BSG / ACP Annual GI Pathology Course

Inflammatory and infectious conditions of the GIT, liver and biliary tree

Primary biliary cirrhosis and its variant

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Primary biliary cirrhosis (PBC)

- **Primary biliary cirrhosis is an autoimmune disorder of unknown aetiology in which humoral + cellular autoimmunity are considered central to induce and maintain the selective destruction of small intrahepatic bile ducts**
  - **Combination of genetic and environmental risk factors**
    - **Genetic**

      High concordance rate of PBC in monozygotic twins
      Familial clustering

    - **Environment** (**Through molecular mimicry - loss of tolerance to target self antigen**)

      Bacteria (*Mycobacteria, E coli, Lactobacillus)*
      Xenobiotics
      Viruses (*Betaretrovirus)*

Primary biliary cirrhosis (PBC)

- The term PBC (Ahrens et al,1950) is inaccurate cirrhosis being only a late manifestation ‘Chronic non-suppurative destructive cholangitis’ more accurately describes the lesion

- Familiarity with the clinical and laboratory aspects of the disease is essential in establishing a diagnosis as biopsy needle often fail to sample pathognomonic features

Primary biliary cirrhosis (PBC)

Clinical features

- Middle-aged women – not in children (unlike PSC)
- F : M = 9-10 :1

Presenting features

- Pruritus, lethargy, pigmentation
- Cholestatic jaundice = late (but pregnancy or drug)
- Rarely hepatic decompensation
- Associated immune disorders

Sjögren syndrome or the 'sicca complex', CREST syndrome

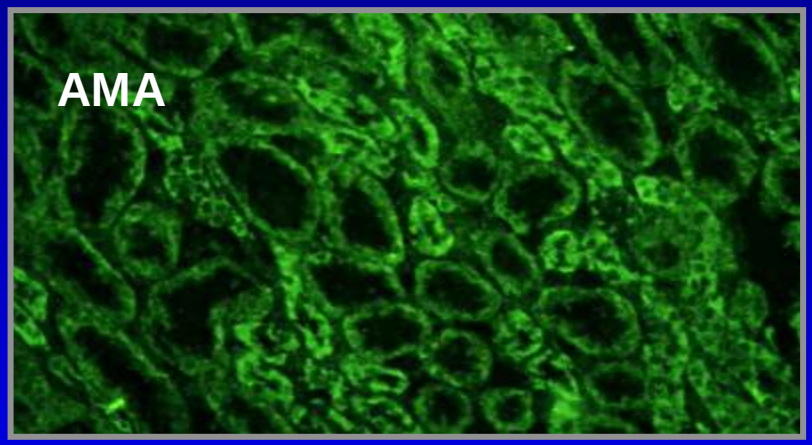
Sero+/-ve arthritis, autoimmune thyroiditis, coeliac disease, SLE

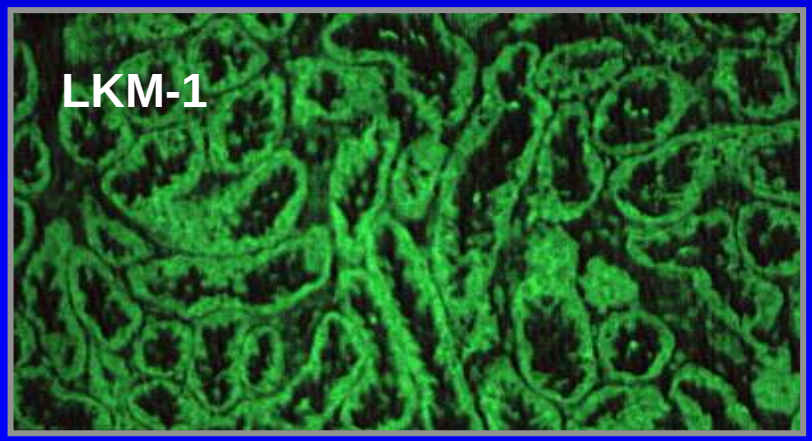
- Raised Alk phos, γGT, ± bilirubin, ↑IgM

Primary biliary cirrhosis (PBC)
Laboratory

- AMA : antimitochondrial Abs
  = hallmark of the disease (95%)
  Reactive with epitopes in E2 components of the pyruvate dehydrogenase complex (PDC-E2)

- Immunofluorescence pattern (kidney) may be confused with LKM-1



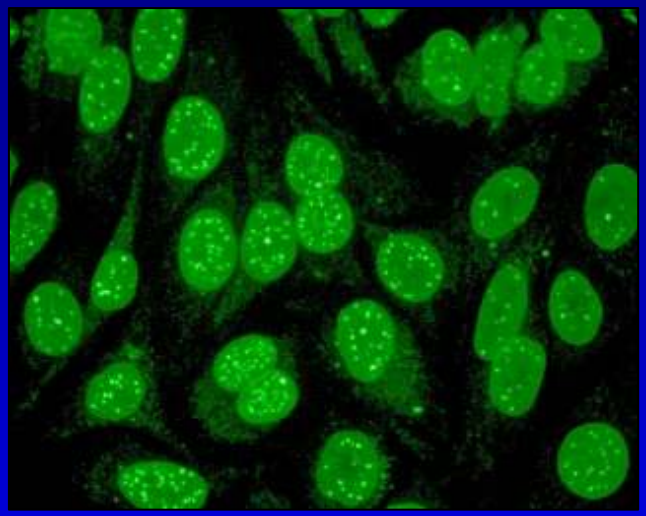


Antinuclear autoantibodies in PBC

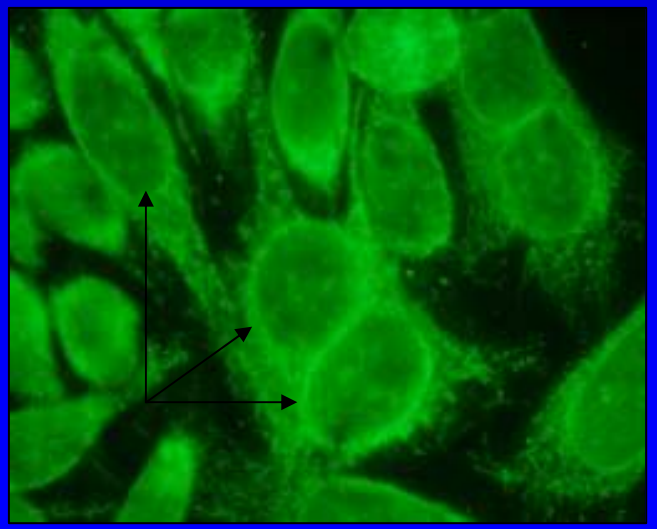
ANA in up to 70% of PBC cases

- Non PBC-specific ANA
- **PBC-specific ANA: up to 50% of patients**
  sp100, gp210 / NUP62

Nuclear proteins as molecular targets:
sp100 = IFL pattern: 3-20 dots →



Nuclear pore complex (NPC) proteins →
as molecular targets (gp210 / NUP62)
= punctated perinuclear rim
(? More severe course of disease)



Yang W, Clin gastroenterol Hepatol 2004; 2(12): 1116-22
Nakamura M, J Hepatol 2005; 42:386-92

Primary biliary cirrhosis : autoantibodies

Study in Systemic Sclerosis patients N = 817
Including 16 (2%) with PBC

	Sensitivity	Specificity
• AMA (MIT3 ELISA)	81.3%	94.6%
• sp100	31.3%	97.4%
• gp210	lower	

