Cancer Imaging (2011) **11,** 179–183
DOI: 10.1102/1470-7330.2011.0035

CI

e-med
www.e-med.org.uk

CASE REPORT

Concomitant lung and gastroenteropancreatic neuroendocrine tumors and the value of gallium-68 PET/CT

Daniel Kaemmerer[a], Karl Khatib-Chahidi[a], Richard Paul Baum[c], Dieter Hörsch[b], Norbert Presselt[e], Jörg Sänger[d], Almut Kunze[d] and Merten Hommann[a]

[a]Department of General and Visceral Surgery, Zentralklinik Bad Berka, Germany; [b]Department of Internal Medicine, Gastroenterology, Oncology and Endocrinology, Zentralklinik Bad Berka, Germany; [c]Department of Nuclear Medicine/ Center for PET, Zentralklinik Bad Berka, Germany; [d]Laboratory for Pathology and Cytology, Bad Berka, Germany; [e]Department of Thoracic and Vascular Surgery, Zentralklinik Bad Berka, Robert-Koch-Allee 9, Germany

Corresponding address: Dr Daniel Kaemmerer, Department of General and Visceral Surgery, Zentralklinik Bad Berka, Robert-Koch-Allee 9, 99437 Bad Berka, Germany.
Email: daniel.kaemmerer@zentralklinik.de

Date accepted for publication 17 October 2011

Abstract

Well-differentiated neuroendocrine tumors (NETs) of the lung occur as typical and atypical carcinoids. Little is known about the biology of these tumors in respect of their ability to metastasize or the probability of development of concomitant neuroendocrine tumors. Here we report a patient diagnosed with a second neuroendocrine tumor of the ileum 4 years after curative resection of a typical carcinoid of the left lung. The intestinal neuroendocrine tumor was successfully detected by gallium-68 based somatostatin receptor positron emission tomography (PET)/computed tomography (CT) and surgically removed using gamma probe detection based on the same labeling. This case report underlines the utility of somatostatin receptor PET/CT based detection and follow-up of NETs.

Keywords: *Typical carcinoids of the lung; gamma probe detection; somatostatin receptor PET/CT, TTF-1.*

Introduction

Neuroendocrine tumors of the lung include atypical and typical carcinoids, large cell neuroendocrine carcinomas and small cell lung carcinomas. Typical carcinoids (TCs) and atypical carcinoids (ACs) of the lung have rapidly increased in the last 30 years with an incidence of 1.57/ 100.000 in 2003[1].

TCs are often regarded as benign due to their low proliferation rate (Ki-67 <2%). They demonstrate an excellent prognosis with a 5-year survival rate of 88%[1].

The treatment of choice is surgery, which can be curative in most cases. Although TCs share histologic features with gastroenteropancreatic neuroendocrine tumors (GEP-NETs), they exhibit a lower tendency to form secondary tumors. The immunohistochemical patterns of GEP-NETs and TCs may be different. TCs express thyroid transcription factor-1 (TTF-1) and CD56, whereas GEP-NETs do not[2,3]. Despite their low proliferation rate, TCs may recur and metastasize[4]. Currently, there are no specific guidelines for preoperative staging or follow-up of typical lung carcinoids. Follow-up of these patients is often individualized and somatostatin receptor (SSTR) based positron emission tomography (PET)/ computed tomography (CT) is rarely performed[5].

Case report

A 1.4-cm nodule in the lingula (Fig. 1A) was detected in a 68-year-old woman. This nodule showed criteria of malignancy by thoracic CT (Fig. 2). Bronchoscopy was normal. Preceding surgery, a [^{18}F]fluorodeoxyglucose (FDG)-PET/CT scan was performed as recommended for staging of pulmonary tumors. It demonstrated diminutive glucose uptake without suspicion for mediastinal lymphadenopathies.

