Update on Autoimmune Liver Disease

Role of Liver Biopsy
in
Autoimmune Hepatitis, PBC and PSC

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Autoimmune Liver Disease
Diagnostic Criteria and Role of Liver Biopsy

- AIH, PBC and PSC diagnosed on basis of combination of clinical, biochemical, immunological, radiological and histological findings
- Liver biopsy rarely diagnostic in isolation.
- In AIH histological assessments are important in establishing a diagnosis and determining therapeutic options.
- For cases of PBC and PSC with other typical findings, liver biopsy no longer required for diagnosis.
- Liver biopsy useful in assessing disease severity
  - Inflammatory activity , fibrosis stage
  - Important implications for prognosis and treatment

Autoimmune Hepatitis

Autoimmune Hepatitis – Laboratory Investigations
Diagnostic Criteria

Biochemistry	Hepatitic LFTs • Raised AST/ALT
Immunology	Autoantibodies • ANA, SMA (type 1) • LKM , LC-1 (type 2) Immunoglobulins • Raised IgG
Histology	Presence of typical/compatible features Absence of atypical features (e.g. biliary features)

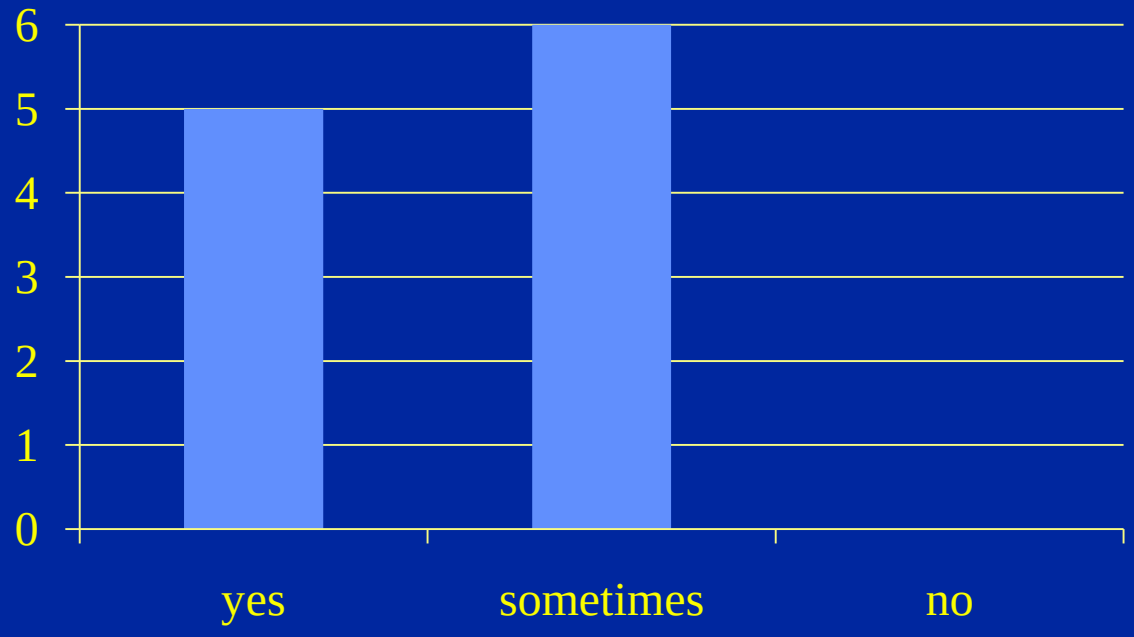
Role of Liver Biopsy in the Diagnosis of AIH

1. Still recommended in expert reviews/ practice guidelines
   (Hennes 2008, Manns 2009, Lohse 2011)

2. Others suggest mainly useful in cases where other findings are equivocal or atypical, e.g.
   - Autoantibodies in low titre
   - Features suggesting an alternative diagnosis (e.g. fatty liver disease or biliary disease)

Survey of Consultant Hepatologists, Birmingham Liver Unit
Role of Liver Biopsy in AIH
12 Hepatologists – 11 responses

Question 1. I recommend obtaining a liver biopsy for the initial diagnosis of AIH



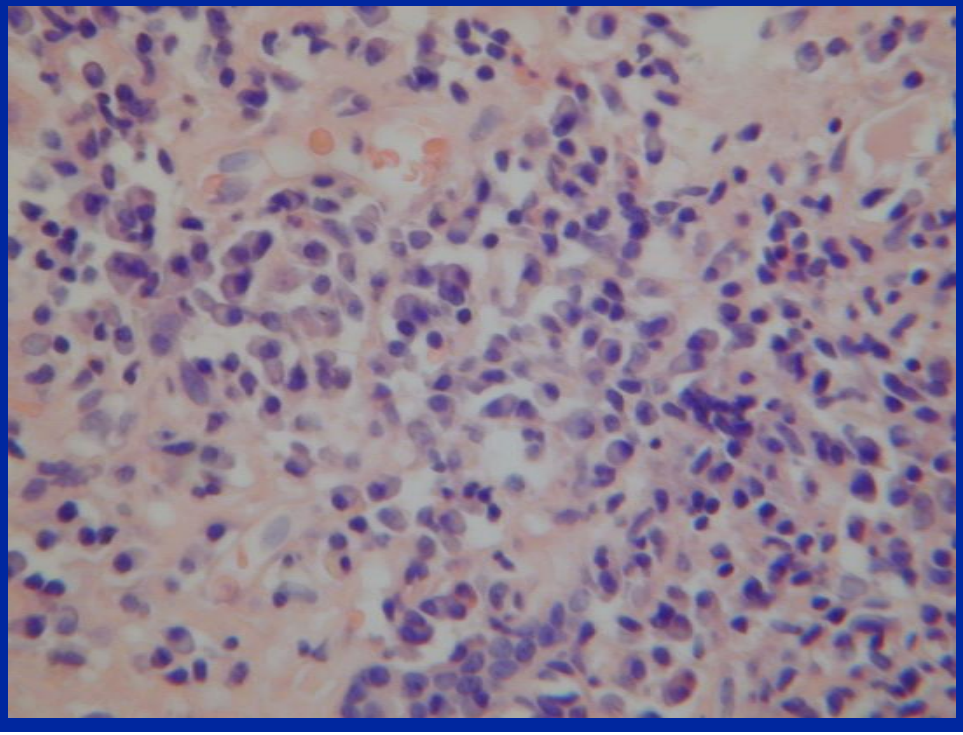
Yes (n =5)

- "usually"(1) or "most of the time"(1)

Sometimes (n=6) - please specify when

- Uncertainty about diagnosis /atypical features (4)
- Possible overlap/alternative aetiologies (3)
- To determine presence/absence of cirrhosis (2)

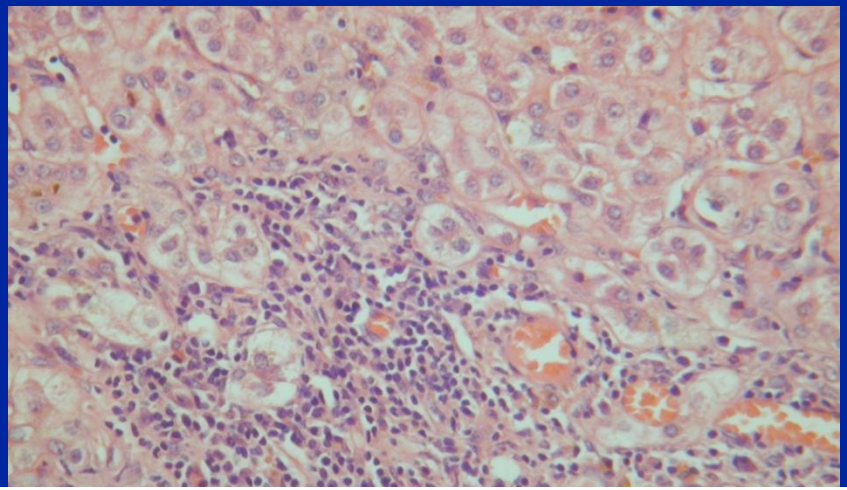
Chronic Autoimmune Hepatitis -Typical Features
Plasma cell rich portal inflammation

