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# Hepatic Epithelioid Hemangioendothelioma Discovered Incidentally on Computerized Tomography

Luke Johnson, M.D.[1], Ryan Ford, M.D.[1], Paul A. Johnson, M.D.[2]
[1]University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Internal Medicine
[2]University of Kansas School of Medicine-Salina, Salina, KS

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## INTRODUCTION

Hepatic epithelioid hemangioendothelioma (HEHE) is an exceedingly rare vascular tumor first described by Weiss and Enzinger in 1982.[1] It is a neoplasm that can arise in many different parts of the body, but most frequently involves the liver, lung, and bone.[2] It disproportionately affects females with a ratio of 3:2 and 50% of cases are discovered incidentally. HEHE is misidentified in up to 80% of cases. It can be mistaken for angiosarcoma, metastatic carcinoma, hepatocellular carcinoma (HCC), or cholangiocarcinoma. While 25 - 40% of patients are asymptomatic, common presenting symptoms include right upper-quadrant pain, fatigue, nausea, vomiting, weakness, ascites, anorexia, and weight loss.[2-4] Up to 37% of patients have distant metastases at the time of diagnosis and rapid progression is seen in up to 75% of cases where there are multifocal lesions.[2,4] This report presents a unique case of HEHE found incidentally on computerized tomography (CT).

## CASE REPORT

A 40-year-old female with no known past medical history presented to the emergency department (ED) with fatigue and shortness of air. The shortness of air gradually worsened over a period of weeks until she presented to the ED. Her vitals were stable and she did not require supplemental oxygen. Chest x-ray was unremarkable for any acute cardiopulmonary process. CT angiography of the chest was negative for pulmonary embolism, but demonstrated a heterogenous liver with discrete hypoattenuating areas concerning for metastatic lesions.

Laboratory evaluation was unremarkable aside from a slight leukocytosis. Magnetic resonance imaging (MRI) of the abdomen days later demonstrated multiple peripheral, contrast enhancing 3-centimeter nodules throughout the liver (Figure 1). Subsequent needle biopsy showed scattered nodular fibrotic lesions, a small number of slightly atypical cells within the fibrotic tissue, and focal hepatic necrosis with scarring. Immunohistochemistry (IHC) stains were positive for CD34 and CAMTA-1. All of these findings were consistent with the diagnosis of hepatic epithelioid hemangioendothelioma. The patient was not a candidate for resection or ablation due to the amount and distribution of her lesions. She was referred for evaluation for liver transplantation and subsequently underwent orthotopic liver transplantation less than one year after diagnosis (Figure 2).

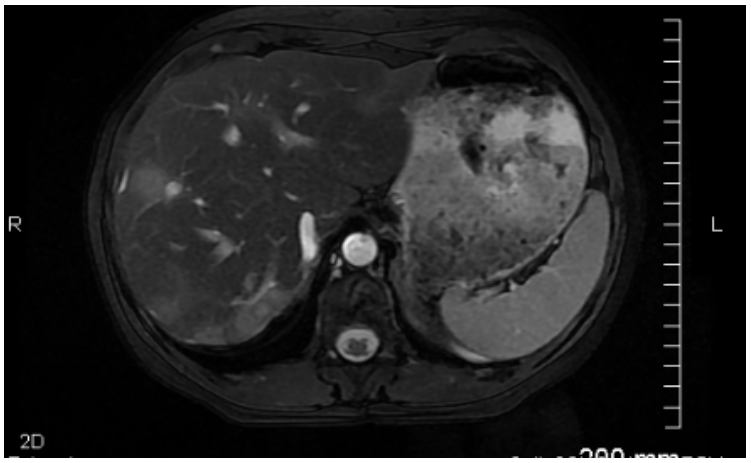


Figure 1. T2 sagittal view of MRI abdomen shows multiple, predominantly peripheral, contrast enhancing nodules in the liver.

