

Focal nodular hyperplasia mimicking hepatocellular adenoma and carcinoma in two cases

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SUMMARY Focal nodular hyperplasia (FNH) is a solid benign tumor of the liver, predominantly in young women. A correct diagnosis of FNH is essential for making appropriate clinical decisions and avoiding unnecessary liver resection. Herein, we reported that two male cases with FNH, who initially presented with persistent abdominal discomfort, were misdiagnosed with hepatocellular adenoma (HCA) and hepatocellular carcinoma (HCC) on contrast-enhanced magnetic resonance imaging and computed tomography scans, respectively. After surgery, a histological diagnosis of FNH was finally established. In this paper, we also reviewed the knowledge regarding diagnosis and differential diagnosis of FNH on imaging examinations, which are helpful for avoiding misdiagnoses and guiding clinical interventions.

Keywords Focal nodular hyperplasia, hepatobiliary contrast agents, contrast-enhanced ultrasound, hepatocellular adenoma, hepatocellular carcinoma

1. Introduction

Focal nodular hyperplasia (FNH) is a benign tumor of the liver with a prevalence of 0.3-3% in the general population (1,2). It is predominant in women aged 35-50 years old (3). In pathophysiology, arterial malformation leads to abnormal blood perfusion and secondary hyperplasia in the liver parenchyma (4). In histology, FNH is composed of hyperplastic hepatocytes separated by fibrous septum which contains hyperplastic bile ducts, tiny arterial branches, and infiltrating inflammatory cells (4). Most FNH patients are asymptomatic (4). Imaging examinations can usually achieve a definite diagnosis; if obscure, liver biopsy is recommended (3,4) with a great diagnostic accuracy of 95% (5). FNH patients mostly need conservative treatment alone (3,4,6), and undergo interventions when the symptoms are persistent and/or the diagnosis is unclear (3,7-9).

Hepatocellular adenoma (HCA) is another benign liver tumor with a prevalence estimated to be 0.001-0.004% (4). Unlike FNH, HCA has a risk of haemorrhage and malignant transformation. Lifestyle change, close imaging follow-up, and surgical resection are major treatment options for HCA (10).

Hepatocellular carcinoma (HCC), the most common primary liver malignancy, mainly develops in patients with liver cirrhosis secondary to viral hepatitis and alcohol abuse (3). Current treatments of HCC include liver transplantation, liver resection, transarterial chemoembolization, radiofrequency ablation, and molecular targeted therapy (11,12).

The use of modern imaging techniques, including contrast-enhanced magnetic resonance imaging (CE-MRI), computed tomography (CECT), and ultrasound (CEUS), is valuable for the diagnosis of liver tumors, further guiding the treatment selection. However, atypical FNHs can mimic HCA or HCC on imaging, because all of them are hypervascular. Therefore, a differential diagnosis of FNH with HCA and HCC is of particular significance.

2. Case presentations

2.1. Case 1

On June 1, 2020, a 55-year-old male complained of persistent abdominal pain for half a year at our department. He had been treated with continuous oral

