Received: 15 September 2021 | Revised: 4 January 2022 | Accepted: 5 January 2022

DOI: 10.1002/jcu.23141

CASE REPORT

WILEY

# Three cases of hepatic epithelioid hemangioendothelioma evaluated using conventional and contrast-enhanced ultrasound: Case reports

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**Funding information**
This work was supported by the Xianyang Natural Science Foundation (grant numbers: 2019k02-102).

## Abstract

Hepatic epithelioid hemangioendothelioma (HEHE) is a very rare vascular endothelial cell tumor, which lacks typical clinical manifestations and specificity of imaging features. Whether the background of fatty liver and the difference in Contrast enhanced ultrasound (CEUS) characteristics between large and small lesions has not been well defined. In this case reports, we described the ultrasound image features of three patients with HEHE. These three patients with HEHE have certain similar characteristics of conventional ultrasound and CEUS. CEUS imaging features include large nodules show earlier perfusion than liver parenchyma, with rim-enhancement, nonenhancing regions in the center, while small nodules show earlier perfusion than liver parenchyma, with hyperenhancement. All nodules show faster washout than hepatic parenchyma, showing heterogeneous hypoenhancement, and more washout lesions can be found in the PVP and LP. Conventional ultrasound and CEUS not only help to improve the diagnostic confidence of HEHE of rare liver tumors, but also can guide the biopsy area, making it easier to make accurate pathological diagnosis.

**KEYWORDS**
contrast enhanced ultrasound, focal liver lesions, hemangioendothelioma, hepatic neoplasm, rare tumors

## 1 | INTRODUCTION

Hepatic epithelioid hemangioendothelioma (HEHE) is a very rare vascular endothelial cell tumor, with an incidence of approximately 1 to 2 per million.[1] HEHE is generally considered as a low-grade malignant tumor with a clinical course between hemangioma and angiosarcoma. HEHE has an uncertain malignant potential[2] with uneven clinical course, its survival time ranges from 2 weeks[3] to 27 years[4] after diagnosis, the mortality rate ranges from 40% to 65%..[1]

HEHE lacks typical clinical manifestations and specificity of imaging features, and the tumor markers are often negative, which leads to high misdiagnosis rate,[5] it is often misdiagnosed as liver metastasis, liver hemangioma and intrahepatic cholangiocarcinoma, etc.[6,7] The imaging diagnosis of HEHE is difficult, and the diagnosis mainly depends on the histopathological and immunohistochemical.[8] However, histomathological diagnosis can also be challenging. Makhlouf et al.[4] reported that only 25% of HEHE's pathological diagnosis was

**Abbreviations:** HEHE, hepatic epithelioid hemangioendothelioma; CEUS, contrast-enhanced ultrasound; CT, computerized tomography; MRI, magnetic resonance imaging; AP, arterial phase; PVP, portal venous phase; LP, late phase; APHE, arterial phase hyperenhancement.

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correct. The nonspecific symptoms and rarity of HEHE entity make the diagnosis challenging for pathologists, radiologists, oncologists and surgeons.[9] Recently, some scholars believe that it is very important for the final pathological diagnosis of HEHE to be suspected by imaging doctors.[10] In particular, it is of great significance for ultrasound doctors to master the contrast-enhanced ultrasound (CEUS) characteristics of HEHE to avoid misdiagnosis.[7]

In this paper, the conventional ultrasound and CEUS findings of 3 HEHE patients diagnosed in our Hospital from September 2019 to February 2021 were introduced, in order to improve the sonographer's understanding and diagnostic sensitivity of HEHE.

## 2 | CASE REPORT

All examinations were obtained using ultrasonic instruments (LOGIQ E9, GE Medical Systems Ultrasound and Primary Care Diagnostics, LLC, Wauwatosa, WI, USA) with a transducer C 1–5, frequency: 1–5 MHz. All conventional ultrasound and CEUS examinations were performed by a sonicologist (FJQ) who had 5 years experiences in liver CEUS. For each patient, we subjectively assessed the background echo of the liver parenchyma, dividing the liver into normal (grade 0), mild fat (grade 1), moderate fat (grade 2), and significant fat (grade 3) based on the increased liver echogenicity compared to the renal cortex, decreased conspicuity of hepatic vasculature, decreased ability to visualize the diaphragm and deeper liver parenchyma.[11,12] The contrast agents used in CEUS was SF6 (SonoVue, Bracco), 2.4 mL injection into the anterior elbow i.v. and 5 m L of 0.9% saline rinse.

