Liver Biopsy for Cirrhosis

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Introduction

Cirrhosis and chronic liver disease (CLD) are ranked 12th in the top 15 causes of death in the United States, and account for 9.7 per 100,000 deaths. Furthermore, while overall life expectancy increased in 2007 compared with 2006, mortality from cirrhosis and CLD increased 3.4% in the same time period [1].

Cirrhosis: Definition

Cirrhosis is a term derived from Greek κιρρός, meaning tawny, or yellow, and linked to an amber-colored wine; the ancient Greeks described a disease of the liver with tan-yellow micronodules. The actual term, cirrhosis, is credited to Laennec, in the 1800s. For clinicians, the term implies end-stage liver disease with a variety of partially manageable complications (encephalopathy, ascites, bleeding) as well as life-threatening complications (bleeding and hepatocellular carcinoma). For pathologists, the term has evolved over the years to connote diffuse remodeling of the liver parenchyma that includes, in its simplest iterations, vascular remodeling with septal/scar formation surrounding nodules of hepatocytes with or without aberrant portal tract-like structures. Subtleties of this description can be found in discussions by leading experts [2, 3].

Underlying Causes of Cirrhosis in the United States: Overview

The leading etiologies for cirrhosis include, broadly:

(1) primary liver diseases, i.e. post-hepatitic, including viral hepatitides C, B, and D, autoimmune hepatitis;
(2) diseases that destroy the bile ducts, including PBC, PSC, IAD, Alagille's, biliary atresia;
(3) ingested toxins such as alcohol;
(4) inherited or acquired metabolic diseases and/or systemic diseases such as diabetes mellitus, nonalcoholic steatohepatitis, hereditary hemochromatosis, alpha-1-antitrypsin disease, Wilson disease, tyrosinemia, cystic fibrosis;
(5) diseases of the vascular outflow tract such as Budd-Chiari or cardiac sclerosis;
(6) drug-induced liver injury (DILI) including methotrexate, amiodarone and others,
(7) the diseases for which a cause has yet to be identified, i.e. cryptogenic.

The Role of Liver Biopsy for Cirrhosis

When a liver biopsy is done for which “cirrhosis” is the diagnostic request on the requisition, what does that tell the pathologist? Most often, it tells us two things: 1. That the patient has portal hypertension, i.e. encephalopathy, varices or variceal bleed, ascites,
splenomegaly, depressed platelets; 2. that the clinically “obvious” causes have likely been ruled out. Therefore, it is highly unusual in modern practice for a pathologist to receive a liver biopsy to "confirm" cirrhosis; rather, the primary reason currently is to determine the underlying cause(s). Often, therefore, the real question is determination of the underlying cause of clinically evident portal hypertension.

Thus, what causes portal hypertension (pHTN)? In the West, cirrhosis is by far the #1 cause. Other processes to be aware of, however, are previously unrecognized advanced biliary fibrosis, and advanced alcoholic hepatitis. Throughout the world, the #1 cause of pHTN is schistosomiasis with the resultant characteristic Symmer’s pipestem fibrosis. Over 200 million people worldwide are infected and it is estimated that up to 400,000 people currently living in the US have schistosomiasis, so this is not a problem to which we can be indifferent.

Classifications of Portal HTN[^4]

pHTN is due to increased vascular resistance. One of the reasons this occurs is the peculiarity of the portal venous system: there are no valves. Thus increased pressures within this normally low-pressure system, are transmitted proximally. Increased pressures may occur from obstruction at 3 different sites: splenic vein thrombosis (pre-hepatic, extra-hepatic), cirrhosis (sinusoidal, intra-hepatic) and/or large outflow veins, right heart, IVC, constrictive pericarditis (post-hepatic). pHTN is commonly classified broadly into 2 (or 3) categories: pre-sinusoidal and hepatic, based on wedged hepatic vein measurements, or pre-sinusoidal, sinusoidal, and post-sinusoidal, based on the organ's structure. Utilizing the pressure gradient categories, presinusoidal is further subdivided into extra-hepatic and intra-hepatic, and the latter is further subdivided into intra-hepatic and post-sinusoidal. These categories carry clinical significance: pre-sinusoidal causes of pHTN are not associated with abnormal liver function and liver failure following variceal bleeding is rare, whereas hepatic causes of pHTN will have abnormal liver function (and tests), and liver failure is common following a variceal bleed.

