PBC/PSC

Definition

- Chronic cholestatic liver disease
- Serum anti-mitochondrial antibody
- Non-suppurative destructive cholangitis on liver histology

Natural History

- Epidemiology
- Prognosis

Overview

- Definition
- Natural history
- Clinical features
- Diagnosis
- Pathology
- Management
- Complications
- Transplantation
Epidemiology

- 30 studies since 1986
- Incidence varies: 1-50 cases/million/year
- Prevalence: 7-402 cases/million
- Prevalence rising in many geographic areas
- Affects all ethnic groups

Clinical Features at Presentation

- Asymptomatic
- Fatigue
- Pruritus
- Sicca symptoms
- Hepatomegaly
- Splenomegaly
- Jaundice
- Xanthelasma

Survival in Asymptomatic PBC

- 40-80%
- Patients who remain asymptomatic
- Matched control population
- Patients who become symptomatic
- Patients who experience a decline in health

Natural History: Risk Factors

- Female gender
- Autoimmune thyroid disease
- Prior urinary tract infection
- History of previous tonsillectomy
- Smoking
- Inflammatory skin disease (psoriasis, eczema)
- Genetic predisposition

Howel D et al, Hepatology 2000
Parikh-Patel A et al, Hepatology 2001
 Springer et al., Am J Gastro 1999

Fatigue in PBC
- Most common symptom
- Frequency 0 - 80%
- No association with age, sex, histological stage, bilirubin, and Mayo Risk score
- Etiology unknown

Biochemical Features of PBC
- Alkaline Phosphatase almost always elevated (generally 3-4x normal)
- AST, ALT < 200 U/L
- Bilirubin - usually rises late
- Cholesterol elevated in 85%
- IgM - commonly elevated

Serum Antibodies in PBC

<table>
<thead>
<tr>
<th>Type</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>AMA</td>
<td>++++</td>
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<tr>
<td>ANA</td>
<td>+++</td>
</tr>
<tr>
<td>ASMA</td>
<td>++</td>
</tr>
<tr>
<td>Anti-Centromere</td>
<td>+</td>
</tr>
<tr>
<td>Anti-Gp210</td>
<td>++</td>
</tr>
<tr>
<td>Anti-Sp100</td>
<td>++</td>
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<tr>
<td>p-ANCA</td>
<td>+</td>
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</tbody>
</table>

AMA-Negative PBC
- Occurs in 5%-10% of all cases
- No evidence of extrahepatic biliary obstruction
- No difference in clinical presentation, natural history and prognosis compared to AMA-positive cases
- Response to medical therapy similar to AMA-positive individuals
- High prevalence of serum ANA
Positive predictive value for PBC is 98% when
- Alk Phos > 1.5x normal
- AST < 5x normal

Biopsy needed when
- AMA is negative
- ? AIH-PBC overlap
- Staging desired
Primary Biliary Cirrhosis

Stage 4: Cirrhosis

Histological Staging – PBC – Stage 4

Ludwig, et al., Virch Arch Pathol Anat 1978; 379:103

Inhomogenous Fibrosis

Bridging fibrosis

No fibrosis

Jig Saw Pattern of Cirrhosis

Pruritus

- Frequency between 20-60% of cases
- Insidious onset
- May be intractable
- No association with age, sex, histological stage, and Mayo Risk score
- Etiology unknown

Primary Biliary Cirrhosis

Risk of Pruritus Over Time

% with pruritus

Years

Primary Biliary Cirrhosis

Sicca Syndrome

• Present in up to 70%

• Keratoconjunctivitis and xerostomia are most common symptoms

• Therapies include
  • increased fluid intake
  • oral sialogogues
  • artificial tears
  • vaginal lubricants

Primary Biliary Cirrhosis

Xanthomata

• Frequency: 15 - 50%

• Involve extensor tendon surfaces

• Xanthelasma affects eyelids

• Associated with elevated serum cholesterol levels

• May resolve with disease progression or with UDCA therapy
Asymptomatic Disease

- Frequency: 13 - 61%
- Increasingly common
- Asymptomatic phase may last up to 10 years
- Liver tests and autoantibody profiles same as for symptomatic patients