**TABLE 1** The results of laboratory tests were normal (Table 1)

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Labs | | | |
| AFP (ng/mL) | 2.02 | 6.49 | 3.74 |
| CEA (ng/mL) | 1.49 | 2.19 | / |
| CA125 (U/mL) | 8.29 | 27.68 | / |
| CA199 (U/mL) | 7.52 | 11.71 | / |
| Immunohistochemical results | | | |
| CD31 | + | + | + |
| CD34 | + | + | + |
| Ki-67 | 5% | <1% | 2% |

### 2.1 | Case 1

An 59-year-old female, presented intermittent pain and discomfort in the right upper abdomen with no obvious cause 20 days ago, denying the history of viral hepatitis. The results of laboratory tests were normal (Table 1). Conventional ultrasound indicated that the liver parenchyma had a fatty liver background, and there were five hypoechoic lesions with a diameter of 0.7–4.8 cm, with vague boundary and irregular shapes(Figure 1A). Color Doppler showed that there was no obvious blood flow signal in the hypoechoic lesions (Figure 1B). CEUS showed that the largest nodule (4.8 cm × 4.3 cm) showed rim arterial phase hyperenhancement (APHE) with early wash out in the portal venous phase (PVP) and late phase (LP) (Figure 1C–E, Figure 4A). The perfusion of smaller nodules (1.4 cm × 1.2 cm) demonstrated APHE with early washout in the PVP (Figure 1F–G，Figure 4C). CEUS indicated that malignant lesions were possible, and ultrasound-guided puncture biopsy was performed. Pathology of puncture showed that liver tissue fibrous tissue increased and inflammatory cell infiltration, and large number of single scattered epithelioid cells were found, some of them were small glandular structure, and nature was difficult to define. Laparoscopic partial resection was performed to determine the nature of the lesion, pathologic results indicated: HEHE.

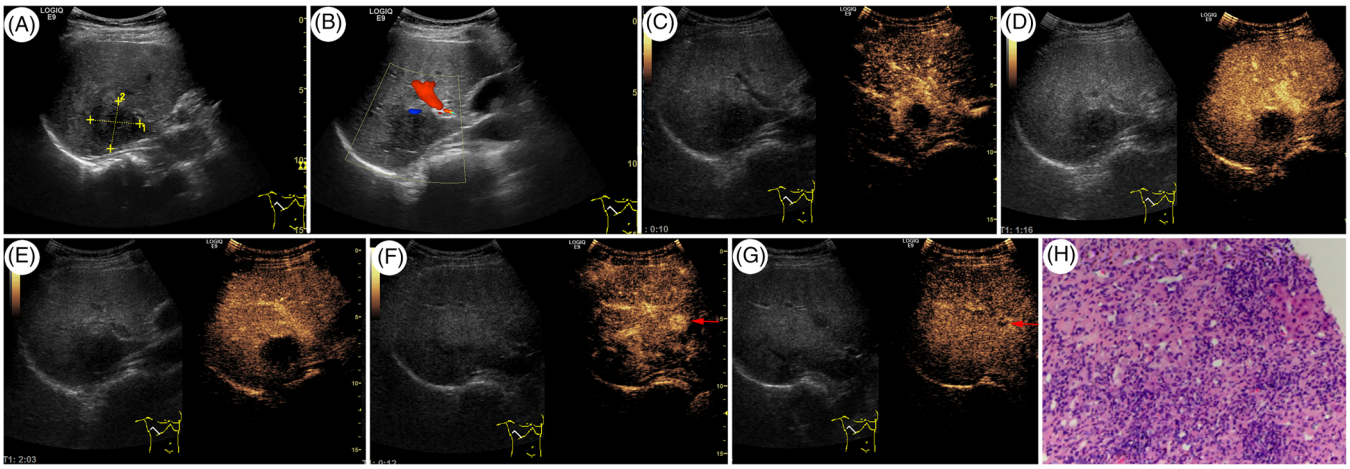


**FIGURE 1** CASE 1 (A) The hypoechoic lesions (4.8 cm × 4.3 cm) was visible under the background of fatty liver, with vague boundary and irregular shape; (B) Color Doppler showed no obvious blood flow signal within the lesions. (C–E) CEUS demonstrating a rim APHE (C) with early washout (D–E). (F–G) The smaller nodules showed APHE (F) with early washout in the PVP (G). (H) HE×4. Irregular vascular-like lacunae were found in the liver tissue, some of which were lined with flattened to cubic epithelium, and some were single-celled lumens. Residue hepatic cord (cytoplasmic red) at upper right

