Nuclear Medicine and Molecular Imaging (2019) 53:144–147
https://doi.org/10.1007/s13139-018-0558-1

CASE REPORT

ISSN (print) 1869-3482
ISSN (online) 1869-3474

Gallbladder Paraganglioma Associated with *SDHD* Mutation: a Potential Pitfall on ^{18}F-FDOPA PET Imaging

Zahraa Abdul Sater[1] · Abhishek Jha[2] · Adel Mandl[1] · Sheila K. Mangelen[2] · Jorge A. Carrasquillo[3] · Alexander Ling[4] · Melissa K. Gonzales[2] · Osorio Lopes Abath Neto[5] · Markku Miettinen[5] · Karen T. Adams[2] · Pavel Nockel[1] · Mustapha El Lakis[1] · Karel Pacak[2]

Received: 9 August 2018 / Revised: 25 October 2018 / Accepted: 26 November 2018 / Published online: 19 February 2019

Abstract

A 36-year-old male patient initially presented with hypertension, tinnitus, bilateral carotid masses, a right jugular foramen, and a periaortic arch mass with an elevated plasma dopamine level but an otherwise normal biochemical profile. On surveillance MRI 4 years after initial presentation, he was found to have a 2.2-cm T2 hyperintense lesion with arterial enhancement adjacent to the gallbladder, which demonstrated avidity on ^{68}Ga-DOTATATE PET/CT and retrospectively on ^{18}F-FDOPA PET/CT but was non-avid on ^{18}F-FDG PET/CT. Biochemical work-up including plasma catecholamines, metanephrines, and chromogranin A levels were found to be within normal limits. This lesion was surgically resected and was confirmed to be a paraganglioma (PGL) originating from the gallbladder wall on histopathology. Pheochromocytoma (PHEO) and PGL are rare tumors of the autonomic nervous system. Succinate dehydrogenase subunit D (*SDHD*) pathogenic variants of the succinate dehydrogenase complex are usually involved in parasympathetic, extra-adrenal, multifocal head, and neck PGLs. We report an unusual location of PGL in the gallbladder associated with *SDHD* mutation which could present as a potential pitfall on ^{18}F-FDOPA PET/CT as its normal excretion occurs through biliary system and gallbladder. This case highlights the superiority of ^{68}Ga-DOTATATE in comparison to ^{18}F-FDOPA and ^{18}F-FDG in the detection of *SDHD*-related parasympathetic PGL.

ClinicalTrials.gov Identifier: NCT00004847.

Keywords Gallbladder · Paraganglioma · *SDHD* · ^{68}Ga-DOTATATE · ^{18}F-DOPA · ^{18}F-FDG

Introduction

Pheochromocytoma (PHEO) and paraganglioma (PGL) are rare tumors of the autonomic nervous system. Around 35–40% of PHEO/PGLs are related to germline mutations in one of the susceptibility genes [1, 2]. The succinate dehydrogenase subunits (SDHx) proteins are part of the SDH complex and mutations in these gene-encoding subunits result in several familial PHEO/PGL syndromes. Succinate dehydrogenase subunit D (*SDHD*) pathogenic variants are usually associated with parasympathetic, extra-adrenal, and multifocal head and neck PGLs [1]. We report a rare case of

✉ Karel Pacak
karel@mail.nih.gov

[1] National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD 20892, USA

[2] Section on Medical Neuroendocrinology, Developmental Endocrine Oncology and Genetics Affinity Group, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 10 Center Dr. MSC-1109, Bldg. 10, CRC, 1E-3140, Bethesda, MD 20892, USA

[3] Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, MD 10065, USA

[4] Radiology and Imaging Sciences, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD 20892, USA

[5] Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD 20892, USA

SDHD-related PGL involving the gallbladder wall, a rare site not to be overlooked in these patients.

