

HISTOPATH UPDATE

PATHOLOGY OF CHRONIC HEPATITIS

VIRAL & AUTOIMMUNE HEPATITIS & THE OVERLAP SYNDROMES

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INTRODUCTION

Chronic hepatitis is defined as chronic inflammation in the liver continuously for at least six months. From a practical point of view, though, it refers to viral, drug-induced and autoimmune hepatitis as well as some inherited liver diseases and excludes the chronic biliary and metabolic disorders. As one of the most common patterns of liver disease, chronic hepatitis is a problem that is commonly encountered in liver biopsies. Biopsies are taken for a number of different reasons and it should be remembered that the particular information being sought by the clinician differs in certain circumstances. Many biopsies are taken for grading and staging, and in these patients the diagnosis is known prior to histological examination. In other cases there may be abnormalities of liver function that remain of uncertain aetiology, or the presence of more than one disease needs to be confirmed or excluded. Additionally, because the risk of malignancy is increased in this group, premalignant changes need to be excluded.

This lecture will describe the general approach to the biopsy showing a 'chronic hepatitis' pattern and will consider the features that are of use in guiding the differential diagnosis. Specific diseases and the current views on the overlap syndromes will then be discussed.

I. THE PATTERN OF CHRONIC HEPATITIS

When assessing the liver biopsy, it is useful to do so in a blinded fashion without recourse to the clinical details. A number of basic patterns can be recognised and help to guide the decision-making algorithm. At first, low-power glance, I generally loosely categorise a biopsy into one of several (overlapping) patterns.

1. Fatty liver

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2. Acute hepatitis
3. Chronic hepatitis
4. Biliary / cholestatic
5. Nodular / vascular (non-fibrotic)
6. Pigment accumulation
7. Invisible
8. Cirrhosis
9. Tumour

Biopsies of chronic hepatitis can often be readily recognised because of the portal fibrosis and mononuclear portal inflammation. If fibrosis is not present then the clinical history of abnormality of liver function tests for over 6 months must be known to make the diagnosis. Three basic causes should be kept in mind – viral, drug and autoimmune – and other diseases listed below should also form the differential diagnosis. As discussed later, differences in the histology can guide the decision as to the probable diagnosis.

It is also important to consider the possible presence of a second contributing cause of liver dysfunction. Currently, alcoholic and metabolic steatohepatitis are the commonest co-aetiologies in chronic hepatitis, and the presence of fatty change, Mallory's hyaline or extensive pericellular fibrosis should alert the pathologist to suggest the possibility of a contributing cofactor.

DIFFERENTIAL DIAGNOSIS IN CHRONIC HEPATITIS

This pattern should initially prompt the potential diagnoses of **viral, drug and autoimmune** hepatitis (Table 1). This same appearance can be mimicked in the biliary diseases primary biliary cirrhosis and primary sclerosing cholangitis, and can also be seen in inherited diseases such as Wilson's disease and alpha-1-antitrypsin deficiency. The presence of ground glass inclusions, confirmed by the Shikata orcein stain, is diagnostic of chronic hepatitis B infection. It should be remembered, though, that co-infection with hepatitis C occurs in some instances. Hepatitis C may be suspected by the presence of **lymphoid aggregates, steatosis** and sinusoidal lymphocytosis, but this is far from a specific appearance. Autoimmune hepatitis should be suspected when **plasma cells** are a prominent component of the inflammatory infiltrate, particularly when there is a moderate or greater degree of interface hepatitis and acinar hepatitis. Primary biliary cirrhosis can have prominent portal inflammation and inflammatory cell aggregates similar to hepatitis C, but these are generally made up of mixed lymphocytes and **plasma cells** rather than purely lymphocytes. Careful examination may reveal granulomatous cholangitis, epithelial degeneration in bile ducts, bile duct loss or peripheral bile ductular proliferation. Deposition of copper associated protein at the periphery of some acini may also be of diagnostic use. Cases of primary sclerosing cholangitis with heavy portal inflammation can be impossible to distinguish from other causes of chronic hepatitis, and a high degree of suspicion needs to be maintained in cases where there is elevation of biliary enzymes. A significant proportion of these patients has a PSC/autoimmune hepatitis overlap including autoantibodies.¹ Generally, most progress as PSC.

