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Case Report

Contrast-enhanced ultrasound in the diagnosis of infiltrative hepatocellular carcinoma: A report of three cases ☆,☆☆

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ABSTRACT

Infiltrative hepatocellular carcinoma (HCC) is a challenging imaging diagnosis due to its ill-defined appearance and variable enhancement, which may be difficult to distinguish from background changes from cirrhosis. The literature on the role of contrast-enhanced ultrasound (CEUS) in the diagnosis of infiltrative HCC is currently limited. CEUS has greater sensitivity for contrast enhancement due to its temporal resolution, and can be used when there is contraindication to CT or MRI contrast. We present 3 cases where CEUS aided in the diagnosis of infiltrative HCC in patients with equivocal CT and MRI findings and/or renal failure, with significant implications for management. As current guidelines focus on the role of CEUS in characterizing defined focal liver lesions or discrete observations on pre-contrast US, further studies are warranted to validate the utility of CEUS in the noninvasive diagnosis of infiltrative HCC and delineate its role in algorithms for imaging workup.

Introduction

Hepatocellular carcinoma (HCC) ranks as the fifth most common neoplasm worldwide and is the third leading cause of cancer-related mortality [1]. More than 20% of patients with cirrhosis may develop HCC over a 10-year period [1]. HCC is classified based on pathological characteristics into nodular, massive, and infiltrative [2]. Of these, the infiltrative subtype makes up 7%-13% of all HCC but carries an especially poor prognosis due to often late diagnosis and incompatibility with surgical resection or locoregional treatments such as radiofrequency ablation [3].

As such, timely diagnosis of infiltrative HCC can have major implications for management. However, infiltrative HCC in particular presents a diagnostic challenge due to its

Abbreviations: CEUS, Contrast-enhanced Ultrasound; HCC, Hepatocellular Carcinoma; AKI, Acute Kidney Injury.

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ill-defined appearance on imaging and difficulty distinguishing it from underlying cirrhotic changes on routine ultrasound, contrast-enhanced CT, or MRI [2]. Additionally, the routine use of contrast-enhanced CT or MRI for routine screening in this patient population may be contraindicated due to underlying comorbidities and concomitant renal impairment.

Contrast-enhanced ultrasound (CEUS) utilizes intravenously injected microbubble contrast agents and contrast specific software to produce real-time images. The primary advantage of CEUS is its capacity to directly visualize changes in regional perfusion over time and therefore yield additional diagnostic information important to the diagnosis of HCC [4]. CEUS is now a widely accepted imaging technique for a variety of applications, including the diagnosis of HCC, and was added to the American College of Radiology Liver Imaging and Data Reporting System (LI-RADS) in 2016 [5]. However, as most published studies have focused on discrete observations visible on precontrast ultrasound, there remains a gap in the literature and in current guidelines on the potential role of CEUS in the imaging of infiltrative HCC in particular.

Here, we present 3 cases of infiltrative HCC where CEUS findings improved confidence in diagnosis, and proved an especially valuable tool in patients with renal failure or equivocal diagnoses with other imaging modalities. All CEUS examinations were performed according to the standard technique described in the CEUS LI-RADS technical recommendations, utilizing a curved 5-1 MHz transducer (Philips; Bothwell, WA, USA) and Definity (Lantheus; Billerica, MA, USA) contrast agent (which is approved for imaging of the liver in Canada) [5]. Informed consent was provided by patients as part of routine clinical care.

Case descriptions

Case 1

A 64-year-old male with a history of nonalcoholic steatohepatitis and decompensated cirrhosis presented to clinic with persistent diarrhea and refractory ascites. He showed clinical signs of severe dehydration and acute kidney injury with creatinine rising to 258 μmol/L, and was therefore admitted directly to the hepatology unit. During his workup, a grayscale ultrasound revealed a nodular liver with a large, ill-defined and geographic hypoechoic area in the right hepatic lobe (Fig. 1A). Due to the renal failure, further characterization of the lesion was attempted though an unenhanced CT scan, which showed an ill-defined region of hypoattenuation and heterogeneity in the corresponding region of the right hepatic lobe (Fig. 1B). As his condition worsened, the patient experienced massive variceal hemorrhage, resulting in worsening renal function despite multiple transfusions.

As such, CEUS was performed and demonstrated a large area of early arterial hyperenhancement, corresponding to the hypoechoic region in the right hepatic lobe (Figs. 1C and D). There was corresponding subtle washout in this region during the delayed phase, most concerning for infiltrative HCC (Fig. 1E). In addition, there was echogenic thrombus in the portal vein, which demonstrated early arterial enhancement prior to contrast filling the lumen of the portal vein, consistent with tumor thrombus or tumor in vein (Fig. 1D).

