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Contrast-enhanced ultrasound of benign liver lesions

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Abstract

Liver lesions are often incidentally detected on ultrasound examination and may be incompletely characterized, requiring further imaging. Contrast-enhanced ultrasound (CEUS) was recently approved by the Food and Drug Administration in the United States for liver lesion characterization. CEUS has the ability to characterize focal liver lesions and has been shown to be superior to color Doppler and power Doppler ultrasound in the detection of tumor vascularity. Differentiating benign from malignant liver lesions is essential to characterizing liver lesions. The CEUS imaging characteristics of benign liver lesions are reviewed, including hepatic cysts, hemangiomas, focal fat, focal nodular hyperplasia, hepatocellular adenomas, abscesses, and traumatic lesions.

Key words: Contrast-enhanced ultrasound—Liver lesions—Benign—FNH—Adenoma—Cyst—Abscess—Hemangioma

Contrast-enhanced ultrasound (CEUS) has been used widely throughout European and Asian countries for many years and was recently approved by the Food and Drug Administration (FDA) in the United States for use in characterizing liver lesions. Focal liver lesions are commonly found during abdominal ultrasound exams either incidentally or in patients undergoing surveillance in chronic liver disease or cirrhosis. At times, benign liver lesions can be characterized by conventional gray scale and color Doppler if they have characteristic appearances of an anechoic cyst or a homogeneous hyperechoic hemangioma. However, often lesions that are detected on ultrasound examination are incompletely characterized and require further imaging. CEUS has the ability to characterize focal liver lesions based on enhancement pattern. CEUS has been shown to be superior to color Doppler and power Doppler ultrasound in the detection of tumor vascularity [1].

In CEUS, the arterial phase starts within 10–20 s and persists for approximately 35–40 s after injection. The portal venous phase lasts for up to 2 min after injection and is characterized by homogeneous enhancement of the liver parenchyma [2]. The late phase persists through approximately 5–6 min. Ultrasound contrast agents are smaller than the size of a red blood cell, and most are purely intravascular agents. As such, there is not a corresponding equilibrium or interstitial phase in CEUS to correlate with that seen on contrast-enhanced CT or MR [3].

The late phase of the CEUS exam has been shown to be the most critical in distinguishing benign from malignant liver lesions [4]. Benign liver lesions generally have persistent enhancement with hypervascular or isovascular appearance relative to the adjacent liver parenchyma [4]. Malignant lesions generally have washout and become hypovascular in appearance; although, hepatocellular adenomas may washout, and therefore the appearance can overlap malignant lesions [5–8]. As with all other modalities, CEUS evaluation of liver lesions should take into account the clinical context, particularly considering the presence or absence of risk factors for HCC.

Herein, the CEUS imaging characteristics of benign liver lesions will be reviewed; including the CEUS appearance of hepatic cysts, hemangiomas, focal fat, focal nodular hyperplasia (FNH), hepatocellular adenomas (HCA), abscesses, and traumatic lesions (summarized in Table 1).

Cystic liver lesions

Liver cysts are commonly found incidentally and are usually benign with little clinical significance. Simple cysts appear as completely anechoic, rounded, or ovoid lesions at gray-scale ultrasound with imperceptible walls and posterior acoustic enhancement. At CEUS, there is

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Table 1. Benign liver lesion enhancement patterns

	Arterial phase	Portal phase	Late phase
Hemangioma	Peripheral discontinuous nodular hyperenhancement with centripetal filling. Small lesion may rapidly and completely enhance	Slow centripetal filling	Complete filling. Iso or hyperenhanced. Can have non-enhancing component
Focal nodular hyperplasia	Hyperenhanced in the center of the lesion (central vessel) with fast centrifugal filling due to radial vascular branches: ''spoke-wheel sign''	Iso or hyperenhanced. May have central area of non-enhancement: ''central scar''	Iso or hyperenhanced. Sometimes the unenhanced central scar can be seen
Adenoma	Hyperenhanced with complete or near complete filling	Iso or hyperenhanced, may have regions of non-enhancement	Iso or hyperenhanced, may have delayed washout
Cyst	No enhancement	No enhancement	No enhancement
Abscess	No enhancement centrally, rim may have irregular enhancement	No enhancement centrally, rim may have irregular enhancement	No enhancement centrally, rim may have irregular enhancement
Focal fat	Isoenhanced	Isoenhanced	Isoenhanced

