# Benign Liver Tumors

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## Abbreviations

| | |
|---|---|
| FFI | Focal fatty infiltration |
| FNH | Focal nodular hyperplasia |
| GSD | Glycogen storage disease |
| HA | Hepatic adenoma |
| HAFLD | Nonalcoholic fatty liver disease |
| HCA | Hepatocellular adenoma |
| HCC | Hepatocellular carcinoma |
| HCH | Hepatic cavernous hemeangioma |

## 5.1 Hepatic Hemangioma

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### 5.1.1 Terminology

**Definition**

- Hepatic hemangiomas are known to be the most common benign liver tumors.
- Hepatic hemangiomas have five types, including cavernous hemangioma, sclerosing hemangioma, capillary hemangioma, hepatoinfantile hemangioma, and hepatic vascular malformation with capillary hyperplasia.
- Hepatic cavernous hemangioma (HCH) is the most common type among the hepatic hemangioma.
- HCH of liver is a kind of benign hemangioma composed of honeycomb thin-walled vascular cavity.
- The cause of hepatic hemangiomas is not known. It may be congenitally determined, mesenchymal origin, congenital hematoma, or abnormal vasculogenesis.

### 5.1.2 Imaging

#### 5.1.2.1 Conventional Ultrasound Findings

- A single lesion or more than one lesion with round or slightly oval shape in the liver.
- Typical hepatic hemangiomas are hyperechoic and well-defined lesion with less than 3 cm in diameter (Fig. 5.1a) [1, 2].
- With or without small central regions with decreased echogenicity (Fig. 5.1b).
- Most hypoechoic lesions have a mesh structure (Fig. 5.1c).
- Larger hepatic hemangiomas are mix-echoic, inside echogenicity including irregular nodules or strips of hypoechoic areas (Fig. 5.1d, e).
- A hypoechoic or isoechoic mass with a hyperechoic periphery is also highly suggestive of HCH (Fig. 5.1f).
- Some lesions may be cystic or hemorrhagic necrosis.
- Color Doppler can detect the venous blood flow in or around the HCH tumor (Fig. 5.2a, c), and the vascular structure can be seen.
- Possible detecting the feeding or draining vessel in color Doppler ultrasound [3]. In a few cases, the arterial blood flow with low flow rate and low resistance index can be measured, and RI < 0.6 in most cases (Fig. 5.2b, d).

#### 5.1.2.2 Contrast Enhanced Ultrasound Findings

- Contrast enhanced ultrasound (CEUS) was considered definite for liver hemangioma if a typical enhancement pattern was present (centripetal fill-in during the arterial phase, hyper-enhanced lesion during portal venous and late phases) according to current WFUMB and EFSUMB guidelines [4] (Fig. 5.3).

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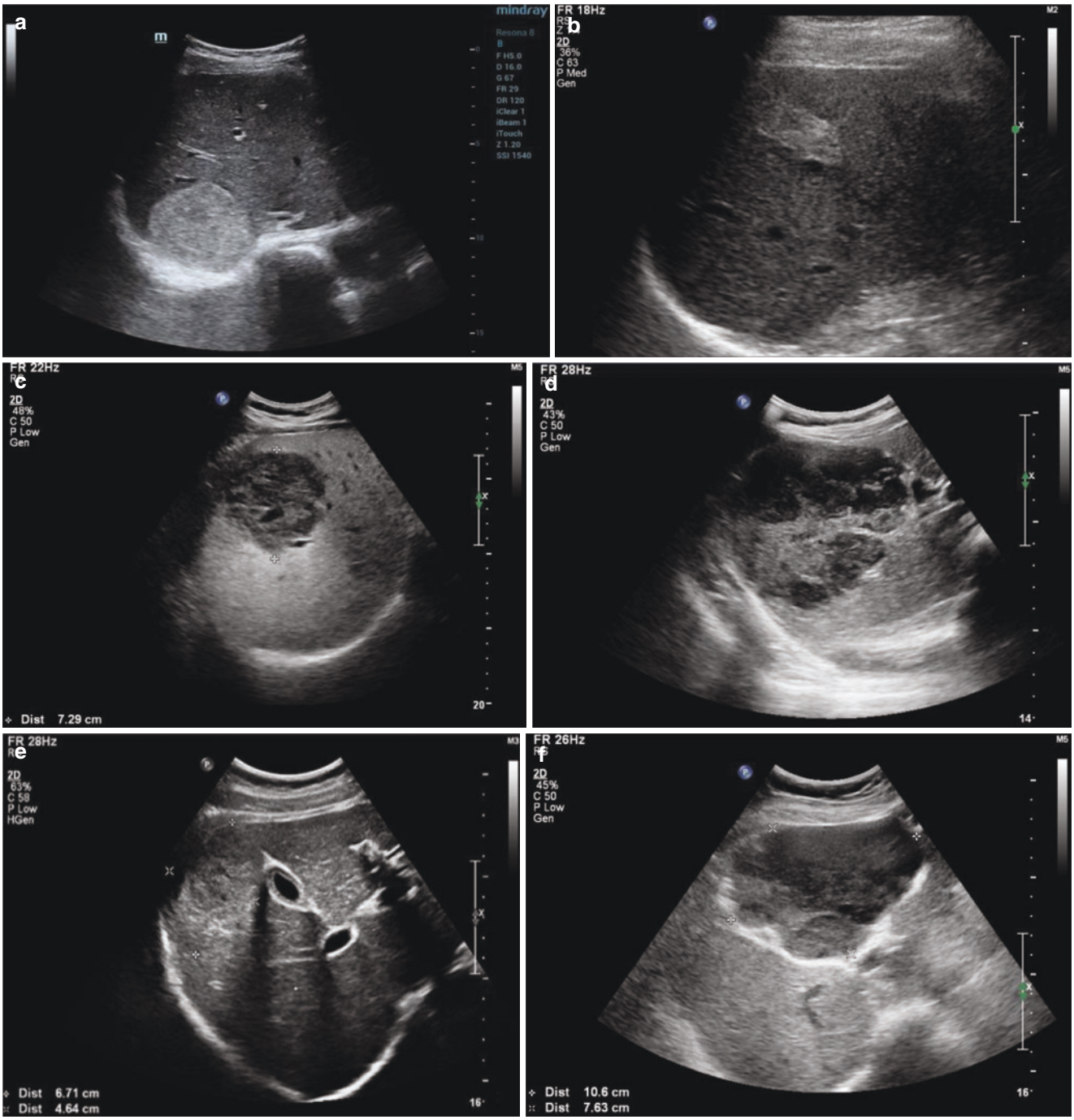



**Fig. 5.1** Features of hepatic hemangiomas on B mode ultrasound. Hyperechoic and well-defined lesion (**a**). Hyperechoic lesion with hypoechoic regions (**b**). Hypoechoic lesion with mesh structure (**c**). Larger mix-echoic (mainly hyperechoic) lesion with network structure or strips of hypoechoic areas (**d**, **e**). Hypoechoic lesion with a hyperechoic periphery (**f**)

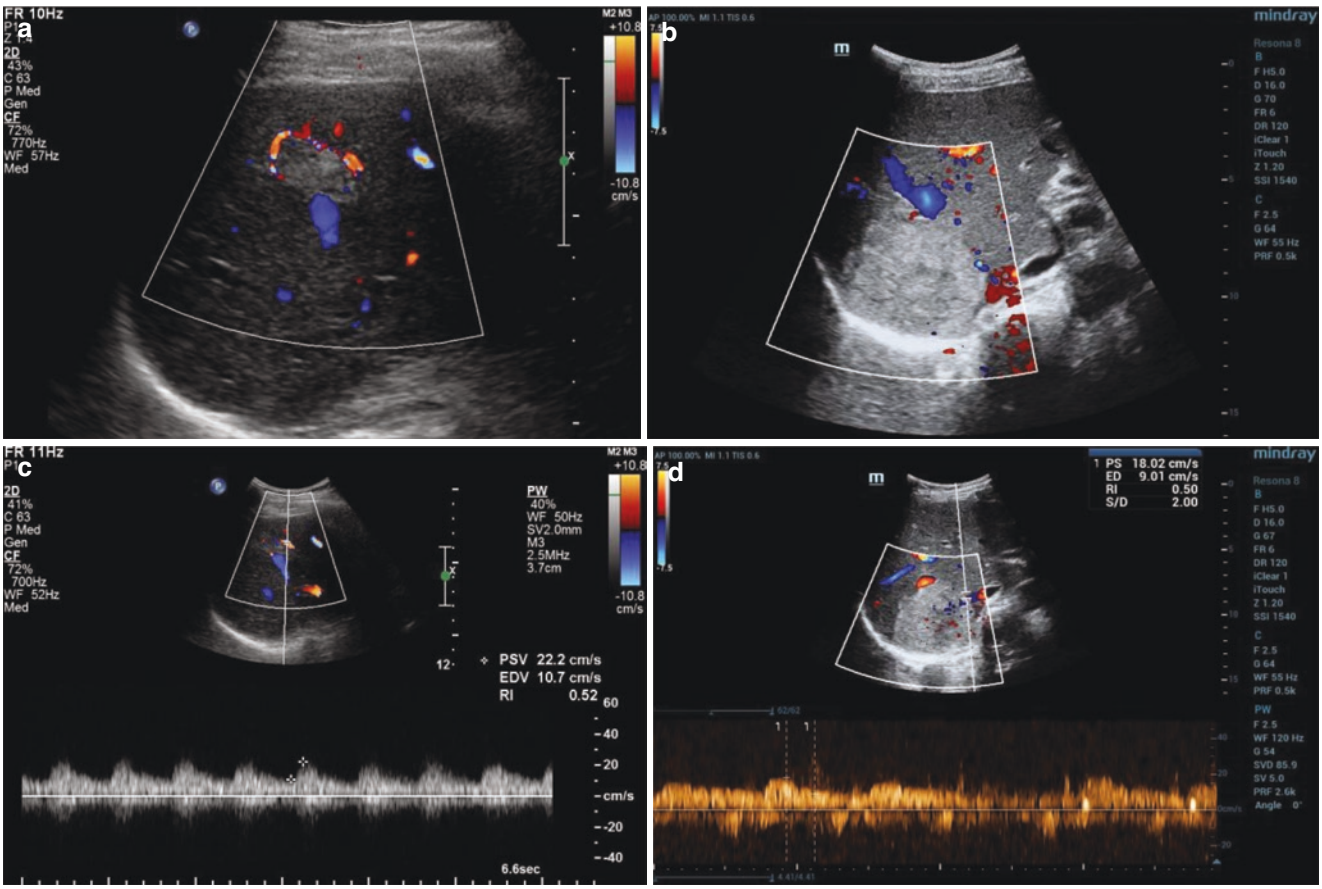



**Fig. 5.2** Color flow signals, especially peripheral flow signal could be detected in most of hepatic hemangioma lesions (**a**, **c**). Arterial Doppler spectrum with low resistance index (RI) could be measured (**b**, **d**)

- Peripheral nodular arterial enhancement and complete portal venous fill-in or no complete (inhomogeneous, incomplete iris diaphragm sign, with non-enhancing solitary necrotic nodule) fill-in can be seen (Fig. 5.4) [1, 5].
- A complete fill-in enhancement pattern without peripheral nodular enhancement can also be seen (Fig. 5.5) [1, 5].
- Small hemangiomas (<10 mm) tend to lack the typical enhancement patterns on CEUS.

#### 5.1.2.3 CT Findings

- Most of HCHs were low density with clear boundary, and a few of them were iso-density or high density because of fatty liver on CT scan.
- Early peripheral discontinuous nodular or globular enhancement in arterial phase with progressive centripetal enhancement [6].
- The lesions often show "filling-in" with hyperenhancement or isoenhancement on delayed scan [6].
- Atypical hepatic hemangioma can show non-enhancing intralesional spots that can occur with fibrosis, thrombosis, or necrosis.

#### 5.1.2.4 MRI Findings

- Typical MRI appearance of liver hemangioma lesions appears as a smooth, well-demarcated homogeneous nodule that has low signal intensity on T1-weighted images and high signal intensity on T2-weighted images [3].
- The signal intensity of the lesion increases with the extension of the echo time, showing a characteristic "bulb sign"-like high signal.
- The lesions show nodular enhancement at the edge in the arterial phase, enlarged enhancement in the portal phase.
- The contrast agents gradually advance to the center in the delay phase.

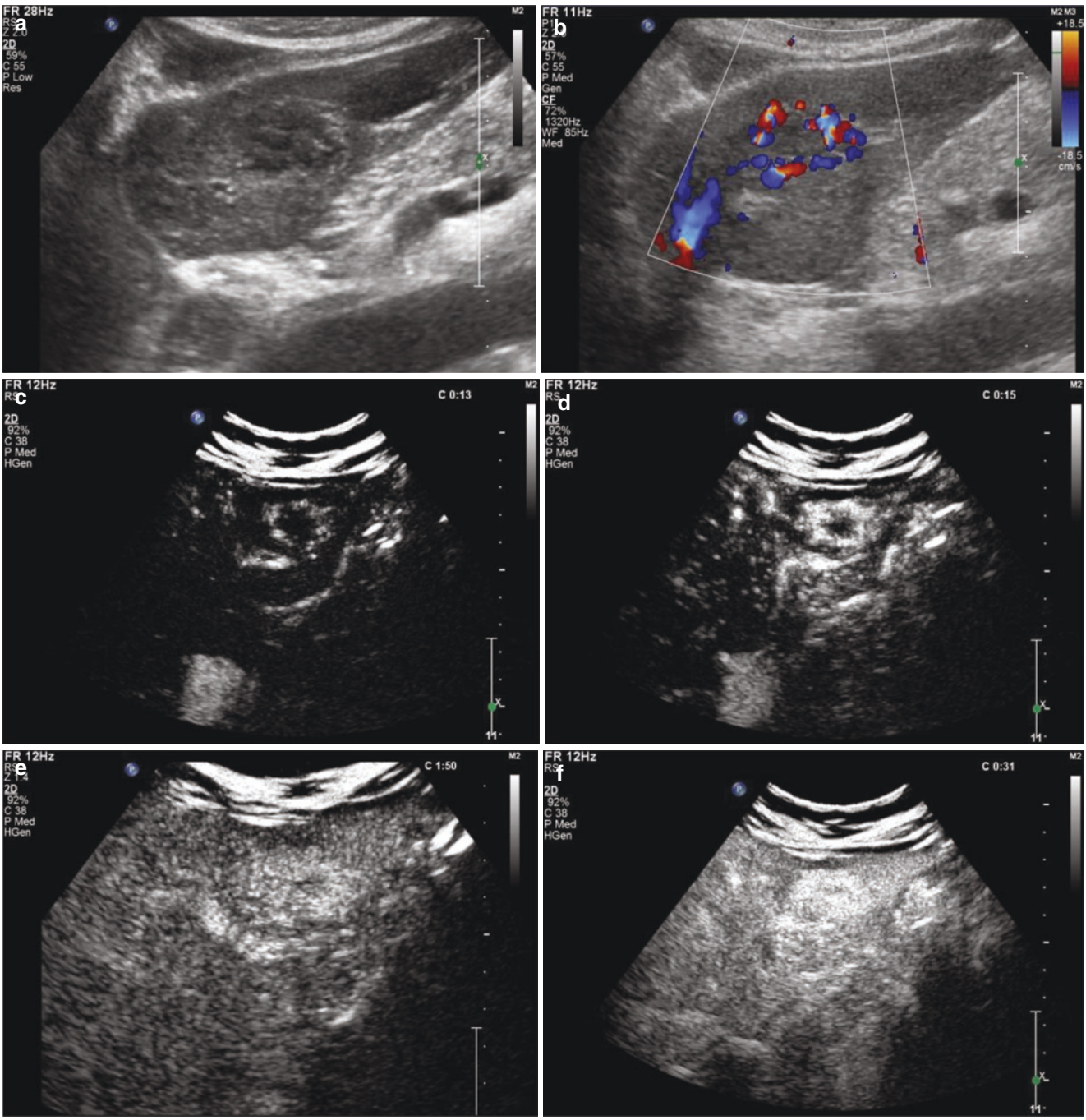



**Fig. 5.3** A case of an incidental hepatic hemangioma of a 50-year-old man. B mode ultrasound revealed a slightly hypoechoic focal liver lesion in left hepatic lobe (**a**). Peripheral color flow signals could be detected around the lesion (**b**). The lesion showed typical peripheral rim-like and centripetal hyperenhancement during arterial phase on contrast enhanced ultrasound (**c**–**e**) and persistent hyperenhancement in portal venous and late phases (**f**)

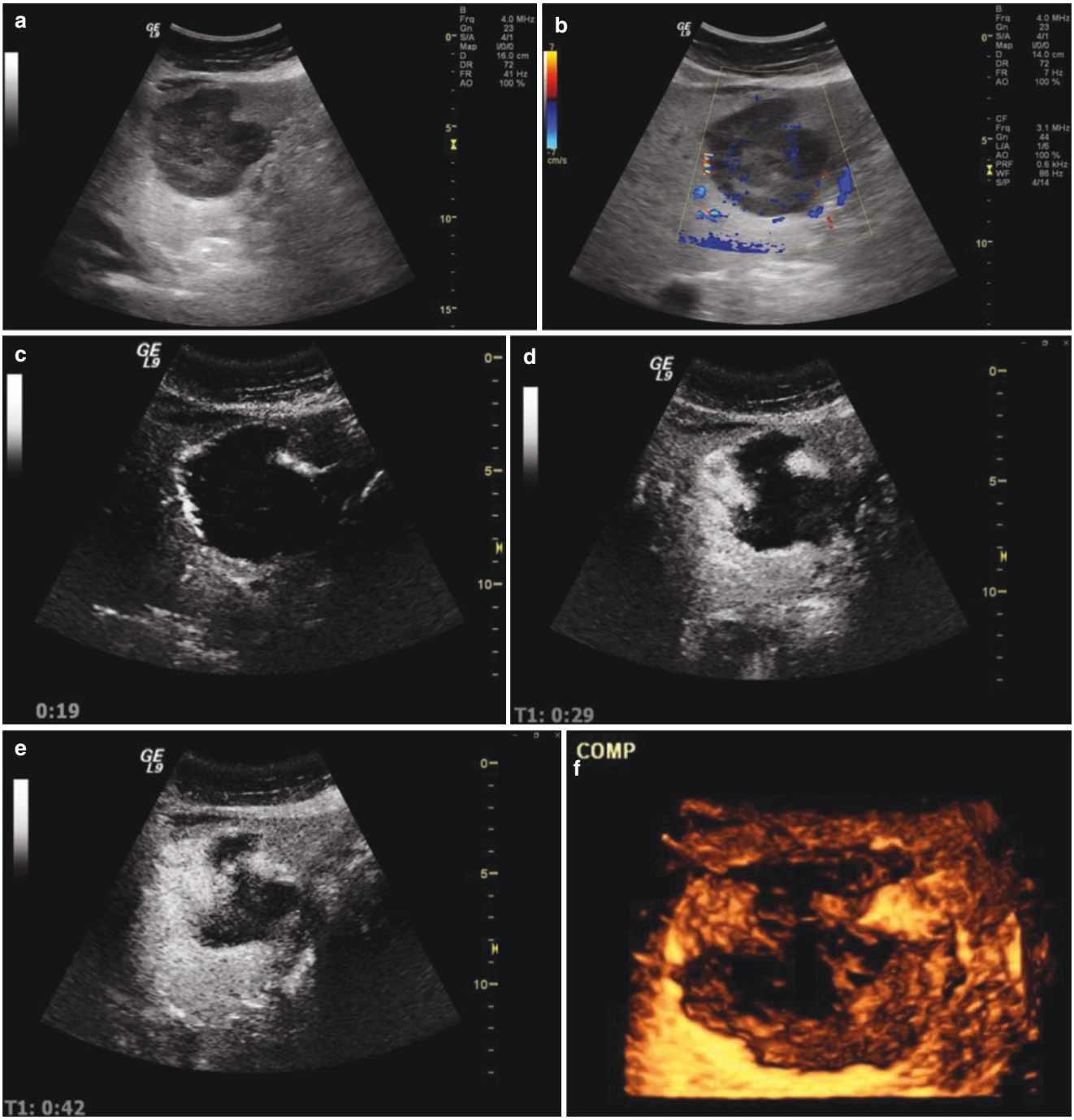



**Fig. 5.4** A case of an incidental hepatic hemangioma of a 36-year-old woman. B mode ultrasound revealed a hypoechoic lesion with a clear boundary (**a**). Color flow signals could be detected around the lesion (**b**). The lesion showed typical rim-like and nodular hyperenhancement in the peripheral region of the lesion during arterial phase on contrast enhanced ultrasound (CEUS) (**c**–**e**). Dynamic three-dimensional CEUS can demonstrate the spatial relationship of the inner nodular enhancement of the lesion clearly (**f**)

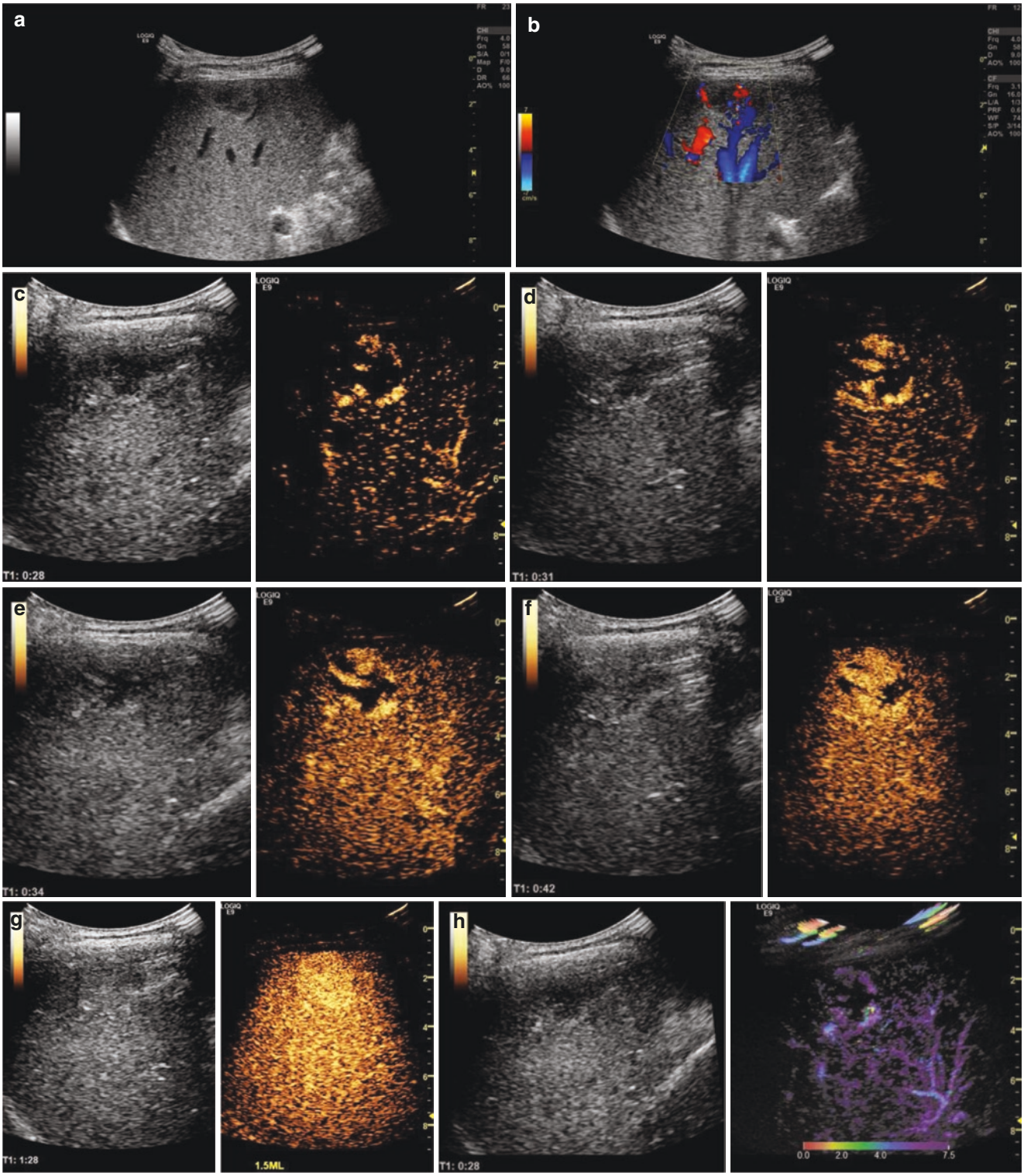



**Fig. 5.5** A case of an incidental hepatic hemangioma of a 27-year-old man. B mode ultrasound revealed a heterogeneously hypoechoic lesion in right hepatic lobe (**a**). Color flow signals could be detected inside and around the lesion (**b**). The lesion showed typical fill-in hyperenhancement from the peripheral region of the lesion during arterial phase on contrast enhanced ultrasound (**c**–**f**). It showed isoenhancement in portal venous and late phases (**g**). Parametric perfusion imaging can reveal the peripheral hyperenhancement in the arterial phase (**h**)

#### 5.1.2.5 Other Imaging Findings

- Technetium-99m pertechnetate-labeled red blood cell scintigraphy shows initial hypoperfusion during arterial flow, which is followed by a gradual increase of tracer peaking 30–50 min after the injection.
- Selective hepatic angiography has the highest specificity for hepatic hemangiomas.

