Liver Biopsy in the Assessment of Medical Liver Disease

Tuesday 30 September 2014

Held at

The Royal College of Pathologists
2 Carlton House Terrace
London
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Liver Biopsy in the Assessment of Medical Liver Disease

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5 CPD Credits

This course will provide a practical diagnostic approach to reporting medical liver biopsies, focusing on the importance of clinico-pathological correlation in assessing common patterns of liver damage. Recommended for senior trainees in Pathology and Hepatology and consultant histopathologists and gastroenterologists who are regularly involved in liver biopsy assessment (without necessarily working in a Liver Unit).

09.20 Registration and Coffee

09.50 Welcome and Introduction – Professor Stefan Hübscher, Birmingham

Clinical Indications and General Approaches to Liver Biopsy Interpretation

10.00 Patterns of abnormal LFTs and their differential diagnosis – Professor Matthew Cramp, Plymouth

10.25 Indications for liver biopsy in investigating common medical liver diseases – what information is required from a liver biopsy report? – Dr Steve Ryder, Nottingham

10.50 Coffee

11.20 How to handle liver biopsy specimens – specimen fixation, processing and staining methods Dr Alberto Quaglia, Kings College Hospital, London

11.45 Basic patterns of liver damage – what information can a liver biopsy provide and what clinical information does the pathologist need? – Professor Rob Goldin, Imperial College, London

12.10 Lunch

Clinico-Pathological Assessment of Common Medical Liver Diseases

13.10 Fatty liver disease – Dr Judy Wyatt & Dr Mervyn Davies, Leeds

13.55 Chronic biliary disease – Dr Sue Davies & Dr Graeme Alexander, Cambridge

14.40 Tea

15.10 Chronic hepatitis – viral and autoimmune – Dr Chris Bellamy & Dr Andrew Bathgate, Edinburgh

15.55 Acute hepatitis, including acute liver failure – Professor Stefan Hübscher & Dr Ahmed Elsharkawy, Birmingham

16.40 Panel Discussion, Questions and Answers. Concluding remarks and close
Abstracts and References

Patterns of abnormal LFTs and their differential diagnosis
Professor Matthew Cramp, Plymouth

- Distinguish liver function from liver function tests
- Interpret patterns of liver enzyme abnormality
- Understand the cellular and sub-cellular sources of various liver enzymes
- Understand the major causes of abnormal liver function
- Assessment of liver disease severity
- Form a differential diagnosis on the basis of LFTs and limited history

‘Liver function tests’ (LFT’s) refers to the quantitative measure of bilirubin, albumin and various liver enzyme levels in the blood. The enzymes measured are present normally, but raised levels serve as an indicator of liver damage and the degree of abnormality gives some measure of its severity. The pattern of liver enzyme elevation gives an indication of the type of liver injury, with raised hepatocellular enzymes (AST / ALT) indicating a hepatitic process and raised biliary enzymes (alkaline phosphatase and GGT) suggesting biliary pathology. A straightforward array of blood tests can be used to diagnose the major common causes of liver disease. Assessment of liver synthetic function using albumin and pro-thrombin time can be used to measure severity of liver damage or as an indicator of liver recovery. An understanding of how to interpret LFTs, full blood count and clotting results can allow a differential diagnosis to be established even with the limited history present on many histological request forms.

Indications for liver biopsy in investigating common medical liver diseases – what information is required from a liver biopsy report?
Dr Steve Ryder, Nottingham

Learning points
- The commonest cause of death from liver disease in the UK is alcohol and this is a co-factor in many other causes of liver disease
- Staging of liver fibrosis in diseases such as hepatitis C is less frequent now that therapy is more effective and other methods which are non-invasive exist.
- Staging of liver biopsy is critically dependent of the size of the biopsy and inadequate size is a key factor in any liver biopsy report for this indication.
- Assessment of alcoholic liver disease is primarily to establish the presence or absence of alcoholic hepatitis and to confirm stage and exclude other causes of liver injury. The presence of peri-cellular fibrosis is clinically important.
- The commonest diagnosis made on liver biopsy for abnormal liver enzymes is non-alcoholic fatty liver disease. In this disorder the differentiation between simple steatosis and NASH is important clinically.