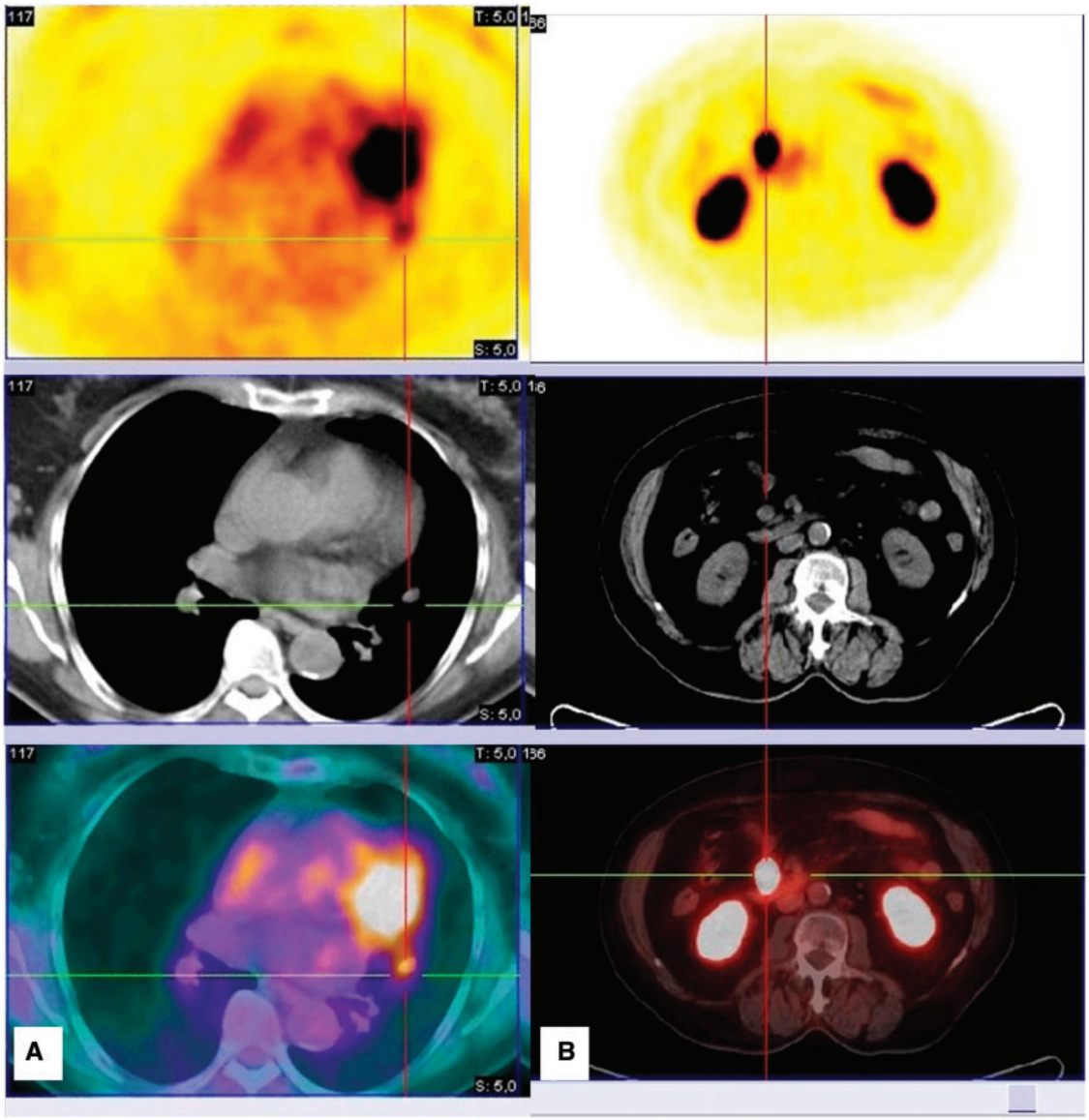

Figure 1 **(A) [^{18}F]FDG PET/CT located a tumor with low glucose uptake in the lingula. (B) [^{68}Ga]SSTR-PET/CT detected somatostatin receptor positive lesions in the terminal ileum and peripancreatically.**

The resection of the lingula and the mediastinal lymphadenectomy was performed in January 2007. Pathology demonstrated a 12 mm typical carcinoid (Ki-67 <5%, see Fig. 5B) with positive expression of chromogranin A, synaptophysin (see Fig. 4D) and TTF-1 (see Fig. 5D)[2]. None of the lymph nodes removed were invaded; the final staging was pT1 pN0 cM0. After surgery, follow-up was performed every 3 months by CT of the chest.

It was noted that tumor marker chromogranin A was increasing in December 2010 and the patient was complaining about recurrent abdominal pain. SSTR-PET/CT with [^{68}Ga]DOTA-Tyr3-octreotide PET/CT ([^{68}Ga]DOTATOC) was performed and demonstrated a tumor in the terminal ileum associated with an enlarged parapancreatic lymph node (Fig. 1B). No other suspicious lesions were found. A radical right hemicolectomy encompassing lymphadenectomy was performed in February 2011, using gamma probe detection after [^{68}Ga]DOTATOC was given as tracer. The gamma probe located the single peripancreatic lymph node during surgery.