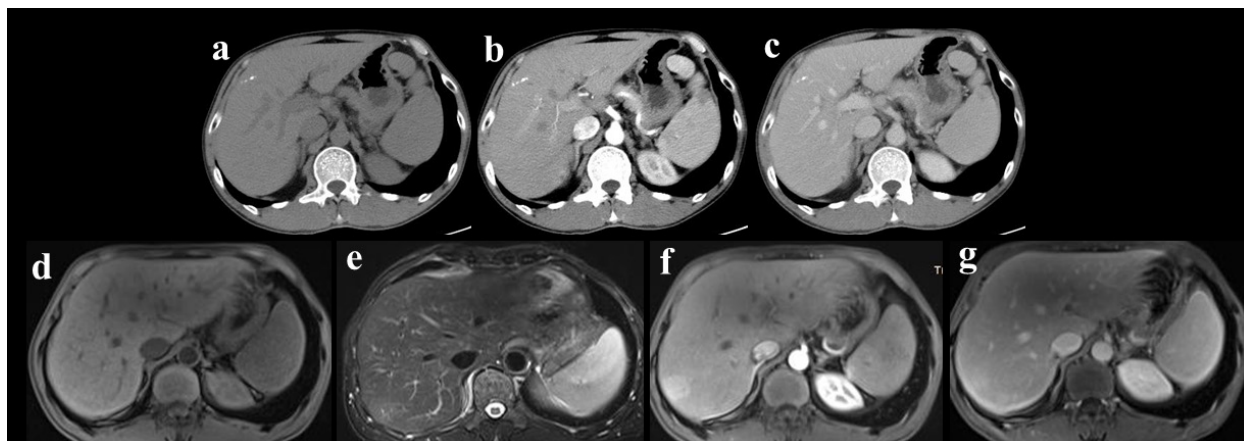


Figure 1. Imaging features of FNH in the case 1. (a-c) On multiphase CECT, no abnormal liver lesions were found, except for intrahepatic bile duct stones or calcification. (d-g) On conventional CE-MRI, a mass was not well-circumscribed in the 7th segment of the liver, which showed isointensity on T1-weighted images (d), slight hyperintensity on T2-weighted images (e), homogeneous and strong hyperintensity on arterial phase (f), and slight hyperintensity on portal phase (g).

clopidogrel bisulfate and hydroxyurea for essential thrombocythemia for 5 years. He also had histories of tuberculosis, appendectomy, and smoking and alcohol cessation as well as a family history of liver cirrhosis. No positive abdominal signs were found on physical examinations. On laboratory tests, the platelet count was 549,000/mm³ (reference range: 125,000-350,000/mm³); fecal occult blood was negative; serum lipase and amylase, liver function parameters, and serum albumin were within the reference range; tumor markers, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), β 2-microglobulin (β 2-MG), carbohydrate antigen-50 (CA-50), CA19-9, and CA24-2, were negative; hepatitis B virus antigen and hepatitis C virus antibody were negative. No positive lesions were found on esophagogastroduodenoscopy and X-ray gastrointestinal fluoroscopy. Neither superior mesenteric artery occlusion/stenosis nor left renal vein compression was found on abdominal color Doppler ultrasonography. Abdominal CECT showed intrahepatic bile duct stones or calcification, splenomegaly, and splenic infarction (Figure 1). Abdominal CE-MRI further found a mass, which was not well-circumscribed, in the 7th segment of the liver, with isointensity on T1-weighted images, slight hyperintensity on T2-weighted images, homogeneous and strong hyperintensity on arterial phase, and slight hyperintensity on portal phase (Figure 1). A possible diagnosis of HCA was considered.

On June 17, 2020, this patient underwent surgery at the Department of Hepatobiliary Surgery after obtaining his and his relatives' written informed consents. A mass with a diameter of about 3 cm was detected in the 7th segment of the liver under ultrasonic guidance, and then the 7th segment of the liver was completely resected. Histology confirmed a diagnosis of FNH (Figure 2). After surgery, abdominal pain disappeared, but liver dysfunction developed with increased serum alanine aminotransferase (ALT) level of 310.32 U/L (reference

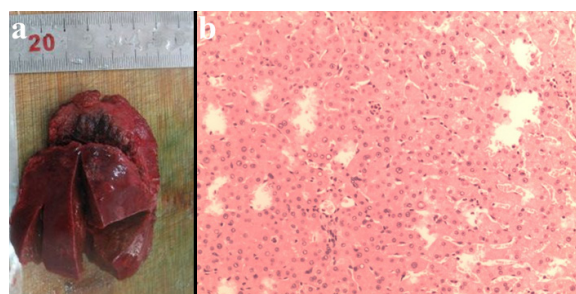


Figure 2. Surgical specimen and microscopic image of FNH in the case 1. (a) Surgical specimen had a diameter of about 3 cm. (b) Histology confirmed the diagnosis of FNH combined with focal steatosis (hematoxylin and eosin, \times 100).



Figure 3. Postoperative abdominal CT scan showing that the 7th segment of the liver was absent in the case 1.

range: 9-50 U/L), serum aspartate aminotransferase (AST) level of 514.61 U/L (reference range: 15-40 U/L), serum total bilirubin (TBIL) level of 152.0 μ mol/L (reference range: 5.1-22.2 μ mol/L), direct bilirubin (DBIL) level of 97.5 μ mol/L (reference range: 0-8.6 μ mol/L), alkaline phosphatase (AKP) level of 169.39 U/L (reference range: 45-125 U/L), and gamma-glutamyltransferase (GGT) level of 60.93 U/L (reference range: 10-60 U/L), and a decreased serum albumin (ALB) level of 29.4 g/L (reference range: 40-55 g/L). Conservative treatment was given for liver dysfunction.