Case Report

A 36-year-old Caucasian male was found to have an *SDHD* mutation after he presented with multifocal PGLs. His initial presentation included mild hypertension, tinnitus, bilateral carotid masses (measuring 2.5 cm and 2.3 cm), a right jugular foramen mass (2.3 cm), and a periaortic arch mass (1.7 cm). This was associated with an elevated plasma dopamine level of 435 (normal: 3–46) pg/ml but an otherwise normal biochemical profile. The bilateral carotid body tumors and mediastinal paraaortic lesion were surgically resected; however, the right glomus jugulare tumor was unresectable due to a significant risk of stroke and, hence, was stabilized with 5400 cGy of intensity-modulated radiation therapy. A few years later, surveillance magnetic resonance imaging (MRI) of the abdomen and pelvis showed a T2 hyperintense 2.2 cm lesion with arterial enhancement adjacent to the gallbladder (Fig. 1a). This lesion was intensely avid on ^{68}Ga-DOTA(0)-Tyr(3)-octreotate (^{68}Ga-DOTATATE) positron emission tomography-computed tomography (PET/CT) (SUV_{max} = 285) and retrospectively on ^{18}F-fluorodopa (^{18}F-FDOPA) PET/CT (SUV_{max} = 69) but lacked avidity on ^{8}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT (Fig. 1b–d, respectively). Biochemical work-up including plasma catecholamines, metanephrines, and chromogranin A levels was within normal limits. He subsequently had an uneventful laparoscopic cholecystectomy. The surgical pathology confirmed a 2.1-cm PGL originating from the gallbladder wall near the fundus with negative tumor margins. Immunohistochemistry confirmed tumor cells were positive for synaptophysin, chromogranin, and S100 (Fig. 2).

Discussion

We describe a case of a parasympathetic PGL associated with *SDHD* mutation that arose from the gallbladder wall. The human gallbladder is innervated by branches of the sympathetic and parasympathetic fibers derived from the left vagus nerve and celiac plexus [3]. Thus, the occurrence of PGL in this location can be explained by migration of ganglionic cells from nearby plexuses. PGL in the gallbladder was first reported by Miller et al. and Wolff et al. in 1972 and 1973, respectively [4, 5].

On histopathologic examination, the tumor was composed of round to polygonal nests with a finely granular cytoplasm with delicate fibrous septa containing prominent capillaries (Fig. 2) and was positive for chromogranin A, synaptophysin, and S100 on sustentacular cells [3, 4].

A genetic etiology for PGL in the gallbladder has only twice been reported and associated with a *RET* gene mutation [6, 7]. To the best of our knowledge, gallbladder PGL associated with an *SDHx* mutation has not been reported in the past [3–9]. *SDHx* genes encode the four subunits of SDH complex

