Clinical Case Report

Medicine®

OPEN

Complete metabolic response to therapy of hepatic epithelioid hemangioendothelioma evaluated with ^{18}F-fluorodeoxyglucose positron emission tomography/contrast-enhanced computed tomography

A CARE case report

Romina Grazia Giancipoli, MD[a,b], Serena Monti, PhD[c], Olca Basturk, MD[d], David Klimstra, MD[d], Mary Louise Keohan, MD[e], Orazio Schillaci, MD, PhD[f,g], Giuseppe Corrias, MD[a,h], Peter Sawan, MD, FRCR[a], Lorenzo Mannelli, MD, PhD[a,*]

Abstract

Rationale: Hepatic epithelioid hemangioendothelioma (EHE) is a rare malignant vascular tumor of endothelial origin with a highly variable clinical presentation and natural history. Given its vascular origin, new therapies with inhibitors of vascular endothelial growth factor (VEGF) have been introduced in the treatment of these patients and have shown promising results. Few reports have described the role of ^{18}F-Fluorodeoxyglucose positron emission tomography/contrast-enhanced computed tomography (^{18}F-FDG PET/CT) in the evaluation of this tumor after treatment with anti-angiogenic agents. Our case reports how ^{18}F-FDG PET-CT scan was critical in the assessment of this tumor after treatment with an anti-angiogenic agent, Pazopanib, demonstrating complete metabolic response.

Patient concerns: A 30-year-old man with no previous significant medical history presented with pain in the right upper quadrant for over a year.

Diagnoses: Multiple hepatic masses were found on abdominal ultrasound. Liver biopsy confirmed the diagnosis of epithelioid hemangioendothelioma. ^{18}F-FDG PET/CT was performed for staging. Multiple FDG-avid hepatic, splenic, and lymph nodes lesions were detected on ^{18}F-FDG PET/CT. A subsequent spleen biopsy confirmed splenic involvement. Immunohistochemistry was positive for CD31, CD34, and ERG, supporting the diagnosis of epithelioid hemangioendothelioma.

Interventions: A 1-year cyclophosphamide treatment was provided followed by Pazopanib for 17 months.

Outcomes: Six years after the first ^{18}F-FDG PET/CT, ^{18}F-FDG PET/CT performed for restaging demonstrated complete metabolic response to therapy. Follow-up CT demonstrated no interval changes in size of some of the treated lesions.

Lesson: ^{18}F-FDG PET/CT is useful for baseline assessment and posttreatment follow-up of this rare cancer.

Abbreviations: CT = computed tomography, EHE = epithelioid hemangioendothelioma, ERG = ETS (erythroblast transformation-specific) related gene, FDG = fluorodeoxyglucose, MIP = maximum intensity projection, PET = positron emission tomography, SUVmax = maximum standardized uptake value, VEGF = vascular endothelial growth factor.

Keywords: abdominal pain, computed tomography, epithelioid hemangioendothelioma, liver, mass, positron emission tomography

Editor: N/A.

Grant support was provided by MSK Cancer Center Support Grant/Core Grant P30 CA008748.

Work by Romina Grazia Giancipoli and Giuseppe Corrias was partially supported by a scholarships awarded by ISSNAF Imaging Science Chapter.

The authors have no conflict of interest to disclose.

[a] Department of Radiology, [b] Department of Nuclear Medicine, Sapienza University of Rome, [c] IRCCS SDN, Naples, [d] Department of Pathology, [e] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, [f] Department of Biomedicine and Prevention, Nuclear Medicine Unit, Tor Vergata University, Rome, [g] IRCCS Neuromed, Pozzilli, [h] Department of Radiology, University of Cagliari, Cagliari, Italy.

[*] Correspondence: Lorenzo Mannelli, 300 East 66th Street, New York, NY, 10021 (e-mail: mannellilorenzo@yahoo.it).