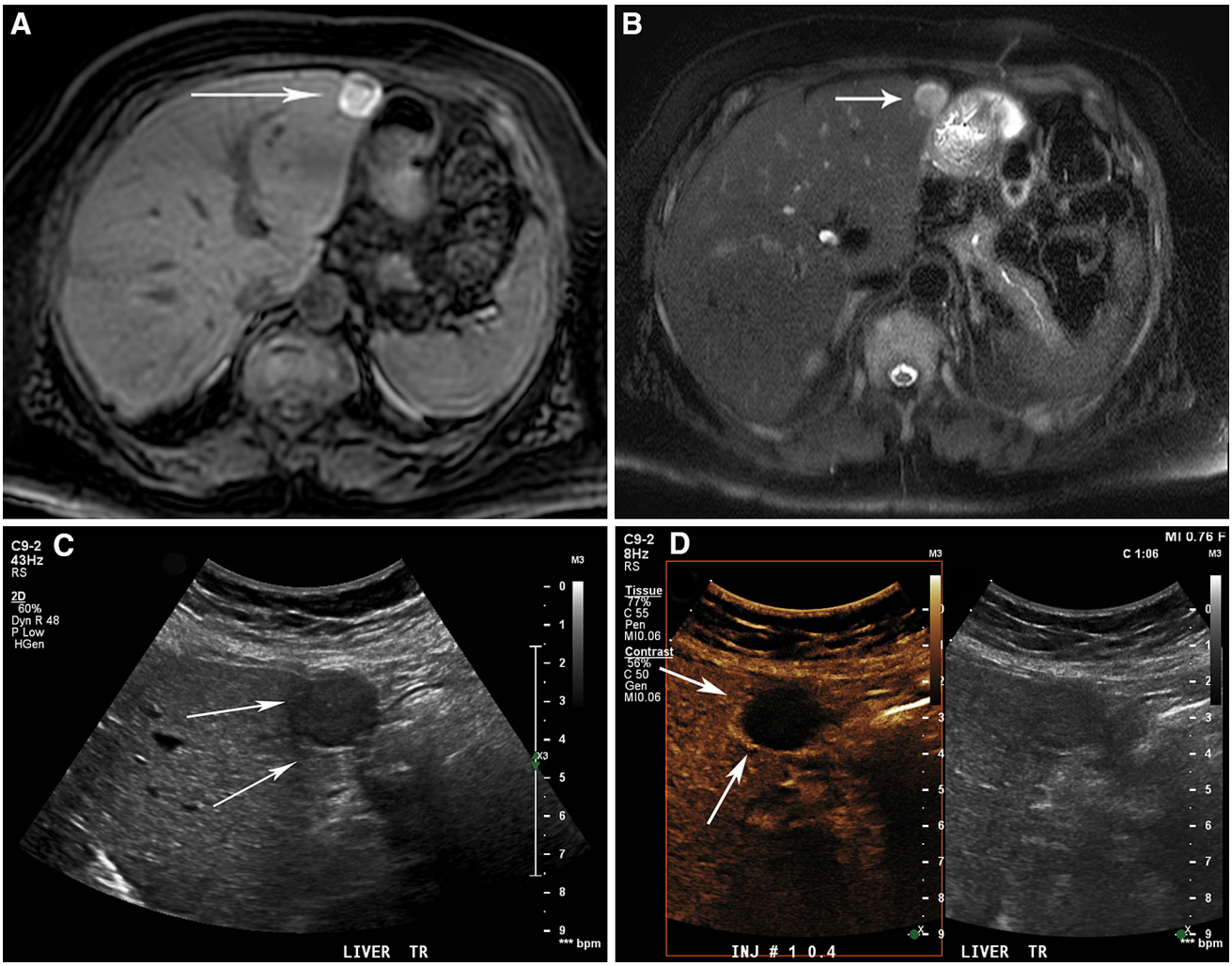

Fig. 1. Benign liver cyst. 79-year-old female with multiple myeloma and multiple liver lesions, imaged to evaluate for metastatic disease within the liver. Two lesions in the liver were indeterminate on CT and MRI. **A**, **B** Lesion within the lateral segment left hepatic lobe (arrow) with high signal on precontrast T1 (**A**) and T2 SPAIR MR (**B**). This lesion had restricted diffusion and possible mild enhancement (not shown); the examination was limited by motion. Findings favored a hemorrhagic cyst; however, this lesion was indeterminate on MR, given limitations. **C** Hypoechoic lesion (arrows) had internal echoes within on gray scale US, indeterminate. **D** Hypoechoic lesion (arrows) without enhancement with CEUS.

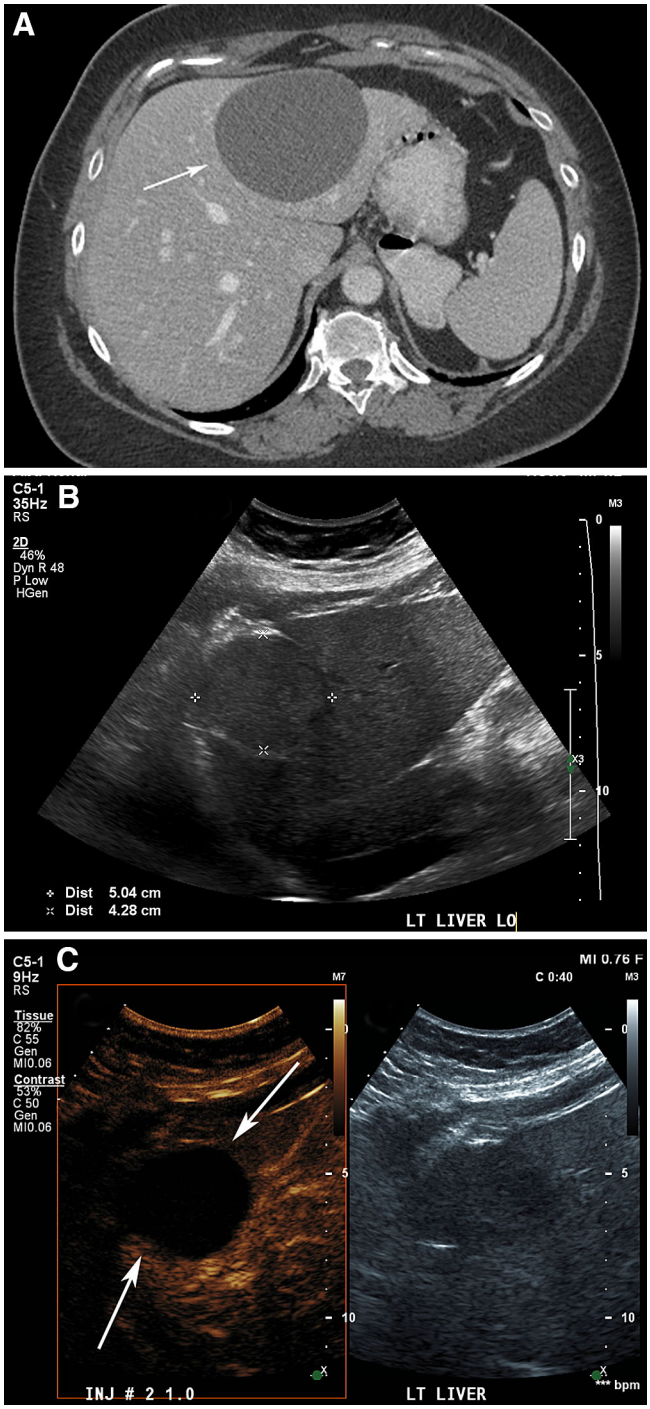

Fig. 2. Benign liver cyst. 55-year-old woman with hepatic mass. **A** Large cyst in left lobe (arrow) on CT measuring 23 HU, indeterminate. **B** Complex cyst (cursors) on gray scale US, with innumerable internal echoes, indeterminate. **C** No enhancement on CEUS (arrows).

complete non-enhancement within the cyst during all phases of the exam [9] (Fig. 1). However, there can be some overlap in the appearance between benign cysts and malignant lesions with cystic components, and CEUS may be useful for distinguishing these two possibilities.

Complex cysts can have a variable appearance, but CEUS findings suggestive of benignity include the absence of internal enhancement and the lack of persistent septal or nodular enhancement in the venous phase. Internal enhancement or persistent septal or nodular enhancement can be seen in cystadenomas or abscesses [10]. A typical pyogenic abscess appears as a hypoechoic lesion on gray-scale ultrasound with thick or irregular walls and usually has a peripheral rim of contrast enhancement surrounding the central necrotic component [11]. CEUS findings of malignancy are arterial enhancement of the septations or mural nodularity with rapid washout in the portal and late phases, which can be seen with a cystadenocarcinoma or cystic metastasis [9, 10].

The echogenic debris seen within a complex hemorrhagic cyst on gray-scale ultrasound may mimic a cystic metastasis or biliary cystadenocarcinoma [10]. CEUS can be useful for distinguishing these entities, as no enhancement will be seen within the debris of the hemorrhagic cyst [12] (Fig. 2). Similar to other cross-sectional imaging, CEUS cannot reliably distinguish between a cystadenoma and a cystadenocarcinoma, but the presence of large (> 1 cm) enhancing nodules is suggestive of malignancy [10].

Hemangioma

A hemangioma is the most common benign liver neoplasm and is generally straightforward to characterize using imaging. At gray-scale ultrasound, a hemangioma appears as a solid, homogeneous, hyperechoic lesion and may have posterior acoustic enhancement [3]. At CEUS, there is peripheral discontinuous globular enhancement in the arterial phase with centripetal filling in the portal and late phases [4], similar to the appearance on contrast-enhanced CT or MR (Fig. 3). The fill-in appears complete in 40–50% of the cases [13]. The combination of peripheral nodular enhancement with complete fill-in has 98% sensitivity for the diagnosis of a hemangioma [14]. In small lesions, the whole lesion may enhance in the arterial phase and may remain hyperenhancing or isoenhancing, but never hypoenhancing in the portal and late phases [6]. The finding of sustained enhancement in the portal and late phases is the most reliable finding of a benign lesion [3]. CEUS is also useful for evaluation of hemangiomas that are atypical in appearance on conventional ultrasound [15] (Fig. 4).

