

Hepatic Epithelioid Hemangioendothelioma: Vascular Penetration in the Tumor as a Characteristic Imaging Finding

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Abstract

Primary Hepatic Epithelioid Hemangioendothelioma (HEH) is a rare, low-grade, malignant hepatic neoplasm. Here we present the typical CT and MRI features of HEH in a 35 year old young woman, which were confirmed by needle biopsy. The most significant CT and MRI imaging findings were capsular retraction and peripheral location with slow progression. In addition, there were multiple hypermetabolic liver tumors seen on FDG-PET/CT and hepatic arterial penetration of the tumor on Dynamic CT (DCT), which may be useful in the diagnosis of HEH.

Keywords: Hepatic epithelioid hemangioendothelioma; CT; MRI; PET; Gadoxetic acid

Introduction

Epithelial Hemangioendothelioma (EH) is an uncommon tumor of vascular endothelial origin, which was first characterized by Weiss and Enzinger in 1982 [1]. Hepatic Epithelioid Hemangioendothelioma (HEH) is a rare neoplasm with an incidence of less than 1:1,000,000 in the general population, and was first reported by Ishak et al. [2]. The clinical course and prognosis of HEH are variable and unpredictable. The clinical manifestations include right upper quadrant pain, hepatomegaly, ischemic stroke [3] and body weight loss, but it has also been discovered incidentally in an asymptomatic patient [4]. Since it is a low-grade malignancy, it may be treated with surgical resection or transplantation, even in the presence of distant metastases [5]. Therefore, it is important to distinguish it from other hepatic malignancies, and diagnostic radiologists should be familiar with the imaging features. In this report, we discuss general imaging findings as well as some new findings of HEH.

Case Report

A 35-year-old female with symptoms of chest pain received an unenhanced CT from chest to abdomen. Multiple lung nodules and hepatic tumors were found, and she was referred to our university hospital for further evaluation. No specific abnormalities were found on her physical examination. Laboratory hematological examination revealed normal values, except for a mild increase of carbohydrate antigen 19-9 (CA19-9; 64 U/mL). She was a smoker (Brinkman index=300), but no other factors such as oral contraceptive use, hepatitis, alcohol abuse, or family history of carcinoma were reported. She was not taking any medication.

During the patient's workup, several imaging studies were performed. Abdominal sonography revealed multiple hypoechoic masses measuring 2.0–4.0 cm in both hepatic lobes. Following a pre-contrast CT, a liver Dynamic CT (DCT) was performed (injection rate of iodine Contrast Media (CM): 2 mL/sec; volume of CM: 100 mL (iohexol 300 mg I/mL); slice thickness: 5 mm (reconstructed by 1.25 mm)). On unenhanced CT, multiple lesions showed hypoattenuation in both hepatic lobes, and the largest lesion had a tiny calcification (Figure 1A). Most of the lesions were located in the hepatic subcapsular

regions. The DCT showed peripheral enhancement of the liver tumors in the arterial phase (Figure 1B) and gradual fill-in enhancement (delayed enhancement) in the portal phase (Figure 1C). In addition, the hepatic artery penetrated the largest mass in the right hepatic lobe in the arterial phase (Figure 1D). All lesions exhibited mild high signal intensity (Figure 2A) on T2-weighted (T2W) MRI images, and low signal intensity on T1-weighted (T1W) images, compared to the liver

