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Benign focal liver lesions: spectrum of findings on SonoVue-enhanced pulse-inversion ultrasonography

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Abstract The prevalence of benign focal liver lesions (BFLL) is high both in the general population and in patients with known malignancies. The gray-scale ultrasound (US) technique is usually the first-line imaging modality used in the radiological workup of such lesions, but unfortunately it lacks specificity. Furthermore, Doppler examination may often be unsatisfactory owing to motion artefacts, or when small or deeply located lesions are evaluated. Recently, microbubble-based contrast agents used in combination with gray-scale US techniques, which are very sensitive to nonlinear behavior of microbubbles, have led to a better depiction of both microvasculature and macrovasculature of focal hepatic masses, thus improving the reliability of using US in the assessment of liver tumors. This review illustrates the spectrum of enhancement patterns of BFLL on contrast-enhanced ultrasonography with SonoVue, a second-generation microbubble-based contrast agent.

Keywords Liver · Liver neoplasms · Pulse inversion imaging · Contrast media

Introduction

Worldwide, the ultrasound (US) technique usually plays a role as the first-line imaging technique in the diagnostic workup of patients with liver disease. The high prevalence of benign hepatic lesions both in the general population—up to 52% in autoptic studies—and in patients with known malignancies explains the need of accurate characterization

[1, 2]. Unfortunately, the gray-scale US technique is commonly considered not to be a specific technique in the diagnosis of hepatic liver tumors, owing to the lack of a peculiar echo pattern apart from for simple liver cysts and typical hemangioma [3, 4]. Furthermore, color and power Doppler examination may often be unsatisfactory owing to motion artefacts, or when small or deeply located lesions are evaluated. Even when US contrast agents are administered, blooming artefacts may hamper color Doppler assessment [5, 6].

Some studies have demonstrated that contrast-specific US techniques, such as pulse inversion (PI), after the injection of a first-generation, air-based contrast agent (SH U 508A) are helpful in diagnosing hepatic tumors [7, 8]. PI works by transmitting in the medium two identical pulses with reverse polarity and adding the two resultant returned signals: the fundamental linear components, mainly arising from tissues, are canceled, whereas the nonlinear harmonic components—which originate from the interaction of the US beam with the microbubbles of the contrast agent—are preserved, thus making this technique extremely sensitive to microbubble-based US contrast agents [9]. SonoVue is a second-generation, stabilized microbubble preparation containing sulfur hexafluoride. This latter is a low-solubility isotonic and does not contain antigenic potential gas [10]. An early report showed that SonoVue could enable the identification of some specific contrast-enhancement patterns in different focal liver lesions [11].

The objective of this pictorial review is to illustrate the spectrum of enhancement patterns of benign focal liver lesions (BFLL) on contrast-enhanced ultrasonography (CEUS) with SonoVue.

Technical note

First-generation microbubble-based contrast agents used in combination with gray-scale US techniques, which are very sensitive to the nonlinear behavior of microbubbles, have led to a better depiction of both microvasculature and macrovasculature of focal hepatic masses, thus improving the reliability of using US in the assessment of liver tumors [7, 8, 14–19]. Nevertheless, the relatively short half-life of first-generation air-based contrast agents, such as Levovist, does not allow adequate time for a complete liver imaging; in adjunction, the wall rigidity of air-based microbubbles requires intermittent US for high US output imaging with limited scanning planes [20]. This makes the examination technically difficult and unsuitable for an exhaustive study of the entire liver parenchyma in the various contrast phases [21]. Microbubble destructive modes with Levovist at high mechanical index (MI), such as stimulated acoustic emission or loss of correlation, may be useful in both in the detection and in the characterization of liver tumors [22–24].

Second-generation microbubble-based contrast agents, such as SonoVue, allow the radiologist to perform continuous imaging at low acoustic power instead of intermittent imaging at high acoustic power and to scan the entire liver in all the vascular phases, providing an easier and more accurate depiction of tumor vascularity [10, 25–27]. Early studies reported that SonoVue enabled the identification of some specific contrast-enhancement patterns in different focal liver lesions [11, 28–30].

