Ga-68 Somatostatin Receptor PET/CT in von Hippel-Lindau Disease

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Abstract Von Hippel-Lindau (VHL) disease is a dominantly inherited familial cancer syndrome with a variety of benign and malignant tumors such as retinal and central nervous system hemangioblastomas, endolymphatic sac tumors, renal cysts and tumors, pancreatic cysts and tumors, pheochromocytomas, and epididymal cystadenomas. Cross-sectional modalities (computed tomography and magnetic resonance imaging) as well as ultrasound play a major role in the initial evaluation and follow-up of the various manifestations of VHL disease. Ga-68-labeled somatostatin receptor analogs already have a significant role in the diagnosis, staging, and therapy management of neuroendocrine neoplasms and neural crest tumors. Herein, we report a case presenting a variety of malignancies in VHL and showing the usefulness of Ga-68 somatostatin receptor PET/CT as a one-stop-shop imaging modality in the management of VHL disease.

Keywords Ga-68 DOTA-TOC PET/CT · Ga-68 DOTA-TATE PET/CT · Ga-68 DOTA-NOC PET/CT · von Hippel-Lindau disease · Hemangioblastoma · Pheochromocytoma

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Introduction

Von Hippel-Lindau (VHL) disease is a dominantly inherited familial cancer syndrome caused by mutations in the VHL tumor suppressor gene with a prevalence of 1 in 39,000–53,000 [1]. VHL is characterized by the development of a variety of benign and malignant tumors, including retinal and central nervous system hemangioblastomas, endolymphatic sac tumors, renal cysts and tumors, pancreatic cysts and tumors, pheochromocytomas, and epididymal cystadenomas [2]. Although genetic testing is available, imaging modalities such as x-ray computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) or endoscopic ultrasound (EUS) play a major role in the initial evaluation and follow-up of the various manifestations of VHL disease [2–4].

Positron emission computed tomography (PET) is increasingly being used for imaging disease based on molecular characteristics of malignant cells and by metabolic characterization of tumors. Ga-68-labeled somatostatin receptor (SSTR) analogs such as 1,4,7,10-tetraazacyclododecane-N, N',N'',N'''-tetraacetic acid (DOTA)-1-Nal³-octreotide (DOTA-NOC), DOTA-Tyr³-octreotide (DOTA-TOC), and DOTA-Tyr³-octreotate (DOTA-TATE) already have been shown to be clinically useful for the diagnosis, staging, and therapeutic management of neuroendocrine neoplasms and various other somatostatin receptor expression tumors [5, 6]. Herein, we report a patient with VHL syndrome (developing a variety of tumors) where Ga-68 somatostatin receptor PET/CT proved useful in the management and follow-up of this rare disorder.

Case Report

A 36-year-old woman who was diagnosed with von Hippel-Lindau disease in 1996 underwent resections eight times for cerebellar and intramedullary hemangiomas from 1996 to 2008, and an additional craniocervical decompression with laminectomy and laminoplasty from C2 to C4 vertebrae in 2007. She suffered from vertigo, ataxia, dysphagia, dysarthria, quadriplegia, and neurogenic bladder and bowel paralysis associated with postoperative sequelae in von Hippel-Lindau disease. During the cervical spine operation, performed in October 2007, she developed sudden hypertension and tachycardia. The norepinephrine level in 24-h urine was elevated, suggestive of overproduction of catecholamines in the body. Abdominal MRI demonstrated a left adrenal mass with a diameter of 19×30 mm and high signal intensity in T2-weighted images and strong contrast enhancement, characteristic of the presence of a pheochromocytoma. The patient was referred to our department for evaluation of the presence of metastases and for determination of the somatostatin receptor status of the left adrenal tumor by molecular imaging. The first PET/CT scan (Biograph Duo, Siemens Healthcare, Munich, Germany) was performed from the skull to the thighs 75 min after the injection of 94 MBq of Ga-68 DOTA-NOC. Intravenous furosemide (20 mg) was applied together with the injection of the radiopharmaceutical to accelerate renal excretion. Then, a low-dose spiral CT was performed after intravenous contrast.

