

Occurrence of 'Redifferentiation akin' phenomenon on [⁶⁸Ga]Ga-DOTATATE PET-CT following CAPTEM chemotherapy in Metastatic Neuroendocrine Tumours with intermediate MiB-1 index: what could be the molecular explanation?

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Abstract

In this report, we present the [⁶⁸Ga]Ga-DOTATATE PET-CT images (pre- and post-chemotherapy) of a patient with intermediate grade metastatic neuroendocrine tumor (NET) with intermediate grade/Ki-67 index who had minimal somatostatin receptor positivity at baseline [⁶⁸Ga]Ga-DOTATATE PET-CT, but had demonstrated high grade positivity on somatostatin receptor imaging (Krenning score III-IV) on follow-up scan after chemotherapy. This 'redifferentiation-akin' phenomenon in intermediate grade NETs following chemotherapy can have potential implications for the feasibility of peptide receptor radionuclide therapy (PRRT) in this group of patients in their course of disease at a later phase.

Introduction

PRRT with [¹⁷⁷Lu]Lu-DOTATATE has recently emerged as a front-runner therapy for well-differentiated and intermediate grade neuroendocrine tumors which can be attributed to its better patient tolerability, convenient treatment schedule and intervals of cycles and its excellent efficacy in alleviating the symptoms in symptomatic patients. However, few intermediate grade neuroendocrine tumors show minimal somatostatin receptor positivity, thus, rendering them unsuitable for PRRT. In our set-up, few such cases which have been followed up following chemotherapy (such as capecitabine-temozolamide abbreviated as

CAPTEM or everolimus) with molecular PET imaging, have shown enhancement of tracer uptake with high grade positivity on somatostatin receptor imaging (1). This small subset of patients can be potential candidates who can receive PRRT.

Case Report

A 58 years-old-female, diagnosed patient of metastatic grade 2 gastric NET (Histopathology demonstrating well - differentiated neuroendocrine tumour, positive for AE1/AE2/AE3, synaptophysin and chromogranin and negative for C-kit and DOG-1, Mib - 1 index 7-8%). was referred for PRRT feasibility opinion. The contrast enhanced CT demonstrated Soft tissue lesion seen, probably arising exophytic soft tissue mass arising from stomach and abutting left lobe of liver. There were also multiple liver lesions, largest in right lobe, with areas of necrosis. The [⁶⁸Ga]Ga-DOTATATE PET-CT showed low grade SSTR expression in the soft tissue mass, involving lesser curvature of stomach (measuring 10x6x5.3cm, maximum standardized uptake value 9.09), consistent with known primary and minimal uptake in the metastatic liver lesions (Krenning score ≤ 1) with largest lesion in segment VII/VIII (Fig 1). In view of low/minimal uptake on somatostatin receptorbased PET imaging and Mib - 1 index 7-8%, she was considered for chemotherapy with capecitabine and temozolamide (CAPTEM). She showed clinical response in terms of reduction of pain in the abdomen. Following 6 cycles of CAPTEM, a follow-up [⁶⁸Ga]Ga-DOTATATE -PET-CT was undertaken (Fig. 1, 2, 3) scan, showed increased SSTR expression (Krenning score level 3) at the gastric mass and the liver lesions with significant reduction in the sizes of the gastric mass and the liver lesions.

Discussion: The uptake in the [⁶⁸Ga]Ga-DOTATATE -PET-CT based molecular imaging is an important prerequisite for choosing PRRT in metastatic NETs. The Krenning score is used to grade the uptake intensity of NETs on somatostatin receptor based imaging (2); typically, PRRT is considered when the Krenning score is greater than 2. CAPTEM based chemotherapy are used successfully in patients with intermediate grade neuroendocrine tumours, especially in cases with poor or minimal somatostatin receptor expression.

To our knowledge, existing literature is limited on the topic of chemotherapy induced enhanced uptake on SSTR based PET imaging, with only one communication till date (1). This observation in the parlance of NET is presently unexplained and we have observed this ‘redifferentiation akin’ phenomenon in the context of intermediate grade NETs. Basu et al (1) had cited examples of three cases in which patients of intermediate grade progressive metastatic NET presented with minimal uptake on initial work up with ⁶⁸Ga-DOTATATE-PET-CT. As a result, these patients were treated with CAPTEM based chemotherapy or Everolimus, and showed intense tracer uptake on subsequent [⁶⁸Ga]Ga-DOTATATE -PET-CT, making them eligible for PRRT at a later period. While we noted enhanced uptake on ⁶⁸Ga-DOTATATE in limited population, it is premature to state that SSTR increase in every NET patient who has treated with CAPTEM or Everolimus. This could be clarified at a later stage in a prospective setting.

The present case upholds the similar observation and brings forth the requirement for an appropriate clinical protocol to benefit such subset of patients who can be later benefitted by PRRT if follow up scans show increased SSTR expression.

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Fig. 1.

