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Case Report

Ovarian neuroendocrine tumor metastasis on DOTATATE PET/CT ☆,☆☆

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ABSTRACT

This case report follows a 63-year-old female patient with a history of a gastroenteropancreatic (GEP) neuroendocrine tumor of the terminal ileum who developed ovarian metastasis and later progressed to peritoneal carcinomatosis. The patient was found to have worsening metastasis on CT that was subsequently confirmed with (^{68}Ga)-DOTATATE PET/CT imaging. This case outlines the rare metastatic nature of a primary ileal neuroendocrine tumor and emphasizes the efficacy of (^{68}Ga)-DOTATATE PET/CT imaging in the localization, progression, and treatment of neuroendocrine metastatic disease.

Introduction

Neuroendocrine tumors (NETs) are rare neoplastic growths that originate from the cells of the neuroendocrine system. These cells share properties of both nerve and endocrine cells and are responsible for hormone production, secretion, and regulation across various organs. NETs are diverse and can present with wide-spread clinical syndromes mediated by excessive hormone secretion. The most common neuroendocrine neoplasms are those of gastroenteropancreatic (GEP) and pulmonary origin. Immunohistochemistry evaluation of cellular differentiation is used to characterize NET's into slow-growing, low-grade tumors or aggressive, high-grade tumors with elevated risk of metastasis. This case report describes a 63-year-old woman who developed ovarian and later peritoneal metastasis from terminal ileum neuroendocrine primary. Ovarian metastasis of primary GEP-NETs is exceedingly rare and not often encountered in existing literature. Focal uptake of radiotracer on (^{68}Ga)-DOTATATE PET/CT imaging is consistent with well-differentiated primary or metastatic NETs. Additionally, this form of functional imaging can be used as a powerful tool to monitor disease progression in established cases. As such, the following case explores the role of (^{68}Ga)-DOTATATE PET/CT in the localization of neuroendocrine neoplasms and the monitoring of GEP NETs of metastatic nature.

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Case report

We present a 63-year-old woman with a history of a stage IV neuroendocrine tumor with metastasis to the right lower quadrant (RLQ) mesentery. Six years prior, the patient presented to the emergency department (ED) with abdominal pain and nausea. A computed tomography (CT) scan of the abdomen revealed a porcelain gallbladder and a RLQ mesenteric mass measuring 2.2 × 2.2 × 2.4 cm. The patient, 3 months later, underwent an elective open cholecystectomy with biopsy of the RLQ mesenteric mass. Grossly, the mass appeared fibrotic and calcified. It was deemed unresectable because of its proximity to mesenteric vessels and calcification. Histopathological examination reported a well-differentiated NET. Immunohistochemistry staining yielded positive results for synaptophysin, CDX2, and CDH17 with a Ki-67 index of 15%. These findings suggested a grade 2 NET of gastrointestinal origin. The patient was then referred to oncology for further workup.

A (^{68}Ga)-DOTOTATE PET/CT was preformed to assess for the primary along with urine levels of 5-HIAA and chromogranin A for clinical correlation. The results of the initial scan redemonstrated the RLQ mesenteric mass, and a 2.6 cm mass in the terminal ileum showed increased uptake, likely the primary tumor (Fig. 1). A focus of uptake in the left adnexa was suspicious for ovarian metastasis. Additionally, urine chromogranin A was elevated at 130 (ng/mL), although urine 5-HIAA was within normal limits. The patient was started on somatostatin analog therapy. The patient continued this therapy for 46 cycles over approximately 2 years, tolerating it well. During this period, multiple CT scans of the abdomen and a repeat (^{68}Ga)-DOTATATE PET/CT scan showed stable disease along with down trending urine chromogranin A levels.

Approximately 3 years and 8 months after her initial diagnosis and apparent stable disease, the patient presented to her primary care provider with complaints of intermittent abdominal pain. A CT scan of the abdomen was performed and showed a mildly enlarged left ovary and enlargement of the previously identified mesenteric lymph node. A DOTATATE PET/CT scan revealed significant disease progression (Fig. 2). Uptake was seen in the enlarged left ovary and in the intraperitoneal compartment suggestive of peritoneal carcinomatosis. Additionally, multiple foci of avid uptake were seen in both liver lobes confirming hepatic metastasis. Urinary chromogranin A levels had now climbed to 198 ng/mL.