A pathologically-based classification of pHTN is cirrhotic and non-cirrhotic (NC-pHTN).

Pre-sinusoidal Portal Hypertension

This group of disease processes is characterized by wedged hepatic pressures that are either normal, or less than measured portal vein pressure. Examples include diseases characterized by portal infiltrates (sarcoidosis, schistosomiasis, PBC), developmental abnormalities (hereditary hemorrhagic telangiectasia, adult polycystic liver disease, congenital hepatic fibrosis), phlebosclerotic processes of the portal vein (hepatoporal sclerosis, biliary diseases, toxins, nodular regenerative hyperplasia).

The extra-hepatic causes of pre-sinusoidal portal hypertension include splenic vein thrombosis, pylephlebitis and other neoplastic and non-neoplastic disease processes that can lead to structural disruption of the main portal vein. This group of diseases will not be further discussed.

Hepatic Causes of Portal Hypertension
Some authors group these into sinusoidal and post-sinusoidal. This grouping of diseases are characterized by wedged hepatic pressures that either exceed, or are equal to measured portal pressure, but are not normal. Causes include many infiltrative processes (amyloid, alcoholic-induced sinusoidal fibrosis, Gaucher's disease, etc), malignancies of the sinusoids (epithelioid hemangioendothelioma, angiosarcoma) all forms of cirrhosis, and venous outflow disease, including cardiac causes.

**Steps in Histologic Determination of Presence and Types of Portal Hypertension:**

**#1: Cirrhosis or Not**

This is a process that can be simple and recognized by "gestalt" within the first minutes of evaluation, or it can be quite challenging, and take conscious efforts to work through. Fragmentation is no longer as reliable a feature as previously, unless the clinician is continuing to utilize a suction biopsy needle; the transjugular needle biopsy technique, and the percutaneous gun biopsy will not yield this type of specimen. Intact core biopsies must, therefore, be evaluated for other "clues": presence of vascular structures (portal tracts and outflow veins); vascular relationships/spacing; cord nodularity and cord integrity; nuclear features: bi-nucleates, homogeneity or anisonucleosis, and cytologic alterations of hepatocytes. One can be highly suspicious of cirrhosis when no well defined portal tracts and predictably-spaced outflow veins are present; increased numbers of vascular/lymphatic-like channels within enlarged fibrous tracts; increased numbers of ductular profiles within enlarged fibrous tracts; delicate fibrous outlines defining rounded edges of hyperplastic, nodular cords are also suggestive of cirrhosis. The presence of an ectatic open sinusoid-like vascular structure adjacent to a septum is a concern for approximation of an outflow vein and loss of intervening parenchyma.

Hepatocyte cords without an outflow vein present but that have small portal-tract like structures may represent a macro-regenerative nodule. Nodules or non-anatomic groups of hepatocytes with distinct but seemingly monoclonal cytologic alterations clearly different from neighboring hepatocytes, i.e. deeply oncocyic, fatty, clear, lack of stainable iron in an otherwise iron-loaded liver, small cell change, large cell change, may represent dysplastic hepatocytes or nodules. The reader is referred to expert reviews \[5, 6\] for more in-depth discussions of this latter and very important topic. Hepatocellular carcinoma may actually be encountered in unguided liver biopsies performed for "cirrhosis".

