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Imaging benign hepatocellular tumors: Atypical forms and diagnostic traps

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Adenoma;
Focal nodular hyperplasia

Abstract Management of patients with a benign hepatocellular tumor relies largely on imaging data; the diagnosis of focal nodular hyperplasia (FNH) must be made with certainty using MRI, because no other clinical or laboratory data can help diagnosis. It is also essential to identify adenomas to manage them appropriately. The radiological report in these situations is therefore of major importance. However, there are diagnostic traps. The aim of this paper is to present the keys to the diagnosis of benign lesions and to warn of the main diagnostic pitfalls.

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Benign hepatocellular tumors are rare, making up 10% of benign hepatic tumors \cite{1,2,3}. Two large groups of benign hepatocellular tumors can be differentiated: reactive regenerative lesions — focal nodular hyperplasia (FNH), and tumoral lesions — hepatocellular adenomas. The common feature of these two groups of lesions is that they develop most often in young women \cite{1,2,3}.

It is essential to use imaging to diagnose these lesions in order to decide how to manage the situation. This can range from no therapeutic treatment to surgical resection, with monitoring or a biopsy for confirmation as intermediate stages \cite{1,2,3}. In recent years, identification of molecular alterations within benign hepatocellular tumoral lesions has provided better understanding of the pathophysiology and genesis of the tumor \cite{4}. Correlation of the genotypic and phenotypic data of hepatocellular adenomas seems to be important for determining their management \cite{5}. While diagnosis and management of these lesions is
multidisciplinary — involving clinicians, hepatologists, surgeons and histopathologists along with radiologists — the radiologist is in the front line for studying their signs. MRI is nowadays the reference examination for characterizing benign hepatocellular tumors [6], sometimes with the use of liver-specific contrast agents [7]. Nevertheless, all is not simple: atypical forms or particular terrains may still make diagnosis of FNH difficult. Adenomas are now classified in pathomolecular subtypes, depending particularly on their MRI profile [8].

The aim of this paper is to provide an overview of the typical presentation of benign hepatocellular lesions, before illustrating the atypical forms or the most common diagnostic traps.

**Typical presentations of benign hepatocellular lesions — an overview**

**Focal nodular hyperplasia (FNH)**

**MRI**

*Typical MRI appearance of focal nodular hyperplasia (FNH) after injection of gadolinium chelates*

MRI diagnostic criteria for FNH were proposed by Mattison et al. based on the analysis of six criteria on non-contrast enhanced MRI sequences [9], then improved by Mathieu et al. with the study of the contrast uptake kinetics of these lesions after dynamic injection of gadolinium chelates [10].

The MRI pathognomonic features of typical FNH following injection of conventional gadolinium chelates are the following five characteristic signs:

- T1-weighted isointensity or discreet hypointensity, associated with T2-weighted isointensity or discreet hyperintensity;
- the presence of a T2-weighted hyperintense central stellate scar;
- homogeneity outside of the central stellate scar;
- intense homogeneous arterial uptake of contrast, the lesion returning to isointensity with the liver in the portal and late phases;
- the absence of a capsule.

The majority of studies show that MRI has a high diagnostic value for FNH, with sensitivity of about 80% and specificity of 98% [1,11]. Fig. 1 (a–e) shows an example of typical FNH in MRI.

**Focal nodular hyperplasia and liver-specific contrast agents: do they provide additional specific help?**

Liver-specific contrast agents (the liver-specific gadolinium chelates Gd-BOPTA, Multihance®, Bracco, Italy or GD-EOB-DTPA, Primovist®, Bayer Schering) are excreted in the bile [12]. The liver-specific contrast agent enters the hepatocytes via a transporter in their sinusoidal membrane which belongs to the organic anion transporting peptide (OATP) family. The contrast agent is excreted into the bile by a hepatocyte canalicular membrane transporter, the multidrug resistance-associated protein 2 (MRP2). The liver-specific contrast agents accumulate in the FNH due to the lack of communication of the intratumoral bile ducts with the rest of the biliary tree. The FNH therefore appears hyperintense or isointense relative to the adjacent liver in the hepatocyte phase, from one hour after injection of the liver-specific contrast agent in the case of Gd-BOPTA, or from about 20 minutes after injection of Gd-EOB-DTPA [13].

