Liver Biopsies in Chronic Viral Hepatitis
Beyond Grading and Staging
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Context.—Knowledge of the etiology and pathogenesis of chronic viral hepatitis has grown immensely during the past 50 years. The terminology used to assess liver biopsies with chronic viral hepatitis and the role of the liver biopsy itself have also evolved during this time. Although the focus of much discussion regarding diagnostic assessment of liver biopsies in patients with viral hepatitis has been on grading of activity and staging of fibrosis, each biopsy is also an opportunity to assess many other important features.

Objectives.—To discuss opportunities provided by biopsies to assess features such as the presence of virus-associated premalignant or malignancy-related changes, and the presence of other concomitant diseases, including fatty liver disease of diverse causes, and hemochromatosis, hereditary or otherwise.

Data Sources.—The data were obtained from published literature and professional experience.

Conclusions.—The evaluation of liver biopsies with chronic viral hepatitis has evolved beyond grading and staging. Pathologists need to be aware of the other features that may have important clinical implications.

namely steatosis, siderosis, concomitant diseases, and features associated with an increased risk of hepatocellular carcinoma (HCC).

PROGRESSION OF CHRONIC HEPATITIS

Clinically, chronic hepatitis, regardless of etiology, is defined as continuing disease without improvement for at least 6 months, although in many cases the diagnosis can be made before that time. Serum aspartate and alanine transaminase levels are increased in almost all patients with chronic hepatitis, but the levels do not necessarily reflect the severity of the necroinflammatory activity present on liver biopsy. The major causes of chronic hepatitis are hepatitis C, hepatitis B with or without hepatitis D, autoimmune hepatitis, and drug/toxin-induced chronic hepatitis. Other diseases, namely primary biliary cirrhosis, primary sclerosing cholangitis, Wilson disease, and α1-antitrypsin deficiency, can share histologic and clinical features with chronic hepatitis but are not included under the heading chronic hepatitis.

In most clinical practice independent of clinical trials, the degree of activity, unless particularly severe, is not as important as the stage of fibrosis in the decision on whether or not to pursue treatment. However, depending on the etiology of the hepatitis, severe activity, meaning confluent necrosis (Figures 1 and 2), implies specific events that may have important implications for patient care. In hepatitis C, the inflammatory activity typically waxes and wanes (Figure 3), and the presence of confluent necrosis on a biopsy specimen may simply represent an acute flare of activity. However, it may also indicate other concomitant conditions, such as drug/toxin-mediated injury, acute coinfection with another hepatotropic virus (hepatitis A or B with or without D), autoimmune hepatitis, or immunosuppression (including coinfection with human immunodeficiency virus [HIV]); all of these would require further investigation and possibly treatment.

On the other hand, fibrosis progression in hepatitis C is believed to be essentially linear with time, and therefore, fibrosis stage, rather than activity grade, is a better predictor of disease progression. A large cross-sectional study by Poynard et al identified 3 categories of progression in patients with chronic hepatitis C: (1) rapid fibrosing, chronic hepatitis C that progresses to cirrhosis in less than 20 years; (2) intermediate fibrosing, chronic hepatitis C with a median progression of 30 years; and (3) slow fibrosing, chronic hepatitis C that will not progress for at least 50 years (Figure 3). Older age at infection and male sex are independent risk factors for progression of fibrosis.

The natural history of hepatitis B infection is dynamic, and the outcome of a given individual may be difficult to predict. The disease can be divided into 4 major phases, which may occur after acute infection: (1) the recovery phase; (2) the inactive carrier-state phase; (3) the immune-tolerance phase, which is thought to occur primarily in perinatally infected patients; and (4) the chronic hepatitis-B phase. In both the carrier-state phase and the recovery phase, the liver histology is inactive with variable, usually minimal, fibrosis. The immune-tolerance phase, which may represent the earliest phase of chronic infection, typically shows minimal activity and scant fibrosis. The chronic hepatitis-B phase can be separated into (1) the hepatitis B e antigen (HBeAg)–positive (or immune, active) state, and (2) the HBeAg–negative, antibody

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Figure 1. Perivenular confluent necrosis in a patient with proven hepatitis C and concomitant autoimmune hepatitis. Note prominent plasma cell infiltrate (hematoxylin-eosin, original magnification ×400).

