Morning Report Presentation

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Primary Biliary Cirrhosis

- PBC is a chronic, progressive, cholestatic liver disease of unknown cause that usually affects middle-aged women eventually leading to liver failure and the need for transplantation.

- Disease is caused by granulomatous destruction of the interlobular bile ducts, which leads to progressive ductopenia with subsequent cholestasis, fibrosis, and cirrhosis.
Epidemiology

- PBC affects members of all races
- Accounts for 0.6-2% of deaths from cirrhosis worldwide
- Prevalence ranges from 19-151 cases per million
- 95% of cases are women
- Onset usually between 30-65 years old
Genetics

- Prevalence in families with index case is estimated to be 1000 times greater than general population.
- Weak association with haplotype HLA-DR8
- Environmental triggers are also thought to be important
Pathogenesis

- Characterized by T-lymphocyte mediated attack on bile duct epithelial cells as well as the toxic effect of retained bile acids
- AMA reacts against E2 subunit of the 2-oxo-acid dehydrogenases
- PDC-E2, normally found on inner mitochondrial membrane of all cells, is aberrantly expressed on luminal surface of bile duct cells in patients w/ PBC.
  - Bile duct epithelial cells expressing this epitope are then targeted by CD8+ T lymphocytes
  - Expression of this antigen may also provoke an Ab-mediated attack by IgA, the antibody present in bile.
- A number of environmental triggers have been implicated in initiation of this autoimmune attack (retroviruses, \textit{P. acnes}, \textit{C. pneumoniae}, \textit{N. aromaticivorans})
Primary biliary cirrhosis

Low power view of liver biopsy in primary biliary cirrhosis. A damaged bile duct is visible in the center of an intense inflammatory cell reaction in an enlarged portal triad. The bile duct appears to be the target of this inflammatory reaction. Courtesy of Sanjiv Chopra, MD.

Primary biliary cirrhosis

Light micrograph showing a portal triad from a woman with stage II primary biliary cirrhosis. There are no normal bile ducts, but there are many bile duct-like structures, called atypical bile duct hyperplasia. The inflammatory cells are primarily lymphocytes. (Reprinted by permission from Kaplan, MM, N Engl J Med; 1996; 335:1772.)
Pathogenesis of PBC  

The initial requirement is a genetically susceptible host, which may involve an inability to suppress an immunologically mediated attack on bile duct cells once it has begun. Some triggering event is required to set this process in motion; it could be any event that damages bile duct cells and exposes the unique PBC bile duct cell antigen to the cellular or humoral immune system. Progressive damage to bile duct cells causes cholestasis. This sets up a vicious cycle in which retention of toxic substances, such as bile acids, cause chemical damage to hepatocytes. Cholestasis also causes increased expression of HLA Class I and II antigens on bile duct cells and hepatocytes which make them better targets for activated lymphocytes. The gradual loss of bile ducts causes progressive scarring, cirrhosis, portal hypertension and eventually, liver failure.
Clinical Manifestations

- Fatigue & pruritus are the most common presenting symptoms
- Fifty to 60% of patients are asymptomatic at diagnosis
- Up to 84% of patients may have at least one other autoimmune disease (thyroiditis, scleroderma, RA, Sjogren’s syndrome)
- Diagnosis should be considered in any person who reports unexplained itching, fatigue, jaundice, or unexplained weight loss.
Clinical Manifestations

- Pruritus
  - May occur initially during pregnancy and be mistaken for pruritus of pregnancy, but persists
  - Is unusual for it to remit spontaneously
  - Often is not recognized as a sign of cholestasis and many people are referred to dermatologists
  - Is not due to retention of bile acids or their sequestration in the skin
  - Increased opiodergic tone related to chronic cholestasis
Clinical Manifestations

- Skin Hyperpigmentation
  - Seen in roughly 25-50% of new patients
  - Due to melanin deposition, not jaundice
  - Cause remains unknown
  - Jaundice is a later manifestation but may be seen at presentation in some
Clinical Manifestations

- Rheumatic Symptoms
  - MSK complaints occur in ~40%, frequently due to an inflammatory arthropathy
  - Classic Rheumatoid arthritis develops in 5-10%
  - “Arthritis of PBC” is observed in another 10%
    - (transient non-deforming RF-negative synovitis of peripheral joints)
  - Forty to 60% have symptoms of Sjogren’s
  - Five to 15% have limited Scleroderma (CREST)
Clinical Manifestations

- Unexplained RUQ discomfort
- Striking hepatomegaly is often found
- Hemorrhage from varices, ascites, or encephalopathy
- Marked osteoporosis (unconjugated bilirubin inhibits osteoblast formation & function in vitro)
- Gallstones
- Asymptomatic bacteruria or frequent UTI
Physical Exam

- Excoriations
- Skin hyperpigmentation
- Xanthomas
- Hepatomegaly
- Splenomegaly
- Temporal & proximal limb muscle wasting
- Spider nevi, ascites, edema
Manifestations of PBC

Specific to PBC
- fatigue
- pruritus
- portal hypertension
- metabolic bone disease
- xanthomata
- fat soluble vitamin malabsorption
- urinary tract infection
- malignancy

Associated Disorders
- thyroid dysfunction
- sicca syndrome
- CREST
- Raynaud’s syndrome
- rheumatoid arthritis
- celiac disease
- inflammatory bowel disease
Laboratory Studies

- Alkaline phosphatase
  - Almost always elevated
  - Up to 5 times normal
  - Tends to plateau early then fluctuate within 20% of this value

- Aminotransferases
  - Normal or slightly elevated
  - No prognostic importance
Laboratory Studies