There have been several studies concerning the contribution made by liver-specific contrast agents to characterize benign hepatocellular tumors. Grazioli et al. found enhancement of FNH in 96.3% of cases three hours after injection of Gd-BOPTA whereas none of the adenomas showed any enhancement [7]. A recent study using Gd-EOB-DTPA showed that contrast between the FNH lesion and the adjacent liver was slightly positive, whereas it was strongly negative for adenomas. The ratio of the signal from the lesion and the adjacent liver in the hepatocyte phase allowing differentiation between the two types of hepatocellular tumor was 0.97, with sensitivity of 92% and specificity of 91% [14]. Another study has shown that reading the hepatocyte phase increased the diagnostic sensitivity for FNH: FNH was correctly diagnosed in 74.3 to 97.1% of cases before the hepatocyte phase and in 97.1% to 100% after reading the hepatocyte phase [15].

An example of typical FNH using Gd-BOPTA is shown in Fig. 1 (f and g).

**FNH and ultrasonography with injection of an ultrasound contrast agent**

Using ultrasonography with intravenous injection of an ultrasound contrast agent, the central artery penetrating the lesion can be visualized in real time: there is early centrifugal spoke-wheel contrast uptake by the FNH, before uptake by the normal parenchyma. The lesion is completely enhanced, outside of the central stellate scar, at the end of the arterial phase, and becomes hyperechoic relative to the adjacent hepatic parenchyma. In the portal and late phases (60 seconds to 3 minutes), discreet hyperechogenicity or isoechogenicity of the lesion persists in most cases. The central stellate scar is not enhanced in the late phase but remains hyperechoic in all phases due to the strictly intravascular character of the contrast agent used in ultrasound [16,17].

In the literature, the sensitivity of contrast enhanced ultrasonord for diagnosis of FNH varies depending on the studies between 80 and 100%, with specificity of between 85 and 95% [18,19].

An example of typical FNH using contrast enhanced ultrasound is shown in Fig. 2.

Note that the typical criteria for FNH are summarized in Table 1.

**Hepatocellular adenomas**

**Overview of the molecular classification of adenomas**

Hepatocellular adenomas are a heterogeneous group of tumors, with their potential to evolve into hepatocellular carcinomas (HCC) and the risk of hemorrhagic complications being closely linked to their molecular characteristics [20].

There are four recognized molecular types of adenoma [5,20,21]:
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Figure 1. Typical focal nodular hyperplasia. A 30-year-old woman with no noteworthy history. Chance discovery of a hepatic nodule of the right liver. MRI characterization: a: the nodule is isointense with in-phase T1-weighted 2D GE; b: no decline in intensity with opposed-phase T1-weighted 2D GE; c: the nodule is isointense with T2-weighted FSE F5, with a central stellate scar appearing hyperintense with T2-weighting; d: the nodule takes up contrast intensely and uniformly in the arterial phase with T1-weighted 3D GE after injection of gadolinium chelates; e: the nodule is isointense relative to the adjacent liver in the venous phase and shows contrast uptake by the central scar; f and g: in the hepatocyte phase, after injection of a liver-specific contrast agent, the nodule is isointense with the adjacent liver with in-phase (f) and with opposed-phase (g) T1-weighted 2D GE. Note that the central stellate scar appears hypointense with T1-weighting in the hepatocyte phase.

- adenomas with HNF1α mutations (35–45%), characterized by their marked steatosis and their benign evolution, resulting in a conservative approach;
- telangiectatic or inflammatory adenomas (35–40%), characterized by their occurring preferentially in obese patients or in patients with metabolic syndrome or steatohepatitis. These adenomas have a higher hemorrhagic risk when they are more than 5-cm in size [3]. An associated mutation of the β catenin gene can exist in about 10% of this adenoma subtype, with a risk of evolving into HCC;
Figure 2. Focal nodular hyperplasia (FNH) with contrast enhanced ultrasound. A 27-year-old woman. Nodule at the junction of segments VI and VII suggesting focal nodular hyperplasia. Contrast enhanced ultrasound found centrifugal contrast uptake typical of FNH (a–g).
• non-specific adenomas (10–20%), with no molecular or phenotypic characteristic known to date.

