI scan of the head and neck demonstrated a vagal glomus tumor and a small carotid body tumor on the left.

An abdominal MRI revealed two enlarged lymph nodes with a pathological aspect in the iliac fossa. Therefore, a second operation was performed to try to remove recurrent tumor tissue. However, a residual tumor with multiple peritoneal metastases was seen which could not be radically resected. Treatment with ^{131}MIBG was considered not to be effective for lack of uptake on diagnostic MIBG scans. Patient 5 is currently treated with external radiotherapy because of progressive local tumor growth, and lutetium-labeled octreotide is considered. The patient tested positive for the SDHD D92Y mutation.

Discussion

We describe five patients with a SDHD (D92Y) mutation and malignant paraganglioma in a group of approximately 200 SDHD (D92Y) mutation carriers. This indicates that malignant paragangliomas may occur more frequently in carriers of SDHD (D92Y) mutations than hitherto recognized. Moreover, the same SDHD mutation resulted in remarkable variations in clinical presentation of the disease. Therefore, this case series indicates that patients with SDHD (D92Y) mutations can develop malignant forms of paraganglioma with divergent clinical phenotypes.

There appears to be a distinct genotype-phenotype correlation for the different genes associated with familial paraganglioma syndrome (5, 6). Head-and-neck paragangliomas and multifocal tumors are more prevalent in patients with a SDHD mutation than in SDHB mutation carriers (6, 15). On the other hand, a high frequency of malignant disease in SDHB mutation carriers is reported. Neumann *et al.* (6) report 34% of SDHB mutation carriers to have distant metastases, whereas another study even found 71.4% malignant disease in SDHB patients (7). Moreover, Young *et al.* (8) presented two cases with a malignant catecholamine-producing paraganglioma associated with a SDHB mutation. SDHD-related malignant disease, however, is rare. There are two large series of SDHD mutation carriers reported in the literature, one is population-based (6) and the other is an international consortium of referral-based patients (5). Remarkably, none of their SDHD mutation carriers presented with malignant disease. However, this does not exclude that malignant paragangliomas develop during prolongation of follow-up. In accordance, of the 28 affected SDHD mutation-positive patients in the report by Benn *et al.* (5), none presented with malignant disease at first surgery, but two patients developed metastases during follow-up. In another study, Astrom *et al.* (12) found four SDHD subjects who developed malignant tumors (6.9%). However, an important issue is that our cases all have the D92Y mutation, the most frequently occurring founder mutation in The Netherlands (14), whereas other reports described patients with other mutations in the SDHD gene. One might argue that malignant disease is pe-

culiar to the D92Y mutation *per se* and/or a gene-environment interaction peculiar to The Netherlands.

This seminar indicates that clinical behavior and survival of malignant paraganglioma in patients with the same mutation is highly variable. Metastasis and/or local tumor invasion was documented 0 (n = 2), 1, 18, and 30 yr after the initial diagnosis of paraganglioma. Because there are no clear-cut histopathological characteristics of malignant dedifferentiation, malignancy was proven by paraganglioma bone metastases (n = 2), intrathoracic paraganglioma with lymph node metastases, locally invasive head-and-neck paraganglioma with destruction of the petrosal bone, and locally invasive paraganglioma of the bladder with lymph node metastases. In patients 1 and 5, systemic ^{131}MIBG therapy was considered but was thought to be ineffective for lack of uptake. Because of very rapidly progressive disease and octreotide uptake, patient 5 will be treated with lutetium-labeled octreotide as was described by van Essen *et al.* (16). Although in malignant pheochromocytoma 5-yr survival rates have been published to range from less than 50% to 74% (depending on the paraganglioma location inside or outside the adrenals) (17, 18), it is at present not possible to estimate specific survival data in SDHD mutation-related malignant paragangliomas because of their low incidence.

SDHD mutation carriers are at risk for developing catecholamine excess due to pheochromocytomas and/or extraadrenal paragangliomas (13). This risk is further exemplified by the current series. Four of the five patients in the present report had catecholamine excess due to pheochromocytoma and/or extraadrenal paraganglioma. Moreover, in this respect it is relevant to note that these tumors can change their hormonal profile during the course of disease and that their hormonal production and secretion can be different in mature or less differentiated tissue (4, 19). These observations emphasize the need to screen SDHD mutation carriers for catecholamine excess on a regular basis.

In conclusion, we report five patients with malignant paraganglioma associated with a germline SDHD (D92Y) mutation. The data indicate that SDHD (D92Y) mutations are associated with a malignant form of paraganglioma with divergent clinical phenotypes.

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