Hepatic Epiteloid Hemangioendothelioma, a Diagnosis to keep in mind when finding Incidentalomas

Introduction

Hepatic Epiteloid Hemangioendothelioma (HEH) is considered a rare tumor with vascular origins that has an overexpression of vascular endothelial growth factor (VEGF) and its receptors VEGFR (Weiss SW, Enzinger FM. Cancer 1982 Sept; 50(5): 970–981). Until now, there has been no standardized treatment for this pathology, the only suitable treatment being surgery, including liver resection, liver transplantation, or considering recent studies, transcatheter arterial chemoembolization (Mehrabi A et al. Cancer 2006 Nov; 107: 2108–2121; Cardinal J et al. Arch Surg. 2009; 144: 1035–1039). The evolution of a HEH is unpredictable. Sometimes the tumor has a quiet and stable course but it can also evolve aggressively and become metastatic (Sangro B et al. Rare Tumors 2012 Apr; 4(2): e34).


HEH exhibits great heterogeneity regarding the imaging findings (Lyburn ID et al. American Journal of Roentgenology. 2003 May; vol.180: 1359–1364). Studies show that it can appear as a single or multiple avascular masses with calcification, and can involve the entire liver (den Bakker MA et al. Pathol Res Pract 1998; 194; Issue 3: 194–198; EH, Rha SE, Lee YJ et al. Abdom Imaging. 2015 Mar; 40(3): 500–509). Some imaging suggestions have been proposed in order to improve diagnostic accuracy, such as the retraction sign (capsule retraction of the liver, near the lesion) (Miller WJ et al. American Journal of Roentgenology. 1992; 159: 53–57). Another is the halo sign, which is related to the i.v administration of contrast medium (a hyperintense layer between the hypointense center and periphery) (Linand J, Ji Y. Hepatobiliary and Pancreatic Diseases International. 2010; 154–8), even though HEH is often misdiagnosed as being a metastatic tumor. In this report we shall present a case of a young woman diagnosed with multiple liver tumors that proved to be HEH. We shall likewise discuss related imaging aspects.

Case Presentation

A 27-year-old woman, asymptomatic, without other known pathology, was incidentally diagnosed with multiple liver masses after a routine abdominal ultrasound. The clinical examination and biochemical tests did not reveal any abnormalities. Tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and alpha-fetoprotein were also normal.

Baseline US showed multiple lesions, hypo/hyperechoic, \( \text{Fig. 1,2} \), with a maximum diameter of 20 mm. CEUS examination revealed a “rim like” enhancement of the most representative lesion of the left hepatic lobe (LHL) \( \text{Fig. 1} \), with wash-out pattern in the portal and late phase. CEUS examination of the right hepatic lobe (RHL) lesion (the largest one) \( \text{Fig. 2} \), showed a slightly hyperenhanced pat-
tern in the arterial phase, with evident washout in the portal and late phase, sug-
gesting malignancy. Subsequently, an ab-
dominal MRI confirmed multiple lesions (☞ Fig. 3), with discreet hyperintensity in
T2, hypointensity in T1, and with restrict-
ed diffusion (diffusion coefficient of 0.96 – suggestive of malignancy) (☞ Fig. 3). Precontrast (☞ Fig. 4a) and (☞ Fig. 4b–d)
dynamic postcontrast T1 weighted fat-
saturated axial images at the same level showed slight peripheral ring-like en-
hancement in the arterial phase (☞ Fig. 4b)
and progressive enhancement during the portal venous phase (☞ Fig. 4c) and delayed phase (☞ Fig. 4d). In the delayed phase the lesions presented as a halo sign, thus confirming the literature (Paolantonio P, et al. J Magn Reson Imaging 2014; 40: 552–558). The same pa-
tient in a postcontrast image (axial portal venous and coronal delayed phase) at a
superior level exhibited another subcapsu-
lar lesion producing retraction of the liver capsule (☞ Fig. 4e–f).

The patient was also evaluated with trans-
vaginal and thyroid ultrasound examina-
tions which were unremarkable. A thorax CT was performed and demonstrated a
small nodule (12 mm) in the right lung that could be characterized in the clinical-
imaging context as metastatic.

Finally a core biopsy was performed that
through immunohistochemistry staining
disclosed the diagnosis of HEH. The biop-
sy indicated an infiltrating tumor resem-
bling epithelioid cells that spread within
sinusoid and small veins with marked
atrophic hepatocyte. The cells had a pleo-
orphic aspect, some of them having intrac-

toplasmic vacuoles (containing red
blood cells), mimicking the “signet ring”,
negative for AA-PAS coloration. Imuno-

histochemically the tumor cells stained
positive for vascular markers CD31, CD34,
and Factor VIII antigen, underlying the
endothelial origin of the tumor. Demon-
strating the histological and immunohisto-
chemical features, the diagnosis of He-
patic Epithelioid Hemangioendothelioma
was established (☞ Fig. 5). With this diag-
nosis the patient was referred to the On-
cology department.

