Autoimmune liver diseases: an update

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Spectrum of autoimmune liver disease

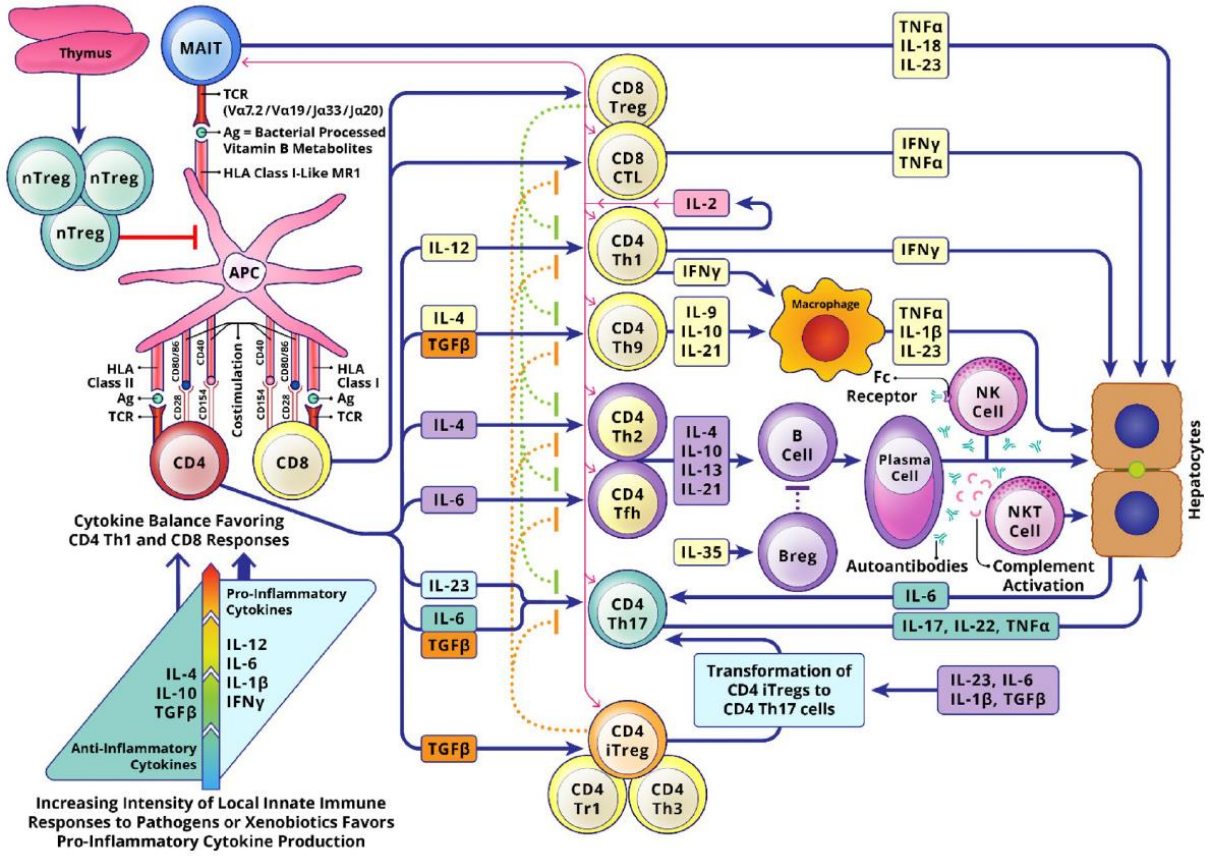
- Autoimmune hepatitis
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- (IgG4-associated cholangitis)

- Outlier syndromes
  - Autoimmune cholangiopathy

- Overlap syndromes
  - simultaneous
  - consecutive (‘crossover’)

Autoimmune hepatitis: key features

- Clinical presentation variable
- More common in females
- May be asymptomatic (approximately 20%) or present with non-specific symptoms
- Acute presentation: may be fulminant hepatic failure
  - Acute on chronic
  - Recent onset
- Significant proportion cirrhotic at presentation
- Bridging and pan-acinar necrosis more likely in those with acute presentation



Subtypes of AIH

	Type 1	Type 2	Type 3
Autoab	SMA/ANF	LKM	SLA/ANF
Age	10-20; 45-70	2-24	30-50
Female	78%	89%	90%
Ig elevation	+++	+	++
Steroid response	+++	+	++
Cirrhosis	45%	82%	75%

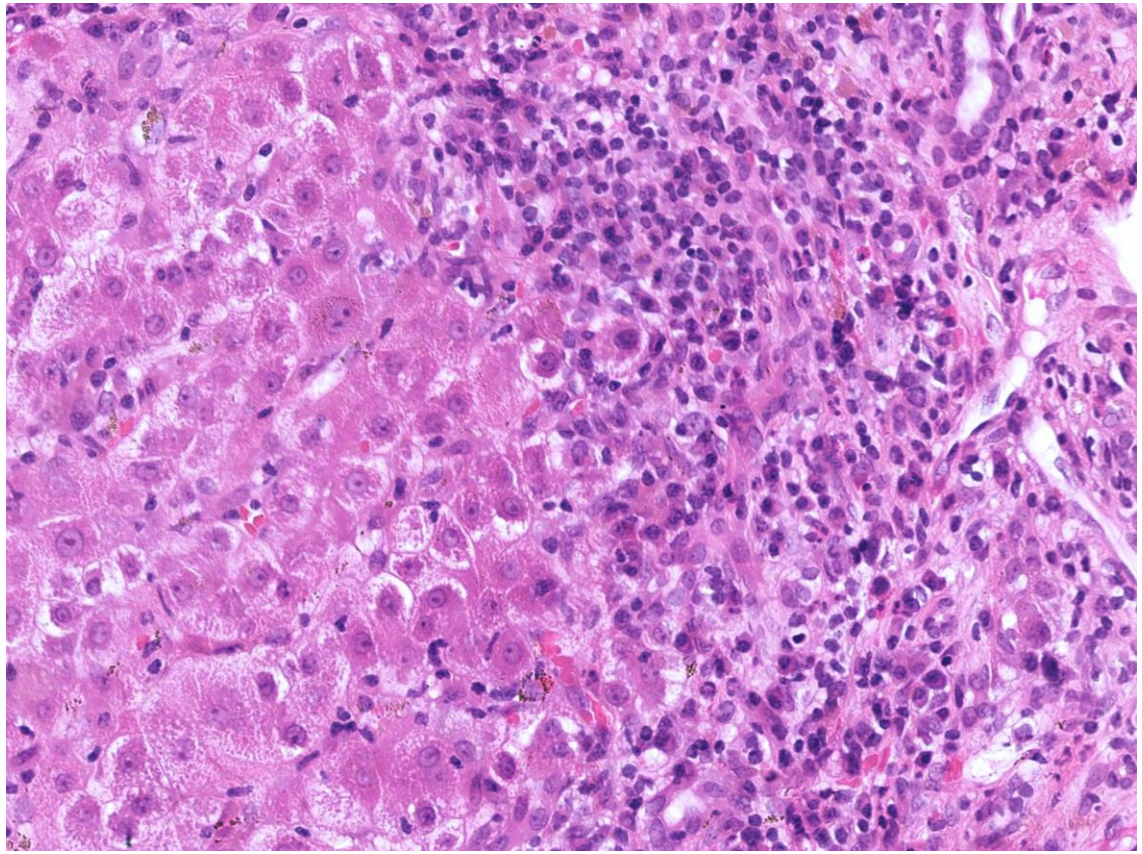
Simplified criteria for diagnosis of AIH

Variable	Cutoff	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	
or LKM	≥1:40	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥6: probable AIH
		≥7: definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

Histological features of AIH

- Interface hepatitis
  - ++ plasma cells
- Portal inflammation
- Spotty necrosis: apoptotic bodies
- Confluent necrosis
- Bridging necrosis
- Panacinar necrosis



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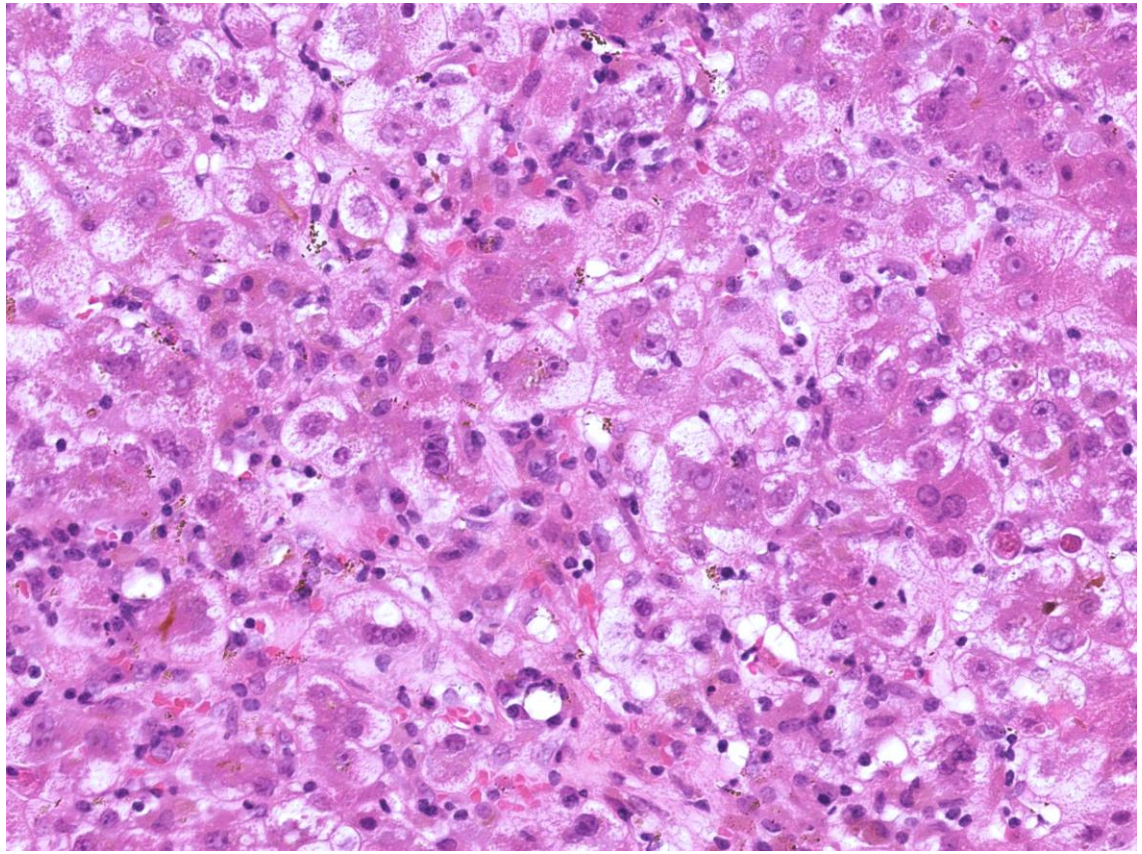

