

A PRACTICAL APPROACH TO THE LIVER BIOPSY

AILEEN WEE, MBBS, MRCPATH, FRCPA

Department of Pathology, National University Hospital, National University of Singapore, Singapore.

Summary

A stepwise practical approach to the histological interpretation of liver biopsy specimens is presented. To avoid bias, liver biopsies are analysed blind initially to arrive at a morphologic diagnosis. The possible differential diagnoses are then considered in order of likelihood. The final diagnosis is made only after clinicopathologic correlation; the importance and necessity of discussion with the referring clinician cannot be overemphasized. Common morphologic categories are given as guide-lines. Helpful histopathologic features for the various differential diagnoses including diagnostic problems and pitfalls are highlighted.

Keywords: Cholestasis, cirrhosis, fibrosis, granulomas, hepatitis, necrosis, steatosis

INTRODUCTION

The histopathologic interpretation of liver biopsies should be a systematic process whereby the biopsy is first examined under low magnification for an appraisal of the adequacy of the specimen and overall appearance in order to get a general idea of what the problem might be or where it might be principally located.

Serial 4 µm thick paraffin-embedded histologic sections stained with haematoxylin and eosin and a connective tissue stain usually suffice. Periodic acid-Schiff (PAS) reaction before and after diastase digestion, Perls' Prussian Blue reaction for iron, other special stains and immunohistochemical techniques are performed whenever indicated.

The most useful general textbook of liver pathology is by R.N.M. MacSween, P.P. Anthony and P.J. Scheuer entitled *Pathology of the Liver.* For a concise illustrated text, *Liver Biopsy Interpretation* by E.I. Scheuer is recommended.¹ The best illustrations can be found in the *Atlas of Liver Biopsies* by H. Poulsen and P. Christoffersen.² For terminology and nomenclature used in this article refer to the coding manual *Liver Biopsy Diagnoses and Reports* by J. Ludwig.⁴

DIAGNOSTIC APPROACH

An initial blind approach to avoid bias followed by a stepwise method of reporting is recommended. Firstly, a general morphologic

diagnosis is made. The next step is to consider all the possible differential diagnoses in order of likelihood. The final diagnosis is based on clinicopathologic correlation - the importance and necessity of discussion with the referring clinician cannot be overemphasized as the final diagnosis has significant prognostic and therapeutic implications.

A morphologic diagnosis is non-specific. Unless this initial diagnosis is inaccurate, there should be no necessity to change it; only to fine-tune it as additional information is made available with the passage of time. In many instances, the pathologist may not be able to take the case further either due to lack of clinical work-up or because the biopsy was performed very early on in the course of a disease when histopathologic changes are likely to be minimal and non-specific. In such instances, the morphologic diagnosis serves as a useful interim "working diagnosis" for communication purposes.

The common morphologic categories encountered are listed in Table 1. The term 'hepatitis' is used in the broadest sense possible to mean a diffuse inflammatory process in the liver. More than one morphologic diagnosis may apply in some instances. Table 2 gives same useful histologic pointers towards the making of the final diagnosis. The details will be discussed briefly under the relevant sections.

(I) LOBULAR HEPATITIS GROUP (Table 3)

Classically, the liver shows lobular disarray, ballooning and acidophilic degeneration (apoptosis) of hepatocytes, spotty necrosis, diffuse lymphoplasmacellular infiltrate, central phlebitis and Kupffer cell proliferation (Fig. P), Haemmerin-laden Kupffer cells and PAS-positive diastase-resistant ceroid pigment in portal tract macrophages and Kupffer cells may be present. Bridging hepatic necrosis and confluent (multilobular, massive or submassive) necrosis may be seen in severe cases. The possible clinical diagnoses are discussed below in order of likelihood.

Acute viral hepatitis (AVH): This is the clinical prototype of classic lobular hepatitis. However, patients with uncomplicated disease of ≤ 1 month's duration usually do not have their livers biopsied.

