A 40-YEAR FOLLOW-UP OF A PATIENT WITH MULTIPLE PARAGANGLIOMAS AND A SDHD MUTATION

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Abstract

Context. Germline mutations in Succinate Dehydrogenase Complex Subunit D gene (SDHD) predispose to predominantly benign head and neck and/or thoracic-abdominal pelvic paragangliomas (PGLs).

Objective. We present the case of a patient carrying a germline SDHD mutation responsible for multiple PGLs, who was followed for 40 years. He was initially diagnosed with a left cervical PGL at the age of 23 years, treated by surgery. Then, he recurred and developed a multifocal disease. The second-line therapeutic option was a three-dimensional conformal radiotherapy performed in 2008. In 2013 the patient had clinical, hormonal, PET- and SPECT-CT data revealing a disease progression. The treatment with the long-acting somatostatin analogue Octreotide Lar was carried out till the patient's death caused by pulmonary embolism in December 2014.

Results. Complex treatment led to a long clinical and biochemical remission and control of tumor growth.

Conclusions. Despite their usually benign behavior, multicentric SDHD-related PGLs can require a multimodal approach involving surgery, radiotherapy and medical treatment for providing a long-term control of the disease and maintaining a good quality of life.

Key words: paraganglioma, succinate dehydrogenase, multicentricity.

INTRODUCTION

Although the first case of paraganglioma (PGL) was described in 1891 (1), only studies from the last two decades threw light on genetics of this rare neuroendocrine tumor. Germline mutations in the genes encoding the four subunits of the mitochondrial enzyme succinate dehydrogenase (SDHA, SDHB, SDHC and SDHD) and SDHAF2 gene (encoding SDH-complex assembly factor 2) have been shown to be responsible for the development of paragangliomas/

pheochromocytomas (PPGLs) (2-5). Strong genotype-phenotype correlations were established. SDHB mutations predispose predominantly to abdominal and thoracic paragangliomas (PGLs) and about half of them have a malignant behavior whereas SDHD mutations are most often associated with multiple head and neck tumors (HNPG) (6-8). A heterozygous germline SDHA mutation was firstly identified in 2010 by Burnichon *et al.*, in a woman with a catecholamine-producing abdominal PGL (5). SDHC mutations are rare and cause PGLs which usually exhibit a SDHD-related phenotype (4). Metastatic PPGL are rare in SDHD mutation-carriers compared to SDHB ones (4% versus 40% of the cases in retrospective series). SDHD-mutation carriers have a good prognosis and a slow progression of their disease even in cases with a multifocal disease (6, 9).

CASE PRESENTATION

We summarize the 40-year history of a man initially seen in 1975, at the age of 23, for complaints of hearing loss and tinnitus in the left ear. A left side neck tumor was initially detected by examination of the ear and neck area and some years later visualized on the CT scan (the corresponding medical records and images were lost). He had a negative family history of PPGL. At the beginning the patient declined surgery and was followed up for 20 years. He was finally operated on in the University Neurosurgical Department, Sofia in 1994. Two years later (1996), magnetic resonance imaging (MRI) visualized bilateral carotid PGLs. The patient refused second surgery and was lost-to-follow up from 1996 to 2005.

In 2005 he was admitted at the University Specialized Hospital of Endocrinology, Sofia, Bulgaria and a significant increase of both tumors size was

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observed on the CT scan (Fig. 1). Furthermore a slightly elevated 24-hour urinary noradrenaline and dopamine concentrations (Table 1) were measured associated with a mild hypertension controlled by monotherapy with a selective α 1-blocker (Doxazosin, 2 mg/d).

A multinodular euthyroid goiter and impaired glucose tolerance were diagnosed and antidiabetic treatment (Metformin, 1500 mg/d) was initiated. The main laboratory parameters (lipid profile, liver function tests, haematology, electrolytes, TSH, FT4, Calcitonin, Parathyroid hormone, etc.) were within the reference ranges. A PPGL genetic testing was carried out by the molecular genetics laboratory of the Genetics Department of the European Hospital “Georges Pompidou” in Paris (France). A pathogenic germline mutation in the exon 4 of the SDHD gene, (c.479_480insGT; p.X160TrpextX*8) was identified allowing to diagnose a SDHD hereditary paraganglioma.

