


Incidental Finding of Squamous Cell Carcinoma on a ⁶⁸Ga-DOTATATE PET Scan

Journal of Investigative Medicine High Impact Case Reports
Volume 9: 1–4
© 2021 American Federation for Medical Research
DOI: 10.1177/23247096211035232
journals.sagepub.com/home/hic


Sanjana Mullangi, MD¹, Manidhar Reddy Lekkala, MD² ,
Charumathi Raghu Subramanian, MD³, Omar Nemer, MD²,
Jagmeet Singh, MD⁴, Asim Kichloo, MD⁵ ,
and Bahar Moftakhar, MD²

Abstract

Neuroendocrine tumors (NETs) are a relatively rare entity; however, the incidence and prevalence of these tumors are increasing, likely attributed to improved diagnostic accuracy. The diagnosis of suspected NETs is facilitated by clinical symptoms, laboratory test abnormalities such as elevated chromogranin-A, and other diagnostic modalities such as the use of computed tomography scans, magnetic resonance imaging scans, positron emission tomography (PET) scans, and biopsy. The expression of high levels of somatostatin receptors in NETs enables the use of a specialized PET scan using the radiolabeled somatostatin analogues ⁶⁸Ga-DOTATATE. The sensitivity and specificity of ⁶⁸Ga-DOTATATE PET is very high for the diagnosis of NETs, but the specificity decreases especially with no clear symptoms and with only borderline elevated tumor markers. We present a case of a suspected NET, which was initially diagnosed as a metastatic NET by virtue of a positive ⁶⁸Ga-DOTATATE PET scan; however, on biopsy it was revealed to be a squamous cell carcinoma originating from the head and neck.

Keywords

squamous cell carcinoma, PET DOTATATE, neuroendocrine tumor, NET, oncology

Background

Neuroendocrine tumors (NETs) are thought to be a rare entity; however, with improved diagnostic parameters, the incidence and prevalence of these cases are increasing.¹ These tumors arise from the neuroendocrine cells and most commonly occur in the gastrointestinal tract, lung, and pancreas although they can appear in various organs within the body.² NETs are best known for their ability to secrete bioactive peptides causing symptoms like diarrhea and flushing; however, the majority of NETs do not secrete hormones and have non-specific symptoms.³ Due to low incidence, nonspecific symptoms, and variable organ involvement, delays in the diagnosis of NETs are frequent.⁴ Biochemical testing with chromogranin-A, imaging with computed tomography and magnetic resonance imaging scans, along with the help of functional imaging like the somatostatin receptor (SSTR) scintigraphy, which takes advantage of the overexpression of the SSTRs and positron emission tomography (PET) scan using radiolabeled somatostatin analogues like the ⁶⁸Ga-DOTATATE help in the diagnosis of NETs. ⁶⁸Ga-PET DOTATATE have high sensitivity and specificity for the diagnosis of suspected NET. In this article, we present a case

of a suspected NET, which was initially diagnosed as a metastatic NET by virtue of a positive ⁶⁸Ga-DOTATATE PET scan; however, on biopsy it was revealed to be a squamous cell carcinoma originating from the head and neck.

Case Description

A 70-year-old man with a past medical history of coronary artery disease, hypertension, hyperlipidemia, obstructive sleep

¹Hillcrest Medical Center, Tulsa, OK, USA

²University of Rochester Medical Center, Rochester, NY, USA

³University of California San Francisco, CA, USA

⁴Geisinger Commonwealth School of Medicine, Scranton, PA, USA

⁵CMU Medical Education Partners, Saginaw, MI, USA

Received May 8, 2021. Revised July 2, 2021. Accepted July 7, 2021.

Corresponding Author:

Manidhar Reddy Lekkala, MD, Department of Hematology and Oncology, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642, USA.

Email: manidhar.lekkala@gmail.com



apnea, and remote history of renal cell carcinoma with prior radical nephrectomy. During a surveillance scan for his prior renal cell carcinoma, an incidental pulmonary embolism was noted as well as a cystic lesion on the pancreas. He was referred to gastroenterology for further workup of the pancreatic cystic lesion. As part of the assessment, a chromogranin-A level was obtained. Chromogranin-A was elevated at >600 ng/mL with normal 5-hydroxyindoleacetic acid. Octreotide scan was negative and endoscopic ultrasound was negative for any solid component of the pancreatic lesion. It was postulated that the patient had elevated chromogranin-A levels related to his chronic kidney disease, recent thrombosis as well as being on a proton pump inhibitor (PPI). The patient was asymptomatic from the pancreatic lesion without complaints of diarrhea or flushing. A repeat chromogranin-A level a few months later decreased to 157 ng/mL after PPI was held but remained elevated beyond the upper limit of normal. Over the next several years he continued surveillance for the pancreatic cyst and elevated chromogranin-A level. On surveillance scans he was noted to have an increase in the size of cystic lesions on the pancreas as well as a peripancreatic lymph node enlargement. The chromogranin-A rose to 400 ng/mL.