Pathology revealed a well-differentiated NET from the ileocecal valve (size 10 mm, Fig. 3A) with a single lymph node metastasis (Fig. 3B). The final Union for International Cancer Control (UICC) staging was pT2, pN1, pM0, G1, L0, V0, R0, pN0. The immunohistology was positive for chromogranin A, synaptophysin

(Fig. 4C), somatostatin receptor 2A and CDX-2, but negative for TTF1 (Fig. 5C) indicating an intestinal origin without any relation to the TC removed 4 years earlier[6,7].

Discussion

This case report describes the occurrence of two non-related well-differentiated NETs in a single patient detected within 4 years. The first NET demonstrated pathologic features of a pulmonary TC and the second, also a well-differentiated NET, originated from the ileocecal valve. This second NET was detected by [^{68}Ga]DOTATOC. The intraoperative exertion of a gamma probe often results in the extension of the planned surgical procedure, especially in an extended lymph node resection. It permits the identification of previously occult metastases and the localization of hidden lymphatic lesions[8,9]. Although little is known about development of second NETs in patients without multiple endocrine neoplasia syndromes, follow-up of patients with NETs using SSTR-PET/CT will help in the detection of tumor recurrence or other non-related NETs[10]. In our patient, the second NET was only detected by a somatostatin receptor PET/CT 4 years after curative surgery of the TC of the left lung. Due to a slow proliferation rate of this second NET (Fig. 5A), it can be assumed that this tumor was already present in 2007, however [^{18}F]FDG/PET usually does not detect GEP-NETs with a low proliferation rate. In our case, after removal, we performed only local staging using thorax CT and bronchoscopy.

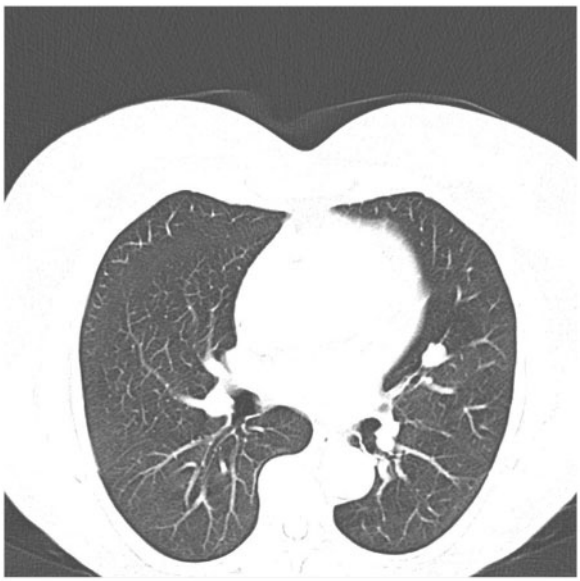

Figure 2 **Thoracic CT (lung window).**

If the NET diagnosis is discovered after surgery, similar to GEP-NETs, systemic molecular imaging ([^{68}Ga]SSTR-PET/CT or octreotide scintigraphy) must be performed postoperatively. This rules out occult metastases and provides reference imaging for further comparative follow-up studies. However, because of the limited availability of this molecular imaging technique, it does not allow routine staging after surgery. In our opinion, this imaging procedure should be reserved for when increasing levels of biomarkers or clinical symptoms indicate a recurrence.

[^{68}Ga]SSTR-PET/CT has excellent sensitivity[10,11]. If the NET diagnosis is known or presumed

