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Benign focal liver lesion: The role of magnetic resonance imaging

Gatti M *et al.* Liver MRI in benign liver lesion

Abstract

Liver lesions are common findings in radiologists' daily routine. They are a complex category of pathology that ranges from solitary benign lesions to primary liver cancer and liver metastases. Benign focal liver lesions can arise from different liver cell types: Epithelial (hepatocytes and biliary cells) and nonepithelial (mesenchymal cells). Liver magnetic resonance imaging (MRI) is a fundamental radiological method in these patients as it allows with its multiparametric approach an optimal non-invasive tissue characterization. Furthermore, advanced liver MRI techniques such as diffusion-weighted imaging and hepatobiliary contrast agents have improved the detection of focal liver lesions and can be highly effective in differentiating pseudotumor from tumors, as well as benign from malignant lesions, and can also be used for differential diagnosis. Although histological examination can be useful in making a definitive diagnosis, liver MRI is an important modality in the diagnosis of liver lesions with a significant impact on patient care. This aim of this review is to provide a comprehensive overview about benign liver lesions on MRI.

Key Words: Magnetic resonance imaging; Liver neoplasms; Biliary tract; Hepatocytes

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Core Tip: Liver magnetic resonance imaging (MRI) is a fundamental radiological technique in patients with focal liver lesion as it allows with its multiparametric approach an optimal non-invasive tissue characterization. Liver MRI can be highly effective to distinguish pseudotumor from tumors, as well as benign from malignant lesions and can also be used for differential diagnosis. Although histopathological assessment sometimes has an important role to make a definitive diagnosis, liver MRI is

a key imaging modality in the diagnosis of liver lesion with a great impact on patient management.

INTRODUCTION

Liver lesions are common findings in radiologists' daily routine. They are a complex category of pathology that ranges from solitary benign lesions to primary liver cancer and liver metastases^[1-4].

Benign focal liver lesions can arise from different liver cell types: Epithelial (hepatocytes and biliary cells) and nonepithelial (mesenchymal cells)^[5] (Table 1). The diagnosis is often straightforward, although sometimes distinguishing between malignant primary and secondary lesions may represent a diagnostic challenge due to atypical tumor appearance and features.

To avoid misdiagnosis, radiologists must cope with the key characteristics of the lesion and decide which imaging procedure [i.e., ²⁵ultrasound (US), computed tomography (CT) and/or magnetic resonance imaging (MRI)] will most likely provide the diagnosis^[3,4,6-8].

The use of advanced liver MRI techniques such as diffusion-weighted imaging (DWI), multiarterial phase technique, hepatobiliary contrast agents and artificial intelligence have improved the detection and differentiation different focal liver lesions^[2-4,8-11] (Figure 1). Furthermore, liver MRI is often the last imaging technique used in the diagnostic algorithm before liver biopsy.

Therefore, it is important to know the characteristics of different focal liver lesions on MRI and how to differentiate between benign and malignant ones in order to make the correct diagnose, recommend the best follow-up when necessary, cut the costs of unnecessary diagnostic tests and, last but not least, reduce patient anxiety.

This aim of this article is to provide a comprehensive overview about benign liver lesions on MRI. Table 1 shows a histological classification that was used in this review. Table 2 provides an overview of the MRI contrast agents currently used in clinical practice.

EPITHELIAL TUMORS (HEPATOCELLULAR AND BILIARY)

Hepatocellular adenoma

Hepatocellular adenoma (HCA) is a rare benign monoclonal neoplasm of the liver, composed of hepatocytes arranged in sheets or in a cord-like fashion with a lack of portal venules and biliary ductules^[12-14]. Hepatocytes sheets are separated by dilated sinusoids. They are perfused solely by high-pressure peripheral arterial feeding vessels, resulting in a remarkable hypervascular nature. Hepatocytes might contain a variable amount of intracellular fat or glycogen.

HCA has an annual incidence of about 1-1.3 million cases per year in North America and Europe; 85% of cases occur in women of childbearing age (15-45 years old)^[15].

An increased incidence of HCAs has been reported since 1960s following the introduction of oral contraceptive pills (OCP's)^[14,16]. Long-term users of OCP have 25-fold increased risk of developing HCA compared to general population^[14]. Some studies suggested that OCP discontinuation might lead to tumor regression, but remains controversial^[17]. Similarly, long-term use of anabolic androgen steroids (AAS) has been associated to a great risk of developing HCA. Glycogen storage disorders (GSDs), in particular type 1 and type 3, have been linked to an increased incidence of HCAs^[14].

Hepatic adenomatosis, was first described in 1985, is a condition in which 10 or more adenomas are present in an otherwise normal liver^[18]. These cases are at higher risk for complications: 63% risk of hemorrhage and 10% risk of malignant transformation^[19].

Other risk factors for HCA are diabetes (both type 1 and 2), metabolic syndrome, obesity, Fanconi's anemia, familial adenomatosis polyposis, beta thalassemia and tyrosinemia^[14].

