Hepatology for Gastroenterologists and Hematologists. Part Three: Pathology of Chronic Necroinflammatory Liver Disease

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Abstract

Necroinflammatory liver diseases are one of the most frequently encountered pathologies when interpreting a liver biopsy. In a histopathological study, we faced several questions including: What is it? How severe is the illness? And what does the clinician expect? This article attempts to answer these questions.

Keywords

Liver, biopsy, necroinflammatory disease, Hepatitis C (VHC), Hepatitis B (HBV), autoimmune hepatitis (AIH).

As we saw earlier, necroinflammatory diseases have either an acute or chronic pattern in which we find evidence of inflammation and cell death (apoptosis and/or necrosis). Multiple etiologies including viral hepatitis, autoimmune hepatitis and drug-induced hepatitis are common.

Much of the usefulness of a liver biopsy is in differentiating chronic liver disease into either acute hepatitis or chronic hepatitis. This article focuses on chronic hepatitis which is defined from the morphological point of view by the presence of portal inflammation and damage to hepatocytes manifested by interface hepatitis and/or lobular inflammation. Fibrosis observed as a fibrous expansion of established cirrhosis is a characteristic hallmark. There is a tendency to call any biopsy chronic hepatitis if portal inflammation is found, but it should be remembered that this consideration involves a significant risk of progression which requires very different management and monitoring of patients.

In the practice of hepatology, when we find portal inflammation, we must differentiate among those conditions that typical present as Hepatitis C, Hepatitis B and autoimmune Hepatitis. We should also differentiate among chronic cholestasic diseases, drug-induced hepatitis, and metabolic diseases such as hemochromatosis, Wilson's disease and alpha-1-antitrypsin deficiency. Since all of these have patterns that resemble chronic hepatitis, a clinical pathological correlation is essential. Otherwise it would be possible for the pathologist to make a purely descriptive diagnosis of observed morphological findings such as "portal inflammation, lobular and interface activity."

In chronic hepatitis, the clinical diagnosis is usually established by clinical history, background, and serological tests for viruses prior to the decision to perform a biopsy. One of the main objectives in a physician's decision to perform a biopsy is to establish degree of necroinflammatory activity as accurately as possible and to classify whether or not fibrosis is present.

There are many systems for grading and staging a liver biopsy, some are more complex than others, and all have been modified over time.

Table 1 provides a comparison of three major systems used for grading activity and staging chronic hepatitis: Knodell's original system which was subsequently modified by Ishak, the system based on pictograms that Batts and Ludwig popularized in 1995, and the Metavir European system. (1,2,3) Some systems do not include stage 0 which can sometimes be observed in autoimmune hepatitis after treatment, in some

Table 1. Classification of activity.

Score	Ishak's modification of Knodell System (3)	Batt and Ludwig (2)	Metavir (11)
0	Inflammation and necrosis: Absent No Fibrosis	Mild portal inflammation or no inflammation, either interface necrosis or lobular nflammation No Fibrosis	A0: no inflammation or necrosis F0: no fibrosis
1	Portal and periportal inflammation in some areas, with focal necrosis 1 focox10X Fibrous expansion of some portal areas with or without short septa	Minimum portal inflammation, patchy interface-necrosis and occasionally apoptotic hepatocytes Portal fibrosis	A1: mild necroinflammatory activity F1: portal fibrosis
2	Mild swelling in portal areas with necrosis shown in zone 3 and some in zone 2. Focal necrosis two-4x10X Fibrous expansion of most portal areas, with or without short septa	Mild portal inflammation with interface hepatitis in some portal tracts and mild apoptosis Periportal fibrosis	A2: moderate necroinflammatory activity F2: portal fibrosis with few septa
3	50% or moderate inflammation with necrosis in most of Zone 1, and focal necrosis 5-10x10X Fibrous expansion of most portal areas with occasional P-P bridges	Moderate portal inflammation, interface and lobular hepatitis, frequent necrotic hepatocytes Septal fibrosis	A3: severe necroinflammatory activity F3: portal fibrosis with numerous septa
4	Severe swelling in most portal tracts with necrosis in Zone 1, occasional PC, bridges and focal necrosis 10x10X. Fibrous expansion of most portal areas with frequent PP and PC bridges	Severe portal inflammation, interface hepatitis with necrosis prominent on bridges and diffuse hepatocellular damage Cirrhosis	F4: cirrhosis
5	Portal and lobular inflammation, necrosis in Zone 1 with multiple PC areas Numerous PP and PC bridges with incomplete cirrhosis or incomplete nodules.		
6	Portal inflammation, lobular and pan-glandular necrosis. Cirrhosis		