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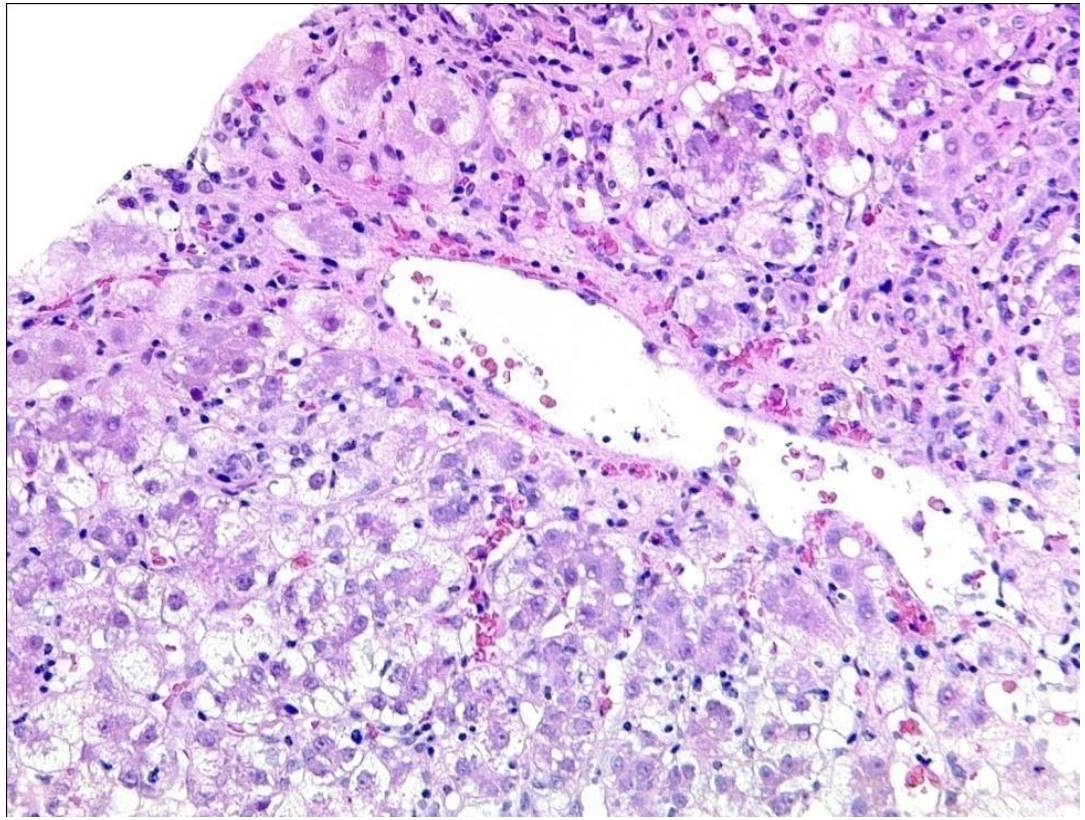

Central perivenulitis in acute presentation AIH: similar to forms of allograft rejection

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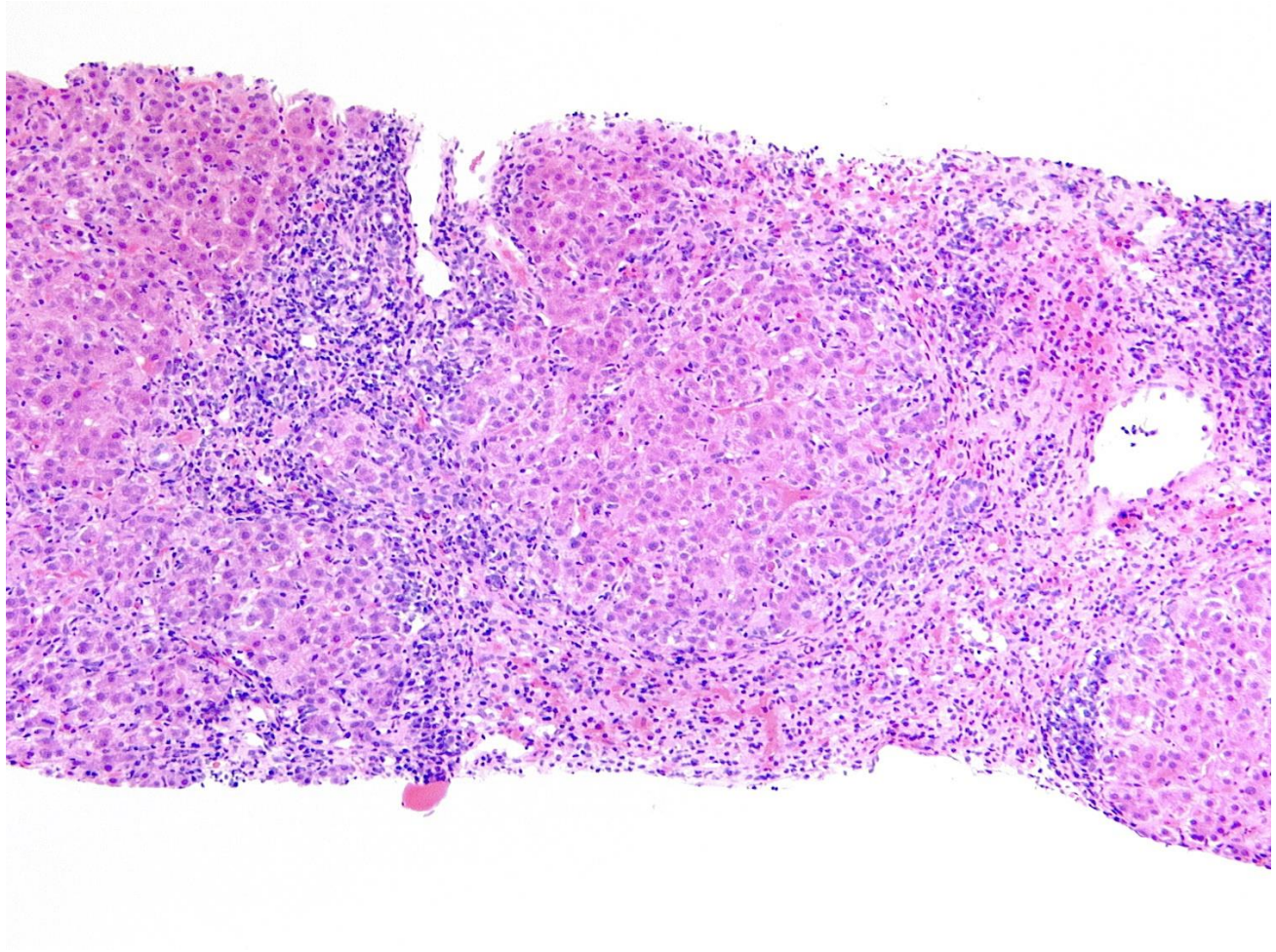

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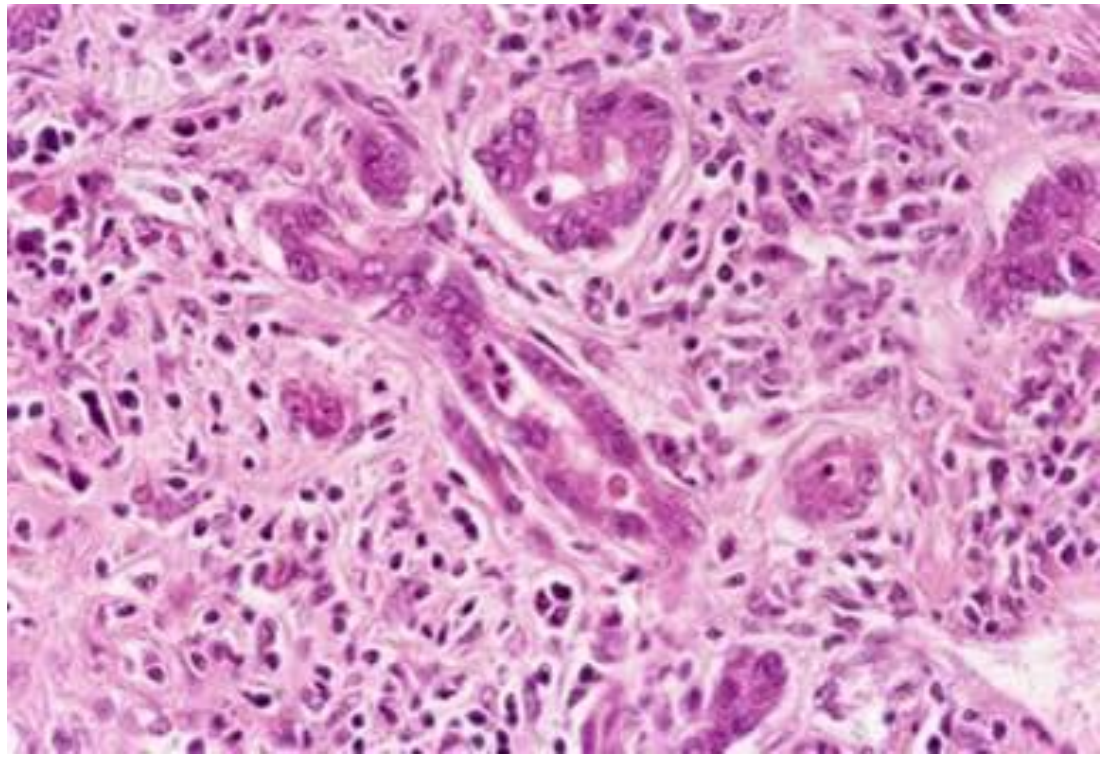
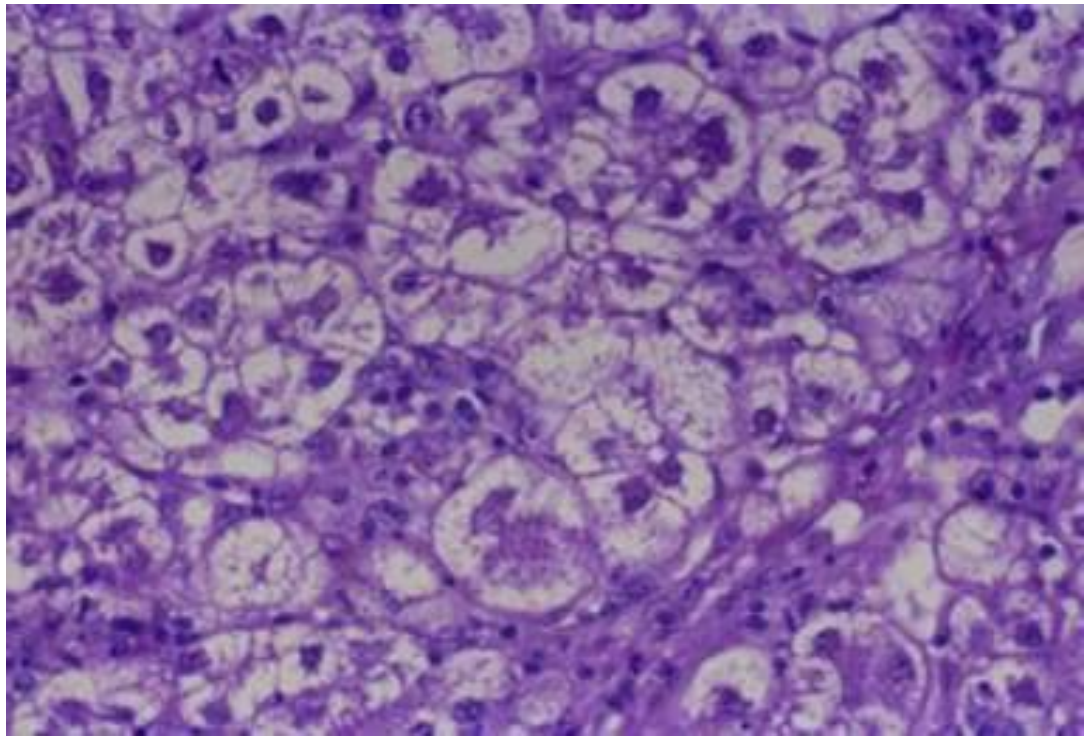