#### 5.1.2.6 Best Imaging Protocol Advices

- Conventional ultrasound or contrast enhanced ultrasound is the first choice for imaging diagnosis in most cases, then secondary MRI and spiral CT.
- The sensitivity for the combination of peripheral nodular arterial enhancement and complete portal venous fill-in in contrast enhanced ultrasound 98% (91–100%).
- The combined application of multiple examination methods can greatly improve the diagnostic accuracy of hepatic hemangioma.
- Considering the high diagnostic performance of imaging methods of hepatic hemangioma that can diagnose up to 95% of the cases, biopsy is not warranted in those typical cases.
- In patients with suspected metastatic disease and therapeutic implications for management, biopsy is still necessary.

### 5.1.3 Differential Diagnosis

Hepatic hemangioma has a high incidence in the normal population. For some patients of high risk of HCC, liver metastases, or other liver diseases, definitively differential diagnosis of hepatic hemangioma from liver malignancy is critical for clinical therapy management (Figs. 5.6, 5.7, and 5.8). Furthermore, hepatic angiosarcoma, hepatic abscess, and hepatic adenoma may be likely to be confused.

#### 5.1.3.1 Hepatocellular Carcinoma

- Hepatocellular carcinoma patients generally have a history of chronic liver diseases such as chronic hepatitis and cirrhosis.
- The shape of hepatocellular carcinoma is irregular, the boundary is unclear, and the internal echo of the mass is uneven.
- The serum AFP is often elevated, and larger tumors are more likely to have a portal vein invasion and tumor thrombus.
- Abundant blood flow signals can be seen inside and around hepatocellular carcinoma.
- Hepatocellular carcinomas often decline rapidly in contrast-enhanced imaging methods.

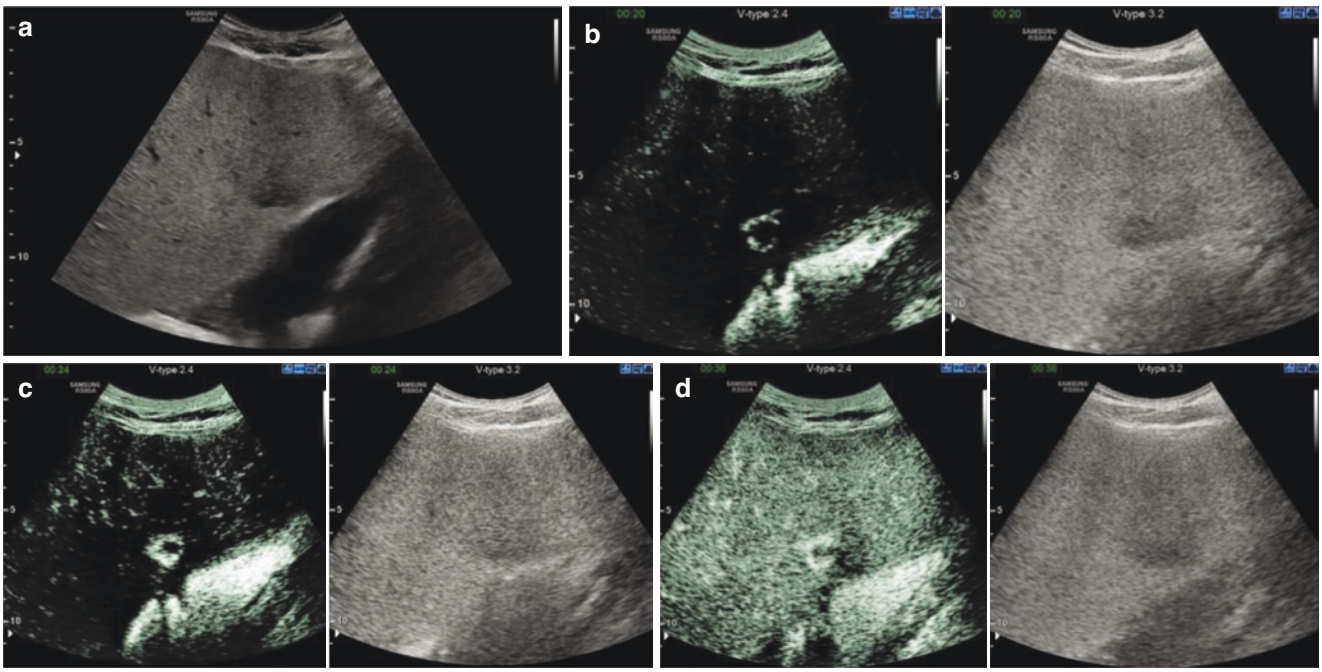
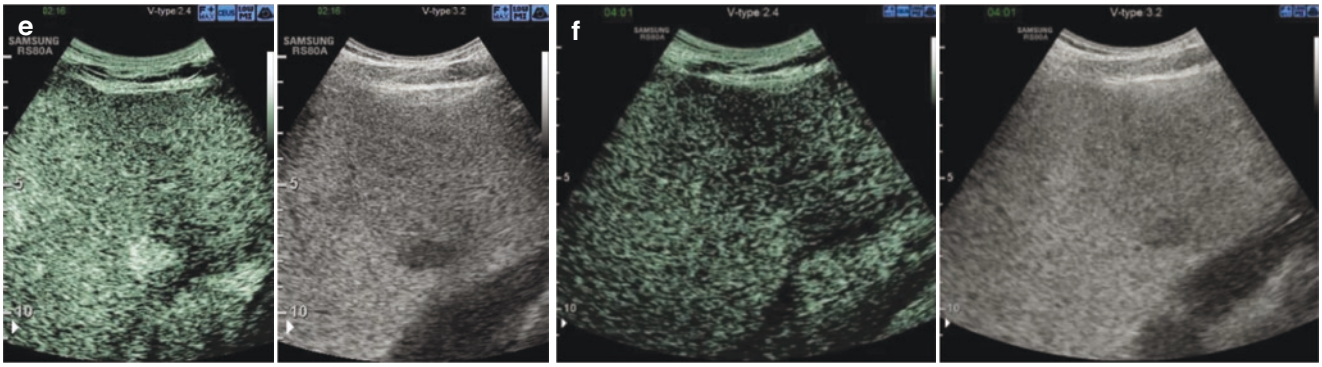



**Fig. 5.6** A case of an incidental lesion of a 48-year-old woman with a history of gastric carcinoma surgery 2 years ago. B mode ultrasound revealed a slightly hypoechoic lesion with an unclear boundary near the top of diaphragm (**a**). The lesion showed typical centripetal hyperenhancement during arterial phase on contrast enhanced ultrasound (**b**–**d**) and persistent hyperenhancement in portal venous and late phases (**e**, **f**). Hepatic hemangioma was diagnosed by various imaging examinations and clinical follow up of 3 years

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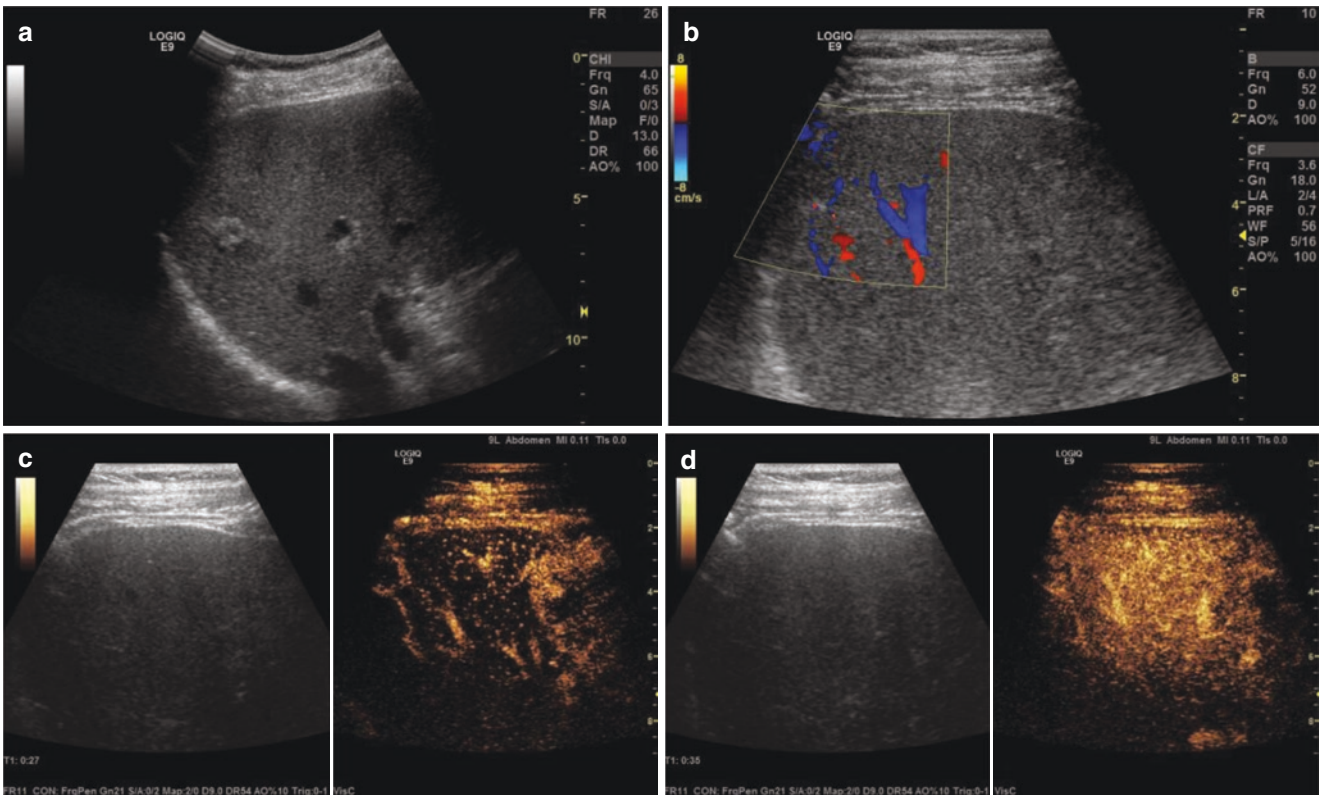
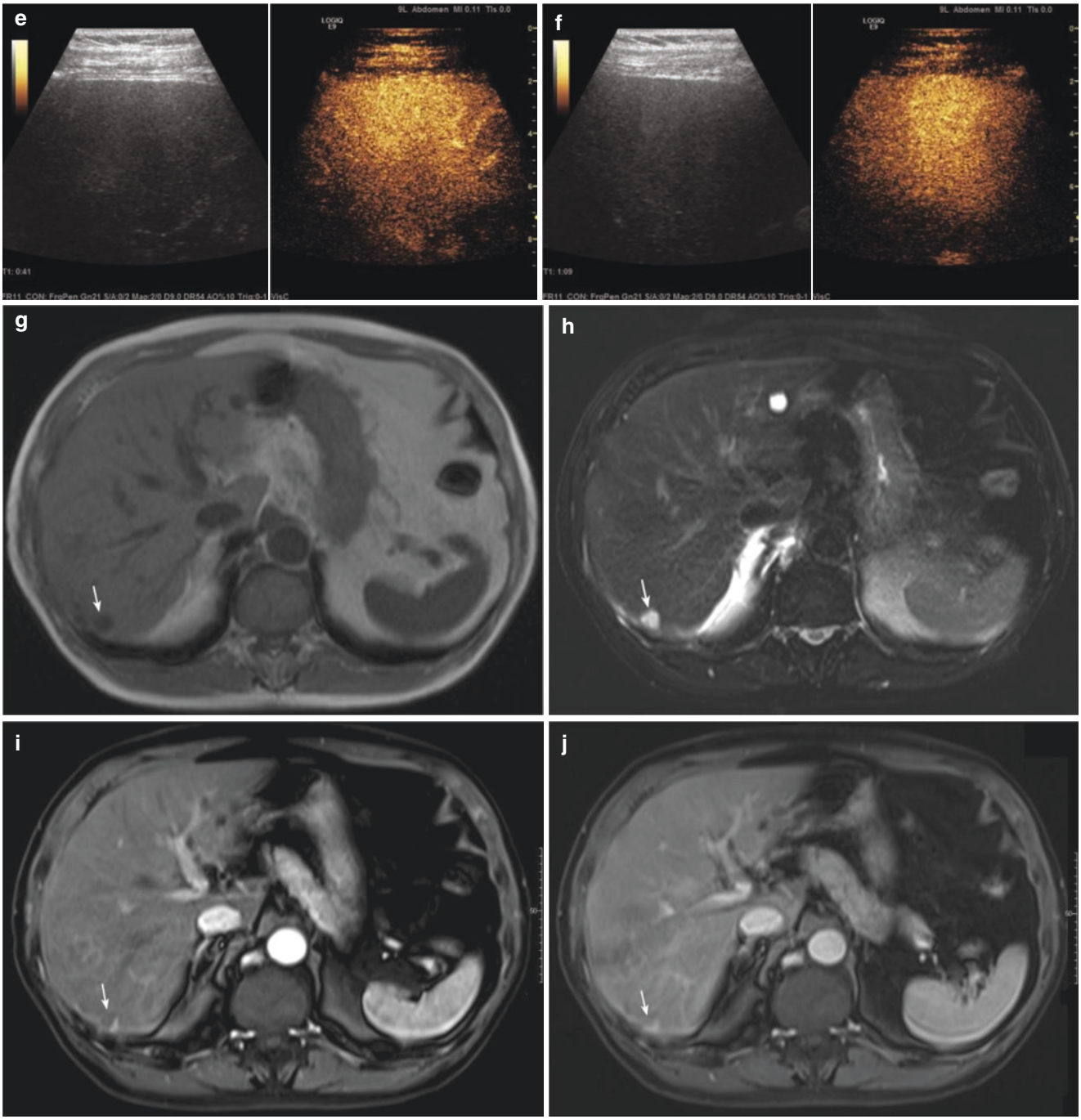



**Fig. 5.7** A case of an incidental lesion of a 64-year-old man with a history of colon carcinoma surgery 1.5 years ago. B mode ultrasound revealed a hyperechoic lesion in the right hepatic lobe near the diaphragm (**a**). Intratumoral dot-like color flow signals can be found (**b**). The lesion showed peripheral hyperenhancement during arterial phase on CEUS (**c**–**e**), and persistent isoenhancement in portal venous and late phases (**f**). The lesion showed homogeneous hypointense on T1 weighted image (WI) (**g**) and hyperintense on T2WI (**h**) of MR. It showed enhancement at the edge in arterial phase (**i**) and gradual enhancement in portal venous phase (**j**). In the late phase, the lesion showed an entire hyperenhancement (**k**). Hepatic hemangioma was diagnosed by various imaging examinations and clinical follow-up of 4 years

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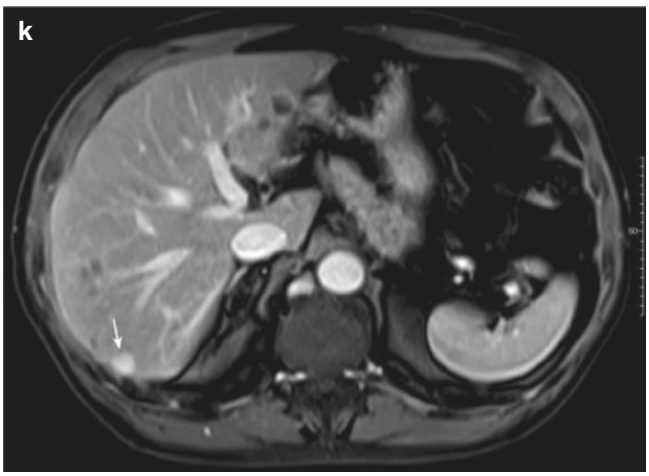


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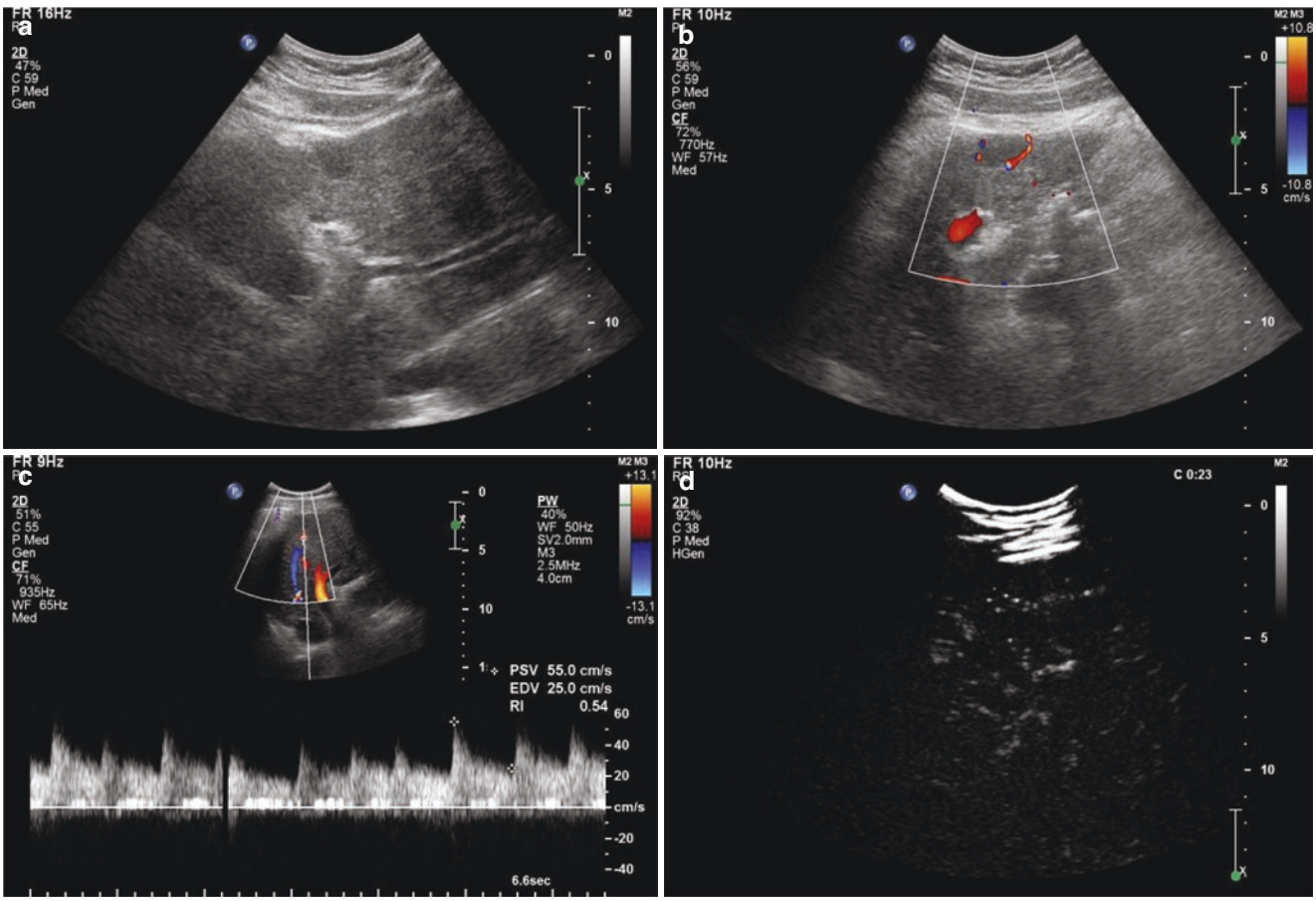


**Fig. 5.8** A case of an incidental lesion of a 57-year-old man with a history of liver cirrhosis for over 30 years. B mode ultrasound revealed a slightly hypoechoic lesion in the right hepatic lobe near the diaphragm (**a**). Peripheral color flow signals can be found (**b**). Arterial Doppler spectrum with resistance index (RI) as 0.54 was measured (**c**). The lesion showed complete hyperenhancement during arterial phase on CEUS (**d**–**g**), and persistent isoenhancement in portal venous phase and late phases (**h**). Hepatic hemangioma was diagnosed by various imaging examinations and clinical follow up of more than 10 years

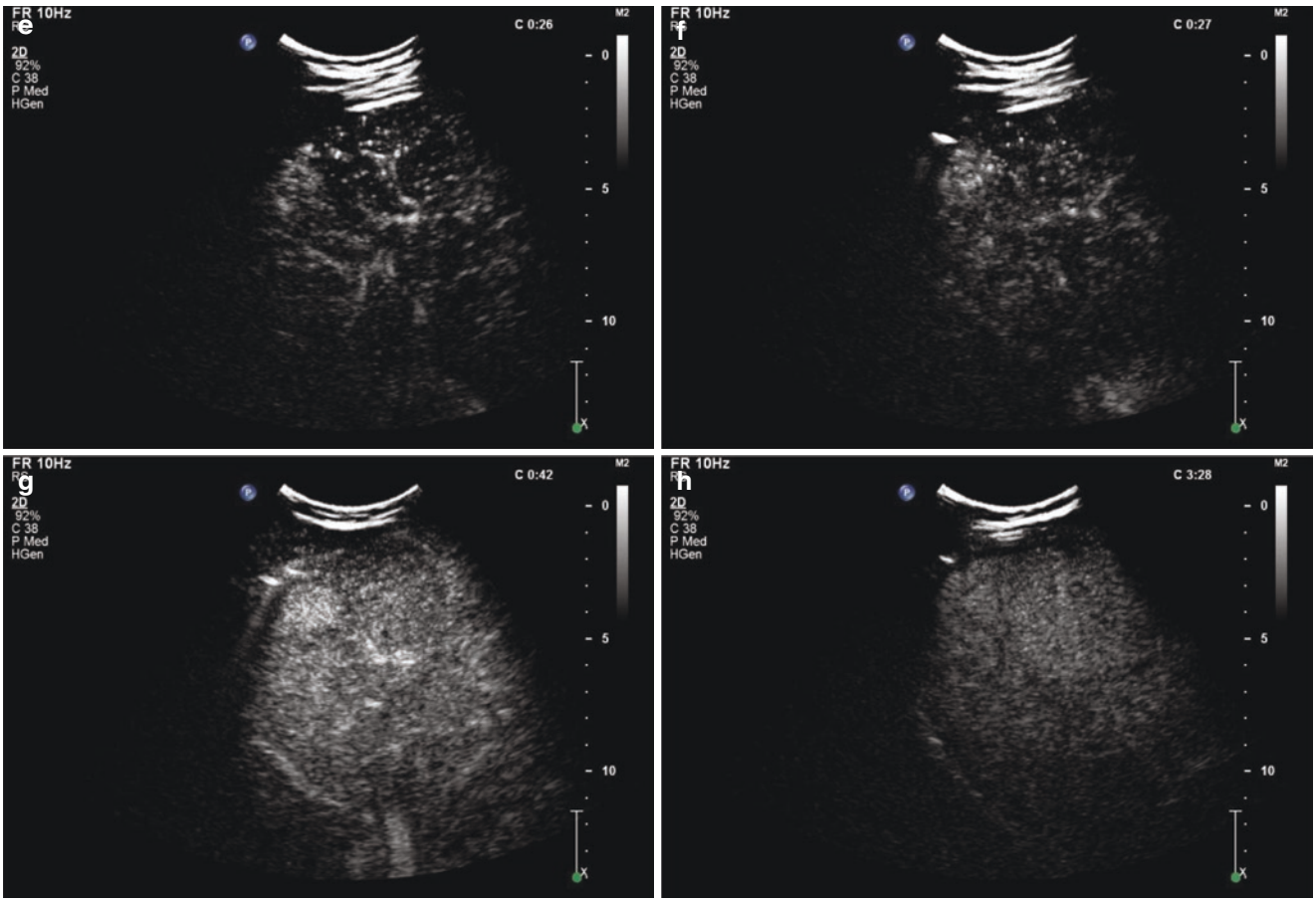


**Fig. 5.8** (continued)

#### 5.1.3.2 Metastatic Hepatic Carcinoma

- Patients often have a history of primary tumor, and serum CEA and CA199 are often elevated.
- Metastatic hepatic carcinoma is accompanied by sound attenuation in the rear, often accompanied by halo around it, showing bull's eye.