Medicine (2018) 97:42(e12795)

Received: 9 May 2018 / Accepted: 19 September 2018

http://dx.doi.org/10.1097/MD.0000000000012795

1. Introduction

Epithelioid hemangioendothelioma (EHE) was originally described by Studer and Selby[1] as "a rare vascular tumor, composed of epithelioid and histiocytoid vascular endothelial cells in myxoid or fibrotic stroma." It can arise in multiple locations throughout the body. In the liver, EHE usually presents as multifocal, heterogeneously enhancing nodules, and is usually an incidental finding on imaging; patients usually report non-specific abdominal symptoms. The histopathological examination has a decisive role for the diagnosis.[2] Imaging modalities such as ^{18}F-Fluorodeoxyglucose positron emission tomography/contrast-enhanced computed tomography (^{18}F-FDG PET/CT) and contrast-enhanced CT scans can be useful in the assessment of EHE. Given its vascular origin, new therapies such as inhibitors of vascular endothelial growth factor (VEGF) have been introduced in the management of these patients and have shown promising results.[3,4] In the literature, the importance of ^{18}F-FDG PET/CT for detecting EHE and determining its recurrence has been described widely.[5–9] However, few reports have described the impact of ^{18}F-FDG PET/CT in the evaluation of the extent of disease after treatment with anti-angiogenic agents.[3] Our case reports how ^{18}F-FDG PET-CT was critical in the assessment of EHE after treatment with an anti-angiogenic agent, Pazopanib, showing a complete metabolic response. In agreement with the literature to date, our PET and CT findings point toward stabilization of the disease.

2. Case presentation

A 30-year-old man presented to the emergency department with pain in the right upper quadrant for over a year. He reported no other clinical symptoms. The pain was not associated with fever, chills, or night sweats. Laboratory findings, liver function tests, and electrocardiogram results were unremarkable. Palpable masses were present on physical examination. Viral markers for hepatitis B and C viruses were negative. Abdominal ultrasound was performed, and the presence of multiple hepatic masses was confirmed (not shown). Liver biopsy confirmed the diagnosis of EHE (not shown), revealing the presence of hyalinized nodules containing individually arranged atypical epithelioid cells, many of which had intracytoplasmatic lumina. There were entrapped non-neoplastic bile ducts between the nodules of tumor, and the interface with the hepatocytes was ill defined. Malignant cells were present within the sinusoids and focal intravascular growth was also noted.

An ^{18}F-FDG PET/CT was ordered for staging. PET/CT was performed after the patient underwent a 6-hour fasting period with a blood glucose level of 98 mg/dL. Images were obtained 40 minutes after intravenous injection of 12 mCi (444 MBq) ^{18}F-FDG. Low-dose CT and PET images from the mid-skull to the upper thighs were acquired with a GE Discovery 690-A PET/CT (GE Healthcare, Chicago, IL). The CT protocol used for the PET/CT study was designed for attenuation correction and anatomic localization of PET abnormalities. The standardized uptake values (SUV) were normalized to patient body weight and indicated the highest activity concentration (SUVmax) in a given disease site. In PET/CT images, normal physiologic biodistribution was observed throughout the whole body with multiple FDG-avid hepatic, splenic, and retroperitoneal lymph node lesions (Fig. 1A–D). The PET scan showed mildly increased FDG uptake in the liver (lesion in hepatic segment 4, SUVmax: 5.7; lesion in hepatic segment 8, SUVmax: 5.4; lesion in hepatic

