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Contrast-enhanced ultrasound features of hepatic angiomyolipoma: comparison with AFP-negative and non-viral hepatocellular carcinoma

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ABSTRACT

Purpose This study aimed to compare contrast-enhanced ultrasound (CEUS) features of hepatic angiomyolipoma (HAML) and challenging cases of HCC, mainly those with no hepatitis infection but also with a low level of AFP (non-viral AFP- HCC).

Materials and Methods The study included pathologically confirmed HAMLs and non-viral AFP- HCCs undergoing CEUS from 2012 to 2023. Sonovue (SV) CEUS and Sonazoid (SZ) CEUS characteristics of the two groups were compared.

Results The study included 50 HAMLs (24 % on SZ-CEUS) and 88 non-viral AFP- HCCs (21.6 % on SZ-CEUS). The CEUS characteristics on SZ-CEUS were similar to those on SV-CEUS to a certain extent. HAMLs more frequently displayed no washout and partial washout with partial no washout, so-called PWNW, in the late phase and post-vascular phase, whereas HCCs more commonly exhibited mild washout. In the post-vascular phase, all non-viral AFP- HCCs exhibited washout, thereby facilitating differentiation from no-washoutHAMLs, superior to SV-CEUS, where some non-viral AFP- HCCs still exhibited no washout in late phase that could not be distinguished from HAMLs. It is noteworthy that PWNW was exclusively found in nodules exhibiting hyper- and hypoechoic separation of the nodules, and hyper- and hypoechoic separation of HAMLs in the post-vascular phase on SZ-CEUS demonstrated PWNW more frequently compared to the late phase, which can potentially help distinguish nodules with hyper- and hypoechoic separation as either HAML or non-viral AFP- HCC. Conclusion: This study highlighted the usefulness of SV- and SZ-CEUS for distinguishing HAML and non-viral AFP- HCC and filled in existing gaps regarding the SZ-CEUS features of HAML.

Background

Hepatic angiomyolipoma (HAML) is an uncommon mesenchymal liver tumor consisting of smooth muscle cells, adipose tissue, and thick-walled blood vessels. It lacks distinct features on clinical examination or laboratory results. For instance, hepatitis B virus (HBV) infection often linked with other liver tumors shows no clear relationship with HAML and alpha-fetoprotein (AFP) levels usually remain low (AFP < 15ng/ml) [1, 2]. However, due to its benign nature and rich blood supply, HAML should be distinguished from hepatocellular carcinoma (HCC), which is the most common primary malignant liver cancer.

Typically, HCC presents distinctive clinical and laboratory traits, including a significant correlation with HBV and elevated AFP levels, facilitating straightforward diagnosis. Nonetheless, HCC with negative hepatitis virus and low AFP levels (non-viral AFP- HCC) can easily be mistaken for HAML. The management strategies of these two types of tumors differ significantly. Conservative treatment is generally recommended for HAML, while HCC, as an aggressive cancer, necessitates more comprehensive treatments like surgery and transhepatic arterial chemotherapy [3, 4]. In recent years, we have observed a global increase in HCC cases in non-hepatitis individuals [5, 6]. A survey from Japan reported that the proportion of HCC patients with non-viral etiologies has continued to increase from 10.0 % in 1991 to 32.5 % in 2015 [7]. Among individuals without HCC risk factors, HCC appears as the most frequent primary malignant liver tumor [8]. Notably, non-viral HCC cases with a low level of AFP may be relatively rarer, but it can be quite easily confused with benign hyper-vascularized HAML. Therefore, understanding their imaging features and distinguishing them carefully is extremely significant.

Imaging plays a crucial role in the diagnostic process as a non-invasive approach. Contrast-enhanced ultrasound (CEUS) has demonstrated remarkable accuracy in detecting focal liver lesions with high sensitivity and specificity [9]. SonoVue (SV; sulfur hexafluoride; Bracco SpA, Milan, Italy) and Sonazoid (SZ; perflubutane; GE Healthcare, Oslo, Norway) are second-generation ultrasound contrast agents. SV is a pure blood agent; SZ exhibits an extra post-vascular phase (10 minutes after injection and lasting at least 1 hour) with a high affinity for Kupffer cells in the liver [10]. Previously, several research studies described conventional ultrasound (US) and SV-CEUS manifestations of HAML in detail [11–13]. However, it appears that fewer studies have explored SZ-CEUS features of HAML. Hence, it is essential to investigate SZ-CEUS traits of HAML to improve accurate diagnosis.

This retrospective study aimed to compare CEUS features between HAML and challenging cases of HCC, mainly those with no hepatitis infection but also with a low level of AFP (non-viral AFP- HCC). We also compared the CEUS features of two different contrast agents, Sonovue and Sonazoid.

Methods

Patients

This retrospective study was approved by the institutional review board of our hospital and informed consent was waived.