Liver biopsy remains a valuable diagnostic test for clinicians treating parenchymal liver disorders. It use and value depend on the clinical context. There are 2 broad areas where liver biopsy is used
currently, staging diseases where the diagnosis has already been established by other means (serology or history) and for investigation of situations where a hepatological diagnosis is uncertain, most commonly abnormal liver enzyme levels. There is a further subset where more than one pathology may be present and biopsy may be helpful in pointing to the major cause of liver injury, in this context it is important to note that alcohol is a co-factor in liver injury from many other causes such as HCV. When considering staging of liver disease there are now alternative methods of assessing hepatic fibrosis such as fibroscan.

How to handle liver biopsy specimens – specimen fixation, processing and staining methods
Dr Alberto Quaglia, Kings College Hospital, London

Learning points

- Optimal handling, processing and tissue-sparing sectioning are essential to avoid loss of information from needle core biopsy specimens
- Paired-mounted sections on 8 slides with H&E on slides 1 and 8 and special stains (reticulin, Perls’, orcein and dPAS) in-between are ideal leaving plenty of tissue in the paraffin block.
- Needle samples of focal lesions are best evaluated on H&E first, holding as much tissue for immunohistochemistry which should be highly selective and guided by histology appearances and clinical information.
- Freezing tissue for enzymatic study and molecular techniques are generally the remit of specialized centres; the type of material required should be planned before the biopsy is undertaken
- TEM is demanding and only rarely provides additional features of diagnostic value.

Percutaneous needle biopsy of the liver is an invasive procedure associated with significant morbidity and an exceedingly low but existent risk of mortality. It is therefore mandatory to secure that the best information is obtained from these tiny specimens, an estimated 1/50 000th of the whole liver, probably less since US guided biopsy performed by radiologists have produced thinner and often shorter and fragmented tissue cores.

A correct handling, high quality processing, tissue-sparing sectioning and a judicious selection of staining methods are therefore essential. The number of sections and stains routinely cut and applied vary from one laboratory to another and this account reflects experience in our laboratory rather than a policy extracted from the literature.

Immediate immersion of the specimen in 10% buffered formalin or formal saline is sufficient for most purposes. The specimen is left floating in the fixative, avoiding blotting paper. Rough packing in foam sponge leading to artefactual tears in the sections can be prevented using small bore cassettes.

In our laboratory 20 consecutive sections are cut from the block and pair mounted on 10 slides which are sequentially numbered, levels 1 and 10 are stained with H&E, 2 and 3 are held unstained and 4 to 9 are stained with the Gordon-Sweets’ silver method for reticulin, Perls’ for iron, modified Shikata’s orcein and PAS after diastase digestion.

Other laboratories use van Gieson / Sirius red or other trichrome methods such MSB for collagen, the former having a tendency to underestimate fibrosis as they mostly stain type I collagen, the
latter on the contrary somewhat enhancing fibrosis as they do stain matrix proteins. Routinely we prefer the untoned silver method for reticulin without counterstaining which detects subtle distortion of the black reticulin meshwork while staining gold-brown the collagenous fibrosis. Perls’ is the method used for the detection of blue haemosiderin granules within hepatocytes or macrophages. A thin blue blush is said to represent ferritin iron, but may at times be artefactual. We attached a great importance to routine orcein stain, not so much for the demonstration of hepatitis B which is of low sensitivity, but mainly for the demonstration of copper-associated protein, the best marker of early cholangiopathies. Rhodanine may be used for the confirmation of copper, but it must be remembered that the metal can be lost during fixation. PAS is not performed routinely; besides demonstrating the extent of liver cell loss or entrapped hepatocytes in fibrous tissue it does not add significant information and happens to give negative result in glycogen storage disorders due to the high glycogen solubility. PAS after diastase digestion is used routinely for the detection of α1-antitrypsin globules, scavenger macrophages and bile duct basement membranes.

