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Case Report

A Liver-Derived Vascular Lesion: Hepatic Hemangioma or Hepatic Epithelioid Hemangioendothelioma?

Roham Gholami[1], Moslem Soltani[2], Naghmeh Salarieh[3], Pardis Ketabi Moghadam[4*]

[1]Fellowship of Gastroenterology, Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Department of Internal Medicine, Islamic Azad University of Mashhad, Mashhad, Iran
[3]Gastroenterologist and Hepatologist, Guilan University of Medical Sciences, Guilan, Iran
[4]Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Hepatic epithelioid hemangioendothelioma (EHE) is an uncommon vascular endothelial cell tumor of the liver with numerous symptoms and features. The median affected age is 41, and females are more frequently affected than men. In the following article, a 37-year-old nurse is presented who was referred to the hospital with severe right upper quadrant pain. She had been misdiagnosed with hepatic hemangioma for years, which finally turned out to be hepatic EHE. Liver transplantation has been recognized as the therapeutic method of choice due to the considerable extent of liver involvement and nonresponse to medications.

Keywords: Vascular endothelial cell tumor, Hepatic hemangioma, Hepatic hemangioendothelioma

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Introduction

Hepatic endothelial cell-derived lesions are a spectrum of lesions from hepatic hemangioma, which is a benign lesion, to hepatic epithelioid hemangioendothelioma (EHE) and hepatic angiosarcoma with borderline malignant and malignant potential, respectively. Hepatic EHE is known as an infrequent vascular endothelial cell tumor of the liver.[1,2] Hepatic EHE is a low-to-moderate-grade tumor associated with an intermediate malignant potential between hemangioma and hemangiosarcoma.[3] Various non-specific clinical manifestations are expected. The usual symptoms included right upper quadrant pain (48.6%), hepatomegaly (20.4%), and weight loss. Constitutional syndrome with progressive liver damage resembling Budd-Chiari syndrome has also been attributed to hepatic EHE (15.6%). Consequently, liver failure and death are expected in some patients with hepatic EHE. Some of these symptoms are attributed to extrahepatic involvement in the disease.[4] Laboratory findings indicate abnormal liver function in most cases.[1] From an ultrasound point of view, they are multifocal hypoechoic lesions commonly originating from the periphery of the liver, which gradually coalesce and form a heterogeneous echotexture. They are also reported to be hypoattenuated and hypointense on computed tomography (CT) and T1-weighted magnetic resonance imaging (MRI), respectively. Reported capsular retraction and compensatory hypertrophy of the unaffected parts on CT scans are attributed to the extension of lesions to the periphery of the liver. The expected central fibrosis and peripheral rim of cellular proliferation lead to halo signs on contrast-enhanced imaging. The sudden termination of hepatic vasculature at the edge of the lesion resembles a typical radiologic sign which is called a lollipop sign in the contrast-enhanced study.[5] In many cases, asymptomatic hepatic EHEs are distinguished from other hepatic lesions by ultrasound or CT scans.[6] Since the behavior of tumors is not completely understood and the probability of disease progression to liver failure cannot be ruled out, definite treatment of the lesion is suggested. However, some studies prefer observation and assessment of tumoral behavior before stepping into the aggressive ablation of the lesion.[7] Suggested therapies include medication, hepatic resection, liver transplantation, radiotherapy, and chemotherapy, which should be tailored to the patient's symptoms and signs. Choosing among the mentioned therapies is controversial. Liver transplantation and surgical resection have acceptable outcomes.[8]

Case Report

A 37-year-old woman with a history of asymptomatic hepatic hemangioma from 5 years ago presented with persistent right upper quadrant pain during the last 6 months. The patient's reported pain was neither meal-related nor positional. It was not associated with nausea, vomiting, or any changes in bowel habits. Long-term patient's slight elevation of serum aminotransferases had been attributed to non-alcoholic fatty liver disease. She also

