Biliary tract disease

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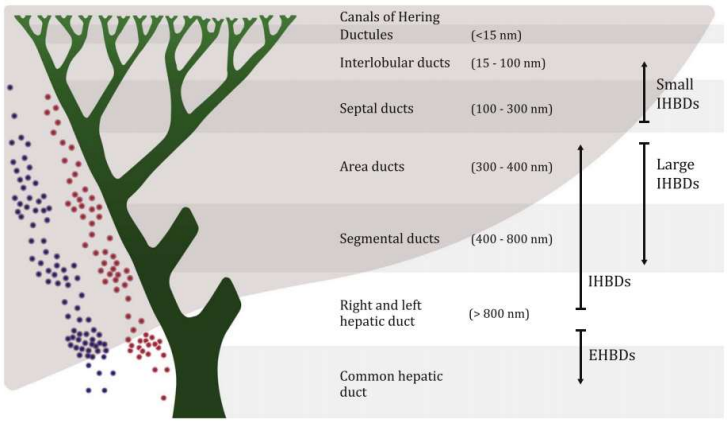
Normal biliary tract



I.E.M. de Jong et al. BBA - Molecular Basis of Disease 1864 (2018) 1524–1531

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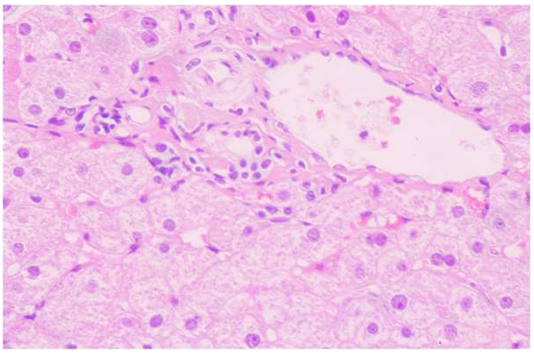
Portal tract



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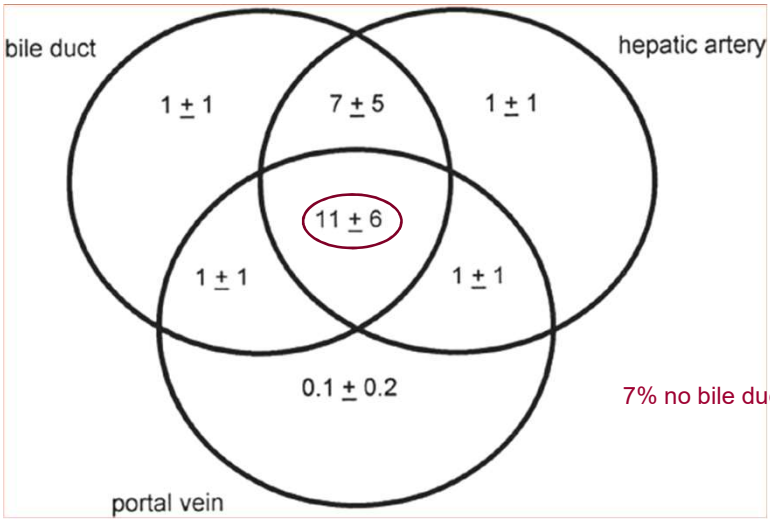
Portal tract



7% no bile duct

Crawford et al. Hepatology 1998;28:323-331

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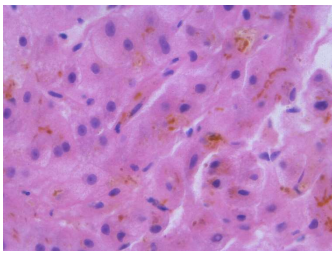
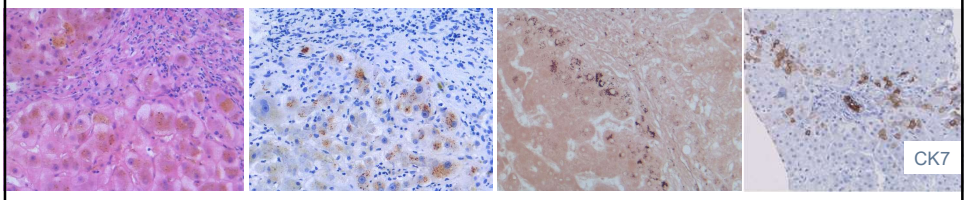
Biliary tract disease

Cholestasis

- Bilirubinostasis
- Cholatestasis
- Ductular reaction
- Copper-deposition





rhodanin orcein

Clark et al. Adv Anat Pathol 2017;24:199

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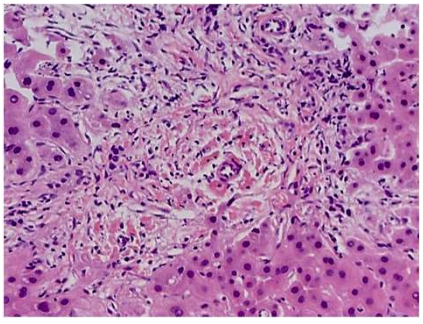
Biliary tract disease

Ductopenia

- 50% rule
  - Absence of bile ducts in > 50 % of portal tracts in an adequate sample
    - Autopsy/resection specimen
    - Adequate sample:
      - 10 portal tracts in a biopsy
      - 5 complete portal tracts in a biopsy



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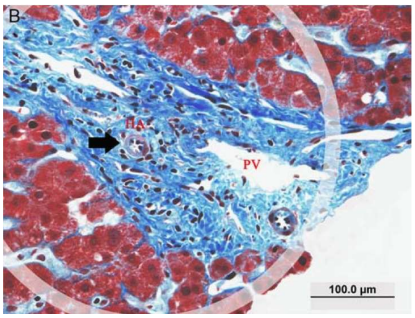
Biliary tract disease

Ductopenia

- Unpaired hepatic artery
  - Presence of 2 or more portal tracts, containing unpaired HA, representing at least 10% of all portal tracts in biopsy sample



Moreira et al AJSP 2011

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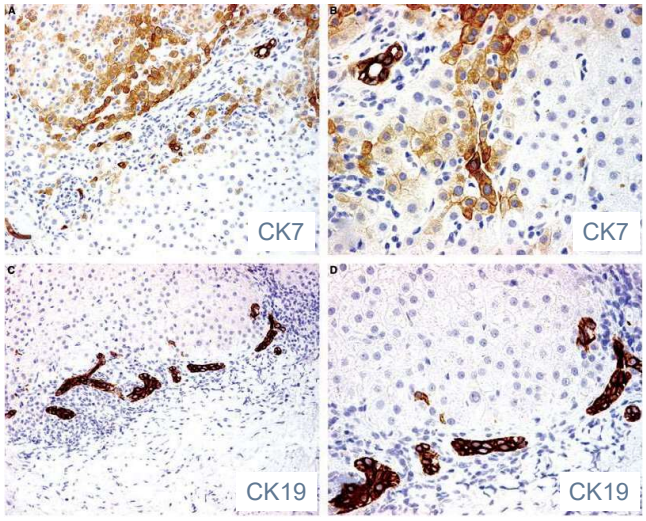
Biliary tract disease



