Focal nodular hyperplasia vs hepatocellular adenoma:
Benign hepatic tumors with overlapping imaging features -
The role of the new specific contrast agents

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Learning objectives

To illustrate the typical and atypical features of focal nodular hyperplasia (FNH) and hepatic adenoma as well as overlapping imaging features.

To demonstrate the use of gadobenate dimeglumine (Gd-BOPTA) in dynamic and delayed MRI in differentiating focal nodular hyperplasia (FNH) from hepatic adenoma.
Background

- MR imaging of the liver is often performed to detect and characterize focal liver lesions.
- Protocols usually include intravenous administration of nonspecific extracellular contrast agents (gadolinium chelates), which evoke the same perfusion mechanism of iodinated contrast-enhanced CT. Although its high accuracy, dynamic liver imaging is not always sufficient to convey a confident diagnosis.
- Compounds have been developed for contrast-enhanced MR imaging of the liver, that combine the excellent contrast resolution of MR imaging (MRI) with increased and prolonged contrast between normal and pathological tissues and also improve specificity.

Liver-Specific Contrast Agents

- Liver-specific contrast media are administred intravenously and accumulate in normal liver cells through anion receptor-mediated endocytosis but not in metastases or other tissues foreign to the liver.
- These agents are highly lipophilic Gadolinium (Gd) or Manganese (Mn) complexes.
- The route of elimination is biliary (enterohepatic circulation) and renal.
- **Gd-BOPTA** or gadobenate dimeglumine accumulates in the liver parenchyma after 30-60min following an initial phase that is rather unspecific. Only 2-7% of the administered agent is excreted in the bile. The fact that this contrast medium preparation acts both as an unspecific gadolinium agent with the capacity to alter plasma relaxivity due to its predominantly intravascular distribution as a result of reversible albumin binding and as a liver-specific agent in the subsequent liver phase opens up new fields of application in MR angiography, imaging of cerebral lesions, and in the detection of breast and liver metastases.
- **Gd-EOB-DTPA** or gadoxetate disodium has the highest specific absorption rate with about 50% hepatobiliary elimination. It enhances normal liver tissue about 10-20minutes after IV administration. Lesions not taking up the contrast medium thus show negative contrast and are delineated as low-signal-intensity areas against the bright background of normal liver tissue on T1-weighted images. Only in patients with biliry obstruction will there be little or no uptake of the contrast medium into liver cells. Apart from improving detection of focal liver lesions, Gd-EOB-DTPA may also have a potential for use in MRCP imaging, where it provides positive contrast of the bile ducts due to its biliary elimination.
There are three main clinical situations that require contrast-enhanced MR imaging with liver-specific contrast agents:

1. Incidental finding of a focal liver lesion in an otherwise healthy patient, suspected to be focal nodular hyperplasia (FNH) or adenoma

2. Staging for HCC in a patient with liver cirrhosis or hepatitis

3. Staging for hepatic metastases in a patient with suspected or known extrahepatic malignancy

**FOCAL NODULAR HYPERPLASIA (FNH)**

- Is the second most common benign hepatic tumor (after hemangioma), thought to represent a hyperplastic response of the hepatic parenchyma to a preexisting arterial malformation.
- Is most commonly detected in women of reproductive age but can rarely occur in men and children.
- Most cases are found at autopsy, surgery, or imaging studies and are asymptomatic. Large lesions may be symptomatic because of distention of the liver capsule or mass effect on adjacent organs.
- Oral contraceptives medications do not initiate development of FHN; however, the relationship between oral contraceptive medication use and growth of FNH is less clear.
- Solitary in 80% to 95% of patients.
- Is composed of nodules of hyperplastic hepatocytes and small bile ductules surrounding a central fibrous scar (containing dense connective tissue and blood vessels).
- Hemorrhage and necrosis are unusual, and rupture of FNH is extremely rare.
- Mean diameter is 5cm.

- **T1-WI**: isointense or slightly hypointense to liver; central scar hypointense.
- **T2-WI**: isointense or slightly hyperintense to liver; central scar hyperintense.
- **Arterial phase**: markedly enhancement.
- **Portal venous phase**: becomes isointense to adjacent liver parenchyma
- **Delayed images**: slightly hyperintense
- **Central Scar**: hypovascular to mass on arterial phase with increased enhancement on delayed phase. At unenhanced MRI, the central scar is typically hyperintense on T2-WI
Atypical Focal Nodular Hyperplasia:

- heterogeneous lesion (e.g. internal hemorrhage on T1W, abnormal signal intensity on T2W)

