

Cirrhosis

Prof. Muhammad Saeed Khokhar

Cirrhosis of the liver is the end stage of a complex process resulting from hepatocyte injury and the response of the liver that leads to partial regeneration and fibrosis.

Cirrhosis poses a difficult challenge for management and engenders major health costs in prevention, detection, and therapy. Diagnostic imaging offers diverse modalities used in the noninvasive evaluation of the liver, and interventional techniques, which may be used to treat complications such as portal hypertension or neoplasia. The contribution of these techniques to diagnosis, management, and therapy are reviewed in this article.

Pathophysiology

Cirrhosis may develop as a chronic, insidious process, most commonly from continued exposure to toxic agents (such as long-term ethanol abuse), chronic viral infection, or to disorders of metabolism such as hemochromatosis, of biliary origin, or resulting from autoimmune disease. It may occur in response to massive injury from toxins, infection, or ischemia that has resulted in acute hepatocyte necrosis. Occasionally, the etiology is never determined and is labeled “cryptogenic.”

The role of marrow stem cells in the cycle of hepatocyte renewal only recently has been recognized through work by Alison et al. Regeneration and scarring lead to gross morphologic and pathophysiologic changes in hepatic circulation, both of which contribute to morbidity in terms of reduced metabolic function and elevation of portal venous pressures, with resultant risk for fatal variceal hemorrhage. Hepatocellular carcinoma (HCC) is a frequent and usually fatal complication. Patients with cirrhosis due to primary sclerosing cholangitis may develop cholangiocarcinoma, which is also invariably fatal.

Cirrhosis and chronic liver disease comprise the 10th most common cause of death in the United States since 1994. In the United States, Schultz et al report that chronic liver disease and cirrhosis accounted for 26,050 deaths per annum as of 1987, with disability in more than 100,000, and accounted

for 300,000 hospitalizations and 1 million physician office visits. US Department of Health and Human Services statistics indicate that alcohol is a contributing factor in 50% of deaths. However, the age-adjusted death rate for chronic liver disease has decreased 23% from 1980-1989, from 13.5-10.4 per 100,000. Worldwide, the WHO estimates that cirrhosis is responsible for 1.1% of all deaths.

Hepatic Morphologic Changes

Regardless of etiology, gross morphologic changes of cirrhosis are recognized by a variety of image techniques. Enlargement of the left lobe and caudate lobe, believed to be the result of lobar-relative regeneration rather than fibrosis, secondary to an accident of vascular supply, is recognized by any cross-sectional technique such as CT, MRI, or ultrasound (US). Often, concomitant volume loss occurs in the right lobe because of progressive fibrosis (The degree of scarring is variable and occasionally results in regions of retraction extending to the capsule in wedge-shaped or irregular patterns.

In contradistinction to alcoholic and viral cirrhosis, cirrhosis from primary sclerosing cholangitis has a different morphology, including atrophy of the lateral segment of the left lobe and massive enlargement of the caudate lobe. This pattern also can be seen in autoimmune cirrhosis. Cirrhosis from hepatic veno-occlusive disease (Budd-Chiari) has a characteristic massive enlarged caudate lobe that should not be confused with a neoplasm.

A recent study by Okazaki et al using MRI determined that alcoholic cirrhosis is associated more frequently with caudate lobe enlargement and the presence of a right posterior hepatic notch than with virus-induced cirrhosis. Harbin et al, Giorgio et al, and Hess et al have described a number of indices, including the ratio of transverse caudate lobe width to right lobe width, multidimensional caudate lobe indexes that can be obtained by USG or CT, and volume analysis of each liver segment, based on cross sectional area by CT or MR imaging as described by Torres et al. Lafortune et al suggest that a reduction in the medial segment of the left hepatic lobe diameter is a helpful adjunct finding of cirrhosis in the USG

Investigation.