- Serum Bilirubin
  - Usually normal early in course
  - Becomes elevated as disease progresses
  - Poor prognostic indicator

- Increased number of eosinophils have been demonstrated in blood & liver
Laboratory Studies

- Antimitochondrial antibodies
  - Serologic hallmark of PBC
  - 95% sensitive; 98% specific

- Serum immunoglobulins
  - Are generally increased
  - Particularly IgM
Laboratory Studies

- Serum lipids
  - Cholesterol levels increased in 50%
    - May exceed 1000mg/dL in those with xanthomas
    - HDL is also high
    - Patients do not appear to be at increased risk of death from atherosclerosis in early disease
    - LDL becomes higher and HDL lower as disease progresses
Xanthelasma  Bilateral xanthelasmata (due to cholesterol deposits in the periorbital skin folds) in a patient with marked hypercholesterolemia resulting from primary biliary cirrhosis. Courtesy of Sanjiv Chopra, MD.

Planar xanthomas  Bilateral planar xanthomas in the palms of a 35-year-old woman with primary biliary cirrhosis. Xanthomas started in the creases and expanded. At the time that the xanthomas began to form, the serum bilirubin level was 18.5 mg/dL and serum cholesterol concentration was 970 mg/dL (25.2 mmol/l). Courtesy of Marshall M Kaplan, MD.
Diagnosis

- PBC likely if:
  - Alk Phos is elevated
  - IgM levels are high
  - AMA is positive

- Diagnosis & staging should be confirmed by liver biopsy
  - Florid bile duct lesion (pathognomonic)
  - Hyaline deposits in portal areas
  - Foamy degeneration
**Diagnosis of PBC**

Florid bile duct lesion in PBC

High power view of a liver biopsy from a patient with primary biliary cirrhosis shows a portal bile duct with degeneration and periductal granulomatous inflammation ("florid" bile duct lesion). Courtesy of Robert Odze, MD.

Foamy degeneration in primary biliary cirrhosis

Foamy degeneration of hepatocytes adjacent to portal triads in a patient with PBC. There are hyaline droplets in many of these swollen hepatocytes which are similar to those seen in alcoholic hepatitis. The lesion is thought to be due to the toxic effect of retained bile acids (Masson trichrome, x496). Courtesy of Marshall M Kaplan, MD.
Natural History & Prognosis

- Median survival
  - Asymptomatic at diagnosis: 10-15 yrs
  - Symptomatic: ~7 yrs
- Symptoms develop in 2-4 yrs in asymptomatic patients; 1/3 remain asymptomatic for many years
- AMA titer does not affect survival
- Granulomas on biopsy are associated with better prognosis
- Follow serum bilirubin, albumin, and PT
Treatment of Symptoms

- Pruritus
  - Cholestyramine (4-16g daily)
    - Binds bile acids
    - Also binds oral meds like ursodiol, thyroxin, digoxin and OCPs -- take 4hrs after
    - Adverse effects: unpleasant to take, constipation
  - Rifampicin (150mg BID-TID)
    - Not effective in all; works within ~1 month
    - AE: hyperbilirubinemia, dark urine, hepatitis, thrombocytopenia, and renal tubular damage
Treatment of Symptoms

- Pruritus (cont)
  - Opioid antagonists
    - Naloxone (IV)
    - Naltrexone (PO), also improves fatigue & depression
  - UV light exposure
  - Plasmapharesis
  - Liver Transplant
Treatment of Symptoms

- Sicca Syndrome
  - Artificial tears
  - Regular visits to dentist, mouth moisturizers

- Raynaud’s Phenomenon
  - Stop smoking
  - Avoid exposure to cold
  - Calcium channel blockers
Treatment of Symptoms

- **Osteoporosis**
  - Bone mineral density should be assessed at diagnosis and every 2 years after
  - Vitamin D & Calcium supplements
  - HRT where appropriate
  - Bisphosphonate once present

- **Thyroid disease**
  - Hypothyroidism affects ~20%
  - Serum TSH should be checked at diagnosis & periodically thereafter
Treatment of Underlying Disease

- **Ursodiol (12-15mg/kg per day)**
  - Increases rate of transport of intracellular bile acids across the liver cell and into the canaliculus (cytoprotective)
  - May also act as an immunomodulator
  - Improves serum biochemical markers of cholestasis
  - Relieves pruritus in some patients
  - Decreased hepatic inflammation in 1 of 4 studies
  - Extended the time to transplant or death as compared with placebo
  - Appears to be more effective in early vs. late disease
Treatment of Underlying Disease

- **Colchicine (0.6mg BID)**
  - Significantly improves serum markers
  - Improves pruritus in some; increased survival in one study
  - Has been shown to be synergistic with ursodiol

- **Cyclosporine (4mg/kg/day)**
  - Showed to stabilize fatigue & itching
  - Decreases serum levels of cholestatic markers and AMA
  - Adverse effects: hypertension, renal toxicity
  - Overall survival is not improved
Treatment of Underlying Disease

- Methotrexate (15mg per week)
  - Decreased cholestatic markers in pilot study
  - All patients had improvement in fatigue, itching, or both
  - Did not benefit those with advanced cirrhosis or decompensated liver disease
  - Response is slower than ursodiol, but may be additive w/ it
  - Interstitial pneumonitis is a serious problem (14%)
Treatment of Underlying Disease

- Liver Transplantation
  - Only treatment that clearly improves natural history of disease
  - 85-90% survival at one year
  - Survival rates thereafter resemble those of healthy persons matched for age and sex
  - Disease rarely recurs if appropriate immunosuppression is used
References:


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