



CASE REPORT

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Unusual Metastasis of Neuroendocrine Tumors Seen in 68Ga-DOTATOC PET/CT: Cases Report and Literature Review

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Introduction

Neuroendocrine tumors (NET) are a group of heterogeneous malignancies derived from the neuroendocrine system which more frequently develop in the small bowel, pancreas, stomach and colorectal [1]. The World Health Organization uses cellular proliferation markers as the mitotic count and the nuclear protein Ki-67 for the staging of the neuroendocrine tumors, classifying them in well differentiated tumors of low (G1) or intermediate (G2) grades and poorly differentiated tumors of high grade (G3) [2].

The main treatment of the NET is surgery regardless of the origin of the tumor, however, the localization of distant metastasis can change the intention of the surgical procedure from curative to palliative [3]. It has been documented that 20% of the patients have metastatic disease at the moment of the diagnosis and in 50% of those patients the primary tumor is not identified in initial studies. The most frequent sites of NET's metastasis are the liver, the peritoneum, the lungs and the bones [4].

Positron emission tomography/ computed tomography (PET/CT) with Gallium 68 bound to the chelator agent DOTA and somatostatin analogues (TOC, NOC, TATE) is a molecular diagnostic image widely used in the actuals diagnostic, staging and following algorithms of the NET given the capacity of detect the NET's characteristic high somatostatin receptor expression, reaching a respective sensibility and specificity of 93 and 91% for the detection of the primary tumor and 94% and 89% for the detection of recurrence [5], showing a better capability of detecting metastasis that aren't detected by other images modalities such as the CT or MRI, modifying the course of treatment in around 60% of all the patients [4,5].

Unusuals metastasis of the NETs have been reported in retrospective studies with an incidence of 2,25%, being the heart, breasts, retro-orbital region, uterus, skin, intramuscular, spleen, testicles and the seminal vesicles some of the reported sites [6].

In this article we show two cases of unusual metastasis detected with PET/CT with 68Ga-DOTANOC which initially were thought to be synchronous tumors. All the studies were made according to the institutional protocol, injecting 4 mCi of the radiotracer

and approximately 45 minutes later the images were acquired in a hybrid PET/CT detector siemens Biograph.

Description of the Cases

Case 1

A 59-years-old female with a 17-years history of a nonfunctional pulmonary neuroendocrine tumor that compromised the right lung's middle and lower lobes. The tumor had an initial histology that showed a typical carcinoid tumor with a size of 3 cm with Ki67 2%, mitosis 0-1x10 HPF and the immunohistochemistry was positive to TTF1 and chromogranin. The patient had a scintigraphy with 99mTc-HYNITOC that showed multiple blastic bone lesions with high expression of somatostatin receptors suggestive of metastasis and increased expression of somatostatin receptor in the pancreas. ⁶⁸Ga-DOTANOC PET/CT (figure 1) was performed for a better evaluation of the extent of the disease and to evaluate the possibility of administering therapy with Lutetium177, and showed tumor-free lung's surgery area, multiple lymph nodes at the cervical, perigastric, peripancreatic, splenic hilum levels with high expression of somatostatin receptor (krenning score 4/4), also paravertebral soft tissue, bone lesions; all suggestive of metastasis, and kidney and brain lesions, the latter studied with brain MRI and CT which was characterized as a meningioma. The pancreatic increased expression of somatostatin receptor with no anormal morphologic finding on low dose CT was initially considered to be a metachronous tumor and was referred to a biopsy through endoscopic ultrasound which showed compromise by neuroendocrine tumor with Ki67 of 1%, negative to P16, CDX2 and positive to TTF1 and chromogranin, showing that the pancreatic lesions expressed the marker TTF1 which is considered a marker of lung primary and being finally categorized as a metastasis instead of a new tumor.