#### 5.1.3.3 Focal Angiosarcoma

- It is the malignant transformation of hepatic hemangioma.
- Clinical manifestations are important, the tumor grows rapidly and is accompanied by cachexia.

#### 5.1.3.4 Abscess

- High fever, right upper abdominal pain, hepatomegaly, and tenderness in the liver are the main symptoms and signs, while hepatic hemangioma generally has no obvious symptoms.
- The liver abscess has a thicker wall and irregularity.
- The interior of the abscess may present heterogeneous mixed echo with liquid dark areas.

#### 5.1.3.5 Hepatic Adenoma

- Hepatic adenoma is a benign liver tumor with potential risk of malignant degeneration.
- Hepatic adenoma is prone to spontaneous bleeding, necrosis, and rupture.
- Hepatic adenoma often displays a heterogeneous or centripetal enhancement during arterial phase followed by persistent enhancement or a slight wash-out in late phases.

### 5.1.4 Pathology

#### 5.1.4.1 General Features

- Hepatic hemangioma lesions are well circumscribed, often surrounded by a thin capsule. The cut surface may exhibit a red-brown appearance with a spongy consistency that may indicate hemorrhage, scarring, or calcification.
- On microscopy observation, the tumor is composed of cavernous vascular spaces of different sizes. The cavern-

ous vascular spaces are filled with blood and lined by a single layer of flat endothelium. They are separated by thin fibrous septae and may contain thrombi.

### 5.1.5 Clinical Issues

#### 5.1.5.1 Presentation

- The incidence is higher in adults, and the general age of the initial diagnosis is 30–50 years old.
- The ratio of men to women in the Western world is 1:4.5 or 1:5.
- The vast majority of hepatic hemangioma patients are asymptomatic, typically discovered incidentally during an imaging examination.
- Lesions (>4 cm) are more likely to cause symptoms.
- The most common symptoms are abdominal pain at right upper quadrant, discomfort, and fullness. Acute abdominal pain may be caused by thrombosis or bleeding within the tumor and associated stretching and inflammation of Glisson's capsule.

#### 5.1.5.2 Prognosis

- Symptomatic hemangioma with no tendency to malignancy generally has a good prognosis after treatment.
- Asymptomatic hemangioma is generally followed up for a long time and the prognosis is good.

#### 5.1.5.3 Treatment

- Most hepatic hemangiomas do not need special treatment.
- If there are obvious clinical symptoms, further treatment can be carried out, including nonsurgical treatment and surgical treatment [7].
- Nonoperative treatment includes hepatic artery embolization (TAE), microwave coagulation and radiofrequency therapy or microwave curing, etc. [7].

## 5.2 Focal Nodular Hyperplasia

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### 5.2.1 Terminology

**Definition**

- Focal nodular hyperplasia (FNH) is the second most common benign focal liver lesion after liver hemangioma.
- FNH is essentially a proliferative response to the abnormal perfusion of a localized vascular malformation, not a true liver neoplasm.

### 5.2.2 Imaging

#### 5.2.2.1 Conventional Ultrasound Findings

- FNH lacks specific signs on grayscale ultrasound.
  - Most FNH lesions appear as well-defined, oval, and hypoechoic, and faint dark ring may be detected around the lesion (Fig. 5.9).
  - The characteristic central scar may appear relatively hypoechoic or hyperechoic, but is rarely seen or hardly distinguished (Fig. 5.10). The ability of grayscale ultrasound to show central scar in FNH lesions is worse than that of CT/MRI.
- Almost all FNH lesions occur in normal liver, rarely in liver cirrhosis.
- The characteristic "spoke-wheel" pattern of radiating artery branches (Fig. 5.11) can be seen in about one-third of the FNH lesions on color flow images.
- Color flow image is helpful to observe the distribution and course of the feeding artery (Fig. 5.12).
  - Color flow signals could be measured in the center of almost all FNH lesions.
  - A large distorted feeding artery can be found around almost all lesions.
- Pulse Doppler can detect the flow signal in the lesion which is mostly arterial spectrum with low impedance. The resistance index (RI) is usually measured less than 0.60.

#### 5.2.2.2 Contrast Enhanced Ultrasound Findings

- Contrast enhanced ultrasound (CEUS) can reveal the characteristics of intralesional blood flow in real time, with sensitivity and specificity reaching 80.9% and 85.7%, comparable to MRI and CT with contrast agents [8].
- On CEUS, the FNH lesion mostly appears homogeneous hyperenhancement in arterial phase, without wash-out in portal and late phases.
- Centrifugal filling (Fig. 5.13) or "spoke-wheel" enhancement pattern with its detection rate in 17.9–36.3% are used as signs in diagnosis of FNH, reflect the pathophysiological features of FNH [9].
- Central scar is also a diagnostic clue with a detection rate of 17.9–28.3%, which is located in the central area of the lesion that is not enhanced in all phases.
- A tortuous feeding artery may be observed in the peripheral area of the lesion (Figs. 5.14, 5.15, 5.16, and 5.17).

#### 5.2.2.3 CT Findings

- The FNH lesions usually show isodensity or slightly hypodensity on nonenhanced CT. It might also be hyperdensity when accompanying with hepatic steatosis.
- On contrast enhanced CT, the FNH lesions display a markedly homogeneous hyperenhancement in arterial

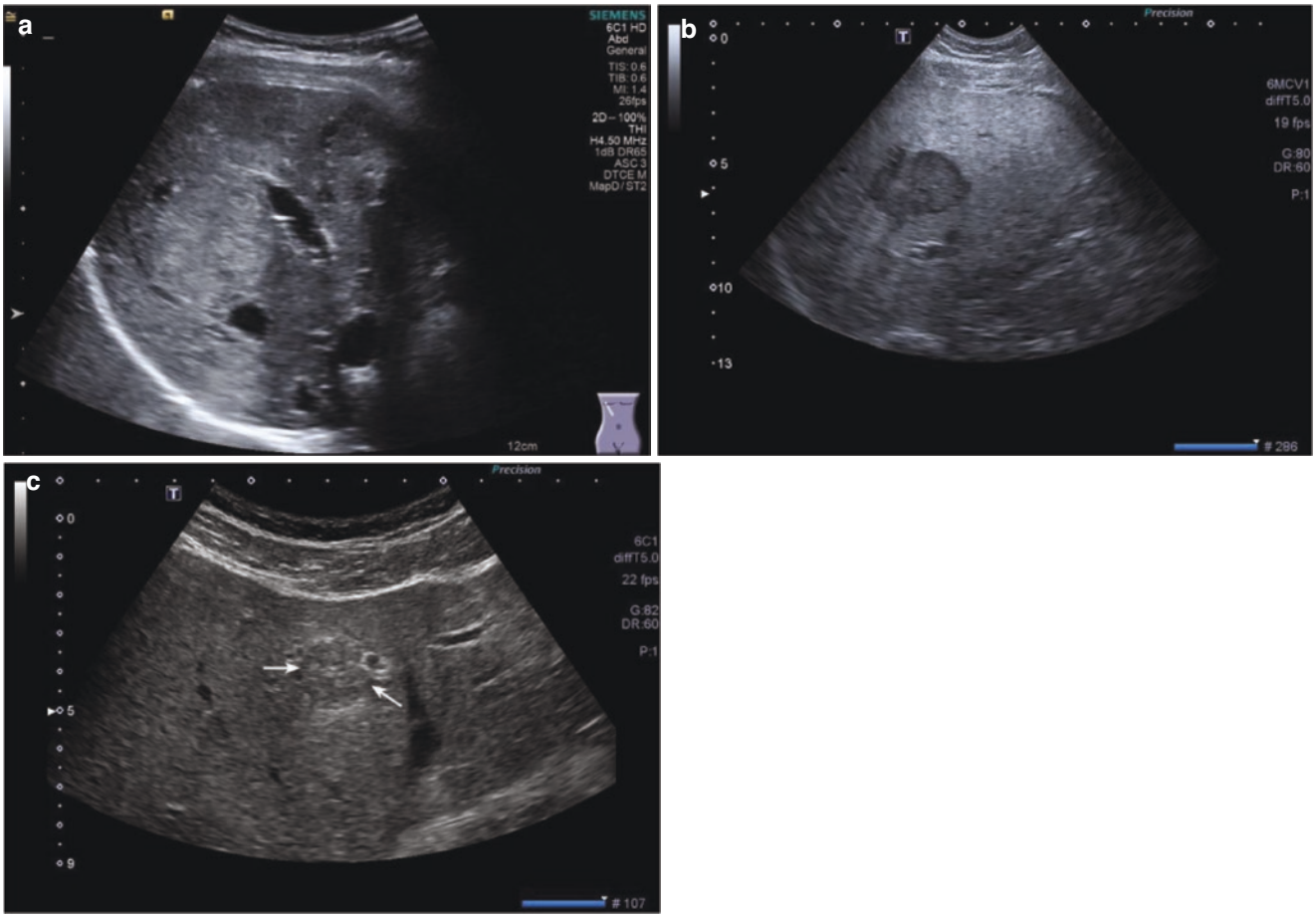



**Fig. 5.9** Different appearance of several cases of focal nodular hyperplasia (FNH) on B mode ultrasound. They are hyperechoic (**a**), hypoechoic (**b**), and isoechoic (**c**, arrow), respectively

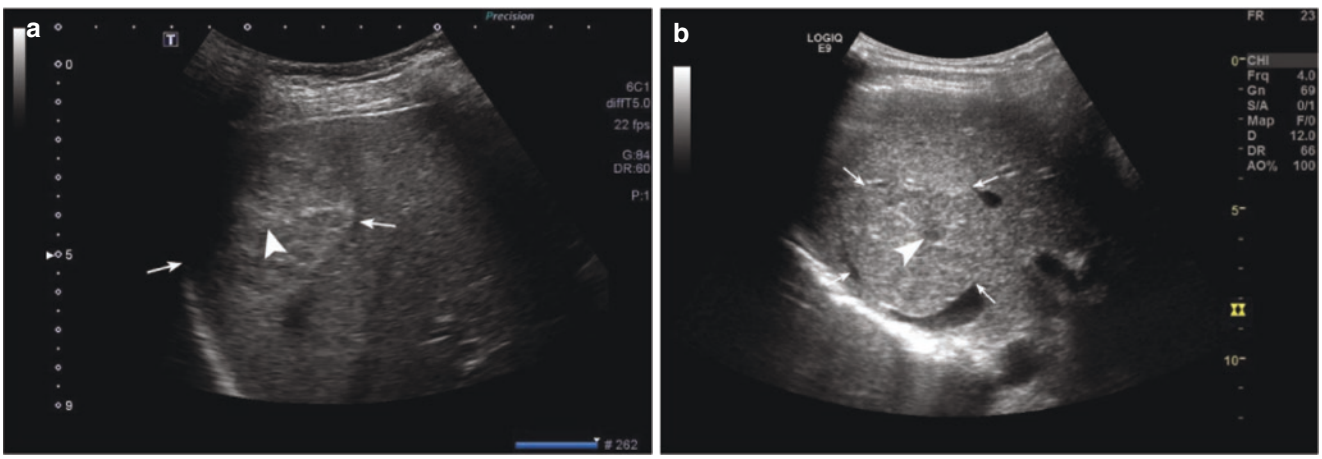
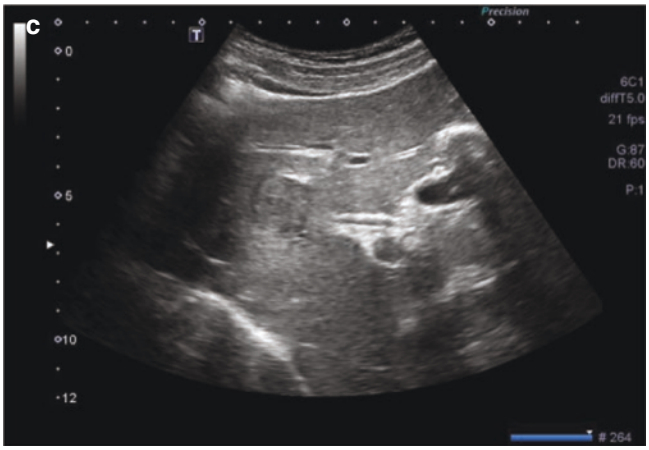



**Fig. 5.10** The characteristic central scar of focal nodular hyperplasia (FNH) may appear relatively hyperechoic (**a**, arrow: lesion; triangle arrow: central scar), hypoechoic (**b**, arrow: lesion; triangle arrow: central scar), and inapparent (**c**)

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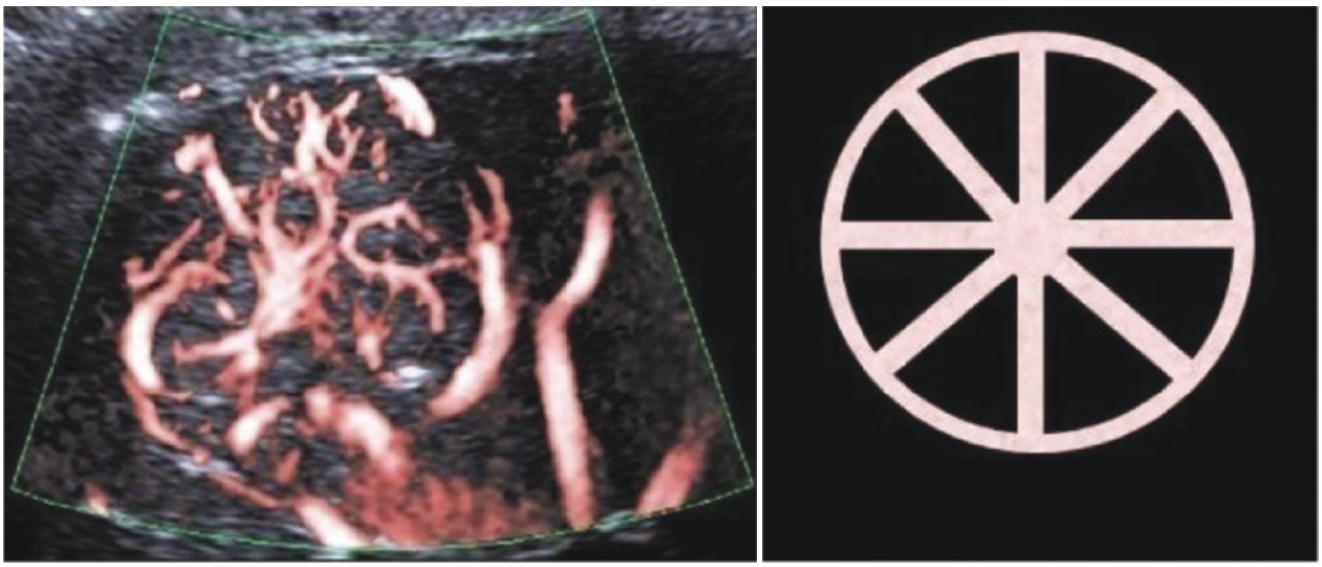


**Fig. 5.11** A diagram of "spoke-wheel" pattern

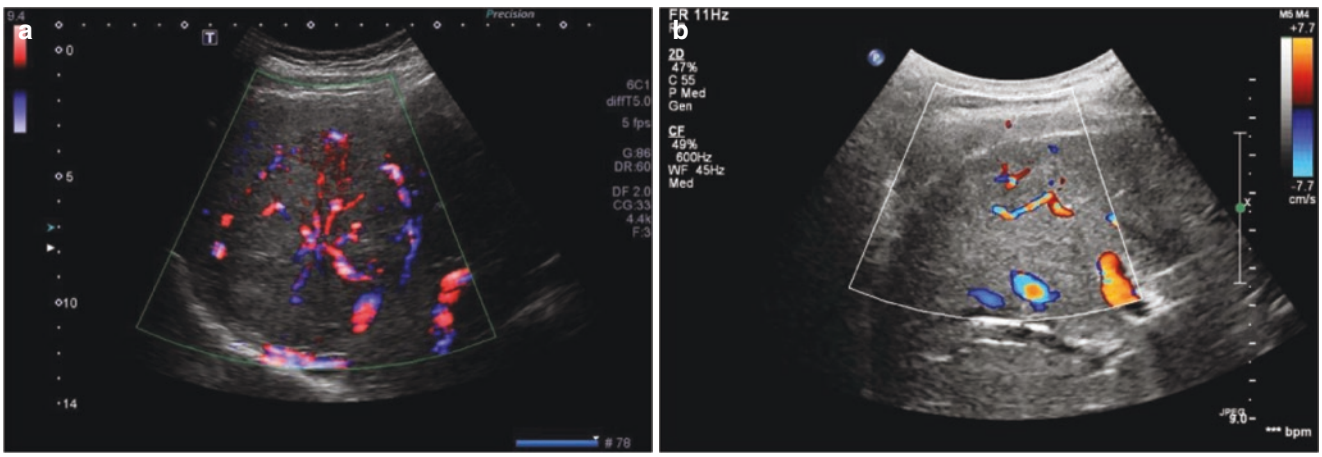
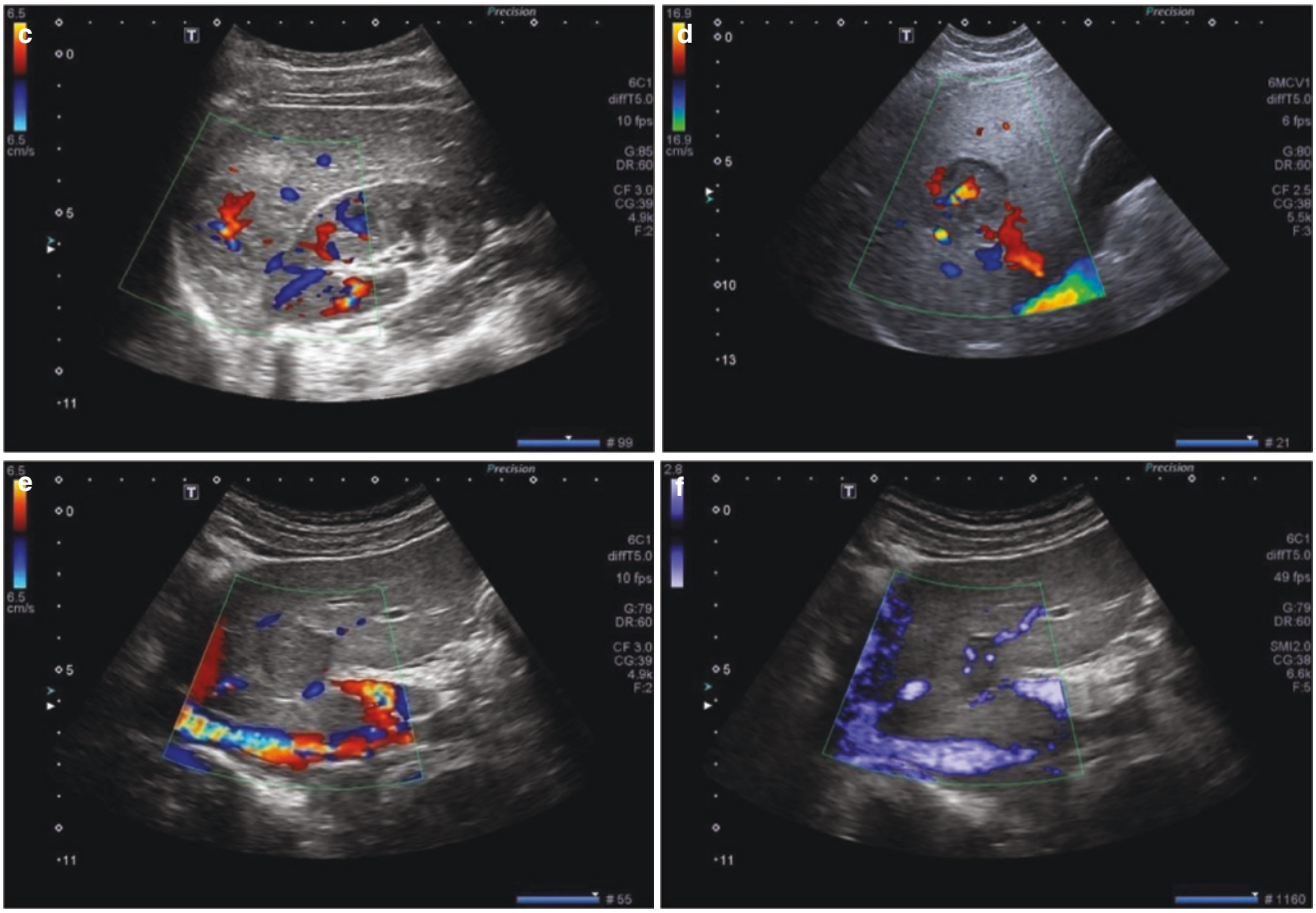



