Clinical Case Report

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Diffuse hepatic epithelioid hemangioendothelioma with multiple splenic metastasis and delayed multifocal bone metastasis after liver transplantation on FDG PET/CT images

A case report

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Abstract

Rationale: Malignant hepatic epithelioid hemangioendotheliom (HEH) is a rare vascular tumor of endothelial origin, with multiple metastases to the spleen. This report describes a diffuse HEH with splenic metastasis on 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) images and delayed mutifocal bone metastasis after liver transplantation (LTx).

Patient concerns: A 30-year-old male was admitted to our hospital with a complaint of abdominal distension, fatigue, and anorexia for 2 months.

Diagnoses: Mild to moderate FDG uptake in the whole liver, and multifocal FDG uptake in the spleen were observed on 18F-FDG PET/CT scan. Ultrasound guided liver biopsy was performed, and a diagnosis of HEH was confirmed.

Interventions: The patient underwent LTx and splenectomy.

Outcomes: The patient developed low back pain due to unknown etiology, 3 months after surgery. A follow-up 18F-FDG PET/CT scan demonstrated multifocal bone destruction. Unfortunately, the patient died 12 months after surgery.

Lessons: It is noteworthy that despite liver transplantation for the treatment of HEH, there may be a risk of recurrence. For these patients with extrahepatic lesions, adjuvant chemotherapy may be a useful alternative treatment method for the prevention of recurrence.

Abbreviations: AFP = alpha-fetoprotein, CA 125 = carbohydrate antigen 125, CA 19–9 = carbohydrate antigen 19–9, DB = direct bilirubin, FDG = fluorodeoxyglucose, HEH = hepatic epithelioid hemangioendothelioma, LTx = liver transplantation, PET/CT = positron emission tomography/computed tomography, PTT = partial thromboplastin time, PT = prothrombin time, SUVmax = maximum of standardized uptake value, TBA = total bile acid, TB = total bilirubin.

Keywords: bone metastasis, computed tomography, epithelioid hemangioendothelioma, fluorodeoxyglucose, liver transplantation, positron emission tomography, spleen

1. Introduction

Malignant hepatic epithelioid hemangioendothelioma (HEH) is a rare vascular tumor of endothelial origin.[1] It can present as diffuse, multifocal, or solitary nodular form [1–4]; the diffuse form is considered to be the advanced stage due to coalescence of the lesions; this is associated with vascular infiltration of hepatic and/or portal veins,[4] and may be prone to metastasis. To the best of our knowledge, there are a few reports on the diagnosis and treatment evaluation of HEH using fluorodeoxyglucose positron emission tomography (FDG PET) or PET/computed tomography (CT) findings; moreover, such reports have mainly focused on the multifocal or solitary nodular form.[5–10] The degree of FDG uptake may be helpful in suggesting a diagnosis of HEH as opposed to other hepatic malignancies. Moreover, ^{18}F-FDG PET/CT has a significant advantage in its ability to detect potential metastasis in HEH patients, especially in the diffuse form.

2. Case description

A 30-year-old male was admitted to our hospital with a complaint of abdominal distension, fatigue, and anorexia for 2 months. He was not an alcoholic. Physical examination revealed jaundice, hepatomegaly, and hard liver with moderate ascites. Viral markers for hepatitis A, B, and C were negative. The levels of carbohydrate antigen 19–9 (CA 19–9), carbohydrate antigen 125 (CA 125), ferritin, and alpha-fetoprotein (AFP) were 50.33

