REVIEW

Severe acute liver disease in adults: Contemporary role of histopathology

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Liver biopsies have consistently contributed to our understanding of the pathogenesis and aetiologies of acute liver disease. As other diagnostic modalities have been developed and refined, the role of biopsy in the management of patients with acute liver failure (ALF), acute-on-chronic liver failure (ACLF) and acute hepatitis, including acute liver injury (ALI), has changed. Liver biopsy remains particularly valuable when

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Abbreviations: ACLF, acute on chronic liver failure; AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; ALF, acute liver failure; ALI, acute liver injury; ANA, antinuclear antibody; ASH, alcohol-related steatohepatitis; DI-ALH, drug induced autoimmune like hepatitis; DILI, drug induced liver injury; HAV, hepatitis A virus; HEV, hepatitis E virus; LKM, liver kidney microsomal antibody; MASH, metabolic dysfunction associated steatohepatitis; MASLD, metabolic dysfunction associated steatotic liver disease; MLN, multilobular necrosis; OTC, over the counter; SLA, soluble liver antigen; SMA, smooth muscle actin; WD, Wilson disease.

first-line diagnostic algorithms fail to determine aetiology. Despite not being identified as a mandatory diagnostic tool in recent clinical guidelines for the management of ALF or ACLF, many centres continue to undertake biopsies given the relative safety of transjugular biopsy in this setting. Several studies have demonstrated that liver biopsy can provide prognostic information, particularly in the context of so-called indeterminate hepatitis, and is extremely useful in excluding conditions such as metastatic tumours that would preclude transplantation. In addition, its widespread use of percutaneous biopsies in cases of less severe acute liver injury, for example in the establishment of a diagnosis of acute presentation of autoimmune hepatitis or confirmation of a probable or definite drug-induced liver injury (DILI), has meant that many centres have seen a shift in the ratio of specimens they are receiving from patients with chronic to acute liver disease. Histopathologists therefore need to be equipped to deal with these challenging specimens. This overview provides an insight into the contemporary role of biopsies (as well as explant and autopsy material) in diagnosing acute liver disease. It outlines up-to-date clinical definitions of liver injury and considers recent recommendations for the diagnosis of AIH and drug-induced, autoimmune-like hepatitis (DI-AIH).

Introduction

Acute liver disease is a common clinical problem; the main patterns and aetiologies are outlined in Table 1. The surgical pathologist has a role in the management of a subset of patients, often those with a more confusing or severe course. There are several different clinical presentations, with a wide range of severity. In many cases, the pathologist will be asked to determine the pattern of injury and give the most probably aetiology. This most commonly occurs in the setting of acute liver dysfunction, where initial screening tests such as viral hepatitis studies and autoimmune serology are negative, although on occasion a biopsy may be performed before these test results are available. In other cases, particularly with severe liver dysfunction and signs of liver failure, biopsy may be performed to confirm a clinical suspicion or to rule out specific diagnoses such as malignancy, which would preclude consideration for transplantation. Increasingly this uses transjugular liver biopsies. Although they can be smaller and more fragmented than percutaneous specimens, they are suitable for diagnostic purposes in up to 98.5%,[1,2] with some reports suggesting that median total lengths may be comparable to percutaneous biopsies.[1] Finally, the pathologist may be asked to confirm a suspected diagnosis in an explanted liver or at autopsy (Figures 1–3).

This review is designed to provide a framework for pathologists faced with biopsies from patients with acute liver disease with a particular focus on those considered to be immune-mediated (active hepatitis). It is not intended to be comprehensive and does not, for example, consider acute injury in the setting of liver transplantation or major hepatic surgery, but draws upon some of the issues that were discussed in recent years by an international group of hepatopathologists, the International Liver Study Group,[3] during several of its annual meetings.

Spectrum of acute liver disease

Acute liver disease may result in a spectrum of clinical presentations from those with life-threatening impairment of liver function leading to transplantation or death to those who may be entirely asymptomatic, where the diagnosis may be made incidentally on liver biochemistry. Clinically, this is often subdivided into three groups: (i) acute liver failure (ALF), (ii) acute on chronic liver failure (ACLF) and (iii) acute liver dysfunction or injury (acute liver injury, ALI). While this is a pragmatic approach, the lines between these are somewhat blurred and there may be temporal changes whereby within an individual patient, at presentation there can be preservation of synthetic function, but the disease severity may increase over time with the development of ALF.

ACUTE LIVER FAILURE AND ACUTE-ON-CHRONIC LIVER FAILURE

The designation ALF is often (inappropriately) used as a generic term for any form of significant acute liver dysfunction.[4] However, from a clinical perspective it should be restricted to those in which there is (i) a significant abnormality of liver function tests in a patient with no underlying chronic disease and (ii)