Biopsy changes provide important prognostic information: degree of necrosis/fibrosis

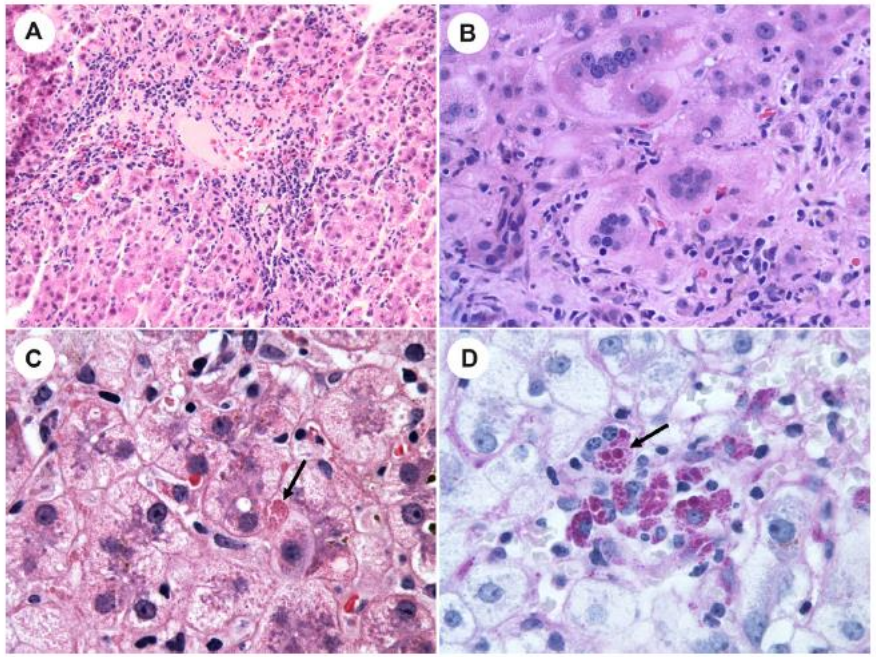
Histological features of AIH

- Interface hepatitis
  - ++ plasma cells
- Portal inflammation
- Spotty necrosis: apoptotic bodies
- Confluent necrosis
- Bridging necrosis
- Panacinar necrosis
- Liver cell rosettes



Histological features of AIH

- Interface hepatitis
  - ++ plasma cells
- Portal inflammation
- Spotty necrosis: apoptotic bodies
- Confluent necrosis
- Bridging necrosis
- Panacinar necrosis
- Liver cell rosettes
- Giant cell transformation
- Kupffer cell hyaline globules



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Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Consensus recommendations for histological criteria of autoimmune hepatitis from the International AIH Pathology Group

Results of a workshop on AIH histology hosted by the European Reference Network on Hepatological Diseases and the European Society of Pathology

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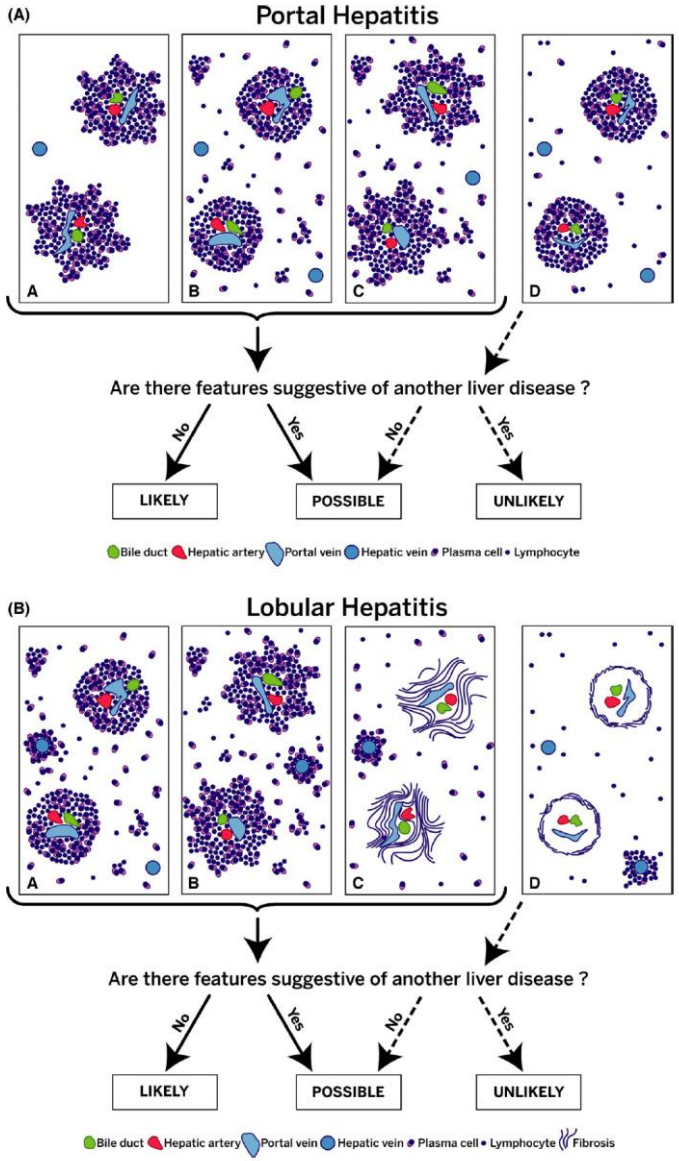


TABLE 5 Diagnostic criteria for autoimmune hepatitis in the settings of both portal lobular hepatitis

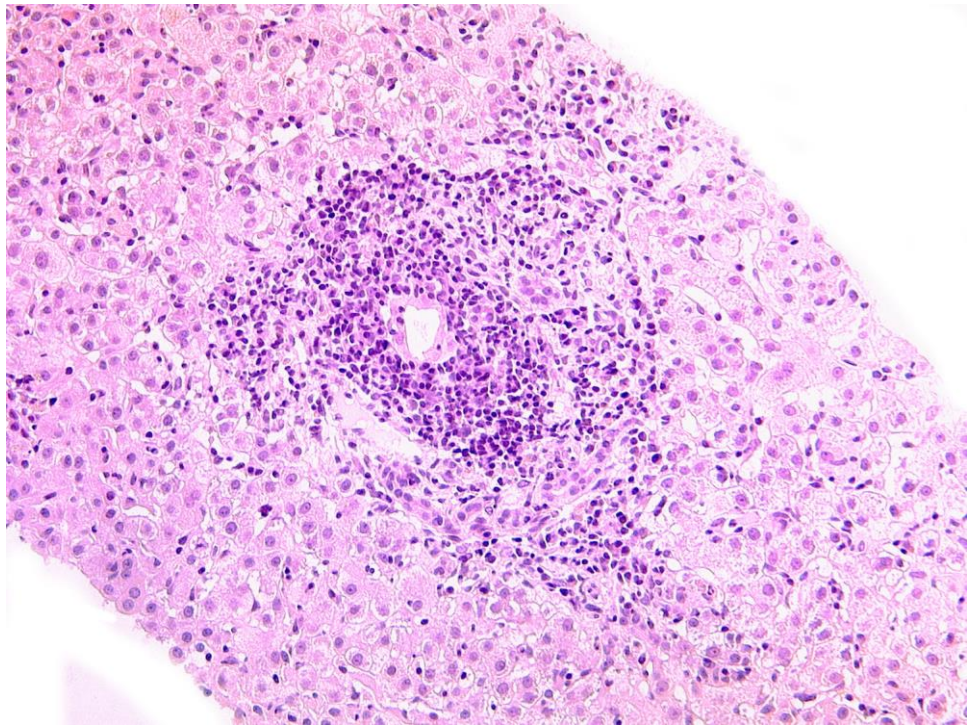
	Portal hepatitis	Lobular hepatitis
Likely AIH	Portal lymphoplasmacytic infiltrate PLUS one or both of the following features 1. more than mild interface hepatitis 2. more than mild lobular inflammation • in the absence of histological features suggestive of another liver disease	More than mild lobular hepatitis (+/− centrilobular necroinflammation) PLUS at least one of the following features 1. lymphoplasmacytic infiltrates 2. interface hepatitis 3. portal-based fibrosis • in the absence of histological features suggestive of another liver disease
Possible AIH	Portal lymphoplasmacytic infiltrate • without either of the likely features 1 or 2 above • in the absence of histological features suggestive of another liver disease OR • with one or both of likely features above • in the presence of histological features suggestive of another liver disease	Any lobular hepatitis (+/− centrilobular necroinflammation) • without any of the likely features 1–3 above • in the absence of histological features suggestive of another liver disease OR • with any of the likely features above • in the presence of histological features suggestive of another liver disease
Unlikely AIH	Portal hepatitis • without either of the likely features above • in the presence of histological features suggestive of another liver disease	Any lobular hepatitis • without any of the likely features above • in the presence of histological features suggestive of another liver disease

Note: Criteria for the diagnosis of likely, possible or unlikely AIH in the setting of portal or lobular hepatitis are shown.