The US technique used in the cases illustrated in this article consisted of continuous scanning performed by using an HDI 5000 unit (ATL, Bothell, WA, USA) provided with a C5-2 convex-array probe and PI imaging software. The US contrast agent used was SonoVue (Bracco, Milan, Italy), injected intravenously as a bolus in a 2.4 ml (equivalent to 0.003 ml/kg for 70-kg body weight) followed by 5 ml of normal saline flush, by using a 20- or 22-gauge peripheral intravenous cannula [13]. A low frame rate (5 Hz) was used. Even if the recommended MI for a SonoVue-enhanced US study of the liver is 0.3–0.5 [25] in order to minimize microbubble disruption a very low MI (0.05–0.08) was used as previously reported [31]. Digital cineloops were registered during both baseline and postcontrast US scanning in the arterial (i.e., 10–35 s from the beginning of contrast agent bolus injection), portal-venous (i.e., 55–80 s from the beginning of injection), and delayed (i.e., 235–260 s from the beginning of injection) phases. All cineloops were digitally stored as raw data in a PC-based workstation connected to the US unit via a standard Ethernet link. All cineloops were reviewed off-line in order to evaluate the dynamic enhancement pattern of each lesion in comparison with adjacent liver parenchyma.

Benign focal liver lesions

Hemangioma

Hemangioma is the most common benign tumor of the liver, with a prevalence ranging from 1–2 to 20% among the general population and having a higher incidence in females than in males (ratio 2:1–5:1) [4]. The differential diagnosis between hemangiomas and other hepatic tumors is of clinical relevance since hemangioma, although frequently an incidental finding of abdominal ultrasonography, is rarely symptomatic or requires treatment.

According to previously reported data with a first-generation air-based US contrast agent, CEUS may be very helpful in characterizing hepatic hemangioma, especially when these latter show atypical gray-scale US appearance [32, 33]. Integration with color Doppler is of limited value in evaluating hemangiomas, except for the demonstration of absent or poor intralesional vascularization. CEUS enables one to demonstrate the peripheral nodular enhancement in the arterial phase followed by a progressive centripetal fill-in in the portal-venous and delayed phases, which are considered by spiral computed tomography (CT) and gadolinium-