*Corresponding Author: Pardis Ketabi Moghadam, Email: ketabimoghadam.p@gmail.com

had a history of hypothyroidism, for which she took 100 µg once-daily levothyroxine once daily. Her family history was unremarkable. Regarding the elevated liver enzymes, investigations for viral hepatitis, autoimmune liver disease, and Wilson's disease were requested, which were all negative. Further laboratory tests revealed aspartate transaminase (AST) = 44 U/L, alanine transaminase (ALT) = 54 U/L, alkaline phosphatase (ALP) = 204 U/L, Bil(T) = 1.8 mg/dL, Bil(D) = 0.8 mg/dL, ALB = 4.4 g/dL, erythrocyte sedimentation rate (ESR) = 6 mil/h, C-reactive protein (CRP) = negative, alpha-fetoprotein (αFP) = 1.57 ng/mL, carcino-embryonic antigen (CEA) = 1.5 ng/mL, CA19-9 = 25 U/mL, international normalized ratio (INR) = 1.2, white blood cell (WBC) = 7700 cells/mm^3, Hb = 14.7 g/dL, platelet (PLT) = 265 000 cells/µL and SPEP = normal, which were not suggestive of liver cirrhosis or any particular disease. The tumor marker levels were all within normal ranges. Physical examination, endoscopy, and colonoscopy findings were unremarkable. Liver sonography showed three ill-defined hypoechoic lesions. The hypoechoic echotexture of the lesions prompted us to conduct further investigations because hypoechoic lesions are not typical of hemangiomas. Further evaluation of the hepatic lesions was followed by a triphasic CT scan, which revealed multiple hypoattenuating foci of variable sizes (Figure 1). Contrast-enhanced CT revealed that the lesions were fused with each other to form a larger hypoattenuating region with peripheral nodular enhancement and halo enhancement on the arterial phase for smaller lesions and larger lesions, respectively. Gradual centripetal filling was detected during the portal and delayed phases. Two-sided radiological evidence raised suspicion of lesions other than hemangiomas in the present case. Biopsy and immunohistochemical staining were performed to distinguish the definite pathology of the lesions. Hematoxylin and eosin (H&E) staining of the specimen revealed epithelioid and histiocytoid cells in a dense fibrous stroma. Intranuclear pseudoinclusions (INPIs) were detected by H&E staining of the lesions. Immunohistochemically, the specimen was positive for cluster of differentiation (CD34) and negative for cytokeratin (CK) (Figures 2 and 3). Histological evaluation of the lesion revealed a rare EHE. The patient's whole-body scan result was unremarkable. She was primarily started on combination therapy with propranolol and prednisolone, which was not effective

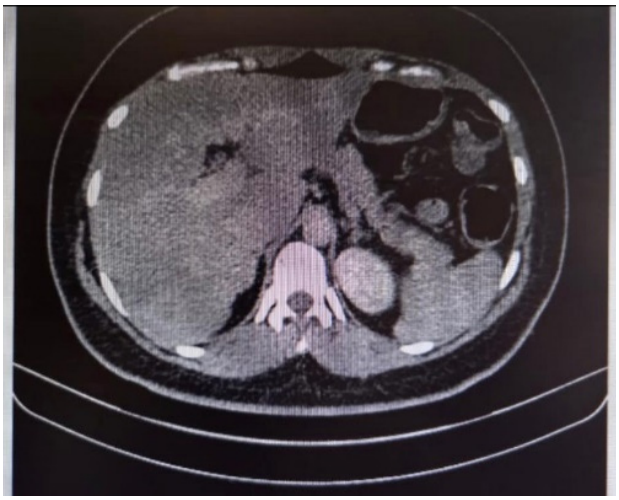

Figure 1. Multiple hypoattenuating foci of variable sizes are seen predominantly in the right hepatic lobe involving a large volume of the liver

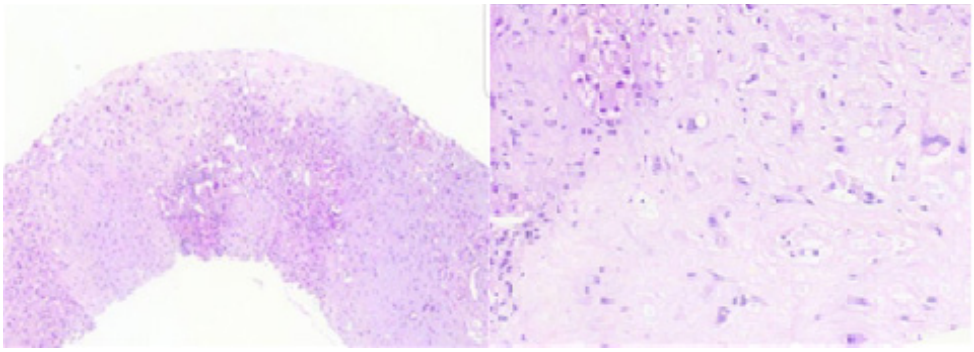

Figure 2. H&E examination of the specimen revealed epithelioid and histiocytoid cells in a dense fibrous stroma. INPIs were found in H&E staining of the lesion

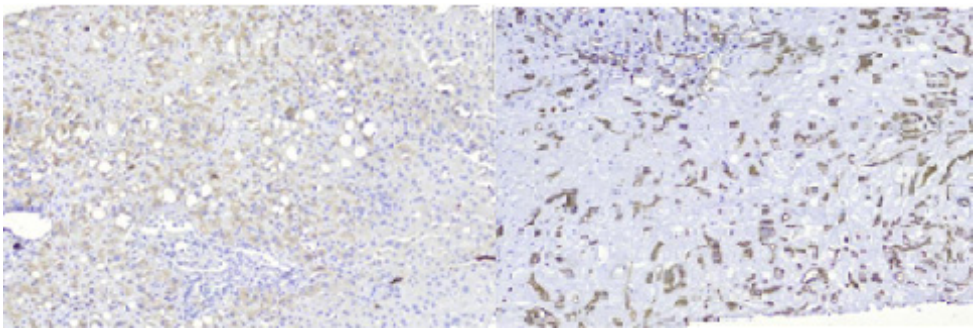

Figure 3. IHC study of the specimen was positive for CD34 and negative for CK

in the 6-month follow-up of the patient. Eventually, she was scheduled for liver transplantation because the resection and ablation of an extensive hepatic lesion were not logical.