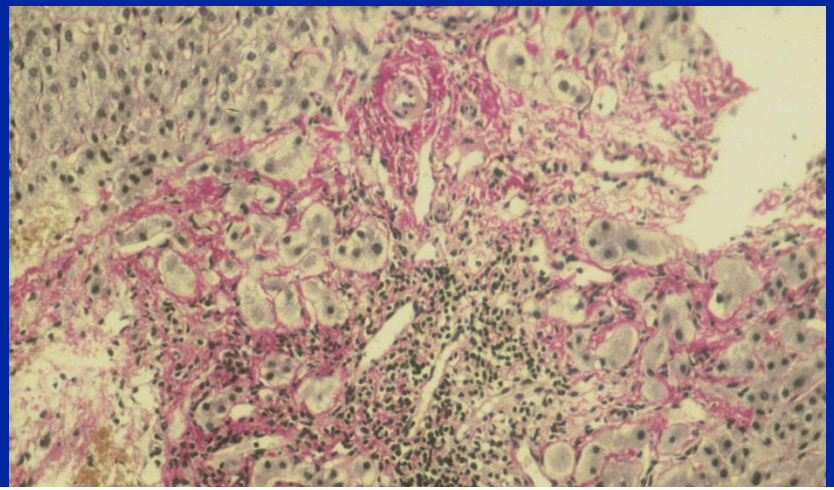


BUT:

- Plasma cells not essential to support/confirm diagnosis of AIH
- Plasma cells also seen in other diseases associated with features of chronic hepatitis (e.g. PBC)

Chronic Autoimmune Hepatitis -Typical Features
Interface Hepatitis ("piecemeal necrosis")





Interface Hepatitis - Clinical Significance

Prognosis

- Presence/severity predicts development of fibrosis
- Persistence after treatment associated with increased risk of fibrosis

Treatment

- Indication for commencing immunosuppression (newly diagnosed AIH)
- Indication for maintaining immunosuppression (treated AIH)
  - Portal inflammation alone - relapse rate 50%
  - Interface hepatitis - relapse rate >80%

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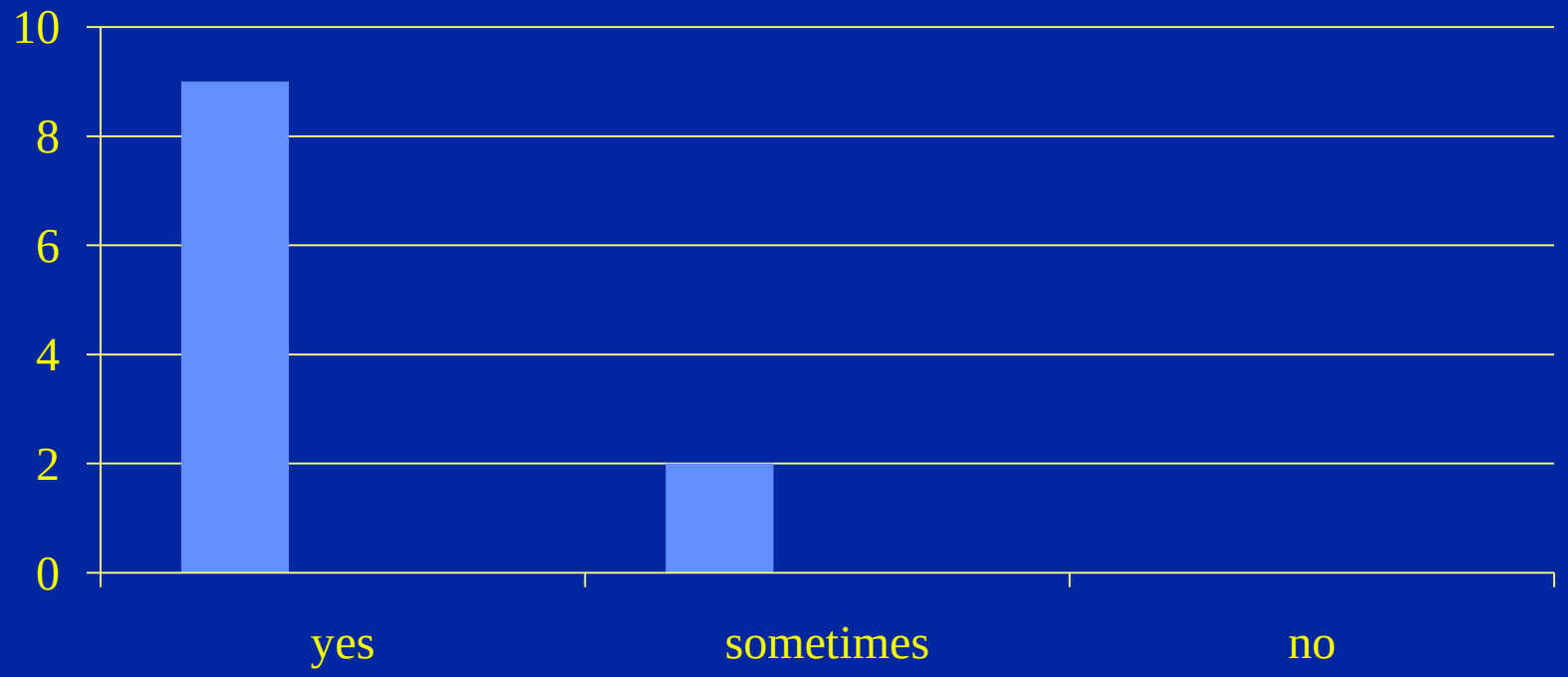
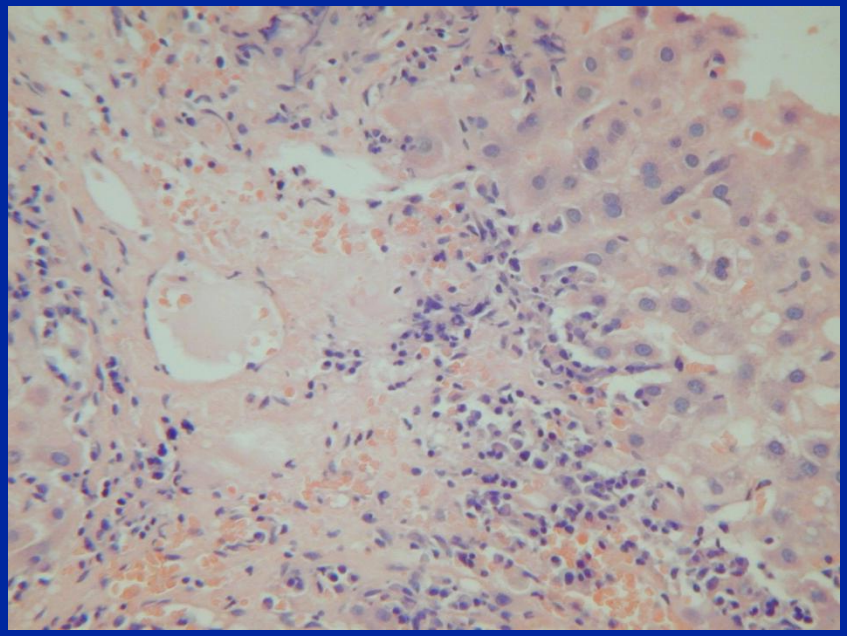
Question 2. Following a successful biochemical and immunological response to immunosuppression, I would recommend obtaining a liver biopsy before deciding to withdraw immunosuppression.

