Review

Histopathologist and clinician interface in diagnosis and management of autoimmune hepatitis

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ABSTRACT

Diagnosis of AIH is based on a combination of clinical, laboratory and histological information. It has been formalised by diagnostic scoring systems, to which liver biopsy contributes substantially. Diagnostic biopsy is thus, desirable in nearly all patients. An adequate biopsy size, provision by clinicians of adequate information to histopathologists and active discussion at regular meetings are all important for accurate histological diagnosis. Recently, the specificity of some features previously thought to suggest AIH has been questioned, and new recommendations for histological diagnosis have been proposed, although not yet validated. The histology of acutely presenting AIH and that of severe or fulminant AIH include some characteristic features. Primary biliary cholangitis, primary sclerosing cholangitis and non-alcoholic fatty liver disease may co-exist with AIH on biopsy. Liver biopsy also enables grading of severity of inflammation and staging of fibrosis. Presence of cirrhosis is a poor prognostic marker. Repeat liver biopsy after achieving biochemical remission, although not performed routinely, enables assessment of (a) histological remission, a favourable prognostic indicator and (b) fibrosis progression. It can thus help determine further management.

Key messages

- ⇒ Diagnosis of autoimmune hepatitis (AIH) is based on a combination of clinical, laboratory and histological information. It has been formalised by diagnostic scoring systems, to which liver biopsy contributes substantially. Diagnostic biopsy is, thus, desirable in nearly all patients.
- ⇒ Recently, the specificity of some features previously thought to suggest AIH (such as rosettes and emperipolesis) has been questioned, and new recommendations for histological diagnosis have been proposed.
- ⇒ The histology of acutely presenting AIH differs from that with an indolent presentation; severe or fulminant AIH also has some specific features.
- ⇒ Other diseases may coexist with AIH on biopsy: primary biliary cholangitis, primary sclerosing cholangitis and non-alcoholic fatty liver disease.
- ⇒ Liver biopsy also enables grading of severity of inflammation and cell damage and allows for staging of fibrosis. Presence of cirrhosis is a poor prognostic marker.
- ⇒ Repeat liver biopsy after achieving biochemical remission, although not performed routinely, enables assessment of (a) histological remission, a favourable prognostic indicator, and (b) fibrosis progression. It can thus help determine further management.
- ⇒ Finally, liver biopsy can determine the cause of persisting or recurrent liver test abnormalities in patients with treated AIH.

INTRODUCTION

The role of liver biopsy in diagnosis and management of liver disease has become more selective, particularly in patients with hepatitis B (HBV) and C (HCV), haemochromatosis and primary biliary cholangitis (PBC). Reasons include availability of laboratory tests allowing accurate diagnosis, lower thresholds for offering treatment and availability of non-invasive tests to assess fibrosis severity. However, liver biopsy still plays a central role in diagnosis and ongoing management of other liver diseases, and a good example is autoimmune hepatitis (AIH)

AIH is a chronic inflammatory liver disease.[1–3] It is probably immune in origin, showing associations with a wide

Box 1 Clinical presentations of autoimmune hepatitis

⇒ Anorexia, fatigue, weight loss, nausea, joint pains, amenorrhoea.
⇒ Jaundice in 30%.
⇒ Complications of cirrhosis—ascites, variceal bleeding (mainly older patients).
⇒ Acute hepatitis±acute liver failure.
⇒ Asymptomatic in 25%.

Features suggesting other diseases (see table 1) include:

⇒ Neurological or psychiatric symptoms, Kayser-Fleischer rings (Wilson's disease).
⇒ Haemolysis, especially Coombs negative (Wilson's disease).
⇒ Prominent itching (primary biliary cholangitis or primary sclerosing cholangitis (PSC)).
⇒ 'Biliary' pain or rigours (PSC).

Box 2 Non-invasive work-up of suspected autoimmune hepatitis

Serum immunoglobulins: IgG–elevated in 78%–87%; IgA/IgM–usually normal.

