Acute Viral Hepatitis: Beyond A, B, and C

Venancio Avancini Ferreira Alves, MD, PhD

KEYWORDS

• Acute viral hepatitis • Hepatotropic viruses • Icteric hemorrhagic fevers • Immunosuppression

Key points

- Acute hepatitis due to any of the hepatotrophic viruses produces a histologically similar generic lobular hepatitis pattern.
- The non-hepatotrophic viruses do not produce a lobular hepatitis pattern histologically, but instead exhibit distinctive histologic features.
- Viral hemorrhagic fevers can produce severe acute hepatitis with characteristic histologic features.

ABSTRACT

From the standpoint of the surgical pathologist "hepatitis" is defined as the set of histologic patterns of lesions found in livers infected by hepatotropic viruses, by non-hepatotrophic viruses leading to liver inflammation in the context of systemic infection, or due to an autoimmune disease, drug, or toxin involving the liver. This article is centered on the histologic patterns of injury in acute viral hepatitis, encompassing the hepatotropic viruses A, B, C, D, and E and the "icteric hemorrhagic fevers" (dengue, hantavirus, yellow fever). A brief mention of viruses causing hepatitis in immunosuppressed patients also is presented.

OVERVIEW

The epidemiology of viral hepatitis has substantially changed over the past decade due to progress in vaccine development and protocols for prevention, diagnosis, and treatment.[1–3] However, marked differences in incidence of each type of viral hepatitis still remain. In 2015, Gupta and colleagues[4] reported a series of 206 cases of acute viral hepatitis from India and determined that hepatitis E virus (HEV) infection was responsible in 95 cases, hepatitis A virus (HAV) in 36, hepatitis B virus (HBV) in 18, and concurrent infections of these viruses in an additional 27 cases. Hepatitis C virus (HCV) was detected in only 1 patient, whereas the other 29 cases were ascribed to CMV or EBV. In the United States, a summary of reports of acute hepatitis from the Centers for Disease Control and Prevention (CDC) for 2014 include 1239 cases of HAV and an increase to 1390 cases in 2015. A total of 2791 cases of acute HBV hepatitis was reported in in 2014 and an increase to 3370 in 2015. Newly reported acute HCV hepatitis cases totaled 2194 in 2014 with an increase to 2436 in 2015. The CDC also reported that cases of acute HCV infection increased more than 2.9-fold from 2010 through 2015, with an increased incidence each year during this period. Unfortunately no data regarding case numbers for acute HEV were reported, but elsewhere on the Web site, the CDC states that in the United States, HEV infection is believed to be uncommon, and when symptomatic hepatitis E does occur, it is usually in individuals who are from or have traveled to a country where hepatitis E is endemic.[5]

Acute liver failure may result from viral hepatitis. In 2015, the CDC reported 8 deaths in the United States ascribed to fulminant HAV infection.[5] Deaths due to acute hepatitis B infection were reported in 20 cases. In contrast, chronic HBV hepatitis was considered the cause of

Department of Pathology, Surgical Pathology, University of Sao Paulo School of Medicine, Sao Paulo, Brazil
E-mail address: venancio@uol.com.br

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death of 1715 patients. The CDC report did not mention death due to acute HCV hepatitis, but chronic HCV hepatitis was considered the cause of death of 19,629 patients.[5] Acute liver failure due to acute HEV infection is not mentioned by the CDC, but in other countries, acute liver failure occurs in 0.1% to 4.0% of infected patients, with a predilection for pregnant women, 30% of whom may develop acute liver failure.[6]

