Autoimmune Liver Disease

University of California, San Francisco
Liver and Gastrointestinal Pathology Update

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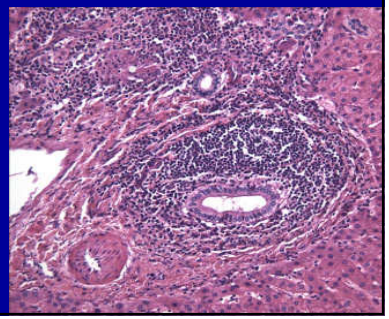


Key Points

- Three main categories of autoimmune liver disease
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
- Characteristic morphologic patterns of injury

Key Points

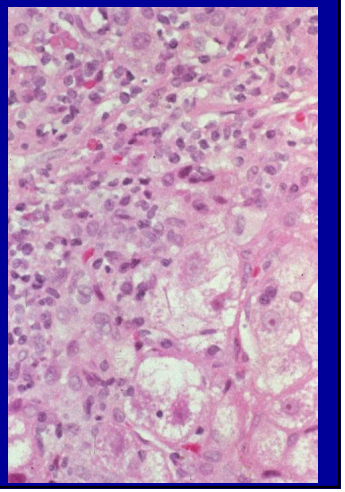
- Overlap syndromes (primarily of AIH with PBC or PSC) may comprise up to 10% of cases
  - Sequential syndromes are rarer
- Diagnosis is based upon a constellation of clinical, serologic, and biopsy findings.

Recent Developments in Autoimmune Liver Disease

- Asymptomatic AIH
- AIH in the elderly
- New simplified scoring system for AIH
- Autoimmune liver disease associated with celiac disease
- IgG4 cholangiopathy
- Response to UDC in PBC
- More focused studies of overlap syndromes

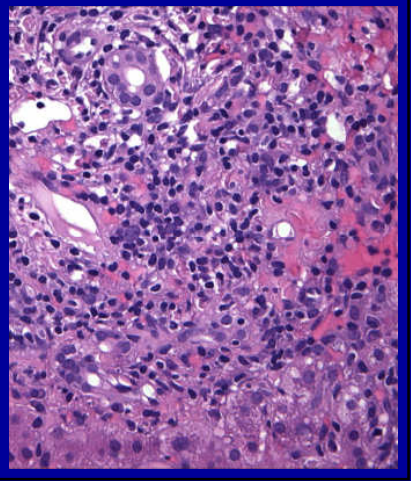
Autoimmune Hepatitis: Topics

- Definition and Epidemiology
- Etiology and Immunology
- Clinical Features
- Serology
- Histologic Features
- Special Problems
- Differential Diagnosis



Autoimmune Hepatitis: Definition

- **Unresolving hepatitis**
- **Increased IgG levels**
- **Tissue directed autoantibodies**
- **Responds to immunosuppression**



Autoimmune Hepatitis: Epidemiology

- Prevalence of ~ 1 per 100,000 in North America
- ~20% of chronic hepatitis
- Associated with HLA A1-B8-DR3 in European populations and DR4 in Japan
- More common in women
- Wide age distribution

Immunology of AIH

- Loss of self-tolerance
- Cause usually unclear
- ? Viral trigger- anecdotal reports of AIH following HAV, HBV, HSV, EBV infections
- Unlikely to be triggered by HCV: anti-LKM antibodies in HCV are directed against different epitopes
- Small heritable component; complex genetic trait

Autoimmune Hepatitis: Clinical Features

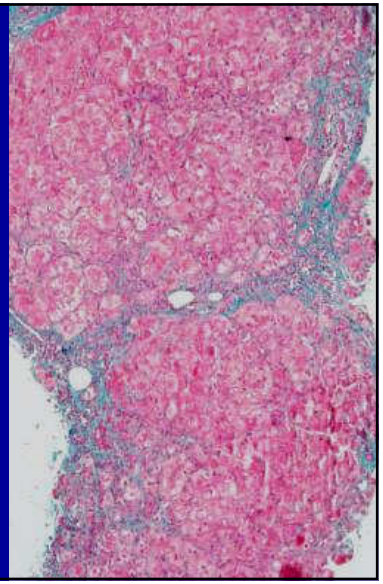
- Presentation is highly variable (asymptomatic to fulminant hepatic failure)
- 1/3 are cirrhotic at presentation
- 1/3 have acute presentation mimicking viral hepatitis
- 1/3 have prodromal phase
- 20% are asymptomatic
- ~50% will have other autoimmune disorders

Asymptomatic Presentation of AIH

- ~20 to 25% are asymptomatic at diagnosis
- Discovered on routine liver testing
- Older patients
- Less activity in liver biopsy
- 25% will develop symptoms upon follow up
- Survival is similar to patients with symptomatic presentation

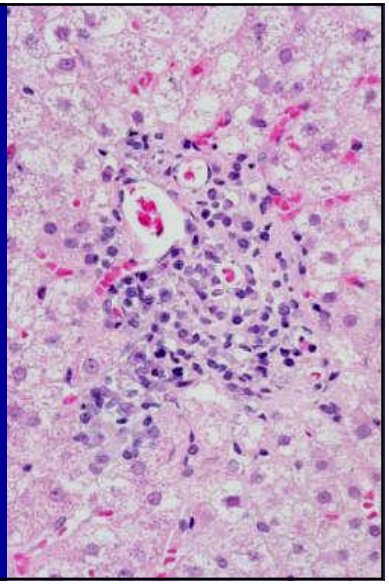
Two Groups of Asymptomatic Patients

- "Burned out" cirrhosis and nearly normal liver tests
  - 36%; similar to that seen in symptomatic patients
  - Less favorable outcome (62% vs. 94% 10-year survival)
- Mild hepatitis without cirrhosis



AIH in the Elderly

- Over 20% are diagnosed after age 60
- More likely to be cirrhotic at presentation
- Responds to corticosteroid therapy, even in setting of cirrhosis
- HLA DR4 more common



Diagnosis of AIH: Serum Studies

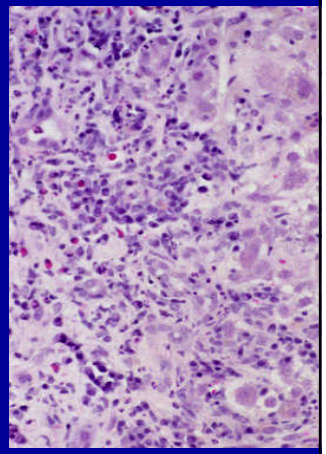
Autoantibody	Target Antigen	Frequency
ANA and/or SMA	ANA-ds DNA & histones; laminin; SMA- actin	70-80%
LKM1	Cytochrome p450 (CYP) 2D6 (endoplasmic reticulum)	3-4%
SLA/LP	UDA suppressor serine tRNA-protein complex	10-30%
p-ANCA	Multiple targets; actin	60-90%

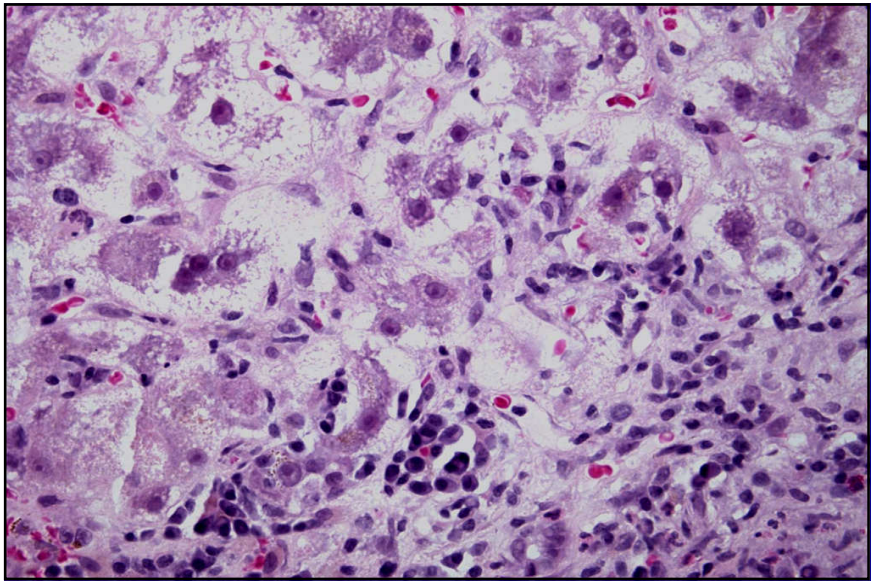
Autoimmune Hepatitis: Classification

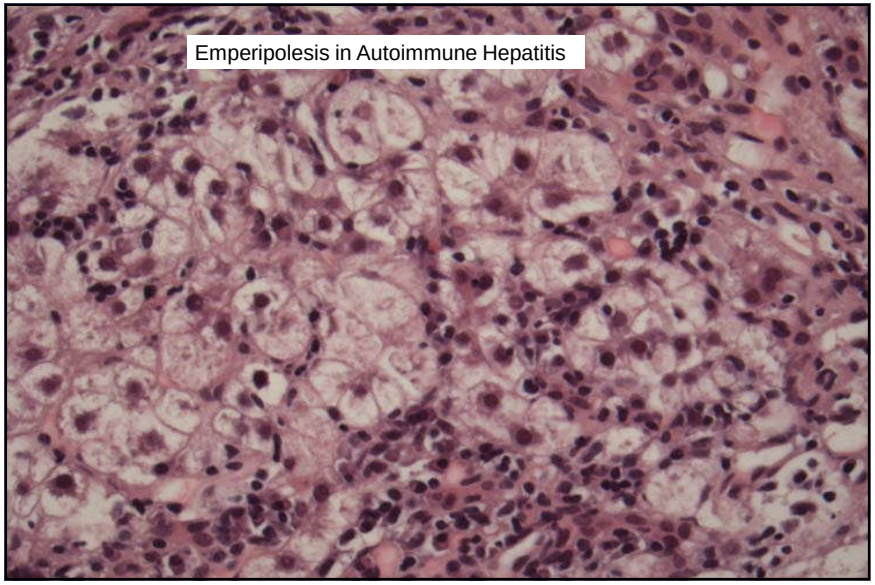
Type	Autoantibodies	Comment
Type I	ANA +/- SMA	Most common
Type II	LKM1	Young women with severe disease
Type III	SLA/LP	Indistinguishable from Type I

