Liver Biopsy

Evolving Role in the New Millennium

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Abstract: Since the origination of the liver biopsy, the technique has evolved into an essential diagnostic tool, with very few complications. In addition to the percutaneous approach, a liver biopsy can also be obtained via transjugular, laparoscopic, or intraoperative approach. While in the early 1960s and 1970s the liver biopsy was used for making a diagnosis in cases of clinically suspected medical liver disease, today it is more often performed to assess disease prognosis and evaluate therapeutic strategies. As a result, indications for the liver biopsy have evolved over the past 2 decades. However with advances in serologic diagnosis of viral/autoimmune hepatitis and laboratory tests for genetic disorders, the role of liver biopsy in certain clinical settings is currently debated. This review discusses the technique, indications, contraindications, and the changing role of liver biopsy in some of the common disorders and the associated controversies.

Key Words: liver biopsy, role, indications, contraindication, NASH, chronic hepatitis

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Since its original description by Ehrlich in 1883, the role of liver biopsy has changed dramatically in current medical practice. Initially, it was used for determination of glycogen stores in livers of diabetic patients, while today the indications for a liver biopsy are numerous.[1] Liver biopsy was accepted only slowly as a standard medical procedure in the medical community, despite large studies from Huard et al from France and Baron et al from United States in 1937. Only after Menghini described "one-second needle biopsy of the liver" in 1958 did the procedure come into more widespread use.[2] In Menghini's technique, the duration of the needle biopsy within the liver significantly decreased to less than a second, in contrast to 6 to 15 seconds with earlier techniques, thus dramatically reducing the complication rates and physician apprehension.

During the last 50 years as the result of a better understanding of liver disorders, appearance of newer entities, and advent of novel hepatic imaging techniques, the indications for liver biopsy have evolved. Whereas in the past liver biopsy was often performed as the initial investigation in the workup of liver disease of unknown etiology, today the most common indication for liver biopsy includes staging of chronic hepatitis following a serologic diagnosis. In this setting, the role of the liver biopsy has also changed from a diagnostic to a prognostic tool, with histologic grades of inflammation and stage of fibrosis guiding therapy. This dramatic shift has resulted in part from the recent developments in serologic diagnosis of chronic hepatitis, particularly hepatitis C and autoimmune hepatitis. The other common indications for a liver biopsy in current practice include nonalcoholic steatohepatitis (NASH), drug reactions, biliary disorders, hemochromatosis and other metabolic diseases, cirrhosis of unclear etiology, and tumors. In this article, we will review the technique, indications, contraindications, and evolving role of liver biopsy in some of the common conditions.

TECHNIQUES AND METHODS OF LIVER BIOPSY

There are different approaches for obtaining liver tissue, percutaneous, transjugular, laparoscopic, and intraoperative, each having advantages and disadvantages. The percutaneous liver biopsy technique remains the standard training and practice in all Gastroenterology fellowship programs. Most of the training programs require fellows to perform approximately 20 percutaneous biopsies under the supervision of a trained hepatologist, gastroenterologist, or a transplant surgeon, before performing liver biopsies independently in an outpatient facility. Despite this rite of passage for all gastroenterology trainees, in clinical practice liver biopsies are performed more often by hepatologists than general gastroenterologists. Whenever a percutaneous biopsy is contraindicated (eg, presence of significant ascites or coagulopathy), a transjugular biopsy is preferred. However, a transjugular liver biopsy is performed by interventional radiologists and is available only at a limited number of tertiary care facilities. An important advantage of the transjugular approach is the ability to obtain intrahepatic portal pressures that aid in the diagnosis and management of select group of patients, particularly those with cirrhosis. However, transjugular biopsies are often smaller and fragmented making pathologic assessment somewhat difficult. While percutaneous or transjugular biopsies are adequate for obtaining tissue when the abnormalities are diffuse, image-guided biopsies are necessary for focal

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diseases/lesions. Laparoscopic liver biopsy enables the gross features of the liver to be assessed as demonstrated in one study where lesions were detected in 48% patients who had negative pre-procedure imaging.[3] However, laparoscopic liver biopsy also has added costs and complications and is used in select settings at most centers.

