Correspondence

DOI: 10.5582/irdr.2022.01113

Updated information regarding management of hepatic epithelioid hemangioendothelioma

Kaijian Chu[1,2], Zhizheng Li[1], Wei Tang[2,3], Xiaoqing Jiang[1,*]

[1] Biliary Surgery Department No. 1, Eastern Hepatobiliary Surgical Hospital, Naval Medical University, Shanghai, China;
[2] Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;
[3] International Health Care Center, National Center for Global Health and Medicine, Tokyo, Japan.

SUMMARY Hepatic epithelioid hemangioendothelioma (HEHE) is a rare hepatic vascular tumor with a borderline biological behavior between hemangioma and hemangiosarcoma. It tends to be multiple or diffuse subcapsular lesions across the liver but has no characteristic clinical manifestations or imaging findings. On computed tomography and magnetic resonance imaging, these lesions usually have a hypodense appearance with heterogeneous enhancement and a "halo sign" or "lollipop sign" may be evident in some cases. HEHE is diagnosed mainly based on a pathological examination along with differential immunohistochemical markers such as CAMTA1, CD31, CD34, CD10, vimentin, and factor VIII antigen. Currently, there are no standardized treatment guidelines for HEHE, and surgery (curative resection and liver transplantation) remains the mainstay of treatment. Studies have indicated that extra-hepatic metastasis might not be a contraindication for resection or transplantation. Systemic chemotherapeutic agents including doxorubicin, vincristine, interferon-a, 5-fluorouracil, and thalidomide, as well as VEGF-related agents are being investigated, but no agents have been approved for the treatment of HEHE.

Keywords hepatic epithelioid hemangioendothelioma, differential diagnosis, pathology, curative resection, liver transplantation

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor with an estimated incidence of less than 0.01 per million (*1*). The World Health Organization has classified it as a tumor condition with a full potential of malignancy (*2*). It can occur anywhere in the body but mostly affects the liver (*3,4*). Hepatic epithelioid hemangioendothelioma (HEHE) is diagnosed predominantly in females (female-to-male ratio: 3:2) (*1*). The hallmark of HEHE is its unpredictable clinical course, which can be indolent, stable, or aggressive due to its borderline biological behavior between hemangioma and hepatic hemangiosarcoma (*5*). Clinical diagnosis and management of HEHE is a challenge. Due to its rarity and inconsistent behavior, there are no standardized treatment guidelines for HEHE at present. This article has reviewed the recent literature and analyzed updated data regarding the diagnosis and management of HEHE.

1. Clinical presentation and diagnosis

HEHE has no characteristic clinical manifestations and may present as right upper quadrant or epigastric pain (60-70%), weight loss (20%), an impaired general condition (20%), or jaundice (10%) (*1*). A study has noted that approximately one-quarter of patients are asymptomatic at the time of diagnosis (*6*). HEHE has a more aggressive course than EHE arising in bone or soft tissue. Clinically, HEHE is misdiagnosed in approximately 60-80% of cases (*7*). HEHE is most often confused with disease entities such as angiosarcoma, cholangiocarcinoma, metastatic carcinoma, and hepatocellular carcinoma. HEHE tends to be multiple or diffuse throughout the liver with a peripheral or subcapsular growth pattern. One study found that HEHE was multifocal in 81% of patients and solitary in the remaining 19% (*7*). Another study found that the multinodular type of HEHE is an intrahepatic metastatic disease arising from a single clone (*8*). The tumor size (> 3cm) and mitotic index (> 3mitoses/50HPF) have been found to be poor prognostic factors for HEHE (*9*). Extrahepatic involvement was found in 36.6% of HEHE cases (*7*). The most common sites of metastasis are the lungs, regional lymph nodes, peritoneum, bone,

and the spleen.

