

The Diagnosis and Management of Benign Hepatic Tumors

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Abstract: Benign hepatic tumors include a broad spectrum of regenerative and true neoplastic processes. Because of advances in imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) as well as progress in immunohistochemistry, accurate diagnosis can now be made in a large percentage of patients without surgical laparotomy or resection. This article will focus on the pathogenesis, diagnosis, and management of focal benign lesions of the liver. Many of these tumors present with typical features in various imaging studies. On occasions, biopsies are required and/or surgical removal is needed. The most common benign hepatic tumors include cavernous hemangioma, focal nodular hyperplasia, hepatic adenoma, and nodular regenerative hyperplasia. In the majority of cases of benign hepatic tumors, patients are asymptomatic, and no treatment is indicated. The main indication for treatment is the presence of significant clinical symptoms or suspicion of malignancy or fear of malignant transformation.

Key Words: liver, benign tumor, diagnosis, review

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Benign hepatic tumors are increasingly reported with the widespread use of sensitive imaging studies and occasionally present significant diagnostic and therapeutic challenges. They usually occur in asymptomatic patients with or without underlying liver disease. Using simple imaging techniques such as ultrasound (US), benign hepatic tumors can be categorized as solitary or multiple and as solid or cystic as shown in Table 1.¹⁻³ In general, a single imaging study is insufficient for a definitive diagnosis, and further studies may be necessary. Most benign hepatic tumors follow a fairly indolent clinical course. However, some of them are associated with serious complications. Thus, the understanding of clinical, radiologic, and pathologic characteristics of each tumor is important for accurate diagnosis and appropriate treatment of these tumors. This article will review several benign hepatic tumors that are commonly encountered in adults. We will categorize them as solid or cystic tumors and describe key differential diagnostic criteria for each tumor. We will also propose a stepwise approach for diagnosis and

treatment of asymptomatic patients with benign hepatic tumors (Fig. 1).

SOLID HEPATIC TUMORS

Hemangioma

Pathogenesis and Pathology

Hemangioma is the most common benign hepatic tumor. The pathogenesis is not well understood. Some of these tumors have estrogen receptors, and accelerated growth has been observed with high estrogen states such as those associated with puberty, pregnancy, oral contraceptive use, and with androgen treatment. These findings suggest that hormonal effect may be one of the pathogenic mechanisms.⁴⁻⁶ Growth of hemangioma is thought to be due to ectasia rather than hypertrophy or hyperplasia.⁷ According to autopsy series, the prevalence of hemangioma ranges from 3% to 20%, and most of them are seen in middle-aged women. The female-to-male ratio is 5 to 6:1.^{5,8}

Hemangiomas are usually located in the subcapsular region of the right lobe, with size ranging from less than 1 cm to more than 20 cm. Grossly, it is a well-circumscribed and compressible tumor with dark color.⁷ Microscopically, it arises from the endothelial cells that line the blood vessels and consists of multiple, large vascular channels lined by a single layer of endothelial cells and supported by collagenous walls.^{8,9} Their blood supply arises from the hepatic artery.¹

Clinical Presentation

The most common clinical presentation of hemangiomas is an incidental finding during ultrasonographic examination of the abdomen for unrelated reasons.⁵ Hemangiomas are usually less than 5 cm. Only a few patients with large tumors (>5 cm) may present with nonspecific abdominal symptoms. Intermittent symptoms can also occur when there is necrosis, infarction, or thrombosis of the tumor.⁷ Although hemangiomas can occur at any age, most of them grow very slowly and are rarely diagnosed during childhood. Major complications such as spontaneous hemorrhage are distinctively rare in even large hemangiomas.⁵ Kasaback-Merritt syndrome is a rare clinical entity with thrombocytopenia and disseminated intravascular coagulopathy associated with giant hemangioma. These patients can present with upper abdominal pain and bleeding due to progressive consumptive coagulopathy, which is often triggered by a surgical or dental procedure.¹⁰

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TABLE 1. Differential Diagnosis of Benign Hepatic Tumors

	Solitary	Multiple or Diffuse
Solid	Hemangioma	Hemangioma
	Focal nodular hyperplasia	Focal nodular hyperplasia
	Hepatic adenoma	Hepatic adenoma
	Macroregenerative nodule	Macroregenerative nodule
	Focal fatty change	Focal fatty change
	Intrahepatic bile duct adenoma	Nodular regenerative hyperplasia
	Mesenchymal hamartoma	
	Lipomatous tumor	
	Inflammatory pseudotumor	
Cystic	Simple hepatic cyst	Polycystic liver disease
	Echinococcal cyst	Echinococcal cyst
	Choledochal cyst	Von Meyenburg complexes
	Biliary cystadenoma	Peliosis hepatis
	Caroli disease	

Imaging

The majority of hemangiomas can be diagnosed accurately by imaging studies alone since hemangiomas usually have characteristic imaging features. They may be isolated or multiple as in up to 50% of patients.⁹ On US, hemangioma typically appears as a well-defined, lobulated, homogeneous hyperechoic mass, but it may also have hypoechoic portion due to hemorrhage, fibrosis, or calcification. The accuracy of US is reported to be 70% to 80%.²⁸ Contrast-enhanced harmonic US imaging demonstrates peripheral nodular enhancement in the portal phase and the absence of intratumoral vessels in the arterial phase, which is often present in hepatocellular carcinoma (HCC).^{11,12}

Hemangiomas are frequently missed on standard CT, but they can often be diagnosed by multiphasic CT. In early enhanced images, they show peripheral nodular or globular enhancement. As time goes by, contrast enhancement progresses centripetally. In delayed enhanced images, they appear as uniformly enhanced tumors.¹³ The best, although most expensive, imaging study for hemangiomas is MRI with sensitivity and specificity between 85% and 95%. Bright signal intensity on T2-weighted images and similar enhancement pattern to enhanced CT are very specific and effective for accurate diagnosis (Fig. 2).^{14,15} Single photon emission computed tomography (SPECT) with technetium-labeled red blood cell has similar sensitivity and specificity to MRI for hemangioma only if the tumor is larger than 3 cm and close to the surface.^{4,5} Because of these limitations, SPECT should be used as a supplementary test.

