Primary biliary cirrhosis and its variant

Prof Bernard Portmann
Institute of Liver Studies
King’s College Hospital - London
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, $\gamma$GT, $\pm$ bilirubin, $\uparrow$ 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
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

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

**Hepatitis (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)
- Development of porto-portal bridging fibrous septa
- Site previously occupied by bile duct
- Biliary interface activity with ‘halo’
Biliary cirrhosis (Stage 4)

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

Biliary cirrhosis

[Image of liver tissue with reticulin staining]
PBC: late interface changes

Cholate stasis
(Mallory bodies →)

Cu-ass granules

Cholestasis

Orcein
Primary biliary cirrhosis

*Progressive fibrosis - Staging*

- Stage 1  Inflammation / fibrosis confined to portal tract
- Stage 2  Interface 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
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.
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
     - General view is that autoimmune cholangitis is synonymous with AMA-negative PBC and does progress as PBC
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

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
- 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
Primary biliary cirrhosis

Sarcoidosis

AIH/PBC overlap syndrome

Autoimmune hepatitis

AMA-ve PBC
‘Autoimmune cholangitis’
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 \( \uparrow \) alk phos, \( \gamma \)GT, 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)
Thank you for your attention.

Institute of Liver Studies

King’s College Hospital