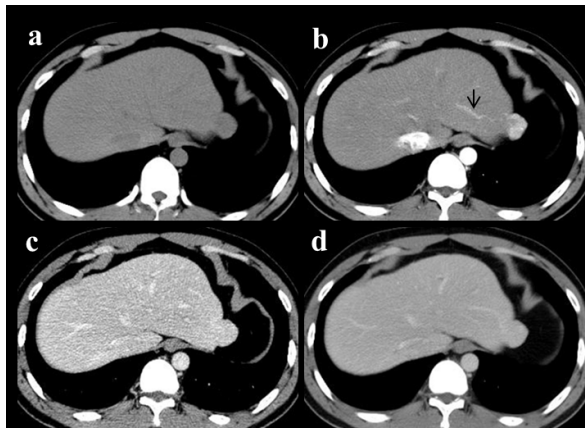


Figure 4. Abdominal multiphase CECT imaging features of FNH in the case 2. There was an irregularly exogenous mass in the left lateral segment of the liver on unenhanced phase (a), hyperintensity on arterial phase (b), and iso-intensity on portal (c) and delayed (d) phases. Notably, there were a thickened vessel (arrow) and its tiny branches into the lesion on arterial phase (b).

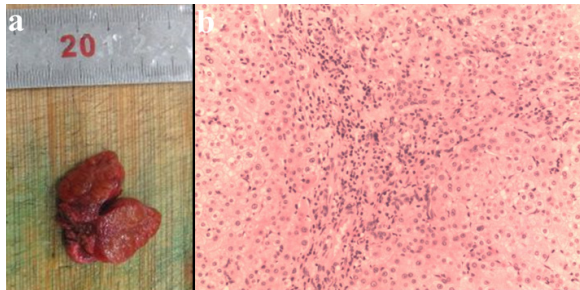


Figure 5. Surgical specimen and microscopic image of FNH in the case 2. (a) The lesion resected was lobulated in appearance with about 2.6×2.3 cm in size. (b) Histology showed nodular hyperplasia of hepatocytes with atypical hyperplasia and lymphocytes infiltration in the portal regions (hematoxylin and eosin, $\times 100$).

Abdominal CT was re-examined and showed that the 7th segment of the liver was absent (Figure 3). He was discharged on June 28. On a recent telephone follow-up visit, he was diagnosed with a hepatic vein stenosis, and at a liver transplantation waiting list.

2.2. Case 2

On May 10, 2020, a 26-year-old male complained of intermittent diarrhea for more than one year and abdominal pain for 20 days at our department. He had histories of upper limb fracture and smoking. He denied the history of alcohol or drug abuse and family history of liver diseases. No positive signs were found on physical examinations. On laboratory tests, fecal occult blood and fecal bacterium cultures were negative; complete blood cell count, serum lipase and amylase, liver function parameters, and serum albumin were within the reference range; tumor markers, including AFP, CEA, $\beta 2$ -MG, CA-50, CA19-9, and CA24-2, were negative; hepatitis B virus antigen and hepatitis C virus antibody were negative. Esophagogastroduodenoscopy

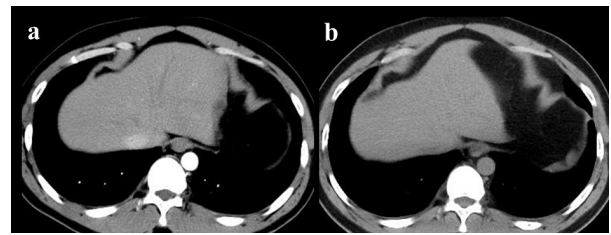


Figure 6. Postoperative abdominal CT scans showing that the left lateral segment of the liver was absent in the case 2. (a) Abdominal CECT in the first postoperative month. (b) Abdominal unenhanced CT scan in the 6th postoperative month.

and colonoscopy revealed verrucous gastritis and proliferative changes of terminal ileum lymphatic follicles, respectively. Abdominal CECT revealed an irregularly exogenous mass with a size of about 2.6×2.3 cm in the left lateral segment of the liver, with hyperintensity on arterial phase and iso-intensity on portal and delayed phases (Figure 4). Notably, there was a thickened vessel and its branches into the lesion on arterial phase. Thus, a possible diagnosis of HCC was considered.

