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SSAT/AHPBA Joint Symposium on Evaluation and Treatment of Benign Liver Lesions

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Abstract

Background—Benign liver lesions are common incidental radiologic findings.

Methods—Experts convened in 2011 at a Society for Surgery of the Alimentary Tract/ Americas Hepato-Pancreato-Biliary Association joint symposium to discuss the evaluation and treatment of benign liver lesions.

Results—Most benign liver lesions can be accurately diagnosed with high-quality imaging, including ultrasonography, multiphase computed tomography, and magnetic resonance imaging, particularly with hepatocyte-specific contrast agents. Percutaneous biopsy is reserved for lesions that cannot be characterized radiographically, and its accuracy is improved with immunophenotypic markers. Hepatic cysts are the most commonly diagnosed benign liver lesions; these must be distinguished from malignant cystic lesions, which are rare. Among the solid benign liver lesions, hemangiomas and focal nodular hyperplasia seldom require treatment. In contrast, hepatocellular adenomas are associated with a risk for complications. A new classification system for hepatocellular adenomas based on genetic and phenotypic features can help guide patient care. In patients who are symptomatic or at risk for complications, multidisciplinary evaluation and treatment based on clinicopathologic, radiographic, and molecular analysis is needed.

Conclusions—Most benign liver lesions can be accurately diagnosed radiographically and do not require treatment. Treatment is necessary for patients with symptoms or at risk for complications.

Keywords

Liver; cyst; hemangioma; adenoma; focal nodular hyperplasia

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Introduction

To treat or not to treat benign liver lesions is an important clinical issue because some can be life-threatening whereas most are not. The risk-benefit ratio for treatment must be evaluated for each patient on the basis of radiologic, biologic, and clinical characteristics. In 2011, the Society for Surgery of the Alimentary Tract and the Americas Hepato-Pancreato-Biliary Association held a joint symposium at which experts addressed the evaluation and treatment of benign liver lesions. Harmeet Kaur, MD, and Evelyne Loyer, MD, of the Department of Diagnostic Radiology at MD Anderson Cancer Center discuss advances in imaging of benign liver lesions. Valérie Paradis, MD, of the Hôpital Beaujon in Clichy, France, discusses the pathology and biology of hepatocellular adenoma (HCA). Michael G. House, MD, of the Indiana University School of Medicine discusses the treatment of complex cysts, polycystic liver disease, Caroli's disease, and cystadenoma. Finally, Yun Shin Chun, MD, of Fox Chase Cancer Center provides a concise but thorough review of treatment recommendations for patients with focal nodular hyperplasia (FNH), adenomas or adenomatosis, and hemangiomas.

Imaging of Benign Liver Lesions

This discussion will focus on the more commonly encountered benign liver lesions, including cysts, hemangiomas, FNH, nodular regenerative hyperplasia (NRH), biliary hamartomas, and HCAs. The imaging arsenal at our disposal in the evaluation of liver lesions includes multiphase computed tomography (CT); magnetic resonance imaging (MRI) with liver-specific contrast agents; ultrasonography, particularly contrast-enhanced ultrasonography (CEUS); and nuclear medicine studies such as sulfur colloid imaging, positron emission tomography-CT, and tagged red blood cell scan. The primary focus of this discussion will be cross-sectional CT and MRI.

A diagnostic algorithm for liver lesions begins with their characterization as homogeneously or heterogeneously hypervascular, hypovascular, or cystic.[1] The list of conditions to be considered in the differential diagnosis can be narrowed by incorporating additional data such as signal characteristics on MRI, patterns of delayed enhancement, and secondary imaging findings, including the presence of fat, central scars, calcification, and hemorrhage.

Benign hypervascular lesions of the liver

Hypervascularity relative to the liver is seen on the arterial phase images obtained after administration of a contrast agent and reflects higher arterial flow to the lesion than to the normal surrounding liver parenchyma. Common hypervascular lesions are hemangioma, FNH, HCA, and, in the cirrhotic liver, regenerating and dysplastic nodules and transient hepatic intensity difference.[2]

While patterns of enhancement on postcontrast CT and MRI play a vital role in lesion assessment, precontrast images can also be helpful in the differential diagnosis and are frequently underutilized. For instance, hemangiomas, the most common benign liver neoplasm, are composed of dilated vascular spaces lined by endothelium and are consequently sharply circumscribed and hypodense on precontrast images. HCAs containing intralesional fat are hypodense on CT and hyperdense on T1-weighted MRI. HCAs with necrosis or hemorrhage may be heterogeneous on precontrast imaging. In contrast, FNH, transient perfusion defects, NRH, and regenerating and dysplastic nodules generally have a density similar to that of normal liver.