HCAs may be complicated by the presence of intralesional fat, hemorrhage, or malignant transformation with a subsequent wide range of imaging appearances resulting in a challenging diagnostic process. In 2006, four subtypes of HCA have been identified based on genotype-phenotype analyses according to the genetic and

histopathological features of lesion: (1) Type 1: Hepatocyte nuclear factor (HNF)-1 α HCA; (2) Type 2: Inflammatory HCA (I-HCA); (3) Type 3: β -catenin activated HCA; and (4) Type 4: Unclassified HCAs^[12].

Several hypervascular benign and malignant hepatic lesions may mimic HCA: Focal nodular hyperplasia (FNH), hepatocellular carcinoma (HCC), hemangioma (HA), angiomyolipoma and metastases.

The use of hepatocyte-specific contrast agent allows differential diagnosis between HCA and FNH with very high sensitivity and specificity (respectively 91% to 100% and 87% to 100%)^[20]. On hepatobiliary phase (HBP) most HCAs present low signal compared to surrounding parenchyma while FNHs have iso- or hyperintense signal. Some HCAs, however, generally I-HCAs, may have iso- or hyperintense signal on the HBP.

Type 1: HNF-1 α HCA

HNF-1 α HCA is the second most common subtype of HCA, representing 30% to 35% of lesions; it is almost exclusively found in women, the majority of whom (> 90%) with a history of OCP use in anamnesis^[20]. This type of HCA might be associated with maturity-onset diabetes of the young and familial adenomatosis. HNF-1 α HCA generally has an indolent biological behavior and among all types of HCA it has the lowest risk of malignant degeneration. HNF-1 α HCA may be associated with mutations of the transcription factor 1 gene on chromosome 12q24.43, an anti-oncogene involved in hepatocyte differentiation, whose inactivation can promote proliferation of such cell line^[14].

Because of intracellular fat content, HNF-1 α HCA typically exhibits diffuse intratumoral signal loss on chemical-shift T1-weighted imaging (*i.e.*, signal loss on opposed-phased images compared to in-phase images); this finding alone demonstrates 86.7% sensitivity and 100% specificity for this subtype. HNF-1 α HCA is often hyper- or isointense on T1-weighted images and iso- or hyperintense on T2-weighted images, with no apparent signal restriction on diffusion imaging. HNF-1 α HCAs often show

hyper-enhancement in the arterial phase after contrast injection, however this does not persist in the portal venous phase^[14,21]. (Figure 2)

Type 2: I-HCA

It is the most frequent subtype, accounting for 40% to 50% of all HCAs; it is linked to mutations in the interleukin 6 signal transducer gene, which is located on chromosome 5q11 and codes for glycoprotein 130. This mutation causes the Janus kinase (JAK) signal transducer to be activated indefinitely, resulting in aberrant hepatocyte proliferation. Type 2 HCA is most common in young women on OCP medication, as well as in those with metabolic syndrome or obesity.

I-HCA is the HCA type with the highest risk of bleeding, occurring in up to 30% of cases. Malignant transformation of HCAs into HCC occurs in 5% to 10% of cases.

On MRI, I-HCA generally shows heterogeneous high signal on T2-weighted sequences, more intense in the peripheral part of the lesion (“atoll” sign) and arterial enhancement that persists in portal venous and delayed phases. Such features are due to the presence of dilated sinusoids. Intralesional steatosis is rare, more frequently focal or with patchy and heterogeneous pattern. Intratumoral hemorrhage, reported in up to 30% of cases, results in increased lesion heterogeneity (Figure 3). Acute hemorrhage presents high signal on T1-weighted sequences due to the presence of methaemoglobin; chronic hemorrhage has low signal on T1 and T2-weighted sequences because of hemosiderin content^[14,21].

Type 3: β -catenin-activated HCA

β -catenin activated HCAs account for 10% to 15% of all HCAs. Mutations in the β -catenin gene (CTNNB1) on chromosome 3p21 cause continuous activation of the β -catenin protein, resulting in uncontrolled hepatocyte growth. It is more common in men and is linked to GSDs, AAS, and familial adenomatosis polyposis. β -catenin mutation is strongly associated with malignant degeneration^[14].

β -catenin-activated HCAs do not have typical MRI features. Such lesions generally do not contain intratumoral fat. Malignant transformation may be suspected in case of growth, local invasion, or contrast medium washout on portal-venous or delayed phases. β -catenin-activated HCAs present arterial enhancement and washout on portal-venous and delayed phase, making differential diagnosis with HCC challenging^[14,21,22].

Type 4: Unclassified HCAs

This category includes roughly 10% of all HCAs with an adenoma-like appearance but no distinguishing genetic and/or clinical characteristics. There is a scarcity of information about these lesions. Such tumors have no pathognomonic characteristics on MRI^[14,23].

FNH

After HA, FNH is the second most common benign hepatic tumor (representing around 8%-9% of all primary liver tumors) and is frequently an incidental finding on imaging because most individuals are asymptomatic.

FNHs are more common in females than in males (8:1), in the third to fifth decades, and, unlike HCAs, the relationship with OCP is uncommon.