Table 1. Differential diagnosis of chronic hepatitis (major conditions)

<i>Cause</i>	<i>Specific Diagnosis</i>	<i>Hints</i>
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Chronic Hepatitis

Viral hepatitis	hepatitis B (\pm D), hepatitis C	ground glass cells
Drug	eg nitrofurantoin	nil specific
Autoimmune	types I, II, III	plasma cell predominance
Biliary diseases	PBC, PSC	lymphoplasmacytic,
copper		
Inherited diseases	Wilson's disease, α 1AT deficiency	special stains reveal
copper/globules		

II. CHRONIC VIRAL HEPATITIS

Because of the high frequency of the hepatitic viruses in many communities, viral hepatitis is a common indication for liver biopsy. This is particularly true for chronic hepatitis C, where liver biopsy is a prerequisite for interferon/ribavirin therapy. Full reviews on chronic hepatitis are readily available²⁻⁴ and this lecture will outline only selected points related to current practice.

AETIOLOGY AND NATURAL HISTORY

It is well known that hepatitis B and hepatitis C are the most common causes of chronic viral hepatitis. Hepatitis A & E cause only self-limited disease in most patients and do not cause chronicity. Delta virus requires co-infection with hepatitis B for division but is not common in Australia. Recent studies of hepatitis G suggest that it is unlikely to be a significant cause of either fulminant or chronic hepatitis. It is possible that rare, as yet undiscovered viruses can also cause chronic hepatitis, since a proportion of patients transplanted for idiopathic fulminant hepatitis subsequently develop chronic hepatitis in their grafts.

Hepatitis B and hepatitis C differ in their natural histories, as shown in Table 2. The majority of patients infected with hepatitis C, around 85%, develop chronic disease of variable severity. The 15% who clear virus appear to do so by inducing a productive Th1 cytokine response (IL-2 and IFN- γ dominant). Even with chronic disease, the outlook for chronic hepatitis C is not bleak. Between 20 and 30% of patients eventually develop cirrhosis but most of these remain well compensated. About 1/5 (4%) develops end-stage liver disease and a further 2-4% develops hepatocellular carcinoma, usually after period of 20 to 30 years of infection. Some patients progress more rapidly. Transplantation may be required but if patients with cirrhosis can be maintained in a compensated state long survival is possible.

Table 2. Natural history of chronic viral hepatitis.

	<i>Hep B</i>	<i>Hep C</i>	<i>Hep D</i>
Immune	85% (adult) 5% (neonate)	15%	
Chronic hepatitis	5%	85%	5% coinfection

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Carrier	10%	80% superinfection	
Cirrhosis	1% (adult)	25%	
Hepatocellular carcinoma	<<1%	2-4%	as for Hep B

Hepatitis B becomes chronic in up to 10% of infections and cirrhosis develops in 1% of infected patients. Many patients have subclinical infection with the early development of protective antibodies to surface antigen (anti-HBsAb) but the time taken to develop “immunity” with conversion to anti-HBs Ab varies. In many cases where the disease is acquired early in life, productive infection occurs until early adulthood followed by seroconversion to anti-HbeAb positive (no longer infective) and then, in some, to anti-HBs Ab (immune). Recent evidence suggests that the virus is probably never cleared completely, even when anti-HBsAb develops, and this occult infection may be important in the subsequent development of hepatocellular carcinoma and cirrhosis.⁵ For this reason, patients with chronic hepatitis B should be monitored for life.

Mutations of the viruses occur in both chronic hepatitis C and hepatitis B. The development of hepatitis C quasi-species is one reason why immunity and immunisation are problematic. Hepatitis B also develops mutations including the precore mutation (causing loss of eAg during productive infection) and other mutations (eg. YMDD mutation) that inhibit the action of antiviral drugs such as lamivudine.