Bateman Histopathology 2010

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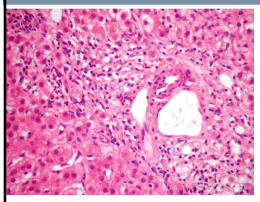

Bateman Histopathology 2010

Vanishing bile duct syndrome	
Developmental	Biliairy atresia
	α1-antitrypsindeficiency
	Cystic fibrosis
Immune-mediated	Primary biliary cirrhosis
	Primary sclerosing cholangitis
	Autoimmune overlap syndromes
	IgG4 systemic sclerosis
	Sarcoidosis
	GVHD, chronic liver rejection
Vascular	Arterial disease e.g. vasculitis
	Portal vein obstruction
Infection	Bacterial, viral, protozoa, ….
Drugs	Phenothiazines, Ab, anticonvulsants…
Neoplastic	Langerhans cell histiocytosis
	Systemic mastocytosis
	Hodgkin
Idiopathic	

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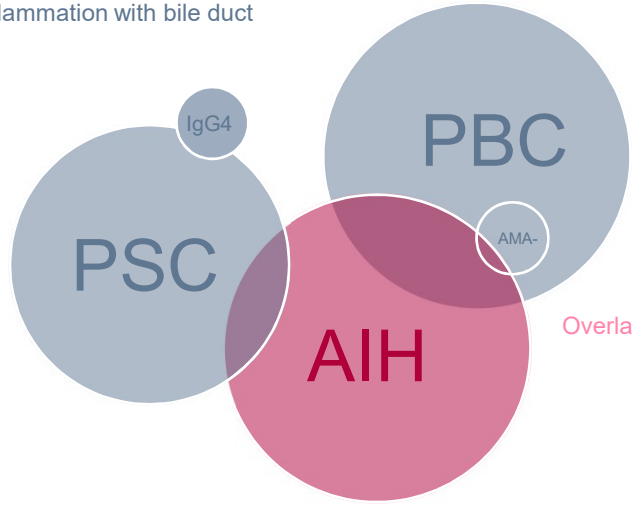
Biliary tract disease

Chronic inflammation with bile duct pathology



Overlap syndrome

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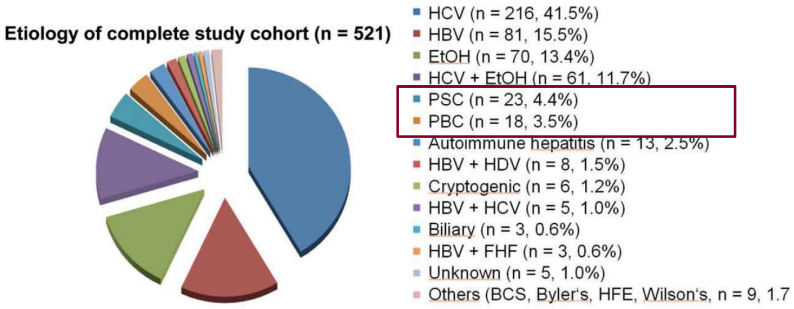
Biliary tract disease



Hartmann et al., Hepatology 2011

1988-2014: ± 16% of the liver transplants in the USA for cholangiopathies

Lazaridis Mayo Clin Proceedings 2015

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Primary biliary cirrhosis (PBC)

- 1950 Ahrens et al: Primary biliary cirrhosis
  - End stage disease
  - Cirrhosis
- Nowadays: diagnosis at early stage → cirrhosis in limited number of patients
  - Disease characterized by a chronic non-suppurative cholangitis

Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'☆☆

Ulrich Beuers[1,*], M. Eric Gershwin[2], Robert G. Gish[3], Pietro Invernizzi[4], David E.J. Jones[5], Keith Lindor[6], Xiong Ma[7], Ian R. Mackay[8], Albert Parés[9], Atsushi Tanaka[10], John M. Vierling[11], Raoul Poupon[12]

Journal of Hepatology **2015** vol. 63 | 1285–1287

→primary biliary cholangitis

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Primary biliary cholangitis

Feature	PBC
Gender	Females: >90%
Age	Typically age group 30-65 years. Not diagnosed in children
Aminotransferases	Normal or slightly elevated
Alkaline phosphatase	Moderately - markedly elevated
Bilirubin	Variable increase, but normal in majority at diagnosis
Immunoglobulins	IgM increased in most patients
Autoantibodies	
ANA	ANA in >30% (anti-gp210 and anti-Sp100 highly specific)
SMA	SMA may be present
Anti-LKM	
Anti-SLA/LP	Anti-SLA/LP may be detected
pANCA	
AMA	AMA in 90-95% (AMA anti-PDC-E2 pattern highly specific)
Cholangiography	Normal or signs of liver cirrhosis
IBD	Rarely associated with PBC

Symptoms
- 50% asymptomatic
- Fatigue
- Jaundice
- Pruritus
- Abdominal pain

Riskfactor
- First degree relative

Boberg et al.
J Hepatol 2011

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Primary biliary cholangitis

Diagnosis

- Serology:
  - AMA: anti-mithochondrial antibody M2
  - Antinuclear antibodies anti-sp100/anti-gp210
- Imaging:
  - Ultrasound
  - MRCP
  - ERCP
  - EUS
- Liver biopsy not required for diagnosis

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Primary biliary cholangitis

- Indications for a liver biopsy
  - AMA-negative 10%
  - DD progressive chronic cholestatic disease: PSC; sarcoidosis; vascular disease e.g. congestive hepatopathy, amyloidosis; drug-induced cholestatic liver injury; idiopathic adulthood ductopenia
  - Suspected overlap syndromes
  - PBC with suspicion of another diagnosis
    - PBC + NASH

