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

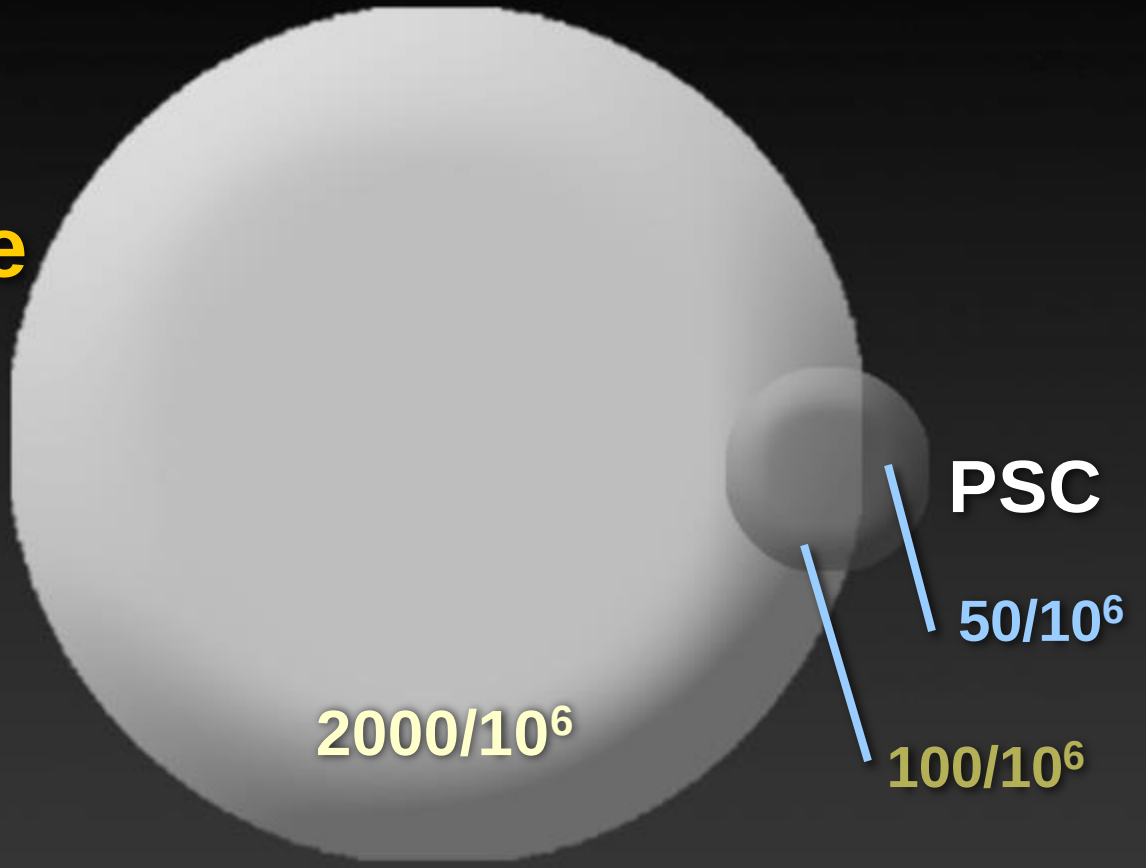
Clinical Presentation

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

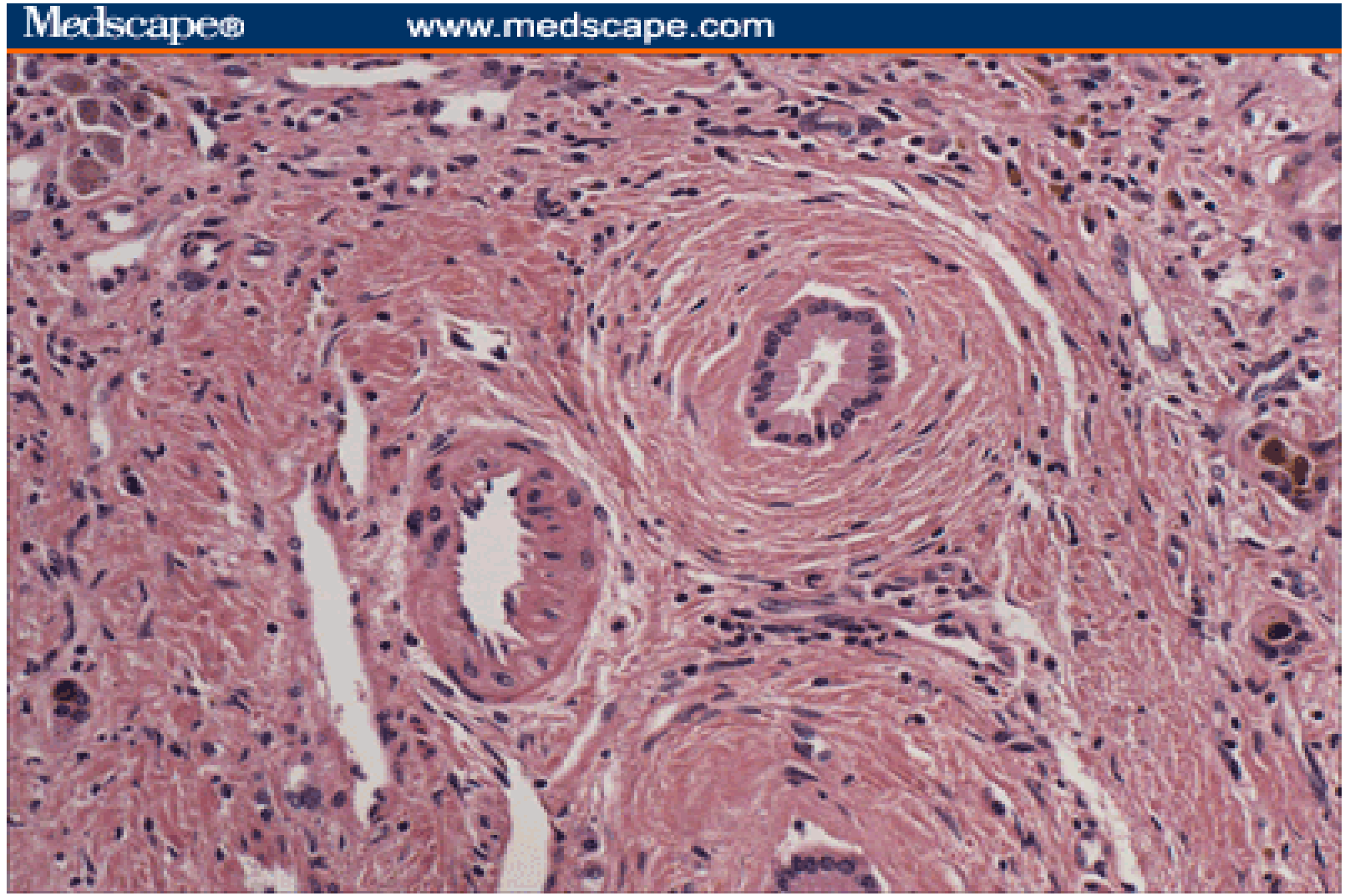
Prevalence of Autoantibodies in PSC

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

Diagnosis - Cholangiography

- ERCP most commonly used
- 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
- Chronic pancreatitis
- 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

