

# Chronic Cholestatic Liver Disease

Stefan Hübscher,  
 Institute of Immunology & Immunotherapy, University of Birmingham  
 Department of Cellular Pathology, Queen Elizabeth Hospital, Birmingham

## Cholestasis - Definition

### Biochemical

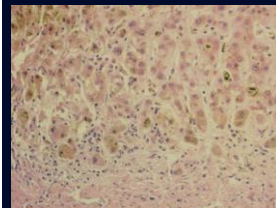
- Defect in bile secretory mechanisms leading to accumulation in blood of substances normally excreted in bile.
- In some conditions where defect is incomplete (e.g. partial obstruction) or patchy (e.g. PBC) cholestasis may be present without jaundice or elevated serum bilirubin levels
- Abnormal biochemical tests characteristically seen in cholestasis are elevations in Alk Phos, gamma GT and bile acids

## Cholestasis - Definition

### Histological

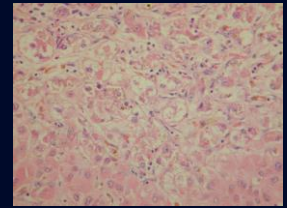
- Accumulation of bile pigment in tissue sections - **"bilirubinostasis"**
- In some conditions where defect is incomplete (e.g. partial obstruction) or patchy (e.g. PBC) bilirubinostasis occurs as a late event
- In chronic cholestasis morphological changes occur due to toxic effects of retained bile acids - **"cholate stasis"**

## Histological Manifestations Of Cholestasis



**"Bilirubinostasis"**

- Bile pigment accumulation (cytoplasmic, canalicular)
- Typically perivenular in acute cholestasis (e.g. drugs)
- May be periportal in chronic cholestasis (e.g. PBC)



**"Cholate Stasis"** (toxic effects of retained bile acids)

- Feathery degeneration & ballooning
- Mallory-Denk bodies
- Usually associated with CAP deposits

## Cholestasis - Mechanisms

INTRAHEPATIC	EXTRAHEPATIC
Hepatocellular	Obstruction of large bile ducts
Canalicular	
Bile ductule	
Bile duct	

- Distinction between intrahepatic and extrahepatic cholestasis somewhat artificial as areas of overlap exist (e.g. PSC)
- Cholestasis may be seen as a component of many liver diseases e.g. acute viral hepatitis, alcoholic liver disease, decompensated cirrhosis
- Majority of chronic cholestatic syndromes seen in clinical practice are ones associated with bile duct loss (vanishing bile duct syndromes)

## Pathology of Ductopenic Syndromes (Vanishing Bile Duct Syndromes)

1. Causes of VBDS.
2. Assessment of bile duct loss.
3. Bile duct lesions (PBC and PSC)
4. Role of liver biopsy in PBC and PSC

## Pathology of Ductopenic Syndromes (Vanishing Bile Duct Syndromes)

1. **Causes of VBDS.**
2. Assessment of bile duct loss.
3. Bile duct lesions (PBC and PSC)
4. Role of liver biopsy in PBC and PSC

## Diseases Associated With Bile Duct Loss

1. Developmental
2. Immune-mediated
3. Vascular
4. Infective
5. Drugs/toxins
6. Neoplastic
7. 'Idiopathic'

## Bile Duct Loss - Developmental Causes

### Extrahepatic Biliary Atresia

### Intrahepatic Biliary Atresia

- syndromic (Alagille's)
- non-syndromic

### Other

- alpha-1-antitrypsin deficiency
- cystic fibrosis
- bile transporter deficiencies (BSEP, MDR3)
  - (previously known as Byler's disease, progressive familial intrahepatic cholestasis)
- Zellweger syndrome

## Bile Duct Loss - Immune Causes

### Primary biliary cirrhosis

### Primary sclerosing cholangitis

### Autoimmune overlap syndromes

### Sarcoidosis

### Liver allograft rejection

### Graft versus host disease

## Bile Duct Loss - Vascular Causes (bile ducts have single blood supply from hepatic artery)

### ARTERIAL

- Hepatic artery thrombosis
- Traumatic injury
- Intra-arterial infusions (e.g. 5-FU, ethanol embolisation)
- Vasculitis (polyarteritis nodosa)
- Foam cell arteriopathy (chronic liver allograft rejection)

