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Ultrasound characteristics of hepatic epithelioid hemangioendothelioma: a multi-center case series study

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Abstract

Aims: Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular tumor that primarily affects the liver. This study aimed to analyze the characteristics of conventional ultrasound (US) and contrast-enhanced ultrasonography (CEUS) in HEHE. **Material and methods:** This multi-center case series study enrolled patients diagnosed with HEHE from five hospitals in China between August 2004 and October 2022. Data on conventional US and CEUS characteristics were collected and analyzed. **Results:** A total of 41 patients with HEHE were included, comprising 14 males and 27 females with a mean age of 50.62±11.43 years. The mean size of the lesion was 4.51±2.92 cm. Among these patients, 29 were confirmed through surgical resection and 12 through liver biopsy. Conventional US imaging identified three types of HEHE: multifocal type in 35 patients (85.4%), single nodular type in 1 patient (2.4%), and giant type in 5 patients (12.2%). US revealed proximity to the liver capsule in 29 patients (71%), hypoechoic appearance in 36 patients (88%), heterogeneity in 4 patients (10%), and hyperechoic appearance in 1 patient (2.4%). CEUS also demonstrated three distinct enhancement patterns: peripheral marginal enhancement with centripetal filling in the arterial phase and washout in the portal venous and venous phases (23 patients), heterogeneous enhancement in the arterial phase with washout in the subsequent phases (7 patients), and mild hyperenhancement in the arterial phase with resolution in later phases (9 patients). A hypo-enhancement pattern in the portal venous and venous phases was observed in 38 patients, suggesting a higher degree of malignancy. **Conclusion**: HEHE exhibits specific US findings, primarily presenting as multiple hypoechoic lesions distributed under the liver capsule.

Keywords: hepatic epithelioid hemangioendothelioma; CEUS; ultrasound; liver tumors; diagnostic imaging

Introduction

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular tumor that primarily affects the liver [1]. HEHE originates from the mesenchymal tissue and its malignancy falls between hemangioma and vascular endothelial sarcoma [2]. Similarly, its behavior can vary from an indolent to an aggressive course [3]. It can metastasize to other organs such as lungs, bones, and lymph nodes [4]. While it can occur at an early stage, the peak incidence is usually between the third and fourth decades of life, with an estimated annual incidence of 0.1–1 case per million individuals [5].

The etiology of HEHE is not clearly known. However, consumption of oral contraceptives, viral hepatitis, chronic alcohol ingestion, and exposure to vinyl chloride, asbestos, and thorium oxide colloids, have been identified as common risk factors with the development of HEHE [6,7]. It remains asymptomatic in the early stages. Its common symptoms during late stages include

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abdominal pain, liver enlargement, weight loss, fatigue, and malaise, which vary widely and depend on the size and location of the tumor [8,9]. In some cases, a large tumor may cause liver dysfunction, leading to jaundice and coagulopathy [10]. The common treatment options for HEHE includes surgical resection [11], liver transplantation [12], and local therapies like radiofrequency ablation [13], trans-arterial embolization [14], or the use of chemotherapeutic drugs [8]. The choice of these methods depends on factors such as tumor size and location and the overall health condition of the patient.

The most common diagnostic methods for HEHE include imaging tests such as ultrasound (US) [15], computed tomography (CT) scan [16], and magnetic resonance imaging (MRI) [10,17,18]. These methods are non-invasive, easily accessible, and identify liver lesions. However, sometimes imaging might be non-specific and unable to detect small lesions. Likewise, HEHE is difficult to be diagnosed with the conventional US. Biopsies like core needle biopsy and surgical biopsy are also used for diagnosis of HEHE. These methods provide accurate histopathological information; however, these encounter complications like bleeding, infection, sampling error, and, due to the intra-tumor heterogeneity, false-negative results. Immunohistochemical analysis is also used for detection of certain proteins expressed in HEHE, which help in differential diagnosis from other liver tumors. However, this approach is limited by the subjective interpretation of staining patterns and occasional false-negative or false-positive results. The current diagnostic approaches for HEHE detection are limited by several factors including rarity of the tumor, varied clinical manifestations, similarity of imaging characteristics with other liver tumors, challenges in sample collection, and lack of specific biomarkers [19].