However, there are also atypical findings of hemangiomas such as cystic hemangiomas or small hemangiomas with immediate homogeneous enhancement.^{16,17} In these cases, pathologic conformation via needle biopsy is required, although it is still debatable whether needle biopsy can be safely performed in hypervascular tumors such as hemangioma. One

retrospective study of percutaneous biopsy of 38 patients with suspected hemangiomas using 20-gauge needles reported that it is safe and effective for establishing the diagnosis of hemangiomas. In that study, hemangiomas range in size from 1 cm to 13.5 cm, with a mean of 3 cm.⁴

Management

Treatment is not indicated for asymptomatic patients with hemangiomas that are less than 5 cm after the diagnosis is established and stability can be demonstrated on at least one follow-up study at 6-month interval.⁴ Asymptomatic patients with giant hemangiomas may need to be monitored more closely. Indications for treatment include severe symptoms, complications, and inability to exclude malignancy.¹⁸ Treatment includes surgical enucleation, resection, transarterial catheter chemoembolization, hepatic irradiation, and transplantation.^{5,19} Surgical resection and enucleation are applicable for single hemangioma. Transplantation may be necessary in large unresectable lesions, multiple lesions, or those involving the hepatic hilum.

Summary

Hemangiomas are the most common benign tumors of the liver. They are often asymptomatic and are found incidentally on imaging studies. Complications are uncommon. Diagnosis is usually made by characteristic radiographic features, and MRI is the most sensitive and specific diagnostic modality. Treatment depends on the patient's clinical presentation.

Focal Nodular Hyperplasia

Pathogenesis and Pathology

Focal nodular hyperplasia (FNH) is the second most common benign solid tumor of the liver and makes up approximately 8% of all primary hepatic tumors.^{4,9} The pathogenesis of FNH is not well understood. In the past, FNH was thought to be either a hamartoma or a neoplasm that forms in response to ischemia. However, more recently, it is considered a nonneoplastic, hyperplastic response to a congenital vascular malformation.⁷ Histologically, FNH is defined as a tumor consisting of benign-appearing hepatocytes occurring in the liver that is normal or nearly normal.²⁰ FNH is encountered in as many as 3% of general population, predominantly in childbearing-aged women with a female-to-male ratio of 6 to 8:1.⁵ Oral contraceptive use may be associated with FNH, but its association is not clear. Most investigators agree that the use of oral contraceptive does not induce the formation of FNH, but it acts only to accelerate the growth of already formed tumors.²¹ FNH most often presents as a solitary, less than 5-cm nodule near the hepatic surface, although large masses up to 15 cm in diameter have been reported.⁴

On gross pathology, it is usually a well-circumscribed, globular, lobulated but not encapsulated tumor.²¹ The characteristic histologic features of FNH include a dense, central stellate scar and septa that radiate from the central scar. The septa divide the tumor into several nodules. Microscopically, this scar is composed of bile ductules, cholangiolar

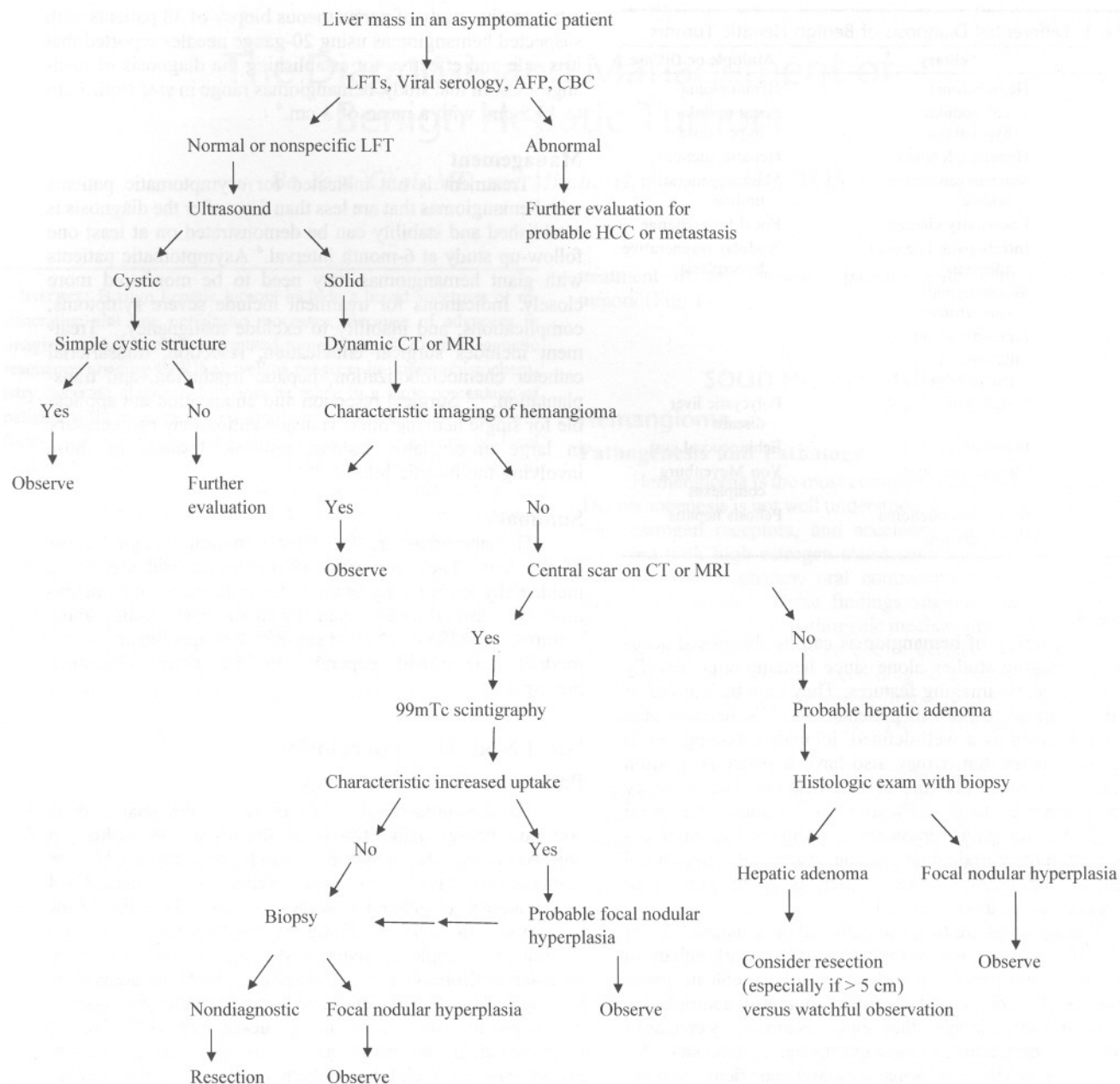


FIGURE 1. Evaluation for asymptomatic liver masses.

proliferation with surrounding inflammatory infiltrates, and malformed vessels including arteries and capillaries but no portal veins.²⁰ All of these proliferating bile ductules are of hepatocellular origin, not the preformed biliary tree.⁷ The hepatic parenchyma between the septa is normally arranged into hepatic cords composed of hepatocytes, sinusoids, and Kupffer cells.

