# Autoimmune Liver Diseases

# 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

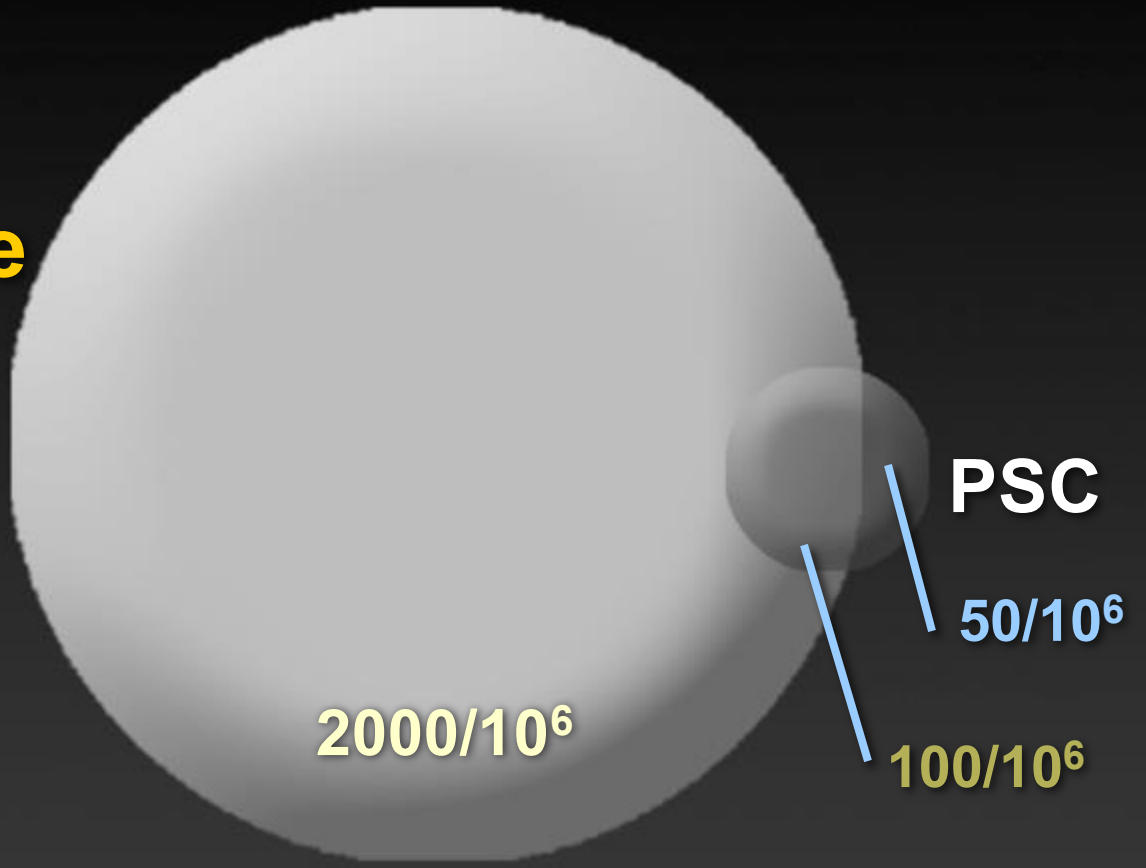
# Clinical Presentation

| | |
|---|---|
| **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 |

# 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

# Primary Sclerosing Cholangitis in Colitis



# 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.

# Diagnostic Criteria

**Exclude:**

- AIDS cholangiopathy
- Bile duct neoplasm (unless previous diagnosis of PSC)
- Biliary tract surgery or trauma
- Choledocholithiasis
- Congenital abnormalities of biliary tract
- Caustic treatment of intrahepatic cysts
- Ischemic stricturing of bile ducts
- Stricturing related to intra-arterial infusion of chemotherapy