The inclusion procedures for the HAML group in our study involved conducting an extensive search of the pathological databases at our hospital using the keyword "hepatic angiomyolipoma" between January 2012 and May 2023. The inclusion criteria for the HAML group were: 1) pathologic diagnosis of HAML confirmed by resection or biopsy; 2) CEUS performed before any treatment; 3) clinical and imaging data were available and of good quality. After adhering to these criteria, we identified and included 50 patients (17 men, 37 women, aged 41 ± 11.3 years) with pathologically confirmed cases of HAML. Of these patients, 12 (24 %) underwent SZ-CEUS.

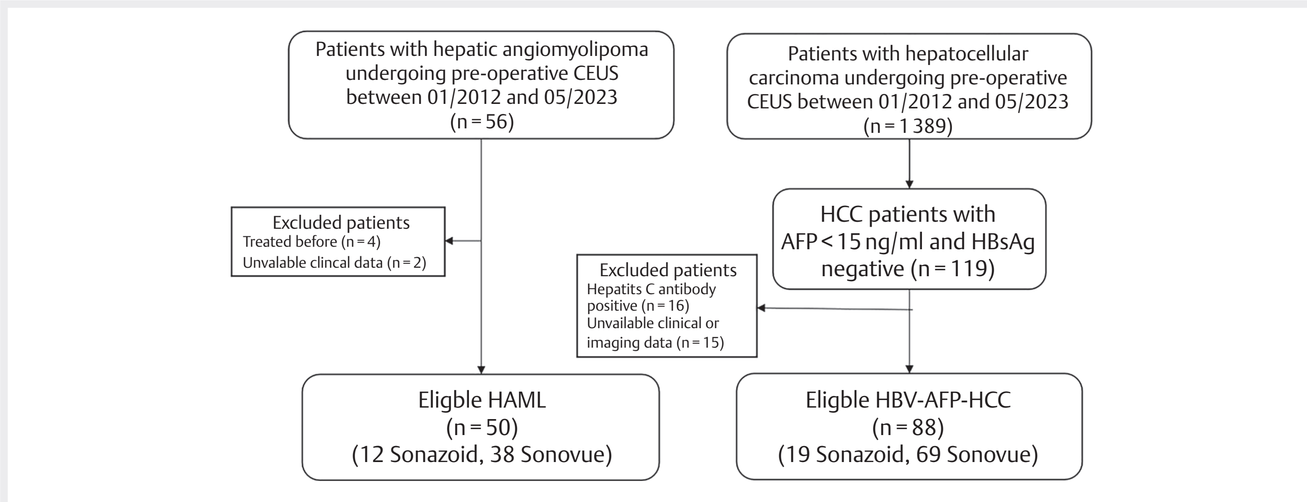
For the non-viral AFP- HCC group, we conducted a similarly comprehensive search for patients that met our criteria. The search spanned January 2012 to May 2023 using the keyword "hepatocellular carcinoma". Non-viral AFP- HCC participants were required to meet the following criteria: 1) resection or biopsy confirmed HCC pathology; 2) AFP levels were not higher than 15ng/ml; 3) hepatitis B surface antigen was negative; 4) hepatitis C antibody was negative; 5) images and clinical data were available and of good quality. Based on these criteria, we identified and included 88 pathologically confirmed HCC patients (81 men, 7 women, aged 61.4 ± 11.2 years). SZ-CEUS was performed on 19 of these 88 patients (21.6 %). The flowchart in ▶ **Fig.1** shows how patients were selected.

Ultrasound and CEUS Examination Technique

SV-CEUS examinations were performed on an Acuson Sequoia 512 (Siemens Healthineers) with a 4C1 convex array probe and Acuson New Sequoia (Siemens Healthineers) with a 5C1 convex array probe, while SZ-CEUS examinations were performed on the Acuson New Sequoia (Siemens Healthcare) with a 5C1 convex array probe. Conventional US examinations were performed on all patients. The contrast pulse imaging mode was used, and the mechanical indices for SV and SZ were set to 0.19 and 0.30, respectively. SonoVue was administered as a 1.5–2.0 mL bolus injection, followed by a saline flush with a volume of 5.0 mL. The target lesion was scanned continuously for the first 1 minute, and then intermittently observed until 5 min. The arterial, portal vein, and late phases were defined as 0–30s, 31–120s, and 121–250s post-injection, respectively. Sonazoid was used at a dose of 0.6–0.8 mL (0.015mL/kg) and injected into the cubital vein by the same method as SV. The arterial, portal vein, and late phases were recorded by the same procedure as SV, and the post-vascular phase was recorded after 10 minutes.

Imaging analysis

Two radiologists with 10 and 4 years of liver CEUS imaging experience independently assessed the conventional US and CEUS images in this study, with any disagreements being resolved through discussion and consensus. The histopathological results were kept blinded from the radiologists. The conventional US characteristics that were evaluated included maximum diameter, shape (rounded, oval, or irregular), boundary (well-defined or ill-defined), the presence of a hypoechoic halo, internal echogenicity (categorized as having hyper- and hypoechoic separation, strong hyperechogenicity with attenuation, hyperechoic, isoechoic, or hypoechoic), and liver parenchyma (homogeneous or heterogeneous). A heter-



▶ **Fig. 1** Flowchart of the selection of patients. The patients with hepatic angiomyolipoma (HAML) and hepatocellular carcinoma with negative hepatitis virus and low AFP levels (non-viral AFP- HCC) were included according to these criteria.

ogeneous internal echotexture, in addition to hyper- and hypoechoic separation and strong hyperechogenicity with attenuation patterns, shall be categorized as hyperechoic, isoechoic, or hypoechoic based on their primary echo features.