Figure 2. Confluent necrosis (gray) is severe necroinflammatory activity that may be present in different degrees.
Acute exacerbation and reactivation

At the time of diagnosis, there may be severe activity in chronic hepatitis B. Subsequently, a review by Guido et al. reported that the ideal sample size found that the incidence of cirrhosis increased linearly. Poynard et al. evaluated the activity and fibrosis progression of chronic hepatitis C. In particular, severe activity with confluent and even bridging necrosis is known to occur with clearance of HBeAg and subsequent conversion to the anti-HBe–positive state. Severe activity in chronic hepatitis B is also present more often in patients coinfected with hepatitis D ("delta hepatitis"). Of course, as with hepatitis C, severe activity in the form of confluent necrosis may be an indication of another condition requiring clinical attention, such as infection with hepatitis A or C, drug/toxin-mediated injury, autoimmune hepatitis, or immunocompromise. Although it may be difficult to predict which patients with hepatitis B are at risk of developing cirrhosis, one large study by Liaw et al. found that the incidence of cirrhosis increased with repeated episodes of severe, acute exacerbation; with severe, acute exacerbation that was not accompanied by seroconversion from HBeAg to anti-HBe–positive states; with viral reactivation; and with increasing age at the time of entry into the study. They found no correlation between cirrhosis and HBeAg superinfection.

Although autoimmune hepatitis is considered a chronic, progressive disease that is ultimately fatal without treatment, it may have an acute clinical presentation. The characteristic (but not pathognomonic) histologic picture is of interface activity composed of lymphoplasmacytic infiltrates with or without lobular activity and bridging necrosis in severe cases. At the time of diagnosis, there may be severe activity but little scarring. However, approximately 30% of patients may have cirrhosis at the time of presentation. In the later stages, liver biopsy specimens may show cirrhosis with mild or “burned out” hepatitis. Given the dynamics of disease progression, liver tissue rarely shows both mild activity and little scarring in untreated patients (Figure 4). With corticosteroid treatment, fibrosis commonly improves, or at least does not progress, and histologic cirrhosis may actually disappear. However, in a few treated patients, fibrosis may actually progress, and that progression has been shown to be associated with heterozygosity for HLA-DR3/DR4.

In summary, the most important points for grading and staging are the following: (1) the standard of care for reporting on biopsy specimens for chronic viral hepatitis is to use words as well as corresponding numeric values derived from the application of a standardized system of grading and staging; (2), the grading and staging system used should be named explicitly in the pathology report to aid in understanding the meaning of the assigned numbers, especially across institutions; and (3), confluent necrosis is a reflection of “severe activity,” and its presence may indicate comorbid conditions with important clinical implications (Table).

**EFFECT OF SPECIMEN SIZE IN THE EVALUATION OF CHRONIC HEPATITIS**

Clinically, obtaining an adequate specimen is of significance because underestimating the degree of fibrosis in patients with chronic hepatitis may cause an unnecessary delay in treatment. Sample size can affect the diagnostic accuracy of liver biopsy specimens, especially in cases of chronic hepatitis, because the biopsy represents approximately only 1/50,000 of the total mass of the liver.

In the past, pathologists were satisfied with a specimen length of 1.5 cm containing at least 6 to 8 portal tracts for the evaluation of diffuse liver disease. For accurate assessment of grading and staging of chronic viral hepatitis B or C, 3 studies are particularly noteworthy. Colloredo et al. reported that the ideal sample size should be 2 cm long and 1.4 mm wide with no less than 11 to 15 portal tracts. They found that shorter and thinner samples resulted in underestimation of both grade and stage, likely the result of fewer complete portal tracts in smaller specimens. Subsequently, a review by Guido and Rugge also concluded that the gold standard for reliably assessing grade and stage is a biopsy specimen that is 2 cm long with no less than 11 portal tracts. In a more recent study, Schiano et al. evaluated the activity and fibrosis scores of 100 liver biopsies from patients with hepatitis C.
to determine the optimal specimen size for accurate grading and staging. They compared the scores of the gold standard size (2 cm or greater) to 3 different lengths (0.5 cm, 1 cm, and 1.5 cm) by physically covering up the slide to the desired length and reassessing the scores. Unlike previous reports, they found that specimens measuring at least 1 cm reliably reflected both grade and stage compared with the gold standard size of 2 cm.