**MRI**

The MRI signs of adenomas appear to be partly correlated with their genotype, at least as far as HNF1α mutation and inflammatory adenomas are concerned [8]:

- telangiectatic or inflammatory adenomas show T1-weighted iso- or hyperintensity, clear T2-weighted hyperintensity, arterial phase contrast uptake, and hyperintensity relative to the adjacent liver on later sequences. Areas of steatosis or intratumoral hemorrhagic changes are possible. In the study by Laumonier et al. [8], the association of ‘obvious T2-weighted hyperintensity’, i.e. at least equal to that of the spleen, and ‘persistent enhancement in the portal and late phase sequences’ had a positive predictive value of 88.5%, a negative predictive value of 84%, sensitivity of 85.2% and specificity of 87.5% for the molecular diagnosis of inflammatory adenomas (Fig. 3);

- steatotic adenomas suspected of being an HNF1α mutation show T2-weighted isointensity or discreet hyperintensity, with a clear, uniform and overall fall in intensity between the in-phase and opposed-phase sequences, corresponding to an increase in fat occupying the majority of the lesion. There is moderate enhancement in the arterial phase, with iso- or hypointensity relative to the adjacent liver on later sequences. According to the study by Laumonier et al. [8], the ‘uniform and overall fall in intensity between the in-phase and opposed-phase sequences’ has a positive predictive value of 100%, negative predictive value of 94.7%, sensitivity of 86.7% and specificity of 100% for the molecular diagnosis of HNF1α mutated adenomas (Fig. 4);

- the β catenin mutated subtype of adenoma cannot at present be characterized by imaging.

**Hepatocellular adenomas and ultrasonography after injection of contrast agent**

In contrast enhanced ultrasound, the enhancement kinetics of adenomas is not specific: it may be centripetal or mixed [22]. A recent study tried to document the contrast-enhanced sonographic features specific for adenoma subtypes. HNF1α-inactivated adenomas was found to have a homogeneous hyperechoic aspect at baseline gray-scale sonography, isovascularity or moderate hypervascularity with mixed filling in the arterial phase, and isoechogenicity in the portal and late venous phases. Inflammatory adenomas, was found to have an arterial hypervascularity with centripetal filling, linear vascularities, peripheral rim of sustained enhancement, and central washout in the late venous phase [23].

Note that the criteria indicating an adenoma are summarized in Table 2.

**Atypical forms and diagnostic traps**

While the typical forms of FNH are easy to recognize in MRI, certain forms are difficult to diagnose and particularly to differentiate from an adenoma. Nevertheless, certain classic traps can be avoided.

**Does FNH occur in men?**

It is generally agreed that FNH is much less common in men than in women. The male/female ratio for the occurrence of this lesion is 1 to 8 [24]. FNH lesions in men are smaller, more often atypical in MRI and age at diagnosis is generally higher than in women [25]. Considerable caution will therefore be used in diagnosing FNH in men from imaging, adhering strictly to the MRI criteria for this non-invasive diagnosis. If one of these criteria is absent, it is recommended to seek an.

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**Table 1 Criteria of typical focal nodular hyperplasia (FNH) (Figs. 1 and 2).**

<table>
<thead>
<tr>
<th>MRI</th>
<th>Contrast enhanced ultrasound</th>
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| Without injection | T1-weighted isointensity or discreet hypointensity  
T2-weighted isointensity or discreet hyperintensity  
Homogeneity outside of the central stellate scar  
Central stellate scar with T2-weighted hyperintensity | Early, arterial, centrifugal, spoke-wheel contrast uptake  
Nodule hyperechoic at the end of the arterial phase  
Nodule iso- or discreetly hyperechoic in the portal and late phases |
| Injection of gadolinium chelates | Intense uniform arterial contrast uptake  
Nodule isointense with the liver in the portal and late phases  
Late contrast uptake by the central stellate scar | |
| Analysis in the hepatocyte phase (only for liver-specific gadolinium contrast agents) | Nodule is iso- or hypointense relative to the adjacent liver |
opinion from a specialized center, and a percutaneous biopsy should be performed where there is the slightest doubt.