The following CEUS scan characteristics were recorded: the type of arterial phase hyperenhancement (APHE, categorized as homogeneous or inhomogeneous), the onset of washout (no washout, < 60s, 60–120s, 120s-5min, or > 5min), and the washout pattern during the late phase (LP) and post-vascular phase. The washout pattern can be categorized as entirely no washout, entirely mild washout, entirely marked washout, or partially with washout and partially with no washout (PWNW).

Statistical Analysis

All statistical analyses were performed using the SPSS software package (version 26.0, IBM, Armonk, NY, USA). The quantitative data was calculated as the mean ± standard deviation. The categorical variables were expressed as count and proportion. Differences in age and diameter were compared using independent sample t-test, and Chi-test or Fisher's exact test was used for categorical variables to compare the clinical, ultrasound, and CEUS characteristics. A *p*-value of < 0.05 was considered statistically significant.

▶ **Table 1** Clinical features.

	HAML (n = 50)	Non-viral AFP- HCC (n = 88)	P
Age in years	41.1 ± 11.3	61.4 ± 11.2	< 0.001*
Sex			< 0.001*
Male	17 (34.0 %)	81 (92.9 %)	
Female	33 (66.0 %)	7 (8.6 %)	
Hepatitis B virus	12 (24.0 %)	0	< 0.001*
AFP			0.972
0~7ng/ml	41 (82.0 % %)	72 (81.8 %)	
7–15ng/ml	9 (18.0 %)	16 (18.2 %)	
Fatty liver disease	10 (20.4 %)	22 (25.0 %)	0.504
Epithelioid subtype⁺	27 (54.0 %)	--	–
Sonazoid	12 (24 %)	19 (21.6 %)	0.744

HAML: hepatic angiomyolipoma; HCC: hepatocellular carcinoma
*indicates significance with $p < 0.05$. ⁺only for hepatic angiomyolipoma.

Results

Clinical characteristics

▶ **Table 1** displays the clinical characteristics of patients with HAML and non-viral AFP- HCC. HAML was more prevalent in females (33/50, 66.0 %), while non-viral AFP- HCC was more common in males (81/88, 92.9 %) (p < 0.001). Patients with HAML had a lower mean age than those with HCC (41.1 ± 11.3 vs. 61.4 ± 11.2, p < 0.001). The epithelioid subtype of HAML accounted for 54 % of cases (27 of 50).

Conventional US image findings

▶ **Table 2** presents the conventional US characteristics of HAML and non-viral AFP- HCC. The echogenicity was quite different between the two tumors. HAMLs demonstrated hyper- and hypoechoic separation (38.0 % vs. 20.5 %, p = 0.025), strong hyperechogenicity with attenuation (13.6 % vs. 0 %, p = 0.001), or hyperechogenicity (34.0 % vs. 13.6 %, p = 0.005) more frequently (▶ **Fig.2**). 88.9 % (24 of 27) of the cases of the epithelioid subtype of HAML exhibited these above three conventional US patterns, and only

3 cases presented as hypoechoic. On the other hand, non-viral AFP- HCC was commonly isoechoic (12.5 % vs. 0 %, p = 0.007) or hypoechoic (53.4 % vs. 14.0 %, p < 0.001). Additionally, a hypoechoic halo was more frequently observed in non-viral AFP- HCC (6 % vs. 22.7 %, p = 0.011). No significant differences were noted in diameter, shape, boundary, and liver parenchyma.

▶ **Table 2** Comparison of conventional US features between HAML and non-viral AFP- HCC.

	HAML (n = 50)	Non-viral AFP- HCC (n = 88)	p
Diameter-mm	46.4 ± 37.8	51.2 ± 24.6	0.375
Shape			0.633
Rounded	7 (14.0 %)	18 (20.5 %)	
Oval	39 (78.0 %)	64 (72.7 %)	
Irregular	4 (8.0 %)	6 (6.8 %)	
Boundary			0.336
Well-defined	39 (78.0 %)	62 (70.5 %)	
Ill-defined	11 (22.0 %)	26 (29.5 %)	
Hypoechoic halo			0.011 *
Yes	3 (6.0 %)	20 (22.7 %)	
No	47 (94.0 %)	68 (77.3 %)	
Echogenicity			
Hyper- and hypoechoic separation	19 (38.0 %)	18 (20.5 %)	0.025 *
Strong hyperechogenicity with attenuation	7 (14.0 %)	0 (0 %)	0.001 *
Hyperechoic	17 (34.0 %)	12 (13.6 %)	0.005 *
Isoechoic	0 (0 %)	11 (12.5 %)	0.007 *
Hypoechoic	7 (14.0 %)	47 (53.4 %)	< 0.001 *
Liver parenchyma			0.308
Homogeneous	49 (98.0 %)	83 (94.3 %)	
Heterogeneous	1 (2.0 %)	5 (5.7 %)	

