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Hepatitic and biliary patterns of injury

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Outline

- Histologic patterns of hepatitic injury
- Histologic patterns of biliary injury
- Case illustrations

Hepatitic vs. biliary

Feature	Hepatitic	Biliary
Liver enzymes	↑ ALT, AST	↑ ALP, GGT
Serology	Hepatitis A, B, C, D, E	Negative
Autoantibodies	ANA, SMA, LKM	AMA
Serum Ig	Elevated IgG (AIH)	Elevated IgM (PBC)

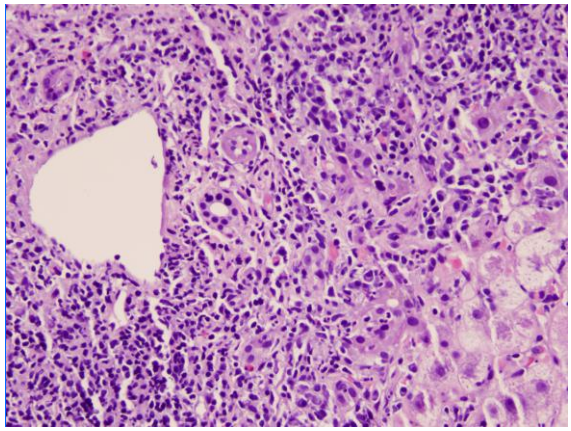
Feature	Hepatitic	Biliary
Portal inflammation	Common	Common
Plasma cells	Often in AIH (not specific)	Often in PBC
Eosinophils	DILI (not specific)	Can be present
Bile duct damage	Absent or minor	Present
Ductular reaction	Associated with necrosis and fibrous septa	Typical of obstruction
Hepatocellular injury	Defining feature	Absent or minor
Periportal copper	Absent	Can be present

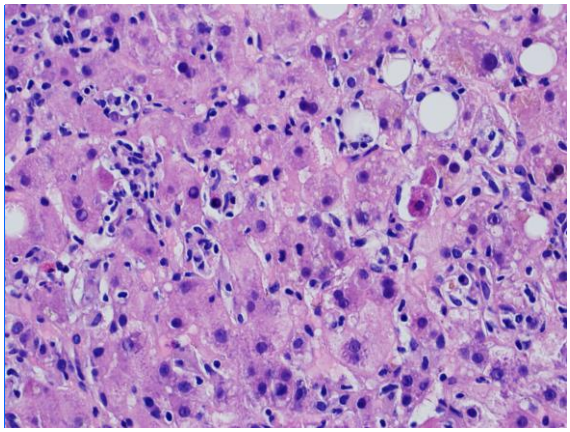
Not covered

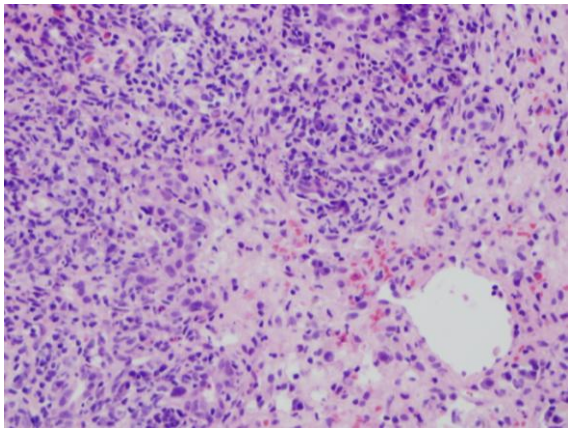
- Steatohepatitis
- Chronic hepatitis: grading and staging
- Individual disease entities in detail

Case 1

Presentation	19/F presented with abrupt onset of abdominal pain, jaundice and signs of liver failure
Liver enzymes	ALT 1250, AST 1100, ALP 230







Diagnosis
morphological and etiological

Inflammation dominant-acute hepatitis	
Viral hepatitis	Serological tests A, B, C Cholestatic hepatitis A Rare cases of acute hepatitis C, E
Autoimmune hepatitis	Prominent hepatocellular injury ↑ IgG ANA, SMA: type 1 AIH; LKM: type 2 AIH
Drug-induced liver injury	Prescription, over the counter drugs, nutritional/herbal supplements
Wilson disease	Age <50 years, steatosis, hemolysis. Low ceruloplasmin, ↑ urinary copper, ↑ quantitative copper
Celiac disease	Serology: TTG, EMA

Diagnosis
morphological and etiological

Inflammation dominant-acute hepatitis	
Viral hepatitis	Negative for A, B, C
Autoimmune hepatitis	ANA, SMA positive
Drug-induced liver injury	Minocycline for acne, no other drugs
Wilson disease	Ceruloplasmin, urinary copper normal
Celiac disease	Serology not done

Drug-related hepatitis with autoimmune markers

Multiple reports	Few reports	Herbal
Minocycline **Methyl-dopa** **Nitrofurantoin** **Oxyphenasitin** **Clometacin**	**Statins** **Infliximab** **Interferon** **Fenofibrate** **Doxycyline** **Rifampin+pyrazinamide** **Hydralazine** **Halothane**	**Germander** **Ecstasy** **Noni juice**

http://livertox.nih.gov/

Drug-related AIH

- Autoantibodies after starting drug
- HLA B8, DR3, DR4 absent
- Resolution of disease on drug withdrawal
- Autoantibodies disappear on drug withdrawal
- Multiple reports for implicated drug
- Recurs on rechallenge

Diagnosis

Minocycline-associated autoimmune hepatitis

Features often seen in DILI

- Centrizonal necrosis
- Eosinophils
- Granulomas
- Cholestasis, often out of proportion to the hepatocellular injury

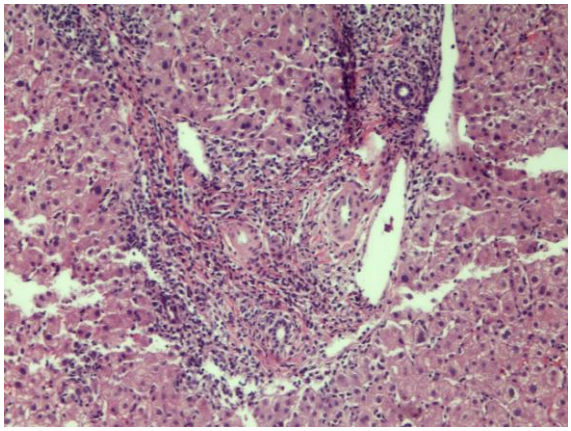
Simplified IAIHG criteria *

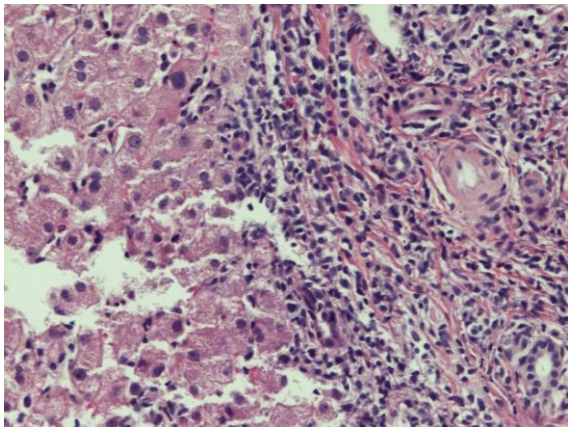
Parameter/Feature	Cutoff	Score
Autoantibodies:[a]		
ANA or SMA	≥1:40	+1
ANA or SMA	≥1:80	+2
LKM-1	≥1:40	+2
SLA	Positive	+2
IgG	>Upper limit of normal	+1
	>1.10 × upper limit of normal	+2
Histologic features	Compatible with AIH[c]	+1
	Typical AIH[b]	+2
Absence of viral hepatitis	No	0
	Yes	+2
Pre-treatment score	Probable AIH	6
	Definite AIH	≥7