Another issue that relates to accurate staging of chronic liver disease is the location where the biopsy was taken. The extent of fibrosis may be overestimated in small biopsies taken from the subcapsular region because there may be a baseline of increased stroma, fibrous septa, or even nodularity present in that region, up to 0.5 cm below the capsule. Thus, if only subcapsular tissue is present in a specimen, it may be considered inadequate for staging. Likewise, if there is subcapsular tissue in a larger specimen and the only increase in stroma is in that portion of the sample, it may be discounted for purposes of staging if the deeper tissue has less scarring.

Differences in grade and stage between biopsies taken from the right and left hepatic lobes have also been reported, particularly in patients with chronic hepatitis C. Regev et al found that 24% of patients had a difference of at least one grade and 33% had a difference of at least one stage between right and left hepatic lobe biopsies, with no consistent unidirectional difference between right and left lobes for either grade or stage. A diagnosis of cirrhosis was given in one lobe but not the other in 14.5% of patients. A more recent study demonstrated a difference of at least one grade or stage in 30% of cases with 16.7% differing in both grade and stage. Both of these studies used a 4-tiered grading and staging system (modified Scheuer and Batts-Ludwig systems, respectively). A smaller study by Fanning et al reported a difference of 2 or more grades in 33%, and a difference of 2 or more stages in 25%, of bilobe biopsies, whereas the hepatitis C viral load was similar between lobes. Single lobe histology would have missed a diagnosis of cirrhosis in 8% of those cases. In contrast, Persico et al found no difference in grade or stage between the right and left lobes, although patients with cirrhosis were excluded from this study. Both of these studies used the Ishak modified histology activity index system, which is a 6-tiered staging system.

These studies suggest that performing bilobe biopsies may reduce sampling error and allow more accurate grading and staging of chronic hepatitis. However, the added risk and expense of performing 2 liver biopsies per patient makes this approach impractical. Because most clinicopathologic studies of viral hepatitis were performed

**Possible Clinical Implications of Severe Activity (Confluent Necrosis) in Liver Biopsy Specimens With Chronic Viral Hepatitis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Implications of Confluent Necrosis</th>
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<tr>
<td>Chronic hepatitis C</td>
<td>Acute flare of activity as part of the natural history of HCV infection</td>
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<tr>
<td></td>
<td>Newly acquired superinfection of other hepatotropic virus (eg, HAV, HBV)</td>
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<td>Immunocompromise (eg, HIV-associated, iatrogenic)</td>
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<td>Drug/toxin-mediated injury</td>
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<td>Concomitant autoimmune hepatitis</td>
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<tr>
<td>Chronic hepatitis B</td>
<td>Activity flare during HBsAg to HBeAb conversion</td>
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<td>Newly acquired superinfection of other hepatotropic virus (eg, HAV, HDV)</td>
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Abbreviations: HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus.
formed using percutaneous biopsies of the right lobe (particularly because they were done when most biopsies were “blind” rather than ultrasound-guided), right lobe biopsy specimens are preferable for the staging of chronic viral hepatitis, unless clinical circumstances require another approach.

**STEATOSIS**

Steatosis is very common in chronic hepatitis C infection, affecting about 50% of patients with a reported range of 34% to as high as 72%. The presence of steatosis is significantly more common in patients with chronic hepatitis C than in patients with either chronic hepatitis B or autoimmune hepatitis. Studies have shown that in patients with hepatitis C, the degree of steatosis correlates with the extent of fibrosis on liver biopsy regardless of genotype, suggesting that steatosis may lead to more rapid progression to cirrhosis in these patients. Some have also reported a relationship between the degree of steatosis and the severity of necroinflammation in patients infected with hepatitis C virus (HCV), another factor that may potentiate the progression of fibrosis.