Liver biopsies (needle or wedge) can also be obtained during abdominal surgery whenever liver disease is suspected. In many instances, an abnormal appearance of the liver during surgery for an unrelated procedure (most often cholecystectomy) is the first indication of an underlying liver disease. While intraoperatively obtained liver biopsies have the added advantage of obtaining tissue from grossly visible/suspicious lesions, they are suboptimal for assessment of liver fibrosis and inflammation, due to preponderance of Glissen's capsule, wider portal tracts in the subcapsular area, and frequent but inconsequential surgically induced hepatitis. Therefore, needle biopsy should be the technique of choice at laparotomy.

The role of ultrasonography has also evolved in the last decade. The practice of ultrasound-guided versus "blind" technique varies among physicians, in part as a result of the training bias and the availability of ultrasonography. In a recent survey by Angtuaco et al, private practitioners referred more than 50% of their patients to radiologists for ultrasound-guided biopsies in contrast to gastroenterologists in academic practice.[4] The use of ultrasound was associated with decreased hospitalization for pain, hypotension, or bleeding. It was also noted that 50% of patients experienced pain when biopsy was performed without using ultrasound compared with 37% patients when biopsy was performed with ultrasound guidance.[5] But the value of this benefit must be weighed against the added cost and use of medical resources. Most studies demonstrate favorable outcomes and shorter hospital stays for patients with liver biopsy complications.[6] Pasha et al evaluated the cost-effectiveness of ultrasound-guided liver biopsy. The added cost from complications per patient with and without ultrasound was $62 and $129, respectively, and 1.2 complications were avoided for every 100 biopsies. The estimated incremental cost to avoid one such complication is $2,731.[7] In examining the impact of ultrasound on biopsy technique at one teaching academic center, Riley et al noted that using the ultrasound changed the biopsy position in 13% (21 of 165) of patients because of intervening structures (lung, gallbladder, large central vessel, rim of ascites or colonic loop) and resulted in aborted procedure in 2.4% (4 of 165) patients (ascites or focal liver lesions).[8] These findings need to be confirmed with multicenter multioperator studies.

The participation of radiologists in liver biopsies has increased, not only because some gastroenterologists prefer to relinquish a procedure they seldom perform but also because of the growth of interventional radiology techniques and high resolution fluoroscopy machines. As the number of outpatient liver biopsies by radiologists increases, it is important that the complications of this planned procedure are reassessed.

Needles for percutaneous liver biopsy are classified into suction needles (Menghini, Klatskin, Jamshidi), cutting needles (Vim-Silverman, Tru-cut), and spring-loaded cutting needles that have a built-in triggering mechanism.

Suction Needles

The device is a special hollow needle attached to a suction syringe as originally described by Menghini. After percussion for liver dullness in the mid-axillary line, the site for the biopsy is appropriately marked (usually in the 7th–8th intercostal space). Local anesthetic is introduced with a 25-gauge needle. The biopsy needle, attached to a saline-filled 10-mL syringe, is inserted at the marked site into but not beyond the intercostal space over the lower rib. The patient holds his/her breath in full expiration. This is the critical step in performing the biopsy to minimize the risk of lacerating the liver and inducing bleeding. While the patient is holding their breath, a small amount of saline is expressed to clear the needle and the plunger of the syringe is subsequently pulled back to create 1 to 2 mL of negative suction. The needle is then inserted into the liver at an appropriate depth and withdrawn quickly, all within 1 second. Vacuum in the syringe created by the plunger, and in some cases the beveling of the cutting edge (Klatskin needle) results in aspiration of the hepatic tissue. The risk of bleeding is increased if the intrahepatic phase of the procedure is prolonged as is needed with cutting needles. The vacuum created by suction needles should be minimized in patients with clinically suspected cirrhosis, as the fibrotic tissue tends to fragment easily and renders pathologic examination difficult or sometimes even impossible. Visual inspection of the biopsy for color and consistency can often provide useful information. A pale to yellow biopsy specimen may imply steatosis while a very green biopsy suggests cholestasis. A fragmented biopsy suggests advanced fibrosis or cirrhosis. The length and volume of the core obtained with Tru-cut and Menghini technique needles are similar.