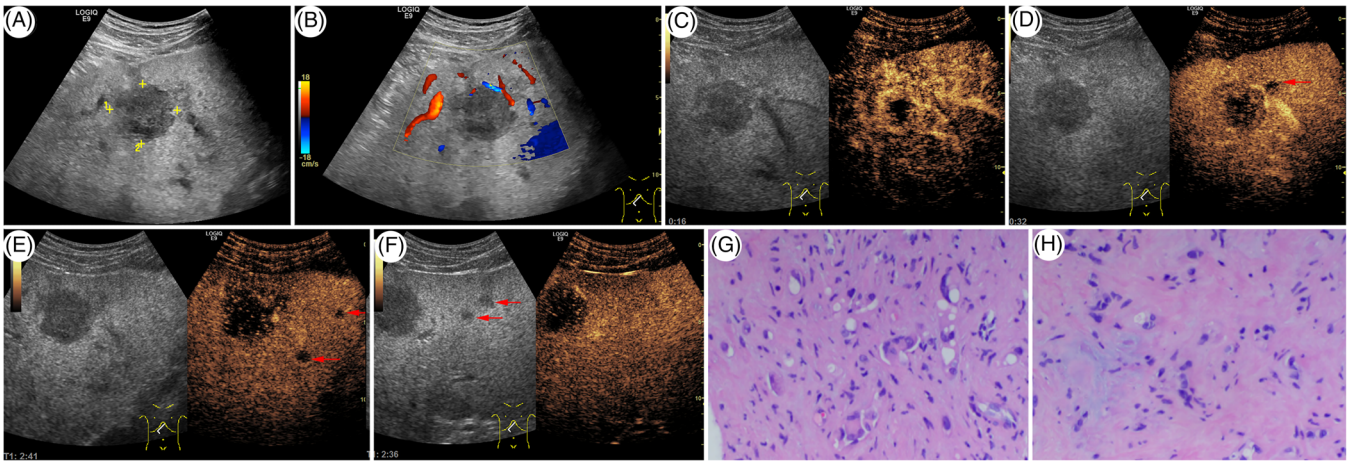


**FIGURE 2** CASE 2 (A) Under the background of fatty liver, a hypoechoic nodule (4.3 cm × 3.9 cm) were seen, with vague boundaries and irregular shapes. (B) Color Doppler imaging shows no obvious blood flow signal in the hypoechoic nodules, with peripheral branching vessels. (C–E) CEUS indicated that the largest nodule demonstrates rim APHE with early washout in PVP and LP. (D–E) More washout lesions (red arrow) were found during the PVP and LP. (F) CEUS demonstrated that some hypoechoic lesions showed isoenhancing in AP, PVP and LP. (G–H) HE×10. Short spindle cells and small dilated or irregular lacunae were seen in the fibrous background (G) and myxoid background (H). Red cells were seen in the lower left lacunae of Figure G

