Case Report

rare tumors

Rare Tumors
Volume 11: 1–5

DOI: 10.1177/2036361319831097
journals.sagepub.com/home/rtu
SAGE

^{68}Ga-DOTA-E-[c(RGDfK)]2 positron emission tomography–computed tomography in the evaluation of hepatic hemangioendothelioma epithelioid

Irma Soldevilla-Gallardo, Sevastian S Medina-Ornelas, Jenny Davanzo and Roberto Pedrero-Piedras

Abstract

Hemangioendothelioma epithelioid is a rare tumor that originates in soft tissues. Imaging evaluation with conventional modalities (tomography and magnetic resonance) is difficult. Novel radiotracers which capably evaluate angiogenesis may have a higher impact on the therapeutic decisions. A 45-year-old man underwent workup for thrombosis and was diagnosed with hemangioendothelioma epithelioid based on the results of liver pathology and immunohistochemistry. The decision of the multidisciplinary board was to begin with thalidomide. After 4 months, progression of disease was documented and right hepatectomy was performed. A ^{68}Ga-DOTA-E-[c(RGDfK)]2 positron emission tomography–computed tomography scan showed residual lesions. After documented angiogenesis by ^{68}Ga-DOTA-E-[c(RGDfK)]2 positron emission tomography–computed tomography, nintedanib was administrated. And 1 year later, progression of the disease was documented by positron emission tomography–computed tomography. Ipilimumab plus nivolumab was started and partial response and excellent clinical response were documented. Molecular imaging with ^{68}Ga-DOTA-E-[c(RGDfK)]2 positron emission tomography–computed tomography is a good biomarker of the response of hemangioendothelioma epithelioid, and ipilimumab plus nivolumab therapy demonstrated a good response.

Keywords

^{68}Ga-DOTA-E-[c(RGDfK)]2, hemangioendothelioma epithelioid, positron emission tomography, angiogenesis

Date received: 24 June 2018; accepted: 21 January 2019

Introduction

Hemangioendothelioma epithelioid (HEE) is a low-grade malignant vascular endothelial cell tumor that originates in soft tissues and rarely occurs in the liver.[1] The diagnosis is made through histopathology and immunohistochemistry because they lack specific clinical and/or radiological characteristics.[2] A new observation was reported regarding a case of HEE that highlights the importance of knowledge of pathophysiology and the close relationship that can be established by molecular imaging with positron emission tomography–computed tomography (PET/CT).

18F-fluorodeoxyglucose (^{18}F-FDG) PET/CT is the radiotracer most commonly used in the evaluation of tumor glycolytic activity, but cannot be used to evaluate angiogenesis.

Department of Nuclear Medicine and Molecular Imaging, Instituto Nacional de Cancerología, Mexico City, Mexico

Corresponding author:
Sevastian S Medina-Ornelas, Department of Nuclear Medicine and Molecular Imaging, Instituto Nacional de Cancerología, México. San Fernando avenue, 22 Col. Sección XVI, Del. Tlalpan, Mexico City C.P. 14080, Mexico.
Email: dr.sevastian@outlook.com