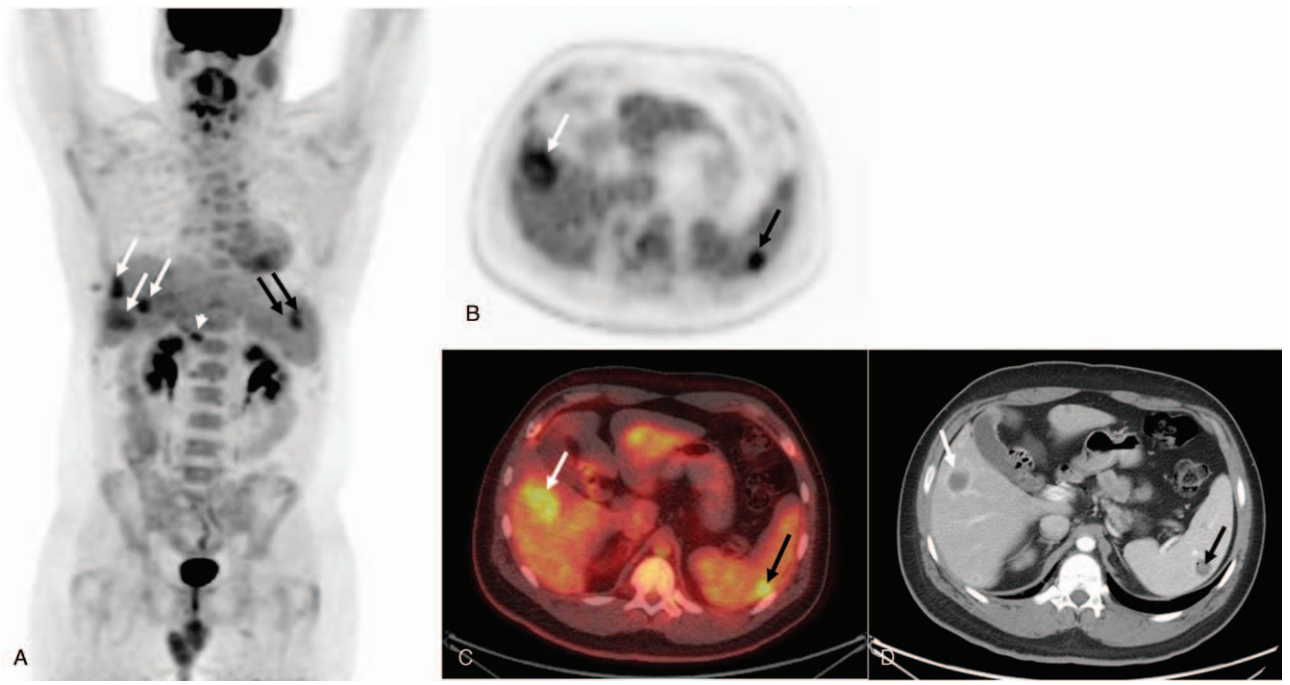

Figure 1. At baseline. ^{18}F-FDG PET/CT scan with contrast. (A) 3D MIP image in coronal view shows multiple hepatic lesions (white arrows), a retroperitoneal lymph node lesion (white arrowhead), and a splenic lesion (black arrows). (B) PET scan shows mildly increased FDG uptake in the liver (lesion in hepatic segment 4, SUVmax: 5.7; lesion in hepatic segment 8, SUVmax: 5.4; lesion in hepatic segment 5, SUVmax 4.8; liver background, SUV mean 2.2), spleen (lesion in the splenic dome, SUVmax 5.7; lesion located more inferiorly, SUVmax 5.0), and retroperitoneal lymph node (lesion in the retroperitoneal lymph node, SUVmax 5.3). (C) FDG PET shows an FDG-avid lesion in hepatic segment 5, SUVmax 4.8 (white arrow) and an FDG-avid lesion in the spleen, SUVmax 5.0 (black arrow). (D) Portal phase post-contrast CT scan shows an enhanced hepatic lesion in segment 5 (white arrow) and an enhanced splenic lesion (black arrow). ^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/contrast-enhanced computed tomography; MIP = maximum intensity projection.

