Cirrhosis

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Daniele Marin and Rendon Nelson

Cirrhosis is a pathologic and clinical entity that occurs following repeated hepatocyte damage and is characterized by extensive fibrosis and innumerable regenerative nodules replacing the normal liver parenchyma. Ultimately, the process can lead to liver failure.

Prevalence and Epidemiology

The true prevalence of cirrhosis remains difficult to ascertain due to the large number of patients with compensated cirrhosis that remain undetected due to a lack of symptoms. Males are affected more commonly than females, with a male-to-female ratio of 4:1. Recent data estimate a prevalence of approximately 0.15% of cirrhosis in the United States, with 400,000 reported new cases in 1998. The prevalence of cirrhosis is even higher in Africa and Asia, where hepatitis B infection is endemic. Cirrhosis represents the tenth leading cause of death worldwide, accounting for 27,000 deaths in 2001. Notably, cirrhosis is the third leading cause of death in males between 34 and 54 years.

Etiology

Cirrhosis represents the terminal stage for a variety of chronic insults to the liver. In the United States and Europe, the majority of cases of cirrhosis are secondary to prolonged consumption of alcohol and/or chronic hepatitis C viral infection. In Africa and Asia, chronic hepatitis B viral infection is the most common culprit for the development of cirrhosis, even though a vaccine exists for hepatitis B. Other less common causes of cirrhosis in adults include chronic biliary obstruction, autoimmune hepatitis, drug-induced hepatotoxicity (e.g., amiodarone and methotrexate), parasitic disease (most importantly schistosomiasis), and genetic disorders, such as hemochromatosis, Wilson disease, glycogen storage disease, alfa1-antitrypsin deficiency.

Recently, nonalcoholic fatty liver disease (NAFLD) has been recognized as a possible predisposing factor for chronic liver damage and cirrhosis (Angulo 2002). NAFLD encompasses a wide spectrum of liver disorders characterized by histologic lesions typical of those in alcoholic liver disease, ranging from mild fatty liver disease to cirrhosis (Clark and Diehl 2003). The so-called nonalcoholic steatohepatitis (NASH) is a subtype of NAFLD, in which fatty liver disease is accompanied by inflammatory cells, hepatocyte necrosis, and fibrosis. By definition, NAFLD is observed in patients with no history of excessive alcohol consumption and is associated with several factors, including obesity, type 2 diabetes mellitus, and dyslipidemia. However, this condition may also be observed on occasion in lean individuals.

Pathology

Cirrhosis is a diffuse process that is triggered by parenchymal necrosis, leading to nodular hepatocyte regeneration and connective tissue deposition.

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Nodular Hepatocyte Regeneration

In cirrhosis, the disruption of hepatic architecture is at the level of the sinusoid, including the portal veins that drain into the sinusoid. During this process of liver regeneration, there is development of a wide spectrum of hepatocellular nodules, ranging from benign regenerative nodules to malignant hepatocellular carcinoma (HCC). In 1994, the International Working Party on Terminology suggested a simplified nomenclature with the intent of promoting a universal classification system for hepatocellular nodules (International Working Party 1995). In the setting of cirrhosis, hepatocellular nodules were defined as: benign regenerative nodule, low- and high-grade dysplastic nodule, dysplastic nodule with foci of HCC, and HCC.

Regenerative nodules (also referred to as, cirrhotic nodules) are nodules composed of hepatocytes circumscribed by fibrous septa. Regenerative nodules are by far the most common nodules in cirrhosis. These nodules tend to be uniform in size (generally smaller than 15 mm) and appearance. At gross inspection, nodules are defined as micronodules (smaller than 3 mm) or macronodules (equal or larger than 3 mm). Anecdotal experience suggests that micronodules are suggestive of alcohol or drug-induced cirrhosis or cirrhosis secondary to metabolic disorders (e.g., NASH). Macronodules, on the other hand, are more often seen in patients with viral-induced or autoimmune cirrhosis. Such distinction, however, has limited clinical value due to the lack of specificity for determining the cause of cirrhosis.

Dysplastic nodules are hepatocellular nodules with histological characteristics suggestive of abnormal growth, but no definitive evidence of malignancy. Evidence suggests that a stepwise progression to HCC may occur in some dysplastic nodules, although causative factors and the frequency of malignant transformation remain uncertain. Differentiation of high-grade dysplastic nodules from HCC may be difficult and sometimes impossible at histopathological analysis. This is largely due to the use of arbitrary criteria for lesion characterization and relatively low yield and sampling variability of liver biopsies. With the introduction into clinical practice of new molecular genetic techniques, the characterization of hepatocellular nodules will likely improve.

Connective Tissue Deposition

Liver fibrosis is the second key factor in the pathogenesis of cirrhosis and related complications. It refers to the abnormal deposition of collagen, proteoglycans, and other macromolecules in the extracellular matrix in response to repetitive liver injury (Afdhal and Nunes 2004). Activation of hepatic stellate cells, the main collagen-producing cells, by fibrogenic cytokines is a central event in fibrosis. Other cells such as portal fibroblasts and bone marrow–derived cells may also be involved in the fibrogenic process. Although fibrosis has been generally considered an irreversible process, recent evidence suggest that this process may be reversible during the early stages.

Liver biopsy remains the reference standard for the quantitative assessment of fibrosis (Ishak et al. 1995). Although widely used in clinical practice, liver biopsy is a suboptimal screening test for the assessment of fibrosis due to the invasiveness, relatively high cost, and sampling variability. Precise noninvasive tests for the quantification of liver fibrosis would be desirable in the screening and follow-up of patients with chronic liver disease.

Clinical Manifestation

The natural history of cirrhosis is insidious with slow progression to terminal stages. Patients may remain asymptomatic or have only mild, nonspecific symptoms until the development of late complications, including portal hypertension (most notably variceal bleeding and ascites) and hepatic failure (hepatic encephalopathy), and renal failure (hepatorenal syndrome). Cirrhosis is also a risk factor for the development of HCC, one of the leading causes of mortality in patients with cirrhosis. While about 70% of patients with HCC have underlying cirrhosis, the incidence of HCC in patients with cirrhosis is about 7%. As a result, HCC is also one of the most common indications for liver transplantation in the United States and Europe.