A contrast-enhanced MRI was eventually carried out when the patient's renal function stabilized 1 week later. The MRI revealed similar findings of heterogeneous hyperenhancement of an ill-defined area of the right lobe during the arterial phase with subsequent washout in the delayed phase, as well as thrombus in the right portal vein (Figs. 1F,G), consistent with infiltrative HCC. Transjugular liver biopsy confirmed the presence of moderately differentiated HCC. Given the patient's decompensated state and infiltrative nature of the disease, he was not a candidate for transplantation or locoregional therapy, and was discharged to his home hospital with plans for external radiation.

Case 2

A 67-year-old male with cirrhosis secondary to chronic hepatitis C presented to clinic for a routine screening assessment. Surveillance grayscale ultrasound scan showed extremely coarse and heterogeneous liver parenchyma with only a few discrete 1-2 cm echogenic lesions seen (Fig. 2A). Alpha-fetoprotein was markedly elevated at 11,000 ng/mL (compared to 5 ng/mL at baseline). Contrast-enhanced CT was subsequently performed and demonstrated diffuse heterogenous nodular and geographic areas of hyperenhancement in the arterial phase, and no significant washout in the portal venous or delayed phases (Fig 2B).

Given that these findings were likely indicative of but not diagnostic for HCC, CEUS was performed. This demonstrated a large geographic and patchy area of arterial enhancement throughout the hepatic parenchyma occurring at 20 seconds in the late arterial phase, after hepatic artery enhancement but before portal vein enhancement (Figs. 2C,D,E). The superior temporal resolution of CEUS added confidence to the imaging diagnosis of HCC, even though no discretely defined lesion or washout was seen on CEUS.

A contrast-enhanced MRI subsequently demonstrated extensive patchy restricted diffusion and high T2 signal corresponding to areas of arterial enhancement in the hepatic parenchyma, without washout (Figs. 2G and H). Based on clinical, laboratory and imaging findings, the presumptive diagnosis of multifocal infiltrative HCC was made by the multidisciplinary tumor board. The patient underwent palliative treatment with transarterial chemoembolization and sorafenib.

Case 3

A 62-year-old woman with a background of cirrhosis of unknown etiology underwent a contrast-enhanced CT to assess for HCC given abnormalities on outside ultrasound. This identified a small filling defect in the ascending left portal vein (Figs. 3A and B). MRI demonstrated inhomogeneous arterial phase enhancement of the left lobe of the liver, without washout. The filling defect in the left portal vein was better visualized on MRI, measuring 1.7 cm and demonstrating possible enhancement suspicious for tumor (Figs. 3C and D).

Given the significant implications for management, a targeted ultrasound was performed. This demonstrated an

