Autoimmune Liver Disease

Kay Washington, M.D., Ph.D.
Vanderbilt University Medical Center

Three main categories of autoimmune liver disease
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Characteristic morphologic patterns of injury

Overlap syndromes (primarily of AIH with PBC or PSC) may comprise up to 10% of cases
  - Sequential syndromes are rarer
- Diagnosis is based upon a constellation of clinical, serologic, and biopsy findings.

Asymptomatic AIH
- AIH in the elderly
- New simplified scoring system for AIH
- Autoimmune liver disease associated with celiac disease
- IgG4 cholangiopathy
- Response to UDC in PBC
- More focused studies of overlap syndromes
Autoimmune Hepatitis: Definition

- Unresolving hepatitis
- Increased IgG levels
- Tissue directed autoantibodies
- Responds to immunosuppression

Autoimmune Hepatitis: Epidemiology

- Prevalence of ~ 1 per 100,000 in North America
- ~20% of chronic hepatitis
- Associated with HLA A1-B8-DR3 in European populations and DR4 in Japan
- More common in women
- Wide age distribution

Immunology of AIH

- Loss of self-tolerance
- Cause usually unclear
- ? Viral trigger- anecdotal reports of AIH following HAV, HBV, HSV, EBV infections
- Unlikely to be triggered by HCV: anti-LKM antibodies in HCV are directed against different epitopes
- Small heritable component; complex genetic trait
Autoimmune Hepatitis: Clinical Features

- Presentation is highly variable (asymptomatic to fulminant hepatic failure)
- 1/3 are cirrhotic at presentation
- 1/3 have acute presentation mimicking viral hepatitis
- 1/3 have prodromal phase
- 20% are asymptomatic
- ~50% will have other autoimmune disorders

Asymptomatic Presentation of AIH

- ~20 to 25% are asymptomatic at diagnosis
- Discovered on routine liver testing
- Older patients
- Less activity in liver biopsy
- 25% will develop symptoms upon follow up
- Survival is similar to patients with symptomatic presentation

Two Groups of Asymptomatic Patients

- “Burned out” cirrhosis and nearly normal liver tests
  - 36%; similar to that seen in symptomatic patients
  - Less favorable outcome (62% vs. 94% 10-year survival)
- Mild hepatitis without cirrhosis

AIH in the Elderly

- Over 20% are diagnosed after age 60
- More likely to be cirrhotic at presentation
- Responds to corticosteroid therapy, even in setting of cirrhosis
- HLA DR4 more common
**Diagnosis of AIH: Serum Studies**

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Target Antigen</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA and/or SMA</td>
<td>ANA-ds DNA &amp; histones; laminin; SMA- actin</td>
<td>70-80%</td>
</tr>
<tr>
<td>LKM1</td>
<td>Cytochrome p450 (CYP) 2D6 (endoplasmic reticulum)</td>
<td>3-4%</td>
</tr>
<tr>
<td>SLA/LP</td>
<td>UDA suppressor serine tRNA-protein complex</td>
<td>10-30%</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>Multiple targets; actin</td>
<td>60-90%</td>
</tr>
</tbody>
</table>

**Autoimmune Hepatitis: Classification**

<table>
<thead>
<tr>
<th>Type</th>
<th>Autoantibodies</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>ANA +/- SMA</td>
<td>Most common</td>
</tr>
<tr>
<td>Type II</td>
<td>LKM1</td>
<td>Young women with severe disease</td>
</tr>
<tr>
<td>Type III</td>
<td>SLA/LP</td>
<td>Indistinguishable from Type I</td>
</tr>
</tbody>
</table>

**Autoimmune Hepatitis: Histologic Features**

- Chronic hepatitis pattern of injury
  - Interface hepatitis
  - Lobular activity
  - Prominent plasma cells (IgG+, rarely IgM+)
- Hepatocyte regeneration
- Centrilobular necroinflammatory activity
- Bile duct injury not rare
Emperipolesis in Autoimmune Hepatitis

Lobular Activity in AIH

Lobular Plasma Cells in AIH
AIH Scoring System:
Positive Weighting

- Female sex
- Low alk phos:AST ratio
- Increased IgG
- Autoantibodies
- Negative viral serology
- Positive treatment response

AIH Scoring System:
Negative Weighting

- High alk phos:AST ratio
- AMA +
- Positive viral serology
- Positive drug history
- High alcohol consumption
- Bile duct damage

- Definite AIH if score > 15 before treatment, 17 after treatment
- Probable AIH if 10-15 before treatment, 12-17 after treatment