When a suction type needle is used, cytologic examination of the aspirated fluid can provide additional information if needed. The size of the biopsy specimen varies depending on the technique and size of the needle used. In one analysis, the average aggregate length of the liver tissue obtained by a 14-gauge Menghini needle was 1.8 ± 0.8 cm, and each centimeter of liver tissue showed an average of 6 portal triads.[9] Minimal size for an adequate liver biopsy is somewhat controversial. Studies have shown that a minimum of 2.5-cm-long biopsy is essential to overcome variation due to sampling in cases of chronic hepatitis.[10] However, in practice this is not always achieved because of operator- and patient-dependent factors. In such circumstances, one has to carefully evaluate the risk of additional passes versus a repeat biopsy at a later date. In our opinion, a biopsy longer than 1.0 to 1.5 cm should be considered adequate for the evaluation of a diffuse parenchymal disease. Longer specimens not only reduce sampling errors but also allow tissues to be sent for microbiology cultures and metal quantification when needed. The approximate percentage of inadequate percutaneous liver biopsies in most institutions is estimated to be generally $<5\%$.[11]

In certain clinical settings, special sample preparation and fixation may be required, such as placing the tissue in appropriate culture medium for suspected infections, metal-free containers for metal quantification, fixation in glutaraldehyde for electron microscopy, frozen tissue for Oil red O stain for estimating microvesicular fat, or simply "RUSH/STAT"

processing in critically ill patients (eg, fulminant liver failure or the posttransplantation situation). It is very important that critical clinical details (eg, liver enzymes, history of medications/toxin exposure, viral and autoimmune serology) and a clinical differential diagnoses be communicated to the pathologist so that appropriate tissue triage and special procedures can be undertaken without loss of time. Most pathology labs will routinely perform trichrome, hematoxylin and eosin, reticulin, iron, and D-PAS (periodic acid-Schiff stain after diastase digestion) stains on liver biopsies for evaluation of a medical liver disorder.

INDICATIONS

Histologic examination remains an essential tool for the evaluation of patients with liver disease, particularly those with persistent unexplained liver function abnormalities. Sorbi et al[12] assessed the role of liver biopsy in asymptomatic patients with persistent (>6 months) elevation of liver enzymes, after negative serology and biochemical screening studies. In this study, the biopsy changed the diagnosis in 14% of cases and resulted in changing the frequency of enzyme monitoring in 13% of patients.[12]

In current practice, the indications for liver biopsy are many (Table 1), and still evolving as treatments for various chronic liver diseases continue to evolve (eg, hepatitis C) and posttransplantation patients live longer. With advances in serologic diagnosis of viral/autoimmune hepatitis and laboratory tests for genetic disorders, the role of liver biopsy in certain clinical settings is currently debated. The following section discusses the changing role of liver biopsy in some of the common disorders and the associated controversies.

Chronic Hepatitis C

Hepatitis C virus (HCV) infection is a major epidemiologic and public health issue. Current estimates amount to about 3 million cases in the United States and over 170 million cases worldwide.[13,14] Immunoassays for diagnosing HCV were introduced in the late 1980s and are now fairly sensitive and specific. Third-generation immunoassays or detection of viral RNA in peripheral blood by PCR are virtually diagnostic of HCV infection; however, they do not predict disease activity. Serum aminotransferases are also unreliable predictors of the grade of inflammation or stage of fibrosis. Although current practice is not to biopsy HCV patients with genotype 1 with normal liver enzymes, recent studies suggest that this practice may need to be reevaluated. A retrospective study from King's College Liver Unit in London, where all HCV patients undergo liver biopsy before treatment, found that all 91 patients with normal ALT had abnormal histology.[15] Moreover, 16% had significant necroinflammatory activity (scores ≥5) and fibrosis (stage 3 or 4; Ishak's scoring system). Thus, these authors concluded that 1 in 6 patients with persistently normal ALT will have significant progressive liver disease that can be only identified on liver biopsy. Also, it is argued that a liver biopsy may be avoided in patients with HCV genotype II/III since approximately 80% of these patients will sustain a virologic response to therapy. In general, a liver biopsy is recommended immediately prior to treatment of HCV to determine if therapy is warranted and to assess prognosis.[16] The absence of bridging fibrosis/cirrhosis in the initial liver biopsy at presentation is an independent predictor of sustained response.[17,18] In addition, the liver biopsy can detect other concomitant findings or disorders that might impact the treatment and prognosis, eg, iron overload, steatohepatitis, alpha-1-antitrypsin inclusions. Thus, liver histology may play a very important role in motivating the patient to undergo the lengthy and arduous treatment process.