Focal fatty infiltration and focal fatty sparing

Fatty change in the liver can manifest in several distinct patterns: diffuse, geographic, focal, subcapsular, multifocal, and perivascular [16]. The most common site for focal fatty change is adjacent to the falciform ligament

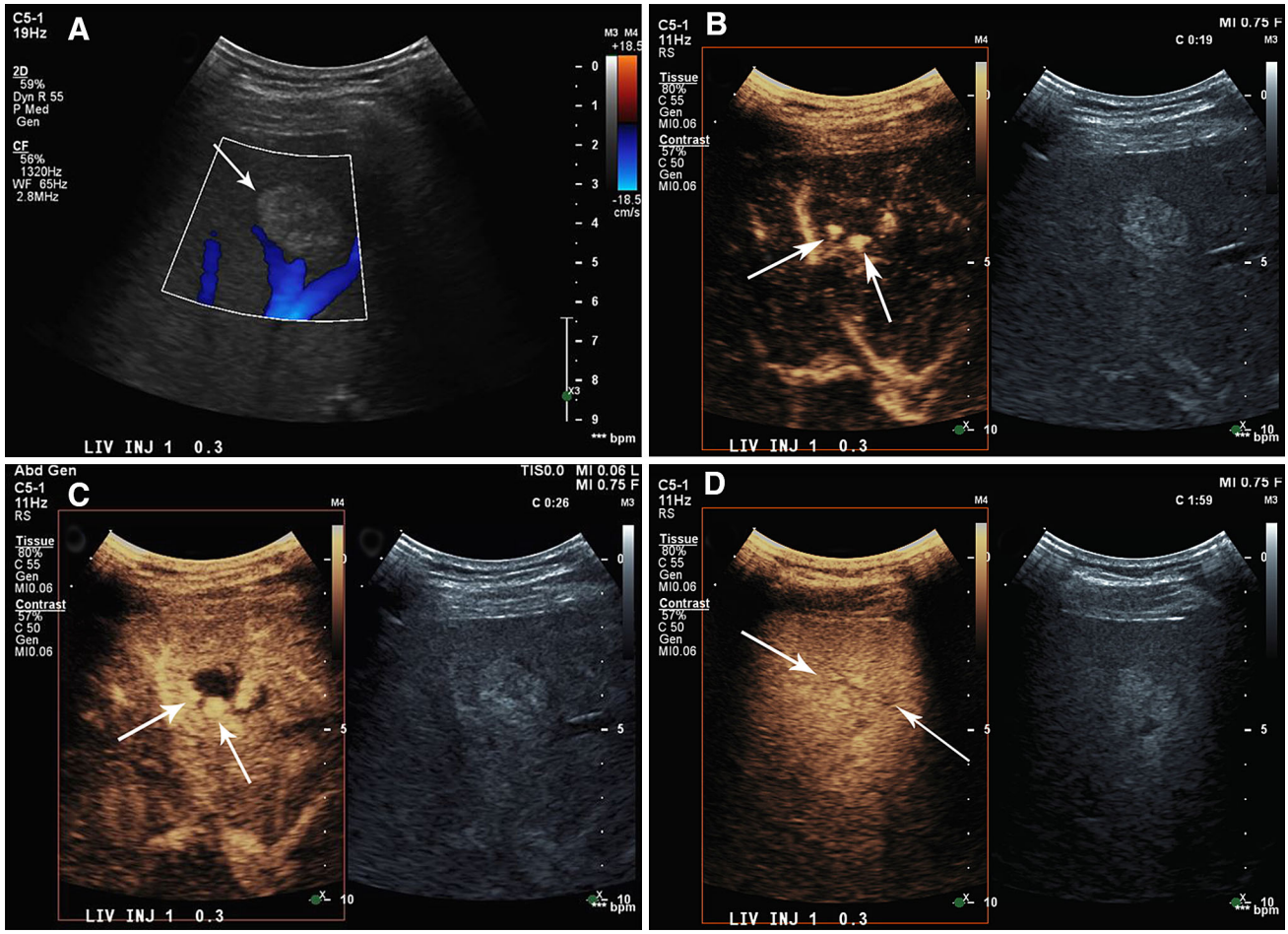

Fig. 3. Hemangioma 71-year-old male with left lower quadrant pain. CT (not shown) showed possible enlargement of posterior segment right lobe liver lesion, characterized as most typical of hemangioma on CT from several years prior. **A** US with color Doppler showed a hyperechoic lesion (arrow) without internal vascularity. **B** Arterial phase CEUS shows peripheral nodular discontinuous enhancement of lesion (arrows). **C** Portal venous phase CEUS showed gradual centripetal fill-in of lesion (arrows). **D** Lesion showed complete enhancement at 2 min (arrows), without washout on delayed phase (not shown).

and is related to alterations in venous supply [17]. However, when the focal fat is in an unusual location or unusual morphology (nodular or multifocal), it can mimic malignancy and pose a diagnostic dilemma. Chemical shift gradient-echo MR is a useful tool for evaluating focal fat with corresponding loss of signal in opposed phase acquisitions [18]. As there are many individuals who cannot undergo MR secondary to claustrophobia or metallic implants, among other reasons, CEUS provides a low-cost alternative for distinguishing focal fat.

Focal fat appears hyperechoic on gray-scale ultrasound as steatotic liver [19, 20]. Focal fatty deposition or fatty sparing does not produce mass effect and has a geographic margin, with undisturbed vessels traversing through the lesion [19, 20]. On CEUS, focal fat or focal fatty sparing generally enhances similar to the surrounding liver parenchyma [3, 21] (Fig. 5). In a study of 25 areas of focal steatosis in 20 patients, 44% demonstrated hypoenhancement, 44% demonstrated isoenhancement, and 12% demonstrated hyperenhancement in the arterial phase [22]. Importantly, all areas of focal fat were homogeneously isoenhancing in the portal venous and late phases, and could not be differentiated from the adjacent parenchyma [22]. Utilization of conventional ultrasound with Doppler to characterize focal fat had 44% sensitivity and 97% specificity (81% accuracy), with CEUS increasing the sensitivity to 88% and the specificity to 100% (96%) accuracy [22].

Focal nodular hyperplasia (FNH)

FNH is the second most common benign neoplasm of the liver and the most common in women between 30 and 50 years old. FNHs are hamartomas, composed of normally functioning hepatocytes, and classically display a central scar. Histologically, FNH is characterized by malformed blood vessels, proliferation of small bile ducts, and nodular architecture [23]. Because of their benign nature, FNHs are typically treated conservatively if the diagnosis can be reliably made by imaging or

