Primary Biliary Cirrhosis and the Management of Chronic Cholestasis - An Update

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Clinical Features of Primary Biliary Cirrhosis

• Middle aged female
• Symptoms: fatigue, pruritus, jaundice, abdominal pain, anorexia, variceal hemorrhage
• Physical findings: jaundice, hepatosplenomegaly, hyperpigmentation, xantholasma, xanthomata, ascites, edema
• Up to 1/3 to 50% of patients today are asymptomatic at presentation
Vanishing Bile Duct Syndromes

- Primary Biliary Cirrhosis
- Sclerosing Cholangitis
- Graft vs Host Disease
- Liver Allograft Rejection
- Cholestatic Drug Reactions
- Sarcoidosis
- Lymphoma
Diseases for which liver transplantation was performed on adults in 1980 to 1986

- Cirrhosis: 168 cases
- Primary Biliary Cirrhosis: 122 cases
- Sclerosing Cholangitis: 57 cases
- Primary Liver Tumors: 35 cases
- Inborn Errors: 25 cases
- Acute Hepatic Failure: 18 cases
- Secondary Biliary Cirrhosis: 10 cases
- Budd-Chiari Syndrome: 9 cases
- Polycystic Disease: 2 cases
- Adenoma: 2 cases
- Congenital Fibrosis: 1 case
- Biliary Atresia: 1 case
- Infection: 1 case
- Trauma: 1 case
- Drug Toxicity: 1 case

The chart indicates the number of cases categorized by age groups: 18 to 49 years and 50 years or more.
Pathophysiology of Vanishing Bile Duct Disease
Site of Bile Duct Epithelial Cell Injury in Vanishing Bile Duct Syndrome
Cycle of Cholestatic Liver Injury

- Initiating insult (immunologic, etc)
- Cholestasis and Accumulation of toxic bile acids
- Damage to hepatocytes and biliary epithelium
- Immune derangement
Pathogenesis of Ductopenia

1) Unknown noxious agents damage bile ducts
2) Macrophages process antigens released from injured bile ducts and present to T-cells
3) Cytotoxic T-cells are activated, release cytokines (TNF-α, INF-γ) resulting in aberrant expression in HLA Class II antigens
4) Cholangiocytes are attacked by cytotoxic T-cells leading to non-suppurative destructive cholangitis and ductopenia
Epidemiology of PBC
Prevalence of PBC per Million Population

- Australia - 19 per million
- Canada - 22 “
- England - 54-129 “
- Sweden - 151 “
- Newcastle - 392 “

Epidemiology (cont.)

- Affects all races
- Female:Male = 9:1
- Occurs worldwide and at all ages
- Prevalence estimates: 19-392 cases/million
- Incidence: 3.9 - 15 cases/million/year
- Genetic Factors: prevalence in families with affected member is ~ 1000 x higher than general population
- Weak association with haplotype HLA-DR8
Etiologic Agents?

- PBC patients develop autoimmunity by losing tolerance to common antigens as a result of molecular mimicry to environmental agents. e.g.

  1. infectious agents?
  2. environmental chemicals (xenobiotics)?
Factors Suggesting an Infectious Etiology for PBC

• Family cases
• Geographic clustering
• Disease in non-related family members
• Disease recurrence in allograft
• Increased incidence in migrant populations moving into high prevalence areas
• Increased prevalence of the disease
Infectious Agents and PBC?

- *E. coli*
- *Mycobacterium gordonae*
- Eubacteria
- Archaeabacteria
- Heliobacter species
- *Chlamydia pneumoniae*
- Retroviruses (human beta retrovirus)
- *Novosphingobium aromaticivorans*
Novosphingobium aromaticivorans

- A gram negative strictly aerobic bacteria
- Found worldwide in soil, water and costal plain sediments
- Its PDC-E2 like protein has the highest homology to human PDC-E2 of any candidate organism
- Metabolizes xenobiotics that react with PBC sera
- + antibodies in 98-100% of sera from PBC patients in two studies (Selmi et al Hepatology 38:1250’03; Olafsson et al AJG 99:2143’04)
- Titers of antibody against lipoyl domain ~1000 X E.Coli’s lipoyl domain

Theoretically, *N. aromaticivorans* may break tolerance by molecular mimicry from subclinical infection or by metabolism of xenobiotics in the environment
Environmental Chemicals?