Adapted from Hennes EM, Zeniya M, Czaja AJ, et al. Hepatology 2008;48:169-76.
[a] Maximum of 2 points total allowed for autoantibodies
[b] Typical AIH: (1) Interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule; (2) emperipolesis (active penetration by one cell into and through a larger cell); (3) hepatic rosette formation (*all 3 required*)
[c] Compatible with AIH: Chronic hepatitis with lymphocytic infiltration without all of the features considered typical
AIH autoimmune hepatitis; *ANA* antinuclear antibody; *IAIHG* International Autoimmune Hepatitis Group; *IgG* immunoglobulin G; *LKM-1* liver kidney microsome-1 antibody; *SLA* soluble liver antigen antibody; *SMA* smooth muscle antibody.

Case 2

Presentation	**45/F presented with 1 month history of abdominal pain and jaundice**
Liver enzymes	ALT 650, AST 500, ALP 210





Diagnosis
morphological and etiological

Inflammation dominant-acute hepatitis	
Viral hepatitis	Negative for A, B, C
Autoimmune hepatitis	ANA, SMA, LKM: negative
Drug-induced liver injury (DILI)	No drugs
Wilson disease	Ceruloplasmin, urinary copper normal
Celiac disease	Serology negative

IgM HEV antibodies: positive

Hepatitis E

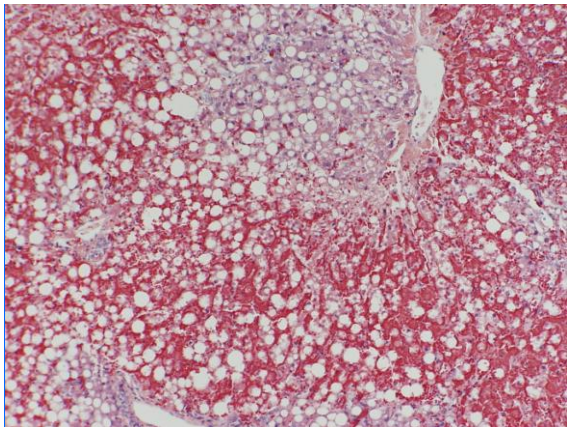
Developing countries
- Genotypes 1 and 2: waterborne
- Acute hepatitis, pregnancy

USA
- History of travel: genotypes 1 and 2
- No history of travel: genotypes 3 and 4
- Seroprevalence in USA: 21%
- Zoonotic: pets, organ meat

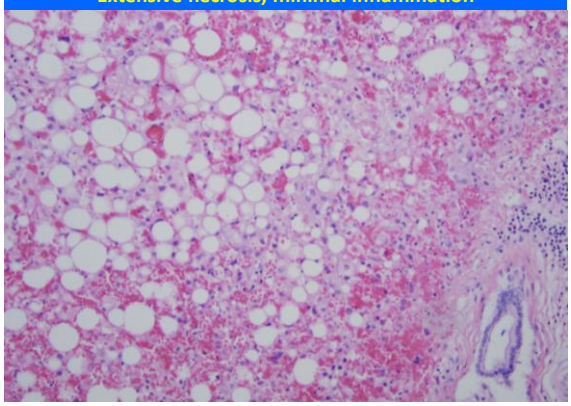
Kuniholm, J Infect Dis, 2009

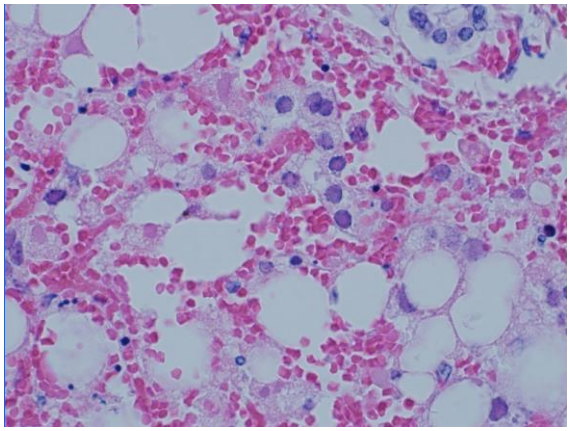
Case 3

Presentation	65/M presented with abrupt onset of fever and abdominal pain
Liver enzymes	ALT, ALT> 1500, ALP 300
Cultures	Negative
Drugs	Aspirin, acetaminophen



Extensive necrosis, minimal inflammation





Diagnosis
morphological and etiological

Necrosis-dominant acute hepatitis	
Drugs	Acetaminophen, halothane Cocaine, ecstasy
Toxins	Mushroom poisoning Herbal agents: pennyroyal Industrial: carbon tetrachloride
Viral infections	Herpes simplex, adenovirus, CMV, EBV
Vascular causes	Ischemia, venous outflow obstruction

DILI: mechanisms

Idiosyncratic (hypersensitivity)
- Dose-independent
- Immunologically mediated

Intrinsic
- Direct toxic effect
- Dose-dependent

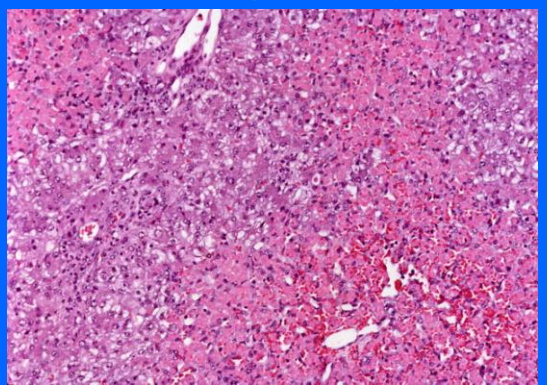
Acetaminophen toxicity

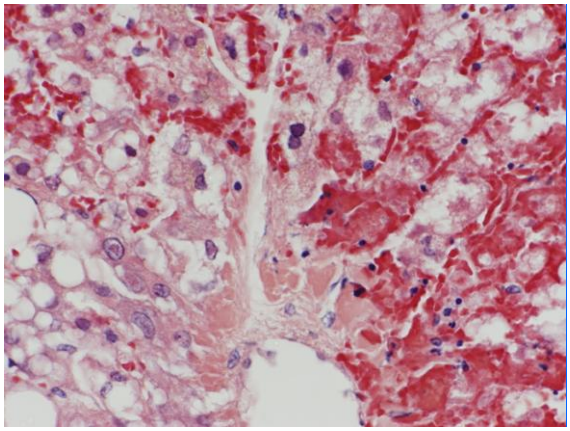
- Most common cause of ALF in the US: 30-40%
- Therapeutic dose safe 3-4g/day
- Toxic dose ~7-10g (>15g significant)
- Alcohol, obesity, drugs like INH, phenytoin, carbamazepine, cimetidine