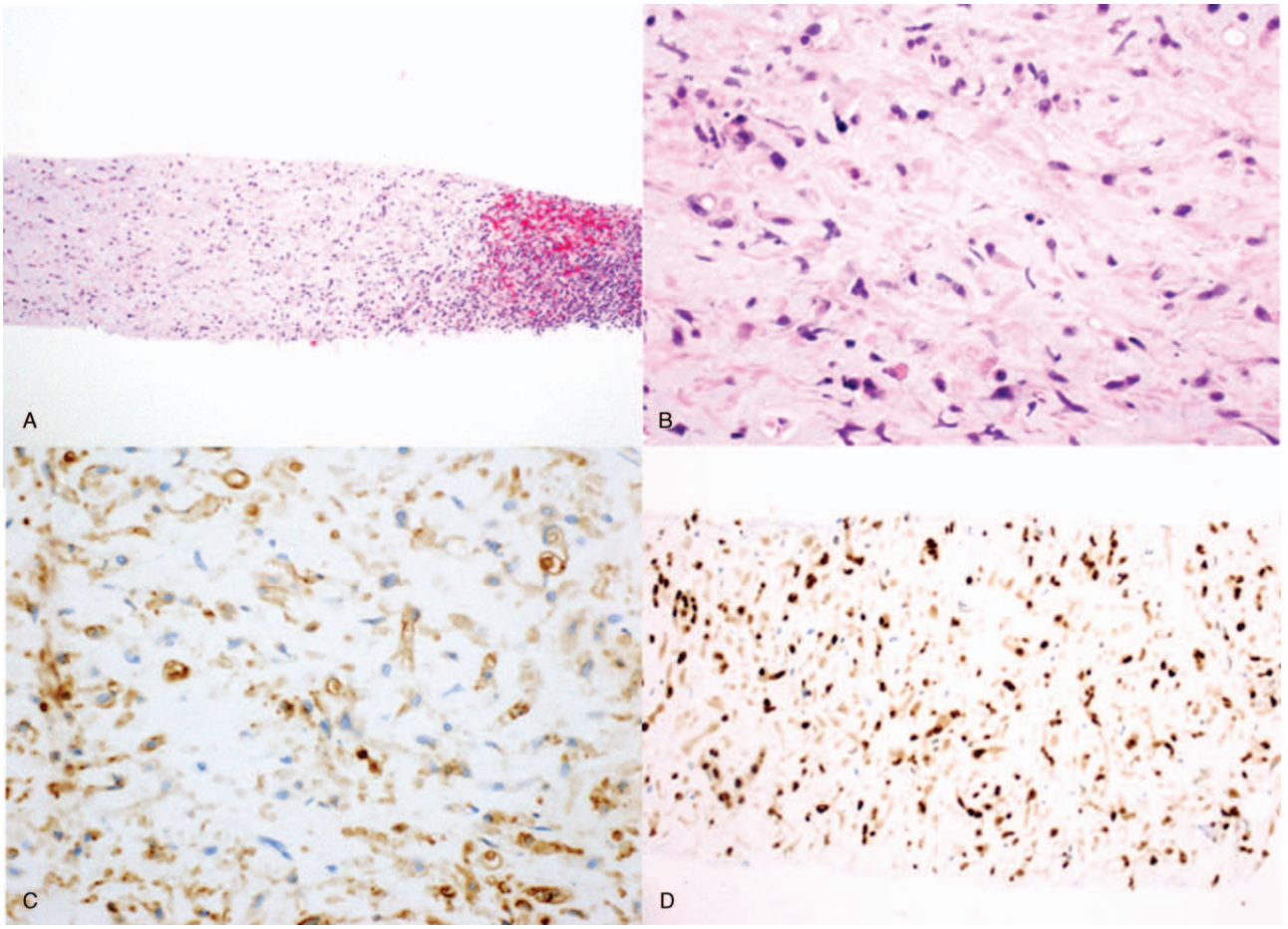

Figure 2. Spleen biopsy revealed (A) an infiltrative tumor, characterized by cords of spindle to epithelioid cells embedded in a fibromyxoid stroma (hematoxylin and eosin stain, 20×). (B) The tumor cells had focal intracytoplasmatic vacuoles containing red blood cells (hematoxylin and eosin stain, 400×). (C) CD 31 and (D) ERG immunohistochemical stains label the tumor cells, confirming the diagnosis of epithelioid hemangioendothelioma (200×). ERG = ETS (erythroblast transformation-specific) related gene.

segment 5, SUVmax 4.8; liver background, SUV mean 2.2), spleen (lesion in the splenic dome, SUVmax 5.7; lesion located more inferiorly, SUVmax 5.0), and retroperitoneal lymph nodes (lesion in a retroperitoneal lymph node, SUVmax 5.3). Spleen biopsy confirmed splenic involvement and revealed an infiltrative tumor characterized by cords of spindle to epithelioid cells embedded in a fibromyxoid stroma (hematoxylin and eosin stain, 20×) (Fig. 2A and B). CD 31 (Fig. 2C) and ERG (Fig. 2D) immunohistochemical stains labeled the tumor cells, supporting the diagnosis of epithelioid hemangioendothelioma (200×).