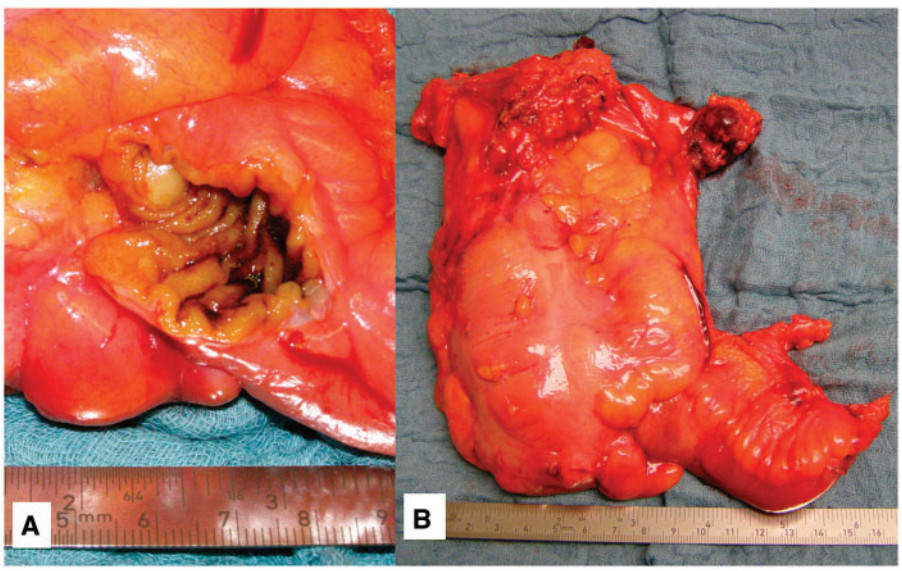

Figure 3 **(A) NET of the ileum (1.0 cm) after ileotomy. (B) Right hemicolectomy compound with a single lymph node metastasis.**

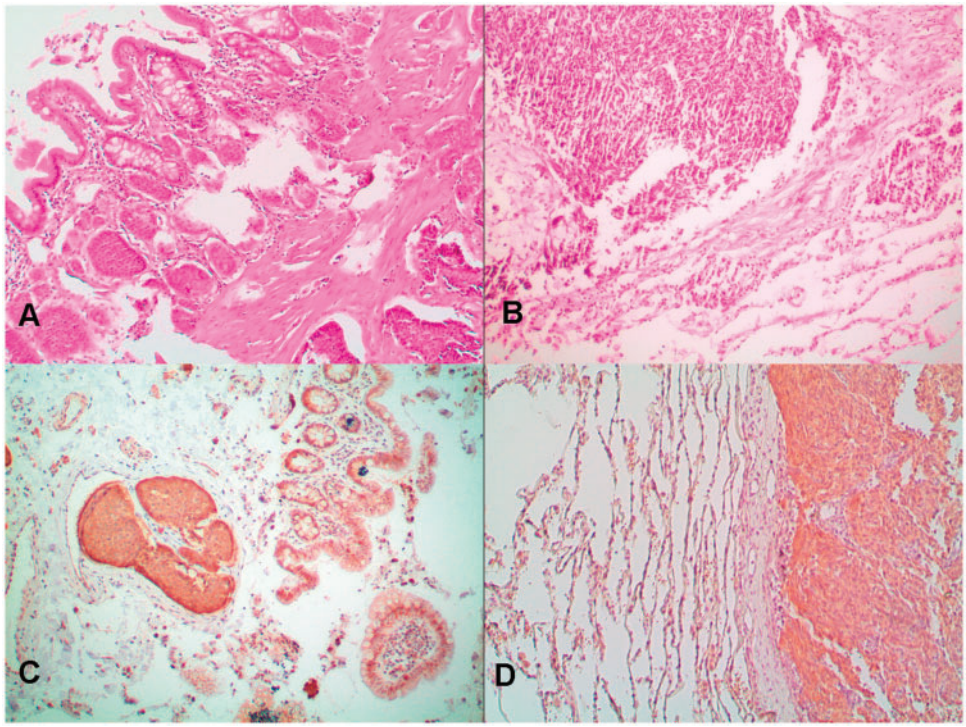

Figure 4 **(A) Hematoxylin–eosin stained light microscopy: ileum. (B) Hematoxylin–eosin stained light microscopy: lung. (C) Synaptophysin: ileum. (D) Synaptophysin: lung.**

