

Acute and Chronic Hepatitis

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Acute Hepatitis

Clinical Features

Classically acute hepatitis is defined clinically as a significant (at least 2X elevation above the upper reference level) elevation of the serum ALT and/or AST levels in a patient without a previous history of liver disease. Serum markers of cholestatic liver injury should not be present. Most patients with acute hepatitis are asymptomatic. The causes of mild elevations in serum ALT or AST are listed in Table 1. In more severe cases fatigue, abdominal pain, nausea and vomiting, muscle aches or jaundice might be present (fulminant acute hepatitis is considered separately below). Serologic tests for hepatitis A, B or C infection and autoimmune hepatitis should be obtained routinely. A careful drug/toxin history must also be sought.

Table 1: Cause of Mild Elevations of Serum AST or ALT

Hepatic: predominantly ALT
Acute viral hepatitis (A-E, EBV, CMV)
Chronic hepatitis B & C
Autoimmune hepatitis
Medications/Herbal preparations/Dietary supplements
Toxins
Steatosis and Steatohepatitis
Genetic hemochromatosis
Alpha-1-antitrypsin deficiency
Wilson's disease
Celiac disease
Hepatic: predominantly AST
Alcoholic steatosis and steatohepatitis
Cirrhosis of any cause
Non-hepatic
Hemolysis
Myopathy
Thyroid disease
Strenuous exercise
Macro-AST

Adapted from Green R, Flamm S. AGA medical position statement. Gastroenterology 2002.

Histologic Features

Biopsy provides little useful information in most cases of acute hepatitis, and therefore is rarely performed by knowledgeable hepatologists. Biopsies are indicated in the following clinical situations:

- 1) When there is clinical suspicion of a second independent hepatic insult (i.e., an underlying chronic liver disease).
- 2) In immunocompromised patients, where an unusual infectious process is possible
- 3) To ascertain the degree of hepatocyte necrosis in a patient with possible submassive hepatic necrosis, who may need to be listed for liver transplantation

The defining histologic pattern for all forms of acute hepatitis is encompassed by the term “**lobular disarray**”. The following features characterize this pattern:

- Hepatocyte ballooning degeneration
- Lobular and sinusoidal inflammatory cell infiltrates
- Scattered acidophil bodies
- Foci of individual hepatocyte dropout
- Kupffer cell hyperplasia

The portal tract changes in acute hepatitis are generally inconspicuous, consisting of sparse mononuclear cell infiltrates. Steatosis is not a histologic feature of any form of acute hepatitis, and when present suggests steatohepatitis or both acute hepatitis and a separate steatotic process. Biliary changes (bile duct proliferation or bile duct loss, cholate stasis, or prominent cholestasis) should also suggest another process.

The diagnosis of acute hepatitis is usually apparent in the H&E stained section. However, special stains can be very helpful in confirming the initial impression. Histologic evidence of acute hepatitis in the resolving phase can be quite subtle and is easily overlooked if a detailed clinical history is not provided. A PAS with diastase stain is very useful in such cases because it highlights the presence of cellular debris in Kupffer cells (a good sign of previous hepatocyte necrosis/apoptosis). A reticulin stain may also highlight foci of individual hepatocyte dropout. In more severe cases the reticulin confirms the presence of zonal or bridging necrosis. No fibrosis should be evident in the trichrome stained section.

Acute Hepatitis C

Clinical: Acute HCV hepatitis is almost always entirely asymptomatic, and therefore is rarely recognized clinically or biopsied. The most common symptom is mild fatigue. A diagnosis is usually made only when an exposure event is recognized (e.g., accidental needle stick). There is no clinical reason to perform a biopsy in a known case, except to rule out a second contributing cause of liver dysfunction.

Histologic features: Biopsies usually exhibit nonspecific features of acute hepatitis, although mild ductular proliferation and cholestasis have also been described in biopsies obtained immediately after infection (see *Johnson K et al Am J Surg Pathol 2007*).

