Histological assessment of the liver

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Abstract

Histopathological assessments play an important role in diagnosis and management of patients with liver disease. For some conditions, histopathology is still regarded as the diagnostic gold standard. In other circumstances, evaluation of morphological changes may provide additional information that is useful for clinical management, for example, grading of inflammatory activity and staging of fibrosis in chronic viral hepatitis, and the distinction between simple steatosis and steatohepatitis in alcoholic and non-alcoholic fatty liver disease. In addition, liver biopsy may reveal abnormalities (e.g. iron overload, alpha-1-antitrypsin globules) 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. Conventional histological assessments can be supplemented by scoring of individual features such as inflammatory grade and fibrosis stage; histological scoring is most appropriate in the context of large clinical trials.

Keywords histological grading/staging; histological scoring; liver biopsy; liver histology; liver pathology

Despite considerable advances in the evaluation of liver dysfunction by non-invasive methods, histopathological assessments continue to play an important role in diagnosis and management of patients with liver disease. For some conditions (e.g. liver allograft rejection), histopathology is still regarded as the diagnostic gold standard. In other circumstances, when a diagnosis has been made by other investigations, evaluation of morphological changes may provide additional information that is useful for clinical management – examples include grading of inflammatory activity and staging of fibrosis in chronic viral hepatitis and the distinction between simple steatosis and steatohepatitis in alcoholic and non-alcoholic fatty liver disease. 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?

- During the past few years, liver biopsy has been increasingly used to assess the presence and severity of non-alcoholic fatty liver disease
- Histological assessments are now used less frequently in the assessment of chronic viral hepatitis
- 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

Types of specimens obtained

Specimens are most commonly taken for histological assessment by percutaneous needle biopsy. Needle biopsies may also be obtained via the transjugular route, if there is a problem with blood coagulation or massive ascites, 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.

Diagnostic difficulties may arise when superficial wedge biopsies are taken for the assessment of diffuse hepatic disease. In particular, fibrous tissue is more prominent in the subcapsular region of the normal liver and this may give a false impression of hepatic fibrosis or even cirrhosis. Other abnormalities (e.g. hypoxic, ischaemic or even immune-mediated liver injury) may also be accentuated in the subcapsular region. Surgical colleagues should therefore be encouraged to take needle biopsies in addition to (or instead of) wedge biopsies when a diffuse liver lesion is suspected.

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 – to determine whether normal vascular relationships between portal tracts and hepatic venules are retained, an intact core at least 1 cm long is generally required. For accurate assessment of fibrosis, a larger core (>2.5 cm long) is desirable.[1,2] 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.

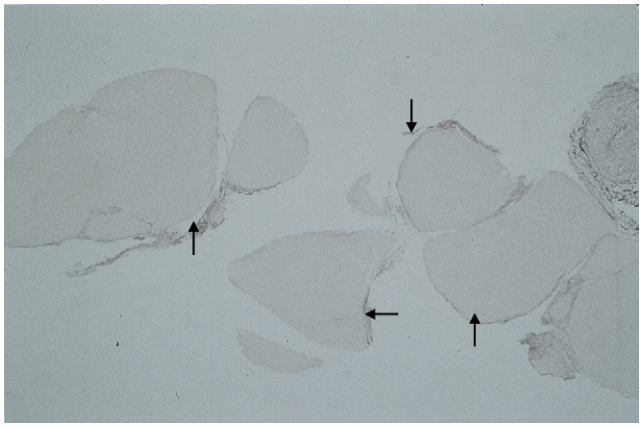

Figure 1 Fragmented liver biopsy in cirrhosis. This small, fragmented needle biopsy of liver comprises cores about 1–2 mm long. Orcein staining reveals thin, fibrous septa along the edges of the fragments (arrows). Although complete nodule formation is not seen, fragmentation and fibrous septum formation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

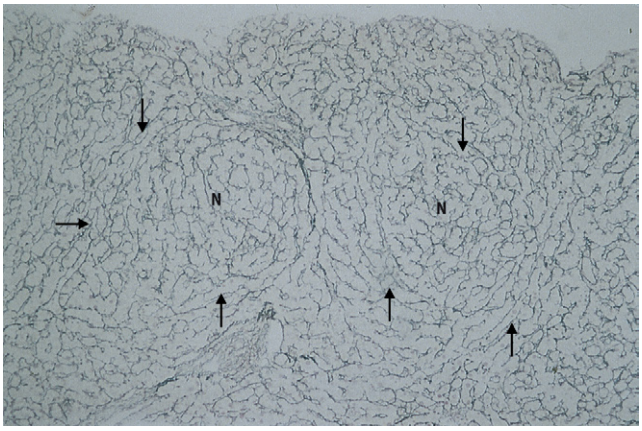

Figure 2 Nodular regenerative hyperplasia. Reticulin staining reveals hyperplastic nodules (N) in which liver cell plates are thickened, alternating with zones in which cell plates are compressed (arrows).

Connective tissue stains (Table 1) are required to distinguish long-standing 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 collagen fibre deposition). This may be a problem in some patients with severe acute hepatitis, in whom surviving hepatocyte nodules surrounded by zones of necrosis/collapse may give the false impression of liver cirrhosis.

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).[3]

Portal tracts are the site at which circulating lymphoid cells first gain access to the liver. 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 term 'interface hepatitis' is now preferred to 'piecemeal necrosis' to describe the spillover of inflammatory cells from portal areas into adjacent liver parenchyma with presumed damage to periportal hepatocytes (Figure 4). This lesion is thought to be important in the pathogenesis of periportal fibrosis, which occurs in many chronic liver diseases.

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 Walls of hepatic vessels	Found in long-standing fibrosis/ cirrhosis
• 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