Contrast-enhanced ultrasound (CEUS) is a diagnostic imaging technique that utilizes microbubble-based contrast agents to enhance visualization of blood flow within the liver vasculature [20]. It is widely used to detect liver diseases, especially focal liver lesions [21,22]. CEUS has proven to be a useful tool for diagnosis and evaluation of HEHE and recently given preference over conventional US. It offers several advantages such as real-time and dynamic imaging of liver tumor as well as allows for the assessment of tumor perfusion patterns, characterization of lesions, and evaluation of treatment response [23]. CEUS shows hypervascular features in HEHE, with arterial phase hyperenhancement and washout in the venous phase [24]. A study demonstrated accurate tumor delineation and improved detection of tumor vascularity compared to conventional US [25] while another study demonstrated improved diagnostic performance of CEUS in differentiating HEHE from other liver tumors with high sensitivity and specificity [20]. However, the findings of HEHE obtained through a CEUS are mostly case reports. Therefore, this study aimed to retrospectively analyze the characteristics of conventional US and CEUS in HEHE.

Material and methods

Study design and patients

This retrospective case series study enrolled HEHE patients from five tertiary hospitals in China, between August 2004 and October 2022. Inclusion criteria: 1) patients with HEHE confirmed by pathological examination. Exclusion criteria: 1) patients with unclear pathological diagnosis; 2) patients with incomplete clinical and imaging data. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University, and informed consent exemption was granted.

Data collection and definition

Various clinical, imaging, and pathological data from all patients were collected, including age, gender, lesion location, size, number, echo, angiographic findings, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), CA 19-9, and CA 125, which were gathered from the Intranet workstation. The number and distribution of lesions were determined through CT and MRI imaging. CEUS was performed on 39 patients. All images were meticulously reviewed by two independent experts with over 10 years of CEUS experience in analyzing liver lesions. In cases where the two specialists had different opinions, a third expert was consulted to reach a consensus.

HEHE was confirmed histologically through hematoxylin and eosin (H&E) staining as well as immunohistochemical staining of tissue specimens. The origin of endothelial cells was verified by detecting endothelial markers like CD31, CD34, and factor VIII-related antigen (FVIII Ag) in the specimens using immunohistochemical staining [26,27].

Procedures

We utilized various ultrasound systems for US and CEUS, including the MyLab system with the CA541 transducer (Esaote, Gen-ova, Italy), the Resona R9 system (Mindray SC5-1U China), the Affiniti 50 system with the C5-1 transducer (Philips, Amsterdam, Netherlands), and the Siemens Acuson S2000 system with the 6C-1 transducer (ACUSON S2000 system, Siemens, Washington, DC, USA).

After undergoing a conventional US examination, 39 patients underwent CEUS using pulse inversion harmonic imaging with a low mechanical index (above). The contrast medium used was SonoVue (Braco Spa). The arterial phase was defined as 10 to 40 s after the injection

of the contrast medium, the portal phase was 30 to 120 s, and the late phase was 121 to 360 s, according to the World Federation for Ultrasound in Medicine and Biology–European Federation of Societies for Ultrasound in Medicine and Biology (WFSUMB-EFSUMB) guidelines [28]. The CEUS data was analyzed and reported. All images were reviewed by two experts with over 10 years of experience in CEUS of liver lesions, and any disagreements were resolved by obtaining an opinion from a third expert with over 20 years of experience in US diagnosis.

The US imaging features of HEHE included the location, number of lesions (single, multiple, and giant), maximum diameter, echo of the lesion compared with the surrounding normal liver parenchyma (hypoechoic, hyperechoic, and isoechoic; homogeneous or heterogeneous), presence of hypoechoic or hyperechoic halos, shape (regular or irregular), border (clear or unclear), and presence of calcification, blood flow, and other indirect signs such as compression of normal peripheral vessels.

The CEUS used different imaging phases to evaluate the enhancement level and pattern of the lesion. The degree of enhancement was categorized as low enhancement, high enhancement, iso-enhancement, and non-enhancement, based on the degree of enhancement of the tumor compared with the surrounding liver parenchyma. Additionally, the enhancement patterns included uniform enhancement, non-uniform enhancement, and peripheral edge-like enhancement [28].