Nonalcoholic Steatohepatitis (NASH) and Nonalcoholic Fatty Liver Disease (NAFLD)

NASH, a disease whose cause is not fully understood, resembles alcohol-mediated liver injury and can progress to cirrhosis.[19] The incidence and the prevalence of steatohepatitis continue to increase in the developed world with increasing obesity, a major risk factor for NASH. The current estimated incidence of NASH is 2% to 3% in the general population. Thus, NASH is the most common liver disease in the United States. Since 20% of these patients may progress to cirrhosis, it is a major health concern. The importance of NASH as a cause of abnormal liver transaminases with negative autoimmune and hepatitis serologies is emphasized in a prospective observational study of 81 "marker negative" patients, where only 2.5% of patients had normal histology. Of the remaining patients, 51% had steatosis, 32% had steatohepatitis, 5% had fibrosis, and 2.5% had cirrhosis.[20] Recently, Skelly et al[21]

TABLE 1. Common Indications for a Liver Biopsy

1. Diagnosis, grading, and staging of alcoholic liver disease, nonalcoholic steatohepatitis, autoimmune hepatitis, and primary biliary cirrhosis
2. Pretreatment evaluation of grading, staging of chronic hepatitis C
3. Diagnosis of liver mass, usually by imaging-guided technique
4. Fever of unknown origin or in immunocompromised patients with hepatomegaly or elevated liver enzymes levels
5. Evaluation of pretransplant living-related donor
6. Evaluation of posttransplant patient with abnormal liver tests (rejection vs. infectious etiology)
7. Evaluation of persistent abnormal liver test after negative serologic and autoimmune workup
8. Evaluation of drug toxicity (eg, chemotherapy, methotrexate therapy)
9. Unexplained hepatomegaly or splenomegaly
10. Definitive diagnosis and pedigree analysis of metabolic and mitochondrial storage liver diseases such as Wilson disease, hemochromatosis, Gaucher's disease
11. Veno-occlusive disease (preferably with transjugular approach with portal pressure measurements)
12. Clinical and research protocols

examined liver histology in 354 patients with elevated transaminases (twice the upper limit of normal range for at least 6 months) and found that 120 (34%) patients had NASH, whereas 115 (32%) patients had only fatty liver. It is well recognized that some patients may have fatty livers without significant inflammatory component (steatohepatitis) and are unlikely to develop progressive fibrosis/cirrhosis. Subsequently, the term nonalcoholic fatty liver disease (NAFLD) has evolved to include the entire spectrum of changes associated with fatty livers.

The role of liver biopsy in evaluating patients with NASH is evolving, as are the diagnostic criteria and staging systems.[22,23] According to a recent AASLD consensus conference the histologic findings of NASH include steatosis, hepatocelluar injury (ballooning, Mallory bodies), mixed lobular inflammation (neutrophils and mononuclear cells), and delicate zone 3 fibrosis in patients with negative serologic tests and minimal alcohol intake.[22] While it is well recognized that many of the histologic features of NASH and alcohol-mediated liver disease (ALD) are indistinguishable, some of the histologic findings seen in ALD are uncommonly observed in NASH. These include central hyaline sclerosis, predominantly microvesicular or foamy degeneration of hepatocytes, venous outflow lesions (veno-occlusive lesions, perivenular fibrosis, or lymphocytic phlebitis), and acute cholestasis or bile plugs. While Mallory's hyaline is seen with both NASH and ALD, the presence of abundant Mallory's hyaline is more indicative of ALD. Disproportionately prominent portal inflammation or fibrosis, bile ductular proliferation, nonzonal steatosis, and prominent hepatocytic necrosis (spotty or bridging) should raise suspicion of disorders other than NASH. Also, while mild zone 1 hepatocytic siderosis can be seen with NASH, the presence of more severe siderosis should lead to a workup for iron overload, including genetic mutational analysis for hereditary hemochromatosis (HHC) (discussed in a later section).