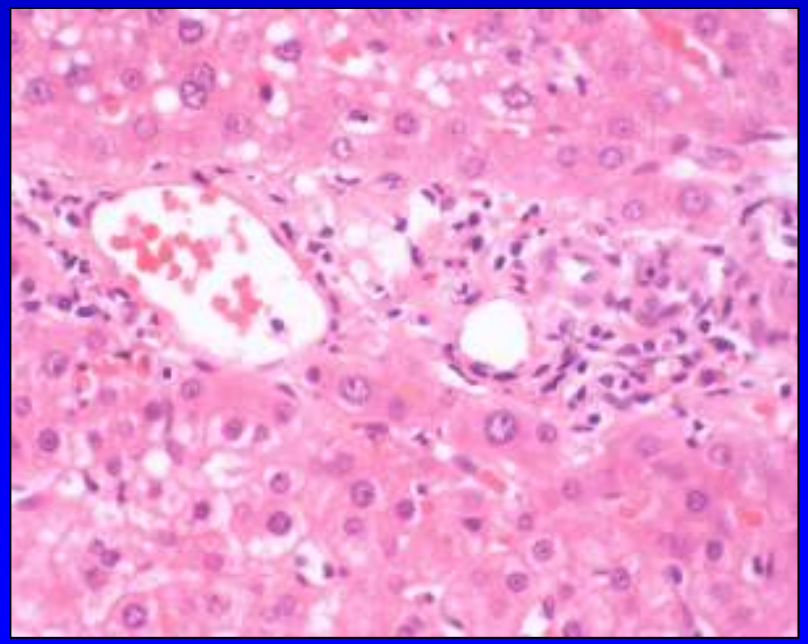
Combined AMA and sp100 detected 100% of PBC

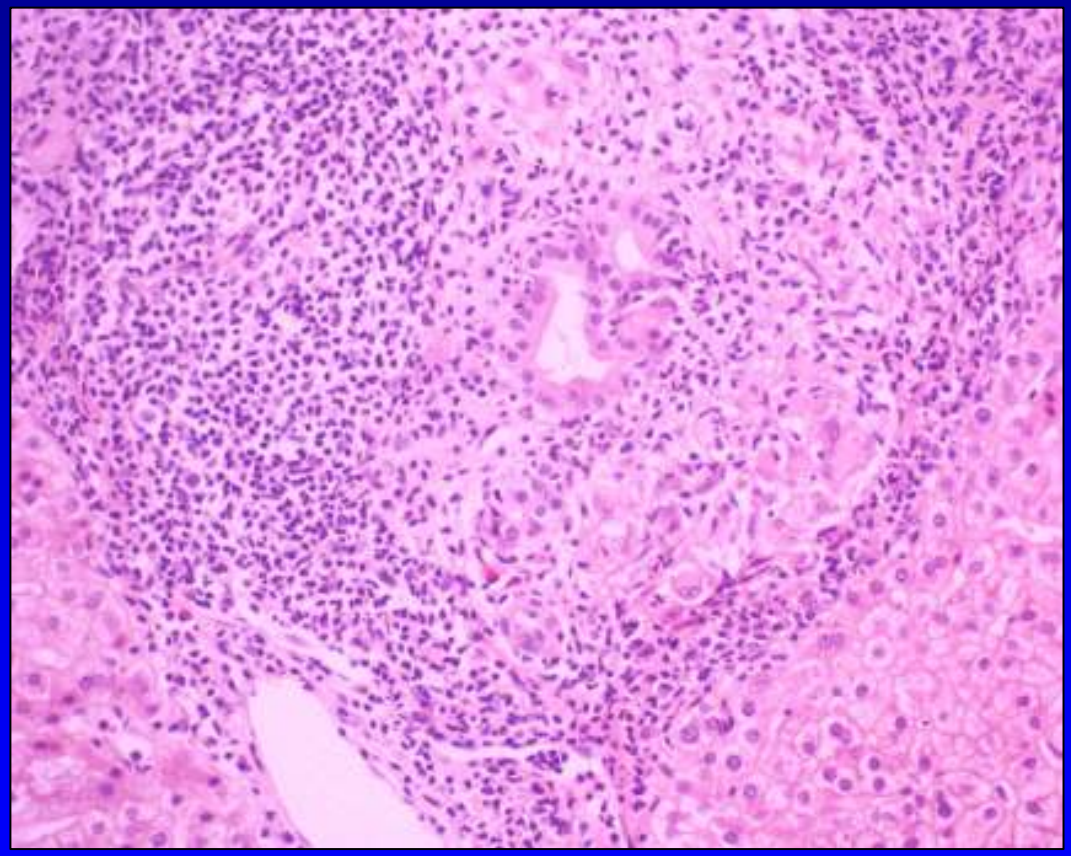
Assassi S et al. J Rheumatol. 2009;36:2250-6.

Primary biliary cirrhosis
Morphology

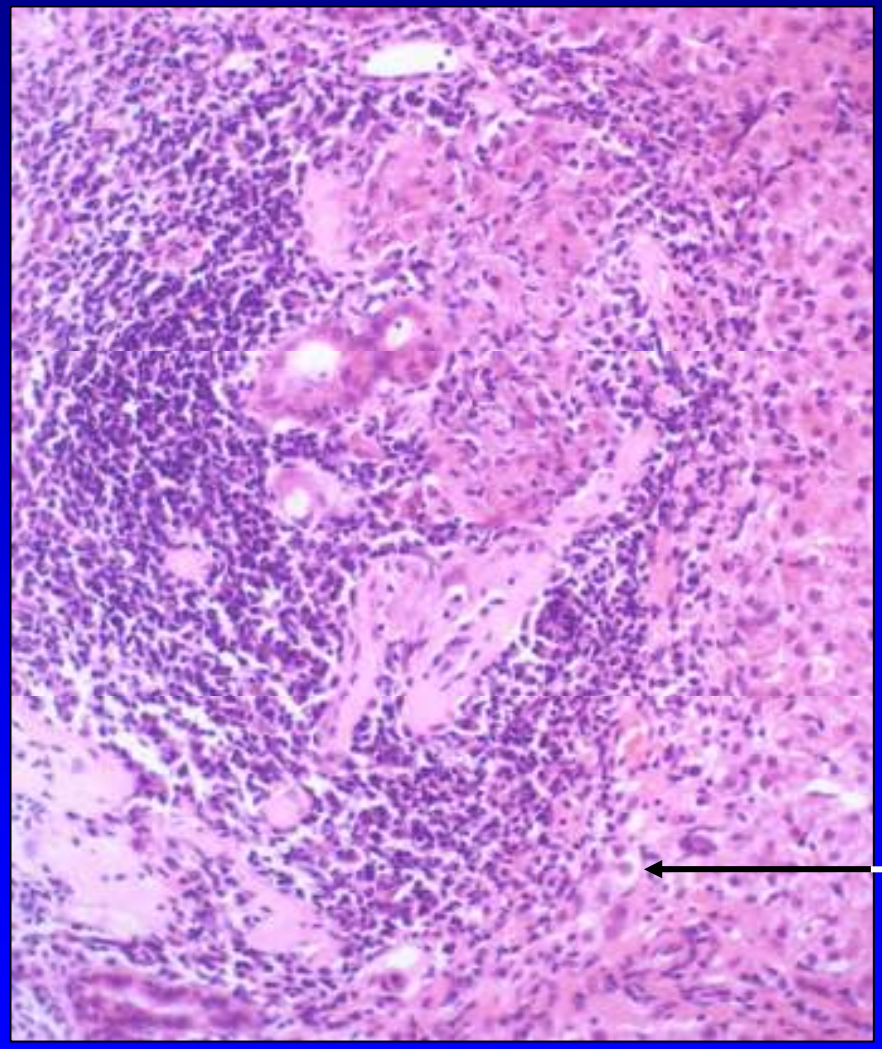
- Non-suppurative destructive ± granulomatous cholangitis
- Interlobular bile ducts 40–80 μm