Autoantibodies: antinuclear (ANA), anti-smooth muscle antibody (ASMA)–either present in 80%.

Anti-mitochondrial antibody–present in 5%–10%.

Additional antibody tests if ANA and ASMA negative:

⇒ Anti-liver–kidney microsomal-1.
⇒ Anti-liver cytosol antibody-1.
⇒ Anti-soluble liver antigen/liver pancreas antibody.

In 10%–20% of patients, no antibodies are detectable.

Exclusion of other liver diseases:

⇒ Viral hepatitis:
  ⇒ All patients: IgM anti-HAV antibody, HBV surface antigen, HBV-core, HCV, HEV.
  ⇒ CMV and EBV antibodies.
  ⇒ Immunocompromised patients: herpes simplex and varicella zoster.
⇒ Biliary obstruction/infiltration/congestion:
  ⇒ Ultrasound (all patients).
  ⇒ Magnetic resonance cholangio-pancreatography (MRCP)if jaundice, rigours or very high serum alkaline phosphatase (ALP)
⇒ Others: serum caeruloplasmin (<40 years), iron saturation, a-1 antitrypsin level.

range of other autoimmune diseases,[4 5] with 'autoimmune' HLA genotypes, non-organ-specific autoantibodies and hyperglobulinaemia, typically serum IgG. Prevalence of AIH in the UK is 19/100 000, and incidence is increasing.[6] Seventy-five per cent of patients are female, and the disease affects all ages (median age at diagnosis about 55 years) and ethnic groups. Prevalence is increased fivefold in first-degree relatives[7] and AIH is associated with HLA genotypes.[8] Environmental precipitants are incompletely characterised. Very occasionally, hepatitis A (HAV), E (HEV), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) infection precede, and so, may precipitate, AIH. Also, some drugs, including minocycline, nitrofurantoin, methyldopa, hydralazine, infliximab and khat have been repeatedly associated with liver injury indistinguishable from AIH.[9 10]

Historically, AIH was considered a chronic disease, and in the 1980s it was named 'autoimmune chronic active hepatitis'. However, in 30%–50% of cases, AIH presents acutely. A more widespread distribution of inflammation throughout the liver lobule (so-called lobular hepatitis) is characteristic of acutely presenting AIH,[11] whereas the more typical portal and periportal distribution is associated more with more indolent presentations. The modes of presentation of AIH are outlined in box 1, the recommended non-invasive work-up in box 2 and the main differential diagnoses in table 1. Importantly, most of these can coexist with AIH.

Is liver biopsy always needed to diagnose AIH?

Liver biopsy is of major help in diagnosing AIH when the non-invasive work-up is equivocal. But is a biopsy always essential? Most clinical guidelines[1–3] say or imply that it is. However, this reflects expert opinion, and the question has not been rigorously tested.

In a study of 257 patients[12] with AIH, histology was 'atypical' in only 5%, and these patients had a similar response to immunosuppressive therapy compared with the other patients. The authors concluded that histology only rarely refuted a diagnosis of AIH based on non-invasive work-up. However, this cohort was preselected as diagnosed with AIH, and it was unclear how many patients had been previously excluded because of liver histology suggesting another disease. In other studies of biopsy-proven non-alcoholic fatty liver disease (NAFLD), 20% met the 1999 IAIHG criteria for probable AIH, and 3% the criteria for definite AIH, based on non-invasive tests (before AIH was excluded by biopsy).[13]

There is an argument that biopsy may not be essential for initial diagnosis of AIH, if non-invasive work-up strongly suggests the diagnosis. However, AIH is a lifelong disease. Response to immunosuppressive treatment is sometimes suboptimal, and in these patients, repeat biopsy may lack diagnostic features due to a partial effect of immunosuppression. Thus, the initial diagnosis of AIH may be questioned, sometimes years later. By helping to avoid such scenarios, a firm biopsy-based initial diagnosis may facilitate management in the longer term.