Recently, another sign of cirrhosis, the expanded gallbladder fossa sign, has been described on MRI examination (based on an evaluation by Ito et al (Radiology, vol. 211, 1999) of 190 patients with cirrhosis and 123 control patients. The criteria were enlargement of the pericholecystic space (i.e. gallbladder fossa), which had to be demarcated laterally by the edge of the right hepatic lobe, medially by the edge of the lateral segment of the left hepatic lobe, or posteriorly by the anterior edge of the caudate lobe, in conjunction with nonvisualization of the medial segment of the left hepatic lobe on the same axial image. This achieved a sensitivity, specificity, accuracy, and positive predictive value for the MR diagnosis of cirrhosis of 68%, 98%, 80%, and 98%, respectively.

On USG examination, the liver contour may appear nodular although Ladenheim et al recently have questioned the specificity of this sign. Similar contour deformities are evident on CT or MRI examination. The echo texture appears coarsened. Increase in echogenicity is caused by fatty infiltration, which may be diffuse in hepatitis or focal in hepatitis or cirrhosis.

Intrahepatic Vascular Changes in Cirrhosis

In cirrhosis, the dynamics of the hepatic arterial and portal venous circulation changes as the degree of fibrosis progresses. As portal hypertension develops, portal flow is reduced and subsequently reversed, with compensatory increase in hepatic arterial flow. The hepatic artery diameter increases, and absolute blood flow increases by as much as 100%. In addition, the vessels appear to elongate and become more tortuous because of the underlying parenchymal architectural distortion. This is recognized classically in angiography as “corkscrewing” of vessels and can be appreciated on cross sectional imaging.

Secondary manifestations of cirrhosis may be seen as morphologic or physiologic evidence; the development of spontaneous shunts has been described in advanced cirrhosis and initially demonstrated by angiography, but now is demonstrable by noninvasive techniques, such as Doppler USG, at an incidence of up to 7%.

The presence of these high-velocity shunts appears to correlate with changes in commonly measured parameters on Doppler evaluation, such as the resistive index (RI) and pulsatility (PI) index in the right and left branches of the hepatic artery. Using criteria for a shunt of a decrease in RI of greater than

20%, and a decrease in PI of greater than 30% in one hepatic lobe relative to the other lobe (all shunts were confirmed angiographically), Bolognesi et al determined that a net increase in RI and PI occurred in patients with cirrhosis with such shunts. Mean RI in patients with a shunt was $35\% \pm 6$ (range, 27%-42%) versus $5\% \pm 4$ in controls (range, 0%-15%; $P < .001$); and mean PI was $50\% \pm 5$ (range, 41%-58%) versus $11\% \pm 7$ (range, 0%-26%; $P < .001$).

Dual-phase CT also can demonstrate these shunts as early opacification of the intrahepatic veins during the early arterial phase injection. They often are accompanied by geographic wedge-shaped perfusion abnormalities.

Some cause for optimism is warranted in terms of reduction in the incidence of HCC in patients with hepatitis C following interferon therapy. A recent meta-analysis by Papatheodoridis et al of 5 studies involving more than 2000 patients determined that the incidence of HCC was reduced to 8.2%, compared to 21.5% in untreated patients, and was even lower in sustained responders (0.9%).

Extrahepatic Manifestations of Cirrhosis Detectable by Imaging Techniques

Alteration in the thickness of the wall of the GI tract also has been reported in patients with cirrhosis by Marshak et al and Karahan et al at a higher frequency than controls (64% vs 7%) and is thought to represent edema. The gallbladder wall may appear thickened.

Prominent mesenteric edema and stranding also occur with increased frequency in 86% of patients in Chopra's recent series. Mesenteric edema occurred alone in 38% and with omental or retroperitoneal edema in 58% of the 69 patients with edema. Although mild in most patients, it can appear as a severe masslike sheath that engulfs the mesenteric vessels. This phenomenon is associated with the presence of ascites, pleural effusions, subcutaneous edema, and low mean serum albumin levels, but not with splenomegaly or varices.

