ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Liver Complications in Patients with Congestive Heart Failure

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G&H What are the underlying causes of comorbid liver disease and congestive heart failure?

CG Individuals with cardiovascular disease, such as congestive heart failure (CHF), are often obese. They may also have nonalcoholic steatohepatitis, which may be related to a history of obesity as well as insulin-dependent diabetes, which also are risk factors for cardiovascular disease. Other causes of comorbid liver disease and CHF include any other diseases or conditions that might reduce the liver reserve, such as viral hepatitis or alcohol abuse. Finally, cirrhosis or diseases such as hepatic venous thrombosis (eg, Budd-Chiari syndrome) can make the liver more susceptible to ischemia—with reduced cardiac output in CHF—because the hepatic blood flow is reduced. Multiple comorbid liver diseases, thus, can exacerbate CHF.

G&H Are there other diseases that place patients at risk for liver involvement in a way similar to CHF?

CG Pulmonary conditions, such as chronic obstructive pulmonary disease and obstructive sleep apnea, place patients at risk for liver involvement due to passive congestion of the liver as a result of an increase in right-sided pressures. Furthermore, such patients tend to have lower arterial oxygenation compared with patients with CHF, leading to hypoxic hepatitis versus ischemic hepatitis seen in patients with CHF. These patients actually have been found to have more dramatic manifestations of liver disease than patients with CHF. Liver diseases such as hypoxic hepatitis can be exacerbated by such pulmonary condition(s).

G&H Do effects on the liver differ depending on whether the right or left portion of the heart is affected?

CG Some studies have examined clinical and histologic evidence of ischemic hepatitis in terms of left-versus-right–sided cardiac disease. For example, right atrial pressures and the degree of zone 3 necrosis on histologic sections in patients with CHF are not correlated, but histologic evidence of necrosis is correlated with acute left-sided heart failure. It has been observed, however, that in clinically apparent ischemic hepatitis more than 90% of patients have some right-sided heart failure. Thus, it appears that hepatic congestion secondary to right-sided heart disease may prime the liver for ischemic insults from low cardiac output and reduced hepatic blood flow and oxygenation due to left-sided heart failure. The right and left sides of the heart act cooperatively in clinical and histologic liver disease related to CHF.

G&H What are the common clinical findings suggestive of associated liver disease in CHF?

CG A number of published case series have looked into what types of clinical findings occur in CHF. One of the largest case series was published about 15 years ago and included 175 patients. These series found that the majority of patients have at least 1 manifestation. For example, 90–95% of patients will have hepatomegaly because of hepatic congestion. There can be associated right upper quadrant pain secondary to stretching of the liver capsule. A smaller percentage of patients—ranging from a few percent up to 25%—will have cardiac ascites. The rate of

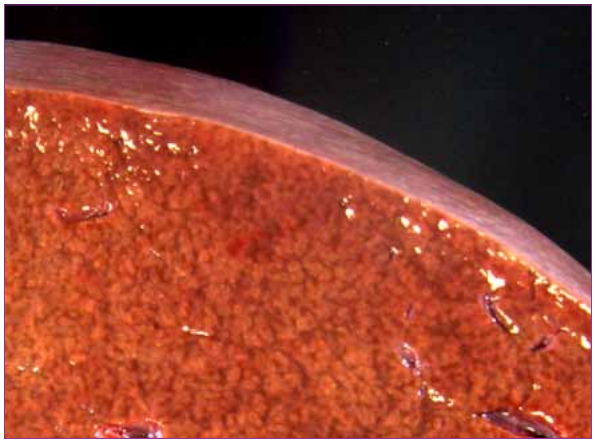

Figure 1. "Nutmeg" liver is characterized by a contrasting combination of reddish hemorrhagic areas, from red blood cells extravasating from the sinusoids, and yellowish portal areas, which represent normal or mild fatty liver. (Image courtesy of James Robert Stone, MD, PhD.)

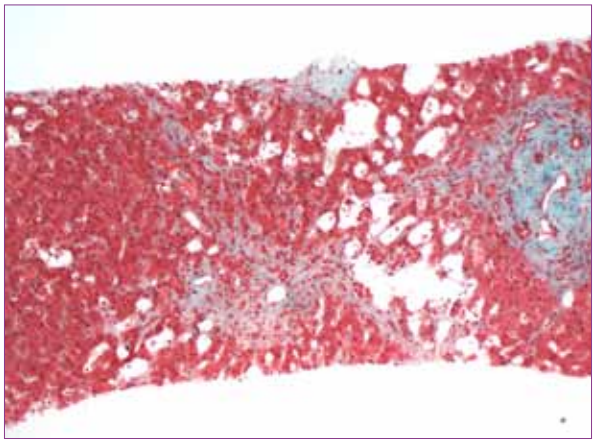

Figure 2. This example of cardiac cirrhosis shows chronic congestion, dilated sinusoids, and reverse lobulation of fibrosis from veins connecting to one another. (Common cirrhosis is portal-linking.) (Hematoxylin and eosin with trichrome stain; image courtesy of Joseph Misdraji, MD.)

splenomegaly is 7–20%. Liver function test (LFT) findings are often mild, usually showing alanine aminotransferase and aspartate aminotransferase level elevations at no more than 2 or 3 times the normal limit. Prothrombin time is also not dramatically affected in patients with CHF-related liver disease due to largely preserved synthetic function.