Acetaminophen toxicity

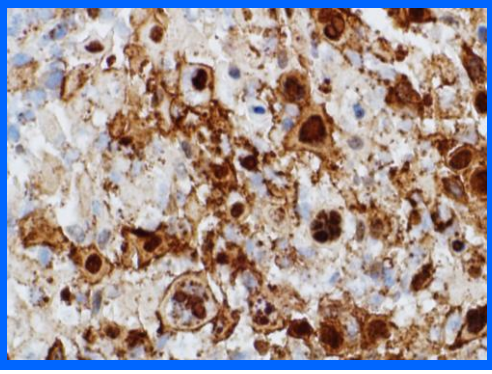
- Latent phase 24 hrs
- GI symptoms for 24-48 hrs
- Acute hepatitis 72-96 hrs

Acetaminophen toxicity



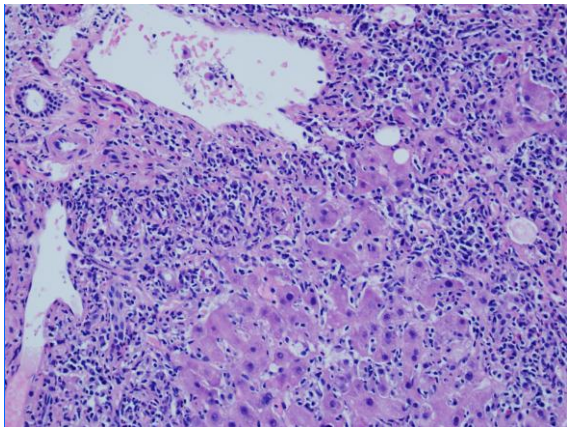


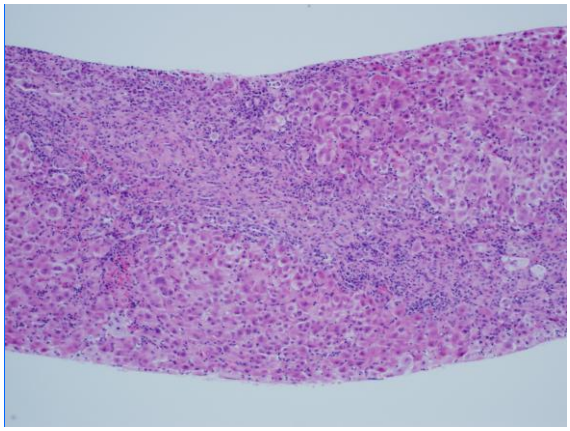
HSV hepatitis

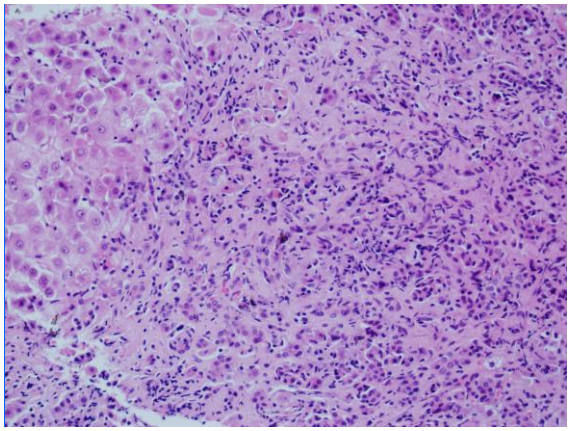


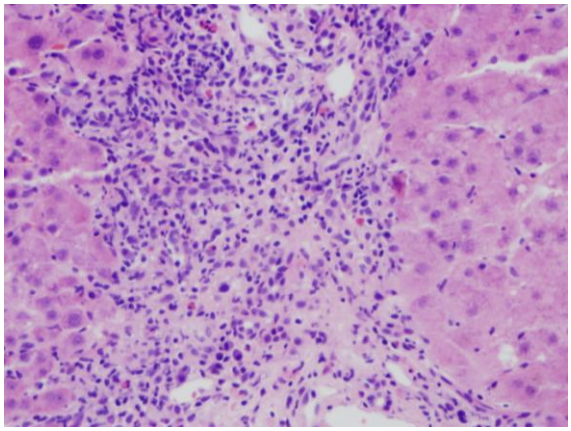
Case 4

Presentation	**42/M jaundice, abdominal pain for 4 weeks. Tender hepatomegaly.**
Liver enzymes	ALT, ALT> 1000, ALP 320
Acute hepatitis work-up	Negative

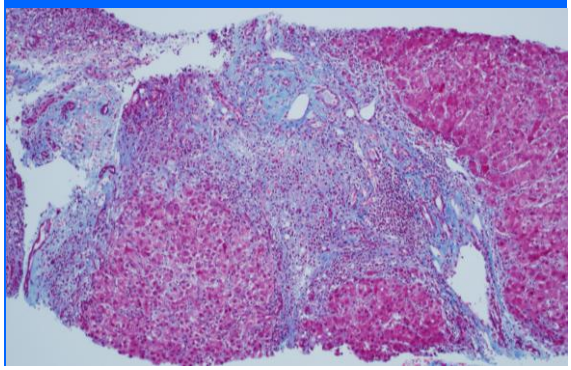






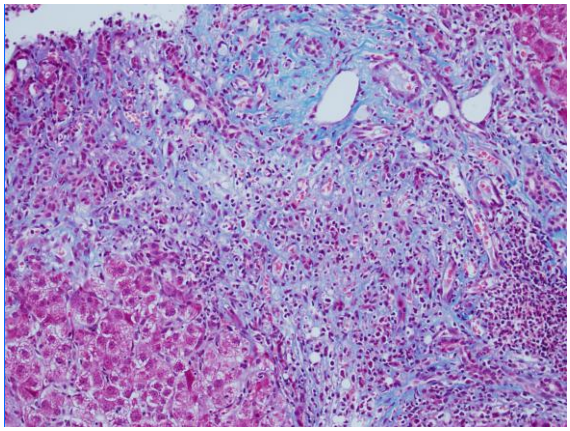


Trichrome: pale and dark areas

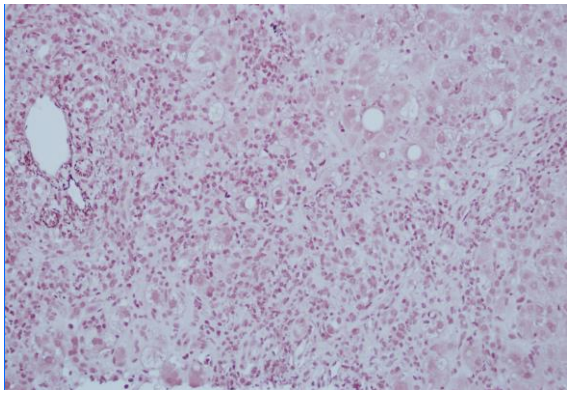


Bridging necrosis or fibrosis

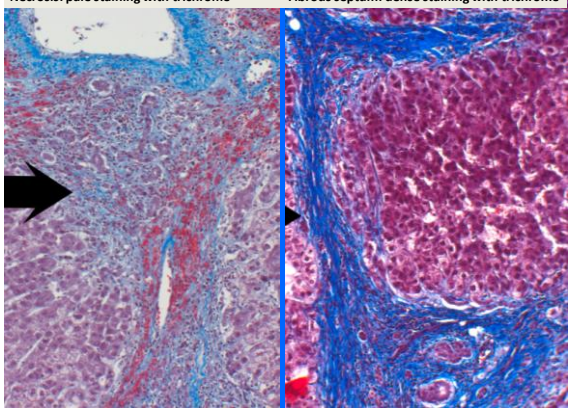
- Distinction has important therapeutic implications
- Trichrome
- Elastic stain