forms of hepatitis B virus (inactive carriers) and in the 5% of cases of hepatitis C in which portal inflammation is observed without necroinflammatory or interface activity. In systems without stage 0, portal inflammation is taken into account for staging even when interface activity is absent. This is one of the reasons these systems tend to indicate quantitatively and qualitatively higher levels of inflammatory activity than do other systems. Number systems are recommended only for research studies that are analyzed by expert pathologists. In daily practice it is definitely more useful and practical to use semi-quantitative methods to indicate inflammatory activity with labels such as minimum, mild, moderate or severe.

Although the biopsy continues to be the gold standard for diagnosing chronic hepatitis, it is important to note that clinical and pathological data can lead to misdiagnoses in between 15% and 50% of cases when these data are interpreted in isolation. In 10% to 15% of cases, a biopsy can provide additional information for the diagnosis and in up to 18% to 20% of cases that information may change how the patient is managed. (4) Despite these facts, widely reported in the literature, we cannot ignore the fact that new techniques like serological and imaging studies have begun to replace the role of liver biopsies in some circumstances and most likely they will be indicated to even more limited extent in the future. (5)

The main reason to conduct a biopsy is if the clinician thinks the outcome will change the diagnosis, treatment and/or prognosis of a patient. Whichever system that is chosen, it must be known by the clinician who is finally going to interpret the result of a pathological study. For this reason interaction between the gastroenterologist and the hepatologist is vital to guarantee that they speak in the same terms.

WHAT IS THE IDEAL BIOPSY FOR ADEQUATE PATHOLOGICAL INTERPRETATION?

We know that liver biopsies are invasive, expensive and not free of complications which can be serious in some cases. Thirty percent of those who undergo liver biopsies experience pain, and in 0.3% of cases severe complications including bleeding occur. In less than 0.01% of liver biopsies the patient dies. Errors may also occur due to lesions which are out of the ordinary, especially parenchymal lesions, espe-

cially due to the heterogeneity of the vast majority of liver diseases and to variations in observations by one or several observers. (6, 7, 8)

Percutaneous fine needle aspersion biopsies and surface and/or sub-capsular biopsies are not recommended for diagnosis of necroinflammatory diseases. The ideal biopsy for the pathologist, and therefore for the patient, is transjugular or laparoscopic biopsy performed with 14 to 19 gauge Tru-cut biopsy needles. Preferably, two biopsies, one from both the right side and one from the left side of the liver should be sent to histopathological study. Fragments for testing should be 2 cm in length and between 1mm and 2mm in diameter. Each piece should contain at least 11 portal triads. A biopsy with these features is considered optimum and corresponds approximately to a value between 1/50,000 and 1/63,000 of hepatic parenchyma. (9, 10)

In this article we focus on the morphological changes observed in the major forms of chronic hepatitis.

VIRAL HEPATITIS C (HCV)

It is well known that after an acute infection develops, up to 85% of cases evolve into chronic hepatitis. Of these cases, 27% develop into cirrhosis, and 25% develop into hepatocellular carcinoma. This is currently the leading cause of death from liver disease and one of the main indications for liver transplantation. From a purely morphological point of view the early stages of the chronic disease are not well documented in the literature. Although HVC is well established, there are not good correlations between the levels of AST/ALT and histopathological findings for this disease. (11) Yano has shown that 30% of patients who show no sign of fibrosis in the initial biopsy will develop it within 13 years. Forty three percent of those with mild to moderate fibrosis will develop chronic conditions within 17 years, and 100% of those with fibrotic bridges or incomplete regenerative nodules will develop chronic conditions within 10 years. (12) When there is serological evidence of HCV combined with clinical suspicion that a chronic liver disease is developing, a biopsy might be useful for its prognostic and predictive value to help evaluate whether treatment should be initiated or discontinued. (13, 14)

HCV has morphological characteristics but no pathognomonic characteristics, and this help differentiate from other forms of chronic necroinflammatory liver diseases since the others share the pattern inflammation described earlier.

