PBC /PSC/AIH overlapping syndromes

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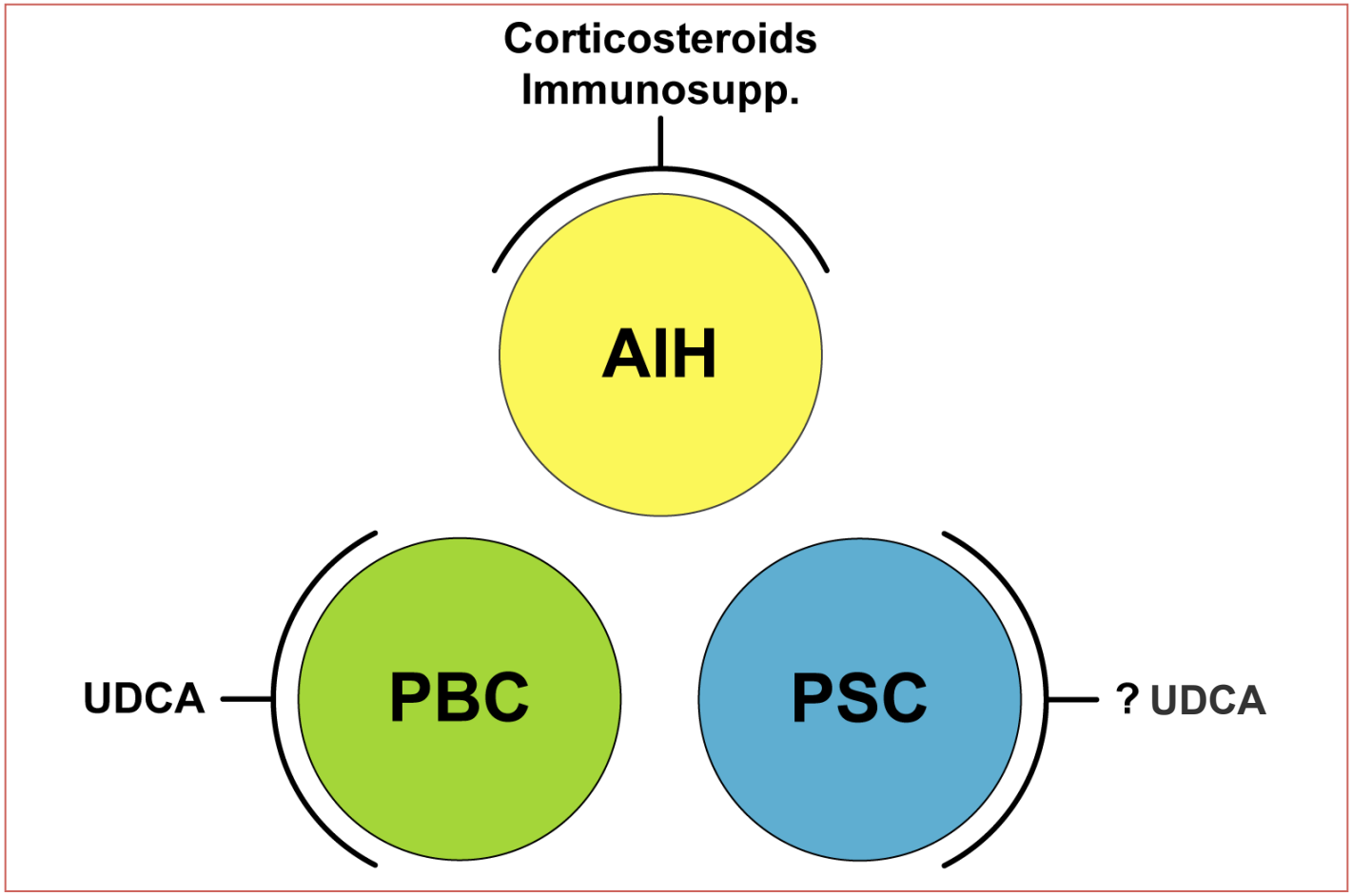
Variants and overlapping syndromes