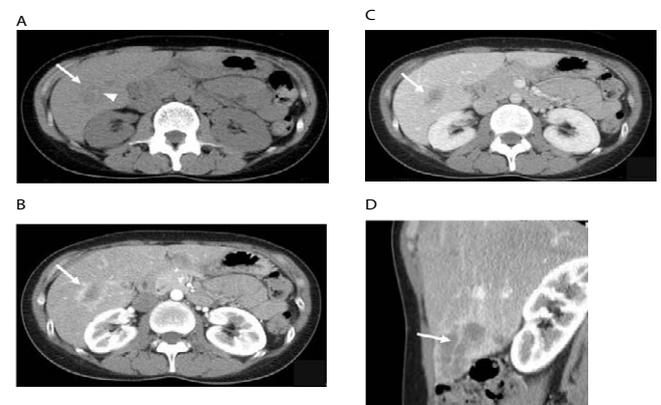


Figure 1: An axial unenhanced CT (A) shows a hypoattenuating lesion (arrow) and a tiny calcification (arrowhead) in the tumor; (B) The arterial phase of a dynamic CT shows peripheral enhancement (arrow) of the tumor and; (C) gradual fill-in enhancement (delayed enhancement; arrow) in the portal phase; (D) The hepatic artery (arrow) penetrates the largest mass on the sagittal image in the arterial phase.

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Received July 30, 2015; Accepted August 25, 2015; Published August 30, 2015

Citation: Iraha R, MOkada R, Kuniyoshi S, Arakaki S, Iraha T, et al. (2015) Hepatic Epithelioid Hemangioendothelioma: Vascular Penetration in the Tumor as a Characteristic Imaging Finding. J Liver 4: 184. doi:10.4172/2167-0889.1000184

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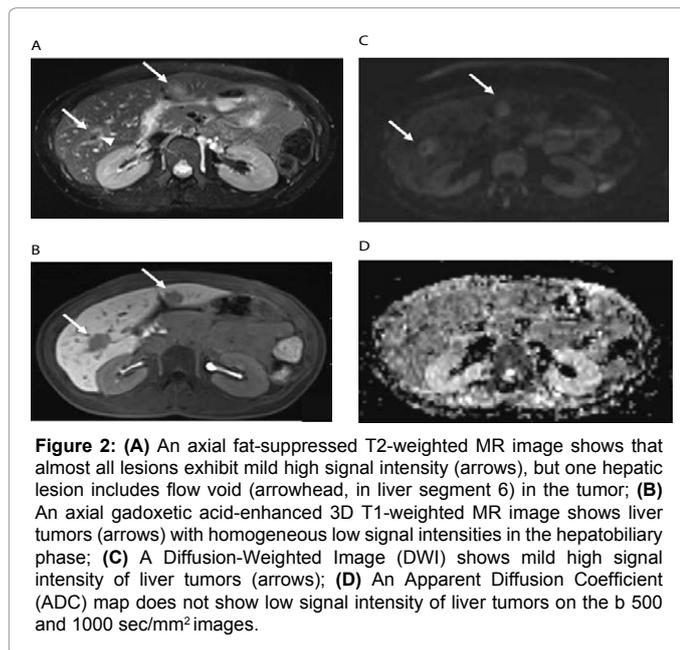


Figure 2: (A) An axial fat-suppressed T2-weighted MR image shows that almost all lesions exhibit mild high signal intensity (arrows), but one hepatic lesion includes flow void (arrowhead, in liver segment 6) in the tumor; (B) An axial gadoteric acid-enhanced 3D T1-weighted MR image shows liver tumors (arrows) with homogeneous low signal intensities in the hepatobiliary phase; (C) A Diffusion-Weighted Image (DWI) shows mild high signal intensity of liver tumors (arrows); (D) An Apparent Diffusion Coefficient (ADC) map does not show low signal intensity of liver tumors on the b 500 and 1000 sec/mm² images.

parenchyma. Gadoteric acid-enhanced MRI (injection rate of iodine CM: 2 mL/sec; volume of CM: 4.2 mL; slice thickness 3 mm) with 3D T1W images showed peripheral enhancement of the liver tumors in the arterial phase, gradual fill-in enhancement (heterogeneous enhancement) in the portal phase, and homogeneous low signal intensities in the hepatobiliary phase (Figure 2B). Diffusion-weighted images (DWI) showed mild high signal intensity of the liver tumors (Figure 2C), but an apparent diffusion coefficient (ADC) map did not show low signal intensity (Figure 2D). ¹⁸F- fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) images showed intense FDG uptake (areas of hypermetabolism compared to the liver parenchyma) of these liver tumors (Figure 3) at 1 hour post FDG injection.