Clinical Presentation

Although FNH may grow to more than 10 cm in diameter, patients are rarely symptomatic.⁸ Clinical symptoms

such as epigastric or right upper quadrant pain are found in less than one third of patients, and pain is usually not acute.²² Spontaneous rupture leading to hemorrhage is extremely rare. Most patients have normal liver function test. Malignant transformation of FNH has not been clearly described. Fibrolamellar variant of HCC is one of malignant hepatic tumors that also has a central scar similar to that of FNH, but there is no definite evidence that FNH is a precursor of fibrolamellar HCC.²³ Because of its benign clinical course, distinction between FNH and other hypervascular hepatic tumors, such as hepatic adenoma, HCC, and hypervascular

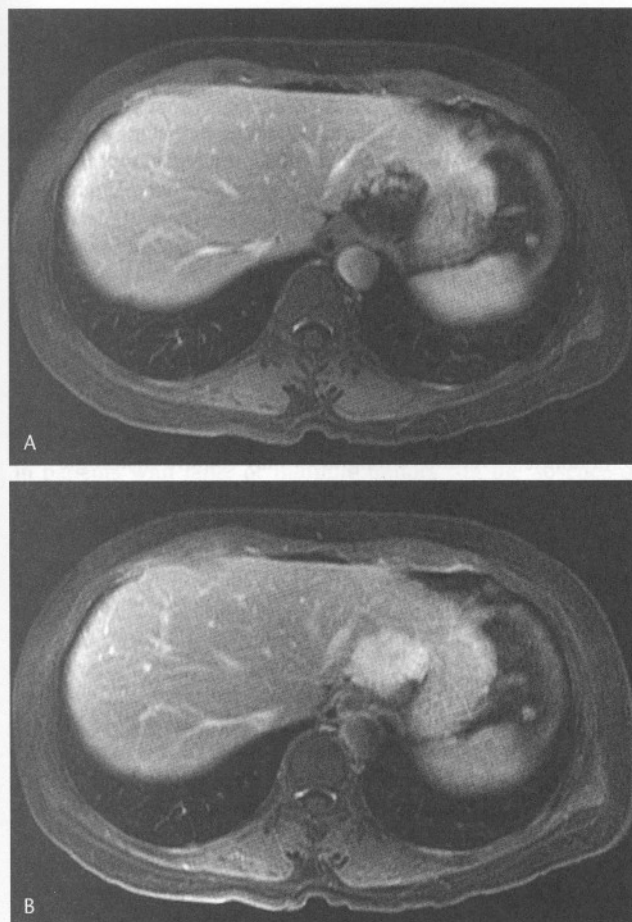


FIGURE 2. Hemangioma. A, Early enhanced T1-weighted image reveals peripheral nodular enhancement of the tumor. B, Delayed enhanced T1-weighted image shows homogeneous enhancement of the tumor.

metastasis, is critical to ensure appropriate treatment and follow-up.

Imaging

As in the case with histologic study, the central fibrous scar is the most characteristic finding in imaging studies. US is often the initial imaging modality that indicates a focal hepatic lesion, but FNH is not well demonstrated by simple sonographic technique. There is only a subtle difference of echogenicity between FNH and the surrounding normal liver. FNH may be slightly hypoechoic, isoechoic, or slightly hyperechoic. Some of them may show a hypoechoic halo surrounding the tumor.²⁰ Color and power Doppler US may be helpful for detecting the vascularity in suspected FNH. In addition, use of US contrast media has been reported. After injection of contrast media (Levovist; Schering AG, Berlin, Germany), FNH demonstrates strong homogeneous activity similar to adjacent hepatic parenchyma. The mechanism of its uptake is thought to be related to Kupffer cell activity. This can be a differential point from other malignant hepatic tumors that typically demonstrate no uptake as focal defects.²⁴ Despite

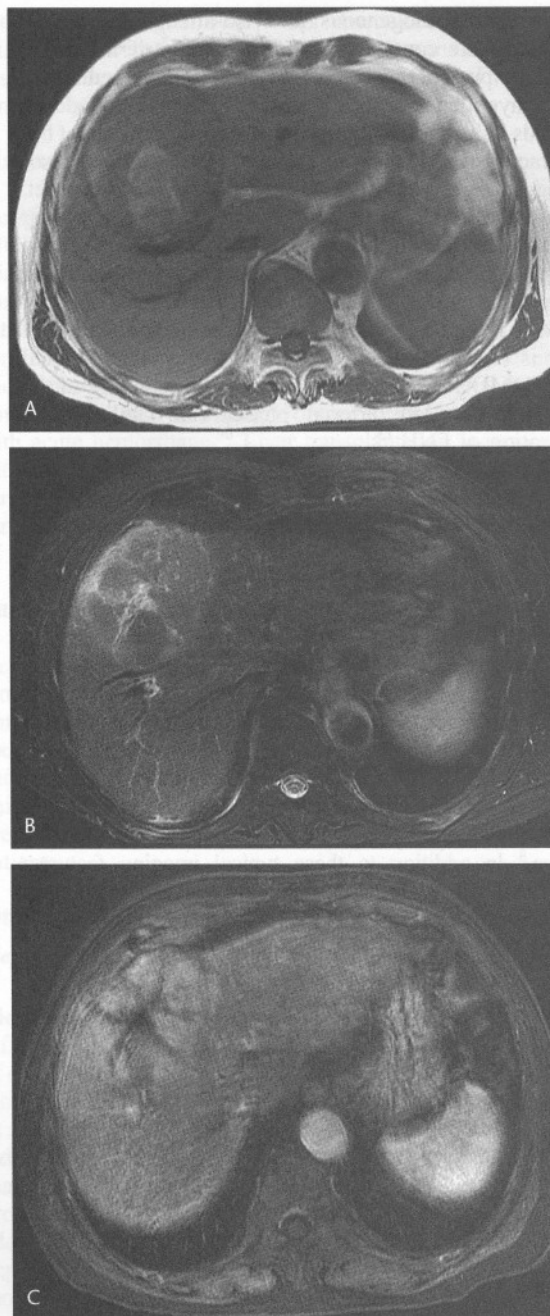


FIGURE 3. FNH. A, Unenhanced T1-weighted image demonstrates a smoothly marginated isointense tumor with a hyperintense portion. B, Fat saturation T2-weighted image reveals slightly hyperintense tumor with a central scar and its intensely bright signal. C, Enhanced T1-weighted image shows a homogeneous enhanced tumor with hypointense central scar.

these possibilities, US is currently not considered the modality of choice for characterization of FNH.