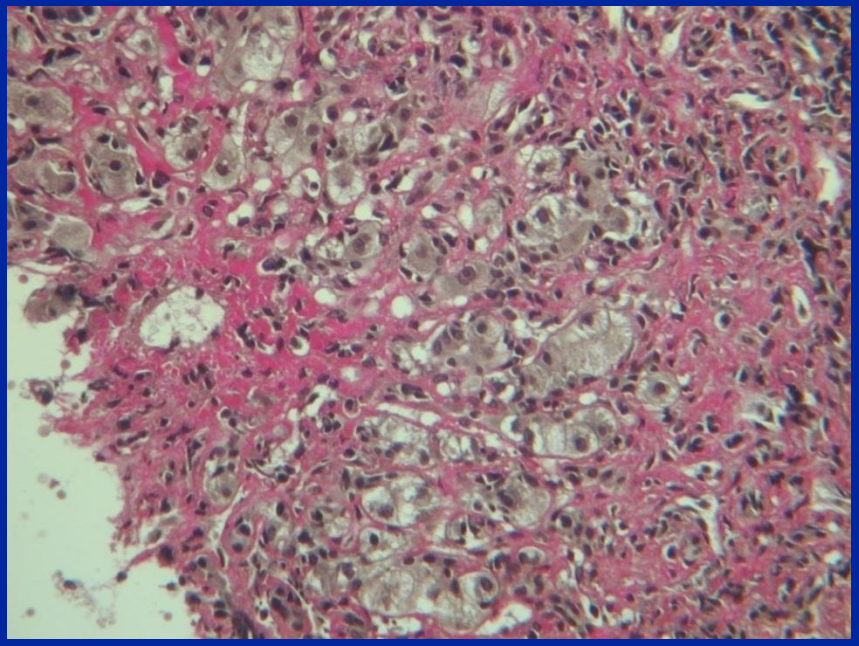


Sometimes (n=2) - please specify when

- If significant fibrosis/cirrhosis suspected
  (progression to cirrhosis associated with very high relapse rate)

Autoimmune Hepatitis - Lobular inflammation





Lobular inflammation in AIH

- Typically plasma cell rich
- Often mainly perivenular (“central perivenulitis”), may be diffuse
- More severe cases associated with confluent / bridging necrosis (and fibrosis)
  - Less responsive to immunosuppression
  - Increased risk of progression to cirrhosis (up to 80% - Cjaza 2007)
- May present as acute hepatitis / acute liver failure

Autoimmune Hepatitis - Acute Presentation
Incidence & Diagnostic Criteria

30- 40% of cases present as acute hepatitis /acute liver failure

(Czaja & Freese 2002, Lohse 2011)

Increasing prevalence of AIH as a cause for acute liver failure

(Fujiwara 2011)

- ? May reflect improved recognition

Autoantibodies unreliable in the diagnosis of acute AIH

- Autoantibodies and hypergammaglobulinaemia may not be present at the time of presentation with acute AIH (Lohse 2011)
- Autoantibodies present in up to 40% of patients with other causes of acute liver failure - e.g viral or drug-induced (Bernal 2007)

Autoimmune Hepatitis - Acute Presentation
Histological Features

Acute presentation of chronic liver disease

- 14-35% have features of chronic hepatitis (Fujiwara 2011, Yasui 2011)
- 10-95% have bridging fibrosis or cirrhosis (Nikias 1994, Burgart 1995, Miyake 2010, Fujiwara 2011)

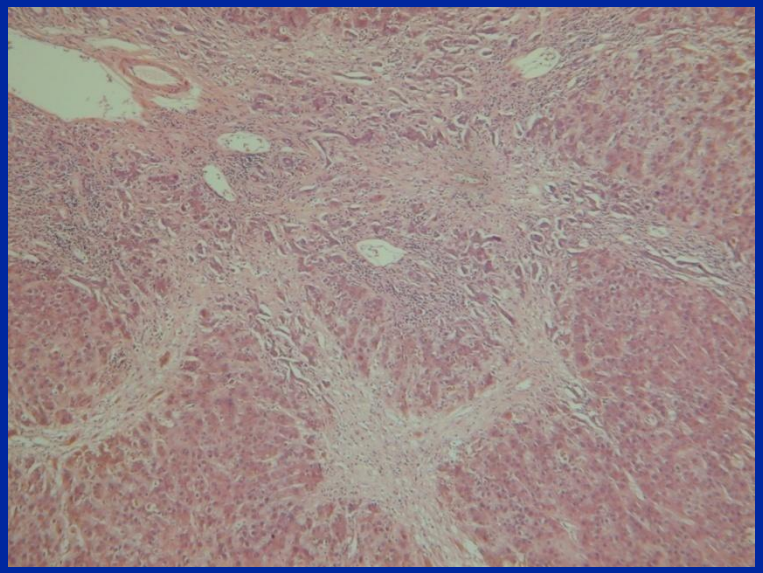
Autoimmune Hepatitis - Acute Presentation
Histological Features

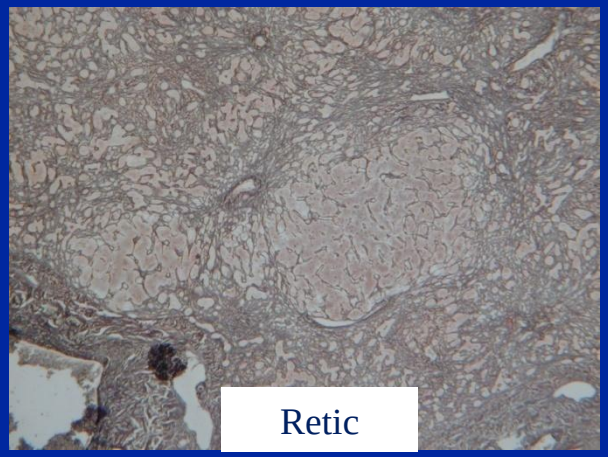
Acute hepatitis (with no signs of chronic liver disease)

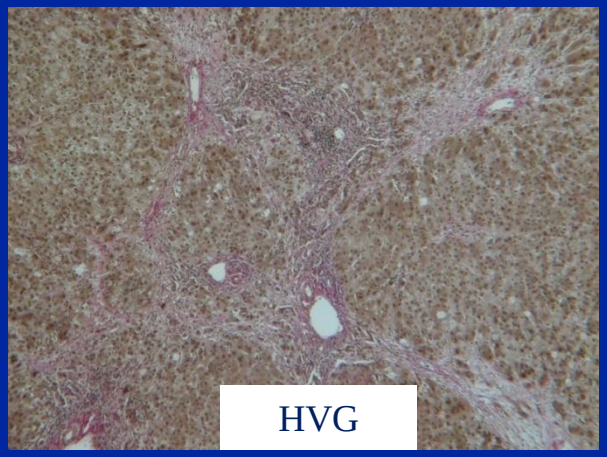
(Te 1997, Singh 2002, Hofer 2006, Ichai 2007, Fujiwara 2011, Stravitz 2011, Susuki 2011, Yasui 2011)

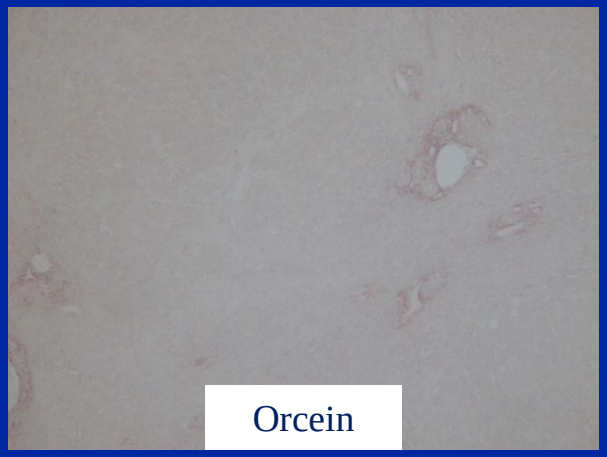
- Classical features of acute lobular hepatitis
- Mainly centrilobular distribution
- Some cases initially have little or no portal inflammation, before subsequently progressing to more classical features of chronic AIH
- Severe cases with bridging or panacinar necrosis
  - Changes heterogeneous in distribution
  - Typical features of AIH may no longer be apparent
  - Can resemble changes seen in cirrhosis

Female, age 34. Subacute liver failure – 3 month history
ANA positive 1 in 400, IgG 33 (normal 8-14.50) ? autoimmune hepatitis
No response to corticosteroid therapy. Liver transplantation









Autoimmune Hepatitis Presenting as Acute Hepatitis/ Acute Liver Failure (Abe 2007, Fujiwara 2008, Stravitz 2011, Yasui 2011)

Histological Features Favouring a Diagnosis of AIH

- Portal inflammation /interface hepatitis (resembling chronic AIH)
- Plasma-cell rich inflammatory infiltrate
- Lymphoid follicles
- Centrilobular necrosis / central perivenulitis (or submassive necrosis with centrilobular accentuation)

One study examined 72 cases where the cause of acute liver failure was uncertain (Stravitz 2011)

- 42 patients with histological features suggesting "probable AIH" had:
  - Higher prevalence of autoantibodies (73% vs 48%)
  - Higher serum globulin levels (3.9 vs 3.0g/dL)
  - Higher incidence of chronic hepatitis in follow up (67% vs 17%)