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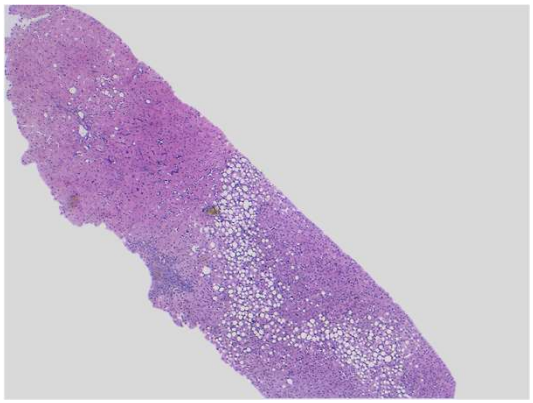
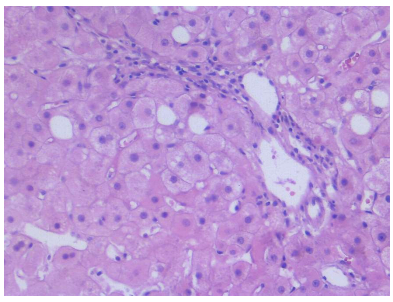
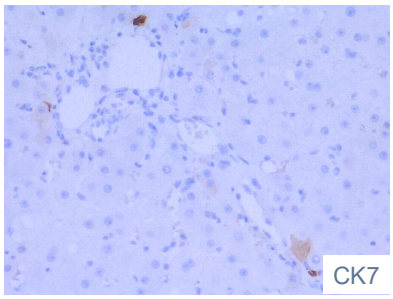
Primary biliary cholangitis

PBC+NASH







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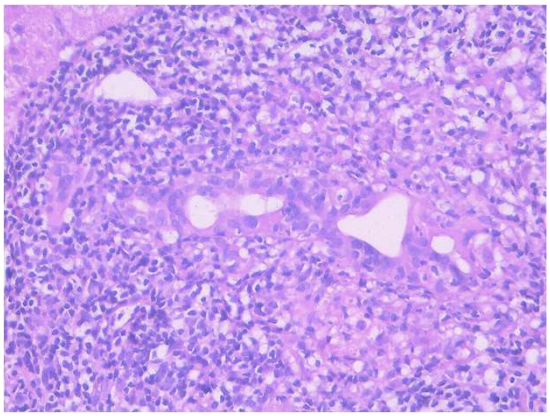
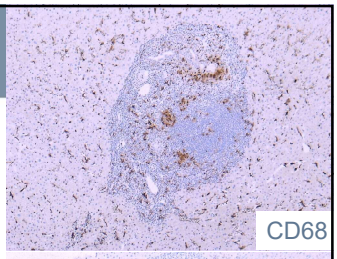
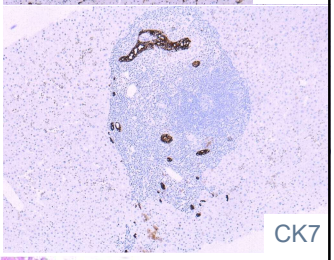
Primary biliary cholangitis

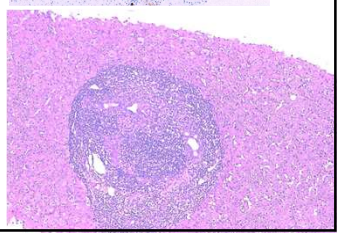
Chronic non-suppurative cholangitis

- Lymphohistiocytic cholangitis
- Canals of Hering, interlobular bile ducts









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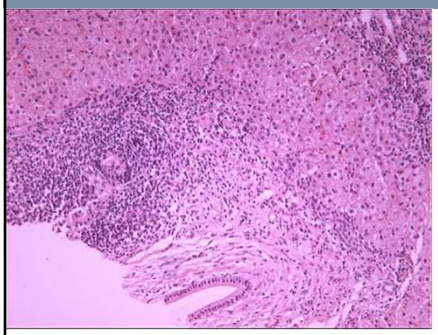
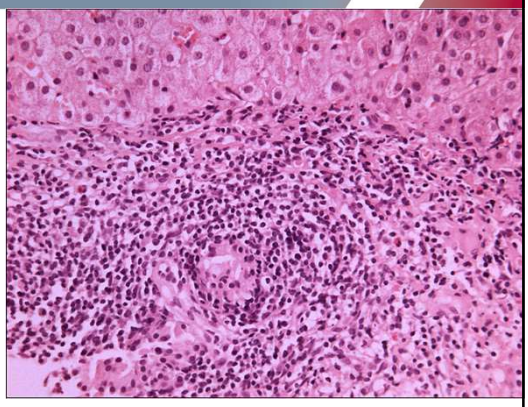
Primary biliary cholangitis





Early stage

- Nonsuppurative cholangitis → florid duct lesion
- Bile ductular reaction
- Problem: patchy distribution

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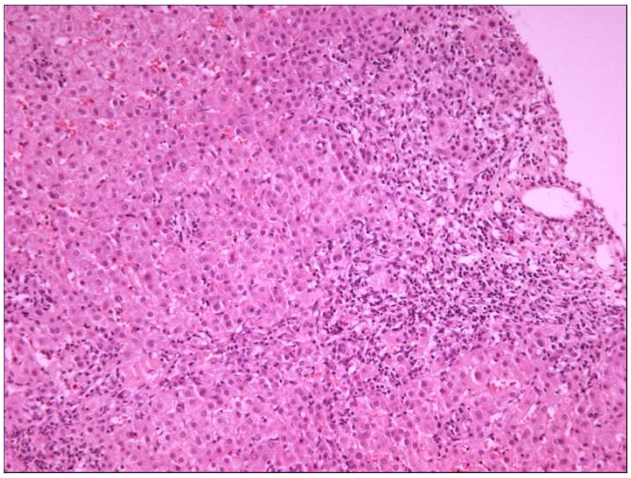
Primary biliary cholangitis