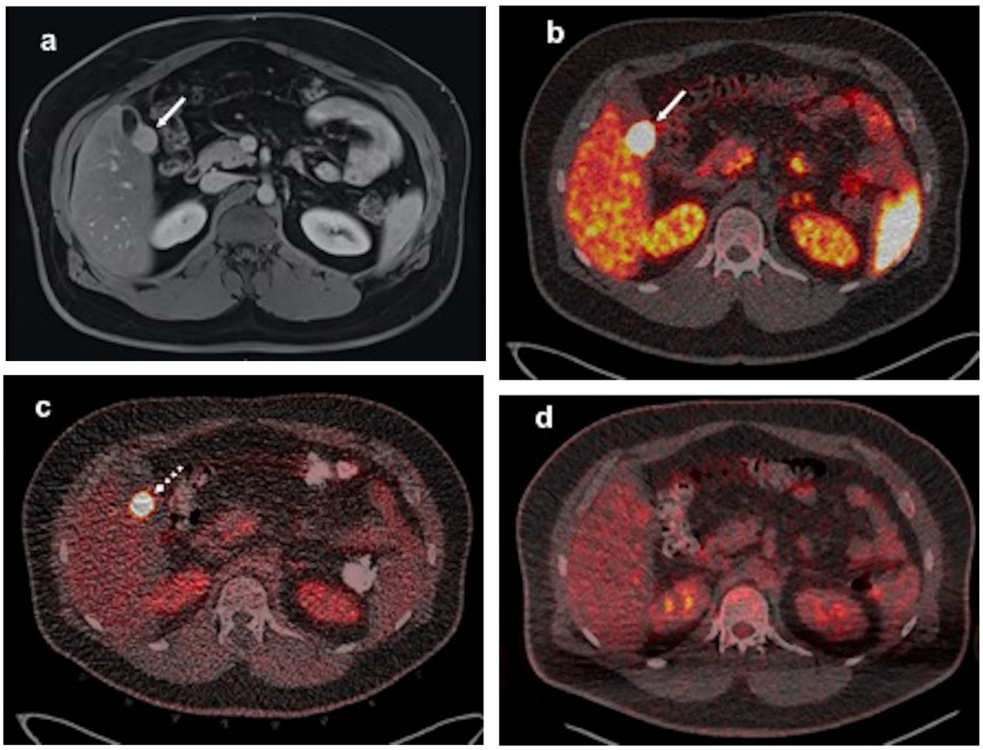

Fig. 1 Anatomic and functional PET imaging of gallbladder paraganglioma. In this figure, an enhancing lesion adjacent to the gallbladder is seen on fat-suppressed delayed post-contrast T1W image (arrow, **a**), which demonstrates uptake on ^{68}Ga-DOTATATE PET/CT (arrow, **b**) and retrospectively on ^{18}F-FDOPA PET/CT (dotted arrow, **c**). However, this lesion lacked avidity on ^{18}F-FDG PET/CT (**d**)

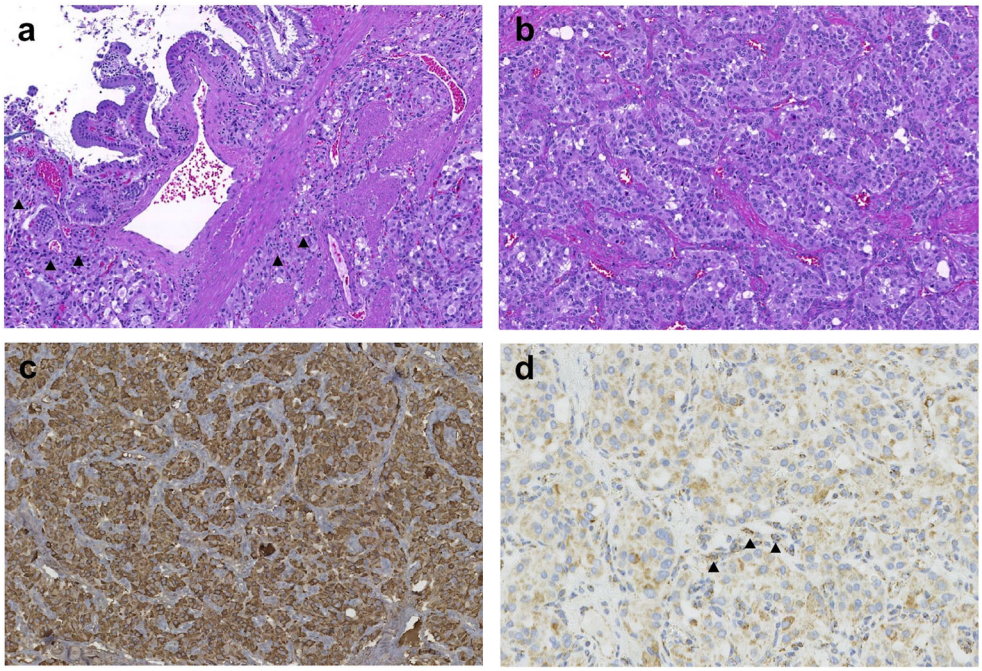

Fig. 2 Histopathologic examination of gallbladder paraganglioma. In this figure, staining with hematoxylin and eosin (**a**, ×100) shows gallbladder mucosa, lined by a single layer of columnar epithelial cells with pale eosinophilic cytoplasm, abutting directly onto muscularis propria. Tumor cells involve the muscularis propria and the mucosa (arrowheads). (**b**, ×100), shows a nested arrangement of paraganglioma cells with fine fibrovascular septa. Neoplastic cells are monomorphic with round nuclei and inconspicuous nucleoli. Chromogranin immunostain (**c**, ×100) is positive in neoplastic cells. Synaptophysin immunostain (not shown) is also strongly positive. SDHB immunostain (**d**, ×200) shows reduced granular cytoplasmic marking of neoplastic cells compared to endothelial cells (arrowheads), indicating an SDH-complex functional aberration