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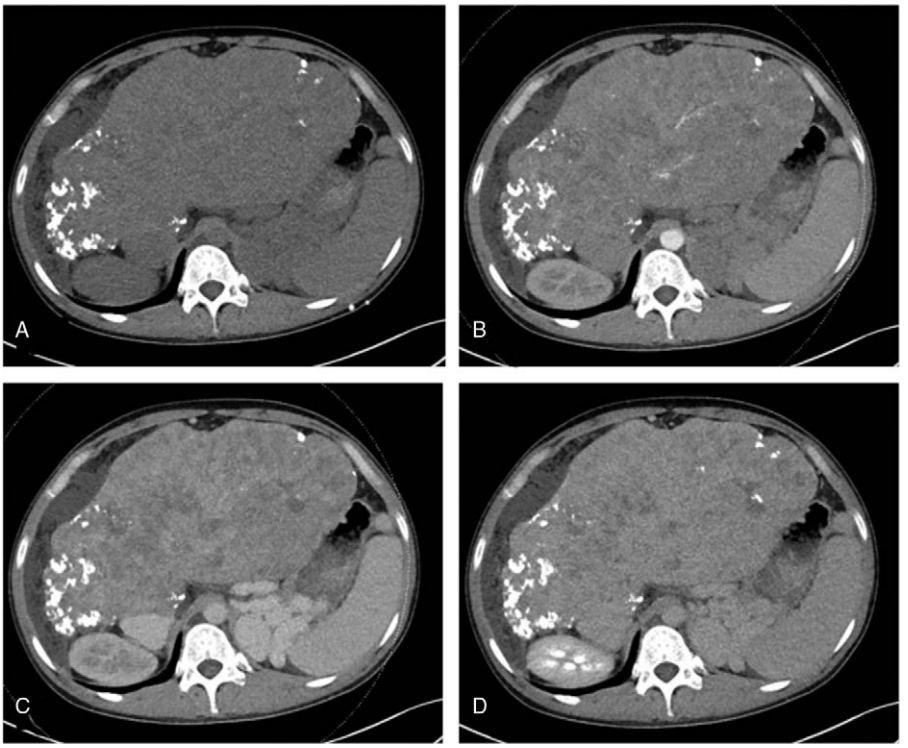

Figure 1. Contrast enhanced computed tomography scan of the abdomen showing multifocal lesions enhanced progressively during the arterial phase, portal phase, and delayed phase.

(normal range < 35.00 KU/L), 362.53 (normal range < 35.00 KU/L), 423.21 (normal range, 0~322.00 ng/mL), and 1.56 (normal range <20 ng/mL), respectively. Liver function tests showed the total bilirubin (TB), direct bilirubin (DB), and total bile acid (TBA) levels to be 441.2 (normal range, 5.1~17.1 μmol/L), 262.1 (normal range, 0~6.0 μmol/L), and 150.3 (normal range, 0~10.0 μmol/L), respectively. Coagulation function test revealed a normal prothrombin time and partial thromboplastin time (PT/PTT). Contrast enhanced CT scan of the abdomen showed multiple soft-tissue density nodules with irregular mild to moderate enhancement (Fig. 1). Moreover, peripheral multifocal calcifications were noted. Liver cirrhosis, esophageal and gastric varices, and moderate ascites were also seen, and multiple low-density nodules were observed in the spleen. ^{18}F-FDG PET/CT was performed due to suspected cholangiocarcinoma or hepatocellular carcinoma with multiple metastases to the spleen (Fig. 2). Axial fusion images demonstrated pervasively mild to moderate FDG uptake in the whole liver, and multifocal FDG uptake in the spleen. Ultrasound guided liver biopsy was performed, and a diagnosis of HEH was confirmed (Fig. 3). The patient then underwent liver transplantation and splenectomy. However, the patient developed low back pain due to unknown etiology, 3 months after the liver transplantation (LTx); bone metastasis was suspected as a result of multifocal lumbosacral destruction observed on lumbar magnetic resonance imaging. A follow-up whole body 18F-FDG PET/CT scan was performed for further evaluation (Fig. 4). The transplanted liver showed normal morphology without abnormal FDG uptake. However, multifocal osteolytic lesions with moderate FDG uptake were observed in the lumbar and sacral vertebrae, and right iliac bone, with a SUVmax of 6.5. Unfortunately, the patient died 12 months after surgery.

3. Discussion

As HEH is a relatively rare malignancy, its imaging findings are not widely reported. There are a few reports describing the FDG PET or PET/CT scan findings for the diagnosis and treatment evaluation of HEH; the reports that exist mainly focus on the multifocal or solitary nodular form.[5–10] This report details the imaging findings of the diffuse form of HEH. Low-density pattern on CT images are the most common abnormal feature, with calcifications accounting for most of the additional CT scan findings.[2] The initial PET images showed diffuse lesions with mild to moderate FDG uptake in the entire liver accompanied by multiple low-density splenic nodules. These imaging findings may be confused with the findings of malignant carcinomas such as cholangiocarcinoma and hepatocellular carcinoma. However, most peripheral cholangiocarcinomas in the nodular form showed intense FDG uptake,[11] whereas most malignant HEH showed relatively mild to moderate FDG uptake.[10] Diffuse lesions with relatively low degree of FDG uptake and patchy calcifications on CT images should be indicative of a differential diagnosis of HEH. However, it should be noted that imaging studies cannot provide a definite diagnosis for the variable patterns of the tumor. The histology, in conjunction with the immunohistology, provides a valuable diagnostic tool.

