Role of ^{68}Ga -DOTATATE PET/CT in a Case of *SDHB*-Related Pterygopalatine Fossa Paraganglioma Successfully Controlled with Octreotide

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Abstract

We describe an unusual case of a 42-year-old female with an unresectable succinate dehydrogenase subunit B (*SDHB*)-related pterygopalatine fossa paraganglioma. She underwent somatostatin receptor imaging with ^{68}Ga -DOTA(0)-Tyr(3)-octreotate (^{68}Ga -DOTATATE) positron emission tomography/computed tomography (PET/CT), which showed uptake in the above mentioned tumor. Hence, the patient was started on octreotide, a cold somatostatin analog, and responded with tumor stabilization and improvement of clinical symptoms for 36 months since initiation of octreotide therapy. This case demonstrates the role of ^{68}Ga -DOTATATE PET/CT in diagnostic localization and its subsequent role in treatment using cold somatostatin analog as a potential choice of therapy in the management of paraganglioma in an unusual location with limited therapeutic options.

Keywords ^{68}Ga -DOTATATE PET/CT · Paraganglioma · Octreotide · *SDHB* · SSTR · Somatostatin analog · PRRT · ^{177}Lu -DOTATATE

Introduction

Head and neck paragangliomas (HNPGLs) are neuroendocrine tumors derived from the parasympathetic nervous system [1, 2], which represent approximately 0.6% of all head and neck tumors [3, 4]. These tumors mainly occur in the carotid body, glomus vagale, glomus jugulare, or glomus

tympanicum regions [5]. Accurate diagnosis of HNPGLs is often challenging because these tumors are typically biochemically silent and lack early symptoms [5]. ^{68}Ga -DOTA(0)-Tyr(3)-octreotate (^{68}Ga -DOTATATE) positron emission tomography/computed tomography (PET/CT) was found to be the imaging modality of choice in diagnosing HNPGLs with a detection rate of 100% (38/38) [4]. ^{68}Ga -DOTATATE PET/CT not only helps in diagnosis but could also determine patients' eligibility for peptide receptor radionuclide therapy (PRRT), where DOTATATE is labeled with therapeutic beta emitters such as ^{177}Lu and ^{90}Y or cold somatostatin analog (SSA) therapy [4]. Optimal therapy for HNPGLs has generated considerable debate and has ranged from surgery to radiotherapy [6–8]. Here, we present a case that reflects the “theranostic” approach with ^{68}Ga -DOTATATE PET/CT imaging in diagnosing an unresectable HNPGL located in an unusual location in the left pterygopalatine fossa caused by mutated succinate dehydrogenase subunit B (*SDHB*) gene, which led to effective treatment planning, achieving symptomatic control, and progression-free survival for 36 months since initiation of treatment with cold SSA, octreotide.

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Case Report

A 42-year-old woman developed headache and blurred vision; workup including magnetic resonance imaging (MRI) revealed an enhancing left pterygopalatine fossa mass. Differential diagnosis at that time included hemangioblastoma, schwannoma, paraganglioma, and neuroblastoma. Surgical debulking achieved only 15–20% mass resection, owing to significant bleeding from the mass. Histopathology of the mass was paraganglioma with germline *SDHB* mutation. For the next 2 years, she remained asymptomatic, and surveillance MRIs showed stable disease. Subsequently, she developed severe headaches and migraines associated with the enlargement of the mass documented on MRI and hence, treated with external beam radiation therapy (5040 cGy) that improved her symptoms. However, 8 months after radiotherapy, she developed intermittent, dull, left retrobulbar pain, blurred vision, and headache despite the stable size of the mass on MRI. ^{131}I -metaiodobenzylguanidine therapy was ruled out owing to negative ^{123}I -metaiodobenzylguanidine scintigraphy (Fig. 1a, b). In 2016, five years after the initial onset of symptoms, she presented to our institute. On evaluation, MRI showed an enhancing multilobular left pterygopalatine fossa paraganglioma extending into the left pterygopalatine canal, orbital apex, middle cranial fossa, and cavernous sinus; displacing and impinging upon intra-orbital structures, and eroding and remodeling adjacent bone (Fig. 2a, dotted boundary; 2b, arrow). The biochemical evaluation revealed elevated plasma dopamine (106 picogram/milliliter (pg/mL), $3.7\times$ upper reference limit,

