Autoimmune hepatitis
Integrating morphologic features with clinical and laboratory findings into a meaningful pathology report

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University of California, San Francisco

Outline
- Scoring system for AIH diagnosis
- Case examples
- Histologic patterns of injury
- Specific clinicopathologic settings
- Overlap syndromes

Diagnosis of AIH
- Serologic: autoantibodies
- Serum IgG
- Exclude viral hepatitis (drug injury)
- Histologic findings

International AIH Group: Simplified score

<table>
<thead>
<tr>
<th>Variable</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>ANA or SMA</td>
<td>1:80</td>
<td>1</td>
</tr>
<tr>
<td>or UKM</td>
<td>1:40</td>
<td>2*</td>
</tr>
<tr>
<td>or SLA</td>
<td>Positive</td>
<td>1</td>
</tr>
<tr>
<td>IgG</td>
<td>&gt;Upper normal limit</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;1.10 times upper normal limit</td>
<td>2</td>
</tr>
<tr>
<td>Liver histology (evidence of hepatitis is a necessary condition)</td>
<td>Compatible with AIH</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Typical AIH</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abstinence of viral hepatitis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Score 6: Probable AIH sensitivity 88%, specificity 97%
Score 7: Definite AIH sensitivity 81%, specificity 99%
**AIH: histologic features**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical (2 points)</td>
<td>- Interface lymphoplasmacytic infiltrate with lobular involvement</td>
</tr>
<tr>
<td></td>
<td>- Emperipolesis</td>
</tr>
<tr>
<td></td>
<td>- Hepatic rosette formation</td>
</tr>
<tr>
<td>Compatible (1 point)</td>
<td>Chronic hepatitis without all 3 features</td>
</tr>
<tr>
<td>Atypical (0 points)</td>
<td>Features of another disease process</td>
</tr>
</tbody>
</table>

**Emperipolesis**

- "Engulfment of lymphocytes by hepatocytes"
- *MacSween’s Pathology of the Liver*
- "Active penetration of one cell through a larger cell"
- *IAIHG Simplified Criteria*

**Is this emperipolesis?**

**Emperipolesis: interpretation subjective**
Rosettes: Boer, Histopathol 2015

5-25% of parenchyma  25-50% of parenchyma

Acute hepatitis-drug injury

Rosette

• ‘Regenerative change where hepatocytes assume the structure of short cylinders’
• Not defined by IAIHG Simplified Criteria

©MacSween's Pathology of the Liver
Limitations of scoring criteria

• Limited sensitivity and specificity: 50-70%
• Inconsistent interpretation
• Rosettes and emperipolesis required for 2 points
• Underscoring of histologic criteria even in otherwise typical cases

Proposed Modified Criteria

Score 1
Mild or mild to moderate hepatitis
(Ishak A2, B1, C2)
CK7, copper: negative
(only for Ishak fibrosis score ≤2)

Score 2
(a) Abundant plasma cells
(b) High necroinflammatory activity
(Ishak ≥A3, B2 and/or C3)

Balitzer/Kakar, USCAP 2015

AIH: spectrum of pathologic patterns

<table>
<thead>
<tr>
<th>Histologic pattern of injury</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or fulminant hepatitis</td>
<td>Viral, drug, Wilson disease</td>
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<tr>
<td>Chronic hepatitis</td>
<td>Viral, Wilson disease, α1-antitrypsin deficiency, biliary diseases, drug (uncommon)</td>
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<tr>
<td>Cirrhosis</td>
<td>Steatohepatitis, viral, Wilson disease, α1-antitrypsin deficiency, biliary diseases</td>
</tr>
<tr>
<td>Nonspecific mild inflammatory pattern</td>
<td>Mild hepatitis of another etiology Biliary diseases</td>
</tr>
</tbody>
</table>

Friedrich Nietzsche

“There are no truths, only interpretations”
Liver pathology: There are no diagnoses, only patterns
Case 1

Presentation: 19/F presented with abrupt onset of abdominal pain, jaundice and signs of liver failure