Interface hepatitis

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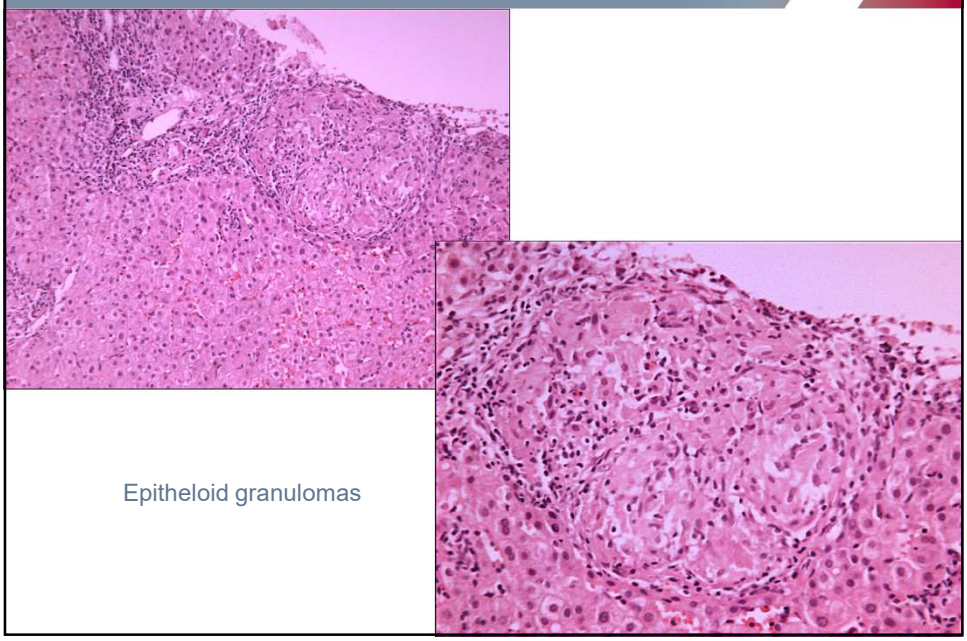
Primary biliary cholangitis



Epitheloid granulomas

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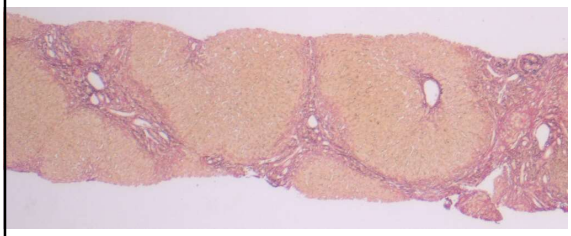
Primary biliary cholangitis

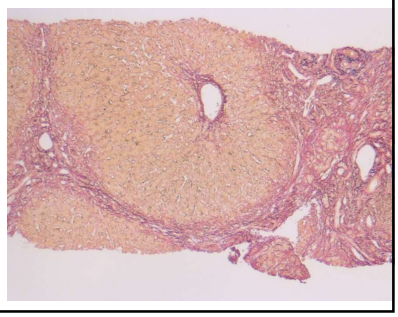
Middle stage

- Destruction of bile duct due to inflammation → ductopenia
- Granulomatous inflammation
- Lobular cholestasis late
- Cholatestase, Mallory bodies

Late stage

- Fibrosis → biliary pattern cirrhosis





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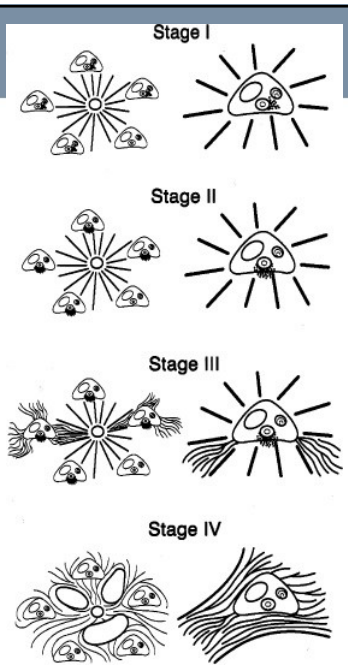
Stages in PBC

Classification of Scheuer



Florid duct lesion

Interfase hepatitis

Fibrosis

Cirrhosis

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Primary biliairy cholangitis

Grading and staging

- Grading: difficult → bile duct injury → chronic inflammation with hepatocellular and bile duct destruction
- Staging: fibrosis → cirrhosis

Table 1
Histologic staging of PBC: comparison of three systems

	Scheuer[6,7]	Ludwig[13]	Nakanuma[14]
Stage 1	Florid duct lesions Bile duct damage Portal inflammation	Portal inflammation	No or minimal progression (fibrosis, bile duct loss, copper binding protein = 0)
Stage 2	Ductular proliferation Portal expansion Interface hepatitis	Periportal inflammation Interface hepatitis	Mild progression (fibrosis, bile duct loss, copper binding protein = 1–3)
Stage 3	Scarring Loss of bile ducts	Fibrous septa	Moderate progression (fibrosis, bile duct loss, copper binding protein = 4–6)
Stage 4	Cirrhosis	Cirrhosis	Advanced progression (fibrosis, bile duct loss, copper binding protein = 7–9)

Simple
Bile duct lesion
Patchy distribution

Viral hepatitis

Clinical trials

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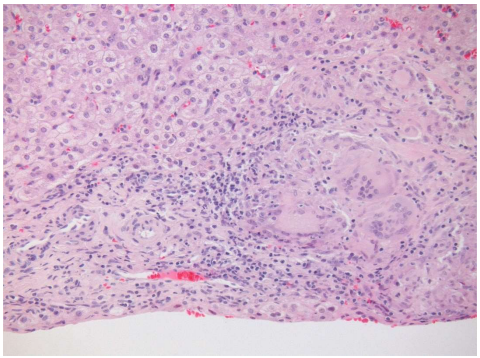
Primary biliairy cholangitis

- Differential diagnosis

- Granuloma
  - Sarcoidosis
  - Tuberculosis
  - CMV infection
  - DILI
  - Crohn disease



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Primary biliary cholangitis

AASLD

- Diagnosis
  - Increase of alkaline phospatase >1,5x the upper limit of normal
  - Presence of positive AMA
  - Diagnostic liver biopsy
    - Florid duct lesion
  - Treatment
    - Ursodeoxycholic acid
    - No steroids

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Primary sclerosing cholangitis

- Cholestatic liver disease,
  - incidence 0-1,3/100000 persons/yr
  - prevalence 0-16,2/100000 persons
- Chronic fibro-obliterative cholangitis with segmental concentric inflammatory fibrosis at the level of intrahepatic and extrahepatic bile ducts → stenosis and ectasia
- Small duct PSC (5%) involvement limited to small interlobular bile ducts
- Pathogenesis unclear
- Increased risk for cholangiocarcinoma (10%)

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Primary sclerosing cholangitis

