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Case Series
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Case Series of Hepatocellular Carcinoma with the Atypical Contrast-Enhancement Ultrasound Enhancement Patterns and a Review of the Literature

*Chen-Shan Wang[1], Bo Zhang[2] and Jin-Tang Liao[2]**

[1]Department of Medical Ultrasound, Wuhan First Hospital, China

[2]Department of Medical Ultrasound, Central South University, China

Abstract

Hepatocellular Carcinoma (HCC) is a common cancer with high mortality worldwide, which typically manifests as "early entry and early exit" in CEUS, CECT and CEMRI. The case series in this study was characterized by the non-fading of the contrast agent. A total of 5 cases with atypical CEUS features confirmed by surgery and histopathological results were identified as HCC, and the possible reasons for this phenomenon were analyzed. Therefore, the diagnosis of HCC with atypical contrast pattern requires a combination of multiple aspects.

Keywords: HCC; CEUS; Atypical contrast pattern; Pathology; Tumor

Introduction

Hepatocellular Carcinoma (HCC) is the sixth most-common cancer and the fourth most common cause of cancer-related death globally, with approximately 841,000 new cases and 782,000 deaths per year [1]. Early diagnosis is critical for patients. The diagnostic performance of CEUS using SonoVue is comparable to that of CECT and CEMRI. CEUS also provides better contrast and spatial resolution as well as better temporal resolution [2]. The typical enhancement feature of hepatocellular carcinoma is hyperenhancement during the arterial phase followed by wash out during the portal venous and late phases, and some patients can see the supplying artery at the early stage of the arterial phase [3,4]. However, some lesions may show sustained enhancement during the portal venous and late phases.

The enhancement pattern of Magnetic Resonance Imaging (MRI) and contrast-enhanced Computer Tomography (CT) is similar to Contrast- Enhanced Ultrasound (CEUS), where the contrast agent presents "fast wash-in and fast wash-out". In this case series analysis, we discuss five cases of HCC with atypical contrast-enhanced ultrasound patterns.

Case Series

Case 1

CEUS: Showed a 50 mm × 28 mm × 50 mm hypoechoic mass in the caudate lobe of the liver.

CDFI: Showed abundant blood flow signals in the mass, and the arterial spectrum was measured as PS 23 cm/s, ED 10 cm/s, RI 0.58. After the contrast agent was injected (2.4 ml for 8 s), the contrast agent began to wash in rapidly. At 13 s, the lesion was completely filled and presented uniform hyper enhancement (Figure 1).

CECT: The CT values were 44 HU (plain scan), 99 HU (arterial phase), 118 HU (portal phase) and 112 HU (delayed phase), which were similar to the enhancement pattern of CEUS.

CEMRI: A lesion was observed in the caudate lobe of the liver, with high DWI signal and low ADC value. In the arterial phase, the lesion was heterogeneous hyper enhancement, and its enhancement degree decreased in the portal phase and the delayed phase. In addition, enhancement degree of tissue around the lesion was significantly delayed.

Postoperative histopathological results showed moderate differentiated hepatocellular carcinoma without satellite nodules. The histological type was solid. There was tumor necrosis, MVI1 (M1) was observed, and no nerve invasion. The adjacent liver tissue presented interstitial inflammation.

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Correspondence:
Jin-Tang Liao, Department of Medical Ultrasound, Xiangya Hospital, Central South University, No. 87, Xiangya Rd, Changsha, 410008, Hunan, China, Tel: 8613973126509;
E-mail: liaojintang@hotmail.com

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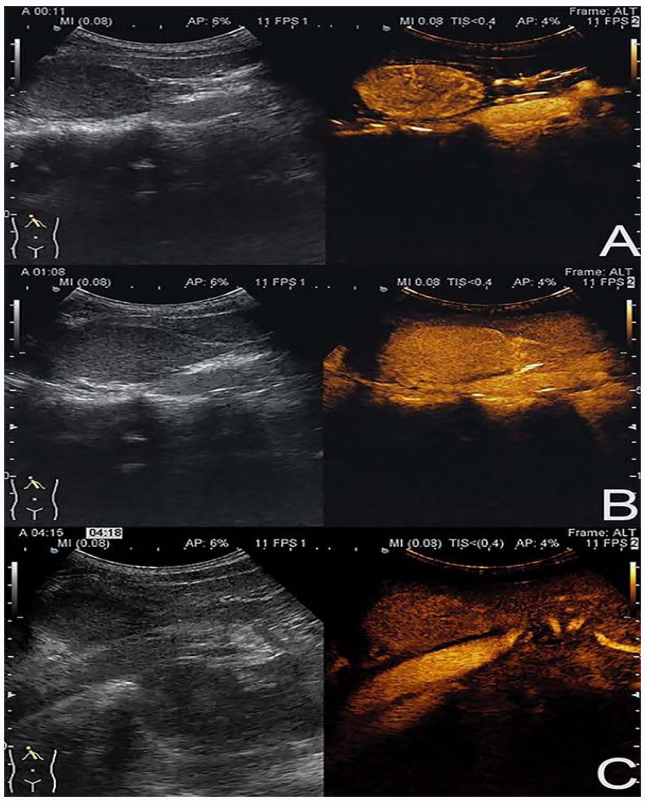