### VENOUS

- Portal vein obstruction (pseudosclerosing cholangitis/ portal biliopathy)

## Bile Duct Loss - Infective Causes

- |                  |                           |                               |
|------------------|---------------------------|-------------------------------|
| <b>Bacterial</b> | - ascending cholangitis   |                               |
| <b>Viral</b>     | - CMV                     | ~ biliary atresia             |
|                  |                           | ~ liver allograft rejection   |
|                  |                           | ~ AIDS sclerosing cholangitis |
|                  | - reovirus 3              | ~ biliary atresia             |
| <b>Protozoa</b>  | - cryptosporidia          |                               |
|                  | - microsporidia           |                               |
| <b>Other</b>     | - Echinococcus granulosus |                               |
|                  | (ruptured hydatid cyst)   |                               |

### Bile Duct Loss - Drug / Toxic Causes

Phenothiazines	Chlorpromazine Prochlorperazine
Antibiotics	Ampicillin Flucloxacillin
Tricyclic antidepressants	Amitriptyline Imipramine
Antiepileptics	Carbamazepine Phenytoin
Other	Cimetidine Methyltestosterone Tolbutamide

### Bile Duct Loss - Neoplastic Causes

- **Langerhans cell histiocytosis**
  - Portal tract infiltration by Langerhans cells (bilio-centric pattern)
- **Systemic Mastocytosis**
- **Hodgkin's Lymphoma**
  - Paraneoplastic phenomenon, often unrelated to direct evidence of liver infiltration

### Bile Duct Loss - Cause Unknown

'Idiopathic Adult Ductopenia' (Ludwig 1987)

- ? Small duct PSC
- ? AMA-negative PBC
- ? Late presentation of non-syndromic paucity of bile ducts

Some cases remain with no identifiable cause:

- May have a familial tendency
- Subtypes with mild disease (type 1) and severe progressive disease (type 2) have been recognised

### Pathology Of Ductopenic Syndromes (Vanishing Bile Duct Syndromes)

1. Causes of VBDS.
2. **Assessment of bile duct loss.**
3. Bile duct lesions (PBC and PSC)
4. Role of liver biopsy in PBC and PSC

### 'Vanishing Bile Duct Syndrome'

#### DEFINITION

- Bile duct loss in more than 50% of portal tracts

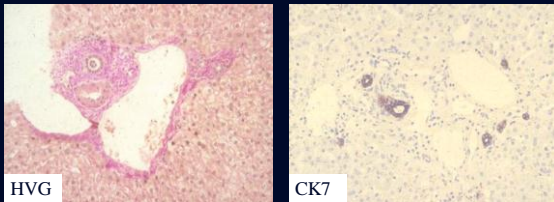
#### DIAGNOSTIC PROBLEMS

- Patchy distribution of bile duct loss in some cases
- Bile ducts versus ductules
- Even if bile duct loss is uniformly distributed, how many portal tracts are required for adequate sampling?

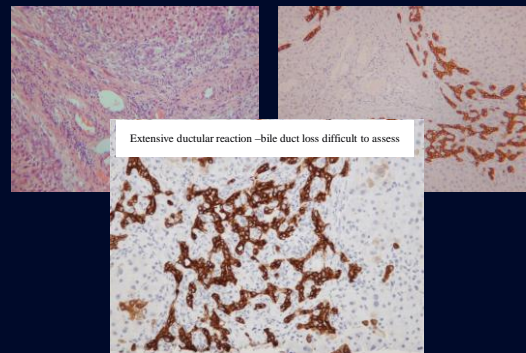
### Interlobular Bile Ducts and Bile Ductules

	INTERLOBULAR BILE DUCTS	BILE DUCTULES
LOCATION IN NORMAL LIVER	CENTRAL (near hepatic arteriole)	PERIPHERAL (near canaliculi/canal of Hering)
SIZE	20-100µm	<20µm
MORPHOLOGY	Cuboidal/columnar epithelium. Clearly identifiable round lumen	Low cuboidal epithelium. Inconspicuous slit-like lumen
CHANGES IN LIVER DISEASE	Targets for damage (immune-mediated, ischaemic etc)	Ductular reaction (increase in number in response to bile duct damage – and other causes of liver disease)