In 2006 the patient was admitted to a hospital for pneumonia and the chest X-ray incidentally revealed a mediastinal enlargement. Thoracic and abdominal CT-scan found two new PGLs: a mediastinal (max. size 65 mm) and a retroperitoneal abdominal (max. size 48 mm). As the patient refused surgery the “wait and scan” management and conservative treatment were proposed. Antihypertensive treatment with Doxazosin was continued. In February 2007, the cervical and mediastinal PGLs presented no change on control CT scan but a new PGL was found in the left retroperitoneal space in the perirenal area. The four PGLs exhibited an equal density and hypervascular phenotype with a strong enhancement in the early arterial phase (Figs 2-4). Later in 2007, while the patient was temporarily working in Torino (Italy), he was admitted to the Department of Endocrinology of “Umberto I” Hospital. An enlargement of the previously detected four tumors

Table 1. 24-hour urinary catecholamines (spectrofluorimetric assay) and free metanephrines (RIA) levels during the follow-up

	A	n.a.	DA	MN	NMN	CgA
MAY 1996	12.08	51.2	449.72	n.a.	n.a.	n.a.
AUG 2005	29.91	108.28	496.74	n.a.	n.a.	n.a.
OCT 2008	<4	122	148	n.a.	n.a.	n.a.
SEP 2009	<4	62	71	45	128	n.a.
AUG 2010	n.a.	n.a.	n.a.	126	499	n.a.
SEP 2011	n.a.	n.a.	n.a.	118	280	n.a.
JUL 2012	n.a.	n.a.	n.a.	126	297	n.a.
OCT 2013	n.a.	n.a.	n.a.	224	669	> 767
FEB 2014	n.a.	n.a.	n.a.	121	481	89.7
OCT 2014	n.a.	n.a.	n.a.	109	392	92.8
Normal range	[< 20 μ g]	[< 60 μ g]	[< 290 μ g]	[< 350 ng]	[< 600 ng]	[$\leq$ 100 ng/mL]

A-Adrenaline; n.a.- not available; DA- Dopamine; MN- Metanephrine; NMN- Normetanephrine; CgA- Chromogranin A.

Figure 1. CT scan of the neck (9-Nov-2005): two solid lesions in the vicinity of the carotid bifurcation on both sides of the neck are visualized with the following dimensions: left mass – 50x37 mm; right mass is almost round, d=43 mm. The carotid arteries are dilated and tortuous with some dislocation in the zone of bifurcation, partially surrounded by the tumors.

Figure 2. CT examination of the neck (contrast enhanced; 12-Feb-2007): there are two symmetrical bilateral heterogeneous soft tissue masses in the paracarotid spaces. Parotid glands are dislocated without sign of direct invasion. There is no sign of bone destruction or periosteal reaction. Internal, external and common carotid arteries could be followed with normal size and homogeneous enhancement. Sternocleidomastoid muscles are dislocated without sign of invasion.

(bilateral cervical, mediastinal and abdominal) as well as a fifth jugulotypanic PGL (23x16 mm) were seen with 123I-MIBG-SPECT-CT and MRI. The patient was considered eligible for radiotherapy. Three dimensional conformal radiotherapy (3DCRT) was performed concomitantly on jugulotypanic (total radiation dose, TRD=50.4Gy) and mediastinal PGL (TRD= 55.8 Gy). Then, carotid PGLs were treated with intensity-modulated radiation therapy (IMRT) (TRD=55.8 Gy) in 2008. Marked improvement in the general condition, arterial hypertension control as well as normalization of the 24-hour noradrenaline and dopamine excretion were observed (Table 1). During the radiotherapy a tumor

Figure 3. CT examination of the mediastinum (12-Feb-2007): a similar solid mass with heterogeneous structure is visualized which upper pole is on the level of the upper mediastinum; caudally the tumor follows the space between the left carotid and left subclavian arteries, lateral margin of the aortic arch and left pulmonary artery. The perivascular fat tissue is engaged without invasion of the vessels. There are no nodules or infiltrates in both lungs. Normal chest wall structures.

Figure 4. CT of the abdomen (12-Feb-2007): Fourth tumor with similar characteristics is found in the left retroperitoneal space on the level of renal vessels without any signs of invasion.

of the ascending colon was incidentally diagnosed, graded as pT3pN0pM0 according to the TNM staging system. In April 2008 the patient underwent right hemicolectomy associated with the resection of the abdominal retroperitoneal PGL. Both diagnoses were histologically confirmed: colon adenocarcinoma and abdominal paraganglioma. After surgery 3 cycles of chemotherapy with Capecitabine were given from May to October 2008. No recurrence was found at the first postoperative follow-up including assessment of specific tumor markers and fibrocolonoscopy.

Significant decrease in the tumor volume of all PGLs was objectified on CT scan in 2009 as well as normal 24h-urine metanephrine levels (Table 1) without any change during surveillance in 2010, 2011 and 2012. The patient had an excellent control of his blood pressure under treatment with a stable dose of Doxazosine (2 mg/d).