Boberg et al.
J Hepatol 2011

Feature	PBC	PSC
Gender	Females: >90%	Females: 30-35%
Age	Typically age group 30-65 years. Not diagnosed in children	Typically 30-50 years, but all age groups
Aminotransferases	Normal or slightly elevated	Normal or slightly elevated
Alkaline phosphatase	Moderately - markedly elevated	Moderately - markedly elevated (typically at least 3 x ULN; but variable levels, may even be normal)
Bilirubin	Variable increase, but normal in majority at diagnosis	Variable increase, but normal in majority at diagnosis
Immunoglobulins	IgM increased in most patients	IgG increased in up to 61% IgM increased in up to 45%
Autoantibodies		
ANA	ANA in >30% (anti-gp210 and anti-Sp100 highly specific)	ANA in 8-77%
SMA	SMA may be present	SMA in 0-83%
Anti-LKM		
Anti-SLA/LP	Anti-SLA/LP may be detected	Anti-SLA/LP may be detected
pANCA		pANCA in 26-94%
AMA	AMA in 90-95% (AMA anti-PDC-E2 pattern highly specific)	AMA occasionally positive
Cholangiography	Normal or signs of liver cirrhosis	Characteristic findings, diagnostic of PSC. Normal cholangiography in small duct PSC
IBD	Rarely associated with PBC	Present in up to 80%

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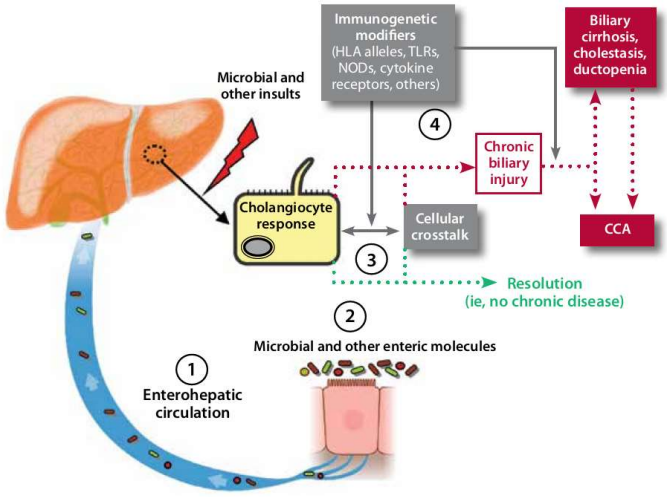
Primary sclerosing cholangitis



Tabibian et al., Gastroenterology & Hepatology 2018

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Primary sclerosing cholangitis

- Diagnosis
  - Serology:
    - Cholestatic profile
    - Auto-antibodies SMA, ANCA → not specific
  - Imaging:
    - To exclude biliary obstruction → ultrasound, CT, MRI
    - Cholangiography: MRCP > ERCP
  - Liver biopsy not required for diagnosis

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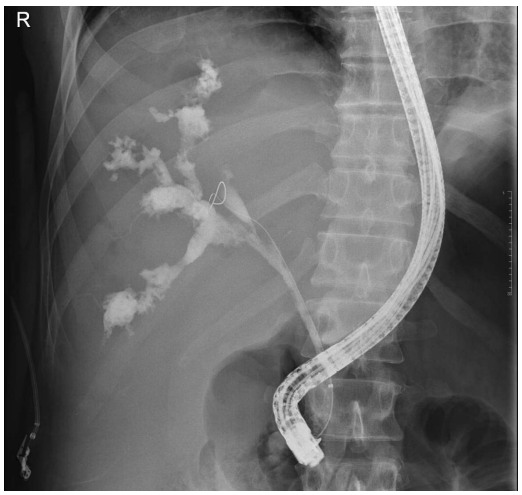
Primary sclerosing cholangitis



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Primary sclerosing cholangitis

- Indications for a liver biopsy
  - Diagnosis of small duct PSC
  - Suspicion of an overlap syndrome with an autoimmune hepatitis
  - To determine the extent of the disease with attention for the stage, activity and degree of involvement of the small interlobular bile ducts
  - To rule out coexisting liver disease

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Primary sclerosing cholangitis

- Problem of a liver biopsy
  - Random distribution of the involved bile duct segments → variable histological changes → sampling error
  - Size of the involved bile duct ↔ size the biopsy needle
  - Characteristic feature namely onion-skin or fibro-obliterative lesion < 40% of the biopsies

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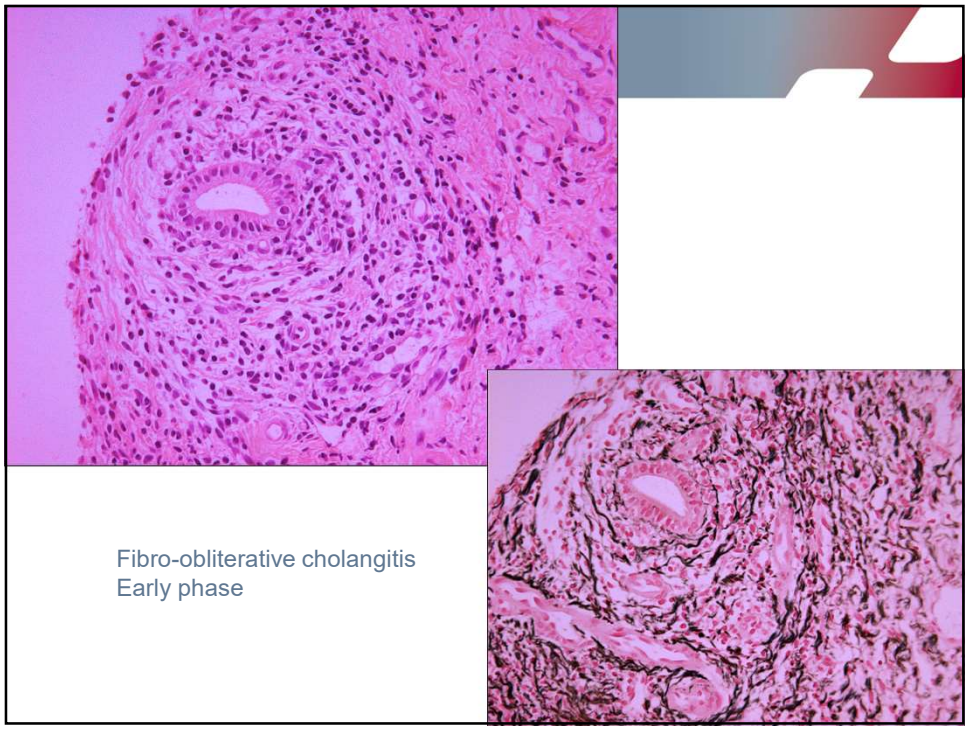