Statistical analysis

Only descriptive analysis was applied. The statistical analysis was performed using SPSS Statistics version 24.0 (IBM, Armonk, NY, USA). Continuous data following a normal distribution were presented as mean ± standard deviation (SD), while categorical data were reported as n (%).

Results

A total of 41 HEHE patients were enrolled, including 14 males and 27 females (mean age: 50.62±11.43 years). The mean size of the lesion was 4.51±2.92 cm. Out of the 41 patients, 25 (61%) patients had no symptoms, 7 (17%) had varying degrees of elevated levels of AFP, CEA, CA 19-9, and CA 125, 5 (12%) patients were found to have hepatitis B virus (HBV) infection. Out of 41 patients, 29 were confirmed to have HEHE through surgical resection, while 12 patients were confirmed through US-guided liver biopsy. The HEHE appeared mostly hypoechoic with a clear boundary (80%), and blood flow signals were mostly undetectable. In giant lesions, minimal blood flow signals were seen at the edges and inside. On conventional US imaging, three types of HEHE were identified: multifocal type in 35 patients (85.4%), single nodular type in 1 patient (2.4%), and giant type in 5 patients (12.2%). Of these cases, 36 showed bilateral liver involvement, while 5 cases had lesions confined to the right liver (Table I). The CEUS revealed features such as proximity to the liver capsule in 29 patients (71%), hypoechoic appearance in 36 patients (88%), heterogeneity in 4 patients (10%), or hyperechoic appearance in 1 patient (2.4%), and regular shape in 34 patients (83%). Occasional observations included acoustic halo in 6 patients (15%) and calcification in 2 patients (4.9%) (Table II).

Table I. Clinical Features and Conventional Ultrasound Features of HEHE Patients

Feature	Value
Number of patients	41
Age (Years), Mean ± SD	50.6 ± 11.4 (range: 23-69)
Gender (Male/Female)	14/27
Mean age (years)	50.62 ± 11.43
Mean lesion size (cm)	4.51 ± 2.92
Symptomatic patients (%)	16 (39%)
Elevated AFP, CEA, CA 19-9, CA 125 (%)	7 (17%)
HBV infection (%)	5 (12%)
Hypoechoic with clear boundary (%)	80%
Detectable blood flow signals (%)	Minimal in giant lesions
Multifocal type (%)	35 (85.4%)
Single nodular type (%)	1 (2.4%)
Giant type (%)	5 (12.2%)
Bilateral liver involvement (%)	36 (87.8%)

Table II. Contrast-enhanced ultrasound features of HEHE patients

Feature	Value
Proximity to liver capsule (%)	29 (71%)
Hypoechoic appearance (%)	36 (88%)
Heterogeneity (%)	4 (10%)
Hyperechoic appearance (%)	1 (2.4%)
Regular shape (%)	34 (83%)
Acoustic halo (%)	6 (15%)
Calcification (%)	2 (4.9%)
CEUS Pattern I (%)	23 (59%)
CEUS Pattern II (%)	7 (18%)
CEUS Pattern III (%)	9 (23%)
Lesions < 3 cm (patterns I & III)	12
Lesions > 3 cm	Irregular non-enhanced areas in the center, walking vascular shadows in the adjacent internal area

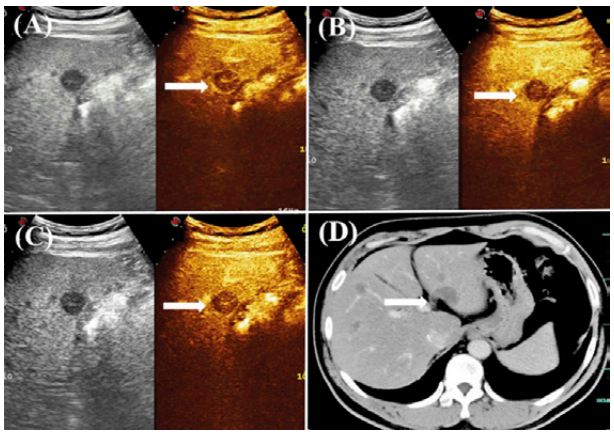

Fig 1. HEHE in a 42-year-old female with elevated CA125 (541.2 ng/ml), negative hepatitis B and AFP: **(**A) CEUS observation of circumferential enhancement in the right liver lesion at 24 s in the dynamic phase, with uneven hypo-enhancement inside; (B) CEUS reveals hypo-enhancement in the portal venous phase at 61 s; (C) CEUS shows hypo-enhancement in the delayed phase at 123 s; and (D) CT image shows multiple lesions in the liver in the delayed phase.