**Do multiple FNH exist?**

About 20% of patients present at least two FNH lesions [24]. It is therefore quite usual to find several FNH nodules in a single patient. A classic differential diagnosis is nodular regenerative hyperplasia (NRH) in its multi-acinar pseudotumoral form which can mimic FNH (Fig. 5) in patients with a particular clinical context: systemic diseases (rheumatoid arthritis, sclerosis, lupus), hematological diseases, certain medicinal products (azathioprine, 6-thioguanine, chemotherapy—in particular oxaliplatin), congenital hepatic vascular abnormalities, hepatic or renal transplant, HIV, cardiac insufficiency, coeliac disease, chronic Budd–Chiari syndrome. Classically, NRH takes up contrast in the hepatocyte phase after injection of liver-specific contrast agent and does not have a central stellate scar [26,27].
Figure 4. Steatotic adenoma with an HNF1α mutation in MRI. Chance discovery of a mass at the junction of segments V and VI in a 29-year-old woman with no noteworthy history: a: the nodule is isointense on the in-phase T1-weighted 2D GE sequence; b: there is an overall, uniform fall in intensity in the opposed-phase T1-weighted 2D GE sequence; c: the nodule is isointense with T2-weighted FSE FS; d and e: it is weakly enhanced in the arterial phase after injection of gadolinium chelates (d) and remains hypointense relative to the liver in the venous phase (e); f: in the hepatocyte phase, the nodule is hypointense relative to the adjacent liver with in-phase T1-weighted 2D GE. The diagnosis of steatotic adenoma with an HNF1α mutation was confirmed on the resected tissue.

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<th>Table 2 Characteristic signs of hepatocellular adenomas.</th>
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<td>MRI</td>
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<td>Inflammatory adenoma (Fig. 2)</td>
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<td>Steatotic adenoma (Fig. 3)</td>
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Are all hypervascular lesions hepatocellular?

Arterial contrast uptake by a nodule is not specific for its being hepatocellular. The range of hypervascular hepatic lesions does indeed include the hepatocellular tumors (adenoma, FNH, HCC), but also vascular lesions (perfusion disorders, angiomatosis), as well as metastases of hypervascular tumors (medullary thyroid carcinoma, neuro-endocrine tumor of the kidney, sarcoma, melanoma) (Fig. 6), which may mean that differential diagnosis is difficult.

Does the presence of fat exclude the diagnosis of FNH?

Fatty transformation of FNH is rare [28]. In a study in 2004, 85% of FNH classified as atypical presented intralesional fat [29]. It has been suggested that subjacent hepatic steatosis might extend into FNH [30]. When fatty transformation is the only atypical feature and particularly when the subjacent liver is steatotic, hyperintensity in the T1-weighted sequences due to the presence of fat within the FNH should not bring the diagnosis into question. In other cases, the presence of fat modifies the characteristics of the signal from the lesion relative to the subjacent liver making differential diagnosis with an adenoma difficult, so that diagnosis of FNH may require the assistance of liver-specific contrast agents or a percutaneous biopsy (Fig. 7).

Is the presence of a central stellate scar synonymous with FNH?

This is a complex question. We must first separate the issues.

Does the absence of a central stellate scar exclude diagnosis of FNH?

The central stellate scar with T2-weighted hyperintensity, enhancing in the venous phase, is among the MRI diagnostic criteria for FNH. However, in many cases, this central stellate scar is not formally visualized in MRI. It is now acknowledged that it may not be seen in small FNH lesions, i.e. those of largest diameter of less than 3-cm [11,24]. If all the other diagnostic criteria are present and there is no particular medical history, the diagnosis of FNH may be made even if there is no central stellate scar in lesions of less than 3-cm. Here again, contrast enhanced ultrasound may be useful because it is more sensitive for detecting the central stellate scar [31]. An MRI with injection of a liver-specific contrast agent and studying the hepatocyte phase may otherwise provide an additional diagnostic argument.

Does the presence of a central stellate scar confirm diagnosis of FNH?

T2-weighted hyperintensity of the central stellate scar and contrast uptake in the venous phase are essential for diagnosis of FNH. T2-weighted hypointensity of the central stellate scar is in fact very unusual and requires additional investigation in order to eliminate diagnosis of fibrolamellar hepatocellular carcinoma, in particular. On the other hand, the central artery, which can sometimes be seen in T2-weighted hypointensity, must not be confused with a T2-weighted hypointense central stellate scar (Fig. 8). In MRI, it can sometimes be useful to wait for several minutes after injecting the contrast agent to identify enhancement of the central stellate scar. Moreover, certain, in particular inflammatory, adenomas may also present a central stellate scar (Fig. 9).