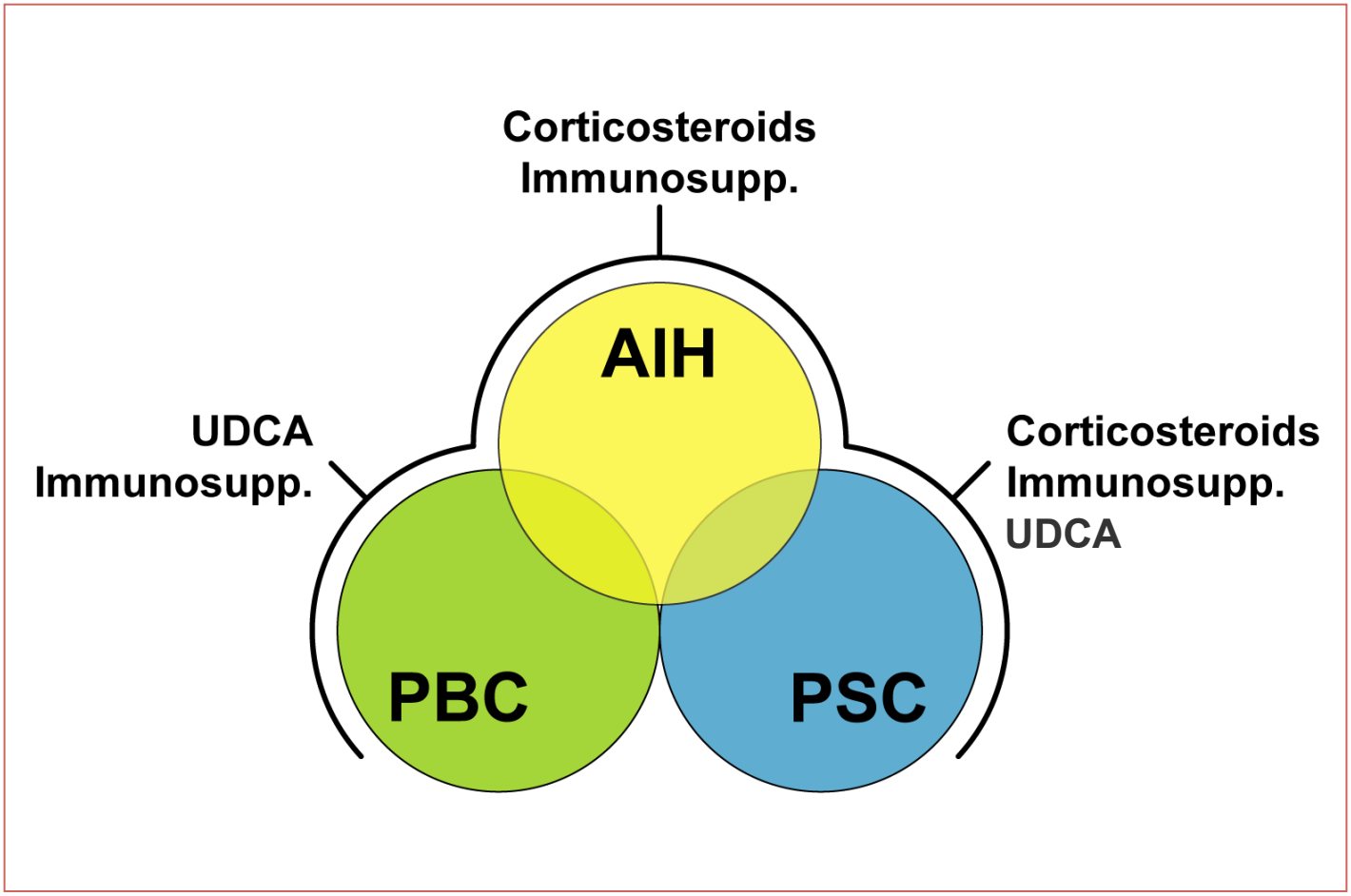
The case of AIH

- AIH with:
  - mitochondrial Ab
  - biochemical cholestasis
  - bileduct injury
- AIH without:
  - autoantibodies or elevated IgG
  - ALT > 5N
  - response to therapy

Autoimmune liver diseases: Definition

- Liver inflammation
- Immune abnormalities:
  - Non-organ non-species autoantibodies
  - Hyperglobulinemia (IgG, IgM)
- Unknown cause


Corticosteroids
Immunosupp.
AIH
UDCA
PBC
PSC
? UDCA


Corticosteroids
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Autoimmune hepatitis: Diagnosis criteria (in practice)

- Elevated ALT or AST
  - fluctuating with spontaneous periods of remission
  - with or without fulminant and/or subacute liver failure
- No other cause of liver disease (except for PBC and PSC)
- Moderate to severe interface hepatitis
- Hyperglobulinemia (IgG > 20 g/L)
  and /or anti SMA, antiactine Ab.
- Response to corticosteroids
  and/or other immunosuppressive drugs
  (Azt, Mycophenolate, Ciclosporine, …)

Diagnosis of PBC

- Cholestasis
- M2 antibodies (AMA)
- Lymphocytic destructive cholangitis

PBC–AIH overlap syndrome

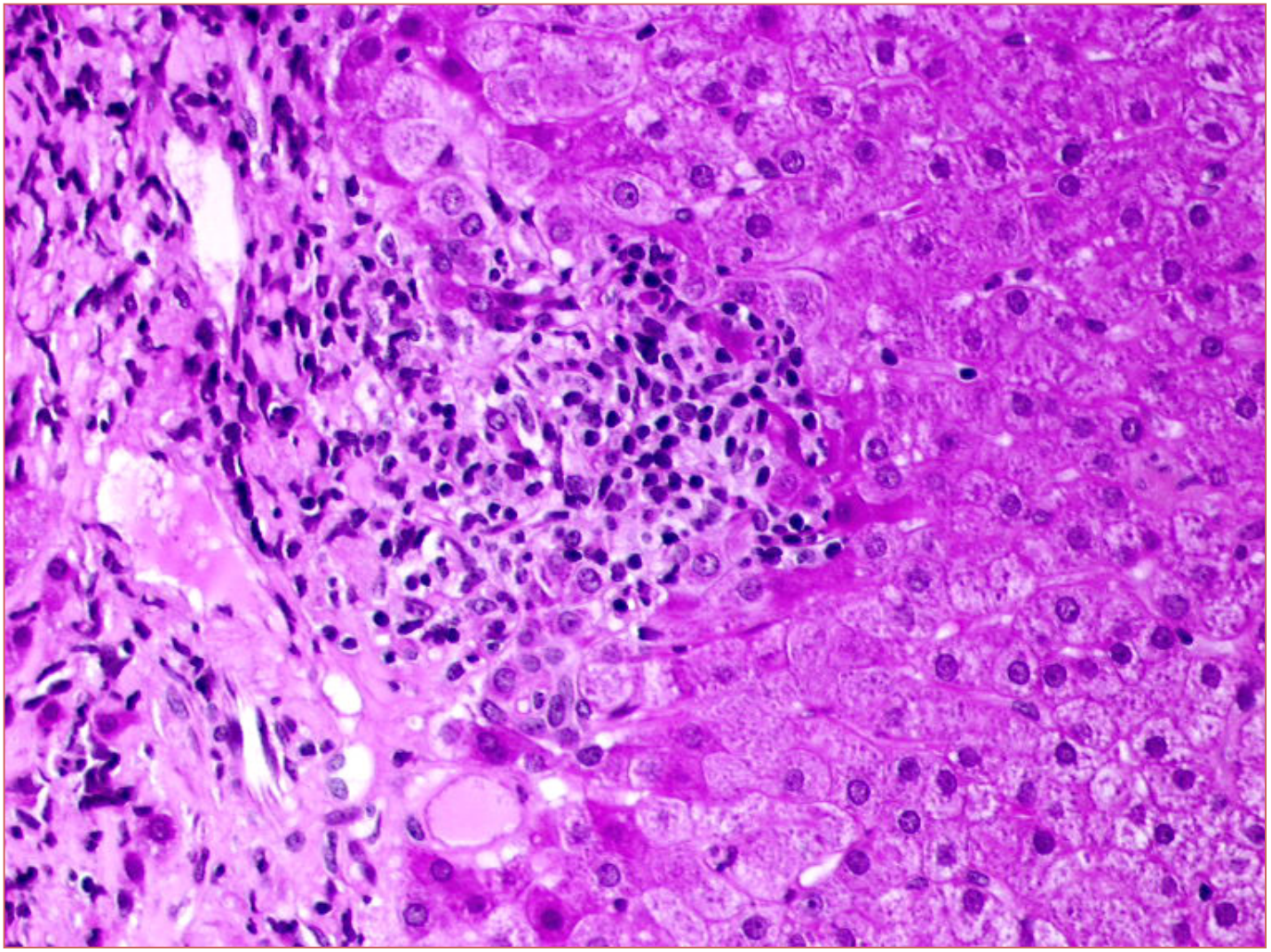
- ***Criteria: association of both diseases***