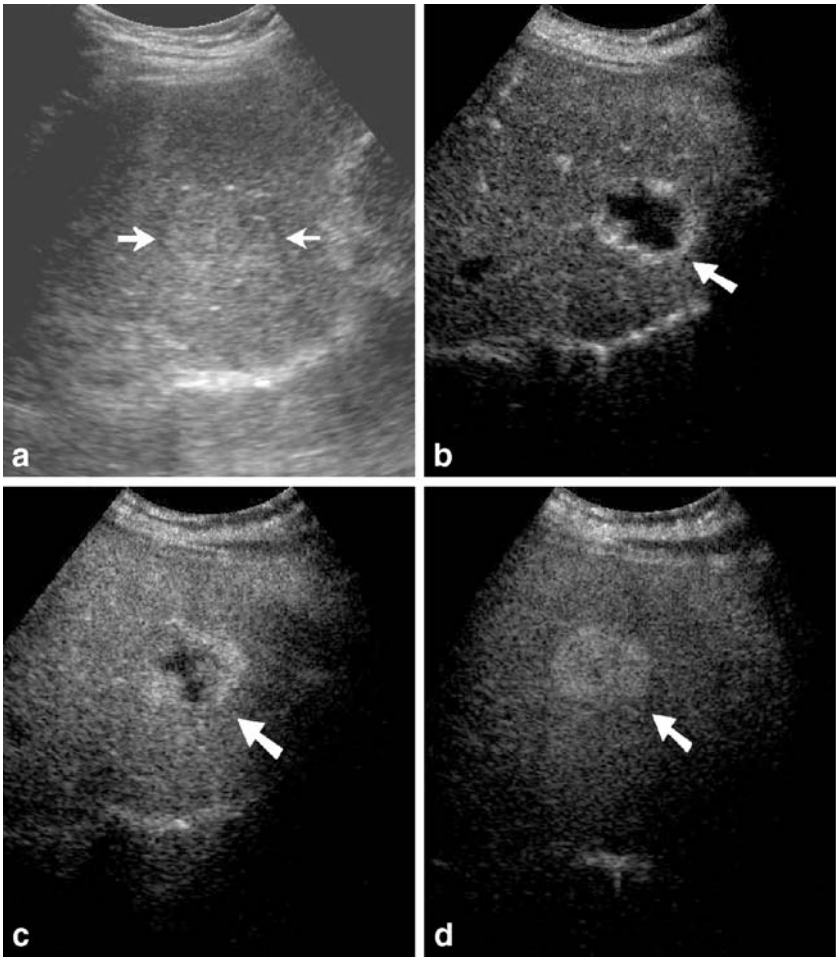

Fig. 1 **a** Hemangioma. Oblique ascending right subcostal baseline image in a 63-year-old man shows an isoechoic lesion (*arrows*) in the VII hepatic segment. **b** On the oblique ascending right subcostal image obtained in the arterial phase (25 s after SonoVue injection) the lesion shows peripheral globular enhancement (*arrow*). **c**, **d** In the portal-venous and delayed phases (60 and 240 s after SonoVue injection, respectively) a progressive and complete centripetal fill-in is shown (*arrows*).

enhanced magnetic resonance (MR) diagnostic studies for this tumor [34, 35] (Fig. 1). The centripetal fill-in may be either complete or incomplete. This latter finding, more frequently occurring in larger lesions, is at least in part referable to the half-life of SonoVue, which is shorter than that of currently used iodinated or paramagnetic contrast agents. However, it must be underlined that centripetal fill-in of hemangioma may require even more than 15 min of CT and/or MRI [35]. In a limited but nonnegligible number of small hemangiomas (diameter smaller than 2 cm) the typical globular peripheral enhancement pattern of the arterial phase may not be documented; instead, a rapid uptake of contrast agent with consequent hyperechogenicity in the arterial phase often occurs. Such semeiological features, though reported in the literature as indicating possible capillary hemangiomas by CT and MRI, represent an atypical pattern and may cause interpretation problems, thus requiring further diagnostic studies. A continuous peripheral rim of enhancement in the arterial phase followed by a progressive centripetal fill-in is also reported in the literature as a possible contrast-enhancement pattern of hepatic hemangioma [33].

Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is the second most common benign hepatic tumor after hemangioma, with an incidence of 1–3% and it is being increasingly discovered, mostly in young women, owing to widespread use of cross-sectional imaging, in particular abdominal ultrasonography [12]. Surgery is not recommended for asymptomatic patients.

The gray-scale US technique is commonly considered to be not a specific technique in the diagnosis of FNH, owing to the lack of a peculiar echo pattern, even if an usually hypoechoic central scar may be detected [25]. In large FNHs color, power and pulsed-Doppler US may show a characteristic spoke-wheel arterial pattern of vessels, thus providing further clues to the diagnosis.

FNHs are very hypervascular tumors and, after contrast agent injection, become hyperechoic in comparison with adjacent normal liver parenchyma in the arterial phase. In the portal-venous and delayed phases all these lesions tend to be slightly hyperechoic or isoechoic in comparison with surrounding liver parenchyma (Fig. 2).