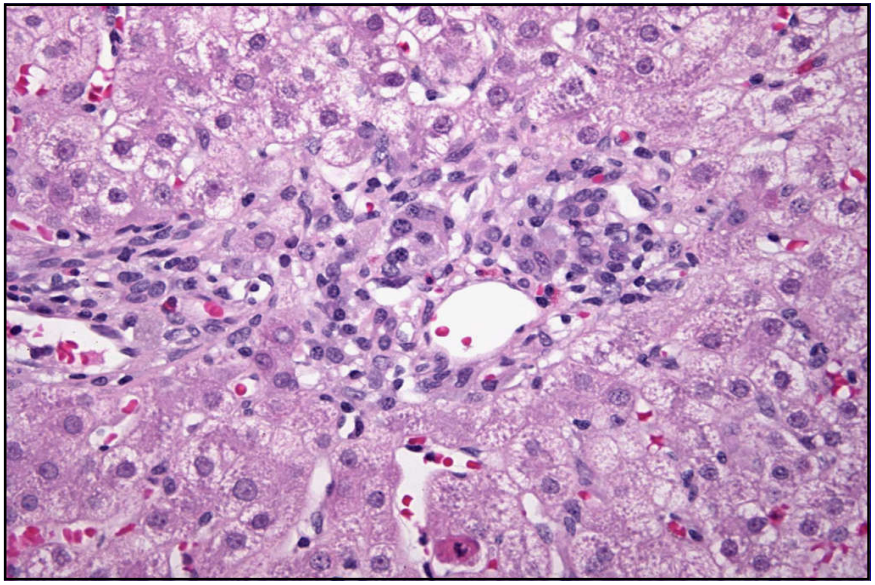
Autoimmune Hepatitis: Histologic Features

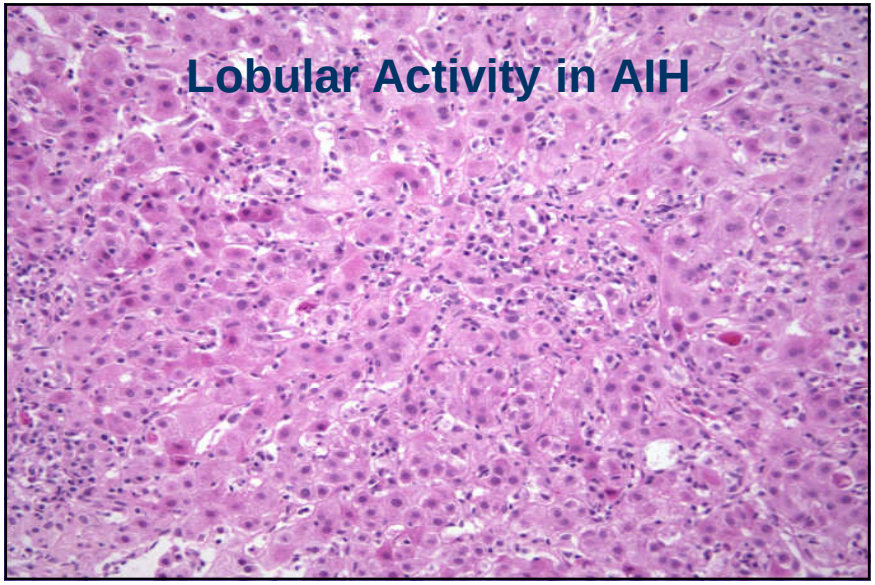
- Chronic hepatitis pattern of injury
  - Interface hepatitis
  - Lobular activity
  - Prominent plasma cells (IgG+, rarely IgM+)
- Hepatocyte regeneration
- Centrilobular necroinflammatory activity
- Bile duct injury not rare