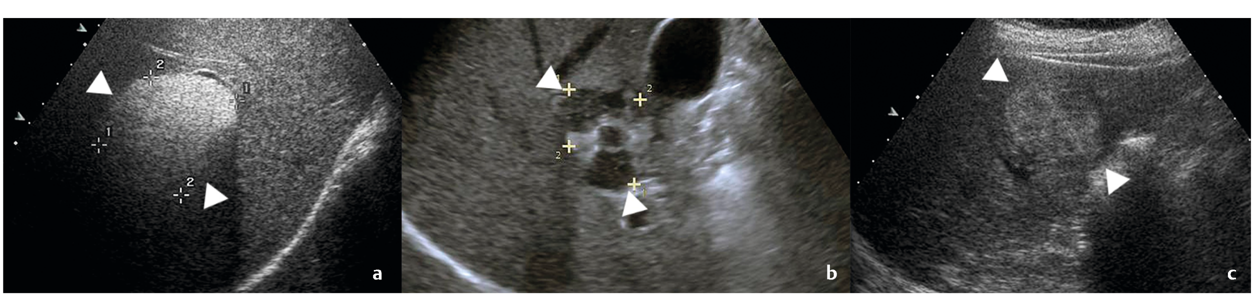
HAML: hepatic angiomyolipoma; HCC: hepatocellular carcinoma. *indicates significance with *p* < 0.05.

CEUS findings using Sonovue and Sonazoid

▶ **Table 3** shows the comparisons of CEUS features between HAML and non-viral AFP- HCC. The CEUS characteristics on SZ-CEUS were similar to those on SV-CEUS to a certain extent. Homogeneous APHE was more frequently observed in HAML with both CEUS techniques, but it was significant when using Sonovue (78.9 % vs. 42.0 %, p < 0.001), not obvious when using Sonazoid (91.7 % vs. 73.7 %, p = 0.217). Using both contrast agents, HAML hardly started to wash out before 120s, while some non-viral AFP- HCCs started to wash out before 120s (7.9 % vs. 33.2 % on SV-CEUS, 0 % vs. 42.1 % on SZ-CEUS). In LP, HAMLs more frequently displayed no washout (50 % vs. 5.8 % on SV-CEUS, 66.7 % vs. 15.8 % on SZ-CEUS) and PWNW (7.9 % vs. 0 % on SV-CEUS, 16.7 % vs. 0 % on SZ-CEUS), whereas non-viral AFP- HCCs more often exhibited entirely mild washout (82.6 % vs. 36.8 % on SV-CEUS, 84.2 % vs. 16.7 % on SZ-CEUS).

In the distinct post-vascular phase of SZ-CEUS, HAMLs still more commonly showed no washout (41.7 % vs. 0 %, p = 0.005) and PWNW (41.7 % vs. 5.3 %, p = 0.022). Despite the fact that 36.8 % of non-viral AFP- HCCs transformed to marked washout in the post-vascular phase, non-viral AFP- HCCs still more frequently exhibited mild washout (57.9 % vs. 8.3 %, p = 0.008). All cases of non-viral AFP- HCC exhibited washout, thereby facilitating differentiation from no-washout HAMLs. This is a slightly superior to SV-CEUS, which only provides an LP where some non-viral AFP- HCCs still exhibited no washout that consequently could not be distinguishable from no-washout HAMLs.

It is worth noting that regardless of the contrast agent being used, PWNW was exclusively found in the nodules exhibiting hyper- and hypoechoic separation with a conventional US pattern (▶ **Table. 4**), with partial washout in the hypoechoic part and partial no washout in the hyperechoic part. However, not all nodules with hyper- and hypoechoic separation showed PWNW. In the LP, PWNW was discernable solely in HAMLs, but the frequency of PWNW in nodules with hyper- and hypoechoic separation was low, only 21.4 % (3 of 14) on SV-CEUS and 40 % (2 of 5) on SZ-CEUS. Interestingly, the HAMLs with hyper- and hypoechoic separation in the post-vascular phase on SZ-CEUS all demonstrated PWNW (5 of 5, 100 %), more frequently compared to the LP (2 of 5, 40 %), which can po-



▶ **Fig. 2** Three types of hyperechoic conventional US patterns of hepatic angiomyolipoma frequently displayed. (**a**) Strong hyperechogenicity with attenuation. (**b**) Hyper- and hypoechoic separation, a clear distinction exists between hyperechogenicity and hypoechogenicity. (**c**) Hyperechoic, heterogeneous (or homogeneous) hyperechogenicity except for the above two patterns. (**b**) and (**c**) could also be observed in non-viral AFP- HCC.

▶ **Table 3** Comparison of CEUS features between HAML and non-viral AFP- HCC using Sonovue and Sonazoid.