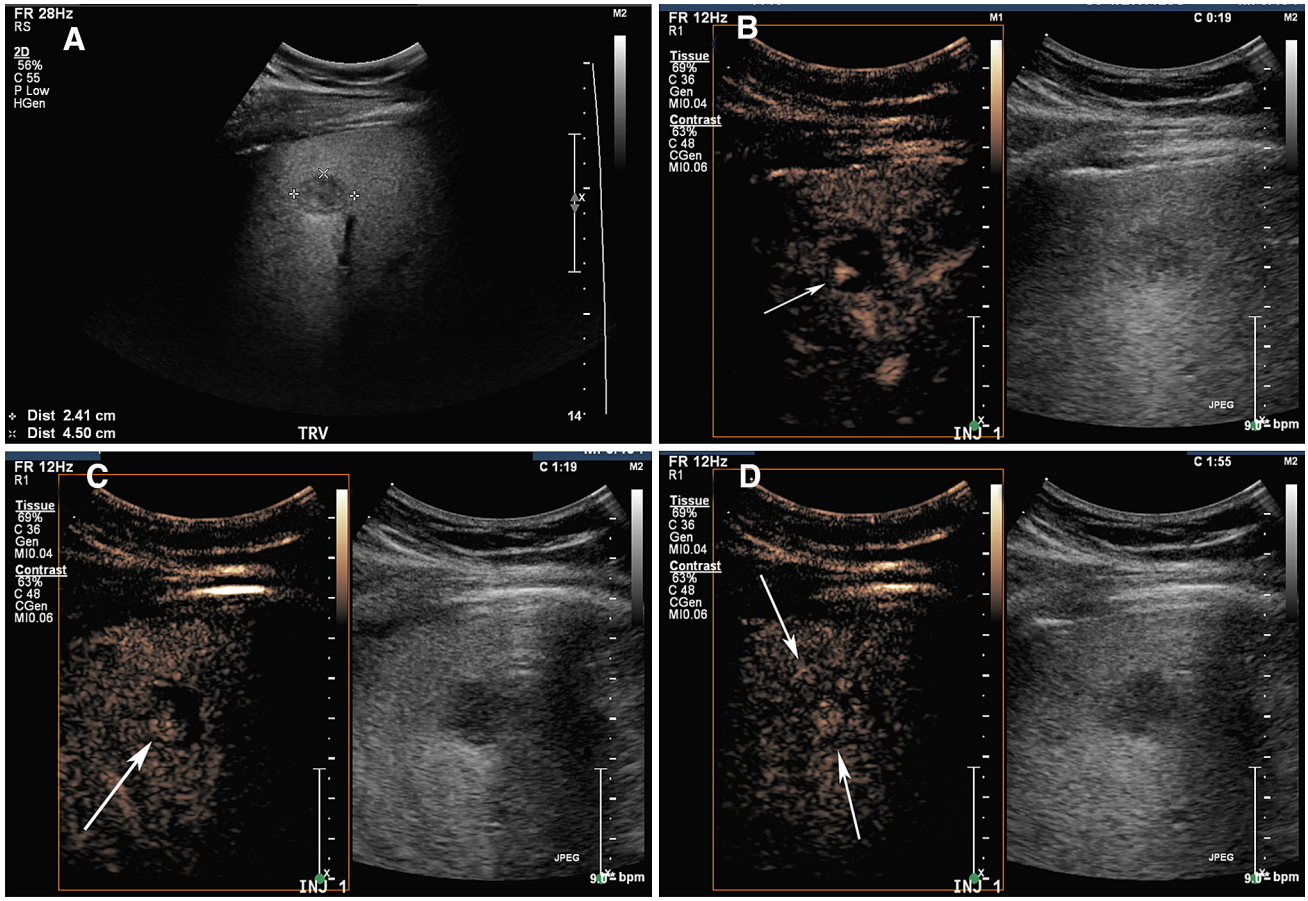

Fig. 4. Atypical hemangioma. 27-year-old male with elevated liver function tests and liver lesion on US. **A** Hypoechoic liver lesion (cursors) in the background of severe steatosis. **B** Arterial phase enhancement shows peripheral nodular discontinuous enhancement (arrow). **C** PV phase shows slightly more centripetal enhancement (arrow) **D** Delayed phase shows near complete enhancement of lesion, without washout (arrows).

pathology. FNHs are characterized by a central feeding artery that branches and then supplies the mass centrifugally [24]. The gray-scale sonographic appearance of FNH is non-specific [3]. FNH may be isoechoic to slightly hypoechoic with respect to the adjacent liver parenchyma on gray-scale ultrasound, and therefore may be difficult to detect unless they are large or displace normal structures [3]. In the setting of diffuse hepatic steatosis, FNH may appear more hypoechoic than the background echogenic fatty liver [25]. The central vessel radiating from the center can sometimes be identified at color Doppler US [3].

A spoke-wheel pattern of arterial enhancement is considered to be a specific sign of FNH [26]. On contrast-enhanced CT, FNHs typically have arterial hyperenhancement with relative isoenhancement in the later phases. Contrast-enhanced MR with a hepatobiliary agent (such as gadobenate dimeglumine or gadoxetate disodium) has an optimal sensitivity (97%) and specificity (100%) for FNH [27, 28].

With the use of CEUS, FNHs are characterized by centrifugal vascularity with sustained enhancement in the portal and late phases [7, 29–31]. The spoke-wheel sign with a central feeding artery has been shown to be a specific finding of FNH [26, 32] (Fig. 6). Specificity for the diagnosis of FNH by CEUS is high (100%), but sensitivity varies based on lesion size (93% for lesions > 3.5 cm and only 7.7% for lesions < 3.5 cm) [33]. Nevertheless, the centrifugal filling is more commonly associated with FNHs < 3 cm, as larger lesions may have increased vascular supply and several feeding arteries [31]. Kim et al. evaluated 43 FNHs with CEUS and found centrifugal filling in the arterial phase (74–91% of the lesions), stellate arteries (60–67% of the lesions), and sustained late phase enhancement (86–91% of the lesions) [7]. In another study of 28 FNHs with CEUS, 42% had centrifugal arterial enhancement, 42% had homogeneous arterial enhancement, 17.9% had spoke-wheel enhancement, and 17.9% had a central scar [30].

When compared to hepatocellular adenomas (HCA), FNHs are more likely to demonstrate isoenhancement in the later phases, whereas HCAs are more likely to become hypoenhancing (10.7% vs. 60%, respectively) [30].