- absence of the central scar or hypointensity of the scar on T2-WIs

- fat infiltration in FNH may also occur but is rare

- presence of a pseudocapsule

- marked T1 or T2 lesion hyperintensity

Focal Nodular Hyperplasia and Gd-BOPTA

- A malformed biliary system is present, in which the primary bile ductules are blind-ending and have no connection to the larger bile ducts, therefore biliary excretion is slowed compared with that occurring in normal hepatocytes and results in accumulation of Gd-BOPTA within the ductules and hence persistent enhancement of the lesion. Over time, as hepatobiliary elimination from the surrounding normal hepatocytes leads to continually decreasing signal intensity enhancement in normal parenchyma, the hyperintense appearance of FNH would be expected to increase, augmented by the re-uptake of Gd-BOPTA from the blind-ending biliary ductules into the hepatocytes of the lesion.

HEPATIC ADENOMA

- Benign hepatic neoplasm occurring most commonly in women taking oral contraceptive medications (the incidence increases with the duration of oral contraceptive medication use and the dosage of estrogen). Anabolic-androgenic steroids and glycogen storage diseases also represent risk factors.

- Composed of benign hepatocytes arranged in large plates or cords without an acinar architecture.

- Adenoma cells contain glycogen and lipid; kupffer cells may be present but usually are nonfunctioning and bile ducts are absent.

- Complications: hemorrhage and rare malignant transformation to hepatocellular carcinoma. Rupture of a hemorrhagic is related to its
proximity to the liver surface and the thickness of the fibrous tumor capsule, if present.

- Mean diameter of 3 to 5cm.
- Heterogeneous MR appearance reflects the variable presence of intralesional steatosis, hemorrhage, necrosis, fibrous encapsulation and large tumoral vessels.

- **T1-WI**: signal intensity (SI) varies with presence of lipid, hemorrhage, and necrosis, but often have components that are hyperintense to liver.
- Intratumoral lipid common, confirmed by chemical shift imaging.
- **T2-WI**: variable SI but usually have some hyperintense components.
- **Contrast-enhanced imaging**: hypervascular on the arterial phase, but not as vascular as FNH
- No central scar

Main **differential diagnosis** for hepatic adenoma includes:

- focal nodular hyperplasia
- hepatocellular carcinoma

Except for the central scar, FNH is typically homogeneously isointense to liver on both T1 and T2-WIs, whereas adenoma is usually of heterogeneous SI. FNH usually contains a central scar, a rare finding in hepatic adenoma.

Hepatocellular carcinoma typically develops in patients with cirrhosis whereas hepatic adenomas occur in young women who have taken oral contraceptive medications.

**Hepatic Adenoma (HA) and Gd-BOPTA**

Bile ductules are absent in HA, therefore the bilirubin metabolism is blocked. While the mechanism of Gd-BOPTA entry into the hepatocytes of HA may be unaltered, the absence of an intracellular transport gradient due to lack of any active transport across the sinusoidal membrane would manifest as hypointensity against normal enhanced parenchyma on delayed images, in which enhancement is derived from the presence of Gd-BOPTA in both the hepatocytes and the adjacent biliary system.
Imaging findings OR Procedure details

FOCAL NODULAR HYPERPLASIA (FNH)

FNH MR Imaging Features (with no liver-specific contrast agent)

Case 1 (Focal Nodular Hyperplasia)

**Fig.**: Figure 1. A In-phase T1-WI shows an FNH (arrows) that is isointense to surrounding liver parenchyma. The central scar is imperceptible.

**References:** Imagem e meios de diagnostico, Radiologia - Porto/PT
Fig.: Figure 1.B Fat-suppressed T2-WI shows a slightly hyperintense FNH (white arrows) and a discrete hyperintense central scar (yellow arrow).

**References:** Imagem e meios de diagnostico, Radiologia - Porto/PT
Fig.: Figure 1.C Arterial-phase CE T1-WI shows marked FNH enhancement (white arrows) and a non-enhancing central scar (yellow arrow).

References: Imagem e meios de diagnostico, Radiologia - Porto/PT
**Fig.**: Figure 1.D - Portal CE T1-WI reveals a discrete hyperintense FNH (white arrows), with a persistent hypointense central scar (yellow arrow) Figure 1.E - Delayed CE T1-WI shows that the FNH becomes isointense to liver except for the hyperintense central scar (yellow arrow)

**References:** Imagem e meios de diagnostico, Radiologia - Porto/PT

**Case 2 (Focal Nodular Hyperplasia)**
Fig.: Figure 2.A In-phase T1W. The lesion is so isointense and so homogeneous that is not clearly identified. Figure 2.B T2W image shows the lesion (arrows) which is markedly hyperintense to liver parenchyma. A very discrete hyperintense central scar is admitted.