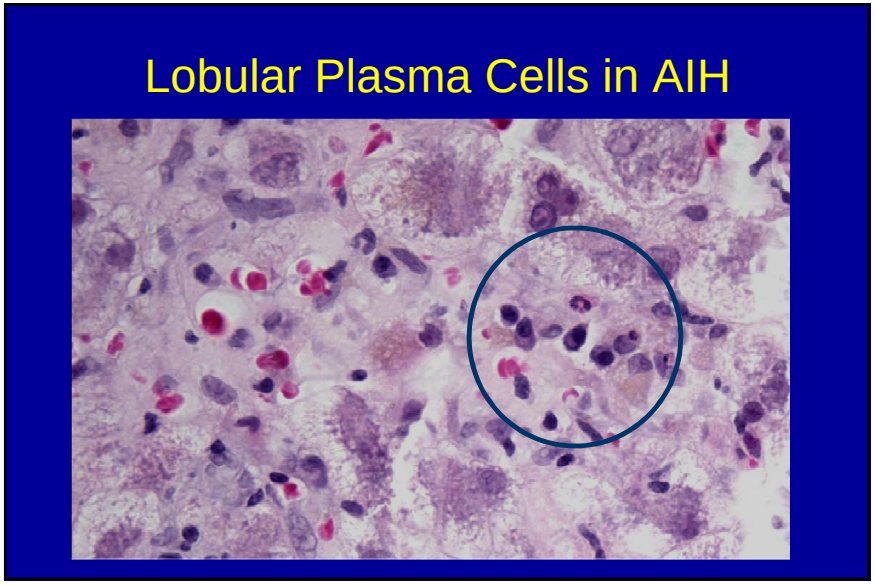


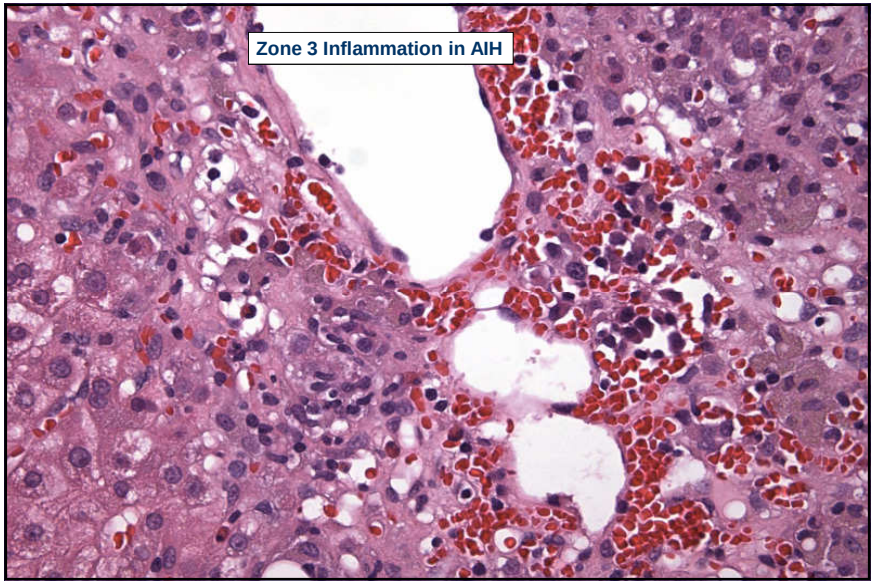


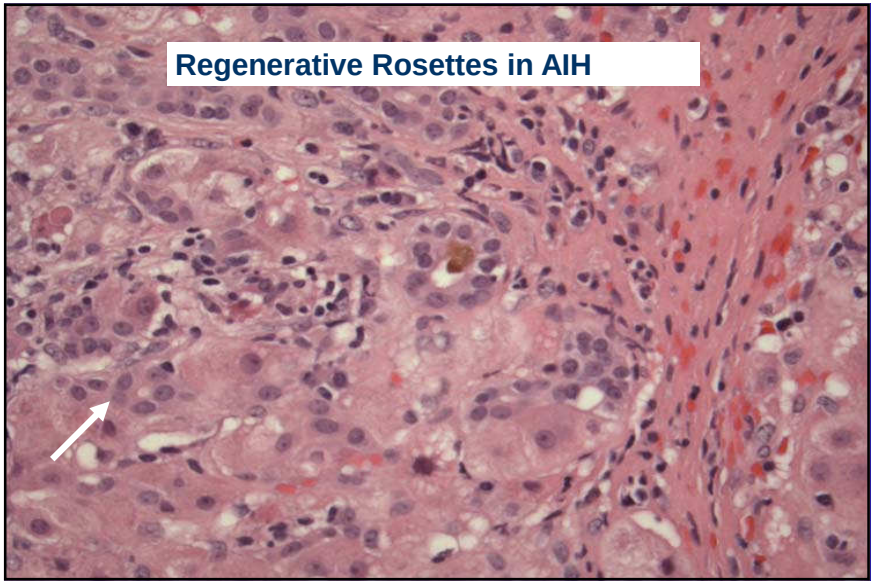

Emperipolesis in Autoimmune Hepatitis



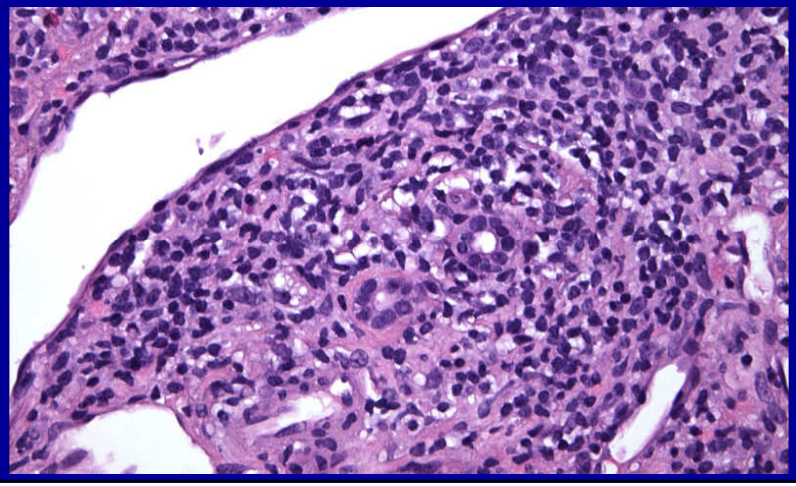

Lobular Activity in AIH

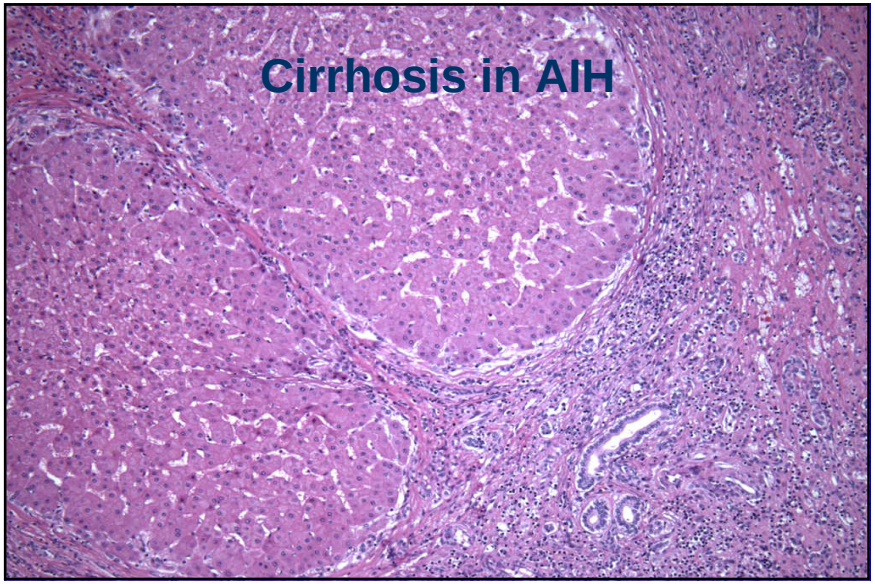

Lobular Plasma Cells in AIH

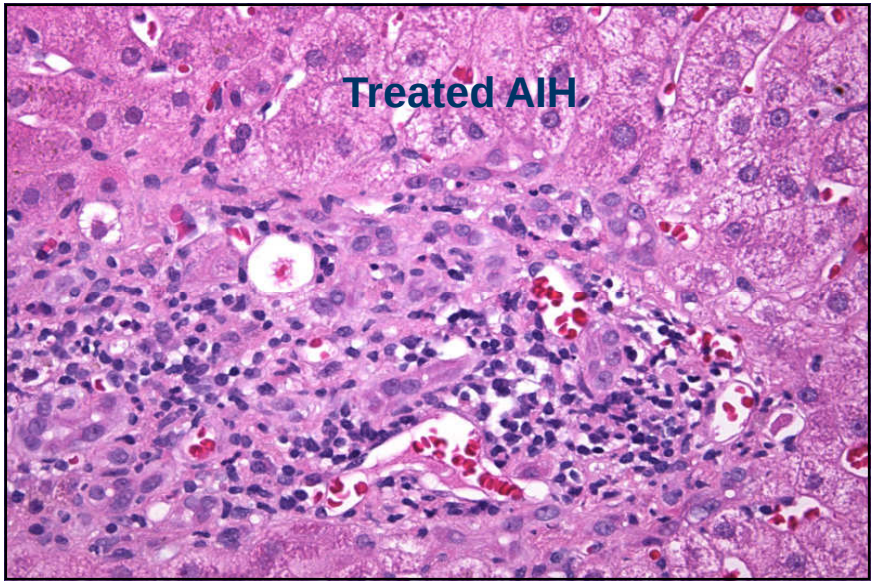




Bile Ducts in AIH







AIH Scoring System: Positive Weighting

- Female sex
- Low alk phos:AST ratio
- Increased IgG
- Autoantibodies
- Negative viral serology
- Positive treatment response
- Negative drug history
- Low alcohol consumption
- **Interface hepatitis**
- Concurrent autoimmune disorders
- + for relevant HLA haplotypes

AIH Scoring System: Negative Weighting

- High alk phos:AST ratio
- AMA +
- Positive viral serology
- Positive drug history
- High alcohol consumption
- **Bile duct damage**

- Definite AIH if score > 15 before treatment, 17 after treatment
- Probable AIH if 10-15 before treatment, 12-17 after treatment

Simplified Diagnostic Criteria for AIH

Feature	Cutoff	Points
ANA or SMA +	≥1:40	1
ANA or SMA +	≥1:80	2*
OR LKM	≥1:40	
OR SLM	Positive	
IgG	> Upper limit of normal	1
	>1.1 x upper limit of normal	2
Liver histology	***Compatible with AIH***	***1***
	Typical AIH	***2***
Absence of viral hepatitis	yes	2
		≥6: probable AIH
		≥7 definite AIH

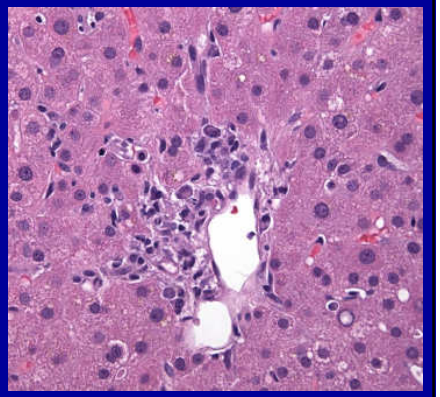
*Addition of points achieved for all antibodies (max 2 points)

Categories for Weighting Histology

- Typical histology (2 points)
  - Interface hepatitis (lymphocytes +/- plasma cells)
  - Emperipolesis
  - Hepatocyte rosette formation (1 point)
- Histology compatible with AIH
  - Chronic hepatitis pattern of injury but lacking some "typical" features
- Atypical histology
  - Features suggestive of other diagnoses

Autoimmune Hepatitis: Diagnostic Difficulties

- **Autoantibody negative patients**
- **Overlap with other autoimmune liver diseases**
- **Viral hepatitis**



Autoimmune Hepatitis and Viral Hepatitis

- True AIH, false positive anti-HCV
- True HCV, autoantibodies at low titers
- True HCV and features of AIH
  - Young women
  - Extrahepatic autoimmune disorders
  - High autoantibody titers
  - Increased serum IgG

Genuine vs. Virus-Induced Autoimmunity

	AIH	***Viral Hepatitis***
Autoantibody titer	↑↑↑	↑
Linear epitopes	+++	+
Conformational epitopes	+	++++
Inhibitory antibodies	++	++
Autoimmune response	Homogeneous	Heterogeneous
Treatment	Immunosuppression	Antiviral agents

Autoimmune Hepatitis: Further Differential Diagnostic Considerations

- Drug reaction
  - Drug-triggered self-perpetuating AIH
- Alpha-1-antitrypsin deficiency in the adult patient
- Wilson's disease
- Celiac disease
- Non-specific spotty hepatocyte necrosis (chronic hepatitis of unclear etiology)

The Liver in Celiac Disease

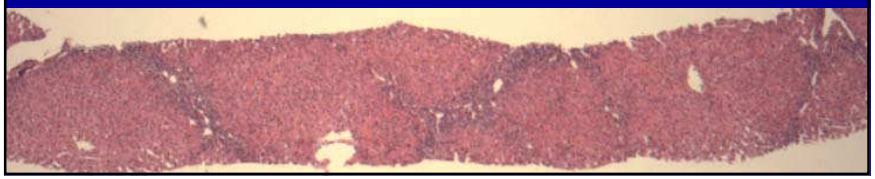
- Increased ALT/AST in 40% adults, 54% children with celiac disease
- Histologic changes are common but non-specific
  - Periportal and portal inflammation
  - Prominent Kupffer cells
  - Steatosis
- Associated autoimmune liver diseases: AIH, PBC, PSC (prevalence varies widely)

AIH versus Drug Reaction

- Drug reaction may trigger an immune attack on the liver
- Centrilobular necrosis and inflammation may be seen in both drug reaction and AIH
- Eosinophils may not be more prominent in drug reaction

Self-perpetuating AIH

- Serologic profile may resemble either Type 1 AIH or Type 2 AIH
- Commonly implicated drugs include
  - Alpha methyldopa
  - Minocycline
  - Nitrofurantoin
  - Interferon

