Liver biopsy plays a central role in treatment algorithms in patients with hepatitis B and remains the gold standard for evaluating hepatic pathology. The pathology of hepatitis B is diverse and reflects the natural history of infection. An acute hepatitic pattern with lobular disarray is seen in acute infection, during acute flares of disease, and with acute hepatitis D superinfection. In chronic hepatitis B, inflammation is less pronounced in the immune-tolerant phase and is prominent during immune-mediated viral clearance. Active inflammation appears to be the driving force for development of fibrosis. Inflammatory grades and fibrosis stage are assigned as is done for hepatitis C. Although current management guidelines recommend liver biopsies only in select patients based on age, viral levels, and hepatitis B e antigen status, these clinical and biochemical parameters do not show consistent correlations with liver histology. Liver biopsy also helps identify preneoplastic lesions including large cell and small cell change. Unlike in other causes of chronic hepatitis, immunostains are widely used and can help determine the phase of infection. Liver biopsies can also identify additional pathology that may contribute to liver disease such as steatohepatitis, iron overload, autoimmune hepatitis, and drug-induced injury. Thus, liver biopsy can play an important role in staging and grading chronic hepatitis B and should be more widely used in assessing the need for therapy. (HEPATOLOGY 2009;49:S61-S71.)

Introduction

The pathology of hepatitis B is diverse and reflects the clinical course of the disease. Following acute infection, most subjects clear the virus whereas others develop chronic hepatitis B. The natural history of chronic hepatitis B is divided into immune-tolerant, immune-reactive, and inactive hepatitis B virus (HBV) carrier phases. Liver biopsy is the traditional gold standard to ascertain the degree of liver injury, including both inflammatory activity and fibrosis stage. In addition, liver biopsy is useful to identify precursor lesions of hepatocellular carcinoma (HCC) and help identify and evaluate confounding diseases such as steatohepatitis, autoimmune hepatitis, and drug-induced liver disease. Current guidelines for management of hepatitis B, however, do not recommend universal liver biopsy in all patients with chronic hepatitis B, but base this decision on several clinical, virological, and biochemical parameters. This article will briefly review the current literature on liver biopsy in hepatitis B.

Salient Histological Features

Acute hepatitis B is characterized by lobular disarray, ballooning degeneration, numerous apoptotic bodies, Kupffer cell activation, and lymphocyte-predominant lobular and portal inflammation. Significant lobular necrosis leads to fulminant hepatic failure. Although patients with acute hepatitis B are usually not biopsied, a similar pattern of injury may also be seen in chronic hepatitis B with acute flares of disease (Fig. 1), acute superinfection with hepatitis D, or a second hepatic insult (such as by drug-induced liver injury). In addition, the virus may develop a precore mutation, leading to an hepatitis B e antigen (HBeAg)-negative chronic, often relapsing, hepatitis with similar histology.

In chronic hepatitis B, there is a varying degree of predominantly lymphocytic portal inflammation with interface hepatitis (Fig. 2) and spotty lobular inflammation. Inflammation is minimal in the immune-tolerant and inactive carrier phases, but is prominent in the immune-reactive phase. Bridging necrosis is identified as
inflammation “connecting” portal tracts to one another or to central veins (Fig. 3). Confluent necrosis, as the name implies, affects multiple contiguous hepatocytes (Fig. 4). Inflammation is typically associated with scarring, which can vary from a mild portal expansion to periportal fibrous strands, bridging fibrosis, and cirrhosis (Fig. 5). Livers that develop central to portal bridging necrosis or confluent necrosis are likely to have higher fibrosis stage. Cells rich in hepatitis B surface antigen (HBsAg) may have “ground-glass” cytoplasm (Fig. 6), and can be highlighted by special immunohistochemical stains, including Shikata’s orcein1 and Victoria blue.2 However, ground-glass hepatocytes may also be seen in other conditions such as drug-induced endoplasmic reticulum hypertrophy, cyanamide toxicity, and storage diseases (e.g., Lafora disease and fibrinogen storage disease).3 Histological studies based on paired biopsies obtained before and after HBeAg seroconversion have consistently demonstrated that seroconversion to antibody to HBeAg (anti-HBe) is followed by a significant improvement or even disappearance of disease activity. This improvement is irrespective of the extent of the liver damage in the baseline biopsy, indicating that liver histology during the HBeAg-positive phase is not predictive of the late outcome of liver disease.4