Fibro-obliterative cholangitis
Early phase

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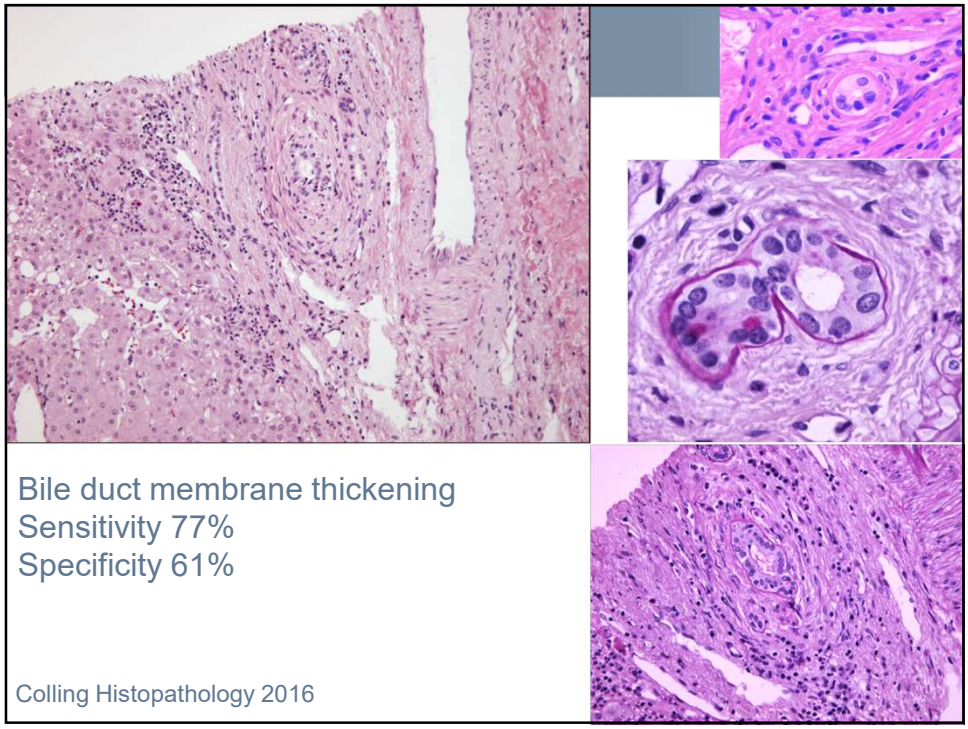

Bile duct membrane thickening
Sensitivity 77%
Specificity 61%

Colling Histopathology 2016

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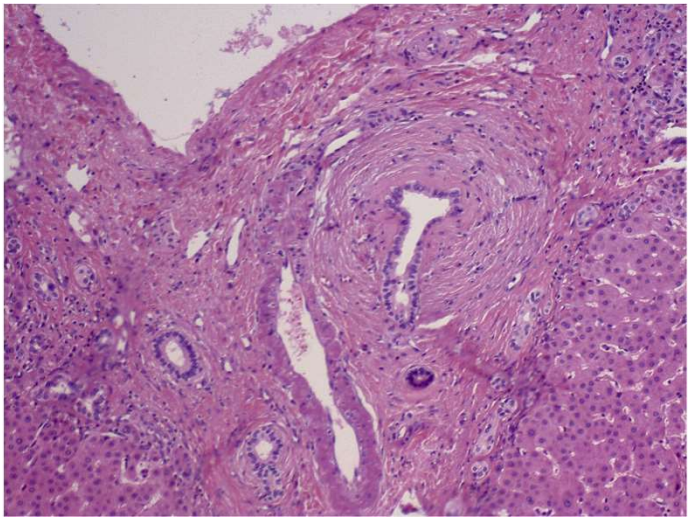
Primary sclerosing cholangitis



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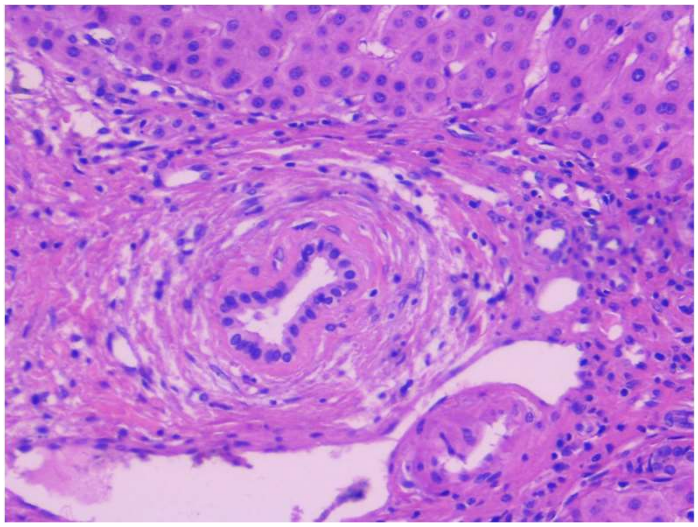
Primary sclerosing cholangitis



Fibrointimal hyperplasia

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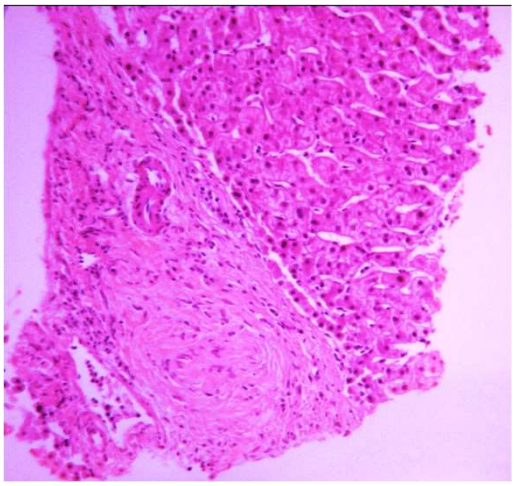
Primary sclerosing cholangitis



Fibrous scar

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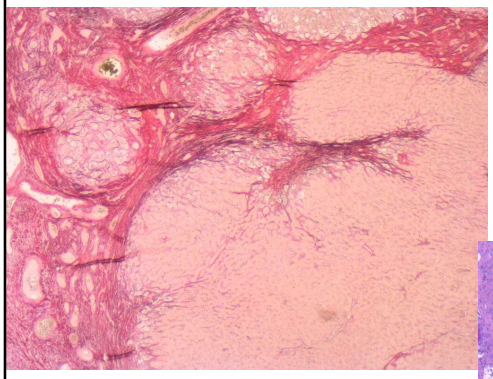
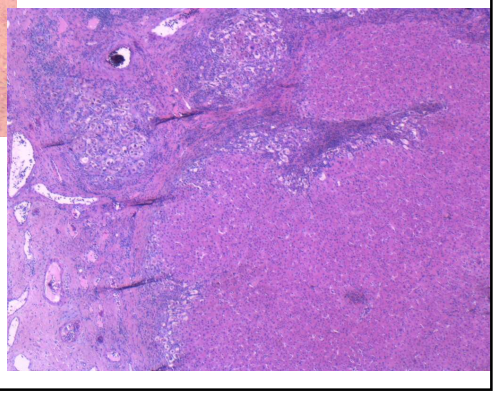
Biliary cirrhosis