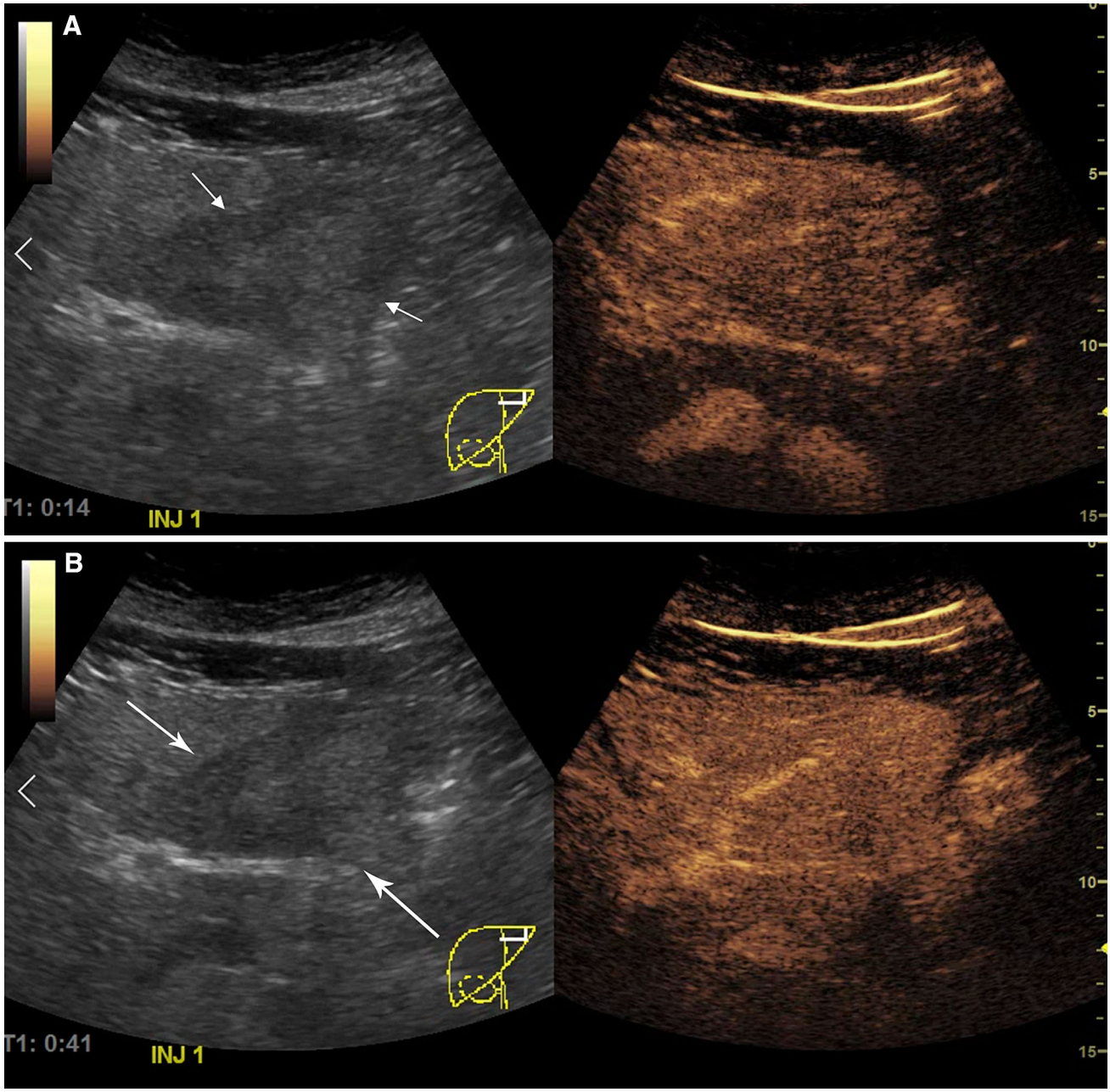

Fig. 5. Focal fatty sparing in a moderately steatotic liver. 40-year-old woman with right upper quadrant pain. Gray-scale US showed geographic hypoechoic area in the left lobe liver, on a background of moderate hepatic steatosis. **A**, **B** Hypoechoic area on gray scale images (arrows) enhances similarly to adjacent liver on arterial (**A**) and portal venous phase (**B**), as well as delayed phase (not shown).

A minority of FNHs demonstrate washout in the portal and late phases and would be considered atypical [7, 30, 31].

A central scar is a characteristic and specific finding of FNH. Because of the fibrous nature of the central scar, it shows sustained enhancement on CT or MR in the portal or late phases due to the diffusion of contrast material into the stroma [34]. The central scar in FNH is not well depicted by gray-scale US, but visualization can be improved with CEUS [30]. Due to the intravascular properties of ultrasound contrast agents, the central scar remains hypoechoic (non-enhancing) during the portal and late phases, as the US contrast will not penetrate into the interstitial space. In smaller FHNs less than 3 cm, the central scar may be less conspicuous [26].

Other liver lesions may have the appearance of a central scar on CEUS (oftentimes related to central necrosis), including fibrolamellar hepatocellular carci-

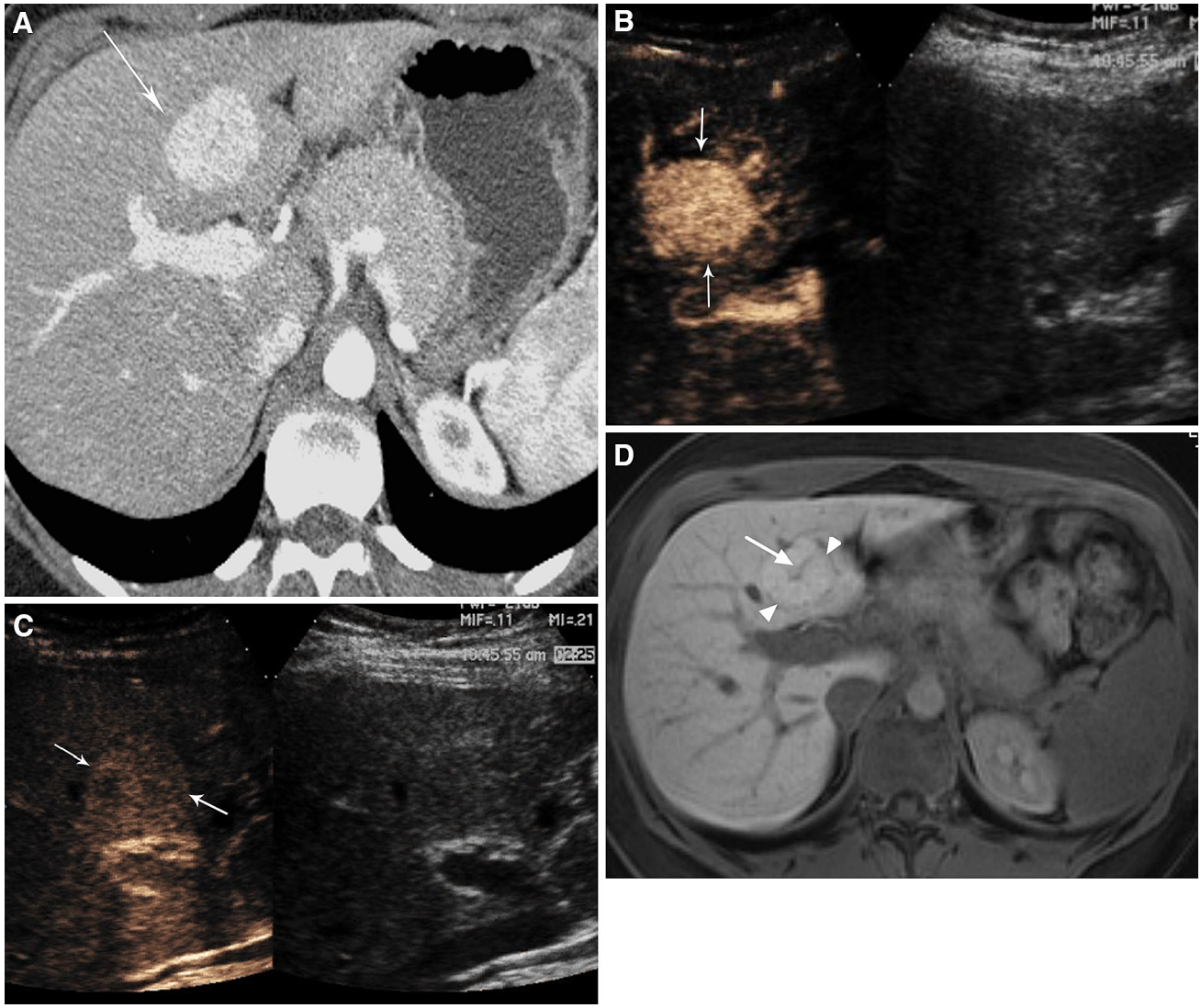

Fig. 6. Focal nodular hyperplasia 25-year-old female presented to the emergency room with right lower quadrant pain. **A** Single-phase contrast enhanced CT showed an enhancing mass in the medial segment of the left lobe of the liver. FNH was suspected and CEUS was subsequently performed. **B** CEUS showed characteristic centrifugal hyperenhancement pattern in the arterial phase. **C** Lesion is isoenhancing to liver on portal venous phase (not shown), and does not wash out on the late phase (arrows). **D** A central scar (arrow) and retention of contrast in the lesion (arrowheads) was seen on delayed T1 fat-suppressed MRI with Eovist.

noma (HCC) and sclerosing or scirrhous HCC. Fibrolamellar HCC is more likely to be large (average size 13 cm) with a lobulated margin [35]. Sclerosing HCC is more likely to have focal atrophy with retraction of the liver surface and contains calcification [24]. Similarly, while the spoke-wheel sign has been shown to be specific for FNH, caution is warranted in the setting of hepatitis and cirrhosis, as scirrhous or trabecular HCC may also have a spoke-wheel sign [26]. Trabecular HCC produces abundant fibrous stroma that separates cords of tumor cells and may demonstrate prolonged central enhancement on CT or MR [36, 37].

Hepatocellular adenoma (HCA)

HCAs are the third most common type of benign liver neoplasm. They occur more commonly in women taking estrogen-containing contraceptives. When HCAs become larger than 5 cm, surgery may be indicated due to the risk of hemorrhage and possible malignant transformation [34]. Subcapsular feeding arteries characterize HCAs and account for the centripetal blood flow into the lesion [38].