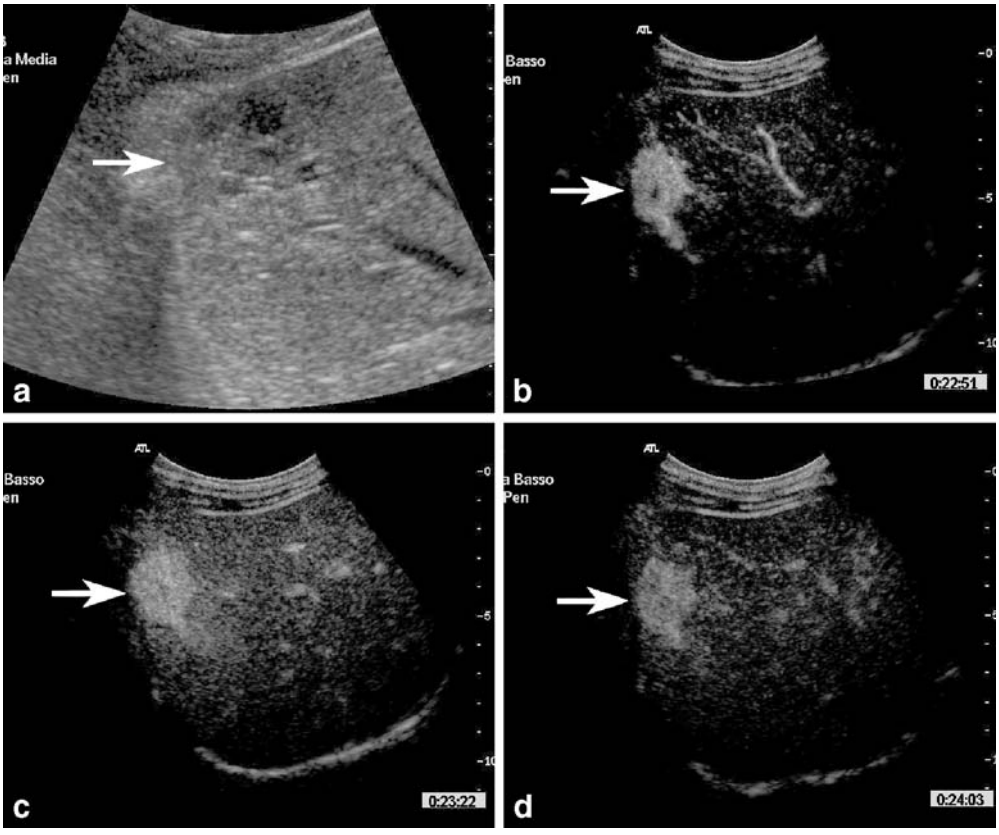

Fig. 2 **a** Focal nodular hyperplasia. Oblique ascending right subcostal baseline image in a 40-year-old woman shows a 2.5-cm mass with inhomogeneous echo texture (*arrow*) in the subcapsular region of the VII hepatic segment. **b** Oblique ascending right subcostal image obtained in the arterial phase (25 s after SonoVue injection) shows strong and homogeneous enhancement of the lesion (*arrow*); an unenhancing hypoechoic central scar is clearly depicted. **c**, **d** Oblique ascending right subcostal images obtained in the portal-venous phase and in the delayed phase (60 and 240 s after SonoVue injection, respectively) still show the tumor as a hyperechoic lesion (*arrows*) with an hypoechoic central scar.

A central starlike fill-in starting less than 30 s after Levovist injection was reported in one study to have a 100% specificity for characterizing FNH [23]. In the same study a diffuse stippled pattern of FNH was also reported, which was identified in three cases of our series. However, the depiction of a starlike fill-in is strictly dependent both on the timing of scanning and on the US technique used. Continuous scanning, which is currently used with a second-generation contrast agent, is better suited for this purpose, yielding better results than those of previous authors using an interval-delay technique [25]. On the other hand, in CEUS the unenhancing central scar is not always easily identifiable in FNH, according to previous CEUS studies and CT and MR findings [7, 11, 36–38] (Fig. 2).

Hepatocellular adenoma

Hepatocellular adenoma (HA) is a quite uncommon primary benign liver tumor of hepatocellular origin. Nevertheless, its incidence has increased with the use of oral contraceptives and androgen steroid therapy, both of which have a causative role in the origin of this tumor [12].