# Liver Tests

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

Primary Sclerosing Cholangitis

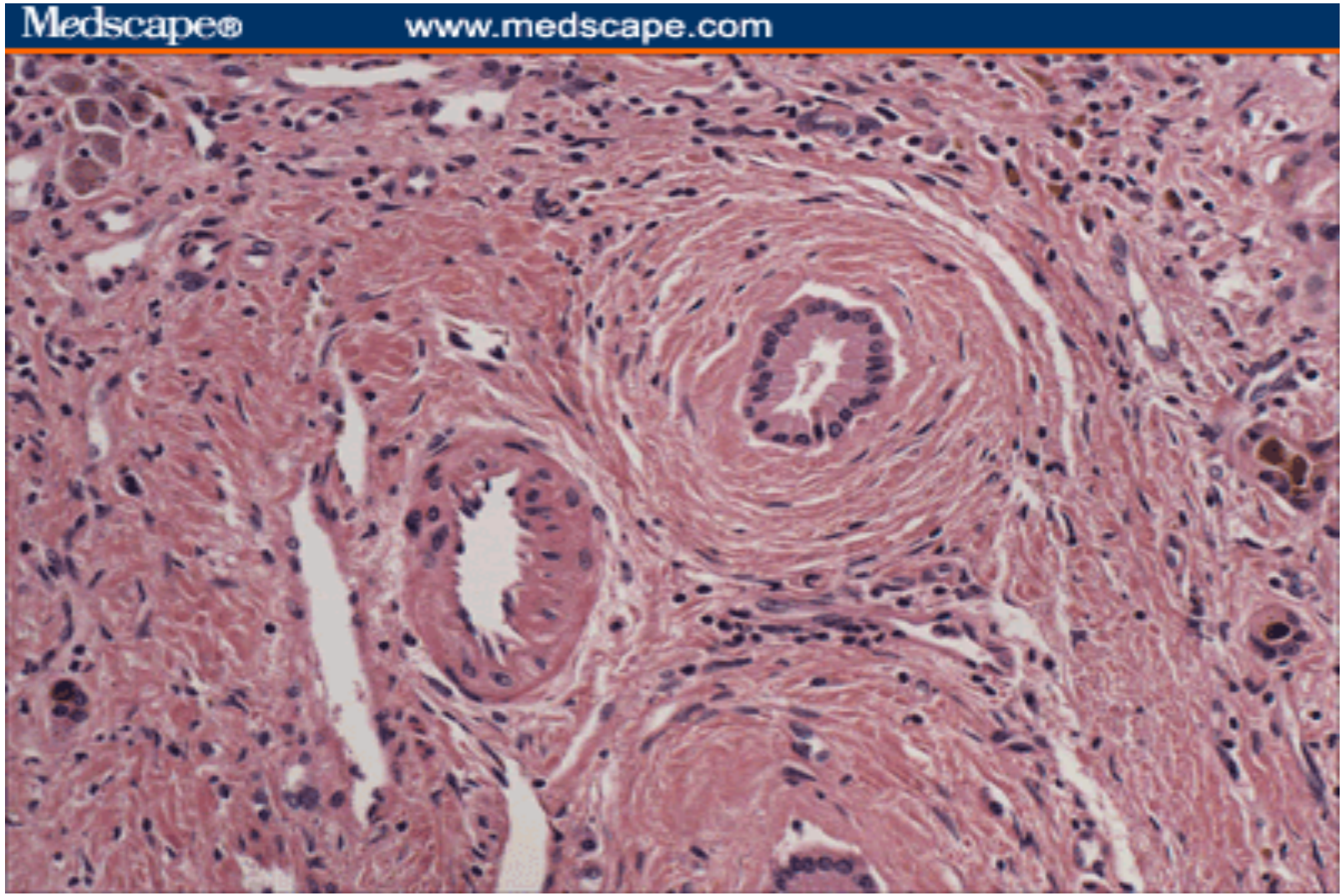
# Prevalence of Autoantibodies in PSC

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

# Diagnosis - Cholangiography

- ERCP should not be used for diagnosis
- Percutaneous cholangiography infrequently used
- Magnetic resonance cholangiography
  - non-invasive
  - no radiation
  - cost-effective

Concentric Fibrosis in PSC



# 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

| | PSC | PBC |
|---|---|---|
| Cholestasis | + | + |
| History of colitis | + | - |
| AMA | - | + |
| Liver biopsy | onion skin fibrosis | florid duct lesion |
| Cholangiogram | abnormal | normal |

# Features Used in Prognostic Models

| Mayo Clinic (n=174) | King's College (n=126) | Multicenter (n=426) | Swedish (n=305) | New Mayo Model (n=405) |
|---|---|---|---|---|
| Age | Age | Age | Age | Age |
| Bilirubin | Hepatomegaly | Bilirubin | Bilirubin | Bilirubin |
| Biopsy Stage | Biopsy Stage | Biopsy Stage | Biopsy Stage | AST |
| Hemoglobin | Splenomegaly | Splenomegaly | | Variceal Bleed |
| Inflammatory Bowel disease | Alkaline Phosphatase | | | Albumin |

