Radiology Case Reports 15 (2020) 2698–2700

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Pulmonary large cell neuroendocrine carcinoma (LCNEC) with confirmed liver metastases negative on ^{18}F-FDG and ^{68}Ga-DOTATATE PET ☆,☆☆

Gaia Ninatti[a], *Heying Duan, MD*[b], *Valentina Ferri, MS*[b], *Brock A. Martin, MD*[c], *Carina Mari Aparici, MD*[b,*]

[a] *Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy*
[b] *Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Stanford University, 300 Pasteur Drive, Stanford, CA, 94305-5281, USA*
[c] *Department of Pathology, Stanford University, Stanford, CA, USA*

ARTICLE INFO

Article history:
Received 24 August 2020
Revised 10 October 2020
Accepted 10 October 2020

Keywords:
Lung neuroendocrine neoplasms
Large cell neuroendocrine carcinoma
^{18}F-FDG
^{68}Ga-DOTATATE
PET/CT
Somatostatin receptors

ABSTRACT

Lung neuroendocrine neoplasms (NENs) encompass the low-, intermediate-, and high-grade entities. Differentiated NENs overexpress somatostatin receptors, which are targeted by ^{68}Ga-DOTA-conjugated peptides in molecular imaging with positron emission tomography. Less differentiated NENs may have lost their expression of somatostatin receptors and thus show lower uptake of ^{68}Ga-DOTA-peptides; however, these tumors express GLUT-1 and can be imaged with (18)F-fluordeoxyglucose (FDG).

We report the case of a 72-year-old patient with a poorly differentiated, high grade lung NEN, which was ^{18}F-FDG-positive at initial diagnosis. After treatment and remission, the patient had histologically confirmed relapse in the liver. Interestingly, these hepatic metastases did not demonstrated radiopharmaceutical uptake at neither ^{18}F-FDG nor ^{68}Ga-DOTATATE positron emission tomography/computed tomography.

Introduction

Lung neuroendocrine neoplasms (NENs) encompass the low-grade typical carcinoid (TC), the intermediate-grade atypical carcinoid (AC), the high-grade large cell neuroendocrine carcinoma (LCNEC), and small cell lung cancer [1].

Differentiated NENs overexpress somatostatin receptors (SSTR). These are targeted by ^{68}Ga-DOTA-conjugated peptides in molecular imaging with positron emission tomography (PET) [2]. Less differentiated NENs like AC, LCNEC, and small cell lung cancer are more aggressive and may have lost their expression of SSTR, thus showing lower or no uptake of

☆ Patient Consent: Informed consent was obtained from the patient for the anonymous use of imaging, histologic, and clinical data.
☆☆ Competing Interests: The authors have declared that no competing interests exist.

* Corresponding author.
E-mail address: drmari@stanford.edu (C.M. Aparici).

https://doi.org/10.1016/j.radcr.2020.10.023

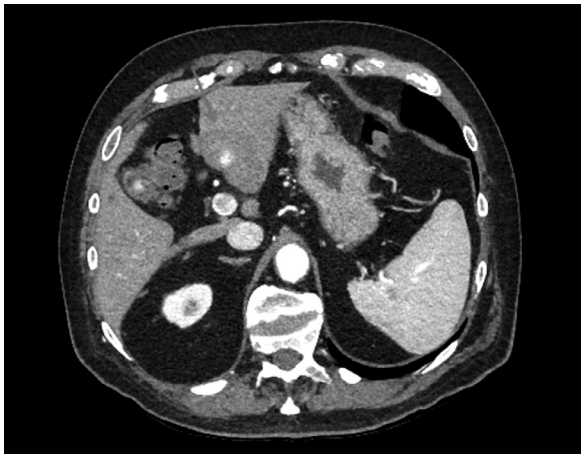

Fig. 1 – Axial contrast-enhanced CT scan showing an enhancing hepatic lesion (red arrow), later confirmed to be a metastasis of the primary lung LCNEC

^{68}Ga-DOTA-peptides. However, they express GLUT-1. GLUT-1 is a proliferation marker indicating glucose metabolism and cell growth and can be imaged with (18)F-fluorodeoxyglucose (FDG) [3].