There is no generally accepted strategy for the treatment of HEH because of its heterogeneous status and variable clinical outcome. Mehrabi et al[2] reviewed the published literature on

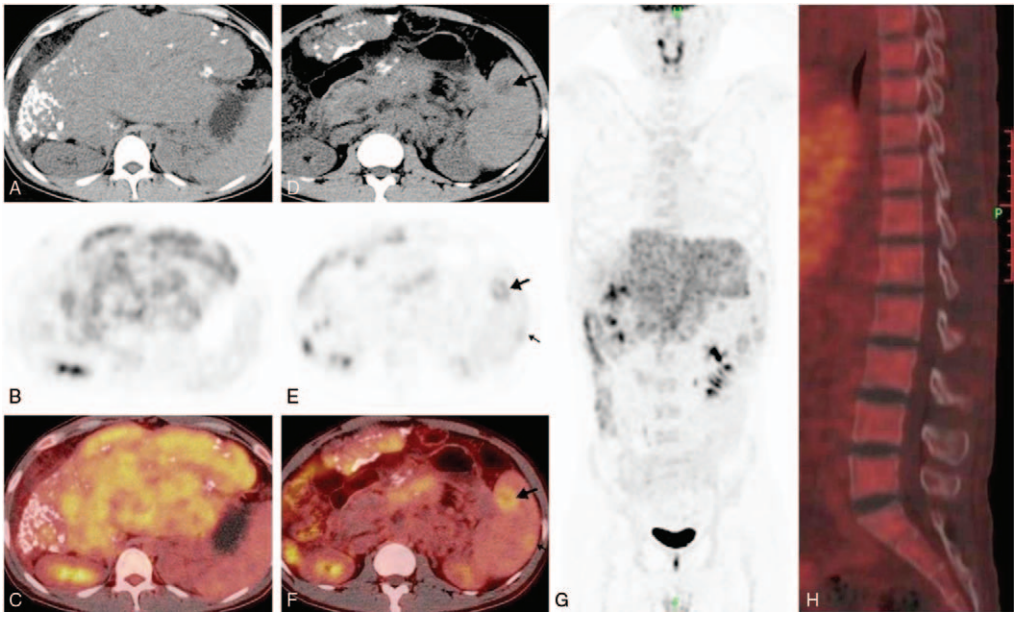

Figure 2. Transverse computed tomography (CT) (A), corresponding positron emission tomography (PET) (B), and fusion (C) images showing abnormally diffuse lesions with moderate fluorodeoxyglucose (FDG) uptake in the entire liver and maximum standardized uptake value (SUVmax) of 4.2. Transverse CT (D) of the spleen reveals multiple metastatic low-density lesions. Corresponding PET (E) and fusion (F) images show peripheral rim FDG uptake with SUV max of 3.6. The maximum intensity projection PET (G) mainly displays diffuse lesions in the liver and multiple nodular splenic lesions. Spinal sagittal fusion image (H) showing normal morphology preoperatively.