the smaller are the first to disappear



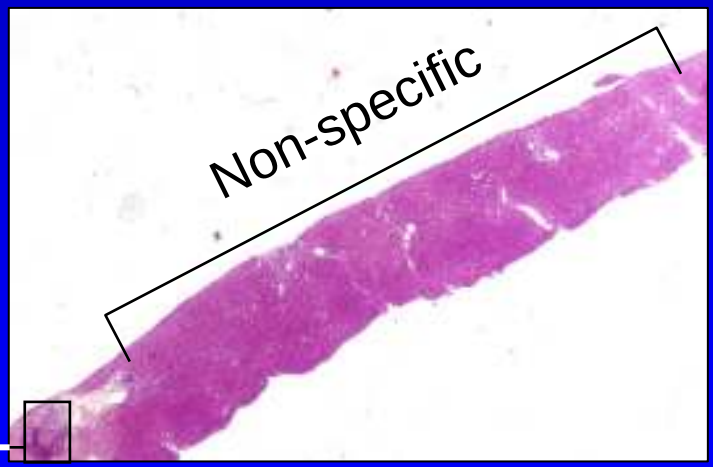


Primary biliary cirrhosis : stage 1-2

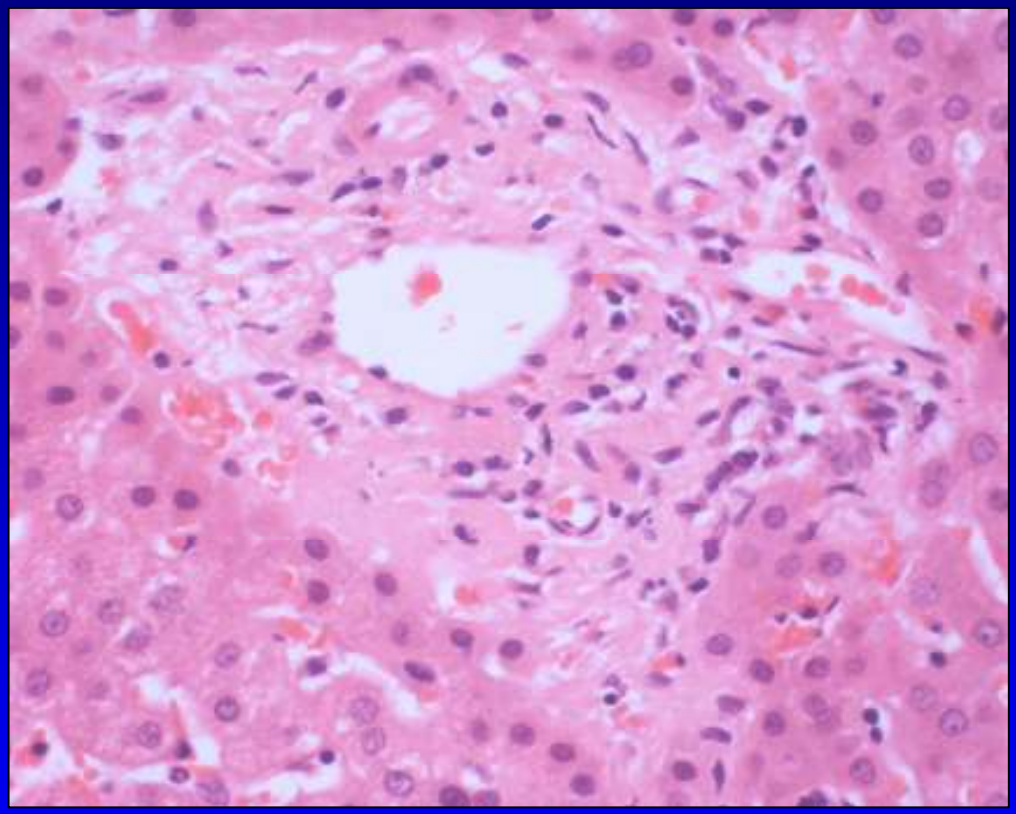


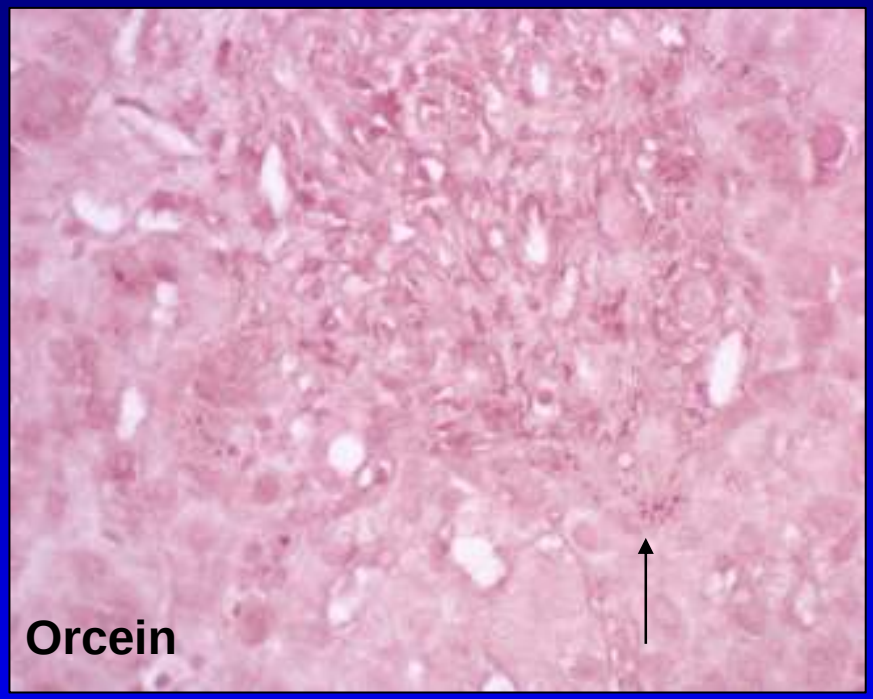
2 important points

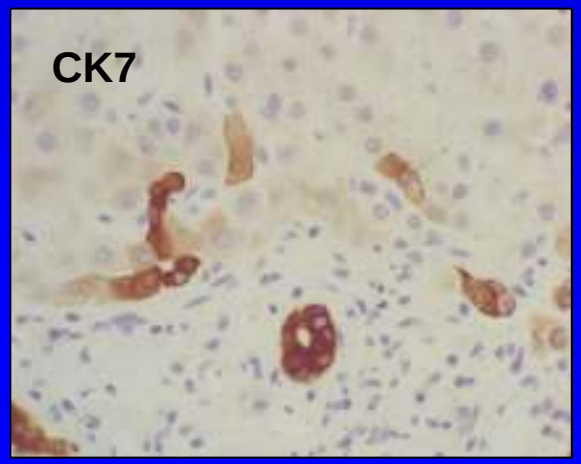
- Heterogenous distribution
- No cholestasis