Initial treatment with oral cyclophosphamide was provided for 1 year followed by treatment with Pazopanib for 17 months. The patient subsequently underwent follow-up CT every 6 months. Six years after the first PET scan, an ^{18}F-FDG PET/CT scan was performed for restaging and showed complete metabolic response (Fig. 3A–C). There was no evidence of FDG uptake in all the treated lesions. Follow-up CT demonstrated that some of the treated lesions showed no interval changes in size but demonstrated partial calcifications (Fig. 3D and E).

3. Discussion

Written informed consent for this case report series was not required, as established by our institutional review board policies. Hepatic EHE is a rare malignant vascular tumor of endothelial origin with a highly variable clinical presentation and natural history.[10–12] It has an estimated incidence of 1 to 2 in 1,000,000 persons.[13,14] CT and magnetic resonance imaging (MRI) characteristics of this tumor are similar to that of cholangiocarcinoma, hepatocellular carcinoma, and colonic adenocarcinoma metastases.[1,15–19] The lung, peritoneum, spleen, lymph nodes, and bone are the most common sites of extra-hepatic involvement.[20] Current management options for hepatic EHE include medical therapy with anti-angiogenic agents, chemoradiotherapy, liver resection, liver transplantation, and a watch-and-wait strategy.[21,22] Given its vascular origin, new therapies with inhibitors of VEGF, such as Pazopanib, have been introduced in the management of these patients and have shown promising results.[4,23] Pazopanib is an anti-angiogenic agent that inhibits VEGF. VEGF receptors are detectable on EHE tumor cells, suggesting that VEGF plays a role in EHE growth.[23] Bally et al[4] previously reported promising results including prolonged disease stabilization in another patient with hepatic EHE who was treated with Pazopanib. They suggested that posttreatment intratumoral changes seen at follow-up CT such as variable tumor density without clear tumor shrinkage and calcifications could be considered highly suggestive of tumor response. In agreement with their report, we found no changes in