URL (29 pg/mL)) and normetanephrine (154 pg/mL, $1.4\times$ URL (112 pg/mL)) values. Somatostatin receptor (SSTR) imaging with ^{68}Ga -DOTATATE PET/CT during initial evaluation showed increased uptake in left pterygopalatine fossa paraganglioma with a SUV_{max} 21.4 (Fig. 2c, arrow), which made her eligible for cold SSA or PRRT with ^{177}Lu -DOTATATE. She was started on 20 mg monthly intramuscular octreotide, a cold SSA therapy due to limited availability and high cost of PRRT at that time. This resulted in symptomatic improvement with no change in tumor size on MRI (Fig. 3a–f, arrows), grossly stable tumor's ^{68}Ga -DOTATATE SUV_{max} (21.4, 21.6, 20.9, 21.3, 21.6, and 26.8, respectively) (Fig. 3g–l, fused axial PET/CT images, arrows), and ^{18}F -FDG SUV_{max} (49.3, 36.9, 26.6, 29.0, 25.4, and 31.1, respectively) (Fig. 3m–r, fused axial PET/CT images, arrows) at 0, 6, 12, 18, 29, and 36 months of octreotide therapy. Her biochemical evaluation after 36 months resulted in normalization (64 pg/mL, $<1.0\times$ URL) of elevated normetanephrine levels ($1.4\times$ URL: before therapy) and lowering of dopamine levels (59 pg/mL, $2.0\times$ from $3.7\times$ URL before therapy). The patient continues to be on octreotide therapy; however, her octreotide dose was increased to 30 mg due to slight increase in her latest ^{18}F -FDG and ^{68}Ga -DOTATATE SUV_{max} values.

Discussion

Surgery has been the mainstay of therapy for HNPGLs [7]. However, the unusual location of this *SDHB*-related PGL

Fig. 1 ^{123}I -metaiodobenzylguanidine scintigraphy of *SDHB*-related pterygopalatine fossa paraganglioma. (a) Whole-body planar anterior and (b) posterior images of ^{123}I -metaiodobenzylguanidine scintigraphy of the patient was found to be negative

Fig. 2 Anatomic and functional imaging of *SDHB*-related pterygopalatine fossa paraganglioma at initial evaluation. **a** Sagittal contrast-enhanced T1-weighted MRI showed a heterogeneously enhancing irregularly shaped mass (dotted boundary) in the left pterygopalatine fossa extending into the left orbit, middle cranial fossa, and pterygopalatine canal. Bone destruction extends from the floor of the orbit to the top of the clivus. **b** Axial fat-suppressed contrast-enhanced T1-weighted MRI demonstrated displacement of the globe, optic nerve,

and extraocular muscles by the mass (arrow) and extension of the mass into the left middle cranial fossa and left cavernous sinus via erosion of the sphenoid bone. **c** Whole-body maximal intensity projection ^{68}Ga -DOTATATE PET/CT of the patient during initial evaluation at our institute showing high uptake of ^{68}Ga -DOTATATE by somatostatin receptors within the mass, with maximum standardized uptake value of 21.4 (arrow) without any evidence of metastasis

presented challenges in offering timely and manageable therapeutic options to the patient. Pheochromocytomas and paragangliomas (PPGLs) express SSTRs, especially SSTR2 subtype [9]. ^{68}Ga -DOTATATE demonstrates a higher affinity for SSTR2 [10]. Therefore, ^{68}Ga -DOTATATE has been used in the imaging of PPGLs and has shown superior detection of PPGLs in comparison to other radiopharmaceuticals in various cohorts of PPGLs, including HNPGLs and *SDHB*-related PPGLs [4, 11–18]. In this rare anatomical position in the pterygopalatine fossa, where complex surgical resection was

not an option, ^{68}Ga -DOTATATE PET/CT emerged as an appropriate diagnostic modality and guided precise therapeutic management, thus, representing an excellent example of “theranostics in action.” The positive uptake on ^{68}Ga -DOTATATE confirms that SSTRs are present in this tumor and hence, can be targeted using “radiolabeled” PRRT or “cold” SSAs. In a prospective study in nine patients with inoperable HNPGLs, PRRT with 2–4 cycles of $^{90}\text{Y}/^{177}\text{Lu}$ -DOTATATE has demonstrated stable disease on RECIST 1.1 with symptomatic improvement in all six patients who were