Unresolved viral hepatitis: This is a useful holdover diagnosis between the acute (< 1 month) and chronic phases (> 6 months' duration). The hepatic picture tends to be less pronounced than in AVH.

Chronic lobular hepatitis (CLH): Milder but appreciable lobular inflammation may be encountered in chronic viral hepatitis. The tendency is for the disease to be self-limiting, representing a prolonged case of unresolved hepatitis.

Chronic active hepatitis (CAH) with "viral features": Patients whose livers show CAH (see "PERIPORTAL HEPATITIS GROUP") may have, in addition, "viral features" (lobular hepatitis). A previous histological

**TABLE 1
LIVER BIOPSY INTERPRETATION -
COMMON MORPHOLOGIC
CATEGORIES**

Morphologic Diagnosis*
Lobular hepatitis
Portal hepatitis
Periportal hepatitis
Cholestatic hepatitis
Pure cholestasis
Steatosis; steatohepatitis
Granulomas; granulomatous hepatitis
Fibrosis
Necrosis
Cirrhosis

* More than one diagnosis may apply in some instances

**TABLE 2
HELPFUL FEATURES IN
DIFFERENTIAL, DIAGNOSES OF
LIVER BIOPSIES**

Abnormal hepatocytes; hepatocellular inclusions
Pigments (except bile)
Abnormal cellular infiltrates
Abnormal bile ducts; loss of bile ducts
Abnormal blood vessels, vascular lesions and haemorrhages

documentation of CAH is necessary before one can confidently differentiate CAH with lobular activity from AVH with periportal involvement. The demonstration of periportal fibrosis suggests chronicity. CAH with "viral features" can have several explanations: (i) spontaneous reactivation or seroconversion in hepatitis B carriers;⁸ (ii) concomitant infection by more than one virus, e.g. a hepatitis B carrier with acute hepatitis A infection or superinfection by hepatitis D; (iii) chronic non-A, non-B infection which is frequently punctuated by relapses making histological separation of the acute and chronic forms difficult.

Drug-induced hepatitis (of the unpredictable type): The histological findings can mimic other conditions. An appropriate history, exclusion of other causes and finding of eosinophils, periportal bile stasis and fatty change are helpful. Some of the drugs¹¹ implicated include isoniazid,¹¹ oxyphenisatin,¹² methyl dopa,¹³ halothane¹⁴ and aspirin.

Non-specific reactive hepatitis: In systemic infections, the liver may show Kupffer cell proliferation, spotty necrosis and varying degrees of portal tract inflammation. The hepatocytes are generally spared.

**TABLE 3
(I) LOBULAR HEPATITIS GROUP**

Differential Diagnoses
Acute viral hepatitis
Unresolved viral hepatitis
Chronic lobular hepatitis
Chronic active hepatitis with "viral features"
Drug induced hepatitis
Miscellaneous disorders
- Non-specific reactive hepatitis
- Surgical "hepatitis"
- Systemic viral infections
- Haematological disorders

Surgical "hepatitis": Intra sinusoidal clusters of neutrophils ("microabscesses") tend to form during abdominal surgery. The hepatocytes are not involved. If a liver biopsy is intended, it is advisable to perform it at the onset of the operation.

Systemic viral infections: Infectious mononucleosis, herpes simplex and cytomegalovirus infections are some examples. In the former, there is pronounced atypical mononuclear cell infiltration in the lobules and portal tracts, far out of proportion to the hepatocytic changes, if any.¹⁶ In fact, the cells may be mistaken for malignant infiltrates. In the other two infections, viral inclusion bodies should be looked for within necrotic foci. The term 'lobular hepatitis' is not very accurate and should be replaced by the aetiological agent.