Liver enzymes: ALT 1250, AST 1100, ALP 230

Viral serologies: A,B,C,E: negative

AutoAb: ANA+, SMA+

Wilson disease: Ceruloplasmin normal
**Diagnosis**

<table>
<thead>
<tr>
<th>Inflammation dominant-acute hepatitis</th>
<th>Viral hepatitis</th>
<th>Negative for A, B, C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune hepatitis</td>
<td>ANA, SMA positive</td>
<td></td>
</tr>
<tr>
<td>Drug-induced liver injury</td>
<td>Minocycline for acne, no other drugs</td>
<td></td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Ceruloplasmin, urinary copper normal</td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Serology not done</td>
<td></td>
</tr>
</tbody>
</table>

**Scoring for this case**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
<th>This case</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA or SMA &gt;1:40 or ANA or SMA &gt;1:80 or LKM &gt;1:40 or SLA positive</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IgG upper limit of normal</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IgG 1.1x normal</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Absence of viral hepatitis</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Histology

- Compatible with AIH: 1 (1)
- Typical of AIH: 2 (2)

If histology score 1, total points 5: Probable AIH
If histology score 2, total points 6: Definite AIH

**Drug-related hepatitis with autoimmune markers**

<table>
<thead>
<tr>
<th>Multiple reports</th>
<th>Few reports</th>
<th>Herbal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline</td>
<td>Statins</td>
<td>Germander</td>
</tr>
<tr>
<td>Methyl-dopa</td>
<td>Infliximab</td>
<td>Ecstasy</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Interferon</td>
<td>Noni juice</td>
</tr>
<tr>
<td>Oxyphenasitine</td>
<td>Fenofibrate</td>
<td></td>
</tr>
<tr>
<td>Clometacin</td>
<td>Doxycycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rifampin+pyrazamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydralazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Halothane</td>
<td></td>
</tr>
</tbody>
</table>

**Drug-related AIH**

- Autoantibodies after starting drug
- HLA B8, DR3, DR4 absent
- Resolution of disease on drug withdrawal
- Autoantibodies disappear on drug withdrawal
- Multiple reports for implicated drug

http://livertox.nih.gov/
Diagnosis
Minocycline-associated hepatitis with autoantibodies, mimicking *de novo* AIH

AIH with acute presentation
• Chronic hepatitis with acute exacerbation
• Histologic acute hepatitis
  Autoantibodies absent
  Serum IgG tends to be lower
  Delay: negative impact on outcome

Acute AIH +

Biopsy with nodular appearance +
Trichrome

Dark: portal collagen, Light: necrosis

**AIH cirrhosis: impact on therapy**

- Planning for transplant
- Budesonide: effective for inducing remission in AIH without cirrhosis
- Less side effects than predinisolone

Manns, Gastroenterology, 2010
**Case 2**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>35/F with history of SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver enzymes</strong></td>
<td>ALT, ALT 250, ALP 140</td>
</tr>
<tr>
<td><strong>Acute hepatitis work-up</strong></td>
<td>ANA+ SMA+ Negative for viral, celiac, Wilson, drugs.</td>
</tr>
<tr>
<td><strong>Clinical suspicion</strong></td>
<td>Autoimmune hepatitis</td>
</tr>
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</table>

**Orcein stain: no elastic fibers in necrotic area**

**Mild portal inflammation**

**Lobule: mild lymphocytic, rare plasma cells**
### Scoring for this case

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<td>2</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compatible with AIH</td>
<td>1</td>
<td>(1)</td>
</tr>
<tr>
<td>Typical of AIH</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

If histology score 1, total points 6: Probable AIH
If histology score 2, total points 7: Definite AIH

### Is this AIH?
- ANA+, SMA+
  - Common in SLE
- Natural history different
  - Cirrhosis and liver failure in AIH
  - Survival 10% at 10 years

### Diagnosis
- ALT, AST <300 U/L
- Biopsy: mild inflammation

Diagnosis: Lupus-related hepatitis
  - (Nonspecific reactive hepatitis)

### AIH: spectrum of pathologic patterns

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**AIH: mild injury**
- Asymptomatic in up to one-third
- Men, lower ALT levels
- 70% become symptomatic on follow-up
- Progression to cirrhosis can occur
- Diagnosis based on overall features, cannot be confirmed by histology alone

AASLD guidelines, Hepatology, 2010

**AIH: Hyaline droplets in Kupffer cells**
- 30% of pediatric cases
- Rare in other hepatitides


**Hyaline deposits vs. lipofuchsin**

**Outline**
- Scoring system for AIH diagnosis
- Case examples
- Specific clinicopathologic settings
- Overlap syndromes
AIH: specific clinical situations