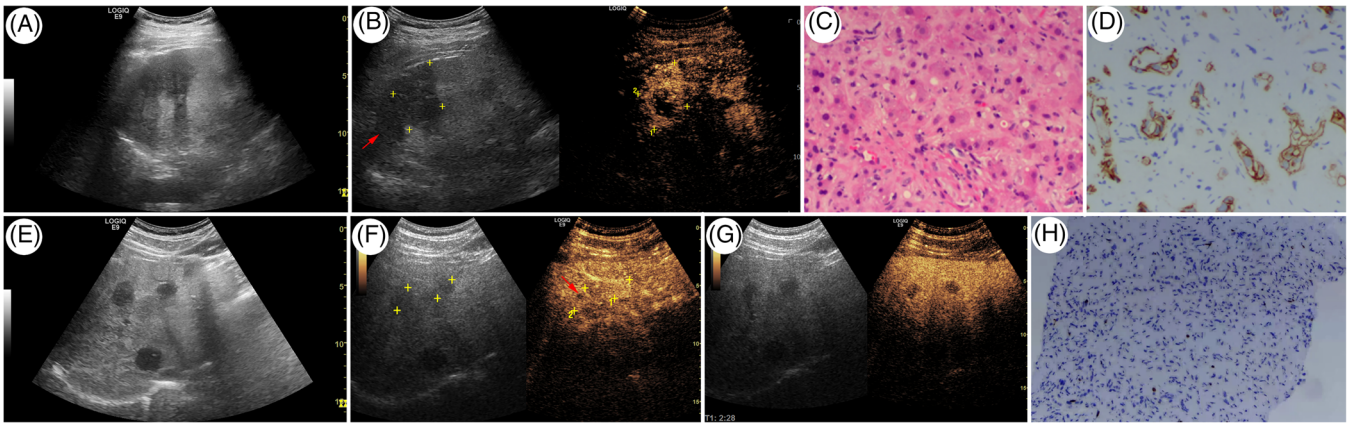


**FIGURE 3** CASE 3 (A, E) The liver parenchyma presents a fatty liver background, with multiple hypoechoic lesions, some of which with vague boundaries and irregular shapes. (B) CEUS indicated that the largest nodule demonstrates rim APHE and early washout in PVP and LP. (F–G) The two small nodules lesion of similar size demonstrate homogeneous or heterogeneous APHE, and early washout in PVP and LP. (C) The structure of hepatic lobule was destroyed, irregular vessels and single-cell lumen were infiltrated, with hepatic cord blurring and sinus disappearance (HE×40). (D) Immunohistochemical staining showed CD34 membrane positive, showing disordered vascular distribution. (H) Ki-67 was about 2%

## 2.2 | Case 2

An 48-year-old male, was hospitalized for cerebral infarction 10 days ago. There was no prior medical history. Abdominal magnetic resonance imaging (MRI) showed early peripheral arterial continuous enhancement, with early wash-out. Conventional ultrasound indicated that the liver parenchyma presented a fatty liver background, with about 10 hypoechoic lesions, 1.0–4.3 cm in diameter, with vague boundary and irregular shapes (Figure 2A). Color Doppler showed no obvious blood flow signal in the hypoechoic lesions (Figure 2B). CEUS demonstrated that the largest nodule showed rim APHE with early washout (Figure 2C–E). In addition, more washout lesions were found during the PVP and LP (Figure 2D–E, Figure 4B), with a total of about 16 lesions, and the minimum size of the lesions was about 0.6 cm × 0.6 cm. Pathological results after ultrasound-guided puncture biopsy performed indicated HEHE, and CAMTA1 gene test was recommended (Figure 2G–H).

## 2.3 | Case 3

A 46-year-old male, chronic hepatitis B for 20 years, no abdominal pain, abdominal distension and other clinical symptoms. During

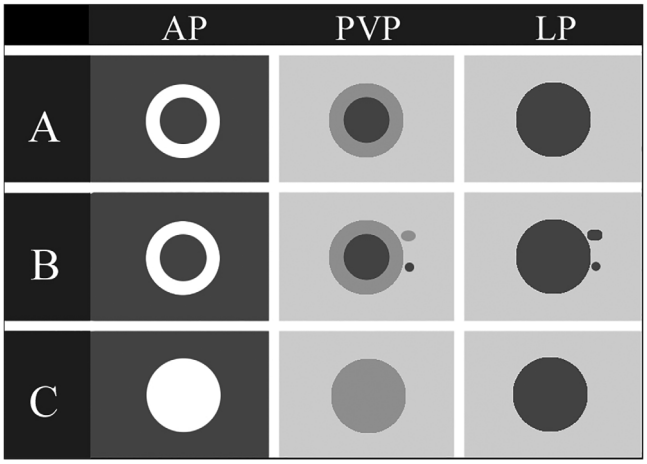


**FIGURE 4** Pattern A: Rim APHE with early washout. Pattern B: Rim APHE with early washout and more washout lesions were appeared during the PVP and LP. Pattern C: APHE with early washout

physical examination, MRI plain and enhanced scan of the upper abdomen suggested multiple intrahepatic occupying, which should be considered (1) right posterior lobe liver cancer with multiple intrahepatic metastasis; (2) multiple intrahepatic metastases; (3) liver cirrhosis, fatty liver. Chest CT plain scan showed: (1) multiple small nodules in bilateral lung, metastatic tumors were considered. Conventional ultrasound indicated that the liver parenchyma was fatty liver background, with about nine hypoechoic lesions, 1.2–5.8 cm in diameter, with vague boundary and irregular shapes (Figure 3A, E). Color Doppler showed no obvious blood flow signal in the hypoechoic lesions. CEUS indicated that the largest nodule (5.8 cm × 5.0 cm) demonstrate rim APHE and early washout in PVP and LP (Figure 3B, Figure 4A). The other two lesion of similar size (S1: 2.2 cm × 1.9 cm, S2: 2.7 cm × 2.6 cm) demonstrate homogeneous or heterogeneous hyperenhancement in AP, and early washout in PVP and LP (Figures 3F–G and 4C). Pathological results of ultrasound-guided puncture biopsy showed that: HEHE.

