Changing indications for liver biopsy: viral hepatitis

Joseph Misdraji

Abstract

Liver biopsy has been an integral part of the management of patients with chronic viral hepatitis. However, several developments have reduced the need for liver biopsy in these patients. Serum based and radiologic non-invasive methods of assessing fibrosis can distinguish between limited and advanced fibrosis and diagnose cirrhosis in these patients. In chronic active hepatitis B infection, antiviral therapy can often be initiated without a liver biopsy as the benefit of treatment extends across all stages of fibrosis. However, the difficulty of determining disease activity and fibrosis by serologic and biochemical data in chronic hepatitis B makes liver biopsy an important tool in the management of a subset of patients. The remarkable progress that has been made in the treatment of hepatitis C is poised to make liver biopsy unnecessary in a large number of patients who previously were treated based on the stage of disease as determined by biopsy. Together, these trends are altering the landscape of liver biopsy in chronic viral hepatitis.

Keywords hepatitis B; hepatitis C; liver biopsy; viral hepatitis

Introduction

In the management of chronic viral hepatitis, liver biopsy has been an integral component of the patient evaluation. The foremost reason for a liver biopsy is to obtain information on the degree of inflammatory activity and stage of fibrosis. Liver biopsy has other supportive roles in the evaluation of patients with chronic viral hepatitis, including assessment for contributing pathologies such as fatty liver disease, evaluation of treatment response, diagnosis of adverse drug reactions, diagnosis of unexpected conditions, classification of hepatic neoplasms that arise in patients with cirrhosis, and determination of recurrent infection in transplant recipients. However, liver biopsy is an invasive procedure associated with a small risk of morbidity and even mortality. Therefore, the decision to obtain a liver biopsy has to be made after considering whether the same information can be obtained through alternative non-invasive means, and whether the information that the biopsy will provide has the potential to change management.

Recent advances in the field of viral hepatitis are already having an impact on the number of liver biopsies obtained in patients with chronic viral hepatitis and the indications for those biopsies. The most dramatic change is the expanding repertoire of agents used to treat viral hepatitis, most notably the introduction of direct-acting antiviral agents in the treatment of hepatitis C. Some practitioners feel that these agents will minimize the need for liver biopsy since nearly all patients with chronic viral hepatitis should be treated, regardless of stage. Although mild fibrosis has been used as a justification to defer treatment, these patients may respond to therapy better and therapy may prevent progression. Conversely, patients with advanced fibrosis may not respond as clearly to treatment but often must be treated given their worse prognosis. The second major change in the management of chronic viral hepatitis is the increasing use of non-invasive techniques to assess liver fibrosis. Together, these developments have reduced the need for liver biopsy in the management of chronic viral hepatitis although there remains a subset of patients for whom liver biopsy is useful or even required.

Joseph Misdraji *M.D. Associate Pathologist, Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. Conflicts of interest: none declared.*

A. Assessing fibrosis in chronic viral hepatitis

One of the primary indications for liver biopsy in chronic viral hepatitis is to assess the degree of fibrosis or stage of disease. The stage of disease has several clinical implications. Since it is a measure of progressive liver damage, increased fibrosis is a factor in the decision to treat viral hepatitis. Also, the stage of disease can provide information on the likelihood of response to treatment. For example, patients with hepatitis C and cirrhosis are less likely to respond to treatment than patients with low stage disease. Finally, the presence of advanced fibrosis and in particular cirrhosis places the patient in a higher risk group for the development of hepatocellular carcinoma, and justifies surveillance.

Although liver biopsy is the gold standard for assessing fibrosis, it is imperfect, as evidenced by the fact that cirrhosis can be missed on a single liver biopsy in up to 30% of cases.[1] Several factors affect the accuracy of a liver biopsy. A liver biopsy samples only a very small portion of the liver and diseases might not affect the liver in a uniform way, creating sampling artifact (Figure 1). Studies have shown that biopsies obtained simultaneously from the right and left lobes show different degrees of activity and fibrosis in a third of cases, due largely to sampling artifact (and partly to interobserver variability).[2,3] Location of the biopsy may also play a role in sampling artifact. The 0.5 cm of parenchyma below the capsule may have increased fibrosis, septae, and even vague nodularity that is not representative of the liver as a whole.[4] Finally, biopsy size can affect diagnostic accuracy of liver biopsy. The shorter the biopsy, the more likely it underestimates the grade of activity and stage of fibrosis.[5]

Establishing the minimum length a biopsy must be to reliably stage chronic hepatitis has been difficult. The factor that influences accuracy of staging is the number of complete portal tracts in a biopsy.[5,6] Five complete portal tracts is considered by some to be the minimum necessary to consider a biopsy adequate although others use the more stringent criteria of 11 complete portal tracts.[5] However, the number of complete portal tracts in a biopsy is determined not only by its length but perhaps equally by its caliber.[5] Studies looking at this question often focus on length, and have arrived at different conclusions about what is the minimum length required to reliably stage chronic hepatitis. Minimum lengths of 1–3 cm have been proposed, with 1.5 cm being adopted as the standard in clinical studies.[6] The American Association for the Study of Liver Diseases (AASLD) recommends a biopsy be at least 2–3 cm in length, that it be obtained with a 16-gauge needle, and that it contain at least 11

