

# Infectious diseases of the hepatobiliary system

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## Abstract

This review will concentrate on commonly encountered infectious diseases in biopsy practice and will consider three scenarios: Firstly, the most frequent, where the biopsy arrives with the infectious disease stated on the request form. Secondly where the patient has a risk factor placing infectious diseases high in the differential diagnosis and, thirdly, where infection is one of several possible aetiologies when a liver biopsy shows a particular pattern of inflammation.

**Keywords** HIV; liver biopsy; opportunistic infection; viral hepatitis

## Biopsy where infection is known

In this section hepatitis C, hepatitis B and HIV will be considered, individually and then as co-infections.

### Hepatitis C

**Context and indications for liver biopsy:** hepatitis C has a global prevalence of approximately 160 million individuals. 80 % of infections progress to a chronic state, many of those affected will be unaware. Of these, 10–20% will develop complications, including cirrhosis, within 2–3 decades, 1–5% will develop hepatocellular carcinoma.<sup>1</sup> The challenge for healthcare providers is to decide who to treat, where treatment is available, and at what point in the disease process, and, to identify cirrhotic patients for screening programmes. Liver biopsy can be used to assist in these decisions. A declining number of biopsies are taken from hepatitis C (HCV) positive patients.<sup>2</sup> The European Association for the Study of the Liver, EASL, clinical practice guidelines in addressing the question ‘how should patients be assessed before treatment?’ regards liver biopsy as the ‘reference method’.<sup>1</sup> Fibrotic stage is acknowledged as one of the three strongest predictors of achieving a sustained virological response (SVR) on treatment, along with host genetics and viral genotype. It is also acknowledged that biopsy is able to assess co morbidities which are weaker predictors of SVR. However these guidelines also state that non-invasive methods of assessing fibrosis can be used with ‘a safe level of predictability’.

Non-invasive methods for assessing liver fibrosis can be divided into biochemical and physical.<sup>3</sup> Biochemical methods are serum markers and these can be either direct measures of collagen deposition or remodelling, such as hyaluronate, or indirect. Indirect markers are those that can be derived from routine blood tests for example the APRI - AST platelet ratio index. Physical methods are those that assess liver stiffness such as Transient Elastography ‘Fibroscan’. Both biochemical and

physical markers are poor at discriminating between intermediate stages of fibrosis. Physical methods outperform biochemical for the detection of cirrhosis and have some prognostic value within the cirrhotic group. Liver ‘stiffness’, however, can be increased by factors other than fibrosis. Whilst these methods are unlikely to completely replace biopsy, their use, particularly in combination, may increase selectivity for biopsy. Treatment naive patients with no co morbidities may not need biopsy. Biopsy might be indicated in certain genotypes of HCV which respond less well to treatment (1 and 4), when results of physical and biochemical methods are discordant, or where treatment has failed.

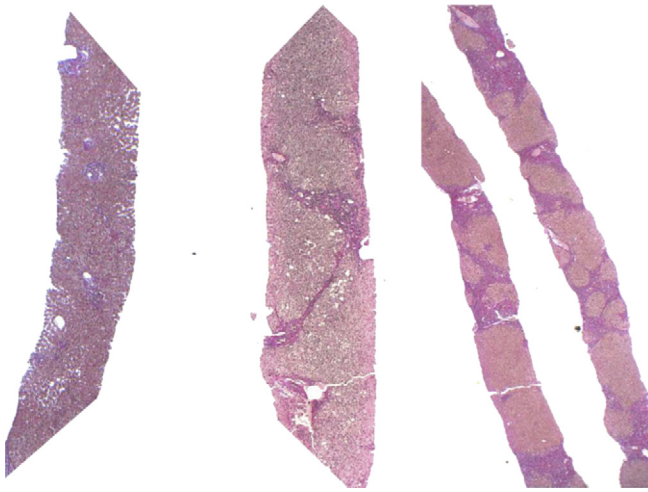
When evaluating non-invasive methods it has to be noted that biopsy is imperfect as a reference standard. Biopsy is not without morbidity and is a static assessment of a single point in a disease process. Small biopsies underestimate disease severity. A frequently quoted adequate biopsy size is 20 mm with at least 11 complete portal tracts,<sup>4</sup> which is not always achieved in practice. As a biopsy only represents 1/50,000 of the total liver, it is perhaps not surprising that biopsies from different areas of the liver give different results for disease severity, although a study comparing biopsies from the two lobes found major differences (of two points on a numerical scoring scale) in fewer than 3% of the study population.<sup>5</sup> The final limitation of biopsy is the variation between individual pathologists in assessing disease severity. This is usually expressed as discrepancies in the application of scoring systems which ascribe a number to the degree of inflammation and fibrosis. A study by Rousselet et al.<sup>6</sup> suggests that it is the experience of the interpreting pathologist, rather than the size of biopsy or sampling variation, that is a major factor in variability, and recommends dual observers whenever possible.