• Seronegative AIH
• AMA+ AIH
• Autoantibodies in steatohepatitis
• Autoantibodies in hepatitis C
• Isolated centrizonal involvement

Seronegative AIH

• Absence of autoantibodies
• Presentation and response to therapy typical of AIH
• Work-up for other diseases: negative

Autoantibodies in AIH

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA, SMA</td>
<td>Present in most cases Type 1 AIH</td>
</tr>
<tr>
<td>Liver kidney microsomal (LKM)</td>
<td>Type 2 AIH More common in children</td>
</tr>
<tr>
<td>Liver cytosol type 1 (LC-1)</td>
<td>Type 2 AIH</td>
</tr>
<tr>
<td>Soluble liver antigen (SLA)</td>
<td>Type 1 AIH Severe disease</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>Type 1 AIH</td>
</tr>
</tbody>
</table>

Autoantibodies in AIH

• Obtain nonstandard autoantibodies before labeling a case as seronegative
• Autoantibodies may appear later in seronegative cases
• Titer does not correlate well with disease activity

AASLD guidelines, Hepatology 2010
AMA+ AIH

• AMA+ in 5-20% of AIH with no evidence of biliary disease
• No difference in natural history

O’Brien, Hepatology 2008

Steatohepatitis with autoantibodies

• Autoantibodies common
  ANA: 30%, SMA: 10%
  Both: 1-2%
• AMA uncommon (<1%)

Cotler, J Clin Gastroenterol 2004

Autoantibodies in Hep C

• Do not necessarily signify an additional component of AIH
• Some studies:
  Higher necroinflammatory activity and fibrosis
• Recent studies:
  No difference in treatment response or disease progression with or without antibodies

Clifford, Hepatol 1995
Muratori, Clin Infect Dis 2005
Mauss S, J Viral Hepat. 2013
Khairy, Liver Int. 2013
**AIH: specific clinical situations**

- Seronegative AIH
- AMA+ AIH
- Autoantibodies in steatohepatitis
- Autoantibodies in hepatitis C
- Isolated centrizonal involvement

Hofer, J Clin Pathol, 2006

**AIH: centrizonal changes only**

- Can progress to typical AIH
- Plasma cells may not be present
- One reported case: no autoantibodies at presentation

Misdraji AJSP 2004
Nakanuma, Hum Pathol 2007

**AIH: Role of the pathologist**

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>- Identify histologic pattern</td>
</tr>
<tr>
<td></td>
<td>- Provide histologic score (if relevant)</td>
</tr>
<tr>
<td></td>
<td>- Note typical AIH features: high necroinflammatory activity, plasma cells</td>
</tr>
<tr>
<td></td>
<td>- Fibrosis (stage)</td>
</tr>
<tr>
<td>Relapse</td>
<td>Grade activity</td>
</tr>
<tr>
<td></td>
<td>Stage fibrosis</td>
</tr>
<tr>
<td>Cessation of therapy</td>
<td>Histologic activity common even if ALT, AST and IgG normal</td>
</tr>
</tbody>
</table>

AASLD guidelines, Hepatology 2010

**AIH: cessation of therapy**

- Interface hepatitis in >50% normal AST and IgG levels during therapy
- Typically relapse after cessation of treatment
- Liver biopsy recommended
  - Histologic activity, fibrosis

AASLD guidelines, Hepatology 2010
Refractory AIH

Confirm diagnosis
• Wilson disease, alpha-1-antitrypsin deficiency
• Celiac disease
• Overlap syndrome

Overlap syndromes

• AIH-PBC overlap
• AIH-PSC overlap

Simultaneous or concurrent
Features of initial disease may not be present

AIH-PBC overlap syndrome

Implications of diagnosis
• PBC: treated with UDCA
  steroids not beneficial
• AIH: UDCA not useful
  can rapidly progress if untreated