Several FNH syndrome is defined as the presence of multiple FNH lesions (up to 20%) and HAs.

To ensure adequate treatment, it is crucial to distinguish FNH from other hypervascular liver lesions such as HCA, HCC, and hypervascular metastases^[24].

FNH should be regarded as a regenerative lesion rather than a neoplasm: It may be caused by the presence of a vascular abnormality (either of the arterial or portal vascular supply) that, when combined with hormonal stimulation, results in mass growth. Histologically, these lesions are known as hamartomatous malformations^[25]. From anatomopathological point of view FNH is a nodule with polycyclic contours, composed of organized hepatocytes, completely or incompletely surrounded by circular

or short fibrous septa originating from a central scar that contains a hypertrophic arterial vessel, originating from hepatic artery.

Surrounding septa's connective tissue contains also numerous capillaries and ductules.

The rich network of capillaries, that arise from the central artery, provide ⁴ arterial blood to the hepatocytes and sinusoids, in accordance with the highly hypervascular nature of most FNH lesions on imaging^[26].

The sinusoids, the malformed arteries and the vein of FNH drain into the hepatic vein. FNH does not have a portal venous supply.

⁴ Normal liver tissue surrounds the FNH and there is no fibrous capsule at the interface of the lesion and the liver^[27].

Because of its vascular physiopathology, FNH is commonly associated (20%-30%) with other hepatic lesions or conditions such as hepatic HA, arteriovenous malformations, anomalous venous drainage, HCA (possible but not proven), congenital absence of portal vein/portal vein atresia and portal shunts^[28].

Because it contains hepatocytes, FNH shows isointense signal on both T1- and T2-weighted sequences with occasional slight hypointensity and hyperintensity on T1 and T2, respectively.

¹⁴ MRI imaging has higher sensitivity (70%) and specificity (98%) for FNH than US and CT.

Both on CT and MRI, after contrast medium administration, FNH shows homogenous and strong contrast enhancement ¹⁰ in the arterial phase with the exception of the central scar^[26].

During portal-venous and delayed phases, it becomes isointense to the liver parenchyma while the central scar remains relatively hypointense.

On HBP FNH appears isointense to hyperintense compared to adjacent liver parenchyma without or with the presence of a central scar^[21], which is hypointense (Figure 4).

On diffusion weighted imaging the average numerical value of apparent diffusion coefficient (ADC) in benign hepatic lesions (FNH, HA, HCA) is about $1.88 (1.326-2.48) \times 10^3 \text{ mm}^2/\text{s}$, while the ADC of malignant liver lesions [HCC, cholangiocarcinoma (CCC), colorectal cancer liver metastasis (CRCLM)] are significantly lower, around $1.15 (1.024-1.343) \times 10^3 \text{ mm}^2/\text{s}$ ^[29].

FNH and HCA have ADC values lower than normal liver but FNH has an ADC higher than HCA^[30].

13 The central scar was more often detected with MRI than with CT (78% and 60%, respectively)^[31].

The central scar appears slightly hyperintense on T2-weighted images and this is an important difference with the central scar of HCC that is generally hypointense in all sequences even if rarely can be hyperintense, mimicking the one of FNH^[32].

At MRI with non-hepatobiliary specific agents (and consequently also on CT imaging) the central scar shows enhancement in delayed phase because of the presence of abundant myxomatous stroma.

With different hepatobiliary specific agents the central scar manifests variously^[32]: (1) With gadobenate dimeglumine (Gd-BOPTA - MultiHance®; Bracco, Milan, Italy) the central scar will enhance in the late phase (hepato-biliary excretion after 1-3 h); and (2) With gadoxetic acid (Gd-EOB-DTPA - Primovist®; Bayer-Schering, Berlin, Germany) the central scar will quite never enhance because the late venous phase overlaps the HBP (that comes on average after 10-100 min) making everything that has not a hepatocellular origin hypointense, including the connective central scar.

Atypical FNH

7 Currently, FNH is divided into two types: Classic and non-classic.

Classic FNH is characterized microscopically by the presence of: (1) Abnormal nodular architecture; (2) Malformed vessels; and (3) Cholangiolar proliferation and on imaging appears with all the characteristics mentioned above. Non-classic FNH lesions lack one of the classic features but always show bile ductular proliferation^[24].

Non-classic FNH may demonstrate “atypical appearance” at imaging that may lead to the following 5 subtypes: (1) No central scar FNH; (2) Large central scar; (3) Intralesional fat; (4) Presence of a pseudocapsule; and (5) Sinusoidal distension (Figure 5).

Biliary cystadenoma

Biliary cystadenoma (BCA) is an uncommon (less than 5% of cystic liver lesions) benign hepatic tumor that arises from intrahepatic biliary channels, most commonly in the right lobe (55%), and rarely from extrahepatic biliary ducts or the gallbladder^[33]. Because of its high prevalence in middle-aged women (> 85%)^[33] it is considered a congenital disorder with potential hormonal influence. Due to its high risk of recurrence (if non-completely removed) and its potential risk for malignant degeneration into biliary cystadenocarcinoma (BCAC), the differential diagnosis with other cystic lesions of the liver is mandatory^[21].