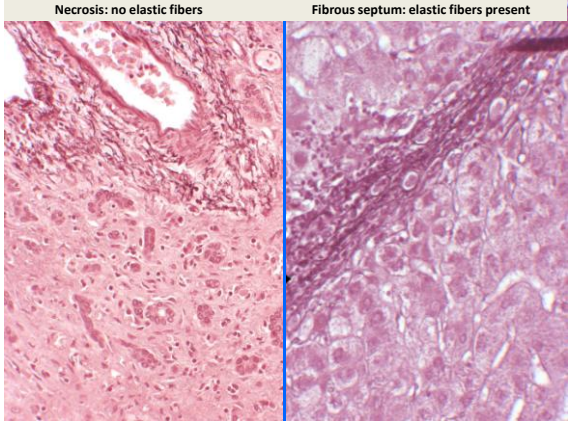
Elastic stain: no elastic fibers in the area of necrosis



Necrosis: pale staining with trichrome | Fibrous septum: dense staining with trichrome



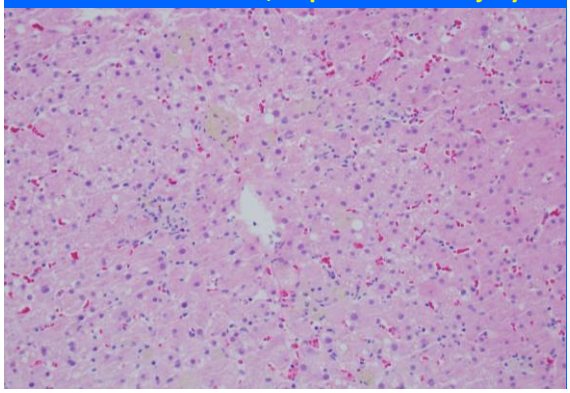
Necrosis: no elastic fibers | Fibrous septum: elastic fibers present



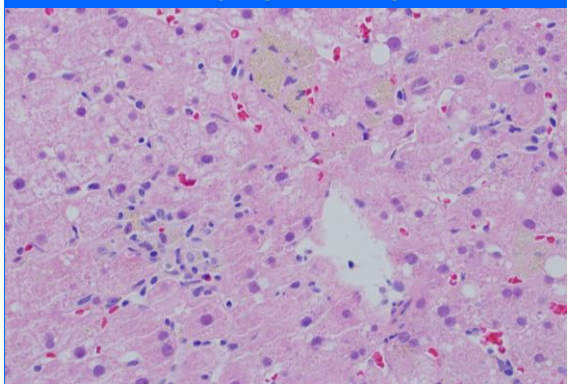
Case 5

Presentation	55/F with abdominal pain 3 weeks after lisinopril for hypertension.
Liver enzymes	ALT, ALT 500, ALP 140
Acute hepatitis work-up	Negative. Drug discontinued.
2 months later	ALT, ALT 150

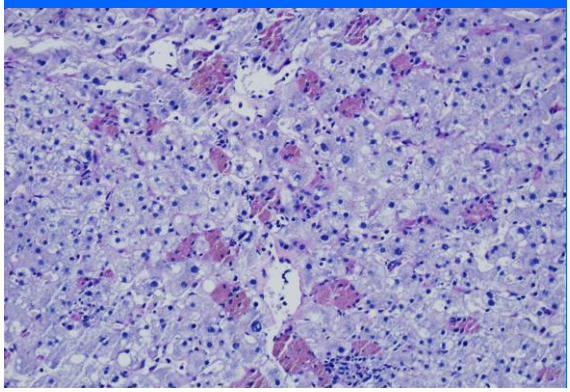
Mild inflammation, hepatocellular injury



Lobular macrophages: 'microgranuloma'



PAS-D stain



Resolving hepatitis

- Most cases are drug-related
- Other causes of acute hepatitis have to be clinically excluded
- Nonspecific reactive hepatitis
  - Abdominal inflammation
    - Cholecystitis, appendicitis
  - Systemic diseases
    - SLE, rheumatoid arthritis, infections

Nonspecific reactive hepatitis

Portal tracts
- Lymphocytes, few eos, plasma cells
- Normal bile ducts, mild ductular reaction can be present

Lobule
- Mild inflammation
- Focal necrosis
- Prominent macrophages

Acute hepatitis: summary of histologic patterns

Pattern	Etiologies
Inflammation-dominant	Viral hepatitis, AIH, DILI, Wilson disease, celiac disease
Cholestatic hepatitis	Usually DILI
Necrosis-dominant	Acetaminophen, toxins, HSV, vascular
Bridging necrosis	Differentiate from cirrhosis
Isolated centrizonal necrosis	DILI, AIH
Resolving hepatitis	Mild inflammatory injury, consider nonspecific reactive hepatitis
Giant cell or syncytial hepatitis	Often AIH in adults, not specific for etiology

Outline

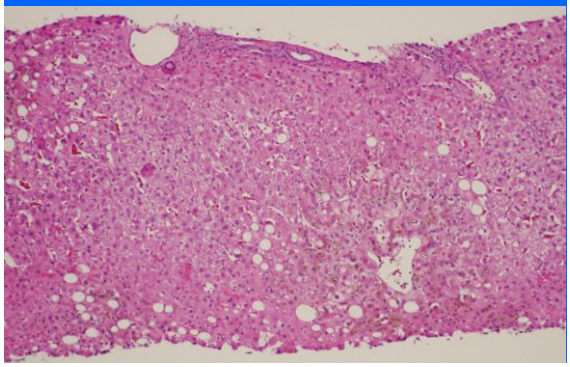
- Histologic patterns of hepatitic injury
- Histologic patterns of biliary injury
- Cases

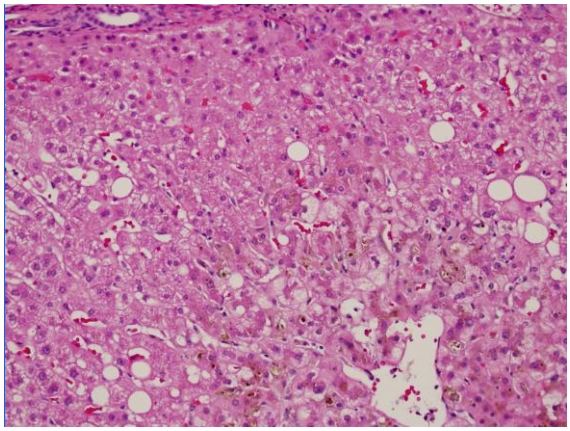
Biliary patterns of injury

Injury pattern	Histologic features
Pure cholestasis	**Cholestasis with no or minimal bile duct/hepatocellular injury**
Obstructive pattern	**Portal expansion, ductular reaction**
PBC-like	**Portal inflammation with bile duct injury**
Cholestatic hepatitis	**Hepatitic pattern with cholestasis**