Primary Biliary Cirrhosis

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

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

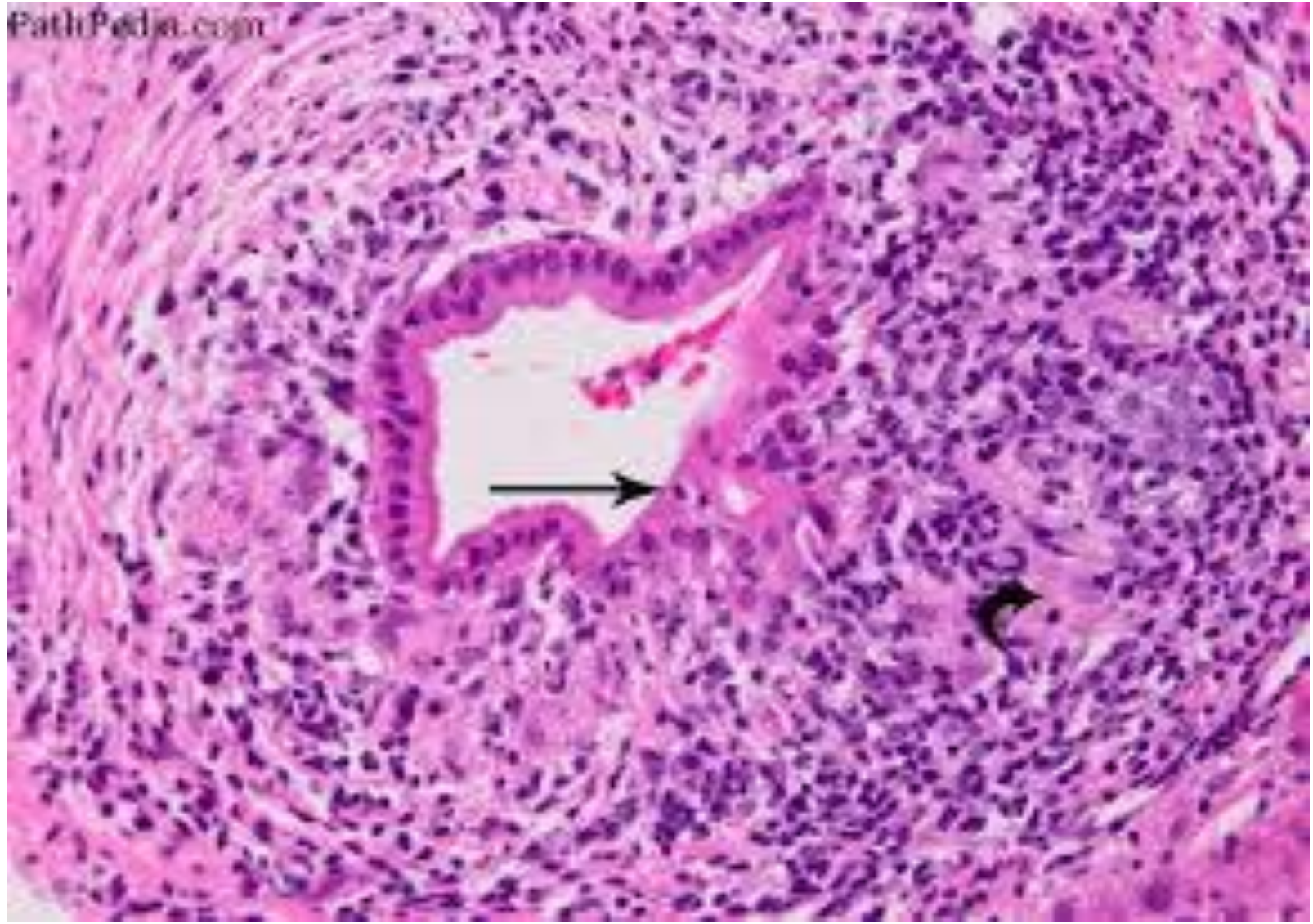
Serum Antibodies in PBC

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

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

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 Cholestasis 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