Acute Hepatitis B

Clinical features: Acute HBV hepatitis is usually asymptomatic, but some patients present with a flu-like illness, jaundice, or lethargy. Serologic testing for acute HBV hepatitis is quite accurate, so there is no role for biopsy in suspected cases.

Histologic features: There are no distinctive histologic features of acute HBV hepatitis. Ground glass hepatocytes are never present in *acute* HBV hepatitis. Likewise, immunohistologic stains with HBsAg and HBcAg antibodies are negative in acute HBV hepatitis.

Acute Hepatitis A

Clinical features: Acute HAV hepatitis is usually asymptomatic in children, but can produce jaundice or a flu-like syndrome in adults. Serologic testing for anti-HAV IgM is diagnostic of acute infection. Although there is no chronic form of HAV hepatitis, there is a relapsing form with a prolonged course (over 6 months), which sometimes takes a cholestatic form. Biopsy is often performed in these cases because of this unusual course, and to rule out any possible superimposed disorder.

Histologic features: Acute HAV hepatitis is usually indistinguishable from other types of acute hepatitis. However, on occasion there is more portal inflammation than is typical, and the infiltrate may include a prominent component of plasma cells. These features can result in an appearance easily confused with autoimmune hepatitis. Thus, the possibility of acute HAV hepatitis should always be considered before making a diagnosis of serologically negative autoimmune hepatitis (unless fibrosis is present).

Acute Autoimmune Hepatitis

Clinical features: Generally autoimmune hepatitis causes significant symptoms, including fatigue, nausea and vomiting, jaundice and muscle aches. Clinical distinction between acute and chronic AIH is usually not possible, and many believe there is no acute form of the disease (i.e., AIH begins with an asymptomatic phase and when diagnosed is by definition “chronic”).

Histologic features: Because chronic AIH often exhibits severe interface and lobular necroinflammatory activity (including bridging *necrosis* in some cases) it is difficult to distinguish from acute AIH. The difficulty in distinguishing between true fibrosis (an undeniable feature of chronic disease) and periportal or bridging necrosis with resultant reticulin collapse (which could occur in either acute or chronic AIH) makes it even harder to histologically separate acute and chronic AIH. Moreover, a prominent component of plasma cells in the portal infiltrates is usually present in acute AIH. The most reliable feature for the diagnosis of *acute* AIH is the presence of a degree of lobular disarray in excess of that expected by the degree of portal inflammation and interface activity. In practical terms histologic distinction between acute and chronic AIH has little importance, since the same treatment with steroids will be instituted regardless. The most important task of the surgical pathologist is to recognize the possibility of AIH and to not overestimate the degree of fibrosis (i.e., avoid confusion with reticulin collapse due to periportal necrosis). In a small subset of cases of acute AIH centrilobular necroinflammatory activity predominates, with relatively inconspicuous portal inflammation.

Drug Induced Acute Hepatitis

Clinical features: Elevation of serum ALT and ALP after institution almost any medication should strongly suggest the possibility of drug induced hepatitis. Unfortunately the temporal relationship between the onset of liver chemistry test abnormalities (or symptoms) and the start of the drug therapy is not of much use (particularly if it is the patient's first exposure to the agent). A Medline search for reports of acute hepatitis caused by the medications the patient is taking is helpful, but no drug can completely be excluded on the basis of lack of prior reports of hepatotoxicity. Antibiotics and anti-epileptics are the most common classes of medications that cause clinically significant liver dysfunction. Of course, the possibility of toxicity due to an herbal preparation or dietary supplement must always be sought assiduously in any case of unexplained hepatotoxicity. Many toxins can also produce acute hepatitis, and again a careful clinical history is key to arriving at the proper diagnosis.

Histologic features: The presence of more than rare scattered eosinophils is very unusual in acute HAV, HBV, or HCV hepatitis, and should raise the possibility of drug toxicity. Unfortunately, eosinophils are not prominent in most cases of drug-induced acute hepatitis. Autoimmune hepatitis is sometimes triggered by a drug exposure, and this possibility should be kept in mind when eosinophils are prominent in a biopsy that otherwise exhibits typical histologic features of AIH. Many toxins produce a distinct centrilobular pattern of hepatocyte injury.