The development of splenomegaly and collaterals from portal hypertension is readily evident by any cross sectional technique and is discussed in the following section. Functional imaging techniques such as technetium Tc 99m-labeled sulfur colloid, which is taken up by reticuloepithelial cells, and the presence of “colloid shift” to the bone marrow in cirrhosis, in addition to recognition of hepatic morphologic changes and splenomegaly, have been helpful in confirming the presence and severity of

cirrhosis.

Portal Hypertension

Portal hypertension occurs once portal pressures are 5-10 mm Hg above normal as a complication of cirrhosis. The pathogenesis is complex, involving increased resistance within the liver and hyperdynamic flow mediated by circulating factors. The effect of increasing portal pressures is well recognized as the development of splenomegaly and collateral portal-venous anastomoses, which occur at numerous sites, including gastroesophageal, paraumbilical, perirectal, and retroperitoneal.

The consequences of portal hypertension include development of ascites, GI tract hemorrhage, or enteropathy. Hepatic dysfunction affecting clotting factors and functional hypersplenism impacting platelet life increase the risk of massive GI hemorrhage. Encephalopathy may worsen significantly if shunts are large. It is not uncommon for patients with unsuspected cirrhosis to present with these manifestations.

Screening Trends

Development of HCC may be expected 10-15 years after the onset of cirrhosis, although rarely, cases may occur in the setting of chronic hepatitis alone. Unlike patients with hepatitis C in whom HCC does not occur without cirrhosis, patients with hepatitis B can develop HCC at any point after infection. The cumulative incidence of cirrhosis in patients with hepatitis C infection has been reported by Aizawa et al to be as high as 42% at 15 years after diagnosis, thus screening such patients represents a major public health challenge.

Regeneration within the liver may result in a host of dysplastic lesions, which form a spectrum from premalignant to frankly malignant and invasive. Neoplasms occur in markedly differing levels of aggressiveness and differentiation, with more aggressive lesions often arising in patients with multiple etiologies, such as alcohol-related cirrhosis in association with hepatitis C.

A search for serologic markers for neoplastic disease has identified a number of promising markers, in addition to alpha-fetoprotein (AFP). Serial measurement of AFP levels remains a mainstay of management, but the test is not particularly sensitive and certainly is nonspecific. However, levels greater than 200 ng/mL are highly suggestive of HCC. Patients with persistently elevated values are at higher risk for developing HCC.

Preferred Examination

1. **USG** is the most widely used worldwide imaging modality in combination with serum AFP screening, based on evidence that increased frequency of examination leads to detection of HCC at an earlier stage.
2. **CT** scan is believed to be equivalent in sensitivity and more specific. However, there are disadvantages related to contrast risk and radiation exposure, particularly if used over a lifetime screening.
3. **MRI** with gadolinium (or other contrast agents) can be used as an alternative (although more costly) study, although in patients with end-stage disease, reduced sensitivity below 50% has been reported, particularly for lesions below 2 cm, similar to USG and CT.

Limitations of Techniques

Real-time USG is used extensively for screening, but biopsy or additional imaging modalities are required for confirmation. USG is a nonspecific test and identifies many nodules, ranging from regenerative nodules, dysplastic nodules, and focal fat to benign neoplasms such as hemangioma, many of which have no uniquely discriminating features on USG.

Therefore, it is necessary to commit either to biopsy all persistent lesions or to corroborate them prior to biopsy with other techniques, such as CT (helical or multislice) or MRI, using dynamic imaging with contrast to obtain multiple vascular phase images. Clinician preferences in the United States surveyed by Chalasani et al suggest a recent, albeit empirical trend toward incorporating CT routinely in screening.