Progressive disease, particularly in hepatitis C, has been linked to age at acquisition (faster if >40 yo), sex (males more severe), portal inflammation, the amount of steatosis and, more recently, to host factors such as body mass index (overweight/obese patients) and polymorphisms in profibrogenic genes such as *TGF*.⁶⁻⁹ Treatment with interferon and antivirals, recombinant interleukin-10 and weight loss have had variable degrees of success, with the current favoured protocol being interferon plus ribavirin for 12 months (genotype 1b) or six months (genotype 3) with a sustained response rate of about 50%. Obesity may inhibit antiviral efficacy.

THE BIOPSY AND CHRONIC VIRAL HEPATITIS

Patients who are biopsied generally have demonstrated abnormal LFTs of varying severity and by definition this should be present for greater than six months. The presence of mature fibrous expansion in portal tracts can be taken as a surrogate marker of chronicity. Clinicians are interested in several factors that impact on prognosis and also on whether the patient should be treated with interferon/antiviral therapy. The important features include:

- Portal inflammation – presence and severity
- Lobular (acinar) inflammation – presence and severity
- Fibrosis – presence and severity
- Pre-neoplastic/neoplastic changes
- Other coexistent disease (eg. alcoholic liver disease, siderosis)

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Apart from ground glass inclusions containing hepatitis B surface antigen, there are no features that reliably distinguish chronic hepatitis B from hepatitis C.

Portal inflammation

Grading systems vary a little in their assessment of portal activity. Ishak's modification of the Knodell classification separates the degree of portal inflammation from the severity of "piecemeal necrosis". (Piecemeal necrosis is now generally referred to as **interface hepatitis** since the mode of cell death is apoptosis rather than necrosis.) Other systems such as the Scheuer score and the METAVIR system grade the lesions together (Table 3). Interface hepatitis refers to disruption of the limiting plates by inflammatory cells and also requires the presence of apoptotic hepatocytes. Particularly in hepatitis C, the cutoff between absent and mild interface hepatitis is often difficult.

The METAVIR system, which has recently come into use in Australia for hepatitis C antiviral treatment, gives an overall activity score that combines severity of piecemeal necrosis (interface hepatitis) (scored 0 to 3) and severity of acinar inflammation (scored 0 to 2). This activity score is an important factor used to determine which patients should be treated (activity score of A2 or more).

Portal fibrosis

Fibrosis scoring in most systems assesses the degree of portal expansion and portal to portal / portal to central linkage. Although not widely assessed, it is possible that acinar fibrosis similar to that developing in steatohepatitis may also play a role. The different systems use slightly different definitions and so the specific scoring system must be specified when a fibrosis score is given numerically. Interestingly, recent evidence suggests that fibrosis is **reversible** following treatment of chronic viral hepatitis.¹³ For this reason, repeat biopsies and serial biopsies may become more common in the future.

Table 3. Scoring systems for chronic hepatitis.

A. Scheuer score¹⁰			
	Portal activity (grade)	Lobular activity (grade)	Fibrosis (stage)
0	none/minimal	none	none
1	mild	inflammation, no necrosis	enlarged by fibrosis
2	mild interface hepatitis (IH)	focal apoptotic bodies	portal-portal linkage
3	moderate interface hepatitis	severe focal cell damage	distortion, not cirrhotic
4	severe interface hepatitis (probable)	bridging necrosis	cirrhosis (or)
B. METAVIR score^{11**}			
	Portal (piecemeal necrosis)	Lobular activity	ACTIVITY GRADE **
0	none	none or mild	A0: no PN or lobular activity
1	focal PN, some tracts	at least 1 focus per lobule	A1: mild PN (grade 1) OR lobular grade 1
2	diffuse PN some tracts OR PN (grade2)	multiple foci per lobule OR	A2: moderate

