Cholestatic and Autoimmune Liver Diseases

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Topics

- Autoimmune Hepatitis (AIH)
- Primary Biliary Cholangitis (PBC)
- Overlap Syndromes/AMA Negative PBC
- Primary Sclerosing Cholangitis (PSC)
- IgG4-Sclerosing Cholangiopathy

Practice Guidelines

- Autoimmune Hepatitis
- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
Autoimmune Hepatitis (AIH)-Introduction

- Wide spectrum of presentation
  - Asymptomatic
  - Symptomatic/Acute severe hepatitis
  - Acute liver failure
- Female predominance (71-95% adults, 60-76% children)
- 28-33% have cirrhosis on presentation
- Concurrent autoimmune diseases common
  - Autoimmune thyroid disease, celiac disease (2.8-3.5%)

AIH-Pathophysiology

- Break in self-tolerance to hepatocyte autoantigens:
  1) Thymic nTregs incapable of response to autoantigens
  2) APC present autogenic peptides
  3) Costimulation
  4) Cytokine secretion by CD4+ Th cells
  5) Failure of CD4+ and CD8+ Tregs and Bregs to control effector mechanisms
  6) Generation of complex portal inflammatory infiltrates of effector cells leading to cytotoxicity
AIH-Classification

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
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<tbody>
<tr>
<td>Autoantibodies</td>
<td>ANA/SMA/Anti-Actin</td>
<td>Anti-LKM1</td>
</tr>
<tr>
<td>Population</td>
<td>96% US Adults</td>
<td>9-12% US Children</td>
</tr>
<tr>
<td>Cirrhosis on Presentation</td>
<td>28-33% adults</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Children &lt;33%</td>
<td></td>
</tr>
<tr>
<td>Overlap Features</td>
<td>PBC-Adults</td>
<td>PBC-Not reported</td>
</tr>
<tr>
<td></td>
<td>PSC-Children (p-ANCA pos)</td>
<td>PSC-Rare (p-ANCA neg)</td>
</tr>
<tr>
<td>Concurrent AI diseases</td>
<td>Autoimmune Thyroiditis</td>
<td>Type 1 DM, Vitiligo</td>
</tr>
<tr>
<td>Remission after drug withdrawal</td>
<td>Possible</td>
<td>Rare, long term treatment</td>
</tr>
</tbody>
</table>

- 20% AIH patients negative for ANA/SMA/Anti-LKM1; 49% with 1 autoantibody: ANA/SMA/Anti-LKM1
- ANA/SMA nonspecific and common in other diseases-PSC (29%/6%); hepatitis C (26%/6%); hepatitis B (ANA-32%); NAFLD (34%/4%); alcohol (ANA-21%)
- Anti-SLA sole autoantibody + in 14-20% (Predictor of severe disease & relapse)


AIH-Diagnosis

- Compatible histological findings
- Elevated serum aminotransferase levels
- Elevated serum IgG level
- Presence of one or more autoantibodies
- Exclusion of other diseases
  - Viral hepatitis
  - Drug-induced injury
  - Other chronic metabolic, cholestatic, or hereditary liver disease

AIH Scoring Systems

Table 2. Simplified Diagnostic Criteria for Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cutoff</th>
<th>Points</th>
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<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>2*</td>
</tr>
<tr>
<td>or LKM</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>1</td>
</tr>
<tr>
<td></td>
<td>&gt;1.10 times upper</td>
<td>2</td>
</tr>
<tr>
<td>Liver histology (evidence of</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>hepatitis is a necessary</td>
<td>condition)</td>
<td></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 autoantibodies (maximum, 2 points).

Drug Induced AIH-Like Liver Injury

- **Commonly Implicated Agents:**
  - Minocycline
  - Nitrofurantoin
  - Infliximab
  - Alpha-methyldopa
  - Adalimumab
  - Halothane

- **Checkpoint Inhibitor toxicity**
  - Lack laboratory and histological features of AIH
  - Majority respond to glucocorticoid therapy
AIH-Histopathology

- Interface hepatitis
- Plasma cell infiltration (66%)
- Lobular hepatitis (47%)
- Centrilobular necrosis (29%)
- Emperipolesis (65%)
- Hepatocyte rosettes (33%)

- NASH features seen in 17-30%
- IgG4+ plasma cells can be present

Images courtesy of Maura O’Neil

AIH-Acute Liver Failure/OLT

- Acute Liver Failure
  - Histopathology
    - Central perivenulitis (65%)
    - Plasma cell infiltrate (63%)
    - Hepatic necrosis (42%)
    - Lymphoid follicles (32%)
  - Eval for OLT if no improvement after corticosteroids for 1-2 weeks

