

Autoimmune Liver Diseases

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Definition

↑ alkaline phosphatase ↑ Gama-GT

- **Chronic cholestatic liver disease**
- **Unknown etiology, frequently associated with Inflammatory Bowel Disease** (ulcerative colitis)
- **Diffuse inflammation and fibrosis of the biliary tree**
- **Leads to biliary cirrhosis and portal hypertension**

↳ common in males

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**

Primary Sclerosing Cholangitis

Clinical Picture

- Cholestasis (elevated alkaline phosphatase)
- Usually in setting of colitis
- May be asymptomatic
definitive diagnosis.
- Abnormal cholangiogram diagnostic
by ERCP or MRCP

Primary Sclerosing Cholangitis

Clinical Presentation

*Asymptomatic	15 - 44%
Symptomatic	
*Fatigue	75
*Pruritus <i>itching</i>	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 <i>if advanced liver disease</i>	2-14
Ascites	2-10

Charcot's triad.

1. right upper quadrant pain

2. Fever

3. Jaundice

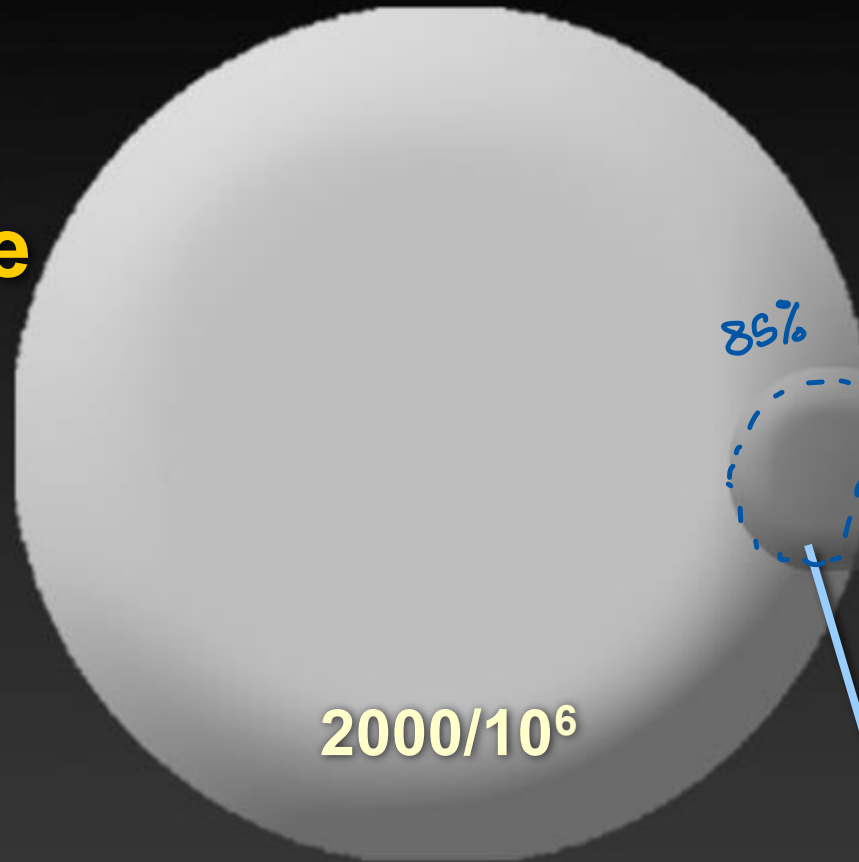
Primary Sclerosing Cholangitis

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

**Chronic
ulcerative
colitis**



85%

isolated PSC
PSC

50/10⁶

100/10⁶

colonoscopy every 5 yrs
in PSC pts.

(Estimated prevalence)

Primary Sclerosing Cholangitis

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.

Autoimmune
IBD
Idiopathic

Primary Sclerosing Cholangitis

Diagnostic Criteria

Exclude: *secondary SC :*

- **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**

Primary Sclerosing Cholangitis

Liver Tests

- **Alkaline phosphatase nearly always elevated**
- **AST and ALT usually <5 times normal**
- **Bilirubin, albumin, prothrombin time usually normal at diagnosis**
 - ↳ With Fibrosis later on will be impaired