On multiphasic CT and enhanced MRI, typical features of FNH are very characteristic (Fig. 3).^{1,22} On multiphasic CT,

FNH is usually homogeneous and iso-attenuating to the normal liver before contrast injection. At late arterial phase, FNH typically presents with a bright homogeneous enhancement and a hypodense central scar. The radiating hypodense fibrous bands or septa, arising from the scar, are infrequent but quite characteristic. At portal phase, FNH returns to iso-attenuating to the normal liver and may be difficult to detect. Delayed phase often shows hyperattenuation of the central scar and septa due to the late opacification of the fibrotic components. Dilated feeding arteries penetrating central scar and draining veins running at the surface of the tumor may be recognized in large FNH.¹³ Because early hyperattenuation of the tumor is the most reliable sign, multidetector computed tomography (MDCT), which allows the rapid scanning of the entire liver at the late arterial phase, can facilitate the characterization of FNH.¹³

On MRI, FNH is slightly hypointense on T1-weighted images and slightly hyperintense on T2-weighted images. FNH may also be nearly isointense on both T1- and T2-weighted images. Unlike hepatic adenoma, FNH rarely has higher signal intensity than the liver on T1-weighted images.²⁵ The central scar is usually hyperintense on T2-weighted images. On dynamic contrast-enhanced MR images, FNH shows similar enhancement pattern to multiphasic CT (Fig. 3). Superparamagnetic iron oxide (SPIO) is an MR contrast agent that undergoes phagocytosis by the RES system (Kupffer cell). On SPIO-enhanced T2-weighted images, FNH is hypointense, whereas the central scar is more conspicuous.^{9,21} On MR images with hepatobiliary contrast agents, FNH appears hyperintense in relation to the normal liver, and the central scar remains hypointense.⁸ In addition to these typical imaging features, atypical CT and MRI findings also occur. These include multiple lesions, heterogeneity or fat component within the tumor, non-visualization of the central scar, and pseudo-capsular enhancement.²⁶

On hepatic scintigraphy with 99m Tc-sulfur-colloid, FNH shows normal (30%), increased (30%), and decreased (30%) colloid uptake compared with the normal liver. In 10% of cases, uptake is intense, and this is a very specific finding for FNH.²¹ Hepatic adenoma usually has decreased uptake.²⁷ The amount of uptake depends on the size and number of Kupffer and fibrous cells. Radiologically, FNH is sometimes mistaken as fibrolamellar HCC, but the fibrous scar of fibrolamellar HCC is usually large and eccentric with broad fibrous bands and calcifications.⁸ If all of the imaging studies fail to establish a firm diagnosis, histologic examination is warranted. By combining different imaging modalities, especially by using MRI, a precise diagnosis of FNH can be achieved in 70% to 90% of cases in centers with expertise in the appropriate imaging techniques.⁸

Management

In asymptomatic patients with FNH, treatment generally includes clinical follow-up to observe for the development of symptoms and radiologic follow-up with US to detect enlarging tumors.²⁹ Most of resected cases are due to the undetermined nature of the tumor, the presence of symptoms, or suspicion of metastasis in patients previously operated for

malignant diseases.²⁸ When surgical resection is not possible, FNH may be treated by transarterial embolization.^{3,21} One special concern in the management of FNH is the fear of accelerated growth of FNH with high-estrogen state such as pregnancy. Although the association between pregnancy and tumor enlargement or development of significant symptoms including tumor rupture have not been clearly established for FNH,⁶ it may be prudent to observe pregnant patients with FNH with more frequent US during pregnancy and the postpartum period.

Summary

FNH is the second most common benign tumor of the liver, next to hemangioma. Patients are rarely symptomatic. Multiphasic CT and enhanced MRI are the most useful diagnostic modalities. Definitive diagnosis may require histologic examination in selected cases. Treatment includes conservative clinical follow-up in asymptomatic patients. Surgical resection is indicated for those with significant symptoms or in whom malignancy cannot be excluded by radiologic and histologic studies.

Hepatic Adenoma

Pathogenesis and Pathology

Hepatic adenoma (HA) is a rare hepatic tumor that is pathologically characterized by the benign proliferation of hepatocytes. As seen with FNH, HA also occurs predominantly in young women with a female-to-male ratio of 4:1.⁵ The pathogenesis of HA remains disputed, but the strong association with oral contraceptive use has been documented. HA was extremely rare before the introduction of oral contraceptives in the 1960s. Since 1960s, the incidence has greatly increased, and HA occurs more frequently in patients with a history of long-term and high-dose estrogen use.³⁰ Withdrawal of oral contraceptives is reported to induce the regression of the tumor, although this may take several months.²² In addition to oral contraceptives, anabolic androgen-containing steroid medications also may increase the incidence, number, and size of HA. Another risk group for HA includes patients with glycogen storage disease. The prevalence is 50% in patients with Type I glycogen storage disease (von Gierke) and 25% with Type III disease.⁴ In these patients, adenomas are also more likely to be multiple and to undergo malignant transformation, although the latter is still rare.³¹

Macroscopically, HA is usually solitary (70%–80%), well-circumscribed, round, unencapsulated, but it often forms pseudo-capsules by compressing adjacent hepatic tissue. They have yellow-tan color with diameter ranging from 5 to 15 cm, and up to 30 cm on rare occasions.⁴ Grossly, intratumoral fat, necrosis, hemorrhage, or large subcapsular vessels are commonly observed. Microscopically, HA includes large plates of cells that resemble normal hepatocytes and are separated by dilated sinusoids. These sinusoids are perfused by feeding arteries, which contribute to the hypervascularity of HA. The presence of hypervascularity, loosely organized connective

tissues, the absence of a true capsule, and the subcapsular location of HA explain its propensity for rupture and bleeding. HA does not contain bile ductules, a key histologic finding that distinguishes it from FNH.³⁰ Kupffer cells may be present but are often few.²⁶

Clinical Presentation

Most patients with no more than a few small adenomas are asymptomatic. In 1 case series with 44 patients, 48% of patients are detected incidentally and 44% have symptoms.⁵ Large HA may cause a sensation of right upper quadrant fullness or discomfort. HA is of clinical importance because of its tendency to spontaneous rupture, hemorrhage. Therefore, acute abdominal pain and catastrophic intraperitoneal hemorrhage are not uncommon presentation of HA.²² Rare cases of malignant transformation have also been reported, particularly in patients with large or multiple tumors.⁸ In the absence of malignancy, serum alpha-fetoprotein and liver function tests are usually normal in patients with HA.