Dynamic postcontrast imaging that incorporates arterial (30 seconds), portovenous (60 seconds), equilibrium (90 seconds), and delayed (3–6 minutes) phases plays a key role in determining the diagnosis. Lesions are characterized according to the initial arterial phase pattern of enhancement and the subsequent behavior of the lesion relative to normal liver. A decline in density of hypervascular lesions relative to normal liver parenchyma in the portovenous and equilibrium phases implies a loss of portal blood supply and possible malignant transformation. For this reason, most benign hypervascular lesions are isodense or faintly hypodense relative to surrounding normal liver on delayed scans. An exception to this is HCAs, which may appear to have lower density than normal liver on delayed imaging.

Hemangioma—Some hypervascular lesions display unique diagnostic features during the arterial phase. For example, hemangiomas classically display nodular peripheral enhancement with a density approaching that of adjacent vessels and retain contrast agent on the subsequent equilibrium phase (Fig. 1). Variants of this classic appearance include capillary hemangiomas, which exhibit uniform enhancement on the arterial phase (flash fill); hemangiomas that appear isodense to liver on the equilibrium phase; and the not uncommon small hemangiomas that appear hypodense on arterial phase as scanning is too rapid relative to the vascular flow within the lesion. These appearances present a diagnostic challenge, which may be resolved by the incorporation of heavily T2-weighted (echo time, 140 msec) MRI, which, combined with the enhancement pattern, has a specificity of 95% in the diagnosis of hemangiomas.[3]

FNH and NRH—After hemangioma, FNH, which represents a hyperplastic response to an arteriovenous malformation, is the most common benign hypervascular lesion. It most commonly presents in young women (male-to-female ratio of 1:8) as a lobular mass with homogeneous arterial enhancement, radiating fibrous septa, and a central, nonenhancing scar. On the equilibrium phase, FNH is isointense to surrounding liver with enhancement of the central scar. This typical pattern of enhancement (Fig. 2) combined with a T2 hyperintense scar permits the radiologist to make a diagnosis with confidence. However, atypical features, such as absence of a central scar, presence of intralesional fat, pseudocapsule, or washout on delayed imaging, are indications for MRI with liver-specific contrast agents. These agents include gadoxetic acid (Eovist) and gadobenate dimeglumine (MultiHance), which are taken up by hepatocytes after an initial extracellular phase. On the hepatocyte phase of imaging with these agents, enhancement occurs because of contrast agent uptake by membrane-bound carriers (organic anion transporting peptide) on functioning hepatocytes. It has been reported that 96% of cases of FNH are either isointense or hyperintense to surrounding liver on imaging with hepatocyte-specific agents (Fig. 2).[4] Superparamagnetic iron oxide particles are taken up by Kupffer cells but are currently not available in the United States. An alternative approach is to use CEUS, which allows real-time assessment of patterns of blood flow within liver masses.

Like FNH, NRH represents a hyperplastic response to a vascular disorder. NRH is an uncommon condition associated with Budd-Chiari syndrome and also occurs with myelolymphoproliferative disorders, in which vascular abnormalities lead to regenerative hepatocellular nodules measuring 0.1 cm to 4 cm in diameter without intervening fibrous septa. As would be expected because of their histologic structure, these nodules are generally of density similar to that of normal liver on T2- and T1-weighted MRI scans. Occasionally, the nodules are hyperintense on T1-weighted scans. On contrast-enhanced scans, NRH is hypervascular on the arterial phase and iso- to hypodense in the equilibrium phase. On delayed hepatobiliary phase MRI with hepatocyte-specific contrast agents, NRH and FNH are hyperintense or isointense to surrounding liver (Fig. 3). In contrast, malignant

lesions lacking functional hepatocytes are typically hypointense to surrounding liver on hepatobiliary phase.