Case report

We present the case of a 72-year-old patient with an incidental finding of a 2 cm right lower lobe mass in a chest X-ray in April 2016. Initial diagnostic evaluation with chest computed tomography (CT), FDG PET/CT, and biopsy revealed a stage IIIA FDG-positive, poorly differentiated lung LCNEC with cytomorphologic overlap with AC (Fig. 4a). The patient underwent radical surgery with right lower and middle lobe lobectomy and mediastinal lymph node dissection, followed by adjuvant chemoradiation therapy. The patient was in remission for 2 years, as a follow-up chest CT (Fig. 1) incidentally revealed a 1.0 cm hyperenhancing lesion in hepatic segment IVb. Magnetic resonance imaging (MRI) showed multiple liver metastases, with the biggest measuring 6.0 × 3.2 cm (Fig. 2a-c T1-weighted images, Fig. 2d T2-weighted image, and Fig. 2e diffusion weighted imaging (DWI)). With the strong suspicion of hepatic metastases derived from the original LCNEC, further assessment with FDG PET/CT (Fig. 3a) was done, but showed no metabolically active disease. Subsequently, a biopsy of the hepatic lesions revealed a NEN within the AC spectrum with cytomorphologic features comparable to the patient's primary lung LCNEC (Fig. 4b). Given the biopsy-verified intermediate grade NEN and FDG negativity, a ^{68}Ga-DOTATATE PET/CT (Fig. 3b) was performed where no uptake was seen in the LCNEC lesions. Therefore, MRI of the abdomen was considered the imaging method of choice. The patient underwent chemotherapy with capecitabine and temozolomide and showed stable disease after 11 cycles.

Discussion

It is not clear why the hepatic metastases from the primary lung LCNEC were negative for both ^{18}F-FDG and ^{68}Ga-DOTATATE. While no or minimal uptake of ^{68}Ga-DOTATATE is expected in intermediate and high-grade NENs, due to their lack of differentiation and lost SSTR expression, FDG negativity is not. De- or undifferentiated NENs, being characterized by a high proliferation rate and thus high glucose consumption, are ^{18}F-FDG-avid [4,5]. Grondahl et al. showed in a study com-

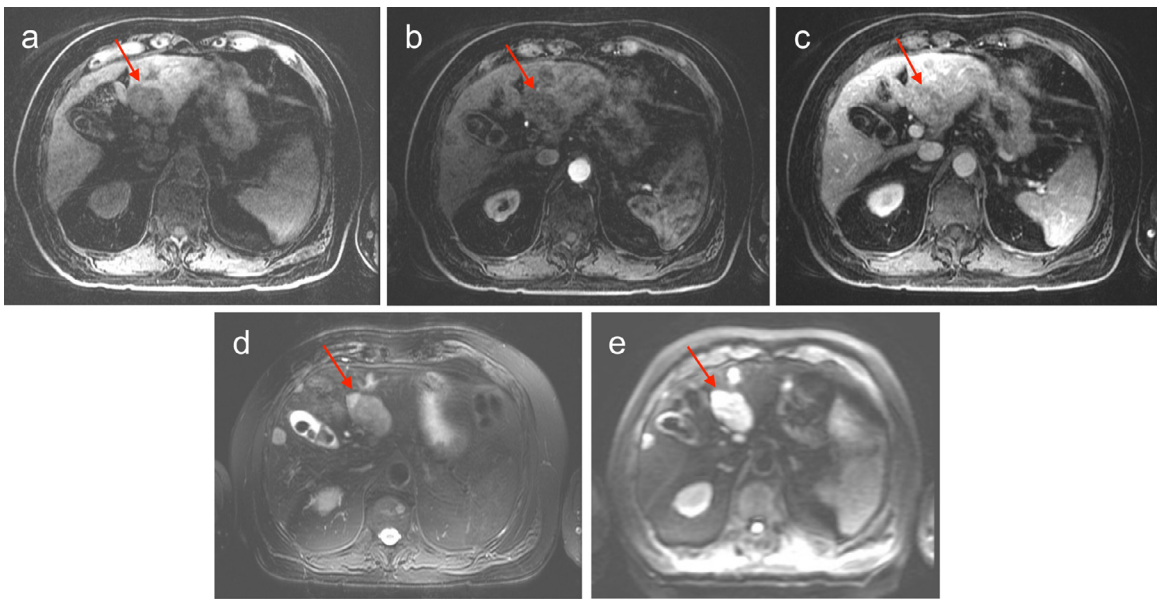

Fig. 2 – (a) axial pre-contrast, (b) arterial phase, and (c) delayed phase T1-weighted images; (d) axial T2-weighted image; and (e) axial DWI