Discussion

Epithelioid hemangioendothelioma is an
intermediate tumor between hemangio-

oma and angiosarcoma indicative of recur-
rence and metastatic activity, and is the
most aggressive member of hemangioen-
dothelioma family (Weiss SW, Goldblum
JR, Soft Tissue Tumors. 2008 5th edition;
681–702). The diagnosis is based on his-
tological and immunohistochemical find-
ings. Histologically the cells have an epi-
thelioid appearance, are mildly pleomor-
phic, and typically show intracytoplasmic
vascular lumina which contain red blood
cells. The intracytoplasmic lumina impart
a “signet ring” appearance which some-
times may be mistaken for an adenocar-
noma. The presence of red blood cells dif-
fertiates them from signet ring cell ad-

carcinoma which contains intracellular
mucin. The tumor typically forms
papillary tufts and glomeruloid struc-
tures within adjacent portal venules and
sinusoidal spaces.

Regarding immunohistochemistry, the
tumor is positive for Factor VIII, CD31, and
CD34. Keratin may be also positive. The
tumor is negative for mucin. Differ-
ential diagnosis can be made with: angio-
sarcoma, hemorrhagic hepatocellular

carcinoma, diffuse metastatic disease in
sinusoids and cholangiocarcinoma (Liang
Cheng et al. Essentials of Anatomy c Pa-

A review of literature from 1984 to 2005
with more than 400 cases demonstrates
female predominance (3:2), and a medi-
an age of 42 years (Mehrabi A et al. Can-
frequent symptom is upper quadrant
pain (49%), and in 81% of cases the tumor
involves both liver lobes, lungs being the
most frequent site of metastases (13% of
patients have metastases), although 63% of
the patients were non-metastatic (Mehrabi A et al. Cancer. 2006: 107:
2108–2121). Keeping in mind the expres-
vion of vascular endothelial growth factor
(VEGF) and its receptor (VEGFR) in HEH
makes reasonable the use of antiangiogen-
ic therapies (Salech F et al. Ann Hepa-
studies published about HEH in last years
report results of antiangiogenic agents
such as bevacizumab, lenalidomide, tha-
lidomide and sorafenib with variable re-

sponse rates (Bruno Sangro et al. Rare
Tumors 2012 Apr 12; 4(2): e34). Some
studies reveal the antiangiogenic effect of
non-steroidal anti-inflammatory drugs that
have been used alone or combined with
other drugs in the treatment of HEH
(Yousaf N. J Clin Oncol 2013; 31 suppl:
abstr 10569). Therefore, antiangiogenic
therapy might be a treatment option for
HEH.

Hepatic epithelioid hemangioendothelio-

ma (HEH) is a rare tumor with variable
malignant potential. The only curative
treatment remains liver transplantation,
extrahepatic manifestation not being a
contraindication for surgery (Mehrabi A,
957; Grotz TE, HPB (Oxford) 2010; 12:
546–553). According to (Komatsu S et al.
World J Gastroenterol 2014 July; 20 (26):
8729–8735) new therapy options can be
taken into consideration, such as the two-

Fig. 3 The 2 nodular lesions (arrowheads), in axial T2 weighted image and ADC map, show target-like appearance with which the central region of the nodule showing higher intensity. On high b value DWI this lesions show restricted diffusion.
stage treatment, hepatectomy and carbon-ion therapy. This, along with the studies of Wang et al. (Wang LR, World J Surg 2012; 36: 2677–2683) and Cardinal et al. (Cardinal J et al. Arch Surg. 2009; 144: 1035–1039) underlining the effectiveness of TACE vs. hepatectomy, opens the possibility of expanding the curative treatment options for multiple bilobar hepatic tumors. Although we should not forget the natural course of the disease, some data from the literature (Makhlof HR et al. Cancer 1999; 85: 562–582; Otrock ZK et al. Lancet Oncol 2006; 7: 439–441) showed a 5-year survival time of patients without any treatment, indicating the borderline malignant nature of the disease. In fact, our patient is currently under imaging and medical surveillance.

The particularity of this case is the clinical and biological silence of the disease. The initial imaging evaluation misleads the first diagnosis characterizing the lesions as being metastatic. Both imaging methods highlight the ring-like/rim-like enhancement and malignant pattern of the lesions, concluding the diagnostic algorithm with a core biopsy.

In conclusion we pinpoint the risk of misdiagnosing the pathology even in tertiary centers and the need for personalizing treatment management according to each patient’s characteristics and local medical experience.

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