PET/CT (Fig. 1) revealed a strong SSTR-positive focal lesion in the head of the pancreas (SUVmax. 19.0), which had not been picked up on abdominal MRI. In contrast, no significantly elevated tracer uptake exceeding normal liver activity (SUVmax. 12.3) was observed in the enlarged left adrenal gland (SUVmax. 11.6). The PET/CT findings were strongly indicative of a second primary tumor in the pancreas with high somatostatin receptor expression, whereas the left adrenal gland exhibited only low somatostatin receptor expression. The patient underwent partial resection of the pancreatic head, left adrenalectomy and lymphadenectomy. Histopathological examinations revealed a primary neuroendocrine tumor in the head of the pancreas, whereas the left adrenal gland was characterized as low-grade pheochromocytoma; the resected lymph node contained a metastasis. Therefore, PET/CT was able to detect a second primary neuroendocrine tumor in the pancreas—one of the clinical manifestations of von Hippel-Lindau disease—and was also helpful in the differential diagnosis of pheochromocytoma.

The second SSTR PET/CT scan was performed 1 year later for the purpose of restaging/detection of recurrence and for evaluation of the somatostatin receptor status. Seventy minutes after the injection of 117 MBq of Ga-68 DOTA-TOC, a PET/CT scan was performed using exactly the same technique as applied for the previous scan. Multiple

hemangioblastomas with low somatostatin receptor expression were newly detected in the left cerebellum and in the spinal medulla (Fig. 2). There was no evidence of recurrence in the abdominal cavity. Because of the relatively low somatostatin receptor density in the cerebellar and spinal lesions, peptide receptor radionuclide therapy was not recommended as a treatment option.

During further follow-up, abdominal MRI revealed an increasing size of the right adrenal gland. PET/CT scan was performed in June 2011 for evaluating the receptor status and for exclusion of metastases; 75 min after injection of 102 MBq of Ga-68 DOTA-TATE, a PET/CT scan was acquired (Fig. 3), which confirmed the already known multiple hemangioblastomas in the cerebellum and the spinal cord, with no significant changes of the somatostatin receptor density as compared to the previous PET/CT scan performed in May 2009. The right adrenal gland showed high somatostatin receptor expression (SUVmax. 10.2) compared to normal liver (SUVmax. of 6.6). In addition, mild focal uptake was detected in a paracaval lymph node, suggestive of a metastasis that was not described in the abdominal MR report. As the right adrenal tumor and the metastatic lymph node were the only abdominal lesions detected by PET/CT and MRI, surgical resection of the tumor lesions was planned.

Discussion

In 1964, Melmon and Rosen used the term “von Hippel-Lindau disease” for a familial disease, summarizing the previous results of von Hippel, Lindau, and others [7]. The VHL tumor suppressor gene, the genetic mechanism of VHL disease, was first identified in 1988 [8] and localized in chromosome 3p25-26 in 1993 [9]. Abnormal or absent VHL protein caused by several effects probably interact to induce formation of various tumors [1, 4]. VHL disease most commonly presents with retinal or CNS hemangioblastomas (60–80 %). Renal cell carcinoma (24–45 %), renal cyst (59–63 %), pancreatic cysts (50–91 %), and epididymal cystadenoma (25–60 %) are also common, followed by pheochromocytoma (10–20 %), pancreatic neuroendocrine neoplasms (5–17 %), and endolymphatic sac tumors (10 %) [1, 4, 7, 10–12]. Because of the various manifestations of the disease and the potency of malignancy, life-long screening and follow-up are necessary.

The diagnosis of von Hippel-Lindau disease is often based on clinical criteria including any one of the following: (1) more than one CNS hemangioblastoma, (2) one CNS hemangioblastoma and visceral manifestations of VHL disease, and (3) any manifestation and a known family history of VHL disease [1, 2]. Several institutions have suggested screening protocols according to afflicted organ, and most of them include imaging follow-up by CT, US, MRI, and sometimes

Fig. 1 Maximum intensity projection (MIP, **a**) and transaxial (**b**, **c**) images of Ga-68 DOTA-NOC PET/CT performed in March 2008. A focal somatostatin receptor-positive lesion (SUVmax. 19.0) indicative of a second primary pancreatic neuroendocrine tumor was detected by PET/CT (**a**, arrow; **b**). In contrast, the left adrenal tumor detected by abdominal MRI had no increased somatostatin receptor density (**c**, SUVmax. of left adrenal gland: 11.6). Histopathology revealed a differentiated neuroendocrine tumor in the pancreas and a low-grade pheochromocytoma in the left adrenal gland

using metaiodobenzylguanidine (MIBG) scintigraphy with I-123 or I-131 MIBG [1, 2, 4]. However, as shown by this case, PET/CT using Ga-68-labeled somatostatin analogs successfully detected a variety of different tumors in one VHL patient and was able to reveal lesions not found by MRI. PET/CT has

become an important molecular-based imaging tool in oncologic practice for detecting and characterizing malignant disease and for determining the glucose metabolism of tumors (which strongly corresponds to the proliferation rate of the lesions). However, there have been only a few reports about