Potential Mechanisms for the Development of PBC

- Microorganism infection
- Xenobiotics
- Genetic
- Apoptosis

Main Autoantigens

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>PDC-E2</td>
<td>95</td>
</tr>
<tr>
<td>E2BP</td>
<td>95</td>
</tr>
<tr>
<td>BCOAD-C-E2</td>
<td>63-71</td>
</tr>
<tr>
<td>CDC-C-E2</td>
<td>30-70</td>
</tr>
<tr>
<td>PDC-E1a</td>
<td>41-66</td>
</tr>
<tr>
<td>gp210</td>
<td>10-42</td>
</tr>
<tr>
<td>p62</td>
<td>22-33</td>
</tr>
<tr>
<td>sp 100</td>
<td>28</td>
</tr>
<tr>
<td>Laminin B receptor</td>
<td>2</td>
</tr>
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</table>

Evidence Against Direct Cytotoxicity of AMA

- Serum titer and disease severity are unrelated
- Variable recurrence of PBC after liver transplantation despite presence of AMA
- AMA is present in unaffected relatives
- In animal models AMA occurs without PBC
### Relative Risk of PBC in Family Members

<table>
<thead>
<tr>
<th>Family member</th>
<th>Risk</th>
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<tbody>
<tr>
<td>Sibling</td>
<td>10.5</td>
</tr>
<tr>
<td>First-degree</td>
<td>18.4</td>
</tr>
<tr>
<td>Offspring</td>
<td>30.6</td>
</tr>
<tr>
<td>Daughters</td>
<td>58.7</td>
</tr>
</tbody>
</table>


### Proposed Etiological Infectious Agents

- *Escherichia coli*
- *Chlamydia pneumoniae*
- Retroviral
- *Novosphingobium aromaticivorans*

### Differential Diagnosis

- Choledocholithiasis
- Biliary strictures
- Malignancy
- Primary sclerosing cholangitis
- Drug-induced cholestasis
- Granulomatous hepatitis
- Autoimmune hepatitis
- Chronic hepatitis C
- Alcoholic hepatitis
- Sarcoidosis
- Celiac Disease

Source: Talwalkar JA, Lindor KD. Zakim/Boyer, 2005

### Extrahepatic Autoimmune Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sicca syndrome</td>
<td>70</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>40</td>
</tr>
<tr>
<td>Arthritis</td>
<td>20</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>15</td>
</tr>
<tr>
<td>Raynaud's phenomenon</td>
<td>10</td>
</tr>
<tr>
<td>CREST syndrome</td>
<td>5</td>
</tr>
</tbody>
</table>

Source: Talwalkar JA, Lindor KD. Zakim/Boyer, 2005
Metabolic Bone Disease: Osteopenia, Osteoporosis, and Osteomalacia

• Etiology related to cholestasis
• Frequency
  - osteopenia: 0% - 50%
  - osteoporosis: 0% - 20%
  - osteomalacia: 0% - 5%
• Risk factors include age, low body weight, smoking, and advanced histological stage
• Independent of menopausal status

Management of Metabolic Bone Disease

Osteoporosis much more common than osteomalacia

• Hormone replacement in women
• Calcium + vitamin D helpful
• Bisphosphonates may be helpful
• Steroid therapy may worsen bone disease
• Calcitonin not helpful

Portal Hypertension

• Most common in cirrhotics
• Esophageal varices from presinusoidal causes in some
• Serum albumin, bilirubin, and platelet count are independent predictors of esophageal varices
• Clinical outcomes similar to other liver diseases

Risk of Hepatocellular Carcinoma in PBC Compared to Cirrhotic Hepatitis C

Primary Biliary Cirrhosis

Management of PBC

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical visit</td>
<td>6-12 months</td>
</tr>
<tr>
<td>Serum liver tests</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Sensitive TSH</td>
<td>Yearly</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Yearly</td>
</tr>
<tr>
<td>Bone density</td>
<td>Diagnosis, 2 years</td>
</tr>
<tr>
<td>Vitamin levels</td>
<td>If total bilirubin elevated</td>
</tr>
</tbody>
</table>

Talwalkar JA, Lindor KD. Therapy of Dig Dis (in press)