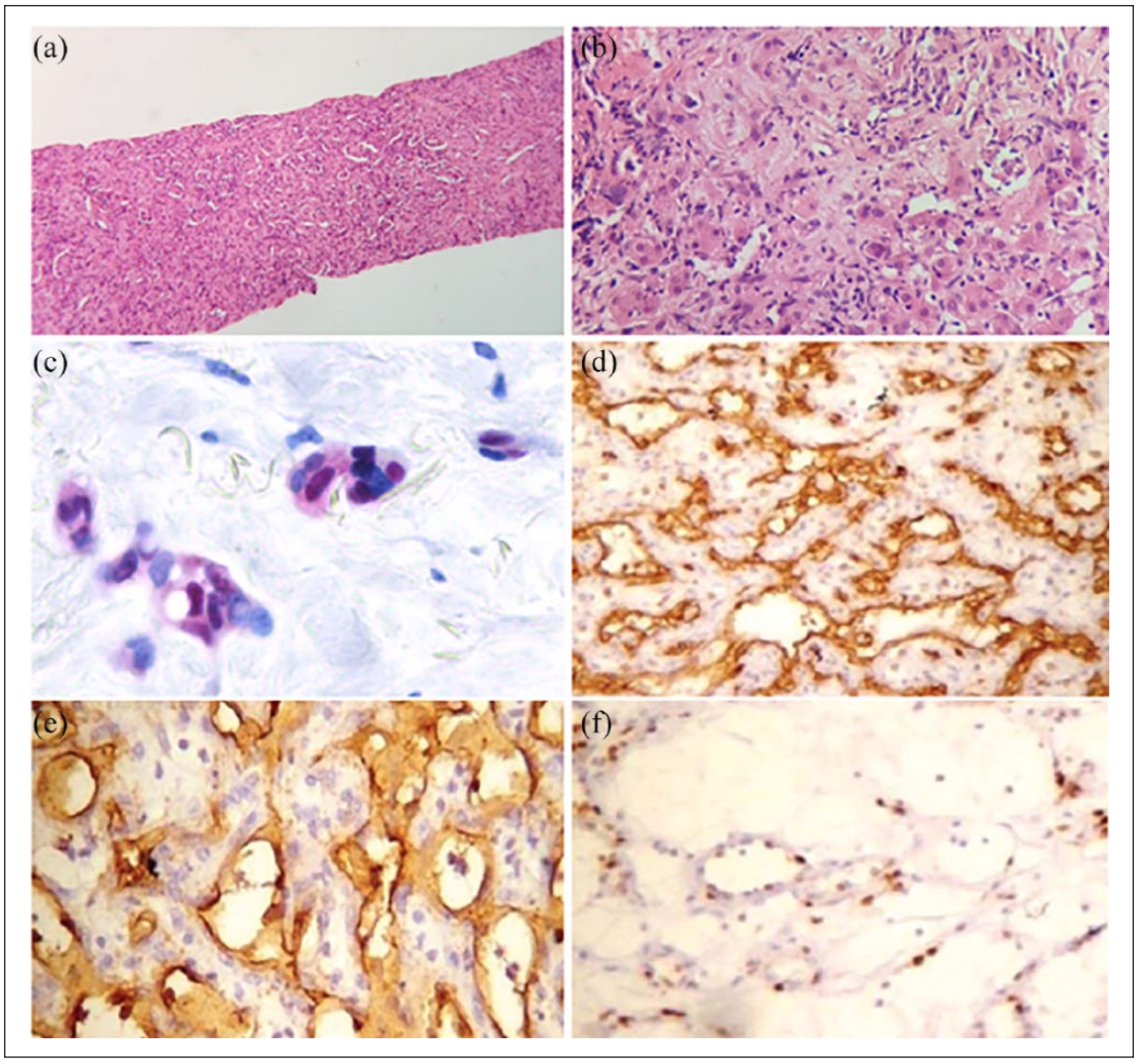

Figure 1. Pathological findings: (a) biopsy liver lesion showing the proliferation of polygonal epithelioid tumor cells with abundant vacuolated cytoplasm (hematoxylin and eosin, 200×); (b) tumor cells showing intravascular expansion, occlusion of larger vessels, and epithelioid cells arranged in strands, cords, and nests (hematoxylin and eosin, 400×); (c) TFE3 showing a nuclear reaction with a WWTR1-CAMTA1 fusion; liver lesion showing strong immunoreactivity to CD31 ((d) inset 400× and (e) CD34 inset 400×); and (f) a low proliferative activity ki-67 (10%).

^{68}Ga-DOTA-E-[(RGDfK)c]2 (68Ga-DOTA-RGD) is a radiotracer that targets integrin αvβ3, and may have an impact as a noninvasive method for assessing neovascularization and allows the follow-up and evaluation of response to the treatment of many pathologies.[3]

We report the case of a patient diagnosed with HEE treated with three different therapies and integral evaluation with a novel radiotracer.