A chronic hepatitis pattern of injury is not specific for chronic hepatitis B, and is also seen with other liver diseases, including chronic hepatitis C, autoimmune hepatitis, drug-induced liver injury, and chronic cholestasis. Unlike in hepatitis C, lymphoid aggregates, duct (Poulsen) lesions, and steatosis are uncommon in chronic hepatitis B. However, Peng et al. found steatosis to be more frequent in chronic hepatitis B than in the general
population, and they hypothesize that this may be due to metabolic factors or the ability of HBV to indirectly facilitate the development of steatosis. Autoimmune hepatitis tends to have a prominent plasma cell infiltrate and more significant lobular injury. Chronic cholestasis shows cholate stasis (manifested by pseudoxanthomatous change and copper accumulation) in periportal hepatocytes, while drug-induced liver injury can show varying histology. Clinical correlation and serologic investigations are therefore of paramount importance in arriving at a specific diagnosis. It must also be remembered that multiple etiologies may be responsible for liver injury in a given patient.

HBV replicates in hepatocytes but is not directly cytotoxic. Liver damage appears to be immune-mediated, with HBV-specific T cells playing a key role both in disease pathogenesis and viral clearance. The inflammatory infiltrates of chronic hepatitis B and C show similar cellular composition, with CD4-positive T cells predominating over CD8-positive T cells. In the same study, B cells comprised 15% of the inflammatory infiltrate, while natural killer (NK) cells totaled 10%. Expression of human leukocyte antigens paralleled inflammatory activity. Portal lymphadenopathy was found more often in hepatitis C (54.5%) than in hepatitis B (30.6%). CD8-positive T cells help clear acute infection and, in the presence of an effective HBV-specific CD8 response, inhibition of virus replication can be independent of liver damage. When the HBV-specific CD8 response is unable to control virus replication, it may contribute to liver pathology not only directly, but also by causing recruitment of non–virus-specific T cells. The non–virus-specific CD8 T cells have an aberrant functional profile and may impede proliferative antiviral effector function, while contributing to the proinflammatory cytokine environment. NK cells may also cause hepatocyte death by a non–antigen-specific mechanism. NK cells and CD4/CD8 ratio are reportedly significantly decreased in livers with advanced fibrosis; pathways regulating the interactions of hepatic stellate cells with specific lymphocyte subsets may be important in the pathogenesis of fibrosis. Liver-infiltrating lymphocytes may functionally differ from peripheral blood lymphocytes in terms of cytokine production and may allow HBV to persist in the absence of significant hepatic destruction. Irrespective of the patient’s viral levels or degree of liver pathology, the infiltrating T cells may be clonally restricted. Further, T-regulatory subsets in the infiltrate may be either beneficial or detrimental by either limiting liver immunopathology or by suppressing protective T cell responses. Immunoexpression of adhesion molecules such as beta-catenin have shown correlation with necroinflammatory scores in chronic hepatitis B. The pathology of hepatitis B is modified in the presence of coinfection with hepatitis C virus (HCV) and/or...
human immunodeficiency virus (HIV), with most studies showing a higher degree of necroinflammation and fibrosis in co-infections. In individuals infected with HIV, the significant hepatotoxicity associated with antiretroviral drugs may further exacerbate liver injury. Super-infection with hepatitis D virus increases the risk of hepatitis flares, cirrhosis, hepatic decompensation, and death in patients with HBV/HIV coinfection.

**Grading and Staging**

Numerous grading systems are available for assessing the severity of necroinflammation and the degree of fibrosis. Histological responses in most trials have been defined as a two-point decrease in inflammation scores (using the Knodell or Ishak scales) or a one-point decrease by the Metavir system, without worsening of fibrosis between pretreatment and posttreatment biopsies, although the clinical significance of these degrees of improvement has not been shown. Active inflammation is the driving force leading to fibrosis, and increasing grade is associated with more fibrosis. Because the goal of treatment is to stop ongoing necroinflammation and prevent progression to cirrhosis and HCC, follow-up biopsies may be helpful, at least in protocol settings, if not in community practice. Liver fibrogenesis is an active, dynamic process that may progress as well as regress spontaneously or after therapy. Reversal is a slow process taking years and may only occur if the patient becomes immune-tolerant or if the virus is eliminated. Some authors suggest that histological classification of the severity of cirrhosis could identify features to predict the potential for its reversal.