All patients underwent CT and/or MRI examination. CEUS was performed in 39 patients. Three different CEUS patterns were observed: (I) peripheral marginal enhancement with centripetal filling in the arterial phase and regression in the portal venous and venous phases (fig 1); (II) heterogeneous enhancement in the arterial phase and regression in the portal and venous phases (fig 2); and (III) mild hyperenhancement in the arterial phase with resolution in the portal and venous phases (fig 3). For lesions smaller than 3 cm (12 cases), most showed types I and III, with no significant differences between the two. Lesions larger than 3 cm typically had irregular non-enhanced areas in the center and walking vascular shadows in the adjacent internal area. Patterns I, II, and III were observed in 23, 7, and 9 patients, respectively. Hypo-enhancement pattern in the portal venous and venous phases often indicates a higher degree of malignancy, as was observed in 38 patients in this study. Only one case still showed annular hyperenhancement in the portal venous phase, which then subsided to hypo-enhancement in the venous phase.

Discussion

This study found that lesions were typically hypoechoic with clear boundaries, and blood flow signals were rarely observed. Overall, HEHE exhibited specific US characteristics, presenting as multiple hypoechoic lesions near the liver capsule. The findings of this study may help in making accurate diagnoses and appropriate treatment decisions for HEHE patients.

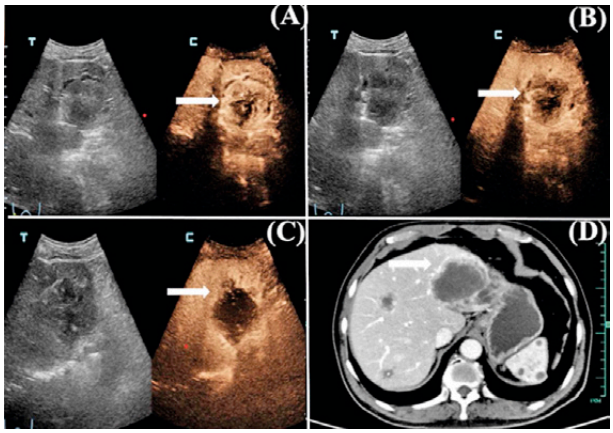

Fig 2. HEHE in a 58-year-old male with negative hepatitis B and tumor markers: (A) At 15 s in the arterial phase, a slightly hyper-enhanced lesion is observed in the left liver, with an uneven and non-enhanced central area. (B) At 30 s, the lesions show regression and exhibit uneven hypo-enhancement, with non-enhancement observed in the central area. (C) At 90 s, the lesions show obvious hypo-enhancement, with no enhanced area in the interior. (D) Low-density lesions are visible in the right liver.

