YW is 59 yo referred for HCV
• s/p cholecystectomy 6 months prior to referral
• HCV antibody positive
• No risk factors for acquiring HCV, no ethanol
• ANA 1:2560
• Alk phos 603, bilirubin (0.2/0.8), AST 106, ALT 79
• Normal ultrasound

Mild epigastric pain and generalized pruritus
• Dry eyes and mouth
• Minimal epigastric tenderness
• 11cm liver (minimally tender)
• Multiple excoriation entire body
• Xanthelasma both eyes
• Parotid enlargement
• Excoriations

HCV-RNA -nondetectable
• Positive AMA 1:1240
• Liver biopsy: lymphocytic infiltrate in the bile ducts, ductopenia
• Treated with Ursodeoxycholic acid (12-15mg/kg)

Primary Biliary Cirrhosis
• Slowly progressing cholestatic liver disease of unknown etiology
• Female predominance
• Often asymptomatic at initial diagnosis
• Most patients develop symptoms over 5-20 years
  – fatigue, pruritis, abdominal pain, jaundice, xanthomas, portal hypertension, liver failure
• Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) are typically elevated
• ALT, AST, bilirubin, cholesterol may be abnormal
• AMA is positive in over 90% of patients
Primary Biliary Cirrhosis: Bile Duct Inflammation

Hyperbilirubinemia

- Unconjugated Bilirubin
  - Can cause kernicterus (brain damage) in the newborn

- Conjugated Bilirubin
  - Bilirubin elevation itself is relatively benign
  - Elevation is often the initial presentation of liver disease
  - May be a marker of severe liver disease
  - May have concomitant abnormalities of hepatic transport or metabolism which are not as “easily seen”
Bile Salts

- Important for fat digestion and absorption
- Prevent gallstone formation
- Important for cholesterol metabolism and lipid homeostasis
- Excess concentrations of hydrophobic bile salts
  - Disrupt hepatocyte membranes, injure hepatocytes, induce apoptosis
- Can cause/treat severe pruritis
- Modulate hepatocyte intracellular signaling mechanisms
  - Calcium, PKC, IFN-α
- Regulate MHC II expression in the liver
- Inhibit eosinophil granulation
- Transcriptionally regulate genes (likely via FXR)

Clinical Uses of Bile Salt (Ursodeoxycholic Acid) Therapy

- Treatment of cholestatic liver diseases
- Therapy for the pruritis associated with cholestasis
- Gallstone dissolution therapy
- Induce choleresis in PSC

Schematic Diagram of the Pathogenesis of Primary Biliary Cirrhosis

Mitochondrial M2 Antigens which React with AMA in Primary Biliary Cirrhosis
Primary Biliary Cirrhosis: Associated Systemic Abnormalities

- Pruritus
- Metabolic Bone Disease
- Hypercholesterolemia
  - 90% of patients have plasma cholesterol < 200
  - Severe elevations not uncommon
  - xanthelasma and xanthomas (<10%)?
  - ? risk of atherosclerosis
- Malabsorption and steatorrhea
- Vitamin (Fat soluble) deficiency
  - Vitamin A, D, E, K
- Hypothyroidism 20% of patients
- Anemia

Xanthelasma in Primary Biliary Cirrhosis

Planar Xanthomas in Primary Biliary Cirrhosis

Tuberous xanthomas in Primary Biliary Cirrhosis
PBC and Hepatic Osteodystrophy: Metabolic Bone Disease

- Osteoporosis
  - Decrease in absolute decrease in amount of bone
  - Plasma Vitamin D and calcium are usually normal
  - Bilirubin inhibits osteoblast function
- Severe disease occurs in up to 30% of patients
- Osteomalacia is rare
  - May be associated with 25-hydroxyvitamin D deficiency
- Treatment
  - Calcium (1500 mg/day) and Vitamin D (400-800 IU/day)
  - Avoid alcohol and tobacco
  - Monitor lumbar spine density
  - ?? Estrogen therapy
  - Biphosphonates

