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CASE REPORT

Successful chemotherapy of hepatic metastases in a case of succinate dehydrogenase subunit B-related paraganglioma

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Abstract Compared to other familial pheochromocytoma/paragangliomas (PHEO/PGLs), the succinate dehydrogenase subunit B (SDHB)-related PHEO/PGLs often present with aggressive and rapidly growing metastatic lesions. Currently, there is no proven effective treatment for malignant PHEO/PGLs. Here, we present a 35-year-old white man with primary malignant abdominal extra-adrenal 11 cm paraganglioma underwent surgical successful resection. But 6 months later, he developed extensive bone, liver, and lymph nodes metastasis, which were demonstrated by computed tomography scan and the ^{18}F-fluorodeoxyglucose positron emission tomography. However, his ^{123}I-metaiodobenzylguanidine scintigraphy was negative; therefore, the cyclophosphamide, vincristine, and dacarbazine (CVD) combination chemotherapy was initiated. The combination chemotherapy was very effective showing 80% overall reduction in the liver lesions and 75% overall reduction in the retroperitoneal mass and adenopathy, and normalization of plasma catecholamine and metanephrine levels. However, plasma levels of dopamine (DA) and methoxytyramine (MTY) were only partially affected and remained consistently elevated throughout the remaining period of follow-up evaluation. Genetic testing revealed an SDHB gene mutation. Here, we present an SDHB-related PHEO/PGL patient with extensive tumor burden, numerous organ lesions, and rapidly growing tumors, which responded extremely well to CVD therapy. We conclude patients with SDHB-related PHEO/PGLs can be particularly sensitive to CVD chemotherapy and may have an excellent outcome if this therapy is used and continued on periodic basis. The data in this patient also illustrate the importance of measuring plasma levels of DA and MTY to provide a more complete and accurate assessment of the biochemical response to therapy than provided by measurements restricted to other catecholamines and *O*-methylated metabolites.

Keywords Paraganglioma · Chemotherapy · Succinate dehydrogenase

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Introduction

Pheochromocytomas/paragangliomas (PHEO/PGL), in particular those associated with genetic mutations of the

mitochondrial enzyme succinate dehydrogenase subunit B (SDHB), are rare neuroendocrine tumors that can affect a patient's overall survival. Compared to other familial tumors that have very low rate of malignancy, metastases occur in 34–83% of patients with SDHB-related PHEO/PGL [1–5]. Some of these tumors produce only dopamine (DA) [6, 7] and therefore do not present with the typical signs and symptoms of catecholamine excess. The asymptomatic presentation can delay diagnosis and may contribute to progression to metastatic disease [1]. Furthermore, SDHB-related PHEO/PGLs appear to be aggressive tumors with metastatic lesions found in bones, lymphatic nodes, liver, and lungs [1–3].

Currently, there is no proven effective treatment for malignant PHEO/PGL. Partial responses are observed in only up to one-third of patients with various combinations of drugs and regimens [8, 9]. Here we present a patient with an SDHB-related extra-adrenal PGL and hepatic and bone metastases who exhibited a marked response of hepatic lesions to cyclophosphamide, vincristine, and dacarbazine (CVD) chemotherapy.

Case report

First presentation

A 35-year-old male with a 5-year history of hypertension presented to the community hospital emergency room with severe acute lower back pain in October 2004. At that time the patient also reported a history of chronic lower back pain that was previously evaluated by an orthopedic surgeon and a magnetic resonance imaging (MRI) of the lumbar spine that revealed only minor degenerative arthritic changes. Non-steroidal anti-inflammatory drugs were given; however, symptomatic improvement was minimal.

Medical history of the patient was significant for mild hypertension after 1999, with episodes of high blood pressure (190/100 mmHg) found during three sinus surgeries, one of which occurred at the induction of anesthesia. The patient also reported other symptoms such as night sweats, diaphoresis, occasional palpitations, and anxiety.