Currently, there are no specific laboratory tests or imaging procedures that can distinguish NASH from other disorders. Current imaging modalities may not detect hepatic steatosis if $<33\%$ of the liver is involved and cannot differentiate between steatosis from different causes or assess the severity of fibrosis. However, a liver biopsy may not be necessary to suspect fatty liver in an obese patient with diabetes, abnormal liver transaminases, and an echoic liver on ultrasongrapic imaging. In such a setting, in the absence of a universally effective therapy, one could argue that a liver biopsy may add little to the management of a NASH. However, the biopsy still remains the diagnostic gold standard and is necessary to stage fibrosis, exclude potentially confounding factors such as alcoholic liver disease, chronic viral hepatitis, autoimmune hepatitis, drug toxicity, and identify other comorbid liver diseases (eg, iron overload, alpha-1-antitrypsin deficiency). Liver biopsy is also the only way to distinguish steatosis from steatohepatitis. A diagnosis of NASH increases the likelihood of progression to cirrhosis and can thus help to effectively plan for monitoring and treatment of the sequelae of possible future decompensated liver disease. The clinical scoring systems predicting disease progression in NASH are still imprecise, and serologic markers of hepatic fibrosis still need to be validated in clinical studies. The histologic staging systems are still evolving and need validation in long-term prospective studies.[22,23] It is clear that while noninvasive methods of diagnosis and disease progression continue to evolve and treatment modalities (eg, oral hypoglycemic medications, antioxidants, and antifibrotic drugs) become increasingly available, the resolution of histologic abnormalities on follow-up biopsy will remain a gold standard for evaluating treatment outcome in the management of NASH patients.

Hereditary Hemochromatosis (HHC)

Trousseau first described the syndrome of diabetes, skin pigmentation, and liver cirrhosis in 1865,[24] and then in 1889 von Recklinghausen[25] named the syndrome "hemochromatose," noting the pigment as iron. A century later, developments in molecular medicine and genetics linked the disease to the HLA-A3 locus.[26] Feder et al in 1996 linked the HLA locus to the short arm of chromosome 6, which was subsequently determined to be the HFE gene.[27,28] Two major mutations involving HFE gene are commonly referred to as C282Y and H63D. It is now recognized that the C282Y mutation accounts for approximately 90% of all cases of HHC in white populations, but not in patients from Asia or Africa. The clinical effects of HHC often evolve insidiously over decades, from clinically insignificant iron accumulation to multiorgan damage (skin, joints, liver, and pancreas). Thus, it is imperative that HHC be diagnosed in its early stages.

The pattern of iron deposits in periportal regions in the liver was first described in HHC patients and their relatives in 1962.[29] In advanced HHC, iron deposition is seen throughout the hepatic parenchyma, reticuloendothelial system, and biliary epithelium. Preferential deposition of iron in the Kupffer cells is associated with iron overload due to multiple transfusions or chronic hemolytic anemia, and had been referred to as "secondary hemochromatosis or hemosiderosis pattern." It is now well recognized that there is overlap in these histologic patterns, and in severe iron overload the patterns could be identical. Also, mild to moderate iron deposition can be seen with alcoholic liver disease, NASH, chronic viral hepatitis, and cirrhosis from any cause, raising the possibility of HHC. Before the discovery of HFE gene, the diagnosis of HHC depended on determining the hepatic iron index (HII) and the patterns of iron deposition noted on the liver biopsy specimen. As biochemical iron quantization is not always available detailed iron grading systems based on distribution and staining intensity of iron on histologic slides were designed to estimate "histologic" HHI.[30] In experienced hands, histologic HHI correlates very well with biochemical HHI. However, subsequent studies have shown limitations to this approach. In a study of 103 patients by Brunt et al, only 42 of 73 cases with predominantly HHC-type iron deposition pattern were homozygous for the C282Y mutation.[31] None of the remaining patients with HHC pattern on liver biopsy was compound heterozygous. Therefore, the pattern of iron deposition alone cannot be used to diagnose HHC. In a multicenter multiethnic group study in the United States by Kowdely et al, 93% of patients homozygous for the HFE gene had a hepatic iron index of >1.9.[32] There was also a trend toward higher mean HII with increased fibrosis and cirrhosis. Press et al evaluated