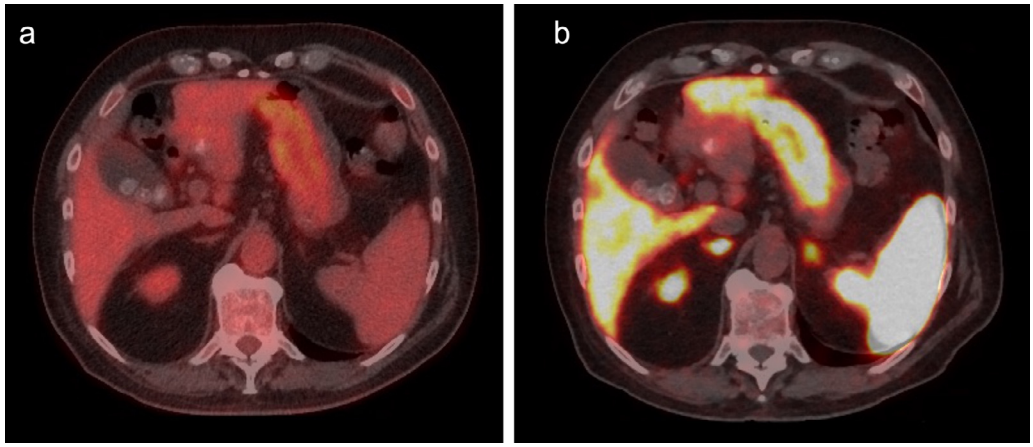

Fig. 3 – (a) axial fused ^{18}F-FDG and (b) ^{68}Ga-DOTATATE PET/CT images demonstrating no lesion uptake of either radiopharmaceutical

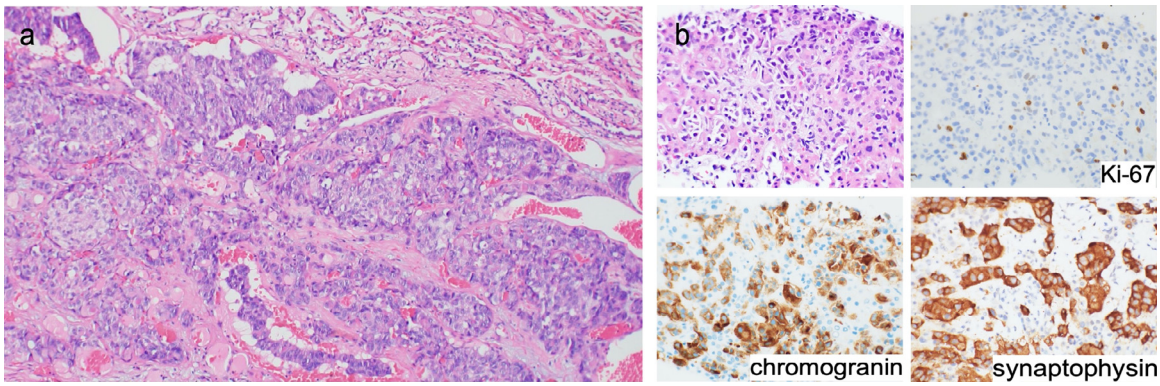

Fig. 4 – (a) Low-power microscopic examination of the lung resection specimen using hematoxylin and eosin (H&E) staining. A LCNEC with cytomorphological features overlapping with AC is revealed.
(b) Microscopic examination of the liver biopsy specimen. Immunohistochemical analysis of Ki-67, synaptophysin, and chromogranin evidences a NEN within the AC spectrum

prising of 252 bronchopulmonary NENs that all LCNEC showed FDG uptake as compared to 93% of TC and 96% of AC.

We excluded a potential technical issue: the injected dose of FDG was proportional to the patient's body weight, and the patient preparation and blood glucose levels before the scan were appropriate. A regular biodistribution with normal background uptake is observed.

This unusual and unique case suggests that negative findings on both ^{18}F-FDG and ^{68}Ga-DOTATATE PET do not rule out NEN lesions. Further histopathological analysis on the diverse SSTR-subtype expression may clarify the different clonal behavior of the hepatic metastases and explain negativity of both radiopharmaceuticals.

REFERENCES

[1] Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 2018. https://doi.org/10.1038/s41379-018-0110-y.

[2] Virgolini I, Ambrosini V, Bomanji JB, Baum RP, Fanti S, Gabriel M, et al. Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA- conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE. Eur J Nucl Med Mol Imaging 2010;37:2004. –10 https://doi.org/10.1007/s00259-010-1512-3 .

[3] Kayani I, Conry BG, Groves AM, Win T, Dickson J, Caplin M, et al. A comparison of 68Ga-DOTATATE and 18F-FDG PET/CT in pulmonary neuroendocrine tumors. J Nucl Med 2009. https://doi.org/10.2967/jnumed.109.066639.

[4] Jiang Y, Hou G, Cheng W. The utility of 18F-FDG and 68Ga-DOTA-Peptide PET/CT in the evaluation of primary pulmonary carcinoid: A systematic review and meta-analysis. Medicine (Baltimore) 2019. https://doi.org/10.1097/MD.0000000000014769.

[5] Grøndahl V, Binderup T, Langer SW, Petersen RH, Nielsen K, Kjaer A, et al. Characteristics of 252 patients with bronchopulmonary neuroendocrine tumours treated at the Copenhagen NET Centre of Excellence. Lung Cancer 2019;132. 141–9 https://doi.org/10.1016/j.lungcan.2019.03.013 .