Autoimmune Hepatitis – Assessment of Fibrosis

- At least 1/3rd of patients have cirrhosis at presentation (Lohse 2011)
  - Includes cases with acute presentation
    (important to distinguish true cirrhosis from post-necrotic collapse)

- Patients with cirrhosis at presentation
  - Have worse outcome (Feld 2005, Verma 2007)
  - Less responsive to immunosuppression (Muratori 2009)
    - But reversal of cirrhosis following treatment can occur (Czaja 2007)
  - At risk of developing HCC - approx 1.1%/year (Yeoman 2008)

Primary Biliary Cirrhosis

Primary Biliary Cirrhosis – Diagnostic Criteria

EASL Clinical Practice Guidelines – J Hepatol 2009; 51: 237-267

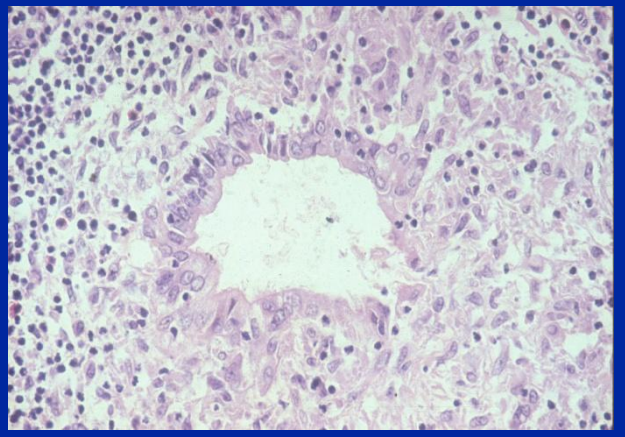
AASLD Practice Guidelines – Lindor. Hepatology 2009; 50: 291-308

1. Cholestatic liver biochemistry (raised Alk Phos)
2. Anti-mitochondrial antibodies (with M2 specificity)
3. Diagnostic or compatible histological findings.

Changing role of liver biopsy:

1. 2 of 3 criteria generally considered adequate

Biopsy not required in cases with other typical features



2. Diagnostic duct lesions patchy in distribution

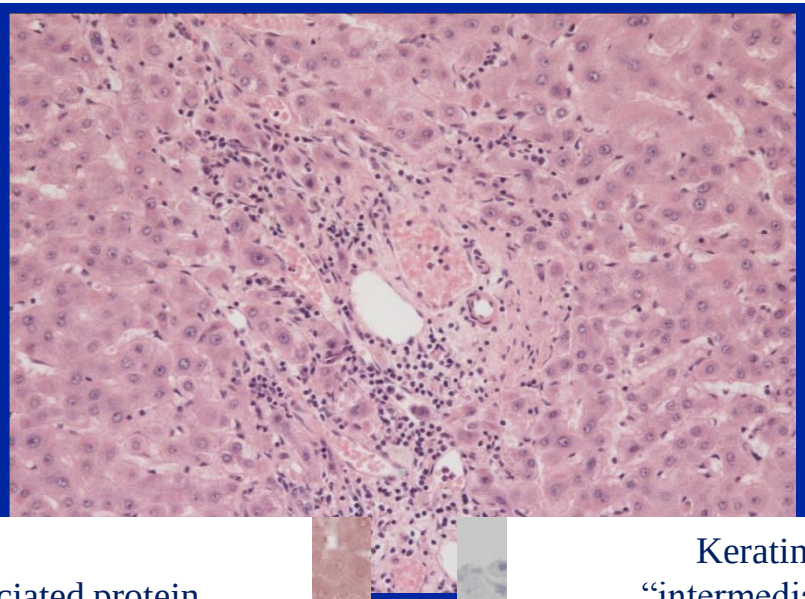
Present in 30-50% of biopsies (Wiesner 1985, Drebber 2009)

Histology alone unreliable in distinguishing PBC from other chronic biliary diseases associated with duct loss (incl. PSC)

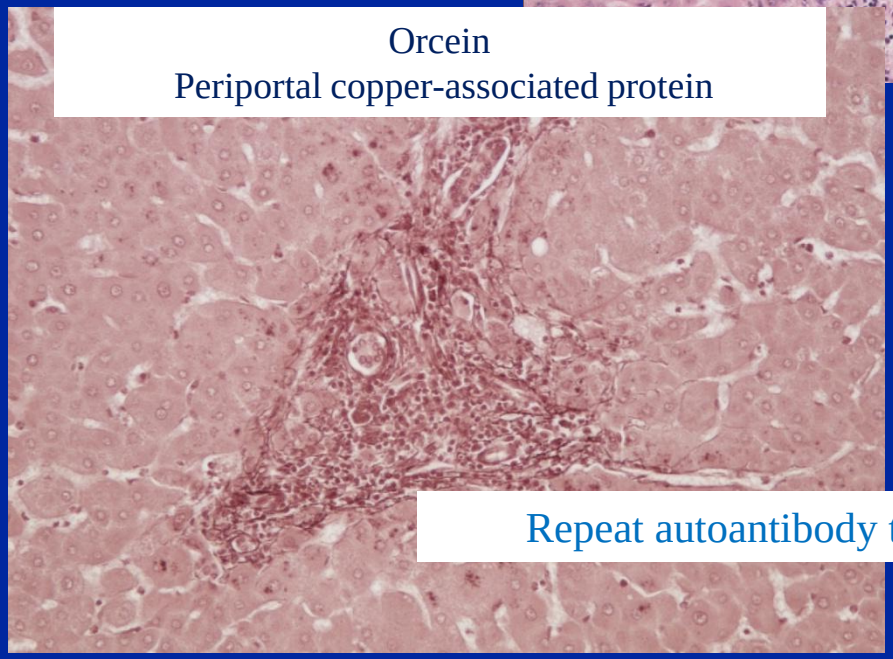
BUT: Subtle features of chronic cholestasis may identify early chronic biliary disease before this has been diagnosed clinically

Referred Biopsy – Diagnosis Chronic Hepatitis ? Cause
Raised AST & Alk Phos. Autoantibody screen negative.

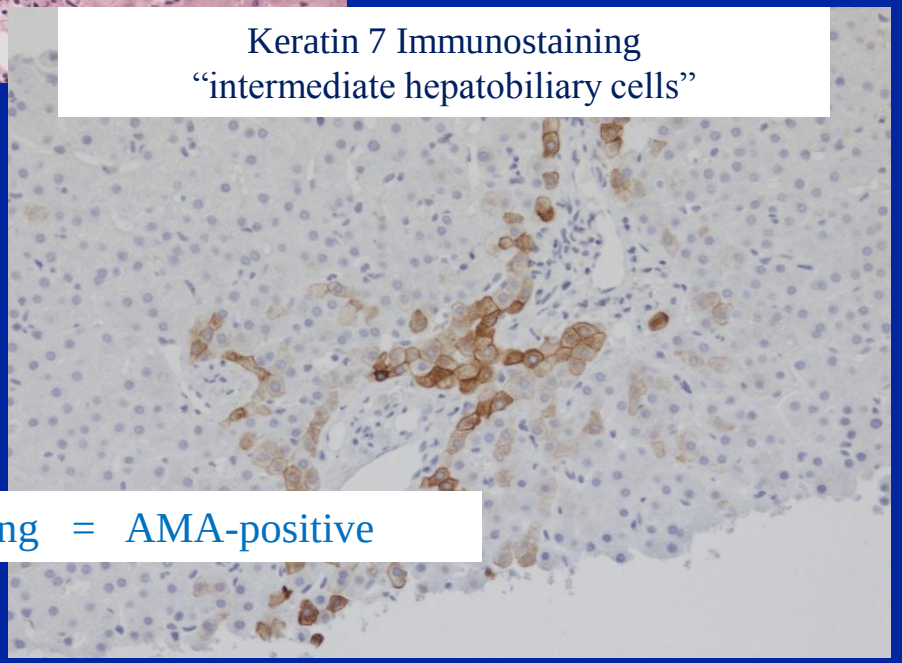
- Portal inflammation and interface hepatitis
- Biliary features not conspicuous



Orcein
Periportal copper-associated protein



Keratin 7 Immunostaining
"intermediate hepatobiliary cells"