Patient Management

Although liver damage from cirrhosis cannot be reversed, treatment is critical to stop or further delay disease progression and reduce complications.

Liver transplantation is the only curative therapy for cirrhosis. Certain conditions, however, such as primary sclerosing cholangitis, can recur in the transplanted liver, as well.

Appropriateness of Different Imaging Modalities

Although cirrhosis is a histopathological diagnosis obtained with liver biopsy, imaging provides critical information in the assessment of the severity of the liver damage and the presence of late complications, such as portal hypertension and HCC. Imaging plays also a critical role in the preoperative assessment of surgical candidates, such as patients with HCC undergoing liver resection or liver transplantation. Finally, because many patients with compensated cirrhosis are asymptomatic, thus remaining clinically undetected, it is not uncommon that the first diagnosis of cirrhosis is suggested based on unexpected findings on an imaging study performed for unrelated reasons.

Different imaging modalities – including ultrasonography, computed tomography (CT), and magnetic resonance (MR) imaging – have been used in the evaluation of patients with cirrhosis. The choice of an imaging modality is based on different factors, including the diagnostic accuracy of the test, clinical indication, practice preferences, and cost-effectiveness. In addition, patient-related factors must also be contemplated in the decision of the optimal imaging modality, including the patient's age and gender, cumulative radiation exposure history, body habitus, presence of ascites, and capacity to cooperate with breathing commands.

Computed Tomography (CT)

CT has become the most commonly used modality in the preoperative diagnosis, staging, treatment planning, and follow-up of patients with cirrhosis, particularly in the presence of a known or suspected hepatic tumor. With the advent of multidetector-row CT scanners, substantial anatomic volumes can be acquired within a short scan time, with submillimeter section thickness and virtually no penalty in increased radiation dose. These technologic advances have led to image acquisition during peak vascular enhancement yielding uniform enhancement along the entire scanned volume, decreased motion artifacts, and the capability to generate high-resolution reformations in different planes.

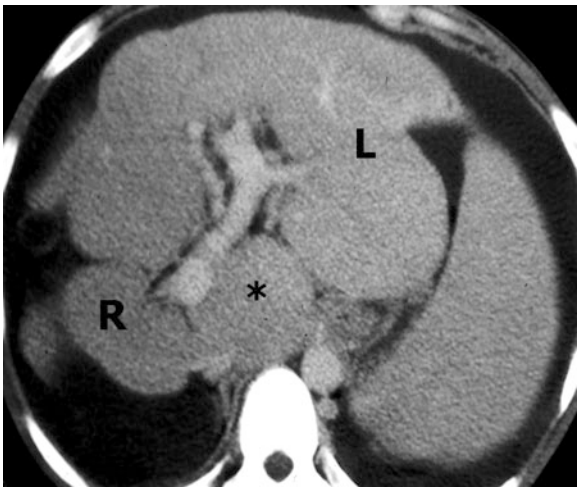

Fig. 69.1 CT scans show advanced primary biliary cirrhosis in a 71-year-old woman. (**a**) Transverse hepatic venous phase CT scan shows morphologic changes consistent with advanced cirrhosis, with atrophy of the right hepatic lobe (R) and hypertrophy of the lateral segments of the left hepatic lobe (L) and caudate lobe (*asterisk*)

During the initial stages of cirrhosis, CT demonstrates a normal or slightly increased hepatic volume. However, as the liver damage progresses, fibrosis and nodular hyperplasia ensue with progressive decrease of liver volume. In addition, characteristic alterations of the hepatic architecture occur with disease progression (Ito and Mitchell 2004). This includes: (a) atrophy of the right hepatic lobe (segments V to VIII) and medial segments of the left hepatic lobe (segments IVa and IVb), (b) widening of the porta hepatis and gallbladder fossa, and (c) hypertrophy of the lateral segments of the left hepatic lobe (segments II and III) and caudate lobe (segment I). Although these morphologic changes are characteristic of cirrhosis regardless of the underlying cause, some distinct appearances have been described in association with specific etiologies. For example, hypertrophy of the left lateral segment with atrophy of the right lobe and the left medial segment tends to be more pronounced in patients with viral-induced cirrhosis. On the other hand, marked caudate lobe hypertrophy is typically associated with alcohol-induced cirrhosis and primary sclerosing cholangitis (Dodd et al. 1999) (Fig. 69.1). In patients with primary biliary cirrhosis, the liver remains enlarged and smooth until the later final stages of disease (Blachar et al. 2001).

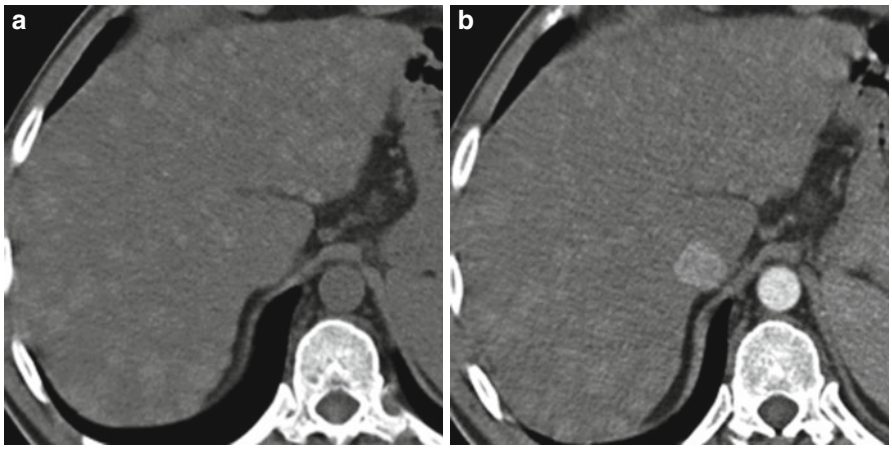

Fig. 69.2 CT scans show macronodular cirrhosis in a cirrhotic liver. (**a**) Transverse nonenhanced CT scan shows numerous hyperdense regenerative nodules scattered throughout the liver. (**b**) Corresponding image obtained during the hepatic arterial phase demonstrates no contrast enhancement of the lesions. Note: hepatic arterial phase image could be misleading without the corresponding unenhanced image because enhancement of the lesions could not be excluded