The degree of uptake on ^{68}Ga DOTOTATET PET/CT serves as a predictive value for lutetium-177 (^{177}Lu) DOTATATE peptide receptor radionuclide therapy response and can thus be used to identify patients who are likely to benefit from radiotherapy treatment (PRRT). Because of clear disease progression, the patient was approved for treatment using ^{177}Lu-DOTATATE

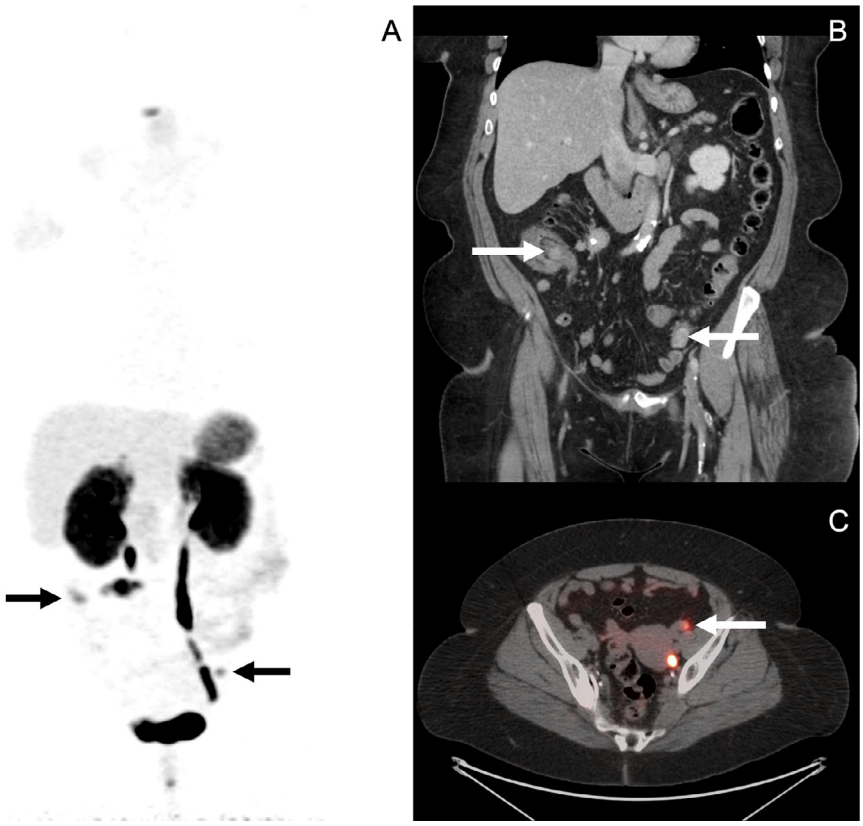

Fig. 1 – Whole body MIP (maximum intensity projections) image (A) from (^{68}Ga)-DOTATATE PET/CT shows focal uptake in the right lower quadrant (black arrow), corresponding to the enhancing focus on the diagnostic CT (B), localizing the primary neuroendocrine tumor in the terminal ileum. Focal uptake is also seen in the metastatic mesenteric lymph node, seen as a calcified focus on CT. Focal uptake in the left lower quadrant corresponds to the left ovary as seen on the CT image (B) and the fused PET/CT image (white arrow on C).

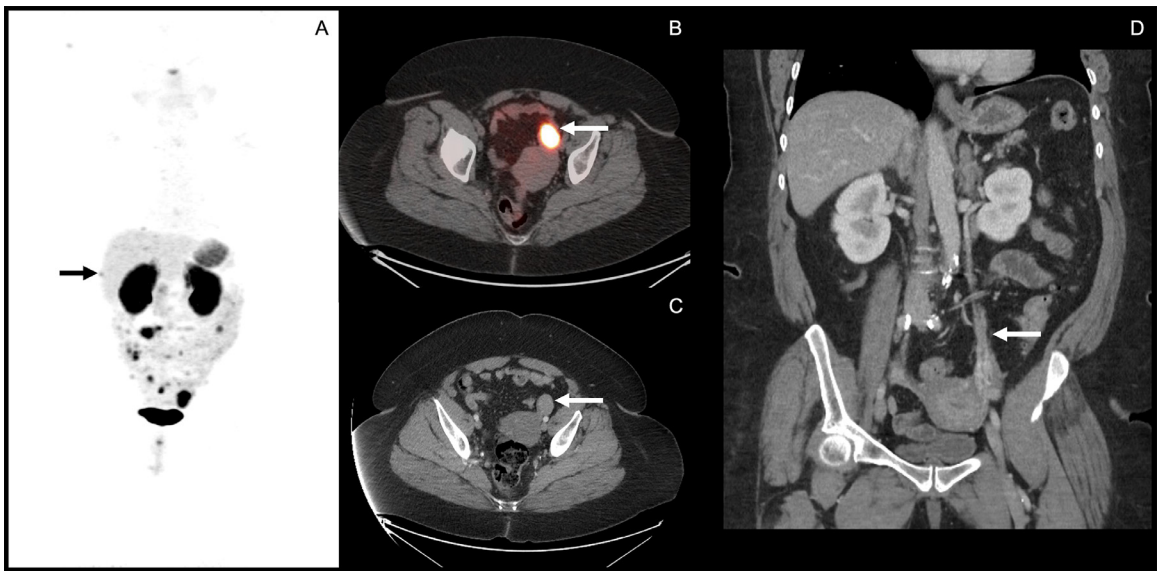

Fig. 2 – Follow up imaging showing multifocal intraperitoneal uptake, seen on MIP image (A) from (^{68}Ga)-DOTATATE PET/CT, secondary to peritoneal carcinomatosis (black arrow points to a focus abutting the right lobe of liver). Intense uptake is seen in the enlarged left ovary on fused PET/CT image (B), and the corresponding diagnostic CT (C). The coronal image (D) shows venous drainage of the mass into the left ovarian vein, proving the presence of ovarian metastasis.

