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Review

Budd-Chiari Syndrome and hepatic regenerative nodules: Magnetic resonance findings with emphasis of hepatobiliary phase

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ABSTRACT

Budd-Chiari syndrome (BCS) is a disorder with numerous causes that is a result of hepatic outflow obstruction, in the absence of right heart failure or constrictive pericarditis. Acute Budd-Chiari syndrome is uncommon and clinically characterized by ascites, hepatomegaly, and hepatic insufficiency. In the majority of cases, patients present with chronic BCS, showing a dysmorphic liver disease with variable fibrosis deposition. In chronic Budd-Chiari syndrome, hepatocellular carcinoma (HCC) and benign regenerative nodules (called large regenerative nodules or FNH-like lesions) have been described in the literature. Very few studies have reported magnetic resonance imaging (MRI) findings about these nodules, using hepatobiliary contrast medium. The aim of our review is to describe the magnetic resonance imaging findings of hepatic regenerative nodules in BCS, with emphasis on the hepatobiliary phase, and to compare the imaging features of benign nodules with those of HCC.

1. Introduction

Hypervascular regenerative nodules are benign hepatocellular nodules related to vascular disturbances of the liver such as BCS, congenital portosystemic shunt, portal cavernoma and Rendu-Osler-Weber syndrome [1–3]. These nodules have been called “large regenerative nodules” or alternatively “FNH-like lesions”, because they strongly resemble FNH (Focal Nodular Hyperplasia), both in imaging studies and histopathologically, but are connected to different clinical settings, typically chronic liver disease [1–3]. Particularly, these nodules have been associated with BCS and they have been reported more frequently as a result of higher-resolution imaging techniques associated with multiphasic contrastographic studies. By contrast, they have received relatively little attention in the radiology literature. Indeed, previous studies exhibit multimodality imaging findings of regenerative nodules in BCS and only few papers describe the hepatobiliary pattern of these nodules, with only few images [1–3]. Therefore, the hepatobiliary imaging of regenerative nodules in BCS has not been supported by an extensive scientific evidence. We propose a more comprehensive review which describes the key MRI features of regenative nodules in patients with BCS, with detailed information about their signal intensity in each MRI sequences, and with emphasis of hepatobiliary pattern. The cases of regenerative nodules showed in our paper are proved by biopsy or follow-up with evidence of benignity. Furthermore, we described the differential diagnosis with HCC and other hepatic lesions, providing all the diagnostic findings to confidently interpret magnetic resonance imaging results.

2. Pathogenetic and clinical aspects of Budd-Chiari Syndrome

BCS is a rare disorder characterized by hepatic venous outflow obstruction, without right heart failure or constrictive pericarditis [4]. Obstruction may have different causes and may be anywhere along the venous system from the smaller hepatic veins to the junction of the inferior vena cava (IVC) to the right atrium. Differently from BCS, in the sinusoidal obstruction syndrome (SOS), previously called veno-occlusive disease, the outflow obstruction arises at level of the sinusoids and terminal hepatic venules rather than the hepatic veins.

BCS can be classified into primary or secondary depending on the origin of the obstruction. When an endoluminal venous lesion, such as thrombus, causes the hepatic venous outflow obstruction, BCS is considered primary [5]. Primary BCS is the most common form and is often associated with hypercoagulable states leading to vascular thrombosis, from several diseases [6]. An other rare cause of primary BCS, more

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frequent in Asia, entails membranous web-like obstruction of the IVC that extends to the hepatic veins, probably with congenital origin. Budd-Chiari syndrome is considered secondary when the hepatic venous outflow obstruction arises from extrinsic compression or from vascular invasion by tumors including hepatic neoplasms (i.e. hepatocarcinoma), nephroblastoma, renal adenocarcinoma, adrenocortical carcinoma, leiomyosarcoma of the IVC, or myosarcoma of the right atrium [5]. To increase the intrahepatic sinusoidal pressure the involvement of at least two hepatic veins is required. Thus, a single vein obstruction is often asymptomatic or paucisymptomatic and does not cause BCS [6]. The obstruction of two or more major hepatic veins increases the sinusoidal pressure, resulting in sinusoidal dilatation, liver congestion and hepatomegaly. The result of these hemodynamic changes is portal hypertension with developing of intrahepatic and extrahepatic venous collaterals, typically seen in patients with BCS. BCS is more common in women and can occur at any age. The clinical presentation is related to the extent and rapidity of hepatic vein occlusion and the developing of venous collaterals. Indeed, BCS can be classified as acute (fulminant or non-fulminant), subacute, or chronic. In acute forms (7%) [7], typical signs and symptoms are hepatomegaly, abdominal pain, ascites, and hepatic insufficiency. Most patients present with sub-acute and chronic forms (48% and 45% respectively) [7], with a dysmorphic liver associated with variable parenchymal fibrosis. In fact, BCS results in severe centrilobular congestion, hepatocellular necrosis and atrophy, so parenchymal fibrosis develops within a few weeks after venous obstruction. Since hepatic atrophy and progressive fibrosis, regenerative nodules develop during the course of disease and have been described in some prevoius studies. Because these regenerative nodules may be numerous, may increase in size and often arise along the portal spaces, they can contribute to increase of portal hypertension, compressing the portal branches and obliterating the central vein.

3. MRI diagnosis of Budd-Chiari Syndrome

Imaging plays a pivotal role in the diagnosis of BCS, mainly through ultrasound and MR imaging. Digital subtraction angiography represents the gold standard for the diagnosis of BCS. Since it is an invasive procedure associated with radiation exposure, MRI has been considered as the best alternative imaging modality for diagnosing BCS. Doppler ultrasound is considered the first line imaging technique in patients with suspected BCS, but it is operator dependent and maybe limited by intestinal gas and ascites. Furthermore, Doppler ultrasound is less accurate in evaluating the extrahepatic venous collaterals and the hepatic focal lesions. Computed tomography (CT) is less accurate than ultrasound in detecting venous abnormalities. Moreover, failure to detect the hepatic veins on CT imaging does not confirm the diagnosis of BCS. The advantage of MRI consists in the possibility of evaluating all the aspects of BCS with or without contrast medium administration, in particular in patients with decreased renal function. Indeed, hepatic veins thrombosis can be detected as hypointensity avoiding the contrast agent administration, using a steady-state free-precession (SSFP) or a grandient echo sequences. Another finding of hepatic veins thrombosis is the lack of signal void on T2-weighted imaging.

The imaging features of BCS are variable and depend on the temporal phase of the disease [8,9].

3.1. Acute BCS

In acute BCS, the liver usually is normal or enlarged, and the hepatic veins occlusion (Fig. 1a) associated with severe ascites is the typical feature [8,9]. Enhancement of the liver is reduced, heterogeneous and delayed since the parenchymal congestion [8,9]. The liver shows patchy, decreased peripheral enhancement caused by blood stasis and more evident enhancement of the central part of the liver parenchyma including the caudate lobe, called “zonal enhancement” (Fig. 1b) [9]. The peripheral portion of the liver appears heterogeneously hyperintense on T2-weighted imaging, due to the hepatic congestion (Fig. 1c) [9,10]. The hepatic artery diameter is usually larger than that of the splenic artery (Fig. 1d) since the increase in arterial perfusion to compensate for the decrease in portal flow. The typical finding of chronic Budd-Chiari syndrome is the so-called “mosaic” enhancement pattern (Fig. 1e,f) [9]. This is characterized by a mottled, heterogeneous and reticulated enhancement on arterial and/or portal venous phases that typically leads to a partial or complete homogenization of the liver parenchyma on the late phase. This finding is related to sinusoidal dilatation, so it may be found in other diseases [9]. Importantly, the caudate lobe is spared from sinusoidal congestion, due to its own venous drainage; for this reason it is enlarged in about half the patients (Fig. 1g) [9].