On May 18, 2020, this patient underwent surgery at the Department of Hepatobiliary Surgery after obtaining his and his relatives' written informed consents. Intraoperatively, an exogenous mass with a diameter of about 3 cm was seen in the left lateral segment of the liver, and then the left lateral segment of the liver was completely resected. Histology confirmed a diagnosis of FNH with atypical hyperplasia (Figure 5) and the immunohistochemical staining revealed the absence of focal malignancy. He was complicated with mild liver dysfunction after surgery, with increased ALT level of 76.14 U/L (reference range: 9-50 U/L) and AST level of 48.98 U/L (reference range: 15-40 U/L). He was discharged on May 28. Abdominal CT at one month and six months after surgery showed that the left lateral segment of the liver was absent (Figure 6).

3. Discussion

A minority of FNH cases may present with abdominal pain or discomfort, which is secondary to the compression of large FNHs on adjacent organs (1). Retraction of FNHs after therapy can relieve abdominal pain, which may explain a potential correlation of abdominal pain with FNHs (9). In the case 1, abdominal pain alleviated after resection of this lesion, indicating that his abdominal symptoms might originate from FNH. Certainly, abdominal pain could also be attributed to other comorbidities (13), such as dyspepsia (14). In the case 2, abdominal pain remained after surgery.

Based on the CECT findings, the diagnosis was inaccurate in the case 2, and even hepatic lesion was not visualized in the case 1. CE-MRI has a higher diagnostic performance of focal liver lesions than

Table 1. The main imaging characteristics of FNH, HCA, and HCC

Items	Hepatocyte-targeted CE-MRI	Contrast-enhanced computed tomography
FNH	<p>Lesion parenchyma T1WI: iso-/slight hypointensity; T2WI: iso-/slight hyperintensity; Arterial phase: hyperintensity; Portal phase: slight hyper-/isointensity; Delayed phase: iso-/slight hyperintensity; Hepatobiliary phase: iso-/hyperintensity.</p> <p>Central scar T1WI: hypointensity; T2WI: hyperintensity; Arterial phase: hypointensity; Portal phase: hypointensity; Delayed phase: hyperintensity; Hepatobiliary phase: hypointensity (4,5,17,18,21).</p>	<p>Arterial phase: typical centrifugal enhancement pattern, sometimes with a spoke-wheel morphology (mainly in lesions less than 3.1 cm); atypical centripetal and diffuse enhancement patterns (mainly in lesions larger than 3.1 cm); Portal and/or delayed phases: sustained enhancement (23).</p>
HCA#	<p>T1WI: iso-/hypointensity; T2WI: mostly hyperintensity; Arterial phase: hyperintensity; Portal phase: iso-/hyper-/hypointensity; Delayed phase: iso-/hyper-/hypointensity; Hepatobiliary phase: hypointensity (4,18,21).</p>	<p>Arterial phase: typical centripetal enhancement pattern; atypical diffuse enhancement pattern, without a spoke-wheel morphology, and unaffected by the lesion size; Portal and/or delayed phases: wash-out appearance (25).</p>
HCC#	<p>T1WI: variable; T2WI: variable/hyperintensity; Arterial phase: hyperintensity; Portal phase: iso-/hypointensity; Delayed phase: hypointensity; Hepatobiliary phase: hypointensity (3,26).</p>	<p>Arterial phase: hyperenhancement; Portal and/or delayed phases: wash-out appearance (28).</p>

Notes: The signal intensity refers to the signal intensity relative to the normal liver parenchyma surrounding the lesion. # the signal intensity of the lesion on MRI is sometimes inhomogenous. Abbreviations: CE-MRI, contrast-enhanced magnetic resonance imaging; FNH, focal nodular hyperplasia; T1WI, T1-weighted images; T2WI, T2-weighted images; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma.