An ultrasound-guided needle biopsy (18G) was performed on the largest lesion in the right hepatic lobe, and the diagnosis of HEH was histologically established based on the morphological and immunohistochemical findings. Microscopically, tumor was composed of atypical epithelioid cells with fibrosis. The myxomatous region was observed in the tumor, and no fibrous capsule was observed around tumor. Immunohistochemically, tumor cells were positive for endothelial cell markers; Factor VIII, CD31, and CD34 (Figure 4A). In addition, we carried out immunohistochemical staining for organic anion transporting polypeptide (OATP8) to examine hepatocyte function in the tumor cells. However, in our case, OATP8 was not expressed on the tumor cell membrane although the one was expressed on the hepatocyte cell membrane (Figure 4B).

Discussion

HEH is a vascular tumor appearing mostly in lung, bone, brain, liver, and small intestine [6]. In contrast to other primary liver tumors, HEH does not originate from a background of chronic liver disease, and its risk factors are unknown. The gender incidence rate of HEH is 3:2 (females to males) with an age range of 25–58 years (average age, 43.5 years) [1,4,7]. In most HEH patients, liver function tests, including serum bilirubin, alkaline phosphatase, and aspartate aminotransferase levels, are mildly elevated. Tumor marker levels, such as Alpha-Fetoprotein (AFP) and CA19-9, are almost always normal, although Carcinoembryonic Antigen (CEA) levels can be elevated in a small

number of patients [8]. In our patient, Cholangiocellular Carcinoma (CCC) was not a probable diagnosis, because there was no dilatation of the intrahepatic bile ducts, although the CA19-9 level was slightly increased. HEH is usually defined as a low-to-intermediate-grade malignancy. Histopathologically, the tumor cells are composed of epithelioid and dendritic cells [5,8,9]. The stroma is fibrous with myxohyaline areas. Immunohistochemical reactivity with factor VIII, CD31, and CD34, which are endothelial cell markers helps to confirm the diagnosis [8].

On ultrasound, the most common type of echogenicity of HEH is hypoechoic (66.3%) relative to the adjacent hepatic parenchyma; however, other patterns of echogenicity are heterogeneous (22.5%), hyperechoic (6.2%), and isoechoic with a hypoechoic rim (5%) [4]. As described in past reports [5,7] no blood flow within the tumors was

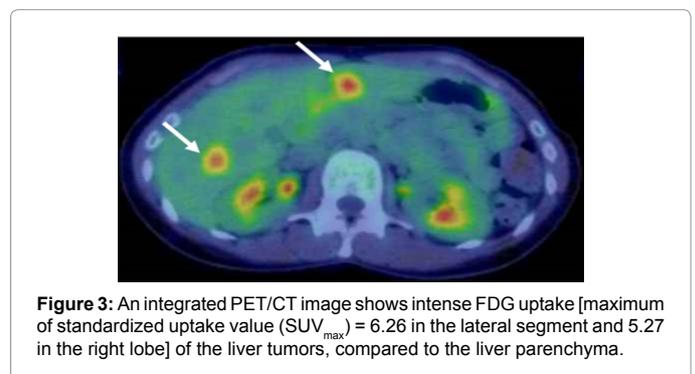


Figure 3: An integrated PET/CT image shows intense FDG uptake [maximum of standardized uptake value (SUV_{max}) = 6.26 in the lateral segment and 5.27 in the right lobe] of the liver tumors, compared to the liver parenchyma.