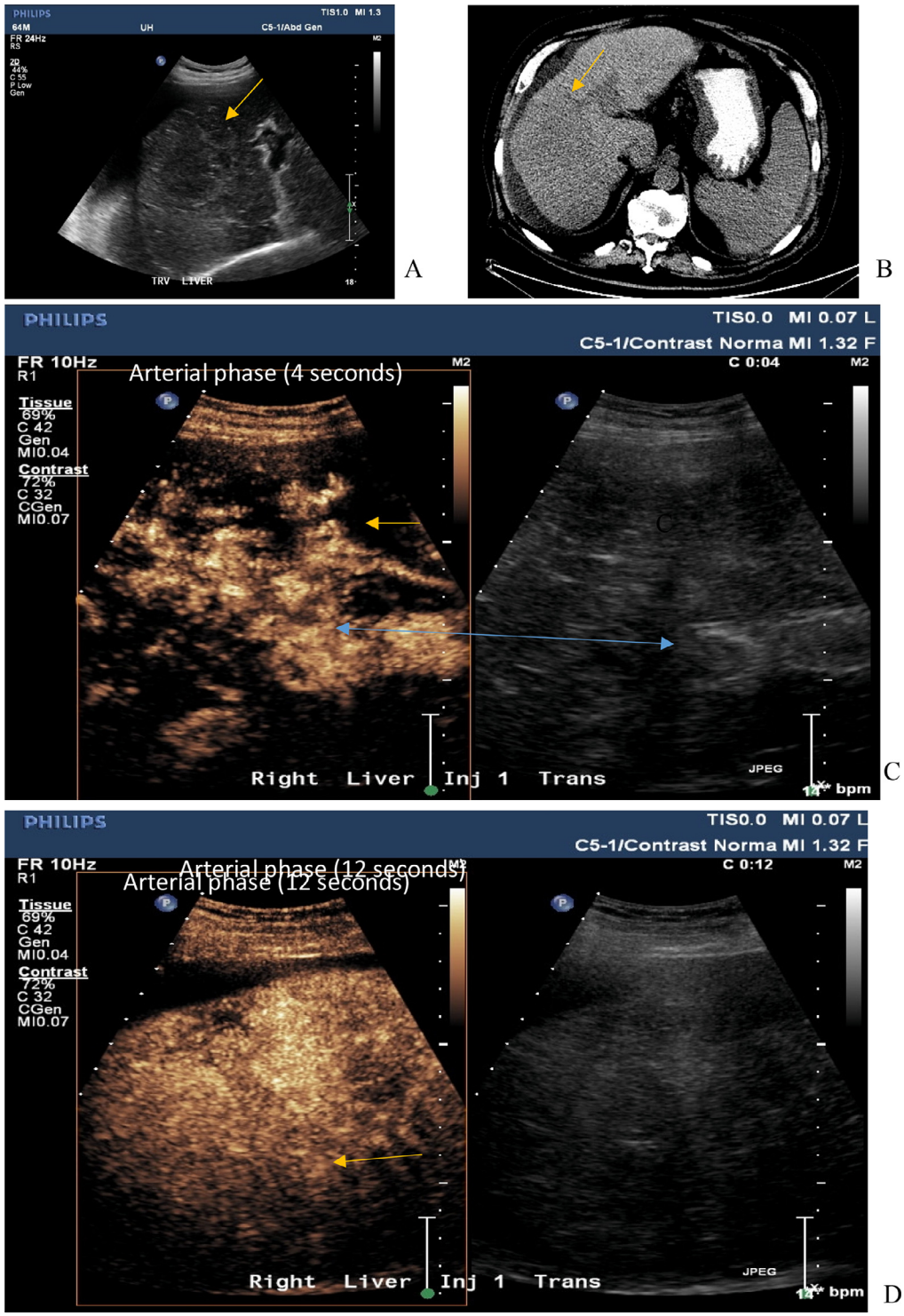


Fig. 1 – A, Transverse grayscale US of the liver demonstrates an ill-defined, geographic hypoechoic area in the right hepatic lobe (orange arrow). B, Subsequent unenhanced CT demonstrates a nodular, cirrhotic liver with subtle ill-defined parenchymal heterogeneity and hypoattenuation in the right hepatic lobe (orange arrow). C and D, CEUS of the right hepatic lobe demonstrates a large area of early (C) and mid-arterial phase (D) hyperenhancement in the right hepatic lobe (orange arrows) along with arterial enhancing, echogenic tumor in the portal vein (C, blue arrows). E, Subtle washout in the right hepatic lobe on delayed phase imaging (arrows). F and G, Axial post-gadolinium MRI demonstrates heterogenous arterial hyperenhancement of an ill-defined area within the right hepatic lobe (green circle) along with tumor in the portal vein (orange arrow) (F), followed by subtle washout of the area in the right hepatic lobe (green circle) on the delayed phase (G), corresponding to CEUS findings.