Table 1. Major patterns and causes of acute liver injury in adults

Acute (immune-mediated) hepatitis
Infections (primarily viruses)
Hepatotropic viruses: HAV, HBV, HCV, HEV
Non-hepatotropic viruses: CMV, adenovirus, EBV, dengue, enterovirus, COVID, herpes viruses (herpes simplex, herpes zoster)
Bacterial: syphilis, brucellosis
Drug, herbal and supplement-induced idiosyncratic reactions
Autoimmune hepatitis
Indeterminate (non-A–E or seronegative hepatitis)
GVHD (hepatitic variant)
'Bystander hepatitis' (associated with systemic immune activation)
Direct toxins leading to zonal parenchymal necrosis
Paracetamol (acetaminophen)
Amanita phalloides toxin (α-amanitin)
Other toxins, e.g. phosphorus
Drug idiosyncrasies leading to cholestasis
Antibiotics
Contraceptive and anabolic steroids
Vascular/ischaemic
Hepatic vein and portal vein thrombosis (may be combined)
Shock liver (ischaemic hepatitis)
HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome
Sinusoidal obstruction syndrome
Metabolic
Steatotic liver disease—ALD and MASLD/MASH
Wilson disease
Microvesicular steatosis (acute fatty liver of pregnancy, Reye syndrome, alcohol-related foamy degeneration)
Neoplastic (diffusely infiltrating tumours)
Lymphoma/myeloma
Carcinoma (lobular breast, lung small cell, colorectal)
Melanoma
Miscellaneous
Heatstroke
Macrophage activation syndrome/adult still disease
Radiation injury
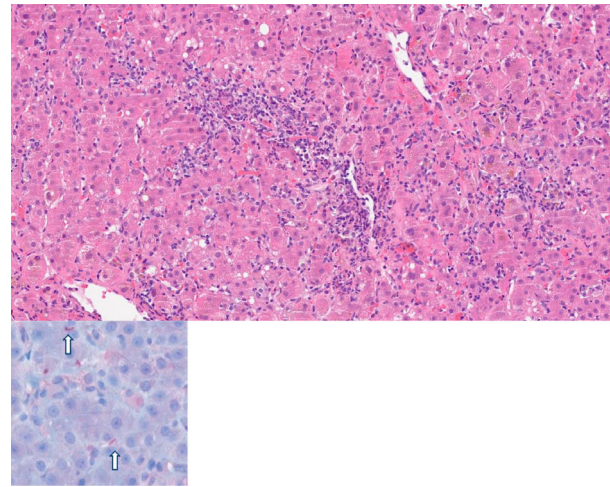
Figure 1. Syphilitic hepatitis. This is manifest by a dramatic lobular lymphohistiocytic infiltrate and accompanying portal inflammation. The diagnosis can be made histologically using immunohistochemistry for *Treponema pallidum* (inset).
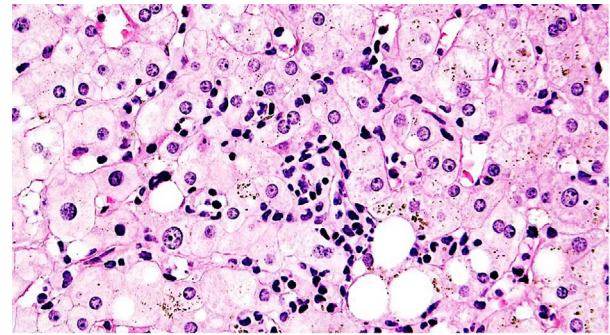
Figure 2. Hepatitic form of graft-versus-host disease (GVHD) in a young male patient treated by chemotherapy and stem cell transplantation for myelodysplastic syndrome. The bile ducts showed only minimal changes of GVHD but there was a moderate lobular inflammatory infiltrate.

the development of liver-related coagulopathy and hepatic encephalopathy; this is frequently associated with multi-organ failure. This term is not recommended for acute dysfunction where there is known chronic liver disease, where the manifestations may reflect rapid deterioration of established cirrhosis or an acute exacerbation of chronic disease (as can occur in autoimmune hepatitis)[5,6]; the term 'acute on chronic liver failure' (ACLF) is a preferred term for the latter.[7] Furthermore, the term ALF should not be used to describe the constellation of hepatic abnormalities that occur in systemic diseases such as haemophagocytic lymphohistiocytosis.[4] ALF can be subclassified based on the time from onset of clinical
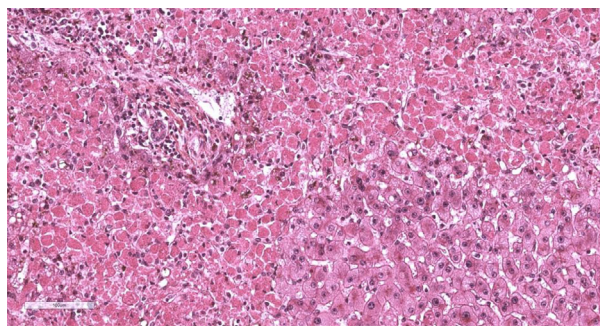
Figure 3. Zonal necrosis involving acinar zone 1 in explant tissue obtained at the time of orthotopic transplantation in a young child for suspected accidental phosphorous exposure.

symptoms to the onset of encephalopathy/coagulopathy[4,8,9]; several systems exist, the most common ones subclassifying into (i) hyperacute, acute and subacute ALF or (ii) fulminant or subfulminant liver failure. The accurate use of these definitions is important in the context of patient management pathways, as the approaches taken in ALF differ from those in ACLF.