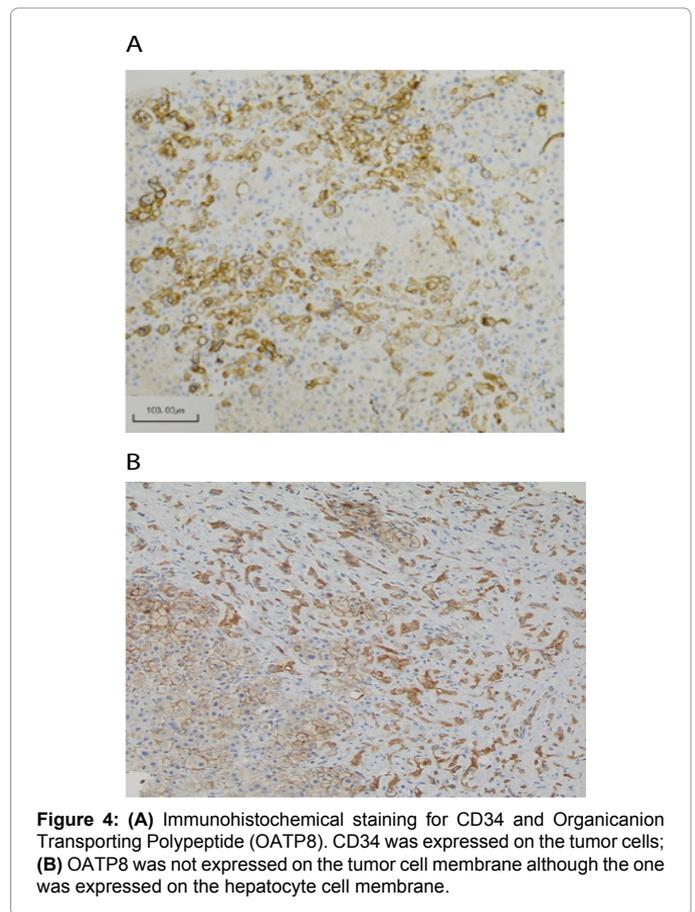


Figure 4: (A) Immunohistochemical staining for CD34 and Organic anion Transporting Polypeptide (OATP8). CD34 was expressed on the tumor cells; (B) OATP8 was not expressed on the tumor cell membrane although the one was expressed on the hepatocyte cell membrane.

seen on color Doppler ultrasound imaging in our patient. There were hypoechoic masses on ultrasound, but no significant features were seen. However, we think that contrast-enhanced sonography may be a promising technique to view hepatic artery penetration of the tumor, due to higher spatial and contrast resolutions.

The CT findings of HEH include multiple hypoattenuating nodules located along the liver periphery, which coalesce over time to form large liver masses [5,9]. Capsular retraction (10.6%) due to fibrosis and calcification (12.7%) have also been seen [4]. The tumor enhancement pattern of HEH has been linked to a halo or target pattern (peripheral enhancement) in the arterial phase of DCT. On delayed images, the tumor centers may be either enhanced or unenhanced [4,5,7-9]. In our patient, hepatic artery penetration in the largest mass was seen on DCT (Figure 1), and this finding may be an additional important appearance.

MR imaging findings of HEH include low signal intensity on unenhanced T1W images relative to the surrounding liver parenchyma [5,9,10]. In one report, several lesions showed foci of high signal intensity on T1W images because of hemorrhage and/or proteinaceous debris [9]. The lesion signal intensity on T2W images was substantially high signal, high or mixed signal center with low signal rim [4,5,7]. Thus, T2W images may be useful in differentiating HEH from hepatic hemangiomas, because hemangiomas show very high signal intensity on T2W or heavily T2W images. A dynamic contrast enhancement MRI of HEH using gadopentetate dimeglumine (Gd-DTPA) or gadoxetic acid may show a halo or target pattern (peripheral enhancement) in the early phase, followed by some progressive centripetal filling in the later phase [9-11]. Central nodular enhancement has also been described on contrast-enhanced T1W images in 37.5% cases of HEH [4]. The peripheral enhancement pattern on DCT or MRI may be interpreted on pathology by the presence of a central zone of myxoid stroma and a peripheral zone of cellular proliferation [8]. Thus, in our patient, the presence of peripheral high tumor cellularity and a central myxomatous region may reflect the high vascularization and the lack of central unenhancing areas.

