Large Regenerative Nodules and Focal Nodular Hyperplasia-Like Lesions

Definition, Pathogenesis, and Imaging Findings

Paul E. Nolan, MD, Roberta Catania, MD, Camila Lopes Vendrami, MD, Amir A. Borhani, MD*, Frank H. Miller, MD

KEYWORDS

• FNH • FNH-like lesions • Large regenerative nodules • Magnetic resonance imaging • Liver • Hepatic vascular abnormalities

KEY POINTS

- Focal nodular hyperplasia-like (FNH-like) lesions and large regenerative nodules (LRNs) are benign hyperplastic lesions of hepatocellular origin, which are often encountered in patients with underlying hepatic vascular abnormalities.
- FNH-like lesions classically have similar imaging findings to FNH. Occasionally, they may show atypical features, different from classic FNHs, on imaging because of their variant histology or altered enhancement of background liver in the setting of abnormal global perfusion.
- FNH-like lesions can mimic hepatocellular carcinoma (HCC). Differentiation of these two entities can be challenging, especially in patients at risk for HCC.

INTRODUCTION

Hypervascular liver lesions, when not obviously a hemangioma, often cause concern and diagnostic dilemma. One classic and generally benign type of hypervascular liver lesion to consider is focal nodular hyperplasia-like (FNH-like) nodule. Unlike FNH, which by definition occurs within a normal background liver, FNH-like lesions are seen in the presence of underlying hepatic disease. Although FNH-like lesions are classically described as having an identical radiologic appearance to FNH (with arterial hyperenhancement and central scar), they may have variable imaging appearances. Particularly, the contrast-enhanced appearance of these lesions could be affected by the changes in the global hepatic perfusion (such as in the setting of venous congestion). Recognition of FNH-like lesions is of clinical importance as many patients with diffuse liver disease are also at increased risk for HCC, and misdiagnosis of an FNH-like lesion as HCC can result in unnecessary interventions and therapies. In this article, we describe the pathophysiology and imaging findings of FNH-like lesions, review the common conditions wherein FNH-like lesions can be seen, and discuss the pitfalls and challenges in differentiating these lesions from HCC.

Histology and Nomenclature

Regenerative lesions refer to hyperplastic lesions of hepatocellular origin that form in response to

Department of Radiology, Northwestern University Feinberg School of Medicine, 676 North Saint Claire Street, Arkes Family Pavillion, Suite 800, Chicago, IL 60611, USA
* Corresponding author. Abdominal Imaging, Northwestern University Feinberg School of Medicine, Medical Director, NMH Computed Tomography, Northwestern Medicine, 676 North Saint Clair Street, Arkes Family Pavilion, Suite 800, Chicago, IL 60611.
E-mail address: amir.borhani@northwestern.edu

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cellular injury or altered perfusion.[1] They include FNH, large regenerative nodules (LRNs), diffuse nodular hyperplasia, lobar or segmental hyperplasia, and cirrhotic nodules.

Classic FNH is a well-defined lesion composed of benign hyperplastic hepatocytes and portal tracts surrounding a central vascular scar.[2,3] By definition, FNH is found within a normal or nearly normal liver. LRNs, also known as multiacinar regenerative nodules, are typically seen in the setting of cirrhosis or advanced hepatic vascular disorders. They both are composed of benign hepatocytes and portal tracts with occasional scarring. Lesions with identical histologic and radiologic appearances to FNH have been described in diffusely abnormal livers and have been referred to as "FNH-like lesions." Others have categorized these as forms of LRNs given their presence within an abnormal liver.[4] Based on current literature, there is no consensus on how these lesions should be categorized. Despite radiologic and histologic similarities between FNH and FNH-like lesions, there is evidence that they differ in genetic expression suggesting a difference in their pathogenesis.[5] In addition, there is some evidence to support that FNH-like lesions are distinct entities from LRNs.[6] For simplicity, in this article, we refer to these entities as FNH-like nodules.

Pathogenesis

Typical FNH is thought to be a hyperplastic response to abnormal perfusion.[2,3] It is theorized that anomalous intrahepatic vessels result in areas of relatively increased regional arterial blood flow that prompts the hyperplastic response. They are often incidentally discovered in young adults with no history of liver disease or other significant pathology.[7] FNH-like lesions, on the other hand, result from a variety of liver pathologies that alter global perfusion and ultimately increase arterial flow to the liver. There are several proposed mechanisms that can result in increased arterial flow. Impaired venous outflow, such as a result of Budd–Chiari syndrome (BCS) and congestive hepatopathy, increases resistance to both arterial and portal inflow. Owing to the higher pressure of the hepatic artery compared with the portal veins, there is resultant disproportionately increased arterial supply to that part of the liver. This amplified arterial supply increases the propensity for a hyperplastic hepatocellular response, resulting in FNH-like nodules. Similarly, increased portal vein resistance due to cirrhosis or venous thrombosis results in compensatory increased arterial supply and increased likelihood of FNH-like lesion formation. Primary increased arterial flow is another mechanism of FNH-like lesion development, as seen with hereditary hemorrhagic telangiectasia in which there is diminished arterial resistance secondary to hepatic telangiectases and arteriovenous malformations.

Imaging Findings

FNH-like nodules are classically described to have an imaging appearance similar to that of typical FNH occurring in normal background liver. However, they can have atypical imaging features, either because of their variant histology or altered enhancement kinetics in the setting of abnormal global perfusion. Distinction of atypical lesions from malignancies can be difficult, often requiring further workup including additional imaging studies (for instance, MR imaging with hepatobiliary agents) or biopsy.

FNH-like lesions are classically referred to as "stealth lesions," similar to conventional FNH, with a signal intensity close to that of the background liver on unenhanced T1-weighted (T1w) and T2-weighted (T2w) images.[8,9] Despite this classic description, they often have slightly different signal intensity compared with the background liver parenchyma,[10] in part due to abnormal signal intensity of the diseased background liver. One can consider FNH-like lesions as being small islands of relatively "normal" liver that stand out against a background of the diffusely abnormal liver in unenhanced and even in non-arterial phase contrast-enhanced images. Increased water content in the setting of venous congestion results in increased signal intensity of background liver parenchyma on T2w and decreased signal intensity on T1w images. As a result, FNH-like nodules can appear as mildly hyperintense on T1w (**Fig. 1**) and mildly hypointense on T2w images, compared with the background liver. Other diffuse processes such as steatosis and iron deposition can affect the relative signal intensity of the nodules. Hyperintensity on T1w images has also been explained by the possible presence of elements such as copper.[11] Hyperintensity on T2w images has been attributed to exaggerated venous congestion and infarction, especially in patients with congestive hepatopathy or BCS.[12] FNH-like nodules may show high signal intensity on diffusion-weighted imaging (DWI), presumably because of their different architecture and higher cellularity compared with the background liver (**Fig. 2**). After injection of gadolinium-based contrast media, there is brisk and usually homogeneous enhancement during the arterial phase. They remain hyperenhancing or become