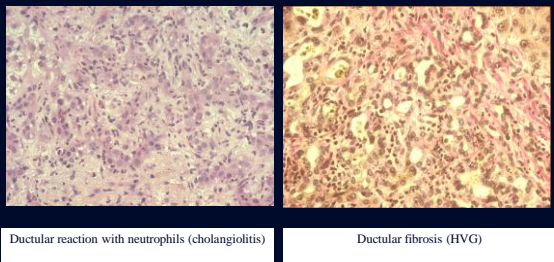
Normal Liver  
bile ducts and ductules



PBC - Bile Duct Loss and Ductular Reaction



Primary Biliary Cirrhosis



How many portal tracts are required to make a diagnosis of significant bile duct loss (SBDL)?

Number of Portal tract arteries	Proportion lacking ducts required to diagnose SBDL
< 4	Not possible
4	100%
8	75%
20	50%

Tadrous and Goldin, J Pathol 1997; 181: 11A

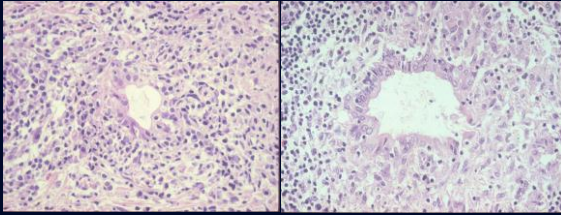
Pathology Of Ductopenic Syndromes  
(Vanishing Bile Duct Syndromes)

1. Causes of VBDS.
2. Assessment of bile duct loss.
3. **Bile duct lesions (PBC and PSC)**
4. Role of liver biopsy in PBC and PSC

Bile Duct Lesions in PBC and PSC

	Ducts Involved	Histological Features
PBC	Small (Interlobular)	Lymphocytic/granulomatous cholangitis
PSC	Intrahepatic	
	• Small (Interlobular)	Usually disappear without trace ("vanishing bile duct syndrome")
	• Medium (septal)	Periductal fibrosis, nodular scars (fibrous cholangitis)
	• Large (hilar)	Dilated, ulcerated & inflamed
	• Extrahepatic	Dilated, ulcerated & inflamed

### Primary Biliary Cirrhosis



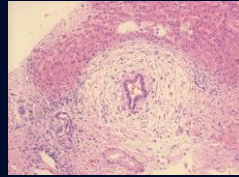
Lymphocytic cholangitis

Granulomatous cholangitis

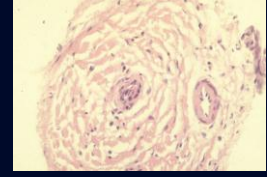
Granulomatous cholangitis more-or-less diagnostic of PBC  
Other rare causes:

- Sarcoidosis
- Hepatitis C (?)

### Primary Sclerosing Cholangitis



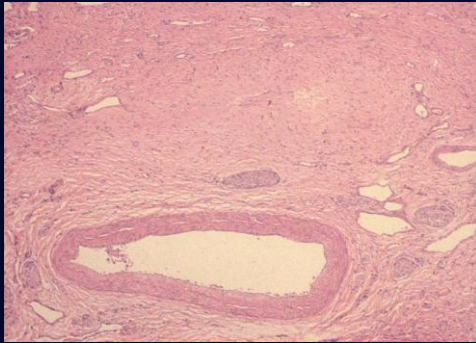
Periductal Fibrosis (early)



Periductal Fibrosis (late)

• Fibrosing duct lesions and duct loss also seen in other causes of sclerosing cholangitis (secondary sclerosing cholangitis)