Simplified Diagnostic Criteria for AIH

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cutoff</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA or SMA +</td>
<td>≥1:40</td>
<td>1</td>
</tr>
<tr>
<td>OR LKM</td>
<td>≥1:40</td>
<td></td>
</tr>
<tr>
<td>OR SLM</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>&gt; Upper limit of normal</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;1.1 x upper limit of normal</td>
<td>2</td>
</tr>
<tr>
<td>Liver histology</td>
<td>Compatible with AIH</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Typical AIH</td>
<td>2</td>
</tr>
<tr>
<td>Absence of viral hepatitis</td>
<td>yes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>≥6: probable AIH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥7: definite AIH</td>
<td></td>
</tr>
</tbody>
</table>

*Addition of points achieved for all antibodies (max 2 points)
Categories for Weighting Histology

- Typical histology (2 points)
  - Interface hepatitis (lymphocytes +/- plasma cells)
  - Emperipolysis
  - Hepatocyte rosette formation (1 point)
- Histology compatible with AIH
  - Chronic hepatitis pattern of injury but lacking some “typical” features
- Atypical histology
  - Features suggestive of other diagnoses

Autoimmune Hepatitis: Diagnostic Difficulties

- Autoantibody negative patients
- Overlap with other autoimmune liver diseases
- Viral hepatitis

Autoimmune Hepatitis and Viral Hepatitis

- True AIH, false positive anti-HCV
- True HCV, autoantibodies at low titers
- True HCV and features of AIH
  - Young women
  - Extrahepatic autoimmune disorders
  - High autoantibody titers
  - Increased serum IgG

Genuine vs. Virus-Induced Autoimmunity

<table>
<thead>
<tr>
<th></th>
<th>AIH</th>
<th>Viral Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibody titer</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Linear epitopes</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Conformational epitopes</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Inhibitory antibodies</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Autoimmune response</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>Treatment</td>
<td>Immunosuppression</td>
<td>Antiviral agents</td>
</tr>
</tbody>
</table>
Autoimmune Hepatitis: Further Differential Diagnostic Considerations

- Drug reaction
  - Drug-triggered self-perpetuating AIH
- Alpha-1-antitrypsin deficiency in the adult patient
- Wilson’s disease
- Celiac disease
- Non-specific spotty hepatocyte necrosis (chronic hepatitis of unclear etiology)

The Liver in Celiac Disease

- Increased ALT/AST in 40% adults, 54% children with celiac disease
- Histologic changes are common but non-specific
  - Periportal and portal inflammation
  - Prominent Kupffer cells
  - Steatosis
- Associated autoimmune liver diseases: AIH, PBC, PSC (prevalence varies widely)

AIH versus Drug Reaction

- Drug reaction may trigger an immune attack on the liver
- Centrilobular necrosis and inflammation may be seen in both drug reaction and AIH
- Eosinophils may not be more prominent in drug reaction

Self-perpetuating AIH

- Serologic profile may resemble either Type 1 AIH or Type 2 AIH
- Commonly implicated drugs include
  - Alpha methylldopa
  - Minocycline
  - Nitrofurantoin
  - Interferon
Recently reported Associations with AIH

- Hepatitis A infection
- Hepatitis vaccine
- Twinrix (HAV + HBV vaccine)
- Interferon tx for HCV, MS
- Terbinafine in HBV
- Atomoxetine
- Phenylpropryluracil
- Black cohosh
- Imatinib
- Infliximab
- Methylphenidate
- Statins
- Kava kava & St Johns wort
- Minocycline
- Respineridone

Primary Biliary Cirrhosis:
Definition

- Chronic cholestatic liver disease, considered autoimmune in etiology
- Morphologic hallmark is inflammatory destruction of intrahepatic bile ducts
- Serologic hallmark is circulating AMA

Epidemiology of
Primary Biliary Cirrhosis

- Affects women (male-female ratio 1:9)
- Median age of onset 50 years (range 21-91)
- Geographical variation: increased prevalence in areas of England, low in developing countries
- More common near "Superfund" sites
- Accounts for up to 2% of deaths from cirrhosis worldwide

Pathogenesis of
Primary Biliary Cirrhosis

Considered an autoimmune disorder
- association with Sjogren’s disease, RA, autoimmune thyroiditis
- ? Multiple hit mechanism triggered by mimicry
- AMA directed against M2 antigen (E2 component of the pyruvate dehydrogenase complex)
Primary Biliary Cirrhosis: Clinical Features

- 50-60% are asymptomatic at presentation
- Most common signs are pruritus and fatigue
- Elevated alkaline phosphatase
- Jaundice occurs in late stages
- Scleroderma, especially CREST syndrome, in 10%
- Gallstones in 50%

Natural History of PBC

- 25% treated with UDC will not progress over 4 years (Stage I and II); improved prognosis with response to UDC at all stages
- Severity of interface hepatitis is associated with progression to cirrhosis in UDC treated patients
- Stage III or IV patients progress to transplant or die with median time of 9.3 years
- Complications of chronic cholestasis and cirrhosis
- Smoking may accelerate progression

