Journal of Clinical and Translational Endocrinology: Case Reports 7 (2018) 8–13

Contents lists available at ScienceDirect

Journal of Clinical and Translational Endocrinology: Case Reports

journal homepage: www.elsevier.com/locate/jctecasereports.com

Successful induction therapy with sequential CVD followed by high-dose lanreotide in for metastatic *SDHB* paraganglioma: Case report

Isabel Tena[a,d,*], José Luis Ponce[b], Marcos Tajahuerce[a], José Luis Vercher-Conejero[c], Manuel Cifrián[b], Katherine I. Wolf[d], Marcela Miret[e], Maribel del Olmo[b], Rosa Reboll[f], Antonio Conde[a], Francisca Moreno[b], Julia Balaguer[b], Adela Cañete[b], Rosana Palasí[b], Alfredo Marco[b], Juan Francisco Merino Torres[b], Carlos Ferrer[a], Alfredo Sánchez[a], José Luis Soto[g], Antonio Llombart[h], Karel Pacak[d]

[a] *Oncology Department, Provincial Hospital of Castellon, Spain*
[b] *University Hospital la Fe of Valencia, Spain*
[c] *Nuclear Medicine-PET Unit, IDI, Bellvitge University Hospital (HUB), Barcelona, Spain*
[d] *Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA*
[e] *Endocrinology Department, Virgen de la Cinta Hospital of Tarragona, Spain*
[f] *University General Hospital of Valencia, Spain*
[g] *Molecular Biology Department, University Hospital of Elche, Spain*
[h] *Oncology Department of Arnau de Vilanova Hospital of Valencia, Spain*

ARTICLE INFO

Keywords:
Paraganglioma
Lanreotide
SDHB
Metastatic

ABSTRACT

Objective: Pheochromocytomas (PHEOs) and paragangliomas (PGLs) arise from adrenal extra-adrenal paraganglia. They often secrete catecholamine and approximately 1/3 are hereditary. Almost 50% of metastatic PGLs are caused by mutations in the succinate dehydrogenase gene, particularly in subunits B and D (*SDHB/D)*. These tumors remain a diagnostic and therapeutic challenge due to a limited number of effective treatment options. To our best knowledge, we present the first report that uses induction therapy to elicit a significant response in both primary and metastatic lesions, followed by complete surgical resection of a primary *SDHB*-related PGL.

Case description: A 45-year-old female presented with an 8.5 cm unresectable primary *SDHB*-related PGL with multiple bone metastases. She had an initial blood pressure of 210/130 mmHg and a heart rate of 150 bpm. Initially, she was treated with cisplatin, vinblastine, and dacarbazine (CVD) chemotherapy and lanreotide (120 mg/sc/28d), which resulted in tumor shrinkage. The patient later progressed, and monotherapy with a shortened interval of lanreotide (120 mg/sc/14d) was initiated. Following 2.5 months at this interval, the patient nearly achieved complete control of her clinical symptoms, and experienced a 30% reduction in ^{18}F-fluorodeoxyglucose uptake in her primary and metastatic lesions. Following the surgical resection of her primary PGL, all prior antihypertensive medications were stopped.

Conclusions: CVD, together with a 14-day regimen of high dose lanreotide, may be an effective treatment option for *SDHB*-related metastatic PGLs. Therefore, further evaluation of somatostatin analogues, preferably lanreotide, in the treatment of metastatic *SDHB*-related PGLs is warranted. We believe that ours is the first report detailing the successful use of lanreotide treatment prior to a surgical rescue after systemic treatment.

1. Introduction

PHEOs/PGLs are normally benign tumors that arise from the adrenal medulla (PHEOs) or from paraganglia along the parasympathetic and sympathetic chains (PGLs). They often secrete catecholamines and thus, they can lead to a premature death when remain long undiagnosed. Approximately 30% of PGLs develop metastases to embryologically unrelated tissues, mainly to the bone, liver, lungs, and lymph nodes. Metastatic PGLs remain a diagnostic and therapeutic challenge due to the limited availability of malignancy markers, including accurate prediction of its metastatic behavior and a lack of effective treatment options [1]. A recent report described a