Imaging

On US, hepatic adenomas have variable and nonspecific appearances depending on the character of the tumor. Hypoechoic, hyperechoic, and mixed-echoic patterns represent simple adenoma, adenoma with fatty metamorphosis, hemorrhage, and necrosis, respectively.³² Color Doppler US sometimes demonstrates peripheral peritumoral and intratumoral vessels with a flat continuous or uncommonly, triphasic waveform. These findings are absent in FNH, so it can be used to differentiate between these 2 types of tumors.³⁰ US findings with contrast enhancement using Levovist may also be helpful. In the hepatic phase, 5 minutes following contrast injection, the tumor shows relatively low uptake in comparison with the surrounding liver. Other benign tumors that have strong Kupffer cell activity such as FNH and some hemangiomas demonstrate strong homogeneous activity similar to adjacent hepatic parenchyma, while malignant tumors such as HCC and metastasis demonstrate no uptake.^{24,33}

On multiphasic CT and MRI, HA may show more specific findings. Unlike FNH, HA is frequently heterogeneous due to intratumoral hemorrhage, necrosis, and fat components on CT. HA containing none of these components is nearly iso-attenuating to normal liver on unenhanced phase as well as portal-venous and delayed phases. HA shows early enhancement because of their rich arterial supply. Peripheral enhancement with centripetally progression is often detected, reflecting the presence of the large subcapsular feeding vessels.²⁶

MRI findings can also be very characteristic. On T1-weighted images, adenomas have been described variously as hyperintense, isointense, or hypointense due to the presence of hemorrhage, necrosis, or fat components. However, 35% to 77% of cases are described as hyperintense. On T2-weighted images, 47% to 74% of adenomas are also predominantly hyperintense.³⁰ On dynamic contrast-enhanced MR images, HA demonstrates early arterial enhancement. SPIO-enhanced MR is useful to distinguish adenomas from HCC. In contrast to HA, which typically shows signal loss on T2-weighted images, malignant hepatic tumors generally lack Kupffer cells

and show no signal loss.³⁴ As discussed earlier, hepatic scintigraphy with ^{99m}Tc-sulfur-colloid demonstrates HA with absent or decreased uptake, reflecting decreased number or function of Kupffer cells.

Management

Because of the risk of spontaneous rupture and malignant transformation, HA must be identified and treated promptly. After the diagnosis of HA, the most common recommended treatment is a surgical resection due to the above complications.^{29,30} However, especially in small (<5 cm) HA, discontinuation of estrogen and follow-up with US can also be considered.³⁵ The treatment options include surgical enucleation, resection, transplantation, and hepatic arterial embolization, which is also an effective option for the treatment of HA with acute hemorrhage.³⁰ Liver transplantation is required for patients with diffuse or multifocal adenomas. Laparoscopic surgery offers an alternative modality for small HA with good surgical outcomes according to one case series with 17 patients of HA.²⁸

Summary

HA is a rare benign tumor; however, it is important to recognize this tumor and to differentiate it from other hepatic tumors because of the risk of hemorrhage and malignant transformation. HA is usually detected with US, but it has no specific features on US. Color Doppler US, multiphasic CT, and MR can offer better characterization of HA. Criteria that guide treatment include the number and size of the lesions, the presence of symptoms, and the surgical risk incurred by patients.

Other Types of Hepatic Adenoma

Hepatic Adenomatosis

Hepatic adenomatosis is defined as more than 10 adenomas, and it is considered a distinct disease entity due to different clinical features.³⁶ It has been reported in the absence of oral contraceptive use or glycogen storage disease with M:F ratio of 1:1. Patients often present with clinical symptoms such as abdominal pain, hepatomegaly, and impaired liver function. Adenomatosis has higher tendency toward rupture, hemorrhage, and malignant transformation, leading to a poorer prognosis.³⁶ The imaging and histologic features are similar to adenomas. Diagnosis is usually made by exclusion of other hepatic tumors, since multifocal HCC or metastasis is much more common in the presence of multiple solid hepatic lesions. Close follow-up is warranted and liver transplantation is sometimes necessary.³⁷

Intrahepatic Bile Duct Adenoma

Bile duct adenoma is a benign and asymptomatic mass that is typically discovered incidentally at imaging studies, surgery, or at autopsy.¹ It is usually a well-circumscribed, subcapsular mass with a diameter of less than 1 cm and composed of bile ductules, inflammatory cell, and fibrosis. Radiologic imaging findings are nonspecific. Histologic analysis is the key in differentiating intrahepatic bile duct adenoma from other hepatic malignancy such as cholangiocarcinoma or metastasis. Treatment is usually not required.

Nodular Regenerative Hyperplasia

Pathogenesis and Pathology

Nodular regenerative hyperplasia (NRH) is a benign proliferative lesion, which has been referred to by many names in the literature including nodular transformation, noncirrhotic nodulation, and partial nodular transformation. It is a distinct disease entity characterized by diffuse involvement of the liver with nodules composed of hyperplastic hepatocytes, and it should not be confused with the regenerative nodules of cirrhosis or FNH.⁹ Macroscopically, NRH is characterized by multiple bulging regenerative nodules in clusters with ranging sizes from 0.1 to 4 cm. This gross finding may not be different from micronodular cirrhosis.⁵ However, microscopic features are very characteristic and readily distinguishable from cirrhosis. Histologic examination reveals the regeneration of hepatocytes with multinucleated hepatocytes and thickened regenerating hepatocytes with centrilobular atrophy. These regenerating nodules also compress the central veins curvilinearly, and there is a lack of fibrotic reactions. On the other hand, NRH and HA share similar benign process and histologic elements and are difficult to be distinguished from each other based on a single-needle biopsy. Multiple biopsies are often helpful as NRH is a diffuse or multinodular process, whereas HA is a solitary process in which the remainder of the liver is normal.²²

The pathogenesis of NRH is not well known. One of the proposed theories hypothesizes that a primary vascular process leads to obliteration of portal vein, which in turn induces ischemia, atrophy of hepatocytes in the central zone, and the proliferation of hepatocytes.³⁸ The other theory proposes that a preneoplastic process leads to NRH due to the reported high prevalence of hepatocyte dysplasia (20%–42%) and HCC formed in livers of patients with NRH.³⁹ According to two large case series, the prevalence of NRH was reported to be 2.1% and 2.6%.⁴ NRH mostly affects patients older than 50 years of age, and the gender distribution of NRH is variable.