Fig. 2 MIP (**a**) and transaxial (**b**, **c**) images of the Ga-68 DOTA-TOC PET/CT performed in May 2009, which depicted somatostatin-positive tumors (**a**, arrows) in the left cerebellum and in the spinal cord, suggesting recurrent hemangioblastomas. Because of the low somatostatin receptor density (**b**, SUVmax. in the left cerebellum: 4.1; **c**, SUVmax. in the spinal cord: 3.8), peptide receptor radionuclide therapy was not recommended as a treatment option

Fig. 3 MIP (a) and transaxial (b, c) images of the third Ga-68 SSTR PET/CT performed using DOTA-TATE in June 2011. Somatostatin receptor density of the lesions in the left cerebellum and the spinal cord were essentially unchanged since the previous PET/CT scan (a, arrows, SUVmax. of the lesions in the left cerebellum and the spinal cord were 3.8 and 2.0, respectively). However, the right adrenal gland

now exhibited significantly higher somatostatin receptor expression (a, arrowhead; b, SUVmax. 10.2, SUVmax. of normal hepatic tissue: 6.6). PET/CT also detected a receptor-positive paracaval lymph node metastasis that had not been picked up by abdominal MRI (a, curved arrow; c, SUVmax. 5.5). Because of localized disease revealed by PET/CT, surgical treatment was planned

the use of PET/CT in VHL disease. Kaji et al. reported that F-18 fluorodopamine PET was useful in detecting VHL-related adrenal pheochromocytoma [13]. Kok et al. advocated the potential use of F-18 fluorodeoxyglucose PET/CT in a pancreatic neuroendocrine tumor in a VHL patient [14]. Recently, Ambrosini et al. reported on Ga-68 DOTA-NOC imaging in a case with cerebellar hemangioblastoma in VHL disease [15]. Our report is, to our best knowledge, the first where Ga-68 somatostatin receptor PET/CT identified multiorgan involvement in VHL disease.

Ga-68-labeled somatostatin receptor analogues such as DOTA-NOC, DOTA-TOC, and DOTA-TATE already have a significant effect in the diagnosis, staging, and therapy management of neuroendocrine tumors and various other somatostatin receptor-positive tumors, and have proved to be clearly more sensitive (and specific) compared to In-111 pentetertotide imaging (Octreoscan) and F-18 FDG PET/CT [5, 6]. In a recent study, Ga-68 DOTA-TOC PET/CT was proven to be superior to I-123 MIBG scintigraphy for the diagnosis of pheochromocytoma and neuroblastoma [16]. Most of the lesions in VHL disease are treatable by surgical resection. Ga-68 receptor PET/CT could be helpful in the preoperative staging and in postoperative evaluation, as well as for the detection of recurrences or metastatic disease during follow-up. In cases with high morbidity, associated

with repetitive operations for CNS hemangioblastoma, and with extensive metastases of different neuroendocrine neoplasms or other unresectable tumors, Ga-68 receptor PET/CT is able to identify those candidates with high somatostatin receptor expression suitable for peptide receptor radionuclide therapy. Contrast-enhanced CT (which is part of the PET/CT scan) provides additional information (e.g., in various cystic lesions) important for the management of VHL disease. The present case demonstrated that all three radiopeptides can successfully detect various SSTR-positive tumors. However, because the degrees of uptake (SUVmax.) differ according to each radiopeptide, the use of a single radiopeptide would be recommended for the follow-up and monitoring of treatment response.

In conclusion, Ga-68 somatostatin receptor PET/CT was useful for the detection of a variety of different tumors in the presented case with VHL syndrome and provided clinical impact in the management of the disease, detecting malignant lesions not identified by other imaging modalities. PET/CT also provided valuable information on the tumor differentiation, i.e., the expression of somatostatin receptors, which is essential for making a decision on peptide receptor radionuclide therapy. Ga-68 somatostatin receptor PET/CT has the potential to become an integral part in the management of VHL disease as a one-stop-shop imaging modality.

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