There have been few studies of gadoxetic acid-enhanced MR images in the hepatobiliary phase. According to Paolantonio et al. [12], there was homogeneous low signal intensity relative to the surrounding liver parenchyma in 5 (62.5%) of 8 patients and entrapment enhancement (internal enhancement surrounded by a hypointense ring) in 3 (37.5%) of 8 patients in the hepatobiliary phase on the gadoxetic acid- or gadobenate dimeglumine-enhanced MRI. Kim et al. [10] reported that all lesions (100%) of 5 patients showed hypointensity, and 2 (40%) of 5 patients showed a target-shaped hypointense lesion composed of a central low signal intensity area with a peripheral intermediate signal intensity rim in the hepatobiliary phase. In our patient, the findings of DCT, pre-contrast/dynamic MRI, and gadoxetic acid-enhanced MRI in the hepatobiliary phase were similar to previous reports. However, the findings of a tiny intratumoral calcification and capsular retraction may be useful in the diagnosis of HEH, although the extracellular enhancement patterns of DCT and MRI in the liver-specific phase, such as the hepatobiliary phase of gadoxetic acid-enhanced MRI, have limitations in differentiating HEH from liver hemangiomas, CCC, and liver metastases.

The main purpose of FDG-PET/CT is to detect a primary malignancy. Moreover, it is useful for investigation of extrahepatic lesions of HEH, such as lung, abdominal lymph nodes, omentum, mesentery, and peritoneum, because 27% of HEH patients have metastatic lesions [8]. A quantitative standardized uptake value (SUV) is useful to know the metabolic activity of HEH, although

inflammatory pseudotumors and liver metastases also show a higher SUV on PET-CT. Generally, liver hemangiomas do not show hypermetabolism of the tumor on PET/CT; therefore, the presence or absence of FDG uptake may be useful in differentiating HEH from liver hemangiomas. According to previous reports on PET/CT imaging for HEH, the lesions had mild-to-moderate FDG uptake or similar FDG uptake to the surrounding liver parenchyma [10,11]. Kitapci et al. have emphasized that a delayed PET/CT scan (3 hours post FDG injection) is better than a routine PET/CT (1 hour post injection) for evaluation of the metabolic activity of lesions on dual-time-point PET/CT. Their case showed similar FDG uptake to surrounding liver parenchyma in the 1-hour post-injection images, but significantly increased FDG uptake to the liver lesions on delayed images [13]. Since our patient had multiple hypermetabolic liver tumors depicted at 1 hour post injection on PET/CT, the additional delayed PET/CT image was not required.

The CD34 marker is enough to diagnose HEH on pathology, but we did OATP8 staining to compare gadoxetic acid-enhanced MRI findings with a transporter of CM. In the human liver, OATP8 is substantially expressed on the cell membrane of hepatocytes at the sinusoidal side and is the most probable uptake transporter of gadoxetic acid. Several reports have indicated that OATP8 correlates with the enhancement in the hepatocyte phase on gadoxetic acid-enhanced MRIs. There was no expression or weak expression of OATP8 on the hepatic cell membrane, and a gadoxetic acid-enhanced MRI showed hypointensity in the hepatocyte phase [14-16]. In our case, when a section of HEH was also stained with OATP8, the pathological findings correlated with the MRI findings. OATP8 was non-specifically expressed on the tumoral cytoplasm, but not expressed on the cell membrane. Therefore, we believe that the low signal intensity of HEH matches the findings of OATP8 staining in our patient.

In conclusion, the mild high signal intensity of the tumor on T2W images, the ring enhancement of the liver tumors in the arterial phase, and the gradual fill-in enhancement (delayed enhancement) in the portal phase, together with the location in the hepatic subcapsular regions, are all suggestive for the diagnosis of HEH. Moreover, we consider that the hypermetabolic appearance on FDG-PET/CT and the hepatic arterial penetration of the tumor on DCT may be additional important findings of HEH.

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