In the past, many studies attempted to identify quantitative metrics for the diagnosis of cirrhosis based on early alterations of liver morphology at imaging. One popular method is the assessment of the caudate-to-right lobe ratio proposed by Harbin et al. (1980). This method divides the maximum transverse dimension of the caudate lobe from the maximum transverse dimension of the right liver lobe, using the right lateral wall of the main portal vein approximately 1 cm below the bifurcation as a reproducible boundary between the two lobes. Using this method, a ratio greater than 0.65 (which is substantially higher than the average 0.37 ratio in normal liver) may yield high diagnostic accuracy for the diagnosis of moderate to advanced cirrhosis, particularly in patients with chronic hepatitis B viral infection, primary sclerosing cholangitis, and primary biliary cirrhosis (all conditions associated with greater ratio values). The caudate-to-right lobe ratio, however, is not sensitive to diagnose early cirrhosis and is not commonly used in daily practice. Other imaging and clinical data are needed in most patients with cirrhosis.

Measurement of liver attenuation (in Hounsfield units) on unenhanced CT images has little clinical value in the diagnosis of cirrhosis. Liver attenuation may vary from normal values (typically +45-65 Hounsfield units [HU] or 10 HU greater than the spleen on unenhanced CT with a single energy CT technique) to slightly decreased or increased values. Decreased hepatic attenuation is common in early stages of cirrhosis and is almost invariably related to increased deposition of fat. This finding is nonspecific and may be also seen in patients with fatty liver but no evidence of cirrhosis. Increased hepatic attenuation may be associated with hepatic deposition disorders, such as hemochromatosis or hemosiderosis (iron deposition), Wilson's disease (copper deposition), and glycogen storage disease (deposition of glycogen). Increased liver attenuation has also been reported with some drugs, such as amiodarone, methotrexate, and gold. When liver attenuation on an unenhanced CT exceeds +70 HU, it may be a clue for hereditary hemochromatosis. However, liver attenuation may be normal in patients with this genetic disease when there is only mild hepatic iron overload or in patients with simultaneous hepatic deposition of iron and fat.

Although regenerative nodules are innumerable in patients with cirrhosis, these lesions may be detected in only a minority of patients at CT. These lesions may be seen on unenhanced CT when encapsulated by a peripheral hypoattenuating rim of fibrous tissue or when abutting the liver capsule (Baron and Peterson 2001). This pattern is commonly seen in patients with primary biliary cirrhosis. Occasionally, regenerative nodules may manifest increased attenuation compared to the surrounding liver due to accumulation of iron or glycogen. These lesions may create a diagnostic pitfall when unenhanced CT images are not acquired because it is not possible to differentiate between the inherent high density of the nodule and arterial hyperenhancement (Fig. 69.2).

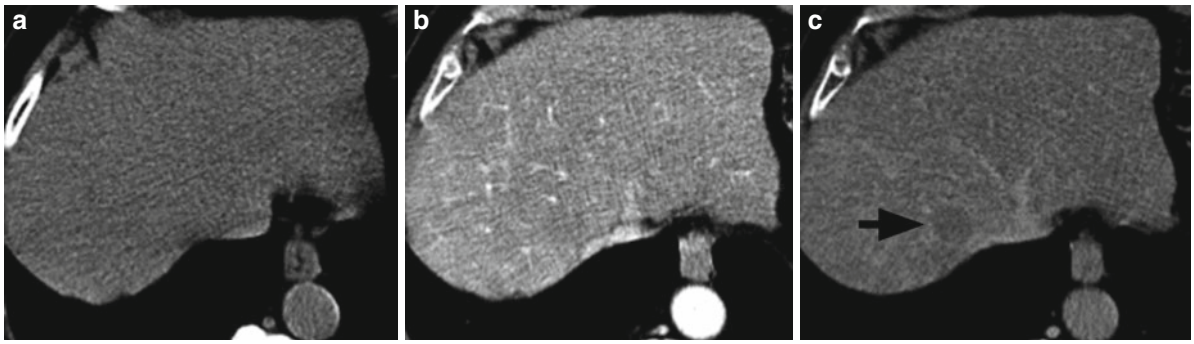

Fig. 69.3 CT scans show a dysplastic nodule in a cirrhotic liver. On the (**a**) unenhanced and (**b**) hepatic arterial phase images, no definite lesion can be identified. (**c**) Corresponding image obtained during the delayed phase demonstrates a hypoattenuating nodule (*arrow*) in segment VIII, interpreted to be HCC. Results of US-guided percutaneous liver biopsy demonstrated that the lesion was a high-grade dysplastic nodule

Imaging findings of dysplastic nodules are similar to those of regenerative nodules at CT. Dysplastic nodules should be suspected when a nodule is solitary and/or larger than 2 cm (Borzio et al. 2003). Because the main blood supply to dysplastic nodules is from the portal venous system and that to HCC is from the hepatic arterial system, a dysplastic nodule often can be distinguished from HCC at dynamic contrast-enhanced CT based on the absence of hyperenhancement on the late arterial phase (Choi et al. 1999). Although generally effective, this rule may not apply to high-grade dysplastic nodules due to increasingly higher arterial vascularity (Krinsky et al. 1998; Jeong et al. 2002). Dysplastic nodules may manifest hypoattenuation compared to the surrounding liver on delayed images (acquired 3–10 min after contrast injection), simulating the imaging appearance of hypovascular, well-differentiated HCC (Bolondi et al. 2005) (Fig. 69.3).

Besides hepatocellular nodules, it is also important to recognize and accurately characterize other liver lesions that are commonly encountered in cirrhosis, including peribiliary cysts, hemangiomas, and transient hepatic attenuation differences (THAD). Peribiliary cysts occur because of obstruction of the periductal glands of bile ducts. The typical appearance of peribiliary cysts is the presence of multiple, small and well-defined, hypoattenuating round structures adjacent to the biliary ducts in the hepatic hilum.