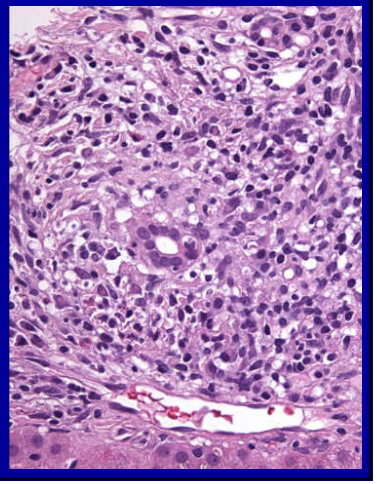


Recently reported Associations with AIH

- Hepatitis A infection
- Hepatitis vaccine
- Twinrix (HAV + HBV vaccine)
- Interferon tx for HCV, MS
- Terbinafine in HBV
- Atomoxetine
- Phenylpropyluracil
- Black cohosh
- Imatinib
- Infliximab
- Methylphenidate
- Statins
- Kava kava & St Johns wort
- Minocycline
- Respineridone

Primary Biliary Cirrhosis: Definition

- Chronic cholestatic liver disease, considered autoimmune in etiology
- Morphologic hallmark is inflammatory destruction of intrahepatic bile ducts
- Serologic hallmark is circulating AMA



Epidemiology of Primary Biliary Cirrhosis

- Affects women (male-female ratio 1:9)
- Median age of onset 50 years (range 21-91)
- Geographical variation: increased prevalence in areas of England, low in developing countries
- More common near “Superfund” sites
- Accounts for up to 2% of deaths from cirrhosis worldwide

Pathogenesis of Primary Biliary Cirrhosis

Considered an autoimmune disorder

- association with Sjogren’s disease, RA, autoimmune thyroiditis
- ? Multiple hit mechanism triggered by mimicry
- AMA directed against M2 antigen (E2 component of the pyruvate dehydrogenase complex)

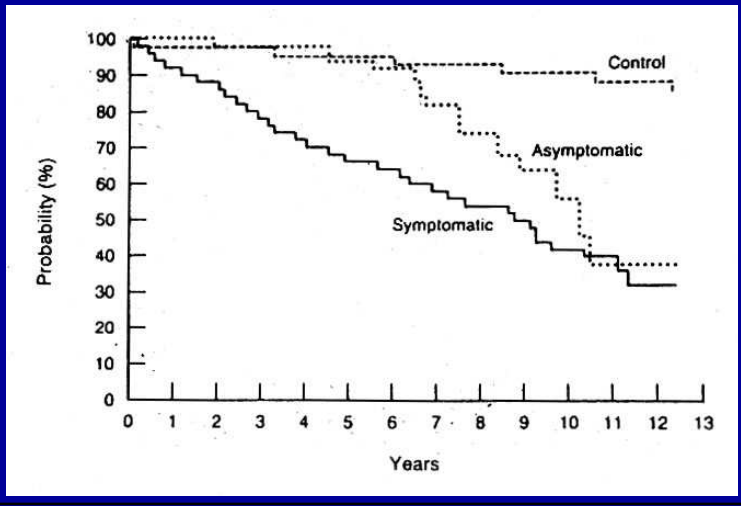
Primary Biliary Cirrhosis: Clinical Features

- 50-60% are asymptomatic at presentation
- Most common signs are pruritis and fatigue
- Elevated alkaline phosphatase
- Jaundice occurs in late stages
- Scleroderma, especially CREST syndrome, in 10%
- Gallstones in 50%

Natural History of PBC

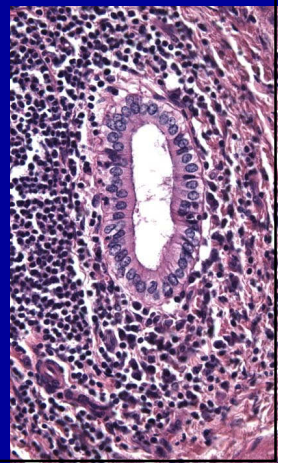
- 25% treated with UDC will not progress over 4 years (Stage I and II); improved prognosis with response to UDC at all stages
- Severity of interface hepatitis is associated with progression to cirrhosis in UDC treated patients
- Stage III or IV patients progress to transplant or die with median time of 9.3 years
- Complications of chronic cholestasis and cirrhosis
- Smoking may accelerate progression

Survival in PBC: Untreated



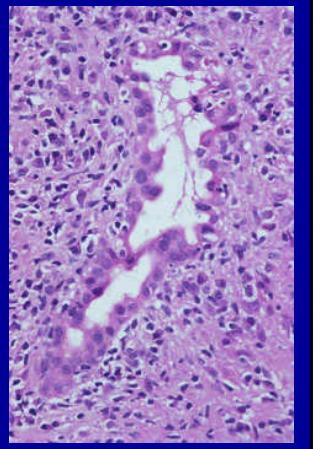
Antimitochondrial Antibodies

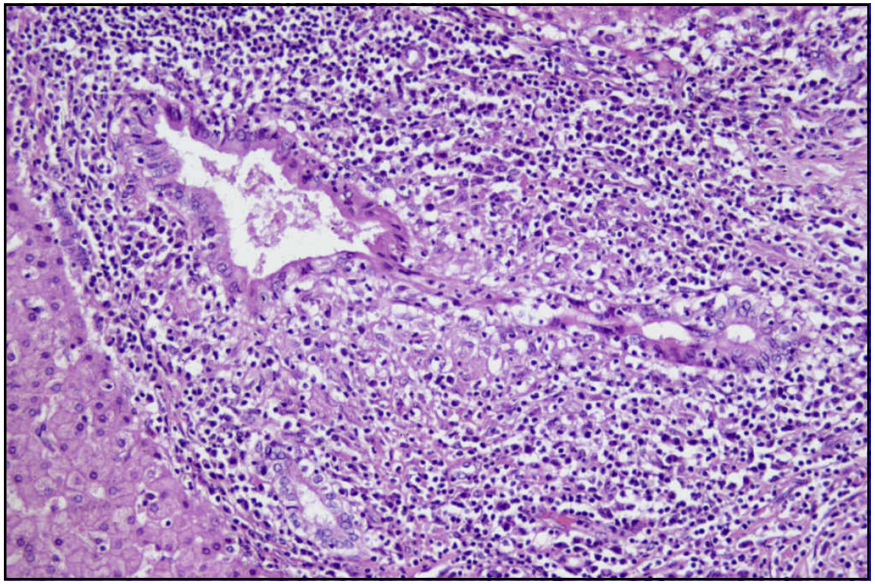
- Immunoblotting may be more sensitive than indirect IF
- Using cloned mitochondrial antigen (rMT3) or bead assay may identify AMA
- Increased expression of PDC-E2 has been demonstrated in biliary epithelium

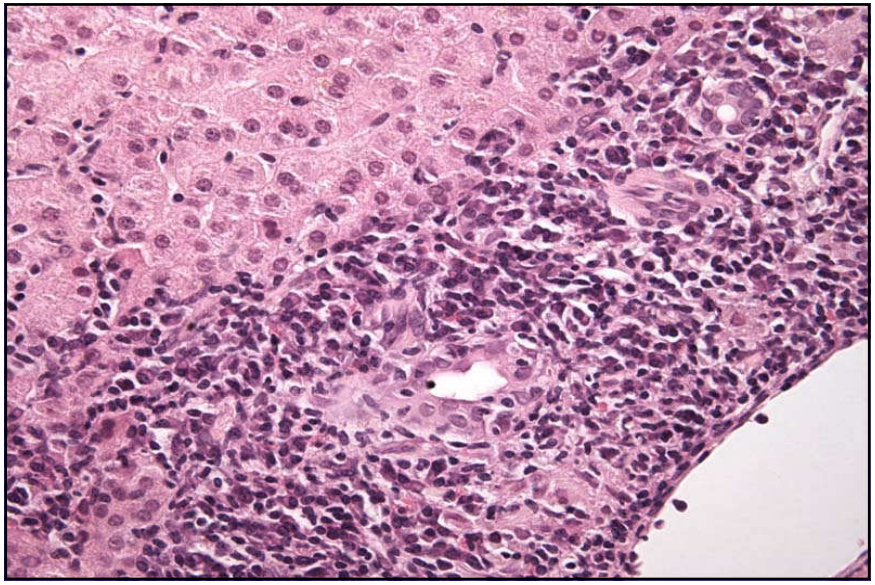


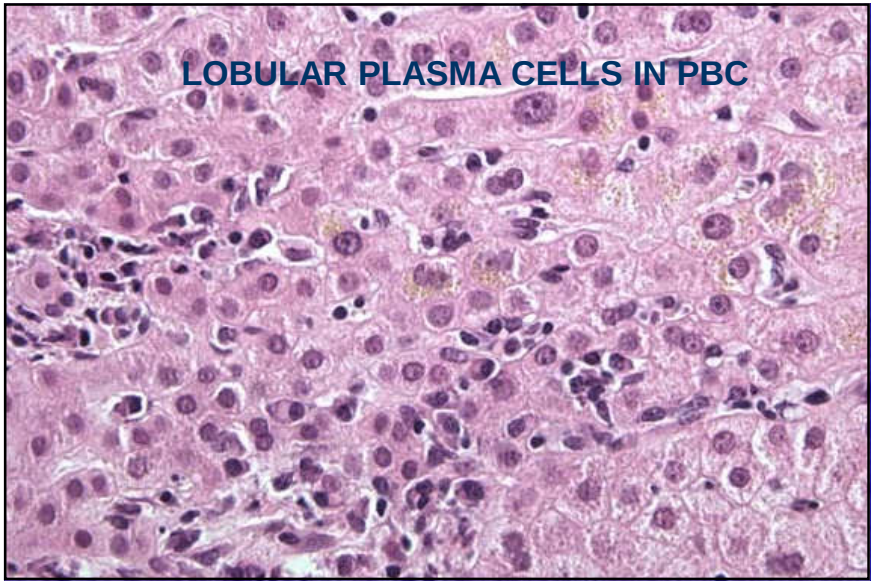
Pathology of PBC

- Florid duct lesion:
  - inflammation
  - injury to bile duct epithelium
  - disruption of basement membrane
- 40 to 80 microns bile ducts
- Segmental destruction