[1, 2]. The latter not only catalyzes the oxidation of succinate into fumarate in the tricarboxylic acid cycle but also transfers electrons to the ubiquinone pool in the respiratory chain [1]. Defects in SDH lead to activation of the hypoxia pathway and thus, cause tumor development. SDHD is one of the two anchorage proteins in SDH and is commonly affected by pathogenic mutations. The germline heterozygous mutations in *SDHD*, together with the loss of heterozygosity, cause highly penetrant multifocal tumor development with a characteristic paternal transmission [1].

Functional imaging is the backbone of PHEO/PGL diagnosis [2]. The patient's genetic mutation has an important effect on the PET tracer utilization. The various functional imaging radiopharmaceuticals target different mechanisms of tumorigenesis in PHEO/PGLs. Somatostatin receptors (SSTR) are expressed in PHEO/PGLs especially SSTR2 subtype [10] and ^{68}Ga-DOTATATE demonstrates higher affinity for SSTR2 [11]. ^{18}F-FDOPA targets the cell via the large amino acid transporter system which is found in PHEO/PGLs [12], whereas ^{18}F-FDG is a nonspecific radiopharmaceutical that enters the cell via glucose transporters [13] and its increased uptake in *SDHx*-related PHEO/PGLs occurs due to altered glucose metabolism that is related to genotype-specific tumor biology [14, 15]. In a recently published meta-analysis by Han et al. in PHEO/PGL of unknown genetic status, ^{68}Ga-DOTA-SSTR PET demonstrated a superior detection rate compared to ^{18}F-FDOPA and ^{18}F-FDG [16]. Further, ^{68}Ga-DOTATATE PET/CT is known to demonstrate superior detection in *SDHB*-related metastatic PHEO/PGL compared to ^{18}F-FDOPA and ^{18}F-FDG [2] and similarly in *SDHD*-related PHEO/PGL when compared to ^{18}F-FDOPA [17]. In this patient, ^{68}Ga-DOTATATE PET/CT (Fig. 1b) was able to detect the gallbladder PGL whereas on ^{18}F-FDG PET/CT (Fig. 1d), it was not detected. On ^{18}F-FDOPA PET/CT (Fig. 1c), this lesion was detected only retrospectively after gaining knowledge of the lesion on ^{68}Ga-DOTATATE PET/CT (Fig. 1b) due to the observed physiologic uptake of ^{18}F-FDOPA in the gallbladder attributed to the normal excretion of ^{18}F-FDOPA through the biliary system and gallbladder and, hence, can be a potential pitfall on ^{18}F-FDOPA PET/CT imaging [18, 19]. Therefore, correlative anatomic imaging should be performed in order to avoid overlooking any gallbladder PGLs on ^{18}F-FDOPA PET/CT, as was the case described above.

Conclusion

Based on the 2017 WHO Classification of Endocrine Tumors, primary PGLs can be found in any tissue except bone and lymph nodes. Here, we present a very unusual location of possible *SDHD*-related primary PGL in the gallbladder wall

associated with *SDHD* mutation which could present as a potential pitfall on ^{18}F-FDOPA PET/CT. Moreover, this case shows the superiority of ^{68}Ga-DOTATATE in comparison to ^{18}F-FDOPA and ^{18}F-FDG in the detection of *SDHD*-related parasympathetic PGL. Therefore, careful surveillance imaging including functional imaging using ^{68}Ga-DOTATATE is necessary for the follow-up of any patient with hereditary PGL, including those associated with *SDHD* mutations.

Acknowledgements We express our sincere gratitude to the patients and families with PGL for their participation and support.

Funding Information This study was funded by the National Institutes of Health (grant number: Z1AHD008735) awarded to Karel Pacak.