PBC:

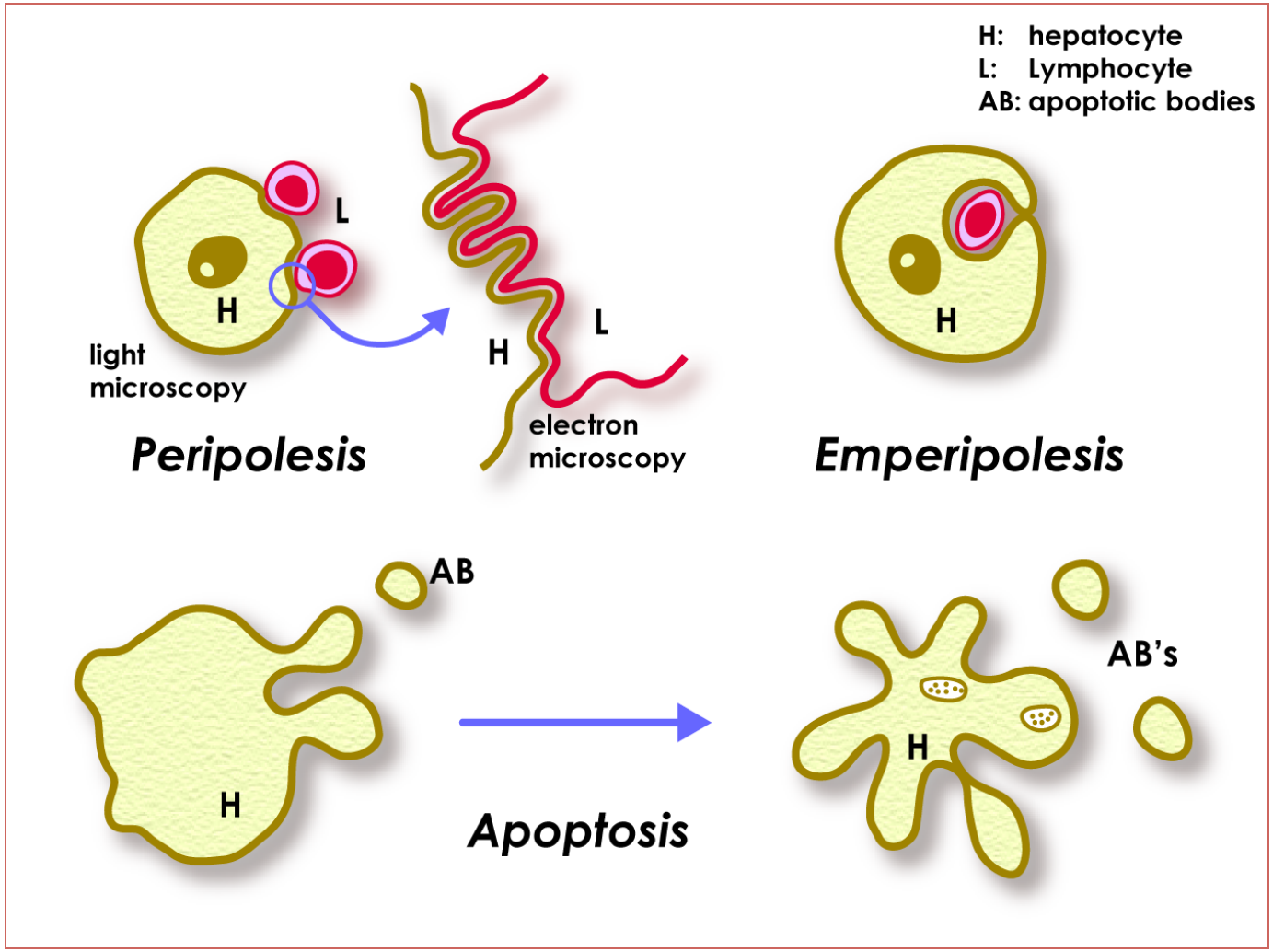
- ***Cholestasis***
- ***M2 antibodies***
- ***Lymphocytic cholangitis***

AIH:

