Cholestatic Liver Diseases: Update on Diagnosis and Management

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Cholestatic Liver Diseases: Location of Injury Determines Phenotype

- Nuclear receptors
  - Genetic input suspected
  - Susceptibility to cholestatic disease
  - Severity of cholestatic disease
- Plasma membrane transporters
  - Drug-induced liver injury
  - Sepsis/cytokines
  - A co-factor in PSC disease progression
- Ductules
  - “Small duct PSC”
  - IgG4-associated cholangitis
- Ducts
  - PBC (small)
  - PSC (small and large)
Cholestatic Liver Diseases: Update on Diagnosis and Management

- PSC
  - Small-duct variant
  - AIH overlap syndrome
- PBC
  - AIH overlap syndrome
- IgG4-associated cholangitis
- Care of the patient with cholestatic liver disease

Case: Small-Duct PSC

- 56 YO W male referred for increased AP (428 IU/L)
- Bilirubin 0.4 mg/dl; GGT elevated
- PMH: osteoporosis
- ROS: negative (no pruritis, diarrhea)
- Exam: normal
- Negative AMA, ANCA, ANA, ASMA
- Liver biopsy at presentation: "bile duct proliferation and acute pericholangitis, no inflammation; portal fibrosis."
- MRC: normal ducts.
PSC: FU of Case #1

- Stable for 3 years, then
- Developed diarrhea; ulcerative colitis
- Developed jaundice shortly after UC diagnosis
- Developed ascites shortly after jaundice
- MRC:

PSC: Case #1 Take home lessons

- “Small duct” variant may evolve into typical large duct PSC
- PSC activity was temporally associated with UC disease activity
- PSC is often indolent, but may be aggressive:
  - No fibrosis to portal HTN in 3 years
  - Portal HTN to florid liver failure in 1 year
Primary Sclerosing Cholangitis: Diagnosis

- Cholangiography
  - ERC, gold standard
  - MRC, 85-90% sensitivity
- Histology
  - *Mild* portal inflammation
  - “onion-skin” fibrosis
  - Useful to stage disease, not confirm diagnosis
- Autoantibodies (ANCA)
  - Lack sensitivity or specificity

Diagnostic Algorithm for PSC: AASLD Guidelines

Primary Sclerosing Cholangitis: Presentation and Natural History

- Male predominance (2:1)
- Concurrent IBD 70%
- Asymptomatic at presentation 40-50%
- Transplant-free survival from diagnosis 7-18y
- Predictors of adverse outcome:
  - Age
  - Stage of fibrosis
  - Symptoms
  - Laboratories
  - Cholangiography

Role of Bacterial Cholangitis in the Progression of PSC

- Culture of bile is usually sterile unless biliary tree has been instrumented
- Dominant strictures increase risk of cholangitis
- Recurrent cholangitis increases progression of disease.
- AASLD Practice Guidelines:
  - antimicrobial therapy should be administered with correction of bile duct obstruction in dominant strictures… (1A).
  - In patients with recurrent bacterial cholangitis, long-term prophylactic antibiotics should be administered (1B).
  - In patients with refractory bacterial cholangitis, liver transplantation evaluation should be considered (1B).
High-Dose Ursodiol (28-30 mg/Kg/d) for PSC

Primary end-points: death, OLT, met listing criteria for OLT, development of Cx, varices, and/or cholangiocarcinoma


PSC: Dominant Strictures

- Definition: total or subtotal stenosis of CBD (≤1.5mm), or left/right hepatic ducts close to the bifurcation (≤1.0mm)

- MRC should be performed prior to biliary intervention to look for associated mass lesion

- Suspicion of CCA after MRC should prompt referral to liver transplant center with a protocol for management
  - prior to instrumentation, if possible

- Balloon dilation rather than stenting may be preferred

- Dilation results in prompt improvement
Balloon Dilation vs. Stenting of Dominant Strictures in PSC


<table>
<thead>
<tr>
<th>Complication</th>
<th>Balloon N=34</th>
<th>PTC N=23</th>
<th>ERCP N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median No. Procedures/Pt</td>
<td>2.1</td>
<td>7.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>3%</td>
<td>43%</td>
<td>14%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0%</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>Duct Perf.</td>
<td>6%</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Fistula</td>
<td>0%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>6%</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Infection</td>
<td>3%</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>18%</td>
<td>100%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Simtuzumab for PSC