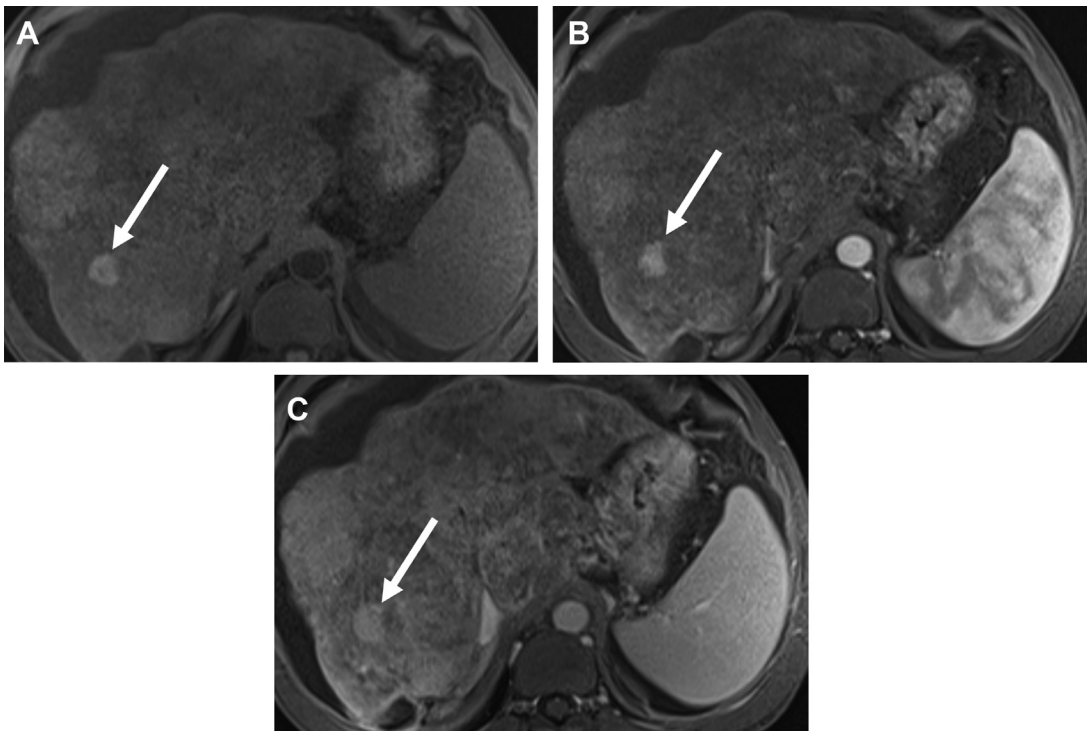

Fig. 1. A 40-year-old man with history of chronic Budd–Chiari syndrome. (*A*). Axial unenhanced T1 FS MR images show hyperintense lesion in segment 8 (*arrow*). Axial T1 FS MR images obtained during hepatic arterial phase (*B*) and venous phase (*C*) show persistent hyperenhancement on both phases. The lesions remained stable for 5 years consistent with benignity.

isointense to the background liver during portal venous and equilibrium phases[8,13,14] (see **Fig. 1**). Their relative signal intensity can be affected by the signal intensity of the diseased background liver. Many of the conditions associated with FNH-like lesions result in a dampened time-enhancement curve with longer time to peak. The delayed enhancement of the surrounding liver parenchyma during the equilibrium and delayed phases may result in relative hypointensity of the FNH-like lesions mimicking the washout appearance seen in HCC (**Fig. 3**). FNH-like lesions are classically iso- or hyperintense to the background parenchyma during the delayed hepatobiliary

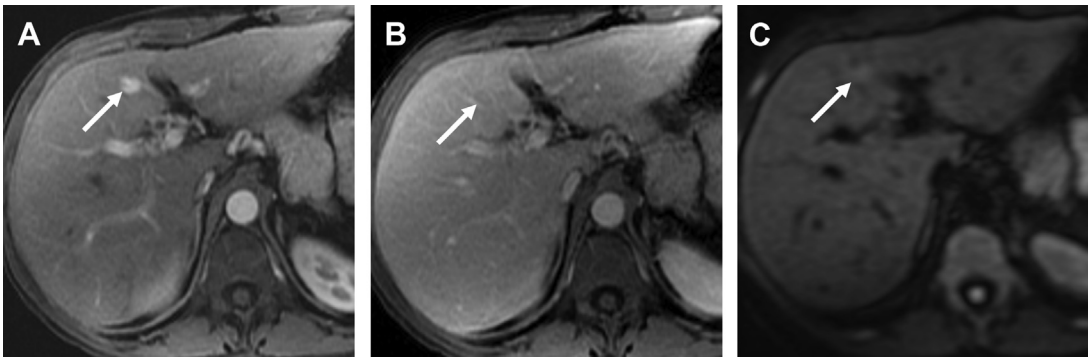

Fig. 2. A 37-year-old woman with history of common variable immune deficiency (CVID). Axial MR image obtained during hepatic arterial phase (*A*) shows an avidly enhancing lesion in segment 2 (*arrow*) which becomes isointense to the background liver during the venous phase (*B*). The lesion showed mild hyperintensity on diffusion-weighted image (b value = 500 s/mm^2) (*C*). Biopsy was consistent with nodular regenerative hyperplasia.