AIH vs. PBC

<table>
<thead>
<tr>
<th></th>
<th>AIH</th>
<th>PBC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver enzymes</strong></td>
<td>Elevated</td>
<td>Typically &lt;400 U/L Elevated</td>
</tr>
<tr>
<td>ALT/AST ALP</td>
<td>Elevated, often mild</td>
<td>Elevated</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td>Typical of AIH, type 1</td>
<td>Can be seen in PBC</td>
</tr>
<tr>
<td>ANA, SMA, AMA</td>
<td>Uncommon in AIH</td>
<td>Typical of PBC</td>
</tr>
<tr>
<td><strong>Ig levels</strong></td>
<td>↑IgG typical of AIH</td>
<td>↑IgM typical of PBC</td>
</tr>
</tbody>
</table>
### Histological features

<table>
<thead>
<tr>
<th></th>
<th>AIH</th>
<th>PBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular injury</td>
<td>Often prominent</td>
<td>Mild or absent</td>
</tr>
<tr>
<td>Interface activity Plasma cells</td>
<td>Often prominent</td>
<td>Mild or absent</td>
</tr>
<tr>
<td>Bile duct inflammation Bile duct loss Cholestasis, ductular reaction</td>
<td>Absent/focal Absent/rare Can be present</td>
<td>Typically present Can be present</td>
</tr>
<tr>
<td>Periportal CK7, copper</td>
<td>Absent (except in late stages)</td>
<td>Often present</td>
</tr>
</tbody>
</table>

#### AIH-PBC overlap syndrome

<table>
<thead>
<tr>
<th>PBC</th>
<th>AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP 2x</td>
<td>ALT 5x</td>
</tr>
<tr>
<td>AMA positive</td>
<td>SMA positive or IgG 2x</td>
</tr>
<tr>
<td>Florid duct lesion</td>
<td>Moderate to severe interface activity</td>
</tr>
</tbody>
</table>

Paris criteria:
2 of 3 from each group should be present for diagnosis of overlap syndrome

Chazouillères, Hepatology 1998

### Case 3

- 40/F with nonspecific abdominal symptoms
- “Elevated LFTs”
- ANA, SMA positive
  - AMA negative
Initial diagnosis

Autoimmune hepatitis
• ANA, SMA+
• Biopsy: mild interface activity
  lobular inflammation
  intact bile ducts

Serial liver enzymes

<table>
<thead>
<tr>
<th></th>
<th>1-2009</th>
<th>9-2009</th>
<th>1-2010</th>
<th>4-2010</th>
<th>6-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>58</td>
<td>62</td>
<td>83</td>
<td>179</td>
<td>190</td>
</tr>
<tr>
<td>AST</td>
<td>40</td>
<td>38</td>
<td>65</td>
<td>100</td>
<td>110</td>
</tr>
<tr>
<td>ALP</td>
<td>292</td>
<td>240</td>
<td>224</td>
<td>288</td>
<td>313</td>
</tr>
</tbody>
</table>
Periportal copper

Repeat biopsy: granulomatous bile duct injury

AIH-PBC overlap syndrome

<table>
<thead>
<tr>
<th>PBC</th>
<th>AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP 2x: yes</td>
<td>ALT 5x: yes</td>
</tr>
<tr>
<td>AMA positive: no</td>
<td>SMA positive or IgG 2x: yes</td>
</tr>
<tr>
<td>Florid duct lesion: no</td>
<td>Moderate to severe interface activity: +/-</td>
</tr>
</tbody>
</table>

2 of 3 criteria from each group should be present for diagnosis of overlap syndrome

AASLD, EASL guidelines

• No definite criteria for diagnosis of overlap syndromes

Lindor, Hepatology, 2009
EASL, J Hepatology, 2009
Case 4
• 44/F with nonspecific abdominal symptoms
• ALT 84, AST 158, ALP 876
• Both IgG and IgM elevated
• ANA, SMA positive
  AMA negative
Primary biliary cirrhosis, no definite AIH component

<table>
<thead>
<tr>
<th>PBC</th>
<th>AIH</th>
</tr>
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<tbody>
<tr>
<td>ALP 2x: yes</td>
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<td>Moderate to severe interface activity: no</td>
</tr>
</tbody>
</table>

Do overlap syndromes exist?