3.2. Subacute or chronic BCS

In subacute or chronic BCS, the occluded hepatic veins show linear signal hypointensity on all sequences and intrahepatic collateral vessels are often demonstrated as a typical finding (Fig. 2). Some authors [11] has classified intrahepatic venous collaterals into 4 types: large collaterals draining into the IVC, subcapsular veins, collateral cobwebs, and veno-venous shunts [9].

Furthermore, the IVC can be compressed by the enlarged caudate lobe and portal vein thrombosis can develop caused by underlying thrombophilia and by portal and sinusoidal stasis. Among portosystemic collateral pathways, esophageal varices (Fig. 2e) are very important because they are a frequent source of gastrointestinal bleeding. In chronic BCS, the liver shows morphologic changes depending on the type of venous involvement, with hypertrophy of healthy territories (in particular the caudate lobe) and atrophy of liver segments with venous outflow obstruction. These hepatic changes result in liver dysmorphy mimicking liver cirrhosis. Finally, in patients with chronic BCS the development of multiple regenerative nodules has been described, as result of vascular imbalance of the liver with decreased portal and venous flow and hyperarterialization.

4. Regenerative nodules in Budd-Chiari Syndrome

In patients with BCS, the liver develops severe vascular congestion and successive fibrosis [4,5,8,9]. The regenerative nodules were discovered only in patients with chronic BCS, not in patients with acute disease. Indeed, the development of fibrosis dominates in the chronic phase and benign regenerative nodules may appear (Fig. 3). The prevalence of these nodules is difficult to determine; a previuos study showed liver nodules in 36% of patients with BCS [12]. Initially, benign regenerative nodules associated with Budd-Chiari termed adenomatous hyperplastic nodules, regenerative nodular hyperplasia (RNH), and regenerative nodules [13–16]. Despite the different terms that have been used to describe these nodules, these lesions are similar pathology features. Some authors [17,18] suggested that the term “RNH” was probably not appropriate for this nodules, due to its big size and the parenchymal fibrosis present in the liver. Indeed, the definition of RNH implies the absence of parenchymal fibrosis between the nodules, and these lesions are monoacinar regenerative nodules, generally with a diameter of 1 mm or up to 10 mm if grouped in clusters. Therefore, these authors preferred the term “large regenerative nodules” or “multiacinar regenerative nodules” in patients with BCS. By contrast, these benign regenerative nodules are similar to focal nodular hyperplasia (FNH), but unlike FNH the surrounding liver parenchyma was not normal [19]. Because they develop on an unhealthy liver, they are also called focal nodular hyperplasia-like (FNH-like) lesions by authors as Vilgrain et al [1]. In our opinion, the term “FNH-like regenerative nodule” (FNH-like RN) could be probably the best name to decribe these lesions at imaging, because suggests the nature (regenerative) and the hypervascular appearance (FNH-like) of these lesions. The

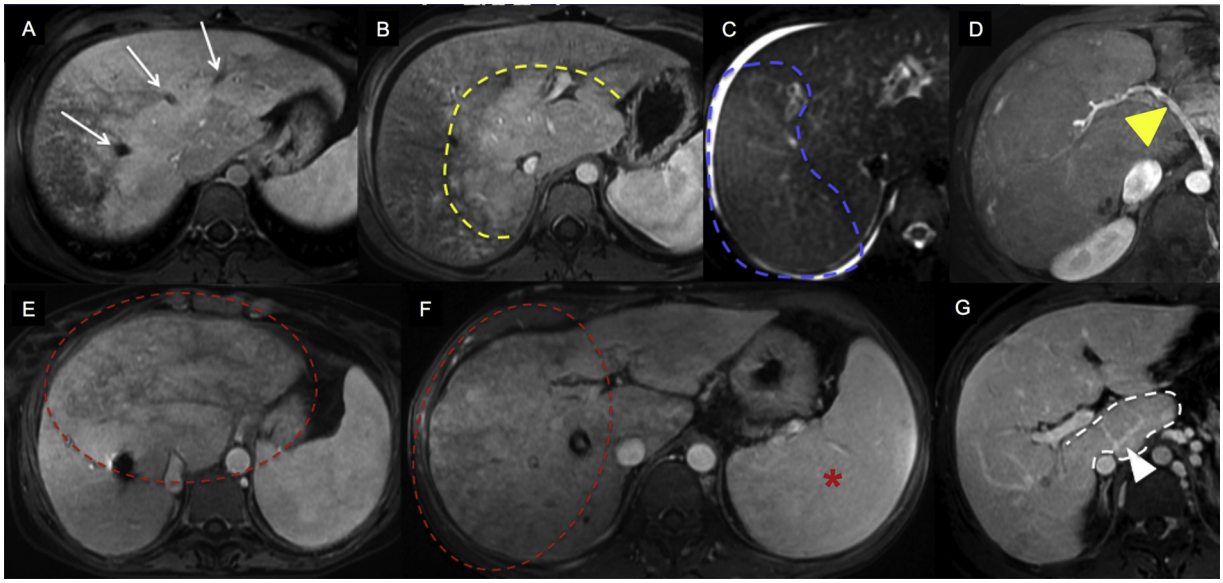

Fig. 1. Magnetic resonance imaging (MRI) findings of Budd-Chiari syndrome (BCS). MR images show occlusion of the hepatic veins (white arrows) (a), zonal enhancement (yellow line) (b), peripheral T2 hyperintensity (c), enlarged hepatic artery (yellow arrowhead) (d), mosaic pattern (red circle) (e,f), splenomegaly (red asterisk) (f) and caudate lobe enlargement (white line) (g) with its own venous drainage (white arrowhead).

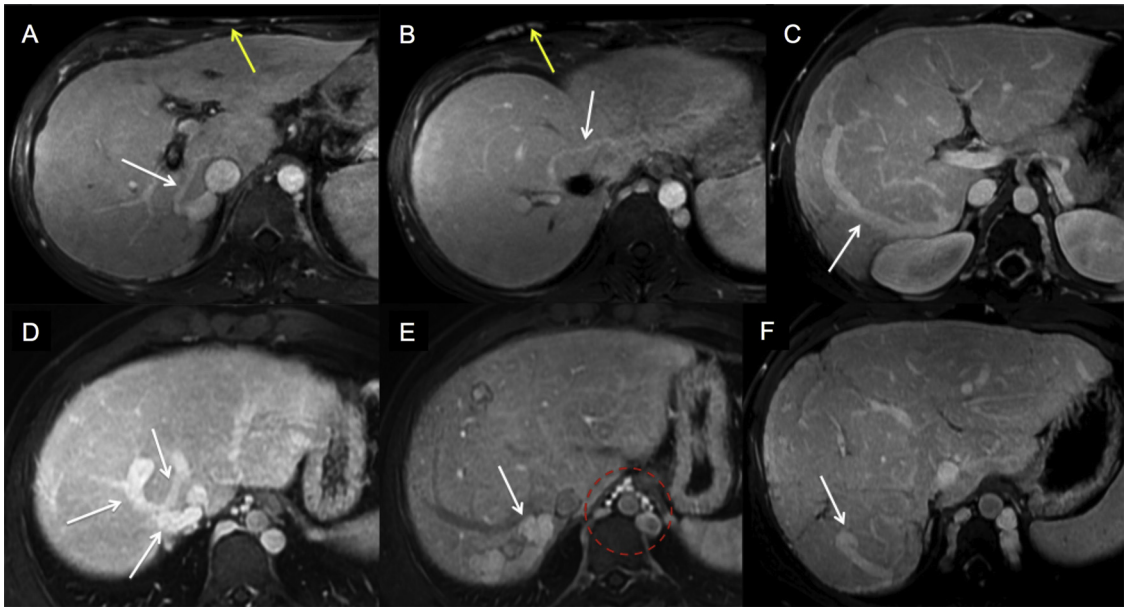

Fig. 2. Venous shunts in BCS. Axial portal phase MR images showing multiple veno-venous shunts (white arrows) in different patients. Notice the caput medusae (yellow arrows) and esophageal varices (red circle) as signs of portal hypertension.