Cholestatic Liver Disease: Osteopenic Bone Disease

- Osteopenia (T-score <-1) is found in approximately 50% of PSC patients at time of referral/diagnosis
- Incidence increases as the liver disease progresses
- Severe osteopenia (T-score <2.5 or Bone Mineral Density of 0.85 gm/cm²) is relatively rare
  - 10% of PSC patients
  - 30% of PBC patients
- Fractures occur in one third of PSC patients after OLT
- Biphosphonates (weekly vs daily)
- Calcium, Vitamin D

Primary Biliary Cirrhosis:

Vertebral Collapse

Periostitis
Primary Biliary Cirrhosis: Medical Therapy

- Ursodeoxycholic Acid (UDCA)
  - improves LFT
  - delays histologic progression
  - improved survival/need for OLT
- Glucocorticoids, cyclosporin, methotrexate, colchicine, azathioprine are unproven or do not alter the natural progression of PBC
- One study demonstrates improved efficacy of oral budesonide and UDCA vs. UDCA alone
  - (Leushner et al. Gastro, 1999)

Treatment of Pruritus

- Topical therapy, antihistamines
- Ursodeoxycholic acid (UDCA)
- Cholestyramine, colestipol
- Rifampin
- Opioid antagonists
- Grapefruit Juice
- Phototherapy
- Plasmapheresis
- Liver Transplantation

Sjogren’s Syndrome

- Keratoconjunctivitis sicca
  - dry eyes
- Xerostomia
  - dry mouth, chronic salivary gland hypofunction
- Salivary gland enlargement
  - labial salivary gland biopsy
- Raynaud’s phenomenon
- Connective tissue diseases (RA, PBC, SLE, MCTD, scleroderma, dermatomyositis)
- Lymphoma and pseudolymphoma
- Upper airway, lung, GI, liver skin, neurologic, kidney, myositis, arthritis, fatigue
- Serologic abnormalities
  - Ro/SSA, La/SSB, ANA, Rheumatoid factor
Primary Sclerosing Cholangitis: Signs and Symptoms

- Fatigue
- Anorexia
- Nausea
- Weight loss
- Pruritus and jaundice (less common in children)
- Hepatomegally and splenomegally

Primary Sclerosing Cholangitis

- Male predominance (2:1)
- Median onset age 40 (range 1-90 years)
- ERCP is the “gold standard” for diagnosis
- Liver biopsy may be useful for staging
- Over 50% of patients have IBD

Primary Sclerosing Cholangitis: ERCP

Primary Sclerosing Cholangitis: MRCP

CBD
Primary Sclerosing Cholangitis:
Periductal Sclerosis and Injured Bile Duct

Primary Sclerosing Cholangitis:
Bile Duct with Concentric Fibrosis

Primary Sclerosing Cholangitis:
Necrotic Bile Duct and Scarred Portal Triad

Hepatobiliary Manifestations of IBD
- PSC and PBC
- Steatosis
  - up to 50% of abnormal biopsies in IBD patients
  - drugs, malnutrition, underlying disease
- Pericholangitis
  - small duct PSC vs nonspecific
- Cholelithiasis
  - 13-34% of patients with ileitis/ileal resection
  - enterohepatic circulation of bilirubin
- Granulomatous Hepatitis
- Hepatic Amyloidosis
Cholestatic Liver Disorders

- Family of slowly progressive liver diseases
- Although these disorders are likely autoimmune in nature, immunosuppressive therapies remain ineffective
- Ursodeoxycholic acid therapy slows the progression of PBC, but is unproven for PSC
- PBC and PSC are associated with many systemic disorders, which are a primary focus of medical therapy for patients with intact liver function
- Orthotopic liver transplantation is a curative procedure for cirrhotic patients with evidence of hepatic decompensation