Item	R1	R2	R3	R4	R5	R6	R7	R8	R9	Median (MAD)	Rating
6.1. Grading of inflammatory activity of AIH											
6.1.1. should be based on the modified Ishak Score (mHAI)	0	0	0	0	0	0	4	2	11	9 (0)	Appropriate
6.1.2. and its category A (periportal or periseptal interface hepatitis)	0	0	0	0	0	0	2	2	13	9 (0)	Appropriate
6.1.3. Category B (confluent necrosis)	0	0	0	0	0	0	3	1	13	9 (0)	Appropriate
6.1.4. Category C (focal /spotty lytic necrosis, apoptosis and focal inflammation)	0	0	0	0	0	0	2	1	14	9 (0)	Appropriate
6.1.5. Category D (portal inflammation) should not be included	0	1	1	0	0	0	2	1	12	9 (0)	Appropriate
6.2. Inflammatory activity should be referred to as 'mild' if											
6.2.1 Category A ≤ 1[a]	0	0	0	1	0	0	1	1	13	9 (0)	Appropriate
6.2.2. Category B =0[a]	0	0	0	0	0	0	2	0	14	9 (0)	Appropriate
6.2.3 Category C ≤ 2[a]	0	0	0	0	0	0	1	0	15	9 (0)	Appropriate

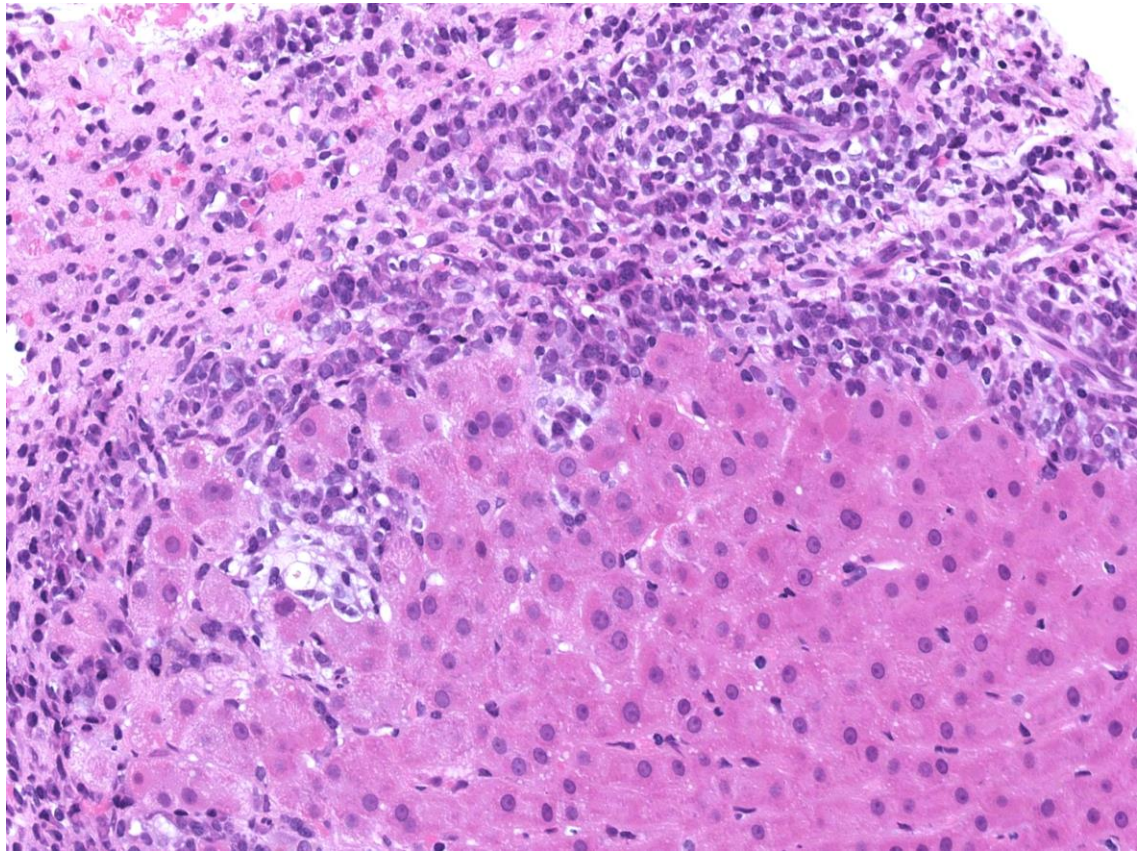
Seronegative autoimmune hepatitis: ‘cryptogenic chronic hepatitis’

- Cases with biopsy features compatible with AIH which are autoantibody – ve
- ++ perivenular injury
- Less since assays for SLA available
- Raised IgG
- HLA susceptibility factors as for AIH (DR3 and DR4)
- Responds to corticosteroids



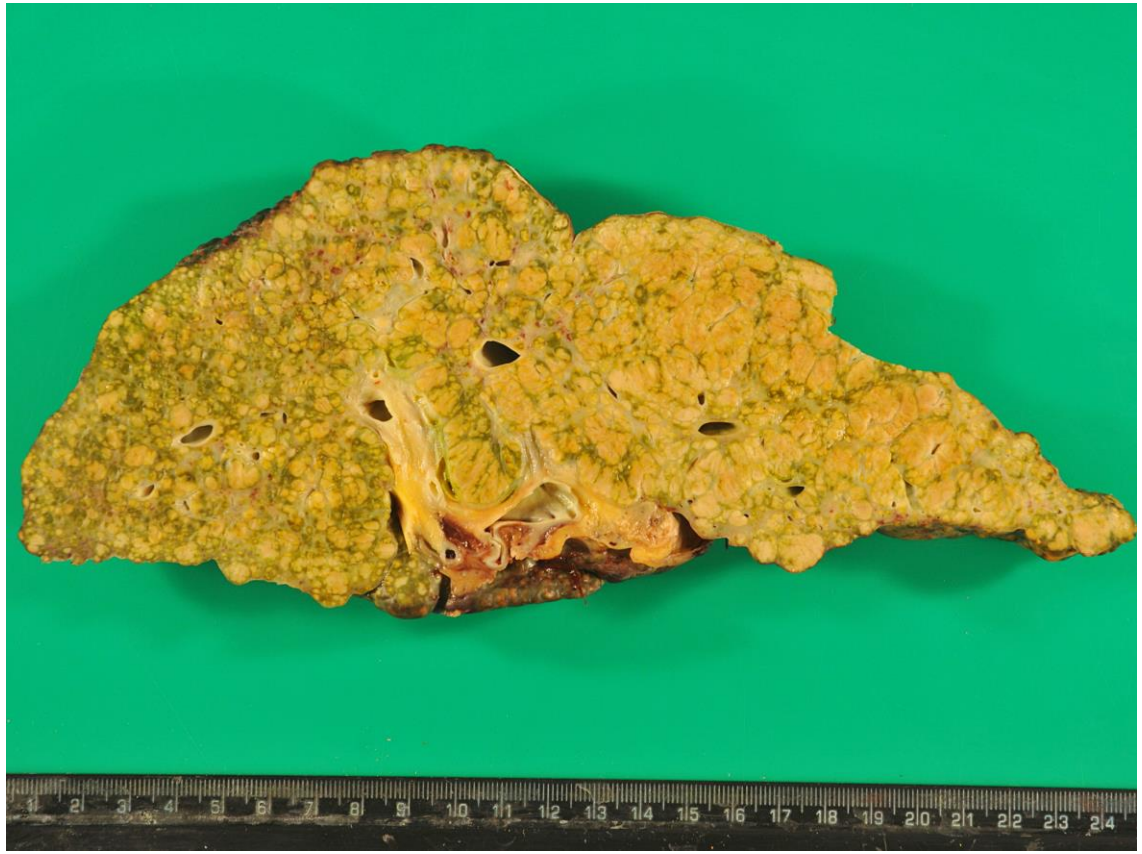
Chronic hepatitis and drug-induced AIH

- Many drugs that cause acute hepatitis can lead to chronic hepatitic process with interface hepatitis and periportal fibrosis
- Frequency probably low
- May resolve on cessation of drug
- Some have histological changes that resemble AIH
- First recognised with oxyphenisatin and subsequently methyl dopa, minocycline, nitrofurantoin etc……..
- Associated with circulating autoantibodies: mainly ANA and SMA
- Some highly specific – anti-CYP2C9 with ticranafen



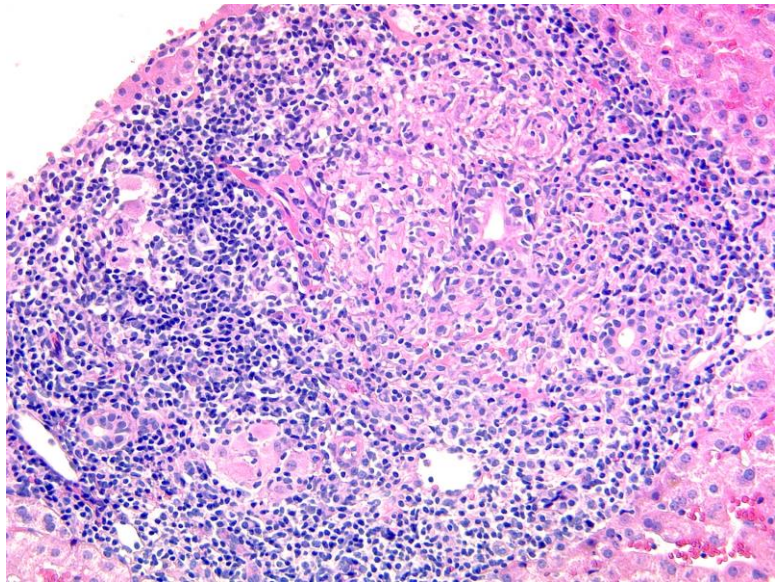
Primary biliary cholangitis

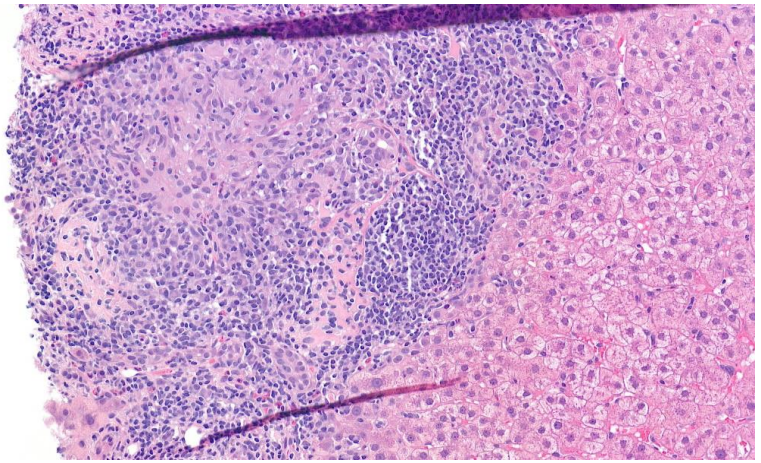
- Chronic cholestatic disease characterised by immune mediated intrahepatic bile duct injury and loss
- Immune signature: high titre AMA; disease specific forms of ANA and high monomeric IgM
- Middle aged females (F:M > 10:1)
- Risk factors: FH autoimmune disease; other autoimmune process; recurrent UTIs
- Presentation with fatigue, pruritis or signs of chronic liver disease but often incidental finding on serology
- Definite diagnosis: ALP elevation; AMA > 1:40; characteristic liver biopsy findings
- Most guidelines **do not** include biopsy in clinical diagnostic algorithms (BSG; AASLD; EASL)



Bile duct lesions in PBC

- Vacuolar degeneration of cholangiocytes and lymphocytic cholangitis
- Apoptosis (CD40-Fas and granzyme B)
- CD8 and CD4 infiltrate
- CD103 +ve cells in infiltrate
- Intraepithelial CD1a Langerhans cells
- Unique coronal arrangement of CD38+ IgG/IgM plasma cells
- Epithelioid granulomas
- Damage to Canals of Hering