genotypic and phenotypic parameters in 37 patients with biopsy-proven hepatic siderosis.[33] In 20 patients with HII >1.9, 9 (45%) were homozygous for the C282Y mutation and 3 of 9 (33%) had cirrhosis. Among the remaining 11 nonhomozygous patients, 10 (91%) had liver cirrhosis. The authors concluded that HII has poor diagnostic specificity for predicting genotypic HHC in patients with cirrhosis. In other studies, it was shown that 15% of genotypic homozygotes for HHC do not have HII >1.9.[34,35] Thus, direct determination of HFE gene (C282Y) is the single best diagnostic test for HHC in patients with cirrhosis, as HII is nonspecific in end-stage cirrhosis.[29]

Although genetic mutational analysis is an integral part of an HHC workup, especially in the early diagnosis and screening of family members, liver biopsy still provides useful information. A quantitative iron analysis is seldom required in routine practice these days and is gradually becoming obsolete. According to AASLD practice guideline for diagnosis and management of hemochromatosis, liver biopsy is indicated in patients greater than 45 years of age, with a transferritin saturation >45%, and a ferritin >1,000 μg/L or elevated transaminases.[36] Liver biopsy reveals the severity of fibrosis and has a significant impact on management of HHC. If needed, liver tissue can also be extracted from paraffin blocks for biochemical iron quantization. Thus, the role of liver biopsy in HHC has shifted dramatically from a diagnostic tool to one for prognostication and surveillance.[37] It is also recognized that many cases of HHC have genetic abnormalities other than HFE (non-HFE HHC). Thus, liver biopsy is critical in evaluating patients with suspected iron overload but lacking HFE gene mutations. This is even more relevant in African and Asian countries where HFE mutations account for only a minority of HHC cases.

Primary Sclerosing Cholangitis (PSC)

The role of liver biopsy in primary sclerosing cholangitis (PSC) is controversial. Radiologic finding of beaded appearance of the biliary ductal system on ERCP remains the gold standard for diagnosis. More typical histologic findings of pericholangitis or "onion-skin fibrosis" are identified in <30% of liver biopsies and frequently the biopsies show only nonspecific findings. Diagnostic "tombstone" lesions are rarely seen. Moreover, the histologic changes in PSC are patchy and biopsies show a poor correlation with disease progression. Burak et al recently evaluated 79 patients with PSC diagnosed by cholangiography, of whom 78 (98.7%) underwent liver biopsy.[38] The biopsy results revealed no additional diagnostic findings and did not change the clinical management of the patients. Histologic evaluation is not a dependent variable in the revised Mayo Clinic model for prediction of the natural history of PSC.[39] Since current treatment of PSC is limited, the utility of routine diagnostic biopsies in PSC is questionable. Liver transplant is the only effective treatment of long-term survival and is reserved for end-stage disease where a liver biopsy is needed in a pre-transplantation evaluation. In summary, currently liver biopsy has a limited role in the diagnosis and management of PSC. However, a small proportion of patients with cholestatic liver chemistries and normal ERCP will have "small duct PSC" or idiopathic adult ductopenia. Liver biopsy is essential in establishing these diagnoses.

Alcoholic Liver Disease (ALD)

Although NASH is emerging as the predominant cause of steatohepatitis, particularly in the Western countries, alcohol still remains a significant cause of liver disease worldwide and in many instances is an aggravating factor in other liver disorders. As previously noted, histopathology of alcohol-mediated liver injury shows considerable overlap with NASH and in milder cases is virtually identical. However, in patients with a history of alcohol abuse, a biopsy not only confirms the diagnosis but is also helpful in staging the disease (fatty liver, alcoholic hepatitis, cirrhosis) and excluding other coexistent disorders. Occasionally, the diagnosis of ALD is established most rapidly with a liver biopsy in someone who presents with acute hepatic decompensation where therapeutic decisions have to be made quickly. Thus, it may be of practical importance to determine if alcoholic hepatitis is present and treatment with steroids or pentoxyphylline is considered. A study by Talley et al reviewed 108 patients who underwent liver biopsy after clinical history and laboratory assessment for ALD.[40] In all cases with a pre-biopsy clinical diagnosis of ALD, the diagnosis was confirmed histologically. Furthermore, no other coexisting diagnosis was revealed by biopsy. However, previous studies before the advent of serologic markers for HCV have demonstrated that in patients with a history consistent with alcohol abuse, a liver biopsy may identify other causes in 10% to 20%.[41] In summary, although a liver biopsy may be useful in establishing the diagnosis and the severity of ALD, its role in guiding the management is somewhat limited.

