Incidental 68Ga-DOTATATE uptake in the pancreatic head
A case report and a unique opportunity to improve clinical care

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Abstract

Rationale: Neuroendocrine tumors (NETs) are neoplasms that can arise from the neuroendocrine cells distributed widely throughout the body. Majority of NETs overexpress somatostatin receptors (SSTR) on their cell surface. This biologic characteristic is exploited by SSTR-based imaging such as 111In octreotide scintigraphy and 68Ga DOTATATE positron emission tomography (PET)/computed tomography (CT), which are considered standard for initial evaluation of NETs. Although highly sensitive and specific, recent reports demonstrate a concerning incidence of “false-positive” physiologic uptake of these tracers in the pancreatic head—a common site of neuroendocrine tumor (NET) involvement. We present false positive uptake on 68Ga DOTATATE PET/CT along with false positive CT findings. Role of other imaging modalities is discussed.

Patient concerns: A 78-year-old woman presented with a year-long history of diarrhea.

Diagnosis: Serum vasoactive intestinal peptide (VIP) levels were slightly elevated at 134.2 pg/mL (normal <75 pg/mL). CT showed a mildly enhancing 2.5 cm × 1.8 cm × 2.8 cm area in the pancreatic uncinate process which corresponded to focal uptake with 68Ga DOTATATE PET/CT. A presumptive diagnosis of pancreatic NET (vipoma) was made, and the patient was scheduled to undergo Whipple’s surgery.

Interventions: She sought a second opinion and a subsequent magnetic resonance imaging (MRI) showed no lesion and the patient’s surgery was deferred. Thereafter, her VIP levels spontaneously normalized. Endoscopic ultrasound (EUS) with fine needle aspiration cytology of the uncinate process showed normal pancreatic acini with no evidence of NET.

Outcomes: Patient is currently pursuing workup for alternative etiologies for chronic diarrhea.

Lessons: Conspicuous physiological uptake has been reported in the pancreatic head on 16% to 70% of 68Ga DOTATATE or 68Ga DOTANOC PET/CT scans, and 26% of the 111In octreotide scintigraphy scans. Image-based quantitative attempts to distinguish physiologic from pathologic uptake using SUVmax have rendered mixed results. When evaluating SSTR-based imaging uptake in the pancreatic head, patients can benefit from a higher index of suspicion of false positive uptake. Such cases require additional confirmation by MRI or EUS. Interestingly, the patient described also had mild contrast enhancement on CT, but without an MRI correlate. Because of potential morbidity and mortality related to false positive uptake, a systematic review with evidence-based recommendations for imaging may benefit patient care.

Abbreviations: CT = computed tomography, EUS = endoscopic ultrasound, MRI = magnetic resonance imaging, NET = neuroendocrine tumor, PET = positron emission tomography, SSTR = somatostatin receptors, SUV = standardized uptake value, VIP = vasoactive intestinal peptide.

Keywords: 68Ga-DOTATATE, neuroendocrine tumors, pNET, somatostatin receptor-based imaging, uncinate process

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1. Introduction
Neuroendocrine tumors (NETs) are epithelial neoplasms that can arise from the neuroendocrine cells distributed widely throughout the body. The majority of NETs overexpress somatostatin receptors (SSTR) on their cell surface. This biologic characteristic is exploited in the somatostatin receptor-based imaging techniques such as $^{111}$In octreotide scintigraphy and $^{68}$Ga DOTATATE positron emission tomography (PET). These modalities are currently considered standard for the initial evaluation of suspected neuroendocrine tumors. Although highly sensitive and specific for NETs, recent reports demonstrate a concerning incidence of “false-positive” physiologic uptake of these tracers in the pancreatic head—an confounding common site of neuroendocrine tumor (NET) involvement. This report is intended to further highlight a persistent concerning issue and to bring to attention the inadequacy of cross-sectional imaging with computed tomography (CT) only in this situation. Potential approaches for when such a finding occurs is discussed.

2. Case report
A 78-year-old woman presented to clinic with a year-long history of diarrhea. Patient had 4 to 5 loose, greasy stools per day. She did not report any blood in stools, weight loss, dyspnea, facial flushing, skin rash, nausea, or vomiting. Patient had previously tried bland diet, cholestyramine, and Pepto-Bismol without any improvement in symptoms. Past medical history was significant for breast cancer diagnosed 5 years ago and treated with lumpectomy, radiation, and anastrozole; hypertension well-controlled on Valsartan; and hypothyroidism treated with levothyroxine replacement. Physical examination did not elicit any abdominal tenderness, guarding, or rigidity. Serum vasoactive intestinal peptide levels were slightly elevated at 134.2 pg/mL (normal <75 pg/mL). CT showed a mildly enhancing 2.5 cm × 1.8 cm × 2.8 cm area in the pancreatic uncinate process which corresponded to mild to moderate uptake with $^{68}$Ga DOTATATE PET-CT imaging (Fig. 1A–B). Based on these findings, a presumptive diagnosis of pancreatic NET (vipoma) was made, with subsequent scheduling for a Whipple’s surgery. The patient sought a second opinion at our institution as part of an IRB-approved trial, and signed informed consent.