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	focal PN all tracts	bridging necrosis	OR lobular
grade 2			
3	diffuse PN all tracts	-	A3: PN grade 2 & lobular gr 2 OR severe PN (grade 3)

Fibrosis

F0	no fibrosis
F1	portal fibrosis without septa
F2	portal fibrosis with rare septa
F3	numerous septa without cirrhosis
F4	cirrhosis

** the METAVIR **activity grade** is derived by considering the portal and lobular grades together to give an overall activity score, which is given the letter **A**

C. Ishak (modified Knodell) score¹²

Necroinflammatory score (see reference for full details)

A 0-4	Periportal or periseptal interface hepatitis (piecemeal necrosis)
B 0-6	Confluent necrosis
C 0-4	Focal (spotty) lytic necrosis, apoptosis, focal inflammation
D 0-4	Portal inflammation

Fibrosis stage

0	No fibrosis
1	fibrous expansion of some portal areas (with or without spurs)
2	fibrous expansion of most portal areas (with or without spurs)
3	fibrous expansion of most portal areas with occasional portal-portal linkage
4	fibrous expansion of portal areas with marked portal-portal and some portal-central linkage
5	marked bridging (P-P and P-C) with occasional nodules (incomplete cirrhosis)
6	cirrhosis

Acinar inflammation

This is characterised by varying degrees of acinar inflammation (generally lymphocytes and macrophages), apoptotic hepatocytes and sometimes confluent dropout. Milder degrees of confluent loss may be randomly distributed, but with increasing severity there may be confluent perivenular cell loss or dropout linking portal and perivenular areas. This last change represents true bridging necrosis. Sinusoidal beading with lymphocytes can be seen in hepatitis C.

Carriers with chronic hepatitis B often have prominent ground glass cells and relatively sparse inflammatory activity. However, some patients show **heightened acinar activity** on a “carrier” background of numerous ground glass cells. In these instances three possibilities should be considered:

1. Seroconversion (from eAg to anti-e antibody)
2. Mutant virus infection (precore mutant, where eAg is not produced)
3. Superinfection with hepatitis D (delta virus)

Steatosis has been described in 60-70% of patients with chronic hepatitis C but can also be seen in hepatitis B. It is due in part to coexistent obesity, but viral factors also play a role in

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genotype 3 infection.^{14, 15} Increasing steatosis and obesity impact on the prognosis of hepatitis C,⁹ and we now report the presence and degree of steatosis in all biopsies. Patients may also show siderosis or steatohepatitis due to coexistent disease and these could have a role in disease progression. A small number of biopsies of chronic hepatitis C contain granulomas that are not due to intravenous drug use. It has been suggested that this feature indicates a greater likelihood of interferon therapy response. Bile duct injury can be seen in the middle of lymphoid aggregates, but these probably represent bile duct diverticula not bile duct loss.

Acinar fibrosis

In typical viral hepatitis the amount of acinar fibrosis is minimal. We have found that some patients with hepatitis C and obesity have deposition of some sinusoidal fibrosis in centrilobular areas¹⁶ but if the change is extensive, and particularly if the fibrosis has a pericellular chicken-wire pattern, the co-existence of previous steatohepatitis (alcoholic or non-alcoholic) should be considered.

NOMENCLATURE

The terms chronic active hepatitis, chronic persistent hepatitis and chronic lobular hepatitis have been superseded with the recognition of their limited clinical usefulness, particularly with chronic hepatitis C. Generally, current reporting indicates the likely aetiology, level of activity and stage of fibrosis. As an example, a current summary could read “**chronic hepatitis (hepatitis C) with mild activity and moderate fibrosis**”.