Autoimmune Hepatitis (AIH)

Since its initial description as "lupoid hepatitis," AIH has become a distinct clinicopathologic syndrome with a wide range of clinical manifestations. No single test is diagnostic, and clinical scoring systems have been developed to aid the diagnosis. According to the International Autoimmune Hepatitis Group (IAHG) guidelines, a definitive diagnosis of AIH not only involves an exclusion of other causes (hereditary, viral hepatitis, alcohol, and drug-related diseases) but also includes characteristic liver biopsy findings.[41] Serologic markers and liver biopsy findings are complimentary in the diagnosis and management of AIH patients. The histology of the IAHG scoring system includes features of interface hepatitis, plasmacytic infiltrates, and hepatic pseudo-rosettes. The histologic findings on liver biopsy have a diagnostic specificity of approximately 80% and a positive predictive value of 68%. The response to immunosuppression is generally good. Liver biopsy can play an important role in monitoring treatment response and monitoring disease progression. There are currently no studies evaluating the prevalence of coexisting liver disease in AIH patients and the impact they might have on the management.

Other Disorders

Liver biopsies continue to play a very important role in the evaluation of liver transplant rejection, staging of primary

biliary cirrhosis, assessment of metabolic and congenital disorders, drug toxicity, and patients with increased transaminases of unclear etiology and hepatic masses. However, detailed discussion of these settings is beyond the scope of this review.

CONTRAINDICATIONS

As for any procedure, the patient that undergoes a liver biopsy should be able to understand and cooperate with the physician's instructions. Occasionally, liver biopsies are performed on patients under general anesthesia or on a mechanical ventilator, requiring appropriate timing with inspirations. A controversial topic is whether bleeding after a liver biopsy correlates with indices of peripheral coagulation, as limited data are available.[43] The consensus guidelines of contraindications for liver biopsy are shown in Table 2. If a patient has relative or absolute contraindication for a percutaneous liver biopsy a transjugular approach should be considered.

COMPLICATIONS

The liver is a very vascular organ with a rich blood supply and complex anatomy. Initially, liver biopsies were performed in an inpatient setting for fear of complications but today are routinely performed in ambulatory centers with minimal risk. In 1993, Garcia et al reviewed 2,166 outpatient "blind" liver biopsies, including their own experience at Yale and found an overall complication rate of 2.8% (60 of 2,166).[44] The highest complication rate (3.7%) was noted by Perrault et al using a Tru-Cut needle,[45] and the lowest (0%) was reported by Rosson using a Klatskin needle.[46] The different complication rates were attributed to variation in technique and to differences in the needles used, as well as differences in the severity of the liver disease and selection criteria in different centers. The most common significant complication was pain and hypotension requiring hospitalization. Minor complications can be expected in up to 20% of patients and include transient and localized abdominal and/or right shoulder discomfort. The risks of liver biopsy should be well communicated to the patient prior to the procedure (Table 3). Severe pain that persists after appropriate analgesia should prompt further evaluation for internal bleeding. Most of the time, these complications can be managed with bed rest, analgesia, or occasional blood transfusion. Rarely, a patient may require interventional hepatic artery embolization or laparotomy to control the bleeding. In a review of more than 10,000 cases of inpatient liver biopsies from 1952 to 1986, the overall mortality ranged from only 0.01% to 0.12%.[45] The highest rate of mortality was noted in patients undergoing biopsies for malignant lesions and in patients with cirrhosis. A multicenter retrospective Italian study of 68,276 percutaneous liver biopsies reported a total of 147 complications and a mortality of 0.09 of 1,000.[47] The reported incidence of liver biopsy complications in AIDS patients remains controversial, but the role of the liver biopsy in the care of an HIV patient remains very important. Many HIV/AIDS patients are coinfected with hepatitis B and C viruses. Viral hepatitis in these coinfected patients can become a greater clinical problem than the HIV infection, as recent advances in antiretroviral therapy have effectively slowed the onset of AIDS. Published experience with liver biopsies in coinfected HIV/AIDS patients is limited. However, one study reported no complications among 60 patients and while another described four deaths within 24 hours after liver biopsy.[48,49] The latter result could be a rare unfortunate consequence or possibly related to the ultrastructural hepatic sinusoidal endothelial cell injury secondary to human immunodeficiency virus infection.[50] This theory needs to be tested in prospective randomized control studies. Zakaria et al examined 14 patients who underwent a percutaneous liver biopsy with sickle cell disease, another high-risk group.[51] Five (36%) suffered serious hemorrhage and 4 (28%) died of complications related to the procedure. Patients with a sickling crisis and histology that reveals chronic venous outflow obstruction, marked hepatic sequestration of erythrocytes, and sinusoidal dilation were associated with complications. Since the biopsy findings did not substantially change the clinical management or prognosis of the patients, patients in acute sickle cell crisis and elevated liver enzymes should be carefully evaluated by other noninvasive methods, as liver biopsy may not be as useful as in other conditions.