Massive and Submassive Hepatocyte Necrosis

Clinical features: The common causes of fulminant hepatic failure include: acute HAV hepatitis, acute HBV infection, acute autoimmune hepatitis, drug and toxin induced injury, ischemic injury (due to decreased portal vein or hepatic vein flow), and Wilson's disease. The later two are not regarded as forms of acute hepatitis. Fulminant HCV hepatitis is extraordinarily rare. Fulminant herpes simplex virus or adenovirus infection can cause massive hepatic necrosis in immunocompromised hosts. Rarely massive infiltration of the liver by tumor (melanoma, leukemia) can cause liver failure. Patients present with signs and symptoms of liver failure. Symptoms include lethargy, encephalopathy, and coma. Laboratory evaluation may reveal AST and ALT levels of 1000 or more, jaundice, coagulopathy, and high serum

ammonia. In many cases of fulminant hepatic failure the etiology is never identified.

Histologic features: Biopsy is not needed in most cases, and is contraindicated in the face of severe coagulopathy. Biopsy is performed in less severe cases as part of the assessment for the need to list the patient for possible liver transplantation. Acute necrosis of more than 30-40% of the parenchyma suggests that the injury may not be recoverable. Marked periportal or panlobular necrosis results in prominent bile ductular proliferation, which should not be misinterpreted as evidence of biliary tract disease. These proliferating ductules, which represent a regenerative response, can transform into hepatocytes to repopulate the liver, assuming that the degree of hepatocyte loss doesn't lead to death before the transformation can occur.

Not infrequently large areas of parenchymal collapse and extinction with subsequent nodular hepatic regeneration can simulate cirrhosis both radiographically and histologically. The deep blue color of true fibrosis in a trichrome stained section can easily be confused with the lighter blue color produced by condensation of reticulin fibers in massive hepatic necrosis, compounding the confusion with cirrhosis. An orcein or reticulin stain is very helpful in such cases.

Histologic Differential Diagnosis

The histologic pattern of lobular disarray in acute hepatitis is distinctive and is not often confused with other entities. Lobular inflammation is present in EBV hepatitis, but in this disorder there is little hepatocellular injury. CMV hepatitis in heavily immunocompromised hosts is characterized by lobular neutrophilic microabscesses but no lobular disarray. In more immunocompetent patients the appearance can be similar to EBV hepatitis. HSV and adenovirus hepatitis produces randomly distributed foci of hepatocyte necrosis. Viral inclusions are usually evident at the edges of the necrotic zones. Severe sudden hepatic ischemia (e.g., "shock liver") causes a distinct centrilobular pattern of hepatocyte ballooning and necrosis. Bacterial infections of the liver (e.g. listeria) produce focal neutrophilic infiltrates with localized foci of hepatocyte necrosis. The presence of

cholestatic hepatitis raises an entirely distinct set of diagnostic considerations, which is beyond the scope of this discussion.

The Bottom Line – how to sign out the case

The term “acute hepatitis” is an acceptable diagnosis to describe the changes in biopsies thought or known to be due to HAV, HBV, HCV, AIH or drug induced injury. A descriptor of severity can also be added (mild, severe) to highlight the degree of hepatocyte injury. The presence of bridging necrosis should be mentioned in the diagnosis, if present, since it may indicate a greater risk for the later development of cirrhosis. In cases of massive hepatic necrosis a rough estimate of the percentage of hepatocytes that are necrotic or have dropped out is useful to the clinician. The appearance of remaining viable hepatocytes should also be mentioned. In many cases of acute hepatitis an exact etiology is never determined.