GRADING AND STAGING OF DISEASE

As listed earlier (Table 2), several systems to grade inflammatory activity and stage the fibrosis have been described. These assign numerical grades and are required to gain access to some drugs. Scoring has the advantages of standardising reporting (within limits) and focussing the pathologist's attention on the different aspects that can be seen in a biopsy. However, the necroinflammatory score components have imperfect reproducibility, although the inter-observer agreement for fibrosis scoring is generally excellent. Moreover, a sum score for inflammatory grade has the disadvantage of potentially giving a similar number for completely different lesions. Finally, there is sometimes the erroneous impression that a series of numerical scores imparts greater precision to a histopathological assessment. Scheuer has suggested that scoring should be performed when needed, for clinical studies and specific clinical indications.¹⁷

DYSPLASIA AND NODULES IN CHRONIC VIRAL HEPATITIS

Dysplasia and malignancy can develop in both chronic hepatitis B and hepatitis C. Viral integration is important in hepatitis B, but this does not occur with hepatitis C since it is an RNA virus. Rather, the hepatitis C core protein induces proliferation of hepatocytes. Two types of dysplasia have been described; **large cell dysplasia** where nuclei are large and hyperchromatic, and **small cell dysplasia** in which the hepatocyte size is smaller than usual resulting in an elevated nuclear to cytoplasmic ratio. Although hepatocyte dysplasia was initially described in African patients with hepatitis B and hepatocellular carcinoma, subsequent studies have shown that large cell “dysplasia” can also result from chronic cholestasis and I prefer the

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term **large cell change**.¹⁸ Small cell dysplasia is a more worrying lesion and has a higher association with hepatocellular carcinoma. However, areas of atrophy and parenchymal revision are easily misinterpreted, and significant interobserver variation is seen in the assessment of small cell dysplasia.

Generally, three types of nodules can be seen in patients with chronic viral hepatitis, usually in the context of cirrhosis. They are seen in about 25% of explanted livers. The nomenclature for these nodules varies, and although a consensus document exists¹⁹ an earlier classification is more easily applied and understood.²⁰ This appears in Table 4. Macroregenerative nodules, generally in excess of 7-8 mm, are commonly seen in cirrhotic livers and contain bile ducts but no atypical features. The presence of atypical features (Table 4) suggests that individual nodules may be undergoing malignant change. When the atypical changes are extensive, or when bile ducts can no longer be identified in a hepatocellular lesion, hepatocellular carcinoma can be diagnosed.

Table 4. Classification of nodules in cirrhotic liver²⁰

Macroregenerative nodule	at least 7-8mm diameter portal areas throughout lesion contain bile ducts no atypical features
Borderline nodule	focally reduced reticulin focal increased nuclear density (small cell change) focal hepatocyte plates of 3 cell thickness rare acinar structures rare infiltrative foci CD34 staining of sinusoids (< 50% sinusoids)
Hepatocellular carcinoma	uniformly thick plates (> 3 cells) widened sinusoids / floating plates small hepatocytes with increased nuclear density >3 acinar structures usually no portal tracts (unpaired arteries only) usually no iron CD34 staining of sinusoids (>50% sinusoids) ²¹

The development of hepatocellular carcinoma does not impart a poor prognosis if detected early, and this is the reason for screening programmes in patients with chronic viral hepatitis. Transplantation or excision (the latter only if liver function is satisfactory) will be performed if there is 1 lesion <5 cm or 3 lesions <3 cm. In these patients survival is not adversely affected. Larger or more extensive nodules have a poorer prognosis. Importantly, when resection only is performed the risk of subsequent hepatocellular carcinoma increases from 10% per year to 25%, probably because of liver cell regeneration and the elaboration of growth factors stimulating premalignant foci.

III. AUTOIMMUNE HEPATITIS

Chronic Hepatitis

Autoimmune hepatitis (AIH) accounts of 10-25% of chronic hepatitis and can present in adults, particularly women, as well as children. With appropriate immunosuppressive therapy it has an excellent prognosis, with remission in about 90% of patients. The diagnosis of classical AIH relies on a combination of clinical, laboratory and biopsy changes to make a firm diagnosis and depends on the exclusion of viral and other causes of chronic hepatitis, or hepatic injury. Autoantibodies are central to the diagnosis of AIH and have led to the serological subclassification into three distinct types (Table 5).²²

As shown in Table 6, histological features are a part of a matrix that gives a combined score devised by the International Autoimmune Hepatitis Group (IAHG), but clinical and especially laboratory findings (such as autoantibody titres and elevated globulin levels) are important. A definite diagnosis cannot be made on one component alone. Additionally, a negative score is given if features are seen that not typical of AIH (such as destructive cholangitis, a feature of PBC).