Any of the above	Fibrosis
Any of the above	**Ductopenia or loss of bile ducts**

Pure or bland cholestasis

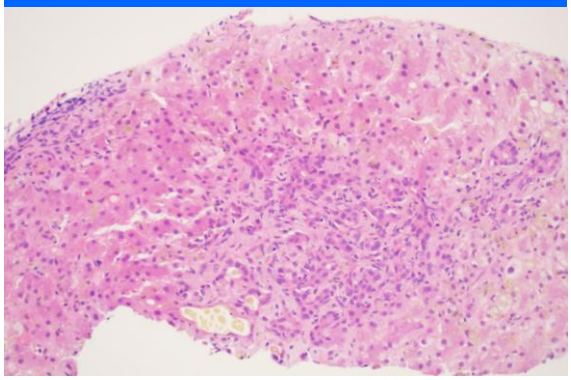




Pure/bland cholestasis

Cause	Clinicopathologic approach
Drugs	**Anabolic steroids, OCs ACE inhibitors like lisinopril Antibiotics: amoxicillin Others: prochlorperazine, thiabendazole, warfarin**
Early obstruction	**Imaging**
Sepsis/shock	**Clinical setting**
Postoperative states	**Clinical setting**
Benign intrahepatic cholestasis (BRIC)	**History, genetic testing**
Paraneoplastic	**Lymphoma**

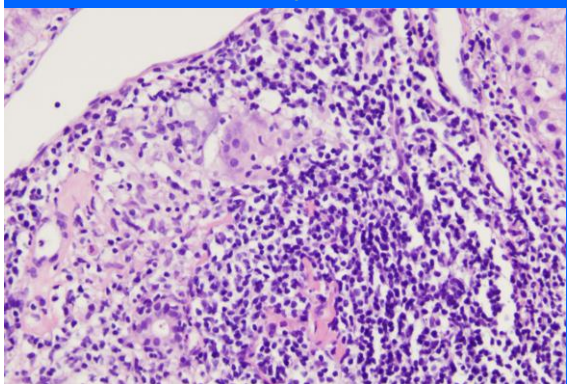
Obstructive pattern: ductular reaction



Ductular reaction

Cause	Clinicopathologic approach
Large duct obstruction	Stone, stricture, neoplasm
Primary sclerosing cholangitis	Clinical setting, autoantibodies, ERCP/MRCP
Sepsis/shock	Clinical setting
Drugs	Anticonvulsant, other CNS drugs Antibiotics
Primary biliary cirrhosis	AMA Duct damage typically more prominent than ductular reaction

PBC-like pattern



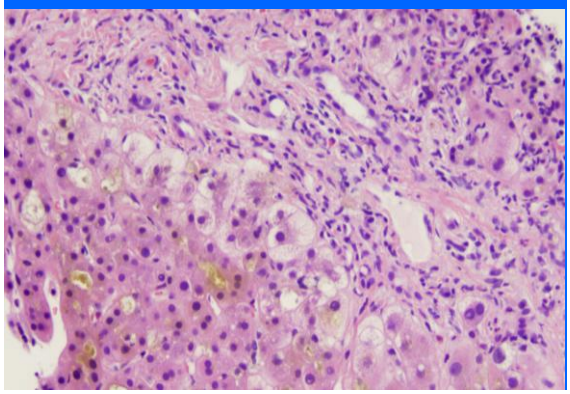
PBC-like pattern

Cause	Clinicopathologic approach
PBC	AMA, serum IgM, exclude other causes
DILI	Review of medications
Primary sclerosing cholangitis	Clinical setting, AMA-negative, ERCP/MRCP
Hepatitis with focal bile duct injury	AMA-neg, positive serology for hepatitis C Clinical features of AIH, hepatocellular injury on biopsy

Chronic cholestasis

- Prolonged cholestasis >3 months
- Fibrosis
- Loss of bile ducts (vanishing bile duct syndrome)

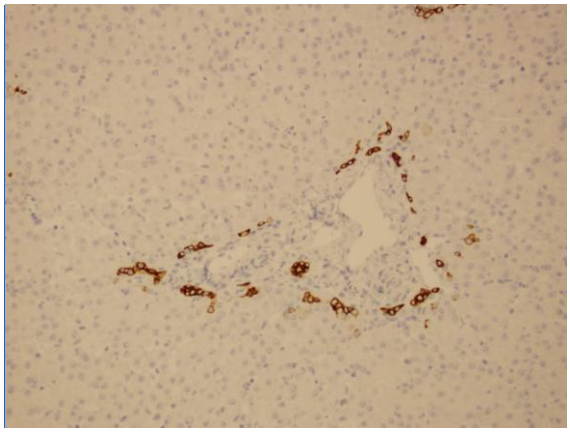
Cholate stasis

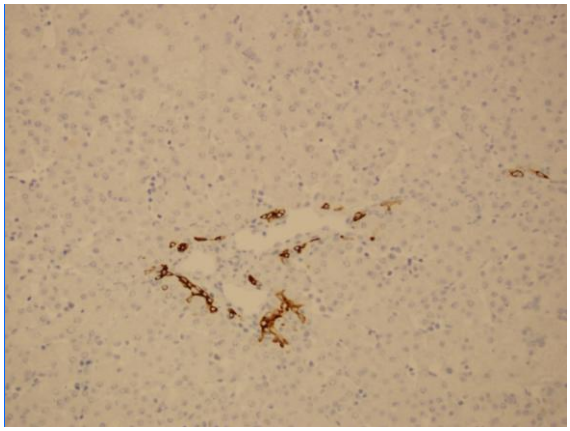


Ductopenia

Different criteria

- Bile duct loss in >50% portal tracts (n=20)
- Bile duct loss in >50% portal tracts (n=10)
- Bile duct loss in >50% portal tracts (n=5)
- Unpaired arterioles in >10% portal tracts

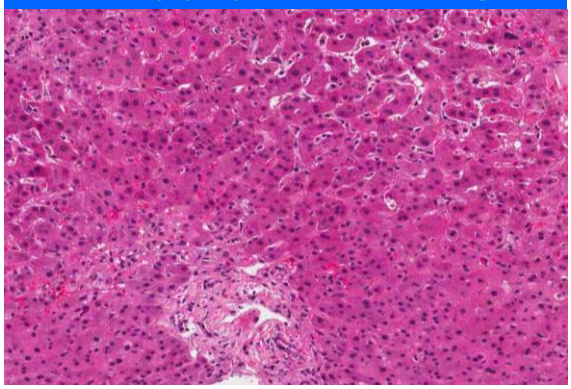




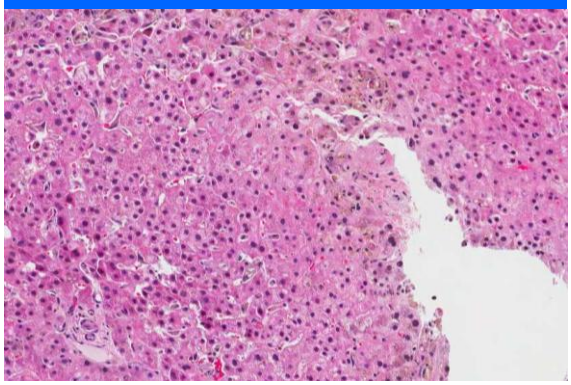
Ductopenia

Cause	Clinicopathologic approach
Drugs	Antibiotics, anticonvulsants, neuroleptics
Biliary diseases	PBC, sclerosing cholangitis
Infections	HIV, CMV
Systemic	Sarcoidosis, Hodgkin lymphoma, ischemic injury
Unknown	Idiopathic adulthood ductopenia

