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Case Report

Delayed and Long-Lasting Response to 177Lu-DOTATATE in a Head and Neck Paraganglioma: Case Report and Literature Review

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Keywords

Paraganglioma · Head and neck · Mutation in succinate dehydrogenase subunit B · 177Lu-DOTATE · Case report

Abstract

Introduction: Malignant paragangliomas (M-PGL) are a group of neuroendocrine tumors that originate from chromaffin cells. The most common location for PGL is the head and neck, which comprise 65–70% of all PGL, and the M-PGL accounts for 0.6% of all head and neck cancers. It is a rare tumor, with an incidence of 2–8 per million. Diagnosing PGL can be challenging, and treatment for metastatic disease is usually not curative. ***Case Presentation:*** A 66-year-old woman was diagnosed with left cervical pain and laterocervical mass in March 2015. Octreotide scintigraphy showed intense uptake in the cervical mass, two pulmonary micronodules of 4–5 mm, and another lesion in the lumbar region (L3–L4). The final diagnosis was malignant nonsecretory PGL with adjacent tissue involvement and distant metastases. After three different treatments with minimal symptomatic improvement, 177Lu-DOTATATE was requested off-label. With a dose of 7,400 MBq until January 2018, the patient showed remarkable symptomatic pain improvement and a decrease in tumor size. ***Conclusion:*** We believe that our case report provides relevant information that can be considered in similar cases. First, the patient tripled the expected survival in such a clinical setting, and this benefit seems to rely on 177Lu-DOTATATE treatment. Second, we documented an early symptomatic response to this treatment but a long-term delayed volumetric radiographic response.

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Introduction

Paragangliomas (PGLs) are a group of neuroendocrine tumors originating from chromaffin cells. They arise in the sympathetic or parasympathetic ganglia. The most common location for PGL is the head and neck area, which comprise 65–70% of all PGL, and the M-PGL accounts for 0.6% of all head and neck cancers [1, 2]. It is a rare tumor with an incidence of 2–8 per million [3]. Parasympathetic PGLs, commonly arise in the head and neck area, are usually nonfunctioning and may cause local compressive symptoms but can also be asymptomatic [4]. On the other side, sympathetic PGLs are mainly located in the retroperitoneum and typically produce and secrete catecholamines or metanephrines [5]. Although most PGL are benign, they are associated with high morbidity and mortality secondary to hypersecretion of catecholamines and metanephrines, leading to hypertension, cardiovascular disease, and even death [3]. Approximately 34% of PGL are malignant as defined by the World Health Organization with the presence of metastases [6]. The clearest association between metastatic risk and the underlying genetic alteration is found in the germline mutations on the gene of the succinate dehydrogenase subunit B (SDHB) [2]. A germline predisposing mutation is found in approximately 40% of PGL in one of at least 12 genes [7, 8]. Furthermore, germinal mutation could be presented as a hereditary paraganglioma syndrome. The SDHB mutation elevates the risk of PGL, pheochromocytomas, renal cell carcinoma, gastrointestinal stromal tumors, or pituitary adenomas. There are no guidelines regarding the screening of asymptomatic SDHx mutation carriers [8]. Diagnosing PGL could be challenging, and treatment for metastatic disease is usually not curative.

There is no clear clinical consensus guideline on the management of PGL. This case report shows a successful outcome of a patient treated with the available scarce options found in the medical literature with limited evidence. The CARE Checklist has been completed by the authors for this case report and is attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000541359).