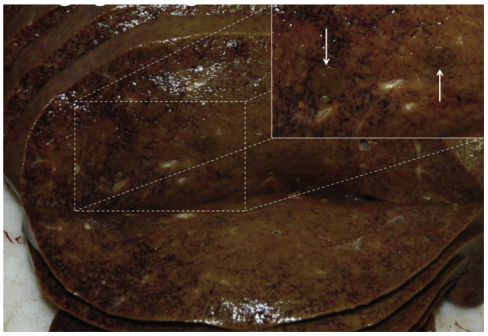

Fig. 3. Photograph of hepatic slice from explanted liver after tranplantation that shows benign regenerative nodules (white arrows) in patient with BCS.

pathogenesis of these regenerative nodules seems to be impaired hepatic blood flow to the liver. Therefore, the cause of benign regenerative nodules is an imbalanced hepatic microcirculation secondary to the hepatic vein obstruction, probably with a decrease of portal flow and an increase of arterial flow. These nodules, in fact, show a bright enhancement on arterial phase of CT and MR imaging, corresponding to an increased arterial supply. It is difficult to determine if TIPS procedures may cause the development of these nodules, since they can grow spontaneously over time [1,20]. The two most characteristic findings concerning these nodules are the number and size of lesions. They are usually numerous, with a typical diameter varying from 0.5 to 3-4 cm [1,2,12] and may increase in size and/or in number spontaneously over time [1,12,20]. FNH-like RNs do not show areas of hemorrhage, fat or calcification. No specific location has been identified and subcapsular nodules may alter the hepatic contours [2]. They are

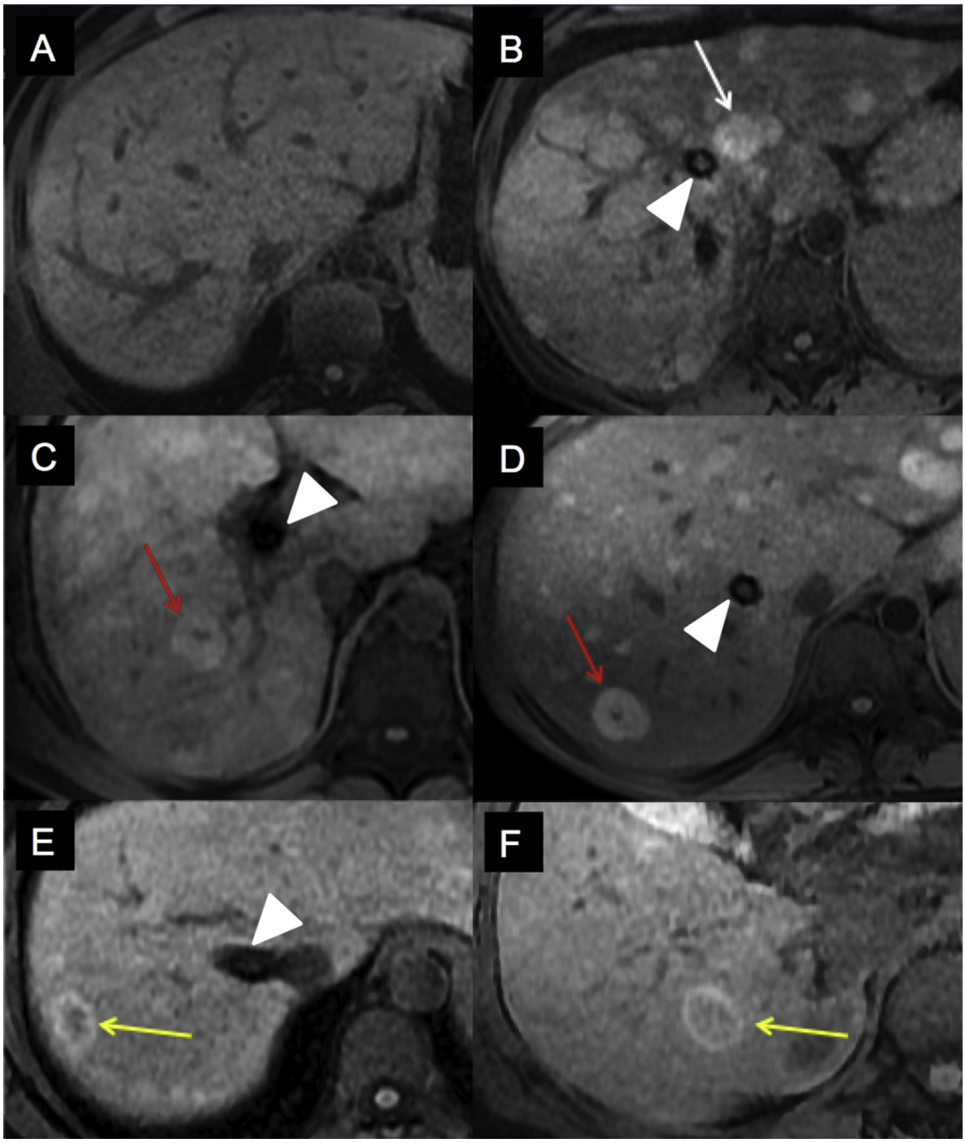

Fig. 4. T1 imaging. FNH-like regenerative nodules (FNH-like RNs) are usually isointense (a) or hyperintense (white arrow) (b). A central area of low signal intensity, due to a scar, is seen in some lesions; this area can be small (red arrows) (c,d) or large (yellow arrows) (e,f). Notice the presence of TIPS (Transjugular Intrahepatic Porto-systemic Shunt) (white arrowheads).

benign liver lesions and are the most common lesions in cronic Budd-Chiari syndrome. There is no existing evidence about transformation of FNH-like RN in HCC, but the number of studies in this field is limited [1,2]. Since hepatocellular carcinoma also can develop in patients with chronic BCS, it is pivotal to distinguish FNH-like RNs from HCC because treatment is radically different. Radiologists should described in the report the number, the location, the size, the imaging features and the presence of dominant lesions.

4.1. T1 and T2 signal intensity of hepatic FNH-like RNs

4.1.1. T1 images

FNH-like RNs are usually hyperintense on fat suppressed T1-weighted 3D imaging (Fig. 4) [2,3,21]. This feature is atypical for benign regenerative nodules, such as hyperintensity on T1-weighted MR imaging is often suggestive of premalignant lesions in patients with cirrhosis. T1 hyperintensity could be explained by the copper deposits found by Wanless et al [22] within these nodules. Another explanation for this T1 hyperintensity might be in part the perinodular parenchymal congestion with lower signal intensity [3,21]. Sometimes, regenerative nodules are isointense relative to the surrounding parenchyma (Fig. 4a). Regenerative nodules often show a central scar of low signal intensity on fat suppressed T1-weighted 3D imaging (Fig. 4c-f), resembling FNH [21].

