

Usefulness of liver biopsy in chronic hepatitis C

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ABSTRACT

Major requirements for performance of liver biopsy (LB) are the benefits for the patient and the impossibility of having the same information by less invasive procedures. In the last two decades physicians have faced the difficult task of convincing a patient positive for hepatitis C, with minimal clinical or laboratory alterations to be submitted to LB in order to evaluate the status of the disease for therapeutic management. The characteristics of the needle used for percutaneous LB interferes with the accuracy of diagnosis. In chronic hepatitis C (CHC), validity is achieved with liver fragments about 25mm in length containing more than 10 portal tracts. Morbidity due to LB is mainly related to bleeding but death is very rare. Severe complications are also uncommon, increasing with number of passes and decreasing with experience of operator and ultrasound guidance. Although CHC is a diffuse disease, the various areas of the liver may not be equally affected and sampling errors are possible. Another potential limitation of LB is the discordance between pathologists in its interpretation. To replace LB, many panels of surrogate markers have been described, aiming to identify extent of fibrosis and inflammation. All of them have used LB as their “gold standard”. Liver biopsy continues to be the most reliable method to evaluate the possibility of therapy for CHC. Universal treatment of all patients with diagnosis of CHC would be ideal. But, there are mainly three drawbacks. Overall efficacy is as low as 50%, side effects are common and may be severe and treatment is prolonged and expensive. The acceptability of the biopsy by the patient is highly dependent on the physician’s conviction of its usefulness.

Key words. Liver biopsy. Chronic hepatitis C. Fibrosis degree. Liver disease. Treatment indications. Biopsy limitations.

INTRODUCTION

The possibility of evaluating hepatic lesions by means of liver percutaneous biopsy started in 1883 when Paul Ehrlich intended to study glycogen content of hepatocytes in diabetes. In the second half of last century risk of bleeding was minimized and the procedure permitted the analysis of structural alterations, inflammatory processes and other various hepatic lesions.¹ Little by little indications of liver biopsy became more and more frequent, since it was a precious instrument of making correct diagnosis as well as prognostic evaluations and therapeutic monitoring in clinical practice.

Liver biopsy is indicated in a wide variety of clinical conditions and the basic requirements for its

performance are the benefits for the patient and the impossibility of having the same information by less invasive procedures. The patient must be aware of its indication, its risks and benefits and nowadays an informed written consent is demanded.

Most of the knowledge about chronic hepatitis was obtained with data derived from liver biopsies. On the other hand, acceptance of the procedure by the patients has been a challenge, due to its invasiveness. Another complain, easy to be removed, is the fear of malignancy, since biopsy procedures in other organs is frequently linked to diagnosis of cancer.

When the patient has symptoms and feels sick it is easier to indicate invasive procedures. It is not the case of chronic hepatitis C. This disease is usually asymptomatic with few laboratory alterations. In the last two decades physicians have faced the difficult task of convincing a patient positive for hepatitis C, with minimal clinical or laboratory alterations to be submitted to liver biopsies in order to evaluate the status of the disease for therapeutic management.

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RELEVANCE OF DIFFERENT TYPES OF PROCEDURES AND NEEDLES

Percutaneous liver biopsy can be performed as a “day-clinic” procedure. General requirements include a hemogram with platelet count, prothrombin time and bleeding time, some days before the procedure. Fasting is required, although only local anesthesia is necessary. Pre-medication and sedation of the patient is optional. Hemodynamic control at short intervals is advisable, meaning pulse and blood pressure during the first six hours, at hospital. As bed rest is essential to control bleeding, patient will be allowed to go home but with minimal physical efforts for the next five days.

In the last decade, with popularization of ultrasound machines and its usefulness in taking hepatic images, with growing degrees of perfection, many physicians preferred to make liver biopsies guided by ultrasound. Replacing the old liver percussion, the use of ultrasound allows the choice of the best place to put the needle, avoiding great vessels, as well as other structures as gall bladder and kidney, sometimes found together with the liver fragment by the pathologist. It also permits the analysis of the liver and its surroundings after the procedure. Early bleeding can be detected as well as hematomas near the capsule, sometimes the cause of a more severe local pain. Nevertheless, it is not mandatory to use ultrasound or other image guiding during routine liver biopsies.