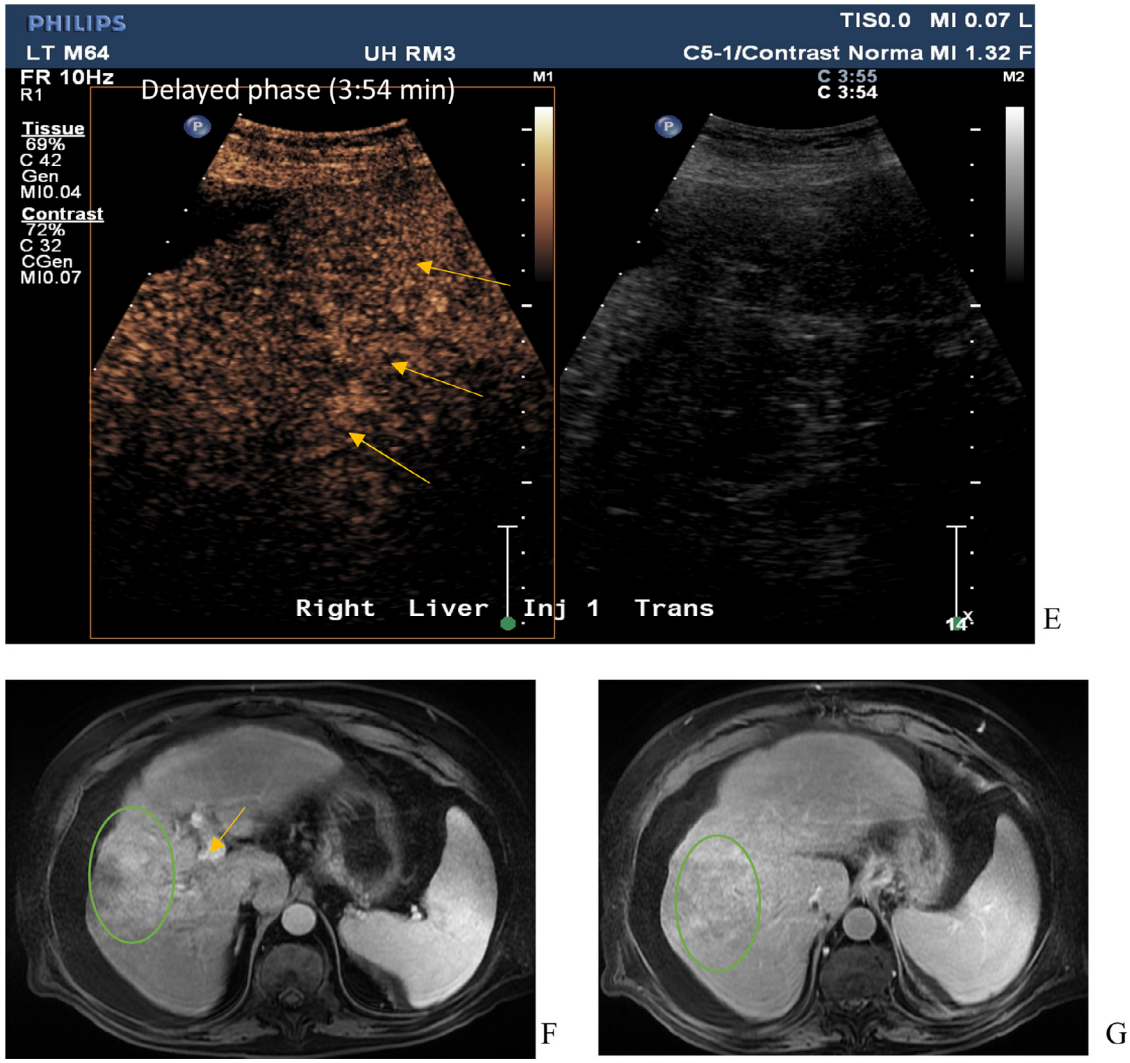


Fig. 1 – Continued

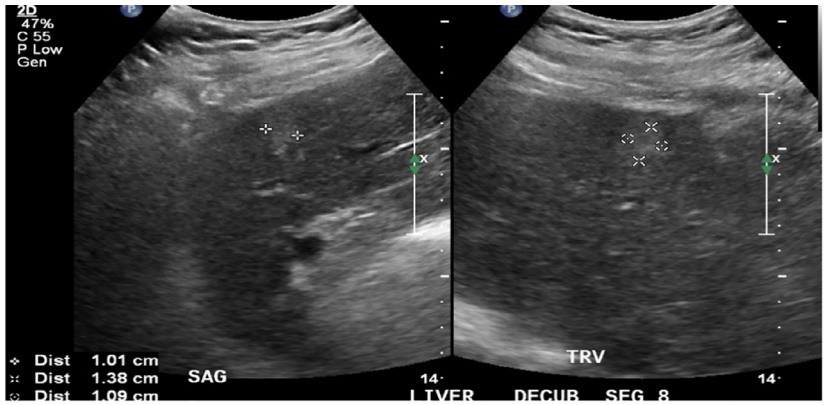
echogenic thrombus within the left portal vein with no detectable internal vascularity on colour Doppler (Figs. 3E and F). CEUS was performed for further characterization, and showed diffuse early arterial enhancement of the thrombus as well as subtle washout of an adjacent 3 cm segment 3 liver lesion (Figs. 3G and H). The diagnosis was therefore consistent with HCC with tumor in vein, according to LI-RADS criteria. The patient subsequently received palliative radiation treatment.