Hepatic hemangiomas are less common in the patients with cirrhosis compared to the general population. This may be due to the spongy texture of these benign vascular tumors that is prone to obliteration and scarring as the process of fibrosis progresses. Serial CT studies demonstrated progressive decrease in size of hepatic hemangiomas, which may be associated with retraction of the liver capsule when the lesion is large and peripherally located (Brancatelli et al. 2001). Loss of some identifying characteristics, such as peripheral nodular enhancement and isoattenuation to blood vessels, may also occur in hemangiomas with progression of cirrhosis. Notably, smaller lesions (<3 cm) commonly demonstrate bright uniform enhancement during the late arterial phase (the so-called, flash-filling enhancement pattern), potentially mimicking small hypervascular HCC. Although isoattenuation with blood vessel during different vascular phases (always present in hemangiomas but not HCC) should lead to unambiguous diagnosis in challenging cases, variability has been reported in reader's identification of this finding (Fig. 69.4).

THAD is another commonly seen entity in patients with cirrhosis. THAD is the result of an increased arterial blood supply in a region of the liver due to arterial-portal shunts. Enlargement and tortuosity of the hepatic artery is a commonly associated finding in patients with THAD. On arterial phase images, THAD is identified as geographic, often peripheral areas of enhancement with characteristic wedge-shaped morphology. Characteristically, THADs demonstrate isoattenuation or only mild persistently higher enhancement relative to the surrounding liver on the hepatic venous and delayed phase images (Fig. 69.5). Although generally straightforward, diagnosis of THAD may be challenging for diminutive lesions that may not show the characteristic wedge-shaped

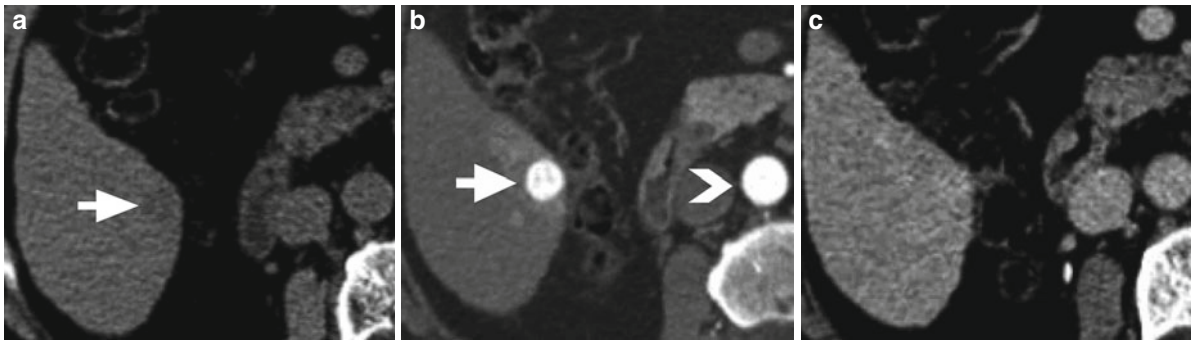

Fig. 69.4 CT scans show a flash-filling hemangioma in a cirrhotic liver. (**a**) On transverse nonenhanced CT image, the hemangioma (*arrow*) is subcapsular and isoattenuating to blood. (**b**) On corresponding image obtained during the hepatic arterial phase, the entire hemangioma enhances homogeneously and almost equally compared with vessels. (**c**) Hepatic venous phase image at the same level. The hemangioma remains isoattenuating to vessels. In such cases, a confident diagnosis of hemangioma may not be possible without additional imaging or biopsy

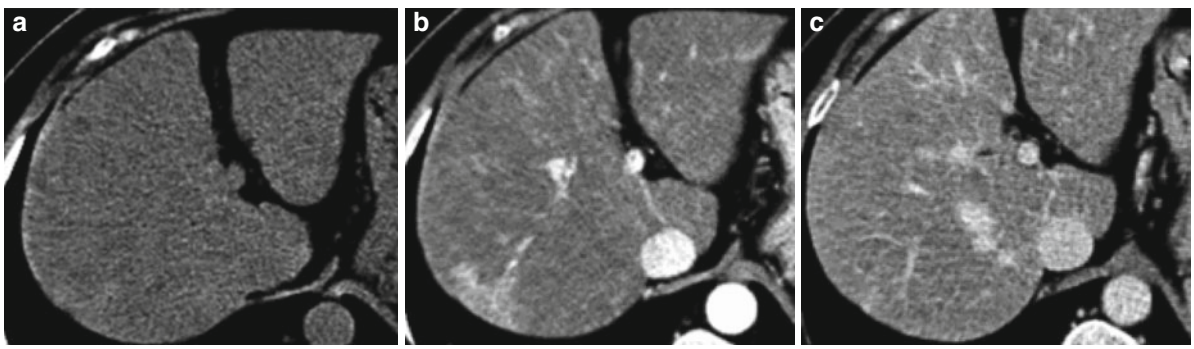

Fig. 69.5 CT scans show transient hepatic attenuation difference (THAD) in a cirrhotic liver. (**a**) Transverse nonenhanced CT image demonstrates no obvious liver lesion. (**b**) Corresponding image obtained during the hepatic arterial phase shows a peripheral wedge-shaped homogeneously hyperattenuating area (THAD). (**c**) Hepatic venous phase image at the same level. The THAD becomes isoattenuating to the surrounding liver. The peripheral location, wedge shape, and enhancement pattern are characteristic features of THAD

morphology. According to recent evidence, THADs represent one of the most common pitfalls in patients with cirrhosis being screened for HCC (Brancatelli et al. 2003). In some cases, THAD may be caused by tumor obstruction of a portal venous branch at the level of the apex of the wedge-shaped area of enhancement.