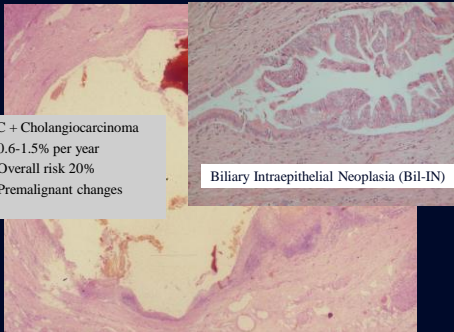
### Primary Sclerosing Cholangitis Fibro-obliterative Duct Lesion



### Primary Sclerosing Cholangitis Large Duct Ectasia



### Primary Sclerosing Cholangitis Large Duct Ectasia



PSC + Cholangiocarcinoma

- 0.6-1.5% per year
- Overall risk 20%
- Premalignant changes

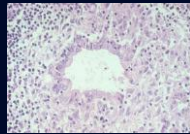
Biliary Intraepithelial Neoplasia (Bil-IN)

### Sclerosing Cholangitis - Other Causes

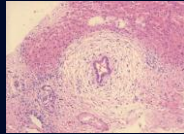
Aetiology	Examples
Developmental/genetic	MDR 3 deficiency
Vascular	Ischaemic cholangiopathy <ul style="list-style-type: none"> <li>• Hepatic artery thrombosis, radiation injury, intra-arterial chemotherapy, "sclerosing cholangitis in critically ill patients (SC-CIP)</li> </ul> Portal vein occlusion ("portal biliopathy")
Infective	Bacterial <ul style="list-style-type: none"> <li>• Recurrent pyogenic cholangitis, septic shock</li> </ul> Viral <ul style="list-style-type: none"> <li>• CMV</li> </ul> Protozoal <ul style="list-style-type: none"> <li>• Cryptosporidia (Immunodeficiency-associated SC - e.g. AIDS)</li> </ul>
Neoplastic	Langerhans cell histiocytosis
Immune mediated	IgG-4 associated cholangitis

### Bile Duct Lesions in PBC and PSC

PBC – granulomatous cholangitis  
(virtually diagnostic of PBC)



PSC – fibrous cholangitis  
(mainly affects septal ducts, also seen in secondary SC)



#### Frequently not seen in needle biopsy specimens

- Granulomatous cholangitis in 30-50% of PBC biopsies (Wiesner 1985, Drebber 2009)
- Fibrous cholangitis in 12% PSC biopsies (Wiesner 1985)
- Histological distinction only possible in 92/318 (28%) cases (Wiesner 1985)

### Pathology Of Ductopenic Syndromes (Vanishing Bile Duct Syndromes)

1. Causes of VBDS.
2. Assessment of bile duct loss.
3. Bile duct lesions (PBC and PSC)
- 4. Role of liver biopsy in PBC and PSC**

### Primary Biliary Cirrhosis

**A Proposal to Change the Nomenclature of PBC : From “Cirrhosis” to “Cholangitis”**  
(EASL Panel – Beuers, J Hepatol Nov 2015 & Beuers, Gut Nov 2015)

- Most patients don't have cirrhosis at the time of diagnosis and some never develop cirrhosis
- Patient groups (mostly female, non-alcohol drinkers) dislike the stigma attached to the term “cirrhosis”
- Other terms proposed to describe PBC (e.g. chronic non-suppurative destructive cholangitis, autoimmune cholangitis) have failed to gain widespread acceptance
- “Primary biliary cholangitis” now proposed as a better term to describe the disease

### Primary Biliary Cirrhosis – Diagnostic Criteria

<b>Biochemistry</b>	Cholestatic LFTs (raised Alk Phos)
<b>Immunology</b>	Anti-mitochondrial antibodies (with M2 specificity) Raised IgM
<b>Histology</b>	Lymphocytic/ granulomatous cholangitis (“diagnostic of PBC”) <ul style="list-style-type: none"> <li>• Only present in 30-50% of liver biopsies (Wiesner 1985, Drebber 2009)</li> <li>Duct loss, ductular reaction, chronic cholestasis (“compatible with PBC”)</li> </ul>

**2 of the 3 criteria now considered adequate to diagnose PBC**  
(EASL Clinical Practice Guidelines – J Hepatol 2009; AASLD Practice Guidelines – Hepatology 2009)