- OLT
  - 5% of OLT recipients in US due to AIH
  - AIH recurrence
    - 6-12% within 1 yr after OLT
    - 36%-66% after 5 yrs
  - Gradual withdrawal of glucocorticoids can be considered

- De Novo AIH
  - Criteria:
    - Indication for OLT other than AIH
    - >6 months after OLT
    - Exclude plasma cell rich rejection/hepatitis
  - Histology: Interface hepatitis features with lymphoplasmacytic infiltrates
  - Treatment: Similar to AIH

**AIH-Treatment**

- **First line**
  - Steroids
    - Prednisone -or-
      - Adults: 20-40 mg/d
      - Peds: 1-2 mg/kg/d
    - Budesonide 9 mg/d
  - Azathioprine (AZA) 50-150 mg/d
    - Check TPMT activity prior to start

- **Second Line**
  - MMF
  - Tacrolimus/Cyclosporine

- **Salvage Therapies**
  - Anti-TNF
  - Anti-CD20

- **AIH Cirrhosis**: Do not use budesonide-risk for PV thrombosis
- **Acute Severe AIH**: Prednisone 60 mg/d or IV steroids
- **Do not use AZA in decompensated cirrhosis or acute severe AIH**

**AIH-Treatment Withdrawal**

- Treatment withdrawal option after biochemical remission ~2 years (normal ALT, IgG levels)
- Liver biopsy may not be mandated in all adults
- Prewithdrawal liver biopsy advised in children
- Relapse in 50-87% of adults, 60-80% children
Primary Biliary Cholangitis (PBC)-Introduction

- 9:1 Female:Male predominance
- 15% become decompensated over 5 years
- Etiology due to genetic and environmental triggers
- Loss of humoral tolerance (AMA) and increase of (CD)4+CD8+ pyruvate dehydrogenase complex (PDC-E2) specific T-cells in the liver
- Specific environmental agents (xenobiotics) may lead to loss of tolerance to PDC-E2
  - 2-octynoic acid – Cosmetics
  - 6,8-bis- (acetlythio) octanoic acid – Acetaminophen metabolite

PBC-Diagnosis

- Biochemical cholestasis
  - Alkaline phosphatase elevation
  - Can have mild AST/ALT elevations
- Antimitochondrial Antibody (AMA)-Targets lipoic acid present on the 2-oxo-aciddehydrogenase complexes on the inner mitochondrial membrane
  - Found in 95% of PBC patients
  - 0.5% population AMA positive
  - AMA+ 17% 5 year incidence of PBC
- Increased serum IgM
- ~50% may have + ANA or SMA
- Biopsy not required for diagnosis
PBC-Histopathology

- Chronic non-suppurative cholangitis
- Florid duct lesion
  - Inflammatory changes and periductular necrosis
- Epithelioid granulomas (early stage)
- Portal venules compressed / occluded
- Ductopenia

PBC-Clinical Features

- Symptoms: Fatigue 50-80%, Pruritis 20-70%, RUQ abdominal pain 17%, Sicca syndrome
- Concomitant autoimmune conditions: Sjogren syndrome, CREST, scleroderma, Raynaud disease
  - Possible: Autoimmune thyroid, celiac disease
- Exam findings: Excoriations, xanthelasma, xanthoma, hepatomegaly
PBC-Prognostic Models

- Prognostic Models:
  - **GLOBE score**:
    - Bilirubin
    - Albumin
    - Alk phos
    - Platelet count
    - Age at treatment start
    - [https://www.globalpbc.com/globe](https://www.globalpbc.com/globe)
  - **UK-PBC score**:
    - Alk phos
    - AST/ALT
    - Bilirubin
    - Albumin
    - Platelet

PBC-Treatment

**Ursodeoxycholic Acid (UDCA)**

- Dosed 13-15 mg/kg/d
- Mechanism: Choleretic, cytoprotective, anti-inflammatory, immunomodulatory
- Improved biochemistries, survival, reduced need for OLT
- Cholestyramine may affect absorption
- 40% inadequate response to treatment
  - Defined as Alk phos >1.67 ULN after 6-12 months
- Side effects: Diarrhea, thinning of hair
- Rebound pruritis and ↑ in ALP, AST/ALT with withdrawal/discontinuation of UDCA

Figure 1. Probability of Responding to Treatment with Ursodiol (Solid Line) or Placebo (Dotted Line).