Compliance with Ethical Standards

Conflict of Interest Zahraa Abdul Sater, Abhishek Jha, Adel Mandl, Sheila K. Mangelen, Jorge A. Carrasquillo, Alexander Ling, Melissa K. Gonzales, Osorio Lopes Abath Neto, Markku Miettinen, Karen T. Adams, Pavel Nockel, Mustapha El Lakis, and Karel Pacak declare that they have no conflict of interest.

Disclosure This work was supported, in part, by the Intramural Research Program of the National Institutes of Health, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and was supported, in part, by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from the individual participant included in the study.

References

1. Neumann HP, Pawlu C, Pęczkowska M, Bausch B, McWhinney SR, Muresan M, et al. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. JAMA. 2004;292:943–51.
2. Janssen I, Blanchet EM, Adams K, Chen CC, Millo CM, Herscovitch P, et al. Superiority of [68Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. Clin Cancer Res. 2015;21:3888–95.
3. Ece I, Alptekin H, Celik ZE, Sahin M. Gallbladder paraganglioma. Ulus Cerrahi Derg. 2015;31:244–6.
4. Wolff M. Paraganglioma of the gallbladder. Arch Surg. 1973;107:493.
5. Miller TA, Weber TR, Appelman HD. Paraganglioma of the gallbladder. Arch Surg. 1972;105:637–9.
6. Mehra S, Chung-Park M. Gallbladder paraganglioma: a case report with review of the literature. Arch Pathol Lab Med. 2005;129:523–6.
7. Hirano T. Paraganglioma of the gallbladder: report of a rare case. Am J Gastroenterol. 2000;95:1607–8.
8. Koplay M, Sivri M, Alptekin H, Erdogan H, Nayman A. Gallbladder paraganglioma: computed tomography and magnetic resonance imaging findings. Prague Med Rep. 2014;115:145–8.
9. Cho YU, Kim JY, Choi SK, Hur YS, Lee KY, Kim SJ, et al. A case of hemorrhagic gallbladder paraganglioma causing acute cholecystitis. Yonsei Med J. 2001;42:352–6.
10. Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. Eur J Nucl Med. 2001;28:836–46.
11. Reubi JC, Schar JC, Waser B, Wenger S, Heppeler A, Schmitt JS, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med. 2000;27:273–82.
12. Santhanam P, Taieb D. Role of 18F-FDOPA PET/CT imaging in endocrinology. Clin Endocrinol. 2014;81:789–98.
13. Belhocine T, Spaepen K, Dusart M, Castaigne C, Muylle K, Bourgeois P, et al. 18FDG PET in oncology: the best and the worst (review). Int J Oncol. 2006;28:1249–61.
14. Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, Eisenhofer G, et al. Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. J Natl Cancer Inst. 2012;104:700–8.
15. Favier J, Brière JJ, Burnichon N, Riviere J, Vescovo L, Benit P, et al. The Warburg effect is genetically determined in inherited pheochromocytomas. PLoS One. 2009;4:e7094.
16. Han S, Suh CH, Woo S, Kim YJ, Lee JJ. Performance of ^{68}Ga-DOTA-conjugated somatostatin receptor targeting peptide PET in detection of pheochromocytoma and paraganglioma: a systematic review and meta-analysis. J Nucl Med. 2018. https://doi.org/10.2967/jnumed.118.211706.
17. Archier A, Varoquaux A, Garrigue P, Montava M, Guerin C, Gabriel S, et al. Prospective comparison of (68)Ga-DOTATATE and (18)F-FDOPA PET/CT in patients with various pheochromocytomas and paragangliomas with emphasis on sporadic cases. Eur J Nucl Med Mol Imaging 2006;43:1248–1257.
18. Balan KK. Visualization of the gall bladder on F-18 FDOPA PET imaging: a potential pitfall. Clin Nucl Med. 2005;30:23–4.
19. Chondrogiannis S, Marzola MC, Al-Nahhas A, Venkatanarayana TD, Mazza A, Opocher G, et al. Normal biodistribution pattern and physiologic variants of 18F-DOPA PET imaging. Nucl Med Commun. 2013;34:1141–9.