	Sonovue			**Sonazoid**		
	HAML (n = 38)	**Non-viral AFP-HCC (n = 69)**	**p**	**HAML (n = 12)**	**Non-viral AFP- HCC (n = 19)**	**p**
Homogeneous APHE^H	30 (78.9 %)	29 (42.0 %)	< 0.001 *	11 (91.7 %)	14 (73.7 %)	0.217
Washout onset						
No washout	19 (50.0 %)	4 (5.8 %)	< 0.001 *	5 (41.7 %)	0 (0 %)	0.002 *
< 60s	0 (0 %)	7 (11.5 %)	0.049 *	0 (0 %)	1 (5.3 %)	0.419
60–120s	3 (7.9 %)	16 (21.7 %)	0.048 *	0 (0 %)	7 (36.8 %)	0.026 *
< 120s +	3 (7.9 %)	23 (33.2 %)	0.003 *	0 (0 %)	8 (42.1 %)	0.012 *
120s-5min	16 (42.1 %)	42 (60.9 %)	0.062	4 (33.3 %)	8 (42.1 %)	0.625
> 5min	N/A	N/A	…	3 (25.0 %)	3 (15.8 %)	0.527
Late phase						
Entirely no washout	19 (50.0 %)	4 (5.8 %)	< 0.001 *	8 (66.7 %)	3 (15.8 %)	0.007 *
Entirely mild washout	14 (36.8 %)	57 (82.6 %)	< 0.001 *	2 (16.7 %)	16 (84.2 %)	< 0.001 *
Entirely marked washout	2 (5.3 %)	8 (11.6 %)	0.282	0 (0 %)	0 (0 %)	> 0.999
PWNW	3 (7.9 %)	0 (0 %)	0.043 *	2 (16.7 %)	0 (0 %)	0.142
Post-vascular phase						
Entirely no washout	N/A	N/A	…	5 (41.7 %)	0 (0 %)	0.005 *
Entirely mild washout	N/A	N/A	…	1 (8.3 %)	11 (57.9 %)	0.008 *
Entirely marked washout	N/A	N/A	…	1 (8.3 %)	7 (36.8 %)	0.108
PWNW	N/A	N/A	…	5 (41.7 %)	1 (5.3 %)	0.022 *

HAML: hepatic angiomyolipoma; HCC: hepatocellular carcinoma; APHE: arterial phase hyperenhancement; PWNW: partial washout with partial no washout. ^H indicates homogeneous APHE versus inhomogeneous APHE. + Washout onset before 120s including washout onset before 60s and 60~120s. * indicates significance with $p < 0.05$.

▶ **Table 4** The interaction of conventional US features and CEUS washout pattern (Sonovue late phase vs. Sonazoid late phase) between HAML and non-viral AFP- HCC.

No. of cases *	**Hyper- and hypoechoic separation**	**Strong hyperechogenicity with attenuation**	**Hyperechoic**	**Isoechoic**	**Hypoechoic**
Entirely no washout	4/0 | 2/1	3/0 | 3/0	10/2 | 3/1	0/0 | 0/0	2/2 | 0/1
Entirely mild washout	6/11 | 1/5	1/0 | 0/0	3/6 | 0/1	0/7 | 0/3	4/33 | 1/7
Entirely marked washout	1/1 | 0/0	0/0 | 0/0	1/2 | 0/0	0/1 | 0/0	1/4 | 0/0
PWNW	3/0 | 2/0	0/0 | 0/0	0/0 | 0/0	0/0 | 0/0	0/0 | 0/0
Total	14/12 | 5/6	4/0 | 3/0	14/10 | 3/2	0/8 | 0/3	7/39 | 1/8

PWNW: partial washout with partial no washout. * the number of cases is listed as HAML on Sonovue CEUS/ HCC on Sonovue CEUS | HAML on Sonazoid CEUS/ HCC on Sonazoid CEUS.

tentially aid in distinguishing nodules with hyper- and hypoechoic separation as either HAML or non-viral AFP- HCC (▶ **Table. 5**).