Figure 1: CEUS Features of a 30-year-old female. A) The lesion was completely filled and presented uniform hyperenhancement in arterial phase. B) The lesion remained uniform hypernhancement in portal vein phase. C) The lesion remained hyperenhancement until 5 min.

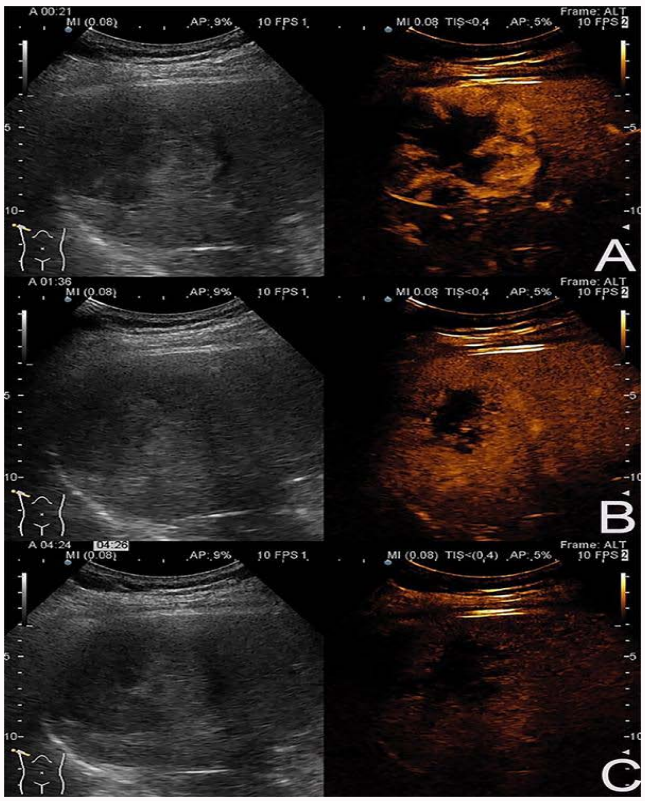

Figure 2: CEUS Features of a 57-year-old male. The lesion presented hyperenhancement during three phases until 5 min; there was an irregular morphology area with three phase's non-enhancement.

Case 2

CEUS: Showed fatty liver, and a mass with size of 67 mm × 61 mm for which echo intensity inequality was found in the upper lobe of the right posterior lobe.

CDFI: Showed a few strip blood flow signals in the mass, and the arterial spectrum was measured as PS 99.1 cm/s, ED 43.7 cm/s, RI 0.56 (Figure 2).

CECT: Marginal patchy hyper enhancement in the arterial phase, but no obvious enhancement in the center of the lesion. Compared with that in the arterial phase, the scope of enhancement in the portal phase was enlarged and the CT value was further increased. In the portal venous phase, the enhancement of lesion edge was weakening, so there was possibility of hemangioma.

CEMRI: The edge of the lesion had mild hyper enhancement in the arterial phase, then further significant enhancement appeared at the portal and late phases. There was no significant enhancement area in the lesion center. It was considered that there was a high possibility of hemangioma, and liver cancer could not be ruled out. According to the performance of Primovist, it was likely considered liver cancer.

Postoperative histopathological results: high-moderate differentiated hepatocellular carcinoma (without capsule), no satellite nodules, fine beam histology, and no MVI (M0). The surrounding liver cells were steatotic, and no cirrhosis was observed.

Immunohistochemical results: Ki67 (approximately 8%), AFP (-), CK19 (-), Hepatocyte (+), glypican-3 (-), ARG-1 (-), CD34 (-). Epatocyte (+), Glypican-3(-), Arg-1(-), and CD34(-).