4.1.2. T2 images

The signal intensity of the nodules on T2-weighted FSE imaging is variable; FNH-like RNs are predominantly hypointense (Fig. 5a,b) or isointense (Fig. 5c) relative to the liver [2,8,21]. Because they are composed of hepatocytes, it is not surprising that they are substantially isointense on T2-weighted FSE MR imaging [2]. The hypointensity could be explained by mineral deposits inside the lesions or in part by the higher hyperintensity of liver parenchyma with congestion and necrosis [21]. The few cases of hyperintense nodules could be explained by lesion infarction (Fig. 5d) [2,8]. Similarly, Kim et al. [23] described infarcted regenerative nodules in cirrhosis as hyperintense lesions at T2 imaging. Indeed, being FNH-like RNs supplied by arteries and drained by hepatic veins, in case of venous outflow obstruction as in BCS, they may udergo congestion and infarction [2]. In some hypointense lesions, especially in nodules larger than 1 cm, a central scar is shown as a

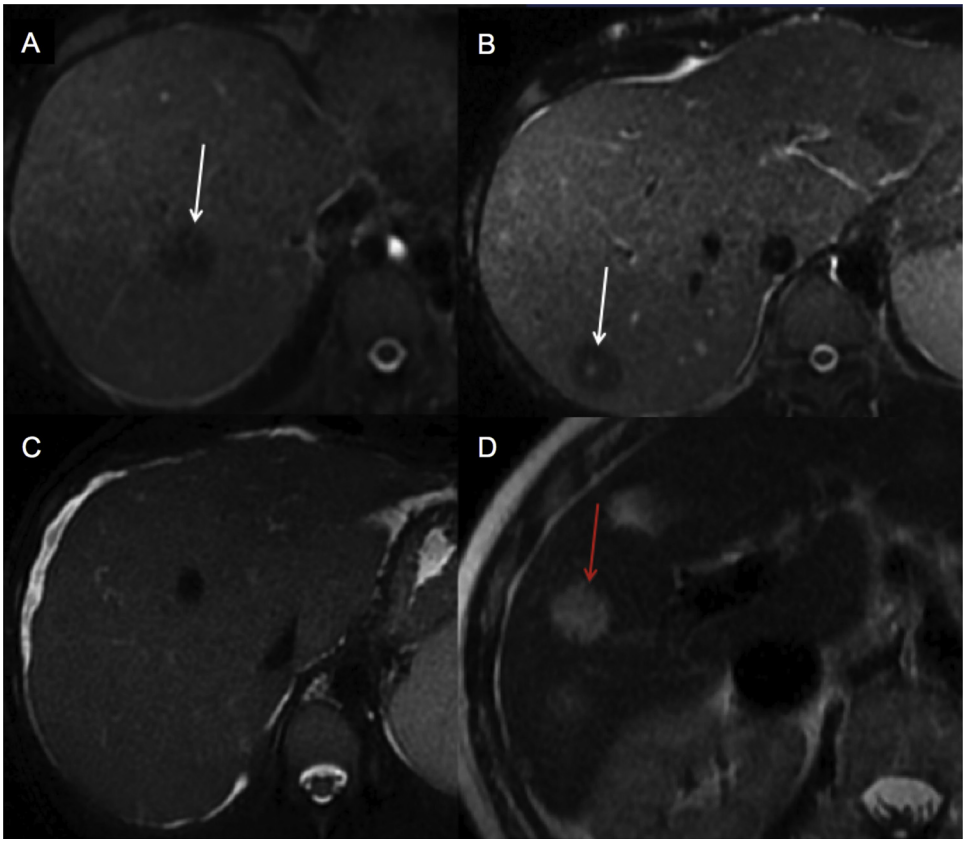

Fig. 5. T2 imaging. FNH-like RNs are usually hypointense (white arrows) (a,b) or isointense (c). Inside the hypointense nodules a central area of high signal intensity (b), which is due to a scar, is seen in some lesions. The few cases of hyperintense nodules (red arrow) (d) are likely the result of lesion infarction.

central hyperintensity area on T2-weighted FSE imaging (Fig. 5b) and central hypointensity area on fat suppressed T1-weighted 3D imaging, resembling FNH [21].

4.1.3. DWI (diffusion weighted imaging) images

Since FNH-like RNs are composed of nearly normal hepaticytes, they are isointense relative to surrounding parenchyma on diffusion weighted imaging, with absence of diffusion restriction on the ADC map. This feature helps in the differential diagnosis between FNH-like RNs and HCC.

4.2. Dynamic enhancement of hepatic FNH-like RNs

4.2.1. Arterial phase

In liver cirrhosis, a T2 hypointense lesion is usually considered as adenomatous hyperplastic nodule [21,24], that typically appears hypovascular [3,21,25]. In BCS, the FNH-like RNs detected on T2-weighted images are usually hypointense but they displayed hypervascularity. Hypervascularization is atypical in benign regenerative nodules but in nodules associated with BCS can be considered as a response to a regional loss of portal flow compensated by hyperarterialization. FNH-like RNs are typically hyperintense on late arterial phase fat suppressed T1-weighted 3D images, showing homogeneous marked enhancement (Fig. 6a), usually without wash-out on portal and late venous phases; this finding distinguishes them from HCC. Because of the their hyperintensity on T1, subtraction imaging from precontrast images must be performed to confirm their hypervascularity. A hypointense ring may be seen surrounding some of the nodules on arterial phase (Fig. 6b). Brancatelli et al [2,8] suggested that this ring consists of atrophic tissue in the periphery of the lesions or sinusoidal dilatation and congestion in the surrounding hepatic parenchyma. If present, the scar inside the nodules is usually hypointense.

4.2.2. Delayed phase

Portal venous phase imaging does not add any further information to evaluate these nodules. Typically, delayed phase MR images (3–5 minutes after administration of extracellular contrast agents) show that the FNH-like RNs are usually slightly hyperintense or isointense relative to the surrounding parenchyma (Fig. 7a,b). However, some lesions can show wash-out mimicking HCC (Fig. 7c–e); some authors suggested that this finding is probably related to surrounding hepatic parenchyma congestion with increased signal intensity and relative hypointensity of the FNH-like RNs [1]. Therefore, it should be better called “pseudo-wash-out”. Recently, some authors found that wash-out was present in close to 1/3 of benign regenerative nodules in BCS mimicking HCC [26]. Since this unacceptably low specificity for the diagnosis of HCC they suggest that the non-invasive diagnostic criteria proposed by the AASLD/EASL for cirrhotic patients cannot be extrapolated to patients with BCS [26]. Furthermore, due to limited value of wash-out for the differential diagnosis between FNH-like RNs and HCC, they suggest that other MRI findings should be carefully analyzed to improve the diagnostic confidence [26]. In light of these results, radiologists should be careful not to label as HCC all lesions showing wash-out in patients with BCS. FNH-like RNs can show a small or large hyperintense central area (scar) and a slightly hyperintense peripheral rim mimicking a capsule (Fig. 7c-e). This scar is very important because helps to distinguish FNH-like RNs from HCC. Therefore, hepatic nodules showing a central scar could be considered benign with acceptable reliability in patients with BCS [21].