There are 2 different mechanisms for the steatosis in chronic hepatitis C depending on the genotype of the virus. One directly affects infected hepatocytes. Most commonly (though not exclusively) seen with genotype 3 infection, this type of steatosis correlates with both intrahepatic and serum genotype 3 HCV RNA levels. Studies have demonstrated that the degree of steatosis improves and even disappears after the achievement of a sustained virologic response with antiviral therapy in patients with genotype 3 only, and therefore, this type of steatosis is thought to be a direct cytopathic effect of HCV genotype 3. Such virus-induced steatosis tends to be patternless and scattered throughout the biopsy in a nonzonal fashion (Figure 5, A), as opposed to the centrilobular pattern of metabolic steatosis or “true” fatty liver disease (Figure 5, B). Steatohepatitis (neutrophilic infiltration and hepatocyte ballooning, with or without Mallory-Denk bodies) and steatofibrosis (pericellular, perivenular, and perisinusoidal collagen deposition) are not features of such virus-induced steatosis.

More recently, HCV infection has been documented to induce insulin resistance and the metabolic syndrome, indirectly leading to hepatic steatosis, a situation most often associated with HCV genotype 1. Such steatosis represents “true” fatty liver disease, which is recognized by the typical zonal pattern of steatosis (beginning in acinus zone 3 and extending with increasing severity toward the portal tract), with or without classic steatohepatitis and steatofibrosis (Figure 5, B). Thus, the steatosis in genotype 1 infections is typically “metabolic” in nature and essentially identical to “true” fatty liver disease, which is often found in patients with diabetes mellitus, central obesity, dyslipidemia syndromes, and the metabolic syndrome and with alcohol use. Studies have shown that the degree of steatosis in these patients is associated with age, body mass index, and insulin resistance. In fact, Fortoux et al suggested that increased circulating insulin is a risk factor for fibrosis in patients infected with genotype 1 via insulin resistance–induced fatty liver disease. The exact mechanism for the development of insulin resistance in hepatitis C infection is not well understood; however, these patients may benefit from therapy to reduce insulin resistance, such as weight loss or use of oral hypoglycemic agents.

It is important for pathologists to attempt to differentiate these 2 forms of steatosis in patients with hepatitis C because the pathogenic mechanisms and treatments differ. A detailed evaluation of “true” fatty liver disease is beyond the scope of this article, but good reviews have been written elsewhere. In the setting of concurrent, chronic hepatitis C and fatty liver disease (not including minor, virus-induced steatosis), scoring of the grade and stage may be inappropriate because distinguishing the contributions of each entity can be difficult or impossible; both diseases may show some degree of portal fibrosis, mild portal mononuclear infiltrates, and apoptotic bodies. Descriptions of the extent of inflammatory activity and fibrosis would suffice in these situations, and examples for wording the diagnosis are given in a separate review.

**COINFECTIONS**

In patients with hepatitis B or C who are coinfected with HIV but who are on successful highly active antiretroviral therapy and who are, therefore, immune competent, the liver biopsy specimens may appear no different than in patients who are monoinfected with either hepatitis B or C. In a state of immune compromise, patients coinfected with HCV/HIV may show more severe inflammatory activity, including confluent necrosis, and a more rapid progression to cirrhosis than do patients who are monoinfected with HCV. Similarly, patients with hepatitis B virus (HBV) and HIV coinfection, who are resistant to or without highly active antiretroviral therapy, may exhibit higher levels of HBV replication, more reactivation episodes, and faster progression to cirrhosis. Of course with immune compromise, one must also beware of lesions like granulomas, infectious organisms, and neoplasms on biopsy.

The prevalence of steatosis in patients coinfected with HCV and HIV is similar to patients monoinfected with HCV. The severity of steatosis correlates with the extent of fibrosis on biopsy in patients with both HCV monoinfections and those coinfected with HCV and HIV, as well. In addition to the factors associated with steatosis in patients monoinfected with HCV that were previously described, patients coinfected with HIV are also at risk for antiretroviral drug–induced fatty liver disease. Nucleoside analogues are known to cause hepatocellular steatosis, especially the microvesicular type, via mitochondrial toxicity. Metabolic syndromes, such as lipodystrophy, which may be caused by both nucleoside analogues and protease inhibitors, may also play a role in the development of fatty liver disease in patients who are coinfected. As might be expected, patients with HBV/HCV coinfection tend to have more severe fibrosis on biopsy and are at greater risk of developing HCC than are patients with either HBV or HCV monoinfections. Interestingly, either virus may interfere with the replication of the other, sometimes making the other virus completely undetectable.
Figure 5. A, Hepatitis C virus–induced steatosis is typically scattered in a nonzonal fashion. B, “True” fatty liver disease (metabolic steatosis) with ballooning degeneration of hepatocytes, Mallory-Denk bodies, and pericellular/perisinusoidal fibrosis (steatofibrosis) in the centrilobular zone (hematoxylin-eosin, original magnification ×100 [A]; trichrome, original magnification ×200 [B]).

