Histological assessment of the liver

Stefan G Hübscher

Abstract

Histopathological assessments play an important role in the diagnosis and management of patients with liver disease. For some conditions, liver biopsy is still used routinely to establish the cause of liver disease. In other circumstances, evaluation of morphological changes provides additional information that is useful for clinical management — for example, when assessing disease severity in chronic viral hepatitis and non-alcoholic fatty liver disease. However, with the increased use of non-invasive methods for assessing the severity of liver injury, particularly fibrosis, the role of liver biopsy in this respect is changing. In cases where a dual pathology is suspected, histological assessment may help to identify the main cause of liver injury. In addition, liver biopsy sometimes reveals abnormalities that have not been detected by previous investigations. Histopathological assessment of liver biopsies involves a systematic evaluation of changes involving individual components of the normal liver. The final interpretation of the abnormalities detected depends on clinicopathological correlation. Sampling variation is a problem, particularly with small-needle biopsies, and should be considered as a possible explanation when there is a disparity between clinical and pathological findings.

Keywords Liver biopsy; liver histology; liver pathology

This article will focus on the role of liver biopsy in the assessment of medical liver diseases, where diffuse hepatic involvement is generally presumed to be present.[1,2] For some conditions (e.g. liver allograft rejection), histopathology is still regarded as the diagnostic gold standard. For other diseases, where a diagnosis is already suspected on the basis of other investigations (e.g. autoimmune hepatitis), liver biopsy is still used routinely, both to identify features supporting the suspected clinical diagnosis and to exclude the presence of features that might suggest an additional or alternative diagnosis. Even in cases where the cause of liver disease has already been identified, the evaluation of morphological changes provides additional information that is useful for clinical management — examples include grading of disease severity (e.g. inflammatory activity in chronic viral or autoimmune hepatitis, steatosis severity in fatty liver disease) and staging of fibrosis in chronic viral, autoimmune and fatty liver diseases. In addition, liver biopsy may reveal abnormalities (e.g. iron overload, α_1-antitrypsin globules) that have not been detected by previous investigations.

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What's new?

- Non-invasive methods are increasingly used to assess the severity of liver disease and have led to a changing role for liver biopsy
- Recent studies have highlighted problems related to sampling variability in liver fibrosis and have emphasized the importance of obtaining samples that are adequate in length and diameter
- Computer-assisted image analysis methods can provide accurate measurements of histological features such as fibrosis and steatosis — these methods are likely to be used increasingly as an adjunct to conventional histology, particularly as the field of digital pathology evolves

Types of specimens obtained

Specimens are most commonly taken for histological assessment by percutaneous needle biopsy.[3] Needle biopsies may also be obtained via the transjugular route, if there is massive ascites or a problem with blood coagulation, or under ultrasound guidance (or, less commonly, at laparoscopy) to sample focal lesions in the liver. Cytological specimens obtained by fine-needle aspiration and wedge biopsies taken at laparotomy are also useful in the evaluation of focal liver lesions.

When interpreting liver histology an adequate sample is vital as samples that are too narrow or too short increase problems with sampling variability and lead to understaging of liver disease. Recommendations for an adequate biopsy include the use of a 16-gauge (or wider) needle, a minimum of 10–12 portal tracts and a length of 20–25 mm.[3] Unfortunately, many of the specimens currently obtained fail to reach these definitions of adequacy.[4] Surgical wedge biopsies taken from the subcapsular area can be misleading as there is more normal fibrous tissue in this region.

Interpretation of liver biopsy

The main features below should be included in the evaluation of all liver biopsies in which a diffuse liver injury is suspected.

Liver architecture

An intact core at least 1 cm long is generally required to determine whether normal vascular relationships between portal tracts and hepatic venules are retained. For accurate assessment of fibrosis, a larger core (at least 20–25 mm long) is desirable.[3,5] There may be problems with fragmentation of biopsies from cirrhotic livers (Figure 1). However, in these circumstances, the presence of fibrous septa with incomplete nodule formation usually enables a reasonably confident diagnosis to be made. In some patients with macronodular cirrhosis, an entire biopsy core taken from within a single macronodule may not show any obvious fibrosis, but the presence of subtle architectural abnormalities can provide a clue to the underlying problem.