US guided biopsy specimens taken for assessment of a focal lesion are best evaluated first on H&E sections, spare sections on poly-L-lysine coated slides being held for potential immunohistochemistry. Due to the scarcity of the tissue a more judicious selection is recommended based on histological appearances and clinical guidance. An immunohistochemical panel including Serum Amyloid A or C-reactive protein, glutamine synthetase, beta-catenin, and fatty acid binding protein is now used to classify hepatocellular adenoma, and the combination of glutamine synthetase, heat-shock protein 70 and glypican-3 are considered to be of help in differentiating between hepatocellular carcinoma and dysplastic nodules. Specific antibodies are available to assess pathogens. Immunostaining for HBs antigen is not required routinely; Hbc antigen and delta may add limited information to that obtained serologically, while CMV, adeno virus and herpes group antibodies may be of diagnostic value in the immunocompromized host. Antibodies against canalicular enzymes such as bile salt export protein (BSEP), multidrug resistant protein 3 (MDR3), have proved to be important in the diagnosis of familial cholestatic disorders in children. Structural antigens such as K7/19 (or pooled antibody AE1/AE3) may be used to assess bile duct loss, ductular reaction and aberrant hepatocyte expression in various liver disorders.

Other techniques must be planned before the biopsy is undertaken. For several molecular techniques, the liver sample needs to be snap-frozen into liquid nitrogen and stored at −80°C until use. Tissue can be embedded in optimal cutting temperature (OCT) compound before freezing, which generally does not interfere with the enzymatic studies required when diagnosis cannot be achieved on blood or urine; small samples of 1 mm³ fixed in ice-cold 3% glutaraldehyde for TEM may be useful in some metabolic disorders, although the technique is generally too demanding for the diagnostic yield; a 5mm length of fresh tissue on wet blotting paper for copper estimation is mandatory when Wilson disease is suspected as staining can be negative in the early stage of the disease. Molecular techniques, such as ‘in situ’ hybridization enabling direct visual recognition of nucleic acid modifications (DNA or RNA) or other ‘ex situ’ techniques requiring preliminary extraction of target molecules followed by molecular biology work-up on the extracted material are generally performed in specialized centres require freshly frozen tissue (see for review ref 4).

References
Basic patterns of liver damage – what information can a liver biopsy provide and what clinical information does the pathologist need?

Professor Rob Goldin, Imperial College London

Learning points

1. You should be able to systematically describe the changes seen in a liver biopsy (including stating the relevant negative findings).
2. You should try and say what the pathological process going on in the biopsy is (e.g. a chronic hepatitis); only sometimes will you be able to make a specific aetiological diagnosis (e.g. hepatitis B).
3. You need to be on the lookout for second diagnoses.
4. You should not issue a final report without having adequate clinical information.
5. Your conclusion should be a synthesis of your observations and the clinical information provided.
6. You should not be shy to suggest further investigations to the clinicians.

Reporting liver biopsies is a clinico-pathological exercise. You should systematically describe the biopsy (adequacy, architecture, bile ducts, inflammation, fatty change, presence of iron etc.) You should try and say what the pathological process is: a cholestatic hepatitis, a chronic hepatitis, fatty change, fatty liver hepatitis, bile duct loss, granulomatous hepatitis, iron overload etc. There may be clues as the cause of this process such as ground glass cells (HBV), lymphoid aggregates, bile duct and fatty change (HCV) plasma cells (autoimmune hepatitis), in a chronic hepatitis. Always be on the lookout for a secondary diagnosis; the commonest are fatty change, a drug reaction and stainable iron. Your conclusion should be based on what you have seen and what you have been told. If necessary suggest additional investigations e.g. exclusion of drug induced liver damage or underlying biliary tract disease.

References


**Fatty liver disease**
Dr Judy Wyatt & Dr Mervyn Davies, Leeds

**Learning points**
- Fatty liver disease includes the morphological spectrum of steatosis, steatohepatitis and cirrhosis, and is classified by aetiology as alcoholic or non-alcoholic. NAFLD is commonly associated with the metabolic syndrome/insulin resistance, but may also be caused by drugs, virus (hepatitis C) or inborn errors of metabolism.
- Biopsy is used for diagnosis: steatosis v. steatohepatitis, to assess fibrosis stage, and exclude other liver disease
- Histological features necessary for diagnosing steatohepatitis – fat, inflammation and hepatocyte ballooning, often with Mallory bodies and pericellular fibrosis
- Steatosis is common; suspect another disease if there is more than mild portal inflammation, or there are features not present in steatohepatitis
- Steatosis disappears in late stage disease, and cirrhosis may look cryptogenic

Hepatocytes metabolise fat but do not normally store it. Fatty change is very common in liver biopsies, and only considered significant when seen in >5% hepatocytes. Pathological accumulation of fat occurs as a result of:
- Metabolic causes – commonly associated with insulin resistance (metabolic syndrome, acquired) and rarely inborn errors (e.g. Wilson’s disease, glycogen storage disease, etc. mainly in children with steatosis)
- Toxic causes – alcohol and drugs
- Infective causes – hepatitis C

Diagnostic criteria and clinical indications for biopsy in patients with suspected fatty liver disease are rapidly evolving - see ref 1 for up to date review.