Sensitivity of CT for detecting fibrosis is low in early stages of cirrhosis. However, fibrosis may prevail in more advanced stages of cirrhosis, particularly when secondary to alcohol abuse or primary sclerosing cholangitis. This may lead to focal areas of confluent fibrosis involving one or more liver segments. Typical imaging findings of focal confluent fibrosis include: (a) peripheral location, (b) involvement of the medial segments of the left hepatic lobe and/or anterior segments of the right hepatic lobe, (c) retraction of the overlying liver capsule, and (d) hypoattenuation compared to the surrounding liver on unenhanced CT followed by mild but persistent contrast enhancement during the late arterial, hepatic venous, and delayed phases (Fig. 69.6). In a small number of cases, focal confluent fibrosis may have a rounded configuration, causing potential problems in the differential diagnosis with HCC (Ohtomo et al. 1993). Other ancillary findings and, as recently suggested, demonstration of a characteristic wedge-shaped morphology on different imaging planes (e.g., sagittal and coronal) may allow a definite diagnosis in challenging cases.

CT has high accuracy in the evaluation of late complications of portal hypertension. By taking advantage of its multiplanar imaging capabilities, CT can readily demonstrate the development of major portosystemic

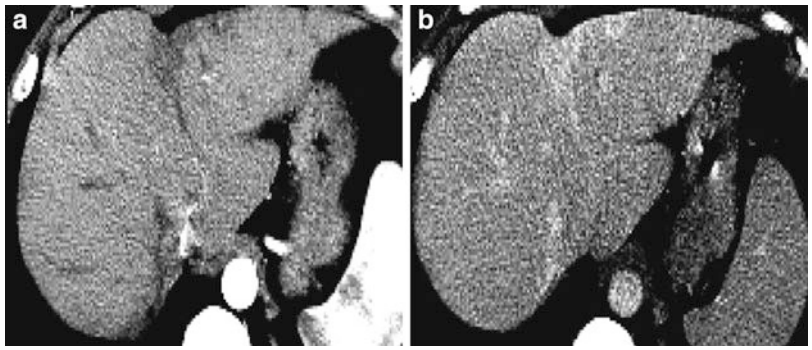

Fig. 69.6 CT scans show focal confluent fibrosis in a cirrhotic liver. (**a**) Transverse hepatic arterial phase CT image demonstrates low attenuation peripherally in segment IV. Overlying capsular retraction is suggestive of fibrosis, since untreated tumor tissue should cause a capsular bulge. (**b**) Corresponding image obtained during the delayed phase shows persistent enhancement of the lesion consistent with contrast material accumulation in the fibrotic tissue

collaterals, including: (a) esophageal and gastric varices, (b) patent paraumbilical veins, (c) splenorenal and gastrorenal shunts, (d) splenomegaly, and (e) ascites.

Magnetic Resonance (MR) Imaging

MR imaging has emerged as an important imaging modality for assessing cirrhosis and its complications (Mitchell 2000). MR imaging is considered the modality of choice in the characterization of liver lesions, particularly when hepatobiliary or reticuloendothelial system (RES) liver-specific contrast agents are used. In addition, MR imaging has higher sensitivity compared to CT for the detection of fat, iron, or the combination of both. Limitations of MR imaging include the longer examination time compared to CT, lower spatial resolution (x-, y-, and z-axes), suboptimal image quality in uncooperative patients and in patients with large volumes of ascites, and higher cost.

MR imaging protocols of the liver include a combination of sequences, most importantly T2-weighted fast spin-echo sequences, dual gradient-echo T1-weighted sequences with opposed-phase and in-phase acquisitions, and dynamic gadolinium-enhanced three-dimensional T1-weighted sequences during different vascular phases (i.e., late arterial, hepatic venous, and delayed phases). When liver-specific contrast agents are used, delayed images during the liver-specific phase are also acquired. More recently, diffusion-weighted imaging has been used in the study of the liver. This sequence may provide important additional information for both improved lesion detection (due to the higher lesion-to-liver contrast and lower susceptibility to blurring at low b values compared to a standard fast spin-echo sequence) and characterization (using the diffusion information at high b-values).

MR imaging provides information similar to CT in the evaluation of morphologic changes of the liver and ancillary findings of portal venous hypertension in cirrhosis. The sensitivity of MR imaging for detection of regenerative nodules remains low, similar to CT. These lesions cannot be discriminated from the surrounding liver on unenhanced and contrast-enhanced T2-weighted and T1-weighted images, as well as images acquired during the liver-specific phase of hepatobiliary and RES-specific contrast agents (Hanna et al. 2008).

However, MR imaging has significantly higher sensitivity compared to CT for detecting regenerative nodules with increased iron accumulation. These nodules, commonly referred to as siderotic nodules in the radiology literature, have been reported in up to one third of patients with long-standing viral or alcoholic cirrhosis (Krinsky et al. 2000). Unlike most regenerative nodules, siderotic nodules demonstrate distinctive low signal intensity on T1-weighted and T2-weighted imaging. This finding becomes more evident with sequences that are particularly sensitive to susceptibility effects from iron molecules, such as T2*-weighted gradient-echo images and fast low angle shot T1-weighted images with longer echo times. Susceptibility effects are also responsible for the characteristic blooming artifact on these sequences, which may be detrimental for the accurate assessment of lesion's size. In approximately 30% of cases, siderotic nodules

may develop pathologic features that are concerning of dysplasia, thus posing the patient at risk for the development of HCC (Krinsky et al. 2000). While clinically relevant, the distinction between benign regenerative and more worrisome dysplastic siderotic nodules is not possible with any of the currently available imaging modalities.

Siderotic nodules may also be seen in the spleen of patients with portal venous hypertension. These lesions (also known as Gamna-Gandy bodies) correspond to amorphous parenchymal deposits of hemosiderin and demonstrate overlapping imaging findings with siderotic nodules in the liver at MR imaging (Sagoh et al. 1989). Gamna-Gandy bodies, however, demonstrate no uptake of hepatobiliary contrast agents during the liver-specific phase. No correlation has been shown between Gamna-Gandy bodies and the severity of portal hypertension.