**Fig. 5.12** Different kinds of flow pattern of focal nodular hyperplasia (FNH) lesions can be detected on color flow imaging, including characteristic "spoke-wheel" pattern (advanced dynamic flow, ADF) (**a**), centrifugal (**b**, **c**), filiform (**d**), and apparent (**e**). The application of super microvascular imaging (SMI) can improve the display ability of color flow of the lesions (**f**)

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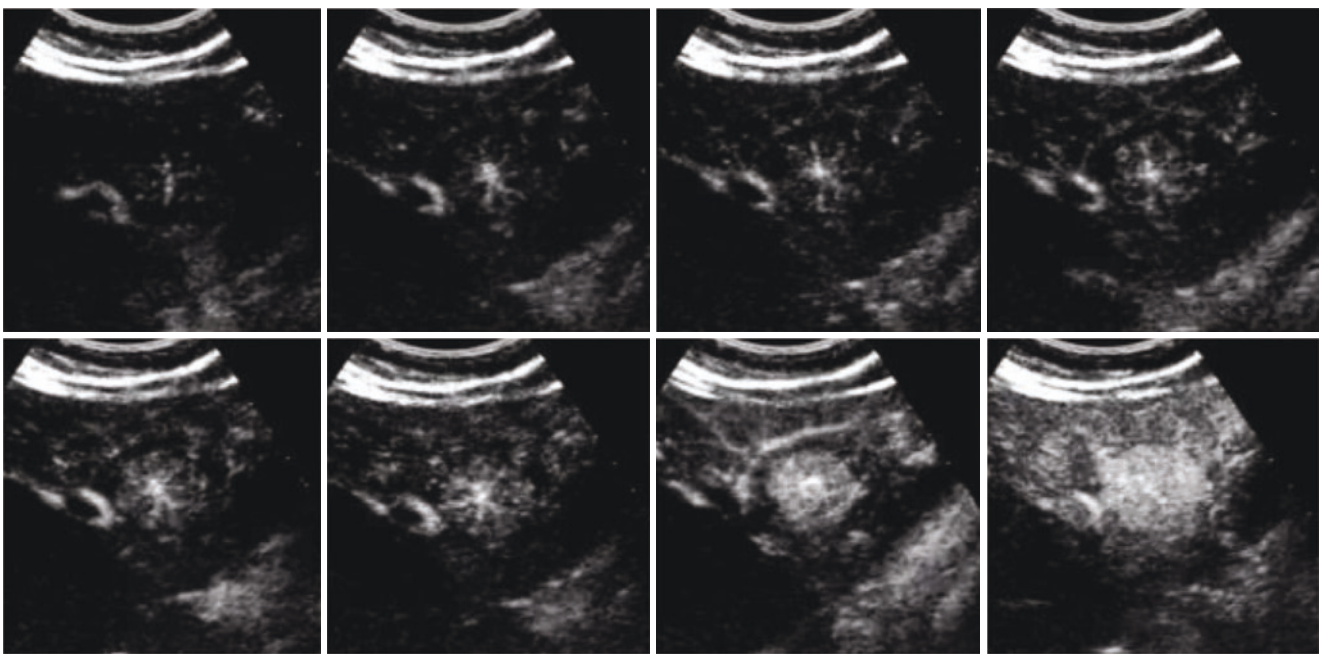


**Fig. 5.13** A focal nodular hyperplasia (FNH) lesion showed typical "spoke-wheel" enhancement pattern in arterial phase of contrast enhanced ultrasound

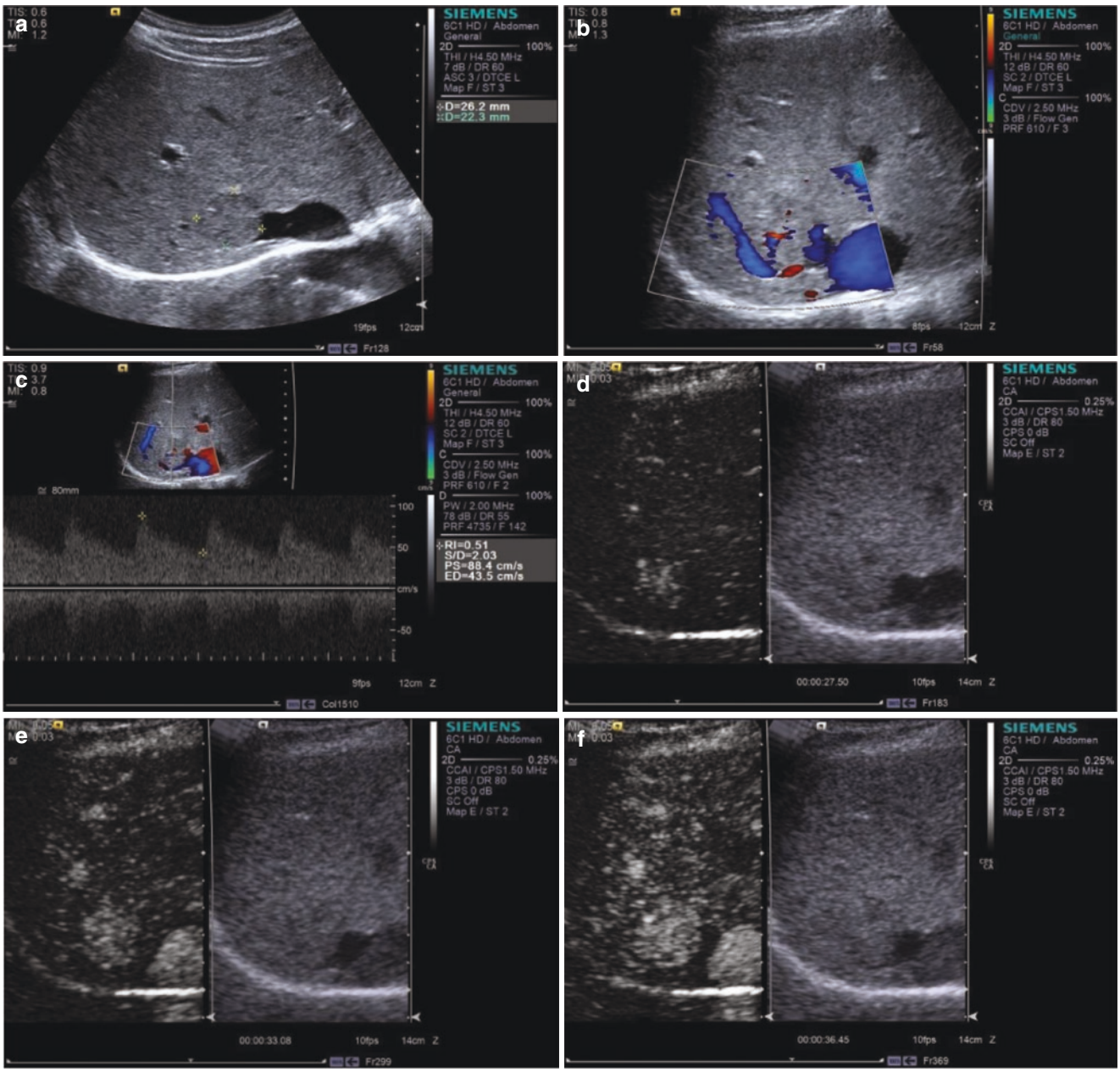
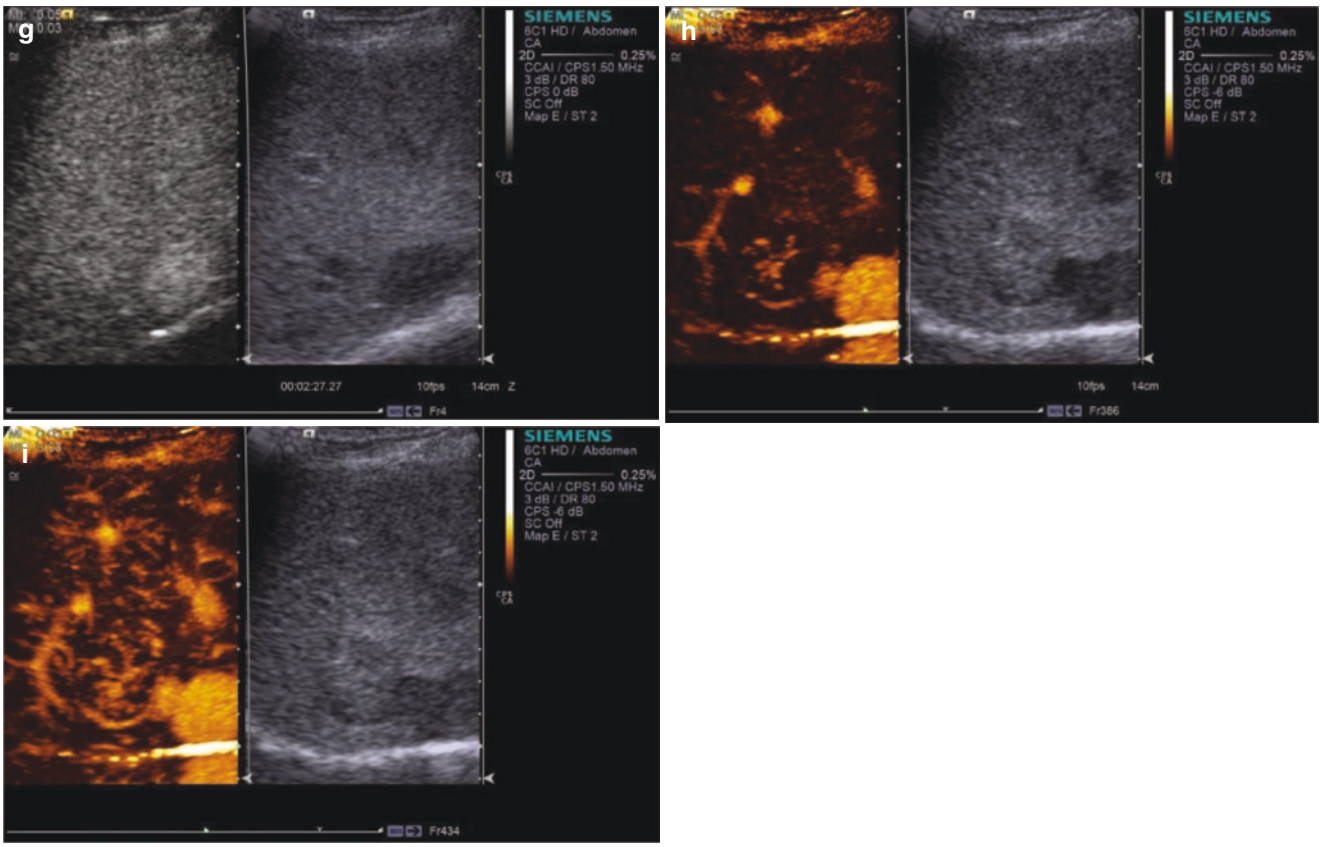



**Fig. 5.14** An incidentally detected focal nodular hyperplasia (FNH) lesion of a 32-year-old man. An isoechoic lesion measured 2.6 cm in maximum diameter could be detected by B mode ultrasound in right lobe of liver (**a**). Short branched color flow signals could be detected in central area of the lesion (**b**). Arterial Doppler spectrum with low resistance index (RI) as 0.51 was measured (**c**). The lesion showed homogeneous starlike hyperenhancement in arterial phase (**d**–**f**). The lesion kept sustained hyperenhancement till late phase (**g**). A similar enhancement pattern could also be observed clearer by microvascular imaging technology (**h**, **i**)

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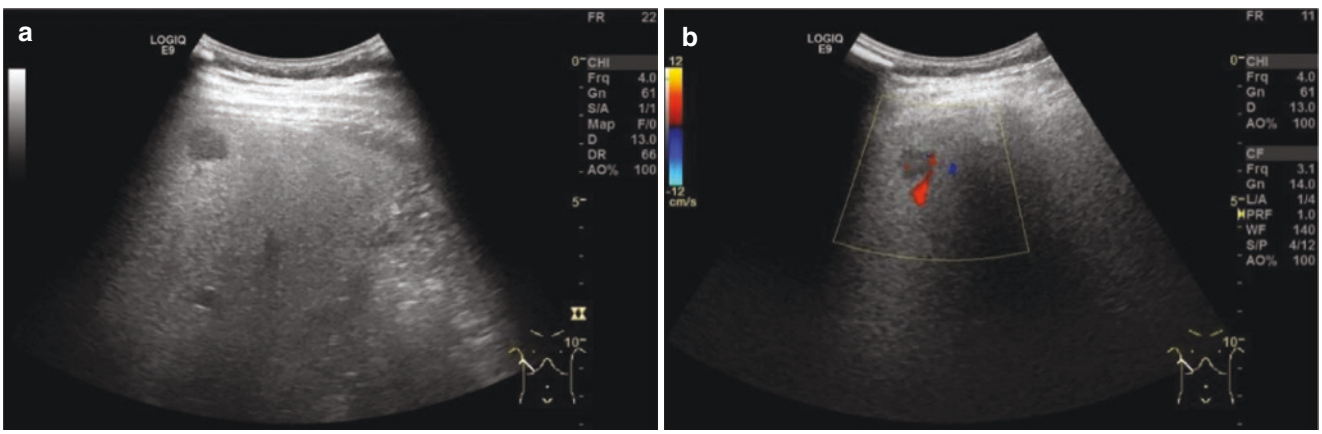



**Fig. 5.15** A case of a small and superficially located focal nodular hyperplasia (FNH) lesion (measured 1.4 cm in maximum diameter) near liver capsule. It was hypoechoic with a clear margin on B mode ultrasound (BMUS) (**a**). Dotted color flow signals were detected in the lesion (**b**). The margin of the lesion was clearer on BMUS performed with high frequency transducer (**c**) and more color flow signals could be detected in the center of the lesion (**d**). The lesion showed centrifugal hyperenhancement in arterial phase (**e**–**i**). It showed isoenhancement in subsequent portal venous (**j**) and late phases (**k**)

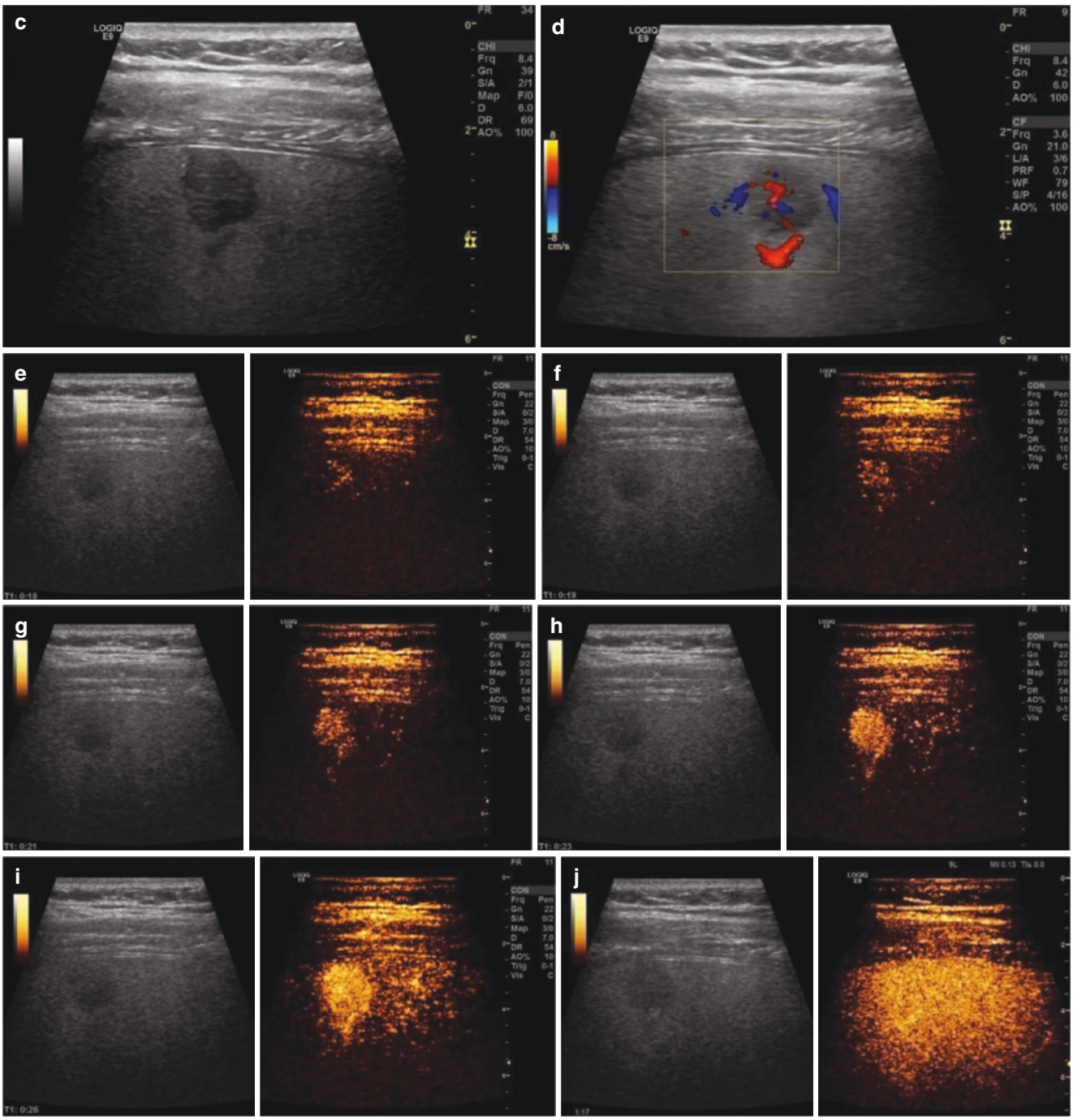
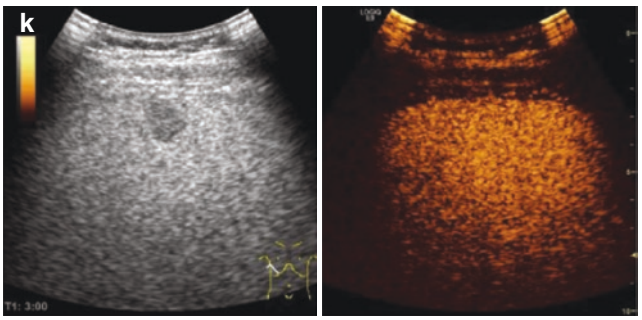



**Fig. 5.15** (continued)

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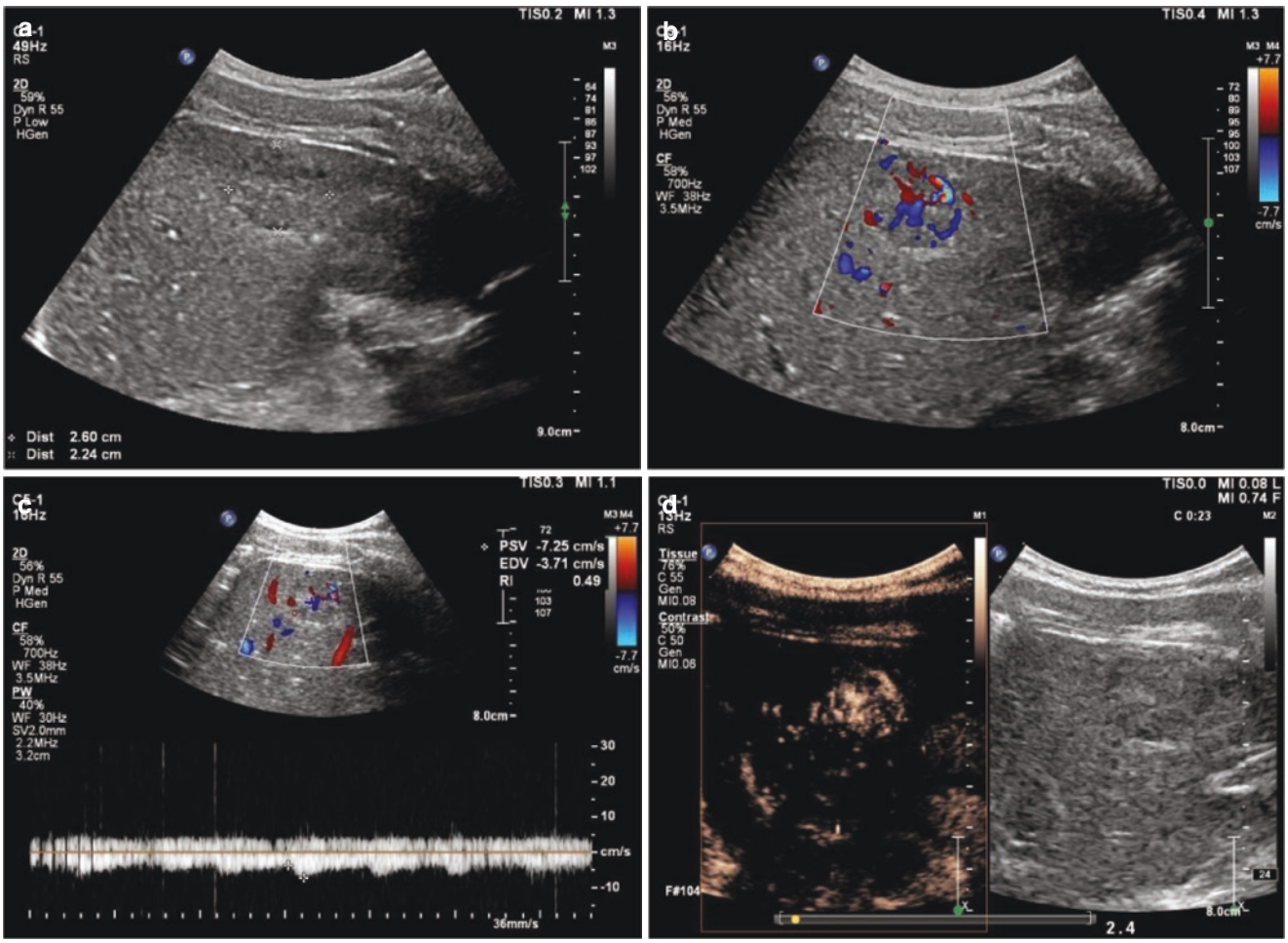
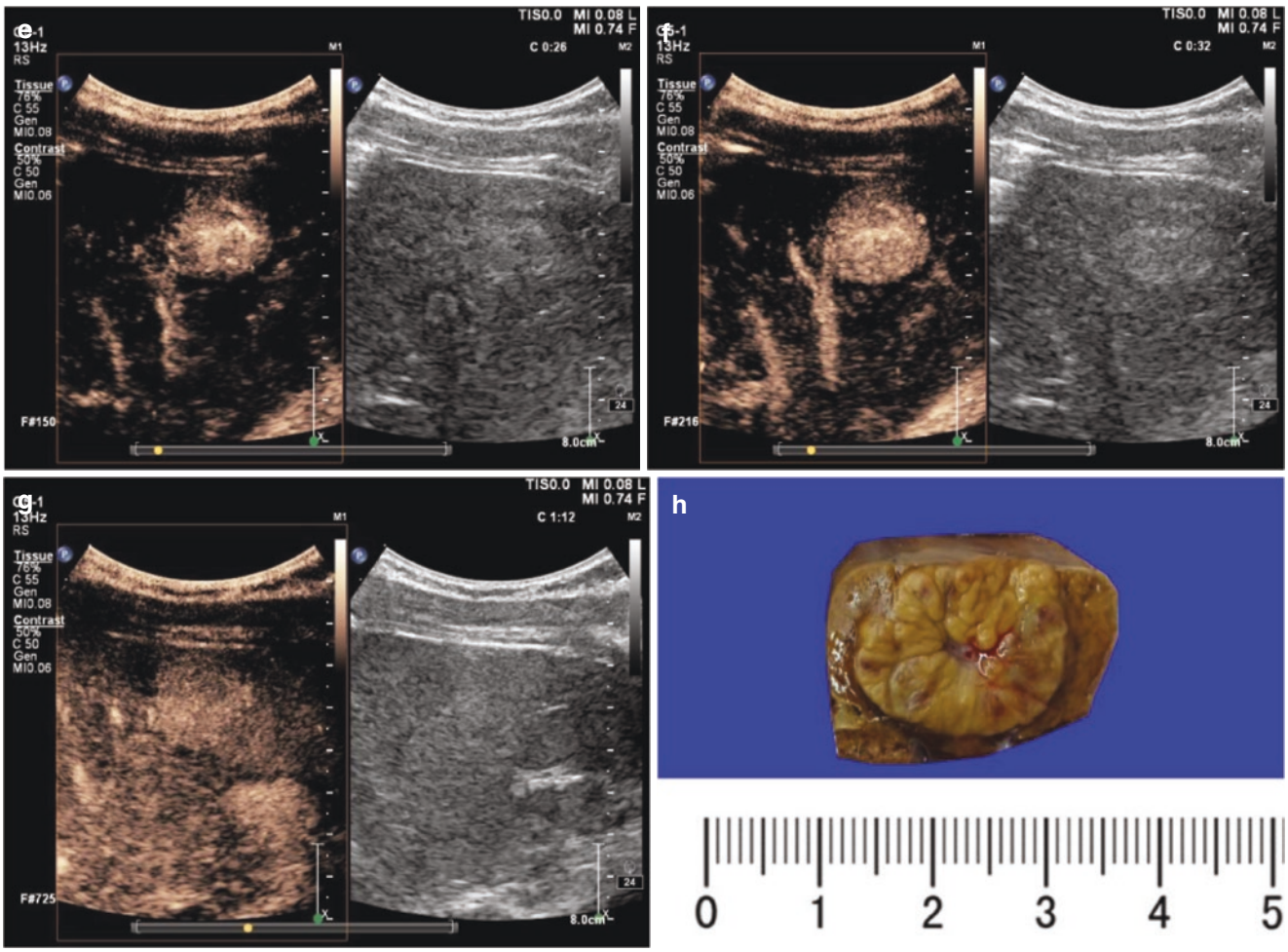