Connective tissue stains (Table 1) are required to distinguish longstanding fibrosis (in which mature elastic fibres are seen) from recent collapse following liver cell necrosis (in which there is condensation of the reticulin framework with immature

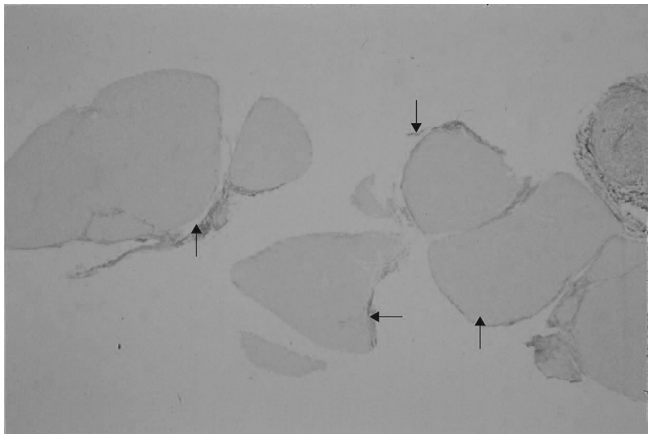

Figure 1 Fragmented liver biopsy in cirrhosis. This small, fragmented needle biopsy of liver comprises cores about 1—2 mm long. Orcein staining reveals thin, fibrous septa along the edges of the fragments (arrows). Although complete nodule formation is not seen, fragmentation and fibrous septum formation strongly suggest cirrhosis.

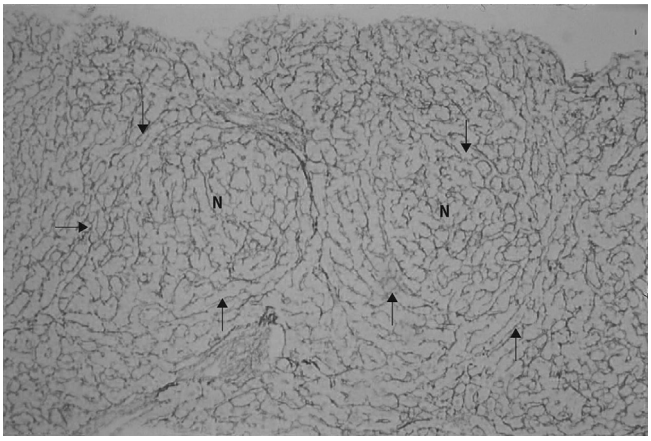

Figure 2 Nodular regenerative hyperplasia. Reticulin staining reveals hyperplastic nodules (N) in which liver cell plates are thickened, alternating with zones in which cell plates are compressed (arrows).

collagen fibre deposition). This may be a problem in some patients with severe acute hepatitis, in which surviving hepatocyte nodules surrounded by zones of necrosis/collapse can give the false impression of liver cirrhosis. The nodular shrunken liver that occurs in such cases can also be mistaken for cirrhosis radiologically.

Nodular regeneration without fibrosis (nodular regenerative hyperplasia: NRH) usually indicates a problem with the vascular supply to the liver, particularly portal venous insufficiency (Figure 2). NRH is seen as part of the histopathological spectrum of 'non-cirrhotic portal hypertension', in which the primary lesion is occlusion of small intrahepatic portal vein branches (hepatoportal sclerosis).[6] Distinction between non-cirrhotic and cirrhotic causes of portal hypertension is important, as patients with the former generally have a more indolent course with well-preserved synthetic function and less frequently progress to liver failure.

Portal tracts

Portal inflammation is common in many liver diseases, but is particularly characteristic of chronic viral or autoimmune hepatitis.

The nature of the inflammatory cells may provide a clue to the liver disease (e.g. numerous plasma cells in autoimmune hepatitis, granulomata in primary biliary cirrhosis — Figure 3, eosinophils in drug reactions).

The extension of inflammation from portal areas into the adjacent liver parenchyma with damage to periportal hepatocytes ('interface hepatitis' — Figure 4) is thought to be important in the pathogenesis of periportal fibrosis, which occurs in many chronic liver diseases.

Bile ducts are the main targets for injury in some cholestatic liver diseases. The term 'vanishing bile duct syndrome' is used to describe cases in which there is substantial bile duct loss (usually defined as ducts missing from >50% of portal tracts) (Figure 5). Counting bile ducts accurately in small biopsy specimens is complicated by sampling variation and the similarity between

Special stains used in routine histological assessment of liver biopsies

Stain	Material demonstrated	Distribution in normal liver	Changes in liver disease
Reticulin	Type III collagen fibres	Portal tracts, hepatic sinusoids	Collapse of reticulin framework in areas of recent liver cell necrosis
			Thickening of cell plates in areas of nodular regeneration
Haematoxylin van Gieson	Type I collagen fibres	Portal tracts, walls of hepatic vessels	Increased in hepatic fibrosis
Orcein	Hepatitis B surface antigen		Present in some patients with chronic hepatitis B virus infection
	Copper-associated protein		Present in chronic cholestasis
	Elastic fibres	Portal tracts	Found in longstanding fibrosis/cirrhosis
		Walls of hepatic vessels	
Periodic acid—Schiff	Glycogen	Hepatocytes	
Periodic acid—Schiff diastase	Mucin	Bile ducts	
	α_1-antitrypsin globules		Present in α_1-antitrypsin deficiency
Perls' reaction	Haemosiderin		Increased in haemosiderosis/ haemochromatosis

Table 1