Letter to the Editor

Metachronous ovarian carcinoma in patient with gastric neuroendocrine tumor diagnosed by ^{68}Ga-DOTANOC and ^{18}F-FDG positron emission tomography/computed tomography

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Introduction

Neuroendocrine tumors (NETs) are a rare heterogeneous group of tumors arising from neuroendocrine cells present at various locations (1). They are frequently associated with synchronous or metachronous malignancies, with rates of associated second primary malignancies (SPMs) reaching 55% (2). The occurrence of SPMs may be due to genetic susceptibility (such as multiple endocrine neoplasia type 1 and 2), delayed cancer treatment, or common etiological factors (such as smoking and alcohol) (3). Metachronous SPMs may also be a consequence of neoplasia-promoting secretory products affecting different types of cells (4).

Herein, we report a rare case of a 77-year-old woman with biopsy-proven localized gastric body NET (Grade 1), who deferred treatment and was diagnosed 6 years later with metachronous ovarian carcinoma with disseminated metastases on positron emission tomography/computed tomography (PET/CT) using two different tracers: [^{68}Ga-DOTA,1-Nal^{3}]-octreotide (^{68}Ga-DOTANOC) and ^{18}F-fluorodeoxyglucose (^{18}F-FDG).

Case presentation

All procedures performed in this study were concordant with the ethical standards of the institutional and/or national research committee(s) and the Declaration of Helsinki (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 77-year-old woman initially presented with abdominal discomfort and distension. Upper gastrointestinal endoscopy (UGIE) revealed atrophic gastritis with multiple small polyps (around 5–10 mm) in the fundus and body, suggestive of carcinoids. Baseline CT of the abdomen showed multiple subcentimetric round, enhancing mural, intraluminal-based lesions in the stomach. Biopsy revealed a Grade 1 NET which was positive for synaptophysin and chromogranin, with cell proliferation marker Ki-67 <2%. The patient was advised to undergo surgery but elected to defer. A follow-up CT of the abdomen 4 years later revealed no significant change in the size, number, or morphology of the stomach lesions. The patient then presented with umbilical swelling 6 years after her initial diagnosis of gastric NET. A CT of the abdomen showed multiple intensely enhancing polypoidal masses in the stomach, a solid mass in the right adnexa, an umbilical nodule, multiple pelvic lesions and nodular thickened anterior peritoneal fold, and swelling of the bilateral inguinal lymph nodes. The patient was diagnosed with metastatic NET and started on octreotide (30 mg) by injection. Serum chromogranin A levels were 68 (<76).

After 6 months, ^{68}Ga-DOTANOC PET/CT was performed to evaluate the patient's status and restage the disease, with consideration of ^{177}Lu-peptide receptor radionuclide therapy (^{177}Lu PRRT) for metastatic NET. The PET/CT imaging showed DOTANOC avid arterially