Regenerating and dysplastic nodules in cirrhotic liver—The regenerating and dysplastic nodules of cirrhosis have a pattern of enhancement similar to that of FNH and NRH on T1- and T2-weighted images. These nodules retain portal flow and are consequently isodense to surrounding liver on delayed images. Dysplastic nodules may develop hypervascularity compared to normal liver, reflecting early malignant change; however, washout on delayed scans remains uncommon. Transient perfusion abnormalities occurring in a background of normal liver are typically wedge-shaped, hypervascular foci. When the diagnosis is uncertain, hepatocyte-specific contrast agents are useful, as transient perfusion abnormalities typically appear isointense to the surrounding liver in the hepatocyte phase.

Hepatocellular adenomas—HCAs are uncommon, generally solitary, hypervascular tumors related to oral contraceptive or anabolic steroid use and also occur in patients with glycogen storage disease. These masses almost always are encapsulated, contain macroscopic or intracellular fat (Fig. 4 a, b), and have a propensity for infarct and hemorrhage. The presence of fat is valuable in distinguishing HCA from FNH. Hepatocyte-specific contrast agents are also useful because HCAs are composed of hepatocytes of decreased function that do not accumulate hepatocyte-specific contrast agent and therefore rarely retain contrast agent on the hepatocyte phase (Fig. 4 c, d).[4] An alternative problem-solving approach is CEUS, which shows centripetal enhancement during arterial phase for HCA and a centrifugal filling pattern for FNH.

Benign hypovascular lesions of the liver

Benign hypovascular liver lesions include biliary hamartomas, which may also appear as cystic lesions, and focal fatty change. While biliary hamartomas are difficult to diagnose, focal fatty infiltration can easily be confirmed in difficult cases by in-phase and out-of-phase MRI and also by characteristic sites of location and shape around the porta hepatis, falciform ligament, and gallbladder fossa. The development of focal fatty infiltration and sparing is related to aberrant blood supply and venous drainage.

Cystic lesions in the liver may represent simple cysts, which are seen in 5% of the population and are thought to arise from congenitally aberrant bile ducts that do not communicate with the biliary tree and become obstructed and dilated. They have a density equivalent to that of water and an imperceptible wall. Cysts seen in polycystic liver disease have a similar appearance. Additional cystic masses include the rare biliary cystadenoma or cystadenocarcinoma, which classically presents as cystic masses with areas of nodularity or thickened wall, and parasitic cysts, such as hydatid cyst.[1] In the evaluation of cystic masses, ultrasonography frequently provides a superior definition of the intralesional characteristics, such as septations or nodules, definition of the cyst wall, or, in the case of hydatid cyst, the presence of daughter cysts. The simple cyst with hemorrhage, however, remains a diagnostic challenge.

Summary of imaging for evaluation of liver lesions

In summary, hypervascular liver lesions may be characterized on multiphase CT or MRI. When findings on CT or MRI are indeterminate, hepatocyte-specific contrast agents or CEUS may be used to problem-solve or increase diagnostic confidence. Cystic lesions of the liver have significant overlap in imaging appearance, and ultrasonography or MRI is superior to CT in the definition of internal characteristics that may assist in diagnosis of cystic lesions.

Pathology and Molecular Biology of Benign Liver Lesions

In the vast majority of cases, benign hepatocellular lesions arise in women without underlying chronic liver disease. Benign liver lesions include 2 main different entities according to their pathogenesis: FNH and HCA. Recent findings regarding the molecular mechanisms underlying the pathogenesis of each lesion (i.e., polyclonal disorders for FNH and monoclonal proliferations for HCA) not only may contribute to accurate diagnosis of these lesions but also indicate their potential clinical behavior and can help guide appropriate management.[5] In recent years, especially thanks to combined genotypic and phenotypic molecular approaches, significant advances have been made in the characterization of HCA, which has been revealed to have great heterogeneity with respect to morphologic, phenotypic, and evolutive features. Therefore, diagnosis of benign hepatocellular tumors requires a multidisciplinary approach based on clinical, imaging, and pathomolecular analysis.