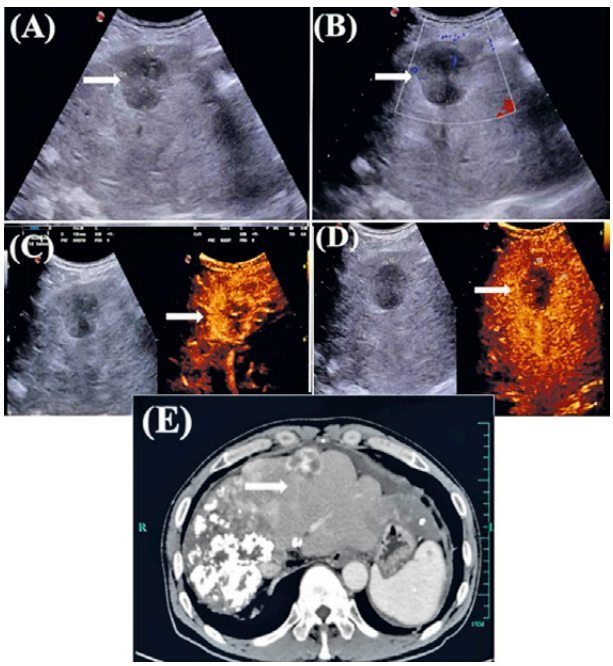

Fig 3. HEHE in a 66-year-old male patient with positive hepatitis B core antibody and negative AFP, CA125: 73.3 ng ml–1, CEA: 5.2 ng ml–1: (A) A hypoechoic lesion with clear boundaries and a size of 3.5 × 3.2 cm was observed under the right liver capsule; (B) Color Doppler flow imaging reveals short strip blood flow signals within the lesion; (C) The lesion displays mild to moderate uneven high enhancement during the arterial phase, observed within 30 s; (D) At 92 s, the lesion shows low enhancement; (E) Multiple lesions and calcifications are detected in the right liver during the arterial phase of CT scanning.

The HEHE is an uncommon tumor and is considered to have a low malignancy compared to other liver conditions such as hepatic hemangioma and a hepatic vascular endothelial sarcoma [29]. A study found that HEHE is more commonly observed in adults, particularly in women, with a higher prevalence in individuals aged 30 to 40 years [30]. However, our study showed a higher proportion of women (65.8%) and a significantly older median age at diagnosis, specifically 60.5 years. Most patients with HEHE do not exhibit obvious clinical symptoms, although a few may experience upper abdominal discomfort, fatigue, weight loss when they present at the hospital. In this study, laboratory examination did not reveal any specificity abnormalities. However, we did observe that 7 cases had varying degrees of elevated AFP, CEA, CA 19-9, and CA 125, of which most were slightly elevated. Interestingly, there was no significant difference in CEUS findings between patients with abnormal laboratory tests and those without obvious abnormal results [31]. Notably, 5 patients in this study had concurrent HBV infection. HEHE can be divided into different types based on imaging findings, including single focal, multiple, and giant mass types [8]. While the single focal type has been reported in about 13-18% of HEHE in a previous study [32], we observed a lower incidence of 2.4% in this study. The majority of patients presented with multifocal lesions (85.4% in this study), primarily located in the subcapsular region of the liver (71% in this study). As the multifocal type progresses, the nodules may fuse together, leading to the appearance of a giant mass type at the time of diagnosis. It is important to note that despite the large size of the lesion, capsular contracture, which is characterized by contraction of the unaffected surrounding tissues of the liver due to fibrosis and compensatory hypertrophy, has been reported in 10-25% of patients, including 7 cases in this study (17%), in line with previous reports [33,34].

In this study, we found that both lobes of the liver were affected in 88% of cases of HEHE. In the remaining 12% of cases, the disease was isolated to the right lobe. This finding is consistent with previous reports who also noted a higher incidence of right-sided and bilateral disease rather than isolated left-sided disease [30,34]. Calcification has also been observed in a portion of HEHE patients, with reported rates ranging from 6-25% [31,35,36]. However, in our data, we only identified 2 cases with multiple calcifications, which accounted for approximately 5% of the cases. This study also revealed that the majority (78%) of patients with HEHE had hypoechoic lesions with clear boundaries. In 5 cases (approximately 12%), hypoechoic was observed. These results align with previous studies [30,36-38]. Despite HEHE being a tumor of vascular origin, the color Doppler US in this study did not detect blood vessels within the lesions. However, a few larger lesions exhibited minimal blood flow signals. This finding is consistent with the color Doppler characteristics of benign hemangiomas, suggesting that the low flow rate of capillaries may explain this observation [36]. It is worth mentioning that this study did not consider the use of power Doppler or flow imaging modalities to assess the vascular condition of the lesion.