4.3. Hepatobiliary pattern of hepatic FNH-like RNs

Two gadolinium-based hepatobiliary contrast agents have been clinically approved: the gadobenate dimeglumine (Gd-BOPTA, Multihance, Bracco, Milano, Italy) and the gadolinium ethoxybenzyl

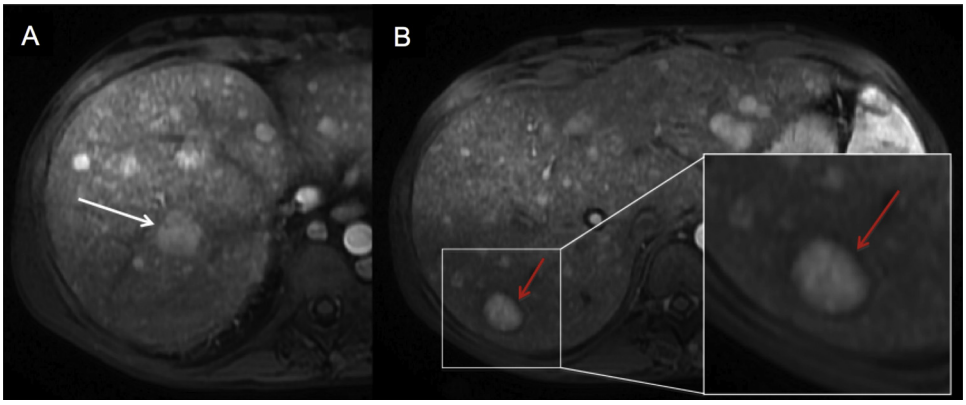

Fig. 6. Arterial phase imaging. FNH-like RNs are typically hyperintense on arterial phase MR images, showing homogeneous marked enhancement (white arrow) (a). A hypoattenuating ring (red arrow) may be seen surrounding some of the lesions (b).

diethylenetriaminepentaacetic acid (gadoxetic acid disodium or Gd-EOB-DTPA; Primovist, Schering, Berlin, Germany). After a first dynamic extracellular-interstitial distribution, both the contrast agents are taken up by functional hepatocytes and subsequently are excreted into the biliary system with a different excretion rate (3–5% for Gd-BOPTA and 50% for Gd-EOB-DTPA). While Gd-EOB-DTPA obtains its hepatobiliary phase as early as 20 min following contrast administration, Gd-BOPTA hepatobiliary imaging is performed more than 60 min following injection. Since FNH-like RNs are composed of nearly normal hepaticytes, they are isointense relative to surrounding parenchyma or slightly hyperintense at MR hepatobiliary phase, after administration of hepatobiliary contrast agents (Fig. 8). Indeed, in this phase they are similar to FNH. This pattern is very important to distinguish typical FNH-like RNs (Fig. 9) from HCC, that is typically hypointense on MR hepatobiliary phase. For this reason, patients with hepatic nodules associated to Budd-Chiari syndrome should be studied with hepatobiliary contrast agents on MRI, (conventional protocols), although the hepatobiliary imaging of FNH-like RNs in BCS has not been supported by an extensive scientific evidence. Particularly, in case of FNH-like RN showing wash-out on 3–5 minutes delayed phase mimicking HCC, hepatobiliary phase can make the difference allowing the diagnosis of benign regenerative lesions (Fig. 10). The hyperintense lesions on hepatobiliary phase could show a hypointense ring (Fig. 8c,d) that, as previously explained, may consist of atrophic tissue in the periphery of the lesions or sinusoidal dilatation and congestion in the surrounding hepatic parenchyma [2,8]. Another finding showed on hepatobiliary phase is a small, large or very large central hypointense area inside an hyperintense nodule (Fig. 8e-g), consisting of the scar showed on T1, T2 and dynamic sequences. This pattern is similar to that described for FNH with scar and the radiologists should be aware that it is a normal finding of FNH-like RNs. In case of very large scar, the nodule could mimick a malignant lesion but for the presence of peripheral hyperintensity (Fig. 8g) that helps in the differential diagnosis. In our experience, we found only few cases of FNH-like RNs slightly hypointense on MR hepatobiliary phase mimicking HCC, as showed on Fig. 11; however, we did not evaluate the diagnostic performance of hepatobiliary imaging for the discrimination

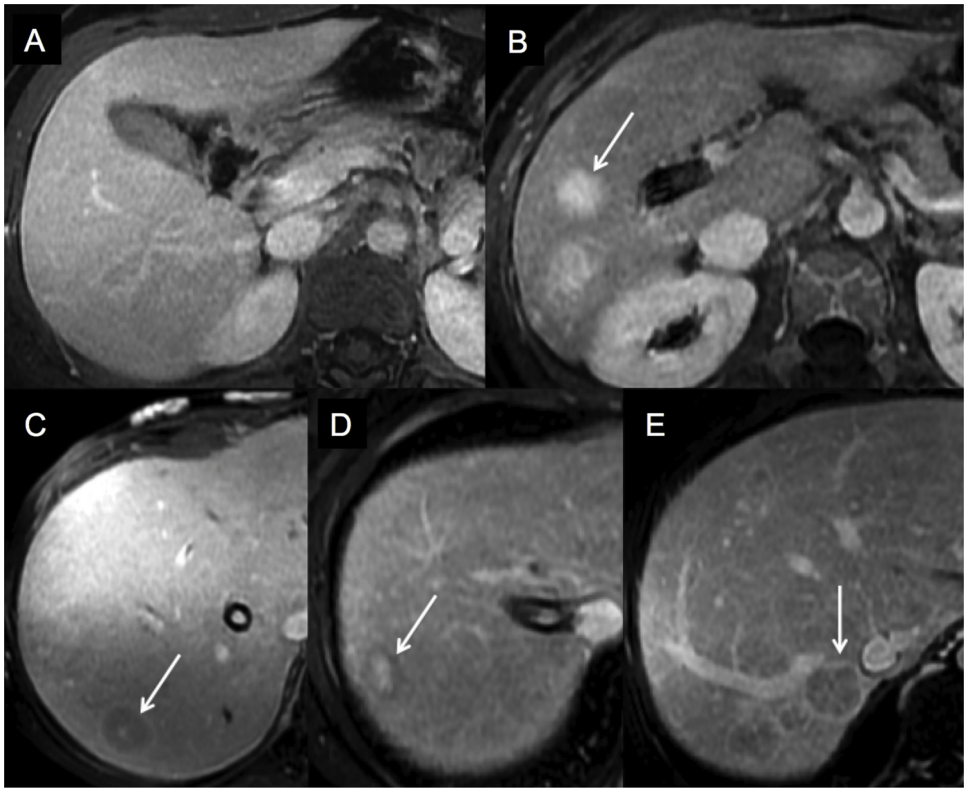

Fig. 7. Late phase imaging. Delayed phase MRI (3–5 minutes) show that the lesions are usually isointense relative to the surrounding parenchyma (a) or slightly hyperintense (white arrow) (b). Some lesions can show wash-out mimicking hepatocellular carcinoma (HCC). These hypointense nodules can show a small (c) or large (d) hyperintense central scar (white arrows) and a slightly hyperintense peripheral rim (e) mimicking a capsule (white arrow).