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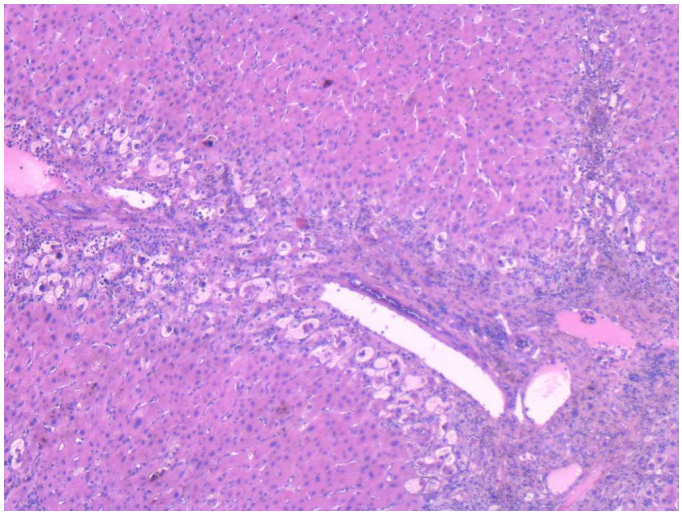
Biliary cirrhosis



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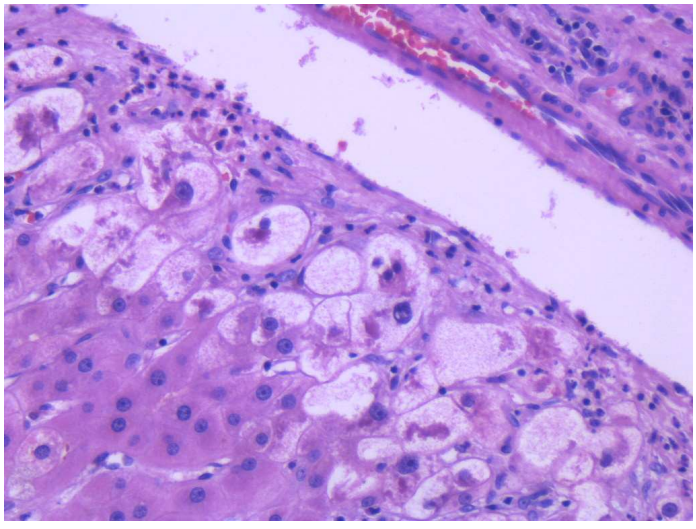
Biliary cirrhosis



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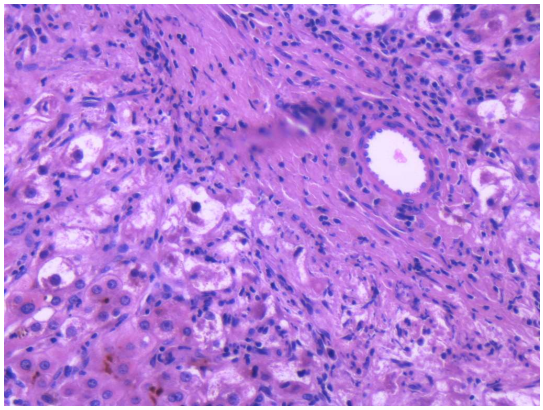
Biliary cirrhosis



Biliary cirrhosis

- Mallory-bodies
- Cholatestasis
- Bilirubinostasis
- Portal lymphoplasmocytic infiltrate
- Variable lobular activity
- Ductopenia

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Primary sclerosing cholangitis

- Staging according to Ludwig (similar to PBC)
  - Stage 1: Portal hepatitis
  - Stage II: Periportal hepatitis with interface hepatitis
  - Stage III: Septal fibrosis with formation of numerous fibrous septa
  - Stage IV: Cirrhosis

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Primary sclerosing cholangitis

Association with inflammatory bowel disease

- Prevalence PSC-IBD 60-80% Western countries
  - Ulcerative colitis 75-80 %
  - Crohn's disease 10-15 %
  - Unclassifiable 5-10%
- Colonoscopy is indicated in patients with a new diagnosis of PSC
- Coexistence of PSC with UC/Crohn → pancolitis
- Increased risk of coloncancer RR 4x

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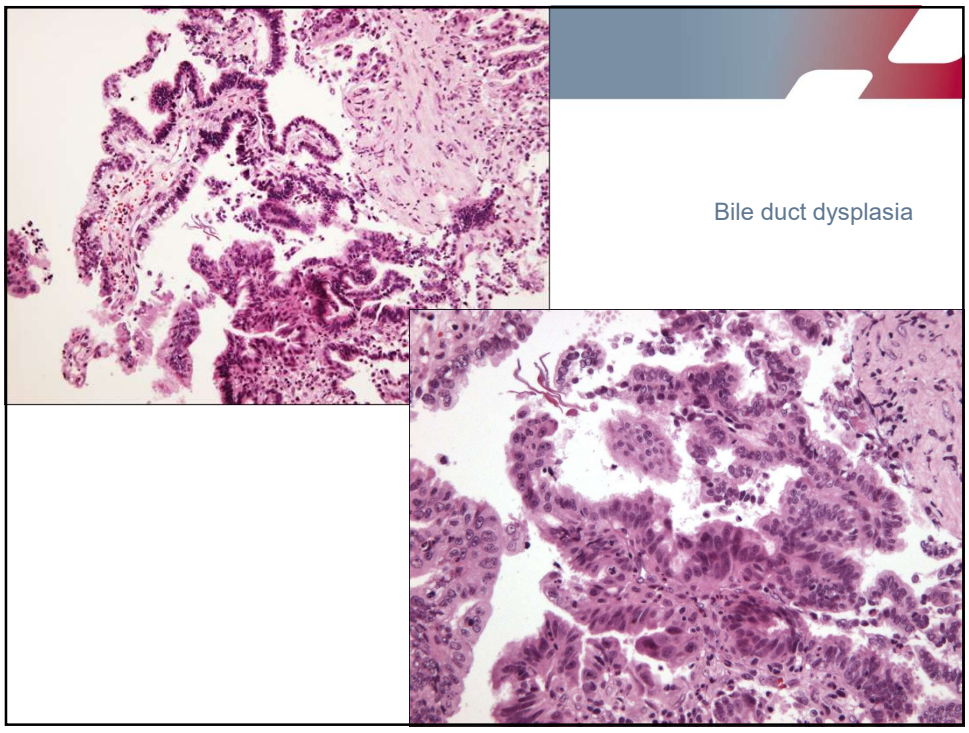