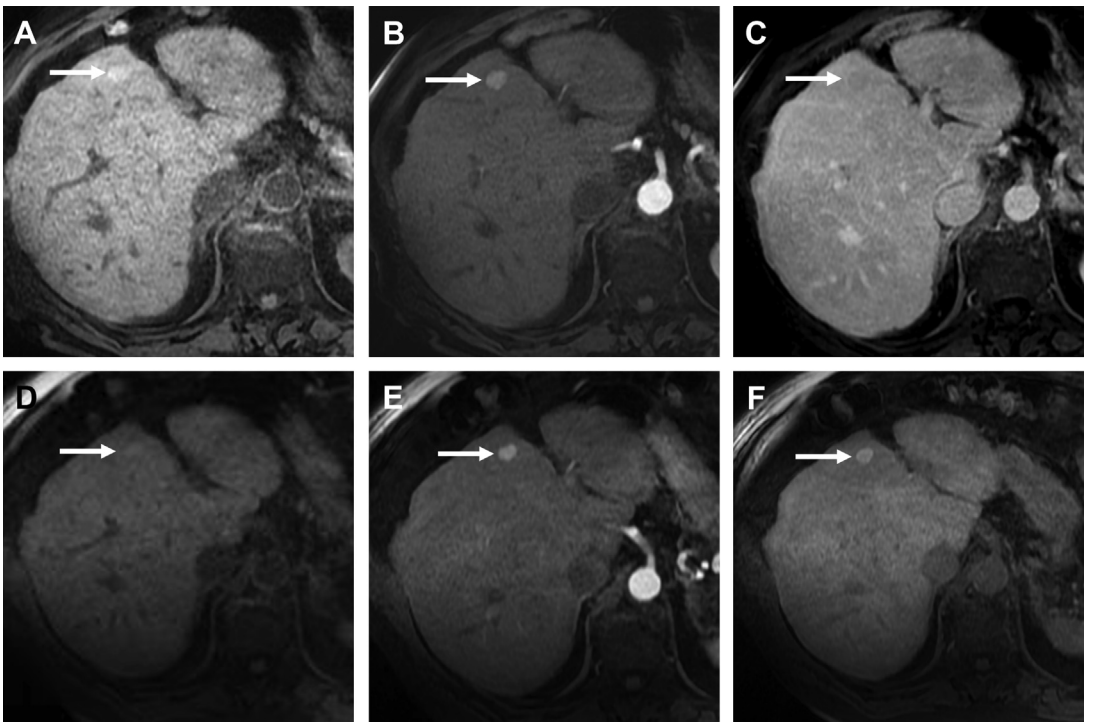

Fig. 3. A 67-year-old woman with history of right heart dysfunction. Axial unenhanced T1w MR (*A*) shows a T1 hyperintense lesion (*arrow*) in segment IV. The lesion showed avid enhancement on arterial phase (*B*) and "wash out" appearance on venous phase (*C*). One-year follow-up MR imaging using hepatobiliary agent (*D–F*) shows stability in size and retention of contrast during the hepatobiliary phase (*F*). Note the decreased signal intensity of liver and delayed excretion of contrast into the biliary tree on hepatobiliary phase (*F*) suggestive of hepatocellular dysfunction in setting of congestive hepatopathy.

phase (when hepatobiliary contrast agents used) owing to overexpression of organic anion-transporting polypeptide (OATP), the main transporter of gadoxetic acid in hepatocytes[15] (**Fig. 4**). A hypointense rim (attributed to peri-lesional sinusoidal dilatation or atrophic tissue) during this phase has also been described.[13] The FNH-like nodules may have a central scar which helps in the diagnosis. The scar tissue typically hyperintense on T2w images and is hypoenhancing during

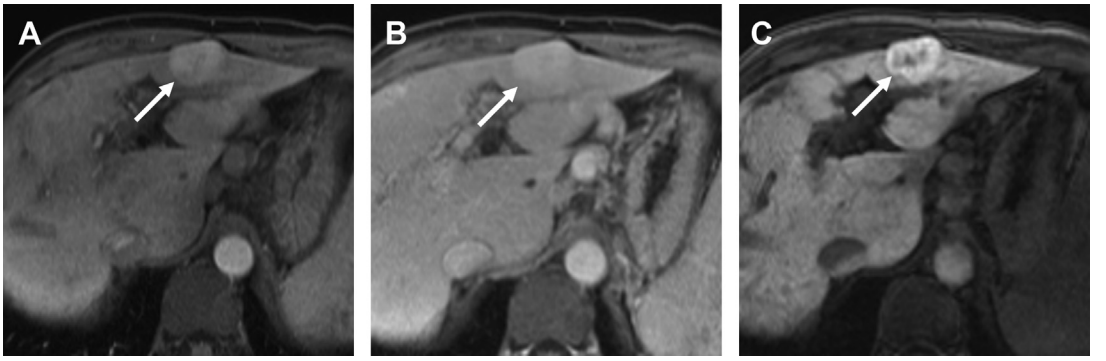

Fig. 4. A 44-year-old woman with history of colon cancer treated with oxaliplatin 13 years earlier. Axial arterial phase T1w MR imaging (*A*) shows an enhancing lesion (*arrow*) in hepatic segment 3 which remained hyperintense on portal venous phase (*B*) and had retention of contrast during the hepatobiliary phase (*C*). Also note the central scar which is slightly hypointense in A and B, becoming more evident on hepatobiliary phase. Percutaneous biopsy was consistent with FNH-like lesion. Lesion differs from metastasis from colon cancer which tends to be hypovascular and hypointense on hepatobiliary phase and not having a central scar.

the arterial, venous, and equilibrium phases while showing delayed enhancement (when extracellular agents used) owing to its larger extracellular compartment. The central scar remains hypointense during hepatobiliary phase (when hepatobiliary contrast agents used) and may appear larger compared with images obtained with extracellular contrast agents, similar to the appearance seen in conventional FNHs (**Fig. 5**).

FNH-like lesions can have variable appearances on ultrasound (US), mostly isoechoic or mildly hypoechoic compared with the liver parenchyma. Contrast-enhanced US is more helpful for characterization by identifying more specific features such as centrifugal arterial enhancement with persistent enhancement during portal venous and late phases.[16] When present, a nonenhancing central scar may be seen.

On CT, FNH-like lesions are typically isodense or slightly hypodense to liver parenchyma on unenhanced phase. After injection of iodinated contrast agents, brisk homogeneous enhancement is usually seen during the arterial phase with persistent homogeneous enhancement during portal venous phase[9,17] (**Fig. 6**). Their appearance on delayed phase is variable ranging from hyperenhancement to hypoenhancement with "washout" appearance (mimicking HCC).[18] As stated earlier, the washout appearance may be due to delayed enhancement of the background liver in the setting of venous congestion. A hypodense central scar may occasionally be seen.

Natural History

Once considered a rare phenomenon, FNH-like lesions are now commonly encountered. Several factors are attributed to this higher incidence. Advances in the medical and surgical management of right heart dysfunction and congenital heart disease (such as the Fontan procedure) have resulted in an increased number of adult patients living with long-standing congestive hepatopathy and with resultant FNH-like lesion formation. Moreover, an increased longevity of oncologic patients treated with oxaliplatin can account for the rising number of FNH-like lesions in these patients. These lesions are believed to have no risk of malignant transformation. Majority of the lesions remain stable over time[19] although growth, regression, and hemorrhagic necrosis have also been reported.[14,20] Despite this preliminary evidence, their natural history and growth rate are not well understood yet, and more longitudinal studies are needed to better clarify the evolution and size changes of these nodules.

DISEASES ASSOCIATED WITH FNH-LIKE LESIONS

Although FNH-like nodules can occur in many scenarios, several disease entities are more classically described to be associated with these nodules and will be discussed in the following.