Focal nodular hyperplasia

FNH, the second most common benign liver process, is considered a hyperplastic reaction resulting from an arterial malformation. FNH is a tumor-like condition predominantly diagnosed in women between 30 and 50 years of age; the incidence of FNH is not influenced by use of oral contraceptives. The vast majority of cases of FNH are asymptomatic and discovered incidentally during liver ultrasound examination. Complications of FNH, such as rupture or bleeding, are rare, and no evidence of malignant transformation of FNH has been reported to date.

In its typical form, FNH is a well-circumscribed, unencapsulated, usually solitary mass with a central fibrous scar. Histologically, FNH is composed of benign-appearing hepatocytes arranged in nodules that are partly or completely delineated by fibrous septa originating from the central scar. In the fibrous septa, large and dystrophic vessels are observed, associated with ductular proliferation and inflammatory cells in varied intensity. Besides this typical form of FNH, several variant lesions are described with increased frequency, including FNH without a central fibrous scar and FNH with prominent steatosis.

Given that FNH is a regenerative lesion rarely associated with complications, no treatment for asymptomatic FNH is required, regardless of the size or number of nodules, when the diagnosis is firmly established.

Hepatocellular adenoma: a heterogeneous entity

HCA is a rare, benign liver neoplasm strongly associated with oral contraceptive use and androgen therapy. HCAs are usually solitary and well delineated, are sometimes encapsulated, and consist of a proliferation of benign hepatocytes arranged in a trabecular pattern associated with small, thin, unpaired vessels. Heterogeneous areas of necrosis and/or hemorrhage may be observed, most commonly in large tumors. Compared to patients with FNH, patients with HCA are more likely to present with symptoms, including spontaneous bleeding and hemorrhage, especially if they have large tumors. The risk of malignant transformation of HCA is low overall but higher for males, lesions larger than 5 cm in diameter, and HCAs in patients with metabolic syndrome (Table 1).[6–8] Thus, surgical resection is required for HCAs larger than 5 cm in diameter and all HCAs in males, regardless of lesion size.

Comprehensive molecular studies have demonstrated great heterogeneity among HCAs and have led to the description of 3 main subtypes: hepatocyte nuclear factor 1 α (HNF1 α)-mutated, steatotic; telangiectatic/inflammatory; and β -catenin-mutated.[7, 9] The β -catenin-mutated subtype is most often observed in men and is associated with a higher risk of

malignant transformation.[6, 7] Finally, a small group of HCAs displays no specific morphologic or genotypic features and are referred to as “unclassified”. Interestingly, telangiectatic/inflammatory HCAs are reported commonly in patients with increased body mass index and are associated with inflammatory syndrome, and about 60% of HCAs of this subtype display activation of the interleukin-6 signaling pathway related to mutations in the *IL6ST* gene. In surgical series of HCA, the steatotic and telangiectatic/inflammatory subtypes together account for 85% of all HCAs, whereas the β -catenin-mutated subtype accounts for 10% to 15% of HCAs. Importantly, surrogate immunophenotypic markers related to genetic abnormalities may be used in the classification of HCA subtypes.[9] These include absence of staining for liver fatty acid binding protein in HNF1 α -mutated HCA, acute-phase inflammatory proteins such as serum amyloid A and C-reactive protein in telangiectatic/inflammatory HCA, and aberrant β -catenin nuclear staining in β -catenin-mutated HCA.[6] Although significant advances have been made in the subtyping of HCA, some tumors remain challenging to classify and may be difficult to differentiate from well-differentiated hepatocellular carcinoma, necessitating use of additional immunophenotypic markers such as Glypican-3.

Role of biopsy in the management of benign hepatocellular nodules

Improvements in imaging have enabled accurate diagnosis of hepatocellular nodules on the basis of imaging studies, and thus biopsy of hepatocellular nodules is restricted to specific situations. Biopsy may be needed to distinguish atypical cases of FNH, especially those without central fibrous scar or with prominent steatosis, from HCA, and diagnostic accuracy in such cases may be improved with immunophenotypic markers. HCA subtypes can be accurately diagnosed with MRI and/or biopsy. Immunohistochemical staining can increase the accuracy of biopsy, particularly for β -catenin-mutated HCA and steatotic lesions.[8]

Treatment of Cystic Lesions

Simple cysts

Liver cysts are present in approximately 5% of adults, and most measure less than 3 cm in greatest diameter. The majority of liver cysts are detected incidentally during sonographic or tomographic imaging of the abdomen. The prevalence of liver cysts is higher in women than in men, especially in the sixth decade of life, when cysts may enlarge.