1.1. Imaging features of HEHE

On a CT scan, HEHE lesions usually display a hypodense appearance and heterogeneous enhancement. Tumors larger than 3 cm in size frequently exhibit delayed heterogeneous enhancement, tumors 2 to 3 cm in size exhibit ring-like enhancement, and tumors smaller than 2 cm exhibit homogeneous enhancement (*10*). A "lollipop" sign with an enhancing portal vein terminating at the edge of a hypodense lesion may be evident in some cases, and a "halo sign" with ring enhancement during the arterial phase and central filling on the delayed phases may be evident in others (*11*). HEHE lesions typically have a hypoechoic appearance on sonography. HEHE displays intratumoral vascularity and is better depicted on color Doppler (*12*). Contrast-enhanced ultrasound (CEUS) can be used to detect multiple foci of HEHE, with high enhancement in the arterial phase and low enhancement in the portal or delayed phase (*13*). 18F-FDG PET-CT is useful in detecting metastatic lesions and determining the spread of HEHE (*14*).

1.2. Histology and pathological differential diagnosis

Due to its nonspecific clinical manifestations and radiological features, HEHE is mainly diagnosed based on a pathological examination (*2*). EHE was first described by Dail and Liebow in 1975 as an epithelial lesion with an epithelioid morphology (*15*). The term "epithelioid hemangioendothelioma" was coined by Weiss and Enzinger in 1982 (*16*). The histology of HEHE is relatively distinctive from normal liver parenchyma, and it displays an infiltrative growth pattern consisting of epithelioid, dendritic, and intermediate cells interspersed in a hyaluronic acid–rich myxoid matrix (*7*). The epithelioid cells in HEHE contain rounded vesicular nuclei, an eosinophilic cytoplasm, and occasional intracytoplasmic vacuoles (*17*). These cells tend to grow along vascular structures and infiltrate hepatic sinusoids, causing atrophy and replacement of hepatocytes (*7*). A subset of HEHE displays a histologic overlap with hepatic angiosarcoma (HA) containing necrosis or cytonuclear atypia, without the typical myxoid stromal component. Pathologists often have difficulty differentiating HEHE from HA (*3*). Immunohistochemical and special staining can help with differentiation. Around 90% of HEHEs harbor the CAMTA1- WWTR1 fusion gene, which has been consistently identified in hemangioendothelioma, irrespective of the primary site (*15,18*). Other vascular endothelial markers include CD31, CD34, CD10, vimentin, and factor VIII antigen (*7*). Immunohistochemical staining of a fine-needle aspiration or biopsy specimen is the best method for diagnosing nonoperative patients. However, a false negative rate of 10% has been observed after a biopsy (*19*). The disease entities that tend to be confused with HEHE and their differential diagnosis are summarized in Table 1.

2. Current management of and the prognosis for HEHE

A standardized treatment algorithm for HEHE has yet to be devised, partly due to its rarity and inconsistent biological behavior. Therapeutic options in clinical practice include radiotherapy, chemotherapy, transcatheter arterial chemoembolization (TACE), anti-angiogenic drugs, locoregional ablation, hepatic resection, and liver transplantation (LT). The treatment modality is determined based on the tumour burden, extrahepatic involvement, resectability, and the condition of the patient's major organs (*20*). Currently, surgery including curative resection and transplantation remains the mainstay of treatment. Curative resection and LT have the best survival rates, with 5-year survival rates of 54.5% and 75%, respectively. In contrast, chemo/radiotherapy and observational follow-up have 5-year survival rates of 30% and 4.5%, respectively (*21*). According to a multivariate analysis, surgery was the only independent prognostic factor for overall survival of HEHE patients (*22*). Chemotherapeutic agents such as doxorubicin, vincristine, interferon-a, 5-fluorouracil, and thalidomide and therapy targeting vascular endothelial grow factor (VEGF) are being investigated (*23*). Thalidomide has been reported to offer potential for the treatment of HEHE (*24*). However, there are no approved systemic treatments for HEHE at present.