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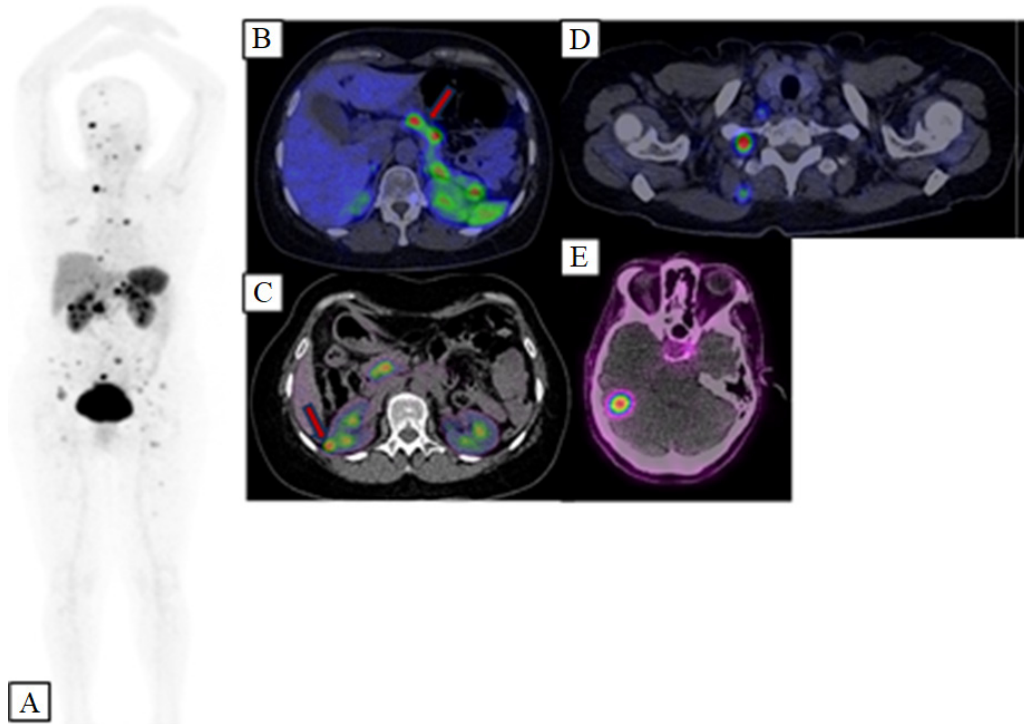


Figure 1: ^{68}Ga -DOTANOC PET/CT. A: MIP (Maximum intensity projection) multiple bone lesions are visualized with high overexpression of somatostatin receptors (SUVmax: 17.4, Krenning 4). B: Hyperuptake foci are observed in the head, body and tail of the pancreas (SUVmax: 10.8, Krenning 3). C: At the outer edge of the lower pole of the right kidney, a nodular image with overexpression of somatostatin receptors can be seen (SUVmax: 17.8, Krenning 4). D: right paravertebral nodes (SUVmax: 17.4). E: lesion with overexpression of somatostatin receptors in the right occipital region (SUVmax: 13.2, Krenning 3)..

Case 2

A 51-years-old female with a clinical history of a neuroendocrine tumor of the colon which was diagnosed a year ago. The initial histology biopsy of a sigmoid polyp showed a well differentiated neuroendocrine tumor grade 2, Ki67 4%, mitotic index of 0 x 10 HFC, positive to chromogranine and synatophysin and negative for PAX 8. As an initial treatment she was taken to a right hemicolectomy, the histopathology of the surgical specimen showed a neuroendocrine tumor of the cecum with a tumoral size of 3x3cm with a Ki67 4%, mitotic index of 2 x 10 HFC and immunohistochemistry showed positive to chromogranine, synatophysin, CD56, cytokeratin, AE1, AE3,

CDX2 and negative to TTF1, also there was metastatic foci in the ileum, peritoneum and ovaries. ^{68}Ga 68-DOTANOC PET/CT was subsequently performed (figure 2), which showed high expression of somatostatin receptors in the adjacent zone to the surgical bed suggestive of tumor relapse, and also in the liver and in the mesentery suggestive of metastases, some nodules were also evident in both breasts with low expression of somatostatin receptors (krenning score 1-2/4). A biopsy was performed showing the same immunohistochemical profile and histopathology of the cecum's tumor and confirming metastasis in the breasts of the neuroendocrine tumor.