Primary Biliary Cirrhosis

Medical Management

<table>
<thead>
<tr>
<th>Unsuccessful</th>
<th>Questionable</th>
<th>Useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>penicillamine</td>
<td>steroids</td>
<td>UDCA</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>colchicine</td>
<td></td>
</tr>
<tr>
<td>azathioprine</td>
<td>methotrexate</td>
<td></td>
</tr>
<tr>
<td>thalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>malotilate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chlorambucil</td>
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</tr>
</tbody>
</table>

Primary Biliary Cirrhosis

Actions of Ursodeoxycholic Acid

- Protects against cytotoxic effects of di-hydroxy bile acids
- Modulates expression of HLA
- Stabilizes bile canalicular membrane
- Choleretic effect
- Decreased apoptosis
- Decreased cytokine production

Primary Biliary Cirrhosis

Transplant-Free Survival With UDCA Therapy

- UDCA

Poupon Gastro 1997; 113:884
Primary Biliary Cirrhosis

Reasons for Non-Response with UDCA Therapy

- Inadequate dose
- Variable bioavailability
- Overlap with autoimmune hepatitis
- End-stage liver disease
- Uncontrolled hypothyroidism
- Occult celiac disease

Survival Unchanged in Non-Cirrhotic PBC Treated With UDCA

Survival after Liver Transplantation

Recurrent PBC after Liver Transplantation

- Cumulative incidence: 20-30% at 10 years
- Requires liver histology for diagnosis
- Normal serum liver tests in > 50% at diagnosis
- Serum AMA titer fluctuates (not diagnostic)
- Older donors and tacrolimus increase risk
- Hepatic re-transplantation is uncommon
Primary Sclerosing Cholangitis

Overview
- Definition
- Clinical picture
- Diagnosis
- Pathology
- Management
- Complications
- Transplantation

Definition
- Chronic cholestatic liver disease
- Unknown etiology, frequently associated with Inflammatory Bowel Disease
- Diffuse inflammation and fibrosis of the biliary tree
- Leads to biliary cirrhosis and portal hypertension

Etiology Unknown
- Disordered immunoregulation
  - T-cell subsets altered
  - T-cell suppressor function abnormal
  - Circulating immune complexes
  - Abnormal complement levels
- Infections and bacterial products
- Portal bacteremia

Clinical Picture
- Cholestasis (elevated alkaline phosphatase)
- Usually in setting of colitis
- May be asymptomatic
- Abnormal cholangiogram diagnostic
Primary Sclerosing Cholangitis

Clinical Presentation

- Asymptomatic: 15 - 44%
- Symptomatic:
  - Fatigue: 75
  - Pruritus: 70
  - Jaundice: 30 - 69
  - Hepatomegaly: 34 - 62
  - Abdominal pain: 16 - 37
  - Weight loss: 10 - 34
  - Splenomegaly: 30
  - Ascending cholangitis: 5 - 28
  - Hyperpigmentation: 25
  - Variceal bleeding: 2 - 14
  - Ascites: 2 - 10

Primary Sclerosing Cholangitis in Colitis

- Chronic ulcerative colitis

- PSC
  - 2000/10^6
  - 50/10^6
  - 100/10^6
  - (Estimated prevalence)

Relationship to Inflammatory Bowel Disease

- IBD in 60-80% of PSC patients
- CUC more common than Crohn's disease (2:1)
- In PSC, Crohn's disease almost always involves the colon
- 4-5% of CUC patients have PSC

Diagnostic Criteria

- Typical cholangiographic abnormalities involving any part of the biliary tree
- Compatible clinical and biochemical findings
  - History of IBD, cholestatic symptoms
  - Two- to three-fold increase in serum alkaline phosphatase level > 6 mos.
Liver Tests

- Alkaline phosphatase nearly always elevated
- AST and ALT usually <5 times normal
- Bilirubin, albumin, prothrombin time usually normal at diagnosis

Prevalence of Autoantibodies in PSC

- p-ANCA 80%
- AMA <2%
- ANA 50-60%
- SMA 35%

p-ANCA is Not Specific for PSC

- Primary Sclerosing Cholangitis 80%
- Idiopathic Ulcerative Colitis 75%
- Autoimmune Hepatitis 80%
- Primary Biliary Cirrhosis 30%