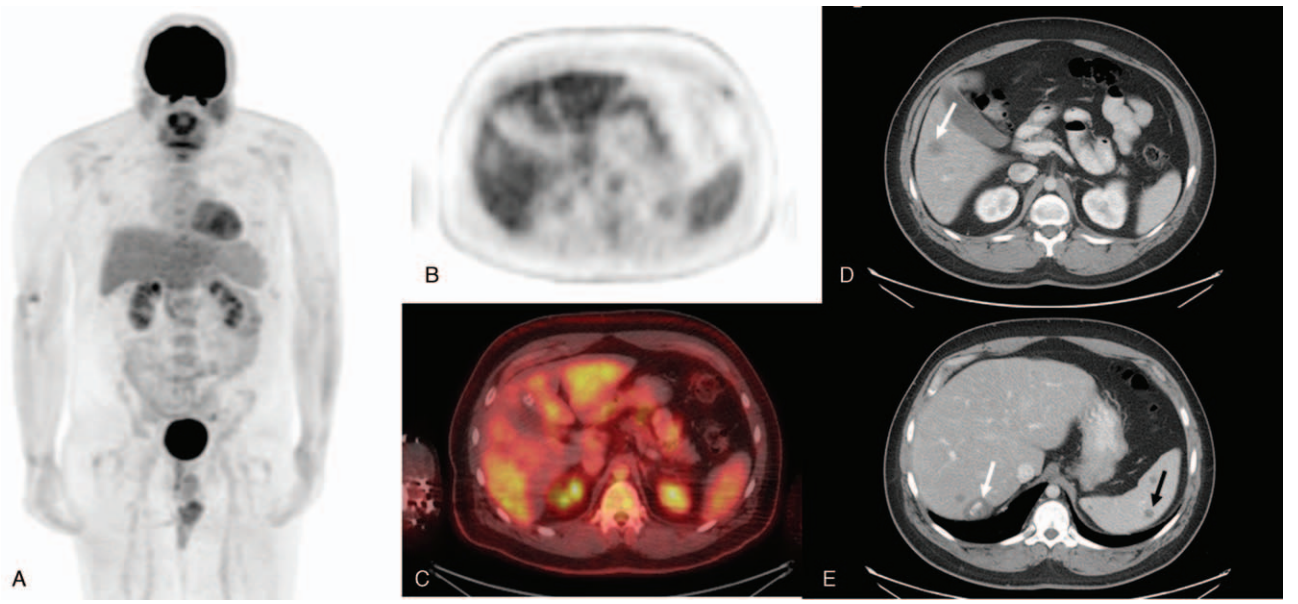

Figure 3. Six years follow-up post chemotherapy treatment with oral cyclophosphamide and Pazopanib. PET/CT scan for restaging shows complete metabolic response to therapy: (A) 3D MIP image, (B) PET scan, and (C) PET/CT scan. No evidence of FDG uptake is seen on the 3D MIP image in coronal view, PET scan, and PET/CT scan. (D) Portal phase post-contrast CT scan shows the treated lesion in hepatic segment 5/6 (white arrow). (E) Portal phase post-contrast CT scan shows that some of treated lesions were unchanged in size but had partial calcifications, e.g., lesion in hepatic segment 7 (white arrow) and splenic lesion (black arrow). MIP = maximum intensity projection, PET/CT = positron emission tomography/contrast-enhanced computed tomography.

lesion size but partial calcifications in some of the treated lesions in our patient at follow-up CT.

The role of ^{18}F-FDG PET/CT for the staging and posttreatment evaluation of EHE, in particular hepatic EHE, has already been described in literature. Several studies reported that all hepatic EHE lesions show intense high glucose uptake on ^{18}F-FDG PET/CT.[5–7] Kitapci et al[8] reported that dual time-point ^{18}F-FDG PET/CT could be important for detecting EHE and determining the extent of disease, because some lesions, missed by the early scan, were detected by the delay scan.

Dong et al[9] reported that FDG PET/CT findings could reflect the histopathological pattern of the tumor. They hypothesized that the degree of glucose uptake of EHE may be related to its cellularity rather than tumor size. Thus, tumors with high cellularity will show increased FDG uptake due to increased glucose metabolism compared with the stroma while tumors with low cellularity and a relative high amount of stroma will show low glucose uptake. Since the majority of patients with high cellularity tumors were also found to have poor outcomes, they suggested that the degree of FDG uptake, correlating to the cellularity of tumor, may be helpful for predicting its clinical behavior.[9] To date, few reports have described a complete metabolic response to therapy seen at ^{18}F-FDG PET/CT scan.[3,24] Suga et al[24] reported the utility of ^{18}F-FDG PET/CT for monitoring radiation therapy response. Seven months after radiotherapy, FDG uptake disappeared in the treated hepatic nodules, while the remaining untreated nodule showed persistently intense uptake. Lastly, Semenisty et al[3] reported a case of metastatic pulmonary epithelioid hemangioendothelioma with long-lasting response to therapy with Pazopanib where response was associated with decreased FDG uptake at PET/CT. In particular, on the PET scan performed for restaging, there was no evidence of glucose uptake in the mediastinal lymph nodes and in the lung lesions, with reduced metabolic response in the liver. In agreement with these studies, in our case, there was no evidence of FDG uptake on the PET scan in all treated lesions in the liver and retroperitoneal lymph nodes.

^{18}F-FDG PET/CT scan was critical in the assessment of our patient, demonstrating complete metabolic response to therapy. In accordance with the literature to date, our PET and CT findings point toward stabilization of the disease. The main limitation of this case study is the lack of further information related to the follow-up of the patient. Furthermore, the data currently available are still limited and should be integrated to deepen the role of ^{18}F-FDG PET/CT for baseline and posttreatment assessment in hepatic EHE.

Author contributions

The authors Romina Grazia Giancipoli, Serena Monti, Olca Basturk, David Klimstra, Mary Louise Keohan, Orazio Schillaci, Giuseppe Corrias, Peter Sawan, and Lorenzo Mannelli were equally involved in acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, technical, and material support of this study.

Writing – original draft: Romina Grazia Giancipoli, Serena Monti, Olca Basturk, David Klimstra, Mary Louise Keohan, Orazio Schillaci, Lorenzo Mannelli.

Writing – review & editing: Giuseppe Corrias, Peter Sawan.

References

[1] Studer LL, Selby DM. Hepatic epithelioid hemangioendothelioma. Arch Pathol Lab Med 2018;142:263–7.

[2] Miller WJ, Dodd GD3rd, Federle MP, et al. Epithelioid hemangioendothelioma of the liver: imaging findings with pathologic correlation. AJR Am J Roentgenol 1992;159:53–7.

