The pitfalls of ^{68}Ga-DOTATATE Imaging. A case report

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Abstract

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors exhibiting diverse clinical and biological characteristics. Despite the diverse nature of these neoplasms, they share common molecular targets which can be used with the help of nuclear medicine techniques for both imaging and therapy.

^{68}Ga-DOTATATE was approved as a PET tracer by the FDA in June 2016 and allows whole-body imaging of cell surface expression of somatostatin receptors (SSTRs). Since then it has become a functional imaging technique that is a mainstay in the initial diagnostic work-up and staging of NETs.

This imaging technique, however, has demonstrated pitfalls which need to be considered. Physiological uptake of ^{68}Ga-DOTATATE occurs in a variety of tissues including the spleen, adrenal glands, kidneys, pituitary glands, liver, salivary glands and thyroid gland. SSTRs are also expressed on leucocytes and macrophages, resulting in inflammatory processes sometimes being misidentified with this imaging technique.

We present a case with a radiological image that could be suggestive for a primary neuroendocrine tumor with desmoplastic reaction. ^{68}Ga-DOTATATE showed no remarkable uptake in the central mass, but only faint uptake in the surrounding desmoplastic reaction. The final diagnosis on histological examination, was an inflammatory reaction surrounding biliary pigment. (Acta gastroenterol. belg., **2023**, 86, **92-94**).

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors exhibiting diverse clinical and biological characteristics. The most common primary sites are the gastro-intestinal and respiratory tract.

NENs are classified according to grade of differentiation into poorly differentiated neuroendocrine carcinoma's with an aggressive behavior with a high Ki-67 index (often above 70%) and well differentiated neuroendocrine tumors (NET) subdivided in grade 1, 2 and 3 according to the Ki-67 index (< 3%, in between 3 and 20%, >20% respectively) (1).

The diagnosis involves the use of functional imaging techniques, 18F-FDG (fluorodeoxyglucose)- and 68Ga-DOTATATE PET(CT).

We present a case of a patient with a chance finding suggestive of metastatic peritoneal disease during a work-up for recurrent cystitis in which final diagnosis ended up being benign.

Case

A 77-year-old patient was referred to us by the urologist in May 2020 with a chance finding suggestive of metastatic peritoneal disease during a work-up for recurrent cystitis.

Relevant past medical history included an abdominal hysterectomy at the age of 40 and more recently, a laparoscopic cholecystectomy for symptomatic gallstones three months previous to referral. The operation was performed elsewhere, and was complicated by post-operative fever requiring readmission and intravenous antibiotics.

The patient initially presented with ongoing right lateral abdominal pain for a few months. In addition to the pain, she reported weight loss, alternating bowel movements and night sweats. Clinical examination was largely unremarkable, and specifically no suggestion of any abdominal mass.

Laboratory findings including tumor markers were all within the normal range - CEA 1.56 mg/L (normal for non-smokers 0 - 3.8 µg/L for smokers: 0 - 5.5 µg/L), CA 19.9 23.7 kU/L (normal 0-34 kU/L), CA 125 28.5 kU/L (normal 0-35 kU/L), Alfa-foetoprotein 3.66 mg/L (normal 0-7mg/L).

The initial abdominal CT scan in May 2020 noted presence of suspected peritoneal or omental lesions with a maximum diameter of 26mm, in absence of a primary tumor.

She underwent a ^{18}F-FDG- PET scan in May 2020 on which multiple hypermetabolic peritoneal lesions were described. With the absence of visualization of a primary tumor and an intense FDG- avid cartwheel lesion in the right abdominal fossa ,see Figure 1a-c, the possibility of a neuroendocrine tumor was suggested.

Additionally she underwent a gastroscopy and colonoscopy which were both negative and urinary 5-HIAA and serum chromogranin were within normal ranges.

Because the presence of the cartwheel lesion and the clinical symptoms (abdominal pain, weight loss and frequent softer bowel habit) arose the suspicion of a neuroendocrine tumor, the patient underwent a further ^{68}Gallium DOTATOC scan in June 2020 on which a 2 cm mass was visualized in the pelvic small bowel. This mass

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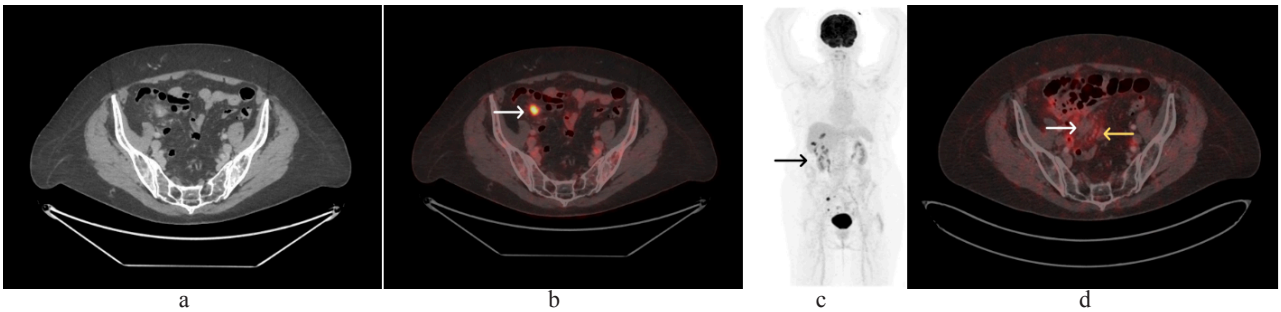

a b c d

Figure 1a-d. — CT and fused ^{18}F-FDG PET/CT images of the pelvis (1a-b), maximal intensity projection (MIP, 1c) showing and intens ^{18}F-FDG- avid cartwheel lesion in the right abdominal fossa (black arrow) and fused 68Ga-DOTANOC PET/CT image (1d) showing no SSR expression in the central mass (white arrow) and faint uptake in the surrounding desmoplastic reaction (yellow arrow).