We will list the most frequently observed patterns. There are infiltrated portal inflammations which are predominantly lymphocytic and which have lymphoid aggregate formations and/or lymphoid follicles with well-formed germinal centers in up to 50% of cases (Figure 1). (15)

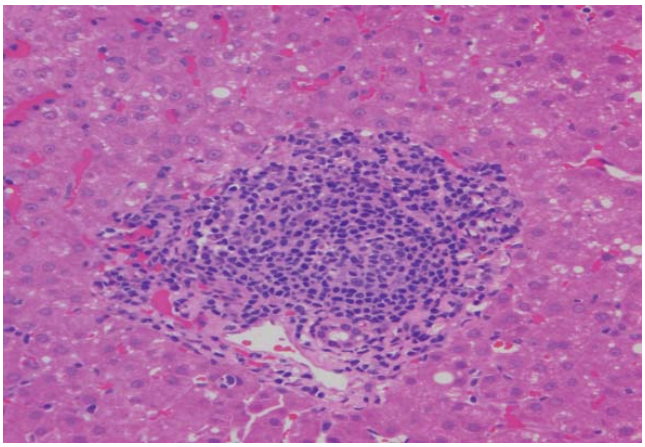

Figure 1. 40X, H & E stain: Portal space with inflammatory lymphocytic infiltrate, lymphoid follicle formation, and focal damage of the limiting plate

In 1969, even though they did not know it was HVC, Poulsen and Christofferson described nondestructive ductal damage or lymphocytic cholangitis and observed intraepithelial permeation of lymphocytes. This sometimes makes ducts dark and difficult to identify. This phenomenon is now known as Poulsen's lesion. (16) In most studies this condition is described in up to one third of the cases. Bach and colleagues have reported this condition in 91% of the HCV biopsies. Poulsen's lesion makes it necessary to establish a differential diagnosis among chronic cholestatic diseases such as primary biliary cirrhosis and ductopenic syndromes. (15)

Steatosis which usually macrovesicular is observed in HCV genotype 3. It is directly related to the virus and has been seen in 70% of cases. Its distribution is also nonspecific, and it usually is not intense. The relationships of other genotypes with the disease are not clear, but in any case they occur less frequently (Figure 2). It is important here to determine any coexistence with steatohepatitis which can be seen in about 10% of the cases. (17)

Mallory's hyaline or Mallory bodies are generally present in more advanced cases of disease and reflect associated cholestasis changes and periportal locational changes. They are reported in 18% of cases. Lobular hepatitis can occur and is accompanied by increased sinusoidal lymphocytic infiltration and hyperplasia of Kupffer cells. In these cases sinusoidal lymphocytes are characteristically arranged in perfectly formed rows. This finding is observed in over 80% of chronic HCV cases. Depending on the severity of necroinflammatory activity, we find isolated apoptotic hepatocytes (Figure 3) or confluent necrosis. Fibrosis which starts in portal areas is progressive. (15, 18)

The differential diagnosis from the morphological point includes other forms of viral hepatitis; primarily hepatitis

B, autoimmune hepatitis, Wilson's disease, drug-induced hepatitis, chronic cholestatic disease, and alpha-1 antitrypsin deficiency. (19)

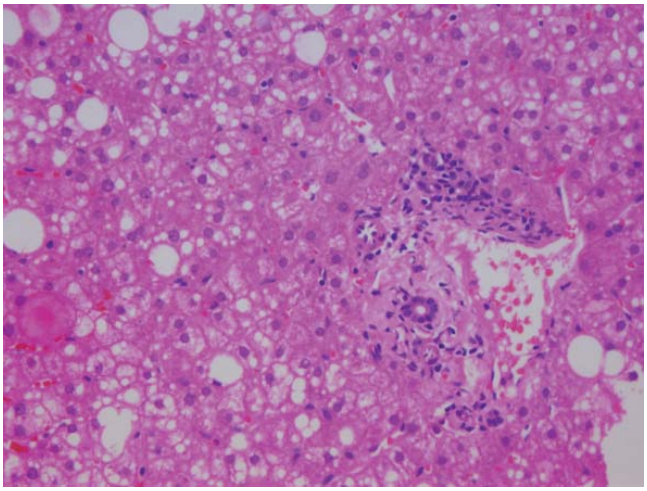

Figure 2. 20X, H & E stain: Minimal portal inflammation with predominantly macrovesicular steatosis