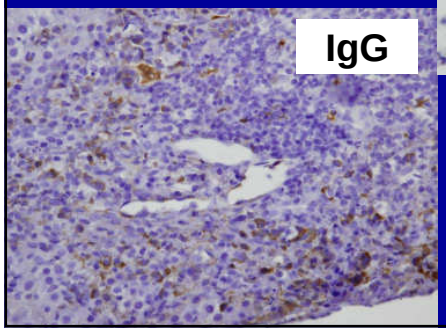


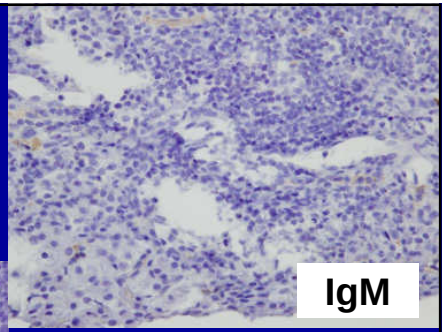




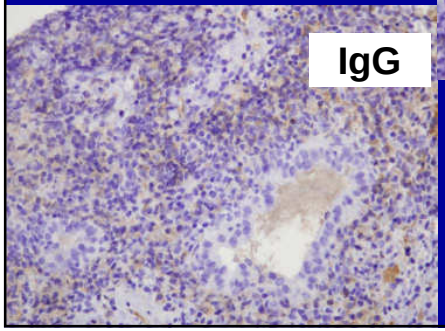


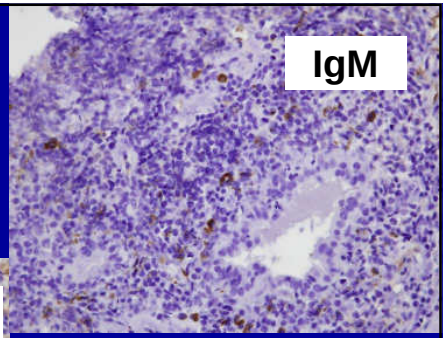
IgG and IgM in AIH





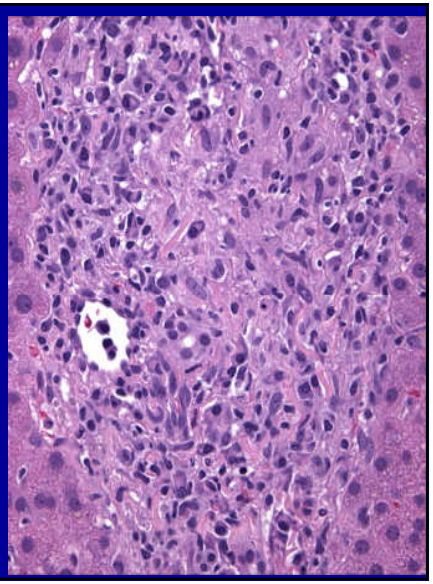
IgG and IgM in PBC





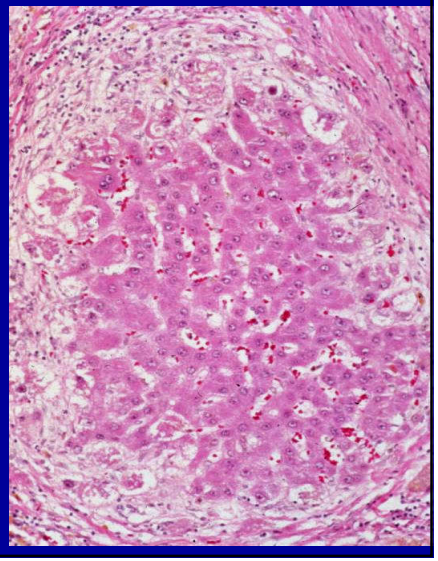
Granulomas and PBC

- Usually found in portal tracts as loose collection of epithelioid histiocytes
- May also be found in lobule and hilar lymph nodes
- Often found in earlier stages, ~50% of patients
- May portend better prognosis



Pathology of PBC

- Chronic cholestasis
  - Feathery degeneration
  - Copper accumulation
  - Hyaline accumulation
- Bile ductular reaction
- +/- interface hepatitis & plasma cells
- Eventual loss of biliary epithelium

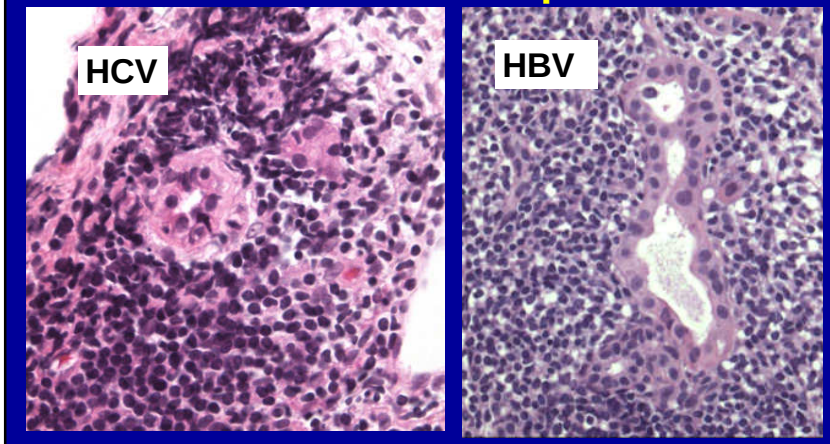


Differential Diagnosis of Primary Biliary Cirrhosis

- *Portal inflammation*
- *Lymphocytic bile duct destruction*
- *Granulomas*
- *Ductopenia*
- *Copper deposition*
- *Ductular reaction*

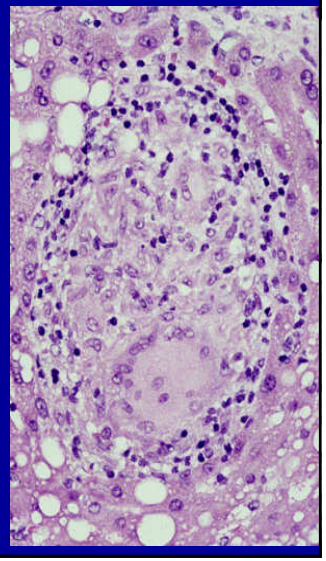
- Chronic hepatitis, drug reaction
- Hepatitis C
- Drug reaction, sarcoidosis
- PSC
- Chronic cholestasis
- Biliary obstruction

Bile Duct Injury in Chronic Viral Hepatitis



Hepatic Sarcoidosis

- Almost 60% of cases of hepatic sarcoidosis showed evidence of cholestasis, usually chronic
- ~20% had bile duct lesions similar to those seen in PBC
- Granulomas of sarcoidosis are better formed and more numerous than PBC



Devaney K, et al. Am J Surg Pathol 17:1272-1301, 1993

Staging of Primary Biliary Cirrhosis

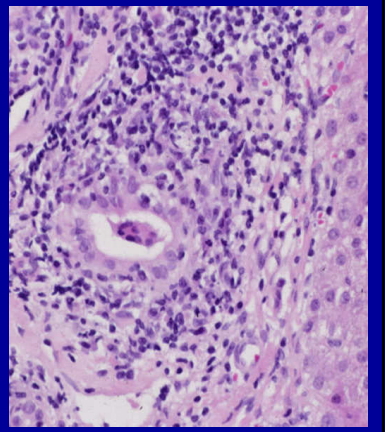
Stage	Ludwig	Scheuer
1	Portal	Florid duct lesion
2	Periportal	Ductular proliferation
3	Septal	Fibrosis
4	Cirrhosis	Nodular cirrhosis

Ludwig J, et al. Virchows Arch A 379:103-112, 1978.

Scheuer P. Proc Royal Soc Med 60:1257-60, 1967.

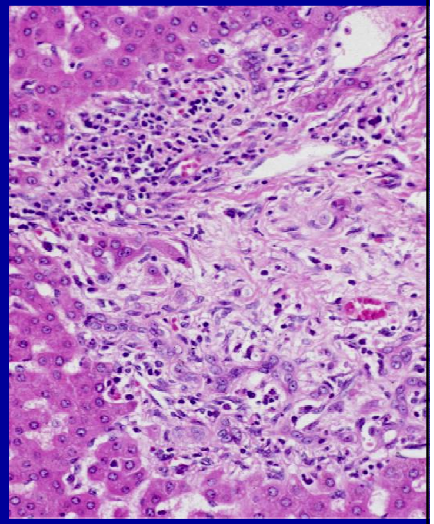
Stage 1

- Florid duct lesion
- Portal inflammation
- Small portal tracts may lack bile ducts
- Kupffer cell aggregates, small granulomas in lobule; small collections of lymphocytes
- Nodular regenerative hyperplasia may contribute to portal hypertension



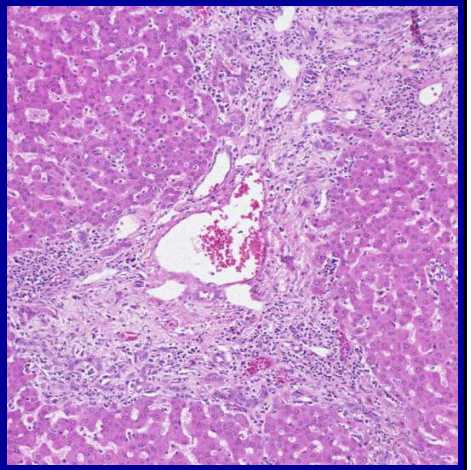
Stage 2

- Periportal changes
- Ductular reaction
- Portal tracts are enlarged
- Biliary piecemeal necrosis
- In some cases, lymphocytic interface hepatitis predominates