Primary biliary cirrhosis: early portal changes

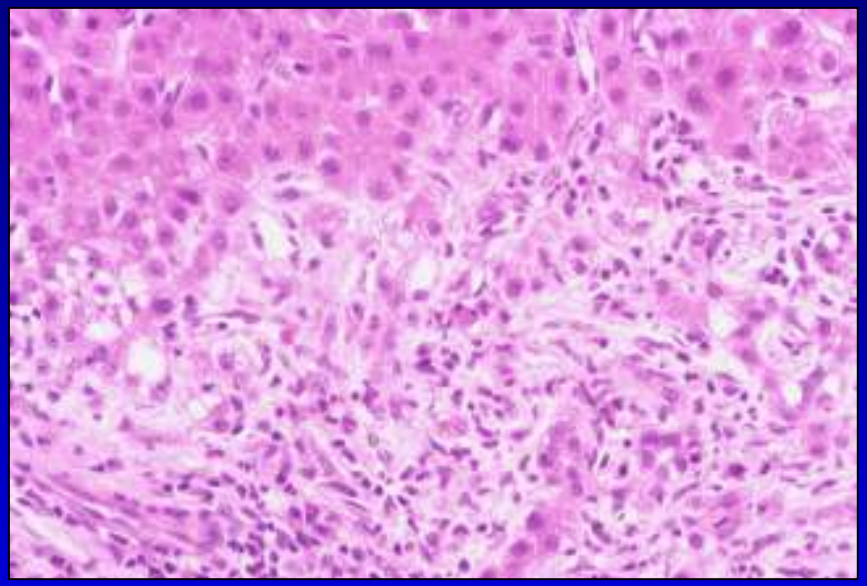


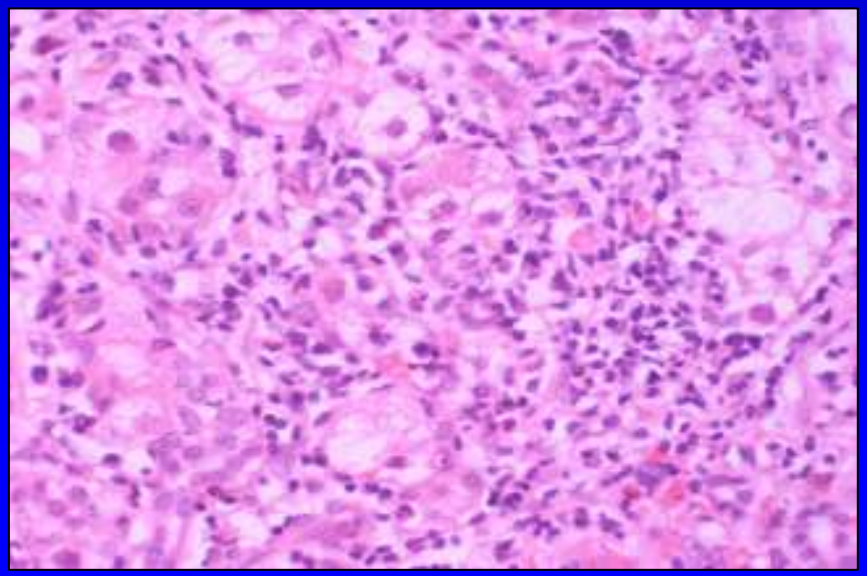




- Portal tract oedema
- Subtle ductular reaction (CK7)
- Light inflammation

Interface activity





Biliary (cholate-static)

PBC / PSC stage 2 to 4

⇒ Interference with bile flow (bile salt toxicity)

⇒ Ursodeoxycholic acid

Hepatitic (lympho-plasmacytic)