After nearly 5 years of surveillance, a ⁶⁸Ga-DOTATATE PET scan was obtained for a suspected NET. This showed an abnormal bifocal uptake in the left neck with a maximum SUV (standardized uptake value) 9, with an additional focus of abnormal uptake in the left neck more medially with a maximum SUV 7. Another abnormal focus of uptake was also appreciated in the right neck with maximum SUV 3.1 (Figures 1 and 2). Due to a high suspicion for metastatic NET, the patient was referred to a medical oncology specialist in gastrointestinal cancers. The patient was thought to have metastatic NET based on laboratory tests and imaging. He was sent for a biopsy of the lymph node for confirmation. To much surprise, the abnormal area on ⁶⁸Ga-DOTATATE PET scan showed squamous cell carcinoma on a core biopsy. ENT evaluation showed a left tonsillar primary lesion. The patient was referred to a head and neck oncology specialist and was not found to have any evidence of a NET.

Discussion

NETs encompass a group of neoplasms that are very rare. These tumors express SSTR, a defining characteristic of NETs.⁵ A combination of clinical signs and symptoms such as diarrhea, flushing, and laboratory test results showing elevated chromogranin-A provides a diagnostic sensitivity approaching 70% to 85%.⁶ However, it is not sufficient for the identification of tumor sites and it is not specific as false-positive chromogranin-A elevations are common with conditions such as atrophic gastritis, renal insufficiency, heart failure, usage of PPI, and gastrointestinal disorders.⁶ Previously, octreotide scans, using a long-acting somatostatin analogue, were used in the evaluation and diagnosis of NETs.^{7,8} However, there were many limiting factors which

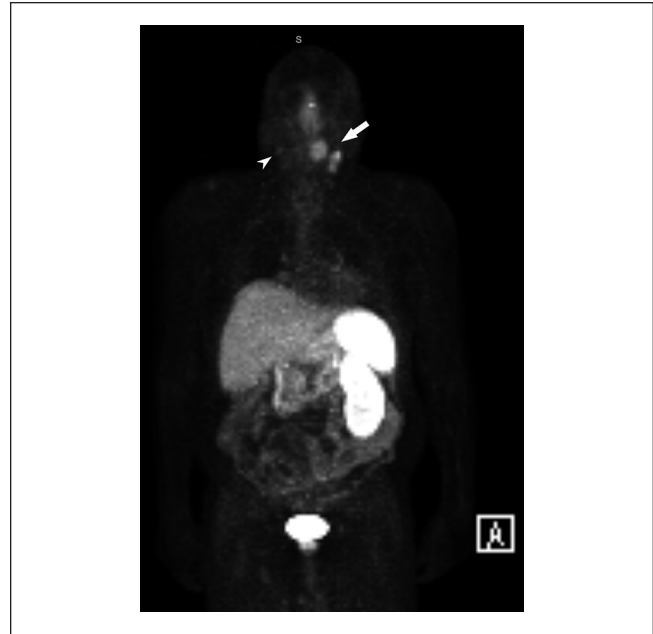


Figure 1. Coronal maximal intensity projection (MIP) image from patient's Ga-68 DOTATATE PET magnetic resonance imaging scan demonstrates abnormal foci of radiotracer uptake in the left neck in the left palatine tonsil medially and left cervical lymph node chain laterally (long white arrow). Subtle increased focus of radiotracer uptake also visualized in the right cervical lymph node chain (short white arrow). Physiologic radiotracer uptake is seen elsewhere in the body, with absence of the right kidney.

led to the low specificity of the test such as low image quality, increased physiological uptake restricting detection of smaller lesions, prolonged imaging protocol, and high-dose radiation.⁹⁻¹²

With the availability of ⁶⁸Ga-DOTATATE PET using radioisotope-labeled somatostatin analogues, the diagnosis of SSTR expressing tumors like NETs has dramatically improved and shown a higher specificity.^{13,14} In addition to improvement in the spatial resolution, lesion detectability, it is also more convenient as the test takes about 2 hours rather than 2 days and has less radiation exposure compared with the octreotide scan.^{13,15-17} Multiple authors evaluated the role of ⁶⁸Ga-DOTATATE PET in diagnosis of suspected primary or metastatic NETs and correlated with gold standard pathology results.¹⁸⁻²⁰ The sensitivity of the ⁶⁸Ga-DOTATATE PET in the diagnosis of NETs is 80% to 90% and the specificity is 82% to 90% compared with the pathology.¹⁴ However, the specificity is found to be low with high false positives in patients with no clear clinical symptoms or borderline elevated tumor markers.¹⁹