Haematological disorders. Conditions ranging from reactive states to lympho-/myeloproliferative disorders can give rise to diffuse and/or discrete cellular infiltrates simulating lobular inflammation. Lymphomatous and leukaemic infiltrates are characterized by the monotony and large number of atypical cells in the absence of appreciable parenchymal changes. Difficulties

in interpretation are often encountered here if the specimens are inadequate or of poor quality. Immunotyping methods are available for confirmation. In haemolytic disorders, haemosiderin is likely to be present in the Kupffer cells. A noteworthy point is that patients with haematological disorders may have a superimposed true lobular hepatitis due to concurrent drug-induced or viral hepatitis.

(II) PORTAL HEPATITIS GROUP (Table 4)

This is characterized by dense portal tract inflammation, usually of the chronic type, with no significant parenchymal changes. The limiting plate is intact (Fig. 2).

Non-specific reactive hepatitis: Portal inflammation, usually mild, can be expected in cases of extrahepatic disease, e.g. inflammatory problems in the gastrointestinal tract. The liver function is usually normal.

Unresolved viral hepatitis: Portal inflammation may be the only significant histologic finding in resolving forms of viral hepatitis (≤ 6 months). Hardly any lobular changes are present except perhaps for spotty necrosis, ceroid pigment, haemosiderin and Kupffer cell proliferation.

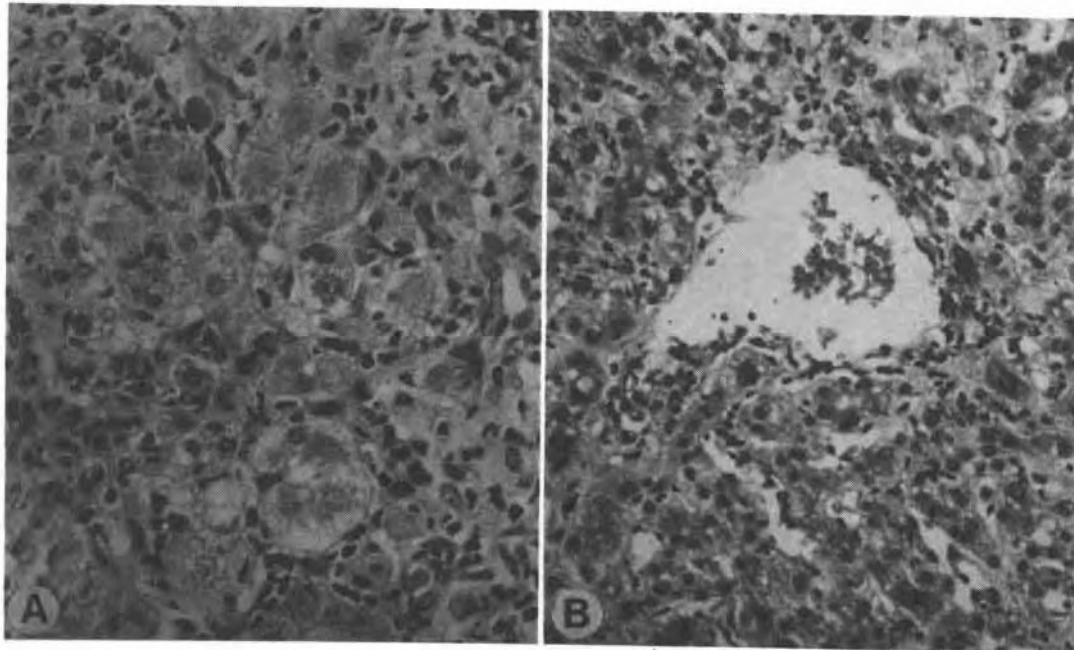


FIG. 1: Classical lobular hepatitis due to acute viral hepatitis, (A) Note the lobular disarray, ballooning of hepatocytes, spotty necrosis, an acidophilic body (arrow) and diffuse lymphoplasmacellular infiltration. (B) Perivenular infiltration of central vein by inflammatory cells (central phlebitis). Haematoxylin & eosin, (A) x 250, (B) x 200.

Chronic persistent hepatitis (CPH): This is the clinical prototype of classic portal hepatitis. The portal **Inflammatory** infiltrates tend to be denser than in non-specific reactive hepatitis. In hepatitis B virus carriers, ground-glass hepatocytes and immunohistochemical demonstration of hepatocytic HBsAg and HBcAg confirm the infection!