**Fig. 5.16** An isoechoic focal nodular hyperplasia (FNH) lesion with typical "spoke-wheel" color flow pattern. An isoechoic lesion was detected near the surface of right liver lobe on B mode ultrasound (**a**). Typical "spoke-wheel" color flow signals were detected inside the lesion (**b**). Arterial Doppler spectrum with low resistance index (RI) as 0.49 was measured (**c**). The lesion showed "spoke wheel" hyperenhancement in arterial phase of contrast enhanced ultrasound (**d**–**f**). It showed homogeneous hyperenhancement during portal venous and late phases (**g**). A typical central scar was observed on gross specimen after surgery resection (**h**)

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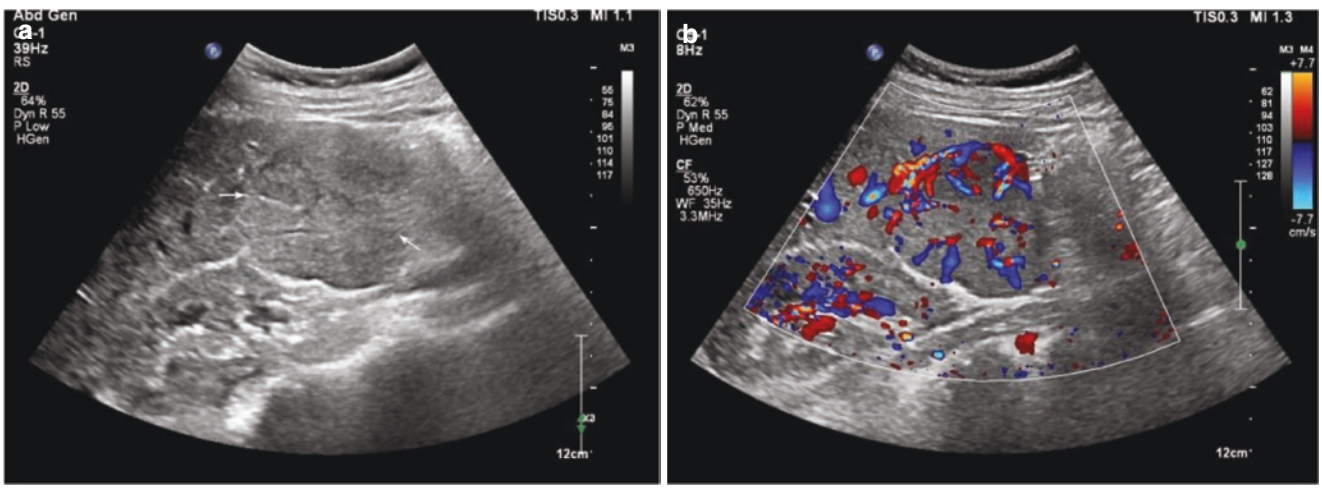



**Fig. 5.17** A focal nodular hyperplasia (FNH) lesion surrounded by a distorted feeding artery. A grayscale image reveals an isoechoic focal liver lesion (arrow) in right lobe of liver (**a**). A characteristic "spoke-wheel" pattern color flow was detected on color flow image (**b**). After injection of contrast agent, the lesion showed "spoke wheel" hyperenhancement during arterial phase of CEUS (**c**). An enlarged torturous feeding artery (arrow) can be observed around the lesion during early arterial phase (**d**). The lesion was observed hyperenhancement in portal venous and late phases (**e**, **f**). An unenhanced central scar could be observed on CEUS (**d**), which was final proved by gross specimen after surgical resection (**g**). Low-power photomicrograph (hematoxylin-eosin staining; original magnification ×20) showing central malformed artery (triangle arrow) and radial fibrous scar (arrow)

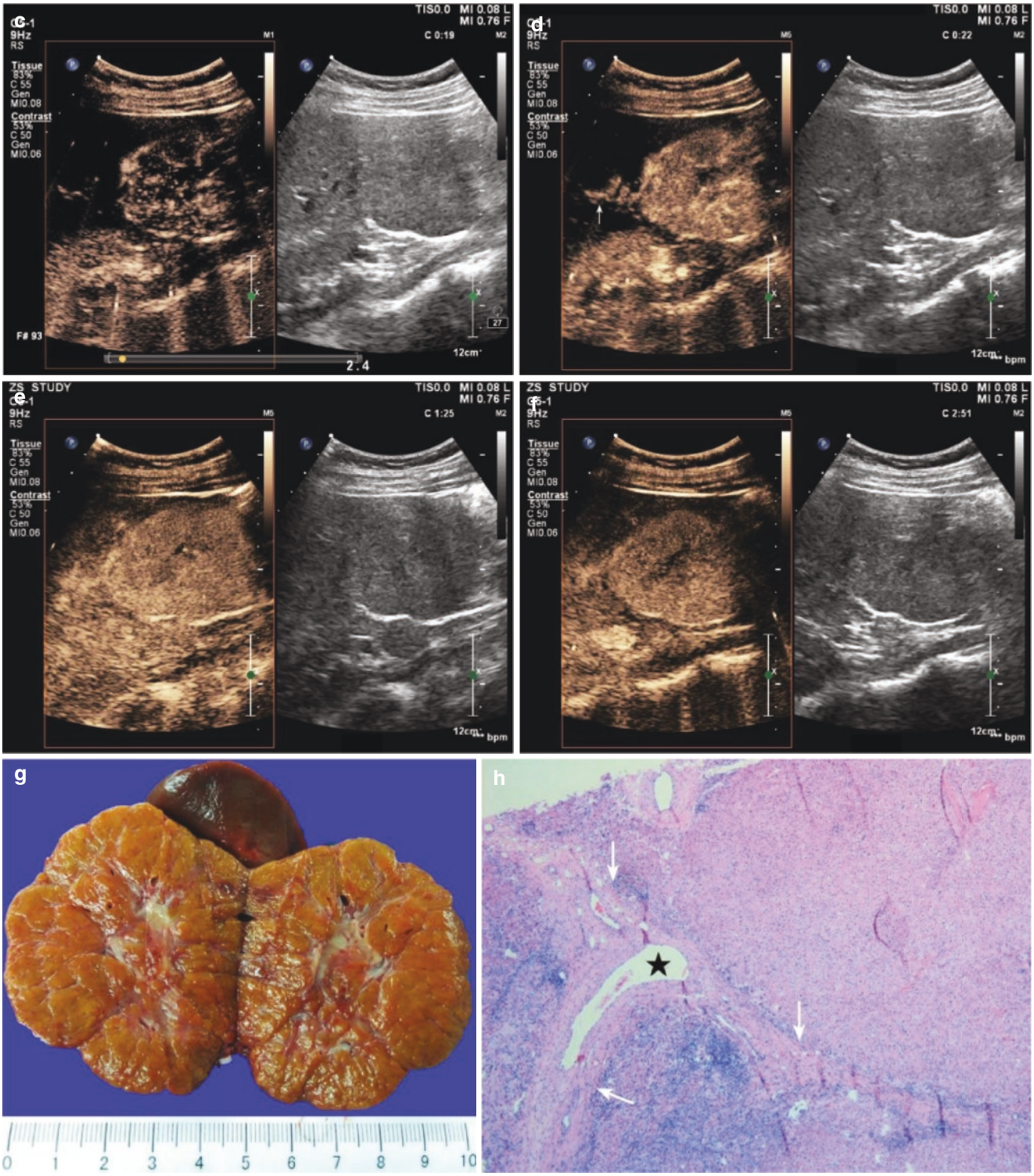



**Fig. 5.17** (continued)

phase, followed by isoenhancement in the portal and delayed phases.
- Central scar displays as an extremely hypodensity area in the center of lesion on nonenhanced CT. It showed nonenhancement in arterial phase, followed by complete filling as hyperdensity in delayed phase.
- The most reliable CT features for the diagnosis of FNH are the marked hyperenhancement of the lesion in arterial phase with central scar.

#### 5.2.2.4 MRI Findings
- Almost all FNH lesions show homogeneously isointense or hypointense on T1-weighted MRI images, and isointense or mildly hyperintense on T2-weighted images. The central scar will demonstrate high signal on T2-weighted images (Fig. 5.18).
- After injection of contrast agent, FNH displays uniform hyperenhancement in arterial phase, followed by isoenhancement in portal and delayed phases [8].
- The detection rate of central scar is higher in contrast enhanced CT/MRI than in CEUS.

#### 5.2.2.5 Other Imaging Findings
- Digital subtraction angiography is mostly used for therapeutic imaging before interventional embolization, rather than diagnostic imaging.
- The characteristic angiographic feature of FNH: a hypervascular lesion with a dominant feeding artery radiating in a spoke wheel pattern from the center to the periphery of FNH lesion, without arteriovenous shunt or portal vein inflow.

#### 5.2.2.6 Best Imaging Protocol Advices
- Diagnosis
  - A lesion presenting typical features (central scar and marked enhancement followed by no wash-out on contrast-enhanced CT/MRI/US, spoke-wheel, or centrifugal enhancement patterns especially on CEUS,

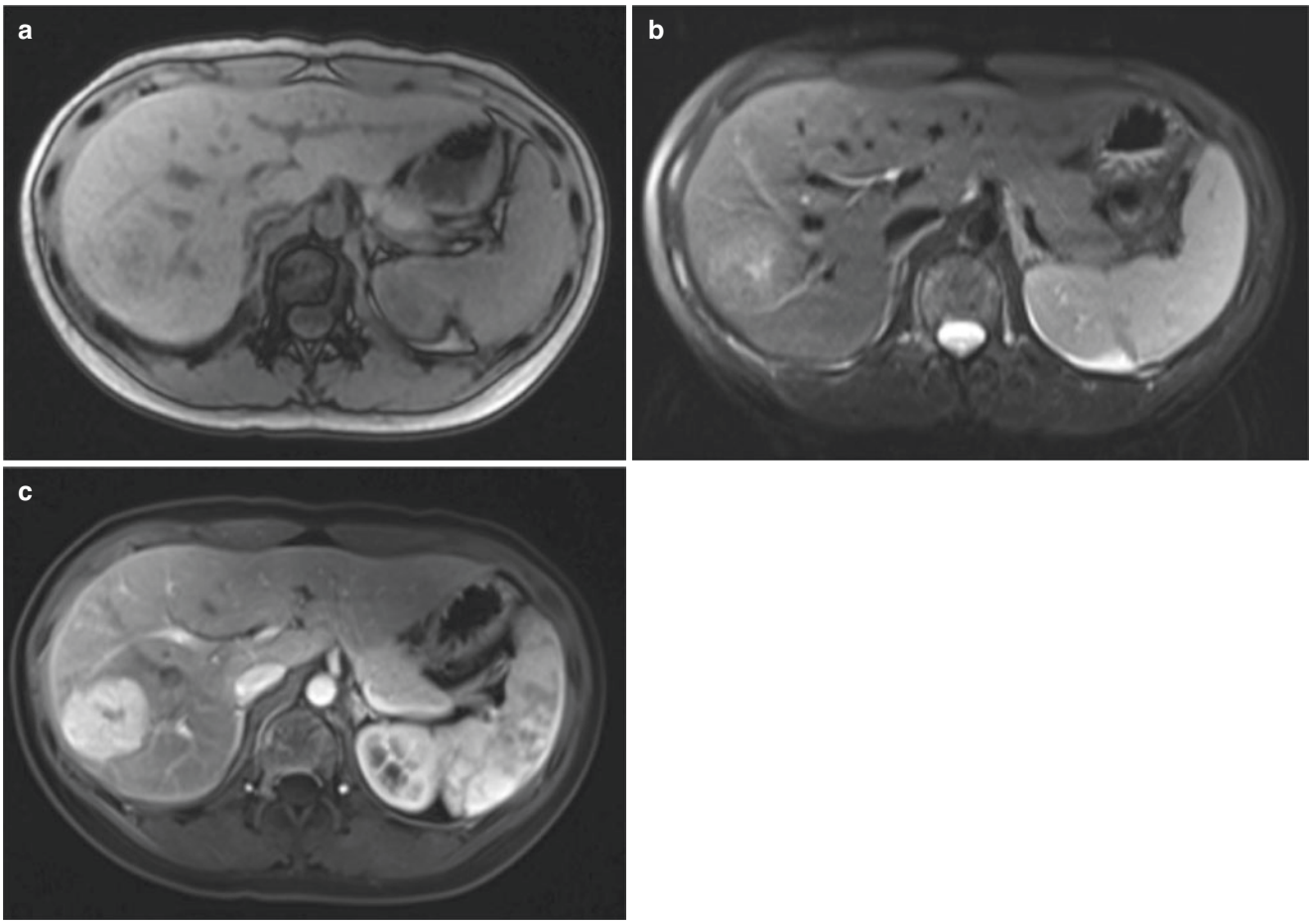



**Fig. 5.18** Non-contrast (**a**, **b**) and contrast-enhanced (**c**–**e**) MRI showed a FNH lesion hypointense on T1-weighted (**a**) and hyperintense on T2-weighted image (**b**), and a central scar was shown hyperintense on T2-weighted image. After injection of contrast agent, the lesion displays homogeneous hyperintense in arterial phase (**c**) and isointense gradually afterward (**d**, **e**). The central scar slowly enhanced in portal venous phase (**d**)

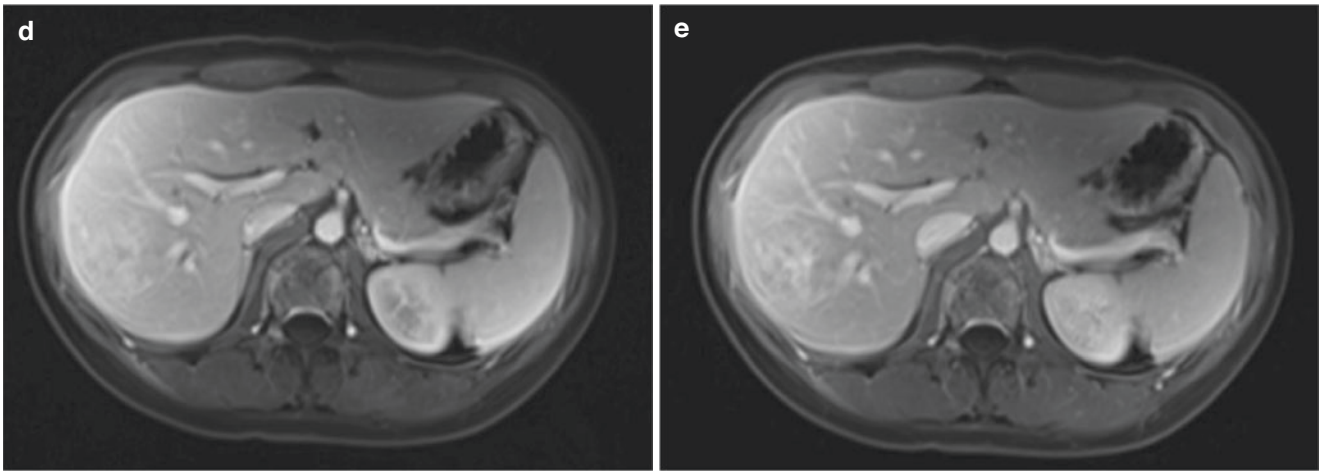



**Fig. 5.18** (continued)

spoke-wheel pattern of radiating arteries detected on color Doppler ultrasound), with no obvious liver cirrhosis and laboratory tests abnormality, a confident diagnosis of FNH can be made [10].

- Suspected diagnosis
  - A lesion suggestive of FNH on conventional ultrasound requires further examination to make a confident diagnosis. Both CEUS and MRI are the best options.
- Surveillance
  - Asymptomatic FNH should be followed up by conventional ultrasound once a year. Once the diagnosis was established, enlargement or steatosis of the lesion may not challenge the diagnosis of FNH.
  - If no typical feature is found by different contrast enhanced imaging modalities, but a persistent enhancement is observed in late phase, surveillance with periodical of every 6 months is recommended.

### 5.2.3 Differential Diagnosis

#### 5.2.3.1 Hepatic Adenoma

- Clinical impression
  - Hepatic adenoma (HA), as a benign liver tumor, often occurs in young women. It is prone to spontaneous bleeding, necrosis, and rupture, with potential risk of malignant degeneration.
- Non-contrast enhanced imaging
  - The presence of fatty components, intratumoral bleeding, and necrosis can produce heterogenous patterns in lesions on nonenhanced images.
- Contrast enhanced imaging
  - After injection of contrast agents, HA lesions often display heterogenous (on CECT/CEMRI/CEUS) or centripetal (on CEUS) enhancement during arterial phase followed by persistent enhancement or a slight wash-out in late phase.

#### 5.2.3.2 Hepatocellular Carcinoma

- Clinical impression
  - HCC usually derives from the liver background of the patients with long-term chronic liver disease caused by HBV or HCV infection. Specific serum AFP could also be elevated.
- Non-contrast enhanced imaging
  - A solidary round lesion in a cirrhotic liver background was a common finding on non-contrast enhanced images. Metastatic thrombus may be found in portal vein of patients with large tumors.
  - Color flow signals with high resistance index (RI) ($\geq$0.60) could be detected in HCC lesions on pulse-wave Doppler ultrasound.
- Contrast enhanced imaging
  - After injection of contrast agent, most HCC lesions display a typical enhancement pattern of rapid "wash-in and wash-out" as early arterial phase hyperenhancement followed by clear wash-out in the portal phase.

#### 5.2.3.3 Fibrolamellar Hepatocellular Carcinoma

- Clinical impression
  - Fibrolamellar hepatocellular carcinoma (FL-HCC) is a histologic variant of HCC. It usually occurs in young healthy patients without sex predilection or liver cirrhosis.
- Non-contrast enhanced imaging
  - Typical FL-HCC lesions show a well-defined and lobulated appearance with calcification inside that is easily noticed on US and CT. There exist a central stellate

scar in FL-HCC lesions as well, which demands differentiation from FNH.
  - The hypointensity of the central scar on T2-weighted MRI images can help differentiate FL-HCC from FNH, as FNH displays a hyperintense central scar on T2-weighted MRI images.
- Contrast enhanced imaging
  - On contrast enhanced imaging, an early heterogenous enhancement with wash-out in late phases of FLC may help differentiating from benign tumors.

### 5.2.4 Pathology

#### 5.2.4.1 General Features

- Macroscopic findings
  - About 90% of FNH lesions are solitary, only a few are multiple.
  - FNH lesions could occur in any lobe of liver. They are often found in the subcapsular regions, even as extracapsular pedunculated mass.
  - FNH lesions are well demarcated and unencapsulated, with an oval or lobulated shape.
  - Cut surface of FNH lesions could show brownish or tawny homogeneous solid mass. The color of the lesion is lighter than the surrounding liver parenchyma. A characteristic stellate scar with radiating fibrous septa could be shown in the center of the lesion. The fibrous septa could divide the lesion into several smaller nodules.
- Microscopic findings [11]
  - FNH lesions could contain all the cell types found in normal hepatic parenchyma, but cytologic atypia may also be seen in variant forms.
  - Proliferating hepatocytes divided into nodules by fibrous septa radiating outward to the periphery of tumor.
  - Stellate central scar contains wall-thickened malformed feeding artery with its branches running through the radiating fibrous septa.
  - Variable degree of bile ductular reaction (most important distinguishing features) and variable amount of mixed inflammatory infiltrate into the lesion.
  - Portal tracts are absent except for arterialized portal tracts.