HISTOLOGIC FINDINGS IN ACUTE VIRAL HEPATITIS

The lobular inflammation and hepatocellular injury in acute hepatitis is much more striking than the portal tract changes, resulting in a low-power pattern that could be termed "lobular hepatitis" (**Fig. 1**). Variable numbers of swollen/ballooned hepatocytes are intermingled with more normal-appearing hepatocytes. Lymphocytes, histiocytes, and plasma cells appear as single cells or in small groups, even in early infection, surrounding the damaged hepatocytes or fragments of dead hepatocytes, a lesion known as lytic necrosis or spotty necrosis.[7] Scattered individual hepatocytes undergo apoptosis and are known as *acidophilic bodies* or *Councilman-Rocha Lima bodies*. Cellular remnants phagocytized by Kupffer cells may be highlighted by use of the periodic acid–Schiff–diastase (PAS/D) stain, which is extremely useful for the diagnosis of resolving acute hepatitis when the appearance in the hematoxylin-eosin (H&E) stain is nearly normal (**Fig. 2**). Portal tract findings are variable; there may be minimal edema and generally sparse to mild mononuclear cell infiltrates that are almost always less impressive than the parenchymal hepatocellular injury and inflammation. Bile duct injury is usually mild, although mild cholangitis has been reported in acute hepatitis E infection.[8] Mild cholestasis may be seen in acute hepatitis, with bile pigment found in the cytoplasm of hepatocytes or in biliary canaliculi. The presence of more significant cholestatic changes rarely may be seen in elderly patients, but also should raise the possibility of drug-induced injury or even bile duct obstruction.

In acute hepatitis, hepatocytes at the interface with the portal tract are usually not damaged, although in acute HAV hepatitis lymphocytes often spill over the limiting plate. Because portal fibrosis and neoangiogenesis are not features of acute hepatitis, when patterns of both acute and chronic hepatitis coexist, the pathologist must consider the possibility of an acute viral infection as a second hepatic insult occurring in the setting of underlying chronic liver disease. An important example of such a scenario is hepatitis D virus (HDV) superinfection of livers chronically infected by HBV.[9]

In most cases of acute hepatitis, especially those due to hepatitis A and E, the loss of individual hepatocytes because of apoptosis and spotty necrosis do not disturb the underlying trabecular architecture, and once the viral infection resolves, usually within 2 to 4 months after infection, regeneration from neighboring hepatocytes leads to complete restoration of structure and function of the liver.

In some cases of acute viral hepatitis, groups of hepatocytes die, resulting in collapse of reticulin framework, known as *confluent necrosis*.[7,10] When confluent necrosis links central veins (terminal hepatic venules) to the neighboring ones, a "vascular bridge" ensues ("central-central bridging" or "central-portal bridging"). Almost 50 years ago, Boyer and Klatskin[11] suggested that confluent necrosis linking central veins to portal tracts might lead to a presinusoidal-postsinusoidal shunt, with a high risk of evolution to cirrhosis (**Fig. 3**). This hypothesis is still a matter of debate, and will require additional sophisticated morphologic and functional assessment in cohorts of affected patients.

Fulminant hepatitis is defined as acute liver failure occurring a few weeks after the onset of acute hepatitis. Viral hepatitis and drugs are reported as major causes of this rather infrequent but potentially severe condition. Confluent necrosis may become extensive, leading to *submassive* or even *massive necrosis* (**Fig. 4**). Because of the irregular distribution of necrosis, histologic features from needle liver biopsies may not predict clinical outcome in such instances[12]

Extensive necrosis may be mistaken as fibrosis; the distinction can be aided by silver impregnation stains, such as the Gomori silver stain. Confluent necrosis leads to approximation of reticulin fibers (collagen III fibers) due to parenchymal collapse, whereas chronic active fibrogenesis leads to deposition of both collagen III and collagen I fibers. Collagen III appears as narrow black fibrils (reticulin fibrils), whereas collagen I bands appear brown. Chronic fibrogenesis is accompanied by production of elastic fibers, visualized by the Shikata orcein, van Gieson, or Weigert stain, whereas acute collapse lacks elastic fibers.[13] These histologic and histochemical features are even more important in the assessment of biopsies demonstrating acute-on-chronic liver failure, to discriminate which lesions are ascribable to acute events