Liver biopsy: reported minimal changes



Subsequent biopsy: marked cholestasis



Biliary patterns of injury

Injury pattern	Histologic features
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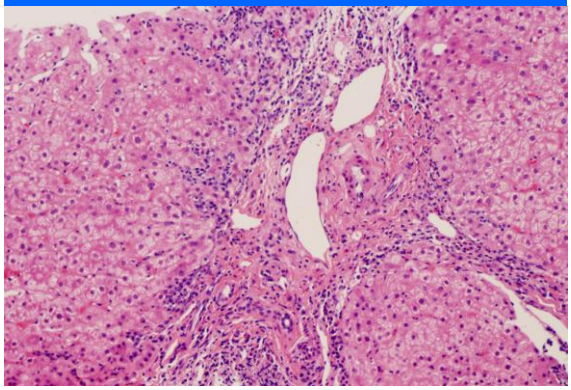
Obstructive pattern	Portal expansion, ductular reaction
PBC-like	Portal inflammation with bile duct injury
Cholestatic hepatitis	Hepatitic pattern with cholestasis
Any of the above	Fibrosis
Any of the above	Ductopenia or loss of bile ducts

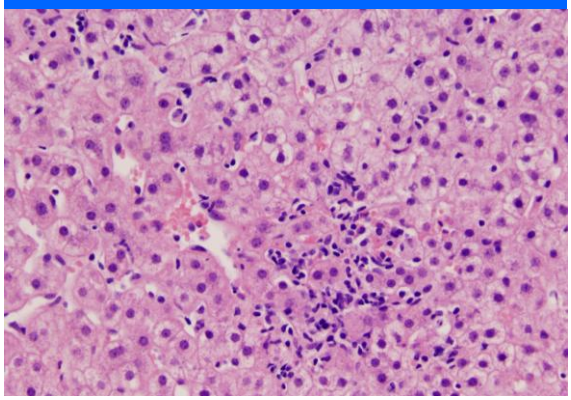
Case 6

- 42/F asymptomatic with elevated ALP on pre-employment screening
- ALT and AST normal
- Antimitochondrial antibodies (AMA) positive

Portal inflammation, no bile duct injury



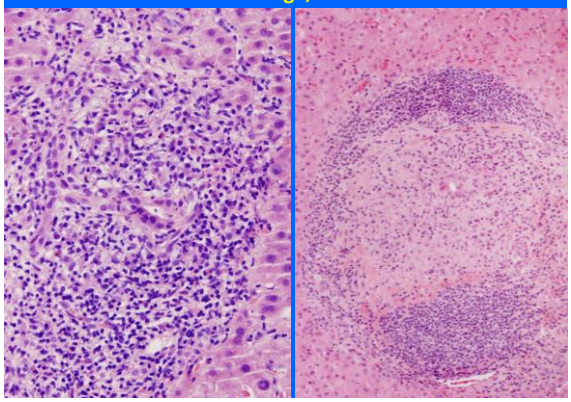
Mild lobular inflammation



Is this primary biliary cirrhosis?

- Specificity of histological findings
- Specificity of positive AMA

PBC: bile duct damage, florid duct lesion



Specificity of AMA

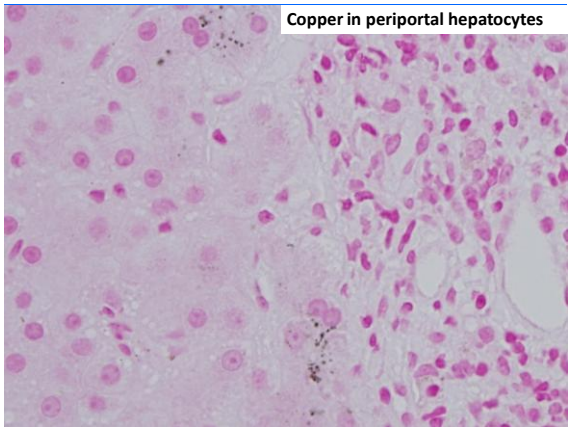
- High specificity for PBC
- AIH, infections like TB
- ELISA-based assay more specific
- Asymptomatic patients with AMA+
  50% symptomatic PBC in 5 yrs
  95% in 20 yrs

Diagnosis

- Diagnosis:
  Mild portal and lobular inflammation, cannot rule out early PBC

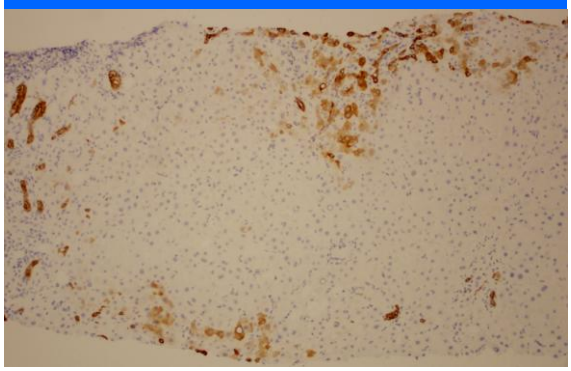
Note:

- Patchy bile duct involvement in early PBC, can be missed on biopsy
- Majority of AMA+ have early PBC, typical disease on follow-up



Copper in periportal hepatocytes

CK7 staining in periportal hepatocytes



PBC diagnosis in different situations

Biopsy findings	Clinical setting	Interpretation
Normal or nonspecific	AMA+	Likely early PBC
Bile duct injury Hepatocellular injury minimal	AMA+ Other causes excluded	Consistent with PBC
Bile duct injury Hepatocellular injury minimal	AMA+ Other causes excluded	Consistent with AMA-negative PBC
Bile duct injury Hepatocellular injury	Hep C or AIH Medications	Hep C or AIH with bile duct injury DILI
Prominent ductular reaction	AMA- ERCP/MRCP	Consider PSC, obstruction

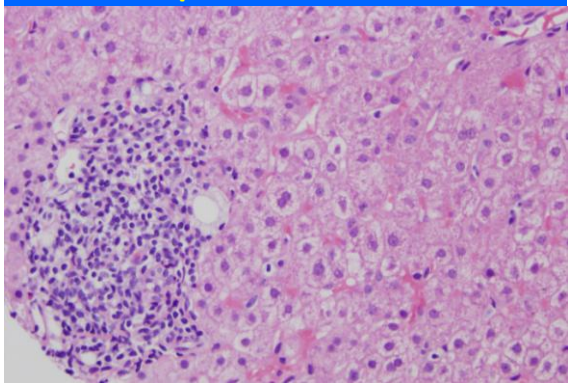
Diagnosis of PBC and PBC

Clinicopathologic feature	Interpretation
Acute or subacute disease with jaundice	Excludes PBC and PSC; cholestasis late feature
AMA+ Prominent inflammation centered on bile ducts	Favors PBC
Inflammatory bowel disease Bile ductular reaction	Favors PSC

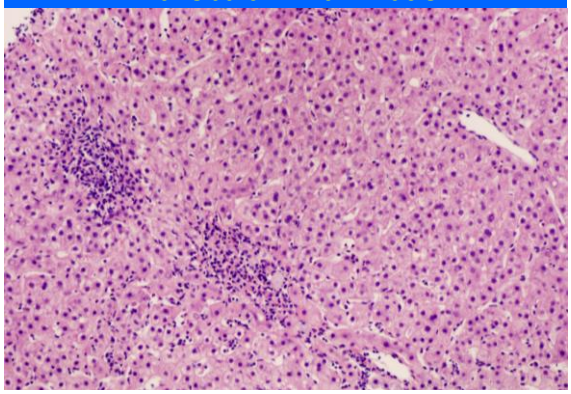
Case 7

- 35/F with history of SLE
- ALT and AST 250 IU/L
- ANA and SMA positive
- Biopsy done to rule out autoimmune hepatitis

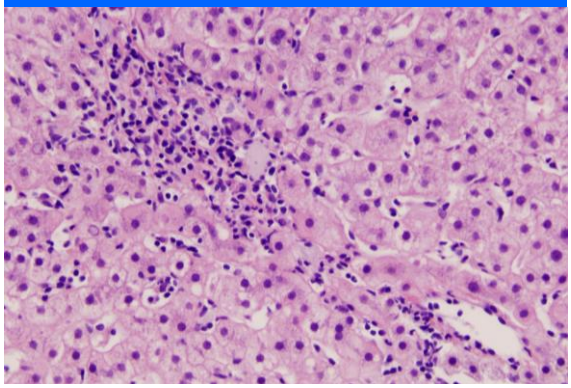
Mild portal inflammation



Mild lobular inflammation



Lymphocytes, rare plasma cells



Is this AIH?