US imaging reveals a massive, lobulated, well-defined hypoechoic or anechoic mass with hyperechoic interior septa or calcifications and solid papillary projections; contrast-enhanced ultrasonography (CEUS) may indicate enhancement of the walls and septa. These features may aid in identifying BCA from other liver cystic lesions^[33].

CT confirms US appearance and CEUS behavior: A single multiloculated cystic lesion with a well-defined thick fibrotic capsule, mural nodules, and rarely calcifications of the capsule^[33].

On MRI, BCA appears as a fluid-containing multilocular lesion that is significantly hypointense on T1-weighted sequences and hyperintense on T2-weighted images with septal hypointensity. On both T1- and T2-weighted images, the signal intensity may fluctuate due to the presence of proteinaceous material or blood products^[21] (Figure 6).

If thinner septa and regular wall are seen in cystadenoma, polypoid excrescences, hemorrhage and evident vascularized septa are more suspicious for BCAC but the differential diagnosis between such lesions may be challenging^[21].

Biliary hamartoma (von Meyenburg Complex)

Multiple biliary hamartomas, also known as von Meyenburg Complex, are rare bile duct malformations, with a very low incidence ranging between 0.4% and 5.5%. There's a higher prevalence in females (F/M = 7/4) with a mean age of 48 years (range 33-68 years). They belong to the spectrum of "fibropolycystic liver disease" and are defined as small duct dilatations within thick bile. The cause is unknown, however it can be present in both non-cirrhotic and cirrhotic livers, as well as in children and adults. However, its prevalence rises dramatically with chronic liver illness, implying an acquired etiology^[34].

Histologically, bile duct hamartomas are generally small, less than 1 cm, often subcapsular, and composed of small dilated biliary ducts surrounded by biliary epithelium^[35].

On T1-weighted images they typically appear as small hypointense lesions, with a strongly increased signal on T2WI due to its intrinsic cystic component especially on heavily weighted T2 sequences. These lesions can show the presence of small mural nodules (1-2 mm) with an isointense signal on T1-weighted and intermediate signal on T2-weighted images. On dynamic sequences, the mural nodules can show enhancement during portal-venous phase in about 90% of cases with no core enhancement. On cholangiography sequences, both intra- and extra-hepatic bile ducts are normally represented^[36,37], while multiple hyperintense cystic lesions on T2-weighted images are uniformly distributed in the liver with no communication with the bile ducts, appearing as "starry sky" configuration^[38] (Figure 7).

Biliary hamartomas should be carefully recognized in order to distinguish it from metastases, microabscess, simple liver cysts, and Caroli's disease (Figure 8).

MESENCHYMAL TUMORS

HA

Hepatic HAs are the most prevalent benign mesenchymal liver lesions, with an estimated frequency of around 20% in the general population, and are up to five times

more common in females than males^[39]. HAs are frequently an incidental finding in asymptomatic patients during routine radiological examinations, however because of its high prevalence, the differential diagnosis can become complex in patients affected by primary liver cancer or liver metastases. HAs are categorized by size: Small HAs are 1-2 cm, typical HA are 2-10 cm and giant HAs have a diameter of more than 10 cm. Recent retrospective cohort studies demonstrated that up to 40% of HAs may grow during follow up, with a slow growth rate (2 mm/year in diameter and 17.4%/year in volume)^[39].

Microscopically, HAs appear as cavernous vascular spaces lined by endothelium and containing a fibrous stroma. Larger HAs may contain a fibrous nodule or a collagen scar.

HAs are usually fed by vessels from the hepatic artery circulation, with a slow blood flow within the vascular spaces.

HAs have been histologically categorized in 3 different subtypes, with some overlap among them: cavernous, capillary and sclerosed.

Cavernous HA

¹⁹ It is the most common subtype, generally smaller than 3 cm with few internal connective components and with a prevalence of large vascular spaces^[21].

The high water content of HAs causes homogeneous hyperintensity on T2-weighted sequences and poor signal intensity on T1-weighted pictures during MRI^[40]. Giant HAs may present a central T2-weighted hypointense component in case of hyalinized or thrombosed areas. If calcifications are present, they show very low signal intensity on all sequences.

On diffusion weighted imaging, HAs show hyperintensity on b_0 s/mm² pictures, with a progressive decrease in signal intensity at higher b values; the signal on the ADC map is greater than that of the nearby liver parenchyma.

Some HAs have residual hyperintensity on high b value images (500-750 s/mm²) because of the “T2 shine through effect” making them more difficult to characterize;

however quantitative assessment with ADC map make differential diagnosis easy as their signal is always higher than that of surrounding liver^[41].

Following contrast injection, typical cavernous HAs exhibit ² peripheral nodular enhancement on the arterial phase, with centripetal progression and progressive filling on the portal venous and delayed phases; because to a lack of hepatocytes, they display a hypointense signal on the HBP^[21] (Figure 9).