Discussion

Greyscale ultrasound has widely been the preferred first step in the surveillance of liver lesions due to its wide availability, low cost of acquisition and lack of exposure to ionizing radiation [6]. This is reflected in the American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines for the surveillance of HCC, with a recommendation for ultrasound screening every 6 months in adults with cirrhosis [7,8]. However, multiphasic CT or MRI is recommended by the American Association for the Study of Liver Diseases for diagnostic evaluation if suspicious lesions are identified on surveillance US [7]. This is in part due to the nonspecific appearance of HCC on noncontrast US, with difficulty distinguishing tumour from regenerative or dysplastic nodules in the setting of cirrhosis [2].

CEUS can accurately display the arterial phase hyperenhancement and later washout characteristics of HCC without ionizing radiation or nephrotoxicity, and at a higher temporal resolution than possible with CT or MRI [1,4]. Additionally, CEUS has superior sensitivity for microbubbles compared to the sensitivity of CT or MRI for iodinated or gadolinium-based contrast agents [9]. Several meta-analyses have demonstrated CEUS to be noninferior to multiphase CT and MRI for the evaluation of focal liver lesions and HCC in patients with cirrhosis [10,11]. However, the efficacy of CEUS in the imaging of infiltrative HCC with its permeative, ill-defined appearance on traditional imaging modalities is not as well known.

In this case series, we demonstrated the additional utility of CEUS in assessing infiltrative HCC in the absence of well-defined target lesions. In case 1, the diagnosis of infiltrative HCC was promptly made in the setting of concurrent renal failure when other contrast-enhanced imaging modalities



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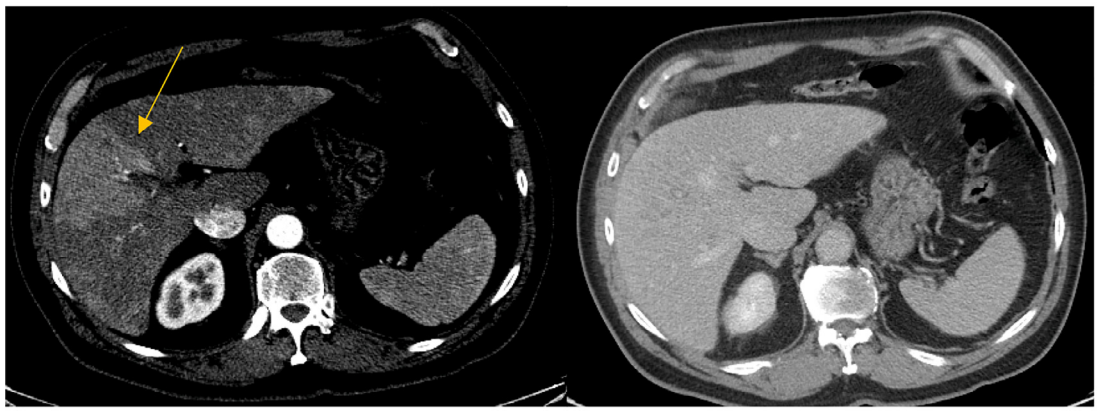