Repeat autoantibody testing = AMA-positive

Primary Biliary Cirrhosis – Role of Liver Biopsy

1. AMA – negative PBC ("autoimmune cholangitis")
2. Assessing inflammatory activity (autoimmune "overlap syndromes")
3. Assessing disease progression (staging)

AMA – negative PBC (‘Autoimmune Cholangitis’)

Prevalence

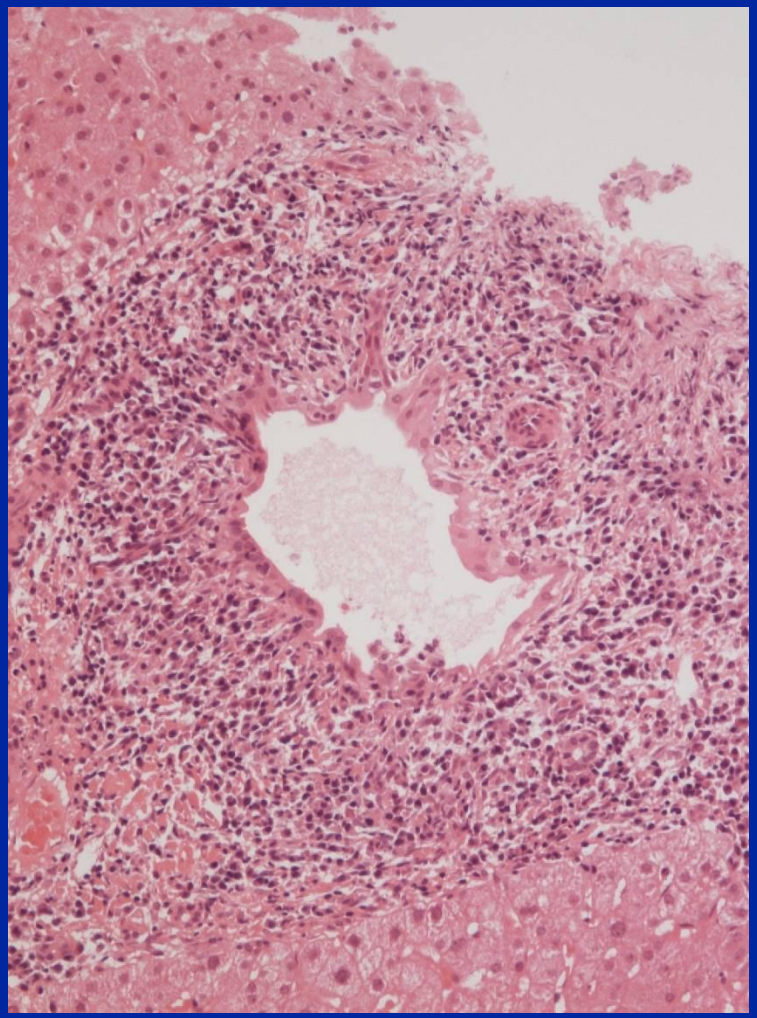
- Approximately 5-10% cases

Diagnostic Features

- Typically have other autoantibodies (ANA, SMA)
- Cholestatic biochemistry and histology

Some differences compared with AMA-positive PBC

e.g. less severe pruritus, higher AST, lower IgM levels, more plasma cells, more T cells



Primary Biliary Cirrhosis – Role of Liver Biopsy

1. AMA – negative PBC ("autoimmune cholangitis")
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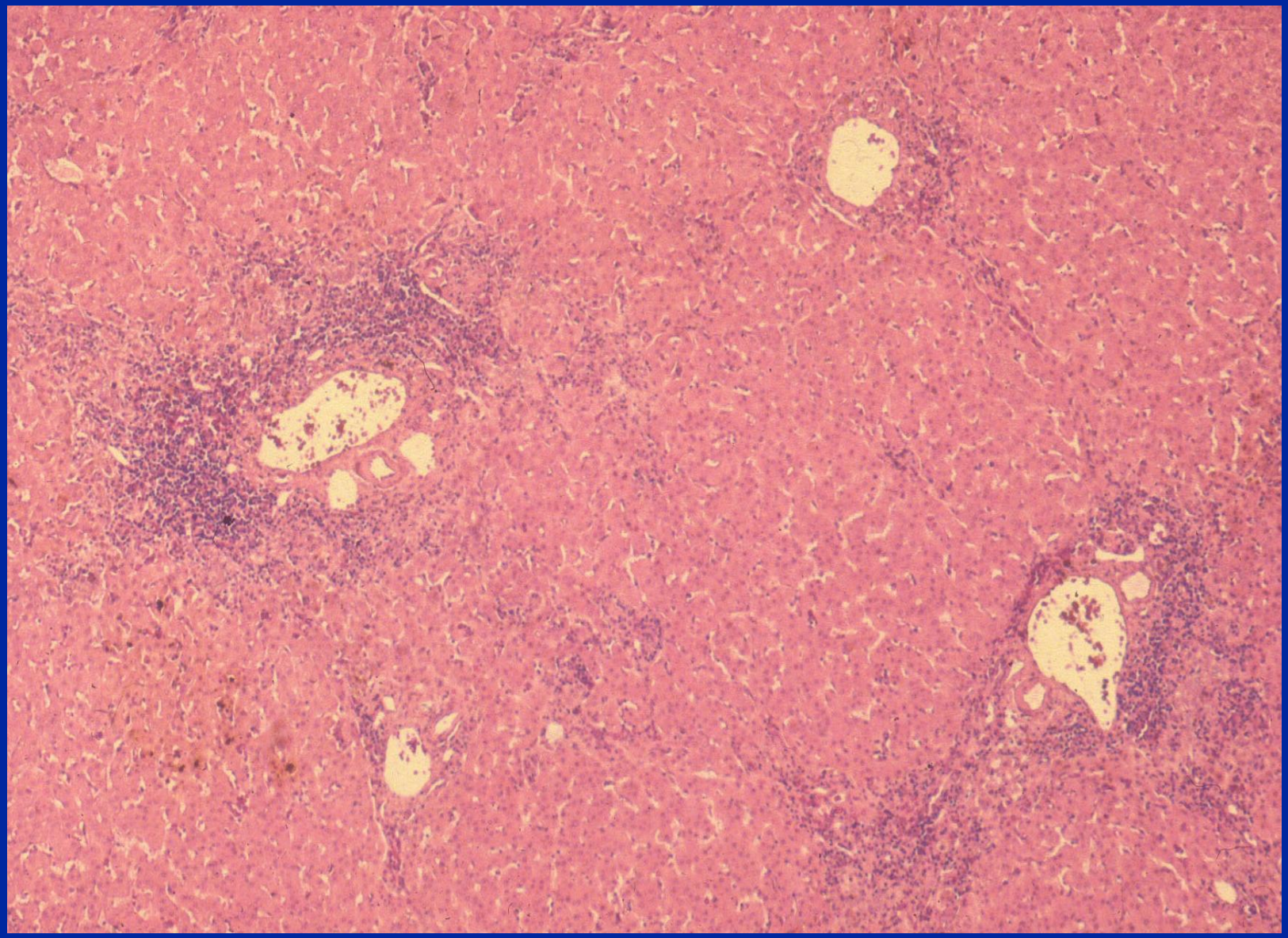
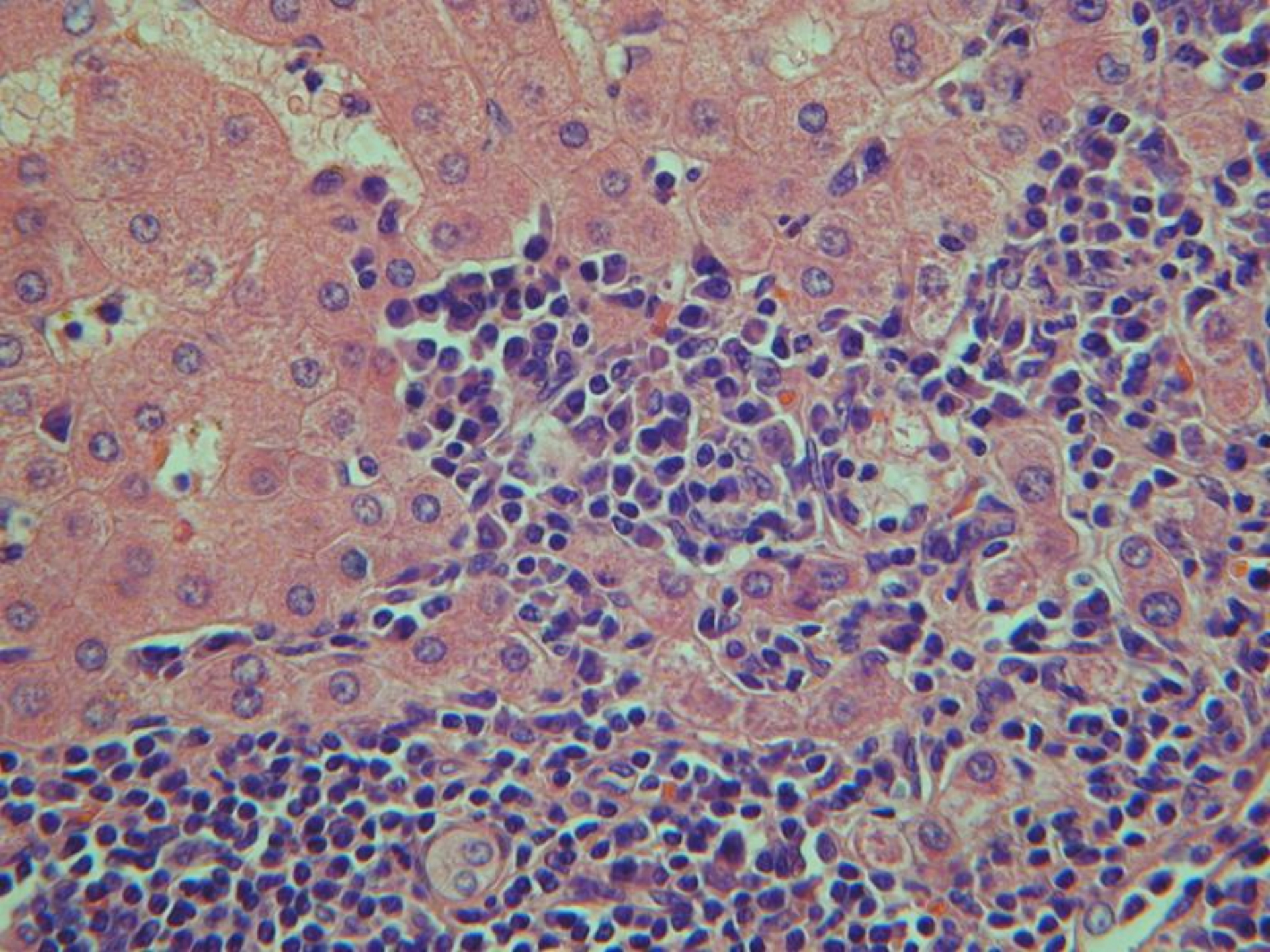
Primary Biliary Cirrhosis
Portal inflammation with interface hepatitis





