Characteristic contrast-enhanced ultrasound findings of hepatic epithelioid haemangioendothelioma: A case report and literature review

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Abstract. Hepatic epithelioid hemangioendothelioma (HEHE) is a rare liver tumor, which is usually diagnosed by pathological examination, since the diagnostic imaging criteria remain to be defined. However, contrast-enhanced ultrasound (CEUS) may reveal the characteristic features of HEHE to aid diagnosis. In the present study, two-dimensional ultrasound examination of a 38-year-old male patient showed a mass in the right liver. CEUS showed an S5 segment hypoechoic nodule, and imaging features resulted in the diagnosis of HEHE. Surgery was shown to be an appropriate and successful treatment for HEHE. In conclusion, CEUS may be valuable for the diagnosis of HEHE, thereby avoiding the serious consequences of misdiagnosis.

Introduction

Epithelioid haemangioendothelioma (EHE) is an extremely rare tumor of vascular origin that may occur in lung (30%), liver (21%), liver plus lung (18%), single lung (12%) and single bone (14%). The incidence of primary liver hepatic EHE (HEHE) is one in a million (1). In most cases, HEHE presents as an inert tumor, with clinical and morphological features intermediate between hemangioma and angiosarcoma. The rarity of HEHE and the non-specific nature of its clinical manifestations mean that rates of misdiagnosis are high, at about 60 to 80% (2). HEHE diagnosis usually relies on histological, immunohistochemical and molecular features but some imaging features are highly suggestive of this lesion. Most existing case reports describe CT and MRI imaging of HEHE, and rarely refer to two-dimensional ultrasound or contrast-enhanced ultrasound (CEUS) (3). The possibility of HEHE should be considered to avoid misdiagnosis, such as when a sign of arterial-phase peripheral nodular hyperenhancement filling internally with washout in the portal and late venous phases, arterial phase marginal ring enhancement, entailing hypoenhancement in the portal and late venous phases, or 'reverse target sign' are presented. The current case report describes the ultrasonographic findings of HEHE with the aim of improving the availability of diagnostic instruments.

Case report

Patient profile, imaging and laboratory results. A 38-year-old man presented for a health examination and reported no physical discomfort. He had no positive signs on physical examination and no significant disease history. Two-dimensional ultrasound revealed a 2.0x1.8 cm hypoechoic nodule in the lower segment of the right anterior lobe of the liver (S5 segment) with a clear boundary and regular shape (Fig. 1A). No blood flow signal was detected in the nodule (Fig. 1B). The patient underwent CEUS (SIEMENS Sequoia) and the S5 segment hypoechoic nodule was found to be synchronously enhanced with the liver parenchyma in the arterial phase, exhibited slight hyperenhancement in the periphery and slight hypoenhancement in the interior, peaking at 19 s (Fig. 2A). The portal phase showed hypoenhancement, slightly higher in the interior than at the periphery (Fig. 2B), no enhancement in the late venous phase and showed 'fast-forward and fast-out' (Fig. 2C). Two possibilities emerged from the CEUS results, cholangiocarcinoma or inflammatory pseudotumor. Abdominal contrast-enhanced computed tomography (CT) revealed a slightly hypodense nodule in the lower segment of the right anterior lobe of the liver with patchy marginal enhancement. Magnetic resonance imaging (MRI) showed an abnormal signal shadow in the lower segment of the right anterior lobe of the liver, indicating a chronic infectious or neoplastic lesion. Laboratory test results were as follows: alpha-fetoprotein: 6.8 ng/ml; carcinoembryonic antigen: 0.47 ng/ml; CA199: 8.09 U/ml; CA125: 12.5 U/ml; hepatitis B surface antigen negative and antibody positive. Remaining laboratory parameters were unremarkable.

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Surgical condition. The patient immediately went to West China Hospital of Sichuan University for treatment. Right hepatic lesion resection, cholecystectomy and intestinal adhesiolysis were performed under general anesthesia. Intraoperative findings revealed the following: ascites was not seen in the abdominal cavity; the greater omentum and the transverse colon adhered to the right hepatic margin, enlarged lymph nodes were not observed and liver color and texture showed no significant abnormality. The S5 segment enclosed mass had the following features: approximately 2.0x2.0x2.1 cm in size, slightly hard consistency, well-demarcated edges, an intact capsule and yellowish color in the cut section.