That said, there are some relative contraindications to liver biopsy. Most commonly, older age and/or frailty. The overall mortality of liver biopsy (usually due to bleeding) is about 1/10 000 and (though not proven) is likely to be higher in older people.

Table 1 Differential diagnosis of AIH following non-invasive work-up*

Condition	Prevalence (vs AIH)	Demography	Risk factors	Raised liver enzymes	Autoantibodies	Raised serum immunoglobulins
Drug-induced liver injury++	Similar	M=F; all ages	Drugs/herbs (medicinal/recreational)	Varies	ANA or ASMA in 20%	Usually not
Primary biliary cholangitis[22]++	Similar	Over 30 years, 90% F	×10-fold in 1st-degree relatives; other autoimmune diseases	ALP usually; ALT rarely >150 U/L	AMA+ in 90% if absent, often ANA+	IgM
Primary sclerosing cholangitis (PSC)[24]++	Similar	M=F; all ages	Inflammatory bowel disease: about 5% of whom have PSC	ALP usually; ALT rarely >150 U/L	None typical	Usually normal
Non-alcoholic fatty liver disease[26]+++	More common	M=F; all ages	Metabolic syndrome	ALT usually; rarely >200 U/L	ANA+ or ASMA+ in 20%[13]	IgG
Wilson's disease[25]†	Rarer	M=F; aged <40 years	Autosomal recessive	Variable	ANA+/ASMA+ described	Sometimes
AIH	–	All ages, 75% F	×5-fold in 1st-degree relatives; other autoimmune diseases	ALT (median 400 U/L) Spontaneously resolves in 20%	80% ANA+/ASMA+, 8% AMA+, 2% LKM+, 30% SLA+	Serum IgG in 80%–90%

Coexists in 5%–10% (++) and in 25%–30% (+++) of patients with AIH.
*Viral hepatitis is not included in the differential diagnosis, as it should have been excluded by serology.
†If suspected, arrange serum caeruloplasmin 24-hour urinary copper, slit-lamp examination for Kayser-Fleischer rings, MRI brain scan and genetic testing.
AIH, autoimmune hepatitis; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; LKM, liver–kidney microsomal-1; SLA, soluble liver antigen.

Diagnostic scores for AIH: contribution of biopsy

The 1999[14] and the simplified (2008)[15] AIH diagnostic scores were introduced to facilitate reporting conformity in published studies on AIH (see UK[1] and European Association for the Study of the Liver[2] Guidelines for full discussion). They are only a guide to diagnosis, which is sometimes made by experienced clinicians without the requisite diagnostic points.

The diagnostic importance of liver biopsy in AIH is illustrated by its contribution to these diagnostic scores. Using the 1999 scoring system, 10 points are required for a definite and 15 for a probable diagnosis of AIH. Liver histology can contribute up to 5 points, if interface hepatitis, rosettes and a plasma cell-rich infiltrate are all present. However, if none of these features are present and there are features suggesting other diseases, such as severe steatosis±steatohepatitis, up to 11 points may be deducted, after which it becomes almost impossible to reach the minimum diagnostic score for AIH of 10 points.

Using the 2008 simplified scoring system, 6 and 8 points are required for a probable and definitive diagnosis of AIH, respectively. Without a liver biopsy, a probable diagnosis of AIH requires all the following: exclusion of relevant viral infections, raised serum IgG (>1.1 times upper limit of normal) and presence of AIH-related autoantibodies. Biopsy can contribute up to 2 further diagnostic points if histology is 'typical', 1 point if 'suggestive' and none, if not suggestive.

