Update on Autoimmune Liver Disease

Role of Liver Biopsy in Autoimmune Hepatitis, PBC and PSC

Stefan Hübscher,
School of Cancer Sciences, University of Birmingham
Dept of Cellular Pathology, Queen Elizabeth Hospital, Birmingham
Autoimmune Liver Disease
Diagnostic Criteria and Role of Liver Biopsy

• AIH, PBC and PSC diagnosed on basis of combination of clinical, biochemical, immunological, radiological and histological findings

• Liver biopsy rarely diagnostic in isolation.

• In AIH histological assessments are important in establishing a diagnosis and determining therapeutic options.

• For cases of PBC and PSC with other typical findings, liver biopsy no longer required for diagnosis.

• Liver biopsy useful in assessing disease severity
  • Inflammatory activity, fibrosis stage
  • Important implications for prognosis and treatment
Autoimmune Hepatitis
## Autoimmune Hepatitis – Laboratory Investigations
### Diagnostic Criteria

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Hepatic LFTs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Raised AST/ALT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunology</th>
<th>Autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• ANA, SMA (type 1)</td>
</tr>
<tr>
<td></td>
<td>• LKM, LC-1 (type 2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunoglobulins</th>
<th>Raised IgG</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Presence of typical/compatible features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absence of atypical features (e.g. biliary features)</td>
</tr>
</tbody>
</table>

## Role of Liver Biopsy in the Diagnosis of AIH

1. Still recommended in expert reviews/ practice guidelines  

2. Others suggest mainly useful in cases where other findings are equivocal or atypical, e.g.  
   • Autoantibodies in low titre  
   • Features suggesting an alternative diagnosis (e.g. fatty liver disease or biliary disease)
Question 1. I recommend obtaining a liver biopsy for the initial diagnosis of AIH

Yes (n=5)
- “usually” (1) or “most of the time” (1)

Sometimes (n=6) - please specify when
- Uncertainty about diagnosis / atypical features (4)
- Possible overlap / alternative aetiologies (3)
- To determine presence / absence of cirrhosis (2)
Chronic Autoimmune Hepatitis - Typical Features
Plasma cell rich portal inflammation

**BUT:**
- Plasma cells not essential to support/confirm diagnosis of AIH
- Plasma cells also seen in other diseases associated with features of chronic hepatitis (e.g. PBC)
Chronic Autoimmune Hepatitis - Typical Features

Interface Hepatitis ("piecemeal necrosis")

Interface Hepatitis - Clinical Significance

Prognosis

• Presence/severity predicts development of fibrosis
• Persistence after treatment associated with increased risk of fibrosis

Treatment

• Indication for commencing immunosuppression (newly diagnosed AIH)
• Indication for maintaining immunosuppression (treated AIH)
  – Portal inflammation alone - relapse rate 50%
  – Interface hepatitis - relapse rate >80%
Question 2. Following a successful biochemical and immunological response to immunosuppression, I would recommend obtaining a liver biopsy before deciding to withdraw immunosuppression.

Sometimes (n=2) - please specify when
- If significant fibrosis/cirrhosis suspected
  (progression to cirrhosis associated with very high relapse rate)
Autoimmune Hepatitis - Lobular inflammation

Lobular inflammation in AIH

- Typically plasma cell rich
- Often mainly perivenular (“central perivenulitis”), may be diffuse
- More severe cases associated with confluent / bridging necrosis (and fibrosis)
  - Less responsive to immunosuppression
  - Increased risk of progression to cirrhosis (up to 80% - Cjaza 2007)
- May present as acute hepatitis / acute liver failure
Autoimmune Hepatitis - Acute Presentation
Incidence & Diagnostic Criteria

30-40% of cases present as acute hepatitis/acute liver failure
(Czaja & Freese 2002, Lohse 2011)

Increasing prevalence of AIH as a cause for acute liver failure
(Fujiwara 2011)
• May reflect improved recognition

Autoantibodies unreliable in the diagnosis of acute AIH
• Autoantibodies and hypergammaglobulinaemia may not be present at the time of presentation with acute AIH (Lohse 2011)
• Autoantibodies present in up to 40% of patients with other causes of acute liver failure - e.g. viral or drug-induced (Bernal 2007)
Autoimmune Hepatitis - Acute Presentation
Histological Features