Capillary HA

It accounts for almost 16% of all HAs, being smaller than 1 cm in about 40% of cases^[42,43]. Microscopically it consists of small vascular spaces with abundant connective components.

⁶ It presents high signal intensity on T2-weighted images and low signal intensity on T1-weighted sequences. In case of hepatic steatosis, it shows hyperintense signal on T1-weighted “chemical shift” images due to peritumoral sparing of fatty infiltration.

After contrast injection it is characterized by a “flash-filling” kinetic of contrast enhancement with early homogeneous enhancement, similar to that of the aorta in all phases^[21].

Because of the presence of arteriportal shunts, fugacious perilesional parenchymal enhancement may be observed in extremely tiny lesions (less than 1 cm).

Relative hyperintensity on delayed phases allows differential diagnosis with hypervascular metastases that are hypointense in portal venous and delayed phases.

Sclerosed/hyalinized HA

Sometimes HAs deteriorate, resulting in the development of severe fibrosis, which usually begins at the core of the lesion, obliterating vascular gaps and causing changes in MRI signal intensity.

Sclerosed HAs may only present slight hyperintensity on T2-weighted images, generally localized at the periphery of the lesion. Because of histologic lesion heterogeneity, the contrast enhancement pattern may be unusual. In most case no early

enhancement is present and there is a slow and inhomogeneous contrast progression. Late centripetal filling of the central scar might be present. Because of its rarity and heterogeneous radiological presentation, that can mimic hepatic malignancies such as CCC or metastases, the final diagnosis of sclerosed HA often remains histological^[8,21,42,44] (Figure 10).

Angiomyolipoma

Hepatic angiomyolipoma (HAML) are mesenchymal benign tumors composed of arteries, fat, and smooth muscle cells that are categorized into four subtypes based on their composition: Mixed (the most frequent form), lipomatous (containing 70% fat), myomatous (containing 10% fat), and angiomatous.

The fat components of a lesion might range from 10% to > 90% of the total lesion volume.

Patients with tuberous sclerosis complex are more likely to have them (5%-10% of the time)^[45].

HAML is classified as a “Perivascular Epithelioid Cell Tumor” and is immunohistochemically positive for beta-hydroxy-beta-methylbutyrate-45, a monoclonal antibody for melanoma: This positivity is a clear diagnostic criterion, while other hepatic tumors are negative for such marker.

The radiological appearance of HAML is completely dependent on the proportions of the three components.

Lipomatous HAML appear hyperechogenic on US, hypodense on non-contrast enhanced CT, hyperintense on in-phase T1-weighted sequences, and hypointense on out-of-phase T1-weighted sequences, indicating intralesional fat components^[46] (Figure 11).

Lesions with minimal fat content (angiomatous or myomatous types) are more difficult to characterize and are frequently classified as HCC because of their appearance on morphologic sequences and after contrast injection: They show moderate to high signal intensity on T2-weighted sequences, hypointensity on T1-weighted

sequences, and early dishomogeneous contrast enhancement during contrast enhanced dynamic studies with CEUS, CT, and MRI, with longer duration^[47].

Recent studies have established the utility of DWI-MRI with ADC values in the differential diagnosis of HAMLs and HCCs with fat components since HAMLs have higher values than HCCs with fat.

Since HAML does not contain hepatocytes, it appears hypointense in HBP^[47].

Lymphangioma

³ Hepatic lymphangioma (HL), a malformation of the lymphatic system is a rare benign liver neoplasm. Most of lymphangiomas are located outside the abdominal cavity, being less than 5% intra-abdominal, affecting primarily the small bowel mesentery, followed by the omentum, mesocolon, and retroperitoneum. Liver location is usually seen when lymphangiomas affect multiple organs, in lymphangiomatosis. Solitary HL is much more rarely seen and could lead to a clinical misdiagnosis^[48,49].

HL are histologically classified into capillary lymphangioma, cystic lymphangioma, and cavernous lymphangioma. It may occur at any age, with average age of 30 years and slightly higher incidence in females^[48,50]

HL may be asymptomatic and incidentally found on cross-sectional imaging. The symptoms, if present, usually depend on compression of adjacent organs by the neoplasm^[51].

Imaging appearances of HL are various. On US it may be non-echoic, low-echoic, and mixed-echoic masses containing cystic and solid components within unicystic chamber or multichambers. On CT scan unilocular cystic mass shows low density and no enhancement. In some cases, it may present like a low-density mass with enhancement. For multilocular mass with mixed components, enhancement is observed for septum and solid parts but not for the cystic components. However, some cases described in literature show atypical appearance, for example with wash-in and wash-out in solid component mimicking malignancy^[48,51].

MRI of HL is low signal on T1-weighted imaging, high signal on T2-weighted imaging, and occasionally mixed signals, related to intralesional bleeding that may occurs. In case of microcystic lymphangioma mistaken for solid mass depending on its enhancement after intravenous injection of contrast, MRI with T2-weighted imaging may be very useful in detection of multiple microcysts. The presentation of enhanced is similar to that of enhanced CT^[48,52].