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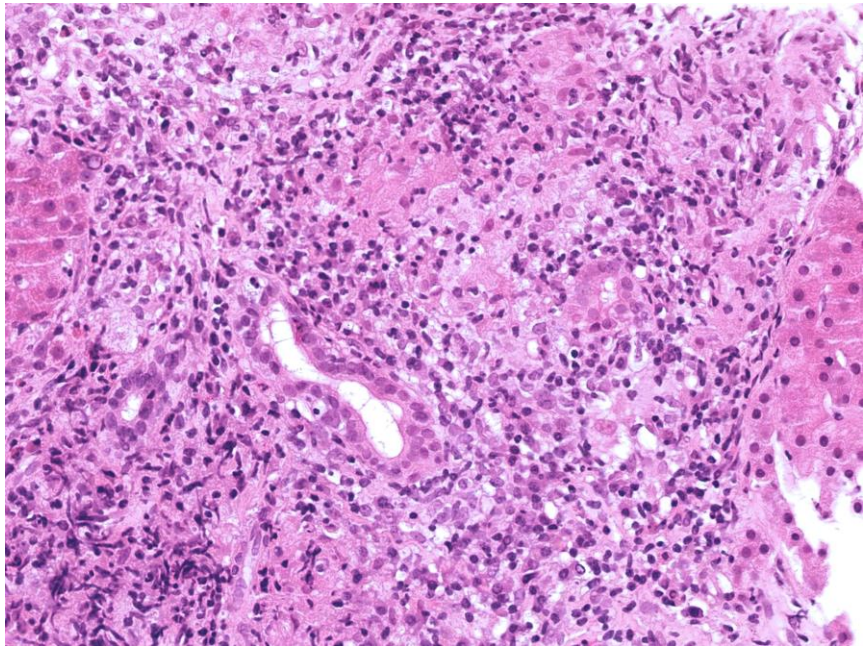

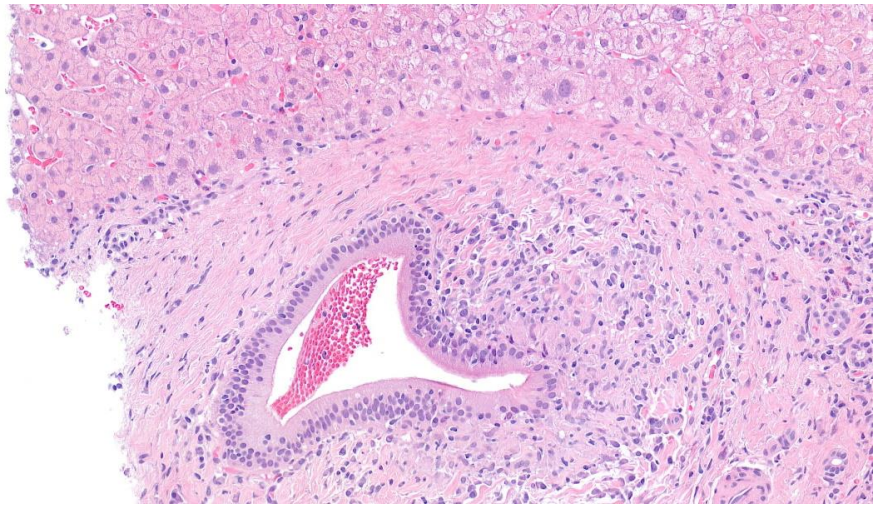

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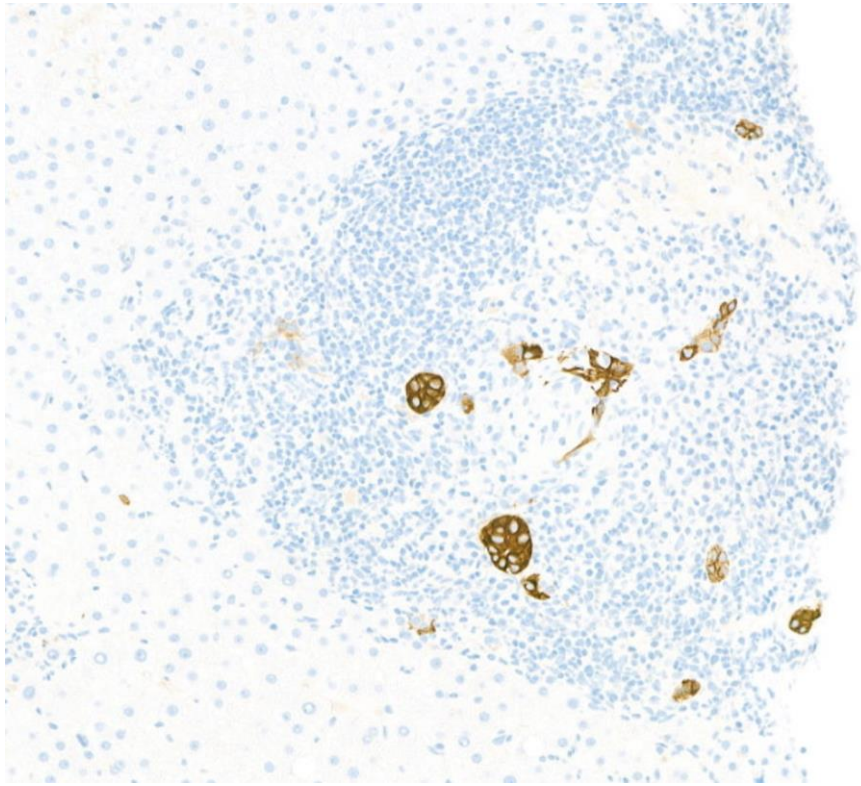
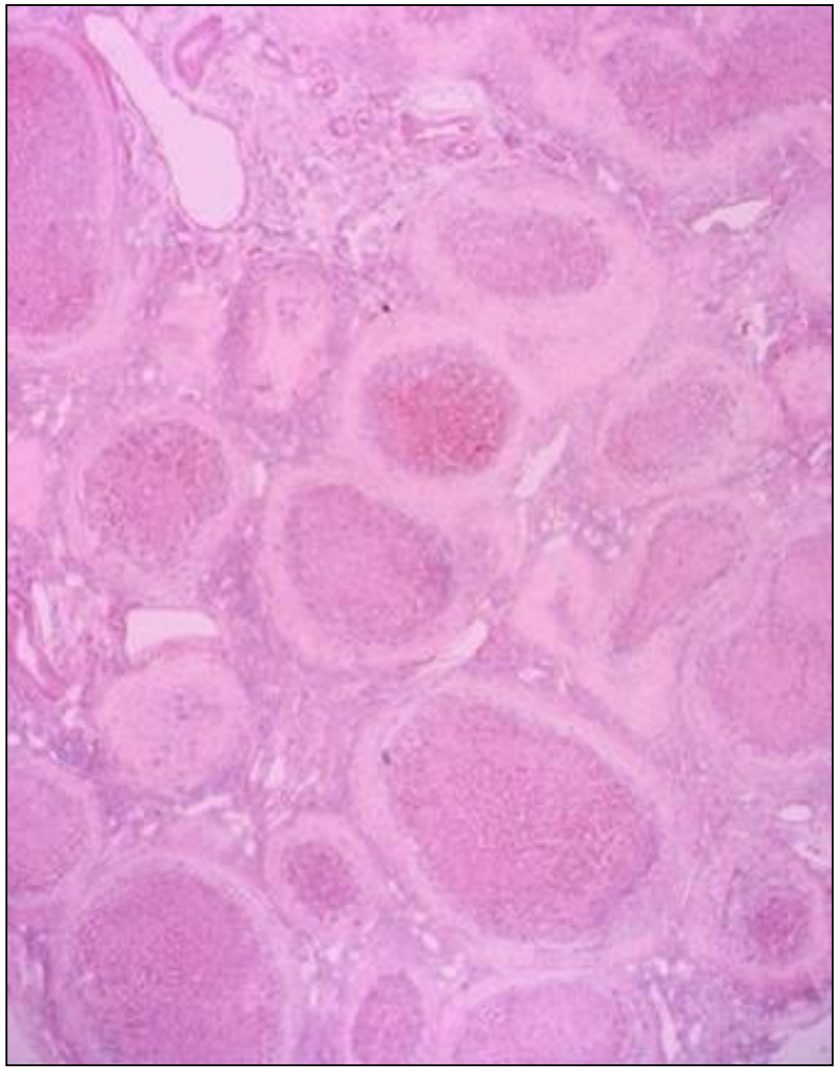


Sequential biopsy changes in PBC

- Progressive ductopaenia
- Four forms of ‘piecemeal necrosis’ described
  - Biliary
  - Lymphocytic
  - Ductular
  - Fibrotic
- Patterns persist in follow up biopsies
- Lobular inflammation common in stages II and III
- Halo and perinodular scars seen in those with marked cholestasis

Portmann et al (1985)



Hiramatsu grading

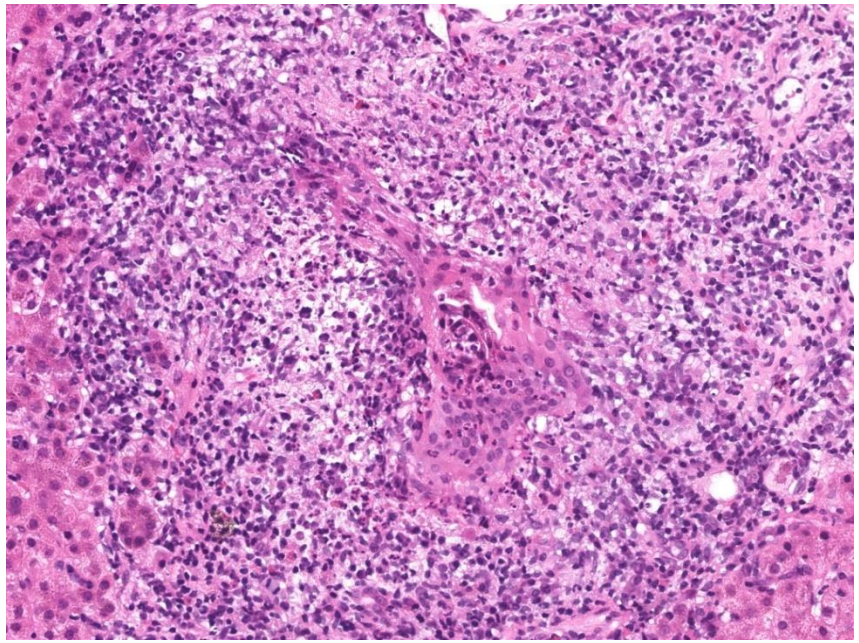
Grade	0	1	2	3
Cholangitis	Absent	Cholangitis in <1/3 portal tracts	Cholangitis in 1/3 – 2/3 portal tracts	Cholangitis in > 2/3 portal tracts
Interface hepatitis	Absent	Focal, mild	Moderate	Severe and extensive
Lobular hepatitis	Absent	Focal, mild	Multiple foci	Zonal and/or bridging necrosis

Hiramatsu staging

Stage	0	1	2	3
Fibrosis	Absent	Periportal septa	Bridging fibrosis	Cirrhosis
Bile duct loss	Absent	< 1/3 portal tracts	1/3 – 2/3 portal tracts	> 2/3 portal tracts
Cholate stasis	Absent	< 1/3 periportal areas	1/3 – 2/3 periportal areas	> 2/3 periportal areas