In 2013 he was hospitalized in our Endocrinology department for uncontrolled hypertension and tachycardia. A slight increase of urinary normetanephrines levels as well as a significant increase of plasmatic chromogranin A (CgA) were observed (Table 1). The 18F-FDG-PET-CT visualized a disease progression with an enlargement of the previously described PGLs in the head and neck region and in the mediastinum, which were metabolically active. The somatostatin receptor SPECT-CT scintigraphy (99mTc Tektrotyd whole-body scan, November 2013) visualized all the above-mentioned lesions with high expression of somatostatin receptors (Fig. 5). Based on these data, a treatment with long-acting somatostatin analogue (Octreotide LAR, 20 mg in monthly intramuscular injections) was initiated

Figure 5. 99mTc Tektrotyd-SPECT-CT-Somatostatin receptor scintigraphy (NOV-2013).

Figure 6. The main clinical features, diagnostic and therapeutic procedures presented as a timeline flowchart.

in December 2013. This therapy was well-tolerated by the patient and resulted in a stable remission. The blood pressure and the heart rate were well-controlled. Chromogranin A and urinary free normetanephrines levels were normalized. A significant reduction of tumor volume of all PGLs was seen in CT and SPECT-CT control scans. Due to the good response, another therapeutic option with Peptide Receptor Radionuclide Therapy (PRRT) was not considered. The patient said having a very good quality of life during his long-term follow-up and continued to actively work. The main diagnostic and therapeutic events as well as tumor and markers progression are represented schematically in a timeline flowchart (Fig. 6).

Unfortunately, the patient suddenly died in December 2014 with clinical symptoms (severe tachydyspnea at rest, cyanosis, tachycardia and syncope) suggesting a massive pulmonary embolism for the emergency care team. The diagnosis was not confirmed by an autopsy which was denied by relatives.

DISCUSSION

SDHD mutation-carriers frequently develop head and neck paragangliomas (HNPGs) but can also have a multicentric disease with extraadrenal abdominal and/or mediastinal PGL. HNPGs are typically slow growing, non-catecholamines-producing, and benign tumors, which may stay long time asymptomatic and can be incidentally revealed by imaging (15). The increase of tumor burden can provoke symptoms caused by compression of regional structures. In spite of the lost documentation, based on the initial complaints of our patient (tinnitus and progressive hearing loss) we could categorize his first tumor as a non-catecholamine producing jugulotympanic PGL (15,16). In line with the classical natural history of SDHD hereditary PGL our patient further developed

bilateral carotid body tumors (CBTs). An issue that should be commented is the co-existence of PGLs and colorectal carcinoma. Is there a causal relationship between these different tumors? Published literature data on this topic are extremely limited. Habano *et al.* demonstrated a loss of heterozygosity at SDHD gene locus in a high per cent of patients operated for colorectal and gastric cancers suggesting a possible role of this tumor-suppressor gene in their pathogenesis (17). Zhang *et al.* observed significantly reduced SDHB expression in human colorectal cancer tissues, correlating with the tumor aggressiveness (18). Dong *et al.* found a significant relationship between certain genetic variations in tricarboxylic acid cycle metabolic enzymes genes (SDHC, SDHD and FH) and the postoperative prognosis in a big cohort of patients with colorectal carcinoma (19). Unfortunately, as colorectal cancer tissue was not available for search for loss of heterozygosity, measurement of SDH enzymatic activity and SDHB immunohistochemistry we can neither confirm nor exclude the hypothesis of an association between SDHD mutation and colorectal carcinoma. Larger studies are needed to explore that hypothesis.

Surgical treatment remains the first therapeutic choice for PGLs while repeated surgical interventions are often needed in SDHD-related disease because of its multicentricity. Incomplete tumor extirpation is often reported in HNPGs due to their proximity to large vessels and nerves as well as their high vascularization predisposing to an increased risk for intraoperative hemorrhages. Permanent postoperative nerve deficits have been reported in one fifth of the patients with CBTs and even more frequently in vagal and jugulotympanic PGLs (20). New retrocarotid and microsurgical techniques are associated with lower rate of intra- and postoperative complications but are curative in the minority of SDHD mutation positive patients (21,

22). Adjunct endovascular embolization procedures in subjects with Shamblin II and Shamblin III CBTs enable more radical surgery with less intraoperative bleeding when performed by experienced specialists (23,24). According to Shamblin classification, CBTs of our patient could be graded as class II (partially surrounding the carotid vessels), predisposing to non-radical surgery (25). Similarly to HNPGLs, surgical treatment of mediastinal PGLs is quite challenging even for experienced surgeons as the tumor could be multiple, catecholamine-secreting and often adjacent to large vessels (26, 27). In contrast, intraabdominal paragangliomas are usually successfully removed as in our case. As SDHD mutation carriers generally develop new PGLs during their lifespan they should undergo annual biochemical screening and whole-body MRI examination every 3 years (28). Regarding the peculiar autosomal dominant inheritance pattern of SDHD-related PGL, which is associated with a maternal genomic imprinting, a presymptomatic genetic testing of the offspring is recommended for those who are at risk of receiving the SDHD mutation from his father. Actually, it has been recently proved that an early determination of the genetic status has a positive impact on the management and clinical outcome of SDHx mutations carriers (29).