Does a mixed or centripetal flow in contrast enhanced ultrasound exclude the diagnosis of FNH?

When there is centripetal or mixed flow in contrast enhanced ultrasound, the first reflex should be to ensure that the plane of the slice is satisfactory, i.e. that it passes through the supplying pedicule, because a poor slice plane may result in false images of mixed or centripetal enhancement. FNH, when large, may however have several supplying pedicles. This may cause contrast enhanced ultrasound results for these large lesions, typically of more than 5-cm, to be atypical by showing mixed or even centripetal flow (Fig. 10). This
Figure 6. Renal carcinoma metastasis. A 52-year-old female patient; discovery of a hypervascular hepatic nodule on a CT scan performed during staging of a renal carcinoma; MRI characterization: a and b: the nodule (arrow) is hypointense on the in-phase (a) and opposed-phase (b) T1-weighted GE sequences; c: it is clearly hyperintense on the T2-weighted FSE FS sequences; d: arterial contrast uptake after injection of gadolinium chelates; e: the nodule is hypointense relative to the liver in the venous phase. It was metastasis of a renal carcinoma.

appearance does not exclude the diagnosis of FNH for large lesions, for which MRI should be preferred.

How should the hepatocyte phase be interpreted after injection of a liver-specific contrast agent?

In the hepatocyte phase, an FNH is typically isointense or hyperintense relative to the adjacent liver after injecting a liver-specific contrast agent, on in-phase or opposed-phase T1-weighted 2D gradient-echo (GE) sequences and on T1-weighted 3D GE sequences with fat saturation. Because of its better spatial resolution, the T1-weighted 3D GE sequence with fat saturation loses contrast resolution, and contrast uptake by the lesion may appear less intense than on a T1-weighted 2D GE sequence. In addition, the signal from the lesion in the hepatocyte phase is assessed relative to the adjacent liver, itself influenced by instrumental parameters such as TE and flip angle. It may therefore be important to perform several sequences in the hepatocyte phase, to avoid missing any contrast uptake by the lesion. It should be noted that in the first study by Grazioli et al. [7], study of the hepatocyte
Figure 7. Focal nodular hyperplasia (FNH) containing fat. A 48-year-old female patient, with no noteworthy history. Chance discovery of a hepatic dome lesion. MRI characterization: a: the nodule (arrow) is hyperintense on the in-phase T1-weighted 2D GE sequence; b: the fall in intensity in the opposed-phase T1-weighted 2D GE sequence is evidence of its fat component; c: the lesion is hyperintense in the T2-weighted FSE F5 sequence, with a hyperintense central stellate scar with T2-weighting; d and e: the nodule is intensely enhanced in the arterial phase (d) after injecting Gd-BOPTA and becomes isointense with the adjacent liver in the venous phase, with contrast uptake by the central part (e); f and g: in the hepatocyte phase, the nodule is hyperintense relative to the adjacent liver in the in-phase T1-weighted 2D GE sequences (f) but above all with opposed-phase T1-weighted 2D GE (g), evidence of the capture of the liver-specific contrast agent favoring diagnosis of FNH.

Phase only concerned the T1-weighted 2D gradient-echo sequences.

Moreover, certain FNH only took up contrast at the periphery, in a ring (Fig. 11), in the hepatocyte phase, with a center remaining hypointense relative to the adjacent liver [32]. This appearance should not call the diagnosis into question.

In MRI, is contrast uptake in the hepatocyte phase after injecting a liver-specific contrast agent synonymous with FNH?

Certain forms of hepatocellular carcinoma may be isointense with or hyperintense to the adjacent liver in the hepatocyte phase [33–35]. Contrast uptake by a nodule in the
hepatocyte phase does not therefore mean that FNH can be diagnosed. It is essential to analyze the terrain, the morphology of the liver and the characteristics of the nodule with no contrast enhancement as well as during the dynamic phases after contrast injection, before diagnosing FNH.