The gray-scale US appearance of HA is not specific but the right diagnosis is of clinical relevance since surgery is a

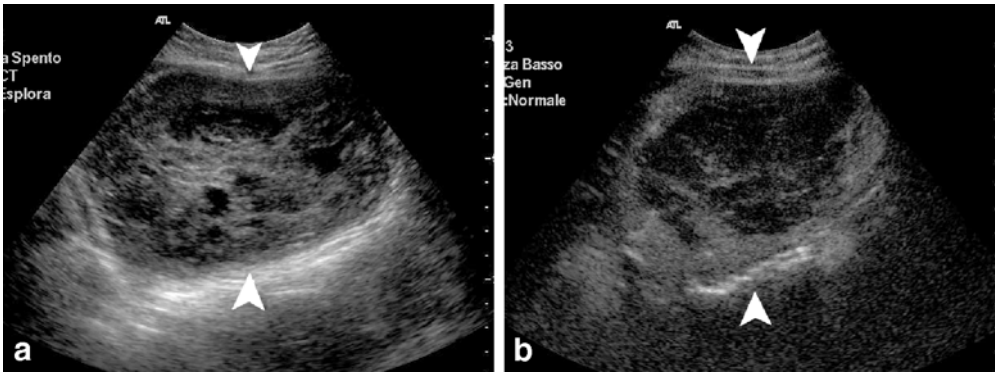

Fig. 3 **a** Hepatocellular adenoma. Parasagittal baseline image of the left lobe in a 31-year-old woman shows a huge mass with very inhomogeneous echo texture (*arrowheads*) in the II–III hepatic segment. **b** Parasagittal image obtained in the arterial phase (25 s after SonoVue injection) shows inhomogeneous enhancement of the lesion (*arrowheads*).

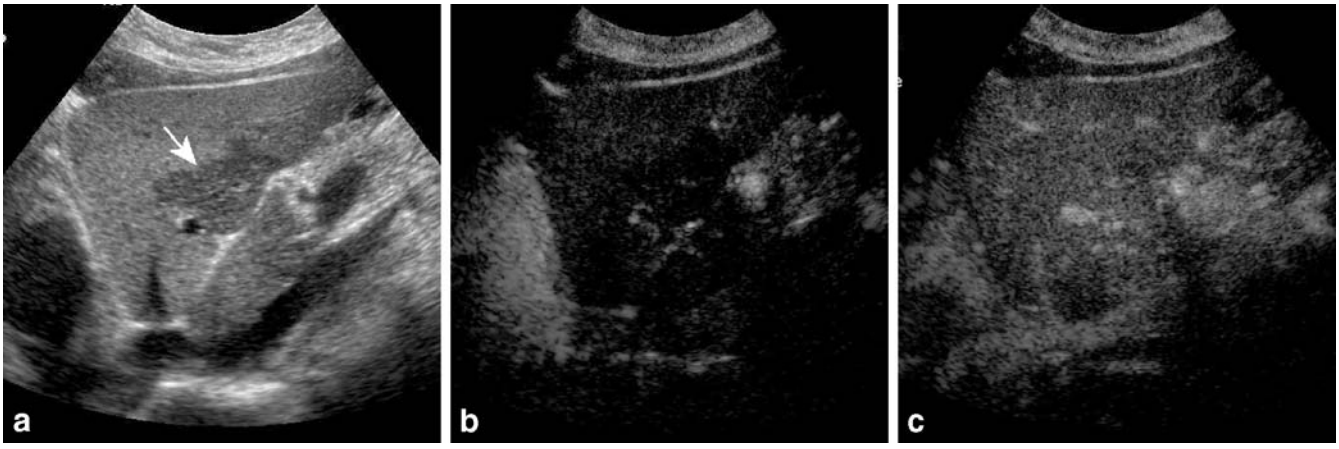

Fig. 4 **a** Focal fatty sparing. Parasagittal baseline image of the left lobe in a 40-year-old woman shows a diffuse "bright liver" with a 4-cm hypoechoic area without mass effect in the III hepatic segment (*arrow*). **b** Parasagittal image obtained in the arterial phase (25 s after SonoVue injection) shows no sign of enhancement of that area. **c** Parasagittal image obtained in the portal-venous phase (60 s after SonoVue injection) shows the same area isoechoic in comparison with the surrounding liver parenchyma.

therapeutic option for HA because of its potential for life-threatening hemorrhage or, more rarely, malignant transformation [12, 39]. Doppler techniques could provide further but not ultimate clues to the diagnosis by demonstrating central or peripheral venous flow in HAs [40].