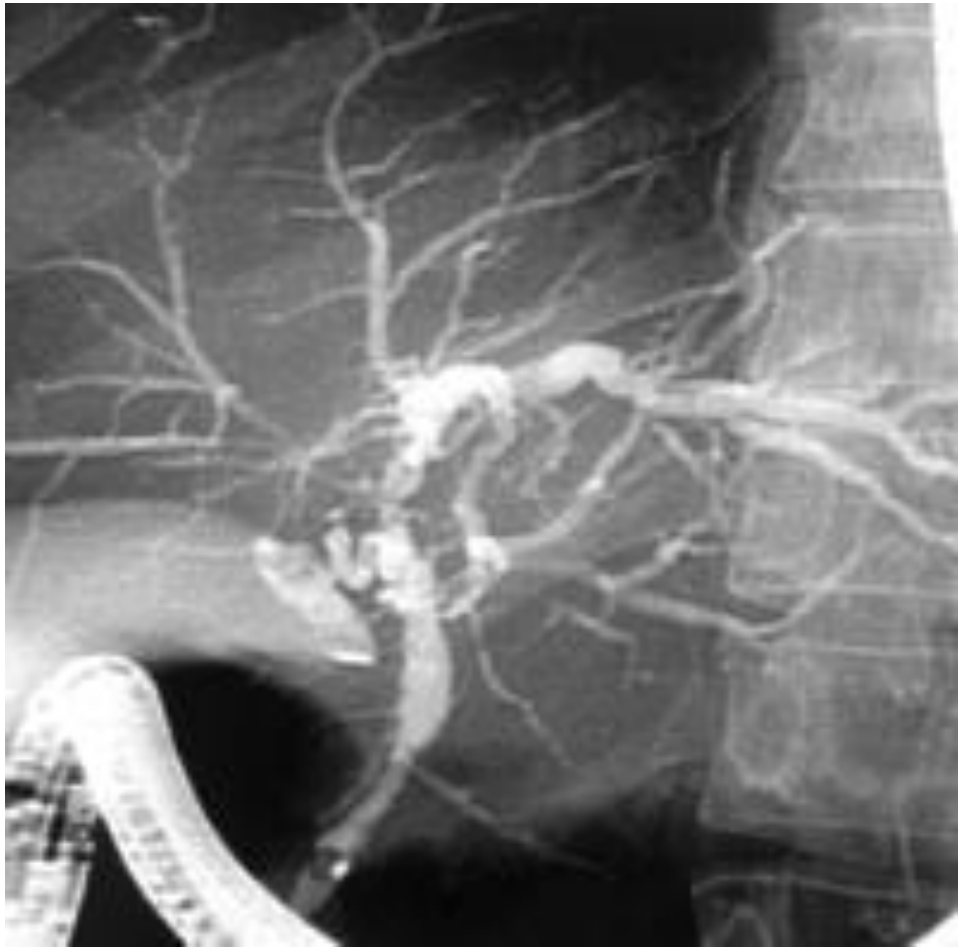
Autoimmune cholangiopathy

- ‘Outlier’ syndrome : part of broad spectrum of autoimmune cholangiopathy
- AMA -
- ANA/SMA +
- Normal ERCP
- Respond well to corticosteroids but course similar to PBC



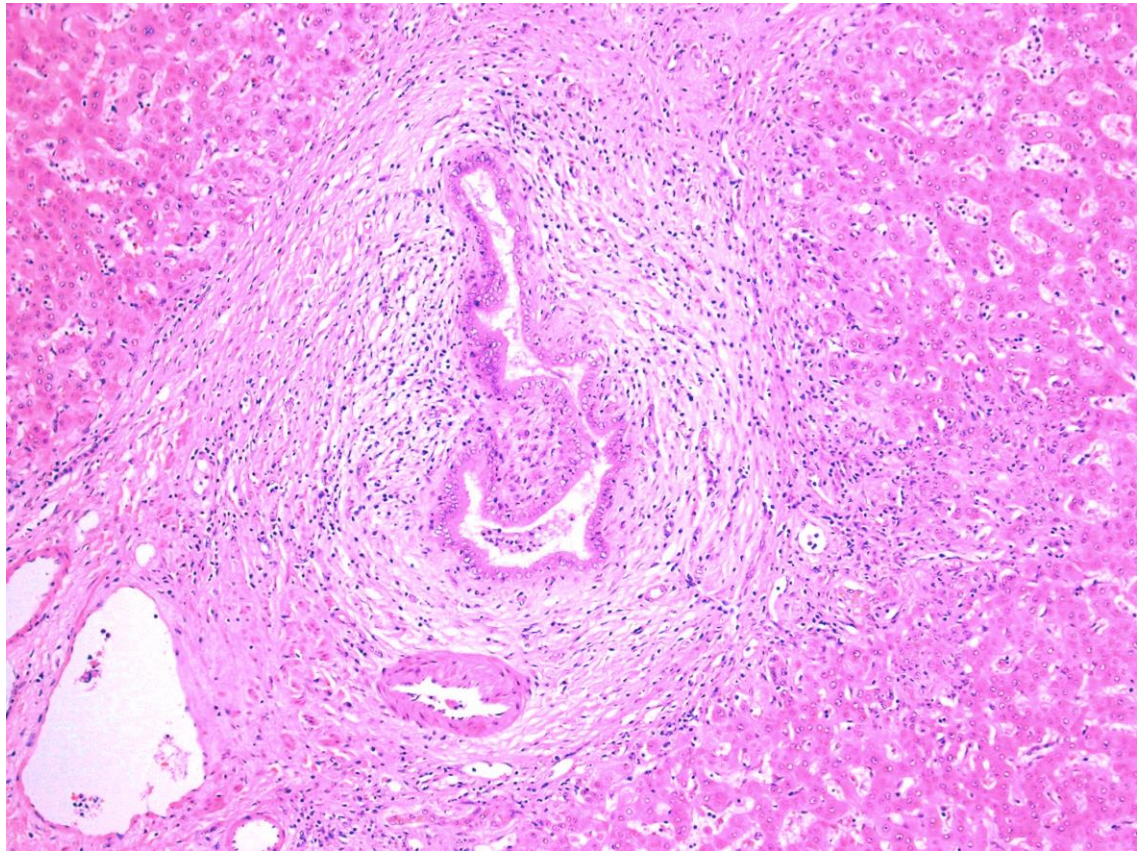
Primary sclerosing cholangitis

- Fibroinflammatory process which may affect any part of the biliary tract
- Extrahepatic > intrahepatic
- 10% small duct disease
- Progressive ductopaenia and cholestasis
- May be seen in infancy
- M:F = 3:1
- >75% associated with IBD



Primary sclerosing cholangitis

- Periductal onion skin fibrosis
- Tombstone lesion
- Rarely granulomas
- May be marked interface hepatitis
- Progressive cholate stasis
- Saccular dilatation of hilar ducts
- Phlebitis: leads to parenchymal extinction and lobar atrophy



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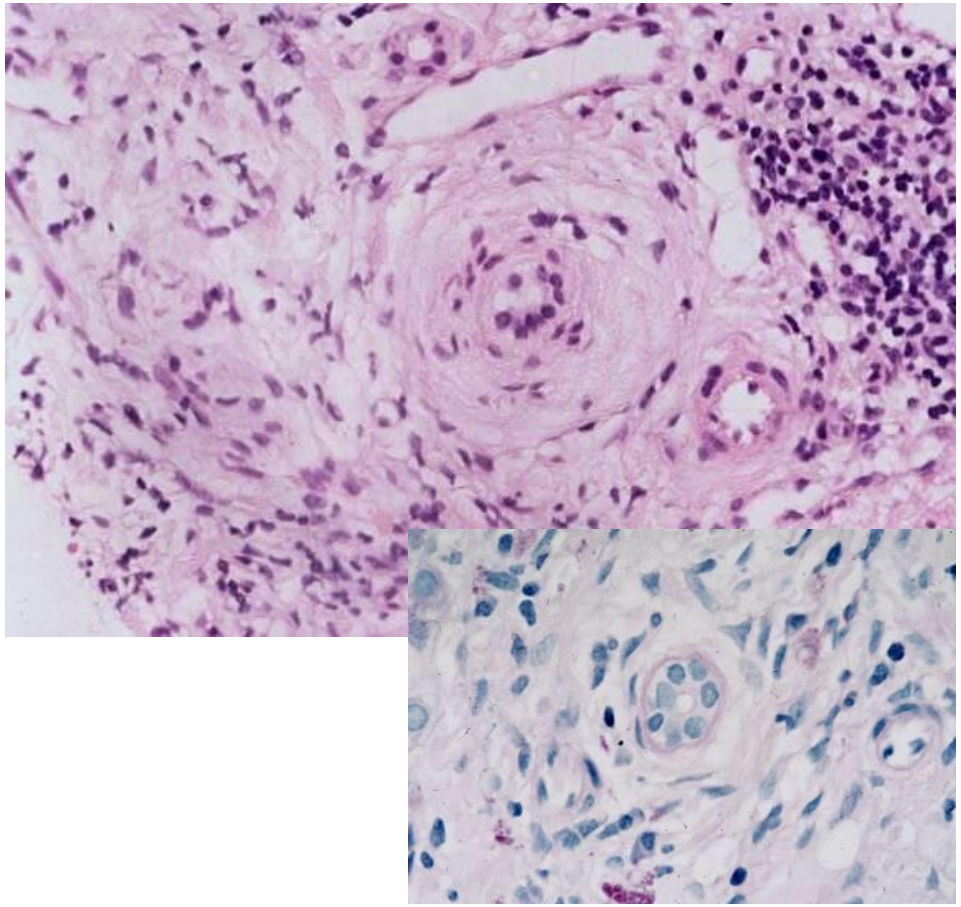

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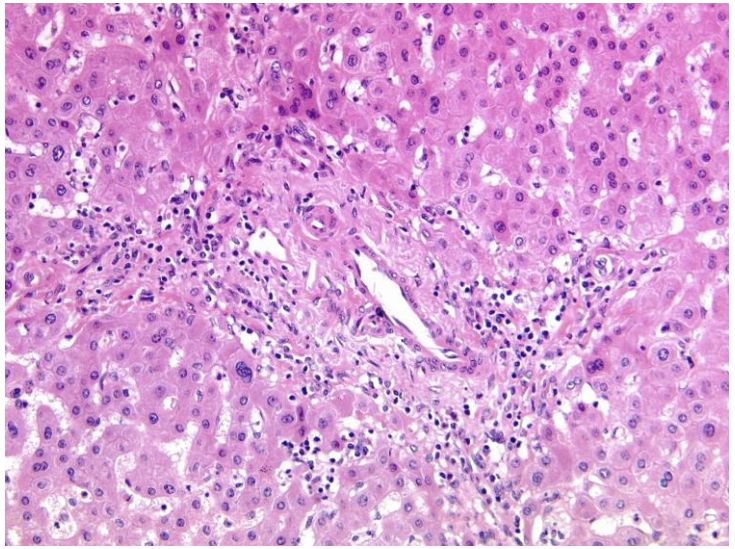