Wide spectrum of systemic diseases and drugs are also associated with NRH such as myeloproliferative disorders, lymphoproliferative disorders, chronic vascular disorders, rheumatologic and collagen vascular diseases (rheumatoid arthritis, Felty's syndrome, polyarteritis nodosa, amyloidosis, and primary biliary cirrhosis), solid organ transplantation (renal and liver transplantation), and use of steroids or chemotherapeutic agents.²²

Clinical Presentation

Clinically, NRH usually cause no symptoms and are discovered incidentally during imaging studies or surgery. Some patients present mainly with symptoms of portal hypertension such as hepatomegaly, splenomegaly, ascites, or esophageal varices due to the compression of the main portal vein at the hepatic hilum. Other cholestatic symptoms can also occur.⁴⁰ Mild and nonspecific elevated liver function tests may be seen. Rarely, hepatic failure, rupture of the liver, or malignant transformation can occur.³⁹ Because of these clinical features, the diagnosis of NRH should be considered in patients with clinical signs of portal hypertension and normal

or mildly abnormal liver function test, in whom other causes of portal hypertension have been excluded.

Imaging

Imaging findings are not specific, and histologic examination is often warranted. In most cases, US shows normal hepatic parenchyma. In a few cases, well-delineated hypoechoic or isoechoic nodules can be depicted. Hyperechoic nodules have been reported in very rare cases.⁴¹ On enhanced CT, NRH shows normal findings or hypoattenuating nodules. Hyperattenuating portion of nodule represents hemorrhage or arteriportal shunting.^{22,41} There are only a few reports on the MR findings. Lesions are described as hyperintense on T1-weighted images and iso- or hypointense to normal liver on T2-weighted images.^{42,43}

Management

Accurate diagnosis should be confirmed with histologic examination prior to treatment. In highly suspicious cases, open biopsy is indicated to obtain adequate sample of hepatic tissue since percutaneous needle biopsies may give falsely normal results.⁴ Management depends on the clinical symptoms. In asymptomatic patients, no treatment is recommended except for periodic follow-up to monitor for development of HCC, although this is very rare. In patients with complications of portal hypertension, appropriate management including drug therapy, endoscopic therapy, or portocaval shunt is necessary.⁴ Rarely, patients may progress to liver failure and finally require liver transplantation.⁵

Summary

NRH is another benign hepatic tumor that is often detected as incidental findings. The diagnosis of NRH usually requires clinical, radiologic, and histologic examinations. Accurate diagnosis is the key, and treatment is indicated based on the patient's clinical presentations.

Macroregenerative Nodule

Pathogenesis and Pathology

Macroregenerative nodule (MRN) was previously classified as adenomatous hyperplasia or high-grade dysplastic nodule (>1 cm).²⁵ MRN occurs on the background of the cirrhotic liver, acute massive or submassive necrotic liver. Nowadays, MRNs are more frequently detected in liver explants after orthotopic liver transplantation.⁴⁴ Clinical importance of MRN is its malignant transformation to HCC, although it is not clear how what percentage of MRN will progress to malignancy. The reported prevalence of MRN varies between 14.2% and 25% on autopsy series.⁴⁴ In acute massive or submassive necrosis, remaining hepatic parenchyma shows compensatory lobular hyperplasia after parenchymal loss. In cirrhotic liver, the hyperplastic reactions occur as a result of even a larger amount of cell loss. Regenerating islets of viable cells are formed between destructed areas, and these islets make up the nodular structures.⁷

Macroscopically, MRN has a greener or paler color compared with the surrounding cirrhotic liver. As compared with HCC, MRN has lower proliferation indices, which is no greater than three-cell thickness.²³ At times, MRN may

demonstrate ischemic coagulative necrosis and hemorrhage, nuclear crowding, and microacinar formation that herald the development of HCC. MRN usually has variable atypia. More specifically, MRN without atypia is classified as Type I and MRN with atypia as Type II.

Clinical Presentation and Imaging

Patients have no specific symptoms since MRN is usually discovered by imaging studies in patients with cirrhosis or advanced fibrosis for evaluation of HCC. Liver function test with viral markers study shows the etiology and severity of underlying liver disease.

MRN is rarely detected on screening US.⁴⁵ On CT, the presence of MRN can be suggested by nodular hepatic contour, and nodules are iso-attenuating to surrounding liver during arterial and portal phases.⁴⁶ On MRI, lesions show variable signal intensities on T1-weighted images and typically hypointensity on T2-weighted images with no enhancement on arterial enhanced phase. These are distinguishable features from HCC, which typically are hyperintense on T2-weighted images with strong enhancement during the arterial phase.^{45,47} Sparse central or peripheral blood supply is found on angiography without neovascularity. HCC emerging from MRN can be demonstrated as nodule-in-nodule pattern on imaging studies due to their histologic uneven growth.⁴⁸

Management and Summary

MRN is a benign but premalignant lesion found in cirrhotic or fibrotic livers. Imaging findings are not characteristic, but MRI findings are useful for the differentiation from HCC. Because of its malignant potential, surgical resection of MRN is sometimes advocated, especially in those with atypia. Optimal management of MRN remains unknown pending ongoing investigation.

Other Solid Tumors

Mesenchymal Hamartoma

Mesenchymal hamartoma of the liver is an uncommon benign lesion composed of bile ducts, immature mesenchymal cells, and hepatocytes.⁴⁹ Most of them are diagnosed during childhood, although a few cases have been reported in adults.⁵⁰ The clinical presentation is nonspecific, and imaging findings reveal solid or multicystic lesions.⁵¹ Although hamartoma can be diagnosed by percutaneous biopsy, diagnosis is usually established after surgical excision.