Survival in PBC: Untreated

Antimitochondrial Antibodies

- Immunoblotting may be more sensitive than indirect IF
- Using cloned mitochondrial antigen (rMT3) or bead assay may identify AMA
- Increased expression of PDC-E2 has been demonstrated in biliary epithelium
Pathology of PBC

- Florid duct lesion:
  - inflammation
  - injury to bile duct epithelium
  - disruption of basement membrane
- 40 to 80 microns bile ducts
- Segmental destruction

LOBULAR PLASMA CELLS IN PBC
**Granulomas and PBC**

- Usually found in portal tracts as loose collection of epithelioid histiocytes
- May also be found in lobule and hilar lymph nodes
- Often found in earlier stages, ~50% of patients
- May portend better prognosis

**Pathology of PBC**

- Chronic cholestasis
  - Feathery degeneration
  - Copper accumulation
  - Hyaline accumulation
- Bile ductular reaction
- +/- interface hepatitis & plasma cells
- Eventual loss of biliary epithelium
**Differential Diagnosis of Primary Biliary Cirrhosis**

- Portal inflammation
- Lymphocytic bile duct destruction
- Granulomas
- Ductopenia
- Copper deposition
- Ductular reaction
- Chronic hepatitis, drug reaction
- Hepatitis C
- Drug reaction, sarcoidosis
- PSC
- Chronic cholestasis
- Biliary obstruction

**Bile Duct Injury in Chronic Viral Hepatitis**

- HCV
- HBV

**Hepatic Sarcoidosis**

- Almost 60% of cases of hepatic sarcoidosis showed evidence of cholestasis, usually chronic
- ~20% had bile duct lesions similar to those seen in PBC
- Granulomas of sarcoidosis are better formed and more numerous than PBC


**Staging of Primary Biliary Cirrhosis**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Ludwig</th>
<th>Scheuer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Portal</td>
<td>Florid duct lesion</td>
</tr>
<tr>
<td>2</td>
<td>Periportal</td>
<td>Ductular proliferation</td>
</tr>
<tr>
<td>3</td>
<td>Septal</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
<td>Nodular cirrhosis</td>
</tr>
</tbody>
</table>

Stage 1
- Florid duct lesion
- Portal inflammation
- Small portal tracts may lack bile ducts
- Kupffer cell aggregates, small granulomas in lobule; small collections of lymphocytes
- Nodular regenerative hyperplasia may contribute to portal hypertension

Stage 2
- Periportal changes
- Ductular reaction
- Portal tracts are enlarged
- Biliary piecemeal necrosis
- In some cases, lymphocytic interface hepatitis predominates

Stage 3
- Scarring stage
- Portal-portal fibrous septa
- Bile ductular reaction becomes less prominent
- Cholestasis may be seen in addition to cholate stasis

Stage 4
- Biliary cirrhosis
- Profound loss of small and medium-sized ducts
- Usually no bile ductular reaction
- Cholate stasis with copper accumulation and Mallory-Denk bodies
Primary Sclerosing Cholangitis: Definition

- Chronic cholestatic liver disease, probably autoimmune in etiology
- Affects extra- and intrahepatic biliary tree

Epidemiology of PSC

- Male predominance (2:1 M/F)
- Median onset 30 years, range 1-90 yrs
- Prevalence in U.S. estimated as 2-7/100,000
- 70% of cases are associated with ulcerative colitis

Genetic Factors and PSC

- Increased prevalence of HLA B8 and DR3
- This haplotype is associated with a number of organ-specific autoimmune diseases
  - autoimmune hepatitis
  - thyroiditis
  - celiac disease
  - myasthenia gravis
- HLA DR4 associated with adverse prognosis

Natural History of Primary Sclerosing Cholangitis

- Clinical course is variable and unpredictable
  - obstructing strictures
  - bacterial cholangitis
  - biliary stone formation
  - cholangiocarcinoma
- Major cause of death in patients with ulcerative colitis
- Median survival from diagnosis 9-12 years
Diagnosis of PSC

- Based on cholangiographic findings of beading and irregularity of biliary system
- 80% are ANCA positive but this is non-specific
- Liver biopsy may not be diagnostic and may even be normal

Diagnosis of PSC

- Gold standard (MRCP)
- Multifocal stricturing and beading
- Involves both extra-and intrahepatic ducts in typical case
- Gallbladder and cystic duct are involved in ~15%

Histologic Clues: PSC

- Concentric periductal fibrosis
- Rounded scars in portal tracts
- Distorted interlobular bile ducts
- Loss of small interlobular bile ducts (60% of cases)
- Superimposed changes of extrahepatic obstruction

Duct Lesions in PSC

- Periductal edema
- Periductal fibrosis
- Duct distortion
- Duct loss
- Often minimal inflammation
Granulomatous Response to Bile in PSC
Small Duct PSC