# Disease Specific Therapy

- Surgical therapy seldom used
- Dilation for dominant strictures
- No proven medical therapy

Primary Sclerosing Cholangitis

# Management of Cholestasis

## Vitamin Deficiency

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

# Management of Cholestasis

## 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**

Primary Sclerosing Cholangitis

# Management of Cholestasis

## Steatorrhea

- Diminished bile salts in gut

- Co-existent celiac disease

## Primary Sclerosing Cholangitis

# 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

# Liver Transplantation for PSC

## Survival

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

## Problems with rejection, infection, recurrence, colon cancer

# 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

# Overview

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

Primary Biliary Cirrhosis

# Definition

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

Primary Biliary Cirrhosis

# 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

## Primary Biliary Cirrhosis

# Clinical Features at Presentation

| | |
|---|---|
| Asymptomatic | 40-60% |
| Fatigue | +++ |
| Pruritus | ++ |
| Sicca symptoms | +++ |
| Hepatomegaly | + |
| Splenomegaly | + |
| Jaundice | uncommon |
| Xanthelasma | uncommon |

Primary Biliary Cirrhosis

# Fatigue in PBC

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

Primary Biliary Cirrhosis

# 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

## Primary Biliary Cirrhosis

# Serum Antibodies in PBC

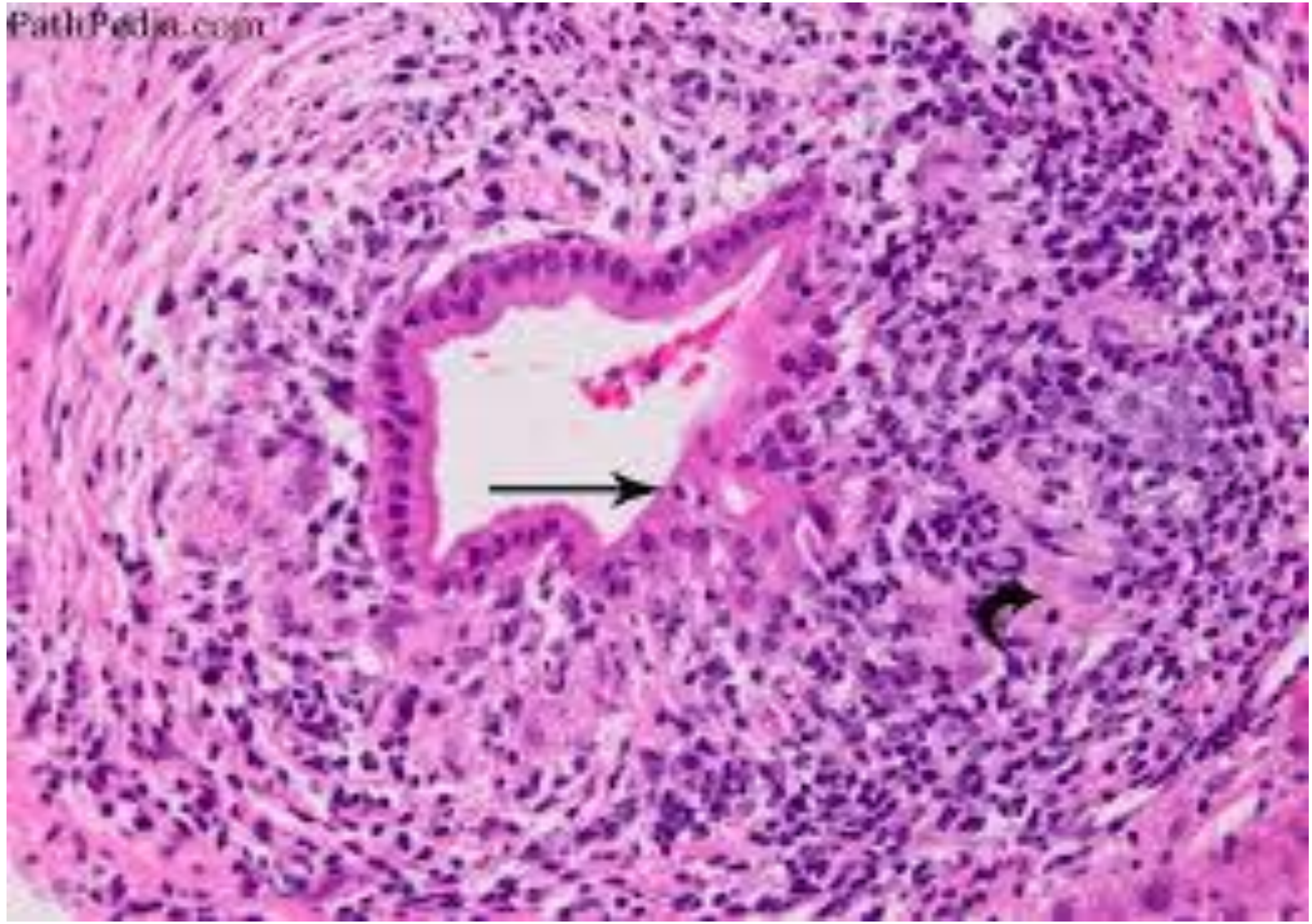
| Type | Prevalence |
|---|---|
| AMA | ++++ |
| ANA | +++ |
| ASMA | ++ |
| Anti-Centromere | + |
| Anti-Gp210 | ++ |
| Anti-Sp100 | ++ |
| p-ANCA | + |