Case presentation

A 45-year-old man, who presented with left extremity edema after a 24-h trip and a deep vein thrombosis documented, was treated with anticoagulation with subcutaneous enoxaparin. The general condition was good, without weight loss. The patient did not have a medical history of relevancy, only smoking suspended 10 years ago. Routine blood cell counts and biochemical investigations were within the reference range. Serological tests for hepatitis B and C were negative. The computed tomography reported hypodense focal lesions with a predominantly peripheral enhancement to the administration of intravenous contrast in segments V and VI, the largest of 26 mm. Magnetic resonance imaging (MRI) reported five hypointense nodular lesions in T1, hyperintense in T2, which restricted in the diffusion sequence and in the dynamic phase presented target enhancement, said lesions located in segments V and VI, the largest of up to 22 mm. The tumor markers, including Alpha-fetoprotein (AFP), human chorionic gonadotropin (GCh), carcinoembryonic antigen(CEA), prostatic specific antigen (PSA), CA 125, and CA19-9, were within normal limits; after these findings, ultrasound-guided biopsy of liver segment V lesion was performed (Figure 1).

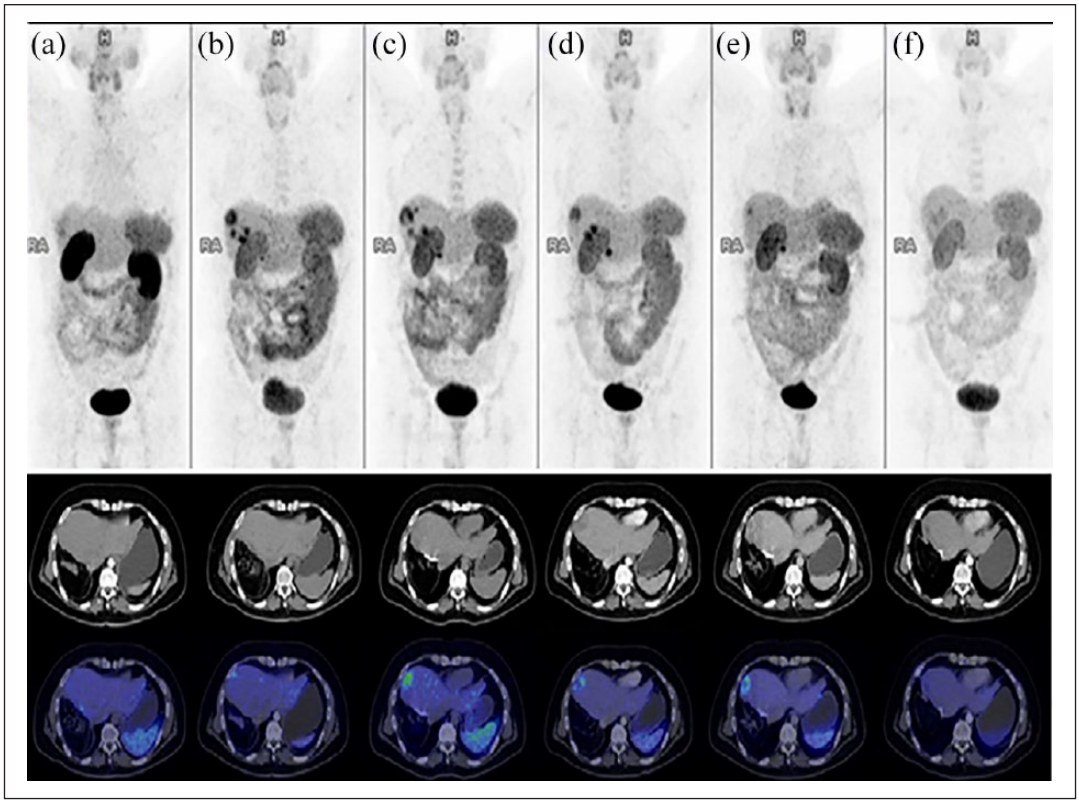

Figure 2. 68Ga-DOTA-E-[c(RGDfK)]2 PET/CT scan: (a) baseline PET/CT in maximum intensity projection (MIP; upper) and PET/CT fusion axial slices (lower) demonstrate normal biodistribution of the radiotracer and residual liver disease post hepatectomy; (b) after 3 months, PET/CT showed new hepatic lesions and progression of disease was documented; (c) after 6 months of the same therapy, a new hepatic lesion was seen; (d) 4 months later, the same lesions was seen and stable disease was documented; (e) 5 months after changing the therapy, morphologic lesions decreased and also molecular uptake of lesions and partial response was documented; (f) the last PET/CT showed a decrease of the lesions with a little uptake.