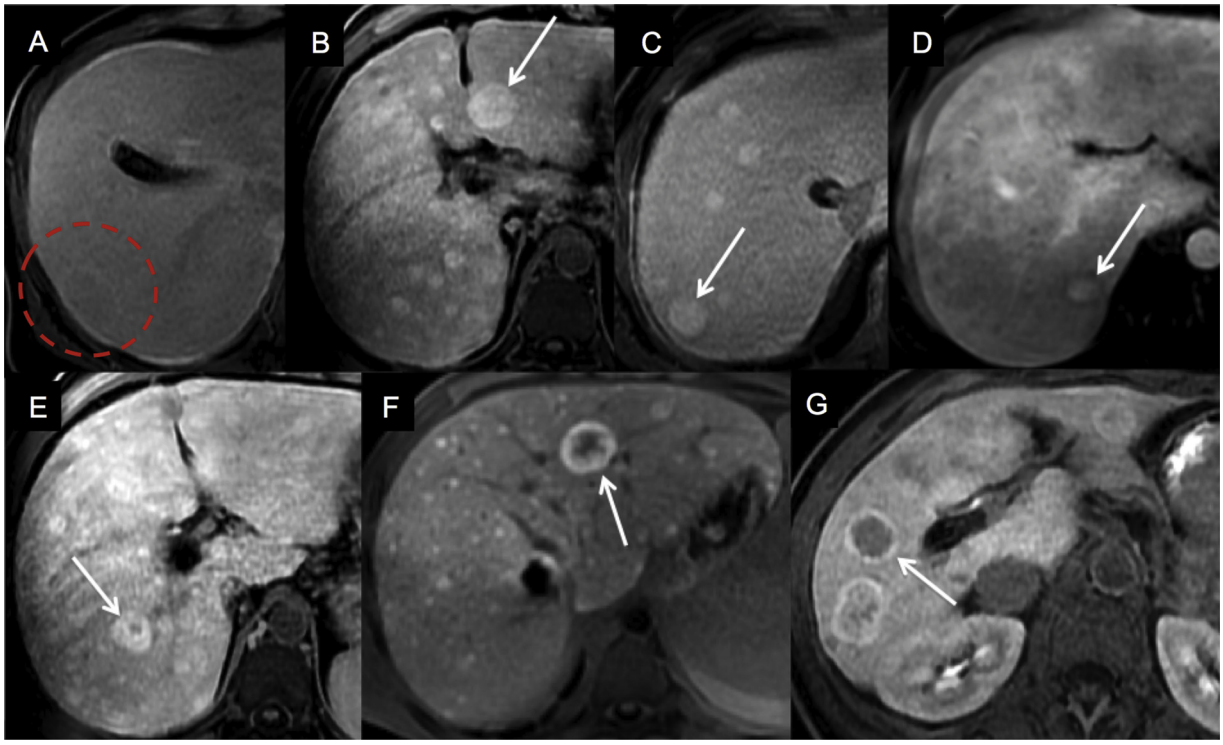

Fig. 8. Hepatobiliary imaging using gadobenate dimeglumine. Because FNH-like RNs are composed of nearly normal hepaticytes, they are isointense (red circle) relative to surrounding parenchyma (a) or slightly hyperintense (white arrow) (b), at MR hepatobiliary phase. The hyperintense lesions could be show a hypointense rim (white arrows) (c,d) or a small (e), large (f) or very large (g) central hypointense scar (white arrows). In the last case (g), the nodule could mimick a malignant lesion but for the presence of peripheral hyperintensity.

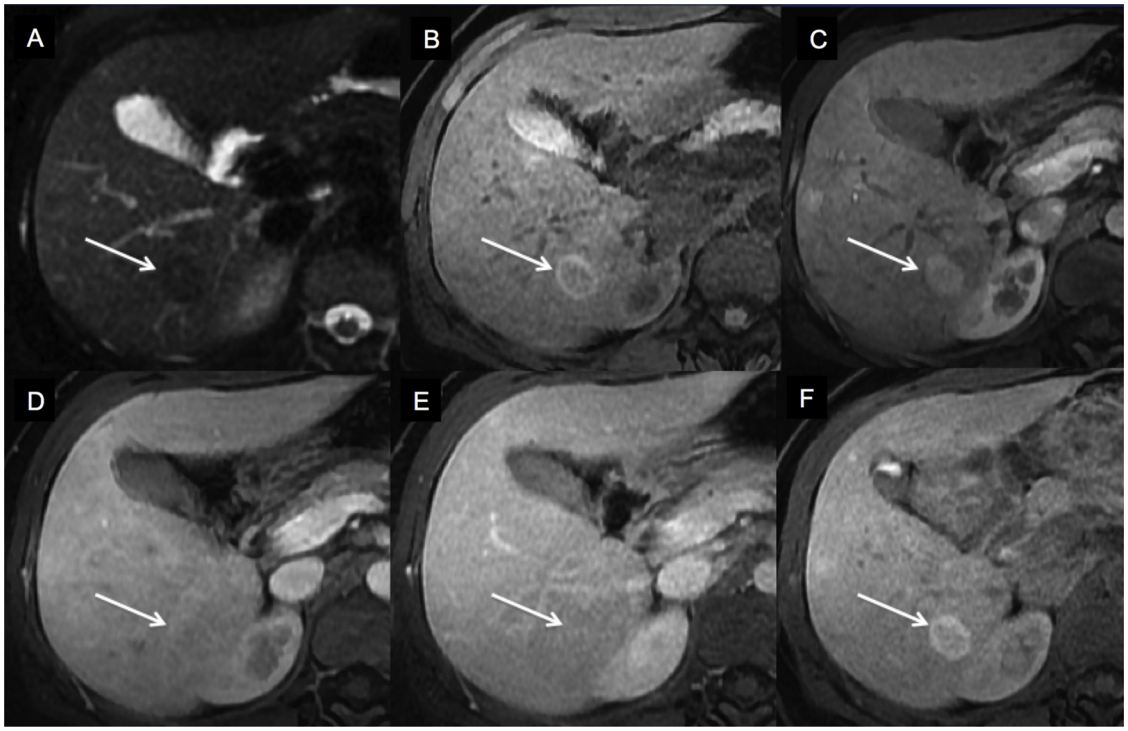

Fig. 9. Typical MR imaging of FNH-like RNs that are usually hypointense on T2 (a), hyperintense on T1 (b), hyperintense on arterial phase (c) (enhancement was also seen on substraction image, not shown), isointense or slighty hyperintense on portal and late phases (d,e) and isointense or hyperintense on hepatobiliary phase (f). Images obtained after intravenous bolus injection of Gd-BOPTA.

between FNH-like RNs and HCC. It is diffucult to explain the hypointensity appearance at hepatobiliary imaging, considering that we found other regenerative nodules with typical hyperintensity on hepatobiliary phase in the same liver. Hypothetically, a different expression of membrane transporters (OATPs) in hepatocytes and/or areas of abnormal hepatic perfusion/congestion, might be related to