CEUS study reflects the hypervascular nature of HA by showing in smaller and more homogeneous lesions a clear contrast enhancement in the arterial phase which usually becomes less intense but still lasts during portal-venous and delayed phases, whereas larger lesions, with mixed echo texture or even hemorrhagic, may show inhomogeneous, mainly peripheral, contrast enhancement after SonoVue injection (Fig. 3).

It is noteworthy that both FNH and hemangioma may present as hyperecoic lesions after contrast agent administration and thus differential diagnosis between HA and other benign hypervascular hepatic tumors, such as FNH and capillary hemangioma, should be considered [10, 33].

Hyposteatosis and hypersteatosis

According to literature data and our personal experience both focal sparing areas—occurring as hypoechoic areas in a diffuse fatty "bright liver"—and focal fatty changes—presenting as hyperechoic areas in otherwise normal liver—usually show no differences in contrast uptake in comparison with surrounding liver parenchyma [23]. In CEUS these pseudolesions do not show contrast enhancement during the arterial phase and become isoechoic in comparison with

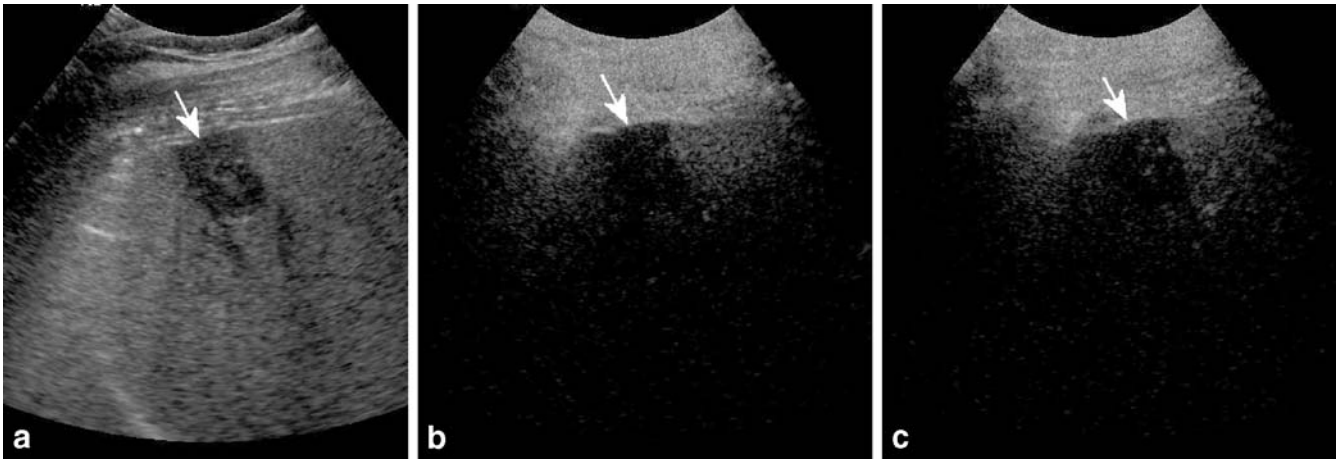

Fig. 5 **a** Solitary necrotic nodule. Oblique ascending right subcostal ultrasound baseline image in a 40-year-old man shows a well-defined, slightly lobulated, hypoechoic lesion in the VI hepatic segment in a subcapsular location (*arrow*). **b**, **c** Oblique ascending subcostal images obtained in the arterial and portal-venous phases (25 and 60 s after SonoVue injection, respectively) show the complete absence of contrast enhancement of the lesion (*arrows*).