Four distinct histologic variants of HCAs have been described [39, 40]. Inflammatory HCAs are most common and tend to have arterial enhancement with an in-

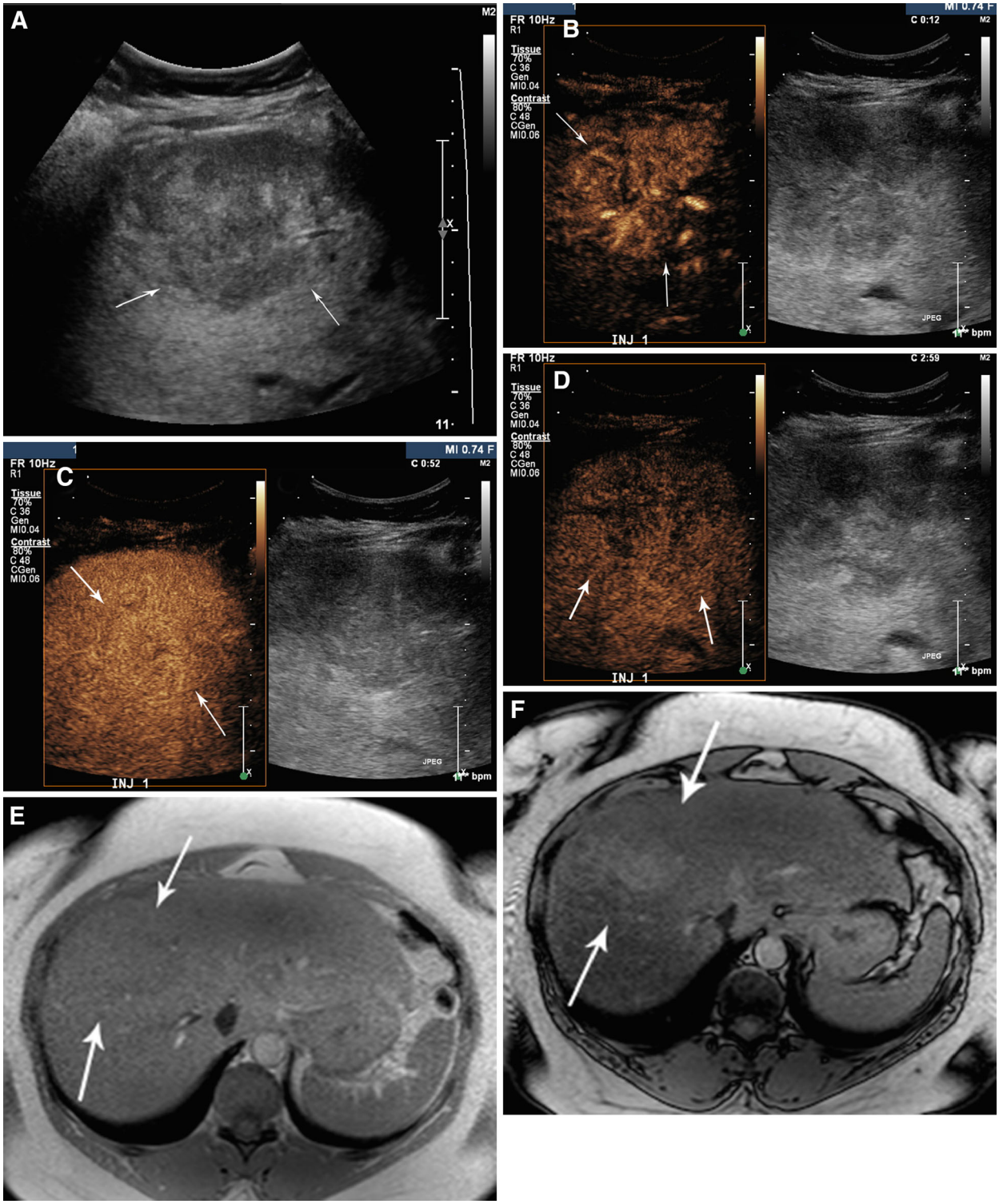

Fig. 7. Adenoma 49-year-old female with elevated alkaline phosphate with liver lesion found on US. 3 phase CT was non-specific. **A** Gray scale US show heterogeneous predominately hypoechoic, ill-defined right lobe lesion (arrows) on a background of moderate steatosis, without cirrhotic-morphology. **B** Early arterial CEUS image shows lesion (arrows) is hypervascular with regards to adjacent liver. **C**, **D** Lesion is isoechoic on CEUS PV (arrows, **C**) and shows partial washout on CEUS late phase, at 3 min (arrows, **D**). **E**, **F**. MRI showed arterial enhancement, diffusion restriction, and does not retain Eovist contrast on delayed sequences (not shown). This lesion is not well seen on T1 in phase images (arrows, **E**), and shows loss of signal on out of phase imaging (arrows, **F**), consistent with intra-lesional fat.

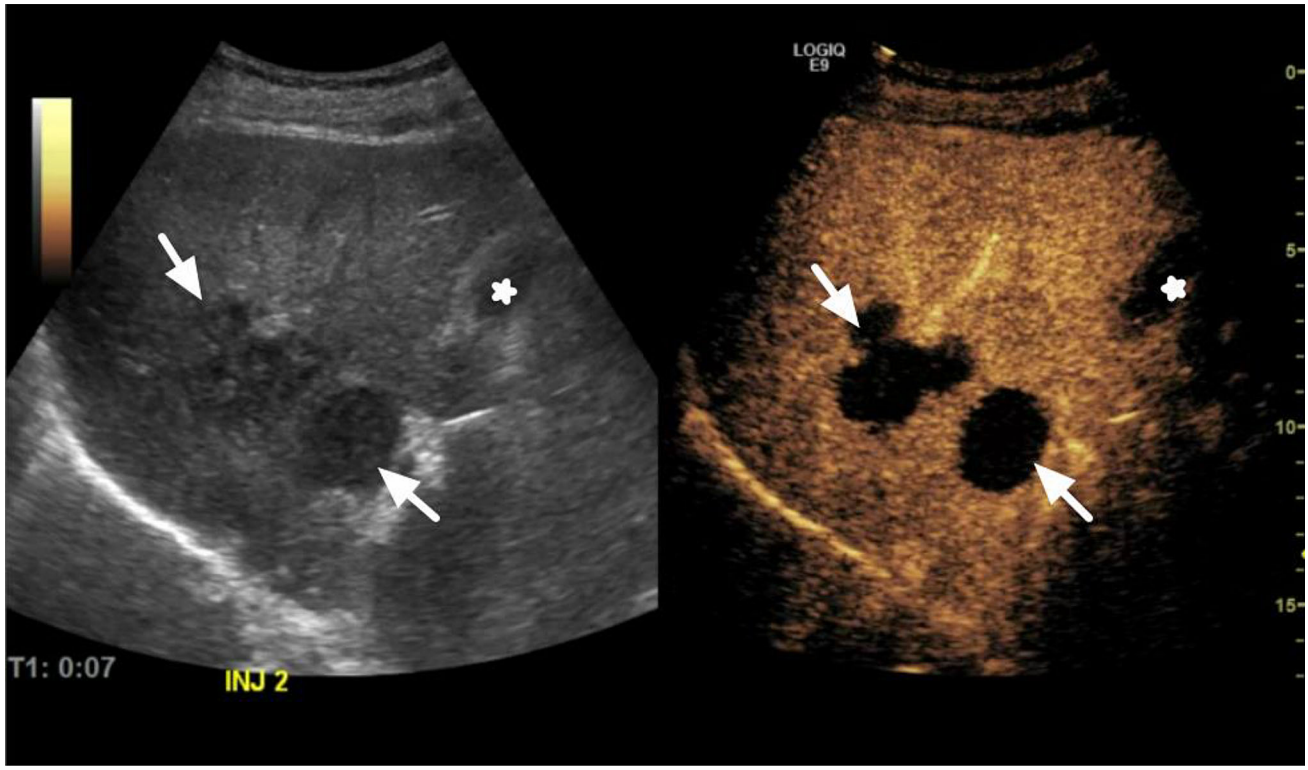

Fig. 8. Liver abscesses 65-year-old man with abdominal pain and fever underwent CT scan of the abdomen without contrast due to renal impairment. The CT (not shown) showed ill-defined hypoattenuating liver lesions that were not fully characterized. Hypoechoic areas within the liver containing internal echoes were seen on the grayscale image (left hand image). Portal venous phase CEUS (right hand image) showed absent flow within the areas of hypodensity seen previously on the CT. No enhancement was seen in these areas in all phases of the CEUS study.