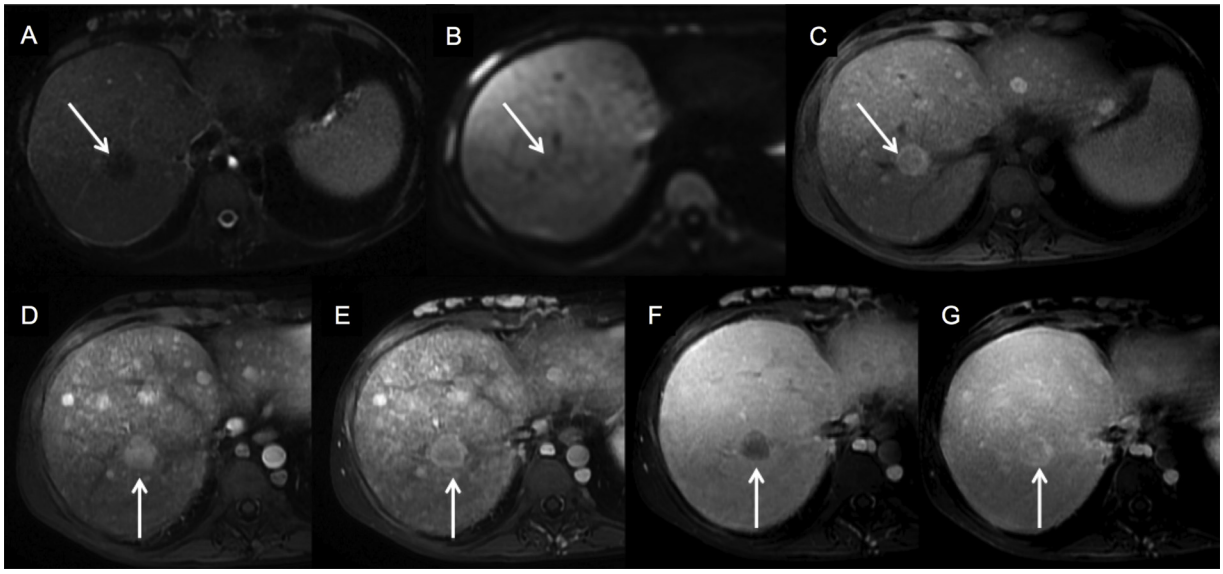

Fig. 10. FNH-like RN mimicking HCC. MRI obtained after intravenous bolus injection of gadobenate dimeglumine show a regenerative nodule (arrow) hypointense on T2 (a), isointense on diffusion weighted imaging (DWI) (b), hyperintense on T1 (c), hyperenhancing on arterial phase (d) (enhancement was also seen on substraction image, not shown) and portal phase (e) and with wash-out on delayed phase (f) mimicking HCC. On hepatobiliary phase (g) the lesion appears inhomogeneously isointense-hyperintense to normal liver. This helps to differentiate FNH-like RN from HCC.

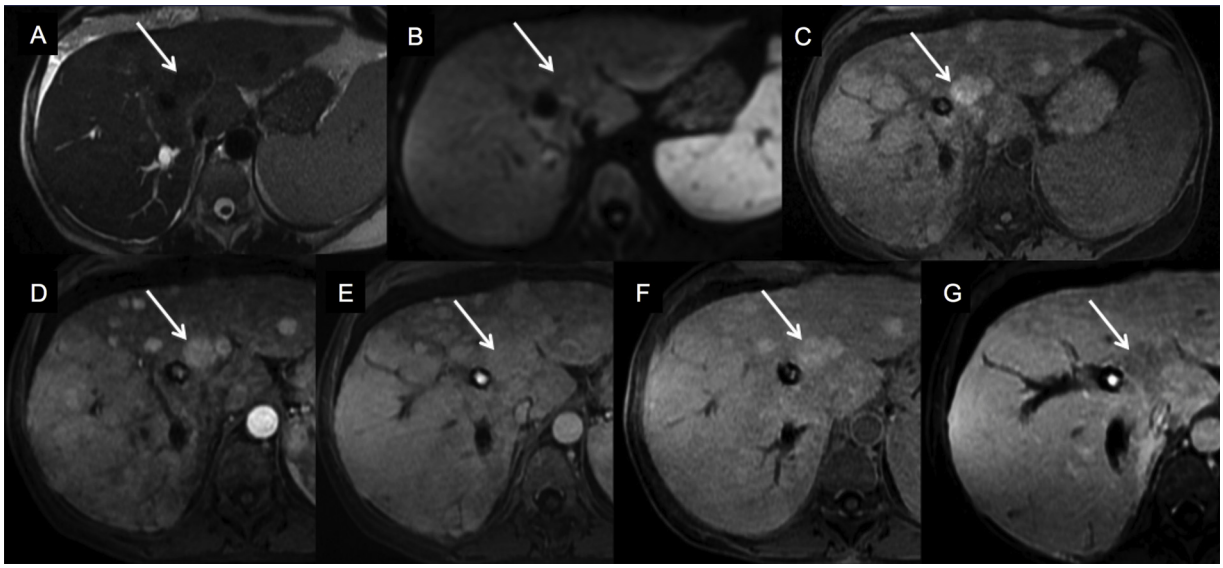

Fig. 11. FNH-like RN mimicking HCC. MRI obtained after intravenous bolus injection of gadobenate dimeglumine show a nodule (white arrow) hypointense on T2 (a), isointense on DWI (b), hyperintense on T1 (c), hyperenhancing on arterial phase (d) (enhancement was also seen on substraction image, not shown) and portal phase (e) and without wash-out on delayed phase. On hepatobiliary phase the lesion appears hypointense mimicking a dysplastic nodule or HCC, but the other typical findings help to reach the correct diagnosis.

this finding. In these cases, the other typical features of FNH-like RNs help to reach the correct diagnosis, such as hypointensity on T2, absence of diffusion restriction, hyperintensity on T1, homogeneous arterial enhancement and absence of wash-out. Another case of FNH-like RN mimicking HCC is the necrotic regenerative nodule. Indeed, this type of FNH-like RN shows hypointensity on hepatobiliary phase associated to hyperintensity on T2, hypointensity on T1 and diffusion restriction mimicking HCC (Fig. 12). However, necrotic regenerative nodule shows absence of arterial enhancement e strong hypointensity in all the dynamic sequences; these features help to differentiate it from HCC.

5. Differential diagnosis

In chronic Budd-Chiari syndrome, hepatic lesions described in the literature include benign regenerative nodules and hepatocellular carcinoma (HCC). The differential diagnosis includes the following arterial phase hyperenhanced hepatic lesions, although some of them are not associated with BCS:

5.1. Small hemangiomas

They are hemangiomas with size less than 1.5 cm, called also flash filling or capillary hemangiomas because of their bright and homogenous enhancement in arterial phase (no gradual filling in) with isointensity to the aorta in portal and late phase [27]. They are solitary or