2.1. Curative resection for HEHE

Lesions that are multiple foci or extensive involvement of the liver pose a challenge to surgical resection. A detailed preoperative plan needs to be devised or surgery needs to be simulated preoperatively, like colorectal liver metastasis (CRLM). Optimal surgery is a radical resection of all HEHE lesions with maximum preservation of liver parenchyma (*2*). The long-term prognosis for patients with extra-hepatic metastasis who underwent surgery was not inferior to the long-term prognosis for patients without extra-hepatic involvement, indicating that extra-hepatic metastasis might not be a contraindication for surgery (*25*).

2.2. LT for HEHE

LT is seldom performed for a benign liver tumor worldwide, and it accounts for only 1% of all LTs in Europe and the US (*26*). However, HEHE is not necessarily considered to be a contraindication for LT when it is bilobar foci or diffuse disease throughout the

Table 1. Differential diagnosis of HEHE and other hepatic disease entities (*4,12,21*)

Entities	Imaging features	IHC markers	Histology
HEHE	Lollipop sign, halo sign, subcapsular growth, capsular retraction	(+)CAMTA1, WT-1, CD31, CD34, vimentin, F VIII,ERG, D2-40; (-)GLUT-1, cytokeratin	Cords and nests of epithelioid cells in a variable fibromyxoid stroma; Occasional intracytoplasmic vacuoles/lumina; minimal cytologic atypia with low mitotic rates; portal tracts intact.
Hepatic angiosarcoma	Heterogeneous centripetal enhancement	(+)WT-1, CD31, CD34, F VIII,FLI-1, ERG; (-)GLUT-1, D2-40, alpha-1-antitrypsin, pan-cytokeratin	More nuclear pleomorphism; more atypia and mitotic activity; well-formed, anastomosing vessels; more solid areas composed of pleomorphic spindle cell; hypercellular whorls of spindled cells; intracytoplasmic eosinophilic globules.
Hepatic hemangioma	Posterior shadowing and centripetal filling	(+)WT-1, CD34, CD31, FVIII,ERG; (-)GLUT-1,D2-40	Circumscribed proliferation of variably sized, dilated and thin-walled vessels lined by a single layer of flat endothelial cells; no cytologic atypia or mitosis.
ICC	Cholangiectasis, capsular retraction	Pan-cytokeratin	Abundant desmoplastic stroma and gland formation or nested neoplastic cells.
HCC	Wash-out	HepPar-1; CD10, CK8/18, glypican3,pCEA	Well-vascularized tumors with wide trabeculae (> 3 cells), a prominent acinar pattern, small cell changes, cytologic atypia, mitotic activity, vascular invasion, absence of Kupffer cells, and the loss of the reticulin network.
CRLM	Bull's-eye sign	Resemble original tumors	Similar to original tumors.

Abbreviation: IHC immunohistochemical staining; ICC intrahepatic cholangiocarcinoma; HCC hepatocellular carcinoma; CRLM colorectal cancer liver metastasis; WT-1: Wilms' tumor 1; FVIII: factor VIII; ERG: Erythroblast transformation, specific-related gene; GLUT-1: glucose transporter-1; D2-40: podoplanin; CAMTA1: calmodulin-binding transcription activator1; TFE3: transcription factor E3.

liver (*27*). Good outcomes of LT for HEHE have been reported from the West, with a 5-year survival of 67% in the US (1987–2005) and 79.5% in Europe (1989–2017) (*28,29*). Both studies found that extrahepatic metastasis did not represent an absolute contraindication for LT (*2*). After transplantation, the 5-year survival rate of patients with HEHE and extra-hepatic metastasis was as high as 72% (*17*). In a study of 110 patients with HEHE, the recurrence rate after LT was 11% (*29*). The independent risk factors for post-LT recurrence of HEHE include macrovascular invasion at pathology, a pre-LT waiting time longer than 120 days, and hilar lymph node metastasis (*29*). Therefore, that study emphasized the importance of routine extensive lymphadenectomy during LT.