Primary Biliary Cirrhosis

# 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

Florid Duct Lesion



Primary Biliary 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

# 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

Primary Biliary Cirrhosis

# 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

## Primary Biliary Cirrhosis

# Extrahepatic Autoimmune Diseases

| | (%) |
|---|---|
| Sicca syndrome | 70 |
| Thyroid disease | 40 |
| Arthritis | 20 |
| Scleroderma | 15 |
| Raynaud's phenomenon | 10 |
| CREST syndrome | 5 |

## Primary Biliary Cirrhosis

# 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

Primary Biliary Cirrhosis

# 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

## Primary Biliary Cirrhosis

# 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

Primary Biliary Cirrhosis

# Management of PBC

| Evaluation | Interval |
|---|---|
| Clinical visit | 6-12 months |
| Serum liver tests | 3-6 months |
| Sensitive TSH | Yearly |
| Lipid profile | Yearly |
| Bone density | Diagnosis, 2 years |
| Vitamin levels | If total bilirubin elevated |

## Primary Biliary Cirrhosis

# Medical Management

| Unsuccessful | Questionable | Useful |
|---|---|---|
| penicillamine | steroids | UDCA |
| cyclosporine | colchicine | |
| azathioprine | methotrexate | |
| *thalidomide* | | |
| *malotilate* | | |
| *chlorambucil* | | |

## 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

# Comparison of Prognostic Models

| Yale | European | Mayo | Oslo | Glasgow | Australia |
|---|---|---|---|---|---|
| Age | Age | Age | Variceal bleeding | Age | Age |
| Bilirubin | Bilirubin | Bilirubin | Bilirubin | Bilirubin | Bilirubin |
| Hepatomegaly | Albumin | Albumin | | Ascites | Albumin |
| Fibrosis | Cirrhosis | Prothrombin time | | Variceal bleeding | |
| Cirrhosis | Cholestasis | Edema | | Fibrosis<br>Cholestasis<br>Mallory bodies | |

Autoimmune Hepatitis

# Overview

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

Autoimmune Hepatitis

# Autoimmune Hepatitis

**Intermittently progressive inflammatory liver disease of presumed autoimmune etiology**

- High gamma globulins, autoantibodies
- Predominately periportal hepatitis
- Usually responds favorably to corticosteroids

# Clinical Features

- Middle-aged (or teenage) woman, non-drinker without viral hepatitis
- Fatigue, arthralgias/myalgias, oligomenorrhea, jaundice
- Increased ALT, AST, gamma globulins
- Positive ANA and SMA
- Interface hepatitis with lymphoplasmacytic infiltrate
- Responds to corticosteroids