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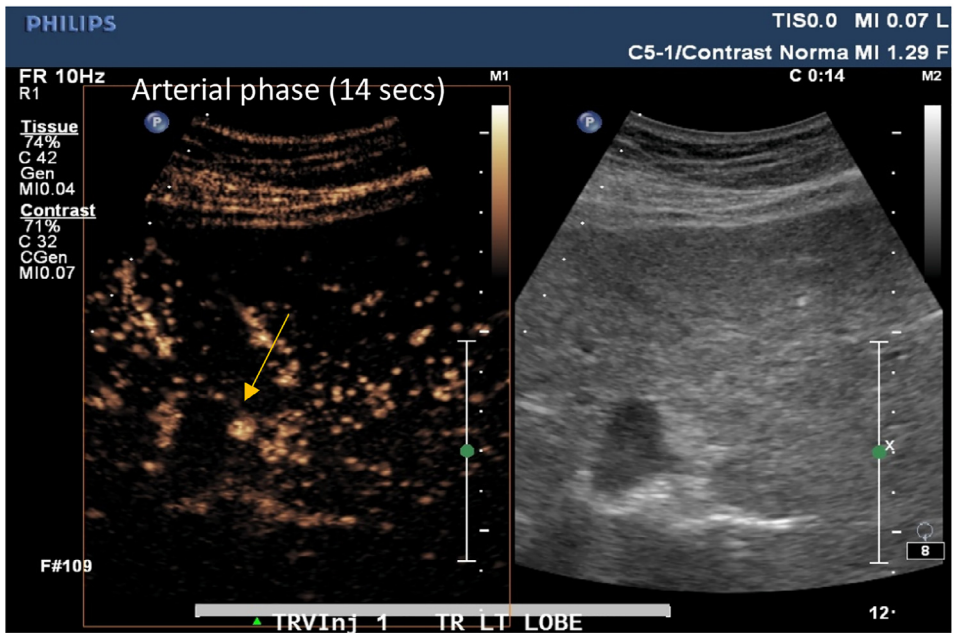
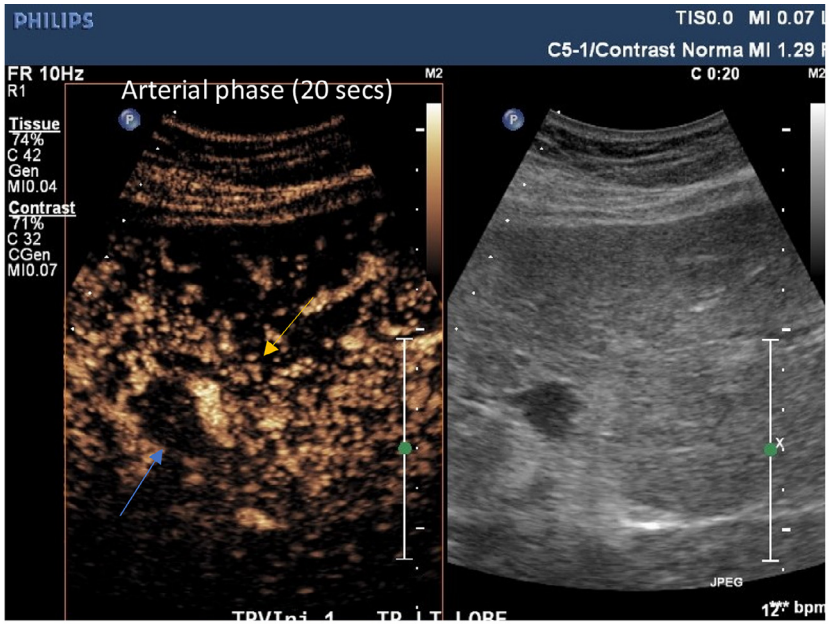


C

Fig. 2 – A, Sagittal and transverse greyscale US of the liver demonstrates very coarse and heterogenous hepatic parenchyma, with scattered 1-2 cm echogenic lesions. B, Contrast-enhanced CT demonstrates diffuse heterogenous nodular and geographic areas of hyperenhancement in the arterial phase (arrow), without definite corresponding areas of washout in the portal venous phase. C, D and E, CEUS demonstrates early arterial phase enhancement of the left hepatic artery (C) followed by late-arterial phase hyperenhancement (orange arrow) of abnormal liver parenchyma prior to contrast opacification of the left portal vein (D, blue arrow) which subsequently occurs in the portal venous phase (E, orange arrows). F and G, Post-gadolinium MRI demonstrates heterogenous arterial phase enhancement (F, orange arrow) without evidence of corresponding washout on the delayed phase (G).



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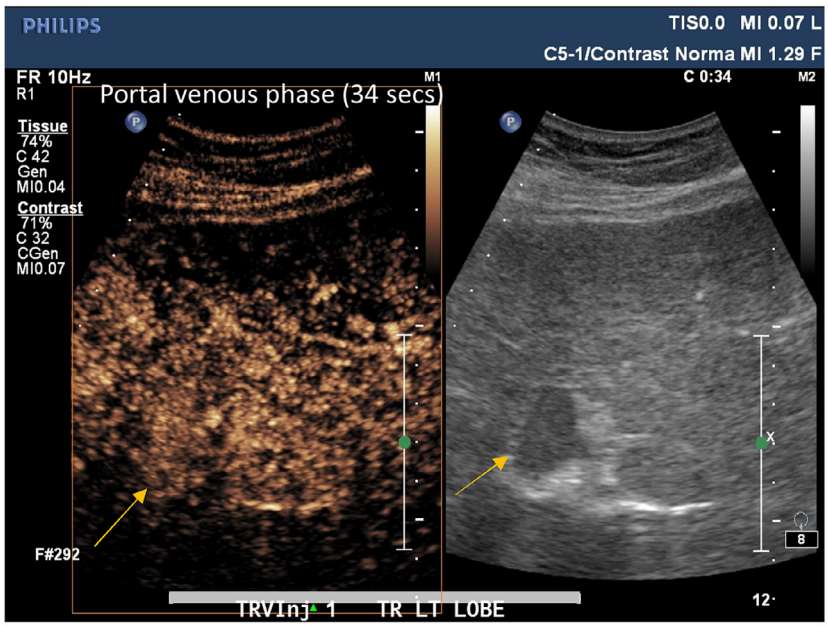