In conclusion, HEHE is a rare borderline liver vascular tumor with an unpredictable clinical course (indolent to progressive), and its pathogenesis is not completely known. Its diagnosis depends mainly on a pathological examination. Immunohistochemistry is helpful in making a diagnosis, along with vascular endothelial markers such as CD10, CD31, CD34, and factor VIII antigen. Currently, there are no standardized guidelines for treating HEHE, and surgery including curative resection and transplantation remains the mainstay of its treatment.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Ostojic A, Mrzljak A, Mikulic D. Liver transplantation for benign liver tumors. World J Hepatol. 2021; 13:1098-1106.
2. Giovanardi F, Larghi Laureiro Z, Meo GA, Hassan R, Lai Q. The challenging surgical management of hepatic epithelioid hemangioendothelioma: A narrative review. Chin Clin Oncol. 2022; 11:27.
3. Hettmer S, Andrieux G, Hochrein J, Kurz P, Rössler J, Lassmann S, Werner M, von Bubnoff N, Peters C, Koscielniak E, Sparber-Sauer M, Niemeyer C, Mentzel T, Busch H, Boerries M. Epithelioid hemangioendotheliomas of the liver and lung in children and adolescents. Pediatr Blood Cancer. 2017; 64. doi: 10.1002/pbc.26675.
4. Cordier F, Hoorens A, Van Dorpe J, Creytens D. Pediatric vascular tumors of the liver: Review from the pathologist's point of view. World J Hepatol. 2021; 13:1316-1327.
5. Cournoyer E, Al-Ibraheemi A, Engel E, Chaudry G, Stapleton S, Adams DM. Clinical characterization and long-term outcomes in pediatric epithelioid hemangioendothelioma. Pediatr Blood Cancer. 2020; 67:e28045.
6. Studer LL, Selby DM. Hepatic epithelioid hemangioendothelioma. Arch Pathol Lab Med. 2018; 142:263-267.
7. Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, Schirmacher P, Weitz J, Friess H, Buchler MW, Schmidt J. Primary malignant hepatic epithelioid hemangioendothelioma: A comprehensive review of the literature with emphasis on the surgical therapy. Cancer. 2006; 107:2108-2121.
8. Errani C, Sung YS, Zhang L, Healey JH, Antonescu CR. Monoclonality of multifocal epithelioid hemangioendothelioma of the liver by analysis of