Table 5. AIH subtypes (based on serology of autoantibodies)²²

	<i>Autoantibody</i>	<i>Frequency</i>
Type 1	ANA, anti-SMA	80%
Type 2	anti-LKM1	4-20% (Europe > USA) ²²
Type 3	anti-SLA/LP	up to 10-20%

Table 6. Histological features that contribute to the International Scoring System²³

<i>Histological/clinical features</i>	<i>Maximum points</i>
Compatible histological features	5
Interface hepatitis	3
Portal plasma cell infiltration	1
Rosettes	1
None of the above	-5
Biliary changes	-3
Other diagnostic features	-3
Compatible clinical features	7
Compatible laboratory features	14
*** Definite diagnosis pretreatment	>15

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*** Probable diagnosis pretreatment

10–15

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HISTOLOGICAL FEATURES

In a report of suspected AIH, it is important to mention not only the presence of interface hepatitis and portal inflammation, but also their severity. Typically, AIH is characterised by moderate or severe inflammatory activity, but this is neither essential nor specific for the diagnosis. In about two-thirds of cases (66%), inflammation is moderate or severe, compared with a lower frequency in chronic viral hepatitis (HCV ~20%).²⁴ Cases with milder inflammation can be seen. The inflammatory infiltrate is typically rich in **plasma cells** in many cases (66%),²⁴ and these tend to be seen at the limiting plate and also in the lobules where they form part of the hepatic process. Because the inflammatory infiltrate has a high turnover, often the absolute number of inflammatory cells is not great in the portal tract, and in this instance it is of importance to carefully assess how much interface activity is present. Ishak's scoring system described above (variable A in Table X) is useful to guide this assessment.

It is common to see brisk lobular activity with many foci of spotty hepatic dropout, apoptotic hepatocytes and often some bridging necrosis. This last change is seen in biopsies as a curved link between portal areas and central veins where hepatocytes are lost, and the reticulin is collapsed. It can look like fibrosis in H&E stains, but the collagen stain shows little or no collagen fibres. Inflammation is variable but at least some is generally present along the bridged areas. As a reflection of the brisk hepatocyte loss, regeneration is upregulated and is seen as clusters of hepatocytes forming **rosettes**. These cells can show cytoplasmic basophilia.

The degree of fibrosis is variable at the time of first diagnosis. Even in patients with an acute presentation, some degree of fibrosis is common, but it can be difficult to distinguish collapsed reticulin from collagenous septa in routine H&E sections and the reticulin and trichrome stains must be read in conduction. Up to 25% of patients are cirrhotic at the time of diagnosis.²²

Giant cell hepatitis

Some hepatocytes can be multinucleated, but in rare cases there will be numerous cells with very large numbers of syncytial-type giant cells, termed (post-infantile or adult) **syncytial giant cell hepatitis**. This change is common in paediatric liver disease but is rare in adults. It has been linked to a variety of causes including AIH,²⁵ viral infection²⁶ (HAV, HBV, HCV, EBV, paramyxovirus²⁷), drugs/herbal remedies²⁸ and primary sclerosing cholangitis. As such, it should be regarded as a pattern of hepatitis from a heterogeneous group.

Centrilobular hepatitis

A rare form of AIH presents as predominantly centrilobular injury.²⁹⁻³¹ A similar lesion has been observed in the transplanted liver,³² and it can evolve into more typical AIH if serial biopsies are taken. The clinical significance of this variant is unknown.