A computed tomography (CT) scan without contrast revealed a large (11 × 9.1 cm^2) left retroperitoneal mass located just below the left renal hilum and partially surrounding the aorta. The relevant lab tests, including chemistry and liver function tests, did not reveal any abnormalities. The preliminary diagnosis of lymphoma versus other solid tumors was suggested.

A subsequent contrast CT scan of the abdomen and pelvis confirmed the mass and identified an extension into the left psoas muscle and aorta as well as moderate left-sided hydronephrosis, likely due to partial obstruction of the left ureter. A CT-guided retroperitoneal biopsy was performed and revealed tissue positive for chromogranin A and synaptophysin, suggesting the diagnosis of PHEO/PGL. The diagnosis was confirmed by elevated urinary norepinephrine (NE) levels of 1338 μg/24 h [upper reference limit (URL) of 100 μg/24 h].

In January 2005, the patient underwent the surgery that included complete resection of the retroperitoneal mass, left nephrectomy, partial resection of paraspinal muscles, and allograft of aorta with partial resection of aorta. The final histopathology reported a 14.5 × 7.5 cm^2 mass with evidence of vascular invasion and extensive necrosis. Microscopic examination showed invasion into the outer third of the aortic wall and into the left kidney.

About 6 weeks after surgery, patient's hypertension had resolved, and the 24-h urine for catecholamines and metanephrines were within normal range. Post-operative ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy was negative and the CT scan of abdomen did not show any evidence of residual, recurrent, or metastatic disease.

Post-operative presentation

In August 2005, about 6 months after surgery, the patient developed a recurrence of back pain, which required extensive evaluation. Biochemical evaluation revealed elevations of plasma normetanephrine (NMN) of 220 pg/ml (URL of 112 pg/ml) and 24-h urine fractionated NMN of 692 μg/24 h (URL of 482 μg/24 h). Plasma and urine catecholamine levels were within normal ranges.

A whole body CT scan in November 2005 indicated retroperitoneal periaortic and left para-iliac lymphadenopathy with a dominant 3.7 cm iliac lymph node, multiple liver lesions, and lytic metastases within the bodies of the spine including fifth thoracic (T5) vertebra. The latter finding required neurosurgical intervention including decompressing laminectomy extending from T4 to T7.

A subsequent ^{123}I-MIBG scintigraphy was negative; however, an Octreoscan revealed three abnormal foci in thoracic vertebral bodies, focal areas of increased uptake in the right hemi-thorax, and heterogeneous areas of increased uptake within the liver.

At that time, the patient was referred to the NIH for further evaluation. Again his biochemical evaluations showed an elevated plasma NMN of 675 pg/ml (URL of 112 pg/ml) and NE of 2649 pg/ml (URL of 498 pg/ml). The patient also showed a substantial elevation of plasma DA of 810 pg/ml (URL of 46 pg/ml). Consistent with the elevation of DA, the *O*-methylated metabolite of DA, methoxytyramine (MTY), was also substantially elevated to 945 pg/ml (URL of 14 pg/ml). Anatomical studies,

including the whole body CT and MRI, confirmed a retroperitoneal mass measuring 4.3 cm along the left para aortic space, multiple hepatic, and bone lesions, and lymphadenopathy. ^{123}I-MIBG scintigraphy was again negative; ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG PET), however, demonstrated numerous metastatic sites located throughout the mediastinum including the thoracic skeleton and a large left retroperitoneal mass. At that time, genetic testing reveled a mutation of the SDHB gene (IVS3-1G>C).

Due to extensive metastases in the liver, we decided to immediately begin chemotherapy using cyclophosphamide 1800 mg on day 1, vincristine 3.4 mg on day 1, and dacarbazine 1440 mg on days 1 and 2 every 3 weeks.

Chemotherapy outcome

After two cycles of CVD, the patient was re-evaluated at NIH to assess tumor response. Plasma levels of NMN and NE were substantially decreased both falling to within the normal range within 6 months after the start of treatment. However, plasma levels of DA and MTY were only partially affected and remained consistently elevated throughout the remaining period of follow-up evaluation (Table 1). The MRI showed a significant decrease in the size of the retroperitoneal mass, hepatic lesions (85% of reduction), and adenopathy (Fig. 1).