- Chemicals that mimic pyruvate dehydrogenase complex autoepitope react with PBC sera (Long et al. J. Immunol 167:2956’01)
- These compounds are halogenated hydrocarbons, widely distributed and found in pesticides and detergents
- Bromohexanoate ester-albumin conjugates induce +AMA in rabbits (Leung et al. J. Immunol 170:5326’03)
6-bromohexanoate – a lipoic acid mimic
(leung et al J. Immunology 170:5326’03)
PBC - Symptoms and Associated Diseases

- Fatigue
- Pruritus
- Abdominal pain
- Dry eyes
- Thyroiditis
- Arthritis
- Osteoporosis
- Gallstones
Laboratory Findings in PBC

- Anti - Mitochondrial Antibody
- Elevated Alkaline Phosphatase
- Elevated Serum Bilirubin
- Elevated Serum Cholesterol
- Elevated Serum Immunoglobulins
Immunologic Abnormalities

- IgM elevations
- Auto-antibodies (AMA, ANA)
- Activated T and B cells in blood
- Impaired T-cell regulation
- Granulomas; plasma cell infiltrates
- Association with other autoimmune disorders (thyroiditis, Sjogrens syndrome, scleroderma, rheumatoid arthritis)
Anti-mitochondrial Antibodies

- Detect antigens in the inner mitochondrial membrane that are part of the pyruvate dehydrogenase complex
- These are the dihydrolipoamide S-acetyltransferase component (E2 antigen complex) of a family of enzymes (2-oxo-acid dehydrogenases)
- Anti-E2 antibodies are specific for PBC (98%)
- AMA’s are not pathogenic or tissue specific
- In PBC, T cells and B cells are autoreactive to PDC-E2
Renal Tubules-with indirect fluorescence
PBC: Pathogenesis

Bile duct necrosis
(immune mediated)

Diminished bile ducts

Cholestasis

Fibrosis/Cirrhosis

Liver failure
Histologic Stages in PBC

- Stage 1: “Florid Duct Lesion”, Granulomas
- Stage 2: Expansion and erosion of the limiting plate; pseudoductular proliferation; portal fibrosis
- Stage 3: Loss of interlobular ducts; bridging fibrosis; canalicular cholestasis
- Stage 4: Established cirrhosis; severe cholestasis
Stage One
Stage Three
Stage Four
Clinical Presentation (PBC)

- Pre-symptomatic
- Asymptomatic
- Symptomatic
- End stage liver failure
Survival of Asymptomatic and Symptomatic Patients with PBC from Time of Diagnosis

(Mahl et al. J. Hep 20:707’94)
Survival of 36 Asymptomatic Patients from the Time of Diagnosis Compared with Controls

(Mahl et al. J. Hep 20:707'94)
## Median Survival of Asymptomatic PBC

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Asymptomatic</th>
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<tbody>
<tr>
<td>Mahl ‘94</td>
<td>7.5 yr</td>
</tr>
<tr>
<td>Nyberg ‘89</td>
<td>8.0</td>
</tr>
<tr>
<td>Springer ‘99</td>
<td>___</td>
</tr>
<tr>
<td>Prince* ‘04</td>
<td>8.0</td>
</tr>
</tbody>
</table>

16 years
12.7
14.0
09.6

* Gut 53:865’04 (mean age at Dx 61.8 in symptoms. vs 63.1 in asymptomatic.) Lack of difference in survival of the two groups may be due to an excess of non-liver deaths in asymptomatic group and minimally elevated bilirubin in symptomatic patients.
Therapy
Therapy in Chronic Cholestatic Liver Injury

- Symptomatic (Pruritus)
- Replacement (Vitamins A, D, E, K)
- Primary (Ursodeoxycholic Acid ? Others)
Therapy for Pruritus

- Anion Exchange Resin - (Cholestyramine or Cholestipol)
- Microsomal Enzyme Inducers - (Rifampin)
- Opiate Receptor Antagonists - (Naloxone, Nalmephine)
- Plasmaphoresis ??
- Charcoal Hemoperfusion ??
- Extracorporeal albumin dialysis (MARS) (AJG 99:1105’04)
Therapy for complications of PBC and other chronic cholestatic diseases

- **Osteoporosis**
  - **Bisphosphonates**: Etretinate, Alendronate, inhibit osteoclast bone resorption; (Zein et al Hepatology 42:762’05)
  - **Raloxifene**, binds to estrogen receptors and inhibits bone resorption and turnover – (Lindor et al Liver Int. 25:117’05)
  - **Transdermal HRT**, increases bone mineral density