## 3 | DISCUSSION

The pathogeny of HEHE is unclear. Possibility factors include exposure to vinyl chloride, polyurethane or silica; using oral contraceptives; primary biliary cirrhosis; viral hepatitis; exposure to asbestos; and alcohol consumption.[13] There was only one case of chronic hepatitis history in this group. Generally, HEHE has no special clinical manifestations and laboratory examinations. In this group, only one case presented clinical manifestations of right upper abdominal pain, and the other two cases were incidentally found by imaging examination. Liver function and tumor markers were normal, that was basically the same as previous reports.[14] Previous reports showed that most HEHE patients were middle-aged females, with the highest proportion up to 89%.[15] However, in this study, there was one female and two male patients, with an average age of 51.0 ± 7.0.

In this group of cases, the intrahepatic lesions presented multiple, hypoechoic, vague boundary, irregular shapes, and no calcification was observed. No blood flow signal was detected in the lesions. These manifestations were basically the same as previous studies. HEHE presented multiple lesions (88%), hypoechoic lesions (92%),[14] vague boundary (77.8%), and no calcification.[7] Although 20% of the patients may have small calcifications,[6] no calcifications were seen in our three cases. In addition, some other studies have reported that branch vessels in the lesion could be detected by color Doppler in about 84% of the cases.[14] By the retrospective analysis of the color doppler images of lesions in the liver, we believe that the lesions and the size of the focal necrosis area, as well as the sensitivity of the equipment used for doppler could be the main reason for the difference of blood vessels. In addition, the background of moderate–severe fatty liver in this group of patients was also a factor affecting the ultrasound findings, especially the lesions located in the deep liver parenchyma.[12]

Klinger et al. reported that CEUS performance of HEHE had three characteristic modes: (1) Peripheral nodular arteries were strengthened with progressive centripetal filling and washout in PVP and LP. (2) Marginal artery enhancement, with washing-out in PVP and LP. (3) Peripheral low enhancement, central isoenhancement ("target sign inversion"), with/without washout in PVP and LP.[7] CEUS imaging features include that large nodules show earlier perfusion than hepatic parenchyma, with rim-enhancement and nonenhancing regions in the center, while small nodules show earlier perfusion than liver parenchyma, with hyperenhancement. The difference in CEUS findings between large lesions and small lesions may be different tumor size, determines the degree of fibrosis, the less blood flow in central part of the large lesions, the more extensive degree of fibrosis,[7] resulting the nonenhancing regions in the central part of the larger lesions. This is consistent with the description of HEHE in the guidelines for CEUS in the liver by EFSUMB update 2020.[16] The different manifestations of HEHE in the AP were very similar to those reported by Antonio Covino for thrombosed hemangiomas and high-flow hemangiomas respectively.[12] However, in PVP and LP, high-flow hemangiomas maintain hyperenhancement, and thrombosed hemangiomas uncentered filling and washout. In this group, all nodules show an earlier washout than hepatic parenchyma in the PVP and LP. Rim APHE of large nodules in this group and early washout of all nodules (<60 s) indicates non-hepatocellular carcinoma, indicates CEUS LR-M. This requires differentiation with the peripheral ICC and liver metastases, the most common in CEUS LR-M type,[16,17] which also provides a basis for further pathological biopsy.

The diagnosis of vascular tumors (including HEHE and angiosarcoma) is more challenging in the liver biopsy of the small sample,[18] and the misdiagnosis rate of HEHE biopsy pathology can be as high as 28.6%.[7] Reviewing these cases and previous literature, the possible reasons are as follows: (1) The disease is rare; (2) The lesions selected for biopsy are mostly large lesions, and the contrast agents perfusion defects are common inside the large lesions, However, there were few active cells in this area, which were mainly composed of necrotic cells, mucous transparent stroma and fibrotic tissue,[8,10,19]