Simple cysts are unilocular and do not contain septa; however, discriminating a simple cyst from more complex and even neoplastic cysts can be challenging when simple cysts cluster or undergo radiographic or sonographic transformation after intracystic bleeding. Once the diagnosis of simple cyst has been established, routine surveillance is not required as these cysts typically demonstrate no appreciable changes over decades. Even when they are large, congenital simple cysts are typically asymptomatic unless they are complicated by intracystic hemorrhage or cause compression of intrahepatic structures, e.g., bile ducts or portal or hepatic veins. Intracystic bleeding can be associated with acute onset of severe pain that can last for several days. The optimal treatment for symptomatic cysts is laparoscopic deroofting with or without ablation of the cyst lining. Morbidity after laparoscopic fenestration is rare, and symptomatic recurrences appear in fewer than 5% of patients.[9]

Polycystic liver disease

Recent findings have improved understanding of the natural history of renal and hepatic cysts in individuals with autosomal dominant polycystic kidney disease (ADPKD) and have shown that medical therapies can alter the progression of such cysts.[10] Polycystin mutations in polycystic liver disease associated with ADPKD have been well characterized. Alterations in polycystin affect the microcilia and secretory properties of cholangiocyte

epithelium and lead to cyst expansion. Somatostatin analogues decrease cyst fluid volume by reducing cyst fluid cyclic AMP.[11] Estrogen receptor overexpression and insulin-like growth factor-1 receptor overexpression are associated with cyst epithelial proliferation; thus, blockade of these receptors could slow disease progression. Disruptions of the mammalian target of rapamycin pathway are also responsible for epithelial proliferation and cyst expansion. Inhibitors of this pathway, such as sirolimus, have resulted in decreased liver volume when deployed for immunosuppression after renal transplantation.[12]

Most individuals with polycystic liver disease are asymptomatic and have preservation of hepatic function. However, some have massive hepatomegaly that can lead to pain, dyspnea, malnutrition, declining functional performance, and poor overall quality of life.[13] Symptomatic patients with polycystic liver disease should be considered for prompt medical therapy and evaluated for surgical intervention. A few classification systems have been developed over the years to select patients with polycystic liver disease for appropriate surgical treatments. Recently, Schnelltdorfer *et al*/proposed a classification system that takes into account not only the number and distribution of cysts but also the volume of liver parenchyma that would be left behind after operative intervention.[14] Individuals with a small number of large, superficial cysts can be treated with laparoscopic cyst fenestration. When at least 1 liver sector can be preserved with normal inflow, outflow, and biliary drainage, partial hepatectomy with cyst fenestration of the liver remnant can produce good results. Combined renal and liver transplantation is reserved for patients in whom no liver sector can be preserved and who have severe symptoms and declining performance status.

Caroli's disease

Type V bile duct cysts of the liver are rare, with an estimated incidence of 1 case per million, and show an autosomal recessive pattern of inheritance. Caroli's disease is characterized by segmental dilatations of the major intrahepatic bile ducts resulting from ductal plate malformations during fetal development. Linkage studies have shown associations between Caroli's disease and deletions of chromosome arms 3p and 8q, autosomal recessive polycystic kidney disease, and medullary sponge kidney.

Cross-sectional imaging with either contrast-enhanced CT or MRI will provide a diagnosis in most cases. The classic central dot radiographic sign results from the vascular pedicle within peripheral portal triads involving dilated segments of minor bile ducts. Several complications are associated with Caroli's disease, including cholangitis, hepatolithiasis, hepatic abscess, and cholangiocarcinoma.[15] Long-standing cholestasis often leads to biliary cirrhosis, hepatic fibrosis, and subsequent portal hypertension.