CECT (15). Notably, CE-MRI is considered as the preferred diagnostic approach in the case where the diagnosis is obscure (4). In a retrospective study involving a total of 124 focal liver lesions undetermined by CECT, the diagnostic accuracy of CE-MRI could be 58% (15). Among the small focal liver lesions (< 2 cm) that cannot be diagnosed by CECT, the diagnostic accuracy of CE-MRI could be 87.7% (16). The main imaging features of FNH on multiphase CE-MRI are summarized in Table 1 (4,5,17).

Several points should be helpful to differentiate between FNH and HCA. First, central scar is of great significance for the diagnosis of FNH, but it is only observed in approximately 50% of FNH cases and is usually present in FNH lesions larger than 3 cm. If such a typical sign is missing, it is difficult to obtain a confident diagnosis of FNH on conventional MRI (18,19). The case 1 with a small hepatic lesion did not have any signal intensity symbolizing the central scar on CE-MRI. Second, in the case 1, gadoterate meglumine, which is an extracellular space contrast agent, was used for multiphase CE-MRI examination. However, the imaging features on CE-MRI using gadoterate meglumine are not significantly different between FNH and HCA (20). By comparison, on hepatobiliary phase of CE-MRI with novel hepatocyte-selective contrast agents, such as gadoxetate disodium

and gadobenate dimeglumine, there is a difference in signal intensity between FNH and HCA. The former often presents as iso-/hyperintensity, but the latter as hypointensity (4,18,21). Of course, some contrasting situations should not be neglected (21-23), which may be related to different expression levels of organic anion transporting polypeptide (OATP) on hepatocyte membrane (24). Third, serious complications, such as spontaneous rupture and haemorrhage, are extremely rare in FNHs (4), but they can develop in HCAs larger than 5 cm (24). Notably, no complication was observed in the case 1. Fourth, the sensitivity of MRI is low for the diagnosis of FNHs less than 3 cm where central scar is often missing (4). In this setting, we could consider CEUS as an alternative diagnostic approach to evaluate small FNHs (23). On CEUS, FNH can present as a typical centrifugal filling pattern with or without spoke-wheel morphology; by contrast, HCA can present as a typical centripetal filling pattern (25). Unfortunately, the case 1 did not undergo CEUS. Fifth, a diagnosis can be further established according to the texture analysis on hepatocyte-targeted CE-MRI (21) as well as a combination of risk factors and imaging features for suspected liver lesions (22).

On CECT or CE-MRI, a “fast-forward and fast-out” enhancement pattern in a focal liver lesion, which shows strong enhancement on arterial phase

and fast wash-out on portal or delayed phases, is one of the most important diagnostic criteria of HCC (3). Such an imaging feature is observed in the case 2. However, he was finally diagnosed with FNH by histology. This may be related to abundant backflow veins inside his hepatic lesion. There are several points to be concerned for a differential diagnosis of FNH with HCC. First, hepatocyte-targeted CE-MRI can be considered for differentiating FNH with HCC. FNHs show iso-/hyperintensity on hepatobiliary phase, but HCCs show hypointensity (26). But it's important to note that a genetic subtype of HCC can also show iso-/hyperintensity on hepatobiliary phase due to its overexpression of OATP 1B3 (27). Second, central scar on imaging usually favors the diagnosis of FNH, rather than HCC. But the scar-like feature can also be observed in fibrolamellar HCC or scalloped HCC (27). The case 2 was lacking of central scar. Third, on CEUS, HCC shows hyperenhancement on arterial phase and wash-out appearance on portal and delayed phases, but FNH often shows continuous enhancement (28). No CEUS examination was further performed in the case 2. Fourth, the natural disease course is often different between FNH and HCC. FNH shows a varied change in size of lesions (slowly increased, stable, or decreased), while HCC often shows a progressively increased size of lesions (27). Fifth, the risk factors and laboratory tests of suspicious liver diseases are often valuable (3,11). The case 2 was a young male without any underlying liver disease, and his AFP level was within the reference range, which were not consistent with the diagnosis of HCC.

In conclusion, FNH larger than 3 cm, rather than HCA and HCC, usually shows the presence of central scar. It is often difficult to distinguish FNH from HCA and HCC on CECT and conventional CE-MRI. By comparison, CE-MRI with hepatocyte-targeted contrast agents can provide more diagnostic clues, where FNH usually shows iso-/hyperintensity on hepatobiliary phase, but HCA and HCC often show hypointensity. Additionally, various CEUS findings and risk factors should be helpful for a differential diagnosis.

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