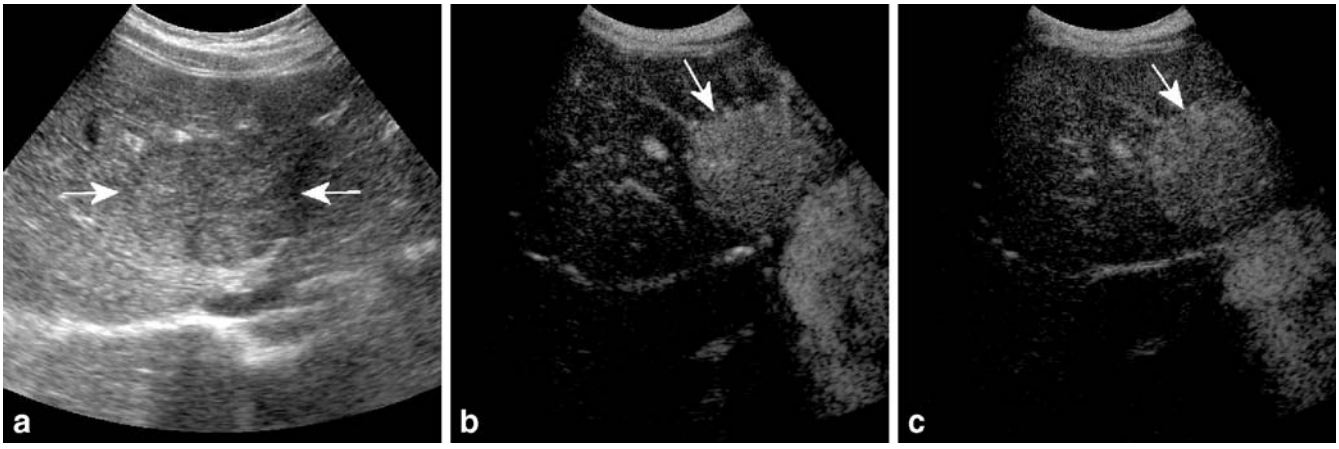

Fig. 6 **a** Intrahepatic extramedullary hematopoiesis. Oblique ascending right subcostal ultrasound baseline image in a 19-year-old woman shows a 5-cm barely defined hypoechoic lesion in the IV hepatic segment (*arrows*). **b** Oblique ascending right subcostal image obtained in the arterial phase (25 s after SonoVue injection) shows strong and homogeneous enhancement of the lesion (*arrow*); no central scar is seen. **c** Oblique ascending right subcostal image obtained in the portal-venous phase (60 s after SonoVue injection) still shows the tumor as a hyperechoic lesion (*arrow*) in the absence of a central scar.

the surrounding liver parenchyma in the portal-venous and delayed phases (Fig. 4).

Other rare lesions

A solitary necrotic nodule of the liver is a possible end stage of a variety of hepatic lesions, such as hemangioma, infected abscesses, parasitic granulomas, and hematomas [41]. CEUS may reveal the absence of vascularization throughout the vascular phase, but the right diagnosis is only made by means of biopsy (Fig. 5). Intrahepatic extramedullary hematopoiesis (IEH) usually presents as hypoechoic lesions in an unenhanced US scan, with intralesional arterial vessels in color/pulsed Doppler evaluation [42, 43]. After SonoVue injection IEH may show strong arterial enhancement, remaining hyperechoic, even to a lesser degree, compared with the surrounding liver parenchyma in portal-venous and delayed scans, thus mimicking a FNH (Fig. 6). In such rare cases, the correct diagnosis is usually possible only after biopsy.

Conclusion

In summary, this pictorial review shows that CEUS may enable the depiction of typical contrast-enhancement patterns, thus providing useful clues for the characterization of BFLL. SonoVue, a second-generation contrast agent, was proved to be effective for this purpose and safe for our patients. Benign liver lesions overwhelmingly appear isoechoic to liver parenchyma in the late phase of contrast enhancement, whereas malignant lesions tend to be hypoechoic [18, 23–25, 28].

Deeply located or tiny lesions could still represent a diagnostic dilemma even for CEUS, even if it is conceivable that CEUS will expand its role in the differential diagnosis of hepatic tumors, especially when they are detected in patients without known cancer.

Further studies are needed to address exactly the cost/efficacy issue and to find the right place for CEUS in the diagnostic workup of patients with focal liver lesions.

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