Operative resection is the best option for individuals with unilateral disease, most of whom have disease affecting the left hemiliver.[16] Bilateral disease is more difficult to manage. Initially, an attempt can be made to clear the hepatolithiasis burden with endoscopic and/or percutaneous lithectomy, but these techniques often fail as the disease progresses. Hepaticojejunostomy with hepatodochoscopy and lithectomy, with or without partial hepatectomy, can be utilized for patients without evidence of extensive hepatic fibrosis. While some institutions have advocated early liver transplantation for patients with Caroli's disease, this option is typically reserved for patients with severe hepatic fibrosis, portal hypertension, and often end-stage renal disease.

Hepatobiliary cystic neoplasms

Intrahepatic biliary cystic lesions represent only 5% of liver cysts but often generate much clinical interest. Unusual cystic lesions of the liver include cystic variants of intrahepatic cholangiocarcinoma, biliary cystadenocarcinoma, and cystic transformation of secondary

liver tumors, e.g., neuroendocrine tumors and mucinous colorectal adenocarcinoma. The 2 most common primary cystic lesions of the intrahepatic bile ducts are biliary cystadenoma, characterized by ovarian stroma, female predilection, and segment IV location, and biliary-type intraductal papillary mucinous neoplasm, characterized by bile duct communication and close resemblance to its pancreatic counterpart. These tumors are typically discovered incidentally during cross-sectional imaging of the abdomen for unrelated indications. When biliary cysts are detected because of symptoms—e.g., abdominal protuberance, dyspnea, or rarely, cholangitis due to biliary mucinosis—they are usually larger than 8 cm in diameter.

Correctly diagnosing cystic neoplasms can be challenging. Liver ultrasonography remains the most useful modality for characterizing liver cysts. Ultrasonography and MRI show multiloculation for almost all cystic neoplasms. Thickened septa, mural nodularity, and intracystic papillary projections are also hallmarks of cystic neoplasms and might indicate malignant transformation. Cyst aspiration with cytologic examination of the aspirate and analysis of CA 19-9 and CEA levels in cyst fluid cannot be used to discriminate cystic lesions from simple cysts.[17]

For noninvasive cystic neoplasms, complete cyst enucleation is favored over fenestration and ablation of the cyst lining. For malignant cysts and biliary-type intraductal papillary mucinous neoplasms, which often recur after enucleation, formal resection with partial hepatectomy should be performed.

Treatment of Hemangioma, FNH, and HCA

A review of recent surgical series on benign liver lesions indicates that most patients with such lesions do not require surgical resection. High-quality cross-sectional imaging is crucial for accurate diagnosis, as discussed earlier in this article. The most common indications for resection of hemangioma and FNH are pain and inability to exclude malignancy. Indications for resection of HCA include lesion size greater than 5 cm in diameter and male gender. HCA is associated with a significant risk of complications, including hemorrhage, rupture, and malignant transformation. Men represent a minority of patients with HCAs, but their risk of malignancy is 47%.[18]

Hemangioma

Hemangioma is the most common benign solid tumor of the liver and represents a congenital vascular malformation. Hemangioma has a female preponderance, with a 5:1 female-to-male ratio.[19] The etiology of hemangioma is unknown, although some hemangiomas have estrogen receptors. The overwhelming majority of patients with hemangiomas should not undergo surgery. Indications for resection are symptoms, inability to exclude malignancy, and complications. Symptoms most often occur with giant hemangiomas (> 6 cm in diameter) and include pain, early satiety, and abdominal distention or mass. Complications, including thrombosis and hemorrhage or rupture, are extremely rare. Kasabach-Merritt syndrome has been reported in up to 3.8% of patients and is caused by trapping of platelets within the hemangioma, leading to activation of the clotting cascade and resultant thrombocytopenia and systemic fibrinolysis.

Radiographic surveillance for asymptomatic hemangiomas is not justified. A series from the Mayo Clinic retrospectively analyzed 289 patients with hemangiomas larger than 4 cm with a mean follow-up time of 11 years.[20] Among the 233 patients (81%) who did not undergo surgery, only 14 patients required intervention during the follow-up period, including resection or enucleation in 11 patients, embolization in 2 patients, and liver transplantation in 1 patient with hemangiomatosis. Eight patients suffered major abdominal trauma without hemangioma rupture.