- Mild hepatitis can occur in autoimmune diseases
- ANA and SMA present in SLE
- AIH and SLE rare
- Both treated with steroids
  - Cirrhosis and liver failure in AIH
  - Survival 10% at 10 years

Lupus-related hepatitis vs. AIH

	Lupus-related hepatitis	Autoimmune hepatitis
Serology		
SMA	+ (30%)	+ (60-80%)
dsDNA	+	Uncommon
Ribosomal P	Often + (40%)	Negative
Histology		
Inflammation	Mild	Moderate/marked
	Not periportal	Periportal
Plasma cells	Not prominent	Prominent
Necrosis	Absent	Often prominent
Cirrhosis	Rare	Common

Diagnosis

Additional information

- Anti dsDNA +
- ALT and AST levels <300 U/L
- Biopsy: mild inflammation
  minimal periportal activity

Diagnosis: Mild portal and lobular hepatitis, most consistent with lupus-related hepatitis

Other autoimmune disorders

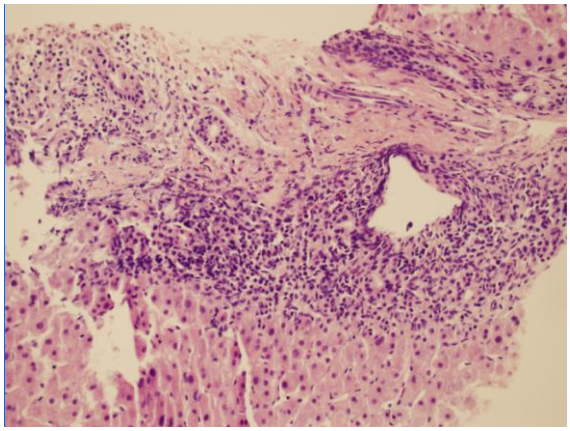
- RA, Sjogren syndrome
- Celiac disease

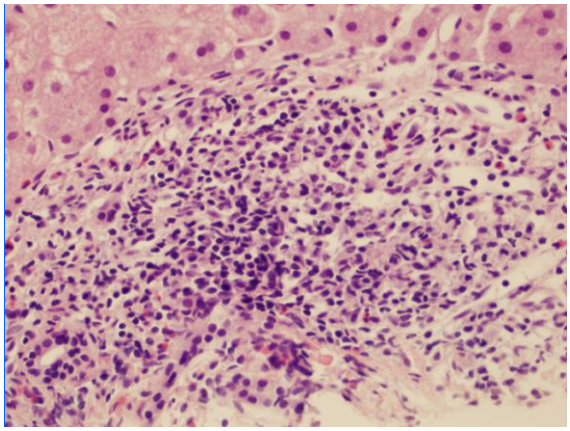
Asymptomatic elevations of ALT, AST
Nonspecific reactive hepatitis
Acute hepatitis
Chronic hepatitis
Cirrhosis

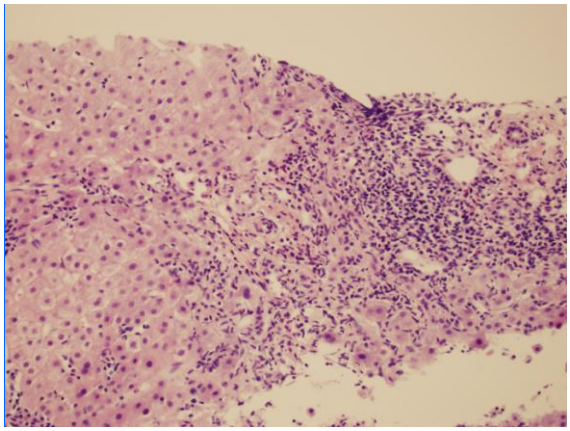
Serological tests in cases with unclear etiology

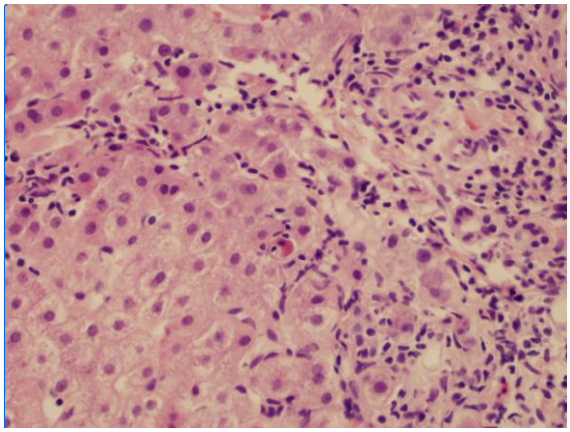
Case 8

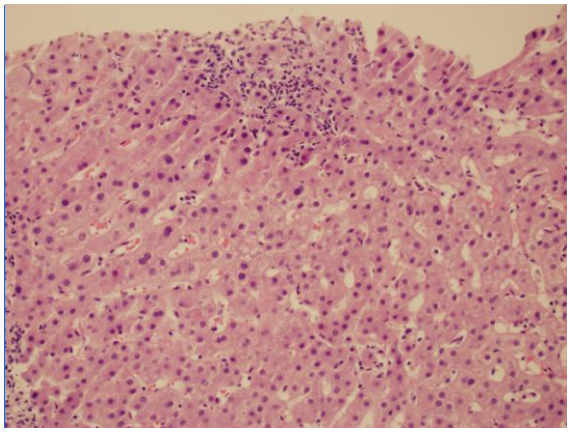
- 40/F with nonspecific abdominal symptoms
- "Elevated LFTs"
- ANA, SMA positive
  AMA negative











Initial diagnosis

- ANA, SMA+
- Biopsy: interface activity
  foci of lobular inflammation
- Diagnosis:
  Autoimmune hepatitis

Serial liver enzymes

	1-2009	9-2009	1-2010	4-2010	6-2010
ALT	58	62	83	159	133
AST	40	38	65	100	110
ALP	192	210	188	224	233

Differential diagnosis

Autoimmune hepatitis	AMA-negative PBC (autoimmune cholangiopathy)	AIH-AMA neg PBC overlap syndrome
Favor	**Favor**	**Favor**
ANA, SMA	ANA, SMA	
Interface activity	ALT low, increased ALP	
	Hepatocellular injury mild	
Against	**Against**	**Against**
Low transminases	Interface activity	
ALP>ALT		
Hepatocellular injury mild		

AIH-PBC overlap syndrome

PBC	AIH
ALP 2x	ALT 5x
AMA positive	SMA positive or IgG 2x
Florid duct lesion	Moderate to severe interface activity