#### 5.2.4.2 Staging, Grading, and Classification

- FNH is divided into two types, including typical and atypical. The latter type includes telangiectatic form, mixed hyperplasia and adenomatous form, and FNH with cytologic atypia [12].
- Typical FNH lesions account for the vast majority (about 80–90%), while the characteristic gross finding of central scar is only seen in 49% of FNH lesions.
- Atypical lesions account for only about 10–20%, in which telangiectatic FNH (tFNH), and "inflammatory FNH," are the major forms. The rest atypical FNH forms are rarely reported.

### 5.2.5 Clinical Issues

- Most FNH lesions are found accidentally on physical examination.
- The ratio of male to female in the Western world is 1:8, while it is close to equal in Asia [13].
- FNH lesions may occur at any age, most under 40 years old.
- Laboratory tests show almost normal, only a few with mildly elevated liver enzymes.

#### 5.2.5.1 Prognosis

- Growth in size can be observed in a few cases. Bleeding or necrosis is rarely observed. And FNH has no tendency of malignancy [14].

#### 5.2.5.2 Treatment

- No specific treatment is required once definite diagnosis is established.
- Surgical resection is only applied for patients with obvious tumor-related symptoms or diagnostic uncertainty.
- Interventional embolization, as a cogent alternative treatment option, is suitable for patients with oversized FNH [15].

## 5.3 Hepatocellular Adenoma

Wen-Ping Wang, Han-Sheng Xia, and Yi Dong

### 5.3.1 Terminology

**Definitions**

- Hepatocellular adenoma (HCA), also known as hepatic adenoma (HA), is a rare, solid, benign, epithelial tumor of liver. It usually appears solitary, and has an inclination to hemorrhage spontaneously. HCA usually occurs in females under the age of 50 years, especially those who are having estrogen-containing oral contraceptive medication. In addition, HCA (often with multiple foci) may

develop in boys with such predisposing conditions as glycogen storage disease (GSD).
- Four distinct subtypes of HCA have been recognized: inflammatory HCA (40–50%, IHCA), HNF1$\alpha$ (hepatocyte nuclear factor 1a)-inactivated HCA (30–40%, H-HCA), β-catenin activated HCA (10–15% b-HCA), and unclassified HCA (10–25%, UHCA).

## 5.3.2 Imaging

### 5.3.2.1 Ultrasonographic Findings

- HCAs are usually present as round, solid, well-defined, heterogeneous mass. Most HCA patients have a single nodule.
- Regarding echogenicity, HCAs are typically isoechoic, but sometimes can also be hypoechoic or hyperechoic due to the content of lesion and the condition of surrounding hepatic parenchyma [16].
  - The typical images of small HCAs are almost isoechoic in comparison to the surrounding hepatic parenchyma. This can be explained by the adenomas' comprising benign-appearing hepatocytes composed of large plates organized in sheets or cords (Fig. 5.19a).
  - HCA lesions may be relatively hypoechoic while the patient also suffers from steatosis, which can cause surrounding hepatic parenchyma to be relatively hyperechoic (Fig. 5.19b).
  - HCA lesions can also be hyperechoic while fat is contained (typically in the case of HNF1$\alpha$-inactivated HCA or patients with glycogen storage disease I and III) (Fig. 5.19c, d).
  - Big HCA lesions (>5 cm) may have a heterogeneous echotexture because of regressive changes such as intratumoral bleeding, necrosis, and calcifications (Fig. 5.19d).
- The centripetal bulky arterial flow with a relatively low resistance index (RI) may be detected in CDFI [17, 18] (Fig. 5.20).

### 5.3.2.2 Contrast Enhanced Ultrasound Findings

- CEUS allows real-time assessment of liver hemodynamic changes, and displays the dynamic "wash-in" and "wash-out" of the lesion, while CDFI can be used in detection of

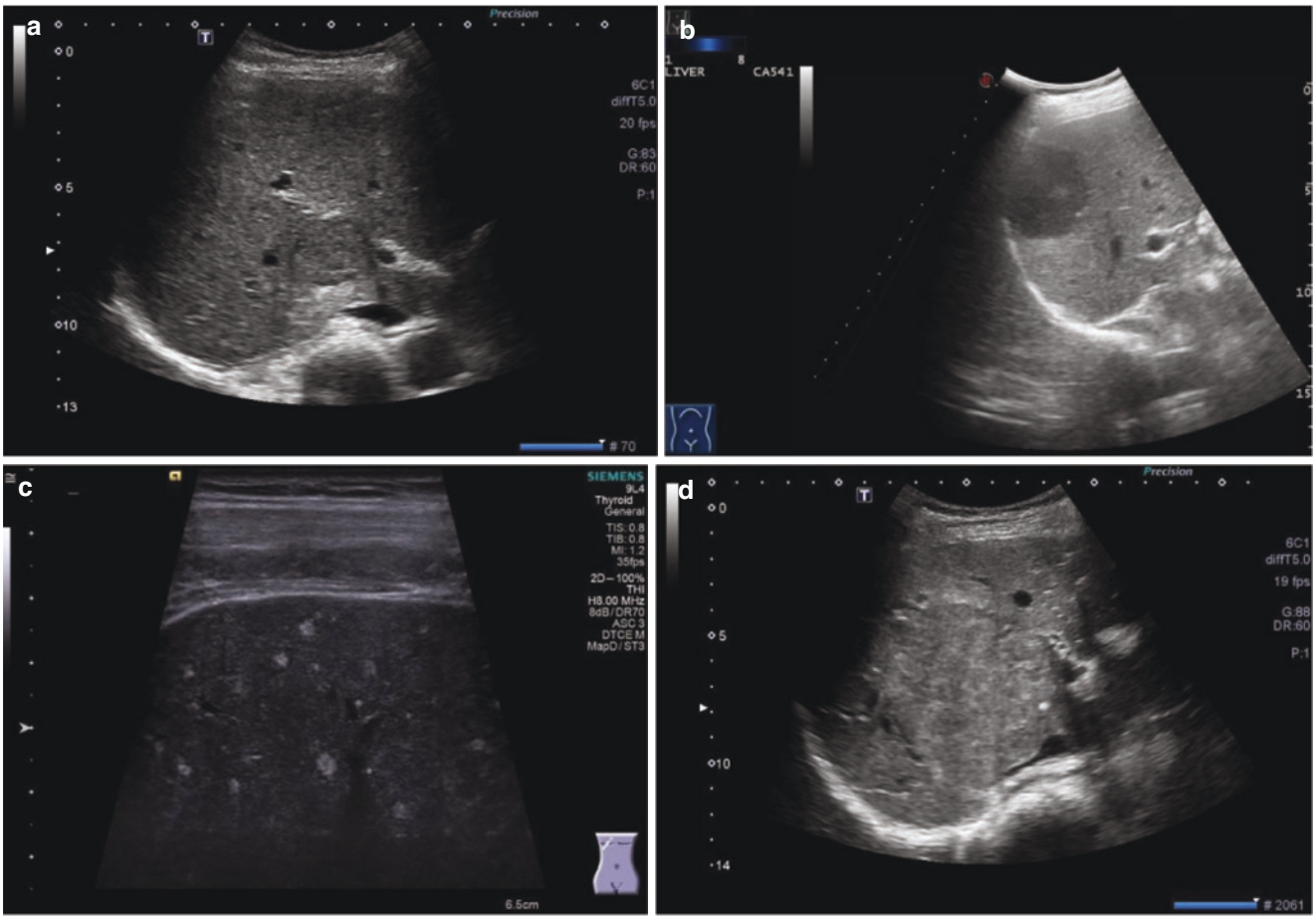



**Fig. 5.19** Different appearances of hepatocellular adenoma (HCA) lesions on B mode ultrasound, including isoechoic lesion (**a**), hypoechoic lesion (**b**), and hyperechoic lesion (**c**, **d**). Calcification can sometimes be observed inside HCA lesions (**d**)

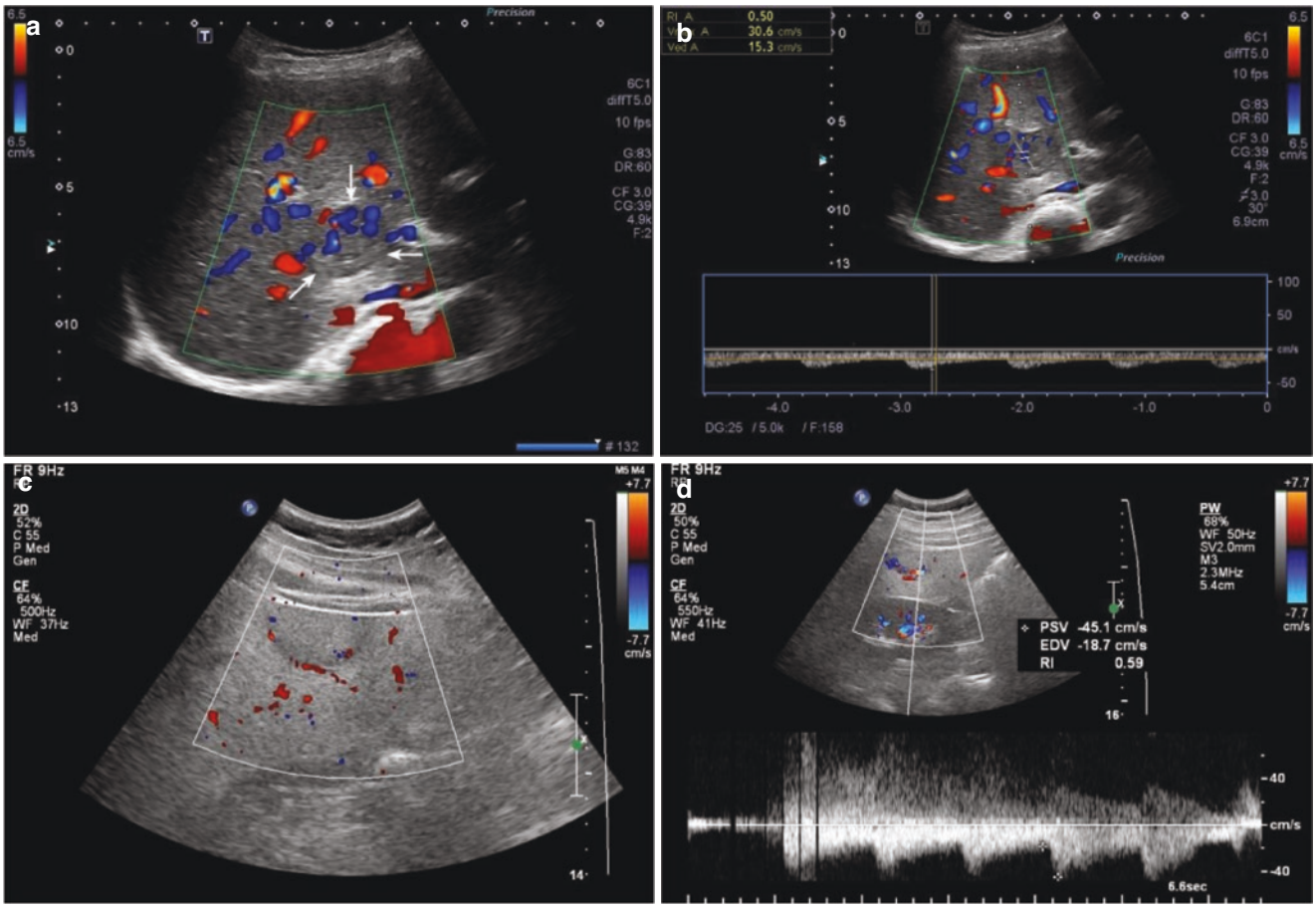



**Fig. 5.20** Branched pattern flow signals were shown inside the lesion on color flow image (**a**) and low resistance index (RI) of 0.50 was detected (**b**). Another case of a histopathologically proved hepatocellular adenoma (HCA) lesion with peripheral blood flow signals (**c**). RI was measured as 0.59 (**d**)

centripetal flow signals. The combination of CEUS and CDFI technology will be helpful to observe real-time filling enhancement mode of HCA, to detect the subcapsular feeding artery, and to make a differential diagnosis of HCA from FNH [16, 19, 20] (Figs. 5.21, 5.22, 5.23, and 5.24).

– Arterial phase

  Rapid and complete enhancement is usually shown. Real-time assessment often reveals centripetal or diffuse filling pattern in arterial phase.

  Abundant blood supply (similar to focal nodular hyperplasia (FNH), although HCAs usually enhance to a lesser degree).

– Portal venous and late phase

  Hypoenhancement in the portal venous phase and wash-out in the later phase.

### 5.3.2.3 CT Findings

- The attenuation of the HCA images is highly influenced by the condition of the lesions, such as fresh hemorrhage (may be hyperattenuating) or fat content (may render the mass to be hypoattenuating); and the hepatic tissue that surrounds the lesions, such as diffuse fatty infiltration, it may cause the lesion appears hyperattenuating.
- Generally, the presentation of HCAs under CT scan is well defined and iso-attenuating to the normal hepatic tissue [18, 20].
- On contrast administration, the images demonstrate transient relatively homogenous enhancement returning to near iso-density on portal venous and delayed phase [18, 20].

### 5.3.2.4 MRI Findings

In common HCA (without hemorrhage), the MRI images usually appear as [17, 20]

- T1: Can be variable from being hypo-, iso-, hyperintense. Most are hyperintense (35–77%).
- T2: Mildly hyperintense (47–74%).
- In/out-of-phase: The presence of fat typically leads to signal drop out on out-of-phase imaging.

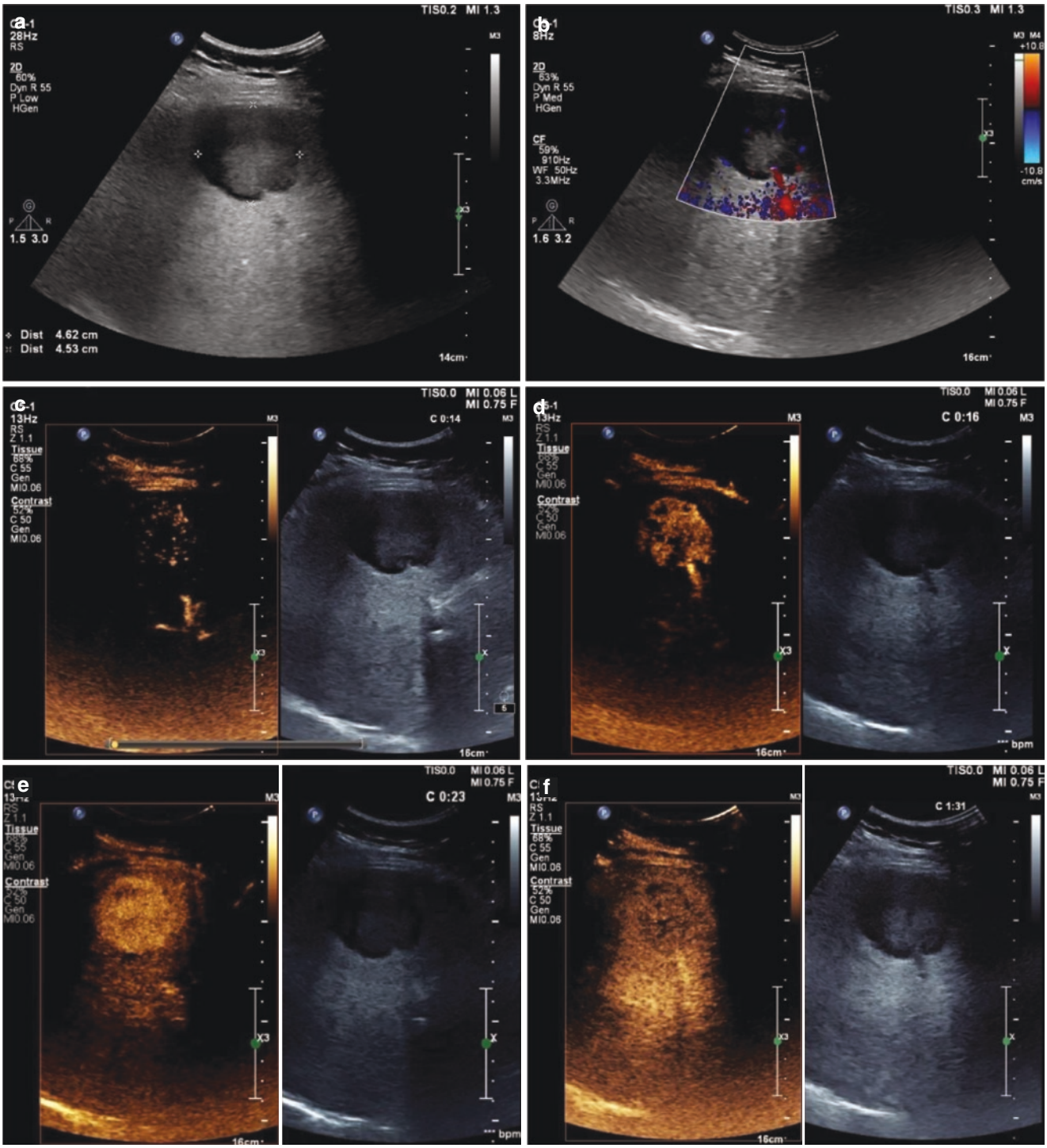
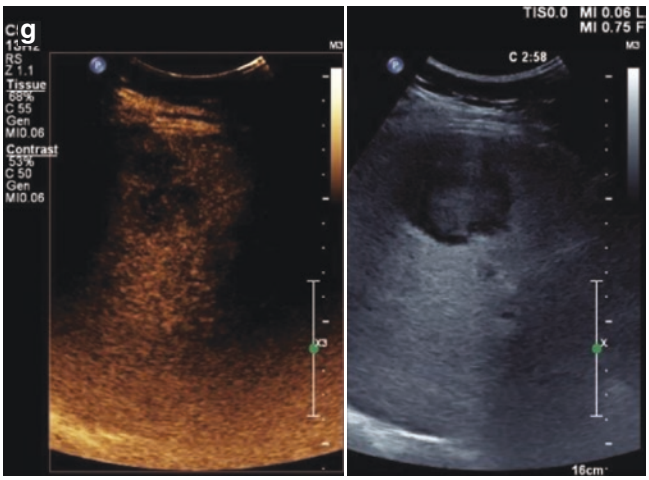



**Fig. 5.21** A 49-year-old man with β-catenin-activated hepatocellular adenoma (HCA). The hypoechoic lesion was located in the right hepatic lobe on B mode ultrasound (**a**). Perilesional blood flow signals were detected (**b**). On contrast enhanced ultrasound, the lesion demonstrated heterogeneously diffuse hyperenhancement in early arterial phase (**c**–**e**). The feeding artery could be observed clearly. The lesion was hypoenhancement in both portal venous and late phases (**f**, **g**)

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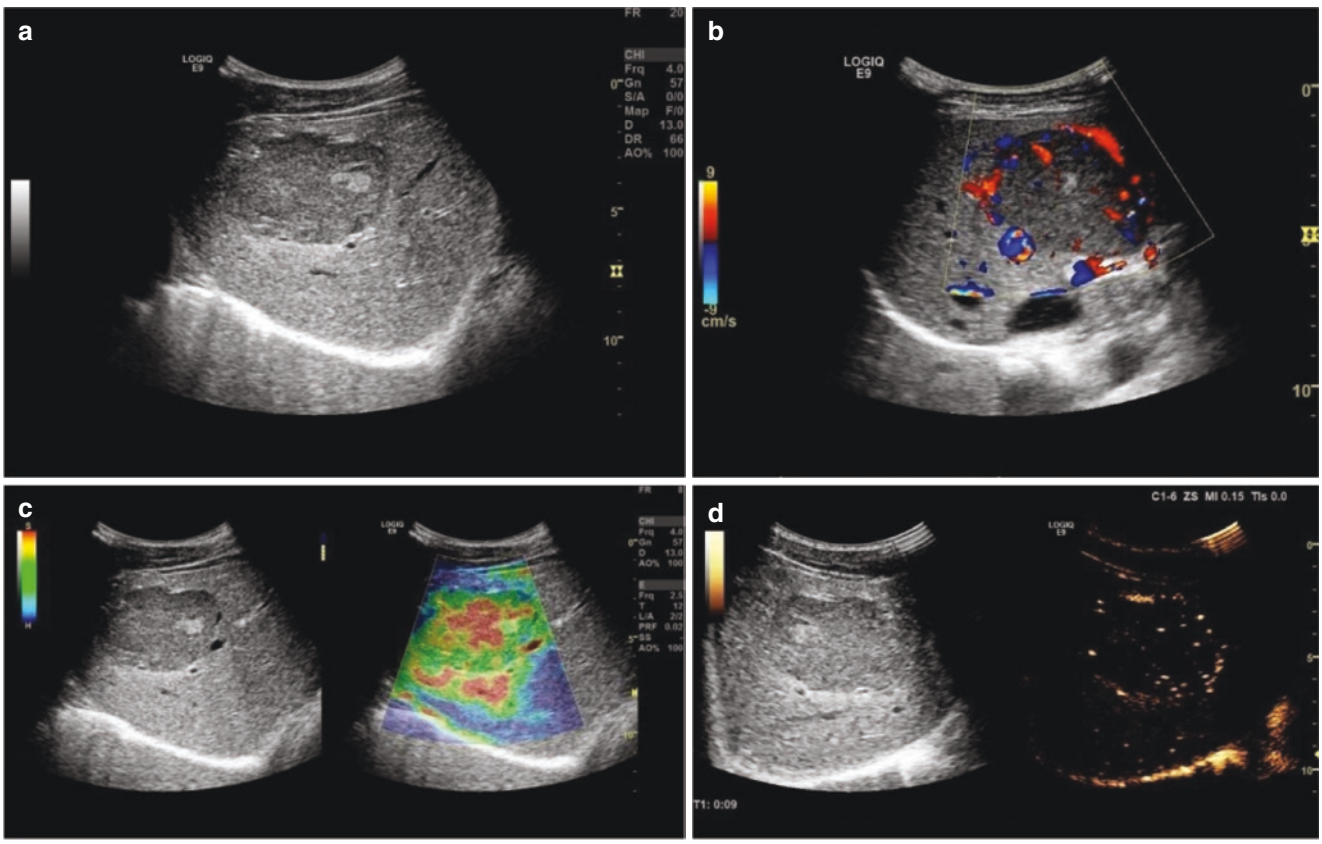
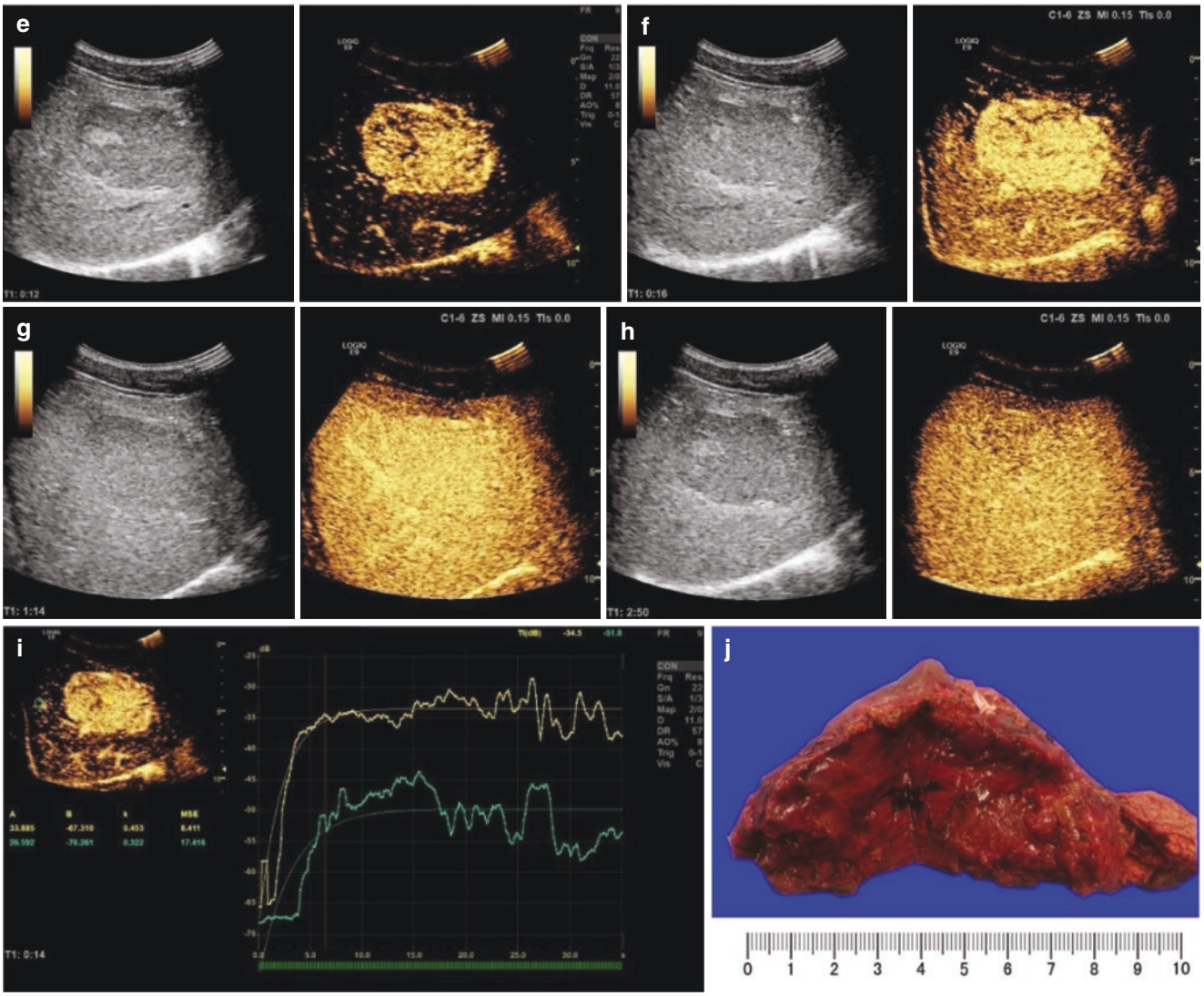