Several professional societies have published recommendations for clinical management of both ALF and ACLF. These have, somewhat surprisingly, concluded that liver biopsy is only indicated in several restricted settings. The American Gastroenterological Association guidelines argued against the use of biopsy, citing evidence that it changed the diagnosis in fewer than 20% but without clarity of the frequency of changing management, and it carries at least some risk of bleeding and death.[8] This was based on limited data, and even at 20% a change in diagnosis can be crucial for the optimal management of a significant number of patients with severe acute liver disease. Furthermore, as noted above, transjugular biopsy is a relatively safe procedure. In the American Association for the Study of Liver Diseases (AASLD) guidelines[7] biopsy is recommended when severe clinically acute autoimmune hepatitis is suspected, particularly when routine serology is negative. They further proposed that it is also helpful where Wilson disease is being considered, in which case histology should be accompanied by the measurement of tissue copper; this is reinforced in recommendations for managing this condition.[9] In addition, these guidelines suggest that biopsy may be indicated where there is a past medical history of malignancy or where there is hepatomegaly and in cases of indeterminate ALF (for example, in unsuspected therapeutic misadventure with paracetamol). The European Association for the Study of the Liver (EASL) guidelines[4] also suggest that the

indications for biopsy in ALF are limited, and if undertaken should preferably be performed via the transjugular route and ideally with access to a specialist hepatopathologist; malignant infiltration should be excluded either on biopsy or by imaging. Recent EASL guidelines for ACLF in 2023[10] have suggested that the indications for biopsy in ACLF are even more limited than in ALF. Histological studies of ALF and ACLF are relatively scarce and are reviewed elsewhere[11–14]; there is currently a lack of standardised systematic descriptions of histopathological features and limited prospective experience in clinical settings, particularly in ACLF.[14]

Despite these guidelines, many centres continue to use liver biopsies in the setting of ALF (and to a lesser extent ACLF) and hepatopathologists need to be aware of how to interpret histological changes to best contribute to patient care. We strongly argue that liver biopsy should be seen as part of the multidisciplinary approach in the management of such patients. They need to be interpreted in the context of clinical, serological, virological and imaging data; the hepatopathologist is well placed to integrate such information. Biopsies can help to establish an aetiology, exclude others or contribute to narrowing the possibilities. Crucially, they can contribute to decision-making regarding possible listing for transplantation. Furthermore, biopsies can provide crucial information regarding the presence or absence of background chronic liver disease (Table 2).

It is important to note that there is significant geographical variation in the most common causes of ALF. In the United Kingdom, for example, paracetamol (acetaminophen) toxicity (intentional and therapeutic misadventure) remains the most common aetiology,[15] while acute viral hepatitis is more common in developing nations and subtropical regions[16]; this refers not only to HBV/HDV but HAV and HEV,[17] and in the tropics other 'exotic' hepatitides need to be considered, such as dengue, yellow fever, hantavirus, etc.[18] In fact, the number of cases of ALF in which the cause remains uncertain despite extensive investigation is relatively low. In a large US ALF registry of 2718 cases, only 303 were 'indeterminate'.[19] Furthermore, when additional review was carried out by an independent causality adjudication committee, together with additional diagnostic tools such as paracetamol adduct detection and HEV/metagenomic next generation sequencing, only 150, or 5.5%, were considered truly indeterminate.[19] In a more recent paper describing a longer-term registry, only 3.4% were considered to be truly indeterminate.[20] However, the histopathologist may face the situation where at the time of biopsy the

Table 2. Distinction between acute liver injury and acute-on-chronic liver injury

Stain	Acute liver injury	Acute on chronic liver injury
H&E	Inflammatory/necrotic lesion with preserved lobular architecture	Inflammatory/necrotic lesion with altered lobular architecture due to regeneration and fibrosis
Trichrome	Usually no fibrosis (necrotic/collapsed areas stain pale grey)	Portal, centrizonal or septal fibrosis (blue stain) according to the aetiology of chronic liver disease
Reticulin	Often preserved reticulin framework (but may be condensed in MHN with some nodularity)	Dense reticulin fibres in fibrotic areas and condensed in areas of more recent collapse
Victoria blue/ orcein	Elastic fibres are absent or sparse	Condensed elastic fibres in collapsed area
Keratin 7/19, EpCAM	Usually, no activation of progenitor cell compartment/ductular reaction	Activation of progenitor cell compartment/ductular reaction
CD34	Usually no sinusoidal capillarisation (no expression of CD34 in sinusoidal endothelial cells)	Increased sinusoidal capillarisation according to the aetiology of chronic liver disease

cause is not apparent. For example, ALF in which there is a severe hepatitis causing panacinar dropout (massive hepatic necrosis, MHN) on biopsy in the absence of an obvious cause presents a difficult problem and, on occasion, a specific diagnosis cannot be made. There is a stereotypical pattern of injury with early loss of hepatocytes and retained reticulin meshwork, but with time the reticulin collapses and a periportal ductular reaction occurs. In patients surviving for more than several weeks there are irregular areas of regeneration that can closely mimic cirrhosis, but the collapsed areas contain immature collagen fibres that stain palely with trichrome (pale grey rather than bright blue) and van Gieson (pale pink rather than dark red) and orcein (or Victoria blue)-positive fibres are absent. Biopsy at this stage can be confusing, as the complete loss of hepatocytes in some areas may not accurately reflect the total liver picture. In some centres, in 20–40% of cases no immediate cause for the MHN is found.[16] Stravitz *et al.*[6] described five patterns of MHN in the biopsies and explants of 72 patients with indeterminate ALF and identified features that suggest a probable autoimmune basis. Non-hepatotropic viral infection needs to be considered in ALF where non-zonal necrosis is present, but this is rare. Herpes infection and adenoviral infection are normally seen in immunocompromised individuals and can present acutely when affecting the liver; characteristic viral inclusions are usually obvious.[17] Histopathologists also play a role in confirming or refuting the working diagnosis in patients who undergo liver transplantation, based on changes in the explant or at autopsy in patients who have died. This information is important for internal clinical audits and the development of learning healthcare systems.