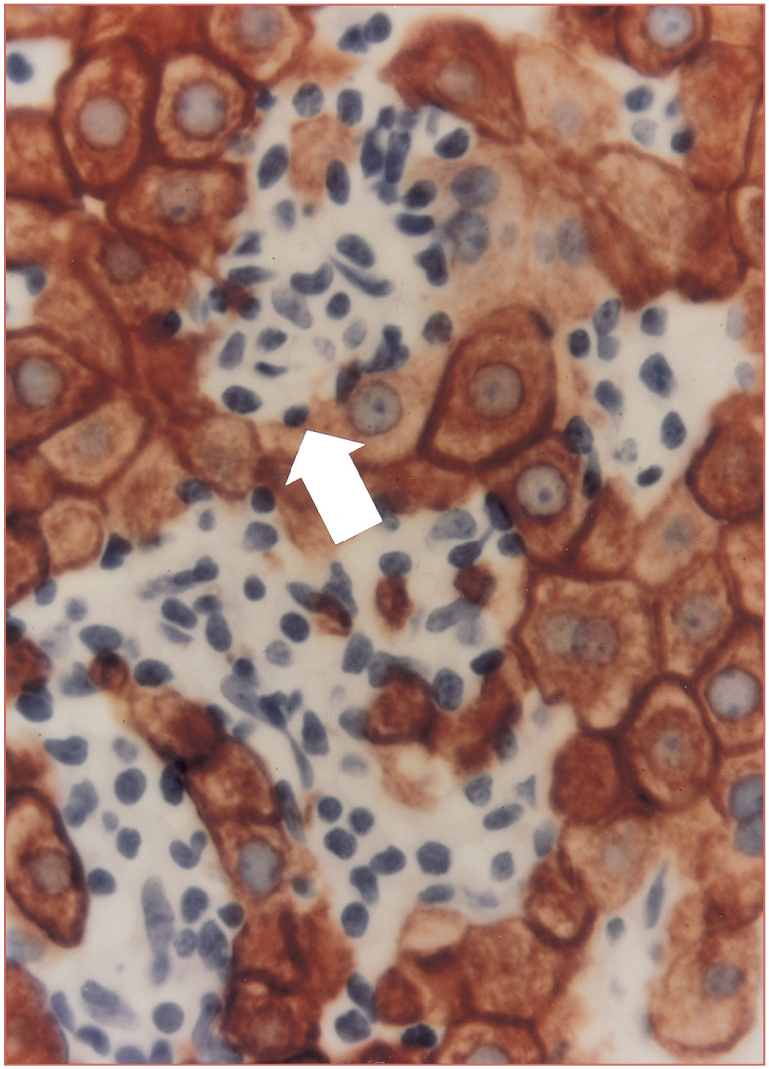
- ***ALT > 5N***
- ***IgG > 20 g/L or SMA (anti-actin antibodies)***
- ***Interface hepatitis***