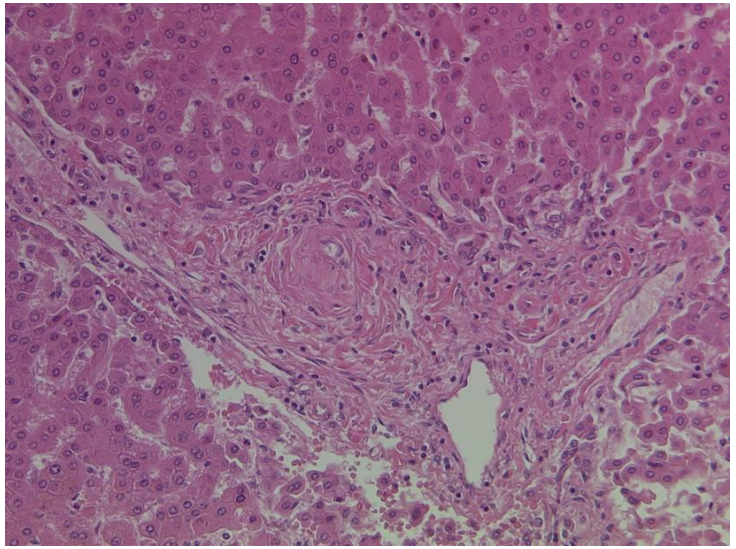

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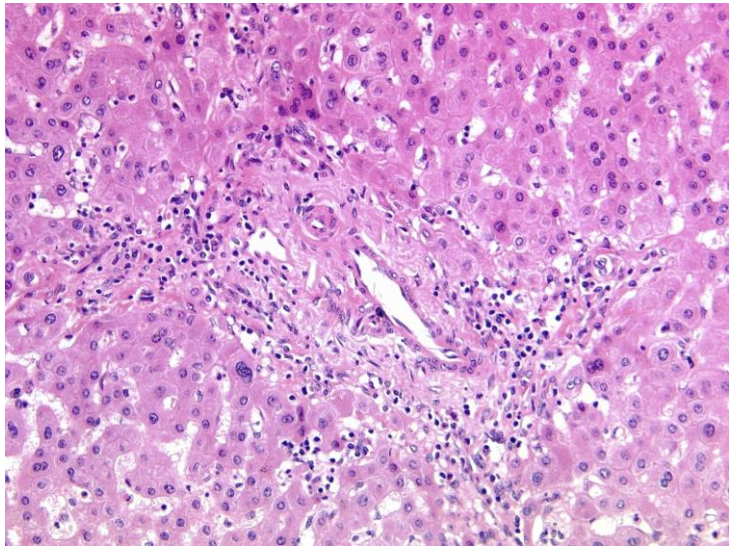

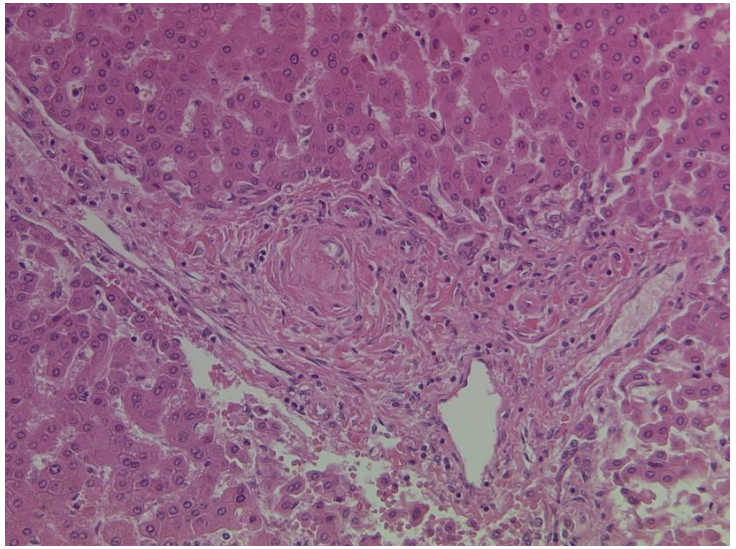

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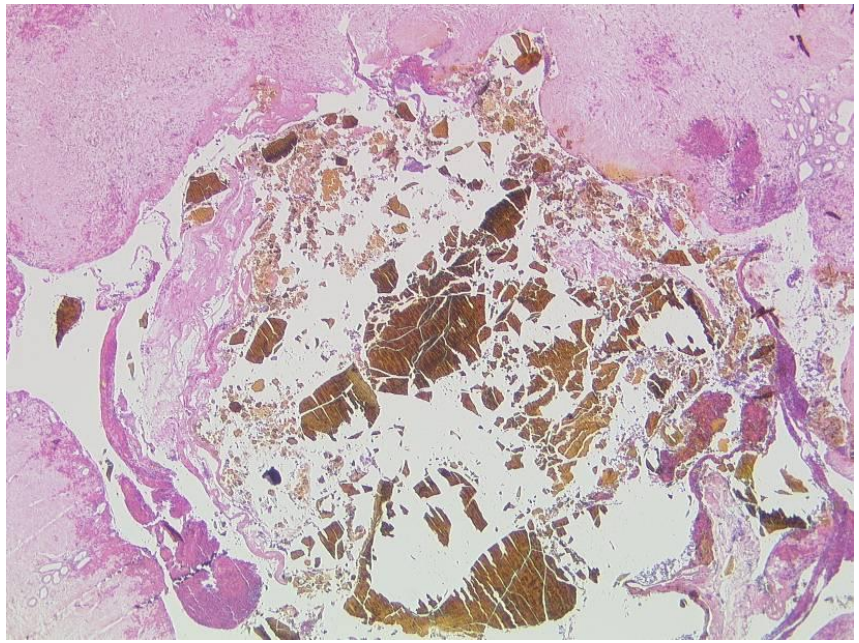

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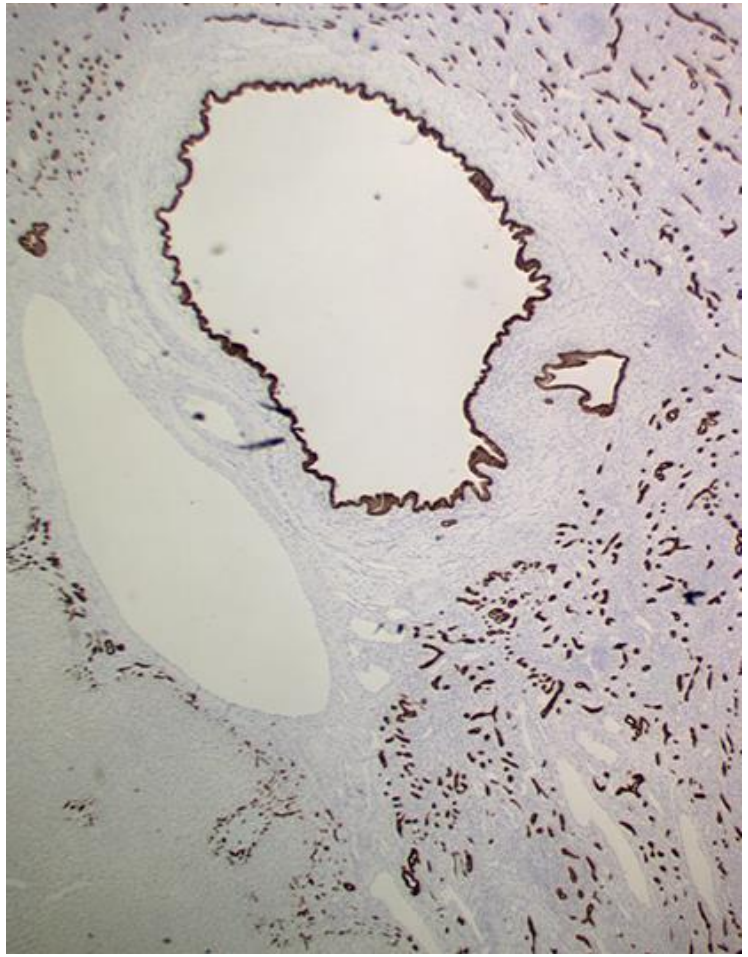
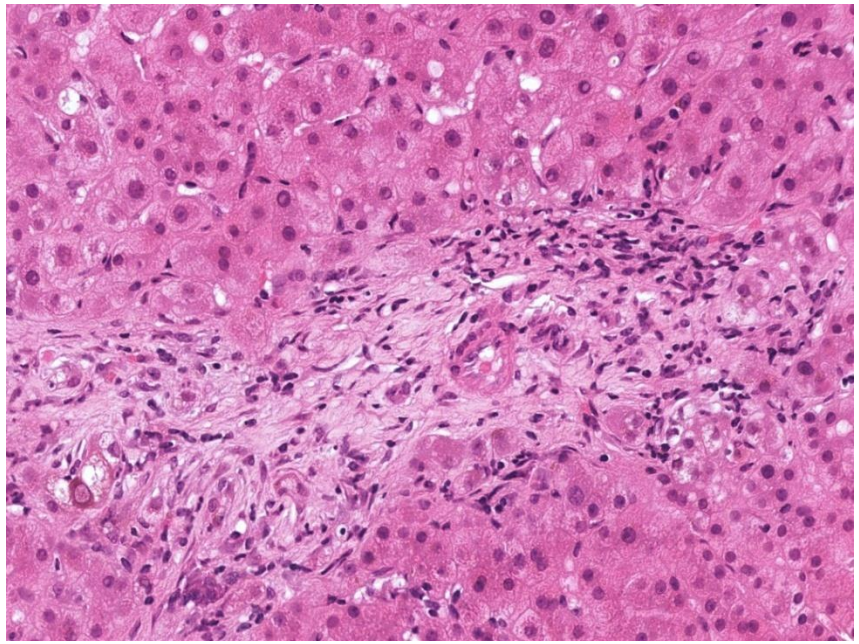


Small duct PSC

- Accounts for 6-16%
- ?Relationship with idiopathic adulthood ductopaenia
- Study of 25 cases: early disease on index biopsy
- Low risk of progression and no transformation to large duct disease
- More frequent in Crohn than UC



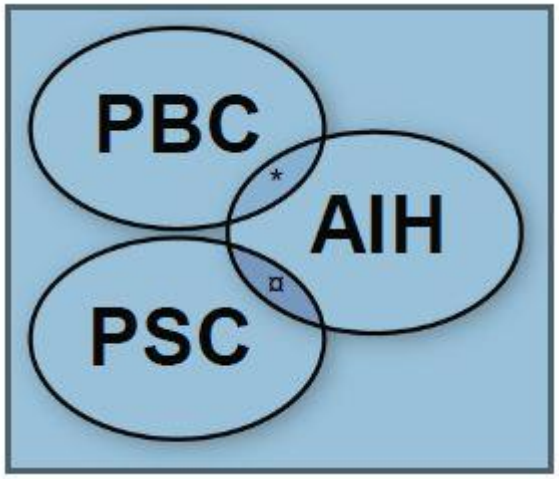
Position Paper

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Overlap syndromes: The International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue

Kirsten Muri Boberg[1,*], Roger W. Chapman[2], Gideon M. Hirschfield[3], Ansgar W. Lohse[4], Michael P. Manns[5], Erik Schrumpf[1], on behalf of the International Autoimmune Hepatitis Group

[1]*Clinic for Specialized Medicine and Surgery, Oslo University Hospital, Oslo, Norway;* [2]*Gastroenterology Unit, John Radcliffe Hospital, Headington, Oxford, United Kingdom;* [3]*Liver Centre, Toronto Western Hospital, Department of Medicine, University of Toronto, Toronto, Canada;* [4]*Department of Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany;* [5]*Department of Gastroenterology, Hepatology and Endocrinology, Medical School of Hannover, Hannover, Germany*



