Role of liver biopsy in autoimmune liver disease

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Abstract

This article will review histological aspects of three chronic liver diseases — autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) — in which autoimmune mechanisms are thought to be involved. The changing role of liver biopsy in the diagnosis and management of patients with autoimmune liver disease will also be discussed. In the case of autoimmune hepatitis, histological assessments remain important in establishing a diagnosis, identifying prognostic features and monitoring therapeutic responses. By contrast, for many patients with PBC and PSC a diagnosis can now be made on the basis of biochemical, serological and/or radiological findings alone and histological confirmation may not be required. Liver biopsy can still be used to assess disease severity in such cases and remains important in establishing a diagnosis in patients with atypical features (e.g. AMA-negative PBC or the small-duct variant of PSC). Liver biopsy is also increasingly used in the assessment of patients suspected to have "overlap syndromes" involving AIH and PBC or PSC.

Keywords autoimmune cholangitis; autoimmune hepatitis; autoimmune overlap syndrome; IgG4-related disease; primary biliary cirrhosis; primary sclerosing cholangitis

Introduction

Liver biopsy continues to play an important role in the diagnosis and management of patients with autoimmune liver disease. The three main diseases that will be discussed in this review are autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). None of these three diseases can be diagnosed on the basis of a single specific test. Instead the diagnosis is based on various combinations of biochemical, immunological, radiological and histological findings. The main diagnostic features are summarised in Table 1. It therefore follows that liver biopsy is rarely diagnostic in isolation and the final interpretation depends on correlating histological findings with the clinical picture and the results of other relevant investigations. Liver biopsy is also used to assess disease severity, including inflammatory grade and fibrosis stage, which may have implications for prognosis and treatment.

Autoimmune hepatitis (AIH)

Clinical presentation

The presenting features are very variable. In most cases the onset is insidious, with non-specific symptoms such as fatigue, lethargy and anorexia - features of chronic hepatitis are usually present by the time that liver biopsies are obtained, with up to one-third of patients already being cirrhotic at the time of presentation. Approximately 30—40% of patients have an acute presentation, typically associated with histological features of acute hepatitis, and sometimes presenting as acute liver failure. Some cases of drug-induced hepatitis may present with features indistinguishable from AIH — in contrast to classical AIH, such cases are not associated with advanced fibrosis and do not relapse following withdrawal of immunosuppression.

Diagnostic features

The diagnosis of AIH is based on a combination of biochemical, immunological and histological findings (Table 1). AIH can be subdivided into three main subtypes of AIH, based on autoantibodies: type 1 is the most common and has a bimodal age distribution with peaks at 10—25 years and 45—70 years; type 2 mainly occurs in children <15 years old and more frequently presents as severe acute hepatitis[1]; type 3 is clinically indistinguishable from type 1 and its existence as a separate subtype is disputed. The diagnosis also requires the exclusion of other diseases that may share one or more of the main features of AIH. Histological assessments contribute to the diagnosis of AIH, both by identifying features that are typical of (or compatible with) a diagnosis of AIH and by excluding features that might suggest an alternative diagnosis (e.g. fatty liver disease or chronic biliary disease). In an attempt to improve diagnostic accuracy, scoring systems have been devised by the International Autoimmune Hepatitis Group: Original-1993: Modified — 1999: Simplified — 2008 (Reviewed by Gleeson & Heneghan[2]). These use various combinations of clinical, biochemical and immunological features, with histological assessments also contributing to all three systems. Points are allocated for features supporting a diagnosis of AIH (and deducted for atypical features in the 1993 & 1999 systems) to produce a total score, which is then classified as "definite, "probable" or "not" AIH. These scoring systems were mainly intended for research purposes, such as clinical trials, but have sometimes been used for routine clinical diagnosis. The extent to which scoring systems are relevant for the assessment of paediatric AIH has been questioned.[3]

"Overlap syndromes" in which features supporting a diagnosis of AIH are present in patients who also have features diagnostic of PBC or PSC are discussed further later. Overlap syndromes involving AIH with hepatitis C, alcoholic liver disease, non-alcoholic fatty liver disease and other chronic liver diseases have also been described. However, it should be noted that autoantibodies are also commonly present in low titre in many chronic liver diseases, where they are considered to be a non-specific response to hepatocellular injury.

Histological findings

The classical histological finding in patients presenting with ***chronic autoimmune hepatitis*** is a plasma cell rich mononuclear infiltrate mainly involving portal and periportal regions. Although plasma cells are typically abundant, this is not always the case and a paucity of plasma cells does not therefore exclude a diagnosis of AIH. Conversely, plasma cells can also be seen, usually in small numbers, in other chronic liver diseases associated with portal inflammation (e.g. PBC). Interface hepatitis is also regarded as a key diagnostic feature of AIH (Figure 1a) — it

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Diagnostic features of AIH, PBC and PSC