Budd–Chiari Syndrome

BCS is a heterogeneous group of diseases resulting from hepatic venous outflow obstruction in the absence of right heart failure or constrictive pericarditis.[21] It is more common in women (in countries outside of Asia) and is usually diagnosed in the third or fourth decade of life, although it can occur at any age.[22] The obstruction may occur at any level along the venous outflow from the smaller hepatic veins to the junction of the inferior vena cava to the right atrium. Primary BCS, the most common type, occurs when a predominantly endoluminal venous process (such as thrombus or

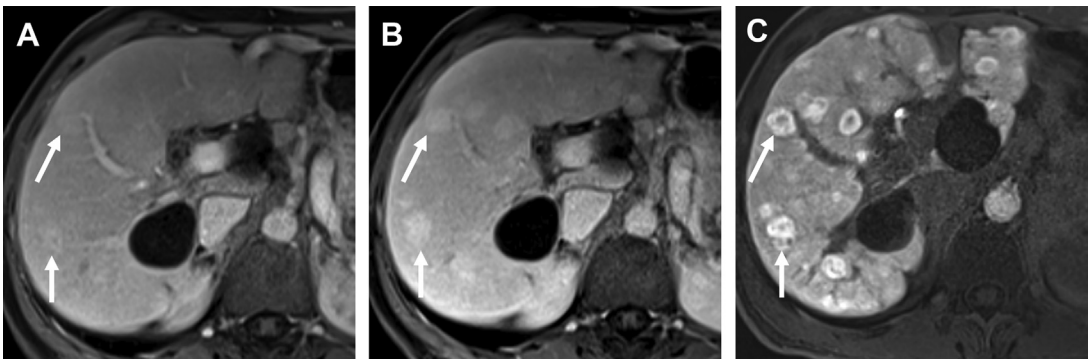

Fig. 5. A 51-year-old woman with history of autoimmune hepatitis. Axial portal venous phase MR imaging (*A*) shows indistinct hepatic lesions (*arrows*). The lesions became more conspicuous during the transitional phase (*B*). All lesions demonstrated intense retention of contrast and central scar during the hepatobiliary phase and central scar (*C*), compatible with FNH-like nodules.

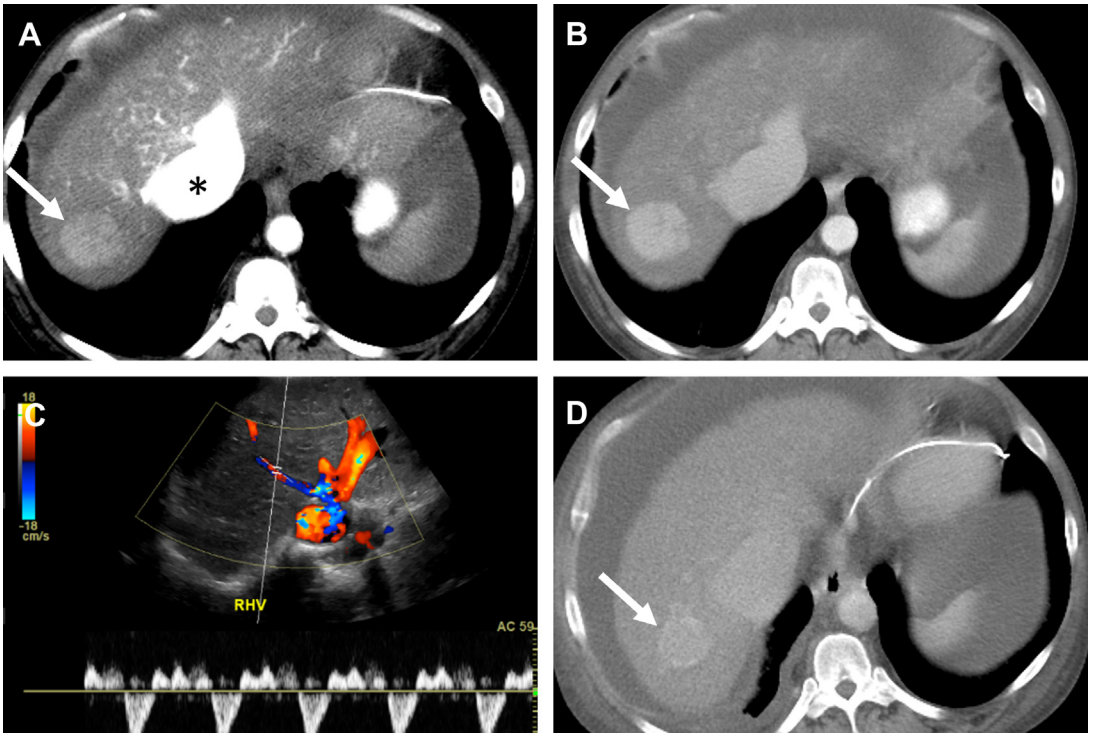

Fig. 6. A 45-year-old man with history of severe diastolic dysfunction and tricuspid regurgitation. Axial contrast-enhanced CT (*A*) shows an avidly arterially enhancing lesion in segment 7 (*arrow*) which remained hyperdense during the venous phase (*B*). Note the reflux of contrast into IVC (*asterisk*) during the arterial phase. Doppler US (*C*) shows abnormal hepatic venous waveform classic for severe tricuspid regurgitation. Contrast-enhanced CT obtained 3 years later (*D*) shows mild decrease in size of the lesion over time.

phlebitis) leads to hepatic venous outflow obstruction. This type is often associated with hypercoagulable states. Secondary BCS applies to hepatic venous outflow obstruction caused by vascular invasion or extrinsic compression. BCS can be also classified as acute (fulminant or not fulminant), subacute, or chronic, based on the chronicity and severity of disease. The majority of the cases are subacute or chronic, associated with dysmorphism of the liver and variable degree of hepatic fibrosis.

Regenerative nodules are commonly seen in the setting of chronic BCS and usually represent FNH-like lesions[23] (**Fig. 7**). Regenerative nodules larger than 5 mm have a reported prevalence of up to 60% to 80% in some pathology series.[12,16,24] No association with any specific etiology of BCS or vascular interventional measures (such as transjugular intrahepatic portosystemic shunt [TIPS]) has been shown.[23] Although their exact pathogenesis remains uncertain, it is thought that they develop as a response to focal loss of portal perfusion and hyper-arterialization in regions of the liver with maintained hepatic venous outflow.[13,17] Patients with BCS are also at risk of developing HCC, accounting for 0.7% of all cases.[8–10] Patients with long-term inferior vena cava obstruction have a higher risk of developing HCC than those with only hepatic vein involvement.