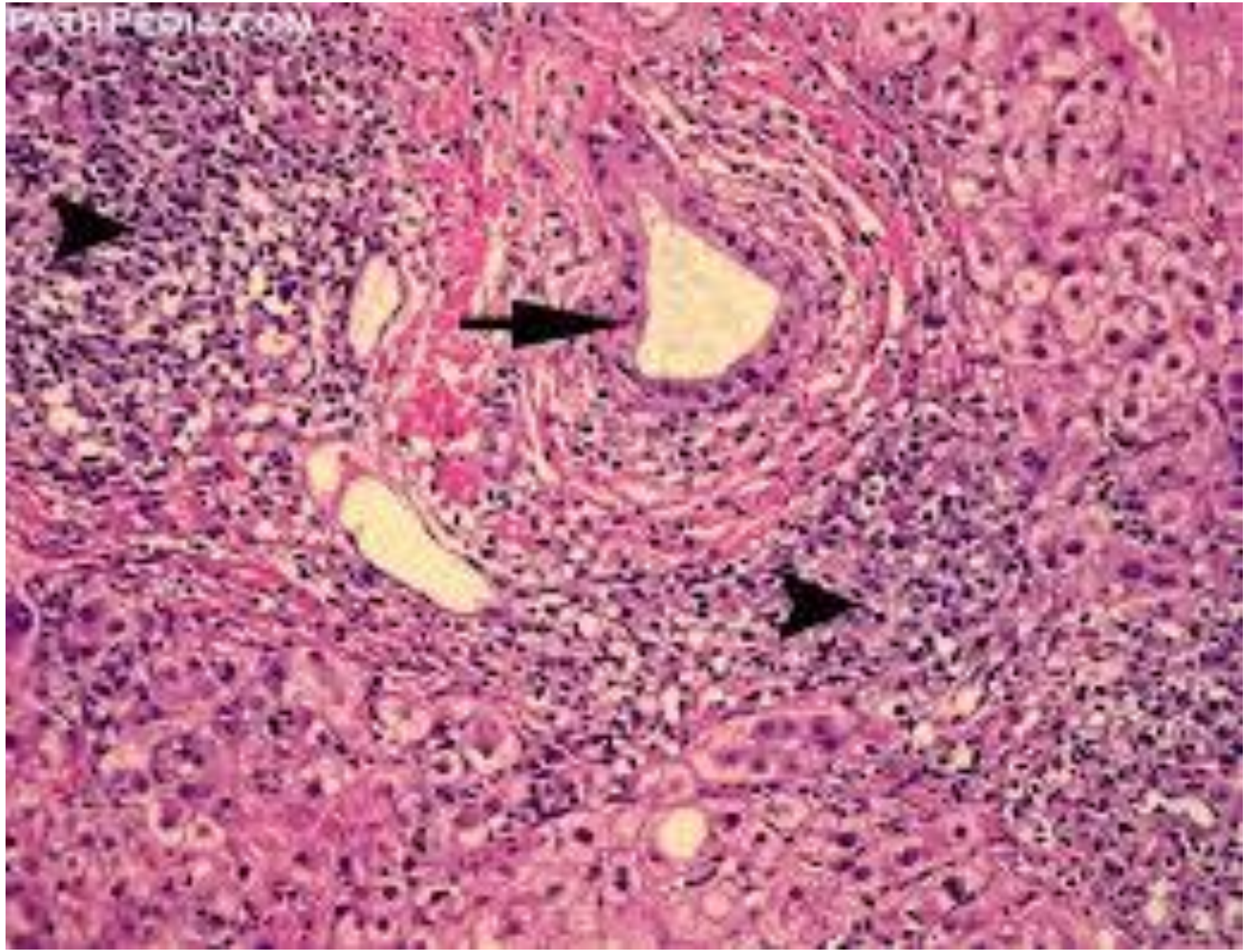
Autoimmune Hepatitis

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) >1.5-2 x normal (+2) > 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) 1:80 (+2) 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 Based on the results of

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