Discussion

Hepatic EHE is a rare vascular endothelial cell tumor of the liver whose known risk factors are oral contraceptives, polyvinyl chloride, asbestos, thorotrast contrast medium, hepatic trauma, and viral hepatitis. A history of hepatic malignancy, chronic liver disease, and biliary system manipulation is not reported to be related to hepatic EHE.[6] EHE was characterized by Weiss and Enzinger in 1982 as a soft-tissue tumor with both a vascular morphology and a histologic phenotype, including benign and malignant potential. Although the disease was first diagnosed in the soft tissue and bone, the liver is now known to be the most common site of involvement.[8] Hepatic EHE is a low-to-moderate grade tumor with an intermediate malignant potential between hemangioma and hemangiosarcoma. The most common sites of metastasis were the lungs (81%), celiac lymph nodes (39%), peritoneum, and diaphragm. The total metastasis rate is estimated to be 27%-45%. 41.7 years is known to be the median affected age, and female-to-male predominance is estimated to be 3:2.[3] The clinical manifestations are not specified for hepatic EHE. The usual symptoms are right upper quadrant pain (48.6%), hepatomegaly (20.4%), constitutional syndrome with progressive liver damage, and weight loss (15.6%).[3] Infrequent symptoms include Budd-Chiari syndrome or liver failure. Laboratory findings may indicate abnormal liver function. Approximately 75% of patients have elevated ALP levels, 2.7% have elevated αFP levels, and 18.8% have elevated serum CEA levels.[2] Generally, tumor markers are always within normal levels, although laboratory findings disclose abnormal liver function tests in almost all cases.[1] This is reflected in the present case, which had near-normal liver function tests and normal tumor markers. One of the comorbidities associated with hepatic EHE is hypothyroidism, which was also reported in the present case.[9] Given the non-specific symptoms of the lesion, the diagnosis is made based on radiological images. Ultrasound is the first utilized modality for diagnosis which mainly demonstrates multiple well defined hypoechoic lesions located near the capsule of the right hepatic lobe leading to capsular retraction.[6] Contrast-enhanced US mostly shows contrast agent wash-out in the portal and late venous phases, finally leaving an enhanced halo sign.[10] Findings of hepatic EHE on MRI are coalescent lesions, subcapsular lesions, capsular retraction, lollipop signs, and target signs.[11] Two radiologic patterns of hepatic EHE are introduced to be a multifocal nodular type and a diffuse type, known to be the early and the advanced stages of the disease, respectively. Therefore, the combination of peripheral multifocal round lesions, thin rim enhancement, late appearance of the low-signal inner thick border, and high-signal central core may be a noticeable feature of hepatic EHE.[6] Pathologist expertise plays an important role in the definite diagnosis of lesions owing to numerous differential diagnoses. Most EHEs are initially misdiagnosed as cholangiocarcinoma, angiosarcoma, hepatocellular carcinoma, metastatic carcinoma, or sclerosing hemangioma.[6] From the perspective of pathology, a composition of epithelioid and histiocytoid cells containing hyperchromatic nuclei and cytoplasmic vacuoles is seen in a dense fibrous or myxohylaine stroma. Occasional INPIs and intracytoplasmic luminas with or without RBCs are also detected in H&E examination of this lesion. An immunohistochemical examination might reveal vascular markers like CD31, CD34, factor VIII, and FLI-1 but not cytokeratin.[12] As could be reflected from (Figures 2 and 3), H&E examination of the specimen shows epithelioid cells in a dense fibrous stroma. INPIs were detected by H&E staining of the lesions. Immunohistochemically, the specimen was positive for CD34 and negative for CK. The prognosis of the disease ranges from a survival rate of > 25 years to death within the year of diagnosis.[6] Treatment with propranolol and prednisolone has not been accompanied by brilliant results, as reflected in the presented case, too.[7] Recently, sirolimus and interferon alfa-2b have been reported to have agreeable results.[11] Liver transplantation and surgical resection of lesions have demonstrated good outcomes.[11] Orthotopic liver transplantation is considered as the treatment of choice in the presented case due to the fact that multiple intrahepatic lesions or single lesions accompanied by extrahepatic metastases are surgically unresectable.[6] Additionally, transcatheter arterial chemoembolization, which is considered a valuable treatment option in the presence of extrahepatic disease or comorbidities,[6] is not reasonable for large and multiple lesions that involve a large volume of the liver. Spontaneous tumor regression has also been reported in uncomplicated hepatic EHEs.[11]

Competing Interests

The authors declare no conflict of interest related to this work.

Ethical Approval

Written informed consent was obtained from the patient.

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