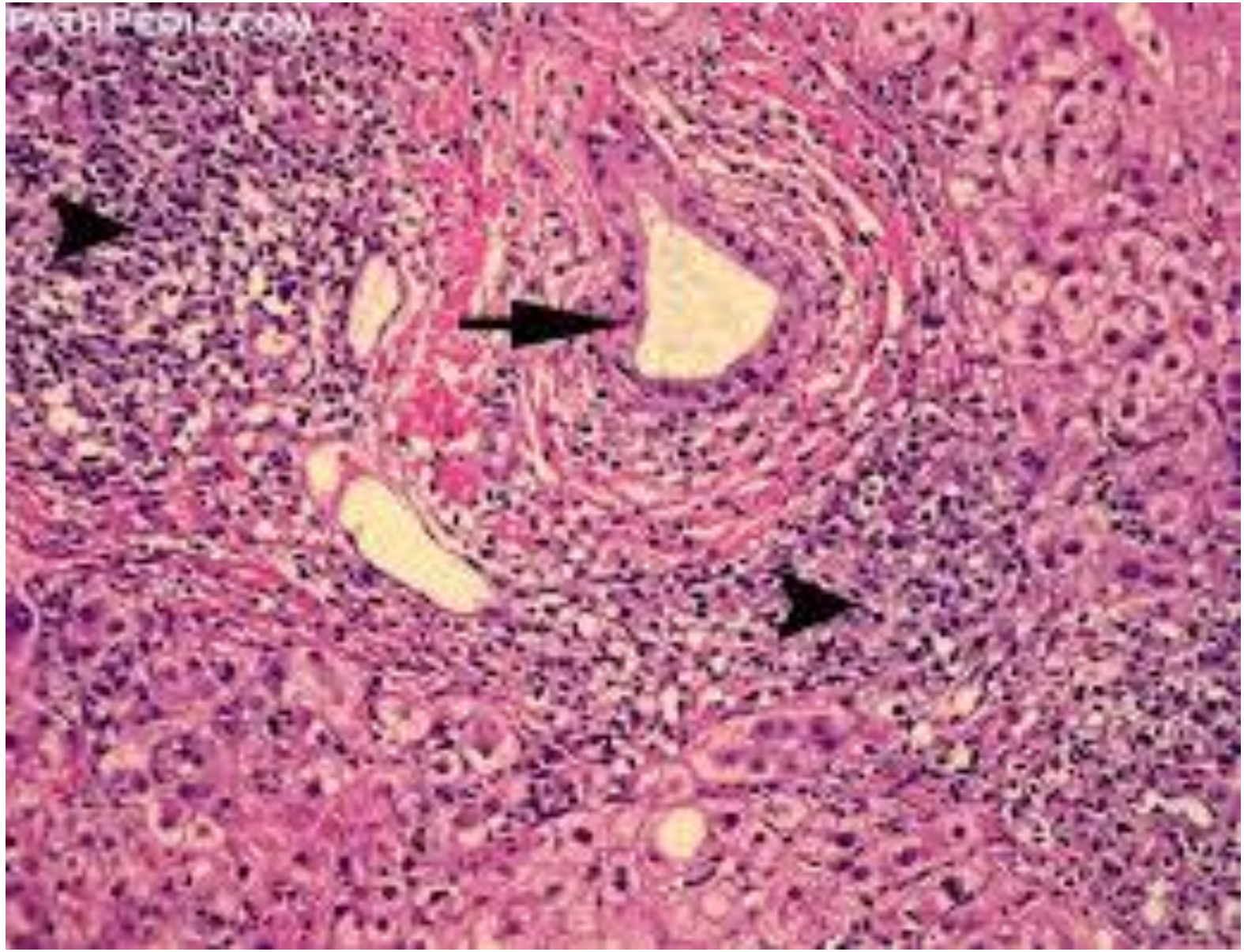
Autoimmune Hepatitis

# Auto-Antibodies in AIH

| Antibody | Target Antigens | Prevalence | Other Disease |
|---|---|---|---|
| ANA | Multiple nuclear proteins | 60-80% | PBC, PSC, HCV, NAFLD |
| SMA | Actin | 60-80% | HCV, NAFLD, Acute viral hepatitis |
| pANCA | Lactoferrin, Other unknown Ag | 65-90% | PSC, PBC |
| LKM-1 | CYP 2D6 | ≈ 4% | HCV |
| SLA/LP | UGA repressor tRNA-associated protein | 10-30% | HCV |

# Sub-Types of Autoimmune Hepatitis

| | Type 1 | Type 2 |
|---|---|---|
| Age at Presentation | Any age | Predominantly children |
| Female:Male | 4:1 | 8:1 |
| Ig G Levels | Elevated IgG | Variable Ig G |
| Ig A Levels | Normal | +/- Low IgA |
| Auto-antibodies | ANA, SMA | LKM-1 |
| Cirrhosis at 3 yrs | ~ 40% | ~ 80% |



# Recognition and Diagnosis of AIH

- Should be considered in patient with elevated AST/ALT or cirrhosis of uncertain etiology
- ANA, SMA and other autoantibody tests are poor “screening tests”
- The diagnosis of AIH must be based on a constellation of findings
- A diagnosis of AIH is often a “work in progress”

| | | Points |
|---|---|---|
| Autoantibodies | ANA or SMA or LKM >1:40 | 1 |
| | ANA or SMA or LKM >1:80 | 2 |
| | SLA/LP Positive (>20 units) | |
| IgG (or gamma-globulius) | Upper normal limit | 1 |
| | >1.10 times normal limit | 2 |
| Liver histology* | Compatible with AIH | 1 |
| | Typical for AIH | 2 |
| Absence of viral hepatitis | Yes | 2 |
| | No | 0 |