A subsequent magnetic resonance imaging (MRI) demonstrated no lesion in the uncinate process and the patient’s surgery was deferred (Fig. 1C–F). On a future measurement, after adequate patient preparation, her vasoactive intestinal peptide (VIP) levels were normal (<50 pg/mL, reference range <75 pg/mL). Endoscopic ultrasound (EUS) with fine needle aspiration cytology of the uncinate process showed no evidence of involvement with NET. Patient is currently pursuing workup for alternative etiologies for chronic diarrhea.

3. Discussion
The case presented here highlights the importance of differentiating physiologic uncinate process uptake from pathological uptake on SSTR-based imaging. A unique aspect of this case was

Figure 1. (A) Computed tomography (CT) scan showing mild enhancement in the pancreatic uncinate process. (B) $^{68}$Ga DOTATATE positron emission tomography (PET)/CT imaging demonstrating uptake in the pancreatic uncinate process. (C–F) MRI with no corresponding anatomic abnormality on (C) T1 post-contrast, (D) apparent diffusion coefficient (ADC), (E) T2-weighted fat suppressed, and (F) diffusion-weighted imaging (DWI).
that the CT scan also demonstrated enhancement in the pancreatic head region suggesting that better cross-sectional imaging modalities are required to characterize the uptake in pancreatic head on SSTR-based imaging. Here we will discuss the available evidence in the literature with suggested clinical approaches when such a finding occurs.

In 2016, Ramos, et al reported 2 cases of clinically suspected NET who underwent $^{68}$Ga DOTATOC PET-CT with presumptively abnormal uptake in the pancreatic uncinate process,[1] without a corresponding anatomical abnormality on EUS. Other case series have corroborated these findings with conspicuous physiological uptake in the pancreatic head reported to be present on 16% to 70% of $^{68}$Ga DOTATATE or $^{68}$Ga DOTANOC PET-CT scans (Table 1).[2–4] Brabander et al found physiologic uptake in the region of the pancreatic head in 26% (46/178) patients who underwent $^{111}$In octreotide scintigraphy. Interestingly, the incidence of physiological uptake was 50% (10/20) in patients on antidiabetic drugs.[4] The abundance of pancreatic polyepitide (PP) cells in the uncinate process of the pancreatic head (90% of all pancreatic PP cells) is thought to be the reason for this physiologic uptake, due to SSTR subtypes 1 to 4 cell surface expression.[4]

Table 1

| Reference | Ligand       | Imaging modality | Localization in pancreas | Incidence |
|-----------|--------------|------------------|--------------------------|-----------|
| Al-Ibraheem et al[5] (2011) | $^{68}$Ga DOTATOC | PET/CT | Head | 20/43 (47%) |
| Castellucci et al[5] (2011) | $^{68}$Ga DOTANOC | PET/CT | Head | 31/130 (31%) |
| Kunikowski et al[5] (2012) | $^{68}$Ga DOTATATE | PET/CT | Uncinate process | 41/250 (16%) |
| Jacobsson et al[5] (2012) | $^{68}$Ga DOTATOC | PET/CT | Uncinate process | 35/50 (70%) |
| Kraus et al[5] (2012) | $^{68}$Ga DOTANOC | PET/CT | Head/uncinate process/body | 38/103 (37%) |
| Mapelli et al[5] (2014) | $^{68}$Ga DOTATATE | PET/CT | Head/uncinate process | 10/38 (26%) |
| Brabander et al[5] (2017) | $^{111}$In Octreotide | SPECT/CT | Head | 46/178 (26%) |
| Boudaoud et al[5] (2017) | $^{111}$In Octreotide | SPECT/CT | Uncinate process | 8/13 (62%) |
| Total | | | | 229/775 (30%) |

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In conclusion, when evaluating somatostatin receptor-based molecular imaging (e.g., $^{68}$Ga-DOTATATE) uptake in the pancreatic head, it is important to consider the possibility of physiological uptake and distinguish it from pathological uptake by using quantitative imaging methods and appropriate imaging techniques.
pancreatic head, this report recapitulates a recommendation of a high index of suspicion of false positive uptake, which can help avoid unnecessary invasive procedures (e.g., biopsy, Whipple’s procedure). Such cases likely require more extensive confirmation, which ideally includes a comprehensive MRI of the pancreas.

Author contributions
Rahul Lakhotia - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing (original draft and review/editing)
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Corina Millo - Conceptualization, Investigation, Visualization, Writing - review & editing
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