TABLE 2. Contraindications for a Liver Biopsy

1. Uncooperative patient
2. History of unexplained bleeding after a surgical procedure
3. Prothrombin time greater than 3–4 seconds than control
4. Platelet counts less than 60,000/mm^3
5. Bleeding time >10 minutes
6. No previous radiologic evaluation of the liver
7. Echinococcal cysts
8. Hemangiomas
9. Recent use of aspirin or other NSAIDs (within last 7–10 days)
10. Extrahepatic biliary obstruction
11. Bacterial cholangitis
12. Right-side empyema
13. Pneumothorax
14. Unavailability of blood products for transfusion
15. Significant ascites

TABLE 3. Liver Biopsy Complications

1. Pain (biopsy site, right upper quadrant and right shoulder pain) (~33%)
2. Vasovagal response and transient drop in blood pressure
3. Intraperitoneal hemorrhage (0.16%–0.32%)
4. Hemobilia (0.059%)
5. Bile peritonitis (0.06%–0.09%)
6. Gallbladder perforation (0.117%)
7. Bowel perforation (0.044%)
8. Bacterial sepsis and local abscess formation (0.088%)
9. Intrahepatic and subcapsular hematoma (0.059%)
10. Puncture of lung leading to hemothorax or subcutaneous emphysema (0.014%–0.35%)
11. Breaking of the biopsy needle (0.059%)
12. Death (0.009%–0.12%)
13. Pneumothorax

Any physician who recommends and performs a liver biopsy should have a complete understanding of the procedure, its indications, and all known absolute or relative contraindications. Laboratory parameters including prothrombin time, bleeding time, platelet count, and prior use of aspirin or other nonsteroidal anti-inflammatory drugs should be known. According to the AGA patient care committee, a liver biopsy should be performed in an outpatient facility in which it is possible to follow the patient closely for at least 6 hours after the procedure. However, many practitioners discharge patients within 3 to 4 hours after the biopsy, as long as vital signs are stable. The patient should be given clear instructions regarding the signs of complications. After discharge, a responsible person should be available to monitor the patient over the next 24 hours. In the event of a complication, the patient should be able to reach a medical facility within 60 minutes for evaluation.

CONCLUSIONS

The indications for performing a liver biopsy have undergone changes in the last decade.[52–57] New and advanced radiologic, immunologic, biochemical, and genetic markers are increasingly available to physicians; however, evaluation of liver histology remains critically important. Studies suggests that the liver biopsy can change the clinical diagnosis in 8% to 14%, management in 12% to 18%, and the frequency of liver test monitoring in 36% of patients.[13,21,54] With a low risk of complications, liver biopsy is a safe outpatient procedure for the majority of patients and continues to be an essential tool in the diagnosis and treatment of appropriately selected patients with liver disease.[55] Clearly, as our knowledge of various liver disorders advances and new especially noninvasive diagnostic tests are developed, the role of liver biopsy in medical practice will continue to evolve. Emergence of better imaging techniques, surrogate "serological" markers of liver fibrosis, understanding of non-HFE iron overload syndromes and objective quantification of liver fibrosis into meaningful clinical groups (especially subclassification of cirrhosis) are among the many new and exciting developments that hold promise for the future.

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