Different studies use different scoring systems, and it is often difficult to compare results and draw unifying conclusions. This difficulty is further compounded by the fact that intraobserver and interobserver reproducibility of scores is moderate. Few studies have compared different scoring systems. In a cohort of patients with chronic hepatitis, Rozario et al. found a good concordance between Ishak and Metavir scoring systems for necroinflammation and an excellent concordance for fibrosis. Goodman has reported that interobserver agreement is high for cirrhosis and fibrosis, but is only moderate for inflammatory grades, and has suggested the use of the terms “mild”, “moderate”, and “severe” instead of using numeric scores to convey grades in routine biopsy reporting. If numeric scores are given, the particular system used should be clearly mentioned, because the patient is likely to be followed at different centers during the prolonged course of disease progression.

Fibrosis stage is, by far, the most relevant histological prognostic factor in chronic hepatitis B. Patients with cirrhosis are at greater risk of flare-related hepatic decompensation. Because liver biopsy is an invasive process, many noninvasive methods have been devised to assess fibrosis. Differing results have been reported with hematological and biochemical parameters such as bilirubin, platelet count, aspartate aminotransferase/platelet ratio, prothrombin time, and prothrombin index as surrogate markers of fibrosis in chronic hepatitis B. Numerous imaging techniques have also been used to evaluate fibrosis, including contrast-enhanced ultrasonography and color doppler portal vein flow velocity profile, transient elastography (Fibroscan), liver apparent diffusion coefficient, and others. However, at present, these tests have not been adequately validated for routine clinical use; histology remains the gold standard for stratification of fibrosis stage.

Sampling error is the most important issue with liver biopsies, because even an “adequate” biopsy can underestimate fibrosis. A biopsy with 11 complete portal tracts is suggested as adequate for staging. On the other hand, ter Borg et al. have found sampling error to be a constant feature, even for biopsies greater than 20 mm in length. Cutting-type needles may yield less fragmented biopsies and are reportedly better than suction-type needles for evaluating fibrosis and cirrhosis.

**Dysplasia and Cancer**

Although cirrhotic livers are at greater risk for HCC, unlike in hepatitis C, patients with chronic hepatitis B can develop HCC in the absence of cirrhosis, supposedly because of direct viral integration in the host genome and the direct oncogenesis effects of HBV. Clinical screening for the development of HCC is routinely performed by noninvasive means including ultrasonography and testing for serum alpha-fetoprotein levels. The role of liver biopsy is to identify precursor lesions including cirrhosis and liver cell dysplasia and to differentiate macrogenerative nodules from well-differentiated HCC. Liver inflammation may contribute to the accumulation of critical mutations in the host genome that contribute to carcinogenesis. Nontumorous liver parenchyma in livers affected by HCC have been reported to have higher inflammatory grades when compared to livers without tumors. In the same study, livers with HCC had a higher incidence of hepatitis B core antigen (HBcAg) positivity, suggesting a significant role of ongoing persistent chronic inflammation and actively replicating HBV in carcinogenesis. Hepatitis B virus–related HCCs may have a worse prognosis and be more aggressive than HCV-related tumors, this difference becoming statistically significant among patients with advanced HCC.