Case Presentation

A 66-year-old woman was diagnosed with no significant previous medical history and a negative family history of cancer. She was studied in the endocrinology service in March 2015 for left cervical pain and the presence of a laterocervical mass. Physical examination reveals a large cervical mass with no other abnormalities. Vital signs and blood pressure were within normal limits. Laboratory results were within normal limits. A contrast-enhanced computed tomography (CT) of the neck was performed, showing a large left mass measuring 65 × 37 mm that displaced the jugular vein and encompassed the carotid artery; no metastases were found. The first diagnostic possibility was PGL or schwannoma, but other diagnoses could not be ruled out. The study was expanded in May 2015 with positron emission tomography/computed tomography (PET-CT) and I-metaiodobenzylguanidine scintigraphy, without finding any relevant result of oncological significance. An octreotide scintigraphy was also performed, which showed intense uptake in the cervical mass, two pulmonary micronodules of 4 and 5 mm, and another lesion in the lumbar region (L3–L4).

In June 2015, a magnetic resonance imaging of the head and neck was performed, revealing a pituitary adenoma; measuring 12 × 12 × 11 mm. The cervical mass measured 65 × 37 mm (shown in Fig. 1a, b). Both biopsies on the primary cervical mass and lumbar vertebra L3 were performed in October 2015. Both pathological samples showed a malignant PGL with immunocytochemistry positive to synaptophysin, chromogranin, vimentin, and S-100. The Ki67 index was 5%. A genetic study showed a germinal mutation in the exon 5 of the gene *SDHB*. Biochemical tests included plasma-free metanephrines and 24-h urine fractionated

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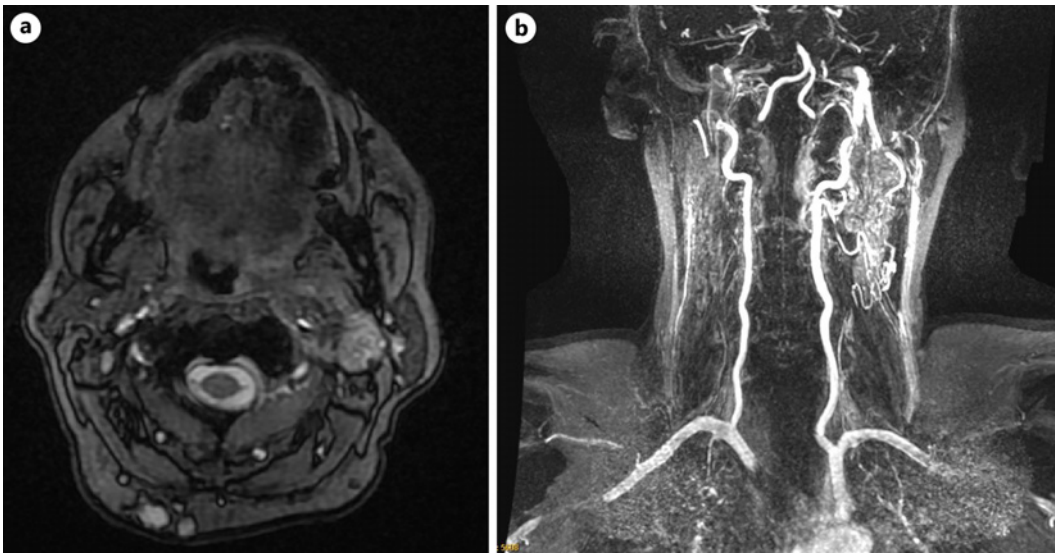

Fig. 1. a Magnetic resonance imaging of the cervical region at time of diagnosis, showing a round neoplasm of 65 mm × 37 mm, in the left carotid space which laterally displaces the jugular vein and encompasses the carotid artery, both vessels maintaining its permeability. It has intense uptake of contrast in T2. **b** Vascular reconstruction of the neoplasm which predominantly irrigates from left vertebral artery.

within normal levels. The final diagnosis was a malignant nonsecretory PGL with adjacent tissue involvement and distant metastases.