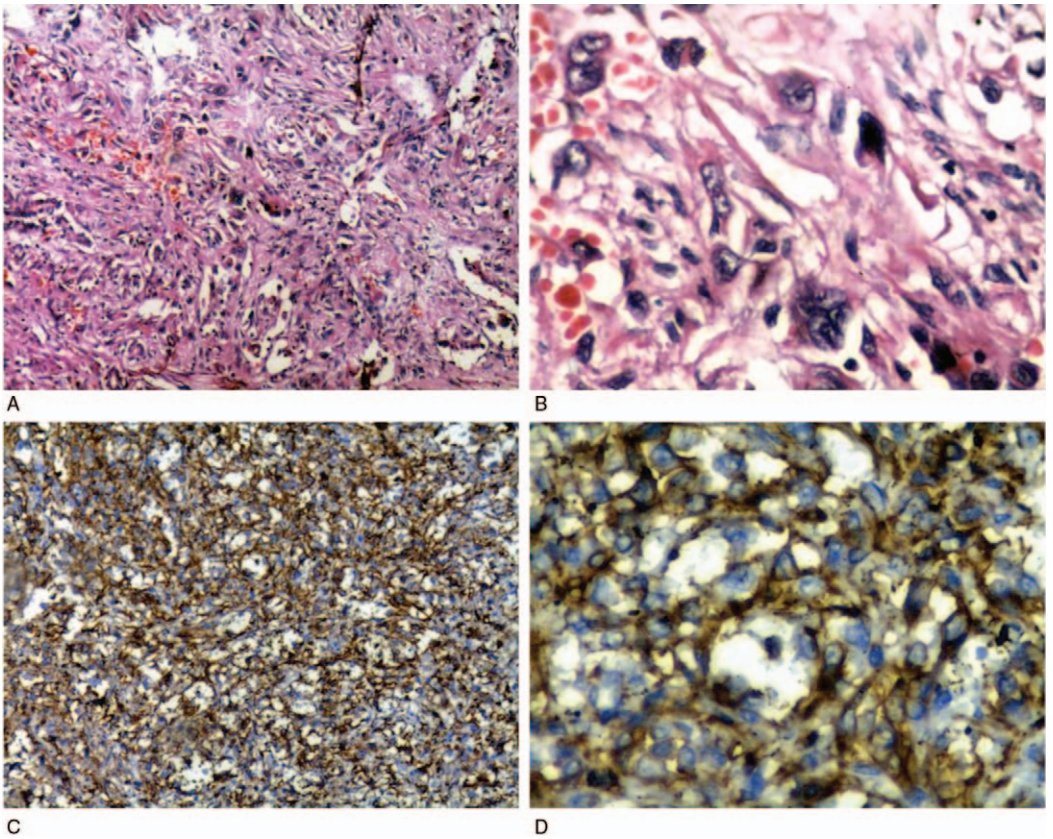

Figure 3. Microscopically, tumor cells with abundant cytoplasm and nuclear atypia, invading hepatic blood vessels are displayed (A, B, hematoxylin-eosin, original magnification 100× and 400×). Tumor cells are immunostained with antibodies to CD31 (C, D, original magnification 100× and 400×).