Primary Biliary Cirrhosis
Significance of Inflammatory Activity

Severity of inflammatory activity (periportal and lobular)

- Predictive for subsequent progession to fibrosis /cirrhosis & liver failure
  (Degott 1999, Corpechot 2002, Corpechot 2008)

- Moderate or severe interface hepatitis also used as a diagnostic criterion for PBC/AIH "overlap syndrome" (PBC with "hepatitic features")
  (Chazouilleres 1998 & 2006, Poupon 2006, &2010, Boberg 2011)
  - 10-15% of PBC have additional features supporting a diagnosis of AIH (biochemical, immunological and histological)
  - PBC with "hepatitic features" - worse outcome than "pure" PBC
  - May benefit from treatment with immunosuppression
    - Normalisation of ALT levels
    - Less severe fibrosis progression

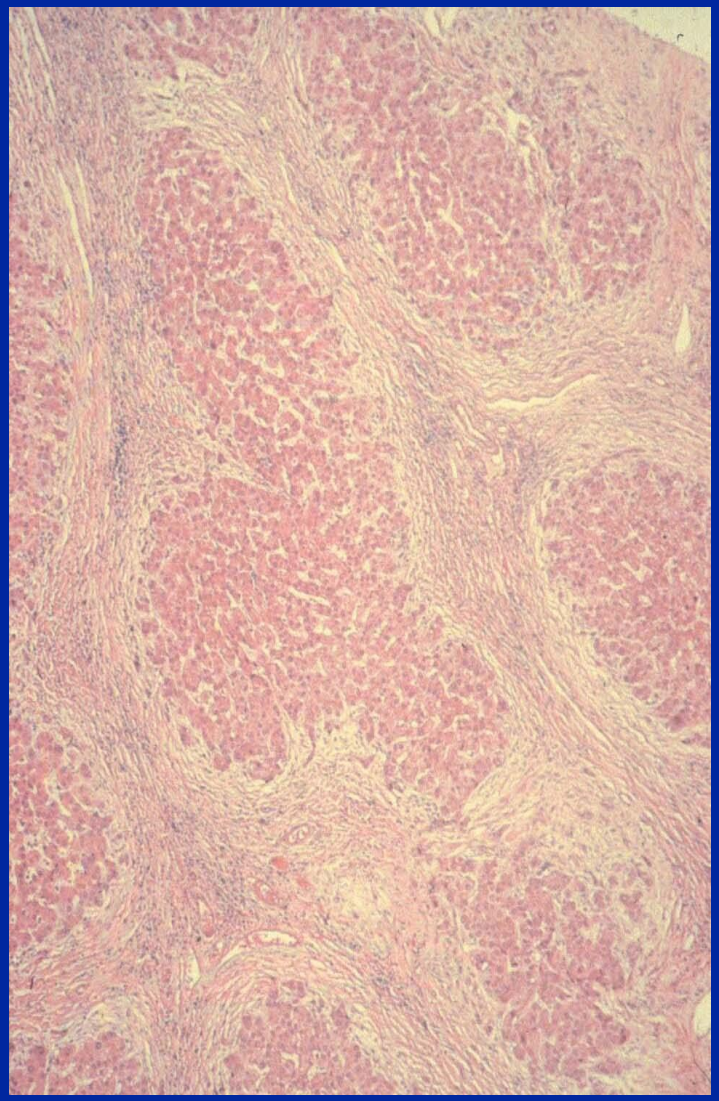
(Similar comments apply to PSC)

Primary Biliary Cirrhosis – Role of Liver Biopsy

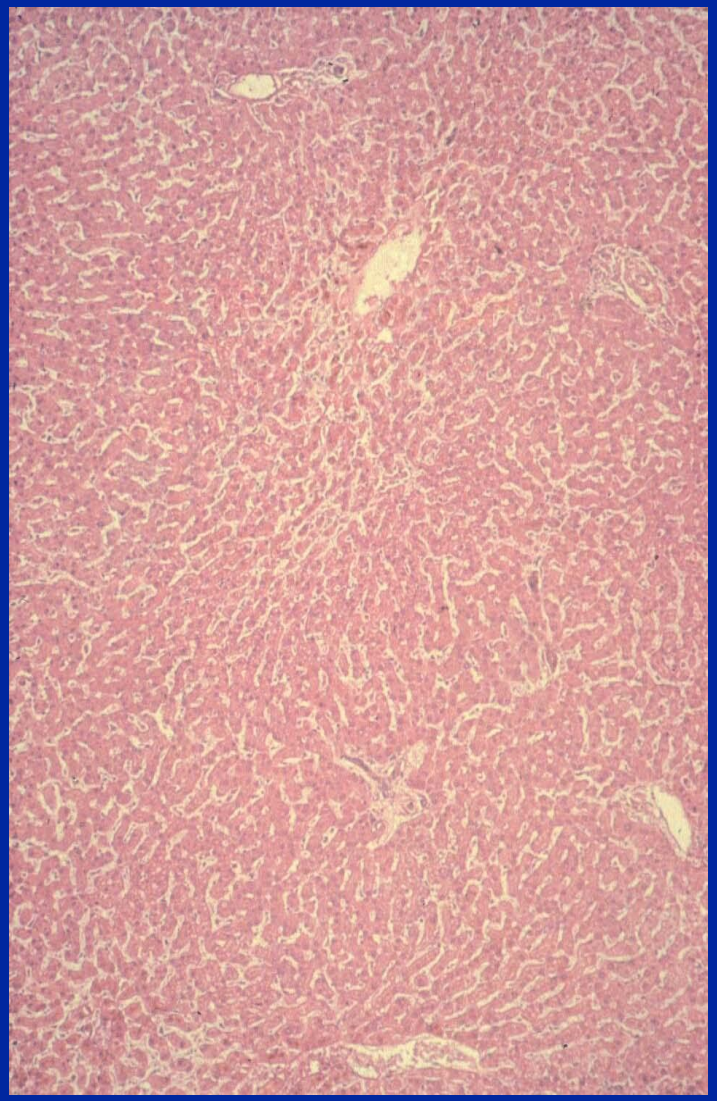
1. AMA – negative PBC ("autoimmune cholangitis")
2. Assessing inflammatory activity (autoimmune "overlap syndromes")
3. Assessing disease progression (staging)
   - Several staging systems described