4. X-rays Findings

Radiography has a modest place in the diagnosis and management of patients with cirrhosis, for example in screening for ascites, seeking evidence for bowel perforation in patients with suspected bacterial peritonitis, and monitoring bowel distension in acutely ill patients admitted for treatment of decompensation or variceal hemorrhage.

5. **Liver Biopsy** Liver biopsy will confirm the cirrhosis and stages of fibrosis.

Treatment

Often, the only required treatment for cirrhosis is removing the offending cause:

- The alcoholic patient must permanently stop consuming alcohol.

- When iron is being retained in the body, chronic removal of blood by vein eliminates large amounts of iron.
- Cortisone medicine helps treat autoimmune hepatitis and cirrhosis.
- Restricting salt and using fluid pills (diuretics) reduce edema and abdominal swelling.
- Toxins and injurious drugs must be avoided.
- Decreasing dietary protein and using certain laxatives generally can prevent changes in mental function.
- Bleeding veins in the esophagus can be injected with sclerosing (clotting) agents or closed with small rubber bands. Occasionally, surgery is necessary to prevent recurrent massive bleeding.
- Ursodiol (Actigall) and other drugs have been helpful in treating primary biliary cirrhosis and primary sclerosing cholangitis.
- Liver transplantation has progressed to the stage where it can now be considered as standard treatment for selected patients.

theesculapio@hotmail.com

References

1. Bosch J, Garcia-Pagan JC: Complications of cirrhosis. I. Portal hypertension. *J Hepatol* 2000; 32 (1 Suppl): 141-56.
2. CDC: Deaths and hospitalizations from chronic liver disease and cirrhosis -- United States, 1980-1989. *MMWR Morb Mortal Wkly Rep* 1993 Jan 8; 41 (52-53): 969-73.
3. Dodd GD 3rd, Baron RL, Oliver JH 3rd, Federle MP: Spectrum of imaging findings of the liver in end-stage cirrhosis: part I, gross morphology and diffuse abnormalities. *AJR Am J Roentgenol* 1999 Oct; 173 (4): 1031-6.
4. El-Serag HB, Mason AC: Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999 Mar 11; 340 (10): 745-50.
5. Ferral H, Male R, Cardiel M, et al: Cirrhosis: diagnosis by liver surface analysis with high-frequency ultrasound. *Gastrointest Radiol* 1992 Winter; 17 (1): 74-8.
6. Giorgio A, Amoroso P, Lettieri G, et al: Cirrhosis: value of caudate to right lobe ratio in diagnosis with USG. *Radiology* 1986 Nov; 161 (2): 443-5.
7. Harbin WP, Robert NJ, Ferrucci JT Jr: Diagnosis of cirrhosis based on regional changes in hepatic morphology: a radiological and pathological analysis. *Radiology* 1980 May; 135 (2): 273-83.
8. Hess CF, Schmiedl U, Koelbel G, et al: Diagnosis of liver cirrhosis with USG: receiver-operating characteristic analysis of multidimensional caudate lobe indexes. *Radiology* 1989 May; 171 (2): 349-51.
9. La Vecchia C, Levi F, Lucchini F, et al: Worldwide patterns and trends in mortality from liver cirrhosis, 1955 to 1990. *Ann Epidemiol* 1994 Nov; 4 (6): 480.
10. Ladenheim JA, Luba DG, Yao F, et al: Limitations of liver surface USG in the diagnosis of cirrhosis. *Radiology* 1992 Oct; 185 (1): 21-3; discussion 23-4.
11. Okazaki H, Ito K, Fujita T, et al: Discrimination of alcoholic from virus-induced cirrhosis on MR imaging. *AJR Am J Roentgenol* 2000 Dec; 175 (6): 1677-81.
12. Tani I, Kurihara Y, Kawaguchi A, et al: MR imaging of diffuse liver disease. *AJR Am J Roentgenol* 2000 Apr; 174 (4): 965-71.
13. Thomas DL, Astemborski J, Rai RM, et al: The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000 Jul 26; 284 (4): 450.