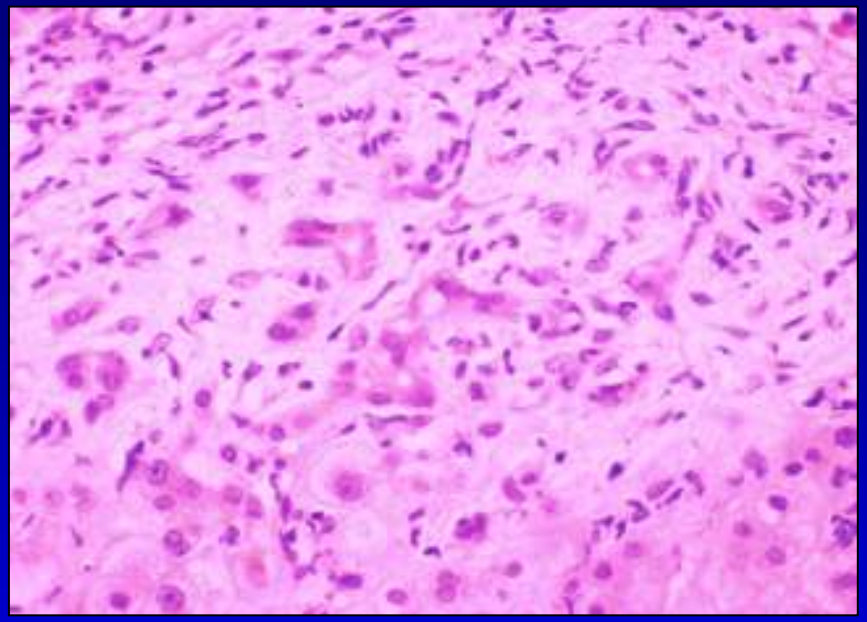
Autoimmune hepatitis

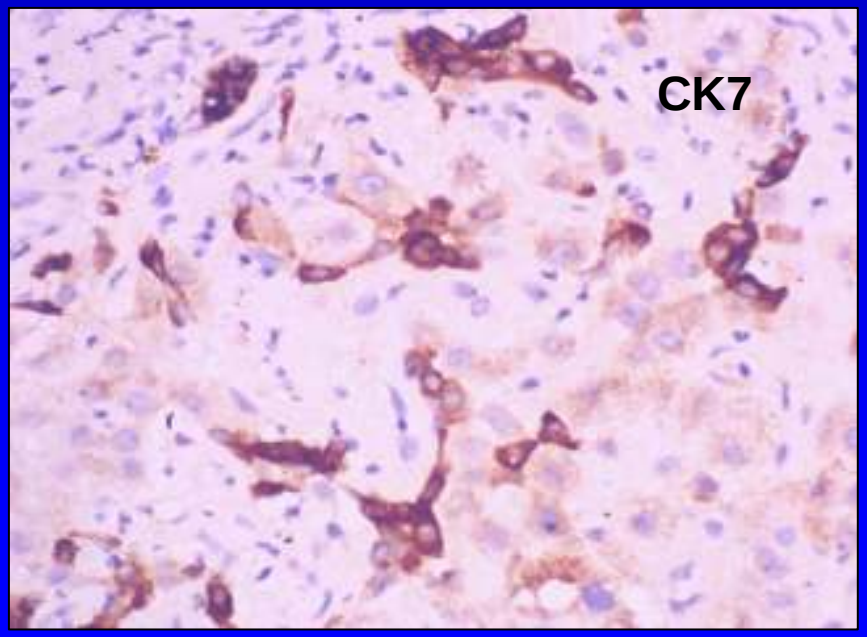
PBC / PSC stage 2

⇒ Immune-mediated injury

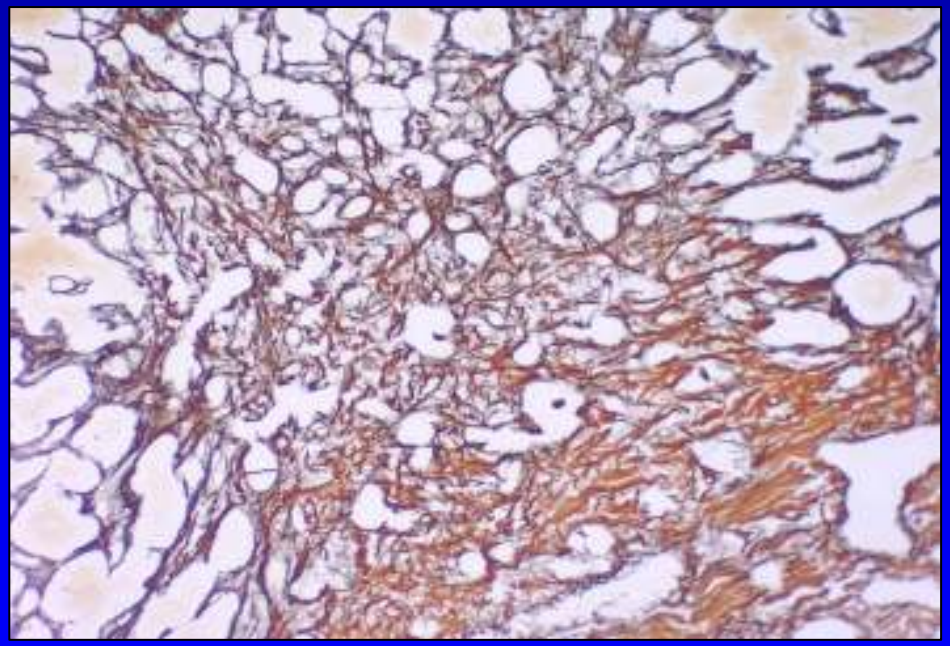
⇒ ? steroid responsive

Ductular reaction



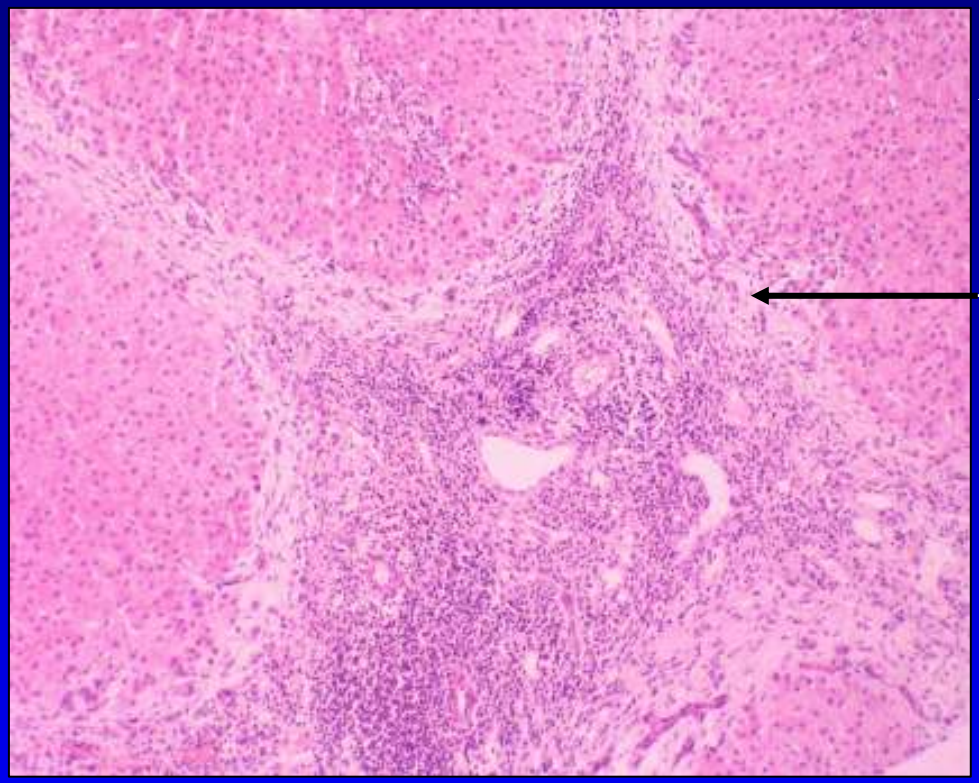


- **Role incompletely understood**
  - **? By-pass mechanism for bile drainage**
  - **? Re-absorption of bile acids**
  - **⇨ Basement membrane ⇨ fibroplasia**



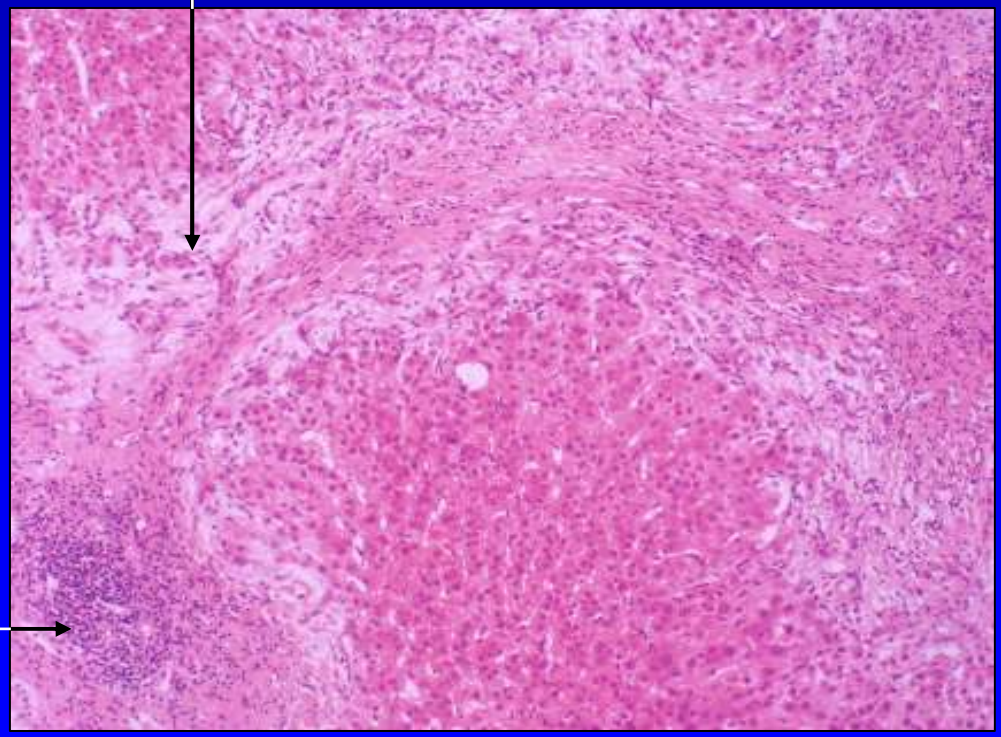
← Shift from hepatocellular to biliary phenotype demonstrated by CK7 immunostaining

Primary biliary cirrhosis : progression



Portal tract expansion + radiating septa
+ absence of bile duct (ductopenia)

Biliary interface activity with ‘halo’