Can an adenoma be formally diagnosed by non-invasive means?

In practice, this question only applies to steatotic adenomas suspected of being HNF1α mutations, since all the other lesions suspected of being adenomas must have at least one hepatic biopsy to look for the β-catenin mutation, the risk factor for evolution into hepatocellular carcinoma. The correlation between MRI and the histopathologic and immunohistochemical diagnosis of the adenoma subtype is excellent for steatotic and inflammatory adenomas, but to date has only been studied in a population of adenomas [8,36]. As regards steatotic adenomas suspected of being HNF1α mutations, the differential diagnosis with a hepatocellular carcinoma is based only on the background of chronic liver disease and arterial contrast uptake by the HCC, because the uniform overall fall in intensity in opposed-phase T1-weighting, very specific for HNF1α mutared steatotic adenomas in a population of adenomas, may perfectly well be encountered in HCC, all the more so when they are small [28]. This must lead to caution and close monitoring of adenomas labeled as steatotic and suspected of being HNF1α mutations without any histopathologic and immunohistochemical evidence.

Can liver overload be a source of diagnostic traps?

A steatotic liver may alter the ratio of the signal between the liver and the lesion. For this reason it is preferable to study the enhancement of a lesion in the hepatocyte phase on a sequence in which the lesion is hypo- or isointense relative to the adjacent liver before injection—in practice, often the in-phase T1-weighted 2D GE sequence—in order to appreciate the behavior of the lesion better (Fig. 12).

Hepatic iron overload also leads to modifications of the ratio of the signal between the liver and the lesion. Iron overload causes an increase in liver intensity on the opposed-phase T1-weighted 2D GE sequence compared with the in-phase T1-weighted 2D GE sequence. Moreover, a lesion appears more obviously hyperintense compared with the adjacent liver in the T2-weighted sequence, making diagnosis of FNH more difficult.

In practice, how do we cope with this?

The diagnosis of benign hepatocyte lesions is based essentially on analysis of MR images. Trap situations and atypical forms of these lesions are now well known. Ultrasonography with the injection of a contrast agent and the use of liver-specific MRI contrast agents could ultimately strengthen the diagnostic arsenal for these lesions further. A proposal for a management algorithm is shown in Inset 1.

Clinical case

This 55-year-old male patient had a liver transplant 3 months ago for alcoholic cirrhosis complicated by hepatocellular carcinoma nodules. He had a hepatic MRI during systematic monitoring because of the high risk of recurrence of his disease. His liver function tests are normal, as is his blood alpha-fetoprotein level. This is his MRI, which shows a single, one centimeter, hepatic nodule (Fig. 13 a–f).

Questions

1. Describe the images. What are your diagnostic hypotheses? Give your reasons.
2. How can diagnostic progress be made using imaging?
3. An additional MRI with injection of a liver-specific contrast agent (Fig. 13 g and h) and a contrast enhanced ultrasound examination (Fig. 14) were performed. How do you interpret them? Can you suggest a diagnosis or suitable management?

Figure 8. Central artery simulating a hypointense scar in a 35-year-old female patient with a typical focal nodular hyperplasia (FNH) seen in imaging: a: on the T2-weighted FSE sequence, the central artery appears hypointense (arrow head), while the central stellate scar appears hyperintense (arrow); b: in the arterial phase, the central artery is enhanced (arrow head), while the central stellate scar remains hypointense (arrow); c: In the venous phase series, the central stellate scar is enhanced (arrow).
Figure 9. Inflammatory adenoma with a stellate scar. A 24-year-old female patient, with no noteworthy history. Chance discovery of a mass in segment VI. MRI characterization: a and b: the nodule is isointense in the in-phase and opposed-phase T1-weighted 2D GE sequences; c: it is discreetly hyperintense in the T2-weighted FSE FS sequence, with a central stellate scar with T2-weighted hyperintensity; d and e: the nodule is intensely, heterogeneously enhanced in the arterial phase after injecting Gd-BOPTA (d), with discreet hyperintensity relative to the adjacent liver in the venous phase (e). Note that the central stellate scar is not enhanced in the venous phase; f and g: in the hepatocyte phase the nodule is hypointense relative to the adjacent liver on the in-phase (f) and opposed-phase (g) T1-weighted 2D GE sequences. This appearance is not indicative of an focal nodular hyperplasia (FNH). The diagnosis of an inflammatory adenoma was confirmed histologically.