- **Osteomalacia**
  - (Vit D and Calcium)
Therapy for complications of PBC and other chronic cholestatic diseases

- **Coagulopathy** (Vit K)
- **Night Blindness**: a concern in children (Vit A)
- **Esophageal Varices** (Beta blockers)
- **Hyperlipidemia** (Cholestyramine, Statins)
- **Fatigue** (ondansetron) – no effect (Hepatology 41::1305’05)
Pathogenesis and Treatment of Vanishing Bile Duct Syndromes

- Immune destruction of bile ducts
  - Rx: AZT, corticosteroids, MTX, cyclosporin

- Retention of hydrophobic bile acids in cells
  - Rx: Ursodeoxycholic acid

- Liver cell injury, apoptosis, necrosis, fibrosis, cirrhosis
  - Rx: Colchicine, D-penicillamine

- Liver failure
  - Rx: Liver transplantation
Ursodeoxycholic Acid-UDCA

YUTAN

(Black Bear Bile)
An ancient Chinese drug
Ursodeoxycholic acid: Also used in Japan
Ursodeoxycholic Acid - Historical Aspects

• 1902 - Hammerstein identified UDCA in polar bear bile (ursocholeiensaeure)
• 1927 - Shoda - Isolated UDCA from Yutan
• 1937 - Iwasaki defined chemical structure
• 1973 - Nakano - First report of gallstone dissolution
• 1981 - Leuschner - During gallstone Rx, chronic hepatitis improved
• 1987 - Poupon et al - First published PBC trial
Biochemical Structure of Bile Acids

Ursodeoxycholic Acid

Chenodeoxycholic Acid
Mechanism of Action of UDCA

• Protection of cholangiocytes against hydrophobic effects of bile acids by enrichment of bile with UDCA

• Stimulation of excretion of hydrophobic bile acids
  • by stimulating cytochrome P-450 and hydroxylation of lithocholate
  • by exocytotic insertion of transport proteins at the canaliculus

• Inhibition of hepatocellular apoptosis
Ursodeoxycholic Acid (UDCA) Stimulates Canalicular Transport Systems
Bile Acids and Transporter Expression

• Cholestasis
  ▲ Bile acids
  ▼ Transporter expression (primary?)

• Ursodeoxycholic acid
  ▲ Bile secretion; bile acid hydroxylations
  ▲ Vesicular exocytosis/targeting
  ▲ Cl⁻/HCO₃⁻ exchanger in PBC

• Effects on transporter expression?
Hepatic Uptake and Secretion of a $\gamma$-Labelled Bile Acid Analogue

Jazrawi et al Gastro 106: 134, 1994
Effect of UDCA on Neat Hepatic Uptake (A) and Hepatic Transit Time (B)

Jazrawi et al Gastro 106: 134, 1994
Effect of UDCA on Net Hepatic Excretory Rate (C) and Absolute Rate (D)

Anti-Apoptotic Effect
Mechanism of Bile Acid Induced Apoptosis

Gores, ‘99
Intracellular Signaling Cascade for Apoptosis Following Fas Ligation

Apoptosis in Liver of Rats Fed Bile Acids

Rodrigues et al JCI 101: 2790, 1998
Clinical Effects of Ursodeoxycholic Acid Therapy

UDCA therapy improves liver function in patients with:

• Primary biliary cirrhosis
• Sclerosing cholangitis
• Pruritus of pregnancy
• Cystic fibrosis

(Survival is increased in PBC in 3 combined international trials)
Summary of UDCA Effects

• Decreases hydrophobicity of bile salt pool
• Acts as a ligand for nuclear receptors that lead to increase detoxification of hydrophobic bile salts and decreased inflammatory mediators
• Acts as an anti-apoptotic drug
• Stimulates bile excretory function
Effect of Ursodeoxycholic acid

Poupon et al NEJM 324:1548’91
Survival in PBC
(3 Combined UDCA Trials)

Poupon, R.E. et al Gastroenterology 113: 884, 1997
Effect of UDCA on Histologic Progression in PBC (French, Mayo, Canadian, Spanish groups)

- 367 patients (200 UDCA; 167 placebo)
- Pre-treatment and post-treatment biopsies (median 25 months)
- No overall effect on histologic progression
- Trend for drug effect in stage I-III
- Significantly lower progression rate in UDCA group with histologic stage I-II

Poupon et al J. Hepatol. 39:12’03
Conflicting evidence for lack of efficacy of ursodeoxycholic acid therapy in PBC


Histologic Stages of Progression in Primary Biliary Cirrhosis

I. Florid duct lesion
II. Portal fibrosis
III. Bridging fibrosis
IV. Biliary cirrhosis
Survival with UDCA in Primary Sclerosing Cholangitis

Predicted Survival with and without liver transplantation in 262 UDCA treated PBC pts.