Chronic Hepatitis

Clinical features: Many patients with chronic hepatitis are completely asymptomatic, even when cirrhosis is present. The most common symptom is fatigue. Symptoms of decompensated liver failure may develop in some patients with end-stage cirrhosis, often precipitated by an intercurrent illness. Variceal bleeding and hepatic encephalopathy may develop. Physical signs of cirrhosis may also be manifested (edema and ascites, spider angioma, palmar erythema, gynecomastia and testicular atrophy in men etc.). Patients with cirrhosis are at particular risk of hepatocellular carcinoma, especially those with cirrhosis due to chronic HBV and HCV hepatitis.

Histologic features: The typical histologic features of chronic hepatitis include portal inflammation, interface activity, spotty lobular inflammation, and scattered acidophil bodies or foci of individual hepatocyte dropout. The severity of each of the changes obviously varies from case to case, and may be absent in some. Prominent lobular disarray, which defines the histologic pattern of acute hepatitis, resolves as conversion to chronic hepatitis develops. Acidophil body formation generally does not result in an increase in the serum AST or ALT levels. Of course the sine qua non of chronic hepatitis is the presence of portal fibrosis, which can ultimately lead to the development of macronodular cirrhosis.

Chronic Hepatitis C

Clinical features: A large majority of patients with chronic HCV hepatitis are asymptomatic. About 85% of patients infected by the HCV infection go on to develop chronic HCV hepatitis. Cirrhosis will develop in about 20-35% of these patients, generally taking more than 20 years to develop. Cirrhosis is a much more likely outcome in patients who become infected as adults.

Histologic features: Before serologic tests were developed the histologic triad of portal lymphoid aggregates, macrovesicular steatosis, and lymphocytic infiltration of bile duct epithelium were identified as features that defined “non-A, non-B” hepatitis. Bile duct loss and granulomas are not features of HCV hepatitis. Steatosis is present in about 50% of cases, and steatohepatitis in about 10%. The presence of steatohepatitis is often overlooked by pathologists, and called simple steatosis instead.

Centrilobular sinusoidal fibrosis, centrilobular hepatocyte ballooning change, and Mallory bodies are not features of chronic HCV hepatitis, and their presence should prompt a diagnosis of superimposed steatohepatitis. Fatty change occurs due to either viral or host factors. Genotype 3 of the HCV virus has been shown to directly cause steatosis, and effective anti-viral treatment will result in resolution of steatosis. In patients infected by other genotypes of the virus host factors are responsible for steatosis and steatohepatitis (e.g., obesity, diabetes, ethanol use, medications, insulin resistance). The presence of steatohepatitis or significant steatosis (>33%) diminishes the efficacy of anti-viral therapy, and therefore these features should be mentioned in the report if present.

The degree of necroinflammatory activity in chronic HCV hepatitis is almost always quite mild (grade 1 or 2). The presence of grade 3 or 4 necro-inflammatory activity should strongly suggest the possibility of another superimposed condition (most often autoimmune hepatitis or drug induced hepatotoxicity). There is some data to suggest that the presence of hemosiderosis may decrease the probability of treatment response and/or increase the risk for subsequent fibrosis. Therefore, a comment regarding the degree of iron deposition should be included in the report.

Chronic Hepatitis B

Clinical features: Chronic HBV hepatitis occurs in 70-90% of patients infected as infants or in childhood, but the majority of adults infected resolve their acute infection and become immune. In 30% of infected patients an identifiable risk factor is not evident. Serologic testing for HBsAg is diagnostic of active infection. A chronic inactive carrier state is defined by an asymptomatic patient with normal serum AST and ALT with positive serum HBsAg and anti-HBeAg tests and negative HBV DNA test.