The questions posed to the histopathologist reporting a liver biopsy with fatty change are:
1. Is this steatosis or steatohepatitis? Alcoholic or non-alcoholic?
2. Could there be another disease instead/as well?
3. How severe is it?

Complete diagnosis including aetiology requires information from the requesting clinician, including history of alcohol consumption, obesity/type 2 diabetes, drugs, hepatitis C status, lipid profile and also clinical evidence of other liver disease to be considered during biopsy interpretation.

1. Is this steatosis or steatohepatitis?
The diagnosis of steatohepatitis depends on seeing macrovesicular steatosis plus specific features of metabolic injury to hepatocytes (ballooning often with Mallory bodies (seen well with CK8/18 or ubiquitin immunohistochemistry2)) together with the non-specific features of inflammation and fibrosis. The lobular inflammation may be very mild. Fibrosis is usually pericellular and seen on stains for mature collagen (van Gieson, sirius red). Portal inflammation and fibrosis may or may not
be present. Just fatty change with chronic inflammation (for example as lipogranulomas or in hepatitis C) but no hepatocyte ballooning should not be diagnosed as steatohepatitis. Non-alcoholic fatty liver disease (NAFLD) is a blanket term that includes steatosis, steatohepatitis (NASH) and cirrhosis in patients with no alcohol history.

Macrovesicular steatosis includes large (single, displaces nucleus) and small (may be multiple, no nuclear displacement) droplet fatty change. True microvesicular steatosis is difficult to appreciate on H&E, may be focally present in either ASH or NASH, while diffusely is a very rare cause of acute liver failure (e.g. acute fatty liver of pregnancy, Reye's syndrome).

In general the histopathologist cannot distinguish among causes of fatty liver disease, and they may be multiple and synergistic (alcohol, obesity, drugs). Glycogenated nuclei are much more common in metabolic syndrome than alcoholic disease. Severe sinusoidal fibrosis, loss of perivenular hepatocytes and numerous Mallory bodies (=central sclerosing hyaline necrosis) is the severe end of alcoholic steatohepatitis, not seen in NASH; steatosis may be absent in this pattern of injury.

Drugs causing fatty liver disease: see ref 3. Includes Tamoxifen, Methotrexate (steatohepatitis), 5FU, and occasionally common medications NSAIDs, antihypertensives (steatosis).

2. Could there be another disease instead/as well?

Other abnormalities in the non-invasive liver screen may prompt biopsy in patients with a clinical diagnosis of fatty liver disease. Alternatively histological findings may prompt consideration of another diagnosis.

Histological differential diagnosis arises when:
  a. the portal tract inflammation and/or fibrosis seem disproportionately severe,
  b. When there are histological features not normally seen in steatohepatitis.
  c. In late stage disease/cirrhosis when steatosis may be absent

a. In steatohepatitis, the portal tract inflammation varies and can occasionally be moderate/marked. When there is more than mild portal inflammation, the clinician should investigate for an additional cause of chronic hepatitis (hepatitis B or C, autoantibodies, drugs, biliary disease).

In particular, steatosis is common in patients with hepatitis C, either as a direct effect of the virus (genotype 3) or as enhanced metabolic syndrome (other genotypes). In non-type 3 HCV it is associated with disease progression and a poorer response to treatment.

b. The following features are not normally seen in fatty liver disease, so consider other diagnoses:

lobular disarray, acute cholestasis (bile plugs), chronic cholestasis (copper associated protein), significant iron, evidence of alpha 1 antitrypsin deficiency, significant eosinophils, granulomas, plasma cells, portal lymphoid aggregates.
When there is clinical evidence of a second liver disease e.g. cholestatic liver function tests or autoantibodies, in a patient with obesity/alcohol history, biopsy can indicate the dominant pathology.

c. As cirrhosis becomes established, the steatosis tends to disappear while portal inflammation may be prominent. Ductular reaction (believed to represent peri-portal stem cell recruitment) develops in late stage steatohepatitis/cirrhosis (especially alcoholic), and may mimic biliary disease. Look out for any residual ballooning or Mallory bodies, which tend to persist longer than steatosis.