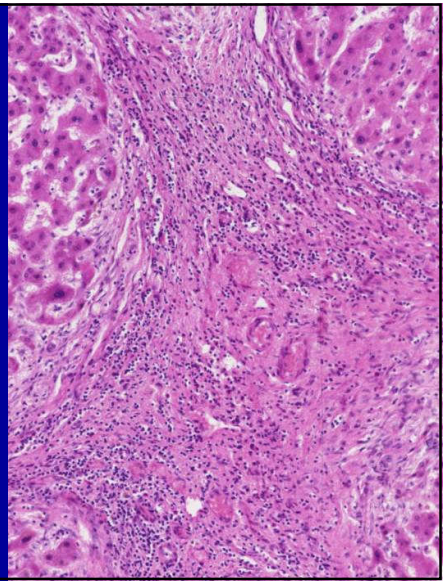
Stage 3

- Scarring stage
- Portal-portal fibrous septa
- Bile ductular reaction becomes less prominent
- Cholestasis may be seen in addition to cholate stasis



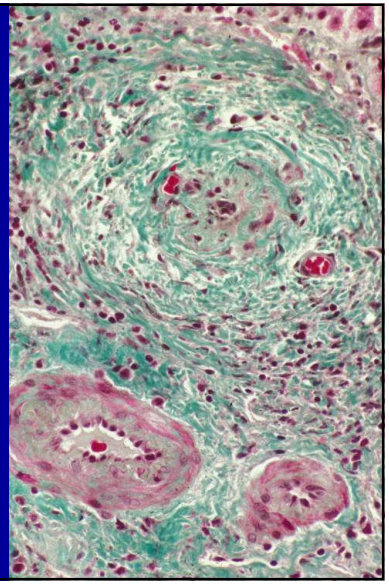
Stage 4

- Biliary cirrhosis
- Profound loss of small and medium-sized ducts
- Usually no bile ductular reaction
- Cholate stasis with copper accumulation and Mallory-Denk bodies



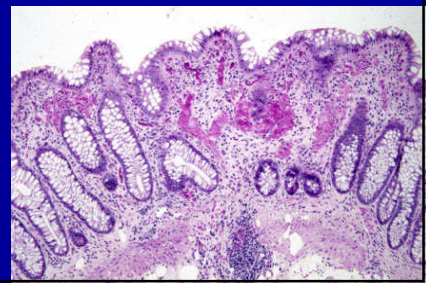
Primary Sclerosing Cholangitis: Definition

- **Chronic cholestatic liver disease, probably autoimmune in etiology**
- **Affects extra- and intrahepatic biliary tree**



Epidemiology of PSC

- **Male predominance (2:1 M/F)**
- **Median onset 30 years, range 1-90 yrs**
- **Prevalence in U.S. estimated as 2-7/100,000**
- **70% of cases are associated with ulcerative colitis**



Genetic Factors and PSC

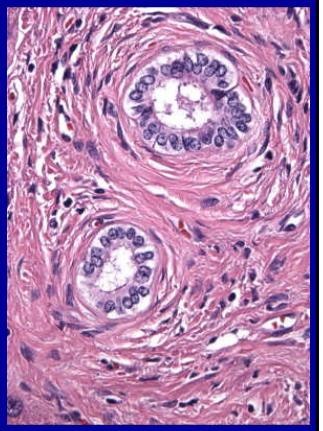
- Increased prevalence of HLA B8 and DR3
- This haplotype is associated with a number of organ-specific autoimmune diseases
  - autoimmune hepatitis
  - thyroiditis
  - celiac disease
  - myasthenia gravis
- HLA DR4 associated with adverse prognosis

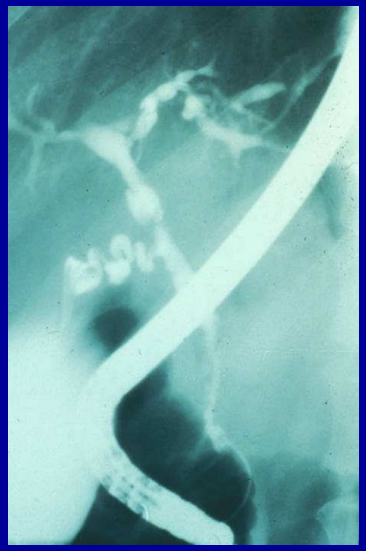
Natural History of Primary Sclerosing Cholangitis

- Clinical course is variable and unpredictable
  - obstructing strictures
  - bacterial cholangitis
  - biliary stone formation
  - cholangiocarcinoma
- Major cause of death in patients with ulcerative colitis
- Median survival from diagnosis 9-12 years

Diagnosis of PSC

- Based on cholangiographic findings of beading and irregularity of biliary system
- 80% are ANCA positive but this is non-specific
- Liver biopsy may not be diagnostic and may even be normal



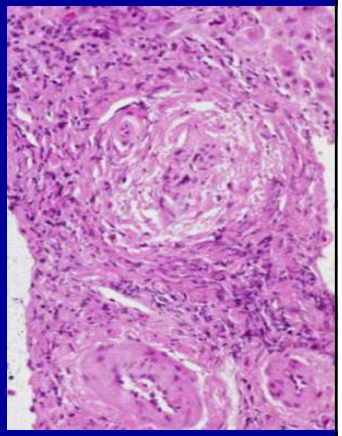


Diagnosis of PSC

- **Gold standard (MRCP)**
- **Multifocal stricturing and beading**
- **Involves both extra-and intrahepatic ducts in typical case**
- **Gallbladder and cystic duct are involved in ~15%**

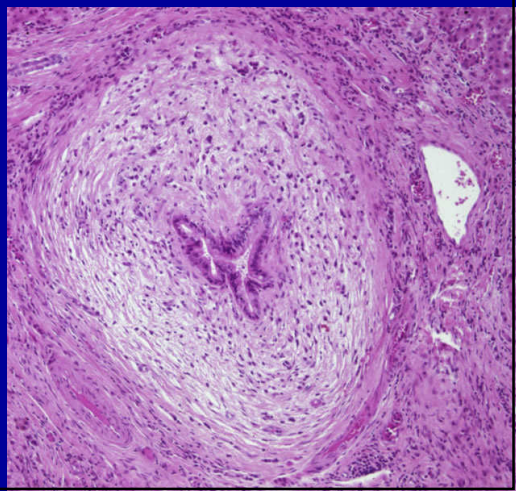
Histologic Clues: PSC

- Concentric periductal fibrosis
- Rounded scars in portal tracts
- *Distorted interlobular bile ducts*
- *Loss of small interlobular bile ducts (60% of cases)*
- Superimposed changes of extrahepatic obstruction