[3] Semenisty V, Naroditsky I, Keidar Z, et al. Pazopanib for metastatic pulmonary epithelioid hemangioendothelioma-a suitable treatment option: case report and review of anti-angiogenic treatment options. BMC Cancer 2015;15:402.

[4] Bally O, Tassy L, Richioud B, et al. Eight years tumor control with pazopanib for a metastatic resistant epithelioid hemangioendothelioma. Clin Sarcoma Res 2015;5:12.
[5] Lin E, Agoff N. Recurrent hepatic epithelioid hemangioendothelioma: detection by FDG PET/CT. Clin Nucl Med 2007;32:949–51.
[6] Rest CC, Botton E, Robinet G, et al. FDG PET in epithelioid hemangioendothelioma. Clin Nucl Med 2004;29:789–92.
[7] Nguyen BD. Epithelioid hemangioendothelioma of the liver with F-18 FDG PET imaging. Clin Nucl Med 2004;29:828–30.
[8] Kitapci MT, Akkas BE, Gullu I, et al. FDG-PET/CT in the evaluation of epithelioid hemangioendothelioma of the liver: the role of dual-time-point imaging. A case presentation and review of the literature. Ann Nucl Med 2010;24:549–53.
[9] Dong A, Dong H, Wang Y, et al. MRI and FDG PET/CT findings of hepatic epithelioid hemangioendothelioma. Clin Nucl Med 2013;38: e66–73.
[10] Makhlouf HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. Cancer 1999;85:562–82.
[11] Errani C, Sung YS, Zhang L, et al. Monoclonality of multifocal epithelioid hemangioendothelioma of the liver by analysis of WWTR1-CAMTA1 breakpoints. Cancer Genet 2012; 205:12–7.
[12] Antonescu CR, Le Loarer F, Mosquera JM, et al. Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. Genes Chromosomes Cancer 2013;52:775–84.
[13] Elleuch N, Dahmani W, Aida Ben S, et al. Hepatic epithelioid hemangioendothelioma: a misdiagnosed rare liver tumor. Presse Med 2018;47:182–5.
[14] Weiss SW, Ishak KG, Dail DH, et al. Epithelioid hemangioendothelioma and related lesions. Semin Diagn Pathol 1986;3:259–87.
[15] Lamba R, Fananapazir G, Corwin MT, et al. Diagnostic imaging of hepatic lesions in adults. Surg Oncol Clin N Am 2014;23:789–820.
[16] Lomas DJ, Mannelli L. Chapter 31: The liver and spleen. Graiger & Allison's Diagnostic Radiology E-Book. Vol 1 6th ed.Elsevier Health Science, Churchill Livingstone:2014;722–76.
[17] Lyburn ID, Torreggiani WC, Harris AC, et al. Hepatic epithelioid hemangioendothelioma: sonographic, CT, and MR imaging appearances. AJR Am J Roentgenol 2003;180:1359–64.
[18] Yarze N, Yarze JC. Radiographic and histologic findings of a rare liver tumor-hepatic epithelioid hemangioendothelioma. Dig Dis Sci 2016;61: 1778–9.
[19] Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. Cancer 1982;50:970–81.
[20] Gurung S, Fu H, Zhang WW, et al. Hepatic epithelioid hemangioendothelioma metastasized to the peritoneum, omentum and mesentery: a case report. Int J Clin Exp Pathol 2015;8:5883–9.
[21] Weitz J, Klimstra DS, Cymes K, et al. Management of primary liver sarcomas. Cancer 2007;109:1391–6.
[22] Ishak KG, Sesterhenn IA, Goodman ZD, et al. Epithelioid hemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. Hum Pathol 1984;15:839–52.
[23] Park MS, Ravi V, Araujo DM. Inhibiting the VEGF-VEGFR pathway in angiosarcoma, epithelioid hemangioendothelioma, and hemangiopericytoma/solitary fibrous tumor. Curr Opin Oncol 2010;22:351–5.
[24] Suga K, Kawakami Y, Hiyama A, et al. F-18 FDG PET/CT monitoring of radiation therapeutic effect in hepatic epithelioid hemangioendothelioma. Clin Nucl Med 2009;34:199–202.