- Monoclonal antibody against lysyl oxidase-like 2 (LOXL2)
- LOXL2: catalyzes lysine oxidation in collagen, promoting their polymerization, promoting hepatic fibrosis
- Phase 2b, 225 patients randomized 1:1:1 to weekly subcutaneous placebo, 75 mg or 125 mg simtuzumab
- Primary end-point: prevention of fibrosis progression (liver biopsy before treatment and at 2 years)
“Small-Duct” PSC: Clinical Characteristics and Natural History

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sm Duct</th>
<th>Lg Duct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>62%</td>
<td>62%</td>
</tr>
<tr>
<td>Age at Dx</td>
<td>38y</td>
<td>38y</td>
</tr>
<tr>
<td>FU</td>
<td>13y</td>
<td>10y</td>
</tr>
<tr>
<td>Stage ¾</td>
<td>28%</td>
<td>34%</td>
</tr>
<tr>
<td>IBD</td>
<td>81%</td>
<td>80%</td>
</tr>
<tr>
<td>CCA</td>
<td>0%*</td>
<td>12%</td>
</tr>
<tr>
<td>Prog to Lg Duct</td>
<td>23% (7.4y)</td>
<td>--</td>
</tr>
</tbody>
</table>

*B1 pt with small duct variant who progressed to large duct PSC developed CCA

IBD in PSC: “A Unique Clinical Phenotype”

<table>
<thead>
<tr>
<th>Feature</th>
<th>PSC-IBD N = 71</th>
<th>Chronic UC N = 142</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancolitis</td>
<td>87%</td>
<td>54%</td>
</tr>
<tr>
<td>Rectal sparing</td>
<td>52%</td>
<td>6%</td>
</tr>
<tr>
<td>Ileitis</td>
<td>51% (23/45)</td>
<td>7%</td>
</tr>
<tr>
<td>Pouchitis</td>
<td>71% (10/14)</td>
<td>30% (13/30)</td>
</tr>
<tr>
<td>Stomal Varices</td>
<td>40% (2/5)</td>
<td>0%</td>
</tr>
<tr>
<td>Incidence of CRC/Dysplasia (7y)</td>
<td>39%</td>
<td>17%</td>
</tr>
<tr>
<td>Survival (5y)</td>
<td>68%</td>
<td>96%</td>
</tr>
</tbody>
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Richard T. Stravitz, MD, FACG

PSC: Risk of Related Malignancies

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Incidence</th>
<th>Features</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CholangioCA</td>
<td>7-10%/10y</td>
<td>CCA Dx early after PSC Dx</td>
<td>??</td>
</tr>
<tr>
<td>GallbladderCA</td>
<td>3%</td>
<td>50% of polyps are malignant*</td>
<td>Annual US</td>
</tr>
<tr>
<td>HepatocellularCA</td>
<td>2-4%</td>
<td>Intermediate risk</td>
<td>Annual US</td>
</tr>
<tr>
<td>ColorectalCA</td>
<td>Risk 4.8-fold over UC alone</td>
<td>Younger age than in US</td>
<td>Scope at PSC Dx and yearly</td>
</tr>
</tbody>
</table>

*A gallbladder polyp of ANY size is an indication for cholecystectomy

Surveillance for Cholangiocarcinoma in PSC: Practice Guidelines are Unhelpful!

- AASLD: “Inadequate information exists regarding the utility of screening for CCA in PSC; in the absence of evidence based information, many clinicians screen patients with an imaging study plus a CA 19-9 at annual intervals.”