Recently, there has been reconsideration regarding what constitutes 'typical' histology. In the original description of the simplified scoring system, 'typical' histology required the presence of all of the following: interface hepatitis, a 'lymphocyte-plasmacytic' infiltrate, mainly in the portal area (proportion of plasma cells was unspecified), hepatocyte rosettes and emperipolesis. However, more recent studies[16–19] (summarised in table 2), while confirming the associations of these features with AIH, have also demonstrated that some (especially rosettes and emperipolesis) are seen in other liver diseases, thus undermining their specificity for AIH. Furthermore, especially in acutely presenting AIH, the distribution of inflammation may be panlobular, with less prominent periportal activity.

An international AIH group of histopathologists and hepatologists met in January 2020 to attempt to reach formal agreement (using a Delphi process) on histological criteria needed for diagnosis of AIH. A consensus statement was recently published[20] and includes the following salient points:

1. Liver biopsies should be taken with least an 18 G needle and preferably 16 G. The minimum length should be 1.5 cm, including at least 6 (ideally 10) portal tracts. As well as an H&E stain, a connective tissue stain is needed to assess fibrosis.
2. While liver biopsy should remain standard for diagnosing AIH (along with clinical and serological information), there are no pathognomonic histological features of AIH.

Table 2 Prevalence of histopathological features in patients with AIH and with other liver diseases

Author	Number		% Interface hepatitis (n)		% Plasma cell prominence		% Rosettes		% Emperipolesis		% Portal tract/bile duct lesions		Other features
	AIH	C	AIH	C	AIH	C	AIH	C	AIH	C	AIH	C	AIH
Suzuki *et al*[16]	28	19*	100	100	86	32	75	41	75	37	57	53	
de Boer *et al*[17]	63	62†	87	63	48	27	49	23	78	50	28	18	Steatosis 3 Granuloma 11
Balitzer *et al*[18]	88	20‡ 13§	80	15 77	49	20 8	33	0 38	65	50 77	46	100 62	Copper, CK-19 stains
Gurung *et al*[19]	43	42†	65	40	60¶	26¶	37	17	51	24	60	25	Endotheliitis Kupffer cell hyaline
Median (range)			**83 (65–100)**	**63 (15–100)**	**55 (48–86)**	**26 (8–32)**	**43 (33–75)**	**23 (0–41)**	**70 (51–78)**	**50 (24–77)**	**51 (28–60)**	**53 (25–100)**	

*DILI (hepatocellular).
†Chronic viral hepatitis.
‡PBC.
§Non-autoimmune.
¶Defined as plasma cell clusters.
AIH, autoimmune hepatitis; DILI, drug-induced liver injury; PBC, primary biliary cholangitis.

3. AIH is likely if there is either:
   - Portal lymphoplasmacytic hepatitis with more than mild interface activity (see figure 1A) and/or more than mild lobular hepatitis, but without features suggesting another liver disease; Ishak necroinflammatory grade is usually >6.
   - More than mild lobular hepatitis with or without centrilobular necroinflammation and ≥1 of the following features: portal lymphoplasmacytic hepatitis, interface hepatitis or portal-based fibrosis, but without features suggestive of another liver disease (see figure 1B).
   - The consensus report also includes criteria for possible and for unlikely diagnoses of AIH.
4. Emperipolesis and rosettes should no longer be considered as diagnostic features favouring AIH because of their limited specificity.

These new criteria are complex and represent only a synthesis of 'expert' opinion. It is unclear to what extent they will replace existing diagnostic criteria. For example, given the high population prevalence of steatosis, it is debatable whether the existence of mild/moderate steatosis, as a 'feature suggestive of another liver disease' should diminish the likelihood of a diagnosis of AIH.

Validation studies of these criteria, incorporating blind assessment of biopsies from patients with AIH and with comparator diseases (drug-induced liver injury (DILI), PBC, viral hepatitis) would help in their general acceptance. Also, if accepted, the 1999 and 2008 diagnostic scores would need to be modified to incorporate the changed histological diagnostic criteria.

Role of liver biopsy in finalising a diagnosis of AIH

Because the non-invasive work-up is usually not definitive (table 1), a biopsy is required for a confident diagnosis of AIH. However, a diagnosis of AIH cannot be made on biopsy alone. The histopathologist needs all relevant pre-biopsy information (detailed in box 3) on the request form.