Fig. 3 Anatomic and functional imaging of *SDHB*-related pterygopalatine fossa paraganglioma at baseline and follow-up evaluation. **a–f** Axial fat-suppressed contrast-enhanced T1-weighted MRI after 0, 6, 12, 29, and 36 months of cold somatostatin analog therapy, demonstrating lack of growth (arrows). **g–l** Axial fused ^{68}Ga -DOTATATE PET/CT images after 0, 6, 12, 18, 29, and 36 months of cold somatostatin analog therapy, demonstrating the gross stability of maximum

standardized uptake values (21.4, 21.6, 20.9, 21.3, 21.6, and 26.8, respectively) by paraganglioma (arrows). **m–r** Axial fused ^{18}F -FDG PET/CT images after 0, 6, 12, 18, 29, and 36 months of cold somatostatin analog therapy, demonstrating gross stability of maximum standardized uptake values (49.3, 36.9, 26.6, 29.0, 25.4, and 31.1, respectively) by paraganglioma (arrows)

symptomatic at presentation [19]. However, due to limited availability of ^{177}Lu -DOTATATE PRRT at the time of initial presentation, our patient was treated with cold SSA, octreotide. Cold SSA therapy with octreotide and lanreotide has demonstrated mixed results in PPGLs based on few published reports [15, 20–23]. However, they showed promising results in terms of progression-free survival in two large prospective clinical trials in patients with gastroenteropancreatic and midgut neuroendocrine tumors [24, 25]. In our patient, tumor growth was not seen on MRI for 36 months, and SUV_{max} on ^{68}Ga -DOTATATE and ^{18}F -FDG have not shown any significant uptake changes. Clinically, the patient has reported dramatic improvement in the stabbing eye sensation and accompanying headaches. This case demonstrates that an *SDHB*-related paraganglioma in an unusual location can be effectively managed with cold SSA therapy. Therefore, further multicentric clinical trials might be conducted to evaluate the efficacy of cold SSAs in managing SSTR positive PPGLs.

Conclusion

This case demonstrates the role of ^{68}Ga -DOTATATE in the diagnostic localization of parasympathetic HNPGLs, even when found in unusual locations, here in the pterygopalatine fossa of our patient. It also plays a vital role in considering treatment using cold SSA, commonly used in gastroenteropancreatic neuroendocrine tumors, as a potential therapy in the management of unusually located paragangliomas with limited therapeutic options.

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Compliance with Ethical Standards

Conflict of Interest Abhishek Jha, Mayank Patel, Eva Baker, Melissa K. Gonzales, Alexander Ling, Corina Millo, Marianne Knue, Ali Cahid Civelek, and Karel Pacak declares no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from the participant included in the study.