The term “liver cell dysplasia” was coined by Anthony et al. in 1973 to indicate a group of cytologic abnormalities found significantly prevalent in HBV-related cir-
rhotic livers harboring HCC. The abnormality is identified as foci of cellular enlargement and nuclear pleomorphism with hyperchromasia and multinucleation, and is frequently noted in chronic hepatitis and cirrhosis. This lesion is now termed “large cell change” (Fig. 7A) to distinguish it from “small cell change” (Fig. 7B). The latter condition, described by Watanabe et al. in 1983,49 is characterized by foci of crowded small hepatocytes with high nuclear/cytoplasmic ratio, increased proliferative activity, and striking morphologic and genetic resemblance to HCC. Different nomenclatures have been used for large cell change, depending on the size of the lesion. “Dysplastic foci” refer to clusters of large cell change measuring less than 1 mm in diameter, while lesions measuring greater than 1 mm in diameter have been termed “nodules”.50 Small cell change is thought to be a true precursor lesion of HCC. Aneuploidy has been observed in liver cell dysplasia,51,52 and these lesions are considered to be an independent risk factor for HCC53; however, others have refuted this based on the presence of low proliferative activity, high apoptotic rate, and no definite histologic continuum to cancer.54,55 More recently, Koo et al. have shown a significantly higher cumulative probability of HCC development in the presence of large cell change and have suggested that its presence may help identify a high-risk subgroup of patients requiring more intensive screening.56

**Immunohistochemistry**

Immunostains for HBsAg and HBeAg allow identification of hepatitis B as the etiologic agent of chronic hepatitis and help differentiate recurrent infection from rejection in allograft livers. Also, the immunoexpression patterns of HBsAg and HBeAg may help determine the phase of infection. HBsAg is usually not expressed in acute hepatitis. In chronic hepatitis B, HBsAg expression may be cytoplasmic and/or membranous (Fig. 8), whereas HBeAg expression may be nuclear and/or cytoplasmic (Fig. 9). Diffuse membranous staining for HBsAg suggests active viral replication. In the immune-tolerant phase (or in immunosuppressed hosts), there is diffuse nuclear HBeAg and membranous HBsAg positivity, without marked inflammation, with an inverse relationship between the degree of diffuse membranous expression and inflammatory activity.6,57 Presence of HBsAg in clusters of hepatocytes (Fig. 8C) along with a negative result for HBeAg may represent an inactive carrier state, without ongoing viral replication.58

Sheen et al. has suggested that nuclear HBeAg expression may predict expression of singly spliced HBV RNA, which, in turn, may play a role in viral persistence.59 Cytoplasmic expression of HBeAg (Fig. 9A) is a target for HBV-specific cytotoxic T cells.6 Cytoplasmic and membrane HBeAg staining is reportedly seen in the viral clearance phase and correlates with liver damage57,60 and hepatocyte regeneration.61 Pure cytoplasmic staining (Fig. 9B) may represent presence of mutations that block the translocation of HBeAg; this association is greater with core promoter mutations than precore mutations.62 However, ter Borg et al. found pure cytoplasmic HBeAg staining to be a strong predictor of high hepatitis B viremia and found no association of HBeAg staining pattern with precore stop codon mutations or grade/stage of liver disease.42 An absence of HBeAg may predict treatment response, especially in patients who are HBeAg-negative. Fibrosis stage and HBeAg-negative/anti-HBe-positive

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**Fig. 7.** Dysplasia occurs either as (A) large cell change with cellular enlargement and nuclear pleomorphism, or as (B) small cell change with crowded small hepatocytes with high nuclear:cytoplasmic ratios. (H&E, 400x).
rate reportedly increase as HBCAg distribution changes from nuclear to cytoplasmic. In the same study, significant differences were also observed in serum alanine aminotransferase (ALT) levels, HBV DNA concentration, and necroinflammatory scores with different nuclear and cytoplasmic distribution of HBCAg.12 Positive HBeAg staining indicates the presence of precore wild-type virus. HBCAg and HBeAg generally have a coincident cellular expression, and strong cytoplasmic HBeAg is a marker of high viral replication.57,63 The hepatitis B x antigen (HBxAg) has been visualized in the hepatocyte nucleus and cytoplasm by immunohistochemistry and is claimed to be more sensitive than HBsAg or HBCAg stains for detecting HBV.64,65 Isolated strong immunoreactivity with anti-preS1 antibody is reported with severe acute HBV reactivation, and may precede HBsAg and HBCAg staining.66 Detection of HBV sequences by in situ hybridization may be more sensitive than immunohistochemistry.57,68 A positive hepatitis D immunostain in the nucleus (and sometimes cytoplasm) is essential in diagnosing active infection, because antibodies to hepatitis D in the serum do not distinguish between ongoing or past hepatitis D virus superinfection.