Case 3

Contrast-enhanced ultrasonography showed an 82 mm × 60 mm × 65 mm hypoechoic mass in the posterior lobe of the right liver.

CDFI: Abundant blood flow signals were observed in the mass. The arterial spectrum was measured as PS 28 cm/s, ED 14 cm/s, RI 0.48 (Figure 3).

CECT: The CT values were 44 HU (plain scan); CT values significantly increased as 69 HU in arterial phase 99 HU in portal phase and 85 HU in delayed phase. This result was considered the possibility of liver Ca.

CEMRI: The mass showed a high DWI signal and low ADC value. Significant hyper enhancement in the arterial phase, hypoenhancement in the portal vein phase and delayed phase were considered with HCC and the formation of the surrounding lesion.

Postoperative pathology result: High-moderate differentiated hepatocellular carcinoma. The histological types were clear cell and pseudoadenoid, with MVI1 (M1), no tumor necrosis, and no definite nerve invasion. Liver tissue adjacent to the lesion presented fibrosis changes. Immunohistochemical results: AFP (-), Arg (+) - 1, and CK19 were (-), Glypican - 3 (+), HepPar (+) - 1, PAX - 2 (-), PAX - 8 (-), RCC (-), Vimentin (-), and Ki67 (5%).

Case 4

Contrast-enhanced ultrasonography: An 86 mm × 68 mm hyperechoic mass was found in the lower lobe of the anterior lobe of the right liver.

CDFI: Abundant blood flow signals were observed in the mass

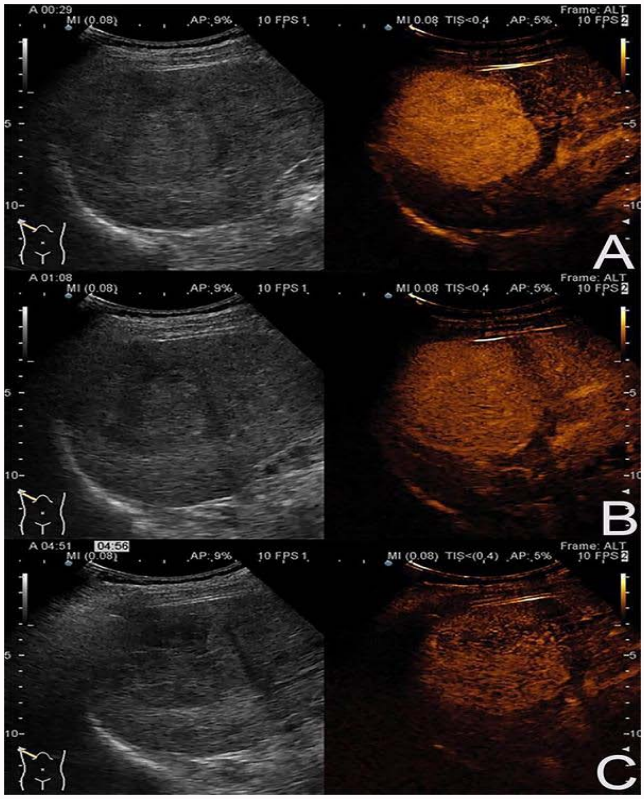

Figure 3: CEUS Features of a 49-year-old male. A) The lesion presented hyperenhancement in arterial phase. B) The lesion turns to isoenhancement in portal phase. C) The lesion turn to hyperenhancement again in late phase.