However, CEUS could potentially have a crucial role in early and accurate diagnosis. In this study we found three distinct patterns of enhancement as we already described. For lesions less than 3 cm, most showed types (I) and (III) with no significant difference. However, for lesions larger than 3 cm, irregular non-enhanced areas were typically observed in the center of the lesion alongside running blood vessels in the adjacent internal area. To date, there have been few reports on the appearance of HEHE on CEUS. Qiu et al reported on 20 cases of HEHE using conventional US and CEUS, with conventional US showing similar manifestations but differences in CEUS findings. We identified only one case of HEHE using conventional US, while Qiu et al reported 8 cases (40%) [35]. However, the number of cases using CEUS was relatively small, and there were frequent differences in contrast-enhancement. Dong et al [36] reported peripheral ring enhancement, similar to CEUS type II in 72% of patients in this study, while heterogeneous enhancement in the arterial phase was observed in the remaining 28% patients. In contrast, Klinger et al reported that 57.1% of cases showed peripheral hypo-enhancement in the arterial phase and iso-enhancement in the portal venous and delayed phases (target ring inversion), consistent with a previous study [38] that showed central iso-enhancement and resolution of peripheral vascular nonuniformity in the portal and delayed phases in a patient (25%). In this study, one patient still displayed iso-enhancement in the portal and delayed phases without significant regression. However, Dong et al [36] reported washout in 100% of their 25 patients in the portal and delayed phases, which differs from our findings. Our CEUS manifestations forms align more closely with Klinger et al [39]. These discrepancies may be due to unique manifestations of HEHE on CEUS. The development of the disease suggests the presence of different pathological stages of HEHE, leading to changes in the proportion of internal blood vessels, parenchymal cells, and stroma [27]. In the early stage of the disease, mild fibrosis is present, and tumor cells are evenly distributed. At this stage, the lesion demonstrates overall concentric hyperenhancement that gradually fills in from the periphery. As extensive fibrosis

occurs inside the lesion, it becomes difficult for the contrast agent to enter, resulting in richer peripheral tumor cells and a transition to wire-like enhancement and ring enhancement in the arterial phase [40]. However, hypoenhancement is observed in both the portal and delayed phases.

In cases in which the CEUS results do not indicate a typical hemangioma, focal fatty liver findings should be considered. In such cases, histological biopsy should typically be performed for localized lesions, regardless of whether tumor markers are elevated [33]. Pathologists should be cautious in diagnosing HEHE. Earlier studies have also noted the potential for misdiagnosis when using core needle biopsy, particularly in dense slitted areas [36,40]. Similarly, a study reported that only 25% of HEHE patients were correctly diagnosed by attending pathologists, with the condition often misdiagnosed as malignant lesions such as intrahepatic cholangiocarcinoma (ICC) [30]. Our study confirms the importance of CEUS criteria in diagnosis and suggests that these findings can improve the accuracy of diagnosing HEHE.

HEHE can be classified into three types based on imaging findings: single type, multifocal type, and giant type. Most cases exhibit multifocal and regular nodular growth, with some nodules merging together. Gross specimens of these lesions typically appear yellow-white and are described as firm, well-defined rubbery brown-grey masses ranging in size from 0.4 to 12 cm, without evident areas of hemorrhage or necrosis [33]. However, we observed vascular preservation in the tumor center in some patients, which is a distinct pattern reported in a previous study [39]. Dige et al noted that the degree of fibrosis depends on the size of the tumor lesion [41], suggesting that differences in enhancement may be attributed to more extensive fibrosis in larger lesions. To confirm the endothelial origin of the lesion, immunohistochemical staining with endothelial markers such as CD31, CD34, and factor VIII-related antigens is necessary. In the study of Makhlouf et al 86%, 94%, and 99% of lesions were tested positive for CD31, CD34, and factor VIII-related antigens, respectively [30].

However, this study had several limitations. Firstly, although it was a multicenter study, some centers provided only several cases, the findings of the study may not be representative of the general populations with HEHE. Secondly, the correlation of different imaging findings with histopathological changes is limited by the fact that not all patients underwent diagnostic testing with all imaging modalities and that not all specimens were available for definitive diagnosis by an expert pathologist.

In **conclusion**, CEUS showed that HEHE exhibits specific US findings, such as multiple hypoechoic lesions under the liver capsule. The study highlights the potential of CEUS as a valuable tool in the imaging evaluation of HEHE and contributes to our understanding of this rare hepatic tumor.

Conflict of interest: none

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