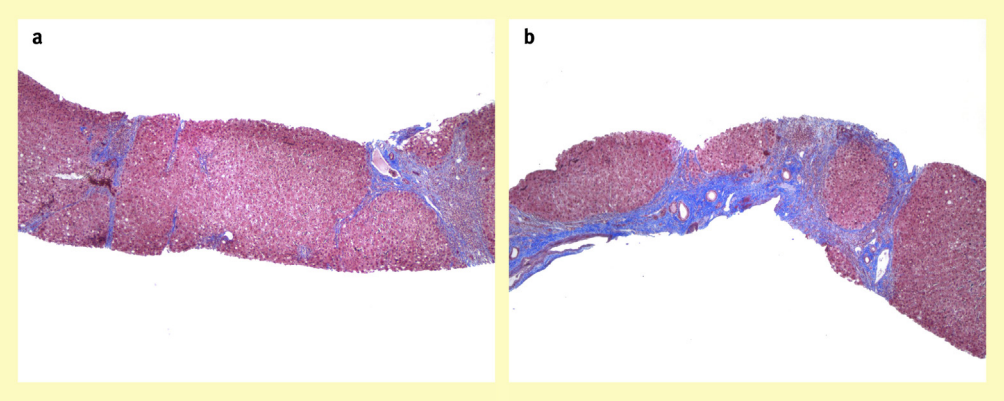

Figure 1 Variable fibrosis in hepatitis C. Panel (**a**) shows bridging fibrosis. Panel (**b**) shows cirrhosis. Both images were taken from opposite ends of a single 2 cm biopsy, demonstrating that fibrosis might not uniformly affect the liver, macronodules can be cause underestimation of fibrosis, and a small biopsy that only sampled the area in panel A might have resulted in under staging of fibrosis. (Trichrome stain.)

portal tracts, but many biopsies in clinical practice fail to meet this standard.[7] The type of needle used may also be important. Cutting needles have been shown to be superior to Menghini suction needles, particularly in the setting of advanced fibrosis, as suction needles cause more fragmentation of fibrotic specimens, hampering evaluation of cirrhotic livers.[1]

Another limitation of liver biopsy in staging chronic hepatitis is interobserver variability. Interobserver variability in liver biopsy interpretation varies according to the pathologic feature. Bedossa et al. found that cirrhosis and portal fibrosis score very high in concordance whereas disease activity and inflammatory features score moderate or fair.[8]

The increasing use of non-invasive methods of assessing fibrosis in chronic viral hepatitis is one of the more recent advances in the management of chronic viral hepatitis that is altering the landscape of liver biopsy. Non-invasive methods of assessing liver fibrosis are either serologic or radiologic. Each has its advantages and disadvantages.

Serologic markers of hepatic fibrosis comprise either direct or indirect measures, and both have very good ability to diagnose advanced fibrosis or cirrhosis (AUROC 77–89).[9] Direct markers of fibrosis reflect the deposition or removal of extracellular matrix in the liver, and include serum hyaluronate, laminin, collagenases and their inhibitors, and cytokines associated with fibrogenesis.[1,9] A major obstacle to widespread acceptance of these markers is lack of availability in many laboratories.[1] The indirect markers of liver fibrosis include various tests such as transaminases, prothrombin time, and platelet count. These routine tests can be combined using formulas to arrive at a score that indicates the probability of increased fibrosis. These formulas can be proprietary ones (e.g., Fibrotest©, Biopredictive, Paris France) or non-proprietary published models such as aspartate-to-platelet ratio index (APRI) or the Forns Index.[9] Indirect serologic markers of fibrosis are easily obtained and fairly accurate for the diagnosis of cirrhosis, but have substantial limitations. Foremost among these limitations is that the various biomarkers are not specific and can be influenced by co-morbid conditions such as Gilbert's syndrome or acute hepatitis.[9] Also, their performance is not as good as transient elastography at diagnosing cirrhosis (see below) and they cannot be used to discriminate between intermediate stages of fibrosis, leaving many patients unclassified.[1,9] Fibrotest-Fibrosure© has the advantage of classifying all patients, but also performs better at the extremes of liver fibrosis than in intermediate stages.[1]

Transient elastography (TE) uses ultrasound to measure the velocity of a low frequency elastic shear wave propagating through the liver. The more stiff the tissue, the faster the propagation of the shear wave.[9] TE is more accurate at diagnosing cirrhosis (correctly classifying 85–94% of cases) than advanced fibrosis (correctly classifying 57–90%).[9] Transient elastography has the advantage of being rapid; however, it requires a dedicated device, the results require interpretation by the operator, and inexperience can lead to incorrect results. Misleading results can also be obtained in obese patients, in patients with ascites, or in patients with narrow intercostal spaces.[9] As with biomarkers, TE cannot discriminate between intermediate stages of fibrosis.[9]

Another radiological method for assessing liver fibrosis is magnetic resonance (MR) elastography. The accuracy of MR elastography may be higher than TE, but data are limited.[9] The advantage of MR elastography is its ability to assess the entire liver and its applicability in patients with obesity or ascites. However, it is limited in patients with iron overload and it is costly and time-consuming.[9]

Although these non-invasive methods of diagnosing cirrhosis or advanced liver fibrosis are limited by their inability to discriminate between intermediate stages of fibrosis, in clinical practice the determination of fibrosis rarely needs to be as finely granular as the various histologic staging systems for viral hepatitis might suggest. With the development of newer agents to treat viral hepatitis, there may be even less of a need for an exact assessment of fibrosis (see below). Additionally, these tests might be used to evaluate patient populations in which they perform with high accuracy, and reserve liver biopsies to patients in whom precise staging is not possible with non-invasive techniques.[1] Furthermore, non-invasive methods have the distinct advantage of being able to be repeated serially without risk to the patient, providing a method of monitoring treatment response or disease progression.[9] These methods may also serve a role in the post-transplantation setting where they allow the segregation of patients with recurrent hepatitis C into those with absent or mild fibrosis in whom a liver biopsy might not be required and those