After four and half months of CVD, the ^{18}F-FDG PET of the abdomen showed an 80% overall reduction in

Table 1

Time	NE (URL 498 pg/ml)	EPI (URL 83 pg/ml)	DA (URL 46 pg/ml)	NMN (URL 112 pg/ml)	MN (URL 112 pg/ml)	MTY (URL 14 pg/ml)	CgA (URL 225 ng/ml)
November 2005[a]	2649	11	810	675	17	945	179
January 2006	244	11	538	188	35	584	28
February 2006	186	25	686	136	41	1088	185
April 2006	172	12	472	116	35	517	344
June 2006	175	7	750	91	15	937	354
September 2006	237	21	518	106	24	516	285
November 2006	185	3	1092	73	16	1088	249
December 2006	246	32	448	75	16	494	277
January 2007	148	–	508	67	14	569	247
March 2007	278	8	418	88	16	426	350

NE norepinephrine, *EPI* epinephrine, *DA* dopamine, *NMN* normetanephrine, *MN* metanephrine, *MTY* methoxytyramine, *CgA* chromogranin A, *URL* upper reference limit

[a] Values before chemotherapy

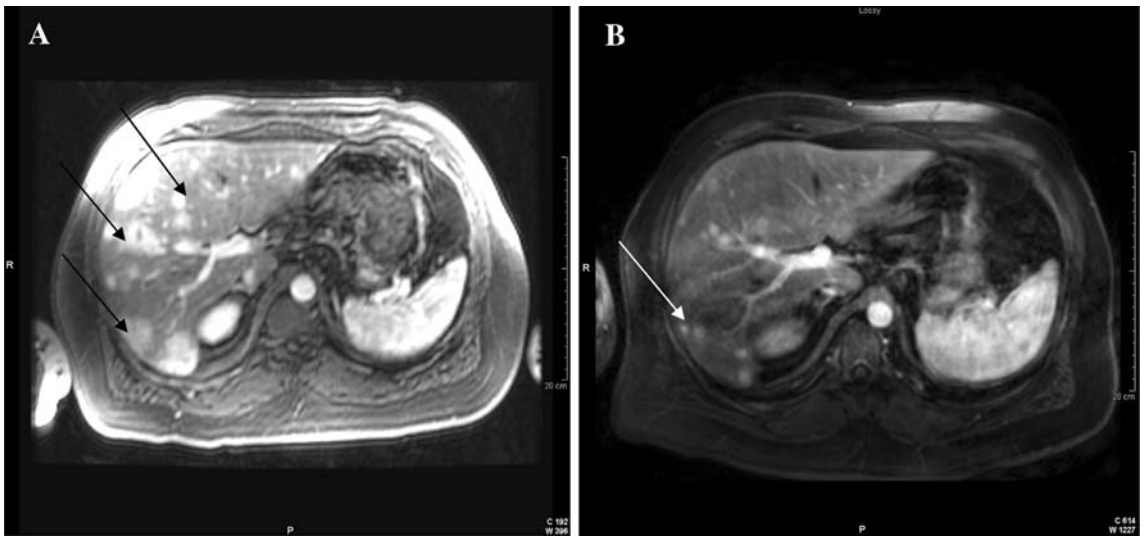

Fig. 1 The abdominal MRI scan of a 35-year-old patient with a previously removed SDHB-related extra-adrenal PGL with extensive metastatic disease including multiple hepatic lesions marked with an *arrow*. **a** Before the chemotherapy, **b** after the chemotherapy