Fluorescence in situ hybridization detection (FISH). The postoperative pathology confirmed that it was HEHE, which was performed at West China Hospital of Sichuan University including HE staining, immunohistochemistry, and FISH. For accurate pathological diagnosis, fluorescence *in situ* hybridization was performed. The reagents used include the first antibody (application: IHC-P=1:400-800 IHC-F=1:400-800), 3% hydrogen peroxide, normal goat serum working solution for blocking, biotin labeled sheep anti rabbit IgG, horseradish enzyme labeled chain enzyme ovalbumin working solution, diaminobenzidine staining solution. Immunohistochemistry was performed on 4-μm formalin-fixed, paraffin-embedded tissue sections after pressure cooker antigen retrieval in citrate buffer using a polyclonal anti-CAMTA1 antibody (15 min incubation; 1:1,000 dilution; Abcam). Immunoreaction was carried out using a universal secondary antibody (OriGene Technologies, Inc.).

Immunohistochemical results. The following immunohistochemical results were obtained: CD34(+), CD31(+), CK7(+), ERG(+), Ki-67(5%+), PCK(-) and EMA(-). CAMTA1 translocation including WWTR1-CAMTA1 gene fusion was detected by molecular biological test. Pathological findings revealed EHE (Fig. 3).

Follow-up. The patient's tumor did not recur during the two-year follow-up.

Discussion

HEHE is very rare and accounts for less than 1% of all vascular tumors (1). HEHE is classified as malignant by the World Health Organization but is clinically and histologically intermediate between benign haemangioma and angiosarcoma and appears indolent in terms of malignancy. The prognosis is usually good with 5-year survival estimates between 40 and 60% (2). No sign of tumor recurrence was found during two year post-surgical follow-up of the current patient. HEHE has a non-specific clinical presentation and the most common symptom is right upper quadrant pain. Other symptoms may include ascites, asthenia, fatigue, anorexia, nausea, vomiting and weight loss. Multiple manifestations are common and 87.3% of HEHE cases in the largest published case series were characterized by multiple lesions (4). Single-lesion types account for only 13 to 18% of all cases (3). The present case involved a rare solitary nodule arising in the right lobe of the liver.