# International Autoimmune Hepatitis Group Scoring System: Patient History

| | Favor AIH (points) | Favor other diagnosis (points) |
|---|---|---|
| Gender | Female (+2) | Male (0) |
| Alcohol | < 25 g/d (+2) | > 60 g/d (–2) |
| Hepatotoxic drugs | None (+1) | Present (-4) |
| Other autoimmune diseases | Present (+2) | None (0) |

# International Autoimmune Hepatitis Group Scoring System: Biochemistries

| | Favor AIH (points) | Favor other diagnosis (points) |
|---|---|---|
| Alkaline phosphatase elevation: ALT elevation | < 1.5 (+2) | > 3.0 (-2) |
| Serum globulins, γ globulin or IgG | > 2 x normal (+3)<br>>1.5-2 x normal (+2)<br>> 1-1.5 x normal (+1) | Normal (0) |

# International Autoimmune Hepatitis Group Scoring System: Serologies

| | Favor AIH (points) | Favor other diagnosis (points) |
|---|---|---|
| ANA, SMA or LKM-1 | > 1:80 (+3)<br>1:80 (+2)<br>1:40 (+1) | < 1:40 (0) |
| AMA | Negative (0) | Positive (-4) |
| Hepatitis Markers | Negative (+3) | Positive (-3) |
| Other autoantibodies | Present (+2) | Absent (0) |
| HLA-DR3 or DR4 | Present (+1) | Absent (0) |

# International Autoimmune Hepatitis Group Scoring System: Histology

| | Favor AIH (points) | Favor other diagnosis (points) |
|---|---|---|
| Interface Hepatitis | +3 | |
| Lymphoplasmacytic Infiltrate | +1 | |
| Rosetting of liver cells | +1 | |
| None of Above | | -5 |
| Biliary Changes | | -3 |
| Other changes | | -3 |

# International Autoimmune Hepatitis Group Scoring System: Response to Therapy

| | Favor AIH (points) |
|---|---|
| **Complete Remission** (normal ALT, IgG, bilirubin within 12 mo and for >6 month duration or: all tests > 50% improved in 1 mo. and AST/ALT < 2x normal within 6 mos. or: liver biopsy with minimal activity) | +2 |
| **Remission with relapse** (return of symptoms, abnormal biopsy and /or > 2 x normal AST/ALT) | +3 |

# Interpretation of International Autoimmune Hepatitis Group Score

| Score | Interpretation |
|---|---|
| **Pre-therapy:** | |
| >15 | Definite AIH |
| 10-15 | Probable AIH |
| **Post-therapy:** | |
| >17 | Definite AIH |
| 12-17 | Probable AIH |

# Indications for Treatment

| Absolute | Relative | None |
|---|---|---|
| AST ≥ 10x normal | Symptoms | No symptoms |
| AST ≥ 5x normal and γ-globulin ≥ 2x normal | AST < 5x normal γ-globulin < 2x normal | Inactive cirrhosis |
| Bridging necrosis | Interface hepatitis | Portal hepatitis |

Autoimmune Hepatitis

# Therapy in Adults

| Interval | Monotherapy | Combination Therapy | |
|---|---|---|---|
| | Prednisone mg/d | Prednisone mg/d | Azathrioprine mg/d |
| Week 1 | 60 | 30 | 50 |
| Week 2 | 40 | 20 | 50 |
| Week 3 | 30 | 15 | 50 |
| Week 4 | 30 | 15 | 50 |
| Daily until endpoint | 20 | 10 | 50 |

Reasons for Selecting Treatment Regimens

# Reasons for Selecting Treatment Regimens

## Prednisone Monotherapy

- Severe cytopenia
- TPMT deficiency
- Prior Aza intolerance
- Pregnancy
- Malignancy

## Combination (Pred+Aza)

- Postmenopausal state
- Osteoporosis
- Brittle diabetes
- Obesity
- Acne
- Emotional lability
- Hypertension

# Liver Transplantation

- Overall 5-year survival rates 80-90%
- Increased frequency of acute allograft rejection
- AIH recurrence in 30-40%
  - Surveillance liver biopsies may be warranted
  - Manage with corticosteroids