which increase the difficulty of pathological diagnosis. Case 1 in this group was the first HEHE we encountered in the puncture biopsy. Due to the insufficient understanding of the disease by ultrasound and pathologists, the possibility of HEHE was not considered. Only the presence of epithelioid cells was indicated in the pathological section. In order to clarify the nature of the disease, we confirmed the diagnosis of HEHE after partial hepatectomy. In Case 2 and Case 3, we considered the possibility of HEHE due to the performance of CEUS, so selected the area of hyperenhancement for puncture biopsy, which provided the direction for pathological diagnosis. The combination of histology and immunohistochemistry enabled the final diagnosis to be made quickly and accurately. HEHE immunohistochemistry often showed CD31 and CD34 positive rates as high as 100%[20] and a low Ki-67 index, which was the same as the results in this group of cases. Ki-67 index >10%–15% proved to be more aggressive.[13] Ki-67 was as high as 40% in the cases reported by Yang et al. the tumor ruptured spontaneously due to rapid expansion and central necrosis, and the patient died 6 months after surgery.[21]

The prognosis of HEHE are vary different, and early diagnosis and treatment are critical,[22] and 5-year survival rate of only 5%[3] without treatment. However, the survival rate of patients treated with surgery was significantly higher than that of other patients (5-year survival rate: 88% vs. 49%, $P = .019$) and was the only independent prognostic factor for survival (hazard ratio: 0.20, $P = .040$),[6] Therefore, radical surgical resection or liver transplantation is the preferred method for patients with local liver involvement,[8] However, HEHE often has multiple lesions and the lack of organ donation, surgical resection and liver transplantation are usually not feasible,[23,24] Other scholars reported that the lesions of some untreated patients were in a stable state during reexamination,[25] and some lesions even disappeared.[7] Thomas et al. proposed a new strategy: Observing the clinical behavior of HEHE may be a key step in management. Immediate treatment may not be the best strategy. Initial observations to assess disease behavior may better stratify treatment options, and surgical treatment should be reserved for candidates who must undergo hepatectomy or transplantation.[1,26] Furthermore, the correct diagnosis of HEHE and its differentiation from other tumors are vital importance for prognosis and treatment.[27] Understanding the imaging features of this rare tumor may help in the detection and timing of further surgical treatment of this potentially curable disease.

## 4 | CONCLUSIONS

In conclusion, HEHE has certain characteristics of ultrasound and CEUS. Ultrasonographic features included fatty liver background, multiple lesions, hypoechoic, vague boundary, irregular shapes, no calcification, and no blood flow signal was detected in lesion. CEUS imaging features include large nodules show earlier perfusion than liver parenchyma, with rim-enhancement, nonenhancing regions in the center, while small nodules show earlier perfusion than liver parenchyma, with hyperenhancement. All nodules show faster washout than hepatic parenchyma, showing heterogeneous hypoenhancement, and more washout lesions can be found in the PVP and LP. These ultrasound features can easily lead us to make the diagnosis of malignant tumor. However, these ultrasound characteristics are not specific and it is difficult to distinguish them from metastatic tumors. Even with CEUS, we cannot make the diagnosis of HEHE directly. We should consider the possibility of HEHE when we again encounter the above ultrasound findings without clear evidence of primary cancer elsewhere. Due to the different clinical management of HEHE from other malignancies, differential diagnosis by pathology is required. Based on the suggestion of CEUS, ultrasound-guided biopsy can avoid puncturing the necrotic area and make accurate pathological diagnosis easier. The convenience of CEUS can be more commonly used in the clinical behavior assessment of HEHE to guide the selection of clinical treatment methods.

## CONFLICT OF INTEREST

This study was funded by the above institutions. All author declare that we have no conflict of interest.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patient consent was not obtained since only unidentifiable ultrasonic and Pathological images were used.

## AUTHORS' CONTRIBUTIONS

FJQ and ZBY contributed to conception and design of the study, and wrote the manuscript; ZWA and JYY contributed to analysis and interpretation of data and critically revised the manuscript; PC and MSY critically revised the manuscript; and all authors have read and agreed to the present version of this manuscript.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, 13 further inquiries can be directed to the corresponding authors.

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**How to cite this article:** Fang J-Q, Ji Y-Y, Zhao W-A, Pu C, Mi S-Y, Zhang B-Y. Three cases of hepatic epithelioid hemangioendothelioma evaluated using conventional and contrast-enhanced ultrasound: Case reports. *J Clin Ultrasound*. 2022;50(6):826-831. doi:10.1002/jcu.23141