Answers

1. This is a steatotic hepatic graft (Fig. 13a and b). The one centimeter, subcapsular nodule is hypointense on in-phase T1-weighted sequences (Fig. 13a) and hyperintense with T2-weighted FS (Fig. 13c). It takes up contrast intensely and uniformly in the arterial phase (Fig. 13d), with discreet hyperintensity relative to the adjacent liver in the portal and venous phases (Fig. 13e and f). There is no central stellate scar.

   With this hypervascular nodule the possible diagnoses are:
   • early recurrence of hepatocellular carcinoma on the graft, but there is no washout in the portal phase; alpha-fetoprotein is normal but the nodule is small;
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Figure 10. Focal nodular hyperplasia (FNH) with mixed flow in a contrast enhanced ultrasound examination. Discovery of a 7-cm left lobe mass in a 37-year-old woman, with no noteworthy history: a: ultrasonography in B mode showing the mass; b–f: contrast enhanced ultrasound shows centripetal and centrifugal, mixed, dynamic filling of the mass, not allowing a differential diagnosis; g–i: the MRI which followed shows the left lobe mass as T1-weighted hypointensity (g), T2-weighted discreet hyperintensity, with a central stellate scar hyperintense with T2-weighting (h) and obvious arterial contrast uptake outside of the central stellate scar (i); j and k: in the hepatocyte phase after injecting a liver-specific contrast agent a mass is seen isointense with the liver on the in-phase T1-weighted 2D GE sequence (j). The diagnosis was therefore of FNH.
• a nodule of focal nodular hyperplasia. There is no central stellate scar, but the nodule is less than 3-cm. The marked T2-weighted hyperintensity and its persistence relative to the liver in the portal and venous phases may be explained by hepatic steatosis;
• an adenoma, of the inflammatory type because of its hypervascular character;
• metastasis of a primary hypervascular tumor;
• a perfusion disorder is excluded because this is a nodule, clearly visible on the morphological sequences without injection. Nor is it an angioma, because the contrast uptake and the T2-weighted signal are not those of an angioma.

2. Performing an MRI with injection of a liver-specific contrast agent might help characterize the nodule better. Contrast uptake in the hepatocyte phase will speak in favor of a hepatocellular lesion, without making it possible to formally exclude a hepatocellular carcinoma. With a contrast enhanced ultrasound examination, the nodule will be characterized better, depending on the

Figure 11. Focal nodular hyperplasia (FNH) after injecting a liver-specific contrast agent. A 45-year-old man. FNH of the right liver proven by histology: a: the nodule is hypointense with non-enhanced T1-weighted 3D GE FS (arrow); b: it shows peripheral contrast uptake in a ring, in the hepatocyte phase, after injecting Gd-BOPTA (arrow).
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Figure 12. Focal nodular hyperplasia (FNH) on a steatotic liver. Overweight 45-year-old man. Discovery of a nodule of the right liver on a steatotic liver. MRI characterization: a: the nodule appears hypointense in the in-phase T1-weighted 2D GE sequence; b: it is hyperintense in opposed-phase T1-weighted 2D GE, due to the fall in signal from the steatotic liver; c: it is discreetly hyperintense in T2-weighted FSE FS, with no evident central stellate scar; d and e: it takes up contrast intensely in the arterial phase (d), with discreet hyperintensity persisting relative to the adjacent liver in the venous phase (e); f and g: in the hepatocyte phase, it is difficult to study the nodule on the opposed-phase T1-weighted 2D GE sequence (f), since it was already spontaneously hyperintense. The in-phase T1-weighted 2D GE sequence shows that the nodule is isointense with the liver in the hepatocyte phase (g), and that it has therefore captured the liver-specific contrast agent, which suggests FNH. This diagnosis was confirmed by histology.

3. Contrast uptake by the nodule on the MRI in the hepatocyte phase can only be analyzed on the in-phase T1-weighted 2D GE (Fig. 13g) and T1-weighted 3D GE FS (Fig. 13i) sequences, since the nodule is already spontaneously hyperintense on the opposed-phase T1-weighted 2D GE sequence (Fig. 13b), due to the hepatic steatosis.