Drug-induced liver injury

Distinguishing DILI from AIH by histology alone can be difficult, especially as some drugs can trigger a reaction indistinguishable from AIH. In a blinded comparative study[16] of biopsies from patients with more typical DILI and with AIH, portal plasma cell-rich inflammation and absence of cholestasis were associated with AIH. Eosinophils were not of diagnostic value. Presence of advanced fibrosis would also favour AIH, as most drug reactions or drug-triggered AIH have acute features rather than chronic ones.

Primary biliary cholangitis

Liver biopsy in PBC[21 22] may show interface hepatitis but also, bile duct injury, bile duct loss and bile duct-associated granulomas. AIH and PBC may coexist,

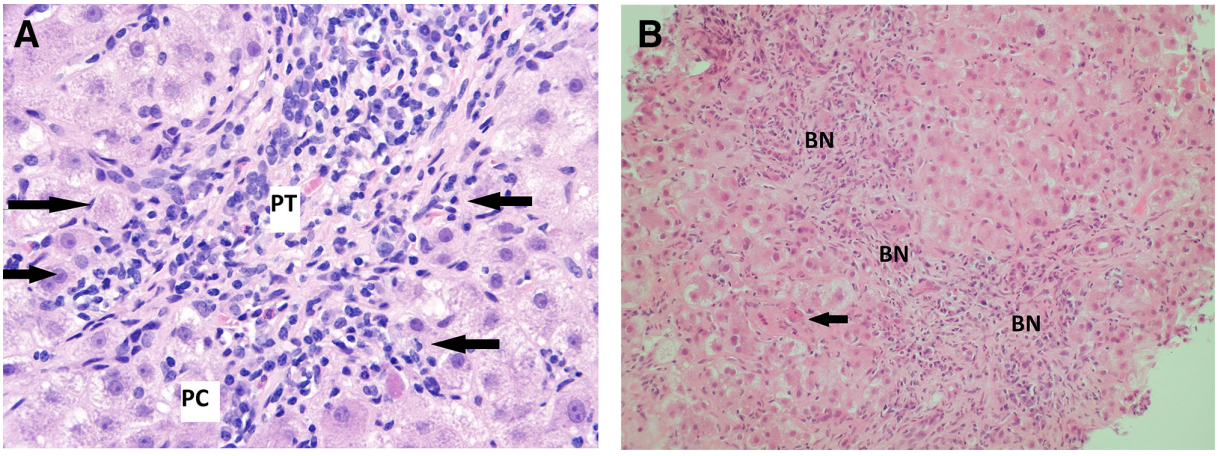

Figure 1 (A) IH. The portal tract (PT) contains a predominantly chronic inflammatory infiltrate, with collections of plasma cells (PC) visible. The interface, normally smooth boundary with the parenchyma, is infiltrated by inflammatory cells at multiple points (arrows). (B) Bridging necrosis (BN) and apoptosis. Lobular hepatitis is present throughout the parenchyma with, in this example, the loss of hepatocytes between structures–BN. An apoptotic cell is also visible (arrow).

and so-called AIH/PBC 'overlap' can only be diagnosed confidently by liver biopsy. Sometimes, treatment of predominant AIH will result in clearing of the associated PBC features on repeat biopsy, but in other patients may lead to unmasking of further PBC features.

Primary sclerosing cholangitis

Liver biopsy adds little to the diagnosis of primary sclerosing cholangitis (PSC)[23] if an MRCP is suggestive. However, in about 10% of patients, the cholangiogram is normal ('small-duct PSC'), and the diagnosis can only be made by liver biopsy,[21 24] which may show portal tract neutrophilic infiltration, cholangitis, periductal oedema, loss of bile ducts, 'onion-skin' fibrosis around the bile ducts, bile ductular proliferation and cholestasis. However, such features are not always present and sometimes biopsy shows minimal abnormalities.