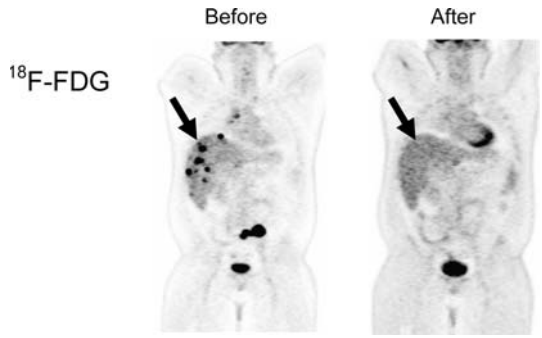

Fig. 2 Whole body ^{18}F-FDG PET scan of a 35-year-old patient with a previously removed SDHB-related extra-adrenal PGL with extensive metastatic disease including multiple hepatic lesions marked with an *arrow*. The left one represents before the chemotherapy and the right one represents after the chemotherapy

hepatic lesions (Fig. 2). The whole body CT scan also showed >50% overall reduction in the size of the retroperitoneal mass and adenopathy. However, there was no change of bone lesions.

One year later, the whole body CT scan showed 80% overall reduction in liver lesion and 75% overall reduction in the size of the retroperitoneal mass and adenopathy. Bone lesions remained unchanged. The patient then stopped the CVD chemotherapy and chose an experimental therapy. Unfortunately, he died quickly from severe toxicity of the experimental treatment.

Discussion

Here we present a patient with SDHB-related metastatic PGL who had an excellent response to CVD chemotherapy. As documented by the ^{18}F-FDG PET and other imaging studies, the reduction of tumor burden was very significant revealing about 85% reduction in hepatic lesions, and 75% reduction in the bulky retroperitoneal mass and adenopathy. The patient also showed normalization of plasma levels of NE and NMN, but interestingly plasma levels of DA and MTY remained elevated.

The divergent biochemical responses may have a number of explanations. The DA and NE and their respective *O*-methylated metabolites may have been derived from different lesions with different responses to chemotherapy. Although the organ lesions showed a marked response to chemotherapy, the bone lesions did not. Thus, the minimal response of DA and MTY to chemotherapy could have reflected their origins from bone but not organ lesions. Alternatively, the normalization of NE and NMN, but minimal response of DA and MTY could reflect a reduction in the activity of dopamine β-hydroxylase (DBH), the enzyme that converts DA to NE.

In previously published reports, responses to CVD in patients with PHEO/PGL were usually partial, and practically no cure was reported. This report suggests that patients with SDHB-related metastatic PGL may be particularly sensitive to CVD chemotherapy and experience an excellent outcome if this therapy is used and continued on periodic basis.

SDHB-related PHEO/PGLs are usually aggressive tumors with a very high rate of metastatic disease. These tumors have been suggested to be more metabolically active than tumors in patients without SDHB mutations. This suggestion may explain both the responsiveness of the SDHB-related tumors to chemotherapy and the so-called "flip-flop" phenomena, in which there is a switch in imaging characteristics of tumors as they exhibit more aggressive behavior. In patients with SDHB-related malignant PHEO/PGL, such a "flip-flop" phenomenon is reflected by a reversal of the normally lower sensitivity of ^{18}F-FDG PET for tumor localization compared to more specific functional imaging approaches, such as ^{18}F-fluorodopamine PET or $^{123/131}$I-MIBG scintigraphy [10]. Those tumors exhibiting such a "flip-flop" phenomenon are suggested to be more susceptible to chemotherapy. Possibly, the more metabolically active nature of these tumors may be related to the mitochondrial defects and subsequent activation of hypoxia-related pathways, rendering the tumors more responsive to chemotherapy.

In conclusion, the case reported here suggests that chemotherapy could be more effective in patients with SDHB-related metastatic PHEO/PGL than in those with other types of metastatic PHEO/PGL. Nevertheless, as previously observed and also found in our patient, any interruption of chemotherapy after few cycles can lead to catastrophic consequences since resistance to subsequent chemotherapy often may occur. The data in this patient also illustrate the importance of measuring plasma levels of DA and MTY to provide a more complete and accurate assessment of the biochemical response to therapy than provided by measurements restricted to other catecholamines and *O*-methylated metabolites.

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