SSTRs are highly expressed in NETs including the pituitary adenoma, endocrine pancreatic tumors, carcinoid of the gastrointestinal tract and lung, small cell cancer but are also present in non-NETs of the prostate, breast, lung, brain tumors, and so on.²¹ Interestingly, studies have shown SSTR expression in

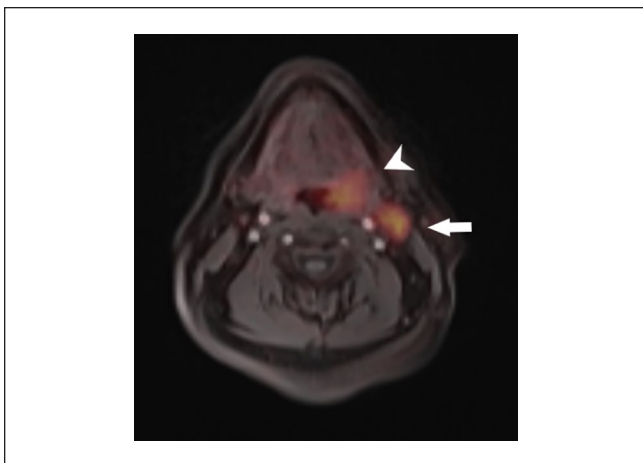


Figure 2. Axial fused DOTATATE PET magnetic resonance imaging image demonstrates asymmetrically increased radiotracer uptake in the left palatine tonsil measuring up to 3.1 cm (short white arrow) and left cervical lymph node chain (long white arrow), with largest cervical lymph node measuring up to 2 cm in the short axis.

squamous cell carcinoma of the lung, head, and neck.²²⁻²⁴ Currently, the pathophysiologic role of the SSTR expression in squamous cell carcinoma is unclear. Due to expression of the SSTR in other cancers, there may be a false positive result for a NET. It is therefore very important to follow the gold standard and obtain a biopsy to establish the final diagnosis.

In our case, in which the patient had no clear clinical symptoms, and the abnormal elevation and a fluctuation of chromogranin-A could be explained by other factors, the specificity of ⁶⁸Ga-DOTATATE PET becomes low. Clinicians need to be aware of sensitivity and specificity of each test and cautiously interpret the results.

Conclusion

⁶⁸Ga-DOTATATE PET scan has high specificity for detecting NETs. The specificity decreases with high false positives in patients with who have no clear clinical symptoms of NETs or have only borderline elevated tumor markers such as chromogranin-A. Tumors not classically thought to have high expression of SSTRs may show positive findings on ⁶⁸Ga-DOTATATE PET and providers cannot use ⁶⁸Ga-DOTATATE PET scan only to make diagnostic conclusions. A tissue biopsy should always be pursued to confirm the diagnosis.

Author Contributions

Sanjana Mullangi: Conception of the idea, acquisition of data, manuscript writing, and final approval.

Manidhar Reddy Lekkala: Conception of the idea, critical revision, manuscript writing, and final approval.

Charumathi Raghu Subramanian: Conception of the idea, critical revision, and final approval.

Omar Nemer: Critical revision, manuscript writing, and final approval.

Jagmeet Singh: Critical revision, acquisition of data, and final approval.

Asim Kichloo: Critical revision, acquisition of data, and final approval.

Bahar Mofthakhar: Conception of the idea, critical revision, manuscript writing, and final approval.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

ORCID iDs

Manidhar Reddy Lekkala  <https://orcid.org/0000-0003-3302-1855>

Asim Kichloo  <https://orcid.org/0000-0003-4788-8572>

References

1. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol.* 2017;3:1335-1342. doi:10.1001/jamaoncol.2017.0589
2. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer.* 2015;121:589-597. doi:10.1002/ncr.29099
3. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. *Neoplasia.* 2017;19:991-1002. doi:10.1016/j.neo.2017.09.002
4. Singh S, Granberg D, Wolin E, et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the First Global Survey of Patients with NETs. *J Glob Oncol.* 2017;3:43-53. doi:10.1200/jgo.2015.002980
5. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26:3063-3072. doi:10.1200/JCO.2007.15.4377
6. Gut P, Czarnywojtek A, Fischbach J, et al. Chromogranin A-unspecific neuroendocrine marker. Clinical utility and potential diagnostic pitfalls. *Arch Med Sci.* 2016;12:1-9. doi:10.5114/aoms.2016.57577
7. Krenning EP, Bakker WH, Breeman WA, et al. Localisation of endocrine-related tumours with radioiodinated analogue