Histologic features: Ground glass hepatocytes are the most diagnostic feature of chronic HCV hepatitis, but are seen in only about 50% of biopsies. Ground glass hepatocytes have finely granular acidophilic cytoplasm, often with a clear halo at the plasma membrane. This appearance is created by a proliferation of the endoplasmic reticulum that contains abundant viral particles. The hepatocyte nucleus is usually pushed to the periphery by the inclusion. A “sanded” appearance of the nucleus may occur rarely. Scattered individual or small clusters of ground glass hepatocytes are usually randomly distributed throughout the lobules. In cirrhotic livers there may be many ground glass hepatocytes in some of the regenerative nodules and none in others. Hepatocytes with oncocytic change can appear very similar, but this change often involves larger clusters of hepatocytes and does not produce a peripheral halo or push the nucleus to the side. Immunohistologic studies can be used to demonstrate that the ground glass cells are reactive with the HBsAg antibody (many other hepatocytes are usually also positive). The HBcAg antibody reveals nuclear reactivity in hepatocytes in which there is ongoing active viral replication. However, the availability of highly accurate serologic tests makes immunohistologic demonstration of HBsAg or HBcAg unnecessary except in specific and very rare situations.

In a chronic inactive carrier there is usually no or very minimal portal or lobular inflammation, but ground glass hepatocytes may be numerous. In patients with active chronic HBV hepatitis there is a variable degree of portal inflammation, interface activity, and lobular necroinflammatory changes. Steatosis is uncommon. At presentation grade 3 necroinflammatory changes are frequently seen. An acute flare of disease may also result in prominent necroinflammatory changes. The possibility of superinfection by hepatitis delta virus should be considered in such patients.

Chronic Autoimmune Hepatitis

Clinical features: Females are much more likely than males to be affected by chronic AIH. There is a bimodal age distribution, with peaks in the teenage years and in the fourth and fifth decades. Although AIH is not completely excluded if serologic tests are negative, a significant elevation of the titer of anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA) or anti-liver/kidney microsomal antibody (anti-LKM) is very helpful in making the diagnosis. The anti-LKM antibody is elevated in less than 5% of patients. In borderline case application of an international consensus scoring system can be utilized. As mentioned previously, AIH can be triggered by exposure to a drug, and this possibility should be kept in mind clinically since withdrawal of the drug can be curative in a small proportion of cases. Minocycline, an antibiotic used in the treatment of acne, is a common drug trigger of chronic AIH. Treatment with high dose steroids is usually rapidly effective in inducing remission, and treatment response actually is useful in confirming the diagnosis. Imuran is then typically introduced as a steroid-sparing agent. Re-biopsy is often performed after several years of tapering treatment to assess the degree of ongoing necroinflammatory activity. If minimal activity is evident histologically an attempt to completely halt steroid therapy may be considered.

Histologic features: In the initial diagnostic biopsy AIH usually exhibits striking necroinflammatory activity (grade 3 or 4). The presence of bridging necrosis should suggest the possibility of AIH. Clusters of plasma cells are often a prominent component of the portal tract inflammatory cell infiltrates, but are not required for the diagnosis. Pseudoacinar formations (hepatocyte rosettes) are a common lobular histologic feature. In a small subset of patients giant cell transformation occurs, but there is no particular clinical significance of this feature. Significant zone 3 inflammation and hepatocyte necrosis or dropout is evident in some patients with autoimmune hepatitis.

Assessment for the presence of fibrosis should be approached cautiously in the initial AIH biopsy, because periportal or bridging necrosis leads to collapse of the reticulin framework. In the trichrome stain the condensed reticulin fibers will produce a grayish (steel) blue staining that can easily be

confused with true (bright blue) fibrosis. The presence of more than rare eosinophils in the portal and lobular inflammatory cell infiltrates should raise the possibility of drug-induced AIH.

Drug-induced Chronic Hepatitis

Clinical features: While several agents are known to trigger autoimmune hepatitis, it is uncommon for a drug to produce a simple chronic hepatitis pattern (See Table 2).

Table 2

<u>Drug induced AIH</u>	<u>Drug induced CH</u>
Diclofenac	Etretinate
Ecstasy (MDMA)	Lisinopril
Methyldopa	Sulfonamide
Minocycline	Trazodone
Nitrofurantoin	Isoniazid
Propylthiouracil	
Dihydralazine	

Histologic features: Other than the presence of a prominent component of eosinophils, which occurs in only a minority of cases, there are no distinctive histologic features of drug induced chronic hepatitis.