Dysplastic nodules cannot be differentiated from benign regenerative nodules at MR imaging (Hanna et al. 2008). Occasionally, imaging findings may give a clue to the diagnosis of dysplastic nodules, including isointensity or slight hypointensity relative to the surrounding liver on T2-weighted images in association with lack of hyperenhancement during the late hepatic arterial phase (Fig. 69.7). High signal intensity on T2-weighted images and arterial enhancement, on the other hand, should raise the suspicion for HCC (Hussain et al. 2004). The imaging appearance of dysplastic nodules on unenhanced T1-weighted images is nonspecific and thus noncontributory to the diagnosis. It is conceivable that higher sensitivity to gadolinium-based contrast agents may improve the detection of subtle areas of arterial enhancement in dysplastic nodules. This sign (also known as the nodule in the nodule sign) strongly favors the presence of foci of HCC within dysplastic nodules. Unfortunately, higher sensitivity to contrast enhancement may also result in higher frequency of false-positive or indeterminate results, thus decreasing the specificity of the test. Liver-specific MR contrast agents may provide important additional information in the characterization of hepatocellular nodules (Gandhi et al. 2006).

MR imaging is also superior to CT in the characterization of nonhepatocellular liver lesions in cirrhosis. T2-weighted and diffusion-weighted images provide critical information in the diagnosis of peribiliary cysts and hemangiomas. In addition, the greater sensitivity to contrast enhancement may result in better visualization of typical enhancement patterns in small atypical hemangiomas. Finally, liver-specific MR contrast agents may help in differentiating atypical, not wedge-shaped THADs from small HCC (Kim et al. 2011).

Sensitivity of MR imaging for detecting fibrosis is greater than that of CT (Faria et al. 2009). Fibrotic septa can be seen in patients with moderate to severe cirrhosis as subtle parenchymal reticulations showing low T1 and high T2 signal intensity. These septa become more conspicuous on T1-weighted gadolinium-enhanced images acquired during the delayed phase (3–10 min after contrast material administration), due to persistent enhancement or delayed washout of fibrotic tissue compared to the surrounding liver (Fig. 69.8). Recently, a double contrast MR technique – with the sequential administration of superparamagnetic iron oxide contrast agents and standard extracellular gadolinium-based contrast agents – has been suggested to further increase the visualization of fibrosis on MR imaging (Aguirre et al. 2006). With this technique, signal intensity of the normal regenerating liver is selectively decreased due to uptake of iron oxide particles by RES cells (Kuppfer cells). This is in distinction with the high signal intensity of fibrotic septa due to prolonged retention of gadolinium extracellular agents. Preliminary experience suggests that a double contrast technique may accurately differentiate severe fibrosis from mild-to-moderate fibrosis. However, high cost and inconveniences associated with the use of two contrast agents remain major limitations that prevented widespread clinical use of this technique.

Ultrasonography

Due to a combination of high spatial resolution and inherent soft-tissue contrast, lack of ionizing radiation, low cost, and wide availability, ultrasonography is frequently the first-line imaging modality for the study of the liver. Operator dependency, substantial image degradation in obese patients, and limited field-of-view, however, represent major limitations of this modality compared to other cross-sectional imaging techniques.

Cirrhosis is typically characterized by a diffusely coarsened and heterogeneous echo pattern, increased parenchymal echogenicity, and increased sound attenuation. These findings, however, are nonspecific and