2 of 3 criteria from each group should be present for diagnosis of overlap syndrome

AIH-PBC overlap syndrome

Implications of diagnosis

- PBC: treated with UDCA
  steroids not beneficial
- AIH: UDCA not useful
  can rapidly progress if untreated

AIH-PBC overlap syndrome
role of the pathologist

Raise possibility of overlap with AIH

- Moderate to severe interface activity
- ALT/AST are high (>400-500 U/L)

Raise possibility of overlap with PBC

- Bile duct damage and ductopenia
- ALP 2x without ALT >5x

Differential diagnosis

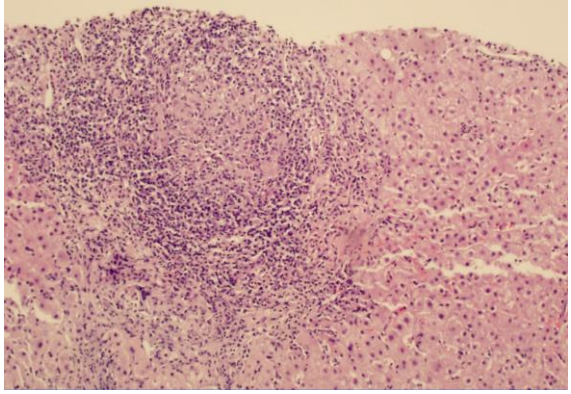
Autoimmune hepatitis	AMA-negative PBC (autoimmune cholangiopathy)	AIH-AMA neg PBC overlap syndrome
Favor	**Favor**	**Favor**
ANA, SMA	ANA, SMA	
Interface activity	ALT low, increased ALP	
	Hepatocellular injury mild	
Against	**Against**	**Against**
Low transminases	Interface activity	Criteria not satisified
ALP>ALT		
Hepatocellular injury mild		

Diagnosis

Portal and interface inflammation with focal bile duct damage, most c/w AMA negative PBC

- Moderate interface activity present
- Mild elevation of ALT/AST and absence of prominent hepatocellular injury does not provide definite evidence of AIH component
- If ALT/AST rise >400-500, overlap syndrome can be considered

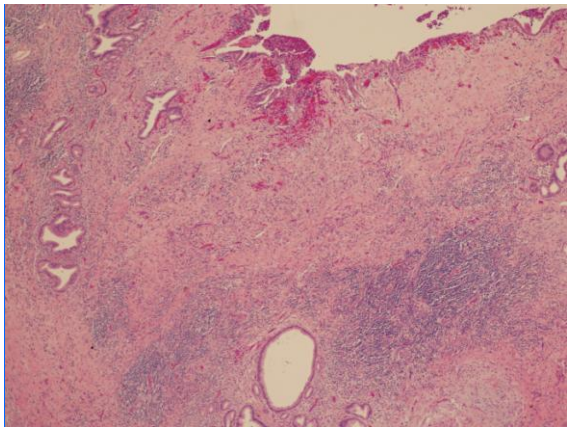
Repeat biopsy: granulomatous bile duct injury

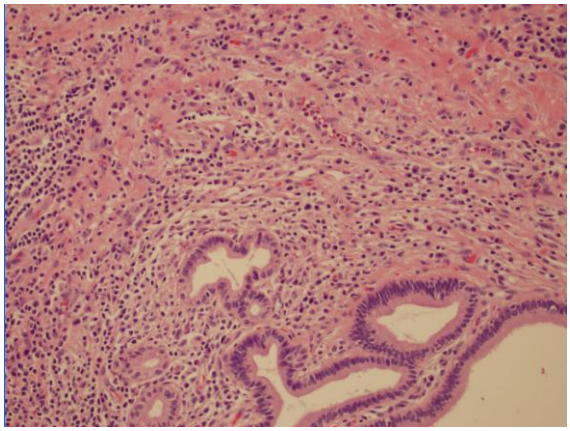


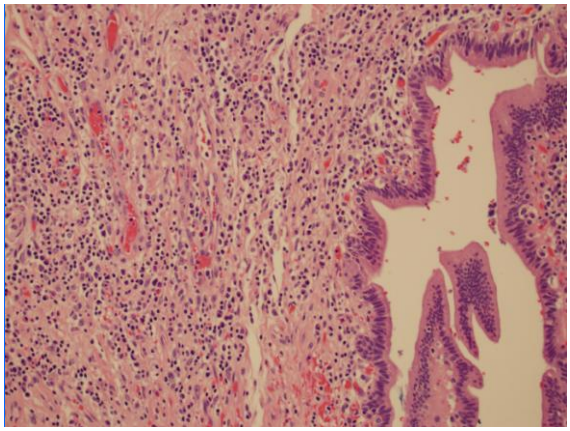
	Hepatitis	Biliary disease
Liver enzymes		
ALT/AST	Elevated	Typically <300 U/L
ALP	Elevated, often mild	Elevated
Serological studies		
Viral hepatitis	Can be positive	Negative
Autoantibodies		
ANA, SMA	Typical of AIH, type 1	Can be seen in PBC
AMA	Uncommon in AIH	Typical of PBC
Ig levels	↑IgG typical of AIH	↑IgM typical of PBC
Histological features		
Hepatocellular injury	Prominent	Mild
Interface activity	Can be prominent	Typically mild or absent
Periportal copper	Absent in early stages	Often present
Bile duct inflammation	Can be present	Typically present
Ductular reaction	Associated with necrosis	Not associated with necrosis
Cholestasis	Can be present	Can be present
Inflammation	Can be prominent	

Case 8

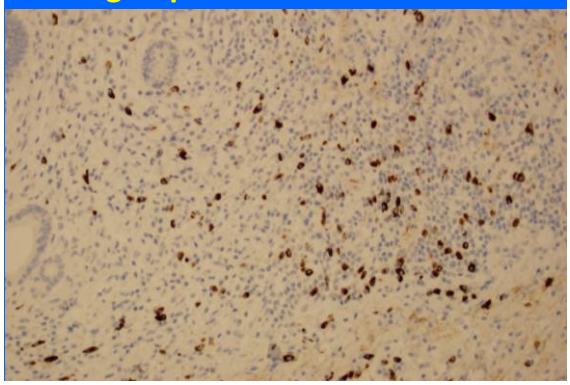
- 55/M with obstructive jaundice
- Imaging: common bile duct stricture, suggestive of cholangiocarcinoma
- Cytology and biopsy inconclusive







IgG4 plasma cells >10 HPF



IgG4 sclerosing cholangitis

- PSC like disease, rare in the absence of pancreatic disease
- Mass forming hilar lesion mimicking cholangiocarcinoma
- Unlike PSC, it is steroid-responsive

PSC and IgG4 sclerosing cholangitis

- IgG4 stain: 23% of PSC have >5 IgG4+ plasma cells per HPF

Absent:

- Portal-based inflammatory nodules: lymphocytes, plasma cells, eosinophils, fibroblasts
- Obliterative phlebitis not seen
- Accentuation of inflammation around bile ducts uncommon

	Hepatitis	Biliary disease
Liver enzymes		
ALT/AST	Elevated	Typically <300 U/L
ALP	Elevated, often mild	Elevated
Serological studies		
Viral hepatitis	Can be positive	Negative
Autoantibodies		
ANA, SMA	Typical of AIH, type 1	Can be seen in PBC
AMA	Uncommon in AIH	Typical of PBC
Ig levels	↑IgG typical of AIH	↑IgM typical of PBC
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