Focal Fatty Change

Hepatic steatosis is generally a diffuse process, but focal distribution of fat is quite common in the liver called focal fatty change.⁵² The pathogenesis is not well understood, but regional hypoxia of hepatic tissue is thought to play a role according to one theory.⁵³ The majority of patients have underlying disease such as diabetes, obesity, and malnutrition. Lesions are often discovered incidentally on imaging studies and characteristically show a fan-shaped or geographic pattern mainly in subcapsular areas or regions adjacent to the falciform ligament.⁵⁴ Focal fatty change can be found as single or multiple lesions with variable sizes in a few cen-

timeters up to 10 cm. These tumor-like lesions may be mistaken for other hepatic tumors, and liver biopsy is often required for a definitive diagnosis.⁵⁵

Lipomatous Tumor

Lipomatous tumors such as hepatic angiomyolipoma or hepatic lipoma are very rare benign tumors. Patients are usually asymptomatic, and lesions are often encountered in patients with tuberous sclerosis.⁸ As their names imply, on the imaging studies, lipoma shows uniform fat component, whereas angiomyolipoma also contains intratumoral vessel and smooth muscle component. Atypical cases should be carefully differentiated from other hypervascular tumors including HCC, FNH, and hemangioma.⁵⁵ Fine-needle aspiration is occasionally required and reveals fat cells, epithelioid smooth muscle cells, and blood vessels.⁵⁶ The prognosis is good, and surgical resection may be needed if patients have symptoms related to mass effect.^{57,58}

Inflammatory Pseudotumor

Inflammatory pseudotumor is an extremely rare benign hepatic tumor. It has the appearance of a malignant tumor but has a benign histology and clinical course.⁵⁹ The etiology is unclear, but underlying infectious agents are strongly suggested as the pathologic process.⁶⁰ The clinical presentation is nonspecific. Patients may have fever, malaise, weight loss, and symptoms related to a mass effect. Routine imaging procedures are not sufficient to make the diagnosis, and a biopsy is necessary to differentiate it from other tumors.⁶¹ Histologic examination reveals myofibroblasts, polyclonal plasma cell, and fibrous tissue. The course of the disease is unpredictable. In most of the reported cases, the patients underwent resection.⁶²

CYSTIC TUMORS

Simple Cyst

Pathogenesis and Pathology

Hepatic cysts are relatively common and most often discovered incidentally. Simple hepatic cysts are usually congenital. During embryogenesis, abnormal or excessive intrahepatic bile ducts develop. These ducts are obstructed or fail to connect with extrahepatic ducts and eventually form hepatic cysts. Despite their pathogenesis, communication with the biliary duct is very rare, and simple cysts usually contain clear fluid with a similar composition to serum.⁶³ Hepatic cysts are recognized with increasing frequency as imaging modalities advance. The US prevalence is reported to be 5%. There is a strong female predominance and presentations occur most frequently in the fifth decade.⁶⁴ Histologically, simple cysts are lined by simple cuboidal epithelium, identical to that of bile ducts and thin underlying rim of fibrous stroma.

Clinical Presentation and Imaging

Patients are usually asymptomatic, and solitary cysts that become symptomatic are generally larger than 5 cm. These can cause mass effects such as right upper quadrant pain. Rarely, other complications such as intracystic hemorrhage and infection may develop and present a diagnostic challenge.⁶⁵ Hepatic cysts can usually be diagnosed by US. On

CT and MRI, simple cysts have water attenuation, with imperceptible and small thin wall, without septations, or with enhancement of its wall or content.⁶⁴ In cases of intracystic hemorrhage, the signal intensity is high, with fluid-fluid level, on the both T1- and T2-weighted images when mixed blood products are present.²

Management

Most simple hepatic cysts do not cause any symptom and are best managed conservatively. The preferred treatment of symptomatic cases is US- or CT-guided percutaneous cyst aspiration followed by sclerotherapy with alcohol (or doxycycline). Surgical treatment is indicated if it is difficult to exclude malignancy or if there is biliary communication or infection.⁶⁶ Laparoscopic fenestration and deroofing have been documented to be safe and effective.^{67,68} The choice between open and laparoscopic surgery depends on the location of the cyst in the liver.

Summary

Hepatic cysts are common benign tumors, especially in older patients and female patients. They are usually asymptomatic and found incidentally. Imaging features are very typical. Complications such as intracystic hemorrhage or infection are very rare. Management includes conservative observation, laparoscopic or open surgical treatment.

Polycystic Liver Disease

Polycystic liver disease is an autosomal dominant disorder often found in association with renal polycystic disease. Patients are usually asymptomatic, but advanced disease can result in hepatomegaly, liver failure, or Budd-Chiari syndrome.^{2,68} Although the diagnosis is easily made with both CT and MR imaging, MR imaging is more sensitive for the detection of complicated cysts.²

Choledochal Cyst

Pathogenesis and Pathology

Choledochal cysts are congenital bile duct anomalies. These cystic dilatations of the biliary tree can involve the extrahepatic biliary ducts, the intrahepatic biliary ducts, or both.⁶⁹ Choledochal cysts are more prevalent in Asia than in the United States or other Western countries. No strong unifying etiologic theory exists for choledochal cysts. The pathogenesis may be multifactorial. In many patients with choledochal cysts, an anomalous junction between the common bile duct and pancreatic duct can be demonstrated. This abnormal union allows pancreatic secretions to reflux into the common bile duct, where the pancreatic proenzymes become activated, thereby damaging and weakening the bile duct wall. Defects in epithelialization and recanalization of the developing bile ducts and congenital weakness of the ductal wall have also been implicated.⁷⁰

Clinical Presentation and Imaging

The clinical history and presentation of patients with a choledochal cyst vary with the patient's age. The classic presentations of adult patients are jaundice, pain, and palpable

mass, but some patients also present with cholangitis symptoms including fever or vague dyspeptic symptoms.⁷¹

For diagnosing choledochal cysts, US is the modality of choice. The communication with the biliary ductal system must be demonstrated. Depending on the type of choledochal cysts, dilatation of the intrahepatic ducts and the presence of intrahepatic cysts may or may not be demonstrated. CT, MRI, and magnetic resonance cholangiopancreatography (MRCP) help to delineate the anatomy of the lesion and of the surrounding structures. These tests can also assist in defining the presence and extent of potential intrahepatic ductal involvement. Invasive studies including percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP) are particularly helpful in demonstrating the presence of an anomalous pancreaticobiliary junction and in delineating associated extrahepatic or intrahepatic strictures and stones.