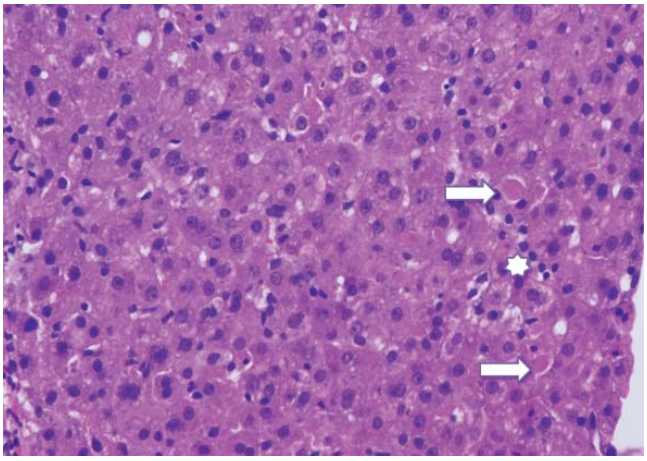

Figure 3. 40X, H & E stain: Lymphocytic infiltrate forming rows (right asterisk) with isolated apoptotic cells (arrows)

VIRAL HEPATITIS B (HBV)

Only 10% of patients with acute HBV infections progress to chronic states. Prevalence has decreased as the result of the use of recombinant vaccines, although it remains high in Asia and Africa.

Portal and periportal inflammation are found in the histopathological study, although they are common to all types of viral hepatitis. Their magnitudes vary according to factors of both the virus and the host. This is also predominantly lymphocytic with some plasma cells and macrophages and significant activity associated with interface and hepatocellular damage. Apoptotic hepatocytes are observed especially in the periportal area. Fibrosis may also begin in the portal area, but its development is not a prerequisite for development of hepatocellular carcinoma.

The most typical histological finding is the presence of ground glass hepatocytes. This is and present in 50% to 75% of cases and reflects the presence of surface antigen (HBsAg) mixed with the endoplasmic reticulum of the cytoplasm of hepatocytes. This produces a fine granular image with a slight, clear peripheral halo. This sometimes moves from the nucleus to the periphery (Figure 4). As described above, histochemical studies including Victoria blue, orcein, aldehyde fuschine and Shikata may be useful for identification. "Sanded" nuclei are pale pink and granular. They containing HBcAg which indicates that the virus is actively replicating. When this occurs massively, it may suggest a state of immunosuppression. We also use immunohistochemistry tests of the cytoplasm and membrane. These include tests for surface antigen HBsAg and core antigen HBcAg for location of the nucleus (Figure 5). (20)

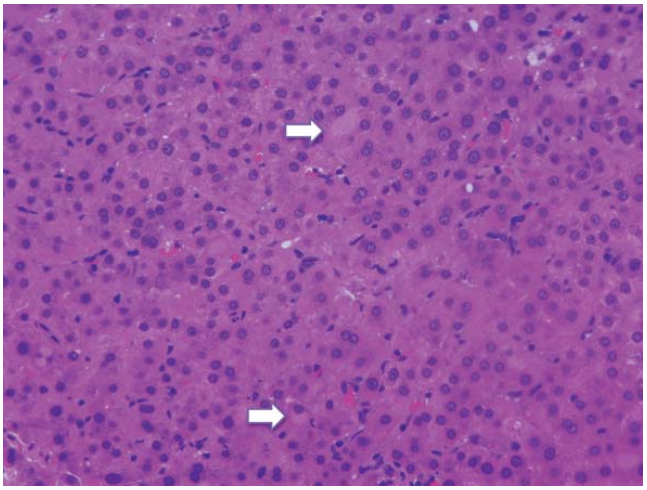

Figure 4. 20X, H & E stain, Hepatitis B with ground glass hepatocytes (arrows) and lobular hepatitis

Histopathological changes help categorize different phases of HBV infection. In the immune tolerant phase observed in perinatally infected patients, we usually find little or no liver damage. In the immune clearance phase of chronic infection there is evidence of progressive liver damage. In this phase the intensity of portal inflammation varies and there is interface activity, lobular hepatitis and the presence of ground glass cells. Inactive carriers may have mild portal and lobular inflammation as well as ground glass hepatocytes which are sometimes prominent. Nevertheless, there is no additional damage to the hepatocytes. Reactivation phases of infection include portal and lobular necroinflammatory activity as well as ground glass hepatocytes. (21, 22, 23)