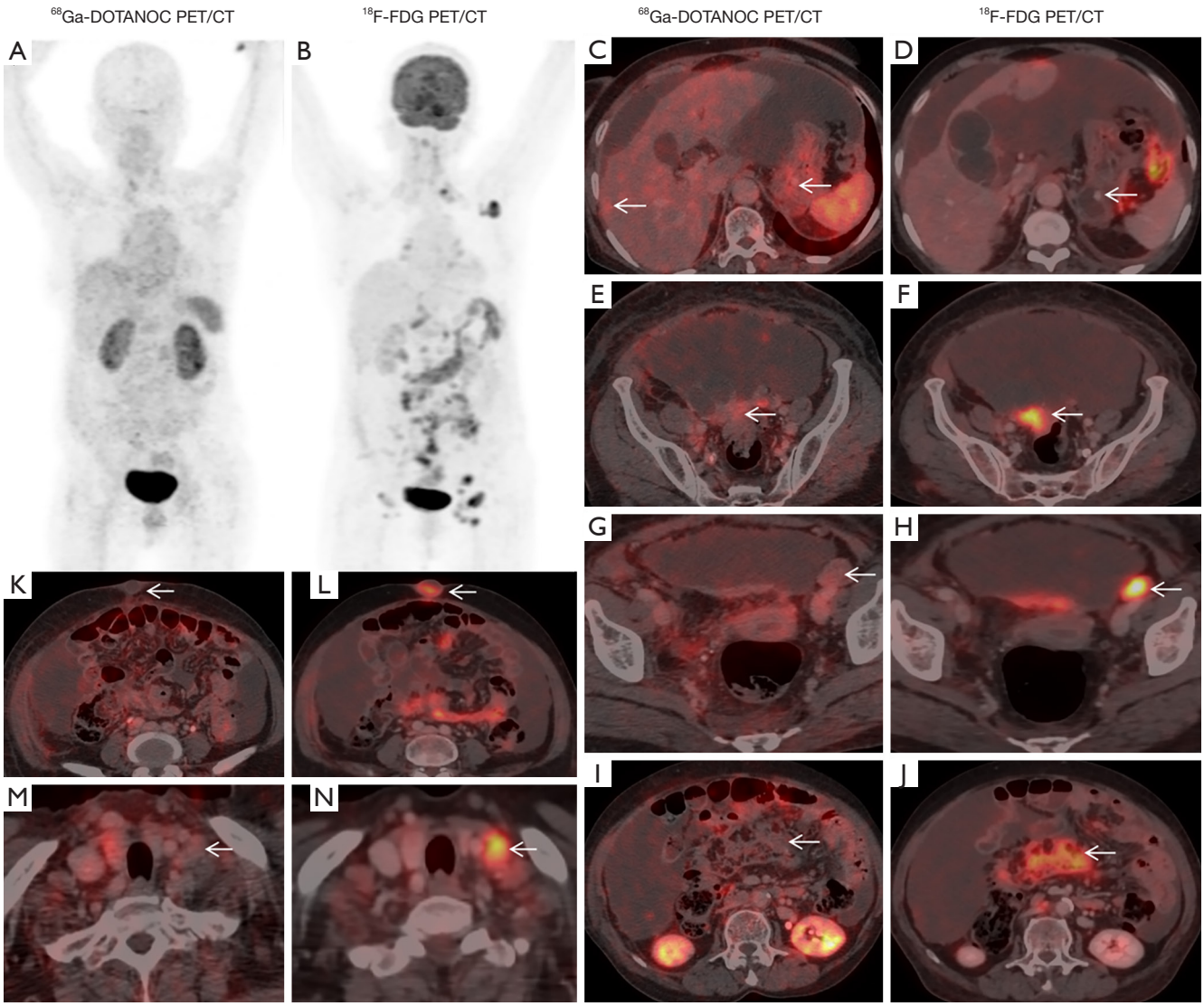

Figure 1 Images from ^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT. (A,B) Show ^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT maximum intensity projection images, respectively. ^{68}Ga-DOTANOC and corresponding ^{18}F-FDG PET/CT transaxial fused images primarily reveal subcentimetric nodular arterially enhancing lesions in the stomach; however, liver lesions also show mild DOTANOC uptake (SUVmax 2.6) and no FDG uptake (C,D) consistent with well-differentiated gastric NET with liver metastases. Increased FDG uptake with no significant DOTANOC uptake is apparent in the following: multiloculated solid cystic right adnexal lesion (E,F); omental caking; mesenteric fat stranding (I,J); diffuse peritoneal thickening; umbilical (Sister Mary Joseph's) nodule (K,L); and multiple abdominal-pelvic (G,H), left axillary and left supraclavicular lymph nodes (M,N). Associated gross ascites in the abdomen and pelvis, and mild bilateral pleural and pericardial effusion are also apparent. In view of the differential uptake, metachronous ovarian carcinoma with metastases is suspected. ^{68}Ga-DOTANOC, [^{68}Ga-DOTA,1-Nal3]-octreotide; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; SUVmax, maximum standardized uptake value; NET, neuroendocrine tumor.

enhancing nodular lesions in the stomach [maximum standardized uptake value (SUVmax) 2.6], mildly DOTANOC avid enhancing lesions in both lobes of the liver (SUVmax 2.5), a mild DOTANOC avid solid cystic lesion in the right adnexal region (identified as a potential second primary), with prominent left supraclavicular, abdomino-pelvic, and bilateral inguino-femoral lymph nodes, omental and peritoneal thickening, and umbilical

lesion, scan features indicative of NET with presence of metastases (*Figure 1*).

As the ^{68}Ga-DOTANOC PET/CT showed low tracer uptake in the lesions, an ^{18}F-FDG PET/CT scan was acquired. The ^{18}F-FDG PET/CT showed non-FDG avid nodular arterially enhancing subcentimetric lesions in the intramural aspect, predominantly in the fundus region (the largest measuring 9 mm) with a few nonmetabolic subcentimetric arterially enhancing lesions in both lobes of the liver (*Figure 1D*). In addition, a large multiloculated solid cystic lesion measuring 5.0×4.8 cm was observed in the right adnexal region closely abutting the rectal wall (*Figure 1F*), with increased metabolic activity in the solid component (SUVmax 6.3). A discrete FDG avid heterogeneously enhancing solid cystic lesion was noted in the umbilicus measuring 1.8×2.6 cm with SUVmax 4.4 (Sister Mary Joseph's nodule, *Figure 1L*). Finally, FDG avid omental caking, mesenteric fat stranding and diffuse peritoneal thickening with multiple bowel wall deposits, and multiple abdominal-pelvic, left axillary, and left supraclavicular lymph nodes (*Figure 1H,1J,1N*) were noted, associated with gross ascites in the abdomen and pelvis and mild bilateral pleural and pericardial effusion.