For patients who require surgery, enucleation is feasible because hemangiomas are surrounded by a sheath of compressed tissue that can be used as a plane of excision to avoid resection of normal liver parenchyma and potential injury to biliary and vascular structures. [21] A retrospective analysis comparing enucleation to lobectomy for hemangiomas showed a significantly lower rate of perioperative complications with enucleation.[22]

Focal nodular hyperplasia

FNH is a hyperplastic response to an arterial malformation and not a true neoplasm. It is most commonly diagnosed in women 30 to 50 years of age and is multiple in 20% to 30% of patients. Concurrent adenomas are diagnosed in 3.6% of patients and concurrent hemangiomas in up to 23% of patients with FNH. The diagnostic hallmark of FNH is a central scar, which can be detected radiographically in 44% of cases. FNH should be distinguished from fibrolamellar carcinoma, which also displays a central scar. Most cases of FNH are less than 5 cm in diameter, with homogeneous enhancement, rare calcifications, no lymphadenopathy, and the central scar on T2-weighted MRI is hyperintense. In contrast, fibrolamellar carcinomas are large, usually more than 10 cm, with heterogeneous enhancement. Up to two-thirds of fibrolamellar carcinomas have calcifications and nodal metastases, particularly in the portal hepatitis, and the central scar is hypointense on T2-weighted MRI.[23]

Although FNH is most commonly diagnosed in young and middle-aged women, FNH is not associated with oral contraceptive use or pregnancy. Patients with FNH rarely require surgery. The most common indication for resection is pain, which typically does not occur until FNH is larger than 7 cm in diameter. Surveillance is not necessary because lesions may regress, the risk of complications is low, and there is no risk of malignancy.

Hepatocellular adenoma

HCAs are rare, benign, monoclonal lesions occurring most often in women with a history of oral contraceptive use. The risk of developing an adenoma increases with the estrogen content and duration of oral contraceptive use. HCAs are also associated with pregnancy, androgen use, glycogen storage disease, and maturity-onset diabetes of the young. Adenomatosis is the presence of more than 10 adenomas and was originally described in patients without risk factors such as oral contraceptive use or glycogen storage disease. HCAs carry a significant risk of complications, including hemorrhage, rupture, and malignant transformation. Poor connective tissue support and high arterial pressure predispose adenomas to rupture and hemorrhage, which occur in 20% to 40% of patients. Risk factors for rupture and hemorrhage include oral contraceptive use, pregnancy, and lesion size greater than 5 cm. Malignant transformation has been reported in up to 10% of patients and is associated with male gender, lesion size greater than 5 cm, androgen use, and β -catenin gene mutations.[18]

As described earlier in this article, HCAs can be classified into 3 subtypes on the basis of their genotypic and phenotypic features. Inflammatory adenomas are the most common subtype and were previously misclassified as telangiectatic FNH.[24] Sixty percent of inflammatory HCAs harbor somatic mutations in the *IL6ST* gene, which cause ligand-independent activation of the interleukin-6 pathway and its downstream effectors, resulting in inflammatory signaling and hepatocyte proliferation.[25] Steatotic adenomas are the second most common subtype and arise from inactivating mutations in the *TCF1* gene, which encodes HNF1 α , a transcription factor involved in hepatocyte differentiation.[6] Inactivation of HNF1 α is associated with increased lipogenesis.[26] Steatotic adenomas lack cytologic abnormalities or inflammatory infiltrates, seldom occur in men, and are associated with adenomatosis and maturity-onset diabetes of the young. The third subtype, accounting

for 10% of HCAs, carries activating mutations in the *CTNNB1* gene, which encodes β -catenin, leading to induction of the Wnt pathway, which is implicated in hepatocarcinogenesis.[6] B-catenin-mutated adenomas occur more commonly in men than other subtypes and are associated with frequent malignant transformation to hepatocellular carcinoma. Adenomas that cannot be molecularly classified comprise less than 10% of HCAs. Occasionally, 2 subtypes co-exist: 10% of inflammatory HCAs harbor β -catenin mutations.