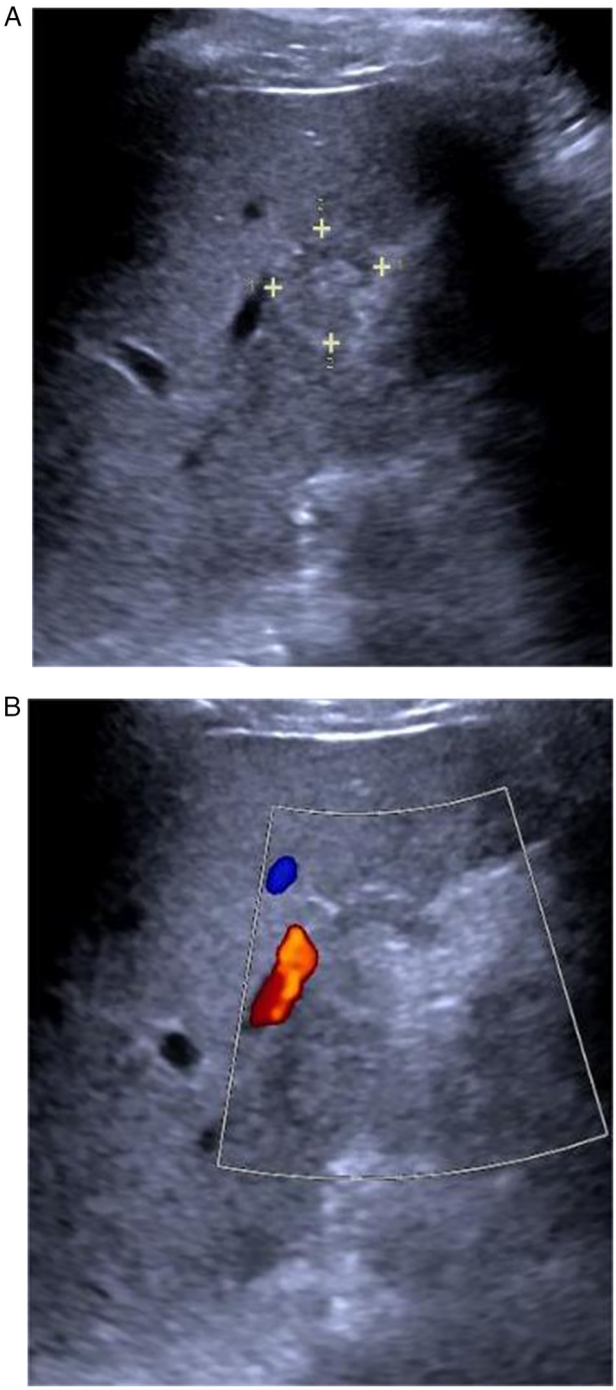

Figure 1. Two-dimensional ultrasound. (A) Hypoechoic nodule in the lower segment of the right anterior lobe of the liver (S5 segment). (B) No blood flow signal detected in the nodule.

Typical laboratory findings of HEHE patients include increased levels of alkaline phosphatase and γ-glutamyl transpeptidase and normal serum levels of alpha-fetoprotein, carcinoembryonic antigen and CA199. Indeed, 15% of HEHE patients do not have abnormal laboratory results (2). Alpha-fetoprotein, carcinoembryonic antigen, CA199 and CA125 were all normal in the current case.

As shown in the figure, typical HEHE staining shows that tumor cells have abundant cytoplasm, light eosinophilic and glassy appearance, small nuclei, and fine nucleoli. Tumor cells can see intracellular vacuoles, similar to the formation

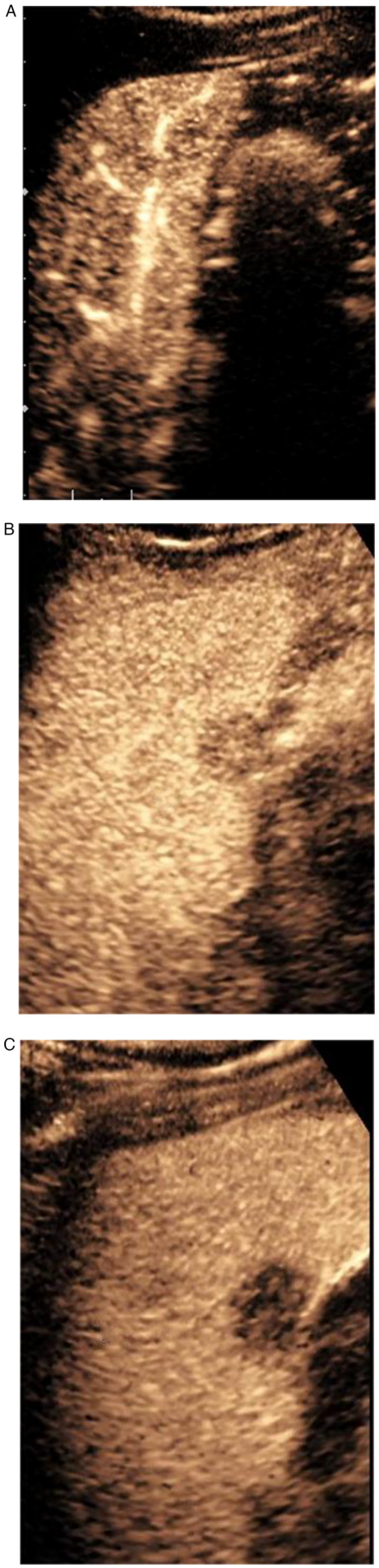

Figure 2. Contrast-enhanced ultrasound. (A) Arterial phase, rim ring enhancement; (B) portal phase, central enhancement greater than peripheral; (C) late venous phase, shows hypoenhancement.