PBC-Treatment

Obeticholic Acid (OCA)

- Dosed 5-10 mg/day
- Indication: Inadequate response to UDCA (alk phos >1.67 ULN) or intolerance of UDCA
- Mechanism: Farnesoid X receptor agonist
- Side effects: Pruritis, abdominal pain, hyperlipidemia
- Use discouraged in decompensated patients (CTP-B/CTP-C)
  - Reduced dosing in CTP-B/CTP-C population (5 mg/week)
  - FDA Box Warning issued 2/2018

PBC-Symptom/Complication Management

- Fatigue
  - Check TSH, consider depression, OSA, anemia
  - Fluoxetine, Ondansetron, Modafinil all no benefit in studies

- Pruritis
  - Anion-exchange resins/Bile acid sequestrants
  - Rifampicin 150-300 mg/d
  - Opiate Antagonists-Naltrexone 50 mg/d
  - SSRI-Sertraline 75-100 mg/d
  - Phenobarbital
  - Antihistamines

- Sicca Syndrome
  - Keratoconjunctivitis Sicca-Artificial tears, Pilocarpine/Cevimeline
  - Xerostomia

- Portal hypertension can develop without cirrhosis
- Esophageal varices
  - EGD at diagnosis if suspected cirrhosis

- Osteopenia/Osteoporosis
  - Calcium 1000-1500 mg/d
  - Vitamin D 1000 IU/d
  - Monitor bone density
  - Alendronate can be used

- Hyperlipidemia
  - Potential ↑ risk for CV disease
  - UDCA lowers LDL

- Fat-Soluble vitamin deficiencies
  - Vitamin A, D, E, K
PBC-Liver Transplant

- Excellent outcomes with OLT
- Graft survival: 1 yr-85%, 3 yr-80%, 10 yr-72%
- Patient survival: 1 yr-90.2%, 3-yr-86.7%, 10 yr-79%
- Recurrent disease in 20-30% over 10 yrs, 50% at 20 yrs
- ? Reduced incidence of recurrence with CSA
- UDCA may lower recurrence rates (21% vs. 62%)

AMA Negative PBC

- Should not utilize nomenclature ‘Autoimmune cholangitis’ interchangeably
- ↑ prevalence of ANA, SMA; lower IgM levels
- Presence of PBC-specific antinuclear antibodies
  - 30% with sp100 and gp210 by direct immunofluorescence
  - 35% anti-kelch-like 12
  - 22% anti-hexokinase 1
- Similar PBC histology with less portal inflammation
**AIH/PBC Overlap**

- Paris Criteria-AIH/PBC Overlap
  - 2 of 3 PBC criteria must be met:
    - Alk phos > 2 fold ULN or GGT > 5 fold ULN
    - AMA positive
    - Florid duct lesions on histopathology
  - 2 of 3 AIH Criteria must be met:
    - Interface hepatitis (Mandatory)
    - ALT > 5 fold ULN
    - IgG > 2 fold ULN or SMA positive

- Clinical description
- Non validated pathologic entity
- May help predict nonresponse to conventional treatment
- ↑ risk of treatment failure, death, or need for OLT
- Treatment: Pred + AZA + Urso

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**AIH/PSC Overlap**

- Autoimmune Sclerosing Cholangitis (ASC) in children
- Presence of UC
  - AIH adults-16%
  - AIH children-20%

- Criteria:
  - Typical AIH features
  - Absence of AMA
  - PSC features:
    - Evidence of large duct PSC on ERCP or MRCP
    - Small duct PSC features on histology
Primary Sclerosing Cholangitis (PSC)-Introduction

- Highly variable natural history
- Diagnosis of exclusion
- No associated autoantibody profile
  - ANA, SMA may be seen in >50% of cases
  - Presence of IgG4+ in PSC (10%) may predict a more aggressive course
- 60-70% male
- Age at diagnosis: ~30-40 yrs

PSC-Diagnosis

- Characteristic multifocal biliary strictures with segmental dilatations
  - Seen on ERCP, MRCP or percutaneous transhepatic cholangiography
- Cholestatic biochemical profile
- Secondary causes of biliary injury excluded
- Small duct PSC: Clinical, biochemical and histological features of PSC with normal cholangiogram
  - Biopsy required for diagnosis
  - 12% can progress to large duct PSC
## Secondary Causes of Sclerosing Cholangitis