Morphological differential diagnosis for HBV must consider hepatitis A, C, CMV, Epstein Barr virus, adenovirus,

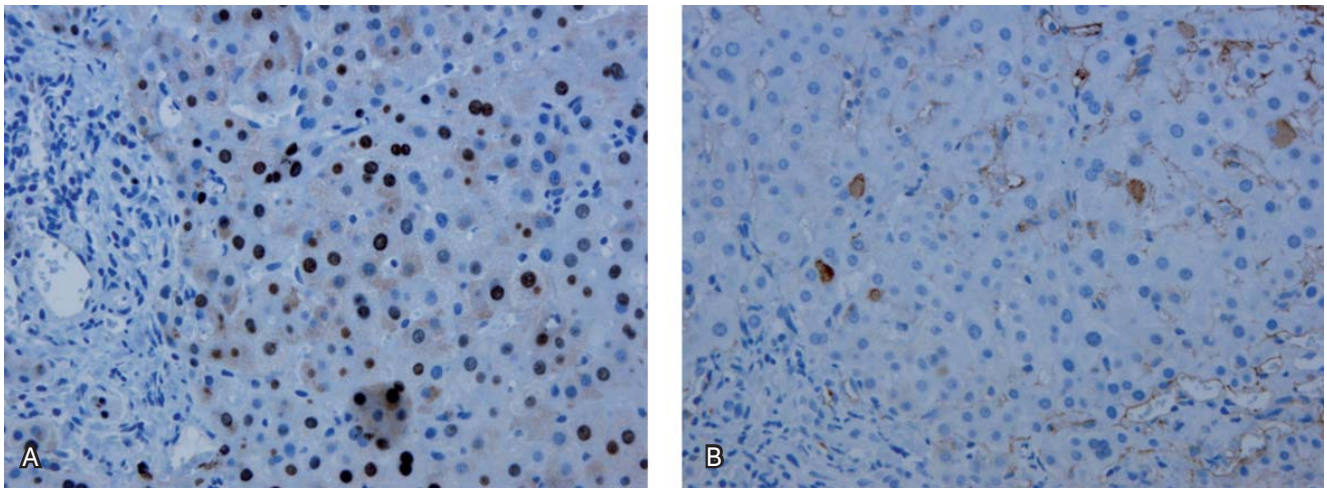

Figure 5. 40X, Immunohistochemical study: A) Hepatitis B core antigen, numerous intensely stained nuclei (brown discoloration) indicating active viral replication. B) Surface antigens indicate ground glass hepatocytes

yellow fever¸ and also include autoimmune hepatitis, and drug induced hepatitis. Correlation with the patient's clinical history and serology is essential. (19)

AUTOIMMUNE HEPATITIS (AIH)

Autoimmune hepatitis (AIH) has a good clinical characterization, and biopsies play an important role in diagnosing acute and chronic forms of this kind of hepatitis as well as in determination of the kind of treatment. AIH progresses rapidly if it is not treated in time, so that even when morphological findings are not pathognomonic a biopsy can help with diagnosis when the clinical diagnosis is not entirely clear. Three types of autoimmune hepatitis have been described on the basis of titers of ANA, ASMA and anti-LKM autoantibodies even though they are all similar from a morphological point. (24, 25)

Autoimmune hepatitis typically appears as a necroinflammatory disease with unevenly distributed portal and periportal infiltrates and with piecemeal necrosis or interface hepatitis. Interface hepatitis is often serious, and in the majority of cases there are increased numbers of plasmocytes which are accompanied by lymphocytes and eosinophils. Lobular compromise, which typically affects Zone 1, is marked and exhibits a pseudoglandular pattern of hepatocytes (Figures 6 and 7). We can sometimes observe giant hepatocyte transformation. (15) Necroinflammatory compromise is rarely found in Zone 3, but has been described with the term "piecemeal necrosis", especially for acute forms (26). Necrosis of hepatocytes with the presence of acidophilic bodies can be seen in isolated cells or in the form of confluent necrosis (Figure 8). This condition results in collapse of the reticular layer and subsequent development of fibrotic bridges since it always starts in Zone 1. (15, 27)