FNH-like lesions in the setting of BCS are usually hyperintense on fat-suppressed T1w images (see **Fig. 1**) and show more variable signal intensity on T2w MR imaging.[13,23] A slightly hyperenhancing rim mimicking a capsule has also been described.[13] Given their inherent T1 hyperintensity, subtraction images may be helpful to confirm their hypervascularity.[13,23] Some lesions may depict a "pseudo-washout" appearance, mimicking HCC.[13] The larger lesions often have a central scar. No predisposition for a specific hepatic location has been identified.

There is overlap in imaging findings of FNH-like nodules and HCC and differentiation of these two entities could be challenging. HCCs are usually heterogeneous and solitary, whereas benign nodules are usually multiple and small (usually <3 cm).[23] The presence of intralesional fat, hemorrhage, or calcification is atypical for FNH-like nodules and should suggest a different process, including HCC. MR imaging with the use of

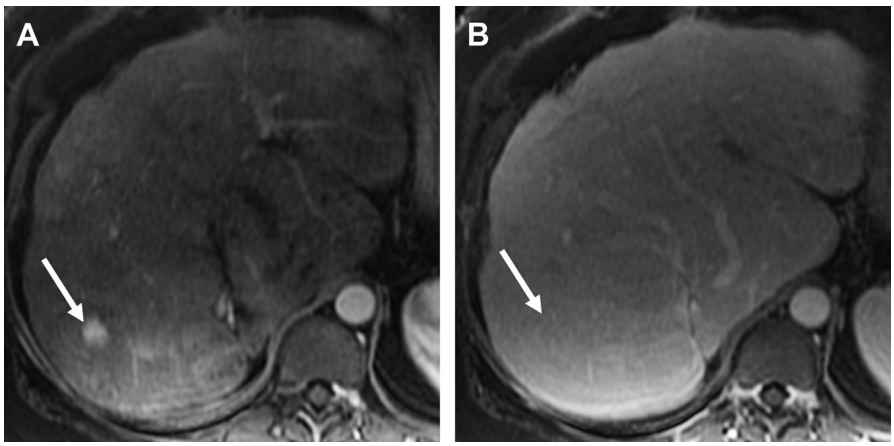

Fig. 7. A 60-year-old man with history of Budd–Chiari syndrome secondary to polycythemia vera. Axial T1 FS arterial phase MR image obtained during hepatic arterial phase (*A*) shows an avidly enhancing lesion in segment 7 (*arrow*). The lesion became isointense to the liver parenchyma on portal venous phase (*B*). The lesion remained stable for 3 years consistent with benignity.

hepatobiliary contrast agents is particularly useful for accurate diagnosis of FNH-like lesions.[23] Retention of contrast during hepatobiliary phase is a common finding with FNH-like nodules while much less common in HCCs. Contrast-enhanced US has also been suggested as a method to distinguish these two entities in the setting of BCS. In a study by Zhang and colleagues most FNH-like lesions showed centrifugal arterial enhancement with persistent enhancement during venous and delayed phases, whereas most HCCs showed heterogeneous enhancement on arterial phase with washout.[16]

Congestive Hepatopathy and Fontan-Associated Liver Disease

Congestive hepatopathy is the umbrella term applied to any hepatic injury as a result of chronic passive hepatic congestion.[25,26] A myriad of diseases (such as myocardial infarction, cardiomyopathy, valvular disease, constrictive pericarditis, and pulmonary hypertension) can result in right-sided heart dysfunction and increased central venous pressure which subsequently transmits to the hepatic venous system.[19] Initial pathologic changes include sinusoidal dilatation with perisinusoidal edema followed by thrombosis, hemorrhage, and loss of hepatocytes surrounding the central veins. Repeated injury results in bridging fibrosis between central veins and regenerating hepatocytes growing along the preserved portal triads, yielding a characteristic fibrosis pattern referred to as reverse lobulation that differs from the more common periportal fibrosis associated with other causes of liver fibrosis.[27] The diminished portal venous flow, as a result of increased sinusoidal pressure, and the compensatory increased arterial flow result in hepatocellular hyperplasia and development of FNH-like nodules (see **Figs. 3** and **6**).

Fontan-associated liver disease (FALD) is a subset of congestive hepatopathy seen in patients with congenital cardiac anomalies who underwent Fontan procedure. First described in 1971, the Fontan procedure results in direct connection of systemic venous return to the pulmonary circulation in patients with univentricular defects and creates a unique blood flow physiology ("Fontan physiology") with the single ventricle pumping blood into the systemic circulation and the pulmonary blood flow being passively driven from the inferior vena cava.[28,29] The resultant increased systemic venous pressure is the main trigger leading to FALD.[30,31] Initially, the hepatic arterial blood flow increases in response to the higher hepatic venous resistance and, similar to other etiologies of congestive hepatopathy, can lead to the development of FNH-like lesions. With time, these patients may develop a low cardiac output that results in decreased arterial hepatic flow.[32] The complexity of inflow and outflow circulation that post-Fontan patients progressively develop explains the complexity of liver lesions reported in FALD.[32] The end result of this chronic hepatic insult is the progressive development of pericentral and perisinusoidal fibrosis.[33–35]

FNH-like lesions are the most common focal liver lesions in post-Fontan patients with a reported prevalence of 27%[36] (**Fig. 8**). A wide variety of other liver lesions (including hepatic adenomas and HCC) also occurs in FALD as a result of the complexity of

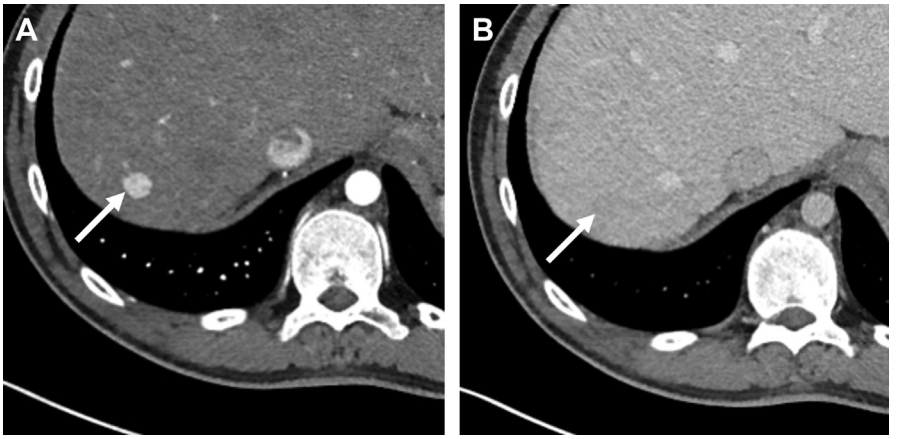

Fig. 8. A 26-year-old boy with history of Fontan procedure as a child for transposition of the great arteries. Axial contrast-enhanced CT (*A*) obtained during hepatic arterial phase shows an avidly enhancing lesion in segment 7 (*arrow*). No convincing associated washout or "capsule" is seen during venous phase (*B*). The lesion remained stable for at least 3 years suggestive of an FNH-like nodule.

