Case Report

Somatostatin Receptor Expression in Renal Cell Carcinoma—A New Front in the Diagnostics and Treatment of Renal Cell Carcinoma

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Clinical Practice Points

- Renal cell carcinoma (RCC) has a poor prognosis and is difficult to treat because of its ability to spread asymptomatically and its resistance to chemotherapy.
- In this patient series, we report that RCC metastases can be identified using gallium-68 (^{68}Ga)-edotreotide (DOTATOC) positron emission tomography/computed tomography (PET/CT).
- Immunostaining of tumor tissue from primary RCC tumors and their matched adrenal, pancreatic, and thyroid metastases showed that RCC cells express membranous somatostatin receptor 2.
- These findings indicate that ^{68}Ga-DOTATOC PET/CT can be used as a new imaging modality in management of metastatic RCC and might contribute to the development of new somatostatin analogue-based methods for the treatment of metastatic RCC.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■
Keywords: Computed tomography, DOTATOC, Positron emission tomography, RCC, SSTR-2

Introduction

Renal cell carcinoma (RCC) accounts for ~3% of all new adult malignancies. Despite surgical resection of localized disease with curative intent, the recurrence rate of RCC is ≤ 30%. RCC can metastasize to endocrine organs such as the adrenal, pancreatic, and thyroid glands. The high rates of tumor recurrence and the need to distinguish RCC metastases from primary tumors underscore the importance of postoperative surveillance.

Conventional computed tomography (CT) is the standard investigation method for monitoring patients with RCC and the detection of recurrent disease. In the adrenal glands and pancreas, RCC metastases are difficult to distinguish from primary tumors in these glands compared with thyroid lesions, which often are available for cytologic examination (with or without ultrasound guidance). Adrenal and pancreatic lesions are difficult to investigate because they are located in the retroperitoneal space. It is not uncommon for patients with suspected RCC metastasis to undergo multiple CT and magnetic resonance imaging examinations and/or other relatively invasive investigations, such as CT- or endoscopic ultrasound-guided cytologic examination before the correct diagnosis is established.

Edotreotide (DOTATOC) positron emission tomography (PET) is a functional imaging study in which the radiolabeled somatostatin analogue (SSA), gallium-68 (^{68}Ga)-DOTATOC, is used as a PET ligand. ^{68}Ga-DOTATOC PET integrated with CT constitutes a state of the art imaging technique for the investigation and follow-up of neuroendocrine tumors (NETs).[1] ^{68}Ga-DOTATOC is accumulated in the tumor tissue (80% within 30 minutes) and has low activity concentrations in tissues without expression of somatostatin receptors (SSRs). Hence, DOTATOC PET/CT results in high tumor to nontumor contrast and allows for the detection of small NET lesions.

In single case reports, it has been shown that RCC cases can be identified using octreotide scintigraphy. To the best of our knowledge, further analysis investigating the pathophysiologic mechanisms of these observations has not been performed. In our

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Submitted: Mar 18, 2018; Accepted: Mar 21, 2018

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1558-7673/$ - see frontmatter
https://doi.org/10.1016/j.clgc.2018.03.011

institution, we have had similar findings in several cases. To investigate these observations, we systematically examined the primary tumors and their matched metastases for expression of SSR type 2 (SSTR-2) to explore the expression of SSR by RCC.

Case Report

The first patient was a 75-year-old man who had undergone right-sided nephrectomy in 2002 for clear cell RCC, Fuhrman grade 2. In 2015, owing to porphyria cutanea tarda, he underwent conventional CT, and a 6-cm tumor in the pancreatic tail was detected. Further investigation using magnetic resonance imaging could not distinguish whether the pancreatic lesion represented a NET or an adenocarcinoma. Endoscopic ultrasound-guided cytologic examination of the pancreatic lesion showed malignant cells with a neuroendocrine phenotype. Hence, the patient underwent with DOTATOC PET/CT, which showed strong DOTATOC uptake in the pancreatic lesion (Figure 1). After pancreatic tail resection, histopathologic examination of the lesion showed a radically removed clear cell RCC metastasis. Subsequent CT follow-up scans for 2.5 years showed no additional signs of RCC metastasis.

The second patient was a 68-year-old man who had previously undergone right-sided nephrectomy in 2006 for clear cell RCC, Fuhrman grade 3. From 2009 to 2012, postoperative surveillance showed metastatic deposits in the right adrenal gland (3 cm) and the right thyroid lobe (2 cm). Thus, he underwent right-sided adrenalectomy and hemithyroidectomy. The pathology reports were consistent with clear cell RCC metastases in both organs. In 2015, conventional CT examination as a part of RCC monitoring showed a 1.5-cm lesion in the left adrenal gland. Radiologically, the lesion was characterized as benign.

Because the patient had metastatic RCC and the right adrenal gland had previously been removed, fluorine-18 fluorodeoxyglucose (FDG) PET/CT was performed to determine whether the left adrenal lesion was benign or malignant and whether other metastatic foci were present before performing metastasectomy of the left adrenal gland. FDG-PET/CT showed no increased FDG activity in the left adrenal (Figure 1) and no sign of metastasis in the abdomen, neck, or thorax.

Based on the clinical evaluation, including comparisons with the previous CT investigations, the lesion in left adrenal gland was considered a RCC metastasis, and the patient underwent adrenalectomy. Histopathologic examination of the left adrenal gland confirmed the lesion as a RCC metastasis. Subsequent CT follow-up scans showed no signs of RCC metastasis.

Histopathologic Investigation

All the original sections from primary tumors and metastases used in the initial routine clinical histopathologic assessment were re-evaluated by experienced pathologists (C.C.J., A.H.). For SSTR-2 immunohistochemistry, tumor tissue (primary tumor and

Figure 1 Gallium-68 (^{68}Ga) Edotreotide (DOTATOC) Positron Emission Tomography (PET). (A) Conventional Computed Tomography (CT) Image Showing Tumor in Pancreatic Tail (Red Arrow). (B) ^{68}Ga-labelled DOTATOC PET/CT Image Showing the Same Lesion Exhibiting High DOTATOC Uptake (Blue Arrow), Demonstrating Expression of Somatostatin Receptor Type 2 (SSTR-2). (C) CT Image Showing Renal Cell Carcinoma (RCC) Metastasis in the Left Adrenal Gland (Red Arrow). (D) Corresponding Fluorine-18 Fluorodeoxyglucose (FDG) PET/CT Scan. Note That the Metastasis Did Not Express FDG (Blue Arrow)