**Acute presentation of chronic liver disease**

- 14-35% have features of chronic hepatitis (Fujiwara 2011, Yasui 2011)
- 10-95% have bridging fibrosis or cirrhosis (Nikias 1994, Burgart 1995, Miyake 2010, Fujiwara 2011)
Autoimmune Hepatitis - Acute Presentation
Histological Features

**Acute hepatitis** (with no signs of chronic liver disease)

- Classical features of acute lobular hepatitis
- Mainly centrilobular distribution
- Some cases initially have little or no portal inflammation, before subsequently progressing to more classical features of chronic AIH
- Severe cases with bridging or panacinar necrosis
  - Changes heterogeneous in distribution
  - Typical features of AIH may no longer be apparent
  - Can resemble changes seen in cirrhosis
Female, age 34. Subacute liver failure – 3 month history
ANA positive 1 in 400, IgG 33 (normal 8-14.50) ? autoimmune hepatitis
No response to corticosteroid therapy. Liver transplantation
Autoimmune Hepatitis Presenting as Acute Hepatitis/ Acute Liver Failure (Abe 2007, Fujiwara 2008, Stravitz 2011, Yasui 2011)

Histological Features Favouring a Diagnosis of AIH

- Portal inflammation /interface hepatitis (resembling chronic AIH)
- Plasma-cell rich inflammatory infiltrate
- Lymphoid follicles
- Centrilobular necrosis / central perivenulitis (or submassive necrosis with centrilobular accentuation)

One study examined 72 cases where the cause of acute liver failure was uncertain (Stravitz 2011)

- 42 patients with histological features suggesting “probable AIH” had:
  - Higher prevalence of autoantibodies (73% vs 48%)
  - Higher serum globulin levels (3.9 vs 3.0g/dL)
  - Higher incidence of chronic hepatitis in follow up (67% vs 17%)
Autoimmune Hepatitis – Assessment of Fibrosis

- At least $\frac{1}{3}$rd of patients have cirrhosis at presentation (Lohse 2011)
  - Includes cases with acute presentation (important to distinguish true cirrhosis from post-necrotic collapse)

- Patients with cirrhosis at presentation
  - Have worse outcome (Feld 2005, Verma 2007)
  - Less responsive to immunosuppression (Muratori 2009)
    - But reversal of cirrhosis following treatment can occur (Czaja 2007)
  - At risk of developing HCC - approx 1.1%/year (Yeoman 2008)
Primary Biliary Cirrhosis
Primary Biliary Cirrhosis – Diagnostic Criteria

1. Cholestatic liver biochemistry (raised Alk Phos)
2. Anti-mitochondrial antibodies (with M2 specificity)
3. Diagnostic or compatible histological findings.

Changing role of liver biopsy:

1. 2 of 3 criteria generally considered adequate
   Biopsy not required in cases with other typical features

2. Diagnostic duct lesions patchy in distribution
   Present in 30-50% of biopsies (Wiesner 1985, Drebber 2009)
   Histology alone unreliable in distinguishing PBC from other chronic biliary diseases associated with duct loss (incl. PSC)

BUT: Subtle features of chronic cholestasis may identify early chronic biliary disease before this has been diagnosed clinically
- 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
Primary Biliary Cirrhosis – Role of Liver Biopsy

1. AMA – negative PBC (“autoimmune cholangitis”)
2. Assessing inflammatory activity (autoimmune “overlap syndromes”)
3. Assessing disease progression (staging)
AMA – negative PBC (‘Autoimmune Cholangitis’)
Primary Biliary Cirrhosis – Role of Liver Biopsy

1. AMA – negative PBC (“autoimmune cholangitis”)
2. Assessing inflammatory activity (autoimmune “overlap syndromes”)
3. 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

- Moderate or severe interface hepatitis also used as a diagnostic criterion for PBC/AIH “overlap syndrome” (PBC with “hepatitic features”)
  - 10-15% of PBC have additional features supporting a diagnosis of AIH (biochemical, immunological and histological)
  - PBC with “hepatitic 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. AMA – negative PBC ("autoimmune cholangitis")

2. Assessing inflammatory activity (autoimmune "overlap syndromes")

3. Assessing disease progression (staging)
   - Several staging systems described
   - 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:

• Advanced stage/established cirrhosis
• Marked ductopenia

A novel system for grading & staging PBC
(Hiramatsu 2006)

<table>
<thead>
<tr>
<th>Grading</th>
<th>Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic cholangitis (0-3)</td>
<td>• Bile duct loss (0-3)</td>
</tr>
<tr>
<td>• Interface hepatitis (0-3)</td>
<td>• Fibrosis (0-3)</td>
</tr>
<tr>
<td>• Lobular hepatitis (0-3)</td>
<td>• Orcein-positive granules (0-3)</td>
</tr>
</tbody>
</table>