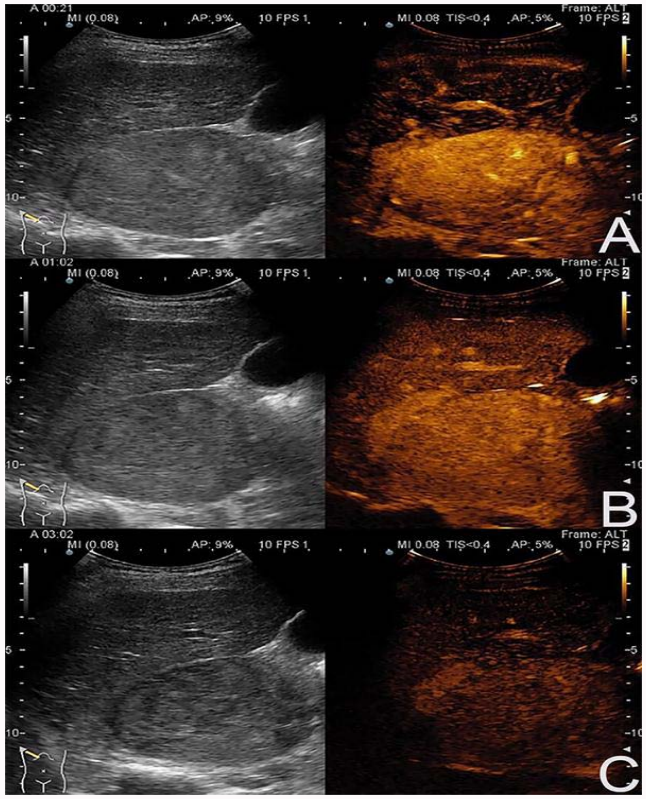

Figure 4: CEUS Features of a 59-year-old male. A) The lesion was hyperenhancement in arterial phase, and trophoblast artery showing. B) The lesion remained hyperenhancement in portal phases. C) After 4 minutes, in the delayed phase, the lesion presented isoenhanced.

(Figure 4).

CECT: The CT value in the arterial phase of the mass was 72 HU, approximately 72 HU in the portal phase, and approximately 64 HU in the late portal phase.

MRI: In the arterial phase, non-uniform hyper enhancement was observed in the lesion, and enhancement degree decreased in the portal and delayed phases. This mass was considered carcinoma and possibly had metastasized. The portal trunk was compressed by the tumor.

Postoperative pathology results: high differentiated hepatocellular carcinoma in liver S7, no satellite nodules, no neoplastic necrosis, and no MVI (M0). The liver tissue adjacent to the cancer presented cirrhosis. Immunohistochemical results: AFP (-), HepPar (+) - 1, Ki67 (15%), Glypican - 3 (+), and CK19 (-).

Case 5

CEUS: An 88 mm × 88 mm hypoechogenic and hyperechogenic mass in the right liver with regular morphology and clear boundary.

CDFI: Striate blood flow signals were observed around and inside the tumor (Figure 5).

CEMRI: Lesions showed uneven high signal on DWI. The lesions showed significant non-uniformity hyper enhanced in the arterial phase and portal phase, and relatively hypoenhanced in the late phase. Therefore, the possibility of HCC was considered to be high.

Table 1: Basic information of five cases.

Case	Sex / Age	Past history	Tumor marker	Viral hepatitis	Pathologic result
Case 1	female / 30Y	2 years history of HBV	negative	Hepatitis B	Moderate differentiated HCC
Case 2	male / 57Y	8-years history of type 2 diabetes, 12-years history of hypertension, more than 30 years of smoking, family history of hypertension	negative	negative	High-moderate differentiated HCC
Case 3	male / 49Y	history of hepatitis B for more than 6 years	negative	Hepatitis B	High-moderate differentiated HCC
Case 4	male / 59Y	diabetes, coronary heart disease history, hypertension found, hepatitis C, and peptic ulcer more than a year	AFP(+) CA199(+)	Hepatitis C	High differentiated HCC
Case 5	male / 65Y	Trauma 30 years ago	negative	Hepatitis B	Moderate differentiated HCC