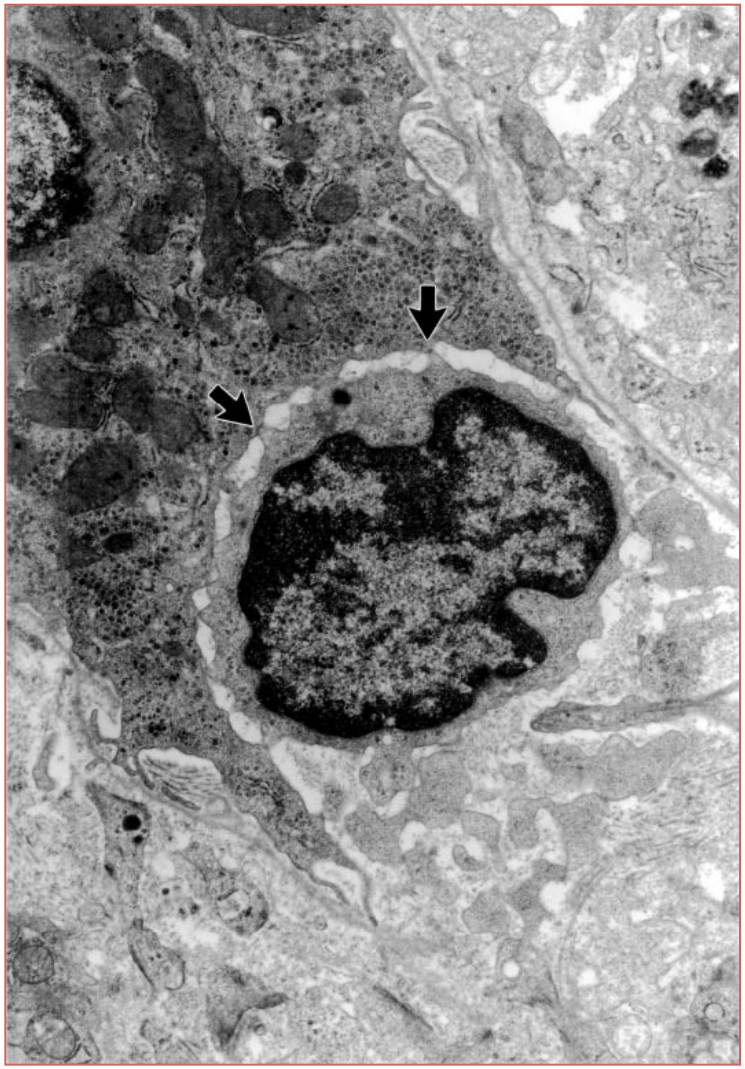


Key features of piecemeal necrosis



adapted from Bianchi L. et al. 1988





Wang et al. Exp Mol Pathol 2001

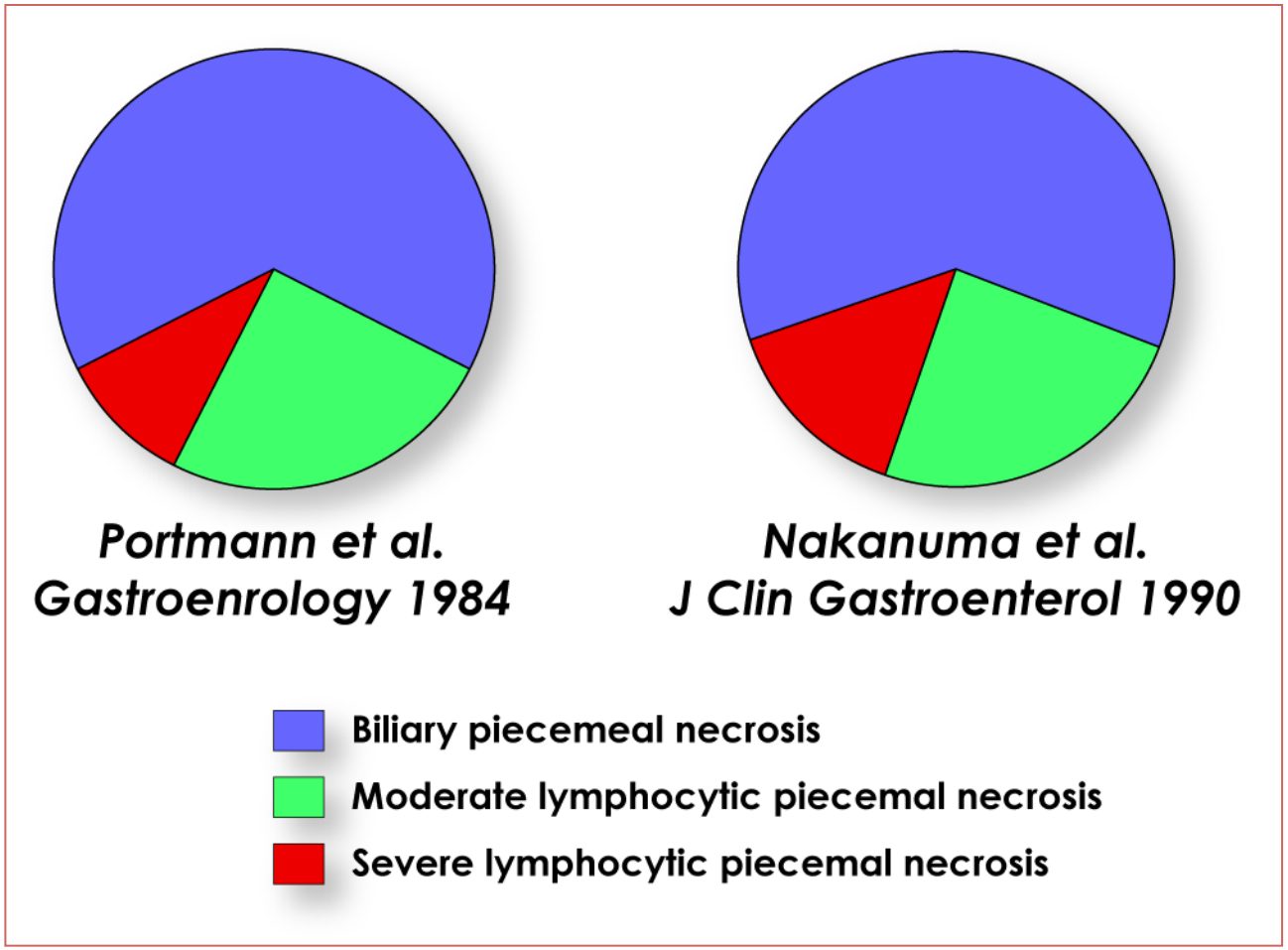
Grading severity of PMN

- Minimal:
  - Not present in all portal tracts (PT)
  - Patchy distribution
- Moderate:
  - Present and restricted at the periphery of at least half of the PT
- Severe:
  - Necrosis surrounding more than half of the circumference of the majority of PT and along fibrous septa

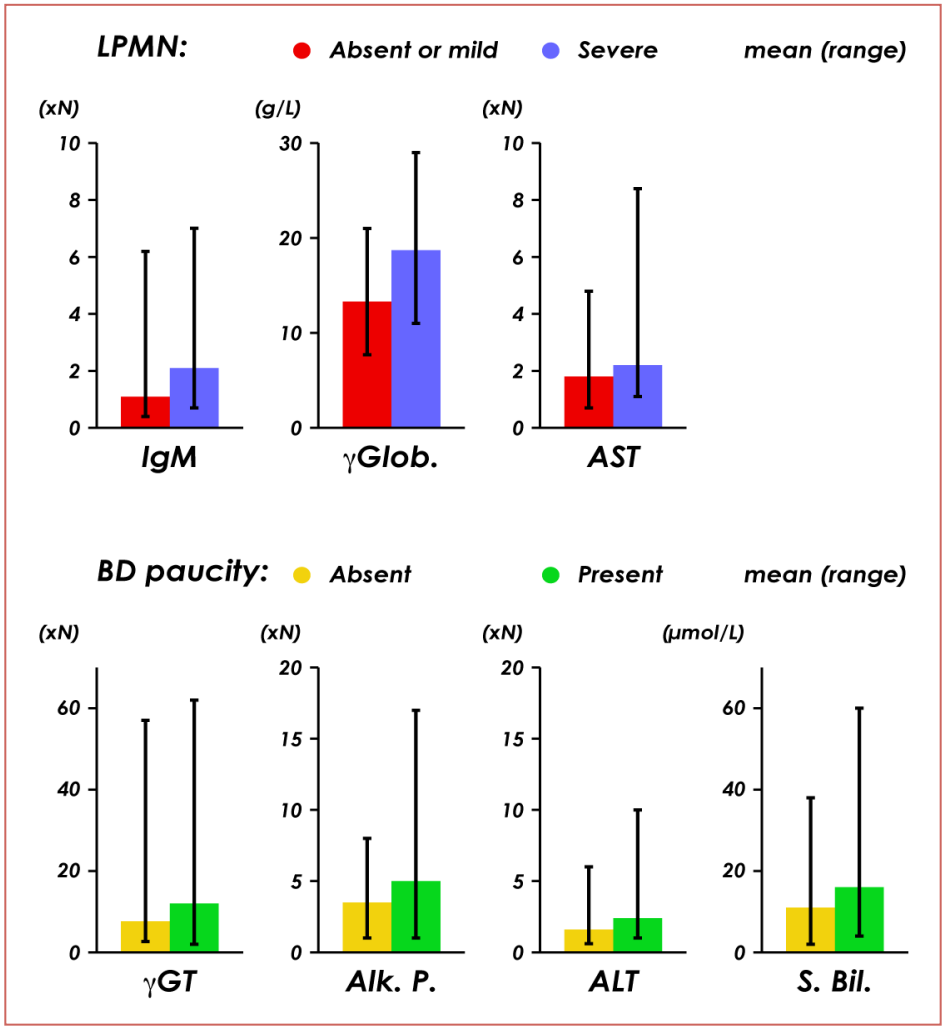
Prevalence and severity of elementary liver lesions in PBC