creased propensity to bleed. They are associated with obesity, hepatic steatosis, and alcohol and may undergo malignant transformation into HCC. The second type is HCAs with HNF-1-α mutation and is associated with adenomatosis. These HCAs typically contain fat. The third type of HCA has a β-catenin mutation and has a high risk of HCC transformation. These HCAs are associated with glycogen storage disease and male hormone excess. The fourth type is unclassified without characteristics to fit in the other groups. Because of the spectrum of genetic and pathologic variation, the imaging appearance of HCAs is variable [40].

The characteristics of HCA at CEUS include visualization of subcapsular feeding arteries in the arterial phase, centripetal filling in the late arterial and portal venous phase, and isoenhancement or hypoenhancement in the late phases [30, 41]. In a study that evaluated 19 HCAs with CEUS, HCAs were characterized by centripetal or mixed arterial filling (84% of lesions) and were more likely than FNH to have washout or hypoenhancement in the late phase (37–53% of lesions) [7]. While hypoenhancement in the portal venous and late phases is a feature suspicious for malignancy [5], several studies have shown a considerable number of HCAs with washout in the late phase [7, 8, 30] (Fig. 7). Any lesion with washout in the portal venous or late phase should be regarded as suspicious (needs follow-up or biopsy) as both HCC and HCA may have this feature [7]. Some HCAs may have a small amount of central necrosis that may be erroneously diagnosed as a central scar [7].

Laumonier et al. evaluated the inflammatory and HNF1α-inactivated HCA subtypes with CEUS [41]. The HNF1α-inactivated HCA was homogeneously hyperechoic at gray-scale sonography, was isoenhancing to hypervascular with mixed filling in the arterial phase, and was isoenhancing in the late phase [41]. Increased echogenicity of the lesion on gray-scale ultrasound was the most specific characteristic and due to the fatty nature of the tumor (91% specificity) [41]. The inflammatory HCA was more likely to have arterial hyperenhancement with centripetal filling, a peripheral rim of enhancement, and late washout [41]. Another study evaluation of the subtypes of HCAs showed a minority of both inflammatory and HNF1α-inactivated HCA demonstrated washout [42]. No specific features were seen in the β-catenin activated or unclassified subtypes of HCA [41]. Unlike the faster washout in metastatic lesions, the timing of the washout in HCAs is more often

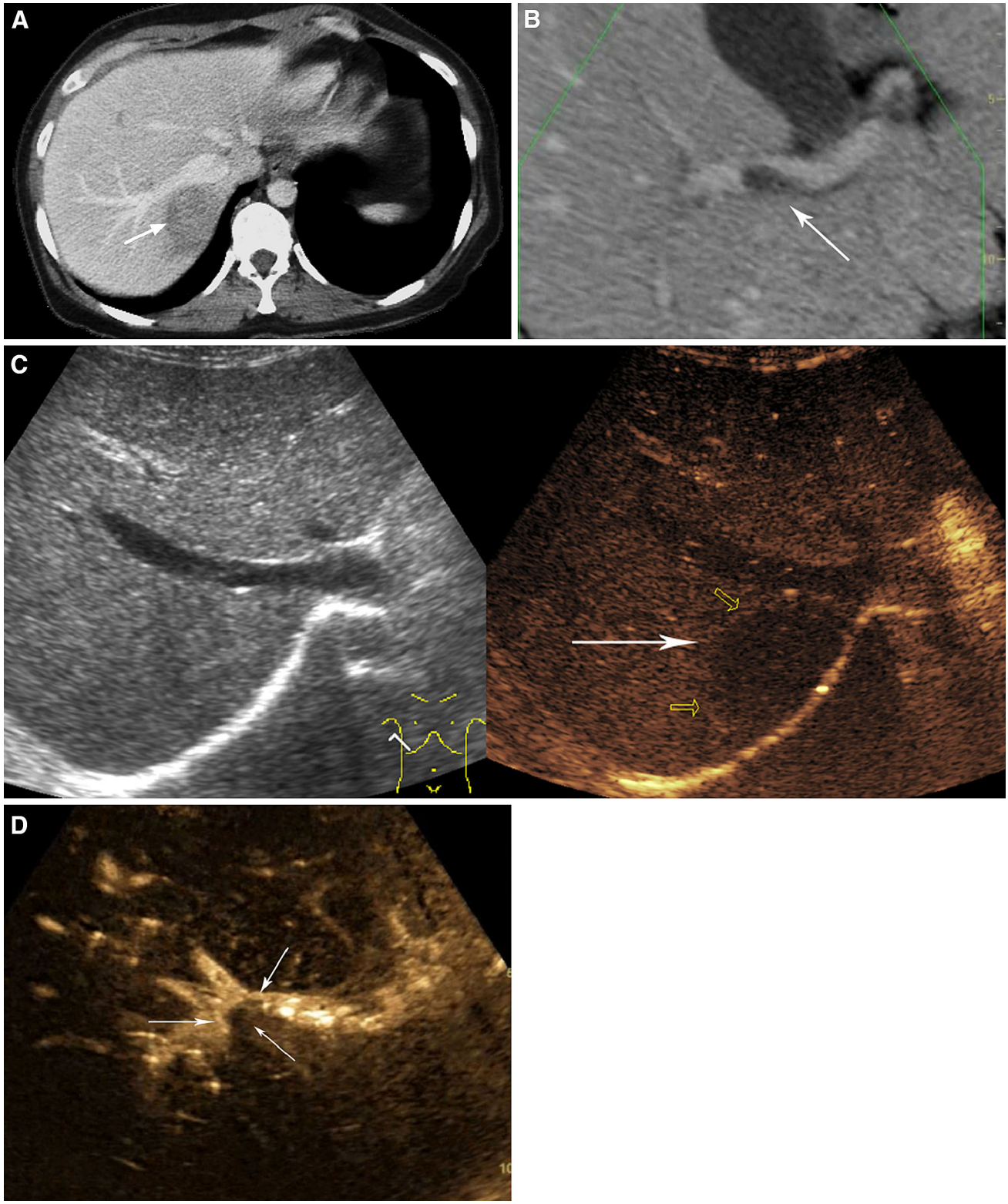

Fig. 9. Portal vein pylephlebitis and hepatic abscess. 55-year-old female with vague abdominal pain. **A**, **B** CT scan of the abdomen showed ill-defined hypodensity in the posterior right lobe of the liver (**A**, arrow) with thrombus in the right portal vein (**B**, arrow), concerning for metastatic disease. Ultrasound guided biopsy of the mass was requested. A CEUS study was performed prior to biopsy to confirm the diagnosis. **C** No enhancement of the lesion was seen on CEUS on the arterial, portal venous or delayed phase (arrows), not consistent with metastasis. **D** Small non-occlusive non-enhancing bland thrombus in the right portal vein (arrows) was also present on CEUS. These findings were consistent with portal vein pylephlebitis and hepatic abscess.