By comparing Fig. 13a, g, and c and i, respectively, it can be seen that this nodule takes up contrast in the hepatocyte phase. The contrast enhanced ultrasound shows the subcapsular nodule (Fig. 14a). The dynamic contrast uptake is centrifugal (Fig. 14b–e).

In all, this one centimeter nodule is compatible with diagnosis of FNH. Added to this is the fact that the liver graft...
Figure 13. MRI: a: in-phase T1-weighted 2D GE sequence; b: opposed-phase T1-weighted 2D GE sequence; c: T2-weighted TSE sequence with fat saturation; d: T1-weighted 3D GE sequence with fat saturation in the arterial phase; e: T1-weighted 3D GE sequence with fat saturation in the portal phase; f: T1-weighted 3D GE sequence with fat saturation in the venous phase; g: in-phase T1-weighted 2D GE sequence in the hepatocyte phase; h: opposed-phase T1-weighted 2D GE sequence in the hepatocyte phase; i: T1-weighted 3D GE sequence with fat saturation in the hepatocyte phase.
Figure 13.  (Continued).

Figure 14.  Contrast enhanced ultrasound: a: without injection of contrast agent; b–e: dynamic arrival of the contrast agent in the lesion.
TAKE-HOME MESSAGES

- MRI is the gold standard for characterizing benign hepatocellular tumors. There is a place for contrast enhanced ultrasound in diagnosing FNH < 5-cm, with typical centrifugal enhancement.
- The MRI criteria for typical FNH are well known. Nevertheless, the presence of intrasosional fat and the absence of a central stellate scar for lesions of less than 3-cm should not call the diagnosis into question.
- Certain molecular subtypes of adenomas, HNF1α mutations and inflammatory adenomas may be suspected from their MRI profile.
- When diagnosis is difficult between an adenoma and FNH, MRI with injection of a liver-specific contrast agent can be offered with analysis of the hepatocyte phase: FNH 'capture' the contrast agent while adenomas do not.
- Take care with the classic MRI pitfalls: liver overload can change analysis of the behavior of a lesion in MRI; not all hypervascular lesions are hepatocellular lesions; the presence of a central stellate scar is not synonymous with FNH.
- In contrast enhanced ultrasound, the presence of centripetal or mixed flow does not exclude diagnosis of FNH for lesions larger than 5-cm.

Once this analysis is complete, several situations could arise.

The lesion suggests:

<table>
<thead>
<tr>
<th>Typical FNH</th>
<th>Steatotic adenoma</th>
<th>Inflammatory adenoma</th>
<th>Other</th>
<th>Non-typical FNH or diagnosis between adenoma and FNH difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action to take</td>
<td>Monitoring?</td>
<td>Biopsy</td>
<td>Biopsy</td>
<td>Contrast enhanced ultrasound if nodule &lt; 5-cm ± MRI with injection of liver-specific contrast agent with the hepatocyte phase</td>
</tr>
<tr>
<td>STOP</td>
<td>Monitoring?</td>
<td>Biopsy</td>
<td></td>
<td>Contrast uptake in the hepatocyte phase and/or contrast enhanced ultrasound suggesting FNH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>= FNH</td>
<td>STOP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Monitoring?</td>
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<tr>
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<td></td>
<td></td>
<td>No hepatocyte contrast uptake</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>= Not FNH</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biopsy</td>
</tr>
</tbody>
</table>

References


came from a female donor cadaver. Given the small size of the nodule and its subcapsular position, difficult to biopsy, a multidisciplinary consultative meeting decided on close monitoring. The various monitoring imaging examinations have shown it remaining stable over a year. This nodule was therefore diagnosed as FNH.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Inset 1. Proposition for the management of hepatic nodules compatible with benign hepatocellular tumors.

   2. Analysis of the overall liver signal: Steatosis? Iron overload?
   3. Analysis of the nodule:
      • Size? < 3-cm? > 5-cm?
      • Presence of fat? Throughout? Focal?
      • T2-weighted signal?
      • Homogeneous lesion?
      • Central stellate scar? T2-weighted signal?
      • Arterial enhancement?
      • Venous phase signal?