Standard definitions lacking

IAIHG system not designed for variants

Suggested categorising according to predominant disease process

Overlap not distinct entities

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Kirsten Muri Boberg[1,*], Roger W. Chapman[2], Gideon M. Hirschfield[3], Ansgar W. Lohse[4], Michael P. Manns[5], Erik Schrumpf[1], on behalf of the International Autoimmune Hepatitis Group

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AUTOIMMUNE HEPATITIS FEATUES (2 OUT OF 3 REQUIRED)	PRIMARY BILIARY CIRRHOSIS FEATURES (2 OUT OF 3 REQUIRED)
Serum ALT > 5x upper limit of normal	Serum ALP >2x upper limit of normal OR Serum GGT >5x upper limit of normal
Serum IgG >2x upper limit of normal OR Positive SMA	Positive AMA
Moderate to severe interface hepatitis or lobular necroinflammation in histology	Florid duct lesion in histology

Standard definitions lacking

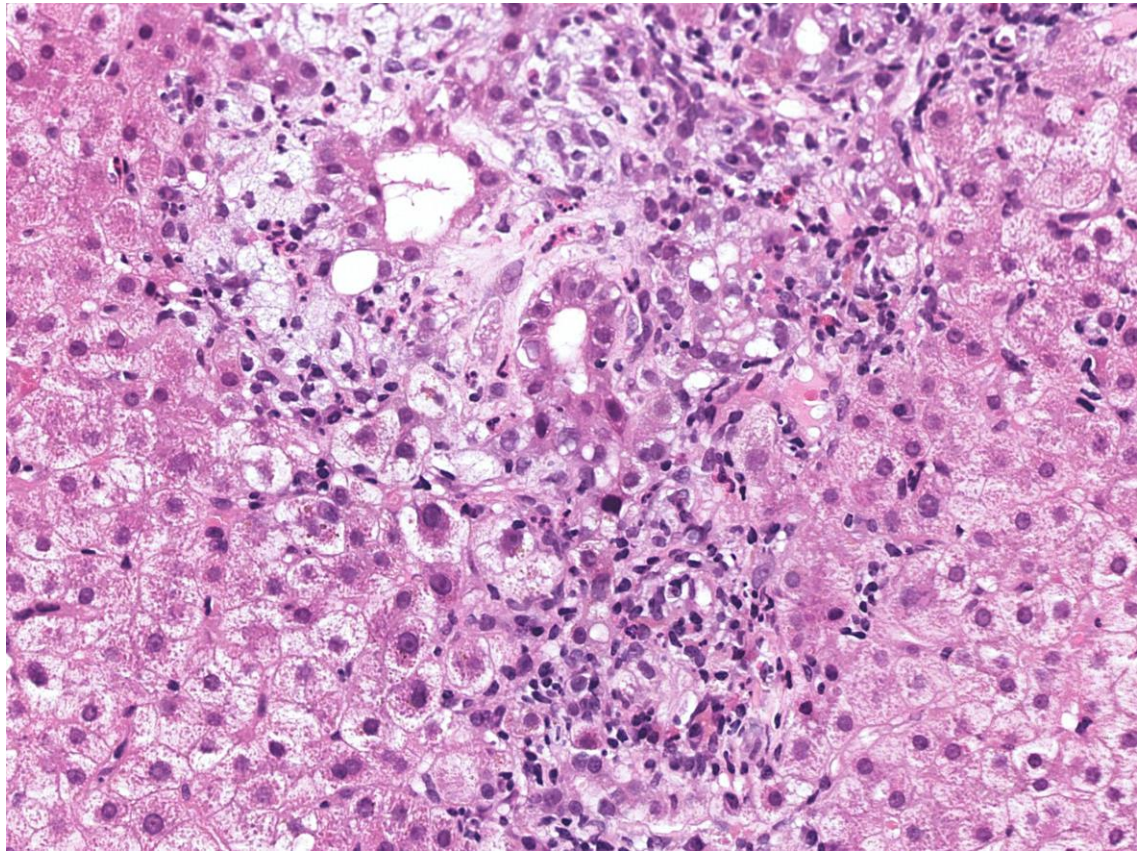
IAIHG system not designed for variants

Suggested categorising according to predominant disease process

Overlap not distinct entities

AIH/PBC overlap

- Co-existence of two conditions presenting simultaneously or developing consecutively
- Blend of PBC-features and AIH
- ALT > 5X normal; SMA+
- Mixed histological picture with marked hepatitic component
- ? Treat with steroids and UDCA



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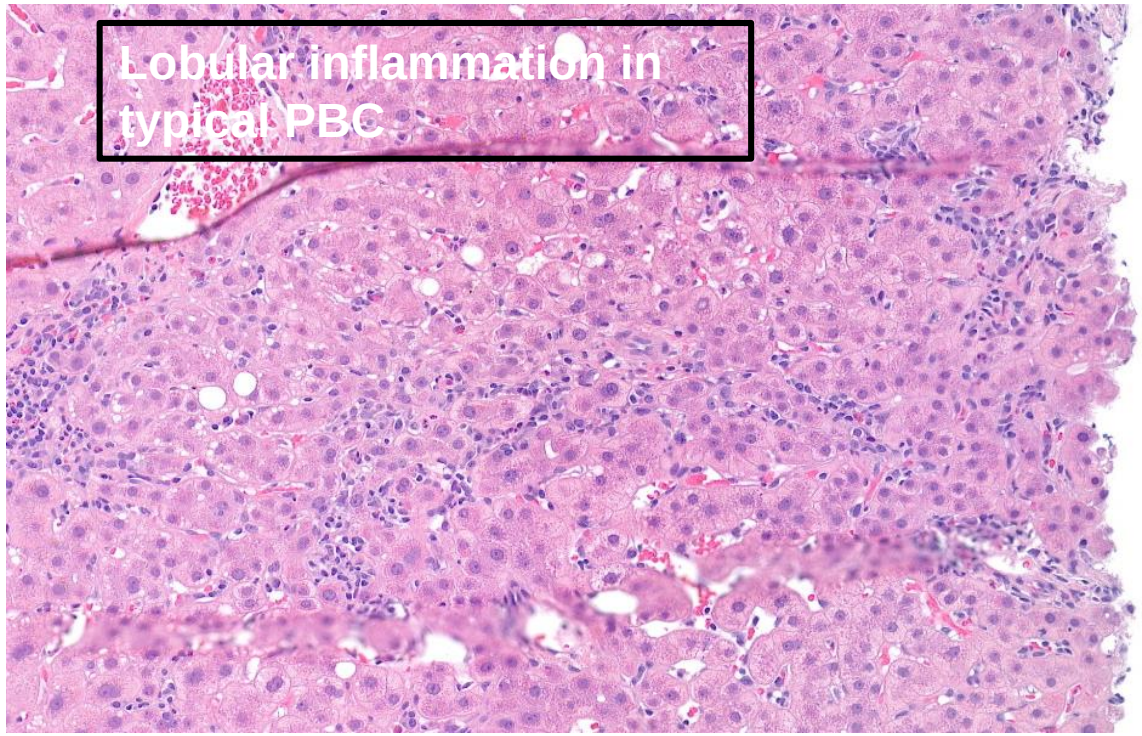
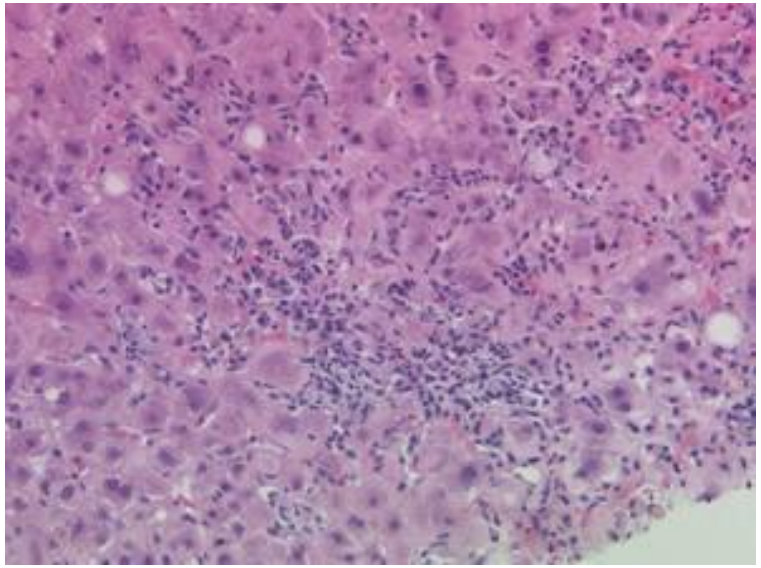
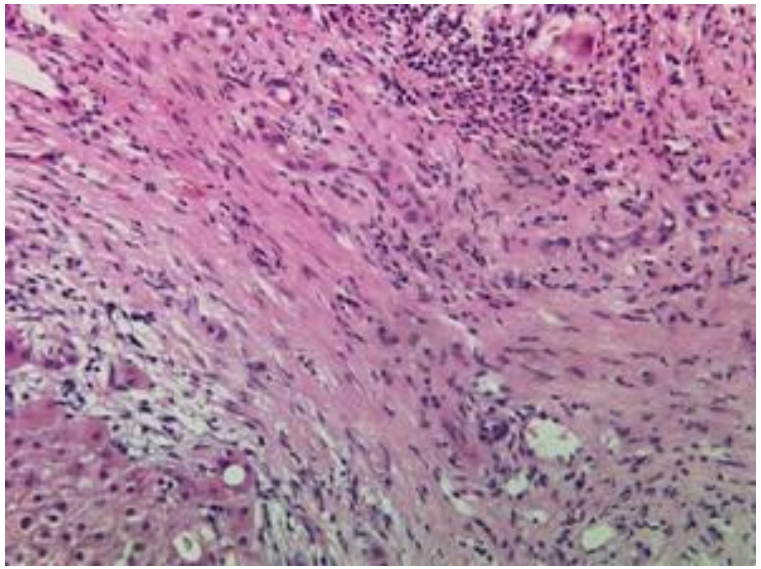


AIH/PSC overlap and autoimmune sclerosing cholangitis

- ERCP and histological evidence of sclerosing bile duct lesions (may only be small duct PSC) with significant hepatitic activity
- Significant proportion of PSC patients are ANF/SMA+
- Some PSC patients score at least probable on International scoring system
- Particularly noted in children with a crossover phenomenon (AIH to PSC): ‘autoimmune sclerosing cholangitis’
- Similar prevalence to ‘pure’ AIH in childhood
- ANA/SMA +; IBD in approx 50% with pANCA in 75%
- Cross over generally AIH to PSC





Summary

- A spectrum of autoimmune liver disease occurs with three principal entities: AIH; PBC and PSC
- Each have characteristic clinical, immunological and histopathological features
- Variants also occur: outliers and ’overlap’ cases are all part of the spectrum
- Needs a pragmatic approach to management: liver biopsy continues to inform this in many patients particularly in AIH