- Diagnostic criteria: chronic cholestatic liver disease with biopsy features suggestive of PSC & normal cholangiogram
- In some studies, diagnosis of IBD is required
- ~25% progress to large duct involvement over 8 years
- Crohn’s Disease in 21% of patients in one study
- Better prognosis than large duct PSC

Staging of Primary Sclerosing Cholangitis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Portal</td>
</tr>
<tr>
<td>2</td>
<td>Periportal</td>
</tr>
<tr>
<td>3</td>
<td>Septal</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>
**Differential Diagnosis:**

**PSC**
- Primary biliary cirrhosis
- Chronic large duct obstruction
- Autoimmune hepatitis (children)
- Intrahepatic artery chemotherapy
- Langerhans cell histiocyte (children)
- Eosinophilic or mast cell cholangiopathy
- Infectious cholangiopathy (AIDS)
- Primary immunodeficiency
- Autoimmune pancreatitis

**Chronic Large Duct Obstruction**
- May be difficult to distinguish from PSC
- Features common to both:
  - Periductal fibrosis
  - Bile ductular reaction
  - Cholestasis
- Bile duct loss does not occur in obstruction
- Finding numerous eosinophils favors PSC

**IgG4 Cholangiopathy**
- Intrapancreatic bile duct is often involved in autoimmune pancreatitis (plasma cell-rich infiltrate with IgG4+ cells)
- Extra-pancreatic biliary involvement in ~15% of cases
- High serum IgG4 levels
- Susceptible to steroid therapy
- Multiple histologic patterns of liver injury in AIP: portal inflammation, large duct damage, portal sclerosis, lobular hepatitis, cholestasis
PSC in Children

• Intrahepatic disease may predominate
• Usually diagnosed in teenage years
• ~50% have inflammatory bowel disease
• ~15% have an immunodeficiency syndrome
• Also associated with Langerhans cell histiocytosis
• Overlap with autoimmune hepatitis

Overlap Syndromes of Autoimmune Hepatopathies

AIH 8-14% 6-8% PBC PSC

Variants of Autoimmune Liver Disease

<table>
<thead>
<tr>
<th>Overlap Syndromes</th>
<th>Outlier Syndrome</th>
<th>Sequential Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIH-PBC</td>
<td>AIC (AMA negative PBC)</td>
<td>AIH ↔ PBC</td>
</tr>
<tr>
<td>AIH-PSC</td>
<td></td>
<td>AIH ↔ PSC</td>
</tr>
<tr>
<td>AIH-AIC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Autoimmune Cholangitis

• Lack of uniform criteria for diagnosis
• Sometimes characterized as a variant of PBC
• Patients typically have high ANA titers, no AMA
• Histology is often similar to PBC, but may not be equivalent to AMA-negative PBC
• May represent an early stage of disease in evolution (AMA titers may fluctuate)
**Autoimmune Cholangitis**

- Identical to PBC except for lack of AMA
- No significant differences with AMA-positive PBC patients—slightly younger in one study
- Similar response to ursodeoxycholic acid
- More sensitive AMA tests may detect AMA

**AMA-Negative PBC**

- Identical to PBC except for lack of AMA
- No significant differences with AMA-positive PBC patients—slightly younger in one study
- Similar response to ursodeoxycholic acid
- More sensitive AMA tests may detect AMA

**AIH + PBC Overlap Syndrome**

- Reserved for cases with “triple overlap”: serology, clinical findings, pathology
- Controversial—? hepatitic form of PBC
- Treatment with both UDCA and corticosteroids
- Similar response to UDCA
**Autoimmune Hepatitis versus PSC**

- Distinguishing PSC from autoimmune hepatitis is more commonly a problem in pediatric patients
- Alkaline phosphatase may be normal
- Cholangiographic findings more subtle
- Concentric periductal fibrosis is rare; usual pattern is loss of small bile ducts
- Portal inflammation may mimic hepatitis

**AIH + PSC Overlap Syndrome**

- 55 children with AIH followed for 16 years
  - 27 developed bile duct changes of PSC
- Term “autoimmune sclerosing cholangitis” proposed
- IBD more common in this group than in AIH
- More commonly p-ANCA +
- Younger than classic PSC patients


**Sequential Syndromes**

- Relatively rare; multiple liver biopsies
- Usually AIH ↔ PBC or AIH ↔ PSC
- Diagnosis of AIH usually precedes PSC

**Autoimmune Liver Disease: Practice Points**

- Diagnosis of AIH is based on combination of findings
  - Numerous plasma cells is suggestive of AIH but no pathognomonic
- Both PBC and PSC can cause ductopenia in biopsies from adult patients
  - Use clinical (demographic, liver tests, serologic, radiographic) findings
- Overlap among autoimmune liver diseases