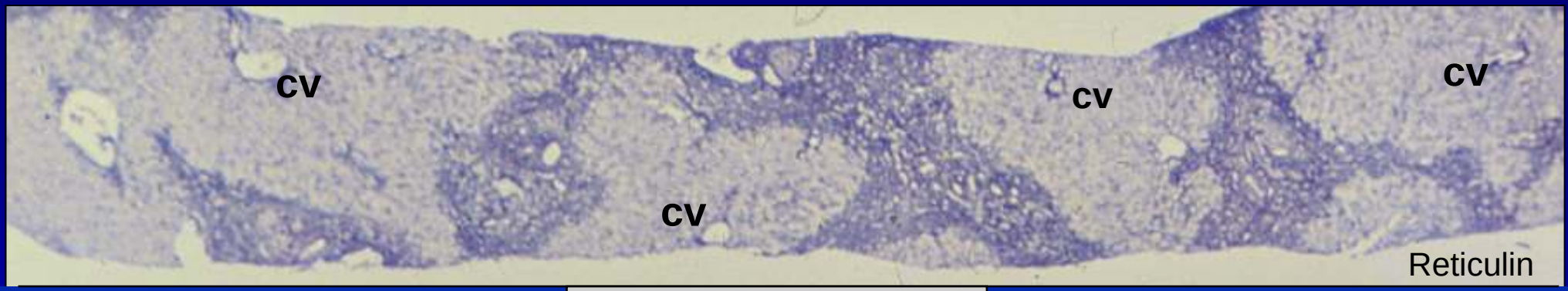


Development of porto-portal
bridging fibrous septa

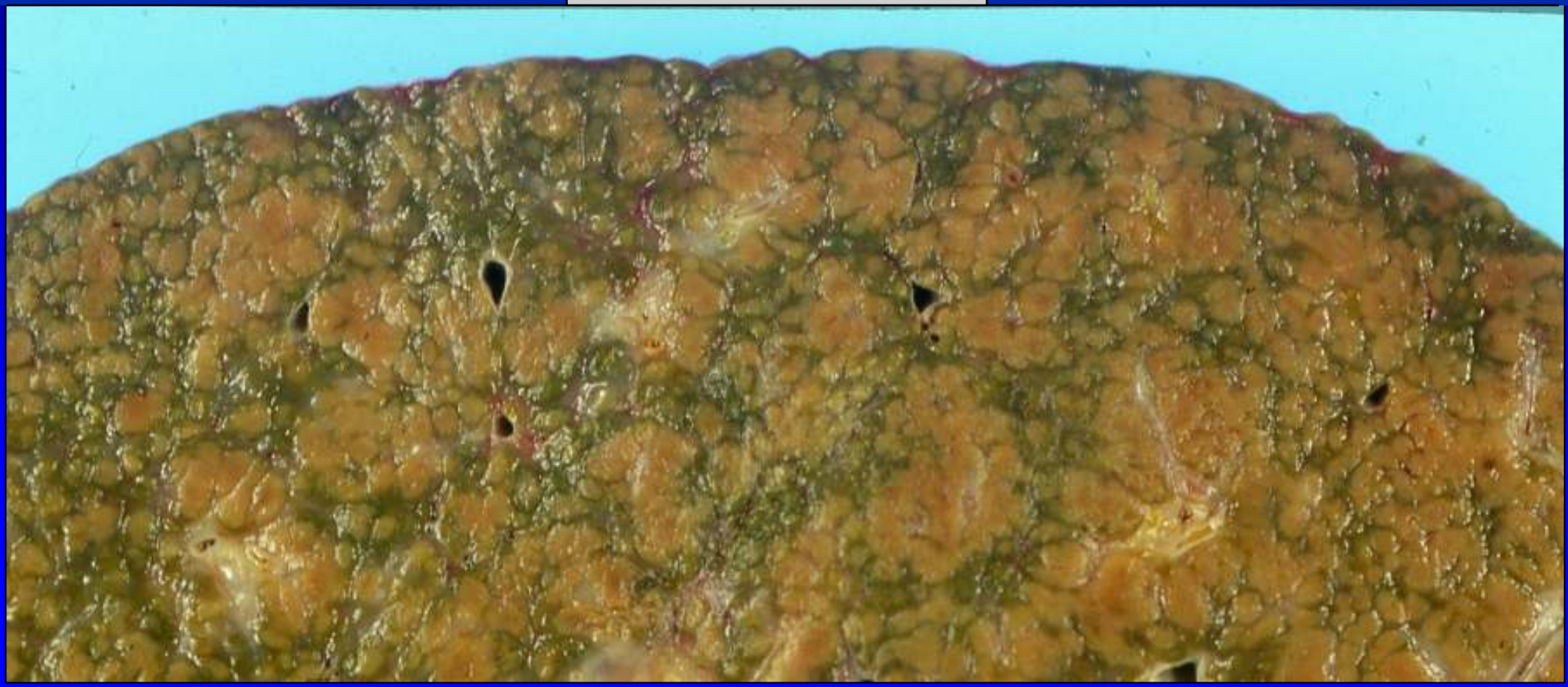
Site previously
occupied by bile duct

Biliary cirrhosis (Stage 4)

- Portal-portal fibrosis with + / - preserved hepatic venules
- Biliary interface (halo)
- Ductopenia