- Liver biopsy no longer required in cases with other typical features

### Primary Biliary Cirrhosis – Role of Liver Biopsy

1. Early PBC
2. AMA – negative PBC (“autoimmune cholangitis”)
3. Assessing inflammatory activity (autoimmune “overlap syndromes”)
4. Assessing disease progression (staging)

### Primary Biliary Cirrhosis – Role of Liver Biopsy

1. Early PBC
  - Subtle histological features of chronic cholestasis may identify early chronic biliary disease before this has been diagnosed clinically
2. AMA – negative PBC (“autoimmune cholangitis”)
3. Assessing inflammatory activity (autoimmune “overlap syndromes”)
4. Assessing disease progression (staging)

Referred Biopsy – Diagnosis Chronic Hepatitis ? Cause Raised AST & Alk Phos. Autoantibody screen negative.

- Portal inflammation and interface hepatitis
- Biliary features not conspicuous

Orcein  
Periportal copper-associated protein

Keratin 7 Immunostaining  
"intermediate hepatobiliary cells"

Repeat autoantibody testing = AMA-positive

**"Minimal Change" Primary Biliary Cirrhosis**  
(Khan, Hepatology 2012)

"Minimal change PBC"      "Minimal change PBC"      Normal control

10 Cases (PBC suspected on clinical/biochemical grounds)

- Nearly normal or mildly inflamed biopsies, with no features to suggest PBC
- Loss of canals of Hering (CoH) demonstrated by K19 immunostaining
- Outcome similar to control population of confirmed early PBC

Loss of CoH may also be a feature associated with disease progression (Kakada 2015)

- Lower CoH density/parenchymal area associated with fibrosis stage, duct loss and orcein-positive granule deposition
- Also associated with higher "hepatitis activity" score, suggesting possible inflammatory destruction of canals of Hering

Primary Biliary Cirrhosis – Role of Liver Biopsy

1. Early PBC
2. **AMA – negative PBC ("autoimmune cholangitis")**
3. Assessing inflammatory activity (autoimmune "overlap syndromes")
4. Assessing disease progression (staging)

AMA – negative PBC ("Autoimmune Cholangitis")

**Prevalence**

- Approximately 5-10% cases

**Diagnostic Features**

- Typically have other autoantibodies (ANA, SMA)
- Cholestatic biochemistry and histology

**Some differences compared with AMA+ PBC**

- e.g. less severe pruritus, higher AST, lower IgM levels, more plasma cells, more T cells, more CD5+ cells, more CD20+ cells

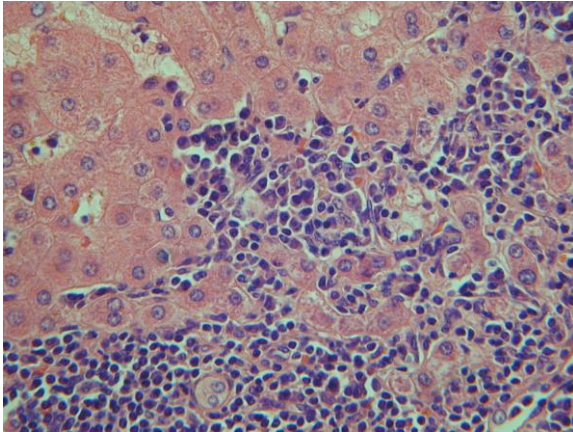
**Overall behaviour similar to AMA+ PBC**

- Including similar response to treatment with UDCA (Lindor 2009)

Primary Biliary Cirrhosis – Role of Liver Biopsy

1. Early PBC
2. **AMA – negative PBC ("autoimmune cholangitis")**
3. Assessing inflammatory activity (autoimmune "overlap syndromes")
4. Assessing disease progression (staging)

Primary Biliary Cirrhosis  
Portal inflammation with interface hepatitis



Primary Biliary Cirrhosis - Significance of Inflammatory Activity

**Severity of inflammatory activity (periportal and lobular)**

Predictive for subsequent progression to fibrosis /cirrhosis & liver failure (Degott 1999, Corpechot 2002, Corpechot 2008)