G&H How is primary liver disease differentiated from CHF-associated liver disease?

CG There are a number of clinical characteristics as well as laboratory tests that help distinguish CHF-related liver disease from primary liver disease due to the former's distinct pathophysiology. For example, patients with CHF-associated liver disease rarely have evidence of portosystemic shunts, such as esophageal varices or hemangiomas. This is in contrast to just about every other type of primary liver disease with cirrhosis. The ascites associated with CHF compared with that seen in primary liver disease tends to be associated with higher lactate dehydrogenase levels, higher protein levels in the ascites (>2.5 g/dL), and higher red blood cell counts (RBCs). These parameters are seen in cardiac ascites as opposed to ascites of primary liver disease due to hepatic congestion and leaking of RBCs into the ascites via lymph tissue, with resulting lysis in the setting of preserved synthetic function (Figure 1). Jaundice is relatively uncommon in CHF-related liver disease. Only about 5% of patients with hepatic disease and CHF will have clinically overt jaundice, but up to 70% of patients may have a mild increase in unconjugated bilirubinemia (<3 g/dL total bilirubin).

If a question persists about the etiology of the liver disease, a liver biopsy may be revealing. Fibrosis in chronic CHF-associated liver disease manifests as a reverse lobulated pattern characteristic of cardiac cirrhosis with relative sparing of the portal regions (Figure 2). This reverse pattern is due to damage starting in zone 3 of the liver triad in CHF and radiating from the central vein, whereas damage is focused in zone 1 in most primary liver diseases. Thus, there are a number of distinguishing clinical characteristics as well as laboratory and histologic findings that distinguish primary liver disease from CHF-associated liver disease.

G&H Should LFTs be routinely performed?

CG LFTs should not be routinely performed to identify or monitor a correlation between liver disease and CHF in the office setting. Furthermore, studies have shown that LFT results vary widely in patients, and researchers were unable to use LFTs to gain information on the type of cardiac dysfunction (ie, right versus left heart dysfunction). Therefore, the literature does not support the routine use of liver function testing in settings regarding CHF beyond monitoring patients for potential treatment-related hepatotoxicity associated with medications. The presence of cardiac disease would not be a primary reason for performing a LFT.

G&H What agents commonly affect liver function in this setting, and, vice versa, what agents are compromised by liver dysfunction?

CG Statins are perhaps the most common class of drugs that can cause hepatic toxicity in patients with cardiac disease. Digoxin, which is metabolized in the liver and regulates cholesterol levels, has a bidirectional impact; it is metabolized by the liver and can affect the metabolism of other compounds in the liver. The antiarrhythmic amiodarone usually does not

cause significant liver abnormalities, but computed tomography scans can reveal that a patient may be taking amiodarone because the liver appears hyperintense compared with the spleen. This does not indicate a reason to stop the medication, though. Some data suggest that hepatic disease from CHF can affect warfarin metabolism or other drug levels; however, there is insufficient evidence that CHF-related liver disease has a substantial and clinically meaningful impact on warfarin or other drug levels.

In general, most cardiovascular drugs—certainly most antihypertensive agents and most diuretics—are well tolerated in the presence of modest liver compromise. However, even with these drugs, indirect effects should be considered to prevent, for instance, intravascular depletion with diuretics, which may exacerbate reduced blood flow in an already compromised liver.

G&H How might recognition and care of CHF-associated liver disease be optimized?

CG Most patients in whom chronic CHF disease leads to cardiac cirrhosis on a biopsy do very well clinically regarding overall morbidity and mortality that is not driven by their liver disease. In addition, most patients with acute ischemic hepatitis secondary to CHF with significant hypotension recover well as long as the underlying insult is reversed. The key to managing patients with CHF is optimizing their cardiovascular dynamics. If that is achieved, the liver is going to do well for the most part.

Suggested Reading

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(continued from page 243)

G&H Is use of these new colonoscopic imaging techniques becoming mainstream?

RK High-definition colonoscopy is rapidly becoming mainstream for colonoscopic imaging. Virtual chromoendoscopy systems are included as part of these high-definition endoscopic systems and are increasingly being used to characterize colorectal lesions. Efforts are being made to avoid histologic examinations because endoscopic diagnosis becomes more accurate with these new techniques (via the resect-and-discard strategy).

Endomicroscopy will be reserved for university or referral centers with a high volume of patients who have an increased cancer risk (eg, patients with ulcerative colitis).

G&H What future developments do you anticipate in this area of endoscopy?

RK Endoscopy is a dynamic field, and new developments are continuously being made. It has been speculated that new optics will provide a nearly 360º overview of the colonic surface, which will further reduce the number of missed lesions. In addition, new fecal or serologic markers will help categorize patients into high- or low-risk groups for colorectal cancer. Then, there will be a shift from diagnostic to therapeutic colonoscopy.

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