Many novel immunohistochemical markers have been reported to help distinguish macroregenerative and dysplastic nodules from early HCC, including C-Kit (CD117).69

**Fig. 8.** HBsAg immunostains can show (A) cytoplasmic (200×) or (B) membranous (400×) patterns; (C) a “clonal” pattern of staining with clusters of positive hepatocytes may represent an inactive carrier state (200×).

**Fig. 9.** HBCAg is usually nuclear, but a positive cytoplasmic stain may also be seen. (A) Mixed nuclear and cytoplasmic positivity is associated with inflammatory activity; (B) pure cytoplasmic staining may represent presence of core promoter or precore mutations (HBC immunostain, 400×).
E-cadherin, matrix metalloproteinases and their inhibitors, tumor markers (e.g., heat shock protein 70, Glypican 3), and markers targeted to evaluate stromal invasion (cytokeratin 7/cytokeratin 19) and vascular pattern (anti-smooth muscle actin and CD34). In a setting of cirrhosis, HCC may be multifocal and difficult to distinguish from metastatic tumors. Immunostains helpful in making this differentiation have been extensively reviewed.

**Role of Liver Biopsy in Clinical Algorithms**

The purpose of a liver biopsy is to grade and stage liver disease, identify precursor lesions of HCC (i.e., dysplasia and small cell change), and exclude confounding diseases such as steatohepatitis, autoimmune hepatitis, and drug-induced liver disease. The clinical guidelines published by the American Association for the Study of Liver Diseases recommend biopsies only in specific groups of patients and state that liver biopsy is usually not necessary in young patients (below 30 years of age) who are HBeAg-positive and have persistently normal ALT levels, because these patients are likely to be in the immune-tolerant phase and would not be candidates for therapy. However, in a retrospective analysis, Tong et al. found that current treatment guidelines for chronic hepatitis B would identify only 20%-60% of the patients who ultimately developed HCC, and only 27%-70% of patients who died of non-HCC liver-related deaths for antiviral therapy. Sigal et al. also found no correlation of inflammatory activity with clinical, biochemical, or virological parameters. Although patients with persistently elevated ALT levels (>70 U/L) may have progression of fibrosis by one stage within 4-5 years of follow-up, others have shown that up to 30% of patients with persistently normal ALT levels may also have significant fibrosis (stage 2-4), can be at increased risk of mortality and may be candidates for therapy. In fact, 10% of patients with normal ALT may have bridging fibrosis or cirrhosis, and patients with high “normal” ALT may also be at risk for progression. There is also no consistent relationship between HBV DNA levels and histology. Although liver histology may correlate with viral loads in patients who are HBeAg-negative, there is no such correlation in patients who are HBeAg-positive, especially if they are in the immune-tolerant phase. Also, liver histology during the HBeAg-positive phase is not predictive of long-term outcomes and progression of liver disease. Liver viral loads may have better histological correlations than serum HBV DNA. The inconsistencies in different studies may relate to selection of subjects in the immune-tolerant phase, patients in transition to the immune-reactive phase, fluctuating HBV DNA levels in HBeAg-negative patients with precore/core promoter mutants, use of variable cutoffs, and very limited prospective studies in literature. Large, prospective, multicenter studies may be required to resolve these issues.

The effect of HBV genotypes on histology is unclear. Although some studies suggest that certain genotypes (especially genotypes C and D) are associated with worse histology and a greater chance of progression to carcinoma, these studies are hampered by the fact that genotypes have different ethnic, geographic, and epidemiologic associations (Table 1).

![Table 1. Association of Genotypes with Fibrosis Stage](image-url)

<table>
<thead>
<tr>
<th>Study</th>
<th>Genotype</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>Mixed</th>
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<tbody>
<tr>
<td>Halfon, France (n = 262)</td>
<td></td>
<td>41</td>
<td>42</td>
<td>32</td>
<td>54</td>
<td>38</td>
<td>NA</td>
<td>44</td>
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<tr>
<td>Ganne-Carrie, France (n = 105)</td>
<td></td>
<td>69</td>
<td>21</td>
<td>65</td>
<td>75</td>
<td>37</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Zeng, China (n = 1096)*</td>
<td></td>
<td>31</td>
<td>6</td>
<td>8</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
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<tr>
<td>Sumi, Japan (n = 254)</td>
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<td>13</td>
<td>33</td>
<td>NA</td>
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<td>Dzierzanowska, Poland (n = 47)</td>
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</tr>
</tbody>
</table>

Studies from different geographic areas differ in the association of genotype with fibrosis stage. All results represent percentages of patients with significant fibrosis or cirrhosis; the study of Zeng et al.* provided proportions of patients with cirrhosis (stage 4 fibrosis), while the other studies provided proportions with fibrosis stages 2 to 4.