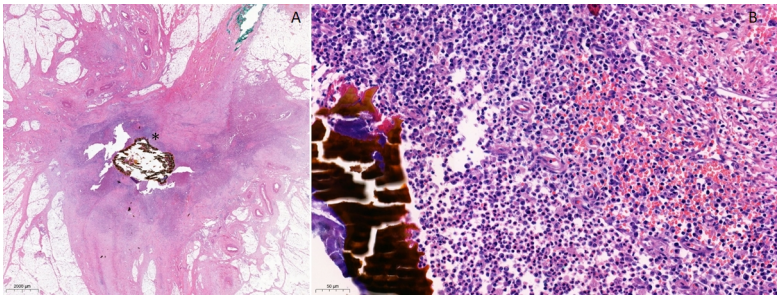

Figure 2. — A. Adipose tissue with brown-yellow bile pigment surrounded by a dense inflammatory reaction and fibrosis. B. Higher magnification of area marked with an asterisk. Bile and a dense inflammatory infiltrate with numerous plasma cells, lymphocytes, macrophages and focal collections of polymorphonuclear cells, surrounded by fibrotic tissue.

showed weak SSR expression which could not rule out a neuroendocrine lesion, see Figure 1d. There were no other suspect lesions seen on the scan

The case was discussed on a multidisciplinary meeting and subsequently the patient underwent laparoscopic removal of 30 cm of her small bowel in August 2020. The pathology report of the resected specimen however did not confirm the diagnosis. The small bowel itself was completely normal and the surrounding mesentery showed a focus of inflammation with abscess formation and fibrosis surrounding biliary pigment, see Figure 2. Eleven lymph nodes were resected and showed no sign of malignancy. In hindsight, the patient could clearly link the onset of the right lateral pain to the time of the laparoscopic cholecystectomy in early 2020. Despite no specific mention of leakage of bile during the procedure, histological findings lead us to draw the conclusion of a biliary leak as a complication post gallbladder surgery.

Discussion

The most common functional imaging techniques used for the diagnosis of NETs are the 18F-FDG- and 68Ga-DOTATATE PET(CT). The role of 18F-FDG-PET is well established in poorly differentiated NEC, but less well documented in well differentiated NET while the use of 68Ga-DOTATATE PET(CT) appears to be mainly restricted to well differentiated NET and rarely advocated for NEC (2).

^{68}Ga-DOTATOC is a commonly used PET tracer for imaging neuroendocrine tumors. Molecular imaging targeting somatostatin receptors (SSTR) has allowed for more specific NET detection. Ga-^{68} DOTATATE PET/CT has an estimated sensitivity of 90.9% (95% confidence interval, 81.4%-96.4%), and specificity of 90.6% (95% confidence interval, 77.8% - 96.1%) (3).

Detection of a cartwheel lesion is highly suspicious for a desmoplastic reaction linked to the presence of a small bowel neuroendocrine tumor. This in combination with weak uptake on ^{68}Ga-DOTATOC therefore prompted the decision for surgical intervention. Urinary 5-HIAA and serum chromogranin may be normal in the non-metastatic setting. Uptake on ^{18}F-FDG- PET scan is not expected in these lesions however, because neuroendocrine tumors of the small bowel are usually low grade NET, typically only showing uptake on ^{68}Ga-DOTATOC (4).

Recent literature has shown that uptake on ^{68}Ga-DOTATOC occurs more frequently than first expected in benign lesions. Somatostatin receptors are overexpressed not only in the neuroendocrine system but also in other tissues. Physiological, anatomical variants and benign tumors expressing these receptors may cause false positive results. A detection of up to 14% of benign lesions has been reported in studies, accessory spleen and

bone hemangiomas being the most known (5). A recent case series describes 5% of benign lesions, divided in anatomic and physiologic variants (45%), osteoblastic activity (11%), inflammatory activity (33%) and benign non-neuroendocrine tumors (11%) (6). These pitfalls are becoming more common knowledge and the appreciation of radiotracer uptake together with the morphological appearance in the CT component enables differential diagnosis. Confrontation is of paramount importance to avoid diagnostic errors, false positives or false negatives. White blood cells including leukocytes and macrophages express SSTR2. Inflammatory uptake is invariably low or very low grade and is commonly seen in reactive lymph nodes, prostatitis or post–radiation therapy change, although any inflammatory process may demonstrate some activity (7). Inflammatory and infectious processes are known to show enhanced uptake on ^{18}F-FDG- PET/CT (8). The combination of findings on ^{18}F-FDG- PET/CT and ^{68}Ga-DOTATOC together with the onset of the clinical picture after the cholecystectomy could have guided us to the eventual diagnosis of a biliary leak as a complication post gallbladder surgery.

Conclusion

We describe a case of a patient who presented with abdominal pain and was suspected to have a small bowel neuroendocrine tumor with desmoplastic reaction. CT scan showed a cartwheel lesion and both ^{68}Ga-DOTATATE and ^{18}F-FDG- PET/CT showed tracer uptake. The final diagnosis was a fibro-inflammatory reaction surrounding bile. The patient had undergone a laparoscopic cholecystectomy recently. In literature, a detection of up to 14% of benign lesions has been reported in studies with ^{68}Ga-DOTATATE, including inflammatory reactions. Inflammatory and infectious processes are known to show enhanced uptake on ^{18}F-FDG- PET/CT. Clinical evaluation and a detailed medical history, in combination with appreciation of radiotracer uptake together with the morphological appearance in the CT component enables differential diagnosis.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Notes on patient consent

Patient consent was obtained for the publication of this case report.

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