The decision of the multidisciplinary board was to begin primary monotherapy with thalidomide. MRI was performed 4 months later, documenting the progression of the disease with an increase of 20% in the size of the lesions; in the same month, a right hepatectomy without complications was performed, resecting all the visible lesions, and the histopathological report remained the same. Baseline ^{68}Ga-DOTA-RGD PET/CT scan was performed (October 2015) that reported two residual lesions in the left lobe with a focal uptake of the radiotracer as well as an increase of 20% in the liver lesions. The therapy is modified to nintedanib 150 mg for 12 h for 6 months, and a control ^{68}Ga-DOTA-RGD PET/CT scan is performed (January 2016) which documents progression of the disease. The treatment is continued without modification and the control ^{68}Ga-DOTA-RGD PET/CT scan is repeated (July 2016), which again reports progression, which is why the dose of nintedanib is increased to 200 mg every 12 h and cyclophosphamide 100 mg is added every 24 h; 4 months later, a ^{68}Ga-DOTA-RGD PET/CT scan was repeated to assess response to treatment reporting stable disease; meanwhile, functional status was poor (November 2016). Changes were decided in the treatment of combined immunotherapy Ipilimumab plus nivolumab posterior and 5 months ^{68}Ga-DOTA-RGD PET/CT scan was performed for assessment of documented partial response (April 2017). With the same treatment, after 8 months, the patient presented a clinical improvement on PET/CT (December 2017; Figure 2); the patient remained clinically asymptomatic.

Discussion

HEE is a rare neoplasm that originates from vascular endothelial cells, which is included within vascular tumors in the classification of soft tissue tumors according to the World Health Organization (WHO) 4th edition.[2] Mehrabi et al. reported less than 500 cases and reviewed 402 patients with HEE treated from 1984 to 2005. The majority of patients with HEE are asymptomatic; the clinical manifestations of the disease are nonspecific and may include pain in the right hypochondrium (48.6%), hepatomegaly (20.4%), and weight loss (15.6%).[4]

The most common treatment is liver transplantation; in a lower percentage, some doctors choose not to give any treatment; others prefer chemotherapy or radiotherapy, and the lower percent of liver resection. No standard treatment

currently exists for HEE; however, many reports suggest that orthotopic liver transplantation represents a good treatment even in cases of metastatic disease, whereas liver resection can be performed when a single lesion is observed, especially in larger lesions.[2,4]

In the present case, the patient suffered left hemiparesis associated with isolated tonic–clonic seizure and, after the event of deep vein thrombosis, hepatic and pulmonary lesions were incidentally documented. Extrahepatic metastases are observed in up to 36.6% of patients, which may include lung, regional lymph nodes, peritoneum, spleen bone, and diaphragm in decreasing order. Some rare manifestations of the disease, such as an ischemic vascular event, have also been reported.[5] The HEE is negative for AFP, ACE, and CA 19-9, which agrees with the patient presented in our case. MRI in the T1W1 sequence shows hypointense lesions with low signal intensity in the center and intermediate to high in T2W2. The sign of "capsular retraction" and a "halo" sign caused by central coagulative necrosis are key manifestations in both CT and MRI that provide diagnostic certainty.[6] The diagnosis depends on the histopathological staining of the cells, despite the infiltrative pattern of the lesions. The tumor is composed of epithelioid or dendritic cells with intracytoplasmic lumen. The diagnosis of HEE must be considered in the presence of one or more of the following aspects evaluated by immunoreactivity to CD31, CD34, and/or factor VIII antigen.[7]

In our case, the typical tumor morphology and the immunohistochemical positivity of endothelial cell markers (such as CD31 and CD34) support the diagnosis of HEE.