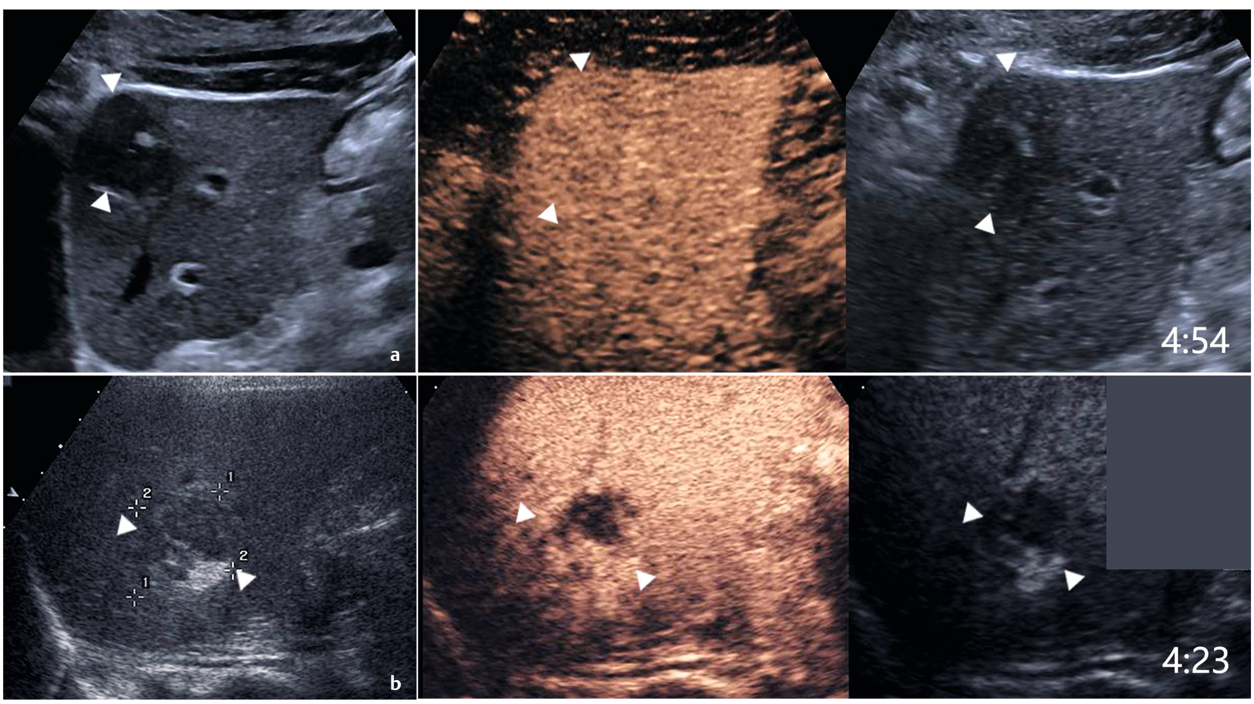
Discussion

HAML, an unusual liver tumor, might not have any noticeable clinical or lab features. For example, HBV doesn't seem to have too much of a connection with HAML, and AFP levels usually stay pretty normal. Generally speaking, this can be distinguished from a typical HCC, which has a strong link with HBV and an elevated AFP. However, there are also HCC cases that don't involve HBV and have low AFP levels. It is a bit tricky to tell the difference between these two since the clinical and laboratory clues are lost. Previous studies have found that Sonovue CEUS was useful for differentiating

▶ **Table 5** The interaction of conventional US features and Sonazoid CEUS washout pattern (late phase vs. post-vascular phase) between HAML and non-viral AFP- HCC.

No. of cases*	Hyper- and hypoechoic separation	Strong hyperechogenicity with attenuation	Hyperechoic	Isoechoic	Hypoechoic
Entirely no washout	2/1 | 0/0	3/0 | 2/0	3/1 | 3/0	0/0 | 0/0	0/1 | 0/0
Entirely mild washout	1/5 | 0/3	0/0 | 1/0	0/1 | 0/1	0/3 | 0/2	1/7 | 0/5
Entirely marked washout	0/0 | 0/2	0/0 | 0/0	0/0 | 0/1	0/0 | 0/1	0/0 | 1/3
PWNW	2/0 | 5/1	0/0 | 0/0	0/0 | 0/0	0/0 | 0/0	0/0 | 0/0
Total	5/6 | 5/6	3/0 | 3/0	3/2 | 3/2	0/3 | 0/3	1/8 | 1/8

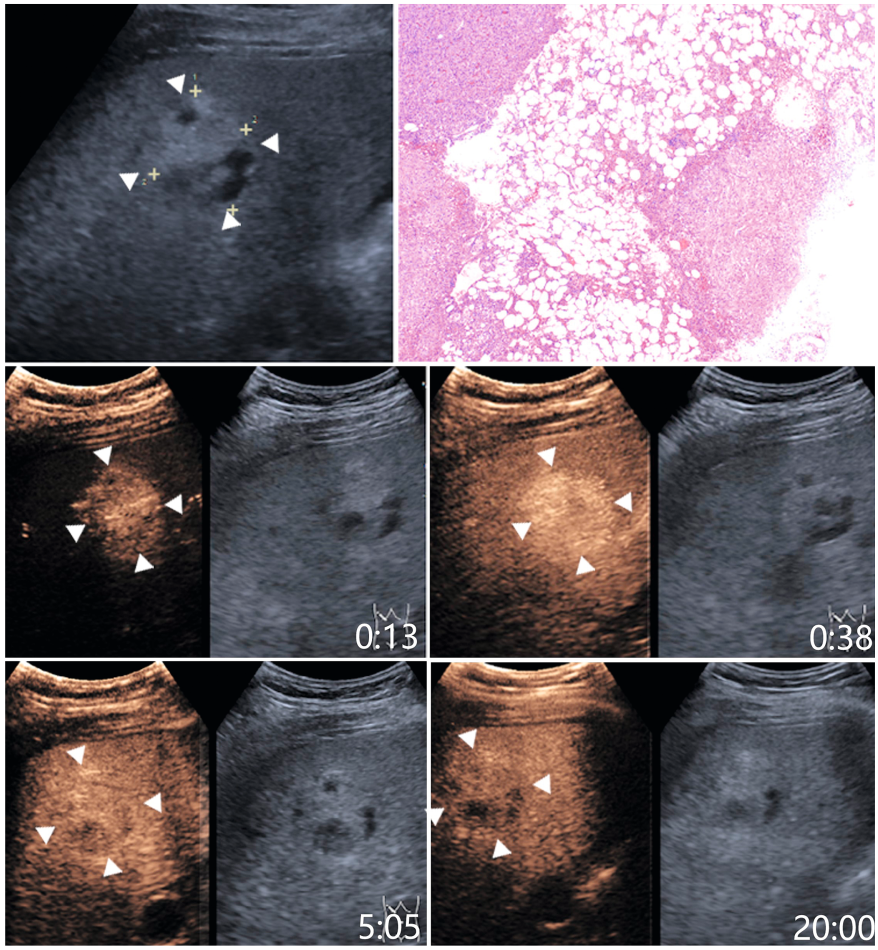
PWNW: partial washout with partial no washout. *the number of cases is listed as HAML in late phase/ HCC in late phase | HAML in post-vascular phase/ HCC in post-vascular phase.