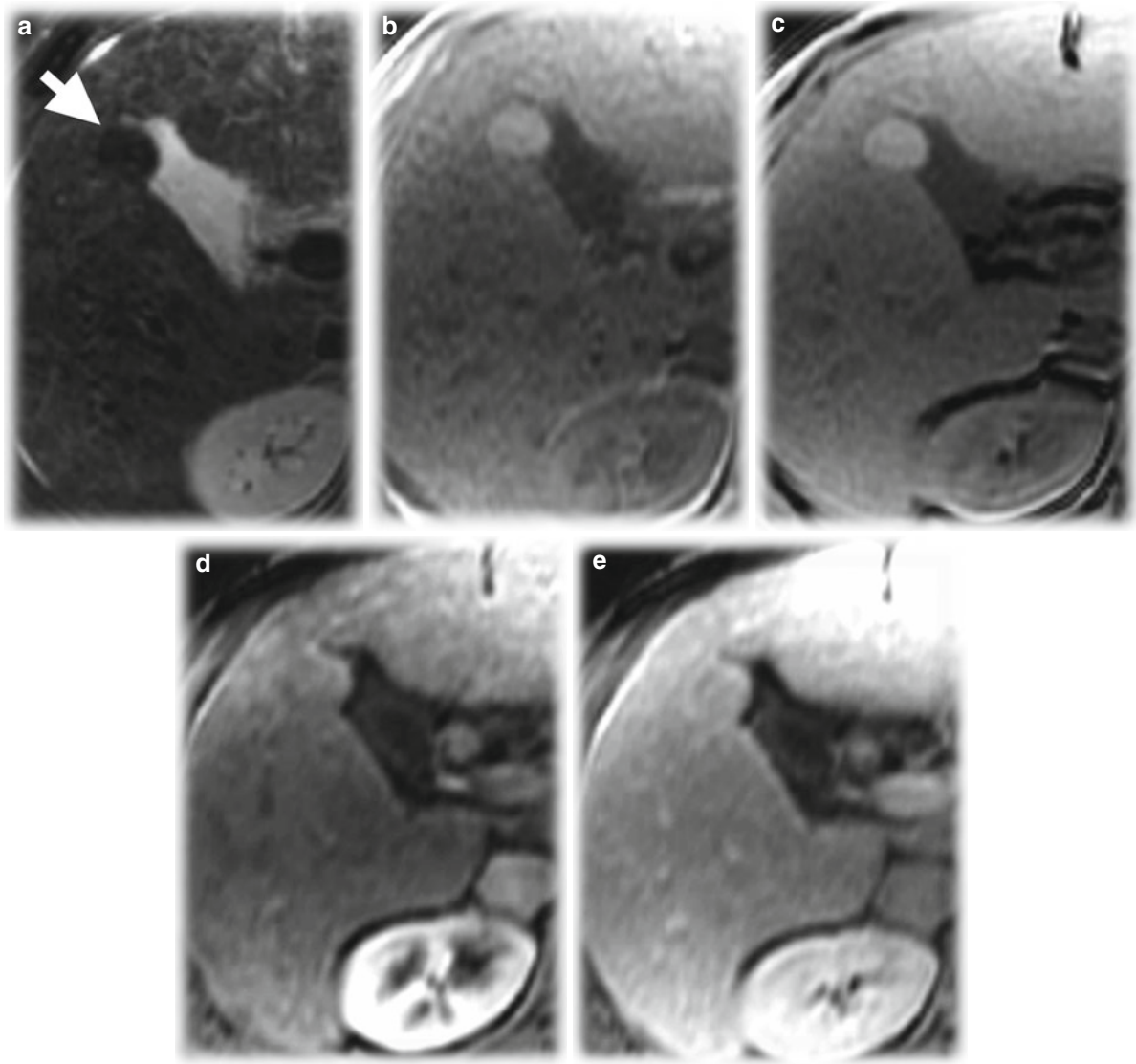

Fig. 69.7 MR scans show a dysplastic nodule in a cirrhotic liver. (**a**) Transverse T2-weighted turbo spin-echo MR image shows a hypointense mass (*arrow*) in the inferior right lobe of the liver. The mass is hyperintense on the T1-weighted breath-hold (**b**) in-phase and (**c**) out-of-phase single breath-hold gradient-echo images. Corresponding transverse (**d**) hepatic arterial phase and (**e**) hepatic venous phase images show isointensity of the lesion compared to the surrounding liver

may also be seen in diffuse fatty liver disease, hepatic lymphoma, and diffuse multifocal metastatic liver disease. Liver surface nodularity is the most specific finding of cirrhosis (Di Lelio et al. 1989). It is more readily visualized in patients with ascites, particularly when high-resolution linear transducers are used.

The role of sonography in the detection of HCC in patients with cirrhosis varies in different parts of the world. In Western countries, sonography is used as a screening test for HCC in conjunction with serologic testing for alfa-fetoprotein. The sonographic appearance of HCC is variable and nonspecific. Small tumors (less than 5 cm in diameter) tend to be hypoechoic and uniform in appearance, while larger masses are usually heterogeneous. In a minority of lesions, fatty deposition causes increased echogenicity that can mimic the appearance of hemangiomas.

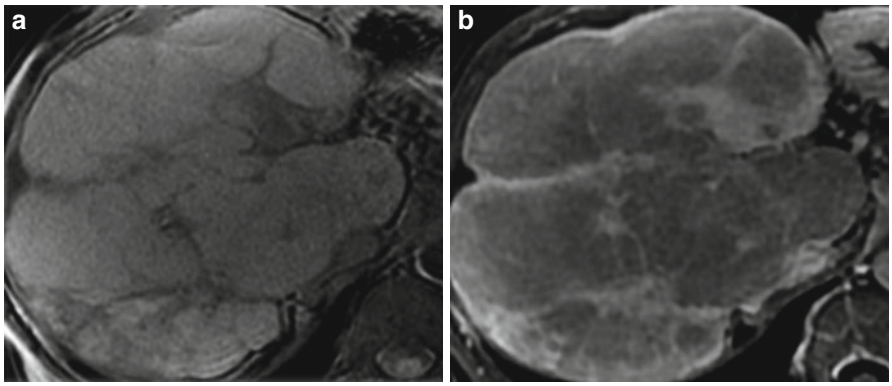

Fig. 69.8 MR scans show liver fibrosis in a patient with advanced alcohol-induced cirrhosis. (**a**) Transverse T1-weighted breath-hold in-phase image demonstrates fibrotic septa and bridges as hypointense reticulations throughout the liver parenchyma. (**b**) On corresponding T1-weighted breath-hold in-phase delayed phase image, fibrotic reticulations demonstrate progressive enhancement and become progressively hyperattenuating compared to adjacent liver parenchyma

Differential Diagnosis

Treated Liver Metastases or Lymphoma

In patients with metastases to the liver, tumor response to chemotherapy can result in areas of retraction and scarring, alternating with other areas of liver regeneration. These findings have been described as pseudocirrhosis and can be observed within weeks to months after starting therapy (Young et al. 1994) (Fig. 69.9). The key feature for the differential diagnosis with cirrhosis is the absence of bridging portal fibrosis at histology.

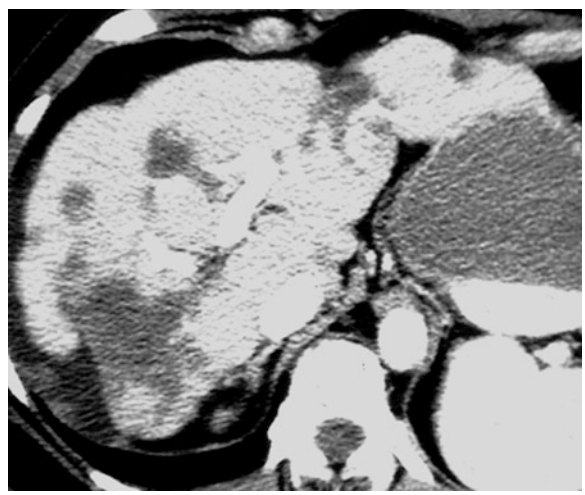

Fig. 69.9 CT scan in a 56-year-old female with breast cancer treated with chemotherapy. Transverse hepatic venous phase image demonstrates diffuse hepatic nodularity and geographic hypoattenuating areas consistent with fibrosis. Findings are of pseudocirrhosis of treated breast cancer metastases; however, without prior studies and clinical history, these findings could suggest diagnosis of cirrhosis

Diffuse Multifocal Metastatic Liver Disease

In patients with advanced metastatic liver disease, particularly when secondary to breast cancer or melanoma, the liver may become entirely replaced by multiple nodules, mimicking the appearance of macronodular cirrhosis. At times, signs and symptoms of portal hypertension also occur. Key findings for the differential diagnosis with cirrhosis include increased liver size (compared to decreased liver size in cirrhosis) and absence of bridging portal fibrosis.

Hepatic Necrosis and Regeneration after Fulminant Hepatitis

In patients with fulminant hepatitis, large areas of liver necrosis lead to disorganized fibrosis and regenerating nodules (Murakami et al. 1996). Although the appearance may simulate that of cirrhosis, clinical history allows a confident diagnosis in most patients.