- Fibrosis
  - numerous septa, cirrhosis 56%
- ILBD paucity (>50%) 68%
- Destructive cholangitis 45%
- Mononuclear portal inflammation
  - moderate 50%
  - severe 12%
- Portal epithelioid granulomas 15%
- Ductular proliferation
  - absent or mild 42%
- Lymphocytic piecemeal necrosis
  - absent or mild 49%
  - moderate 38%
  - severe 13%
- Lobular mononuclear inflammation
  - moderate 12%
  - severe 3%
- Lobular hepatocellular necrosis
  - moderate 14%
  - severe 4%

Prevalence of lymphocytic and biliary piecemeal necrosis



Biochemistries according to severity of BDpaucity and lymphocytic PMN



Poupon et al. J Hepatol 1999

PBC-AIH Overlap Syndrome Clinical Presentation

- Simultaneous forms (PBC + AIH at presentation)
- Consecutive forms (PBC → AIH + PBC)

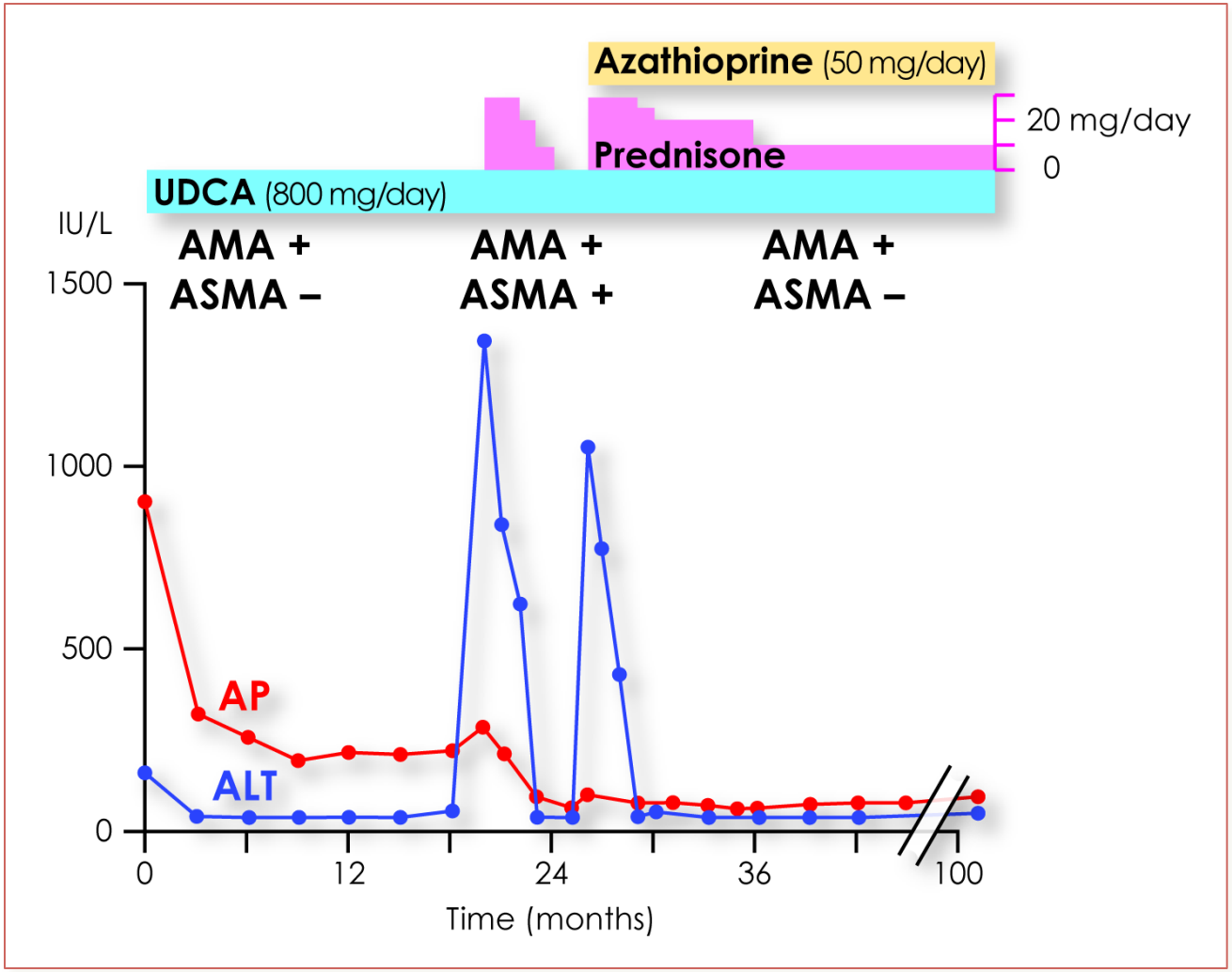
Characteristics of simultaneous overlap syndrome, at the time of diagnosis of PBC

		PBH and AIH simultaneously (n = 22)	*PBC without AIH (n = 78)*
Age	*Yr mean (range)*	*43 (21 – 71)*	*53 (23 – 72)*
S. Bilirubin	*µmol/l*	*25 (8 – 170)*	*19 (5 – 87)*
Alk. Phosphatase	*ULN*	*3.2 (0.8 – 21)*	*4.0 (0.6 – 21)*
ALAT	*ULN*	*5.8 (3.1 – 16)*	*2.7 (0.5 – 12)*
IgG	*ULN*	*1.6 (0.9 – 2.5)*	*1.2 (0.6 – 1.4)*
AMA	*> 1/80*	*95 %*	*95 %*
ANA	*> 1/80*	*77 %*	*67 %*
ASMA	*> 1/80*	*68 %*	*17 %*
Fibrosis	*Numerous septa or cirrhosis*	*41 %*	*29 %*
Interlobular bile duct lesions	*Cholangitis*	*82 %*	*78 %*
Lymph. PMN	*moderate*	*46 %*	*18 %*
	severe	*45 %*	*4 %*