The case was evaluated in a multidisciplinary tumor board. Upfront surgery was initially recommended. However, due to the high risk of mortality, the patient rejected this option, so systemic treatment in the oncology department was initiated. In December 2015, based on the clinical evidence available at that moment, treatment with sunitinib 37.5 mg/day (off-label) was started [9] being ineffective and poorly tolerated. In January 2016 the patient received chemotherapy with CVD scheme (cyclophosphamide at 750 mg/m^2, vincristine at 1.4 mg/m^2, and dacarbazine at 600 mg/m^2 on day 1 and dacarbazine at 600 mg/m^2 on day 2, every 28 days). After 5 cycles, the patient showed poor psychological tolerance and scarce symptomatic improvement [10]. In September 2016, she started temozolamide 150 mg/d for 5 days every 28 days. She completed 5 cycles until June 2017 being also poorly tolerated and with forced delays because of hematological toxicity [11].

At that time, the patient had not achieved any kind of clinical or symptomatic response, so 177Lu-DOTATATE was requested off-label. This treatment was started in June 2017 every 8 weeks with a dose of 7,400 MBq until January 2018 with remarkable symptomatic pain improvement and decreased tumor size (shown in Fig. 2a, b). Progressively, it has been decreasing until achieving 32 × 17 mm (2b) in the last CT in May 2024. The lung metastases have remained stable based on RECIST criteria during the whole follow-up. The patient has undergone oncological medical checkups every year and is currently asymptomatic.

Discussion

Advanced and/or unresectable PGL is commonly classified as an orphan disease. Approximately 70% of all PGL develop in the head and neck region and they are usually non-secretory and slowly growing neoplasms [12]. It is recommended in patients with

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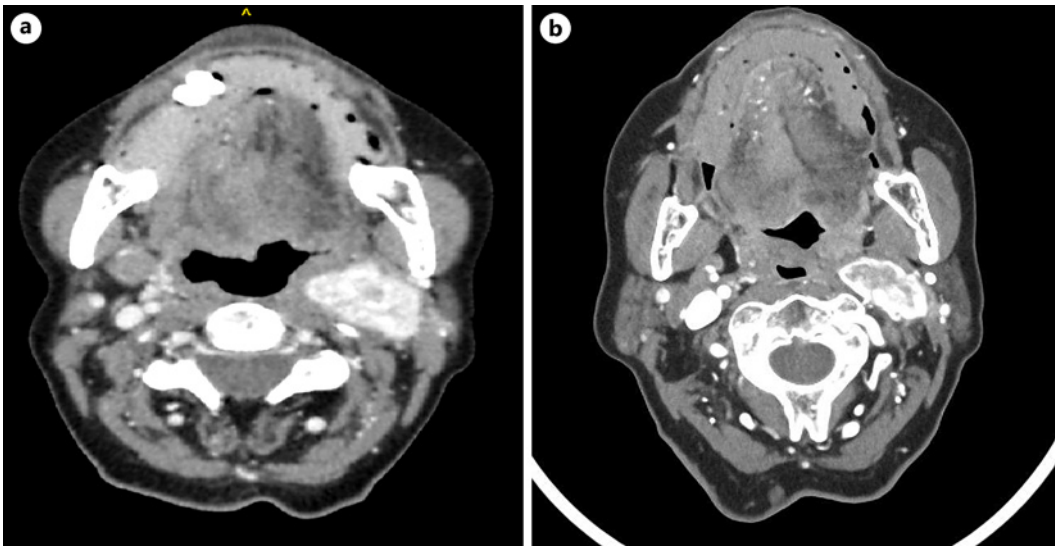

Fig. 2. a CT of the PGL after ending the radionuclide therapy in January 2018 that shows a decrease in tumor size. **b** Last CT in May 2024 after 6 years of ending the radionuclide therapy that shows a stability of the tumor.

PGL to measure biochemical secreted hormones and to perform a head and neck magnetic resonance imaging as the first method to evaluate the local tumor extension [13]. Imaging is vital in the evaluation of patients with advanced PGL. The most important functional imaging is whole-body imaging with PET-CT, preferably with radiolabelled somatostatin analogs due to high sensitivity (100% head and neck or metastatic disease) [13]. If unavailable, other imaging types such as I-MIBG are limited to abdominal PGL [13, 14]. Diagnosis is typically confirmed without the need for biopsies [1].