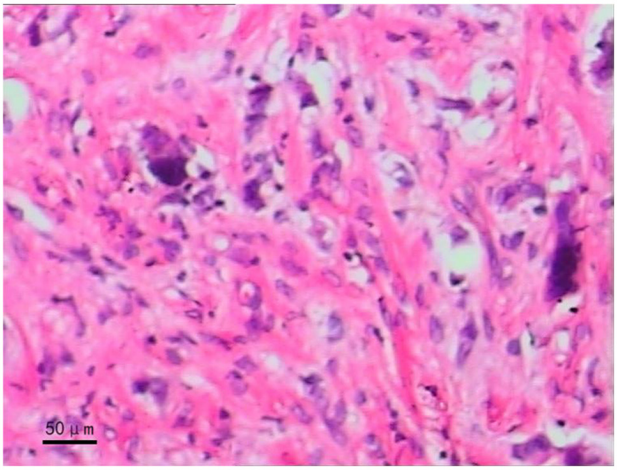

Figure 3. Epithelioid hemangioma composed of well-formed blood vessels lined by epithelioid endothelial cells with eosinophilic cytoplasm and prominent intracytoplasmic vacuoles within a myxoid stroma.

of primitive vascular lumens, in which red blood cells can be seen, with fewer mitotic images, suggesting diagnostic clues for EHE (Fig. 3). The definitive diagnosis of HEHE is based on immunohistochemical findings. Around 90% of tumors showed WWTR1-CAMTA1 gene fusion, 94% were positive for CD34 and 86% positive for CD31 (5). These characteristic features can be used to distinguish HEHE from other lesions, such as epithelioid haemangioma and epithelioid angiosarcoma. The current case showed positive immunohistochemical staining for CAMTA1, CD31 and CD34.

Conventional CT, MRI and ultrasonography produce no obvious specific findings for HEHE. Contrast-enhanced CT/MRI involves an intermittent tomographic scan which is irradiating, costly and has low reproducibility. The great advantages of CEUS are the dynamic sweep in real time, its non-irradiating nature and its high reproducibility. Exploration of HEHE by CEUS gives additional imaging information with utility for diagnosis.

HEHE may be classified into three types depending on imaging findings: uni-nodular, multifocal nodular and diffuse. Early stage EHE may show nodular changes and present as uni-nodular or multifocal nodular types. Nodules grow and merge over time, forming a diffuse lesion (6). EHE nodules often appear hypoechoic with indistinct margins on two-dimensional ultrasound and a few nodules may have hypoechoic halos. The internal echoes of the nodules are usually homogeneous and anechoic areas can be observed inside a few which may indicate hemorrhage and necrosis. HEHE is a vascular tumor but color Doppler often reveals no blood flow-related information in the nodule, perhaps due to the low capillary flow velocity and insufficient color flow sensitivity of ultrasound instruments. Klinger *et al* (7) described 3 types of HEHE from CEUS examination: Type a: arterial-phase peripheral nodular hyperenhancement filling internally with washout in the portal and late venous phases; Type b: arterial phase marginal ring enhancement, entailing hypoenhancement in the portal and late venous phases; Type c: arterial-phase peripheral hypoenhancement and internal isoenhancement ('reverse target sign') with or without washout in the portal and late venous phases. The current case had a

Table I. Different imaging findings of HEHE.

Imaging technique	Image presentation	Formation mechanism
Conventional CT	Slightly hypodense nodule	
Conventional MRI	Halo sign/target ring sign	T1: Low signal core with high signal edge (black target-likesign); T2: Heterogeneous high signal intensity in the centre and low signal intensity at the edge; (whitetarget-like sign) (15)
Enhanced CT/MRI	'Lollipop sign'	The hepatic vein or portal vein and its branches extend and terminate at the edge of the nodule (13)
Two-dimensional ultrasound	Hypoechoic nodules; no blood flow information in the nodules; can be divided into monodular nodular type, multifocal nodular type, and diffuse type (6)	
Contrast-enhanced ultrasound	Type a: Peripheral hyperenhancement in the arterial phase fills internally, with clearance in the portal venous phase and delayed phase Type b: Marginal ring enhancement in the arterial phase, hypoenhancement in the portal venous phase and delayed phase Type c: Peripheral hypoenhancement in the arterial phase and internal isoenhancement ('countertarget sign') (7,8,10)	i) Although the growth is irregular, the structure of glandular vesicle and the system remain intact ii) HE staining is regionally characteristic iii) Arteriovenous fistulas in some areas (9)