In about 5% of patients with AIH (and in a larger proportion of children), there are coincidental features of PSC. Likewise, in about 5% of patients with PSC, there is coincidental AIH. Usually, this manifests as serum transaminases of over 200 U/L, higher than is usual in PSC. In such patients, it is reasonable to perform a liver biopsy to see if there is coincidental AIH; however, usually this is not the case.

Box 3 Information needed by histopathologist

1. The mode of clinical presentation (acute or indolent).
2. Any drugs deemed potentially relevant which the patient is taking.
3. Results of the non-invasive screen (especially negative virology tests).
4. Diagnoses other than autoimmune hepatitis being considered (table 1).
5. Liver function tests at presentation.

We strongly recommend direct discussion of cases at a regular clinical-pathological meeting.

Wilson's disease

Liver histology in Wilson's disease encompasses a range of abnormalities, none of them specific. Occasionally, the appearances even suggest AIH. In patients with acute severe liver injury, copper level should be measured in liver biopsy tissue, sometimes urgently. This is the most reliable single test for diagnosing Wilson's disease. Histochemical staining for copper or copper-associated proteins is not sufficiently accurate and these can occur in chronic cholestatic disorders.[25]

Non-alcoholic fatty liver disease

The presence of prominent steatosis, hepatocyte ballooning, neutrophilic inflammation and pericentral fibrosis on liver biopsy suggests steatohepatitis, rather than AIH. However, some patients with NAFLD and cirrhosis can develop a dense chronic inflammatory cell infiltrate in portal areas and fibrous septa that may contain plasma cells.[26]

NAFLD and AIH can also coexist. Steatosis is present in 25%–35%% of patients on initial biopsy on which AIH is diagnosed.[27 28] This is not surprising, as about 25% of the general population have steatosis on imaging or on biopsy. According to the 1999 AIH diagnostic criteria, no points need to be deducted if the steatosis is mild (which it usually is). Steatosis is more frequent and more severe on follow-up biopsy 2–4 years later, possibly due to corticosteroid treatment.[27]

Although in these studies, steatohepatitis was not observed,[28] coexistence of steatohepatitis on diagnostic biopsy has been described in 12 (16%) of 73 patients with AIH[29] and was associated with a higher likelihood of cirrhosis and worse clinical outcome.

ACUTE, SEVERE AND FULMINANT AIH

In 30%–40% of cases, the presentation of AIH is that of acute liver injury. The term 'acute icteric AIH' is used when the presentation is with jaundice. Acute severe (AS)-AIH is diagnosed when there is jaundice and coagulopathy (defined as an international normalised ratio (INR) exceeding 1.50).[30] Acute fulminant (AF)-AIH requires the presence of hepatic encephalopathy, in addition to jaundice and coagulopathy (usually the INR exceeds 2.0). Transplant-free survival of acute icteric AIH, AS-AIH and AF-AIH is 90%,[31] 66%[32] and 32%,[33] respectively, reflecting increasingly severe acute liver injury. Because of the frequent requirement for liver transplantation, patients with AS-AIH and AF-AIH should be managed in transplant centres.

Liver biopsy, which usually must be via the transjugular route, is often essential for a diagnosis of AIH, especially as autoantibodies are sometimes absent. Biopsies via this route may be smaller than those taken percutaneously and thus present a challenge for the histologist. Such cases often show widespread panacinar necrosis; however, distinction of acute AIH from other causes of acute hepatitis is rarely possible on histological grounds alone. Features favouring AIH include a plasma cell-rich infiltrate, and centrilobular or panacinar necrosis.[34] Again, close liaison with the clinician and review of all investigation results are necessary for a firm diagnosis. The histopathologist can tell the clinician whether the disease present is that of acute hepatitis with an AIH-like pattern or acute exacerbation of a chronic hepatitis, by using histochemical stains to demonstrate the presence of permanent fibrosis with elastic fibres, which can be remodelled but not removed.