Budd-Chiari Syndrome

Budd-Chiari syndrome occurs because of obstruction of the hepatic venous outflow leading to venous

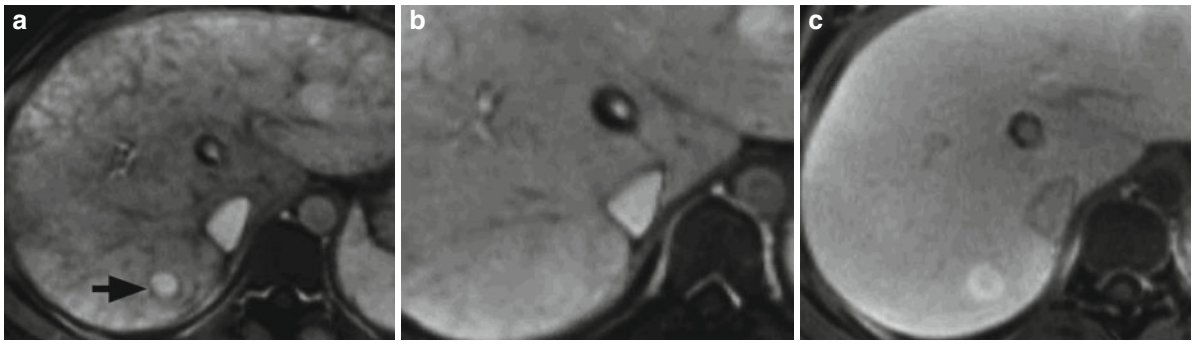

Fig. 69.10 MR scans show a large regenerative nodule in a 37-year-old woman with Budd-Chiari syndrome. (**a**) Transverse hepatic arterial phase image shows a lesion with marked homogeneous enhancement (*arrow*) in the right lobe of the liver. (**b**) Corresponding hepatic venous phase image shows isointensity of the lesion compared to the surrounding liver. (**c**) Delayed phase image acquired during the hepatobiliary phase (180 min after intravenous administration of gadobenate dimeglumine) demonstrates persistent accumulation of the contrast material within the lesion, a finding suggestive of deranged biliary drainage in a large benign regenerative nodule

congestion, centrilobular necrosis, and regenerative hyperplasia. Although findings may mimic cirrhosis, the absence of patent hepatic veins and the atrophy of the peripheral areas of the liver with hypertrophy of the central liver regions (most strikingly the caudate lobe) provide clues for the diagnosis (Brancatelli et al. 2007). Hypervascular large regenerative nodules may develop in many patients with Budd-Chiari syndrome. Although these lesions may mimic hypervascular HCC during the arterial phase, other findings may allow a confident diagnosis in most cases. These findings includes (a) the multiplicity of the lesions, (b) the lack of washout sign, and (c) the characteristic hypointensity on T2- and hyperintensity on T1-weighted images due to paramagnetic metal ions (Brancatelli et al. 2002) (Fig. 69.10).

Cavernous Transformation of the Portal Vein

Cavernous transformation of the portal vein is a physiologic compensatory response that aims to restore portal venous blood flow after complete thrombotic occlusion of the portal vein. Cavernous transformation of the portal vein can develop in as little as a week after portal vein thrombosis and it can lead to profound alterations of liver morphology and vascular hemodynamics, including (a) atrophy of the left lateral segment and/or right liver lobe, (b) hypertrophy of the caudate lobe and medial segments of the left liver, (c) signs and symptoms of portal hypertension, and (d) mass effect on the suprapancreatic portion of the common bile duct (commonly referred to as portal cavernoma-associated cholangiopathy). Recent anecdotal observations also suggest that CTPV may foster the growth of large regenerative nodules. These nodules have similar imaging findings and common pathogenesis with large regenerative nodules in Budd-Chiari syndrome (Bureau et al. 2004).

Nodular Regenerative Hyperplasia of the Liver

Nodular regenerative hyperplasia is described histopathologically as regenerative nodules with little or no hepatic fibrosis and largely healthy hepatic architecture. This entity is associated with signs and symptoms of portal hypertension and may not be differentiated from cirrhosis based on imaging findings. Biopsy is necessary for a confirmative diagnosis.

Key Features

- Cirrhosis is a pathologic and clinical entity characterized by extensive fibrosis and innumerable regenerative nodules.
- Although the definitive diagnosis of cirrhosis is based on the results of liver biopsy, imaging plays a critical role in the assessment of the severity of the

liver damage and in the early detection of complications, particularly hepatocellular carcinoma. In addition, imaging may provide the first clue for the diagnosis of cirrhosis in patients with no or very little clinical symptoms.

- Key findings for the diagnosis of cirrhosis at imaging include: (a) nodular liver contour, (b) atrophy of the right hepatic lobe and medial segment of the left hepatic lobe, (c) widening of the porta hepatis and gallbladder fossa, and (d) compensatory hypertrophy of the lateral segment of the left hepatic lobe and caudate lobe. Ancillary findings of portal hypertension are also critical in the diagnosis and evaluation of severity of cirrhosis.
- CT is the modality of choice in the preoperative diagnosis, staging, treatment planning, and follow-up of patients with known or suspected hepatic tumors. CT is also recommended in uncooperative patients and patients with large volume of ascites due to the lower susceptibility to motion artifacts.
- Due to the higher soft-tissue contrast and increased sensitivity to gadolinium-chelate contrast agents, MR imaging is commonly recommended as a problem-solving modality in patients with indeterminate liver lesions at CT. Liver-specific MR contrast agents provide critical additional information for the characterization of liver lesions and are recommended in cirrhotic patients with indeterminate liver lesions.
- Both CT and MR have low sensitivity for the early detection and quantification of liver fibrosis, thus making serial liver biopsies necessary in the evaluation of the progression of disease.
- Ultrasonography has limited role in the evaluation of cirrhosis and its complications. However, due to the lack of ionizing radiation, low cost, and wide availability, ultrasonography is frequently used in the screening of cirrhotic patients for HCC.

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