References: Imagem e meios de diagnostico, Radiologia - Porto/PT
**Fig.**: Figure 2.C Early phase post gadolinium image shows the lesion with marked contrast enhancement with a non-enhanced hypointense central scar (yellow arrow) Figure 2.D Delayed phase post gadolinium image shows late contrast enhancement within the central scar (yellow arrow). There is contrast wash out in the non scar area of the lesion.

**References:** Imagem e meios de diagnostico, Radiologia - Porto/PT

**Case 3 (Focal Nodular Hyperplasia)**
Fig.: Figure 3.A - Axial fat saturation T2W shows two adjacent FNH in the right hepatic lobe, both lesions are hypointense with a hyperintense central scar (yellow arrows) Figure 3.B - Arterial phase reveals marked contrast enhancement with a nonenhanced hypointense central scars (yellow arrows) Figure 3.c - Portal phase shows that the FNH becomes hypointense and the central scars remain at this phase hypointense

References: Imagem e meios de diagnostico, Radiologia - Porto/PT
Fig.: Figures 3.D and 3.E Both figures reveal the delayed phase post gadolinium that clearly depicts the two hyperintense central scars (arrows). There is contrast washout in the non scar area of both lesions.

References: Imagem e meios de diagnostico, Radiologia - Porto/PT

Case 4 (Focal Nodular Hyperplasia)
**Fig.**: Figure 4.A - In-phase T1 shows an FNH (white arrows) that is minimally hypointense to liver. The central scar (yellow arrow) is hypointense to the remainder of the mass and liver. Figure 4.B - Arterial phase CE T1 WI reveal marked FNH enhancement and a nonenhancing central scar (yellow arrow). Figure 4.C - Delayed CE T1-WI shows that the FNH becomes isointense to liver except for the hyperintense central scar (yellow arrow) that enhanced late.

**References:** Imagem e meios de diagnostico, Radiologia - Porto/PT

**FNH MR Imaging Features (with liver-specific contrast agent, Gd-BOPTA)**

**Case 5 (Focal Nodular Hyperplasia)**
**Fig.**: Figure 5.A - T1-WI shows a hypointense almost isointense lesion (arrows), without a visible scar. Figure 5.B - Fat saturation T2-WI reveals the lesion which is hyperintense to liver parenchyma. Figure 5.C - Arterial phase depicts a hypervascular lesion.

**References:** Imagem e meios de diagnostico, Radiologia - Porto/PT
**Fig.**: Portal phase (figure 5.D) reveals a hyperintense lesion, and 60 minutes after Gd-BOPTA administration (figure 5.E), when the peak enhancement of lesion-to-liver contrast occurs, an enhancing lesion is still present indicating the presence of bile ductules (FNH).

**References:** Imagem e meios de diagnostico, Radiologia - Porto/PT

**Case 6 (Atypical FNH - fat infiltration)**
Fig.: Figures 6.a and 6.b - A very discrete isointense liver lesion is revealed on the in-phase image (6.A). On the opposed-phase image (6.B) there are some lesion areas (arrows) that reveal signal intensity loss, establishing the presence of intracellular lipid. This fact would suggest initially an adenoma. However, the dynamic contrast-enhanced study (6.C, 6.D, 6.E, 6.F) demonstrates a hypervascular pattern (6.C, the arrow points the hypointense central scar) and a late enhancement of the centrally-located scar (arrow in 6.E). On a delayed phase (6.F) (almost 120 minutes after Gd-BOPTA administration), as hepatobiliary elimination from the surrounding normal hepatocytes leads to continually decreasing SI enhancement in normal parenchyma, the lesion (arrows) reveals a more hyperintense pattern due to the augmented re-uptake of Gd-BOPTA from the blind-ending biliary ductules into the hepatocytes of the lesion. This dynamic pattern suggests the presence of FNH.

References: Imagem e meios de diagnostico, Radiologia - Porto/PT
Fig.: Figures 6.a and 6.b - A very discrete isointense liver lesion is revealed on the in-phase image (6.A). On the opposed-phase image (6.B) there are some lesion areas (arrows) that reveal signal intensity loss, establishing the presence of intracellular lipid. This fact would suggest initially an adenoma. However, the dynamic contrast-enhanced study (6.C,6.D,6.E,6.F) demonstrates a hypervascular pattern (6.C, the arrow points the hypointense central scar) and a late enhancement of the centrally-located scar (arrow in 6.E). On a delayed phase (6.F) (almost 120 minutes after Gd-BOPTA administration), as hepatobiliary elimination from the surrounding normal hepatocytes leads to continually decreasing SI enhancement in normal parenchyma, the lesion (arrows) reveals a more hyperintense pattern due to the augmented re-uptake of Gd-BOPTA from the blind-ending biliary ductules into the hepatocytes of the lesion. This dynamic pattern suggests the presence of FNH.