Diagnosis of lymphangioma is difficult because of no typical symptoms and signs and differential diagnosis from simple cyst, BCA, BCAC, hydatid cyst, sclerosing HA, or HCC is very hard^[52].

Definitive diagnosis relied on pathological examination, that can be necessary in a cirrhotic liver with a lesion diameter less than 2 cm and if the cystic appearance isn't predominant on imaging^[48].

Macroscopically, the cysts resemble unilocular cysts or multilocular cysts of varying diameters with septum, some of which have solid material or are filled with clear serous fluid, chylous fluid, and blood clots. Solid components have the microscopic appearance of fibrous hyperplasia, whilst liquid components are made up of a high number of cystic-dilated lymphatic lumens lined by simple squamous endothelium and filled with lymph. If morphology is insufficient to make a diagnosis, lymphatic markers and D2-40 (podoplanin) may be used to confirm the condition. Furthermore, endothelial markers such as von Willebrand factor, CD31, CD34, and two lymphatic markers (LYVE-1 and Prox-1) are utilized to identify lymphatic vessels from blood vessels immunohistochemically^[53].

Solitary fibrous tumor

Solitary fibrous tumor (SFT) is a rare soft tissue neoplasm that originates from mesenchymal tissue. It was first reported in 1931 like an intra-thoracic mass arising from the pleura. Even if cases of SFT have been reported to originate in organ external to the thorax, hepatic location is extremely rare, accounting for less than 100 cases in the literature^[54,55].

Liver SFT show itself like a large, well-defined and heterogeneous single lesion that usually involves the right hepatic lobe, with a median tumor size of 17 cm^[54,56].

It may occur at any age, with prevalence in middle-aged women^[56].

SFT is asymptomatic in 80% of patients. Symptoms depend on tumor effects, including pain, weight loss and nausea, and less frequently weakness, fever and hypoglycemia. Laboratory parameters are usually non-specific^[57].

SFT does not reveal specific findings on imaging examination.

Ultrasonography often shows a heterogeneous mass that may be low-echoic, hyperechoic or both, with or without calcifications. On CT scan it shows early arterial enhancement with delayed venous wash-out. MRI may reveal an heterogeneous lesion, slightly ⁶ hyperintense on T2-weighted sequences and hypointense on T1-weighted sequences, with high signal on DWI^[55]. In some cases reported on the literature about imaging appearance of SFT with gadoteric acid, it shows heterogeneous enhancement on arterial and portal phase images and homogeneous hypointensity on HBP^[54,58].

Being these findings non-specific and mimic those of HCC or leiomyomas, diagnosis of SFT is challenging, also because of no typical symptoms and signs^[55].

A definitive diagnosis relied on histopathological and immunohistochemical studies^[55].

On histology SFT is characterized by fibroblast-like spindle cells within thick collagen bundles, with patternless architecture in which hypo and hypercellular areas coexist; collagenous stroma contains hemangiopericytic vessels. Immunohistochemical reactions is usually positive for CD34 in most of cases, but the specific immunohistochemical marker of SFT is STAT6^[55,59].

The biological behavior of SFT is controversial, in fact it may show malignant potential, as described in some reported cases of metastasis or recurrence^[54,57,59].

England *et al* in 1989 reported malignancy criteria: the presence of intratumoral necrosis or hemorrhage, mitotic changes, pleomorphism of cellular nuclei, metastasis, large dimensions (more than 10 cm) and cellular atypia^[59,60].

Mesenchymal hamartoma

Mesenchymal hamartoma (MH) of the liver is a rare benign tumor that originates from an anomalous development of primitive portal mesenchymal tissue, comprising predominantly of mesenchymal stromal component and aberrant malformed biliary structure with a small amount of hepatic lobules^[61].

This neoplasm usually affects children mostly in the first 2 years with a slightly male predominance and it accounts for 8% of liver tumors in children^[61-63]. Liver MH show itself like a large benign multicystic/solid cystic liver mass, sometimes pedunculated, arising in the right lobe of the liver in 75% of cases^[64].

MH leads with non-specific clinical manifestations, usually depending on the great size of the tumor, which can reach up to 30 cm. Patients may present with hepatomegaly, non-tender abdominal mass causing occlusion of inferior vena cava or dyspnea and sometimes with fever, weight loss or vomiting. Alpha-fetoprotein is usually normal^[61].

Imaging appearance depends on the cystic, solid/cystic or solid predominance of the tumor^[61,64].

US often shows a complex cystic mass with internal septation^[65]. On CT scan it shows a heterogeneous appearance with enhancing stromal elements and cystic components with water attenuation^[64]. The stromal component may be predominant in less cases, although cystic components are more frequent and may vary in size; if the lesion is predominantly cystic it may range from a "swiss cheese appearance" if cysts are small, into a multilocular cystic lesion with septa, if the cystic components have a great size^[61,64]. MRI appearance depends on the cystic *vs* stromal composition of the neoplasm and on the protein content of the fluid. The solid component may be hypointense to adjacent liver both on T1-weighted and T2-weighted sequences because of fibrosis. Cystic components usually show signal intensity similar to water on T2-weighted images and may have variable signal intensity on T1-weighted sequences because of the protein content of cystic areas. After injection of gadolinium only stromal components and septa enhance^[64].