Biopsies in ALF and ACLF can provide prognostic information, but this needs to be provided cautiously; it is important to remember that changes are not always distributed evenly throughout the liver. Indeed, biopsies that are apparently completely devoid of hepatocytes do not invariably preclude recovery. Features indicating poor prognosis, however, include the extent of necrosis > 50–70%,[2,21] the presence of bridging necrosis,[22] low proliferative index in surviving hepatocytes, abundant hepatic progenitor cells (identified by immunohistochemistry for keratin (K)-7, K19 or epithelial cell adhesion molecule (EpCAM),[23] sparse intermediate hepatocytes (small K7+ hepatocytes, often showing submembranous staining)[23] and extensive ductular reaction with ductular cholestasis.[22] Baloda *et al.*[24] compared histological changes in biopsies from patients considered to have ACLF with those from compensated chronic liver disease. Significant necrosis, a dense lobular inflammation, bilirubinostasis and ductular reaction were more frequent in the former group; using multivariate analysis the predictors of increased mortality were absence of advanced fibrosis and the presence of dense lobular inflammation. Li *et al.*[25] studied explant material from patients with decompensated HBV disease. Of 174 patients, 69 showed 'submassive necrosis'; these were regarded as being ACLF rather than decompensation of cirrhosis. This group of patients had a higher rate of multi-organ failure and a shorter interval between acute decompensation and transplantation. They also had evidence of higher cytokine expression in peptide arrays and gene expression microarrays.

ACUTE LIVER INJURY

Histopathologists play a greater role in the management of patients with significant acute liver disease

but without coagulopathy, encephalopathy or multi-system failure. Typically, this will be manifest by a significant rise in serum aminotransferases ± alkaline phosphatase and elevated bilirubin ± detectable jaundice, but with normal synthetic function. Some patients may have borderline coagulopathy in the absence of cognitive impairment. The EASL guidelines, reflecting current usage, stress that this does not amount to an established ALF but should be described as 'acute liver injury' (ALI).[10,26]

ALI has a wide differential diagnosis and comes with a broad spectrum of histological findings. Many, but not all, are characterised by an immune-mediated process. The term 'acute hepatitis' is often applied to this[26]; the clinical definition of acute hepatitis is the presence of acutely elevated aminotransferases within 6 months of onset in a patient with no pre-existing liver disease. Beyond 6 months, it is regarded as chronic hepatitis. The difficulty with this definition is that the time of onset is not always clear. Furthermore, clinical and histological changes do not always correlate well. The nature and severity of any biochemical disturbances may not correspond to the degree of histological injury. For this reason, the term 'acute hepatitis' in biopsy reports should be used with caution; an alternative term preferred by some is 'active hepatitis'. Discussion with the clinicians will often help to identify any probably aetiological culprits often based on virological and immunological studies and consideration of possible drug-induced liver injury (DILI). It may only be possible to describe the injury pattern and give the various possible causes of it, providing guidance with respect to any additional investigations.

Wilson disease (WD) can present as ALI with severe liver dysfunction, relatively high serum aminotransferases, possible coagulopathy but no encephalopathy.[10] These patients may respond to prompt intensive chelation treatment; however, some may progress to ALF. Histological findings may elucidate the aetiology[27]; in children, changes in mitochondrial morphology may be informative.[28]

Immune-mediated ALI is characterised by variable degrees of portal inflammation, interface hepatitis and lobular inflammatory infiltrate of predominantly mononuclear cells with apoptotic hepatocytes and central venulitis. The severity of hepatitis affects the pattern seen, with milder examples showing spotty lobular inflammation or mild confluent hepatocyte dropout only (most commonly of perivenular hepatocytes). Increasing severity sees the development of bridging 'necrosis' between portal and perivenular regions, more marked panacinar or even multiacinar

dropout or 'necrosis' (although the actual mode of cell death is probably predominantly apoptotic). Lobular inflammation is a key element in acute hepatitis and may show predominance over portal inflammation, which can be surprisingly mild. Cases showing bridging necrosis and parenchymal collapse should be differentiated from those with fibrous septa denoting chronicity by using adequate additional stains such as reticulin, trichrome and elastic stains. Macrophages containing pigment (ceroid) are commonly present, and there may be a variable degree of bilirubinostasis. The pattern is not specific and laboratory tests are needed to make a specific diagnosis. The major diagnostic considerations are viral infection, DILI and autoimmune hepatitis (AIH), and all these can appear similar.[29]

DILIs (including some involving dietary supplements) can exactly mimic AIH and induce antinuclear and occasionally antismooth muscle actin (SMA) antibodies; some drugs precipitate autoimmune-like hepatitis and should be mentioned in reports when AIH is being considered. These drugs include nitrofurantoin (Figure 4), minocycline, statins, infliximab, methyldopa, hydralazine, diclofenac, interferon and etanercept, the first two accounting for 90% of cases.[30] Check-point inhibitor-induced liver injury may have a hepatitic pattern in 60% of the cases and antinuclear antibodies (ANA)/SMA positivity in 32%. Following cessation, patients with drug-induced autoimmune-like hepatitis (DI-ALH) can be weaned from steroids after a short period, which is not the case with conventional AIH.[31] Acute hepatitis A can also be strikingly zonal (periportal dropout), leaving a rim of spared
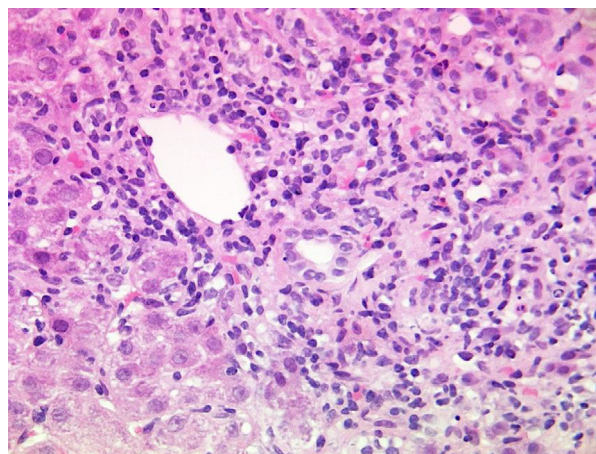