- The outer boundaries of the classical diagnoses are undefined, and the point where a hepatitic PBC meets a cholestatic AIH is unknown
- Clinical acumen rather than fixed algorithm may be the best method of managing these cases

Editorial: Czaja, J Hepatol 2006
**AIH-PBC overlap syndrome**
role of the pathologist

- Raise possibility of overlap with AIH
  - Moderate to severe interface/lobular activity
- Raise possibility of overlap with PBC
  - Bile duct damage and ductopenia
  - Copper/CK7+ hepatocytes in early stage disease

**AIH-PSC overlap syndrome**

- Children, young adults
- IBD often present
- By definition: AIH with cholangiographic features of PSC
- Sequential progression can occur

**Summary**

Diagnosis of AIH, PBC
- Identify histologic pattern
- Discuss differential diagnosis
- Suggest use of scoring system, provide reference
- Consider modified histologic criteria

References:
- Gregorio Hepatol 2001
- Abdo Hepatol 2002
- Czaja, Can J Gastroenterol 2013
- Luth, J Clin Gastroenterol 2009
Summary

Overlap syndrome
- Raise possibility if overlapping features are present, especially if supported by serologic and biochemical tests

*Cannot be diagnosed on biopsy alone*

A mystic assumption prevails in the mind of the clinician that the pathologist can produce a statement of absolute truth based on a small piece of tissue

More dangerous to mankind is the pathologist who thinks the same

Oscar Rambo, UCSF

Interface activity, ductular reaction: minimal
Periportal activity (‘biliary piecemeal necrosis’)

Lobular inflammation in PBC

Bile duct loss

Copper and CK7

Markers of chronic cholestasis
- Periportal hepatocellular copper
- CK7+ periportal hepatocytes
- Not specific for cholestasis if bridging fibrosis or cirrhosis
• importance of recognizing
• excessive inflammatory activity in an otherwise cholestatic
• syndrome and responding to this finding with potent
• antiinflammatory
• medication [5]. There are no objective indices
• that guide this intervention, and there are always legitimate
• concerns regarding corticosteroid-induced bone disease
• [4,6]. The careful selection of patients by histological
• examination and the customization of therapies to
• individual
• need are essential for a favorable benefit-to-risk ratio.
• Previous studies in PBC using prednisolone [14] or
• Journal of Hepatology 44 (2006) 251–252

• From a clinical standpoint, the recognition of a
  disproportionate amount of inflammatory activity in a
  patient with antimitochondrial antibodies and florid
  duct lesions on liver tissue examination is the key
  issue, and the experience of Chazouille `res and
  colleagues indicates that this awareness can direct
  therapy and improve outcome [5]. Whether the
  syndrome is designated atypical PBC or overlap
  syndrome of PBC with AIH is unimportant.
• They are more likely to represent atypical cases of the
  classical disease. As such, they do not warrant
  separate and presumptuous designations such as
  'overlap syndrome'.

• Silveira, AJG 2007
• esophageal varices, GI bleeding, ascites,
  and death and/or OLT were more
  common in the overlap group. The higher
  risk of symptomatic portal hypertension
  and worse outcomes in patients with
  PBC overlap syndrome may justify the
  risks of immunosuppressive therapy

• AASLD guidelines
• In children, the gamma glutamyl
  transferase level may be a better
  discriminator of biliary disease,
  specifically primary sclerosing cholangitis
  (PSC), than the AP level, which can be
  elevated due to bone activity in the
  growing child.77 Neither the gamma
  glutamyl transferase nor AP levels,
  however, discriminate between the
  presence or absence of cholangiopathy
  in children with AIH.36
• AIH can have an acute severe presentation that can be mistaken for a viral or toxic hepatitis. 10,11,58,64,65,67,68,265 Sometimes autoimmune hepatitis may present as acute liver failure. Corticosteroid therapy can be effective in suppressing the inflammatory activity in 36%-100% of patients,11 whereas delay in treatment can have a strong negative impact on outcome. 265-267 In addition, unrecognized chronic disease can exhibit a spontaneous exacerbation and appear acute.92 If extrahepatic endocrine autoimmune features are present in children with severe acute presentation the APECED syndrome must be excluded.268

• Describe the spectrum of morphologic patterns of injury in autoimmune hepatitis
• Incorporate the scoring criteria proposed by the International Autoimmune Hepatitis Group into pathology reports
• Integrate the biopsy findings with clinical and lab data in challenging situations like overlap syndromes and autoantibodies in non-AIH disease settings
AIH: centrizonal involvement