As chronic hepatitis C becomes more common through the years, the therapeutic consensuses have stressed on the need of liver biopsy before treatment, and therefore ultrasound clinics started making liver biopsies. Although they usually use thin needles with imaging control, it is not advisable to make this procedure far from surgical facilities, usually found in a hospital center, since unexpected hemorrhagic complications needing surgical intervention may occur.

Either at surgery or during laparoscopy, wedged liver biopsies may take large fragments of liver, offering also the possibility of liver direct visualization with evaluations of alterations in color, parenchyma consistency and presence of nodules,. It has been largely used in the 70s and 80s. Nevertheless, those advantages are not particularly important in chronic hepatitis C and some disadvantages have to be pointed out. Fear of hemorrhage may lead to very superficial resections or small fragments of liver. The subcapsular area may present structural alterations not representing the whole liver parenchyma.

When specific needles are used for biopsy it is advisable to take fragments at least two centimeters deep in the liver. Another advantage of the needle is regular cut and proximity of the areas, allowing prompt clotting and regeneration.

The transjugular access to make liver biopsies may be indicated in patients with coagulation problems or in cases of intractable ascites. These conditions are usually found in decompensated cirrhosis, but patients with chronic hepatitis C very seldom will need a liver biopsy when they achieve that condition. Another possible indication for transjugular access would be in hemophiliacs with hepatitis C, in which therapeutic doubts or the need of better prognostic evaluation are demanded.

Concerning the needles currently used for liver biopsy different mechanisms can be found. The old Vim-Silverman needle, maintaining the guillotine mechanism, was replaced by Tru-cut needles. They cut a linear fragment of liver avoiding fragmentation and allowing a better evaluation of fibrous septa. The other common type of needle uses the aspiration procedure as in the old Menghini type. It is assumed they are related to less bleeding tendency, but fragmentation is more common and large fibrous septa may be over passed. Metallic needles have been replaced by dischargeable ones. The expertise of manual handling has been replaced by semi-automatic needles, mainly used by experts in ultrasound.

The characteristics of the needle may interfere with accuracy of diagnosis. It is increasingly recognized that longer biopsy samples with larger bore needles are needed to accurately stage and grade the extension of liver damage. In hepatitis C it was shown that biopsies with 15mm length may have only four to six portal tracts. In these specimens grading and staging may be underscored. Validity was achieved with fragments about 25mm with more than 10 portal tracts, what is now mandatory in the evaluation of the representativity of liver biopsy.²

CONTRAINDICATIONS AND COMPLICATIONS

For liver biopsy in general and also in chronic hepatitis C, the main contraindications are coagulation disorders and tense ascites. Prolongation of prothrombin time as well as very low platelet counts are risk factors for bleeding. As patients with clinical evident cirrhosis do not require liver biopsy for treatment purposes, these situations are very rare.

Morbidity due to liver biopsy is mainly related to bleeding. Slight to moderate bleedings can be controlled clinically, but some cases of bleeding urge for surgical intervention and death is rare, mainly linked to advanced liver disease or hemorrhagic tumors.

Local pain or referred pain in the right shoulder are common and may happen in up to 50% of patients, sometimes due to capsule hematomas, seen in ultrasound. Other less frequent related complications are hemoperitoneum, biliary peritonitis, arteriovenous fistulas and septicemia. A nationwide prospective study in France, involving more than two thousands biopsies have shown no deaths but severe complications in 0.57% of cases, that increased with number of passes and decreased with experience of operator and US-guidance.³

SAMPLING AND OBSERVATION ERRORS

Considering the whole liver weight, the liver fragment collected in a biopsy represents about 1:50.000 of the liver parenchyma. Although chronic hepatitis C is a diffuse disease, the various areas of the liver may not be equally affected. Unfortunately macroscopic analysis on surgery or laparoscopy does not evidenciate these small differences. So, there are possibilities of sampling errors.⁴

On the other hand, especially for chronic hepatitis C, a good representativity of the liver fragment may be a guarantee for the accuracy concerning the degrees of alterations. In small fragments that contain less than 10 portal spaces underscoring is frequent. Besides length of the liver fragment, needle bore larger than 18 gauges is also relevant. If the needle is thin or the fragment is short, a second or third pass will be needed to obtain more material for accuracy of diagnosis.⁵