- of somatostatin. *Lancet*. 1989;1:242-244. doi:10.1016/s0140-6736(89)91258-0
8. Deppen SA, Liu E, Blume JD, et al. Safety and efficacy of 68Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. *J Nucl Med*. 2016;57:708-714. doi:10.2967/jnumed.115.163865
 9. Chopra A. (99m)Tc-ethylenediamine N,N'-diacetic acid/hydrazinonicotinamide-Tyr(3)-octreotide. In *Molecular Imaging and Contrast Agent Database (MICAD)*. Bethesda, MD: National Center for Biotechnology Information; 2004.
 10. Al-Nahhas A, Win Z, Szyszko T, Singh A, Khan S, Rubello D. What can gallium-68 PET add to receptor and molecular imaging? *Eur J Nucl Med Mol Imaging*. 2007;34:1897-1901. doi:10.1007/s00259-007-0568-1
 11. Bozkurt MF, Virgolini I, Balogova S, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with (68)Ga-DOTA-conjugated somatostatin receptor targeting peptides and (18)F-DOPA. *Eur J Nucl Med Mol Imaging*. 2017;44:1588-1601. doi:10.1007/s00259-017-3728-y
 12. Etchebehere EC, de Oliveira Santos A, Gumz B, et al. 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. *J Nucl Med*. 2014;55:1598-1604. doi:10.2967/jnumed.114.144543
 13. Antunes P, Ginj M, Zhang H, et al. Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals? *Eur J Nucl Med Mol Imaging*. 2007;34:982-993. doi:10.1007/s00259-006-0317-x
 14. Deppen SA, Blume J, Bobbey AJ, et al. 68Ga-DOTATATE compared with 111In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. *J Nucl Med*. 2016;57:872-878. doi:10.2967/jnumed.115.165803
 15. Poeppel TD, Binse I, Petersenn S, et al. 68Ga-DOTATOC versus 68Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med*. 2011;52:1864-1870. doi:10.2967/jnumed.111.091165
 16. Walker RC, Smith GT, Liu E, Moore B, Clanton J, Stabin M. Measured human dosimetry of 68Ga-DOTATATE. *J Nucl Med*. 2013;54:855-860. doi:10.2967/jnumed.112.114165
 17. Hofman MS, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *J Med Imaging Radiat Oncol*. 2012;56:40-47. doi:10.1111/j.1754-9485.2011.02327.x
 18. Haug AR, Cindea-Drimus R, Auernhammer CJ, et al. The role of 68Ga-DOTATATE PET/CT in suspected neuroendocrine tumors. *J Nucl Med*. 2012;53:1686-1692. doi:10.2967/jnumed.111.101675
 19. Haug AR, Cindea-Drimus R, Auernhammer CJ, et al. Neuroendocrine tumor recurrence: diagnosis with 68Ga-DOTATATE PET/CT. *Radiology*. 2014;270:517-525. doi:10.1148/radiol.13122501
 20. Fallahi B, Manafi-Farid R, Eftekhari M, et al. Diagnostic efficiency of (68)Ga-DOTATATE PET/CT as compared to (99m)Tc-Octreotide SPECT/CT and conventional morphologic modalities in neuroendocrine tumors. *Asia Ocean J Nucl Med Biol*. 2019;7:129-140. doi:10.22038/aojnm.2019.39392.1263
 21. Barbieri F, Bajetto A, Pattarozzi A, et al. Peptide receptor targeting in cancer: the somatostatin paradigm. *Int J Pept*. 2013;2013:926295. doi:10.1155/2013/926295
 22. Nisman B, Heching N, Biran H, Barak V, Peretz T. The prognostic significance of circulating neuroendocrine markers chromogranin a, pro-gastrin-releasing peptide and neuron-specific enolase in patients with advanced non-small-cell lung cancer. *Tumour Biol*. 2006;27:8-16. doi:10.1159/000090151
 23. Yuan A, Liu J, Liu Y, Cui G. Chromogranin A-positive tumor cells in human esophageal squamous cell carcinomas. *Pathol Oncol Res*. 2007;13:321-325. doi:10.1007/bf02940311
 24. Stafford ND, Condon LT, Rogers MJC, MacDonald AW, Atkin SL. The expression of somatostatin receptors 1 and 2 in benign, pre-malignant and malignant laryngeal lesions. *Clin Otolaryngol Allied Sci*. 2003;28:314-319. doi:10.1046/j.1365-2273.2003.00711.x