With regard to multicentricity, in order to avoid repeated surgery, radiotherapy (RT) can be considered in second line treatment or in first line for large tumors. In our case, three dimensional conformal radiotherapy was a good option, which led to a long-term control of the tumor volume. Similarly, the published studies have shown that RT seems to be a safe and efficacious treatment associated with very high overall local control rates and minimal morbidity and recurrence rates (30, 31). ¹³¹Iodine-labeled MIBG (¹³¹I-MIBG) therapy was not discussed in our case as it may be considered only in patients with unresectable or metastatic PPGL when ¹²³I-MIBG scintigraphy is positive (32).

Another option in progressive multiple PGLs could be medical treatment with somatostatin analogues (SSAs) but successful control of tumor volume may be expected in PGLs who exhibit a high somatostatin receptor expression and lack of side effects (33). Our patient met both criteria which can explain the excellent therapeutic response.

At the stage of the multicentric disease comprising mediastinal and extraadrenal PGLs we observed clinical signs of catecholamine hypersecretion - arterial hypertension, sinus tachycardia and impaired glucose tolerance. Based on published data, no

more than 5% of HNPGLs are catecholamine secreting (15). It is important to note that in contrast to adrenal pheochromocytomas these tumors can only produce noradrenaline because of the lack of phenylethanolamine N-methyltransferase in their cells, the enzyme that converts noradrenaline to adrenaline in the adrenal tissue, due to an epigenetic regulation (34, 35). Catecholamines have different affinity to the main subtypes of adrenergic receptors. Adrenaline (A) is considered to have more profound metabolic effects because of its wider range (α , β_1 , β_2 and β_3) then noradrenaline (NA), which acts predominantly on α -adrenergic receptors. Experimental studies with catecholamine infusion techniques in healthy humans have demonstrated more potent action of A compared to NA on both endogenous glucose production (positive effect) and peripheral glucose uptake (negative effect) (36). Thus in theory carbohydrate disturbances in patients with PGLs are expected to be less frequent and milder in comparison with patients with adrenaline producing pheochromocytomas, but there is no specific published study on this topic. Our patient achieved normalization of glucose tolerance with metformin treatment and low-carbohydrate diet.

Another issue that should be discussed is whether there is a causal relationship between PGL and the cause of death. Pulmonary thromboembolism is not considered an expected PPGL-related complication as this tumor is not associated with an increased thrombotic risk. Anecdotic case reports of acute peripheral arterial thrombosis as well as left ventricular thrombosis in patients with PPGLs could be found in the literature (37, 38). Patetsios *et al.* reported only one case of massive pulmonary embolism and two arterial thrombosis in a retrospective study including 29 patients with CBTs for 30-year experience (16). On the other hand, advanced and metastatic colorectal cancer (CRC) is a strong predisposing factor for thrombosis (39). In contrast, most published studies demonstrated very low thrombotic risk (in spite of the adjuvant chemotherapy) in subjects with localized CRC, which is the case with our patient (40). Normal annual colonoscopy and tumor markers levels are reliable indicators for stable remission during the whole six year postoperative follow-up.

Pheochromocytoma is one of the tumors with very strong genotype-phenotype correlations. Extensive genetic research over the past decade revealed new pheochromocytoma susceptibility genes, so at present familial forms are estimated to be almost 40% (29). Uncommon clinical presentation or biochemical

profile as well as unusual comorbidities in patients with PPGL may open a window to new discoveries in the field of genetics of this rare tumor (29, 34, 41).

In conclusion, in spite of their predominantly benign behavior SDHD-related PGLs are usually multiple and require a multimodal approach for management involving often surgery, radiotherapy and medical treatment which can result in a long-term stable clinical and biochemical remission, tumor growth control and good quality of life. As SDHD mutation carriers generally develop new PGLs during their lifespan they should undergo annual biochemical and imaging examination every three years. Genetic analysis for mutations in genes encoding the SDH subunits is recommended in all patients with HNPGLs as well as in the first-degree relatives of subjects with detected mutations.

Conflict of interest

The case was presented as a poster at the 9th Scientific Meeting of the European Network for the Study of Adrenal Tumours (ENS@T), in Turin, 2010 after signing an informed consent by the patient.

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