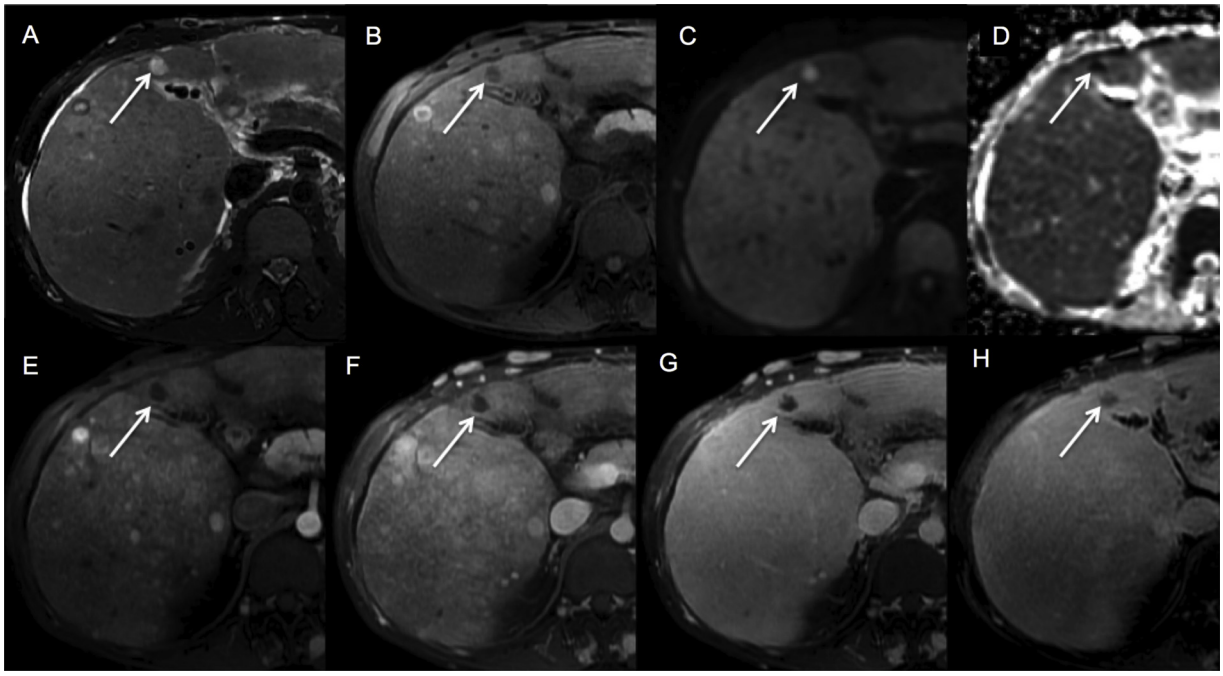

Fig. 12. Necrotic regenerative nodule. MRI obtained after intravenous bolus injection of gadobenate dimeglumine show a necrotic regenerative nodule (white arrow) hyperintense on T2 (a), hypointense on T1 (b), hyperintense on DWI (c) with diffusion restriction on ADC map (d), costantly and strongly hypointense on all contrastographic phases (e–g) and hypointense on hepatobiliary phase (h).

few in number and differ from FNH-like RNs in some features, such as hyperintensity on T2-weighted images, hypointensity on T1-weighted images and hypointensity on hepatobiliary phase.

5.2. Focal nodular hyperplasia (FNH)

The surrounding hepatic parenchyma is healthy, whereas the liver around FNH-like RNs in BCS is usually abnormal. This feature helps to differentiate FNH from most cases of FNH-like RNs. FNH is usually solitary while FNH-like RNs are multiple. Certain FNH-like RN imaging findings differ from those of FNH [28], in particular the former is usually hyperintense on T1 and hypointense on T2 MR imaging. Common findings of FNH are the central scar (visible in about 35% of FNH < 3 cm) [2], the hypervascularity and the isointensity in hepatobiliary phase [28].

5.3. Hepatocellular adenoma

It is usually solitary (liver adenomatosis is a rare condition), no related to BCS and may contain areas of necrosis, fat, hemorrhage, or calcification, showing a heterogeneous aspect [29]; differently from FNH-like RN, adenoma are often hypointense on T1, hyperintense on T2 and hypointense on hepatobiliary phase [29].

5.4. Dysplastic nodules in cirrhosis

Despite they share some features with FNH-like RNs such as enhancement on arterial phase [30], they arise from a cirrhotic liver with typical morphological changes and clinical history, which help to differentiate cirrhosis from the dysmorphic liver of BCS.

5.5. Hypervascular metastases

Typically, these metastases show enhancement on arterial phase but differently from FNH-like RNs they exhibit wash-out on portal and/or late phase and are hypointense on hepatobiliary phase [31]; furthermore, they are usually heterogenous with variable size, they appear hypointense to the liver on T1 imaging, hyperintense on T2 imaging and show diffusion restriction [31]. Finally, many patients are known to have a primary tumor giving hypervascular metastases, such as thyroid carcinoma, renal cell carcinoma, neuroendocrine tumors (NET), melanoma and brest cancer.

5.6. Hepatocellular carcinoma

When HCC arise in a healthy liver, it is usually a solitary, large mass characterized by heterogeneous enhancement on arterial phase images with wash-out on portal and/or late phase images and hypointensity on hepatobiliary phase. It is usually capsulated and characterized by hypointensity on T1 imaging, heterogeneous hyperintensity on T2 imaging. Furthermore, it can show restriction of diffusion on DWI sequence. The incidence of hepatocarcinoma on chronic Budd-Chiari syndrome varies is different from country to country (6%–41% in Japan, 48% in South Africa, 25% in the USA) and accounts for 0.7% of all the cases of HCC [1,9,12,32]. In two studies, HCC is found in 6.4% and 11,3% of patients with BCS [1,12,33], respectively during a 15-year and a 5-yers follow-up period. Despite HCC has been reported in patients with chronic BCS, some of these patients had coexisting chronic viral hepatitis or a simultaneous diagnosis of Budd-Chiari syndrome and hepatocellular carcinoma, leading to speculate that the viral infection could be the cause of HCC [3,32] or that HCC could be the cause of BCS and not the result [3,12]. It should be noted that HCC in chronic BCS is more frequent in case of obstruction of the IVC and in particular in presence of membranous web-like obstruction [9,34,35]. The above-mentioned imaging features of HCC help to distinguish it from FNH-like RNs. However, the differential diagnosis between FNH-like RN and HCC can be argue because the former may increase in size and/or in number, and can show wash-out on portal and/or delayed phase imaging [1]. In these cases, hepatobiliary MR contrast media may help in the differential diagnosis, although they have not been extensively evaluated [1,36]. If hepatic lesions in BCS have the typical findings of FNH-like RNs and low levels of alpha-fetoprotein (AFP) are detected, patients can perform a six months follow-up by clinical-laboratoristic and imaging assessment [1]. Indeed, some authors found

Table 1
Magnetic resonance imaging (MRI) findings of FNH-like regenerative nodules (FNH-like RNs), hepatocellular carcinoma (HCC) and metastases.

MRI FINDINGS	FNH-like RN	HCC	Metastases
T1	Hyperintense or Isointense	Hypointense	Hypointense
T2	Hypointense or Isointense	Hyperintense	Hyperintense
DWI	Negative	Positive	Positive
Arterial phase	Hyperintense (homogeneous)	Hyperintense (inhomogeneous)	Hyperintense (in- or homogeneous)
Hypointense ring on arterial phase	+	–	–
Delayed phase	Hyperintense or Isointense	Hypointense	Hypointense
Scar	+	–	–
Hepatobiliary phase	Hyperintense or Isointense	Hypointense	Hypointense
Hypointense ring on hepatobiliary phase	+	–	–
Scar on hepatobiliary phase	+	–	–
Peripheral hyperintensity on hepatobiliary phase	+	–	–

+ : finding associated with this lesion.
- : finding not associated with this lesion.

that serum AFP levels seems to be a useful tool for HCC screening in these patients [34]. Liver biopsy should be suggested in presence of atypical imaging findings, or significant changes during the follow-up, or increase of AFP levels [1]. Since many of the above-mentioned hepatic lesions listed in the differential diagnosis arise in healthy liver or in cirrhosis, and are solitary nodules, the main differential diagnosis consists of HCC and hypervascular metastases; Table 1 summarizes the MRI findings of the FNH-like RNs and the main differential diagnosis (HCC and metastases).

6. Conclusion

In conclusion, FNH-like RNs are commonly detected in patients with chronic BCS and they are more common than HCC. These lesions are typically small, multiple, hypervascular on late arterial phase and sometime can show different patterns in the same liver. MRI plays a pivotal role in these patients because typical MRI features of these lesions help to reach the correct diagnosis, distinguishing them from HCC with reasonable confidence in most cases. Since the role of hepatobiliary imaging in the differential diagnosis, although it has not been extensively evaluated in this setting, we suggest that patients with chronic BCS associated with hepatic lesions should be studied on MRI with hepatobiliary contrast agents and monitored.

Conflict of interest

We declare no conflict of interest.

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Institutional review board statement and Informed consent statement

The Institutional Research Review Board reviewed and approved this article, with waiver of the informed consent; a written informed consent to the MR procedures was obtained after a full explanation of the purpose and nature of the procedure.

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