* Corresponding author. Section on Medical Neuroendocrinology, National Institutes of Health, NICHD/NIH, 10 Center Drive, Bldg. 10, Room 1E-1-3140, Bethesda, MD 20892-0001, USA.
E-mail address: isabel.tenagarcia@nih.gov (I. Tena).

https://doi.org/10.1016/j.jecr.2017.12.001
Received 15 May 2017; Received in revised form 4 December 2017; Accepted 5 December 2017

catecholamine secreting carotid body PGL that responded well to preoperative treatment with long-acting octreotide-LAR [2]. According to the authors, octreotide-LAR resulted in decreased chromogranin A (CgA), excellent control of catecholamine hypersecretion from the tumor, and contributed to minimal intraoperative blood pressure fluctuations.

In 2009, the PROMID study was the first to show that octreotide LAR, a somatostatin receptor analogue (SSA), had an anti-proliferative effect in neuroendocrine tumors (NETs) [3]. However, until 2013, SSAs were mainly indicated for the relief of various hormone-related clinical symptoms in patients with functionally active NETs. In 2014, the phase III CLARINET trial presented new and compelling evidence regarding the anti-proliferative effect of lanreotide in both well- and moderately-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [4]. Anti-proliferative treatment options using various therapeutic regimens for patients with metastatic, well-differentiated NETs intend to reduce tumor burden and secretory activities, delay tumor progression, and prolong the life of the patients [5].

Like other NETs, PGLs also express somatostatin receptors (SSTs) [6]. PGLs mainly express SST2, as well as SST3 and SST5, but to a much lesser extent. The unique expression of SST2 has been studied in metastatic succinate dehydrogenase subunit B (*SDHB*)-related PGLs, metastatic non-*SDHB* PGLs, and head and neck PGLs. Successful reports using ^{68}Ga-DOTA analogues to image PGLs and other NET's lead to FDA approval of ^{68}Ga-DOTATATE in the localization of NETs [7–9]. Furthermore, the first studies related to the successful radiotreatment of PGLs using these analogues were published in 2007 [10].

Here, we report the case of a patient with an initially unresectable metastatic *SDHB*-related primary PGL who was treated, and responded well, with cisplatin, vinblastine, and dacarbazine (CVD) chemotherapy followed by high doses of lanreotide.

2. Case presentation

A 46-year old female was referred to the Oncology Department of the Hospital Provincial de Castellon for treatment of metastatic *SDHB*-related PGL in May 2013. Prior to her admission, she presented to the emergency room with a hypertensive crisis (blood pressure: 230/130 mmHg) and tachycardia (heart rate: 150 bpm). Her past medical history was significant for pain in her left hip over the last 3 months, which resulted in walking difficulties and neuropathy. Her pain was accompanied by severe episodes of flushing, sweating, and palpitations. Three years prior, she was diagnosed with mild hypertension, which was treated with clorthalidone daily. Her family history was positive for a father and uncle with an *SDHB*-related PGL as well as a cousin who died from *SDHB*-related kidney cancer. Following the patient's admission, an 18-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET/CT) scan was performed, which showed a 75 × 68 mm hypermetabolic mass with a necrotic center around the third portion of the duodenum (target lesion L1). A second lesion (27 × 25 mm) was also identified in the proximal part of the jejunum (L2). Multiple hypermetabolic bone lytic lesions were also found, including in the right iliac bone, which extended to the soft tissue component and measured 100 × 90 mm (L3) (Fig. 1). Initial biochemistry showed increased urine normetanephrine (NMN) levels of 19,000.00 (upper reference limit (URL) of 1933 μmol/dl), 3-methoxytyramine levels of 9500.00 (URL of 2396 nmol/24h), and plasma norepinephrine (NE) levels of 6632.00 (URL of 650 pg/mL). Urine dopamine (D) levels were also elevated at 4264.00 (URL of 2612 nmol/24h),whereas plasma D levels were within the normal reference limits. CgA levels were also elevated at 9.30 nmol/L (URL of 6.0 nmol/L). Plasma and urine epinephrine (E) and urine metanephrine (MN) were normal (Table 1). A multidisciplinary team evaluation determined that the patient was ineligible for surgical resection of her primary PGL. Standard of care CVD chemotherapy was therefore recommended and initiated in May 2013. The patient was placed on 20 mg of nifedipine twice daily to control hypertension. Later, 12.5 mg of hydrochlorothiazide was added to control reoccurring hypertensive crises. The right iliac bone lesion (L3) was biopsied in June 2013, which confirmed a diagnosis of metastatic PGL. Immunohistochemistry was positive for chromogranin, synaptophysin, and SSTs with a Ki-67 of 5% (Fig. 2). After 2 courses of CVD, a mild clinical response was observed, accompanied by normalization of CgA to 1.7 nmol/L. Plasma NE values slightly decreased to 6180 pg/mL, whereas NMN was elevated at 7011.98 pg/Ml. ^{111}In-pentetreotide scintigraphy (Octreoscan®) was performed showing uptake in the primary tumor, as well as in multiple metastatic lesions (Fig. 3). Therefore, in September of 2013, a monthly dose of 120 mg/sc of lanreotide was added to her treatment regimen. In October 2013, following 4 cycles of CVD (the last two in combination with lanreotide), the patient presented with 27% shrinkage of the primary PGL, but with global stable disease based on RECIST criteria 1.1 (L1 5.6 mm, L2 0 mm -not identified- and L3 -bone lesion with soft tissue- 90 mm). In March 2014, after 7 courses of CVD (the last five in combination with monthly lanreotide), the patient presented with clinically worsening moderate bone pain and an increase in the frequency and severity of flushing episodes. Repeat bloodwork revealed biochemical correlation with CgA levels again elevated at 9.82 nmol/L. Also urine NE, 3-methoxytyramine, and NMN levels increased at 2494.61 pg/mL, 7009.59 nmol/24h and 21,000.00 nmol/24h respectively.