### Histological assessment of the liver biopsy in hepatitis C:

having noted that the aetiology is written on the request form, this should not prevent the pathologist from deciding if the pattern of damage is in keeping with hepatitis C or not, and whether there are features of another disease. Assuming a dominant pattern of chronic hepatitis, judgements should be made regarding the amount of fibrosis (the stage, [Figure 1](#)) and the amount of inflammation (the grade). The portal inflammation often includes lymphoid aggregates sometimes associated with lymphocytic infiltration of the bile duct (‘Poulson Christoffersen lesion’). Extension of inflammation beyond the confines of the portal area eliciting damage to the periportal hepatocytes is assessed as ‘interface hepatitis’ and foci of inflammation in the parenchyma as spotty lobular inflammation. Semi quantitative descriptors are used for these and comparisons should be made with previous biopsies. Numerical scoring systems are a frequent adjunct to the pathology report.<sup>7</sup>

Interobserver and sampling variability in the application of histological scoring systems have been alluded to above but it should also be noted that these scoring systems have a number of other inherent limitations.<sup>8</sup> They are not linear scales; ‘4’ is not twice as severe as ‘2’ and two biopsies with quite different patterns of inflammation, predominantly portal versus predominantly lobular for example, can achieve the same numerical score. Despite this their use, particularly in research, is widespread. The Ishak modification of the histological activity index

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**Figure 1** Biopsies from three different patients with hepatitis C stained with Van Gieson for assessment of fibrosis. On the left with a near normal architecture ( $\times 40$ ), centrally with a portal–portal fibrous bridge – moderate fibrosis ( $\times 40$ ), and on the right the nodular architecture of cirrhosis ( $\times 20$ ). As an adjunct to the report these appearances might be given a numerical stage.

and METAVIR systems are most commonly used. An alternative to semi quantitative systems is a quantitative measure of fibrosis by computer assisted image analysis. Calvaruso et al. describe liver collagen as a ‘collagen proportionate area’ (CPA) expressed as a percentage.<sup>9</sup> This group, from the Royal Free Hospital in London, have shown that, post transplantation for HCV, CPA correlates with Ishak stage and with hepatic venous pressure gradient. Furthermore the CPA value at 1 year post transplant is an independent, sensitive and specific predictor of decompensation and CPA can be used to sub classify patients with cirrhosis. A range of CPA values is generated distinguishing ‘early’ from ‘late’ cirrhosis and correlating with liver decompensation. Regardless of genotype, grade and stage correlate with serum HCV RNA levels but insufficiently to predict the level of inflammation and fibrosis in any given individual. Liver function tests are similarly unable to accurately predict histology. Genotype may influence histology. There is evidence that fibrosis shows a more rapid progression in genotype 3.<sup>10</sup> Histological findings are being described according to host genetic factors. Polymorphisms on chromosome 19 close to genes encoding cytokines of the interferon family, including IL28B, predict both spontaneous viral clearance and SVR after treatment.<sup>11</sup> A CC genotype in the IL28B gene, in patients infected with genotype 3 hepatitis C, have more pronounced portal inflammation than patients with alternative IL28B genotypes.