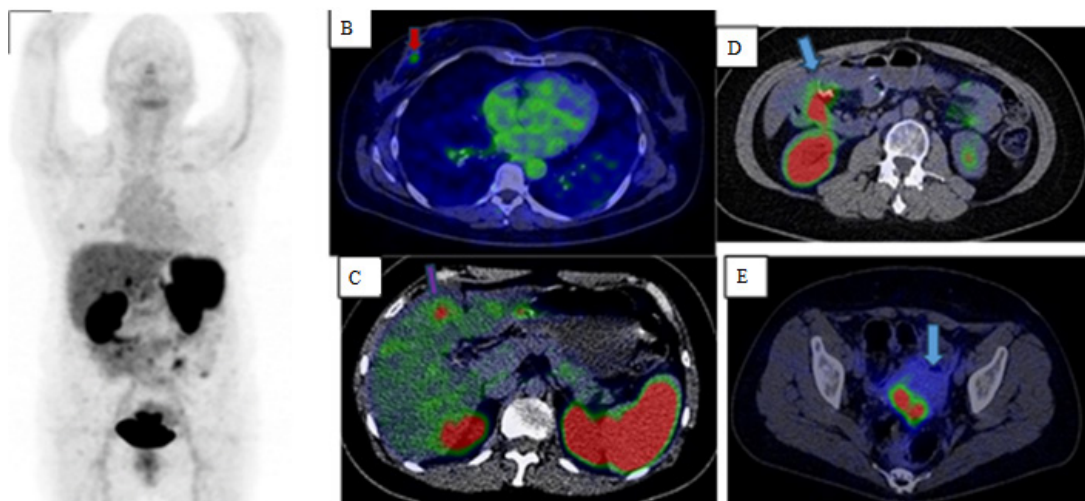


Figure 2: ^{68}Ga -DOTANOC PET/CT. A: MIP (Maximum intensity projection). B: Right breast nodule with slight overexpression of somatostatin receptors (SUVmax: 1.7, Krenning 2). C: liver lesions. D: changes of right hemicolectomy with high expression of somatostatin receptors, Krenning 4. E: hyperuptake in the uterus.

Discussion

Lungs are the second most common site, after the gastrointestinal, for the localization of primary neuroendocrine tumor and represent around 30% of all NETs [7]. The pulmonary NETs are a family of four different subtypes, typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC) and they are clinically categorized in three grades, low grade (TC), intermediate grade (AC) and high grade (LCNEC and SCLC) [8], the patient presented in the case 1 has a disease evolution of 17 years because her tumor was a typical carcinoid of low grade. Only 5 to 20% of the TC metastasize and the main sites for these metastases are the liver or the bone [9].

On the other hand gastroenteropancreatic represent the most common NET subtype, being 55-70% of all NET, and more specifically the pancreas is one of the most prevalent sites of primary NET, especially in the south American population [10] being that the main reason why it was initially proposed that the increased expression of somatostatin receptors in the pancreas corresponded to a metachronous tumor, however and even though the primary pancreatic NET doesn't have immunohistochemical specific markers [11] the lung's NET express TTF1, which is a protein presented in follicular cells of the thyroid and in the respiratory epithelial cells being involved in the regulation of surfactant, and its presence is a sign of pulmonary origin since no other NET express this marker [12] and for this reason the pancreatic lesions in this patient are finally considered a metastasis instead of a new tumor.

Secondary tumor to the pancreas are rare and the stomach is the main site that metastasize to the pancreas principally via direct dissemination, being the lung the second organ [13], according to our search in pubmed, scopus and science direct, there have been reports of cases in metastasis of pulmonary adenocarcinoma [14], small cell carcinoma [15], large cell carcinoma and squamous cell carcinoma [13] to the pancreas, but this is the first case published of a pancreatic metastasis of a typical carcinoid neuroendocrine tumor of the lung.

The breasts are an unusual site of metastasis with an incidence of 2% of all metastasis, even though the majority of the metastasis come from other primary tumors, mainly the contralateral breast, only 0,1% of the metastasis come from NETs. Distinguishing a NET's metastasis from a primary NET of the breast is a challenge, because the incidence of the latter is also approximately 2% [16-18].

Patients with a NET in which a lesion in the breast is documented for any imagenologic method, is essential a complementary histologic study, since the analysis of the estrogen's receptor and progesterone receptor is very useful to differentiate between metastasis from other organ's NET or breast's primary NET [19,20]. The first case of bilateral breast metastasis secondary to a NET was of duodenum, reported in 1996 by Hawley [12]. Until the date, it had been reported less than 15 cases with bilateral compromise of the breasts and a little more of 200 cases including unilateral compromise, in which the primary tumor was located, in frequency order, in the ileum, appendix, duodenum, pancreas, lung and the ovary [21-23].

Conclusion

⁶⁸Ga DOTANOC PET/CT is a nuclear medicine technique for the evaluation of patients with NETs, for initial staging, suspicion of relapse or progression of the disease or to evaluate the possibility of administering radiometabolic therapy with ¹⁷⁷-Lu-dotapeptides, however, through this technique it is not possible to differentiate between metastatic lesions or a second tumor, which is why histopathological evaluation is necessary in these cases to determine its etiology with certainty.

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