Chronic active hepatitis in remission: This diagnosis requires biopsy evidence of previous classic CAH (see "PERIPORTAL HEPATITIS GROUP") because it is histologically indistinguishable from CPH.

Syndrome of primary biliary cirrhosis (PBC), stage I A non-specific-looking portal hepatitis is the usual finding. The so-called "florid duct lesions" characterized by granulomatous destruction of interlobular bile ducts (granulomatous cholangitis) tend to involve scattered portal tracts and are often absent in the early stages; this is made worse by sampling problems inherent in small-sized specimens. There is also difficulty in demonstrating stainable copper (Rhodanine

stain) and copper-protein deposits (Shikata orcein stain) in periportal hepatocytes.* Atomic absorption spectrophotometry is the method of choice for the chemical analysis and quantitation of copper in liver tissue, fresh or paraffin-embedded.*

TABLE 4

(II) PORTAL HEPATITIS GROUP

Differential Diagnoses
Non-specific reactive hepatitis
Unresolved viral hepatitis
Chronic persistent hepatitis
Chronic active hepatitis in remission
Syndrome of primary biliary cirrhosis, stage I
Incomplete extrahepatic obstruction
Chronic hepatitis, stage I, associated with primary sclerosing cholangitis
Miscellaneous disorders
- Drug-induced hepatitis
- Haematological disorders

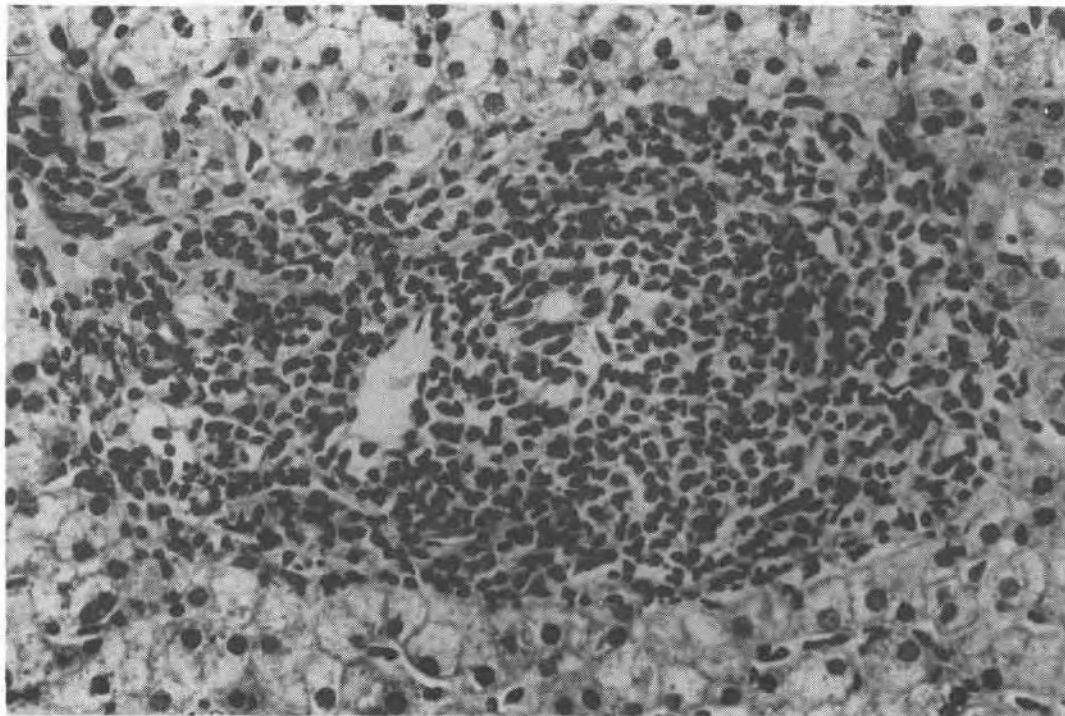


FIG. 2: Classical portal hepatitis due to chronic persistent viral hepatitis, type B. The portal tract is enlarged and inflamed. The limiting plate is intact. Haematoxylin & eosin, x 300.