Biliary changes and AIH

Cholestasis is not a typical feature, but if the hepatitis is severe there may be some reactive ductular proliferation. In weighing up whether this is the major process, I compare the degree of hepatitis with the degree of ductular proliferation – it is generally clear that one is dominant,

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and this should guide the ultimate diagnostic interpretation. Bile duct injury is not a typical feature but it has been described in up to 24% of biopsies.³³ Some of these cases could represent subtle or weak expressions of overlap syndromes. A minority of patients has steatosis prior to the initiation of therapy.

Post-treatment biopsies

Biopsies taken after the initiation of therapy are sometimes performed to determine the response to therapy. Although some centres perform rebiopsy prior to cessation of steroids, more usually it is done if the response clinically has not been complete, or to assess for the presence of cirrhosis. The histological resolution lags the clinical response by 3-6 months²³ and cirrhosis, the persistence of interface hepatitis or in some cases portal inflammation, predicts a high likelihood of recurrence after steroid withdrawal.^{23, 34}

Cryptogenic chronic hepatitis

There appears to be a form of aggressive **cryptogenic chronic hepatitis** that possibly represents a form of autoimmune hepatitis without typical autoantibodies.³⁵ It has similar clinical features and responds to corticosteroid therapy at the same rate as AIH. Without the autoantibody support, histological appearances become of greater importance. This is discussed further below.

IV. OVERLAP AND VARIANT SYNDROMES

Approximately 20-30% of patients with autoimmune liver disease have overlap or variant features that complicate their classification,^{36, 37} and so the literature has tried to address these lesions. Unfortunately the conditions are difficult to diagnose, variably (and sometimes loosely) defined and have empirical treatment regimens. Additionally, it appears that overlap cases can switch dominance from one component to the other, sometimes necessitating a change in treatment strategy. Thus, it is not surprising that enlightenment can be elusive, at best. The following is one interpretation of these syndromes, and it borrows heavily from a large body of work from Czaja at the Mayo Clinic.^{23, 35, 37, 38}

There are 3 main overlap syndromes (**with** autoantibodies) and 2 outlier syndromes (**without** autoantibodies) that are characterised to at least a degree. None are particularly common. They are as follows:

- AIH – PBC overlap
- AIH – PSC overlap
- AIH & chronic viral hepatitis

- Autoimmune cholangiopathy
- Cryptogenic chronic hepatitis

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AIH – PBC overlap

This overlap is well recognised, but it should show serological, biochemical and histological changes of both diseases to qualify for the overlap diagnosis.³⁹ It is not sufficient to find excessive portal inflammation without autoantibodies in otherwise typical PBC (which occurs relatively commonly³⁷) nor is low titre antimitochondrial antibody (AMA) in otherwise typical AIH without duct lesions sufficient to warrant the designation of PBC – AIH overlap, since non-specific AMA (titre < 1:160) can occur in AIH and other liver diseases.³⁷ About 20% of patients with PBC have florid portal inflammation.³⁶ However, 8 % of patients with AIH have a true overlap syndrome. The treatment is unclear – steroids and ursodeoxycholic acid have been tried.⁴⁰ Ultimately, treatment may be guided by the dominant histological change,⁴¹ but this strategy requires validation. It is unclear whether the overlap change is a lesion lying at the centre of a spectrum,⁴² an expression of one disease that evolves into the second, or whether the two diseases co-exist in predisposed individuals.⁴³

AIH – PSC overlap

This overlap is less common than the above and again requires cholangiographic and histological changes of PSC accompanied by clinicopathological changes that, on their own, would be diagnostic of AIH.⁴⁴ When strictly defined as such, it is probably rare in adults but may be commoner in children.^{1, 41} It should be suspected in patients with concurrent inflammatory bowel disease, particularly low-grade pancolitis,³⁷ and also in those diagnosed with AIH who have a poor response to steroids. Because the histological diagnosis of PSC is often difficult in typical disease, the diagnosis may not be considered until cholangiography is performed. An exception is the intrahepatic (small-duct) form of PSC where duct scars and onion-skinning occur without large duct lesions.²³ The optimal treatment and the risk of cholangiocarcinoma remains undefined, but cases reported to date have described a poor response of the bile duct lesions to immunosuppression.^{41, 44}

An AIH – PSC overlap occurs in children and appears to begin as a predominantly AIH-like picture that gradually develops a clinical picture of PSC.¹ It has had the term autoimmune sclerosing cholangitis applied to it. The overlap syndrome appears to be about as frequent as pure AIH in the paediatric age group and requires cholangiography for identification.