Figure 4. Nitrofurantoin DILI. Moderately severe mixed portal inflammation with interface hepatitis and abundant plasma cells in the infiltrate. This case also showed marked perivenulitis but there was no fibrosis.

centrilobular hepatocytes, and may be plasma cell-rich. Rare clinical variants of HAV infection also include relapsing hepatitis A approximately 4–7 weeks after initial recovery and, in approximately 2% of cases, a prolonged cholestatic course.

Cholestatic hepatitis is more commonly seen in association with DILI, but is also characteristic of acute hepatitis E.[32] Although most cases of HEV in Asia and the subcontinent are due to waterborne spread of genotypes 1 and 2, HEV genotype 3 is zoonotic, with reservoirs in pigs, wild boar, deer and camels. It is more common than previously thought, and consumption of undercooked pork or game (particularly liver) is the major cause of acute hepatitis E in Europe and the United States. The disease phenotype in HEV is variable and is determined in part by the patient's immune status and presence or absence of a pre-existing liver condition. Lenggenhager *et al.*[33] assessed biopsies from patients with molecularly confirmed HEV infection for 33 histopathological features; using hierarchical clustering they found three main clusters: cluster 1, that mapped to pre-existing liver disease with mainly features of the underlying disease; cluster 2, in immunocompetent individuals which displayed florid acute portal and/or lobular hepatitis; and cluster, 3 in those who were immunocompromised, showing a smouldering portal hepatitis.

AUTOIMMUNE HEPATITIS: ACUTE PRESENTATIONS AND CHALLENGES

AIH is a relatively rare condition, albeit one which appears to be occurring with a higher frequency than in previous decades.[34] It is generally associated with the presence of circulating autoantibodies (ANA, SMA, LKM, SLA) and raised serum immunoglobulin G (IgG). However, the clinical and histological features are heterogeneous. It may be entirely asymptomatic, but in some the initial presentation is one of ALF. A firm diagnosis may be difficult, as no single laboratory finding is pathognomonic. However, timely intervention with immunosuppressive agents is vital to prevent progression of the disease or the development of ALF. Liver biopsy can contribute to establishing whether it is definite, probable or unlikely AIH; as such it is a component of international scoring systems for the diagnosis of AIH[35] and recent clinical guidelines have underscored the importance of biopsies.[36] However, such scoring systems were based largely on the premise that AIH is a chronic disease. The historical concept was that this was a portal/periportal-based immune-based process that could lead to significant fibrosis and progression to cirrhosis. Pathologists are familiar with such classic features of AIH, but it is now widely accepted that variant patterns can arise.[34] These include centrilobular predominant AIH, fulminant AIH with panacinar necrosis and post-infantile giant cell hepatitis, the latter being a phenomenon seen in a variety of hepatic inflammatory diseases.[37] Some of these variants are most typically seen in the context of an acute presentation of AIH.

Centrilobular hepatitis (or perivenulitis) in AIH is usually seen in association with portal inflammation and interface hepatitis, but it can occur as a pure or predominant lesion in fewer than 5% of cases.[38] Importantly, this can be associated with absence of autoantibodies or a paucity of plasma cells. One case series highlighted the presence of centrilobular sinusoidal dilation, causing some diagnostic confusion with vascular liver disease.[39] Centrilobular AIH may represent an early phase of AIH, with evolution to more characteristic portal/periportal hepatitis over time, but one report suggested more heterogeneity in outcome.[39] The International AIH Pathology Group[40] recently used a Delphi-based approach to reconsider the diagnostic utility of histological findings in AIH, given the acceptance of a broader spectrum of changes in this disease. Some features that were thought previously to be strongly supportive of AIH, notably emperipolesis and liver cell rosettes, are now recognised to be non-specific, being present in several different liver diseases, and probably best regarded as a marker of disease activity. The group addressed the issue of using semiquantitative scoring to assess severity, opting for the modified Ishak system but where only three components are considered relevant: (A) interface hepatitis, (B) confluent necrosis and (C) spotty necrosis; the degree of portal inflammation is no longer thought to be of value. Mild inflammation is defined as $A \leq 1$; $B = 0$; $C \leq 2$. Given that the biological significance of A, B and C is probably not equal, we believe that a summation of these scores in practice is unwarranted and may be misleading. They further defined the diagnostic criteria for probable, possible and unlikely AIH based on patterns of portal and lobular inflammation. This new approach will need to be validated in the setting of acute AIH.[40]

DRUG-INDUCED ACUTE LIVER INJURY (INCLUDING OVER THE COUNTER (OTC), HERBAL AND DIETARY SUPPLEMENTS)