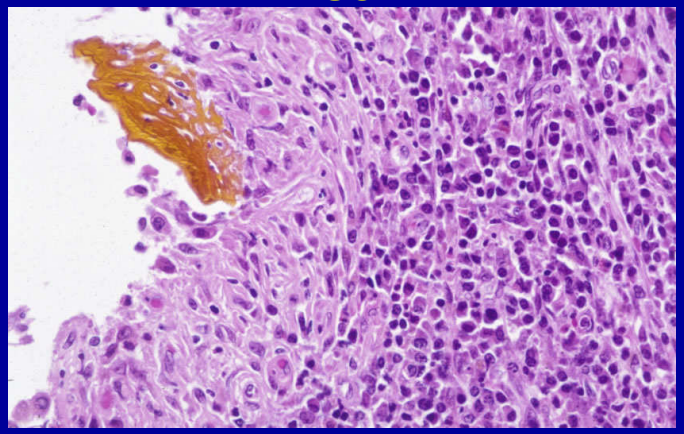


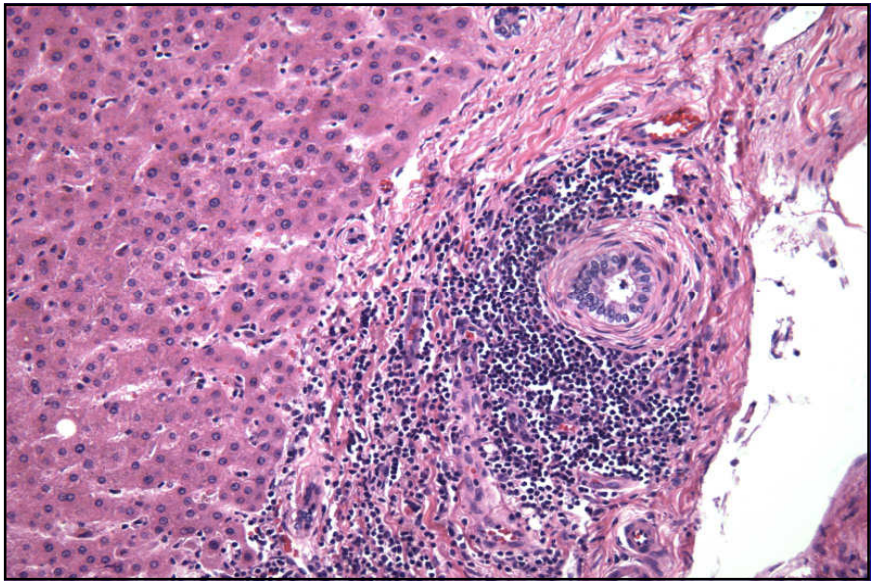
Duct Lesions in PSC

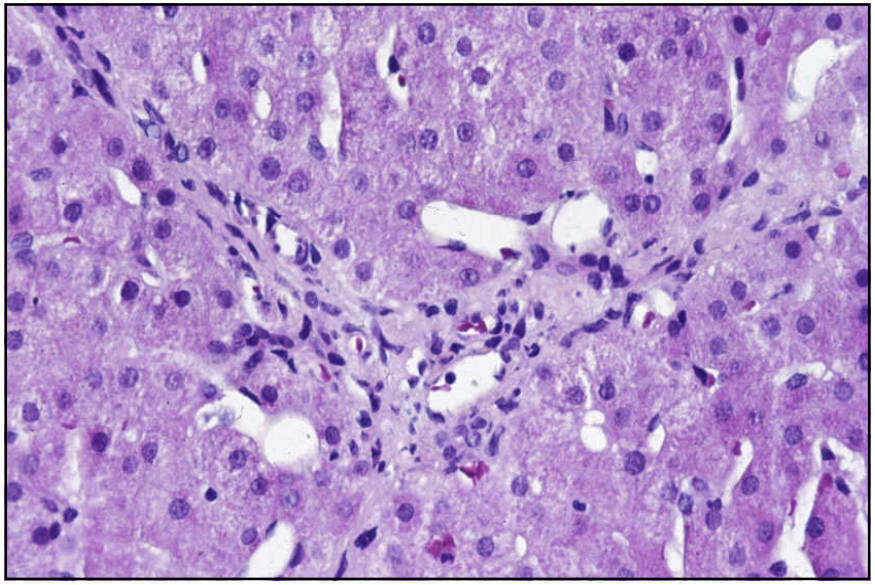
- **Periductal edema**
- **Periductal fibrosis**
- **Duct distortion**
- **Duct loss**
- **Often minimal inflammation**

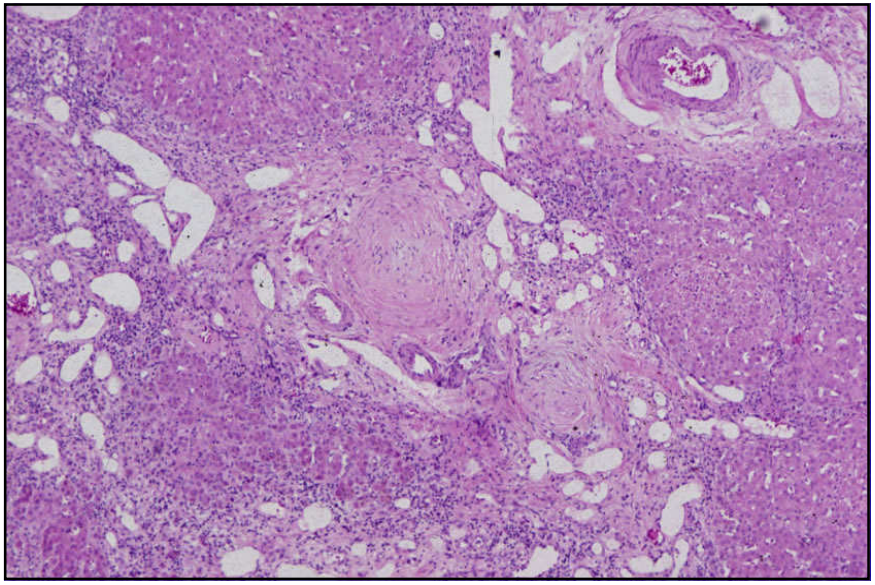


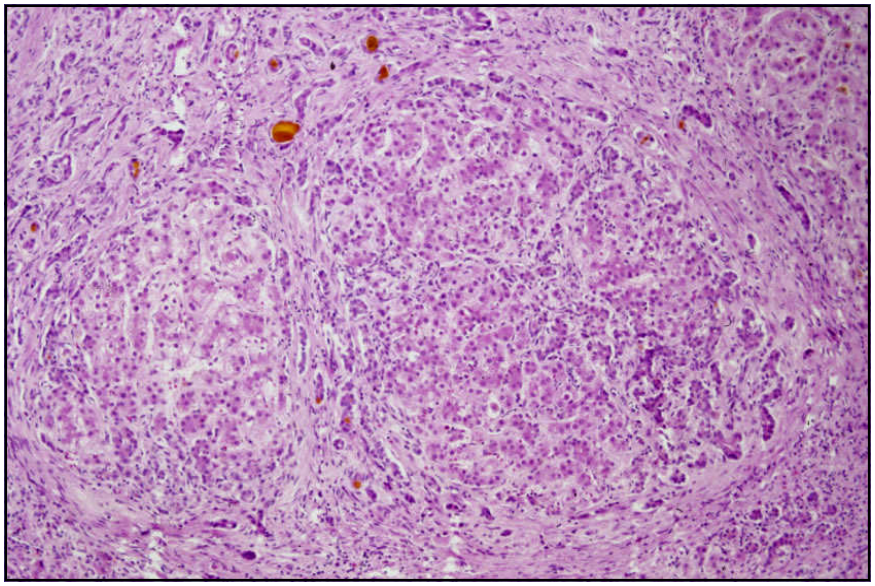
Granulomatous Response to Bile in PSC



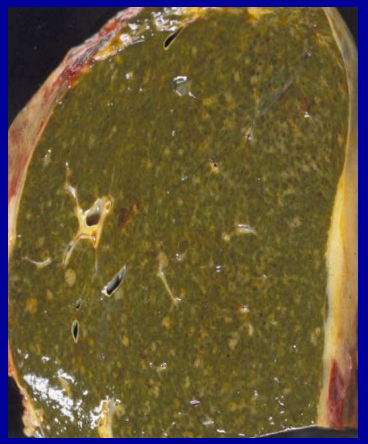


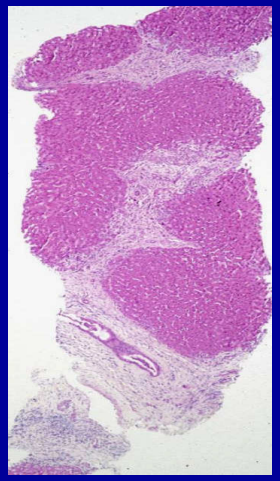






Biliary Cirrhosis in PSC





Small Duct PSC

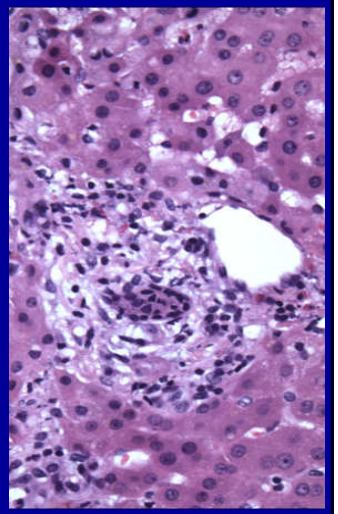
- Diagnostic criteria: chronic cholestatic liver disease with biopsy features suggestive of PSC & normal cholangiogram
- In some studies, diagnosis of IBD is required
- ~25% progress to large duct involvement over 8 years
- Crohn's Disease in 21% of patients in one study
- Better prognosis than large duct PSC

Staging of Primary Sclerosing Cholangitis

	Stage	Features
1	Portal	Duct abnormalities
2	Periportal	Ductular proliferation
3	Septal	Fibrous septa
4	Cirrhosis	Nodular cirrhosis

Differential Diagnosis: PSC

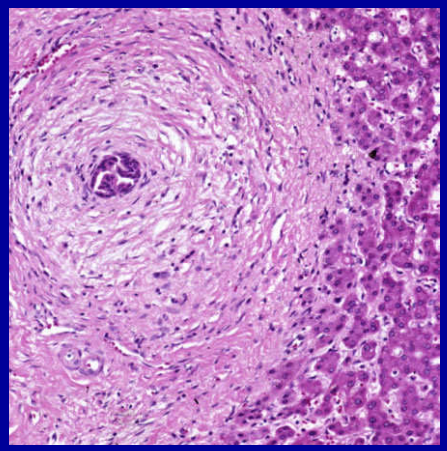
- Primary biliary cirrhosis
- Chronic large duct obstruction
- Autoimmune hepatitis (children)
- Intrahepatic artery chemotherapy
- Langerhans cell histiocytosis
- Eosinophilic or mast cell cholangiopathy
- Infectious cholangiopathy (AIDS)
- Primary immunodeficiency
- Autoimmune pancreatitis



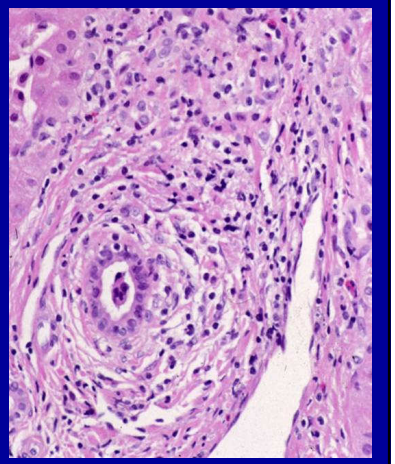
Chronic Large Duct Obstruction

- May be difficult to distinguish from PSC
- Features common to both:
  - periductal fibrosis
  - bile ductular reaction
  - cholestasis
- Bile duct loss does not occur in obstruction
- Finding numerous eosinophils favors PSC