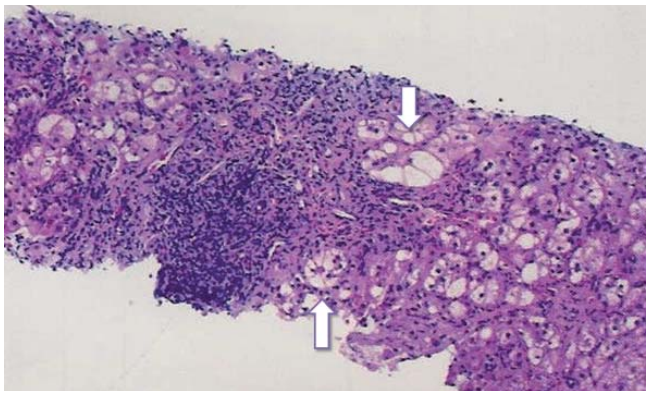

Figure 6. 10X, H & E stain: Autoimmune hepatitis with very severe portal inflammation of lymphocytes and plasmocytes, lobular hepatitis and interface hepatitis with pseudo-acini of the hepatocytes (arrows)

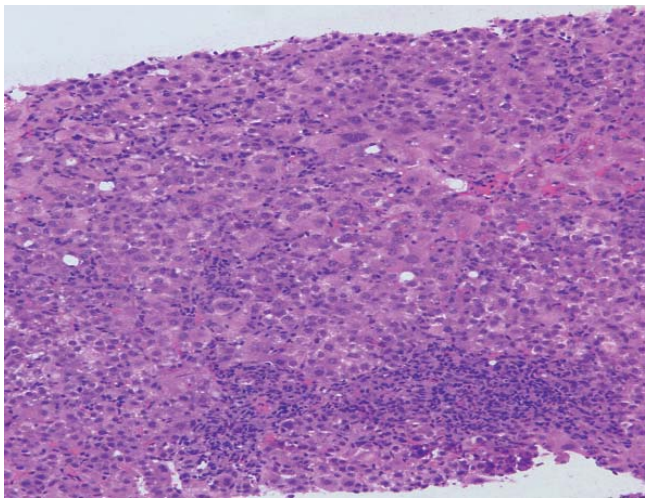

Figure 7. 20X H & E stain: Autoimmune hepatitis with severe portal and lobular inflammation.

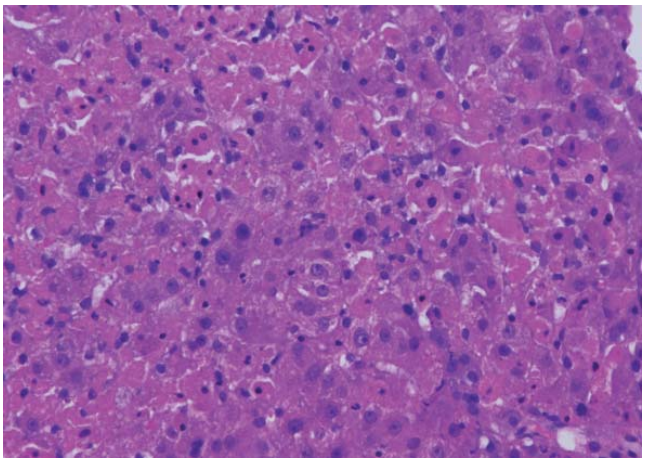

Figure 8. 40X H & E stain: Autoimmune hepatitis with multiple foci of confluent necrosis

AIH is not usually characterized by changes shown in bile ducts, but if they are present a differential diagnosis with chronic cholestatic disorders such as primary biliary cirrhosis is required. In these cholestatic disorders we find portals infiltrated with lymphocytes and plasma cells, but this is characteristic of damaged ducts. Sometimes when ducts are lost, granulomas form. In these cases when a biopsy is performed it will show evidence of chronic cholestatic disease and clinical testing for alkaline phosphatase and elevated levels of antimitochondrial antibodies (AMA) will be positive. We also must discard primary sclerosing cholangitits, overlap syndrome, and HVC. If lymphoid follicles contain primarily lymphocytic infiltrate, HVC with plasmocytosis should be considered in the differential diagnosis. When there are numerous eosinophils, it is important to differentiate drug induced hepatitis which resembles autoimmune hepatitis (19).

Table 2 summarizes clinical and histopathological features of the 3 most important entities in this pattern of liver damage.

IMITATORS OF CHRONIC NECROINFLAMMATORY HEPATITIS

In addition to those already described, many other entities morphologically resemble chronic liver damage caused by necroinflammatory disease.

Table 2. Diagnostic key.