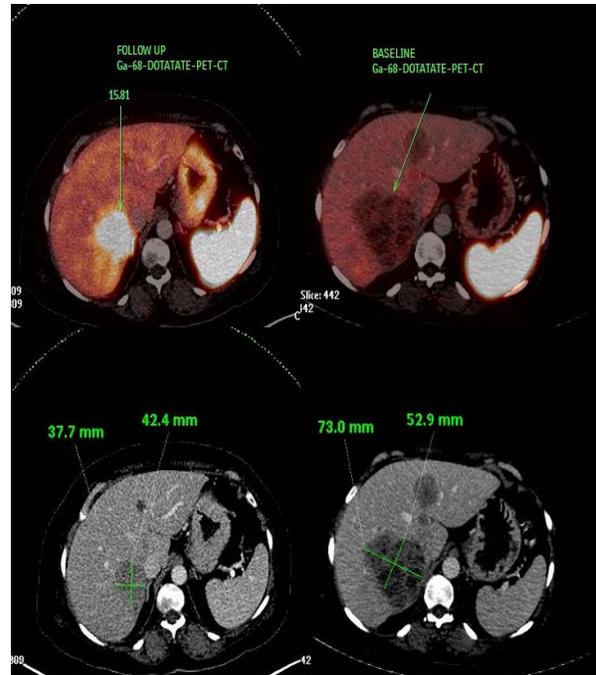


Fig. 2.

Fig. 1. Axial CT and fused PET-CT images demonstrating uptake of tracer in the primary gastric mass (SUVmax: 11.47) in the follow-up axial ^{68}Ga -DOTATATE-PET/CT images (left panel) compared to the baseline (right panel).

Fig. 2. Axial CT and fused PET-CT images demonstrating Krenning score 3 level uptake of tracer in the follow-up axial ^{68}Ga -DOTATATE-PET-CT in the liver lesions in segment VII/VIII (reduced in size as seen in CT images), compared to the corresponding computed tomography and axial ^{68}Ga -DOTATATE-PET-CT images at baseline.

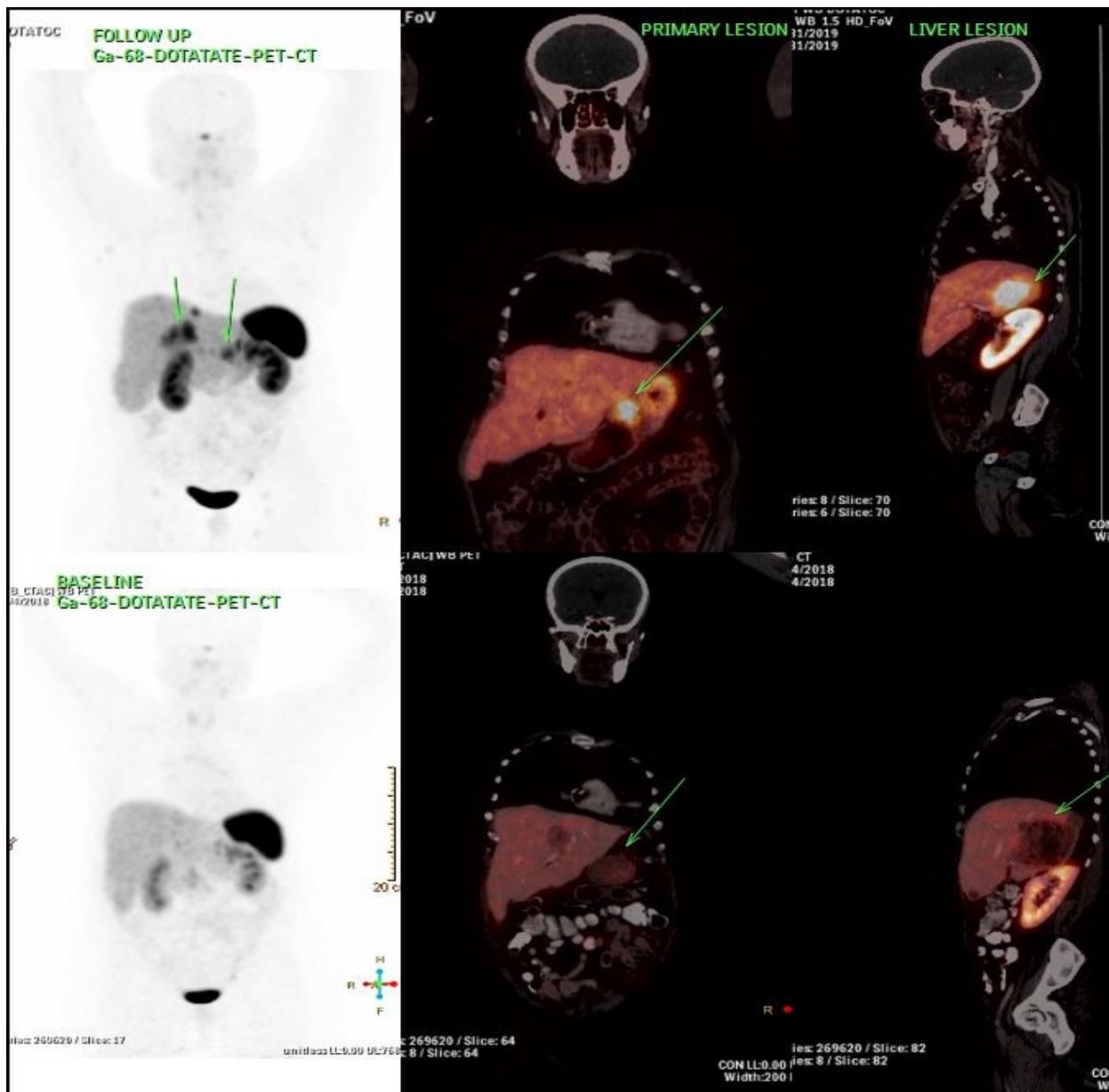


Fig. 3

Fig. 3. Baseline (lower panel) and follow-up (upper panel) maximum intensity projection (MIP), coronal and sagittal images of the [⁶⁸Ga]Ga-DOTATATE –PET-CT demonstrating enhanced trace uptake in t follow-up scan.