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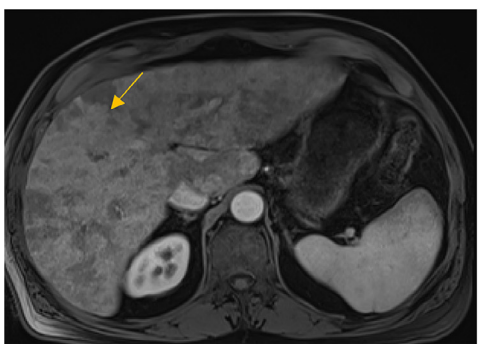

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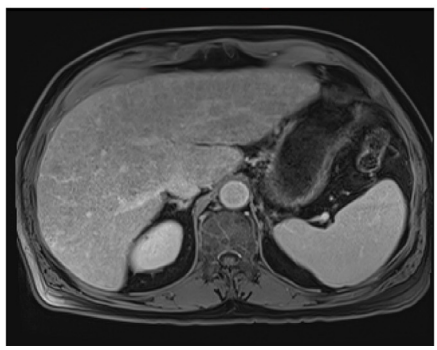

G

Fig. 2 – Continued

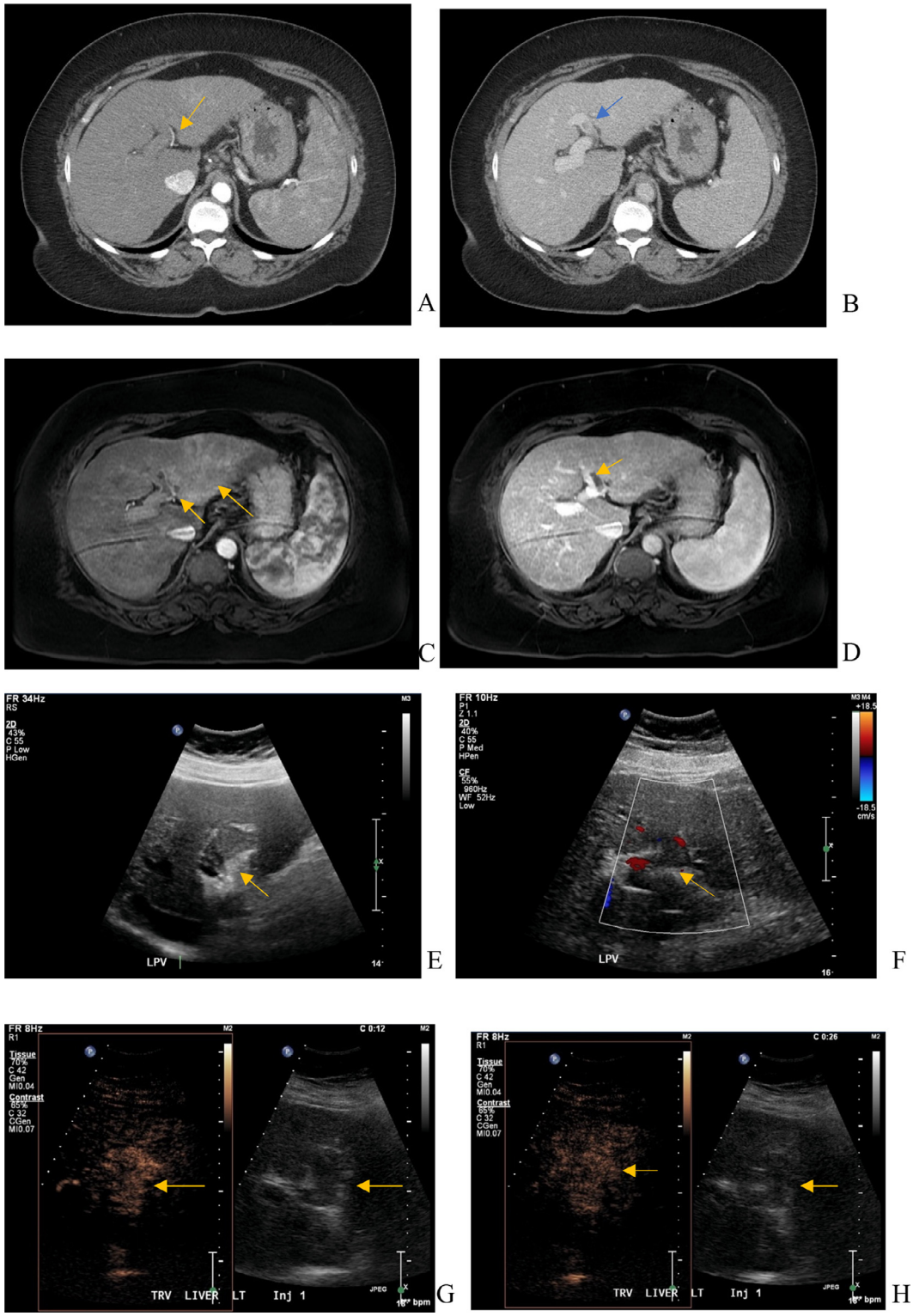

Fig. 3 – A, Contrast-enhanced CT in the arterial phase demonstrates enhancement of the left hepatic artery (orange arrow). B, In the portal venous phase, there is a nonocclusive filling defect in the left portal vein (blue arrow). C, Post-gadolinium MRI in the arterial phase demonstrates a filling defect in the left portal vein, as well as heterogenous arterial enhancement in the adjacent left hepatic lobe (orange arrows). D, The portal vein filling defect (blue arrow) is redemonstrated during the late venous phase; there is no washout in the left hepatic lobe. E and F, Greyscale US demonstrates echogenic thrombus within the ascending left portal vein (E, orange arrow), with no obvious vascularity within the thrombus (orange arrow) on colour Doppler (F). G and H, CEUS demonstrates diffuse arterial enhancement within the left portal vein thrombus, confirming the diagnosis of tumor in vein (orange arrows).

could not be safely utilized, and tumor in vein was not identified on initial CT. In case 2, the increased temporal resolution of CEUS enabled the detection of early arterial hyperenhancement compared to the remaining liver parenchyma, in order to increase confidence in diagnosis of infiltrative HCC. This illustrates the point that real-time nature of CEUS imaging may demonstrate enhancement which is not obvious on CT/MRI due to variations at the point at which arterial-phase images are acquired [12]. CT or MRI only provide a snapshot of enhancement during contrast diffusion, whereas CEUS allows for continuous real-time imaging of microcirculation to capture the whole arterial and late parenchymal phases [13]. This feature is particularly beneficial when differentiating tumor in vein from bland portal venous thrombosis, as the former is associated with infiltrative HCC as in Cases 1 and 3, whereas the latter is a common finding in patients with cirrhosis. CEUS led to superior demonstration of tumor in vein as well as washout of HCC not seen on MRI in Case 3, with significant implications for management.