AIH – viral hepatitis

This entity is not well recognised in the literature but does appear to occur.⁴⁵ Up to 4% of patients with otherwise typical AIH have hepatitis C infection,²³ and a similar number have evidence of hepatitis B infection. Case reports suggest that these patients have greater portal inflammatory activity and respond to steroids, but the increasing experience with post-transplant hepatitis C suggests that a counter-argument against such therapy could be mounted. It is important to note that low-titre autoantibodies of < 1:160 are common in hepatitis C and the overlap syndrome requires high titres.²³

Czaja and Carpenter have looked at this a little differently.⁴⁶ They assessed 60 biopsies and assigned the term **chronic hepatitis C with autoimmune features** if the biopsy showed diffuse portal, interface and acinar hepatitis in any combination with plasma cell infiltration. A proportion of these patients (13%) also had high titre anti-smooth muscle antibody greater than 1:320, representing a true overlap syndrome. It was associated with an increased risk of cirrhosis.

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Patients with lymphoid aggregates, mild interface hepatitis and steatosis have the common changes of hepatitis C and these are **not** compatible with a diagnosis of AIH or an overlap.²³

Autoimmune cholangitis

This disorder was popularised by Sherlock and colleagues⁴⁷ and describes a group of patients with absent anti-mitochondrial antibody, positive ANA, cholestatic LFTs and a histological picture **typical of PBC**.⁴⁸ Immunocholangitis and autoimmune cholangiopathy are other terms that have been applied. The histology does not resemble AIH. It may represent a mixed group that includes AMA-negative PBC and also others.^{23, 49} The treatment generally follows that used for PBC; steroids have been tried in patients with more inflammation and improves the degree of inflammation but does not impact on the biliary loss.⁴⁹

Cryptogenic chronic hepatitis

There is a group of patients with chronic, non-viral hepatitis who have typical histological features of AIH - ie. a significant portal and lobular hepatitis with moderate or severe interface hepatitis and plasma cell predominance – but who lack ANA or anti-SMA and, as such, cannot be classified as definite AIH. The patient characteristics are similar to usual AIH when the hepatitis is moderate or severe,³⁷ and the treatment response to steroids mirrors that of AIH. These patients benefit from further investigation of autoantibodies by a specialist centre,³⁷ which may be present against uncommon antigenic targets such as **soluble liver antigen** (anti-SLA/LP) also known as liver-pancreas antigen.²²

A form of idiopathic chronic hepatitis is described in **transplant patients** but currently its significance remains unclear.³² The term **idiopathic post-transplant chronic hepatitis** has been suggested at a consensus meeting recently (2003, unpublished). There has not been any systematic study of autoimmune markers, treatments or long-term outcomes in these patients, but it appears that some have a fluctuating course requiring reintroduction of steroids into the immunosuppressive regimen, and a small proportion progress to cirrhosis.

Table 7. Distinguishing between typical autoimmune and variant syndromes

	AMA	ANA or aSMA	PBC-like histology	Interface hepatitis	Lobular hepatitis	Abnormal cholangiogram
PBC	+	25%	+	20%	-	-
AIH	-	+	-	++	+	-
AIH – PBC overlap	+	+	+	++	+	-
AIH – PSC overlap	-	+	-	++	+	+
AIH – viral overlap	-	+	-	++	+	-
		(>1:320)				
Autoimmune cholangitis	-	-	+	±	-	-

Chronic Hepatitis

Cryptogenic hepatitis

- -
 (anti-
 SLA)
- ++ + -

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