Moderate or severe interface hepatitis also used as a diagnostic criterion for PBC/AIH "overlap syndrome" (PBC with "hepatic features") (Chazouilleres 1998 & 2006, Poupon 2006, Beuers 2009, Boberg 2011, Czaja 2012)

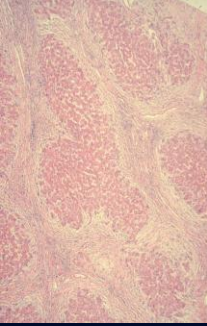
- 5-15% of PBC patients have additional features supporting a diagnosis of AIH (biochemical, immunological and histological)
  - Usually present simultaneously, occasional sequential syndrome (usually PBC → AIH)
- PBC with "hepatic features" - worse outcome than "pure" PBC
- May benefit from treatment with immunosuppression
  - Normalisation of ALT levels
  - Less severe fibrosis progression

(Similar comments apply to PSC)

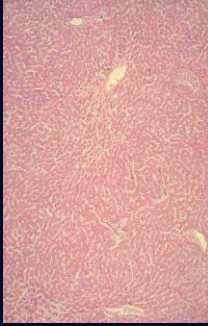
Primary Biliary Cirrhosis – Role of Liver Biopsy

1. Early PBC
2. AMA – negative PBC ("autoimmune cholangitis")
3. Assessing inflammatory activity (autoimmune "overlap syndromes")
4. Assessing disease progression (staging)
  - Several staging systems described (Rubin 1965, Scheuer 1967, Popper & Schaffner 1970, Ludwig 1978)
  - No longer used in routine assessment

Primary Biliary Cirrhosis – Variable Fibrosis (similar changes in PSC & other chronic cholestatic disease)



Cirrhotic area



No fibrosis

PBC – Role of Biopsy in Staging

**Histological features predictive of poor outcome in PBC (including HCC) :**  
 (Vleggar 2000, Bergasa 2004, Mayo 2008, Cavazza 2009, Kumagi 2010, Floreani 2011, Kakuda 2013, Chan 2014)

- Advanced stage/established cirrhosis
- Marked ductopenia
- Orcein-positive granules

Proposal of a new staging and grading system for primary biliary cirrhosis  
 Hiramatsu. Histopathology 2006;49:466-78.

- Factor analysis and correlational analysis
- 17 histological features in biopsies from 188 PBC patients – graded on a scale of 0-3
- Correlated with other clinical and laboratory data (Mayo Clinic Prognostic Model)

<p><b>Grading</b></p> <ul style="list-style-type: none"> <li>• Chronic cholangitis (0-3)</li> <li>• Interface hepatitis (0-3)</li> <li>• Lobular hepatitis (0-3)</li> </ul>	<p><b>Staging</b></p> <ul style="list-style-type: none"> <li>• Bile duct loss (0-3)</li> <li>• Fibrosis (0-3)</li> <li>• Orcein-positive granules (0-3)</li> </ul>
-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------

**Total Staging Scores (0-9)**

0 = stage 1 (no progression)  
 1-3 = stage 2 (mild progression)  
 4-6 = stage 3 (moderate progression)  
 7-9 = stage 4 (advanced disease)



### “Japanese System” for Staging PBC – Further Studies

- Grading simplified into Cholangitis Activity and Hepatitis Activity (combination of interface hepatitis and lobular inflammation) (Nakanuma 2010)
  - Inter-observer agreement “fair” for staging, “slight” for activity
- Subsequent studies have shown that Japanese system for staging PBC correlated better with adverse outcomes than other scoring systems (Kakuda 2013, Chan 2014)
  - CAP deposition score most powerful predictor of adverse outcomes

### Another Histological Scoring System for PBC (Wendum, Liver International 2015)

#### Liver biopsies from 33 newly diagnosed PBC patients

#### Semi-quantitative scoring of features thought to be prognostically important:

1. Fibrosis (F0 – F4)
2. Interface hepatitis (0-3)
3. Bile duct ratio (number of PTs with BD/total number of PTs)

#### Results

- Good correlation with biochemical abnormalities (no liver-related events)
- Better interobserver agreement for each of the 3 features compared with Ludwig & Scheuer systems.