With these additional advantages to using CEUS in the diagnosis of HCC, EASL 2018 guidelines now include CEUS in the diagnostic algorithm for HCC, albeit as a second line measure after CT or MRI based on moderate evidence [8]. The American College of Radiology has also endorsed the use of CEUS in the Contrast Enhanced Ultrasound Liver Imaging Reporting and Data system (CEUS LI-RADS) published in 2017. This utilizes the size of a lesion, type and degree of arterial phase enhancement, and the presence, timing and degree of washout in categorizing focal liver lesions in patients at high risk of developing HCC [5,14]. CEUS LI-RADS includes a total of 8 categories for characterizing focal liver lesions, ranging from definitely benign to definitely HCC. Other categories include probably or definitely malignant, but not necessarily HCC, not categorized due to inadequate image quality and tumor in vein [14,15]. The CEUS LI-RADS algorithm has been found to be highly specific for HCC, thus avoiding the misdiagnosis of intrahepatic cholangiocarcinoma, a previously cited reason for excluding CEUS in the diagnostic imaging workup [16].

In summary, we present 3 cases of infiltrative HCC where CEUS was valuable in confirming the diagnosis in patients with renal failure, problem solving in patients with equivocal CT and MRI findings, and confirming the presence of tumor in vein. CEUS is a safe and effective imaging modality in the diagnosis of liver lesions including HCC, and this is increasingly being reflected in clinical practise guidelines. Further studies are warranted to validate the utility of CEUS in the noninvasive diagnosis of infiltrative HCC and delineate its role in the algorithm for imaging workup.

Patient Consent

All patients gave informed written consent for their anonymized information to be used for education and research. All identifying personal information has been removed.

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