	Hepatitis C	Hepatitis B	Autoinmune Hepatitis
Etiology	Single-stranded RNA virus. Six genotypes with more than 50 subtypes of the Flaviviridae family	Double stranded viral DNA of the Hepadnaviridae family	Unknown/Autoimmune Presence of autoantibodies
Laboratory Test	Anti-HCV HCV RNA viral load Elevated aminotransferases	Serology for antigens HBV: HBsAg, HBcAg, HBeAg. HBV DNA viral load. Elevated aminotransferases	Serum antibodies: Type 1 (ANA and / OSMA) p-ANCA Type 2 (anti-LKM-1) Type 3 (anti SLA or LP) Hypergammaglobulinemia Elevation of aminotransferases. Alkaline phosphatase, normal.
Natural history	80-85% progress to chronic state Slow evolution to chronic state	10% evolution to chronic state	Prolonged clinical course. 30% of cases have multiple relapses. Appropriate response to steroids in 65% cases. Predominantly suffered by women with history of other autoimmune diseases. Bimodal
Prognosis	Hepatocellular carcinoma is more closely related to the development of cirrhosis Its recurrence is common after transplantation.	Increased risk of cirrhosis. Hepatocellular carcinoma without development of cirrhosis. Coinfections with VHC, HIV and HVD are common Post-transplant recurrence is rare.	Rapid progression to cirrhosis and liver failure It depends on the severity at the time of diagnosis.
Histopathological diagnosis Keys	Portal inflammation, predominantly of the lymphocytes. Formation of clusters and lymphoid follicles. Interface activity. Lobular hepatitis with lymphocytes in perfect rows with or without acidophilic bodies. Steatosis	Portal Inflammation with lymphocytes and plasma, interface hepatitis, lobular hepatitis with lymphocytes, Ground glass hepatocytes and sand nuclei.	Portal inflammation marked predominantly by plasma. Strong interface activity. Lobular hepatitis of plasma. Acidophilic bodies Confluent necrosis
Utility of biopsy	Grading and staging. Exclusion of concomitant liver diseases. Determine recurrence of infection after transplants.	Grading and staging Exclusion of concomitant liver diseases. Determination of presence of fibrosing cholestatic hepatitis after transplant.	Grading and staging Exclusion of concomitant liver diseases Overlap syndromes Treatment

Serious lymphocytic portal inflammation can develop in steatohepatitis. When it does it can cause ballooning and subsinusoidal which primarily compromises Zone 3. Understanding this is important for differential diagnosis, especially in cases of HVC.

Infiltration caused by lymphoproliferative disorders such as lymphoma may present as very prominently infiltrated portals. Nevertheless, identifying a monotone appearance of the infiltrate and/or atypical cells combined with immunophenotyping will help in the diagnosis.

Prominently infiltrated portals may also be present in acute hepatitis, but the marked ballooning with lobular hepatitis and loss of the reticular layer - along with the patient's medical history - are the keys to diagnosis.

Obstructive biliary syndromes present infiltrated portals, but polymorphonuclear neutrophils with cholangiolar proliferation and acute cholangitis usually predominate. These are associated with pericentral cholestatic changes. These symptoms combined with the patient's medical history and diagnostic images help guide the diagnosis.

Celiac disease also results in find inflamed portals and infiltrated predominantly by lymphocytes. The patient's medical history, negative serology and the presence of anti-tTG are diagnostic clues.

Wilson's disease is characterized by portal inflammation and steatosis which are usually accompanied with ballooning and glycogenated nuclei. Findings of copper deposits together with, negative viral serology, clinical evidence of cholestasis and decreased ceruloplasmin help interpret the morphological findings.

Alpha1-antitrypsin deficiency is characterized by portal inflammation and interface activity. The finding of cytoplasmic PAS which is positive for diastase in the periseptal or periportal areas together with fibrosis is the key to this diagnosis.

Hemochromatosis has lymphocytic infiltrated portals, iron deposits within the hepatocytes in the endothelium and the ductal epithelium, negative serology and autoantibodies. Taken together, these factors provide the pattern for the differential diagnosis.

Reactive hepatitis frequently presents nonspecific portal infiltration does not present necrosis or interface activity. Lobular inflammation is minimal and fibrosis is definitely absent. A finding of portal and sinusoidal macrophages filled with PAS positive diastase material suggests a recent reactive process such as those secondary to cholelithiasis, cholecystitis and intestinal infections.

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