contrast-enhanced ultrasound pattern consistent with a type b nodule with rapid internal hypoenhancement of the nodule in the arterial phase, slight hyperenhancement of the rim ring and hypoenhancement in the portal and late venous phases. The cases studied by Klinger *et al* (7) were predominantly type c. Eight of 10 cases showed peripheral hypoenhancement and internal isoenhancement in the arterial phase, peripheral washout preceding the internal washout, peripheral hypoenhancement and internal isoenhancement or no enhancement in the portal and late venous phases, visualized as a 'reverse target sign'. Dong *et al* (8) reported 72% of cases to be type b with remaining cases having no obvious characteristics on angiography (Table I).

Pathologically, HEHE is characterized by marginal invasive growth of tumor cells. The growth is irregular and glandular vesicle structure and portal system remain intact. EHE staining has regional characteristics, showing that: i) Tumor peripheral epithelial cells grow along the hepatic terminal veins and sinusoids and arteriovenous fistulas are present in some areas (9), explaining the phenomenon of rapid washout in the portal and delayed phases of type a and b nodules; ii) conversely, the tumor center is less vascularized and shows a significant stromal response and dense sclerosis (9), explaining lower internal enhancement in the arterial phase than in the peripheral phase in type a and b nodules; iii) the difference between a and b types largely stems from peripheral vascular distribution. CEUS results of the current case conformed to the classical EHE staining characteristics in the pathological report. Klinger *et al* and Schweitzer *et al* (7,10) reported low interstitial reaction and dense sclerosis at the center of type c nodules from HE staining and nodules had more internal vascularity than did those at the periphery, resulting in significantly higher internal than external enhancement in the arterial phase of c-type nodules. Moreover, the degree of HEHE fibrosis has been reported to depend on the size of the tumor lesion and blood vessel distribution is affected by the degree of fibrosis (11). Therefore, differences in the enhanced image are related to tumor size and fibrosis degree, explaining the complexity and diversity of HEHE CEUS patterns.

According to previous literature, the blood flow perfusion of the liver and spleen can be affected by liver diseases, such as cirrhosis. However, in this case, the blood flow perfusion of the liver and spleen has not been studied, nor has it been mentioned in the relevant literature, which needs further study (12).

HEHE CT and MRI characteristics include the 'lollipop sign', a well-defined low-density mass on the enhanced image resembling a lollipop. Moreover, venous obstruction in the mass is manifested as a hypointense hepatic vein or portal vein or branches perpendicular to the lesion and terminating at its margins, forming a lollipop stem (13). Other imaging features include local calcification in 20% of cases, capsular retraction in 10-25% of cases, central hypodensity and peripheral enhancement (14,15) (Table I).

The rarity of HEHE means that most case reports are of individual cases, usually found incidentally by imaging

examination and an understanding of the imaging features is, therefore, very important. Most existing case reports describe CT and MRI images and rarely involve two-dimensional ultrasound or CEUS. The current HEHE findings refer to two-dimensional ultrasound and CEUS images with reference to the pathological basis. The identification of slowly progressing nodules in lung, liver and bone which show the characteristic imaging findings should allow the possibility of HEHE to be entertained to avoid misdiagnosis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL, WT, YN and XM contributed to the study conception and design. Data collection was performed by YL. Data analysis was performed by WT and YN. The first draft of the manuscript was written by WT and YN. XM guaranteed the completion of the study. YL and WT confirm the authenticity of all the raw data. WT and YN contributed equally to this manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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