In countries such as the United Kingdom and United States, the number of approved medications that can

be prescribed now exceeds 1000; this number is dwarfed by the number of (less tightly regulated or unregulated) OTC herbal and dietary supplements available to the public. A sizeable proportion of agents in both categories has been associated with DILI.[41] Mechanistically, there are now considered to be three main forms. Direct hepatotoxicity is dose-dependent, predictable and reproducible in animal models. Idiosyncratic hepatotoxicity is less common, shows no straightforward dose relatedness and is unpredictable, although it often reflects a pharmaco-genetic defect. Finally, indirect hepatotoxicity is generally brought about by drugs which interfere with the host immune system, and which may then indirectly adversely affect the liver (see below); this form of DILI is being increasingly reported with the emergence of many immune check-point inhibitors, protein kinase inhibitors and monoclonal antibody therapies. DILI can give rise to a myriad of histological changes; there are few patterns of hepatic injury not described as adverse events.[42,43] However, in broad terms, direct hepatotoxins generally cause either (i) hepatocellular necrosis which may be zonal or panacinar or (ii) microvesicular steatosis. Those responsible for idiosyncratic hepatotoxicity are more prone to causing a bland cholestasis, cholestatic hepatitis or a chronic hepatitis. Some, however, such as nitrofurantoin, may produce ALI. An acute hepatitis with or without bile stasis is the most common histological manifestation of indirect hepatotoxicity.

The diagnosis of any form of DILI is one of exclusion of other possible causes liver disease and a clear understanding of what prescribed medication and OTC herbal and dietary supplements the patient has taken. Because some agents have a long latency period before clinical presentation and can cause liver injury for some time after cessation of therapy, it is crucial to gain an understanding of drug history during a period, not just present exposure. When any agent is suspected as a cause of DILI, one useful resource for finding details of adverse liver reactions to almost all drugs is the publicly available database from the NIH (livertox.nih.gov), which has an easily searchable database with useful case discussions. This is particularly useful, as we see more adverse reactions to newer agents used in personalised medical therapies, particularly in oncology, such as immune check-point inhibitors[44] (Figure 5).

It is not uncommon for pathologists to be asked to help in the context of a differential diagnosis between idiopathic autoimmune hepatitis (particularly where there are equivocal serological findings) and DILI in acute liver injury. However, AIH and DI-ALH may be
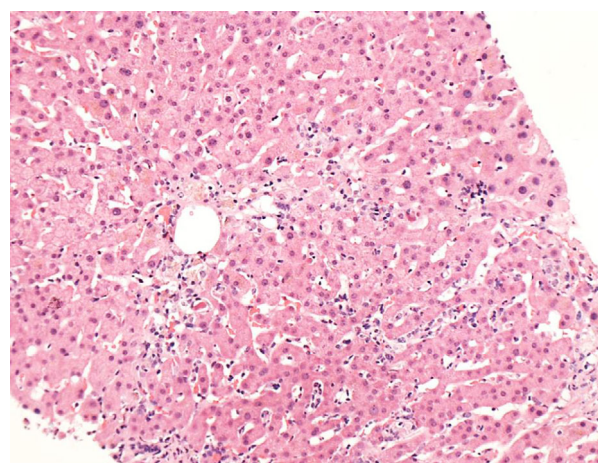

Figure 5. Nivolumab-associated perivenulitis with a prominent lymphohistiocytic infiltrate.

indistinguishable both clinically and histologically.[31] Several groups of pathologists have studied the problematic differential diagnosis. Suzuki et al.[45] showed that a variety of features favoured AIH, including severe interface hepatitis, plasma cell-rich infiltrates and dense portal inflammation. They developed a model which incorporated these features together with eosinophils, rosettes and canalicular cholestasis to predict hepatocellular DILI over AIH. This approach, while attractive, has not been adopted into routine practice. A more recent paper tackled the issue of using histological features to distinguish between AIH and DI-ALH (see above). While there were some subtle cell density differences (e.g. ceroid-laden macrophages being more common in AIH), the main distinguishing feature was the degree of fibrosis as assessed by multiple methods, with advanced fibrosis observed in AIH but not DI-ALH.[46] Recent data suggest that the new International AIH Pathology Group histological criteria may be better in identifying DI-ALH.[47]

ACUTE HEPATITIS DURING IMMUNE ACTIVATION ('BYSTANDER HEPATITIS')

Acute hepatitis developing during immune activation states is now well-recognised in the context of immune check-point inhibitor-associated hepatitis. This is generally regarded as a DILI, but similar injury occurs rarely in other circumstances. Circulating cytokines such as interleukin (IL)-6 are implicated[48] and may activate tolerised, self-reactive lymphocyte clones that induce acute hepatitis, which may be severe. Tumours, particularly renal cell carcinoma,[49] as well as others such as Hodgkin
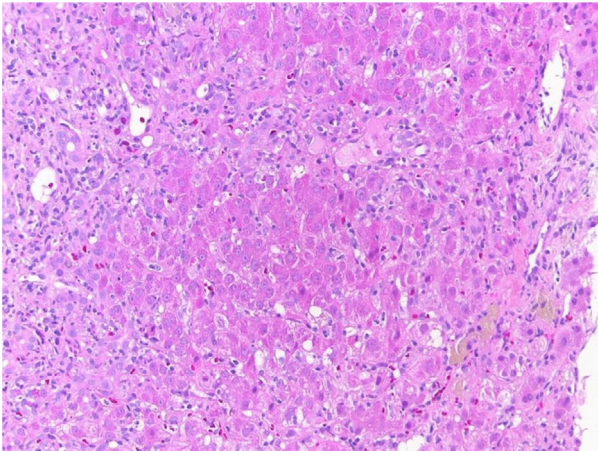
Figure 6. Bystander hepatitis in Stauffer syndrome, a paraneoplastic effect of renal carcinoma. Confluent necrosis is seen, with numerous apoptotic hepatocytes present throughout the lobules.