Characteristics of consecutive overlap syndrome PBC→AIH, at the time of diagnosis of PBC

		PBH and AIH consecutively (n = 12)	*PBC without AIH (n = 78)*
Age	*Yr mean (range)*	*46 (23 – 65)*	*53 (23 – 72)*
S. Bilirubin	*µmol/l*	*14 (7 – 23)*	*19 (5 – 87)*
Alk. Phosphatase	*ULN*	*2.6 (1.9 – 6.1)*	*4.0 (0.6 – 21)*
ALAT	*ULN*	*2.1 (1.1 – 3.7)*	*2.7 (0.5 – 12)*
IgG	*ULN*	*1.2 (0.9 – 1.8)*	*1.2 (0.6 – 1.4)*
AMA	*> 1/80*	*100 %*	*95 %*
ANA	*> 1/80*	*67 %*	*67 %*
ASMA	*> 1/80*	*25 %*	*17 %*
Fibrosis	*Numerous septa or cirrhosis*	*34 %*	*29 %*
Interlobular bile duct lesions	*Cholangitis*	*75 %*	*78 %*
Lymph. PMN	*moderate*	*17 %*	*18 %*
	severe	*25 %*	*4 %*

Consecutive form of overlap syndrome Time course of events



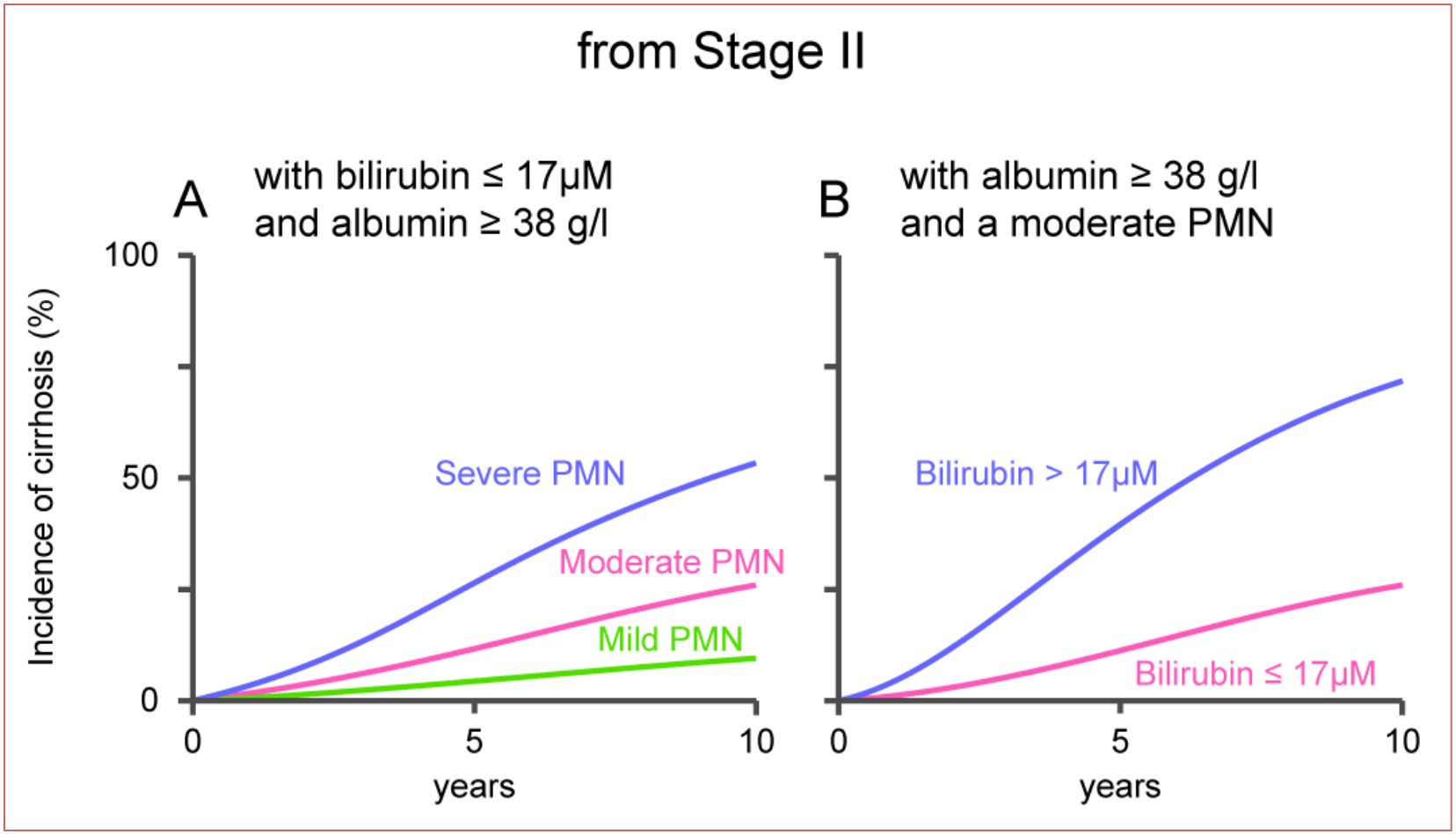
Relationships between fibrosis and other elementary histological lesions

Elementary lesions	Fibrosis 0	1	2	3	P*
Interlobular bile duct lesions					
Biliary cell necrosis	0.50†	0.58	0.54	0.33	NS
Paucity (prevalence)	0.38	0.54	0.80	0.83	0.002
Ductular proliferation	0	0.66	1.03	1.60	0.002
Lymphocytic piecemeal necrosis	0.25	0.71	1.40	1.30	0.002
Mononuclear portal and periportal inflammation	1.50	1.80	0.79	0.70	0.002