CVD was discontinued and the interval of lanreotide was shortened from 4 to 2 weeks. Bimonthly lanreotide in monotherapy resulted in a complete clinical response including control of her blood pressure (110/72 mm/Hg) and heart rate (83 bpm). Additionally, the patient experienced several *hypo*tensive episodes as well as disappearance of sweating, flushing, palpitations, and bone pain after 5 doses (2.5 months). Furthermore, she was able to walk without any pain or assistance. The patient responded biochemically as well, with a decrease in levels of CgA to 4.30 nmol/L and both urine NE and 3-methoxytyramine drop to 1419.86 pg/mL and 2867.46 nmol/24h, respectively. However, urinary NMN levels remained elevated with a value of 28,206.00 nmol/24h and began to decrease in July 2014 (Table 1). A repeat ^{18}F-FDG PET/CT was performed in July 2014, and in correlation with her clinical and biochemical improvement, it showed a 30% decrease in ^{18}F-FDG uptake in the target lesions (Fig. 4). As a result, antihypertensive and analgesic medications were weaned off. However, prior to surgery the patient received standard alpha-beta blockade to avoid intraoperative precipitation of hypertensive intraoperative crises and underwent a complete surgical resection of the primary PGL in September of 2014. No blood pressure fluctuations during the 5-h procedure.

3. Discussion

This report illustrates that sequential CVD followed by a 14-day regimen with high-dose lanreotide may be an effective induction treatment scheme in *SDHB*-related metastatic PGL. This regimen resulted in an initial 27% shrinkage of the primary PGL with CVD, followed by a significant decrease of more than 30% in ^{18}F-FDG uptake in the primary and metastatic lesions, along with a profound clinical improvement including normalization of blood pressure and heart rate, followed by complete surgical resection of the primary PGL.

SDHD was the first mitochondrial gene to be identified as a tumor suppressor in familial PGL [11]. SDH inactivation predisposes mutation carriers to renal cell carcinoma [12], gastrointestinal stromal tumors [13], pancreatic neuroendocrine tumors [14], and pituitary recurrent adenomas [15]. Recently, the first case of pituitary carcinoma has also been described [16]. *SDHx* mutations result in alterations in hypoxia-inducible factor (HIF) [17,18] signaling and hypermethylation [19], which can consequently lead to cancer. SDH dysfunction results in accumulation of the oncometabolite succinate [20], a tricarboxylic acid cycle (TCA) substrate, which acts as a competitive inhibitor of the 2-oxoglutarate (2-OG)-dependent HIF prolyl-hydroxylases [21,22]. This