Because the vast majority of paragangliomas are slow-growing and asymptomatic tumors, frequently, there is no initial need for local treatment, making a wait and see policy a reasonable option, monitored with CT or PET-CT. Treatment is deferred until the progression of the disease or the presence of symptoms [1, 13]. However, surgical resection is indicated if the tumor is locally aggressive, symptomatic, or a progressive disease. Surgery can be curative in most patients, but it should be performed by experienced surgeons because of great vessel involvement [1, 13].

There is no consensus on the management of metastatic PGL in advanced, unresectable, and/or symptomatic disease. Primary therapy for fast-progressing diseases includes chemotherapy (Cth), but it is still controversial, due to toxicity and the need for discontinuation [13, 14].

Targeted radionuclide therapies have been considered in this kind of tumor, and there are two main options to target: metaiodobenzylguanidine (131I-MIBG) and peptide receptor radionuclide therapy (PRRT; 177Lu or 90Y). It is uncertain which treatment is preferred when tumors show uptake equally with MIBG and somatostatin receptors. Recently, high-specific-activity (HSA)-131I-MIBG therapy has been approved by the FDA for the treatment of progressive or symptomatic metastatic PGL or pheochromocytoma (PCC). It is prescribed in patients with positive MIGB scans [15]. In a single-arm phase II trial, 68 patients were treated with high-specific-activity-131I-MIBG. It showed stable disease (69%) with a median overall survival of 36.7 months [15]. It is vital to consider the side effects (most important the hematotoxicity).

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PRRT with 177Lu-DOTATATE was approved by the US Food and Drug Administration (FDA) on January 26, 2018, for adult patients with expression of somatostatin in some NETs, but not yet in PCC (pheochromocytoma) and PGL. In a recent meta-analysis, PRRT with 177Lu-DOTATATE and 90Y-DOTATOC have shown pooled disease control rates of 0.83 (95% CI: 0.75–0.88) and 0.76 (95% CI: 0.56–0.89) respectively, considering them as an interesting alternative to I-131 MIBG and Cth [14].

By attaching the octreotate peptide to 177Lu-DOTATE, the compound can specifically target and binds to these receptors on the surface of neuroendocrine tumor cells, leading to beta radiation which is sufficient to annihilate target cells with effective limited in neighboring normal cells. It represents a less intensive treatment with low toxicity, capturing attention in oncology [14, 15].

When a metastatic or inoperable patient with PGL or PCC hands over to the physician, the MIGB and somatostatin receptor imaging must be evaluated to determine uptake. In our situation, after multiple treatments, we initiated off-label 177Lu-DOTATE due to its uptake; however, there are instances when both exhibit comparable uptake. In these scenarios, we must evaluate the toxicity profile and patient characteristics.

Conclusion

Despite all the different alternatives that can be used in this type of tumors, there is no clinical guideline, just expert consensus [14]. Our case was presented as a locally advanced and metastatic symptomatic disease. The patient achieved a clear symptomatic improvement after we started this treatment, and in the following years, the tumor decreased in size.

We honestly think that our case report provides relevant information that can be taken into account in similar cases. First, the patient has tripled the expected survival for such clinical setting [15], and this benefit seems to rely on 177Lu-DOTATATE treatment. Second, we have documented an early symptomatic response to this treatment but a long-term delayed volumetric radiographic response. This fact should be considered when we use this kind of therapies. Finally, we also provide the experience of a sequential treatment with most of available treatments based on the limited published scientific evidence in this orphan disease.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. After several years of suffering pain and loss of autonomy due to my illness, this treatment was a turning point from which my life progressively got better.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.R.E., S.E.C.R., N.P.P.F., M.L.M.C., F.M.C., P.T.C., A.A.T., and J.M.T. have contributed to writing and reviewing the manuscript. All authors have read and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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