References

- Martin TP, Irving RM, Maher ER. The genetics of paragangliomas: a review. *Clin Otolaryngol*. 2007;32:7–11.
- Taieb D, Boedeker CC, Martucci V, Fojo T, Adler JR Jr, et al. Current approaches and recent developments in the management of head and neck paragangliomas. *Endocr Rev*. 2014;35:795–819.
- Sykes JM, Ossoff RH. Paragangliomas of the head and neck. *Otolaryngol Clin N Am*. 1986;19:755–67.
- Janssen I, Chen CC, Taieb D, Patronas NJ, Millo CM, Adams KT, et al. ^{68}Ga -DOTATATE PET/CT in the localization of head and neck Paragangliomas compared with other functional imaging modalities and CT/MRI. *J Nucl Med*. 2016;57:186–91.
- Erickson D, Kudva YC, Ebersold MJ, Thomson GB, Grant CS, van Heerden JA, et al. Benign paragangliomas: clinical presentation and treatment outcomes in 236 patients. *J Clin Endocrinol Metab*. 2001;86:5210–6.
- Capitana C, Ntali G, Karavitaki N, Grossman AB. The management of head-and-neck paragangliomas. *Endocr Relat Cancer*. 2013;20:R291–305.
- McCrary HC, Babajanian E, Calquin M, Carpenter P, Casazza G, Naumer A, et al. Characterization of malignant head and neck Paragangliomas at a single institution across multiple decades. *JAMA Otolaryngol Head Neck Surg*. 2019;145:641–6.
- Jha A, Nilubol N, and Pacak K. Some Considerations in Treating Malignant Head and Neck Paragangliomas at a Single Institution Across Multiple Decades. *JAMA Otolaryngol Head Neck Surg*. 2019 Nov 14. doi: 10.1001/jamaoto.2019.3444. [Epub ahead of print]
- Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor *sst1-sst5* expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. *Eur J Nucl Med*. 2001;28:836–46.
- Reubi JC, Schar JC, Waser B, Wenger S, Heppeler A, Schmitt JS, et al. Affinity profiles for human somatostatin receptor subtypes *SST1-SST5* of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. *Eur J Nucl Med*. 2000;27:273–82.
- Han S, Suh CH, Woo S, Kim YJ, Lee JJ. Performance of ^{68}Ga -DOTA-conjugated Somatostatin receptor targeting peptide PET in detection of pheochromocytoma and Paraganglioma: a systematic review and meta-analysis. *J Nucl Med*. 2019;60:369–76.
- Janssen I, Blanchet EM, Adams K, Chen CC, Millo CM, Herscovitch P, et al. Superiority of ^{68}Ga -DOTATATE PET/CT to other functional imaging modalities in the localization of *SDHB*-associated metastatic Pheochromocytoma and Paraganglioma. *Clin Cancer Res*. 2015;21:3888–95.
- Janssen I, Chen CC, Millo CM, Ling A, Taieb D, Lin FL, et al. PET/CT comparing ^{68}Ga -DOTATATE and other radiopharmaceuticals and in comparison with CT/MRI for the localization of sporadic metastatic pheochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging*. 2016;43:1784–91.
- Jha A, Ling A, Millo C, Gupta G, Viana B, Lin FI, et al. Superiority of ^{68}Ga -DOTATATE over ^{18}F -FDG and anatomic imaging in the detection of succinate dehydrogenase mutation (*SDHx*)-related pheochromocytoma and paraganglioma in the pediatric population. *Eur J Nucl Med Mol Imaging*. 2018;45:787–97.
- Jha A, de Luna K, Balili CA, Millo C, Paraiso CA, Ling A, et al. Clinical, diagnostic, and treatment characteristics of *SDHA*-related metastatic Pheochromocytoma and Paraganglioma. *Front Oncol*. 2019;9:53.
- Jha A, Ling A, Millo C, Chen C, Gupta G, Viana B, et al. Superiority of ^{68}Ga -DOTATATE PET/CT to other functional and anatomic imaging modalities in the detection of *SDHD*-related pheochromocytoma and paraganglioma – A comparative prospective study. *J Nucl Med*. May 1, 2018 vol. 59 no. supplement 1 46

17. Taieb D, Hicks RJ, Hindie E, Guillet BA, Avrram A, Ghedini P, et al. European Association of Nuclear Medicine Practice Guideline/ Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of pheochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging*. 2019;46: 2112–37.
18. *Taïeb D, *Jha A, Treglia G, and Pacak K. Molecular imaging and radionuclide therapy of pheochromocytoma and paraganglioma. *Endocr Relat Cancer*. 2019;27:R627–R652.
19. Puranik AD, Kulkarni HR, Singh A, et al. Peptide receptor radionuclide therapy with $^{90}\text{Y}/^{177}\text{Lu}$ -labelled peptides for inoperable head and neck paragangliomas (glomus tumours). *Eur J Nucl Med Mol Imaging*. 2015;42:1223–30.
20. Tenenbaum F, Schlumberger M, Lumbroso J, Parmentier C. Beneficial effects of octreotide in a patient with a metastatic paraganglioma. *Eur J Cancer*. 1996;32A:737.
21. Tonyukuk V, Emral R, Temizkan S, Sertcelik A, Erden I, Corapcioglu D. Case report: patient with multiple paragangliomas treated with long acting somatostatin analogue. *Endocr J*. 2003;50: 507–13.
22. Duet M, Guichard JP, Rizzo N, Boudiaf M, Herman P, Tran Ba Huy P. are somatostatin analogs therapeutic alternatives in the management of head and neck paragangliomas? *Laryngoscope*. 2005;115: 1381–4.
23. van Hulsteijn LT, van Duinen N, Verbist BM, Jansen JC, van der Klaauw AA, Smit JW, et al. Effects of octreotide therapy in progressive head and neck paragangliomas: case series. *Head Neck*. 2013;35:E391–6.
24. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J Clin Oncol*. 2009;27(28):4656–63.
25. Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224–33.

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