the hepatic insult post-Fontan procedure.[31,36] These patients are at increased risk of HCC (**Fig. 9**). In a large multicenter retrospective study involving 2470 patients who had Fontan surgery, the prevalence of biopsy-proven HCC was reported at 1.3%.[35] More recently, Sagawa and colleagues reported a higher prevalence of HCC among patients with FALD, up to 9.8%.[37] Given the multitude of liver lesions encountered in these patients and the increased risk of HCC, confident diagnosis of FNH-like lesions can be challenging because of overlap in imaging features of these lesions, including washout appearance after contrast administration.[5] Stability, uniform homogenous arterial enhancement with central scar appearance and retention of contrast on the hepatobiliary phase

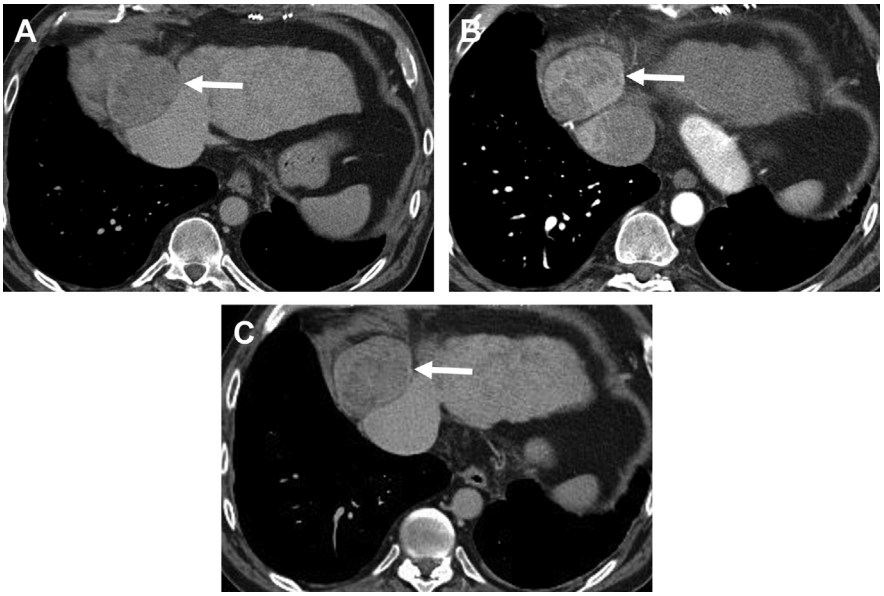

Fig. 9. A 44-year-old man with history of tricuspid atresia status post-Fontan procedure. Axial unenhanced CT (*A*) shows a large hypoattenuating mass in hepatic dome (*arrow*). The lesion shows heterogeneous enhancement during the hepatic arterial phase (*B*) with subsequent washout during the venous phase (*C*). The lesion is heterogeneous and does not have central scar, unlike FNH-like nodules. Percutaneous biopsy was consistent with hepatocellular carcinoma.

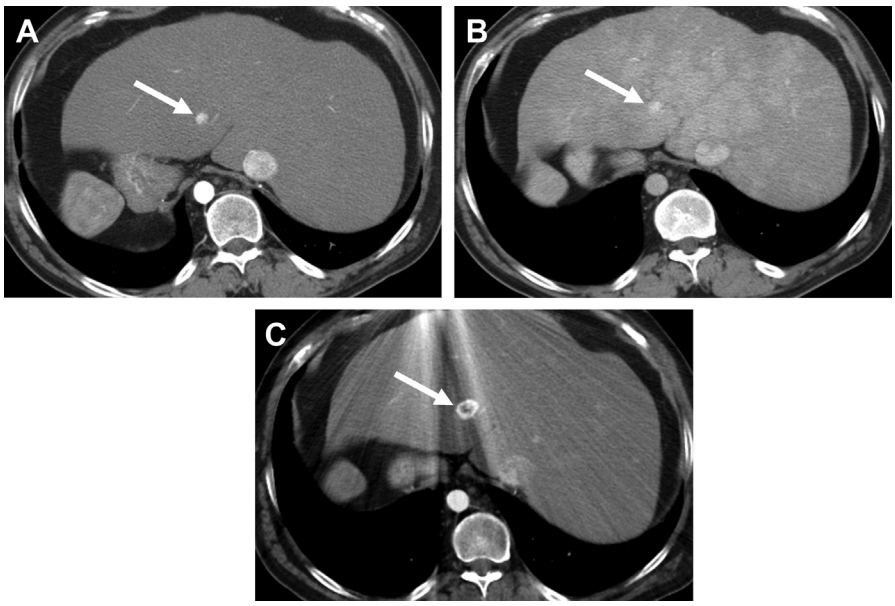

Fig. 10. A 40-year-old man with history of situs inversus and prior Fontan procedure. Axial contrast-enhanced CT images show gradual increase in size of FNH-like nodules over a period of 5 years. Note the homogeneous enhancement and central scar of the dominant lesion (*arrow*) typical of FNH-like nodule.

are features suggestive of FNH-like lesions[32] (**Figs. 10** and **11**). Washout during the portal venous phase (as opposed to washout during delayed phase), mosaic architecture, elevated serum AFP, and higher central vein pressure (CVP) were shown to be associated with a higher risk of HCC.[19] Short-term imaging follow-up (in 3–6 months) and/or tissue biopsy should be considered for atypical lesions.[32]

Sinusoidal Obstruction Syndrome

Sinusoidal obstruction syndrome (SOS), previously known as hepatic veno-occlusive disease,