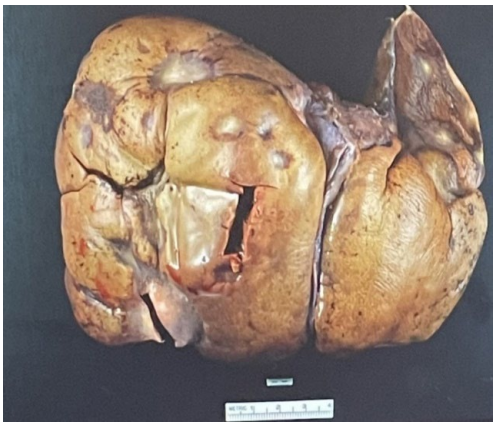

Figure 2. Gross pathology of this patient's liver status-post liver transplantation. [Courtesy of: Mayo Clinic Liver Transplant Program]

## DISCUSSION

HEHE can be differentiated from common mimickers by a combination of histology, IHC, and molecular characteristics. Initial diagnostic workup includes CT, MRI, or ultrasound. Lesions appear hypoechoic on ultrasound.[3] Non-contrast CT shows nodules with a hypodense appearance, while CT with contrast shows small lesions (< 2 cm) with homogenous enhancement and large lesions with peripheral or heterogenous enhancement.[2] Lesions appear hypointense on T1 weighted MRI and hyperintense on T2 weighted MRI.

HEHE lesions vary in size from less than one centimeter to more than ten centimeters in diameter and over 75% of cases have lesions in both liver lobes.[5] When presenting as multifocal, there is a peripheral or subcapsular growth pattern. Lesions also can differ based on disease progression with late disease showing a pattern of coalescence.[2]

Histologically, HEHE manifests as nests and cords of spindle to epithelioid cells with mild to moderate atypia, abundant pale to eosinophilic cytoplasm, indistinct cell boundaries, and intracytoplasmic vacuolations in a fibromyxoid stroma.[4] Older lesions appear sclerotic, calcified, or necrosed.[2]

IHC stained HEHE cell tissues typically are positive for CD34 (94% of cases), CD31 (86% of cases), and Factor VIIIa (99% of cases).[2]

Other positive staining factors include vimentin, type IV collagen, and D2-40 which helps to differentiate from other angiomatous lesions. IHC staining of common mimickers is as follows: (1) metastatic carcinoma does not stain positive for any of the above markers; (2) cholangiocarcinoma does not stain positive for any of the above markers; (3) HCC is negative for the above factors except for CD34 following sinusoidal capillarization; and (4) angiosarcoma stains positive for CD34, CD31, and Factor VIIIa while losing expression of these markers upon undergoing dedifferentiation. In 86% of cases, molecular translocation results in *WWTR1-CAMTA1* fusion.[2] Fine needle aspiration and small biopsy is an effective method for diagnosis; however, it holds a 10% false negative rate.[5]

There is no consensus for a gold standard of treatment, however, there is agreement that treatment should consider the involvement of both liver lobes, lesion size/number, and disease progression.[4] Treatment includes radiation, chemotherapy, liver resection, and liver transplant. While agents targeting anti-angiogenesis have had the most success in clinical trials, common chemotherapeutics include doxorubicin, vincristine, interferon-alpha, 5-fluorouracil, thalidomide, and monoclonal antibodies against vascular endothelial growth factor. Characteristics most favorable to liver resection included: less than 10 lesions, tumor diameter of less than 10 cm, less than four extrahepatic lesions, and single lobe involvement. Liver transplant is the treatment of choice for diffuse, multifocal lesions, and rapidly progressive disease.[4,6]

Patients with radiologically stable disease should undergo an initial three-month surveillance period with subsequent treatment for tumors rapidly enlarging at a rate of more than three centimeters in three months.[6] Survival rates are liver transplant (54.5%), liver resection (75%), chemotherapy/radiation (30%), and surveillance without follow-up intervention (4.5%).[2]

A poor prognosis is associated with a tumor size of more than 10 cm in diameter in patients who received liver resection versus liver transplant.[6] Increased uptake by 18F-fluorodeoxyglucose PET/CT imaging following anti-angiogenic chemotherapy signifies a worse clinical outcome. Risk factors for recurrence are macrovascular infiltration, time to liver transplant of at least 120 days, and hilar lymph node infiltration.[5] A scoring system assessing the risk of HEHE recurrence following liver transplant stated that the five-year disease-free survival rate was significantly higher in patients with a lower score of 2 or less (93.9%) versus a higher score of 6 or more (38.5%).[5]

HEHE is a rare malignancy that often presents with nonspecific clinical symptoms, nonspecific labs, and imaging that easily misdirects. It carries a high misdiagnosis rate and an even worse clinical outcome when treated improperly. It has potential to progress rapidly and there was no consensus for treatment. It is difficult to overstate the need for a multifaceted diagnostic approach that considers imaging, histology, immunohistochemistry, and molecular markers.

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