2nd Pannonia Congress of pathology
Hepato-biliary pathology

Autoimmune Liver Diseases

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Liver diseases suggested to be of immune origin

- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Overlap syndromes
- Sequential or transitional syndromes
Key Points

- Three main entities: AIH, PBC, PSC
- Overlap syndromes: AIH-PBC, AIH-PSC, comprising up to 10% of cases
- Diagnosis results from clinico-pathological data: clinical-serologic examination and histological findings
Topics to be discussed

- Histopathological diagnostic criteria in clinically suspected autoimmune liver disorders. Does histopathological classification of these diseases offer an insight into cholestatic liver lesions?
- Liver biopsy report. Does it meet expectations of physicians in diagnostic decisions and selection of therapy?
Topics to be discussed

- Histopathological scores (grading, staging) are applied to assess severity of liver injury and structural changes.

Is scoring just a diagnostic supplement or does it embrace pitfalls, so as safeguards in diagnostic approach?
What to observe?

The Normal Liver Lobule:
Histological key feature

Portal inflammation
DEFINES
Chronic Hepatitis

“Piecemeal Necrosis”
or, better,
“Interface Hepatitis”
Autoimmune hepatitis – AIH

„definite“or „probable“ clinical diagnosis

- Unresolving hepatitis:
  - acute (mimicking viral), chronic (6 months of onset)
- Increased serum IgG levels
- Tissue directed serum autoantibodies:
  - ANA, SMA, LKM1
- Response to immunosuppressive therapy
  - (corticosteroids)
- Characteristic histopathological picture of liver damage
AIH - Epidemiology

- Prevalence of 1 per 100,000 in Europe; 20% of chronic hepatitis cases
- Associated with HLA A1-B8-DR3 phenotype
- More common in women (4:1)
- Wide age distribution (10-30-60 years)
AIH – Clinical features

- Presenting clinical features are highly variable
- 1/3 are cirrhotic at presentation
- 1/3 begin as acute, mimicking viral hepatitis
- 20% are asymptomatic
- 50% have or will have other autoimmune disorders
AIH – Histological features

- **Chronic hepatitis pattern** of injury: portal and periportal (interface) hepatitis prominent plasma cells in inflammatory infiltrate lobular necroinflammatory activity

- **Hepatocytic changes**: rosettes, syncytial giant hepatocytes, centrolobular necrosis

- **Bile ducts injury**: florid portal inflammation may destroy portal bile ducts
Lobular features
**AIH** – Dilemmas of viral hepatitis

- True AIH, false positive anti-HCV
- True HCV, autoantibodies at low titers
- True HCV and clinico-patho features of AIH: young women
  - extrahepatic autoimmune disorders
  - high serum autoantibody titers
  - increased serum IgG
Liver histology
What needs to be reported?

Necroinflammatory activity (Grading):
- Nature of infiltrate: lympho-plasmacytic, mixed
- Location: portal, periportal, lobular, bridging necrosis
- Severity: mild, moderate, severe

Structural changes or fibrosis (Staging):
- Presence/absence
- Location: portal, septal, bridging fibrosis
- Distorted structure: nodular, cirrhosis (probable, suspicious, definite)
Liver histology
What needs to be reported?

☐ Knodell RG (1981)
☐ Scheuer PJ (1991)
☐ Ishak KG (1995)
☐ Bedossa P (1996)
☐ International AIH group (1999): Revision of diagnostic criteria

*Not to simplify, not to complicate*
Primary Biliary Cirrhosis – PBC

Definition

- Chronic cholestatic liver disease, considered autoimmune in etiology (genetic susceptibility, triggered with infection)
- Serologic hallmark is the presence of AMA
- Morphologic hallmark is inflammatory destruction of intrahepatic bile ducts
PBC - Epidemiology

- Women predominance (9:1)
- Median age of onset 50 yrs (range 21 – 91)
- Geographical variations: increased prevalence in more developed countries
- Accounts for up to 20% of deaths from cirrhosis worldwide
PBC – Clinical features

- Asymptomatic at first presentation (50-60%)
- Most common signs: pruritus, fatigue, jaundice (occurs in late stages)
- Cholestatic markers in serum: raised alkaline phosphatase and gamaGT
- Associated with: scleroderma, CREST syndrome (in 10%), gallstones (in 50%), rheumatoid arthritis, autoimmune thyroiditis...
PBC – Clinical history

- 25% (Stage I, II patients; treated with UDC) will not progress over 4 years
- Stage III, IV patients progress to transplant or die within 9.3 years
- Median time of progression from Stage I, II to cirrhosis (if untreated): 4 – 6 years
- Complications: chronic cholestasis, cirrhosis
PBC – Basic histological features

- **Florid duct lesions** progress to duct destruction, continue to ductular proliferation, followed with chronic cholestasis
- **Interface hepatitis** (similar to any chronic hepatitis)
- Damaged hepatocytes accumulate **copper**
- **Ductal** and **ductular epithelium** vanish
- **Biliary cirrhosis** develops step by step
PBC – Pronounced histology

**Florid bile duct lesions:**
- inflammatory aggregates surround portal ducts
- affected duct epithelium develops abnormal, irregular forms
- basement membrane disruption influences bile leakage

Injury is restricted to larger (portal-septal) ducts, seen in enlarged portal tracts
PBC - Granulomas

- Loose collections of epithelioid histiocytes in portal tracts and in periportal parenchyma
- Absence of this feature does not exclude the diagnosis
- Found mostly in earlier stages, in 50% of patients
- May announce better prognosis
**PBC – Diagnostic dilemmas**

What does histological picture talk about?