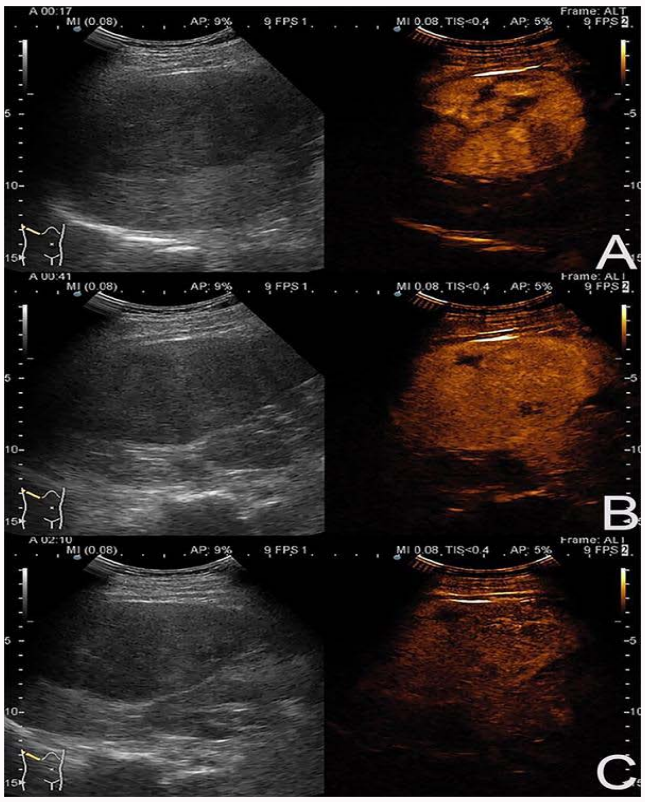

Figure 5: CEUS Features of a 65-year-old male. A) The mass in early arterial phase was significantly hyperenhanced. B, C) in the portal phase and the late phase were still slightly hyperenhanced, and there was a no enhanced area in 3 phases at the center.

Postoperative pathological results: Moderately differentiated hepatocellular carcinoma in the right liver (enveloped) with no satellite nodules; No MVI (M0) was found near or far from the cancer. The surrounding liver tissues are hydrodenatured and steatotic, and in the lymphocyte infiltration in the portal area there is hyperplasia of fibrous tissue (Table 1).

Discussion

Between 2008 and 2014, liver cancer presented the lowest 5-year relative survival rate among all cancers in the United States, at only 18% [5]. The etiology of HCC is mainly related to Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), aflatoxin contamination, excessive sex hormones and alcoholism [6]. Recent studies have found that Non-Alcoholic Fatty Liver Disease (NAFLD) is the root cause of 13% to 38% of non-viral hepatitis and alcohol-related liver cancer cases [7]. It has been estimated that people with type 2 diabetes show approximately 2 to 3 times the risk of HCC as normal healthy people, and HCC development is one of the most worrying liver-related complications in diabetics [8]. The common characteristics of insulin resistance and liver steatosis include the promotion of adipose tissue-derived inflammation [9], hormone changes [10], oxidative stress and lipotoxicity [11-13] and promoting the occurrence of liver cancer by stimulating the IGF-1 axis of hyperinsulinemia [14]. Other factors include diet [15,16], intestinal microbiota [17,18], and very important genetic factors [19]. The patient in case 2 had no history of hepatitis, but had a fatty liver and a history of type 2 diabetes for 8 years.

Hepatocellular Carcinoma (HCC) is a blood-rich tumor, usually supplied by the hepatic artery. In the typical contrast pattern of CEUS, after the contrast agent is injected, the lesions are filled with the contrast agent uniformly and quickly. The echo of HCC in the arterial phase is significantly higher than that of surrounding liver tissue. Sometimes, in the early arterial stage, strong echogenic tumor nutrient artery appears in tumor lesions [20,21]. However, in the portal vein stage, the contrast agent of the lesion disappears rapidly, in contrast with what occurs in the normal surrounding liver tissue.

In this case series, except for case 4, tumor markers in the several other cases were negative. CEUS in the five cases in this study was different from the typical pattern of hepatocellular carcinoma, but presented high enhancement in the arterial phase, no clearance in portal phase and/or delayed phase, most of which were still high enhancement in the delayed phase. However, postoperative pathological results were all hepatocellular carcinoma. On the basis of referring to the relevant literature, we believe that there may be the following reasons for the appearance of this imaging pattern in hepatocellular carcinoma:

1. It may be that the wash-out time of the contrast agent is related to the differentiation degree of the tumor. LIU [22] believed that the time at which HCC began to undergo clearance at CEUS was related to the degree of tumor differentiation, and the clear speed of well-differentiated tumors was slower than that of poorly differentiated tumors. Yang [23] considered that the clearance of highly differentiated HCC in CEUS occurred later. In our case series, there was one case of highly differentiated HCC, two cases of highly differentiated HCC, and two cases of moderately differentiated HCC.

The average number of portal veins in well-differentiated hepatocellular carcinoma was found to be approximately 30% of the para-tumor liver tissue, and there was almost no intratumoral dysplasia of arterioles. However, the average number of portal veins in moderately differentiated hepatocellular carcinoma is approximately 0.5% of the para-tumor liver tissue, and a large number of tumor proliferating arterioles can be seen in the tumor tissue [24].

This pattern indicates that with the malignant transition of the tumor, the degree of differentiation decreases, the tumor portal vein and normal hepatic artery decrease, and the abnormal neoplastic artery increases [25]. These arteries will gradually increase and thicken, become disordered, form an abnormal vascular network, and even form an arteriovenous fistula, which will cause changes in tumor

Table 2: Imaging findings and pathological findings of the five cases.