**Fig. 5.22** A 46-year-old man with surgically proved inflammatory hepatocellular adenoma (HCA). The lesion was hypoechoic on B mode ultrasound (**a**). Rim-like blood flow signals were detected in the perilesional area (**b**). The lesion was soft on ultrasonic elastography (**c**). On contrast enhanced ultrasound, the lesion demonstrated complete homogeneous hyperenhancement in arterial phase (**d**–**f**). It was isoenhanced in both portal venous and late phases (**g**, **h**). Time intensity curve could reflect the intensity change of the lesion (**i**). It was confirmed by pathology after surgery (**j**)

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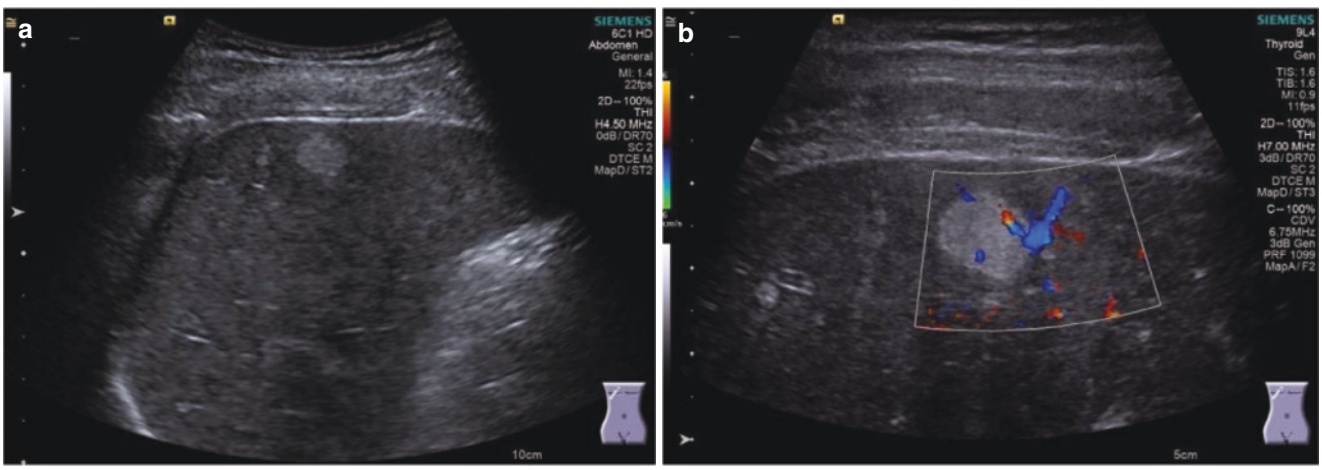
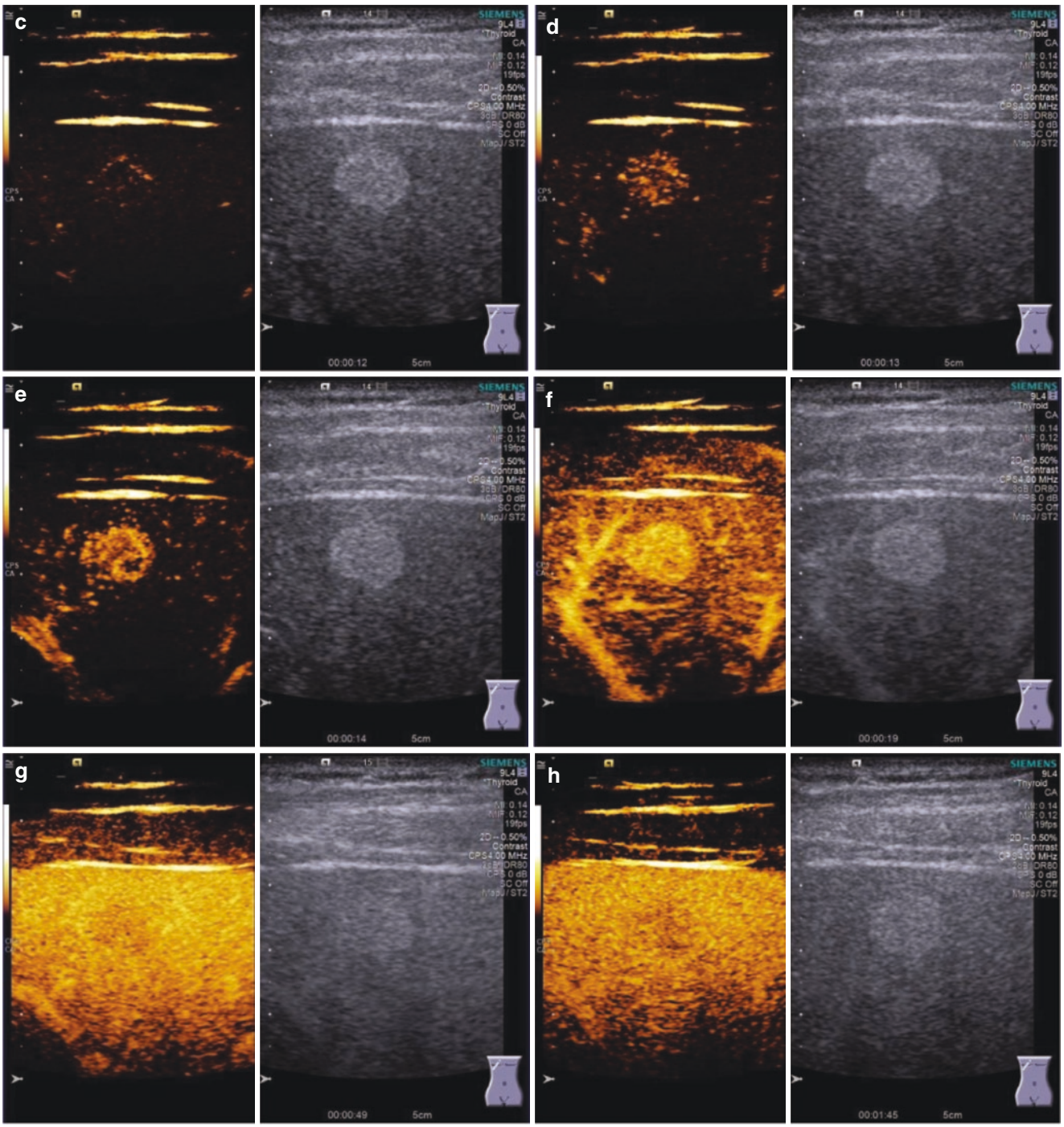



**Fig. 5.23** A case of small hyperechoic hepatocellular adenoma (HCA) lesion. The lesion was near the surface of right hepatic lobe (**a**). It was more clear on high-frequency ultrasound images. Branched color flow signals were detected in the lesion (**b**). It showed complete hyperenhancement during arterial phase (**c**–**f**). It showed mild wash-out in portal venous and late phases (**g**, **h**)

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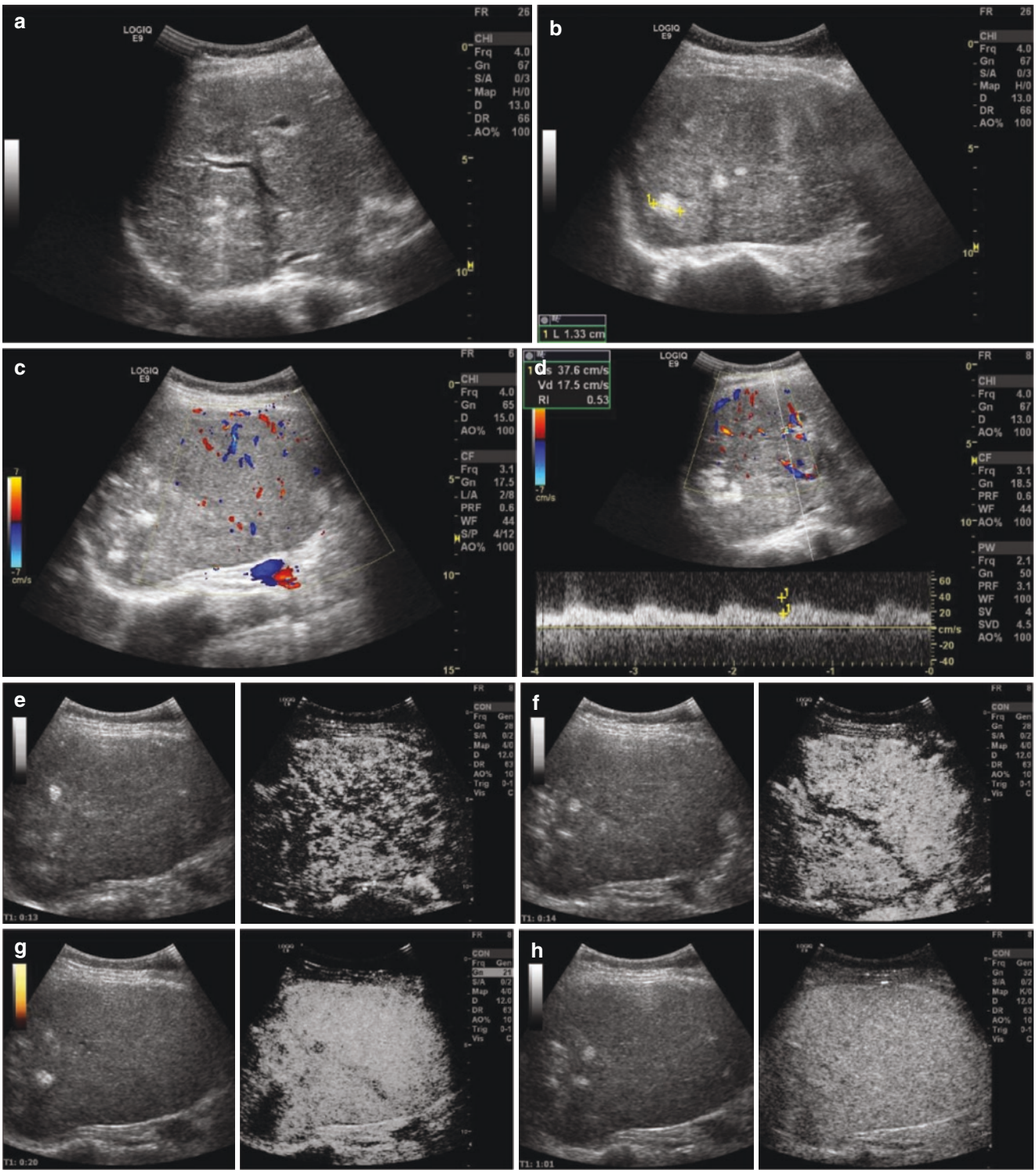


**Fig. 5.24** A case of hepatocellular adenoma with hemorrhage in a 27-year-old woman. B mode ultrasound showing a hypoechoic lesion with unclear boundary in the right lobe of the liver (**a**). Spotty hyperechoic calcification can be observed inside the lesion (**b**). Color flow signals could be detected inside the lesion (**c**). Arterial Doppler spectrum with resistance index (RI) as 0.53 was measured (**d**). The lesion was heterogeneously enhanced with a bulky and tortuous artery under the capsule during arterial phase on contrast enhanced ultrasound (**e**–**g**). Isoenhancement was observed in portal venous phase (**h**) and intratumoral hypoechoic areas were detected in late phase (**i**). Contrast-enhanced computed tomography (CECT) showing multi low-density areas inner nodule (**j**). Gross specimen showed hemorrhage change of the whole lesion (**k**) and low-power photomicrograph (hematoxylin–eosin staining; original magnification ×20) showed multiple hemorrhagic areas and dilated sinusoidal spaces (**l**)

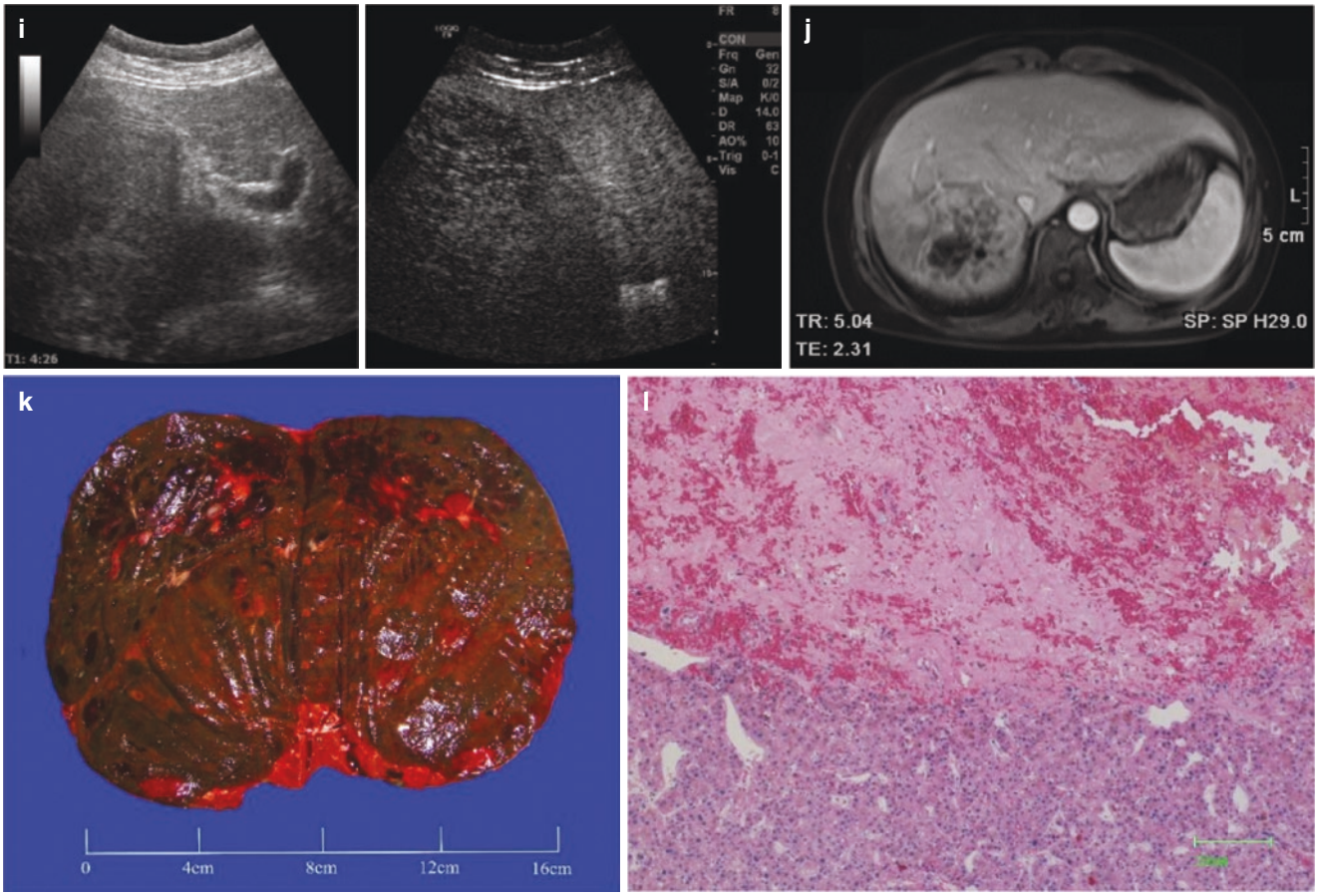


**Fig. 5.24** (continued)

- Contrast studies
  - T1 C+ (Gad)
    On the dynamic postcontrast sequence, adenomas show early arterial enhancement and become nearly isointense about liver on delayed images.
    Some reports suggest that the enhancement becomes isointense to the rest of the liver by 1 min.
  - T1 C+ (hepatocyte-specific)
    Adenomas usually appear hypointense on hepatobiliary phase (20 min after injection) due to reduced uptake of Gd-EOB-DTPA/Eovist (cf. FNH which appears iso- to hyperintense).

#### 5.3.2.5 Imaging Recommendations

- Best imaging tool
  - HCAs are usually detected by imaging, typically by abdominal ultrasound or CT scan.
  - The ultrasound is always considered to be the first choice because of its safety, availability and low cost.
  - Sometimes, the ultrasonic images of lesions of HCA may appear similar to other several liver tumors such as FNH or HCC. In this kind of situation, a multi-phase contrast-enhanced imaging study such as CT or MRI may be applied to provide more diagnostic information.

### 5.3.3 Differential Diagnosis

#### 5.3.3.1 Focal Nodular Hyperplasia

- HCA and FNH are best distinguished with immunohistochemical stains for glutamine synthetase and inflammatory proteins, such as SAA or CRP.
- Combination of the CEUS and CDFI techniques can help to reveal the real-time flow signals of the lesions and detect the subcapsular feeding artery [21–23].
  - FNH is usually observed hyperenhanced in arterial and portal venous phases in more than 90% of cases.
  - The arterial enhancement is typically central (60–70%) or eccentric (<20%) with centrifugal filling patterns.
  - In larger FNHs (>6 cm), more than one central or peripherally supplying artery can be identified.
- MRI scan is also a good way to differentiate FNH from HCA [17].

- T2WI: Bright central scars show late enhancement.
- Retains hepatocyte-specific contrast material [e.g., Eovist (gadoxetate)] on delayed phase MRI.

#### 5.3.3.2 Hepatocellular Carcinoma

- Rapid wash-out.
- Rim enhancement of the pseudocapsule may be observed on the late-phase images of CT/MRI.
- Different demographics.
- May be difficult to distinguish from an adenoma if well-differentiated.

#### 5.3.3.3 Fibrolamellar Hepatocellular Carcinoma

- Radiating/central scar.
- Calcification more common [18].
- Lymph node enlargement common.

#### 5.3.3.4 Hepatic Hemangioma

- Ultrasonic images of hemangiomas typically appear as well-defined hyperechoic lesions with a small proportion (10%) of hypoechoic region (which may be due to a background of hepatic steatosis, where the liver parenchyma is of increased echogenicity).
- On dynamic CT and MRI using conventional ECF agents, a hemangioma may show typically peripheral nodular enhancement in arterial phase with centripetal and prolonged enhancement [17].

### 5.3.4 Pathology

#### 5.3.4.1 General Features

- In the examination of biopsy or resection specimens stained with hematoxylin and eosin (H&E), a HCA lesion is characterized by scattered thin-walled vascular channels within the mass and the absence of portal and central veins and bile ducts or connective tissue [16].
- Depending on the several subtypes of HCA, different degrees of hepatocyte steatosis, inflammatory cells, bile duct proliferation, hemorrhage, or dystrophic blood vessels may be present.

#### 5.3.4.2 Staging, Grading, and Classification

- The classification of HCA [22]
- Four distinct subtypes of HCA are recognized as inflammatory HCA, HNF1$\alpha$-inactivated HCA, β-catenin activated HCA, and unclassified HCA. In these different subtypes, several genetic mutations are identified, resulting in benign proliferation of hepatocytes and in some HCA, malignant transformation.
  - Inflammatory HCA (IHCA): Both serum and lesion indicators of IHCA patients show active inflammatory response. The markers serum amyloid A and C-reactive protein seem to express higher, which are all classic indicators of the acute phase response.
  - HNF1$\alpha$-inactivated HCA (H-HCA): Characterized by a downregulation of the liver fatty acid-binding protein (LFABP, which is caused by inactivating mutations of the HNF-1$\alpha$ gene.); rare malignant progression would happen in this phenotype, which is not apparent in the other HCA subtypes.
  - β-Catenin activated HCA (b-HCA): Defined by activating mutations of β-catenin that resist phosphorylation-mediated downregulation by the GSKB/APC/AXIN complex.
  - Unclassified HCA (UHCA): The genetic mutation of them still remains unclear or unclassified.

### 5.3.5 Clinical Issues

#### 5.3.5.1 Presentation

- The clinical presentation is various due to the size of tumor and the location it occurs.
- Many HCA patients usually have no symptoms, with normal liver function test results and no specific detection of serum tumor markers such as α-fetoprotein [23].
- Few patients may suffer from slightly abdominal pain with nausea, poor appetite or other digestive disorder symptoms [23].

#### 5.3.5.2 Complications

Common complications of HCA include lesion rupture, hemorrhage, and malignant transformation [16].

- Lesion Rupture and Hemorrhage
- Are the most important complications, which can cause hypovolemic shock or even death.
- Common risks are increasing tumor sizes (≥4 cm), subcapsular location, and long duration of contraceptive use.
- Most common presentations are severe abdominal pain and hemodynamic disorders, or even hypovolemic shock.
- Malignant transformation
- Previous reports showed that HCA may have possibility to transform from benign to malignant (8–13%).
- It still remains unclear whether the origin of malignant tissue comes from HCA lesion or periphery hepatic tissue.