Figure 7. Biopsy from a middle-aged female who was found to have grossly abnormal liver function tests following two doses of COVID 19 vaccine. In this case there was an initial response to steroids but there was a relapse following a third dose of vaccine. Lobular inflammation is seen with confluent necrosis and a plasma cell-rich infiltrate.

lymphoma,[50] have been found to induce acute hepatitis as a paraneoplastic syndrome without neoplastic infiltration of the liver (Figure 6). Some reported cases have been severe and may require bridging steroid therapy, but treatment of the underlying neoplasm results in hepatitis resolution. Autoimmune-like hepatitis has also been described in association with SARS-CoV-2 infection and vaccination[51,52] (Figure 7). The number of reported cases is very small, and it remains unclear whether this represents a bystander hepatitis due to immune activation, cross-reactivity of SARS-CoV-2-reactive cells with the liver or is simply a non-causal coincidence.[53] Mycoplasma pneumoniae infection is a rare cause of acute hepatitis and is predominantly seen in younger adults and children. As mycoplasma has not been shown to be hepatotropic the acute hepatitis is postulated to occur because of immune activation, although the exact pathogenesis remains unclear.[54] The histological appearance is identical to typical acute hepatitis, with conspicuous apoptotic hepatocytes, spotty inflammation and lobular disarray.[55]

INDETERMINATE HEPATITIS

Acute hepatitis with a typical 'immunological' pattern may not have any clear aetiology. It remains unclear whether this represents an undetectable viral infection or some other form of immune dysregulation. Brennan *et al.*[56] undertook a systematic review to identify possible aetiological agents, including *PVB19* toga-like virus and *annelloviridae* (including SEN-V), but concluded that there was no compelling 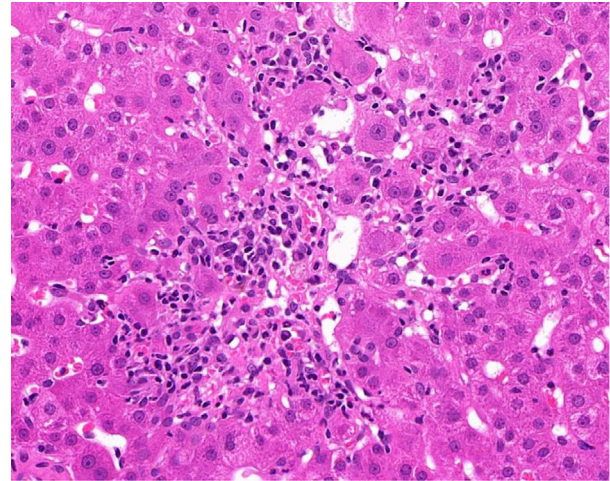evidence. In one study such 'seronegative hepatitis' was responsible for 3% of all patients who presented with jaundice to a non-transplant centre versus 5% for AIH and 7% for viral hepatitis.[57] As many of the patients with a viral cause for hepatitis would not have been biopsied, this seronegative hepatitis is probably over-represented in cases that come to biopsy. The duration of illness was 4–12 weeks, with a mean of 7 weeks. Importantly, early AIH may present before antibodies appear, so follow-up serology is necessary. Some patients with this process present with or develop ALF with a high risk of either death or orthotopic transplantation. This has previously been referred to as (i) non-A, non-B, non-C hepatitis, (ii) non-A-E hepatitis or (iii) seronegative hepatitis. Indeterminate acute hepatitis (IAH) is now the preferred term, severe IAH (sIAH) being used when there is clinical evidence of failure. sIAH is thought to be responsible for approximately 15% of cases of ALF seen in specialist centres. Biopsies were previously discouraged in this setting, but several papers have drawn attention to its use in prognostication and for guiding therapy. Lin *et al.*[58] demonstrated that the presence of multilobular (panacinar) necrosis (MLN) was associated with a higher MELD score and INR and by multivariate analysis was an independent predictor for transplantation or death, the only such histological parameter. These cases had low immunoreactivity for HNF4a and the proliferation marker Ki67, but increased expression of the progenitor cell marker keratin 19 and cell death markers (cleaved caspase 3 and RIPK3). These results are like

those recorded in severe acute presentation AIH. Furthermore, in a retrospective study, they showed that the presence of MLN predicted the beneficial effect of treatment with corticosteroids with a reduction in risk of death or transplantation in 50%.[59]

In some settings, biopsy has been found to be of considerable value in identifying or confirming new and/or emerging causes of severe immune-mediated indeterminate hepatitis. For example, in 2021 there were reports of an outbreak of idiopathic acute hepatitis occurring in children with concurrent adenovirus infection. The biopsy appearances resembled severe autoimmune hepatitis with plasma cell-rich interface activity. Although no adenovirus inclusions were seen, polymerase chain reaction (PCR) testing of biopsy tissue showed enteric adenovirus serotypes 41 (species F) in most cases.[60] In another study, high levels of adeno-associated virus 2 (AAV2) DNA were detected in liver tissue; replication of AAV2 requires coinfection with a helper virus, such as adenovirus, herpesvirus or papillomavirus.[61] The biopsy material therefore helped establish the probably biological mechanisms of the disease.