Diagnosis - Cholangiography

- ERCP most commonly used
- Percutaneous cholangiography infrequently used
- Magnetic resonance cholangiography non-invasive no radiation cost-effective
Multifocal stricturing

Classic Case of PSC

Primary Sclerosing Cholangitis

Comparison of ERC and MRC

Role of Liver Biopsy in PSC

- May help confirm diagnosis
- Can help exclude overlap with AIH
- Needed if cholangiogram normal – small duct PSC possible
- Can provide prognostic information
- May not be needed in all cases
Primary Sclerosing Cholangitis

Histological Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Portal stage: portal inflammation or bile duct inflammation, periductal fibrosis, atrophy</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Periportal stage: portal and periportal fibrosis</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Bridging fibrous septa</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>
Small-Duct PSC

- 5% of PSC
- Normal cholangiogram but biopsy showing PSC
- Can progress to classic PSC
- May exist with or without colitis

Differentiating PSC from PBC

<table>
<thead>
<tr>
<th></th>
<th>PSC</th>
<th>PBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestasis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>History of colitis</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>AMA</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>onion skin</td>
<td>florid duct</td>
</tr>
<tr>
<td></td>
<td>fibrosis</td>
<td>lesion</td>
</tr>
<tr>
<td>Cholangiogram</td>
<td>abnormal</td>
<td>normal</td>
</tr>
</tbody>
</table>

Survival in PSC Compared to Olmsted County Population

Disease Specific Therapy

- Surgical therapy seldom used
- Dilation for dominant strictures
- No proven medical therapy
Medical Therapy Tested to Date

<table>
<thead>
<tr>
<th>Therapy</th>
<th>A</th>
<th>D</th>
<th>E</th>
<th>K</th>
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<tbody>
<tr>
<td>Penicillamine</td>
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<tr>
<td>Colchicine</td>
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<td>Mycophenolate</td>
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<td>Mofetil</td>
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<td>Silymarin</td>
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<tr>
<td>Pentoxifylline</td>
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<tr>
<td>Nicotine</td>
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<td>Azathioprine</td>
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<td>Budesonide</td>
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<tr>
<td>Pirfenidone</td>
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<td></td>
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<tr>
<td>Etanercept</td>
<td></td>
<td></td>
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<tr>
<td>Ursodeoxycholic acid</td>
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</table>

Vitamin Deficiency

- A 40%
- D 14%
- E 2%
- K Unknown

Primary Sclerosing Cholangitis

- Osteoporosis much more common than osteomalacia
- Hormone replacement in women helpful
- Calcium + vitamin D helpful
- Bisphosphonates may be helpful
- Steroid therapy may worsen bone disease
- Calcitonin not helpful

Management of Peristomal Varices

- Pathogenesis similar to esophageal varices
- Local measures seldom effective
- TIPS, surgical shunt, liver transplantation may be effective
Management of Biliary Stricture

- Uncommon
- Cytology insensitive
  - Molecular methods being evaluated
- Long-term stents may cause problems
- Dilatation alone seems preferable

Cancer Risk

Cholangiocarcinoma

- Lifetime risk 7-15%
- Incidence 0.5 to 1%
- Smoking and IBD may increase risk

Other cancers: pancreatic, liver, and colon
Primary Sclerosing Cholangitis

Cholangiocarcinoma

Survival With PSC and Biliary Carcinoma

Survival After Photodynamic Therapy for Unresectable Cholangiocarcinoma

Liver Transplant for Cholangiocarcinoma


Risk of Colon Cancer in CUC and PSC Compared to CUC Alone

Loftus EV et al Gut; 2005;91

Cumulative probability

Years

p=0.0571

CUC + PSC

CUC alone

Survival

1 year 90-97%
5 years 85-88%

Problems with rejection, infection, recurrence, colon cancer

Liver Transplantation for PSC

Treatment Recommendations

• No standard medical therapy
• Cancer surveillance
• Hepatitis A & B vaccination
• Antibiotics for cholangitis
• Screen for varices
• Dilate symptomatic strictures
• Assess for osteoporosis and vitamin deficiency in advanced disease