**1a. If Cirrhosis is Present: Clues to Etiology**

Having established *cirrhosis*, there are histopathologic features that may be clues to the underlying etiology for hepatitic (HBV/metabolic/toxic), cholestatic or vascular disease. Caveats, however, are that once the liver has undergone complete remodeling, acute and chronic cholestasis and vascular alterations may occur in the nodules due to local aberrations, and the vagaries of end-stage liver failure.
Cryptogenic cirrhosis is a term reserved for a biopsy diagnosis for which there is no known clinical or histopathologic etiology. Many disease processes, such as autoimmune hepatitis, alcoholic cirrhosis and nonalcoholic steatohepatitis can "burn-out" and lose features of activity; if the underlying cause has been previously identified, the biopsy is not cryptogenic.

**Regression of Cirrhosis:** Histopathologic lesions of “regressed cirrhosis” have been described; these include thin, incomplete and perforated septa; hepatocyte growth into veins, and small thick collagen bundles in parenchymal sinusoids. These may be challenging lesions to discern in needle biopsies.

#2 If Not Cirrhosis: Clues to Diagnosis

**Noncirrhotic Portal Hypertension**

NC-pHTN can be referred to by many rubrics: Idiopathic portal HTN (IPH), intrahepatic portal venopathy, hepatoportal sclerosis, nodular regenerative hyperplasia, and is a leading cause of pre-sinusoidal pHTN. These processes vary by the amounts of fibrosis and nodularity that define them. Clinically, there is increased intrahepatic portal pressure and features of pHTN; these changes are seen in the presence of patent extra-hepatic portal and hepatic veins, and in the absence of cirrhosis. Portal vein thrombosis is known to develop in the larger portal veins in late stages in up to 50%, and carries a worse prognosis. Overall, these entities have better outcomes than cirrhosis, if the clinical manifestations can be managed. A variety of systemic diseases, toxins and drugs are associated with NC-pHTN/IPH, including autoimmune conditions and vasculitides. Geographic differences between India and Japan have been clearly presented and may be related to poverty in the former and autoimmunity to sinusoidal endothelial cells in the latter. Recent work has shown different mechanisms of fibroobliterative lesions of portal veins and fibrosis within the parenchyma.

Incomplete Septal Cirrhosis (ISC) is a term that, broadly, applies to with parenchymal nodularity and varying degrees of fibrous septal formation, but without the complete parenchymal remodeling of cirrhosis. There is more fibrosis in this disease process than in the other forms of IPH, poorly-defined nodules, increased periportal thin-walled vascular channels ("shunt vessels"). The latter have also been referred to as megasinusoids or herniated veins.

Nodular regenerative hyperplasia (NRH), another manifestation of NC-pHTN, is on the other end of the spectrum and is characterized by nodularity of the parenchyma without the fibrosis of cirrhotic septa. NRH can be challenging to diagnose by needle biopsy; but clues include alternating groups of “thick and thin” cords with nodules 1-3 mm, and compression of the outflow veins into a crescent moon shape. The nodularity may be noted initially by "dilated" sinusoids due to compression of atrophic cords between nodules. Portal veins may be absent in the smallest portal tracts; periportal and perisinusoidal fibrosis may be noted irregularly. NRH may be associated with certain toxins and drugs, and systemic processes that injure the sinusoidal endothelium and result in impaired portal and sinusoidal circulation. This process has become increasingly recognized in patients following the use of various chemotherapeutics.
including 6-MP, azathioprine, and oxaliplatin. Both NRH and HPS have been reported in AIDS\textsuperscript{[9]}.

Hepatoportal sclerosis is a third form of NC-pHTN that may be encountered. The biopsy may seem deceivingly "normal", or the portal tracts may be abnormally enlarged. Portal veins may appear enlarged, as the patent intraparenchymal vessels are bearing the pressure from the obliterated portal venous branches elsewhere. Alternatively, only scarred remnants of a portal vein branch may be present. The megasinusoids described above may be noted, as may cord atrophy, nodular parenchymal changes, and perisinusoidal fibrosis\textsuperscript{[4]}.

REFERENCES


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