## Primary Sclerosing Cholangitis

### Primary Sclerosing Cholangitis – Diagnostic Criteria

EASL Clinical Practice Guidelines – J Hepatol 2009; 51: 237-267  
AASLD Practice Guidelines – Chapman, Hepatology 2010; 51: 660-678

1. Cholestatic liver biochemistry (raised Alk Phos)
2. Cholangiography
3. Exclusion of secondary causes of sclerosing cholangitis

- Liver biopsy no longer required for routine diagnosis
- Diagnostic duct lesions patchy & mainly affect medium-sized (septal) ducts
  - Present in 12% of liver biopsies (Wiesner 1985)
  - Also seen in secondary sclerosing cholangitis (SSC)
  - Histology alone often unreliable in distinguishing PSC from other chronic biliary diseases associated with duct loss (including PBC, SSC)

### Primary Sclerosing Cholangitis – Role of Liver Biopsy

1. Early PSC
2. PSC variants
  - Small-duct PSC
  - IgG4 sclerosing cholangitis
3. Assessing inflammatory activity (autoimmune “overlap syndromes”)
4. Assessing disease progression (staging)

(Early PSC & Staging of PSC – similar to PBC)

### Primary Sclerosing Cholangitis – Role of Liver Biopsy

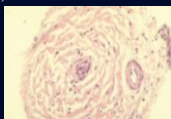
1. Early PSC
2. PSC variants
  - Small-duct PSC
  - IgG4 sclerosing cholangitis
3. Assessing inflammatory activity (autoimmune “overlap syndromes”)
4. Assessing disease progression (staging)

### Small Duct PSC (approximately 5-15 % of cases)

Normal/near-normal cholangiogram

Histological features of fibrous cholangitis

- Extent to which fibrosing duct lesions present not clearly specified (Singal 2011)



#### Outcome variable:

- 10-20% cases progress to large duct involvement (La Russo 2006, Bjornsson 2008)
- Generally more favourable than classical PSC
  - Survival comparable to normal population
  - Low risk of cholangiocarcinoma
- “Overlap syndrome” with AIH may be more frequent
  - 26% of PSC-AIH cases had small duct PSC (Olsson 2009)
- More frequently associated with Crohn’s disease (Bjornsson 2008, Halliday 2012)

### Primary Sclerosing Cholangitis – Role of Liver Biopsy

#### IgG4-associated sclerosing cholangitis

- Part of spectrum of systemic IgG4-associated disease
- Range of lesions involving bile ducts (extra- and intrahepatic)
- Usually associated with type 1 autoimmune pancreatitis (IgG4-related pancreatitis)

Most cases have extrahepatic bile duct lesions

- Histological features resemble those seen in autoimmune pancreatitis
  - Lymphoplasmacytic infiltrates, storiform fibrosis, obliterative phlebitis

Nature of intrahepatic disease less well characterised

- role of liver biopsy in identifying cases with diffuse intrahepatic disease ?
- relationship between IgG4-SC and PSC?

### IgG4 -associated Sclerosing Cholangitis Intrahepatic Disease - Histological Findings

#### Bile Duct Lesions

- Periductal inflammation
  - “fibro-inflammatory nodules”
- Mild periductal fibrosis (no nodular scars)
- Ductopenia uncommon

#### Inflammation (more prominent than PSC)

- Mainly portal, variable interface hepatitis
  - Plasma cells++, eosinophils+
- Lobular hepatitis

#### Fibrosis

- Generally mild
- Bridging fibrosis in up to 40%
- Advanced fibrosis rare

### IgG4-associated Sclerosing Cholangitis Role of IgG4 Immunohistochemistry

> 10 IgG4+ cells/HPF generally accepted as suggestive/diagnostic



#### Problems:

1. Variable size of high power fields
2. 30- 50% of otherwise typical cases have < 10 IgG4+ cells/HPF (Deshpande 2009, Itoh 2009, Kawakami 2010, Oh 2010)
3. > 10 IgG4+ cells/HPF may be seen in other diseases
  - 37-43% of extrahepatic cholangiocarcinoma (Harada 2012, Kimura 2012)
    - Mainly at growing front ? role in invasion