- EASL: “There is at present no biochemical marker or imaging modality which can be recommended for early detection of CCA. ERCP with brush cytology (and/or biopsy) sampling should be carried out when clinically indicated.”
PSC-AIH Overlap Syndrome

- Incidence:
  - 10-20% of adults with PSC have features of AIH
  - 50% of children with PSC have features of AIH ("autoimmune sclerosing cholangitis")

- MRC screening:
  - Not recommended in adults with AIH unless cholestatic chemistries co-exist
  - Recommended in children with AIH

- Differential diagnosis:
  - IgG4-associated cholangitis
  - DILI (α-methyldopa, nitrofurantoin, minocycline, PTU, hydralazine)

- Treatment:
  - Corticosteroids (recommended by AASLD and EASL)
  - PSC component does not improve, resulting in disease progression

PSC/AIH Overlap Syndrome
Recurrent PSC after Deceased Donor Liver Transplantation

Choledocho-jejunostomy

Recurrent PSC 3 Years after LT

“Onion-skin” fibrosis
Diagnosis of Primary Biliary Cirrhosis

- Women: 90%
- Alkaline phosphatase: elevated
- Serum cholesterol: elevated
- Antimitochondrial antibody: positive in ≥95%
- Liver biopsy:

Ursodiol (12-15mg/Kg/d) for PBC: Administration at ALL Stages Improves Patient Survival

N = 62
N = 38

Trends in Liver Transplantation for Cholestatic Liver Diseases in the US

Based on OPTN/UNOS database


Response of Biochemistries to Ursodiol Predicts Transplant-Free Survival in Patients with PBC

Response Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Total cohort</th>
<th>Early</th>
<th>Moderately advanced</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP, AST, Bili</td>
<td>a, met criteria; b, did not meet criteria</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>AP</td>
<td></td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Bili, Albumin</td>
<td></td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
</tbody>
</table>

### PBC: New Approaches to Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Efficacy</th>
<th>Reference</th>
</tr>
</thead>
</table>

Probably not effective: methotrexate, colchicine, mycophenolate, azathioprine.


### PBC-AIH Overlap Syndrome

- Incidence of probable AIH in patients with PBC 2-20%
- Histologic and biochemical features of both diseases:

  - PBC
    - Increased AP
    - Duct injury
    - Portal inflammation
    - Granulomas
  - AIH
    - Increased ALT
    - Piebald necrosis
    - Lobular inflammation
    - Plasma cell-predom

- Progression of fibrosis may be faster than PBC alone
- Treatment:
  - AIH component does not respond to ursodiol
  - Corticosteroids recommended after 3 months of ursodiol if chemistries fail to respond (EASL Guidelines)
Recurrent PBC 10 Years after LT

IgG4-Associated Cholangitis

- Part of a systemic inflammatory disorder involving the pancreas and other tissues (autoimmune pancreatitis)
- Affected organs infiltrated with T-cells and IgG4-expressing plasma cells
- May mimic PSC or cholangiocarcinoma (mass lesion) on imaging
- Labs:
  - Increased alkaline phosphatase (90%)
  - Increased serum IgG4 levels (>140 mg/dl)
  - Immunohistochemistry for IgG4 in liver biopsy
- Treatment: prednisone 40 mg PO QD for 4 weeks, tapering by 5 mg a week

Care of the Cholestatic Patient

• Remove potentially confounding medications:
  – (eg., diltiazem, captopril, Augmentin, nitrofurantoin)

• Screen for and treat low bone mineral density:
  – Screen for low 25-OH-Vitamin D, testosterone; DEXA
  – Replete Vitamin D; topical androgens (low dose); bisphosphonates

• Pruritis:
  – Bile acid sequestrants, rifampin 150 mg PO BID, sertraline 75-100 mg PO QD, naltrexone 25-50 mg PO QD

• Hypercholesterolemia:
  – Treat with statins in patients with co-existing cardiovascular risk factors.

PSC: Summary Update on Diagnosis and Management

• No role for ursodiol

• Manipulate the biliary tree as little as possible

• Balloon dilate dominant strictures rather than stent them

• No recommendation regarding screening for CCA

• Patients with PSC and cirrhosis should have US surveillance for HCC and gallbladder cancer

• Low threshold for antibiotics acutely; and, consideration of maintenance for recurrent cholangitis

• UC in PSC has the highest risk of colon CA!
PBC: Summary Update on Diagnosis and Management

- Ursodiol should be administered at PBC diagnosis
- Improvement in biochemistries after ursodiol predicts improved transplant-free survival
- Liver transplantation for PBC in the US has decreased, probably as a result of ursodiol
- Synthetic bile acid analogues may further improve therapy.