Although the studies quoted above do show a lack of consistency of these individual variables with histology and outcomes, multivariate analyses in different cohorts have shown an association of age over 40 years, male sex, and high HBV DNA levels and ALT values, with significant necroinflammation and advanced fibrosis. In children with hepatitis B, liver biopsy has a limited role but has been suggested as important in staging patients with persistently high ALT levels without HBeAg clearance, in anti-HBe–positive hepatitis B (due to a precore mutant), and for diagnosing cirrhosis.

Most studies report histologic improvement in terms of the percent of patients meeting the two-point inflammation goal. However, the few studies that have provided actual histological data show that the improvement in inflammation often exceeds this goal (Fig. 10). In several large trials of adeovir and entecavir, treated patients lost three to four points of inflammation on average, starting from mean inflammation scores of 7.5 to 8 in the Knodell system. Interferon therapy results in similar improvement in inflammation. In typical end-of-treatment biopsy studies, there is little change in fibrosis stage, even in responders. However, long-term follow-up studies have...
demonstrated less progression of liver disease in treatment responders as compared to nonresponders.99

**Allograft Pathology**

Biopsies have an important role in monitoring patients after liver transplantation. The histopathology of recurrent hepatitis B in the transplant allograft is similar to that seen in native livers. Unlike in hepatitis C, where it can be difficult to differentiate recurrence from rejection, immunostains for HBsAg and HBCAg help identify HBV re-infection. Endotheliitis is an important histological feature of acute cellular rejection, but is not specific, being seen in up to 60% and 35% of patients infected with HCV and HBV, respectively.100 Positive C4d staining has been observed in 89% of liver biopsies in recurrent hepatitis B and 40% of hepatitis C. Staining is greater in the centrilobular sinusoids as compared to periportal staining in autoimmune hepatitis. The high prevalence of C4d reactivity in viral hepatitis strongly suggests that C4d does not represent a useful marker in the differentiation between acute rejection and viral hepatitis relapse in liver transplants.101 Fibrosing cholestatic hepatitis is an atypical pattern of recurrent hepatitis B that occurs in a small number of allografts, but may also be seen after renal transplantation and in other immunocompromised patients.102-105 These patients present with a rapidly progressive severe cholestatic syndrome, which may clinically resemble acute or chronic rejection. Histologically, it is characterized by severe cholestasis, extensive periportal sinusoidal/pericellular fibrosis, moderate to severe parenchymal damage, and relatively little inflammation.106 HBCAg reactivity (nuclear and cytoplasmic) is seen in a very high number of hepatocytes. In allografts, histological grading and staging should only be applied when the changes are related to the recurrent HBV. Cirrhosis after liver transplantation is uncommon and is usually attributable to recurrent or acquired viral hepatitis. Chronic rejection may result in centrilobular fibrosis, but does not lead to cirrhosis.107 Thus, the pathology of hepatitis B after liver transplantation is complex, and clinical correlations are extremely important.108

**Summary and Conclusions**

In summary, the pathology of hepatitis B has many similarities with that of hepatitis C. Liver biopsy assessment in patients with hepatitis B therefore uses the same grading and staging systems. Although liver biopsy is not routinely performed in all hepatitis B patients at diagnosis, due to the presence of an immunotolerant phase, biopsy evaluation can provide important information on the phase of infection (by immunohistochemistry), immunopathology (by nature of infiltrating cells), severity of liver disease (grade and stage), presence of contributing pathology (such as fat and iron), and help in the identification of preneoplastic lesions. At present, there are conflicting data on the effect of viral levels, genotype, and immune status on pathology, and large multicenter studies may be required to resolve these issues.

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