Case	CEUS performance	CEUS diagnosis	CT diagnosis	MRI diagnosis
Case 1	Hyperenhanced-Hyperenhanced-Hyperenhanced	Consider FNH	FNH? Liver Ca?	Liver Ca? FNH?
Case 2	Hyperenhanced-Hyperenhanced-Hyperenhanced	Benign, adenoma? Atypical hemangioma?	Considering the possibility of HCC	Consider the possibility of liver Ca
Case 3	Hyperenhanced-isoenhanced-Hyperenhanced	Consider HCC	Consider liver Ca	Consider HCC
Case 4	Hyperenhanced-Hyperenhanced-isoenhanced	Consider Ca	Considering possibility of hepatic Ca	Consider the possibility of liver Ca
Case 5	Hyperenhanced-Hyperenhanced-Hyperenhanced	Consider HCC	The outcome of the outer hospital	Consider the possibility of liver Ca

blood perfusion. The ultrasound contrast agent is a kind of blood pool contrast agent, which reflects the condition of blood perfusion in the lesion. There was no significant change in the number of highly differentiated HCC portal veins, most of which were supplied by both the portal vein and hepatic artery [26]. After the arterial phase, continuous perfusion may be provided to the tumor through the portal vein, resulting in continuous contrast development of the lesion.

2. The formation of PVTT (Portal Vein Tumor Thrombus) will hinder the portal vein blood flow of the tumor, even the portal vein blood flow of the liver parenchyma around the tumor, to accordingly affect their hemodynamic changes. With the formation of PVTT, hepatic portal vein blood supply gradually decreases. In order to make up for the amount of hepatic blood perfusion, hepatic artery blood expands. In the short term, the blood supply gradually increased, and the arteriovenous fistula of HCC gradually formed [27]. Studies have found that approximately 60% of the HCC lesions combined with PVTT did not show typical hyper enhanced in the arterial phase, suggesting that PVTT has a significant impact on the hemodynamic performance of HCC [28].

3. It may also be related to differences in the uptake of microvesicles by cancer cells with different degrees of differentiation and pharmacokinetic differences of contrast agents in different individuals [29].

4. The observation time may not be long enough; only five minutes of contrast injection has been observed so far. The lesion may wash out after 5 min (Table 2).

In our study, in two cases, CEUS, CECT and CEMRI showed different manifestations and conclusions, which may be because of the following:

i. The time points of CECT and CEMRI were different from those of CEUS. The enhanced CT scan was performed on the patients in the three phases, with the arterial phase of 25 s, the venous phase of 65 s, and the delayed phase of 300 s. The three phases of MRI scan were arterial phase 25 s, venous phase 65 s, and delay phase 180 s. CEUS is a continuous scanning method, which can reveal the perfusion of the lesion more comprehensively and continuously.

ii. The contrast agents used in contrast-enhanced CT and contrast-enhanced MRI are different from those used in CEUS. The method of CT enhancement is to inject contrast agent, usually 85 ml to 100 ml of iohexanol, into the body of the patient intravenously with a high-pressure syringe. MRI enhancement was performed at a rate of 2 ml/s using a high-pressure syringe to inject the contrast agent Gadolinium meglumine pentiate at a dose of 0.1 ml/kg intravenously into the patient. The ultrasonic contrast agent sulfur hexafluoride is a kind of blood pool imaging agent. The diameter of the microbubble ultrasonic contrast agent is mostly between 2 and 8 microns. Even in the case of increased blood tube permeability, such as in the tumor and inflammation, it cannot enter the interstitial space. It is a real blood pool contrast agent [30,31], which only exists in the blood vessels, while the CT/MRI contrast agent can enter the extracellular space [32].

In conclusion, although well-differentiated HCC may suffer from slow or even no contrast wash-out, such radiographic manifestations of HCC were relatively rare in this study. Therefore, for HCC with atypical CEUS manifestations, it is necessary to combine other imaging evaluations and relevant blood tests to confirm HCC. The specific reason for atypical ultrasound imaging model of HCC is not very clear; in addition to the degree of tumor differentiation and the number of contortions in tumor angiogenesis, it may also have to do with the formation of portal venous tumor emboli and cancer cells, the pharmacokinetic differences in uptake and contrast agents, and different individual differences. Thus, further studies are needed.

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