- AIDS Cholangiopathy
- Cholangiocarcinoma
- Choledocholithiasis
- Diffuse intrahepatic metastasis
- Eosinophilic cholangitis
- Hepatic inflammatory pseudotumor
- Histiocytosis X
- Intra-arterial chemotherapy
- IgG4-associated cholangitis
- Ischemic cholangitis
- Mast cell cholangiopathy
- Portal hypertensive biliopathy
- Recurrent pancreatitis
- Recurrent pyogenic cholangitis
- Surgical biliary trauma


## PSC-Liver Biopsy/Histological Features

- Biopsy may be needed for diagnosis if ERCP/MRCP negative-evaluate for small duct PSC or overlap syndromes
- Histology findings nonspecific
- Periductal concentric fibrosis (“Onion-skin”)
  - Infrequently seen
  - Not pathognomonic

Image courtesy of Maura O'Neil
PSC-Treatment

- No specific approved pharmacotherapy
- Symptom directed management
- UDCA
  - Not recommended
  - Trials of high dose UDCA (28-30 mg/kg/d) ↑ risk of death/OLT
  - Improvement in biochemistries at <20 mg/kg dosing, possible improvement in patients who normalize biochemistries
- No benefit: Corticosteroids, AZA, CSA, TAC, MTX, MMF


PSC-Complications

- Dominant Strictures ~50% of PSC patients
  - Biliary sphincterotomy, endoscopic dilatation +/- stent, brushings
  - Percutaneous cholangiography
- Cholangitis
  - Recurrent episodes→Prophylactic antibiotics, eval for OLT
- Cholangiocarcinoma
  - 10-15% of PSC patients
  - Screen with US/CT/MRI +/- CA 19-9 every 6-12 months
- Gallbladder disease
  - Cholecystectomy recommended for any GB mass lesion/polyp
- Metabolic bone disease
- Portal hypertension

PSC and IBD

- Concomitant IBD common: 60-80% UC>>Crohn’s
  - 5-10% of IBD patients have PSC
- Full colonoscopy with biopsies recommended at diagnosis
- Endoscopic findings in PSC/UC:
  - Rectal sparing, backwash ileitis, mild/quiescent course, ↑ risk of pouchitis, ↑ peristomal varices
- Increased risk for colon cancer before and after OLT:
  - Colonoscopy every 1-2 years in UC/PSC patients
  - Colonoscopy annually following OLT in UC/PSC patients

PSC-Liver Transplant

- ~85% 5 year survival rates
- Surgical approach: Roux-en-Y choledochoduodenostomy
- Disease recurrence in 20-25% in 5-10 years
  - ↑ risk with IBD, intact colon, male sex, prior history of CCA, ACR
IgG4 Sclerosing Cholangitis

- Part of IgG4-related disease (IgG4-RD); nearly any organ can be involved
- Epithelial organs primary target for IgG4-RD
- Variable presentation: Biliary strictures to mass-like features, mimicking malignancy
- Slight male predominance in US, mean age ~55 yrs
- 6-10% of IgG4-RD with hepatobiliary involvement
- 6-10% IgG4-SC patients have IBD
- Treatment:
  - Initial therapy: Prednisone 40 mg/d for 4 weeks followed by taper
  - Maintenance/Relapse: AZA, Rituximab

IgG4 Sclerosing Cholangitis-Histology

- Diffuse increase in IgG4+ plasma cells
- IgG4:IgG ratio >40%
- Storiform fibrosis
- Obliterative phlebitis
- Lymphoplasmacytic infiltrate

Images courtesy of Maura O'Neil
## IgG4 Sclerosing Cholangitis vs. PSC

<table>
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<tr>
<th></th>
<th>IgG4 Sclerosing Cholangitis</th>
<th>PSC</th>
</tr>
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<tbody>
<tr>
<td>Age / Gender</td>
<td>50-70 yrs old / M=F</td>
<td>30-50 yrs old / M=F</td>
</tr>
<tr>
<td>Cholangiogram</td>
<td>Long strictures with upstream dilatation</td>
<td>Short strictures with normal caliber duct in between (Beads on string)</td>
</tr>
<tr>
<td>Extrahepatic organ involvement/ Disease association</td>
<td>Pancreas, salivary glands, kidneys, periorbital tissues, aorta, lymph nodes, lungs, meninges</td>
<td>IBD</td>
</tr>
<tr>
<td>IgG4 Elevation</td>
<td>90%</td>
<td>15%</td>
</tr>
<tr>
<td>Histology</td>
<td>Dense IgG+ lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis</td>
<td>Ductopenia, onion-skin periductal fibrosis</td>
</tr>
<tr>
<td>Immunohistochemistry &gt;10 IgG4+ cells/HPF</td>
<td>Usually</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>Yes</td>
<td>No</td>
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