Figure 6. Biopsy from a patient with chronic hepatitis C and grade 1 of 4 hemosiderosis (Prussian blue stain, original magnification ×400).

Figure 7. A, Hepatocytes with large cell change. B, An aggregate of hepatocytes with small cell change (center) (hematoxylin-eosin, original magnifications ×200 [A and B]). Images courtesy of Young Nyun Park, MD, PhD, Yonsei University College of Medicine, Seoul, Korea.

Figure 8. An iron-free focus in a biopsy from a patient with chronic hepatitis B and grade 3 to 4 of 4 hemosiderosis (Prussian blue, original magnification ×100).
In fact, the inhibition of one virus by the other may alternate over time, meaning that at one point the results from the patient’s serum may be positive for hepatitis C RNA and negative for hepatitis B DNA and a few months later, the reverse is true.

### Hemosiderosis

Hepatocellular siderosis may be present not only in hereditary hemochromatosis but also in many chronic liver diseases, including chronic viral hepatitis, alcoholic and nonalcoholic fatty liver disease, and genetic disorders, such as Wilson disease and α1-antitrypsin deficiency. By contrast, reticuloendothelial iron alone is suggestive of hemolytic/hematologic disorders and is not the typical pattern seen in usual or type I hereditary hemochromatosis. However, when it occurs in large quantities, there may be “spillover” into hepatocytes creating a mixed pattern. \(^{(65)}\) (Type IV hereditary hemochromatosis, ie, ferroportin deficiency, results in diffuse and exclusively reticuloendothelial iron, but that genetic condition is not known to actually cause disease.\(^{(66)}\) The role of the pathologist is to assess the quantity and the localization (predominantly hepatocellular, predominantly reticuloendothelial, or mixed) of iron accumulation and to offer a differential diagnosis of its cause based on the liver biopsy findings.

There are many systems for grading hepatocellular iron based on the quantity and/or the natural progression of accumulation (from zones 1 to 3). One example of a simple system based on progression is grade 1–zone 1, some perportal areas; grade 2–zone 1, all perportal areas; grade 3–zones 1 and 2; and grade 4–zones 1, 2, and 3.

Stainable iron can be demonstrated in liver biopsies in up to about 50% of patients with chronic hepatitis C and is usually mild (grades 1 to 2/4; Figure 6).\(^{(67,68)}\) The exact mechanism of iron overload in HCV infection is unknown. Recent studies have shown that patients with chronic hepatitis C have reduced serum hepcidin levels compared with healthy patients, suggesting that downregulation of hepcidin by HCV may contribute to iron overload in those patients.\(^{(69,70)}\) Patients infected with HCV are also at risk for iron overload when treated with ribavirin, which causes a dose-dependant reversible hemolysis. Although ribavirin-induced hemolysis is thought to occur within the reticuloendothelial system, the iron accumulation in those patients is mainly within hepatocytes.\(^{(71)}\) Iron deposition has been shown to be associated with more advanced fibrosis in patients with hepatitis C.\(^{(72)}\) High levels of hepatic iron may also decrease the response to interferon α therapy in patients infected with HCV. Treatment with phlebotomy has been reported to decrease serum transaminase levels and improve the response to interferon α in some patients.\(^{(73)}\) However, that has not become a routine method of treatment.

Type I hereditary hemochromatosis is known to have a variable penetrance.\(^{(74)}\) Liver biopsies may show any degree of siderosis (grades 1 to 4 of 4), and therefore, the presence of only mild hepatocellular iron does not exclude this disease. Because patients with chronic liver diseases like hepatitis C may also harbor mutations associated with hereditary hemochromatosis, it may be impossible to distinguish hereditary from HCV-related or other causes of secondary hemochromatosis without genetic testing. A comment in the diagnostic report can include statements like: “Prussian blue stain highlights increased hepatocyte iron stores in some, but not all, perportal regions. This may be related to hepatitis C infection; however, this small amount does not exclude a diagnosis of hereditary hemochromatosis due to the variable penetrance of this disease. Genetic testing may be helpful, particularly if there is a clinical suspicion of familial liver disease.” Cirrhosis itself can result in hepatic siderosis, and the degree of iron deposition can be highly variable from one nodule to the next and within individual nodules.\(^{(75)}\) Therefore, in biopsy specimens showing cirrhosis, this should also be suggested as a possible cause of iron overload in the comment.