#### 5.3.5.3 Prognosis, Treatment, and Surveillance

The natural prognosis and indication for surgical treatment and surveillance are not well reported.

- For symptomatic patients and/or lesions ≥5 cm (which have a higher risk of rupture or hemorrhage.

- Surgical (laparoscopic) resection or enucleation could be considered if necessary.
- In cases of multiple lesions, resection of the largest tumor and close follow-up of the remaining lesions are considered as a possible management of choice.
- Embolization can be performed if hemorrhage occurs.
- For asymptomatic patients with smaller lesions (<5 cm).
- Conservative therapy should be a better choice.
- Sometimes, HCAs can regress spontaneously while withdrawing oral contraceptives or having dietary for glycogen storage diseases.

## 5.4 Focal Fatty Infiltration

Yi Dong, Pei-li Fan, and Wen-Ping Wang

### 5.4.1 Terminology

**Definitions**

- Focal fatty infiltration (FFI) is a form of fatty liver disease. Obesity, atherogenic dyslipidemia, arterial hypertension (metabolic syndrome), insulin resistance, and glucose intolerance could lead to overnutrition in liver, particularly in genetically predisposed individuals [24].
- FFI occurs in a local area of the liver, showing focal or patchy mass-like appearance on images.
- It is classified into focal steatosis and focal steatosis spare.

### 5.4.2 Imaging

#### 5.4.2.1 Conventional Ultrasound Findings

- Focal steatosis usually shows as a homogeneously hyperechoic irregular area with slight posterior acoustic attenuation (Fig. 5.25) but focal steatosis spare could appear as hypoechoic mass (Fig. 5.26).
- Both focal steatosis and focal steatosis spare are absent of hypoechoic halo.
- They have well-defined margins with irregular shapes.
- FFIs are mostly located in the medial segment of the left liver lobe close to the falciform ligament (Fig. 5.25), the gallbladder bed (Fig. 5.26), the forepart of segment I, and the back of segment IV [25].

#### 5.4.2.2 Contrast Enhanced Ultrasound Findings

- FFIs show arterial phase isoenhancement and persists in all phases on CEUS (Figs. 5.25 and 5.26).
- Several studies found that some focal steatosis lesions have a delayed enhancement, and show hypoenhancement in the arterial phase then become isoenhancement gradually in the portal venous and late phases.
- Several focal steatosis spare lesions show hyperenhancement in all phases on CEUS due to fatty cell-induced exclusion and constriction of blood vessels [26].

#### 5.4.2.3 CT Findings

- FFIs usually appear as typical homogeneous hypoattenuating lesions on CT images.
- The degree of hypoattenuation depends on the amount of fat inside the lesion. The density of focal fatty infiltration

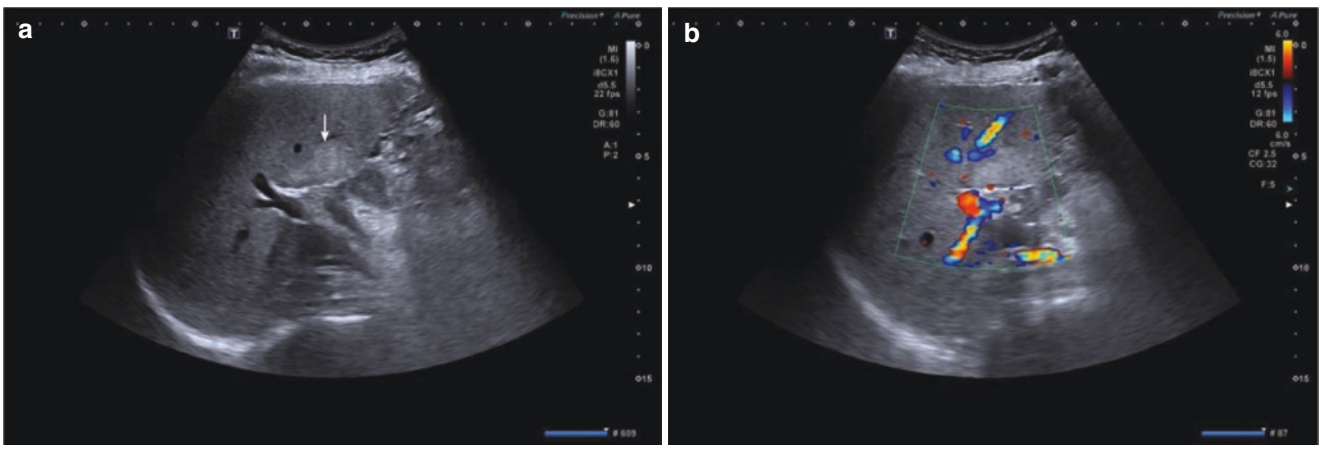


**Fig. 5.25** Features of focal steatosis on B mode ultrasound and contrast enhanced ultrasound (CEUS). B mode ultrasound revealed a homogeneously hyperechoic and irregular-shaped mass in the medial segment of the left liver lobe, close to the falciform ligament (arrow) (**a**). Color flow imaging showed no blood signal inside the lesion (**b**). The lesion showed isoenhancement in all phases on CEUS (arrow) (**c**–**h**). A homogeneously hypoattenuating lesion on non-contrast CT (arrow) (**i**). On dynamic contrast enhanced CT, the lesion showed non-enhancement in arterial phase and hypoenhancement in portal venous and late phases (arrow) (**j**, **k**)

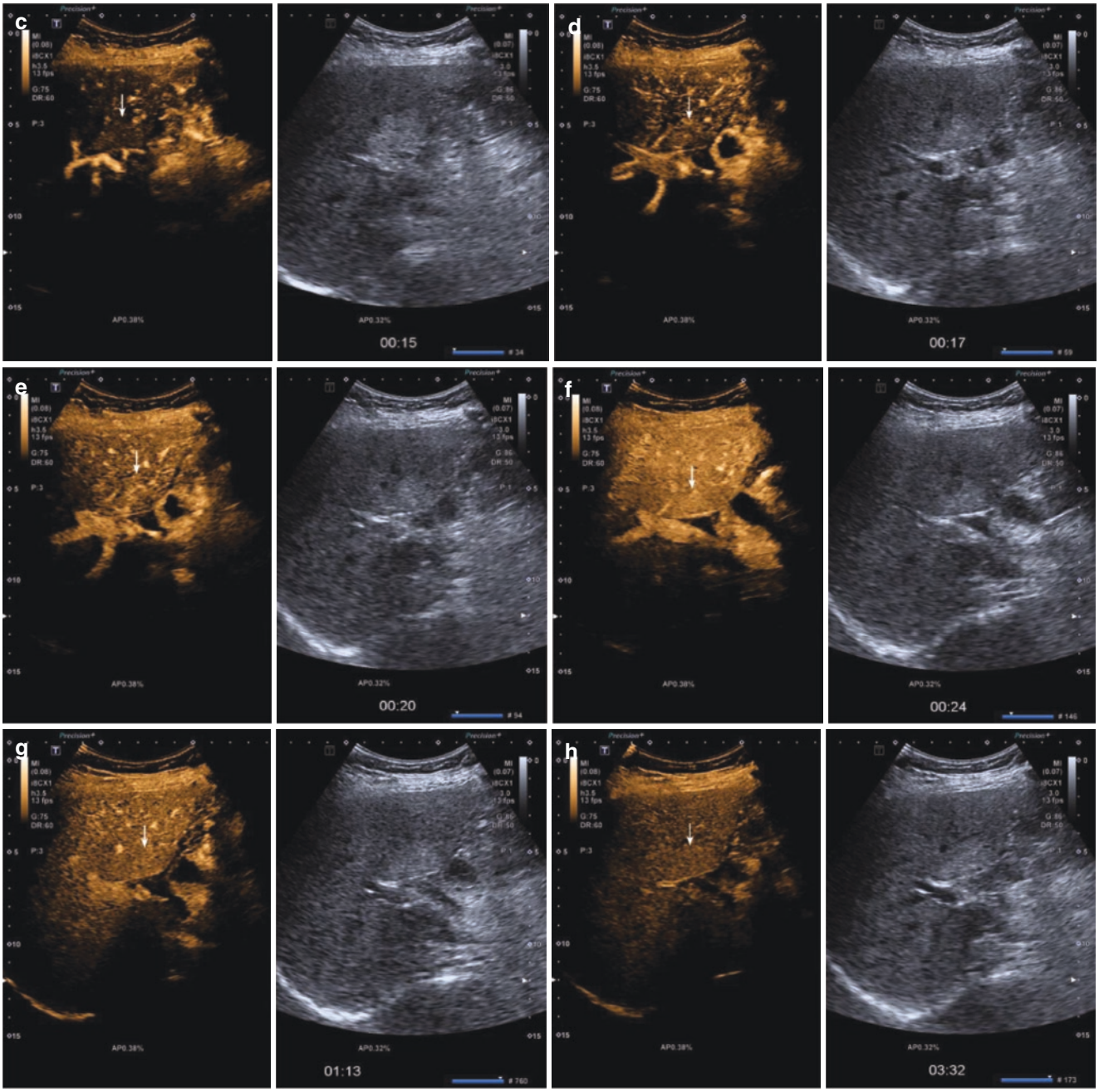


**Fig. 5.25** (continued)

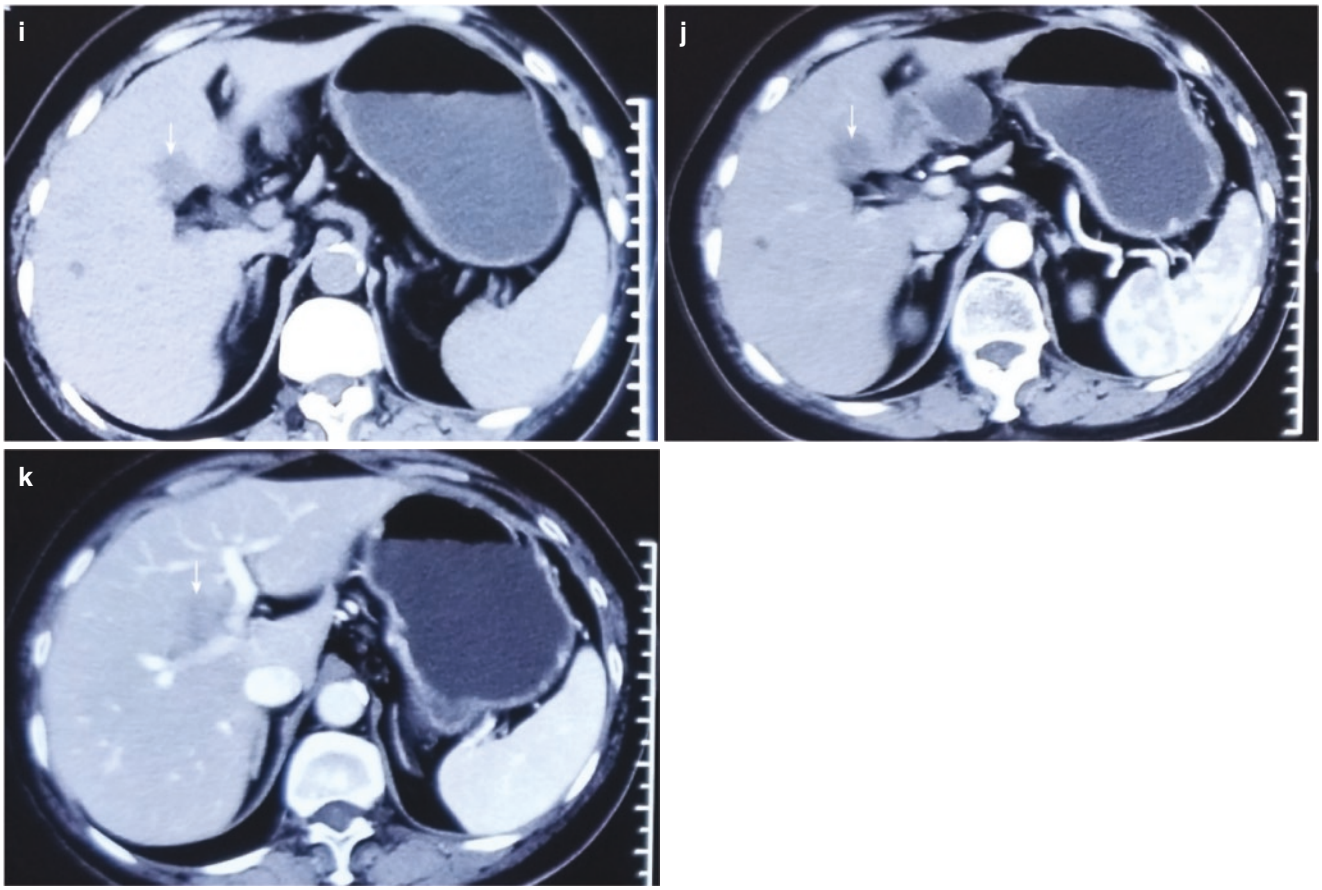


**Fig. 5.25** (continued)

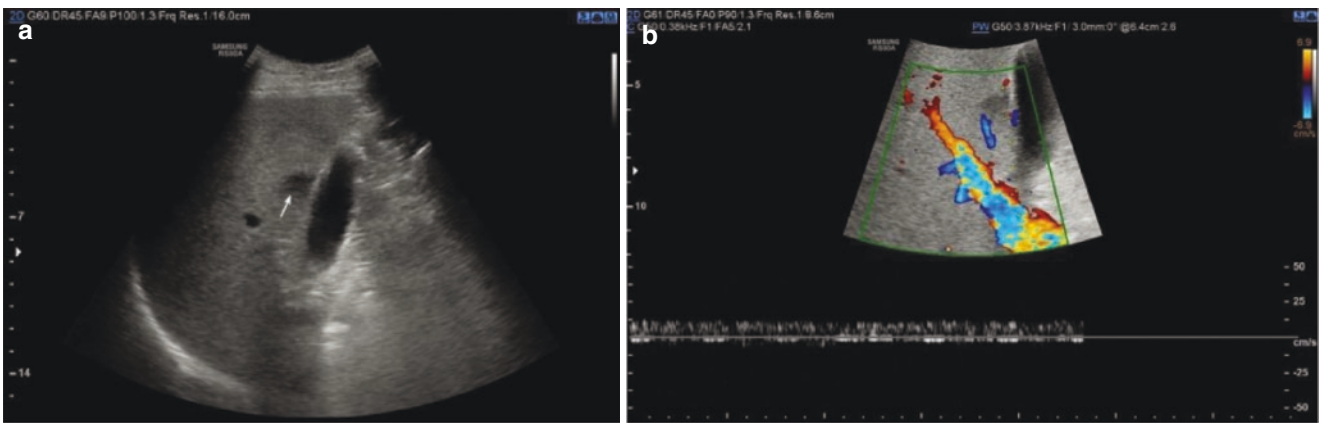


**Fig. 5.26** Features of focal fatty infiltration (FFI) on grayscale ultrasound and contrast enhanced ultrasound (CEUS). B mode ultrasound revealed a hypoechoic mass in the medial segment of the liver, close to the gallbladder bed (arrow) (**a**). CDFI showed portal venous blood signal around the lesion (**b**). The lesion showed isoenhancement in all phases on CEUS (arrow) (**c**–**f**)

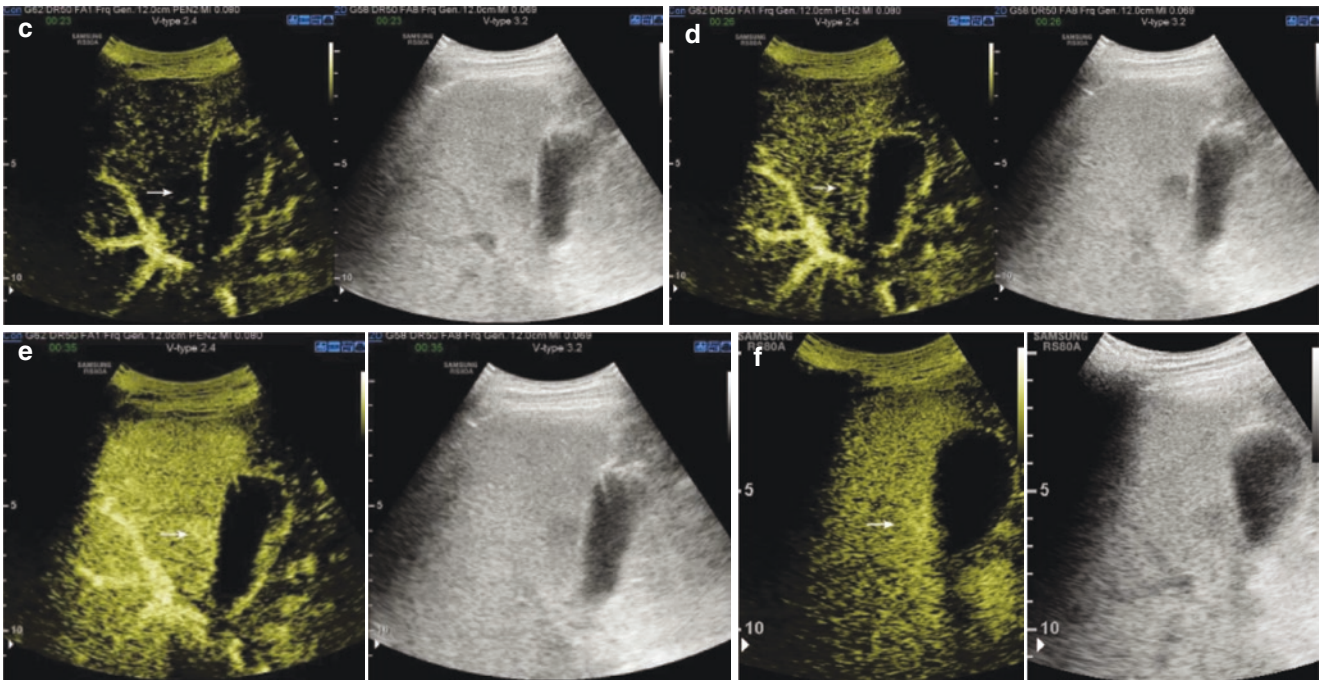


**Fig. 5.26** (continued)

is usually <40 Hounsfield units (HU) or becomes more than 10 HU difference with spleen and surrounding liver parenchyma.
- Most hypoattenuating lesions have irregular shapes without space-occupied effect, and normal hepatic vessels can pass through the lesions [27].

#### 5.4.2.4 MRI Findings
- FFI can be confidently diagnosed when the signal intensity of the lesion decreases on opposed-phase images versus in-phase images (Fig. 5.25), whereas signal intensity of the surrounding liver parenchyma has no difference between the two phases.
- Additional imaging features of FFIs include irregular border, and similar enhancement pattern to the surrounding liver parenchyma [28].

#### 5.4.2.5 Other Imaging Findings
- None

#### 5.4.2.6 Best Imaging Protocol Advices
- Ultrasound: The imaging method of the first choice for the screening and surveillance of patients with chronic liver disease.
- Doppler ultrasound:
  - To evaluate the waveform of blood flow signals.
  - To evaluate the presence of normal portal or hepatic veins through the lesion area.
- Contrast Enhanced Ultrasound:
  - Isoenhancement and wash-out of local hyperechoic lesions on CEUS suggest focal steatosis of the liver.
  - Isoenhancement and wash-out of local hypoechoic lesions on CEUS suggest focal fatty infiltration lesion of the liver.
- MRI:
  - Chemical shift MRI is the current gold standard for diagnosing focal fatty infiltration.
  - Magnetic resonance spectroscopy (MRS) can detect focal fat quantification accurately.
  - Signal intensity of the lesion decrease on opposed-phase images versus in-phase images.

### 5.4.3 Differential Diagnosis

#### 5.4.3.1 Hepatocellular Carcinomas
- HCCs usually show hyperenhancement in arterial phase with a disorder vascular pattern.
- In portal venous and late phases, HCCs commonly show hypoenhancement except that some well-differentiated HCCs may manifest isoenhancement.

#### 5.4.3.2 Metastases

- Liver metastases can be recognized reliably as hypoenhancement during the portal venous phase with previous history.
- Wash-out of liver metastases is often observed in early portal venous phase, and marked.

#### 5.4.3.3 Hemangioma

- Hemangiomas usually appear as well-defined, round-shaped hyperechoic and homogeneous focal liver lesion (FLL) without halo sign on B mode ultrasound. Few vessels were observed inside the lesion at color flow images.
- Hemangiomas show arterial phase peripheral nodular enhancement with progressive centripetal fill-in, partially, or totally. The filling process lasts from seconds to minutes, but is rapid in small lesions. Isoenhancement or hyperenhancement in the late phase on CEUS.

### 5.4.4 Pathology

#### 5.4.4.1 General Features

- Fatty liver can be divided into macrovascular and microvascular steatosis.
  - Macrovascular steatosis, which contains large fat vacuoles and displaced nuclei in the hepatocytes, is typically associated with excessive alcohol intake, non-alcoholic fatty liver disease (NAFLD), and type II diabetes.
  - Microvascular steatosis, which is characterized by small intracytoplasmic fatty inclusions without the displacement of the nuclei, usually occurs with severe impairment of mitochondrial fatty acid beta-oxidation, as either a primary disorder or a secondary to drug toxicity.
- FFI is a form of fatty liver disease due to increased triglyceride content in the liver.

#### 5.4.4.2 Staging, Grading, and Classification

- The etiology of FFI could be divided into alcoholic fatty liver and non-alcoholic fatty liver.
- Pathological subtypes of NAFLD:
  - Simple steatosis
  - NAFLD without steatohepatitis
  - Steatohepatitis
  - With or without fibrosis or cirrhosis
- According to the percent of involved hepatocytes, steatosis is graded 0–III (0 is none; grade I is up to 33%; grade II is 33–66%; grade III is more than 66%). Zonal distribution of steatosis and the presence of microvascular steatosis were noted.

### 5.4.5 Clinical Issues

#### 5.4.5.1 Presentation

- Fatty liver disease is often associated with metabolic syndrome and obesity. It has shown a rapid increase in prevalence worldwide.
- Fatty liver disease is often due to excessive triglycerides accumulation in hepatocytes.
- The predilection sites of FFI are usually without portal venous supply, including the gallbladder bed, the medial segment of the left liver lobe close to the falciform ligament, the forepart of segment I, and the back of segment IV.

#### 5.4.5.2 Prognosis

- Mild degree of fatty liver disease is not life threatening.
- If left untreated, it could progress to a severer degree correlated with inflammation, hepatic impairment, cirrhosis, and even hepatocellular carcinoma.
- The most common death causes are cardiovascular events rather than hepatic diseases among patients with fatty liver disease.

#### 5.4.5.3 Treatment

- Controlling risk factors, such as weight reduction, tight glycemic control, and abstinence.
- When co-existing chronic liver diseases occur and diagnosis is unclear, liver biopsy is recommended to perform in FFI patients.
- There are no specific drugs to treat fatty liver at present.

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