On histology a fibromyxoid connective background with bland spindle cells characterizes MH with branching bile ducts, thick walled vascular channels and scattered island of hepatocytes in the periphery of the lesion^[66].

The biological behavior of MH is benign, even if cases of malignant degeneration in undifferentiated embryonal sarcoma are described in the literature^[65].

PSEUDOTUMOR

Focal fatty infiltration

Focal fatty hepatic infiltration can be easily recognized using the standard liver MRI examination, based on T1-weighted in-phase/out-of-phase and T2-weighted images, which in the latter shows slight hypointense signal. However, in some cases, these focal areas can be misdiagnosed by focal liver lesions and they have to be assessed using dynamic contrast enhancement and HBP imaging. Considering the physiological GD-BOPTA and Gd-EOB-DTPA uptake by normal hepatocytes, the focal fatty infiltration or hypersteatosis areas presented a decreased contrast enhancement due to reduced number of functioning hepatocytes or atypical vascularization. Moreover, in case of nodular-shaped focal fatty infiltration, its differential diagnosis with a fat-containing liver lesion can be challenging. In this setting, wedge or pyramidal shape and the lack of mass effect are useful features to distinguish a focal fatty lesion from a focal liver lesion^[67] (Figure 12).

Yeom *et al*^[68], by evaluating 27 focal fat deposition areas, reported a homogeneous or heterogeneous enhancement during the dynamic study, both in the arterial and portal venous phase, with hypointense signal during HBP.

On the other hand, fat spared areas don't show any signal drop-off during in-phase/out-of-phase imaging and may induce increased signal intensity on HBP due to preserved or increased focal liver function^[69].

Infection-liver abscess

The liver abscess, defined as a localized collection of inflammatory products caused by bacterial, fungal or parasitic agents, can be easily diagnosed with all imaging techniques, best with US and CT. MRI can help to distinguish between uni- and multifocal necrotic lesions disseminated through the liver parenchyma. In this setting, the typical appearance of liver abscess during the standard MRI protocol can support the final diagnosis, based on the iso- to a hyperintense appearance on T1-weighted images due to the presence of proteins, hemorrhagic foci, or inflammatory degradation products, without significant drop-off signal during in-phase/out-of-phase imaging. T2-weighted imaging is useful to determine not only the amount of free water inside the lesion but also to identify the slight peripheral hyperintense area due to edema or peripheral inflammation. Usually, on DWI an abscess presents a high restricted diffusion with very low values of ADC because of the high viscosity of inflammatory debris and cellularity^[21] in the necrotic cavity, while no diffusion restriction is seen peripherally. Furthermore, as reported by Park *et al*^[70], DWI is helpful in differentiating hepatic abscess from malignant mimickers considering the higher peripheral restriction in case of malignancy with 98% of diagnostic accuracy.

During the dynamic study, liver abscess typically shows a peripheral rim enhancement, in particular on the portal-venous and delayed or transitional phase, because of the presence of a pseudocapsule and inflammatory cells. During the HBP the core typically does not change its appearance, while the peripheral area can show an ipo- to isointense signal, due to the edema or to the normal function of hepatocytes, respectively (Figure 13).

Although size, shape, number, and signal intensity can help to establish a differential diagnosis, the only pathognomonic signs are the presence of air bubbles within the lesion or an air-fluid level^[71], seen as a single or multiple flow-void foci.

The most important differential diagnosis of liver abscess is metastasis. As mentioned above, liver metastasis can be recognized due to the different signal intensity on T2-weighted images and DWI with a slight and clear hyperintense appearance respectively, as well as during the dynamic study, in particular with a poor peripheral

ring enhancement due to the presence of pathological cells. On portal-venous and transitional phase, solid liver metastases present isointense signal while abscess shows hypointense signal.

To date, only one study evaluated the importance of Gd-EOB-DTPA in distinguishing between hepatic microabscesses and metastasis: Choi *et al*^[72], by enrolling 72 patients, demonstrated that perilesional edema and arterial rim enhancement maintained during the following dynamic sequences. Also the size discrepancy between T1-weighted and T2-weighted images and between T1-weighted and HBP images, allow obtaining a high diagnostic accuracy for microabscess (90.9%).

Infection-Echinococcus granulosus

Different tapeworms belonging to the echinococcus genus can infect humans, both as the intermediate or definitive host. The two most important types of disease are cystic echinococcosis and alveolar echinococcosis, caused by *Echinococcus granulosus* (*E. granulosus*) and *Echinococcus multilocularis* respectively.

This subsection will focus on *E. granulosus* considering its higher incidence and global distribution in all countries except Antarctica^[73].

Sheeps or pigs are definitive host of *E. granulosus* and typically they excrete hundreds of eggs within their feces. Intermediate hosts, such as dogs, cats, or humans, can eat these eggs directly or indirectly by contaminated water, food, or soil^[74].