▶ **Fig. 3** Sonovue-CEUS images of hepatic angiomyolipoma. (**a**) A hypoechoic nodule demonstrated no washout in the late phase (LP). (**b**) A hyper- and hypoechoic nodule displayed partial washout in the hypoechoic part and partial no washout (PWNW) in the LP. The pathologies were both hepatic angiomyolipoma.

HAML from HCC [1, 14, 15], but no studies have explored the diagnostic potential of Sonazoid CEUS in this respect. So far, only two case reports have demonstrated the characteristics of HAML on Sonazoid CEUS [16, 17]. The purpose of this study was to compare the features of HAML and non-viral AFP- HCC on Sonovue CEUS and Sonazoid CEUS, with the goal of filling in existing gaps regarding the characteristics of HAML on Sonazoid CEUS.

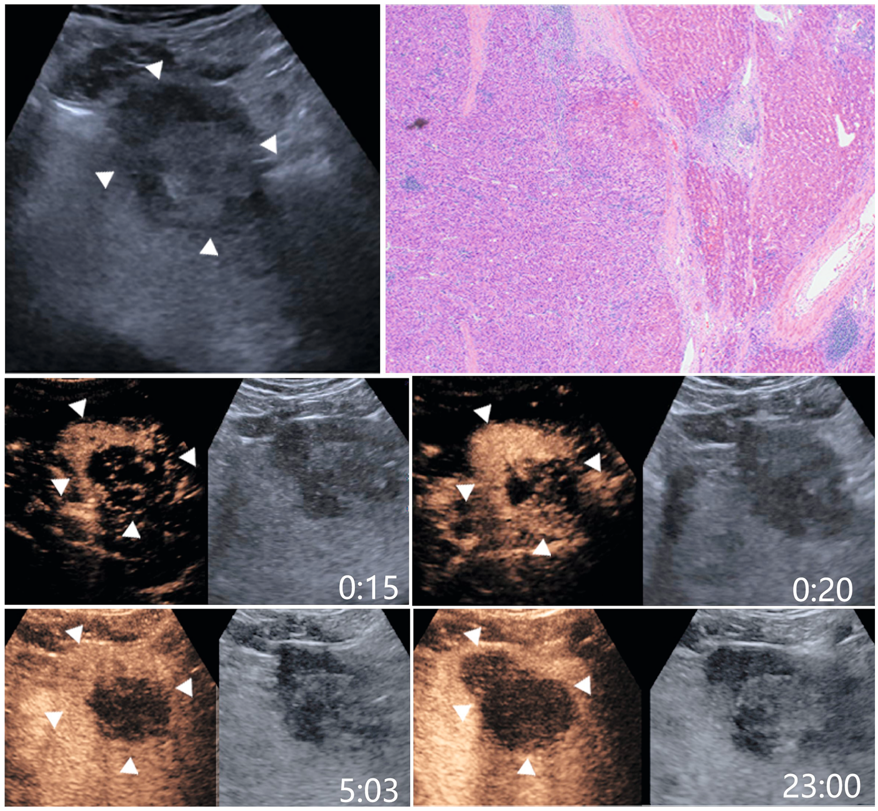
HAML presents diverse compositions and morphologies, resulting in varied echogenicity. Although a US pattern showing strong hyperechogenicity with attenuation seems to have an exclusive link to HAML [11, 18], it may be challenging to distinguish HAML from non-viral AFP- HCC utilizing the conventional US pattern alone. The additional utilization of contrast agents becomes indispensable for extracting enhancement information about nodules, thereby facilitating further diagnostic assessment.



▶ **Fig. 4** Sonazoid-CEUS images of hepatic angiomyolipoma with partial washout in the hypoechoic part and partial no washout in the hyperechoic part. A 35-year-old male presented a 32mm × 29mm well-defined hyper- and hypoechoic separation of the liver lesion (angle). The lesion showed homogeneous arterial hyperenhancement, and began washout at 2 min 50 s. It presented partial washout in the hypoechoic part and partial no washout (PWNW) in the hyperechoic part at 20 min. The pathology was hepatic angiomyolipoma.