Another potential limitation of liver biopsy is the discordance between pathologists in its interpretation. Several studies have shown that observer variation is higher for grading than staging. So, fibrosis scores are usually less affected. Training of pathologists in liver disease is of major importance to reduce observer variations.⁶

Due to those various limitations of liver biopsy, many panels of surrogate markers have been described in literature and some are routinely used in clinical practice of some hepatology centers. Their aim is to identify the extent of fibrosis and inflammations replacing liver biopsy. Among them, the direct markers of extracellular matrix turnover,⁷ the indirect markers of fibrosis or inflammation⁸ as well as

combination of direct with indirect methods and elastography to evaluate liver stiffness⁹ all of them have used liver biopsy as their "gold standard".

INDICATIONS OF LIVER BIOPSY IN CHRONIC HEPATITIS C

The diagnosis of chronic hepatitis C is often made on clinical, laboratory and serological grounds. As the disease develops without symptoms in the great majority of patients the evaluation of real liver damage must be made by liver biopsy. But it would not be necessary if all patients could be safely and efficiently treated, eliminating this viral infection. Much progress has been achieved in the treatment of hepatitis C in the last years, but efficiency could only be reached in small groups of patients. For the great majority of them, side effects and low efficacy levels persists. There are mainly three drawbacks for universal treatment of all patients with a diagnosis of chronic hepatitis C. Overall efficacy is as low as 50%, many side effects may be present, some of them severe, and the costs of the treatment are not easily affordable.

Patients with persistently normal transaminases may have severe hepatic damage; according to some authors a systematic indication of liver biopsy has been proposed. Nevertheless, some recent works, studying paired liver biopsies have found that patients with persistently normal ALT experience significantly milder disease when compared to patients with elevated levels of ALT.¹⁰ Another frequent concern is the cut-off to define normal levels of ALT, which should be lowered when evaluating chronic hepatitis C. Physicians face a dilemma with those patients in terms of an early indicating of liver biopsy and surrogate markers of fibrosis could play a role, in terms of postponing this indication.

On the other extreme, patients with clinical evidences of cirrhosis but without signs of decomposition are candidates for treatment. In these cases there is little profit in confirming the nodular architectural changes of the liver, since F4 cases should be treated. So, liver biopsy is not necessary, considering this approach.

In chronic hepatitis C patients with genotypes 2 or 3 and other indicators of good response, in which therapeutic efficacy reaches 80 to 90%, a liver biopsy is not really needed. Some authors differentiate between genotype 2 more benign and genotype 3, which may have greater percentages of relapses or no response. For genotype 3, in particular, it is important to have histopathological differentiation,

since in cases with cirrhosis or even with F3 and some nodules, a prolongation of treatment for 48 weeks is advisable.¹¹

DIAGNOSIS OF ASSOCIATED DISEASES IN CHRONIC HEPATITIS C

Histological diagnosis of associated diseases may be relevant in the management of chronic hepatitis C. In cases of elevated titers of auto antibodies other clinical data may not be sufficient to assure a correct diagnosis of autoimmune hepatitis and a liver biopsy is mandatory.

A more frequent association is between chronic hepatitis C and steatosis or steatohepatitis. Although epidemiological data can exclude alcohol intake, the diagnosis of nonalcoholic steatohepatitis is made on histopathological grounds. Lately, this association is recognized as relatively frequent and linked to more advanced histopathological changes.¹²

Other metabolic diseases as iron overload and $\alpha 1$ anti-trypsin deficiency can also be easily detected when liver biopsy is available. Although the diagnosis of hepatocellular carcinoma is currently made by use of imaging methods, for small lesions a liver biopsy is still indicated, allowing the detection of very early cases of liver tumor.

CONCLUSION

Liver biopsy is the only approach enabling direct assessment of liver injury. In addition to fibrosis it allows a full histopathological evaluation. In Hepatitis C, besides staging fibrosis and grading necro-inflammatory activity, it may reveal and/or confirm associated liver diseases as steatohepatitis, auto-immune hepatitis, $\alpha 1$ anti-trypsin deficiency, iron overload and others. It is useful not only for diagnosis and treatment indi-

cations but also for prognosis and general management. The acceptability of the biopsy by the patient is highly dependent on the physician's conviction and belief in biopsy usefulness.

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