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 3% affecting 130—210 million individuals. 80% of infections progress to a chronic state. Of these, 10—20% will develop complications, including cirrhosis, within 2—3 decades, 1—5% will develop hepatocellular carcinoma. This is a huge burden.[1] 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 both of these decisions. Numbers of biopsies taken from hepatitis C (HCV) positive patients have varied over the years, influenced largely by the requirement for biopsy in national treatment guidelines. Lipp et al. over a 15-year period, saw a peak in 2003 followed by a steady decline.[2] 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'[1]. 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 (recently helpfully reviewed in the context of viral hepatitis by Castera[3]). 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 other factors than fibrosis. As the capsule does not stretch oedema and congestion will also cause an increase in stiffness. Whilst these methods are unlikely to completely replace biopsy, their use, particularly in combination, may increase selectivity for biopsy. Decisional algorithms are being proposed for combinations of modalities and points at which biopsy might be requested.[4] 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. Sebastiani asks if biopsy is a 'gold' or 'silver' standard and helpfully summarizes its limitations.[4] 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,[5] 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 2 points on a numerical scoring scale) in fewer than 3% of the study population.[6] 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.[7] 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: assuming that at least some biopsies from HCV positive patients cross the desks of pathologists, how are they best assessed? 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). Semi quantitative

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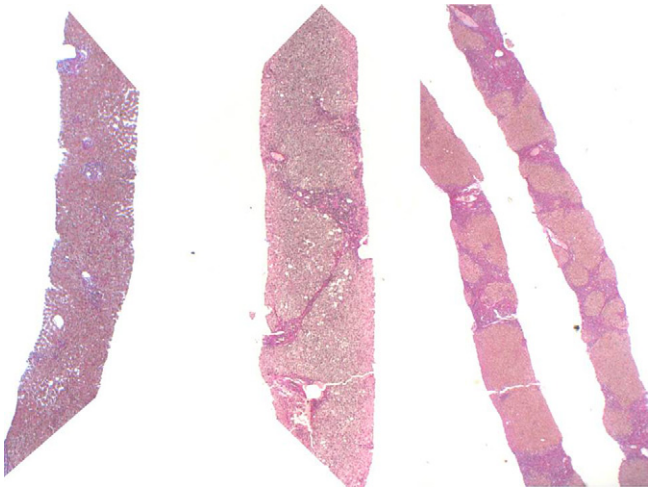

Figure 1 Biopsies from 3 different patients with hepatitis C stained with Van Gieson for assessment of fibrosis. On the left with a near normal architecture (×40), centrally with a portal—portal fibrous bridge — moderate fibrosis (×40), and on the right the nodular architecture of cirrhosis (×20). As an adjunct to the report these appearances might be given a numerical stage.

descriptors are used for these and comparisons should be made with previous biopsies. Numerical scoring systems are a frequent adjunct to the pathology report. A checklist for biopsy reports and discussion of different scoring systems is helpfully given by Guido et al.[8]

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.[9] 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 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.[10] 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.[11] 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.[12] 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.[13] 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.[14] 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 characterized in genotype 3. The virus uses the hepatocellular mechanisms for exporting lipids to export virions and in so doing causes steatosis.[15] Hepatitis C also causes insulin resistance. Non viral causes of steatosis are the metabolic syndrome and alcohol. Concurrent treatment of obesity and diabetes are often 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[16] In univariate analysis the presence of steatohepatitis, but not steatosis, impacts on the likelihood of achieving an SVR on treatment[17] (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.[18]

Hepatitis B

Context and indications for liver biopsy: hepatitis B (HBV) infection affects even more people worldwide than hepatitis C, with over 350 million people infected. 600,000 deaths per annum can be attributed to the development of cirrhosis and hepatocellular carcinoma. Many of those affected are unaware of their