Differential Diagnosis of Chronic Hepatitis

Wilson's disease

Clinical features: Wilson's disease is an autosomal recessive disorder caused by a mutation in a copper binding protein involved in the transport of copper from hepatocytes into bile. Patients usually present in childhood or as young adults. The serum level of another protein, ceruloplasmin, is often decreased, but may rise into the normal range in patients with significant hepatic necroinflammatory activity. Hemolysis (Coombs' negative) is common, particularly at the time of menarche in girls. It is thought to be caused by the sudden release of large amounts from the liver due to massive

hepatic necrosis. Keiser-Fleischer rings are present in patients with significant neurologic involvement, but are less common in patients who present primarily with hepatic disease. A 24-hour urine copper level is helpful in establishing the diagnosis. Genetic testing is difficult to perform because of the size of the Wilson's disease gene and the large number of possible mutation sites. Genetic testing is useful to identify affected family members of index patients with known mutations.

Histologic features: In childhood a liver biopsy may exhibit only steatosis or mild steatohepatitis. A copper stain (rhodanine) may be negative, but quantitative copper determination can be performed from the paraffin embedded tissue. In older patients the biopsy appearance can be indistinguishable from other forms of chronic hepatitis. One subtle clue is the presence of Mallory bodies in periportal hepatocytes, a feature not present in chronic HBV, HCV or AIH. A copper stain usually reveals deposition in periportal hepatocytes. Often considerable fibrosis, or even cirrhosis, is present at the time of diagnosis. The combination of a clinical presentation of severe acute hepatitis and a biopsy showing cirrhosis in a patient less than 45 years old is almost always due to Wilson's disease or autoimmune hepatitis. In fact, Wilson's disease should be ruled out in any patient less than 45 with unexplained chronic hepatitis. In particular, Wilson's disease should be excluded before a diagnosis of seronegative AIH is made. In cirrhotic patients copper deposition can be patchy, with no deposition at all in some regenerative nodules. Quantitative copper deposition can be helpful in such cases.

Primary Biliary Cirrhosis (PBC)

Clinical features: Primary biliary cirrhosis is primarily a disease of middle-aged women. Clinical confusion with chronic hepatitis is not an issue since there is a reliable serologic marker (anti-mitochondrial antibody, or AMA) and because PBC patients demonstrate a cholestatic pattern of liver chemistry test abnormalities (elevated TB, alk P, GGT), rather than a hepatitic pattern. There are patients with PBC/AIH overlap, but this topic is beyond the scope of this review.

Histologic features: If no clinical information is provided histologic confusion between chronic hepatitis and PBC is possible, since both conditions are characterized by dense portal mononuclear cell infiltrates,

including lymphoid aggregates or follicles in some cases of each condition. However, in PBC there are also histologic features of chronic cholestasis, including lymphocytic cholangitis, bile duct loss, and cholate stasis. Mallory bodies may be seen in the periportal zones in advanced PBC. Granulomas are common in PBC and are exceptionally uncommon in most forms of chronic hepatitis.

Non-specific Portal Inflammation

A few scattered inflammatory cells can be found in some portal tracts in a normal liver. The presence of a slightly increased number of portal mononuclear cells is a not uncommon finding in donor liver biopsies and at autopsy. It is possible that subclinical biliary tract disease (i.e., gallstones) or intestinal inflammation may lead to mild portal inflammation. Certainly mild portal inflammation is common with any form of clinically significant biliary obstruction. The possibility of celiac disease should also be kept in mind when a biopsy reveals unexplained mild portal inflammation. Other autoimmune diseases may also cause mild portal inflammation, and the possibility of other as yet unrecognized viral infections can not be excluded.

The Bottom Line – how to sign out the case

The diagnostic term “chronic hepatitis” is best reserved for cases known or thought to be due to chronic HBV or HCV infection, AIH, Wilson’s disease and rare cases of drug toxicity. If these processes have been ruled out the descriptive term “portal inflammation” is more appropriate.

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Clinical Features

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