*P values for the Jonckheere-Terpstra test
†For each lesion, the mean value in the scoring system was calculated

Degott et al. Hepatology 1999

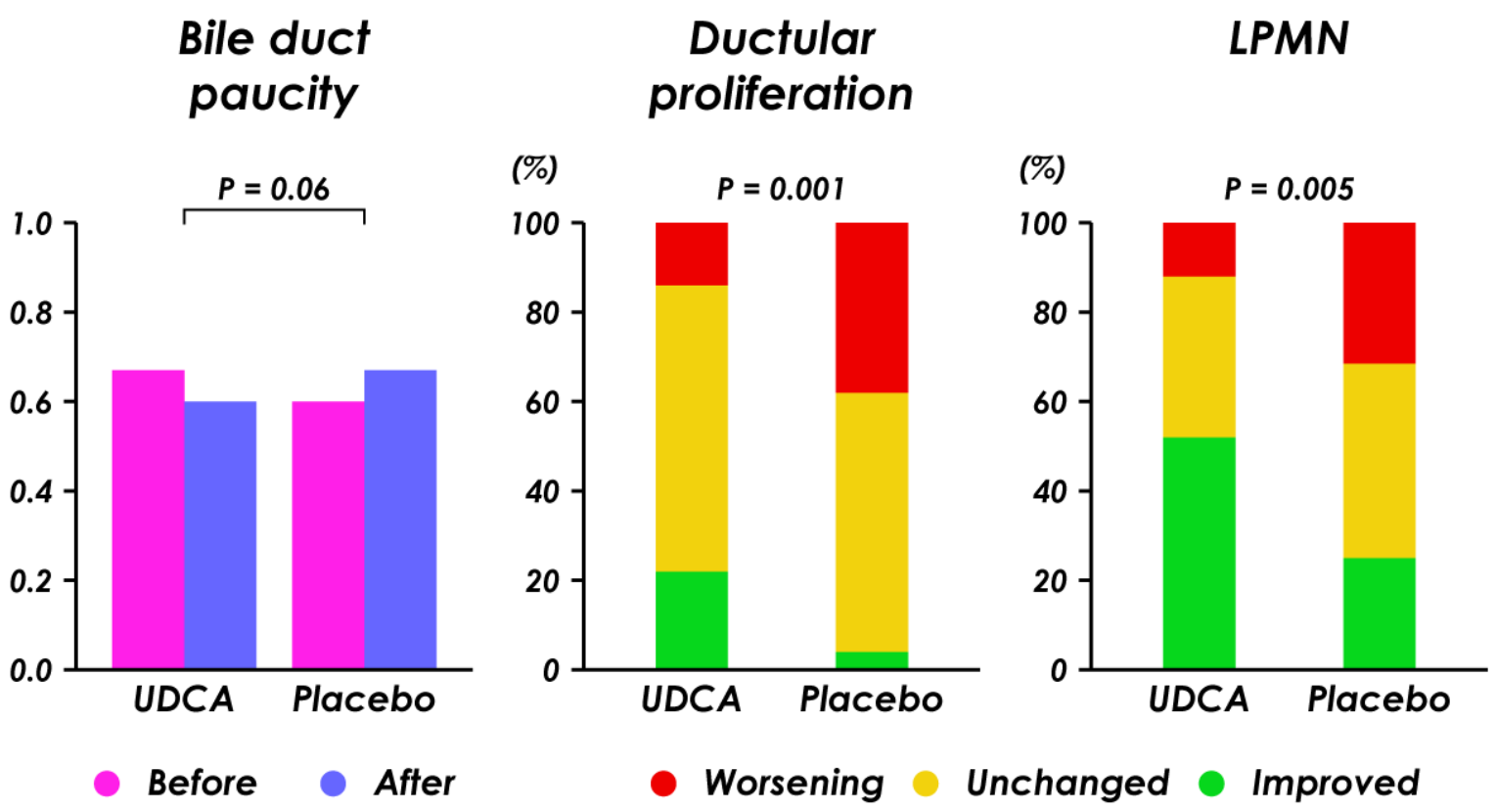
Time profile of cirrhosis development



Main PBC variants responsible for development of liver failure under UDCA therapy

- PBC-AIH overlap syndrome
- Premature ductopenic variant of non cirrhotic PBC
- Regenerative nodular hyperplasia associated-PBC
- Overwhelming fatigue / lack of energy / lethargy / depression

Impact of 2-year UDCA treatment on histology in PBC



Poupon et al. NEJM 1991

PSC:
A heterogeneous group of biliary diseases

- Small BD PSC
- Large BD PSC
- IgG4 -associated PSC
- AIH -associated PSC (« autoimmune sclerosing cholangitis »)

PSC–AIH overlap syndrome

- Criteria: association of both disease

PSC:

- **Cholestasis**
- **ERCP or MRI abnormalities**
- **Fibro-obliterative and inflammation at histology**

AIH:

- **ALT > 5N**
- **IgG > 20 g/L or SMA (anti-actine antibodies)**
- **Interface hepatitis**

Autoimmune sclerosing cholangitis or overlap syndrome: Therapy

- Corticosteroids + Urso ± Azathioprine

- Results *(Mieli-Vergani, Falk Symp. 136, 2003)*
  - median follow-up 10 yrs
  - survival 100 %
  - survival without transplantation 95 %
  - progression of cholangiographic lesions 50 %
  - progression toward cirrhosis 0 %

IAIHG Position Paper Conclusion(2011)

- « definition of diagnostic criteria for overlap conditions can only be arbitrary.
- We propose that patients with autoimmune liver disease should be categorized as AIH, PBC, and PSC/small duct PSC,respectively.
- The IAIHG scoring system should not be used to establish subgroups of patients.
- Patients with PBC and PSC with features of AIH should be considered for immunosuppressive treatment. »