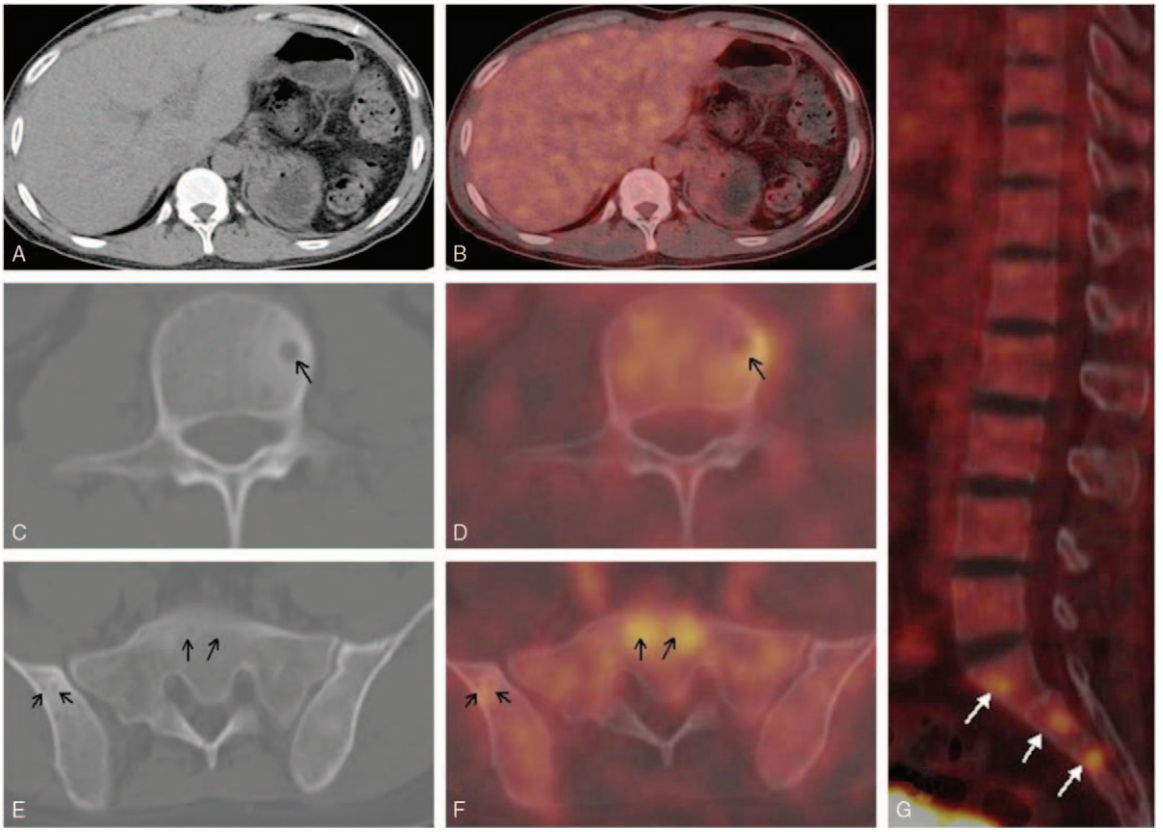

Figure 4. Follow-up whole body positron emission tomography/computed tomography (PET/CT) scan performed 5 months after LTx. The transplanted liver shows normal morphology (A) without abnormal fluorodeoxyglucose uptake (B). Transverse CT and fusion images display osteolytic destruction in the lumbar vertebrae (C, D), sacral vertebrae, and right iliac bone (E, F) with a maximum standardized uptake value of 6.5. Spinal sagittal fusion image (G) shows multifocal sacral lesions postoperatively (arrow).

HEH from 1984 to 2005 with a focus on clinical outcome after different therapeutic modalities, and they found that LTx accounted for the largest proportion (44.8%) of the various therapeutic methods. The proportion of non-treatment, chemotherapy or radiotherapy and partial liver resection was 24.8%, 21%, and 9.4%, respectively. However, some authors have advocated LTx in the presence of extrahepatic involvement because the 5-year survival rate in HEH patients with extrahepatic manifestations who undergo LTx, ranges from 50% to 70%.[12–16] Whereas liver resection can be performed in case of single nodular type,[17] but some patients with the disease confined to the liver developed rapid recurrence and metastasis after LTx.[18–19] The effect of various chemotherapeutic drugs on HEH has been reported and provides a promising treatment method. Some studies reported that the use of sorafenib took more advantages over other anti-angiogenic agents because of its dual anti-tumor activity.[20] In a case report, Kobayashi et al[21] used sorafenib monotherapy in a patient with mutiple unresectable lesions, who did not agree to receive surgical resection including liver transplantation. About 6 months later, CT findings indicated that these tumors were shrinking slightly; even 60 months later, the partial response was still observed with sorafenib monotherapy. Metastatic HEH has been successfully treated with the use of thalidomide via blocking the proliferation of the malignant vascular endothelial cells.[22] Recently, some authors reported a malignant HEH successfully treated with pegylated liposomal doxorubicin.[23] Metronomic cyclophosphamide also has been presented as a new therapeutic alleviative option to treat metastatic and nonoperative patients.[24]

But there is no consensus on preferable or specific medications due to its rare and variable clinical course. In the present case, the patient had multiple metastases to the spleen and underwent LTx and splenectomy; however, he developed multifocal bone metastasis 5 months after surgery. The mechanism involved in the rapid progression of HEH after LTx is uncertain, and may be related to undefined subtypes with varying potentials for progression or recurrence. The reasons for the unpredictable prognosis of patients with HEH after LTx, need to be further investigated. For these patients with extrahepatic lesions, adjuvant chemotherapy may be a useful alternative treatment method for the prevention of recurrence.

4. Conclusion

This case is a reminder that HEH should be considered among the differential diagnoses in case of diffuse liver disease with multifocal calcifications. The relatively low degree of FDG uptake may be helpful in suggesting a diagnosis of HEH as opposed to other hepatic malignancies. Moreover, ^{18}F-FDG PET/CT is advantageous in detecting potential metastasis in HEH patients, especially in the diffuse form of the disease.

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