Incomplete extrahepatic obstruction: The portal tract changes may be minimal, consisting only of stromal oedema, increase in the number of interlobular bile ducts and a mixed inflammatory cellular infiltrate. Cholestasis may be lacking. A point to note is that clinically obvious cases of large duct obstruction are usually not indications for liver biopsies. Hence, the clinical diagnosis would often be unintentionally misleading.

Chronic hepatitis, stage 1, associated with primary sclerosing cholangitis (PSC): Intrahepatic and/or extrahepatic bile ducts are affected. Some patients have inflammatory bowel disease - chronic ulcerative colitis in particular.²⁰ The classic feature is destructive fibrous cholangitis with obliteration of the interlobular bile ducts to form nodular scars. There is also periportal hepatocytic copper retention. However, in early PSC, the same remarks about PBC, stage 1, apply.^{21,22}

Drug-induced hepatitis: The features are variable and non-specific. Eosinophils, when present, are useful.

Haematological disorders: Leukaemic and lymphomatous infiltrates in the portal tracts may simulate portal hepatitis. However, inflammatory infiltrates are characteristically composed of mixed cell populations.

(III) PERIPORTAL HEPATITIS GROUP (Table 5)

This is characterized by portal and periportal inflammation, usually of the chronic type, accompanied by piecemeal necrosis and fibrosis. The piecemeal necrosis at the limiting plate region may be lymphocytic, biliary or fibrosing depending on the condition (Fig. 3). Classically, there is no appreciable centrilobular or midzonal involvement. Periportal hepatitis generally represents a more advanced stage of portal hepatitis.

Non-specific reactive hepatitis: The inflammatory cells in the portal tracts may spill over into the lobules but there is no significant piecemeal necrosis.

Unresolved viral hepatitis: Periportal inflammation and a minor lobular component may be encountered during the course of this condition.

Chronic active hepatitis: This is the clinical prototype of classic periportal hepatitis. The aetiology could be viral, autoimmune or undetermined. The portal infiltrates tend to be denser than in the above two conditions. Lymphocytic piecemeal necrosis is almost always present. In severe cases, bridging hepatic necrosis accompanied by septal fibrosis may be seen.

Syndrome of primary biliary cirrhosis, stage 2: There is a greater chance of finding granulomatous cholangitis and loss of interlobular bile ducts. Copper stains are also more likely to be positive. On the other hand, if the only significant finding is periportal inflammation with paucity of ductal abnormalities, differentiation from CAH may be difficult.²³

Drug-induced hepatitis: Drugs like oxyphenisatin,¹² methyldopa,¹³ halothane¹⁴ and aspirin¹⁵ can cause liver damage mimicking CAH. The hepatic process should resolve following withdrawal of the offending agent.

Incomplete extrahepatic obstruction: Refer to "PORTAL HEPATITIS GROUP".

Chronic hepatitis, stage 2, associated with PSC: The liver biopsies of such patients may be indistinguishable from patients with long-standing mild extrahepatic obstruction.

Classically, however, the former shows destructive fibrous cholangitis and loss of interlobular bile ducts as opposed to increase

TABLE 5

(III) PERIPORTAL HEPATITIS GROUP

Differential Diagnoses

Non-specific reactive hepatitis

Unresolved viral hepatitis

Chronic active hepatitis

Syndrome of primary biliary cirrhosis, stage 2

Drug-induced hepatitis

Incomplete extrahepatic obstruction

Chronic hepatitis, stage 2, associated with primary sclerosing cholangitis

Acute viral hepatitis

Wilson's disease

Miscellaneous disorders

- Acute viral hepatitis in drug addicts

- Haematological disorders