WWTR1-CAMTA1 breakpoints. Cancer Genet. 2012; 205:12-17.
9. Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, Healey JH, Antonescu CR. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. Genes Chromosomes Cancer. 2011; 50:644-653.
10. Zhou L, Cui MY, Xiong J, Dong Z, Luo Y, Xiao H, Xu L, Huang K, Li ZP, Feng ST. Spectrum of appearances on CT and MRI of hepatic epithelioid hemangioendothelioma. BMC Gastroenterol. 2015; 15:69.
11. Alomari AI. The lollipop sign: A new cross-sectional sign of hepatic epithelioid hemangioendothelioma. Eur J Radiol. 2006; 59:460-464.
12. Virarkar M, Saleh M, Diab R, Taggart M, Bhargava P, Bhosale P. Hepatic hemangioendothelioma: An update. World J Gastrointest Oncol. 2020; 12:248-266.
13. Kou K, Chen YG, Zhou JP, Sun XD, Sun DW, Li SX, Lv GY. Hepatic epithelioid hemangioendothelioma: Update on diagnosis and therapy. World J Clin Cases. 2020; 8:3978-3987.
14. Kitapci MT, Akkaş BE, Gullu I, Sokmensuer C. FDG-PET/CT in the evaluation of epithelioid hemangioendothelioma of the liver: the role of dual-time-point imaging. A case presentation and review of the literature. Ann Nucl Med. 2010 ; 24:549-553.
15. Ishak KG, Sesterhenn IA, Goodman ZD, Rabin L, Stromeyer FW. Epithelioid hemangioendothelioma of the liver: A clinicopathologic and follow-up study of 32 cases. Hum Pathol. 1984; 15:839-852.
16. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: A vascular tumor often mistaken for a carcinoma. Cancer. 1982; 50:970-981.
17. Jung H, Kim HN, Jang Y, Park CK, Ha SY. CAMTA-1 Expression in 24 Cases of Hepatic Epithelioid Hemangioendothelioma in a Single Institute: Diagnostic Utility for Differential Diagnosis from Hepatic Angiosarcoma. In Vivo. 2019; 33:2293-2297.
18. Tanas MR, Ma S, Jadaan FO, Ng CK, Weigelt B, Reis-Filho JS, Rubin BP. Mechanism of action of a WWTR1(TAZ)-CAMTA1 fusion oncoprotein. Oncogene. 2016; 35:929-938.
19. Venkatesh SK, Chandan V, Roberts LR. Liver masses: a clinical, radiologic, and pathologic perspective. Clin Gastroenterol Hepatol. 2014; 12:1414-1429.
20. Gigante E, Paradis V, Ronot M, Cauchy F, Soubrane O, Ganne-Carrié N, Nault JC. New insights into the pathophysiology and clinical care of rare primary liver cancers. JHEP Rep. 2020; 3:100174.
21. Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, Schirmacher P, Weitz J, Friess H, Buchler MW, Schmidt J. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. Cancer. 2006; 107:2108-2121.
22. Noh OK, Kim SS, Yang MJ, Lim SG, Hwang JC, Cho HJ, Cheong JY, Cho SW. Treatment and prognosis of hepatic epithelioid hemangioendothelioma based on SEER data analysis from 1973 to 2014. Hepatobiliary Pancreat Dis Int. 2020; 19:29-35.
23. Choi KH, Moon WS. Epithelioid hemangioendothelioma of the liver. Clin Mol Hepatol. 2013; 19:315-319.
24. Raphael C, Hudson E, Williams L, Lester JF, Savage PM. Successful treatment of metastatic hepatic epithelioid hemangioendothelioma with thalidomide:A case report. J Med Case Rep. 2010; 4:413.
25. Brahmbhatt M, Prenner S, Bittermann T. Liver transplantation for hepatic epithelioid hemangioendothelioma is facilitated by exception points with acceptable long-term outcomes. Transplantation. 2020; 104:1187-1192.
26. Bellini MI, Lauro A, D'Andrea V, Marino IR. Benign hepatic tumors and liver transplantation: A literature review. Exp Clin Transplant. 2022; 20:231-236.
27. Lerut JP, Orlando G, Adam R, *et al*; European Liver Transplant Registry. The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: Report of the European Liver Transplant Registry. Ann Surg. 2007; 246:949-957.
28. Rodriguez JA, Becker NS, O'Mahony CA, Goss JA, Aloia TA. Long-term outcomes following liver transplantation for hepatic hemangioendothelioma: The UNOS experience from 1987 to 2005. J Gastrointest Surg. 2008; 12:110-116.
29. Lai Q, Feys E, Karam V, Adam R, Klempnauer J, Oliverius M, Mazzaferro V, Pascher A, Remiszewski P, Isoniemi H, Pirenne J, Foss A, Ericzon BG, Markovic S, Lerut JP; European Liver Intestine Transplant Association (ELITA). Hepatic epithelioid hemangioendothelioma and adult liver transplantation: Proposal for a prognostic score based on the analysis of the ELTR-ELITA registry. Transplantation. 2017; 101:555-564.

Received October 12, 2022; Revised November 4, 2022; Accepted November 6, 2022.

**Address correspondence to:*
Xiaoqing Jiang, Biliary Surgery Department No. 1, Eastern Hepatobiliary Surgical Hospital, Naval Medical University, 225 Changhai Road, Yangpu District, Shanghai 200433, China
E-mail: jxq1225@sina.com

Released online in J-STAGE as advance publication November 9, 2022.