The patient's imaging follow-up was carried out using CT, MRI, and ^{68}Ga-DOTA-RGD PET/CT which is a specific molecular biomarker of angiogenesis when binding to integrin $\alpha v\beta 3$.[8–10]

The detailed characterization of the human genome has allowed better understanding of the molecular basis of carcinogenesis and an improvement in the management of patients through tools for tumor classification, which makes it possible to implement risk assessment tests for relapse or response to treatment in a personalized fashion. It is in this context that the molecular image becomes important, since there are currently multiple clinical trials that have demonstrated the prognostic utility of this through the use of ^{18}F-FDG PET/CT and the evaluation of other biomolecular pathways.[10]

The patient was managed with first-line antiangiogenic therapy with thalidomide, which has been shown to be effective,[11] and subsequently the inhibitor of tyrosine kinase (nintedanib) with the evaluation of response to treatment with ^{68}Ga-DOTA-RGD PET/CT scan, which documented the progression of the disease and led to a change in therapeutic behavior with the establishment of a third line of treatment with immunotherapy (ipilimumab + nivolumab), which remained stable until now in the evaluation with ^{68}Ga-DOTA-RGD PET/CT scan.

Conclusion

Molecular imaging with ^{68}Ga-DOTA-RGD PET/CT is a good biomarker of the response of HEE; since thalidomide is an antiangiogenic therapy and nintedanib is a potent triple tyrosine kinase inhibitor: anti-vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), it is possible to establish integrin $\alpha v\beta 3$ as a molecular target in the evaluation of treatment response and surveillance of rapidly growing neoplasms adding prognostic value.

Acknowledgements

We wish to thank the Nuclear Medicine staff at INCan, Mexico and Dr España for providing pathologic images. I.S.-G. and S.S.M.-O. contributed equally to this work.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Informed consent was obtained from the patient.

ORCID iD

Sevastian S Medina-Ornelas https://orcid.org/0000-0002-5761-2337

References

1. Weiss SW and Enzinger FM. Epithelioid hemangioendothelioma a vascular tumor often mistaken for a carcinoma. *Cancer* 1982; 50(5): 970–981.
2. Mistry AM, Gorden DL, Busler JF, et al. Diagnostic and therapeutic challenges in hepatic epithelioid hemangioendothelioma. *J Gastrointest Cancer* 2012; 43(4): 521–525.
3. Arrieta O, Garcia-Perez FO, Michel-Tello D, et al. Response assessment of 68Ga-DOTA-E-[c(RGDfK)]2 PET/CT in lung adenocarcinoma patients treated with nintedanib plus docetaxel. *J Nucl Med* 2018; 59(3): 403–409.
4. Mehrabi A, Kashfi A, Fonouni H, et al. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. *Cancer* 2006; 107(9): 2108–2121.
5. Zis P, Assi A, Kravaritis D, et al. Ischemic stroke as the first manifestation of hepatic epithelioid hemangioendothelioma. *J Stroke Cerebrovasc Dis* 2014; 23(3): e237–e240.
6. Dong A, Dong H, Wang Y, et al. MRI and FDG PET/CT findings of hepatic epithelioid hemangioendothelioma. *Clin Nucl Med* 2013; 38(2): e66–e73.
7. Flucke U, Vogels RJ, De Saint Aubain Somerhausen N, et al. Epithelioid hemangioendothelioma: clinicopathologic, immunohistochemical, and molecular genetic analysis of 39 cases. *Diagn Pathol* 2014; 9(1): 131–142.

8. Liu S. Radiolabeled multimeric cyclic RGD peptides as integrin α v β 3 targeted radiotracers for tumor imaging. *Mol Pharm* 2006; 3(5): 472–487.
9. Tateishi U, Oka T and Inoue T. Radiolabeled RGD peptides as integrin alpha(v)beta3–targeted PET tracers. *Curr Med Chem* 2012; 19(20): 3301–3309.
10. Blom E, Velikyan I, Estrada S, et al. Ga-labeling of RGD peptides and biodistribution. *Int J Clin Exp Med* 2012; 5(2): 165–172.
11. Raphael C, Hudson E, Williams L, et al. Successful treatment of metastatic hepatic epithelioid hemangioendothelioma with thalidomide: a case report. *J Med Case Rep* 2010; 4(1): 413.