Bile duct dysplasia

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Primary sclerosing cholangitis

- Cholangiocarcinoma
  - Developed countries: PSC most common risk factor for cholangiocarcinoma
  - PSC RR 400x -1500x
  - PSC annual risk 0,5-2%, life time incidence 15%
- Gallbladder carcinoma
  - Life time incidence 3-14%
- Hepatocellular carcinoma
  - Life time incidence 0,3-2,4%

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Overlap syndrome

- 5-10% of patients with PSC or PBC have features supporting a diagnosis of auto-immune hepatitis
- Classic features of auto-immune hepatitis with prominent duct injury/chronic cholestastis
- Diagnostic approach
  - AASLD: classify according to the predominant features as a PBC or PSC
  - EASL: pointing towards the inflammatory pattern of the disease
    - PBC or PSC with hepatitic features or PBC or PSC with auto-immune features

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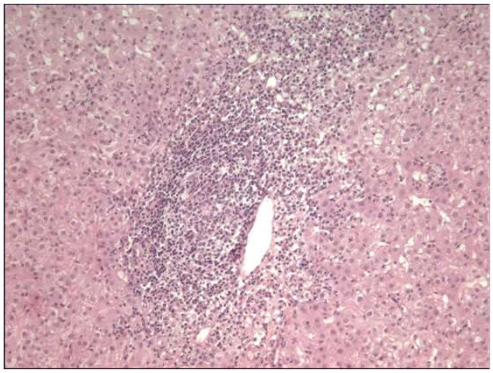
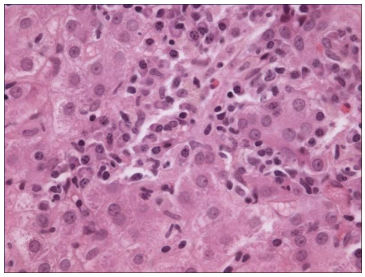
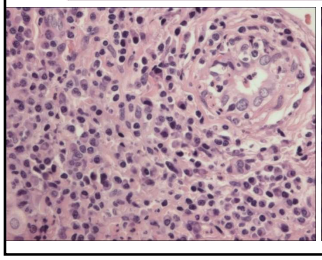
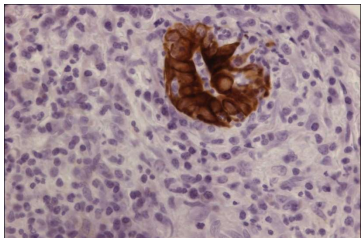
Overlap syndrome

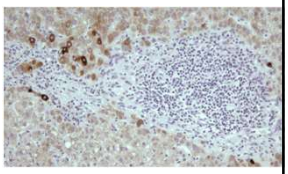


PSC +AIH









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Overlap syndrome

PSC-AIH overlap syndrome

- Laboratory features
  - ANA or SMA
  - Hypergammaglobulinemia
  - ↑ IgG4
  - AST/ALT abnormal
  - ERC/MRC: focal biliary strictures and dilatations
- Histologic findings
  - Lymphocytic portal infiltrate
  - Ductular proliferation
  - Periductular fibrosis
  - Portal edema
  - Cholate stasis
  - Fibro-obliterative cholangitis
  - Ductopenia
  - Increased stainable hepatic copper

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Overlap syndrome

- PBC-AIH overlap syndrome
  - AIH (2 of 3 criteria required)
    - ALT levels > 5x upper limit normal
    - IgG > 2x upper limit or + SMA
    - Liver biopsy: moderate to severe interface hepatitis
  - PBC (2 of 3 criteria required)
    - Alkaline phospatase > 2 or GGT > 5x upper limit normal
    - Positive AMA
    - Liver biopsy: florid duct lesions

→ Diagnosis not only based on histopathological features, but also on clinical features

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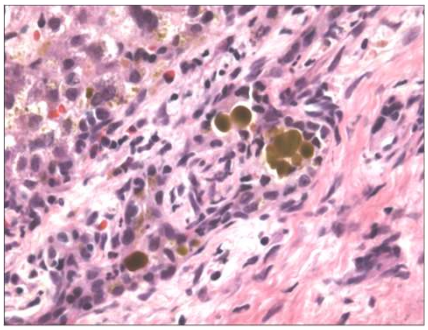
Bilairy tract disease

Differential diagnosis

Cholestasis

- Total parenteral nutrition
- Cholestasis of pregnancy
- Sepsis
- DILI
- Pediatric liver disease



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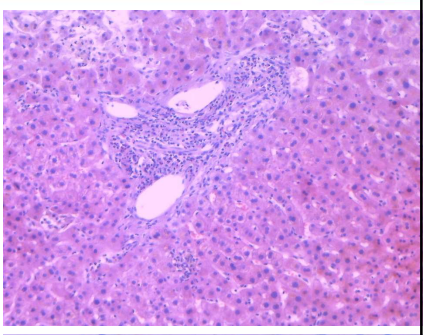
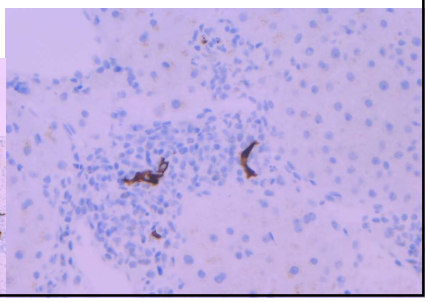
Biliary tract disease

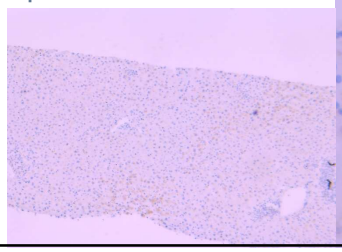
Differential diagnosis

Duct loss/ductopenia

- Iatrogenic adulthood ductopenia
- Chronic ductopenic rejection
- GVHD
- Long-term parenteral nutrition







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Biliary tract disease

- Comprise a whole list of different diseases
- Diagnosis is not only based on the histological findings of a liver biopsy, but should be analysed in relation to the clinical and laboratory data
- Indications for a liver biopsy are limited
- Drawbacks of a liver biopsy
  - Patchy distribution of the involved bile ducts in the liver
  - Size of the involved bile duct may be larger than the size of the needle
  - Absence of cholestasis
  - Overlap syndrome

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