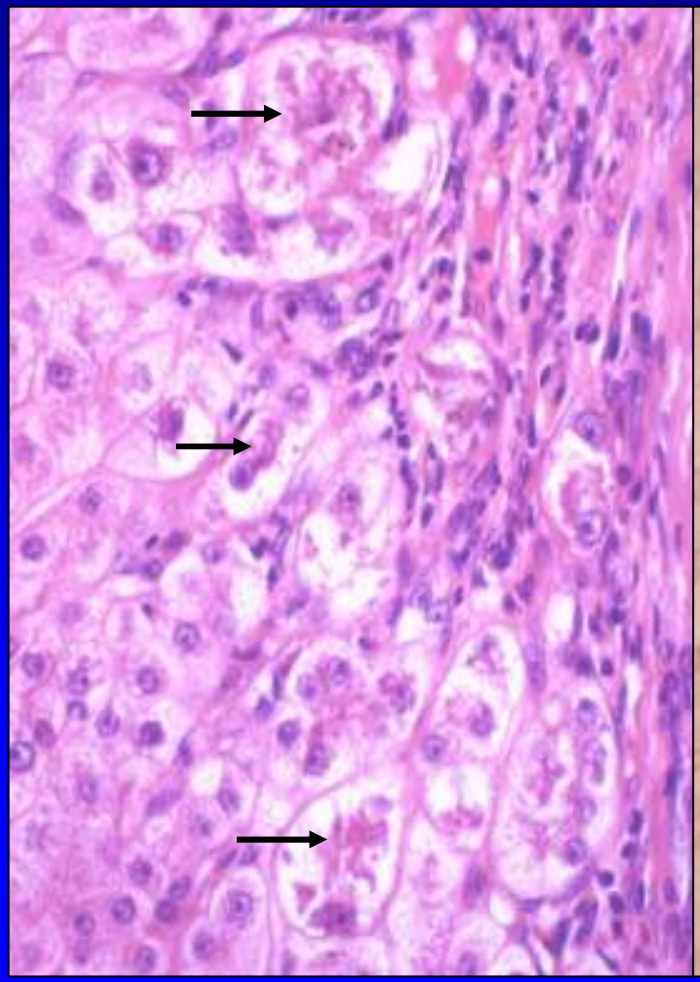
Biliary cirrhosis



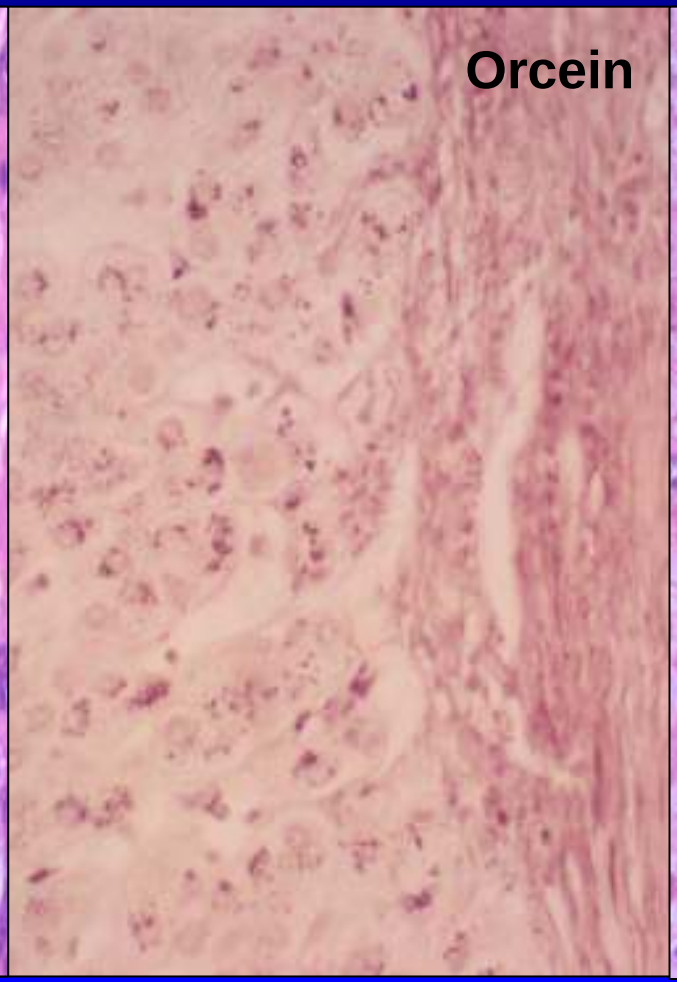
PBC : late interface changes

Cholate stasis

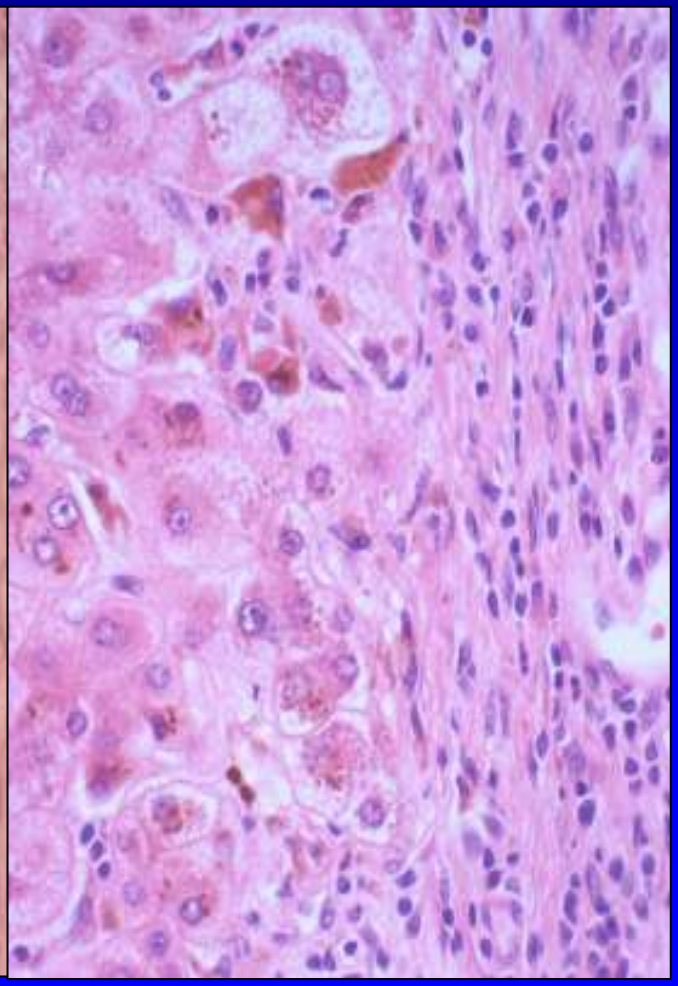
(Mallory bodies ⟶)



Cu-ass granules



Cholestasis



Primary biliary cirrhosis

Progressive fibrosis - Staging

- Stage 1 Inflammation / fibrosis confined to portal tract
- Stage 2 Inter*f*ace activity / short radiating spurs
- Stage 3 Bridging septa (mainly porto-portal)
- Stage 4 Cirrhosis

Proposal of a new histological staging / grading system

- **System using in addition to fibrosis : bile duct loss, orcein positive granules, chronic cholangitis, interface hepatitis and lobular hepatitis**

Hiramatsu K et al Histopathology. 2006 ;49:466-78

Primary biliary cirrhosis
Key points in interpreting needle biopsy

- Exclusion of PBC should be avoided on a needle biopsy specimen
- Histological cholestasis is absent for the largest part of the clinical course
- Staging may have a prognostic value, but is subject to sampling variation (use of additional criteria)
- Interface activity may focally mimic that seen in AIH, a finding not necessarily associated with clinical PBC–AIH overlap

Primary biliary cirrhosis
Variants

1. *AMA negative PBC (autoimmune cholangitis)*

- 'Immunocholangitis' = term used in early studies to described patients with features of PBC but AMA negative and generally high titre of ANA
- High-titre ANA positivity more frequent in AMA-negative than AMA-positive PBC cases in one study

In both instances ANA = PBC-specific ANA
sp100 and / or gp210

⇨ General view is that autoimmune cholangitis is synonymous with AMA-negative PBC and does progress as PBC

Primary biliary cirrhosis
Variants

2. AIH / PBC overlap syndrome

= Association of PBC and AIH in a single patient, either simultaneously or consecutively

Diagnostic criteria

- **Presence in an individual patient of at least 2 out of 3 accepted features**
  for PBC : +ve AMA, florid bile-duct lesion on histology or raised alk phos x5
  for AIH : raised ALT levels x 5, IgG levels x 2 or a +ve ASMA + moderate/severe lymphocytic interface activity

Chazouillères O et al. J Hepatol 2006;44:400-6

PBC–AIH overlap syndrome
Diagnostic criteria

- Incidence varies at the grace of broader or narrower definitions ⇨ Number of cases inversely proportional to expertise of the centre!

- Long-term follow-up with repeat histological examinations may considerably reduce the number of cases initially considered as AIH–PBC overlap