Prognostic value of initial liver biopsy

In cohort studies, cirrhosis (Ishak fibrosis stage 5 or 6) is seen on diagnostic liver biopsy in about one-third of cases and is independently associated with a twofold to fourfold increase in death or transplantation rates, compared with patients without cirrhosis.[1–3 35] It is unclear if lesser degrees of fibrosis affect prognosis.

Grading of necroinflammatory activity in AIH should be based on Ishak's modified Histological Activity Index (HAI). Although widely used, this nonlinear scoring system shows interobserver variation. Thus, grade is usually expressed in words such as minimal, mild, moderate or severe chronic hepatitis. Ishak HAI is not appropriate in the setting of acute hepatitis without fibrosis.

Early studies suggested an association between bridging necrosis in acute hepatitis and early mortality, but this has not been addressed in recent years or in patients with a firm diagnosis of AIH. In AS-AIH, the main determinants of mortality are older age, higher Model for End-stage Liver Disease (MELD) score and presence of encephalopathy. Although histological features are important in making the diagnosis of AIH, they may not provide additional prognostic information.

In one cohort study, lower necroinflammatory score was associated with a better long-term outcome.[36] However, high baseline serum ALT has been a favourable prognostic marker in some,[37] although not in other studies.[38]

Follow-up liver biopsy in AIH

Biochemical remission of AIH was originally defined as serum transaminases and globulins falling to less than twice the upper limit of normal and subsequently, to less than once the upper limit of normal. In the initial randomised trials and in more recent cohort studies, about 60% of patients also achieve histological remission (Ishak necroinflammatory score ≤3). This is a desirable endpoint, being associated with fibrosis regression and a good long-term outlook, not different to that of the general population.[39] Trials of maintenance therapy to prevent relapse in the 1980s were performed in patients who had achieved histological (as well as biochemical) remission.[40]

In the remaining (about 40%) of patients, follow-up biopsy (even in the presence of normal serum transaminases and globulins) indicates an Ishak necroinflammatory score of >3. This persisting histological activity is associated with failure of fibrosis regression and a poorer long-term outcome.[39] However, while immunosuppressive therapy is usually continued and is sometimes changed, such measures have not yet been shown reliably to achieve histological remission and to improve longer term outcome.

More recently, a more rigorous definition of biochemical remission has been proposed, including normal serum ALT, AST and IgG, and termed complete biochemical remission (CBR). CBR is associated with a higher percentage of histological remission (77%–80%),[41 42] with regression of fibrosis on repeat liver biopsy, with stable or improved transient elastography scores over several years[42] and finally with reduced rates of liver-related adverse events[43] and mortality.[44] Given the small but quantifiable risk of repeated liver biopsy, it is likely that many units will rely on a combination of CBR and serial non-invasive assessment of fibrosis (eg, by Fibroscan) to define satisfactory control of AIH.

Repeat liver biopsy has also been suggested[2] to confirm that stopping immunosuppressive therapy is appropriate in patients with sustained CBR. Biopsy is of limited value in predicting AIH relapse but may detect ongoing inflammation or fibrosis progression, which if present might result in continuing (or changing) treatment. However, as the efficacy of such measures in preventing disease progression is not proven, the value of routine biopsy prior to treatment withdrawal remains unclear.

Finally, repeat biopsy may be necessary in the event of persistent (or recurrent) rises in serum transaminases

if non-invasive work-up is inconclusive. The histopathologist may suggest possibilities not previously considered.

CONCLUSION

Although the precise histological criteria for diagnosis of AIH are currently undergoing revision, they illustrate the art of histopathologists in interpreting visible patterns of liver injury. Liver biopsy retains a central role in diagnosis of AIH and should be performed in most patients in whom AIH is suspected. As with all clinical-pathological interactions, the histopathologist needs detailed clinical and biochemical information and discussion, to interpret the biopsy and arrive at a meaningful conclusion.

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