### Malignancy-Related Changes

Patients with chronic liver disease, especially hepatitis B and C, have an increased risk of developing HCC. On liver biopsy, there may be specific microscopic changes that are either malignancy-associated or directly premalignant, even in the absence of fully established cirrhosis. It is important for pathologists to look for these changes and to report them to ensure proper HCC screening for these particular patients.

Large cell change (previously known as large cell dysplasia) refers to enlarged hepatocytes with large, atypical nuclei; multinucleation; prominent nucleoli; abundant cytoplasm; and a fairly normal nuclear to cytoplasmic ratio (Figure 7, A). The cells tend to be intermixed with healthy hepatocytes in periportal/perisepetal regions. Cytogenetic and molecular studies have shown that these cells are polyploid in nature and are usually not directly premalignant because they do not share the same genetic alterations as HCC.\(^{(76)}\) They may thus be thought of as a marker for the kind of chronic injury that, in parallel, leads to malignancy. Patients with cirrhosis and large cell change have a 3 to 5 times greater risk of developing HCC than do patients without large cell change.\(^{(77)}\) A subset of patients infected with HBV, however, have large cell change with molecular alterations that are suggestive of direct premalignancy; thus, the precise nature of large cell change and the possible existence of subcategories within the lesion remains unsettled.\(^{(78)}\)

On the other hand, small cell change (previously small cell dysplasia) does have similar genetic alterations as HCC, suggesting that this lesion is directly preneoplastic.\(^{(79)}\) It consists of clusters or small nodules (usually <1 mm) of small hepatocytes with hyperchromatic (sometimes grooved or irregular) nuclei, basophilic cytoplasm, and an increased nuclear to cytoplasmic ratio (Figure 7, B). It may appear as a zone of nuclear crowding resembling atrophic hepatocytes,\(^{(79)}\) and reti culin stain may show a slight loss of reticulin fibers.

The term dysplasia should be reserved for distinctive macroscopic nodules, usually in established cirrhosis, many with cytologic and/or architectural atypia but without definite histologic criteria of malignancy, that is, dysplastic nodules. Dysplastic nodules are divided into low grade (without cytologic or architectural atypia, other than possible large cell change) or high grade (cytologic or architectural atypia suggestive of malignant progression, inclusive of small cell change). Some high grade dysplastic nodules have clonal proliferations of hepatocytes, so-called nodule-in-nodules, and are considered further steps on the way to the emergence of HCC. Detailed descriptions of the diagnostic criteria have been written elsewhere.\(^{(80,81)}\) Uncommonly, a dysplastic nodule may be
sampled on a random biopsy in a patient with chronic viral hepatitis and can be recognized as an apparently noncirrhotic zone with prominent “unpaired arteries” (angiogenesis without accompanying bile ducts) in an otherwise cirrhotic specimen.

Iron-free foci in liver biopsies with hemosiderosis, either due to genetic or secondary causes, are another finding that may represent a premalignant process (Figure 8). Studies\(^{39,40}\) have suggested that iron-free foci in patients with cirrhosis, with iron overload due to both primary and secondary hemochromatosis, represent premalignant lesions, and this finding on a liver biopsy may warrant more rigorous screening for HCC. Terada et al\(^{41}\) reported that HCCs that develop within siderotic nodules in patients with cirrhosis are also iron-resistant and may appear on magnetic resonance imaging as isointense, iron-free foci within hypointense, iron-rich nodules.

**SUMMARY**

Now that our knowledge of the pathogenesis and progression of chronic hepatitis and hepatits-related changes that can occur in the liver has expanded, the role of the liver biopsy, and therefore, the pathologist, has expanded as well. Simply grading and staging the hepatitis is not enough anymore. Pathologists should be aware of all of the "extras" described in this article, which may have important clinical implications and subsequent impact on patient care.

**References**