### IgG4-associated Sclerosing Cholangitis – A Variant of PSC? (Bjornsson 2006, Hirano 2006, Mendes 2006, Webster 2009, Zhang 2010, Bjornsson 2011, Oseini 2011, Alswat 2012)

- 10-30% of otherwise typical cases of PSC have elevated serum IgG4 levels +/- tissue infiltrates of IgG4+ plasma cells supporting a diagnosis of IgG4-SC
- Appear to behave more aggressively than Ig4-negative PSC
  - Higher prevalence of cirrhosis at time of diagnosis
  - More rapid progression to liver transplantation
  - Higher rate of recurrence post-transplant
- Nature uncertain (variant of PSC or IgG4 sclerosing disease)
  - May benefit from treatment with corticosteroids

### Primary Sclerosing Cholangitis – Role of Liver Biopsy

1. Early PSC
2. PSC variants
  - Small-duct PSC
  - IgG4 sclerosing cholangitis
3. Assessing inflammatory activity (autoimmune “overlap syndromes”)
4. Assessing disease progression (staging)

## PSC/AIH Overlap Syndrome

(Beuers 2009, Chapman 2010, Boberg 2011, Czaja 2012 )

### Diagnostic Criteria

- Similar to those used for PBC/AIH overlap

### Presentation

- "sequential syndrome" more common than in PBC, particularly in children/young adults ( usually AIH  $\rightarrow$  PSC , 6 months -13 years)
- extent to which PSC excluded at time of diagnosing AIH uncertain
  - Using routine cholangiography up to 50% of children (Gregorio 2001) and 2-10% of adults (Abdalain 2008, Lewin 2009) presenting with AIH have features compatible with PSC

## PSC/AIH Overlap Syndrome

### Role of Liver Biopsy in a Patient with a Diagnosis of AIH

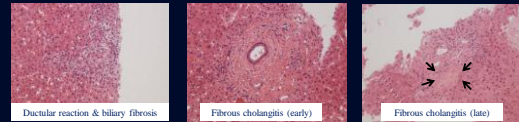
#### New onset AIH (particularly in children)

Subtle features of chronic cholestasis or focal duct loss should raise possibility of PSC and prompt cholangiography.

Liver biopsy occasionally reveals features compatible with PSC in a patient who initially has a normal cholangiogram (Abdalain 2008, Luth 2009)

#### Treated AIH (with persistently abnormal LFTs)

Liver biopsy may help to identify relative severity of inflammatory activity and features of chronic biliary disease



Male, age 30.

AIH diagnosed several years ago. Persistently abnormal LFTs despite treatment with immunosuppression

## Chronic Cholestatic Diseases - Liver Biopsy Assessment

- (1) Most cases of chronic cholestasis are related to bile duct damage and duct loss
- (2) Careful examination of bile ducts is required in any case where there is biochemical or histological evidence of cholestasis
- (3) For some diseases (e.g. PBC, PSC) diagnostic bile duct lesions are often not seen in liver biopsy specimens. Other investigations are therefore required to make a definitive diagnosis
- (4) Bile duct loss may be difficult to assess accurately in small needle biopsy specimens (e.g. incomplete sampling of portal tracts) or when there is extensive ductular reaction
- (5) Secondary features of chronic cholestasis may be an important pointer to a biliary problem

## Role of Liver Biopsy in PBC & PSC - Summary

1. PBC and PSC diagnosed on the basis of a combination of clinical, biochemical, immunological, radiological and histological findings
  - Liver biopsy rarely diagnostic in isolation.
2. For cases of PBC and PSC with other typical findings, liver biopsy no longer required for diagnosis.
  - Liver biopsy still used to diagnose atypical cases (e.g. AMA-neg PBC, small-duct PSC, IgG4-SC, "overlap syndromes" – PBC/AIH, PSC- AIH)
3. Liver biopsy useful in assessing disease severity
  - Inflammatory activity
  - Fibrosis, ductopenia, copper-associated protein
  - Important implications for prognosis and treatment