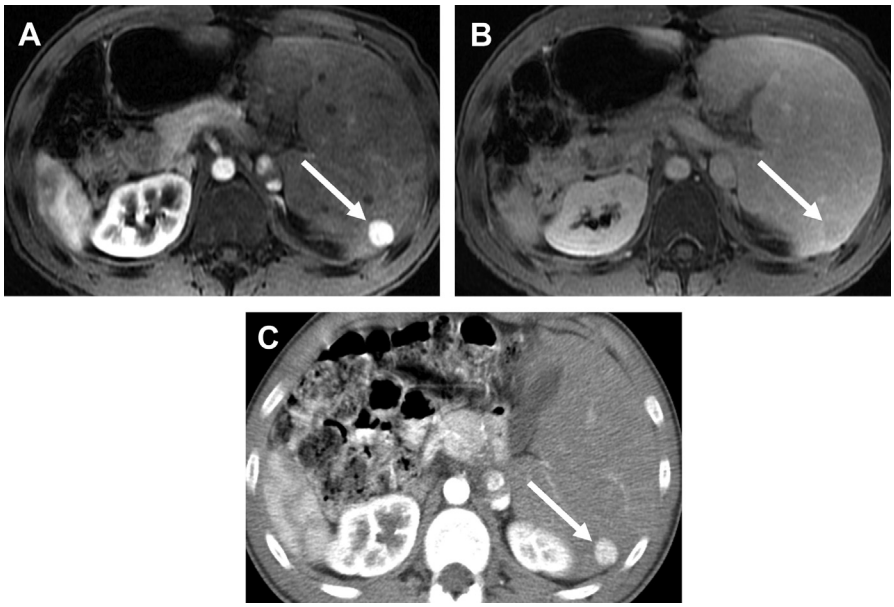

Fig. 11. An 18-year-old boy with history of Fontan procedure and situs inversus. Axial MR imaging shows avidly enhancing lesion (*arrow*) on hepatic arterial phase (*A*) with subsequent washout and enhancing capsule on venous phase (*B*). Contrast-enhanced CT obtained 5 years later (*C*) shows stable size of the lesion suggestive of benignity (despite the worrisome enhancement pattern).

occurs as a result of injury to sinusoidal endothelial cells and is characterized by dilated sinusoids filled with erythrocytes, often associated with centrilobular vein occlusion and perisinusoidal fibrosis.[38] Common causes of SOS include medications, particularly chemotherapy, bone marrow transplantation, and high-dose radiation. Oxaliplatin is one such chemotherapy agent with a known association with SOS.[39] FNH-like lesions have been reported in adults who previously received oxaliplatin for colorectal and pancreatic cancers, with evidence of SOS on pathology.[14] Local perfusion abnormalities related to SOS and centrilobular vein occlusion may account for subsequent FNH-like lesion development in these patients.

FNH-like lesions and nodular regenerative hyperplasia have been reported in 22% of patients treated with oxaliplatin, based on histopathologic examination of hepatectomy specimens.[20] It usually occurs at least 3 to 4 years after the completion of therapy, which is usually later than the interval for the development of hepatic metastases.[14] In addition, they can be distinguished from metastases based on their imaging appearance as these lesions are typically hypervascular often with central scars (FNH-like) and with the retention of hepatobiliary agents during the hepatobiliary phase (see **Fig. 4**), unlike metastases from GI adenocarcinomas that tend to be hypovascular, lack a central scar, and are hypointense on hepatobiliary phase MR imaging.[14] Although oxaliplatin is the most well-documented chemotherapeutic agent associated with FNH-like lesions, these nodules have also been reported in association with other agents including cyclophosphamide-based chemotherapy.[40] FNH-like lesions have also been reported in patients previously treated with chemotherapy for neuroblastoma in childhood. One imaging-based study found FNH-like lesions in 15% of patients who previously received chemotherapy for neuroblastoma.[41]

FNH-like lesions are also reported in the setting of hematopoietic stem cell transplant (SCT). One study reported FNH-like lesion development in 17 of 138 patients who received SCT.[42] All FNH-like lesions were seen in patients who received SCT as children, which may suggest that younger patients are more prone to FNH-like lesion development in the setting of SCT.

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Weber–Rendu disease, is an autosomal dominant disorder characterized by arteriovenous malformations and other vascular abnormalities involving multiple organ systems. Liver involvement is common, with one study demonstrating hepatic vasculature abnormalities in 74% of patients.[43] Liver manifestations include intrahepatic shunts (arterioportal, arteriovenous, and portovenous shunts), telangiectases, regenerative nodular hyperplasia, and FNH-like lesions.[44] In severe cases, intrahepatic shunting can result in diminished distal arterial perfusion and peribiliary necrosis, sometimes necessitating liver transplantation.[45]

Hepatocellular regeneration in HHT can present as nodular regenerative hyperplasia, LRNs, or FNH-like lesions[46] (**Fig. 12**). These patients are not considered at increased risk for primary liver malignancies. As such and given the high prevalence of regenerative lesions in patients with HHT, the diagnosis of FNH-like lesions can be made with higher confidence. It has been suggested that lesions with features indicative of FNH should not undergo biopsy or excision, particularly given presence of vascular abnormalities that may predispose to bleeding.[46]

Cavernous Transformation of the Portal Vein

Cavernous transformation of the portal vein (CTPV) occurs as a response to occlusive portal vein thrombosis in an attempt to restore portal blood flow. Etiologies for portal vein thrombosis include slow flow in the setting of cirrhosis, myeloproliferative syndromes, autoimmune diseases such as antiphospholipid syndrome, and hypercoagulability syndromes. Compensatory increased arterial flow due to reduced portal flow is a possible explanation for the formation of FNH-like lesions in these patients. One study reported a prevalence of 21% of FNH-like lesions in patients with non-cirrhosis-related CTPV.[47] Chronic portal venous thrombosis may result in dysmorphic liver and portal hypertension, even in the absence of fibrosis. FNH-like lesions in this setting can pose a diagnostic challenge because some of these patients are erroneously labeled as having cirrhosis and the lesions may be suspected to be HCC. Familiarity with the association between CTPV and FNH-like lesions and recognizing the typical features of these nodules can help with appropriate management (**Fig. 13**).

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is one of the rare etiologies of hepatitis characterized by chronic nonspecific inflammation of liver parenchyma, thought to be due to an autoimmune reaction against the liver.[48] Patients are usually female and have circulating autoantibodies (antinuclear and/or anti-smooth muscle antibodies in type I;

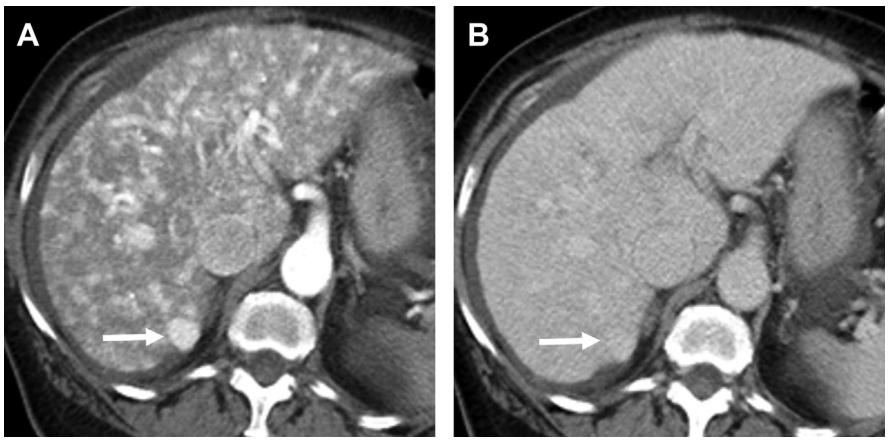

Fig. 12. A 72-year-old woman with history of hereditary hemorrhagic telangiectasia (HHT). Axial hepatic arterial phase CT (*A*) shows an enhancing lesion in hepatic segment VII (*arrow*). The lesion remains mildly hyperdense compared with the background liver on 150-s delayed phase (*B*). Note numerous areas of arterioportal shunting as well as enlargement of hepatic arteries consistent with history of HHT. The segment VII lesion remained stable on follow-up imaging.