	Autoimmune hepatitis	Primary biliary cirrhosis	Primary sclerosing cholangitis
Biochemistry	Hepatitic (raised AST/ALT)	Cholestatic (raised Alk Phos)	Cholestatic (raised Alk Phos)
Autoantibodies	ANA, SMA (type 1) LKM, LC-1 (type2) SLA/LP (type 3)	AMA Anti-M2	ANCA
Immunoglobulins	Raised IgG	Raised IgM	Normal levels or polyclonal elevation
Radiology (ERCP)	Normal	Normal	Abnormal (beading, strictures)
Histology	Hepatitic	Biliary	Biliary
Bile duct lesions	*Mild*	*Inflammatory*	*Fibrosing*
Bile duct loss	*No*	*Yes*	*Yes*
Chronic cholestasis	*No*	*Yes*	*Yes*

Table 1

is typically associated with ballooning and rosetting of periportal hepatocytes and frequently also with emperipolesis of lymphocytes within periportal hepatocytes. Interface hepatitis leads to the development of periportal fibrosis (Figure 1b). Initially this is present as delicate strands of immature collagen enveloping small clusters of hepatocytes. Subsequently, there is development of broader fibrous septa associated with bridging and nodule formation. Progression to cirrhosis occurs in 40–80% of cases. Inflammatory activity often subsides when cirrhosis has developed, making it difficult to distinguish end-stage AIH from other causes of cirrhosis. Small groups of entrapped hepatocytes showing ballooning and/or rosetting can sometimes still be seen within cirrhotic septa and may provide a clue to AIH as a possible cause for cirrhosis. Varying degrees of lobular necro-inflammatory activity are also commonly seen in chronic autoimmune hepatitis. These range from mild spotty inflammation with acidophil body formation through to more severe lesions associated with confluent, bridging or panacinar necrosis. Lobular necro-inflammatory changes tend to be more prominent in cases with an acute presentation (discussed further below).

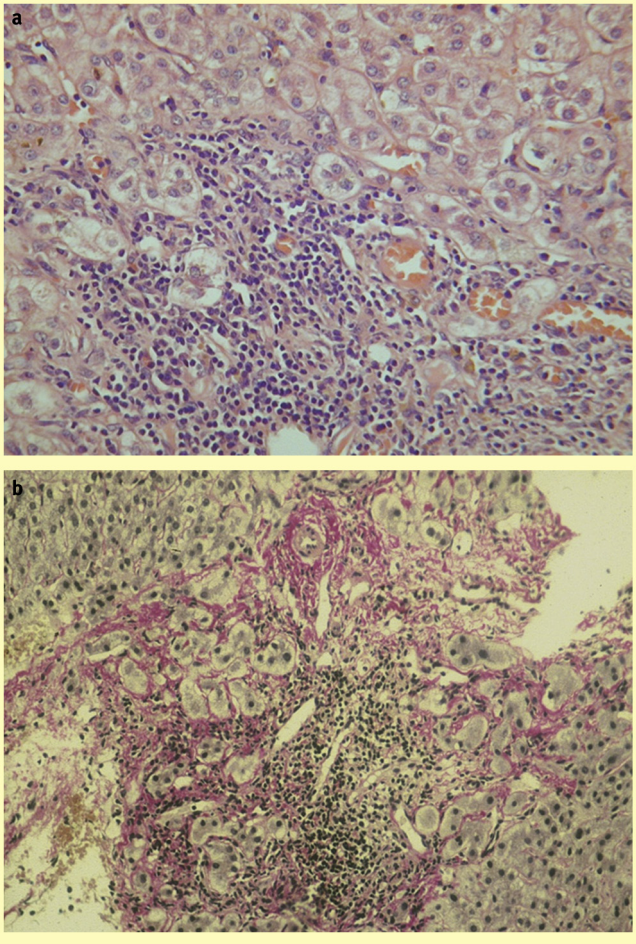

Figure 1 Periportal inflammation and fibrosis in chronic autoimmune hepatitis. (**a**) Portal tract inflammation with interface hepatitis associated with ballooning and rosetting of periportal hepatocytes. (**b**) Interface hepatitis is also associated with the fibrous entrapment of periportal hepatocytes (haematoxylin Van Gieson).

Portal and periportal inflammation, which could be classified histologically as chronic hepatitis, can also be seen in many other chronic liver diseases. These include viral hepatitis (hepatitis B and C), chronic biliary diseases (PBC and PSC), fatty liver disease (alcoholic and non-alcoholic) some metabolic diseases (e.g. Wilson's disease, alpha-1-antitrypsin deficiency) and certain drug reactions (e.g. isoniazid, methyldopa, minocycline, nitrofurantoin). In most cases, careful assessment of pathological features and other clinical findings will lead to the correct diagnosis.

Inflammatory bile duct lesions are also recognised to occur in otherwise typical cases of AIH. Typically the changes seen are mild with focal lymphocytic infiltration of bile ducts that are otherwise well preserved. Less commonly there are more severe changes with biliary epithelial cell damage or disruption, in some instances associated with bile duct loss, although this is rarely extensive. Cases of AIH with destructive cholangitis or duct loss tend to have higher alkaline phosphatase levels than those without biliary changes, but are otherwise similar in terms of disease behaviour and response to immunosuppression.

Autoimmune hepatitis with an acute presentation is typically associated with prominent necro-inflammatory changes involving the liver parenchyma. These frequently have the appearances of acute lobular hepatitis with spotty necrosis and lobular disarray. In more severe cases there is confluent or