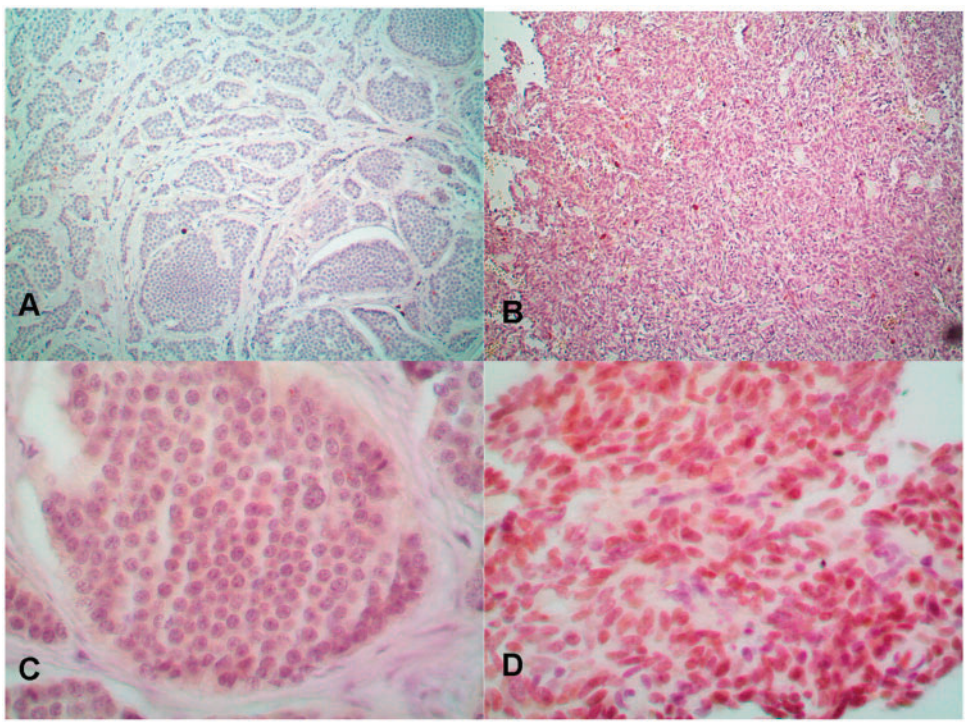

Figure 5 **(A) MIB1: ileum. (B) MIB1: lung. (C) TTF-1: ileum. (D) TTF-1: lung.**

preoperatively, accurate preoperative staging and a postoperative comparative study from the resection results are enabled through this imaging technique.

This case report illustrates the clinical utility of SSTR-PET/CT for the detection and follow-up of patients with NETs of the lung and gastroenteropancreatic system.

Acknowledgments

We thank Maria Spiegler for editorial assistance.

References

[1] Gustafsson BI, Kidd M, Chan A, Malfertheiner MV, Modlin IM. Bronchopulmonary neuroendocrine tumors. Cancer 2008; 113: 5–21. doi:10.1002/cncr.23542.

[2] Du EZ, Goldstraw P, Zacharias J, *et al.* TTF-1 expression is specific for lung primary in typical and atypical carcinoids: TTF-1-positive carcinoids are predominantly in peripheral location. Human Pathol 2004; 35: 825–31. doi:10.1016/j.humpath.2004.02.016.

[3] Lin X, Saad RS, Luckasevic TM, Silverman JF, Liu Y. Diagnostic value of CDX-2 and TTF-1 expressions in separating metastatic neuroendocrine neoplasms of unknown origin. Appl Immunohistochem Mol Morphol 2007; 15: 407–14.

[4] Aydin E, Yazici U, Gulgosteren M, *et al.* Long-term outcomes and prognostic factors of patients with surgically treated pulmonary carcinoid: our institutional experience with 104 patients. Eur J Cardiothorac Surg 39: 549–54. doi:10.1016/j.ejcts.2010.08.010.

[5] Ambrosini V, Castellucci P, Rubello D, *et al.* ^{68}Ga-DOTA-NOC: a new PET tracer for evaluating patients with bronchial carcinoid. Nucl Med Commun 2009; 30: 281–6. doi:10.1097/MNM.0b013e32832999c1.

[6] Liu WH, Wang DG. Apoptosis regulating genes in neuroendocrine tumors. Histol Histopathol 2000; 15: 851–9.

[7] Srivastava A, Hornick JL. Immunohistochemical staining for CDX-2, PDX-1, NESP-55, and TTF-1 can help distinguish gastrointestinal carcinoid tumors from pancreatic endocrine and pulmonary carcinoid tumors. Am J Surg Pathol 2009; 33: 626–32.

[8] Adams S, Baum RP. Intraoperative use of gamma-detecting probes to localize neuroendocrine tumors. Q J Nucl Med 2000; 44: 59–67.

[9] Freesmeyer M, Wurst C, Uberrueck T, *et al.* Intraoperative identification of a neuroendocrine tumour diagnosed by ^{68}Ga-DOTATOC PET but undetectable by surgical palpation or conventional imaging. Nuklearmedizin 2009; 48: N50–1.

[10] Al-Nahhas A, Win Z, Szyszko T, *et al.* Gallium-68 PET: a new frontier in receptor cancer imaging. Anticancer Res 2007; 27: 4087–94.

[11] Jindal T, Kumar A, Venkitaraman B, Dutta R, Kumar R. Role of (68)Ga-DOTATOC PET/CT in the evaluation of primary pulmonary carcinoids. Korean J Internal Med 25: 386–91. doi:10.3904/kjim.2010.25.4.386.