3. How severe is it?

The report should include the fibrosis stage and an assessment of current disease activity. There are criteria for staging/grading steatohepatitis. Features of steatohepatitis can be patchy in fatty livers, and sampling variation exceeds observer variation.

- Fibrosis staging (Kleiner) is 1: perisinuoidal (stage 1a or 1b depending on extent) or periportal (stage 1c), 2: perisinusoidal and periportal, 3: bridging fibrosis, 4: cirrhosis.
- Grading depends on amount of steatosis, inflammation and ballooning, but is not necessary in routine practice; description of severity is sufficient. A recent SAF score separates steatosis from other graded factors.
- Scoring systems developed for chronic hepatitis (e.g. Ishak) should not be used for patients with fatty liver disease.

References
5. Bedossa P. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity and fibrosis (SAF) score in the evaluation of biopsies of non-alcoholic fatty liver disease. Hepatology 2014:60;565-575.

Chronic biliary disease
Dr Sue Davies & Dr Graeme Alexander, Cambridge

Learning points
- Chronic biliary tract disease causes problems for histopathologists.
- The pattern of LFTs and standard serology testing in a typical patient can strongly suggest the correct diagnosis.
• The role of biopsy is limited for typical cases of primary biliary cirrhosis and primary sclerosing cholangitis; staging has not been satisfactory or considered prognostically important.
• Biopsy is indicated in PBC without typical serology or with disproportionately raised ALT or immunoglobulins.
• Biopsy in PSC may be helpful in small duct disease
• IgG4 related disease can involve the liver as well as the pancreateo-biliary tract; there may be some overlap with PSC.
• Drug related bile duct injury may be prolonged and even fatal, despite withdrawal of drug.
• Staging of chronic biliary disease may be helped by assessment of the degree of cholate stasis and extent of ductopenia, in addition to fibrosis.

Symptoms of cholestatic liver disease, including pruritus, cholangitis and occasionally jaundice, require a detailed history of previous surgery, drugs, associated medical disorders and family history. Biochemical confirmation should prompt ultrasound and a detailed immunological profile. The autoimmune disorders of primary biliary cirrhosis and primary sclerosing cholangitis can then often be diagnosed but in some, clinical aspects are missing or there may be more than one condition. Further radiological investigations and liver biopsy make valuable contributions to an accurate diagnosis and to guide therapy.

Biliary injury can be subtle on liver biopsy and additional histochemical demonstration of copper associated protein is important, along with identification of biliary type piecemeal necrosis. Genuine overlap with autoimmune hepatitis is rare and requires good clinical and pathological correlation.

We present a few cases to show the importance of the dialogue between clinician and pathologist in the assessment of biliary disease.

References
5. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. Carbone M for UKPBC Consortium. Gastroenterology 2013; 144: 560-569
Chronic hepatitis – viral and autoimmune
Dr Chris Bellamy and Dr Andrew Bathgate, Edinburgh

Learning points

- Liver biopsy in patients with chronic hepatitis can help both differential diagnosis and management
- An understanding of the background, clinical questions and management decisions awaiting the biopsy interpretation is essential to maximise the value of this investigation
- Liver biopsy identifies the principal pathologic process, its severity and chronicity, but must be correlated with the biochemical, immunologic and clinical findings for definitive diagnosis.
- Discriminating recent onset, acute-on-chronic and chronic disease may be problematic
- Atypical histologic patterns or clinical settings may on the one hand distract from the correct diagnosis, or on the other hand raise appropriate suspicion for a different or second diagnosis that requires further clinical correlation
- Assessment of a small biopsy with chronic hepatitis is particularly prone to sampling error

“Chronic hepatitis” in a biopsy refers to a pattern of changes characterised by evidence of hepatocellular injury and regeneration, inflammatory cell infiltration, and architectural disorder related to fibrosis. Despite quite marked histological changes, liver function tests and other clinical metrics of disease severity can show little or no abnormality in some patients.