(A. early stage 1 and 2)  (B. late stage 3 and 4)

Corpechot et al Gastro 128:297’05
Over-all Conclusions

- Treatment with ursodeoxycholic acid alone normalizes survival rate of patients with PBC when given at early stages (I and II)

- There is a continued need for new therapeutic options in patients with more advanced disease (III & IV)
Alternative Therapies

- **Colchicine** (Cochrane Hepato-Biliary Group - insufficient evidence for efficacy - Am. J. Gastro 100:1876’05)
- **Methotrexate** (Cochrane Database Syst Rev July 20,2005 - methotrexate increased mortality)
- **Glucocorticosteroids** (Cochrane Database Syst Rev April 18,2005 – insufficient data)
Alternative Combination therapy for PBC?

• UDCA and prednisone (Leuschner et al Hepatology 25: 49, 1996)
• UDCA and Sulindac (Leuschner et al Hepatology 32: 309A, 2000)
• UDCA and budesonide (Leuschner et al Gastro 117: 918, 1999; Rautiainen et al Hepatol ‘05)
• Colchicine and methotrexate (Kaplan et al Gastro 117: 1173, 1999)
• UDCA and methotrexate (Combes et al- submitted)
Effect of UDCA on Glucocorticoid Receptor and Suppression of NF-κB Transcription

Recent Preliminary Pilot Trials in PBC/PSC

- Mycophenolate – immunosuppressive agent that inhibits T and B lymphocyte proliferation – lack of effect in PBC and PSC (Mayo Clinic trials)
- Combivar antiviral therapy (150 mg lamivudine and 300 mg zidovudine bid) resulted in improvement in LFT’s and liver histology in a small pilot study (Mason et al AJG 99:2348’04)
Survival after Transplantation in 161 Patients with PBC

Markus et al NEJM 320: 1709, 1989
Summary

- PBC is a prototypical chronic vanishing bile duct cholestatic disorder
- Etiology remains unknown
- Clinical spectrum is varied
- Many therapeutic options for complications of PBC and other cholestatic disorders
- Bile acid therapy (Urso) delays progression of disease, particularly in early stages and benefits other cholestatic disorders
PBC and Autoimmune Hepatitis - an overlap syndrome

- Overlap syndrome with PBC occurs in ~10% of all cases
- Flares of autoimmune hepatitis can occur spontaneously or during UDCA treatment
- Combination therapy with corticosteroids is oftner necessary to achieve a complete remission clinically and biochemically

PBC-AIH Overlap Syndrome

Triple Rx for PCS
(Immuran, prednisolone, UDCA)

Schramm et al Ann Int Med 131: 943, 1999
Indications for Liver Transplantation

- Intractable itching
- Refractory fatigue
- Refractory encephalopathy
- Small cell carcinoma (<5 cm and 3 nodules)
- Malnutrition
- SBP
- Refractory ascites
- Bil > 15 mg%; albumin < 2.5 g%
- Hepatorenal or hepatopulmonary syndrome
Contraindications for Transplant in PBC

Absolute
- Advanced portal and mesenteric thrombosis
- Advanced cardiac/pulmonary disease
- AIDS
- Extrahepatic Cancer
- Sepsis

Relative
- >70 years of age; alcoholism/drug use
- Non-compliance
The End

• Proceed to post test
• Print post test
• Complete post test
• Return post test to Dr. S.K. Oliver
  – 407i TAMUII
Clinical Features include all of the following EXCEPT

1. Middle aged male
2. Symptoms: fatigue, pruritus, jaundice, abdominal pain, anorexia, variceal hemorrhage
3. Physical findings: jaundice, hepatosplenomegaly, hyperpigmentation, xantholasma, xanthomata, ascites, edema
Post test question two

Complete the pathogenesis of PBC:

1. Bile duct necrosis (immune mediated)

2. ________________

3. Cholestasis

4. Fibrosis/Cirrhosis

5. ________________
Post test question three

Circle True or False

• Treatment with ursodeoxycholic acid alone normalizes survival rate of patients with PBC when given at advanced stages (III & IV)