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 (18F-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:
Sebastían 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
68Ga-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).
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 68Ga-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 68Ga-DOTA-RGD PET/CT scan is performed (January 2016) which documents progression of the disease. The treatment is continued without modification and the control 68Ga-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 68Ga-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 68Ga-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. 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%).

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \( \alpha \beta_3 \).\textsuperscript{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.\textsuperscript{10}

The patient was managed with first-line antiangiogenic therapy with thalidomide, which has been shown to be effective,\textsuperscript{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 \( \alpha \beta_3 \) as a molecular target in the evaluation of treatment response and surveillance of rapidly growing neoplasms adding prognostic value.

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**Informed consent**

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**ORCID iD**

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

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