In chronic viral hepatitis, the purpose of the biopsy is to guide management of the usually already diagnosed viral disease, rather than provide primary diagnostic information, and exclude occasional co-morbidities such as steatohepatitis. In autoimmune hepatitis, the biopsy plays a stronger supportive role in establishing diagnosis, in addition to answering clinical questions about the degree of already accumulated chronic damage (fibrosis).

In clinical practice it is not uncommon to find low levels of autoantibodies with slightly abnormal transaminases. As autoimmune hepatitis is treatable with immunosuppression it is an important diagnosis to make. The diagnosis of cirrhosis in all liver diseases is important as patients will require surveillance for both oesophageal varices and hepatocellular carcinoma. Treatment for hepatitis B and C has progressed significantly with the former now being more dependent on biopsy for commencement of treatment. Published guidelines usually incorporate hepatitis B DNA levels, ALT and biopsy findings in their recommendations on starting therapy. As non-alcoholic fatty liver disease increases in prevalence the contribution of this entity to liver enzyme abnormalities in other diagnoses will require information only available from a liver biopsy.

References

3. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. J Hepatol 2014; 60:392-420
Role of Liver Biopsy in the Assessment of Acute Hepatitis
Stefan Hübscher, University of Birmingham & Ahmed Elsharkawy, Queen Elizabeth Hospital, Birmingham

Learning Points

- Most cases of acute hepatitis are now diagnosed on the basis of non-invasive investigations.
- In cases where the clinical diagnosis is uncertain, liver biopsy can help to confirm the presence and severity of acute hepatitis and may provide pointers to a likely aetiology.
- Connective tissue stains should be used to distinguish recent post-necrotic collapse from longstanding fibrosis/cirrhosis.
- The presence of bridging necrosis and/or panacinar necrosis indicates severe liver damage, which has implications for prognosis and treatment.
- Liver biopsy may sometimes reveal that acute liver injury is not due to a hepatitic process.

Many of the classical morphological studies of acute hepatitis were carried out before the main causes had been discovered. Most cases of acute hepatitis are now diagnosed on the basis of clinical, biochemical and serological findings and liver biopsy is rarely indicated. Liver biopsy may still be carried out in cases where the clinical presentation is atypical or the cause is uncertain. Faced with a biopsy from a person with suspected acute hepatitis, there are three main questions that should be addressed:

1. **Is this acute or chronic liver damage?**
   - Some patients presenting with signs of acute liver injury have an acute exacerbation of chronic liver disease. Liver biopsy can identify the presence and severity of any underlying chronic liver damage.
   - Areas of recent bridging necrosis or panacinar necrosis can resemble changes seen in cirrhosis. Use of connective tissue stains to demonstrate collagen and elastic fibres helps to distinguish recent post-necrotic collapse from longstanding fibrosis.

2. **How severe is the liver injury?**
   - The presence of bridging necrosis or panacinar necrosis indicates severe liver damage. This has implications for prognosis (e.g. an increased risk of developing acute liver failure and/or progressing to chronic hepatitis) and for treatment (e.g. poor response to immunosuppression in cases of autoimmune hepatitis). However, these lesions are often patchy in distribution and sampling variability therefore limits the utility of liver biopsy in this setting.

3. **Are there any clues to aetiology?**
   - The three main known causes of acute hepatitis are viral agents (mainly hepatitis A, B and E, less commonly hepatitis C), drugs and autoimmune hepatitis (AIH). Liver biopsy is rarely diagnostic in isolation, but may provide pointers to a likely cause if this is not already known. For example a plasma cell rich infiltrate may suggest a diagnosis of AIH, even in a person who is auto-antibody negative, whereas the presence of disproportionately severe necrosis and/or large numbers of eosinophils favours a diagnosis of drug hepatitis, even if the initial drug history is negative.
   - Most biopsies are obtained from patients in whom the common causes of acute hepatitis have already been excluded by other investigations (“seronegative hepatitis”). Liver biopsy rarely provides strong aetiological pointers in this situation, but may nevertheless be useful to confirm the presence and severity of acute hepatitis.
• In a small proportion of cases presenting with clinical features suggestive of severe acute hepatitis, liver biopsy may reveal another unsuspected cause for acute liver failure. Examples include fulminant Wilson’s disease (in which the liver is usually cirrhotic) or neoplastic infiltration of the liver (usually lymphoma, rarely carcinoma).

References