Combining the results of the ^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT imaging, the subcentimetric nodular arterially enhancing lesions in the stomach as well as the liver lesions showed mild DOTANOC uptake and no FDG uptake, which was consistent with well-differentiated gastric NET with liver metastases. Furthermore, increased FDG uptake with no significant DOTANOC uptake was noted in the multiloculated solid cystic right adnexal lesion, omental caking, mesenteric fat stranding, diffuse peritoneal thickening, umbilical nodule, and multiple abdominal-pelvic, left axillary, and left supraclavicular lymph nodes. In view of the differential uptake (refer to *Figure 1*), metachronous ovarian carcinoma with metastases was suspected.

Patient serology showed that cancer antigen 125 (CA-125) was markedly elevated (1,396.6 U/mL, normal range, 0–35 U/mL) and ascitic fluid cytology was positive for malignancy. The cytology cell block preparation of ascitic fluid was indicative of metastatic adenocarcinoma (probable genitourinary origin). Immunohistochemistry indicated that the neoplastic cells were positive for CK7 and WT1, and negative for CDX2 and chromogranin.

Therefore, the final diagnosis of our patient was well-differentiated gastric body NET (Grade 1) with liver metastases and metachronous ovarian carcinoma with disseminated metastases.

Discussion

Frequently, NETs are associated with synchronous or metachronous malignancies. In their meta-analysis, Habal *et al.* (2) reported NET-associated SPMs in 17% of a cohort of 5,280 patients. This rate is more than double that observed for non-neuroendocrine primary malignancies (5). Prommegger *et al.* (6) reviewed 14 patients with NET and SPM, of whom 5/14 (36%) were diagnosed synchronously and 9/14 (64%) were diagnosed metachronously. The great majority of SPM cases (12/14, 86%) were localized in the gastrointestinal (GI; 7/14, 50%) or genitourinary (5/14, 36%) tracts, and only 1 case of synchronous ovarian carcinoma was reported in this study. Synchronous malignancies with NETs are more common than metachronous cases; however, metachronous malignancies can occur anywhere, and typically present 1–7 years after the NET is diagnosed (7,8). In an autopsy-based study, Pearson and Fitzgerald were the first to demonstrate the association between NETs and increased incidence of SPM, and found that 23% of carcinoid patients harbor SPMs, predominantly arising from the GI tract (15.8% of patients) (9).

Kamp *et al.* (10) published a large population-based study including 459 Dutch patients with GI and pancreatic NETs, and found that 13.7% of patients had a second malignancy, and the presence of an NET was associated with increased incidence of synchronous malignancies. They also reported that the incidence of synchronous, but not metachronous, malignancies was increased in patients with NET of the GI tract and pancreas.

In their recent retrospective review of 30 patients, Verrico *et al.* (11) reported that 11.4% of patients with NET developed additional malignancies. Metachronous lesions accounted for 66.7% of these malignancies (20/30 patients), and the most common locations reported were the colon (15%) and the pancreas (25%). The authors found an association between prostate neoplasia and NET of the pancreas in 2 patients, and reported that only 2 patients (6.7%) had secreting NETs (both in the metachronous group). However, no patients with NET and metachronous ovarian carcinoma were identified in their study. The authors concluded that additional GI malignancies were frequently synchronous, but additional non-GI malignancies were likely to be metachronous.

Kauffmann *et al.* (12) reported an incidence rate for additional cancers in patients with pancreatic or GI NET of 26%, 15% in patients with pancreatic NET, and 34% in patients with GI NET.

Hemminki and Li observed an increased risk of developing metachronous SPM subsequent to the diagnosis of non-Hodgkin lymphoma or an NET in the endocrine glands, small intestine, skin, and prostate in men, and subsequent to the diagnosis of melanoma, leukemia, or cancers of the small intestine, upper aerodigestive tract, colon, urogenital system, and breast in women (13).

Many hypotheses have tried to explain the association between NETs and SPMs: field-effect theory (i.e., common carcinogenic effect stimulates growth of neuroendocrine and SPM cancer cells), a genetic predisposition, exogenous mitogenic effects of secretory products from a primary tumor causing neoplastic transformation [secretory products include various neuropeptides such as gastrin, cholecystokinin (CCK), bombesin, and so on, which have specific growth factor properties, and non-neuropeptide growth factors such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor (TGF)], or a combination of all these factors (4,14).

While there have been a few interesting case reports of NET-associated SPMs (8-17), the majority of these studies have described the association between synchronous malignancies and NETs. Metachronous ovarian carcinoma, as a secondary cancer in patients with biopsy-proven, well differentiated gastric NET, is very rare.

This case highlights the importance of 2 commonly used radionuclide PET tracers in the diagnosis of NET, as well as in decision making regarding PRRT therapy with 177-Lu, 90-Y, or 225-Ac. The differential uptake of tracers reported in this case study was indicative of the development of a metachronous SPM in our patient. We were able to arrive at a diagnosis non-invasively using a combination of ^{68}Ga-DOTANOC PET/CT and ^{18}F-FDG PET/CT, which was later confirmed with ascitic fluid cell cytology and a biochemical tumor marker.

In conclusion, every NET should be regarded as an index tumor and follow-up with thorough investigation, mainly of the GI and genitourinary tracts, is recommended.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-713/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and the Declaration of Helsinki (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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