     (Rubin 1965, Scheuer 1967, Popper & Schaffner 1970, Ludwig 1978)
   - No longer used in routine assessment

Primary Biliary Cirrhosis – Variable Fibrosis
(similar changes in PSC & other chronic cholestatic disease)



Cirrhotic area



No fibrosis

PBC – Role of Biopsy in Staging

Histological features predictive of poor outcome in PBC:

(Vleggar 2000, Bergasa 2004, Kumagi 2010, Floreani 2011)

- Advanced stage/established cirrhosis
- Marked ductopenia

A novel system for grading & staging PBC

(Hiramatsu 2006)

Grading	Staging
• Chronic cholangitis (0-3)	• Bile duct loss (0-3)
• Interface hepatitis (0-3)	• Fibrosis (0-3)
• Lobular hepatitis (0-3)	• Orcein-positive granules (0-3)

- Inter-observer reproducibility assessed in follow-up study (Nakanuma 2010)
  - Agreement "fair" for staging , "slight" for activity
- Utility in prognosis/management not yet demonstrated

Primary Sclerosing Cholangitis

Primary Sclerosing Cholangitis – Diagnostic Criteria

EASL Clinical Practice Guidelines – J Hepatol 2009; 51: 237-267

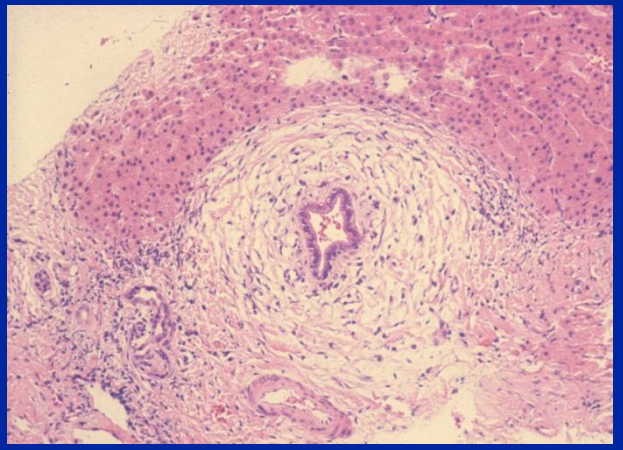
AASLD Practice Guidelines – Chapman, Hepatology 2010; 51; 660-678

1. Cholestatic liver biochemistry (raised Alk Phos)
2. Cholangiography
3. Exclusion of secondary causes of sclerosing cholangitis

Changing role of liver biopsy:

1. No longer required for routine diagnosis
2. Diagnostic duct lesions patchy & mainly affect medium-sized (septal) ducts

- Present in 12% of biopsies (Wiesner 1985)
- Also seen in secondary sclerosing cholangitis (SSC)
- Histology alone unreliable in distinguishing PSC from other chronic biliary diseases associated with duct loss (including PBC, SSC)



Primary Sclerosing Cholangitis – Role of Liver Biopsy

1. PSC variants
   - Small-duct PSC
   - IgG4 sclerosing cholangitis
2. Assessing inflammatory activity (autoimmune “overlap syndromes”)
3. Assessing disease progression (staging)

Primary Sclerosing Cholangitis – Role of Liver Biopsy

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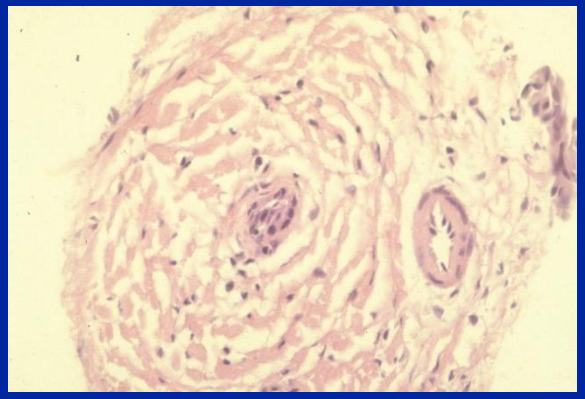
Small Duct PSC



Approximately 10-15 % of cases

Normal/near-normal cholangiogram

Histological features of fibrous cholangitis

- Extent to which fibrosing duct lesions present not clearly specified

- Outcome variable:
  - 10-20% cases develop features of large duct involvement (Bjornsson 2002, La Russo 2006, Bjornsson 2008)
  - Generally more favourable than classical PSC
    - Survival comparable to normal population
    - Low risk of cholangiocarcinoma
  - "Overlap syndrome" with AIH may be more frequent
    - 26% of PSC-AIH cases had small duct PSC (Olsson 2009)

Primary Sclerosing Cholangitis – Role of Liver Biopsy

1. PSC variants
   - Small-duct PSC
   - IgG4 sclerosing cholangitis
     - Part of spectrum of systemic IgG4-associated disease
     - Range of lesions involving bile ducts (extra- and intrahepatic)
     - Role of liver biopsy
       - Identifying cases with diffuse intrahepatic disease
       - Relationship between IgG4-SC and PSC
2. Assessing inflammatory activity (autoimmune “overlap syndromes”)
3. Assessing disease progression (staging)

IgG4 –associated Sclerosing Cholangitis
Intrahepatic Disease - Histological Findings

(Naitoh 2007, Nakanuma 2007, Umemura 2007, Deshpande 2009, Koyabu 2010, Oh 2010, Naitoh 2011, Ryu 2011, Zen 2011)

Bile Duct Lesions

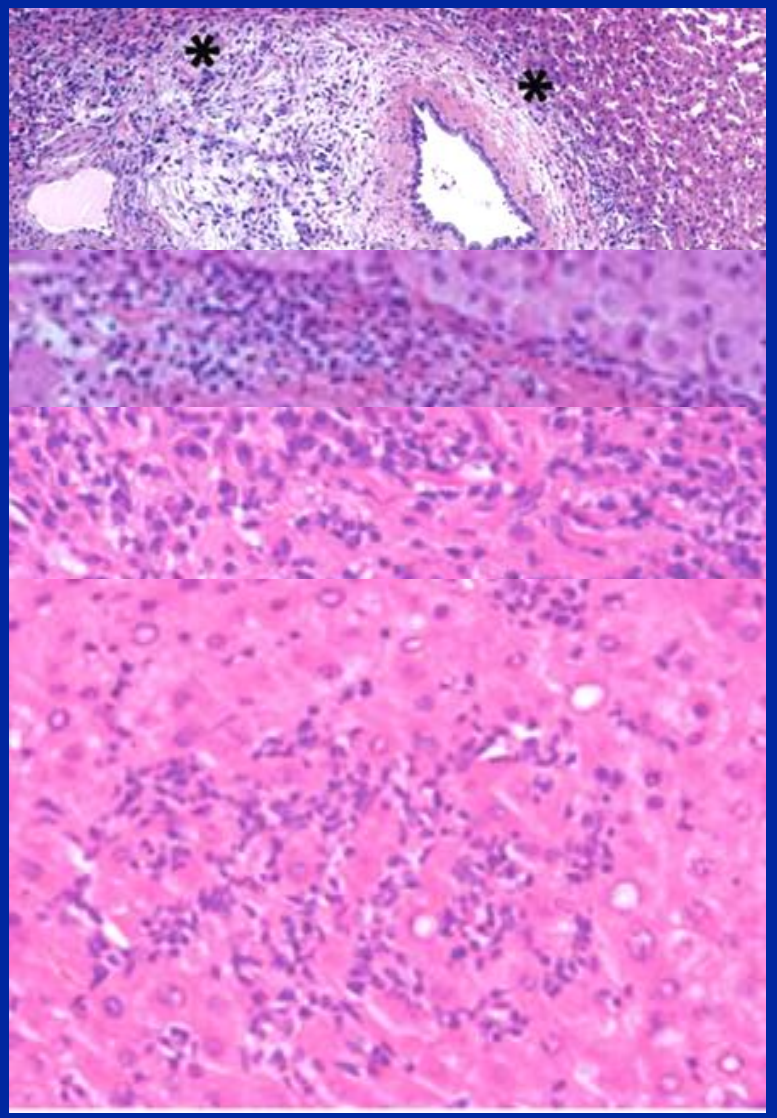
- Periductal inflammation
  - "fibro-inflammatory nodules"
- Mild periductal fibrosis (no nodular scars)
- Ductopenia uncommon