antibodies against liver–kidney microsome and/or liver cytosol in type II). FNH-like lesions have been reported in patients with AIH[49] (see **Fig. 5**), although the exact prevalence is unknown. The mechanism for the development of these nodules in AIH is uncertain. A proposed mechanism is alterations in hepatic microcirculation secondary to diffuse parenchymal inflammation.[49] AIH can progress to cirrhosis. The incidence of HCC in patients with AIH (in absence of other etiologies of chronic liver disease), however, is thought to be lower than other etiologies of cirrhosis, estimated to be less than 1%.[50,51] Given the lower chance of malignancy in these patients, differentiation of FNH-like lesions from HCC should be less of a challenge. Awareness of the association of FNH-like nodules with AIH is critical so that there is not misdiagnosis of HCC. The presence of multiple lesions and stability also favor benignity.[49]

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is the most common primary immunodeficiency in adults, characterized by decreased serum levels of immunoglobulin and antibody production in response to vaccines and pathogens.[52] Besides an increased susceptibility to infections, CVID presents a broad

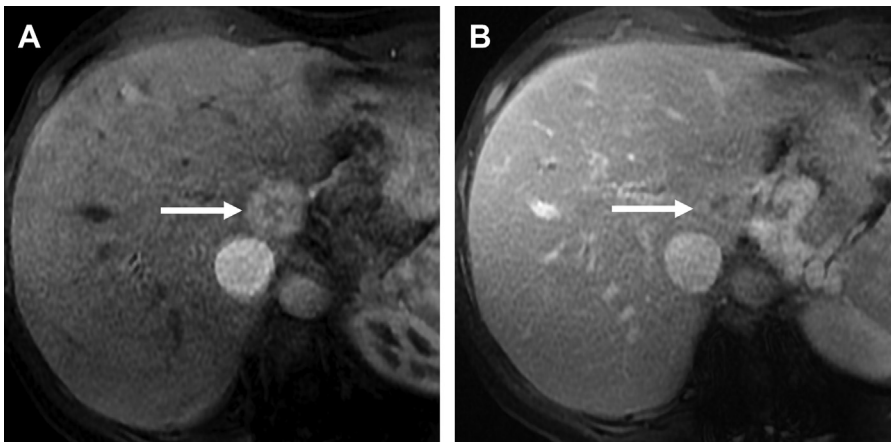

Fig. 13. A 25-year-old boy with history of chronic portal vein thrombosis with cavernous transformation. Axial contrast-enhanced MR imaging obtained during hepatic arterial phase (*A*) shows arterially enhancing lesion (*arrow*) with central scar. The lesion became iso-intense to the background liver on equilibrium phase (*B*). The lesion was stable for 3 years consistent with benign etiology. Of note, this lesion was new compared with prior examinations (not shown).

spectrum of clinical manifestations related to immune dysregulation-related complications. Nodular regenerative hyperplasia is considered the most common form of liver involvement in CVID[53] (see Fig. 2). NRH can lead to chronic cholestasis, noncirrhotic portal hypertension, or cirrhosis.[54] FNH-like lesions seen in these patients likely represent the spectrum of nodular regenerative hyperplasia. These nodules usually have typical radiologic features of FNH-like nodules described earlier. In the absence of risk factor for primary liver malignancies (such as cirrhosis), these lesions can confidently be diagnosed by imaging.

Diagnostic Challenges

Many of the conditions associated with FNH-like lesions are also risk factors for the development of other liver lesions. Furthermore, certain comorbidities (such as history of concomitant chronic liver disease) place the patient at higher risk of HCC development. Confident differentiation of FNH-like lesions from premalignant and malignant lesions (especially HCC) is clinically relevant and critical to guide the management. Clinical and laboratory findings (such as serum AFP level and probability of HCC based on underlying disease) should be considered when making this distinction as in many cases the imaging findings of FNH-like lesions are not specific and overlap those of HCC.[23] Classically described radiologic features of HCC such as arterial phase hyperenhancement and washout appearance are not specific in the setting of global hepatic vascular disorders. Hence, Liver Imaging Reporting and Data System (LI-RADS) classification cannot be applied in this setting.[55] Washout appearance can be seen with FNH-like lesions, with a reported prevalence of up to 10%,[56] although this appearance is likely reflective of abnormal enhancement of the background liver rather than deranged de-enhancement of the lesion (see Fig. 3).

Hyperintensity during the delayed hepatobiliary phase (when hepatobiliary MR imaging contrast agents are used) and presence of central scar are the most helpful features to differentiate FNH-like lesions from HCC. Although most HCCs are hypointense during hepatobiliary phase, FNH-like lesions typically show homogeneous iso- to hyperintensity during this phase.[13] This finding, however, is not definitive as hepatic adenomas and well differentiated HCCs may show retention of contrast during this phase.[57,58] HCCs, however, tend to have more heterogenous signal intensity (on unenhanced and contrast-enhanced T1w and T2w sequences) and lack central scar.[59] Intrahepatic cholangiocarcinoma and some metastases can show central retention of hepatobiliary contrast agent that is thought to be due to aberrant expression of OATP1B3 in their fibrotic stroma. This "targetoid" appearance with peripheral hypointense rim and inhomogeneous central uptake of contrast agent during hepatobiliary phase, however, is different from FNH-like nodules that have more homogeneous iso- to hyperintensity with a hypointense central scar.[60]

Patients with atypical imaging features (such as heterogeneity or significant changes of the nodule on serial imaging) and the ones with elevated serum AFP should be discussed by a multidisciplinary team and may require tissue sampling. Patients with lesions typical for FNH-like nodules should also be considered for follow-up by serial imaging and clinical/laboratory assessment.

SUMMARY

FNH-like lesions, and other similar benign nodules, can be seen in association with multiple liver diseases and are increasingly encountered in daily practice. Their imaging findings overlap with other entities, such as HCC. Familiarity with their pathogenesis and their imaging findings will help with a more informed diagnosis.

CLINICS CARE POINTS

- In cancer patients recieving oxaliplatin-based chemotherapy regimen, FNH-like lesion should be considered as differential diagnosis for new hepatic lesions.
- Signal characteristics similar to FNH, presence of central scar, and retention of contrast during hepatobiliary phase are key features helpful for diagnosing FNH-like lesion and differentiation from other hepatic pathologies.

DISCLOSURE

The authors have nothing to disclose.

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