Both HAMLs and non-viral AFP- HCCs have abundant vascularity [19, 20]. The pattern of APHE could not distinguish between HAML and non-viral AFP- HCC. However, irrespective of contrast agent, HAMLs hardly started to wash out before 120s, and exhibited no washout more frequently, which could help to distinguish them from non-viral AFP- HCCs, since most non-viral AFP- HCCs in our study still maintained typical washout patterns as previously reported [21]. Notably, zero non-viral AFP- HCCs showed no washout in the post-vascular phase, which can be attributed to the size of the tumors. A portion of HCCs demonstrated no washout in the post-vascular phase, but it was more frequently observed in nodules with a size of less than 30mm [22]. Generally speaking, as the size of an HCC increases, there is a greater likelihood of washout during the post-vascular phase [22]. Non-viral HCCs may be commonly detected in more advanced stages, thus having a significantly larger tumor diameter than viral HCCs, culminating in increased washout during the post-vascular phase, aiding differentiation from cases of no-washout HAML.

Another interesting thing is that our study found PWNW was a relatively exclusive feature of HAML, and more frequently occurred in the post-vascular phase on SZ-CEUS. PWNW is a washout pattern solely observed in nodules with hyper- and hypoechoic separation, with contrast agent partial washout in the hypoechoic part and partial no washout in the hyperechoic part (▶ **Fig. 3** and ▶ **Fig. 4**). An earlier instance of this phenomenon also surfaced in a case report [17], yet it did not elicit substantial interest. This phenomenon may be attributed to the following potential reasons: First, the washout pattern may be influenced by the basic conventional US hyperechogenicity to an extent. Besides, the hyperechoic part of HAMLs may be comprised of angiomatous tissue [11, 18, 23, 24] that could hinder contrast agent washout. Thirdly, the hyperechoic part of HAMLs may contain macrophages with uptake of contrast agent in the post-vascular phase [16, 25, 26]. Conversely, the US pattern with hyper- and hypoechoic separation in HCCs, the so-called “mosaic sign”, representing the heterogeneity within HCCs, is probably due to the presence of different grades of HCC differentiation



▶ **Fig. 5** Sonazoid-CEUS images of hepatocellular carcinoma with hyper- and hypoechoic manifestation. A 58-year-old male with normal level of AFP and negative hepatitis B antigen, presented a 66mm × 43mm well-defined hyper- and hypoechoic separation of the liver lesion (angle). The lesion showed heterogeneously arterial hyperenhancement with a non-enhanced necrotized part in the hyperechoic part. The enhanced part stayed iso-enhanced before 5 min, and entirely markedly washed out at 23 min. The pathology was hepatocellular carcinoma.

[27] or fatty metamorphosis [28], but this would not change the washout pattern. In some cases of large HCCs, a necrotic part also exhibited hyperechogenicity, which could be easily differentiated using CEUS (▶ **Fig. 5**).

CT and MRI are valuable tools for distinguishing between benign and malignant liver tumors. The specific features on CT for HAMLs include the presence of fat tissue attenuation within tumors on unenhanced CT, demonstration of dysmorphic vessels, heterogeneous arterial phase enhancement, and prolonged contrast enhancement [18]. The diagnostic signs of HAML on MRI exhibit certain similarities, including: presence of fatty content in fat-saturated T1-weighted sequences, detection of an internal vessel, hepatic vein drainage, and remaining no washout [29]. The most important sign on CT and MRI to differentiate HAML is the presence of fat content, but this can be effective for lipomatous and mixed types of HAML, not for myomatous and angiomatous types that lack lipid [18, 30], resulting in varying accuracy when diagnosing HAML. Nevertheless, these four types of HAML, irrespective of the presence of fat, do exhibit hyperechogenicity on conventional US [18]. Similar results were found in our study. Regardless of epithelioid subtype, a large percentage of HAMLs demonstrated hyperechogenicity more frequently than non-viral AFP- HCCs, which may potentially enhance sensitivity, compared to CT/MRI. Moreover, two head-to-head comparison studies found that LP washout was present in more HAMLs on CT/MRI than on CEUS, reinforcing the pivotal role of CEUS in accurate HAML diagnosis.

The study has some limitations that should be noted. First, the number of included patients was small, due to the rarity of HAMLs and non-viral AFP- HCCs. However, it was acceptable compared to prior studies. Second, we only compared non-viral AFP- HCCs to HAMLs in this study, and other hypervascularized liver tumors were not considered. Other types of hypervascularized liver tumors should be included in future prospective studies.

Conclusion

Our study underscored the utility of Sonovue and Sonazoid CEUS for differentiating HAMLs from non-viral AFP- HCCs, thereby serving to enrich our understanding of distinctive features exhibited by HAMLs on Sonazoid CEUS.

Conflict of Interest

The authors declare that they have no conflict of interest.

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