Inflammation (more prominent than PSC)

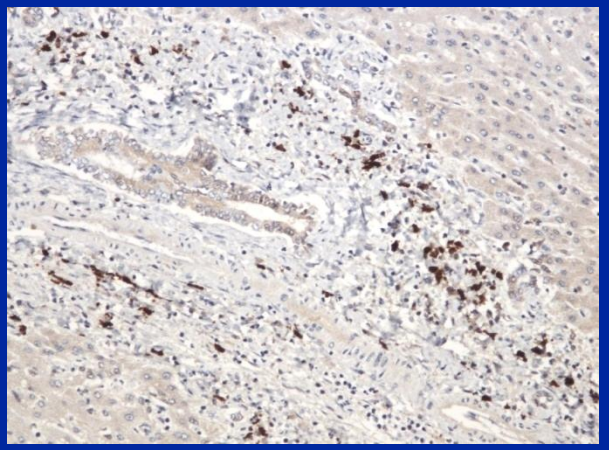
- Mainly portal , variable interface hepatitis
  - Plasma cells++, eosinophils+
- Lobular hepatitis

Fibrosis

- Generally mild
- Bridging fibrosis in up to 40%
- Advanced fibrosis rare



IgG4-associated Sclerosing Cholangitis
Role of IgG4 Immunohistochemistry



> 10 IgG4+ cells/HPF generally accepted as suggestive/diagnostic

Problems:

1. Variable size of high power fields

2. 30- 50% of otherwise typical cases have < 10 IgG4+ cells/HPF (Deshpande 2009, Itoh 2009, Kawakami 2010, Oh 2010)

3. > 10 IgG4+ cells/HPF may be seen in a range of unrelated chronic inflammatory diseases
   - e.g. non-specific dermatitis, rheumatoid synovitis (Strehl 2011)

IgG4-associated Sclerosing Cholangitis – A Variant of PSC?

(Bjornsson 2006, Hirano 2006 ,Mendes 2006, Webster 2009, Zhang 2010, Bjornsson 2011, Oseini 2011)

- 10-30% of otherwise typical cases of PSC have elevated serum IgG4 levels +/- tissue infitrates of IgG4+ plasma cells supporting a diagnosis of IgG4-SC

- Appear to behave more aggressively than Ig4-negative PSC
  - Higher prevalence of cirrhosis at time of diagnosis
  - More rapid progression to liver transplantation
  - Higher rate of recurrence post-transplant

- Nature uncertain (variant of PSC or IgG4 sclerosing disease)
  - May benefit from treatment with corticosteroids

Primary Sclerosing Cholangitis – Role of Liver Biopsy

1. PSC variants
   - Small-duct PSC
   - IgG4 sclerosing cholangitis
2. Assessing inflammatory activity (autoimmune “overlap syndromes”)
3. Assessing disease progression (staging)

PSC/AIH Overlap Syndrome

(Beuers 2009, Chapman 2010)

- **Diagnostic Criteria**
  - Similar to those used for PBC/AIH overlap

- **Presentation**
  - "sequential syndrome" more common than in PBC, particularly in children/young adults (usually AIH → PSC , 6 months -13 years)
  - extent to which PSC excluded at time of diagnosing AIH uncertain
    - Using routine cholangiography up to 50% of children (Gregorio 2001) and 2-10% of adults (Abdalain 2008, Lewin 2009) presenting with AIH have features compatible with PSC

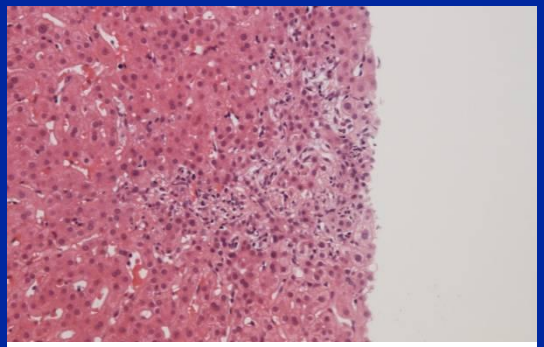
PSC/AIH Overlap Syndrome
Role of Liver Biopsy in a Patient with a Diagnosis of AIH

New onset AIH (particularly in children)

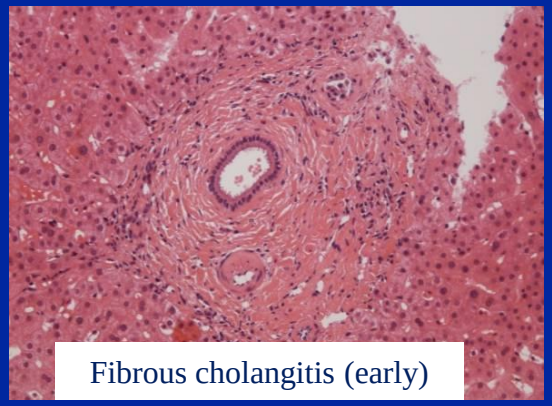
- Subtle features of chronic cholestasis or focal duct loss should raise possibility of PSC and prompt cholangiography.
- Liver biopsy occasionally reveals features compatible with PSC in a patient who intially has a normal cholangiogram (Abdalian 2008, Luth 2009)

Treated AIH (with persistently abnormal LFTs)

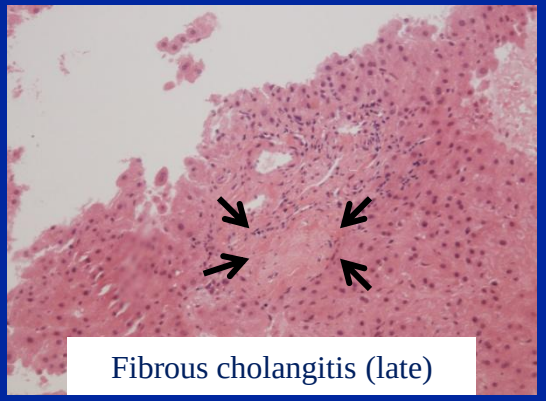
- Liver biopsy may help to identify relative severity of inflammatory activity and features of chronic biliary disease



Ductular reaction & biliary fibrosis



Fibrous cholangitis (early)



Fibrous cholangitis (late)

Is Liver Biopsy Essential for Diagnosis and Management of AIH?

Still recommended in recent expert reviews/guidelines documents

- International Autoimmune Hepatitis Group (Hennes 2008)
  - Histology one of 4 features used in simplified scoring system used to diagnose AIH

- AASLD Practice Guidelines (Manns 2010)
  - Liver biopsy "recommended to establish the diagnosis and to guide treatment decisions"

- Invited Review (Lohse & Mieli-Vergani, J Hepatol 2011)
  - "Histology considered a necessary prerequisite for making a diagnosis", "follow-up biopsies are also generally recommended before considering cessation of therapy"

Autoimmune Hepatitis – Laboratory Investigations
Diagnostic Criteria

Biochemistry	Hepatitic LFTs • Raised AST/ALT
Immunology	Autoantibodies • ANA, SMA (type 1) • LKM , LC-1 (type 2) Immunoglobulins • Raised IgG
Histology	Presence of typical/compatible features Absence of atypical features (e.g. biliary features)

International Autoimmune Hepatitis Group – Scoring Systems for Diagnosis of AIH
(Original –Johnson 1993, Modified – Alvarez 1999, Simplified – Hennes 2008)

- Various combinations of clinical, biochemical, immunological & histological features
- Points allocated for typical features (deducted for atypical features -1993 & 1999 systems)
- Total scores = "definite", "probable" or "not" AIH
- Mainly intended for research purposes – e.g. clinical trials