PRRT. The patient is currently receiving treatment once every month, alternating between radionuclide therapy and somatostatin analog therapy. Thus far, the patient has received 2 out of the planned 4 radionuclide treatments and has tolerated them well.

Discussion

Neuroendocrine tumors (NETs) are rare neoplasms that originate from cells of the neuroendocrine system [1]. Neuroendocrine cells are unique in that they demonstrate properties of both neural and hormone-producing cells [2]. By managing the synthesis and release of organ specific hormones, neuroendocrine cells can control many essential bodily functions [2]. Due to the variety of neuroendocrine cell types in our bodies, the clinical symptoms of NETs vary extensively and are heavily dependent on the site of tumor growth [2,3]. Neuroendocrine cells of gastroenteropancreatic origin, known as enterochromaffin cells, are responsible for the storage and release of bioactive monoamine neurotransmitters such as serotonin (5-HT) [2]. The excessive release of monoamines into systemic circulation causes a distinct clinical presentation known as carcinoid syndrome [4] The hallmark symptoms of this syndrome include diarrhea, flushing, edema, abdominal pain, wheezing, and right-sided valvular heart disease [4,5]. NETs associated with clinical symptoms are characterized as functioning, whereas asymptomatic NETs are referred to as nonfunctioning [6]. Nonfunctioning tumors are far more common and are often diagnosed incidentally or secondary to mass effect [6].

Well-differentiated NETs that run an indolent, non-metastatic course are classified as low-grade [2]. In contrast, high-grade NETs are poorly differentiated and are more commonly associated with distant metastasis and aggressive clinical courses [2]. Most NETs of the gastrointestinal tract arise from the distal ileum of the small intestine and are known to carry a high malignant risk [5]. The most frequent sites of metastatic spread include the mesentery, peritoneum, and the liver [5]. Peritoneal carcinomatosis and metastasis to the surrounding lymph nodes, particularly of the mesentery, may result in fibrosis, obstruction, and ischemia [5,7]. Neuroendocrine metastasis to the ovaries is exceptionally rare with a carried incidence of 2% [8]. The most common primary origin of ovarian NET metastasis are NETs of the small bowel, particularly of the ileum [8]. Patients presenting with ovarian metastasis often have multiple other sites of metastasis, peritoneal seeding, and liver involvement with concurrent carcinoid syndrome [8]. As such, the presence of ovarian metastasis in patients with NETs of other primary origin is often consistent with advanced disease [8].

Somatostatin receptors (SSTRs), encoded by genes $SSTR_1$-$SSTR_5$, are G protein-coupled receptors that modulate protein synthesis and hormone release [5]. Well-differentiated tumors of neuroendocrine origin express SSTRs, particularly $SSTR_2$, in exceedingly high densities [5,9]. Gallium-68 (^{68}Ga) DOTATATE PET/CT imaging correlates with the extent of SSTR expression [5]. Therefore, (^{68}Ga)-DOTATATE PET/CT scanning is a form of functional imaging that allows for the whole-body detection, staging, and localization of NETs - both metastatic and primary [5]. When evaluating imaging results, normal physiologic uptake is often visualized in the following tissues: pituitary, salivary glands, thyroid, spleen, pancreas, liver, adrenals, prostate, urinary and gastrointestinal tract [9]. Normal ovaries are not a site of physiologic uptake of (^{68}Ga)-DOTATATE on a PET/CT, and focal ovarian uptake is considered pathologic [7,9].

Conclusion

Imaging with whole-body (^{68}Ga)-DOTATATE PET/CT accurately stages disease by correctly identifying all sites of metastatic disease, detecting disease progression, and thus guiding treatment decisions. Ovarian metastasis from neuroendocrine primary is rare and may be associated with or progress to peritoneal carcinomatosis.

Author contributions

The authors declare that this is their original work, and they all approve the content of this manuscript. They confirm that this manuscript has not been published previously, in any language, in whole or in part, and is not currently under consideration elsewhere.

Patient consent

A written informed consent was obtained from the patient for the publication of this case report.

Ethical clearance

This project did not involve any research and no ethical clearance was required.

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