The risk of complications with adenomas depends on their molecular subtype, as shown in a study from the Hôpital Beaujon of 122 patients who underwent surgery for single and multiple HCAs.[7] Among 35 patients with steatotic adenomas, 8.6% had macroscopic hemorrhage, and none exhibited malignant transformation. In contrast, among 66 patients with inflammatory adenomas, 30.3% had hemorrhage, and 10.6% had malignant transformation. In another report from Hôpital Beaujon, of 23 patients whose adenomas had undergone malignant transformation, two-thirds of the transformed adenomas had activating β -catenin mutations.[18] Steatotic and inflammatory adenomas can be accurately diagnosed on MRI to help guide patient management.[8, 27] Steatotic adenomas display diffuse signal dropout on T1-weighted chemical shift sequence, indicating intracellular fat. They are moderately enhancing in the arterial phase without persistent enhancement in the portal venous and delayed phases. In contrast, inflammatory adenomas demonstrate strong arterial enhancement, with persistent enhancement in portal venous and delayed phases; high-intensity signal on T2-weighted MRI, correlating with sinusoidal dilatation; and lack of signal dropout on fat suppression images.

Guidelines for surgical management of HCAs include (1) resection of all adenomas in men, regardless of lesion size, given their risk of malignant transformation, (2) resection of adenomas associated with symptoms or hemorrhage, (3) observation off oral contraceptives for adenomas $\leq$ 5 cm in women, and (4) resection of adenomas $>$ 5 cm in women (Figure 5). Adenomas that have ruptured should be treated with hepatic arterial embolization, and oral contraceptives should be discontinued. Surgery can be delayed and enucleation can be used for resection if malignant transformation is not a consideration. Immediate resection of ruptured adenomas is associated with a mortality rate of 8%.[7] The number of adenomas does not increase the risk of malignancy or hemorrhage; therefore, the management of adenomatosis mirrors that of solitary adenomas. Liver transplantation is reserved for the rare patient with symptomatic adenomatosis who cannot undergo resection or ablation. In asymptomatic patients with adenomatosis, large, bilateral adenomas may not be resectable, and close observation after discontinuation of oral contraceptives should be considered.

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Figure 1.

Axial T2 and postcontrast arterial, portovenous phase, and delayed images show a lesion in the left lobe consistent with hemangioma. Lesion is hyperintense on T2-weighted images (a) with nodular enhancement (b) and density similar to that of adjacent vessels that partially fills in during the portovenous phase (c) and completely fills in and retains contrast agent on the delayed 5 minute scan (d).

Figure 2. Axial T2- and T1-weighted arterial phase and delayed 20-minute gadoxetic acid scans show a large, homogeneously enhancing lesion in the posterior portion of the right liver (a) consistent with focal nodular hyperplasia. It retains contrast agent on the hepatocyte (20 min) scan, reflecting the presence of normal hepatocytes, and has a subtle scar (b) that is only faintly visible on the T2-weighted scans (c).

Figure 3.

Axial T1 pre- and postcontrast arterial and 20-minute gadoxetic acid scans in a patient with chronic myeloid leukemia show nodules that are hyperintense on the precontrast image (a). The nodules do not show arterial enhancement on the arterial phase subtraction images (b). The delayed 20-minute hepatocellular phase image shows uptake of contrast agent (c), consistent with nodular regenerative hyperplasia.

Figure 4.

Axial in-and-out phase images show a pedunculated mass arising from the left lobe with fat suppression (a), reflecting intralesional fat that appears hyperintense on the in-phase T1-weighted image (b). The arterial phase T1-weighted image shows no enhancement (c). The 20-minute scan shows no uptake of gadoxetic acid (d), reflecting hepatocytes that lack organic anion transporting peptide receptors, consistent with hepatocellular adenoma.

Figure 5.
Proposed clinical management for hepatocellular adenomas.

Table 1

Risk factors for complications in patients with hepatocellular adenoma[6–8]

Risk factor	Complication	
	Hemorrhage (20%–30%)	Malignant transformation (4%–8%)
Male gender	No	Yes
Size	> 5 cm	> 5 cm
Molecular subtype	Telangiectatic/inflammatory	B-catenin activated
		Telangiectatic/inflammatory
Clinical history	Recent use of oral contraceptives	Metabolic syndrome
	Biopsy	
Number	No	No