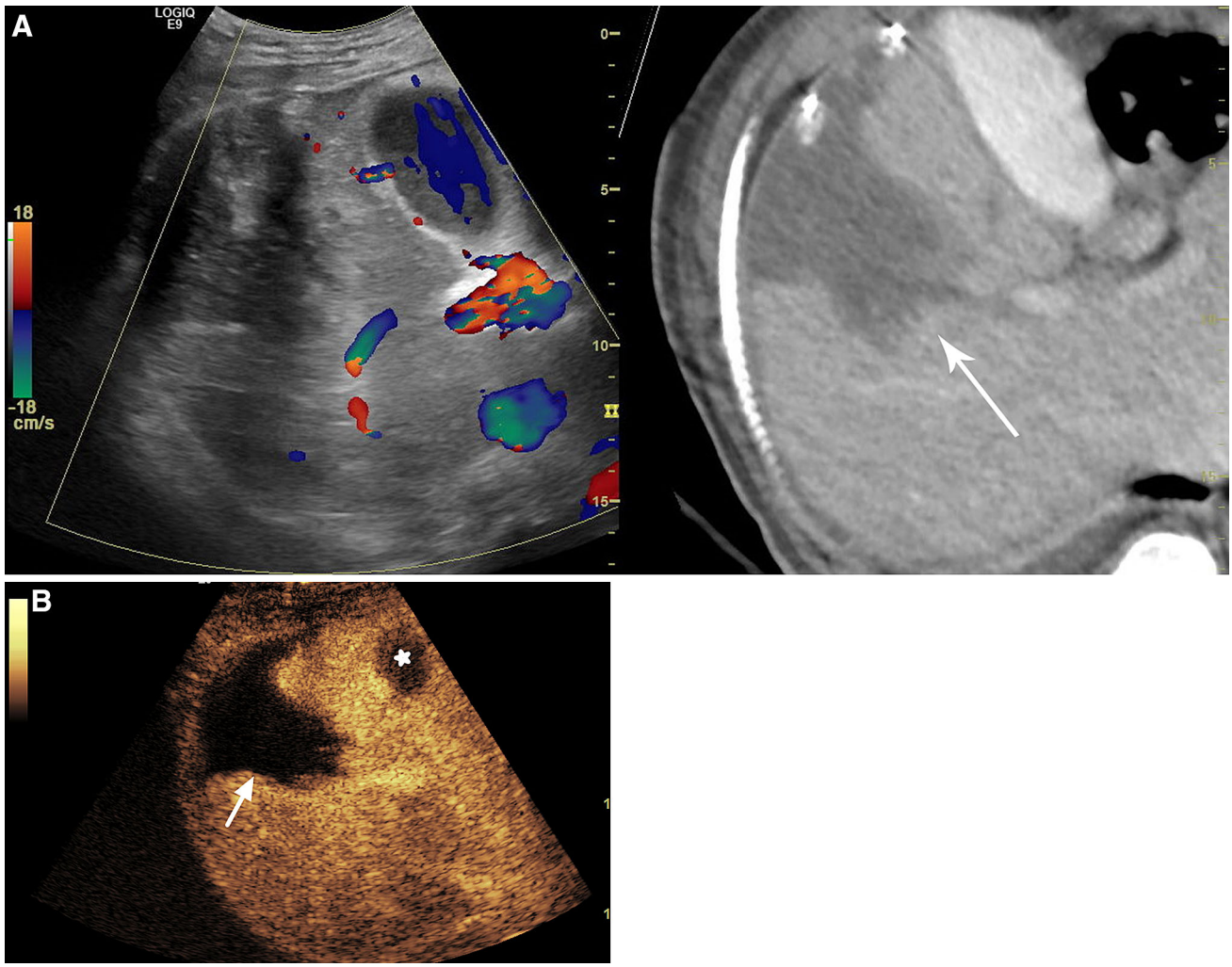

Fig. 10. Liver laceration/intraparenchymal hematoma 36-year-old male with recent MVC with large liver laceration. CT scan on presentation showed large area of devascularization in the right lobe of the liver. Follow-up CEUS was requested to evaluate for pseudoaneurysm. **A** US/ CT Fusion technology was used for exact localization of the injury (arrow). **B** Dynamic CEUS showed the devascularized area in the liver (arrow) corresponding to the CT finding, with no evidence of pseudoaneurysm (* = gallbladder).

observed in the late phase than in the portal venous phase [41]. There is an overlap in the CEUS appearance of inflammatory HCA and well-differentiated HCC, both demonstrating arterial enhancement and delayed washout [41]. However, inflammatory HCA is more likely to have a rim of enhancement at CEUS [2, 41, 43].

Abscess

Contrast ultrasound is instrumental in the evaluation of patients with renal failure when contrast CT cannot be performed to establish the diagnosis of abscess and exclude other entities like tumors, especially in the patient with a history of malignancy. Occasionally, characterization of abscesses solely by gray-scale ultrasound or non-contrast CT may be challenging due to the mass-like appearance of these abscesses. On gray-scale ultrasound, abscesses have a variable appearance due to the degree of internal liquefaction. The typical hepatic abscess cavity will not have significant internal enhancement after contrast ultrasound administration in either the arterial, portal venous, or late phases. Enhancing septations can be seen within the abscess, depending on the age and inflammatory response [44]. There is generally irregular rim enhancement of the abscess cavity in the arterial and portal venous phases with the possibility of hyperenhancement in the surrounding liver parenchyma (thought to be due to perilesional hyperemia) [44]. In the late phase, the rim becomes hypoenhancing and there continues to be a lack of central enhancement. [44] (Figs. 8, 9). Infected granulomas may be hyper or isoenhancing in the arterial

phase, generally washing out in the portal and late phases, overlapping the flow characteristics of malignancy, and may need biopsy for further evaluation [45].

Trauma

Gray-scale ultrasound is often used in the early assessment of polytrauma primarily due to its ability to detect free intraperitoneal fluid, but can also be used for the assessment of solid organs. The addition of contrast-enhanced ultrasound has been shown to be more useful in the detection and characterization of liver injury when compared to gray-scale ultrasound [46, 47]. A liver laceration appears as a sharply demarcated, non-enhancing defect, an intraparenchymal hematoma is non-enhancing but with less well-defined rounded boarders, and a subcapsular hematoma is non-enhancing with lenticular boarders at the periphery of the liver. Active contrast extravasation can be recognized by visualizing microbubbles extravasating into the peritoneum or retroperitoneum [48]. A pseudoaneurysm appears as focal intraparenchymal lobular region with microbubbles circulating within it [49]. If the patient is stable without evidence of active bleeding or pseudoaneurysms, then a follow-up CEUS of the solid organ injury can be performed prior to discharge as follow-up, and to exclude late development of pseudoaneurysms [50, 51]. CT fusion technology during the contrast ultrasound is useful for precise localization of the area of laceration (Fig. 10). The use of CEUS is not only beneficial to make the diagnosis, but also eliminates the need for a second CT scan with contrast thus avoiding radiation exposure, and the potential nephrotoxic side effects of iodinated contrast, of particular importance in pediatric patients.

Conclusion

CEUS is a valuable tool for investigating focal liver lesions and may obviate the need for further imaging and biopsy of some benign lesions. At CEUS, a general finding for a benign liver lesion is one that has arterial enhancement and becomes isoenhancing or remains hyperenhancing in the portal and late phases [4]. Delayed washout is a feature of malignancy that should prompt biopsy; however, this characteristic is also sometimes seen with inflammatory HCAs. In the setting of hepatic cirrhosis, one must have a high suspicion for HCC, as FNH and adenomas are extremely rare in the setting of cirrhosis. CEUS has a high safety profile and is relatively inexpensive. When an incidental lesion is detected on gray-scale ultrasound, CEUS can be employed and may decrease the need for further follow-up.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was waived for the purposes of this review article.

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