Suzuki Y et al. J Gastroenterol Hepatol. 2004;19:699

AIH / PBC overlap syndrome

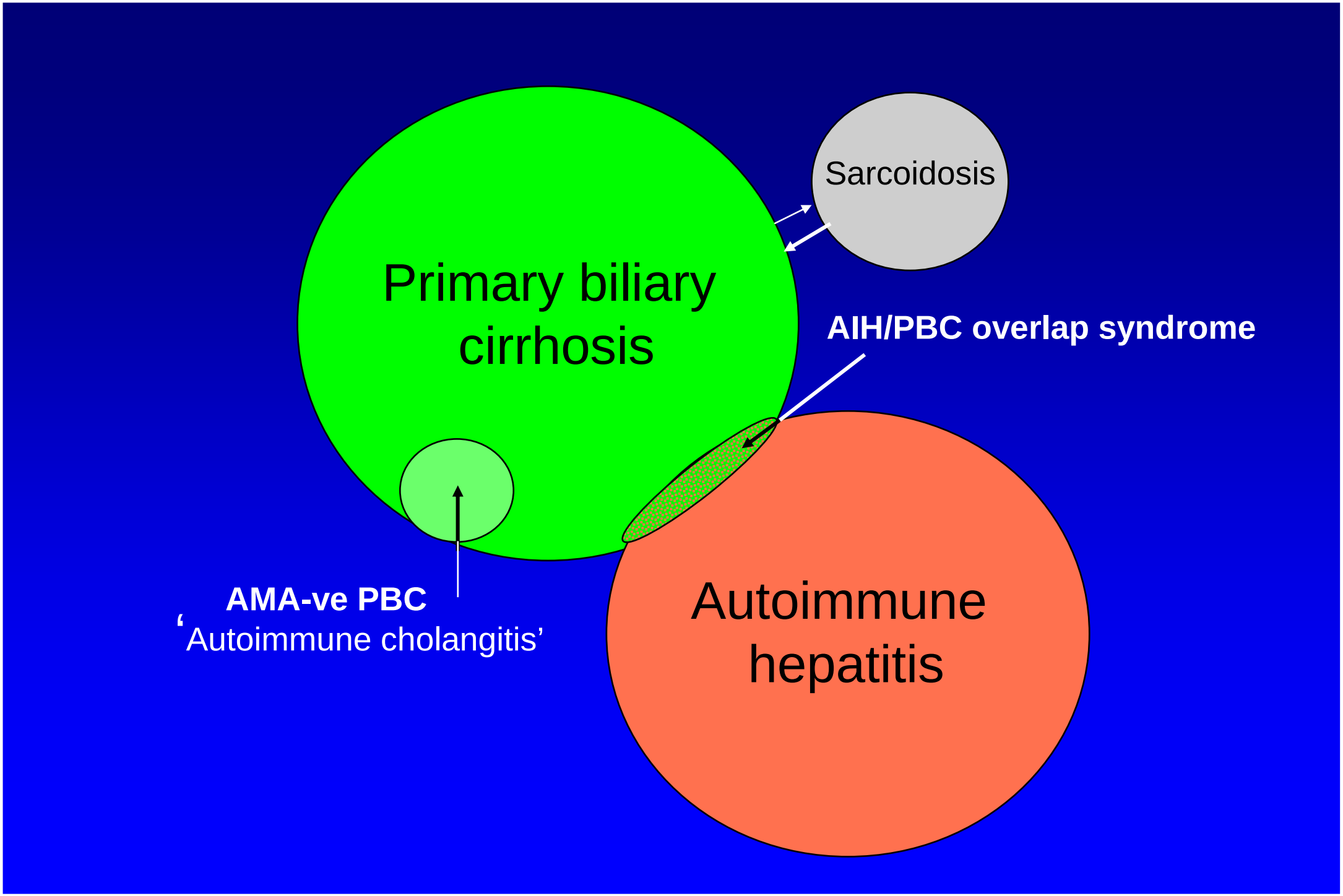
Documented

- Consecutive occurrence of PBC-AIH
- Flare-up of AIH, either spontaneously or during treatment with UDCA
- Clinicopathological features of AIH after transplantation for PBC

→ Steroids +/- Azathoprine

- Classical AIH evolving into a typical PBC → UDCA

- In view of imprecise definition and small number of cases → therapy control trials not possible – beneficial effect to be assessed on individual basis


Sarcoidosis
Primary biliary cirrhosis
AIH/PBC overlap syndrome
AMA-ve PBC
‘Autoimmune cholangitis’
Autoimmune hepatitis

Primary biliary cirrhosis
Differential diagnosis

- Liver involvement in sarcoidosis may mimic PBC
  (AMA –ve, ACE+ve, extrahepatic manifestations)
  but sarcoidosis and PBC may coexist
- Drug induced injury – PBC-like
  but drug may also trigger a true PBC
- PSC, small duct disease (associated UC)
- MDR3 deficiency – late presentation

Primary biliary cirrhosis and variants

Clue to pathological diagnosis

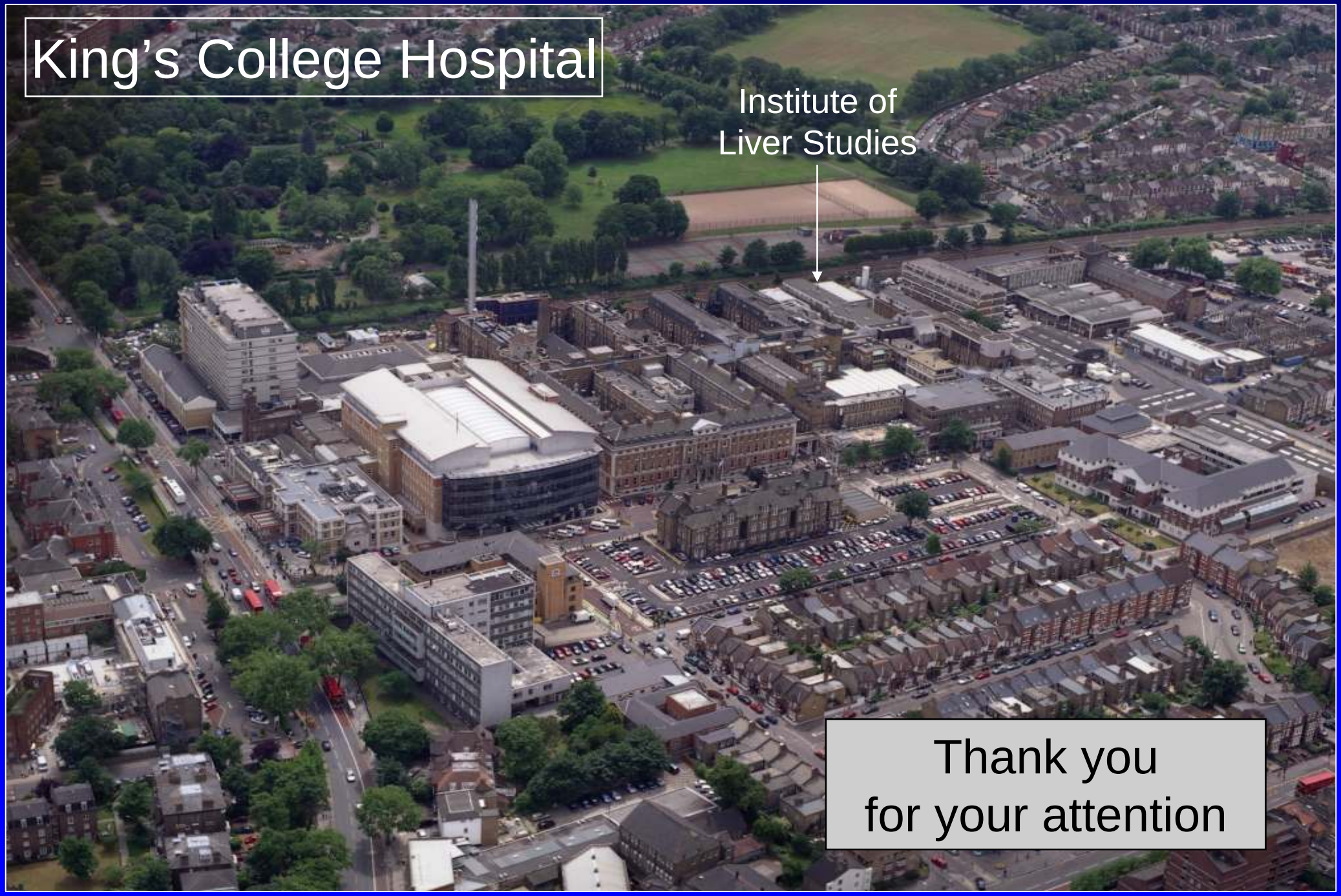
- Be familiar with clinical features

  Evaluation of histological findings in conjunction with clinical / laboratory data (↑ alk phos, γGT, IgM, AMA, ANA)

- Awareness of histology pitfalls
  - **Lack of sampling of characteristic bile duct lesion**
  - **Overlapping features (autoimmune hepatitis)**
  - **Absence of cholestasis until late**

- Recognition of subtle biliary features

  (precholestatic changes / orcein-Cu)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Thank you
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