Other patterns of acute liver injury

STEATOTIC LIVER DISEASE

Steatotic liver disease may present acutely with one of two main histological patterns: active steatohepatitis and microvesicular steatosis. The former is most often seen in the context of an acute presentation of alcohol-related liver disease (often with a clinical alcohol-related hepatitis syndrome).[62] These are largely examples of ACLF and most already on biopsy have advanced fibrosis, if not cirrhosis, at the time of presentation. Biopsy in a such setting can help to distinguish ACLF due to recent alcohol abuse from decompensation of underlying alcohol-related cirrhosis.[63] Histology guides the selection of patients for treatment with corticosteroids, which should be reserved for those with alcohol-related steatohepatitis.[64] Furthermore, detection of bilirubin pigment in hepatocytes,[65] canaliculi and ductules[63,66] can help to detect infection at an early, often subclinical, stage. Substages of alcohol-related cirrhosis and ASH are independent predictors of prognosis in decompensated alcohol-related liver disease. It can also be seen in DILI, the most notable examples associated with more acute presentation being amiodarone and (now historically) highly active antiretroviral therapy (HAART) during treatment for HIV.[41] Conversely, microvesicular steatosis rarely shows signs of chronicity on biopsy. The causes of this pattern of injury are reviewed elsewhere[67] but briefly, the principal factors are (i) DILI, (ii) acute fatty liver of pregnancy, (iii) Reye syndrome, (iv) inherited disorders of urea cycle, fatty acid metabolism and mitochondriopathies and (v) a relative uncommon adverse effect of excess alcohol intake, alcohol-related foamy degeneration.[68]

ACUTE CHOLESTASIS

Acute cholestasis characterised by a bland bilirubinostasis and accompanied by minimal parenchymal inflammation is a common pattern of injury in DILIs such as that due to some antibiotics or anabolic steroids; this can be associated with grossly elevated bilirubin levels and jaundice, but is not typically accompanied by any significant synthetic dysfunction.[69] It is generally reversible on cessation of treatment, although a proportion of individuals may go on to progressive ductopenia. Bland cholestasis is also a feature of some paraneoplastic syndromes, possibly resulting from cytokine-mediated inhibition of bile transporters. Renal cell carcinoma, prostatic adenocarcinoma and haematological malignancies such as Hodgkin disease have been implicated.[70,71]

SINUSOIDAL OBSTRUCTION SYNDROME

Sinusoidal obstruction syndrome is a form of acute liver injury that may complicate haematopoietic stem cell transplantation or be seen in injury from pyrrolizidine alkaloids or oxaliplatin. It presents with abdominal pain and swelling with signs of portal hypertension. Biopsies show narrowing of hepatic veins by loose connective tissue, with central haemorrhage and perivenular hepatocyte loss.[72,73]

INFILTRATIVE PROCESSES

Acute liver disease may also be caused by infiltrative processes, in particular malignant deposits. The number of cases reported in the literature of ALF occurring in this setting is low, but almost certainly this is under-reported. In the largest case series, 27 cases were identified in an ALF registry of 1910 patients.[74] One-third were associated with lymphoma/leukaemia, another third metastatic breast carcinoma (particularly lobular type) with 7% in metastatic colorectal carcinoma. Most patients died within 3 weeks of the onset of ALF. The key role of liver biopsy is to identify the futility of further active treatment.

ISCHAEMIC INSULTS

Finally, ischaemic insults can give rise to clinically important acute liver disease and may lead to ALF. This is sometimes referred to as 'ischaemic hepatitis', although this is something of a misnomer, as it is not an inflammatory condition as such. The typical appearances by histology include zone 3 necrosis with congestion, a pattern not dissimilar to paracetamol toxicity. In contrast with paracetamol (acetaminophen) toxicity, in which zonal necrosis is uniformly present throughout the liver, ischaemic necrosis typically has a more patchy distribution which may not be strictly zonal. Other examples of zonal necrosis include that associated with certain direct hepatotoxins that selectively damage hepatocytes in acinar zone 1 (e.g. phosphorous (Figure 3), ferrous sulphate). Tapper *et al.*[75] undertook a systematic review with a meta-analysis of 24 papers on 'ischaemic hepatitis'. In more than 75% of cases there was an association with an acute cardiac event, and in 24% there was sepsis. Interestingly, a hypotensive event was only documented in 53% of cases. Just over half survived the liver injury to enable discharge.

Conclusions and practical considerations

Despite recent advances in immunoserological and microbiological diagnostics, liver biopsies will continue to play an important role in the multidisciplinary management of patients with acute liver disease. This includes those in whom there is less severe liver injury, and where the abnormalities may have been detected biochemically, to those with ALI, ALF or ACLF. In the context of severe liver injury, urgent processing and reporting of biopsies is essential. This may necessitate rapid processing for 'same-day' reporting, although we would advise against the use of frozen sections as this may be complicated by tissue artefacts. Most centres are now well equipped to use rapid fixation of specimens, with a turnaround of a few hours. Recent studies point to the utility of liver biopsy in the management of severe indeterminate hepatitis, providing invaluable data to predict survival and probable response to medical treatment. We speculate that the future application of deep learning algorithms may further enhance the prognostic value of this approach; however, the data sets required to develop this will be challenging, given the complex nature of the patient cohorts. In the molecular era, liver biopsy leads safely to the identification of patterns of liver involvement and also provides tissue to be submitted to molecular approaches, which may yield aetiological evidence. Importantly, now, each molecular phenomenon and each cell type may be directly assessed in liver tissue using spatial multiplex staining techniques. All these new approaches will be found most useful when interpreted in a strong clinicopathological context.

Conflicts of interest

None of the authors have any conflicts of interest to declare.

Data availability statement

No original data are included in this review article.

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