**Additional findings in the liver biopsy:** having a known infection with a hepatitis virus is no protection against other liver diseases. Nair et al.<sup>12</sup> in 1842 biopsies from patients with hepatitis C, B or co infections found additional diseases in 377 (20.5%). Fatty liver disease, haemochromatosis, hepatocellular carcinoma and dysplastic nodule were the most frequent of 14 different disease categories. The authors make important points that these co morbidities may need treatment and have consequences for the patient in their own right, as well as potentially altering the natural history of the viral hepatitis or its response to

treatment. In patients who come to transplantation for viral hepatitis there may be more than one potentially recurrent disease to consider. Some of the additional diagnoses, often drug reactions, were made because there was ‘too much’ fibrosis and inflammation when compared with viral load or the pattern of inflammation was not typical of viral hepatitis. These are rather subtle distinctions the pathologist is able to make with experience and good clinicopathological correlation.

Steatosis is the most frequently cited ‘additional finding’ in hepatitis C. In a meta-analysis steatosis was shown to be significantly and independently associated with fibrosis.<sup>13</sup> The chances of seeing steatosis increase as fibrosis progresses in all genotypes but fall sharply at the point of decompensated cirrhosis. Steatosis can be seen as a direct cytopathic effect of hepatitis C, best characterised in genotype 3. The virus uses the hepatocellular mechanisms for exporting lipids to export virions and in so doing causes steatosis.<sup>14</sup> Hepatitis C also causes insulin resistance. Non-viral causes of steatosis are the metabolic syndrome and alcohol. Concurrent treatment of obesity and diabetes are advocated in hepatitis C and avoidance of alcohol is also strongly advised as it accelerates fibrosis progression.

In the histological assessment of the spectrum of fatty liver disease, pathologists define ‘steatohepatitis’ as a potentially progressive lesion. The distinction between simple steatosis and steatohepatitis is good practice. Steatohepatitis can ensue when steatosis is induced either by HCV (genotype 3) or the metabolic syndrome and is associated with higher stages of fibrosis than steatosis alone.<sup>15</sup> In univariate analysis the presence of steatohepatitis, but not steatosis, impacts on the likelihood of achieving a SVR on treatment.<sup>16</sup> (Figure 2).

Significant hepatocellular, as opposed to predominantly macrophage, iron deposition in a biopsy from a patient with hepatitis C should prompt genetic testing for coexistent genetic haemochromatosis by means of HFE genotyping. Iron deposition should always be reported, and a semi quantitative assessment of its severity given, as iron deposition has been shown to be associated with poor outcomes irrespective of HFE genotype.<sup>17</sup>

## Hepatitis B

**Context and indications for liver biopsy:** hepatitis B (HBV) infection affects even more people worldwide than hepatitis C, with over 240 million people infected and therefore at risk of developing cirrhosis and hepatocellular carcinoma. Vaccination programmes and migration are changing the profiles of disease, declining in traditionally endemic areas and increasing in some countries in Europe. The natural history of hepatitis B is a dynamic process reflecting the host immune response to HBV replication progressing, not necessarily in sequence, through several phases summarised in Figure 3. The phases are now defined by e antigen status and whether there is deemed to be ‘infection’ or ‘hepatitis’. It is important for the pathologist to recognise the phases in which histological evidence of inflammation, with or without fibrosis, are expected.<sup>18</sup>

In an era of declining liver biopsy numbers the proportion taken in the setting of hepatitis B is increasing.<sup>2</sup> EASL (European Society for the Study of the Liver) guidelines for the management of Hepatitis B<sup>18</sup> state biopsy or a non-invasive test is recommended when the results of other investigations are inconclusive. Discovery of at least moderate inflammatory activity and/or

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