PSC



Obstruction

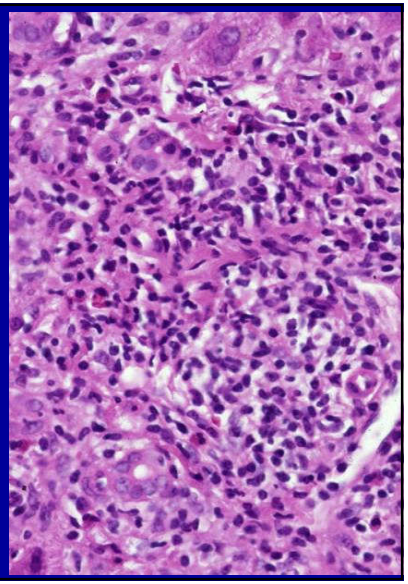


IgG4 Cholangiopathy

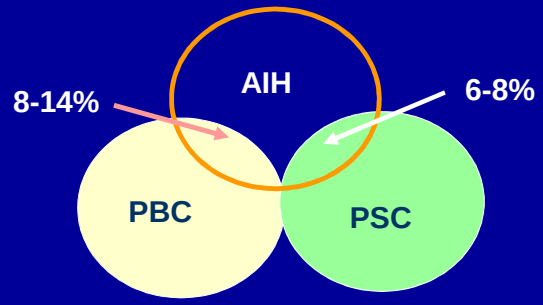
- Intrapancreatic bile duct is often involved in autoimmune pancreatitis (plasma cell-rich infiltrate with IgG4+ cells)
- Extra-pancreatic biliary involvement in ~15% of cases
- High serum IgG4 levels
- Susceptible to steroid therapy
- Multiple histologic patterns of liver injury in AIP: portal inflammation, large duct damage, portal sclerosis, lobular hepatitis, cholestasis

PSC in Children

- Intrahepatic disease may predominate
- Usually diagnosed in teenage years
- ~50% have inflammatory bowel disease
- ~15% have an immunodeficiency syndrome
- Also associated with Langerhans cell histiocytosis
- Overlap with autoimmune hepatitis



Overlap Syndromes of Autoimmune Hepatopathies



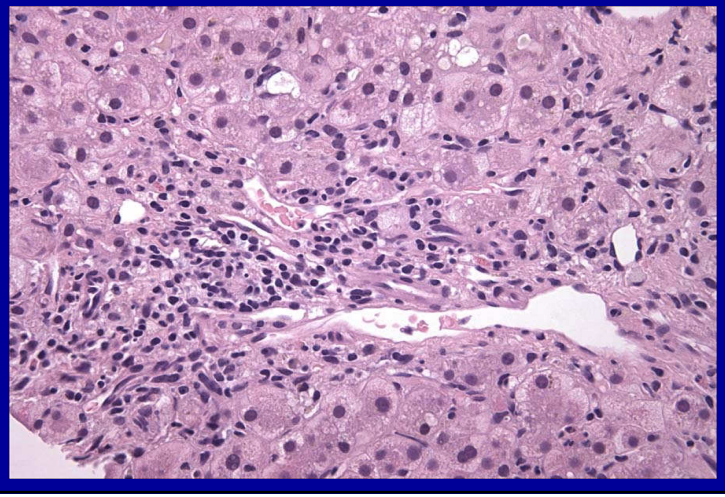
Variants of Autoimmune Liver Disease

Overlap Syndromes	Outlier Syndrome	Sequential Syndromes
AIH-PBC	AIC (AMA negative PBC)	AIH ↔ PBC
AIH-PSC		AIH ↔ PSC
AIH-AIC		

Autoimmune Cholangitis

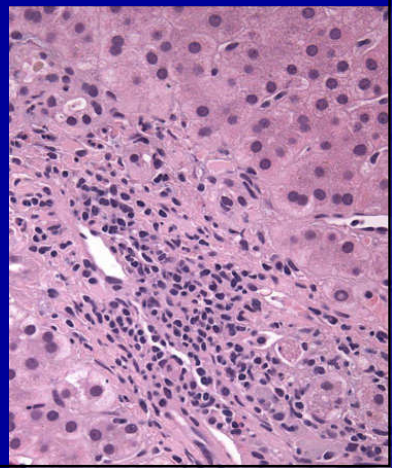
- Lack of uniform criteria for diagnosis
- Sometimes characterized as a variant of PBC
- Patients typically have high ANA titers, no AMA
- Histology is often similar to PBC, but may not be equivalent to AMA-negative PBC
- May represent an early stage of disease in evolution (AMA titers may fluctuate)

Autoimmune Cholangitis



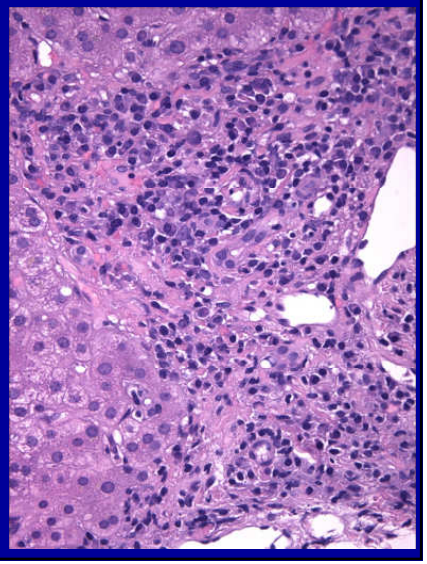
AMA-Negative PBC

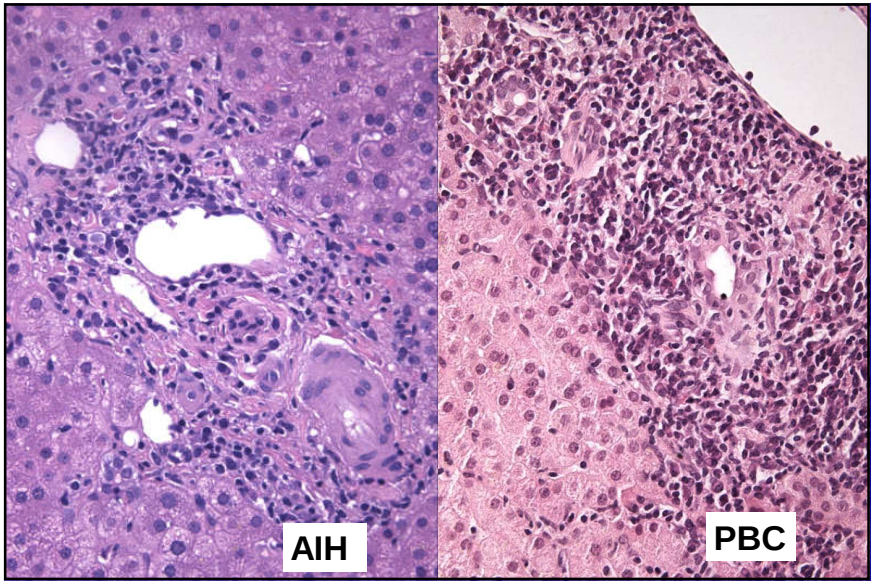
- Identical to PBC except for lack of AMA
- No significant differences with AMA-positive PBC patients- slightly younger in one study
- Similar response to ursodeoxycholic acid
- More sensitive AMA tests may detect AMA



AIH + PBC Overlap Syndrome

- Reserved for cases with “triple overlap”: serology, clinical findings, pathology
- Controversial- ? hepatitic form of PBC
- Treatment with both UDCA and corticosteroids
- Similar response to UDCA





Autoimmune Hepatitis versus PSC

- Distinguishing PSC from autoimmune hepatitis is more commonly a problem in pediatric patients
- Alkaline phosphatase may be normal
- Cholangiographic findings more subtle
- Concentric periductal fibrosis is rare; usual pattern is loss of small bile ducts
- Portal inflammation may mimic hepatitis

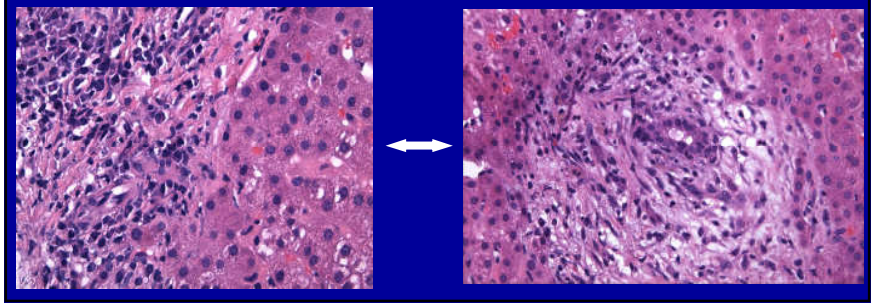
AIH + PSC Overlap Syndrome

- 55 children with AIH followed for 16 years
  - 27 developed bile duct changes of PSC
- Term “autoimmune sclerosing cholangitis” proposed
- IBD more common in this group than in AIH
- More commonly p-ANCA +
- Younger than classic PSC patients

Gregorio GV, et al. Hepatology 33:544-53, 2001

Sequential Syndromes

- **Relatively rare; multiple liver biopsies**
- **Usually AIH ⟷ PBC or AIH ⟷ PSC**
- **Diagnosis of AIH usually precedes PSC**



Autoimmune Liver Disease: Practice Points

- **Diagnosis of AIH is based on combination of findings**
  - **Numerous plasma cells is suggestive of AIH but no pathognomonic**
- **Both PBC and PSC can cause ductopenia in biopsies from adult patients**
  - **Use clinical (demographic, liver tests, serologic, radiographic) findings**
- **Overlap among autoimmune liver diseases**