References: Imagem e meios de diagnostico, Radiologia - Porto/PT

Case 7 (Focal Nodular Hyperplasia)
**Fig.**: Figure 7.A - No liver lesion is revealed on the in-phase image Figure 7.B - Arterial phase shows the lesion a hypervascular mass (arrows) Figure 7.C - The FNH becomes isointense to liver except for the hyperintense central scar (arrow) Figure 7.D - One hour after medium contrast administration, Gd-BOPTA is being eliminated by the biliary system (white arrow indicates the presence of Gd-BOPTA in the gallbladder), the lesion is slightly hyperintense (re-uptake of Gd-BOPTA from the blind ending biliary ductules into the hepatocytes), suggesting the presence of FNH.

**References:** Imagem e meios de diagnostico, Radiologia - Porto/PT

**Case 8 (Focal Nodular Hyperplasia)**
Fig.: Figure 8.A - T1-WI shows a hypo/almost iso-intense lesion (arrows) Figure 8.B - Arterial phase shows the lesion with marked contrast enhancement (arrows) Figure 8.C - Venous phase, FNH is slightly hyperintense (arrow) Figure 8.D - One hour after medium contrast administration, the lesion reveals discrete contrast (Gd-BOPTA) enhancement (arrows)

References: Imagem e meios de diagnóstico, Radiologia - Porto/PT

HEPATIC ADENOMA (HA)

HA MR Imaging Features (with no liver-specific contrast agent)

Case 9 (Hepatic Adenoma)
Fig.: Hepatic Adenoma

Figure 9.A - No obvious nodular lesions are revealed on the in-phase image, however a very discrete hypointense area is delineated at the periphery of the right hepatic lobe (arrow) Figure 9.B - Opposed-phase image shows loss of SI on some intra-lesional areas (arrows), establishing the presence of intracellular lipid Figure 9.C - Arterial phase CE T1-WI shows a hypervascular mass (arrows), but not so hypervascularized as FNH (as described above)

References: Imagem e meios de diagnostico, Radiologia - Porto/PT

Case 10 (Hepatic Adenoma)
**Fig.:** Hepatic Adenoma Figure 10.A - No liver lesions are revealed on the in-phase image Figure 10.B - Opposed-phase image clearly depicts a nodular area (arrows) with loss of SI, suggesting an area with intracellular lipid Figure 10.C - Fat suppressed T2-WI shows a hyperintense nodular lesion (arrows) Figure 10.D - Arterial phase CE T1-WI reveals marked adenoma enhancement (arrow)

**References:** Imagem e meios de diagnostico, Radiologia - Porto/PT

**Case 11 (adenoma with no intratumoral lipid component)**
Fig.: Hepatic Adenoma Figure 11.A and 11.B - In-phase image (11.A) does not reveal any nodular hepatic lesion, and opposed-phase image (11.B) does not show any significant loss of signal intensity. Figure 11.C and 11.D - The dynamic contrast-enhanced study demonstrates a hypervascular pattern (arrows in 11.C), becoming isointense on delayed image (11.D).

References: Imagem e meios de diagnostico, Radiologia - Porto/PT

Hepatic Adenoma MRI Features (with liver-specific contrast agent, Gd-BOPTA)

Case 12 (Hepatic Adenoma)
Fig.: Hepatic Adenoma in a 32-year-old woman Figure 12.A - In-phase image (12.A) reveals a large focal mass (arrows), slightly hyperintense to liver parenchyma. Figure 12.B - Opposed-phase image shows that the mass remains hyperintense (arrows) consistent with no intracellular lipid component. Figure 12.C - During the arterial phase the mass markedly enhances. Figure 12.D - One hour after Gd-BOPTA administration, contrast is being eliminated by the hepatobiliary system (note the contrast inside the gallbladder) and the lesion is not enhanced, suggesting the absence of biliary ductules inside the lesion, thus favoring the diagnosis of adenoma.

References: Imagem e meios de diagnostico, Radiologia - Porto/PT
Conclusion

MR Imaging features of Focal Nodular Hyperplasia and Hepatic Adenoma are often similar but it is important to differentiate them because they have different complications.

Atypical Focal Nodular Hyperplasia can be difficult to diagnose as it may mimic other tumours such as hepatocellular carcinoma or large hepatic adenoma, which should be resected.

The development of new contrast media (each with its pharmacokinetic properties) for hepatic MR Imaging allowed a more accurate diagnosis, thus playing a key role in today's radiology.
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