• Inter-observer reproducibility assessed in follow-up study (Nakanuma 2010)
  • Agreement “fair” for staging, “slight” for activity
• Utility in prognosis/management not yet demonstrated
Primary Sclerosing Cholangitis
Primary Sclerosing Cholangitis – Diagnostic Criteria
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**

Changing role of liver biopsy:
1. No longer required for routine diagnosis
2. Diagnostic duct lesions patchy & mainly affect medium-sized (septal) ducts
   - Present in 12% of biopsies (Wiesner 1985)
   - Also seen in secondary sclerosing cholangitis (SSC)
   - Histology alone unreliable in distinguishing PSC from other chronic biliary diseases associated with duct loss (including PBC, SSC)
Primary Sclerosing Cholangitis – Role of Liver Biopsy

1. PSC variants
   - Small-duct PSC
   - IgG4 sclerosing cholangitis

2. Assessing inflammatory activity (autoimmune “overlap syndromes”)

3. Assessing disease progression (staging)
Primary Sclerosing Cholangitis – Role of Liver Biopsy

1. PSC variants
   • Small-duct PSC
   • IgG4 sclerosing cholangitis

2. Assessing inflammatory activity (autoimmune “overlap syndromes”)

3. Assessing disease progression (staging)
Small Duct PSC

Approximately 10-15% of cases

Normal/near-normal cholangiogram

Histological features of fibrous cholangitis

- Extent to which fibrosing duct lesions present not clearly specified

- Outcome variable:
  - 10-20% cases develop features of large duct involvement
    (Björnsson 2002, La Russo 2006, Björnsson 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)
Primary Sclerosing Cholangitis – Role of Liver Biopsy

1. PSC variants
   - Small-duct PSC
   - IgG4 sclerosing cholangitis
     - Part of spectrum of systemic IgG4-associated disease
     - Range of lesions involving bile ducts (extra- and intrahepatic)
     - Role of liver biopsy
       - Identifying cases with diffuse intrahepatic disease
       - Relationship between IgG4-SC and PSC

2. Assessing inflammatory activity (autoimmune “overlap syndromes”)

3. Assessing disease progression (staging)
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 a range of unrelated chronic inflammatory diseases
   – e.g. non-specific dermatitis, rheumatoid synovitis (Strehl 2011)
IgG4-associated Sclerosing Cholangitis – A Variant of PSC?

- 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. PSC variants
   • Small-duct PSC
   • IgG4 sclerosing cholangitis

2. Assessing inflammatory activity (autoimmune “overlap syndromes”)

3. Assessing disease progression (staging)
PSC/AIH Overlap Syndrome
(Beuers 2009, Chapman 2010)

• 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 → 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 (Abdalian 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

Ductular reaction & biliary fibrosis
Fibrous cholangitis (early)
Fibrous cholangitis (late)
Is Liver Biopsy Essential for Diagnosis and Management of AIH?

Still recommended in recent expert reviews/guidelines documents

• International Autoimmune Hepatitis Group (Hennes 2008)
  – Histology one of 4 features used in simplified scoring system used to diagnose AIH

• AASLD Practice Guidelines (Manns 2010)
  – Liver biopsy “recommended to establish the diagnosis and to guide treatment decisions”

• Invited Review (Lohse & Mieli-Vergani, J Hepatol 2011)
  – “Histology considered a necessary prerequisite for making a diagnosis”, “follow-up biopsies are also generally recommended before considering cessation of therapy”
# Autoimmune Hepatitis – Laboratory Investigations

## Diagnostic Criteria

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Hepatitis LFTs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Raised AST/ALT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunology</th>
<th>Autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• ANA, SMA (type 1)</td>
</tr>
<tr>
<td></td>
<td>• LKM, LC-1 (type 2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunoglobulins</th>
<th>Raised IgG</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Presence of typical/compatible features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absence of atypical features (e.g. biliary features)</td>
</tr>
</tbody>
</table>

## International Autoimmune Hepatitis Group – Scoring Systems for Diagnosis of AIH


- Various combinations of clinical, biochemical, immunological & histological features
- Points allocated for typical features (deducted for atypical features - 1993 & 1999 systems)
- Total scores = “definite”, “probable” or “not” AIH
- Mainly intended for research purposes – e.g. clinical trials