<table>
<thead>
<tr>
<th><strong>PBC</strong></th>
<th><strong>Alternative diseases</strong></th>
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<tbody>
<tr>
<td>Portal inflammation</td>
<td>Chronic hepatitis, drugs</td>
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<td>Lymphocytic aggregates</td>
<td>Hepatitis C</td>
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<td>Granulomas</td>
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<td>Ductopenia</td>
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<td>Ductular reaction</td>
<td>Chronic cholestasis</td>
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<td>Copper deposition</td>
<td>Biliary obstruction</td>
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**PBC – Histological staging**
prognostic data of disease progression

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>1: Portal hepatitis</td>
<td>☐ Florid duct lesions</td>
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<tr>
<td>2: Periportal hepatitis</td>
<td>☐ Ductular reaction</td>
</tr>
<tr>
<td>3: Septal fibrosis</td>
<td>☐ Bridging necrosis, bridging fibrosis</td>
</tr>
<tr>
<td>4: Cirrhosis</td>
<td>☐ Nodular regeneration</td>
</tr>
</tbody>
</table>

- **Ludwig J. Virchows Arch A**
  378:103-12, 1978

- **Scheuer P. Proc Royal S Med**
  60: 1257-60, 1967
Primary Sclerosing Cholangitis – PSC Definition

- Chronic cholestatic liver disease, probably autoimmune in etiology
- Extra and intrahepatic biliary tree is affected
**PSC - Epidemiology**

- Male predominance (2:1)
- Median onset 30 years (range 1-90 yrs)
- 70% of cases are associated with:
  - ulcerative colitis (adults)
  - Crohn’s disease (children)
PSC – Genetic background

Increased prevalence of HLA B8 and DR3, associated with a number of organ-specific autoimmune diseases:

- AIH
- thyroiditis,
- coeliac disease,
- myasthenia gravis
PSC – clinical history

**Clinical course** is variable and unpredictable due to:
- Obstructing strictures
- Bacterial cholangitis
- Biliary stone formation
- Cholangiocarcinoma

**Median survival** from the diagnosis: 9-12 yrs

In patients with ulcerative colitis PSC is the major cause of death
PSC – clinical features

- **Gold standard:**
  - MRCP
  - ERCP (in suspicion but normal MRCP)

- **Cholangiographic findings:** irregular biliary system due to multifocal duct strictures

- **Autoantibodies:** ANA, SMA, pANCA (80%, though nonspecific)

- **Liver biopsy:** may not be diagnostic, may even be normal
**PSC** – Histologic clues to diagnosis

- Rounded scars in portal tracts, **concentric periductal fibrosis**, distorted interlobular bile ducts
- Minimal inflammation, more fibrotic features
- Loss of small interlobular bile ducts (in 60% of cases)
- Superimposed changes of extrahepatic obstruction
PSC – periductal concentric fibrosis
PSC – Histological staging

- **Stage**
  1. Portal phase
  2. Periportal fibrosis
  3. Septal fibrous bridges
  4. Cirrhosis

- **Histological findings**
  1. Duct abnormalities, no destruction, obliterative cholangitis
  2. Ductular proliferation in fibrosis
  3. Bridging septa, disappearing ducts
  4. Biliary cirrhosis
PSC – Diagnostic dilemmas

☐ PBC
☐ Chronic large bile duct obstruction
☐ AIH (children – frequent overlap)
☐ Infectious cholangiopathy (AIDS)
☐ Intrahepatic arterial chemotherapy
PSC - Primary : Secondary SC

- PSC usually has **a component of obstruction** - may be difficult to distinguish
- **Bile duct loss does not occur** in obstruction
- Histological **features, common to both**: periductal fibrosis, ductular proliferation, cholestasis
- **Numerous eosinophils** in portal inflammation favours PSC
Overlap syndromes – Variants of autoimmune liver diseases

**Hepatocellular damage** is the clue of AIH diagnosis

**Bile duct damage** is the clue for PBC diagnosis

**Overlap** means histological spectrum „between“:

- AIH + PBC: 8-9%
- PSC + AIH: 6-8%

- Beuers H. J Hepatol 42: S93-S99, 2005
Autoimmune cholangitis
An example of a nondecisive diagnosis

- Lack of the uniform clinico-pathological criteria for diagnosis
- Sometimes presented as a variant of PBC, or an early stage of disease in evolution
- Autoantibodies: ANA(high), AMA (negative)
- Histology often similar to PBC
- Exact classification or „hepatitic form of PBC“ is controversial!
Autoimmune liver diseases
Practical suggestions

**AIH** diagnosis is based on clinico-pathological findings

- Portal inflammation with numerous plasma cells is highly suggestive of AIH

Both, **PBC and PSC**, can cause ductopenia

- Use clinical findings (liver tests, serology, radiography) to overweight the diagnosis

**Overlap syndromes** mean transition from one autoimmune disease to another

- Still more close clinico-pathological consultation is required
Co-operation works ...
Conclusion

- Liver diseases compose a medical field, where pathologists and clinicians really meet.

- No surrogate methods/markers currently exist to replace the tasks of liver biopsy.

- Sometimes, the meeting point in reality means: „There is no body cavity that cannot be reached with a needle or knife and a good strong arm....“