Management

The treatment of choice for choledochal cysts is the complete excision of the cyst with a biliary-enteric anastomosis to restore continuity with the gastrointestinal tract.⁷² Appropriate antibiotic therapy and supportive care should be given to patients presenting with cholangitis. Laparoscopic resection of choledochal cyst and reconstruction has been reported to be technically feasible.⁷³

Summary

Choledochal cyst is a congenital bile duct anomaly. US findings are diagnostic in many patients; however, complementary studies such as CT, MRI/MRCP, or PTC/ERCP may be helpful in the preoperative period for delineating details of the surrounding anatomy. The best treatment is complete excision with biliary-enteric reconstruction.

Echinococcal Cyst

Pathogenesis and Pathology

Hydatid cysts or echinococcal cysts are still endemic in certain parts of the world and caused by the tapeworms *Echinococcus granulosus* or *Echinococcus multilocularis*.⁷⁴ Humans can become infected upon ingesting the eggs of the parasite directly, through contact with sheep, cats, dogs, cattle, or by contaminated water or food.⁷⁵ The liver parenchyma filters out most of the embryos, and those that are not destroyed transform into small cysts that grow over time. Depending on the condition of the parasite and the host reaction, the cyst can degenerate and may eventually collapse, leaving an area of calcification in the liver. After the initial hepatic involvement, local extension or metastatic spread to the lungs, brain, bones, or bulbous oculi may be seen in *Echinococcus multilocularis* infection.⁷⁶

Microscopically, hydatid cyst is composed of three layers: the outer pericyst, which corresponds to compressed hepatic tissue; the endocyst, an inner germinal layer; and the ectocyst, a translucent thin interleaved membrane. Maturation of a cyst is characterized by the development of daughter cysts in the periphery as a result of endocyst invagination. Peripheral calcifications are common in both viable and nonviable cysts.²

Clinical Presentation and Imaging

The majority of patients are asymptomatic, but some may present with abdominal pain, fever, or hepatomegaly. Anaphylactic shock may occur due to rupture of cysts into the peritoneal cavity. Helpful diagnostic features include eosinophilia, positive serologic tests, and radiologic imaging.

On US or CT, hydatid cysts appear as well-defined lesions with distinguishable walls. Also, calcified rims, intracystic septations, and daughter cysts can be seen.^{77,78} MR images clearly demonstrate the pericyst, the matrix, and daughter cysts. The pericyst is seen as a hypointense rim on both T1- and T2-weighted images because of its fibrous component and the presence of calcification. The hydatid matrix (hydatid "sand") appears hypointense on T1- and markedly hyperintense on T2-weighted images. Daughter cysts are more hypointense than the matrix on T2-weighted images.^{2,74} On the contrast-enhanced images, solid components of the cysts are weakly enhanced.⁷⁴

Management

Surgical treatment can cure the patients if the entire cysts are removed. Special care should be taken not to spill the hydatid fluid during surgery because spillage of the hydatid fluid can induce anaphylactic reaction.⁷⁹ Laparoscopic treatments including simple drainage, unroofing, and pericystectomy have been reported to be safe and effective.⁸⁰ Medical treatment with albendazole or mebendazole only is not effective but can be used as an adjuvant therapy.

Summary

Hydatid cysts are caused by tapeworm infection, which has a worldwide distribution. Most patients are asymptomatic. Diagnosis is made by eosinophilia, positive serologic tests, and characteristic imaging features. Treatments include medical, surgical, and laparoscopic procedures.

Other Cystic Tumors

Biliary Cystadenoma

Biliary cystadenoma is an uncommon, slow-growing tumor and is considered a premalignant lesion.⁸¹ Malignant transformation to cystadenocarcinoma is not uncommon. It occurs predominantly in female patients between 30 and 50 years of age. Histologically, the tumor emerges as multilocular cyst with a single layer of biliary epithelium. On enhanced CT, it is a multilocular cystic lesion with typical enhancement of the cystic walls, internal septations, and mural nodules.¹ The MRI findings vary depending on the protein content of the fluid and the presence of an intracystic soft-tissue component. Imaging findings are similar to cystadenocarcinoma, although the polypoid projection with pedunculated excrescence is more common in cystadenocarcinoma.² For treatment, surgical resection is mandatory if cystadenocarcinoma is suspected.⁸² After surgical resection, recurrence is quite common.

Von Meyenburg Complex

Bile duct hamartomas, also known as von Meyenburg complex, are relatively common benign lesions composed of disorganized proliferation of bile ductules and fibrocollagenous stroma.⁸³ Radiologic imagings are nonspecific, revealing

multiple subcentimeter nonenhanced lesions.⁸⁴ von Meyenburg complex is of no clinical importance, except for mimicking metastasis or microabscess.⁸⁵ Further evaluation or treatment is not required.

Caroli Disease

Caroli disease is a rare, autosomal-recessive developmental disorder characterized by nonobstructive saccular dilatation of intrahepatic bile ducts, multiple intrahepatic calculi, and is associated with polycystic renal disease.⁸⁶ Clinical symptoms include recurrent attacks of fever, right upper quadrant pain, and rarely jaundice. US is the best initial imaging study because it reveals the irregular dilatation of the large intrahepatic ducts. On enhanced CT and MRI, the presence of tiny dots with strong enhancement within dilated intrahepatic ducts ("central dot" sign), reflecting intraluminal portal vein radicles, is very suggestive finding of Caroli disease.⁸⁷ Surgical treatment may be necessary for recurrent or refractory cholangitis. Broad-spectrum antibiotic coverage is indicated in cases of cholangitis.

Peliosis Hepatica

Peliosis hepatis is a rare benign lesion that is characterized by the presence of diffuse blood-filled cystic spaces. It can occur in the liver, spleen, bone marrow, and lungs.⁸⁸ It has been reported to associate with long-term treatment of steroid, estrogen, tamoxifen, immunoglobulin, malignancy (hepatocellular carcinoma and adenoma), hematologic disease (Hodgkin disease, multiple myeloma), renal transplantation, and infections (tuberculosis, AIDS). Radiologic imaging findings are cystic lesions with variable sizes. Sometimes, very small lesions are detected as noncystic or diffuse hepatic lesions.^{88,89} Treatment should include withdrawal of the possible causative agents and specific treatment such as antibiotics in patients with either primary or secondary infections.

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