The tapeworm, following the blood vessels typically stops in the liver more frequently in the right lobe, where starts growing as a cystic lesion, with a growth rate from 1-2 mm to 10 mm per year.

Cysts are composed of two layers of membrane: a germinal and an outer one. The immune system responds to the cyst by forming a capsule that during years will be completely calcified^[74].

When performing MRI, it should be taken into account that cystic echinococcosis can show different imaging features according to the parasitic stage in the infected liver.

In the first stage of infection, a rounded, thin-walled cyst can be recognizable, showing inhomogeneous signal in T1-weighted images, hyperintense in T2-weighted images, with only a peripheral enhancement best seen on the portal-venous or delayed phases. During the cystic growth, it can be possible to catch the typical echinococcosis cyst features, appreciable in about 75% of cases: The daughter cysts within the main cyst may produce a honeycomb-like structure with typical thin peripheral capsule, hypointense both in T1-weighted and T2-weighted images. When the daughter cysts grow up, the pressure inside the whole cyst can lead to their collapse or the rupture into the biliary tree or a peritoneal seeding: Under this circumstance, the internal appearance may vary according to the number of cystic debris, especially on T2-weighted images (Figure 14). Finally, the dead cyst is composed of a solid matrix, due to the immune response manifesting with the peripheral calcified layer, from partial to complete, that can be seen in about 50% of cases^[75].

Inflammatory disorder of the liver-pseudotumor

Hepatic inflammatory pseudotumor, even if rare, has an unknown etiology and can manifest itself as a consequence of different immune responses, such as infective agents, including viruses (firstly Epstein-Barr virus), bacteria and fungi (nocardia and actinomycosis), primary and secondary liver tumors including hepatic lymphoma^[76], and as the hepatic manifestation of immunologic disease, firstly IgG4-related disease^[77], inflammatory bowel disease^[78], and, finally, a response to a foreign body^[79].

Hepatic pseudotumor can present as single or multiple lesions with a wide range of distribution, including liver parenchyma, peri-portal spaces, and peri-biliary ducts. On unenhanced MRI it can show hypointensity signal on T1-weighted images, without any signal drop-off during in-phase/out-of-phase imaging, while variable signal intensity on T2-weighted images strictly linked to the presence of acute edema or, if chronic, fibrosis can be present. In line with T2 signal, pseudotumor can show areas of signal restriction on DWI, typically peripheral, due to the high cellularity of inflammatory cells.

Considering the mixed content within the lesion, during dynamic sequences the enhancement can be different. It can mimic a CCC with a peripheral enhancement during the arterial phase with a delayed central-filling, in case of diffuse fibrotic components; a heterogeneous enhancement can be easily identified in case of acute or subacute findings, while in case of chronic lesion variable enhancement can be present. Sometimes it can also show internal septa with a delayed enhancement. On HBP imaging, pseudotumor typically manifests as hypointense lesion due to the small number of functioning hepatocytes, surrounded by fibro-inflammatory components. The abovementioned features were confirmed by a recent study published by Ichikawa *et al*^[80], in which a typical appearance of pseudotumor was demonstrated, a central hypointense signal with a relatively peripheral hyperintensity on HBP, helping the differential diagnosis with colorectal liver metastasis.

Inflammatory disorder of the liver-sarcoidosis

Even if typically considered a thoracic disease, sarcoidosis can involve all human organs, with an estimated 50% of patients with extra-thoracic manifestation^[81]. Based on the underlying pathophysiology, it can manifest as hepatomegaly with possible jaundice and with manifestations of portal hypertension, even if not commonly reported. Thus, liver MRI should be performed to exclude the presence of focal liver lesions. In patient with sarcoidosis the typical changes due to liver fibrosis were the most common findings, underling that only 25% of patients showed a normal liver morphology with no radiological signs of portal hypertension. In this setting focal hepatic and splenic nodules were seen in about 25% of subjects at presentation, demonstrating coalescing granulomas sometimes confluent and mimicking malignancy^[82]. The sarcoidosis nodules are usually hypointense on T1-weighted images, without any changes on in-phase/out-of-phase imaging, while a variable signal on T2-weighted images can be seen, ranging from hypo to hyperintensity, strictly linked to the amount of edema both intra- and peri-lesional. During enhanced sequences, these lesions may show a slight and peripheral enhancement on the arterial phase while

during the next sequences, including the HPB, the lesions show hypointense signal (Figure 15). Sometimes the sarcoidosis can manifest exclusively with chronic liver failure.

CONCLUSION

Liver lesions are common findings in radiologists' daily routine. They are a complex category of pathology that ranges from solitary benign lesions to primary liver cancer and liver metastases. Liver MRI is a fundamental radiological method in these patients as it allows with its multiparametric approach an optimal non-invasive tissue characterization. Liver MRI can be used to differentiate between pseudotumors and tumors, ²³ as well as benign and malignant lesions, and it can also be utilized for differential diagnosis. Although histological examination can be useful in making a definitive diagnosis, liver MRI is an important modality in the diagnosis of liver lesions with a significant impact on patient care.

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