Primary Sclerosing Cholangitis

Prevalence of Autoantibodies in PSC

* **p-ANCA** **80%**
+ve in ulcerative colitis

AMA **<2%**

ANA **50-60%**

SMA **35%**

ASCA → +ve in crohn's

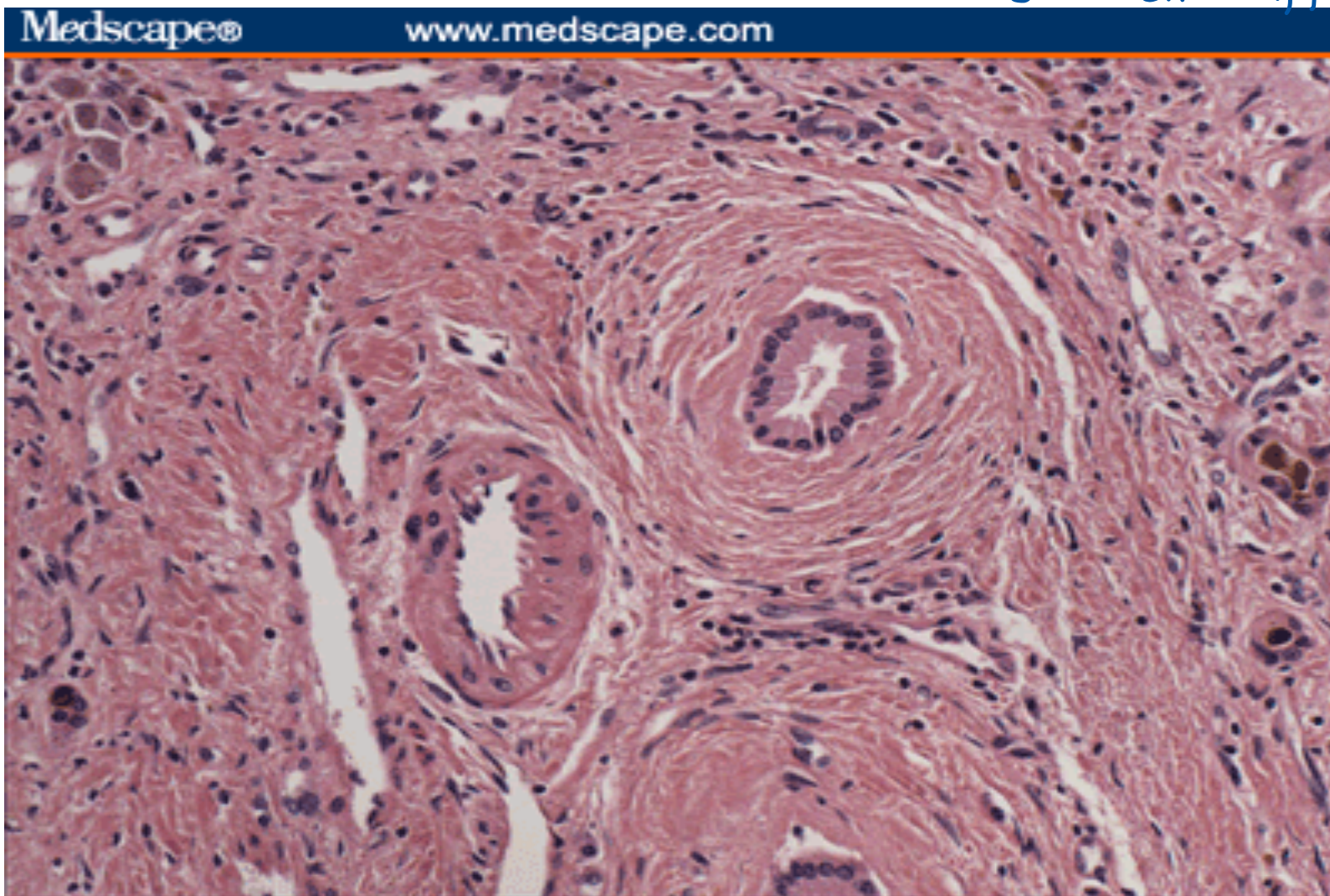
Primary Sclerosing Cholangitis

Diagnosis - Cholangiography

- **ERCP** ^{not} ^{should not be used for diagnosis} **most commonly used** *(used only when indicated)*
** MRCP is usually used **
- **Percutaneous cholangiography**
infrequently used
- **Magnetic resonance cholangiography** *MRCP*
Why preferred? ** non-invasive*
~~no~~ radiation exposure
** cost-effective*



onion skin appearance



Small-Duct PSC

- 5% of PSC
- Normal ^{MRCP} cholangiogram but biopsy showing PSC
- Can progress to classic PSC *with time*
- May exist with or without colitis ^{IBD}

Primary Sclerosing Cholangitis

Differentiating PSC from PBC

	PSC	PBC <i>Primary biliary cholangitis</i>
Cholestasis	+	+
History of colitis	+	-
AMA <i>anti-mitochondrial antibodies</i>	-	+
Liver biopsy	onion skin fibrosis	florid duct lesion
Cholangiogram	abnormal	normal <i>injury to small ducts</i>

Primary Sclerosing Cholangitis

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

مو مطلوب

Disease Specific Therapy

- **Surgical therapy seldom used** *if focal*
- **Dilation for dominant strictures**
by ERCP (used in managing complications)
- **No proven medical therapy**
 - *No steroids use*

Primary Sclerosing Cholangitis

Management of Cholestasis

Vitamin Deficiency

↓ absorption of bile (fat)
soluble vitamins

A	40%
D	14%
E	2%
K	Unknown

Primary Sclerosing Cholangitis

Management of Cholestasis

Metabolic Bone Disease

Osteoporosis much more common than osteomalacia

- **Hormone replacement in women**
- **Calcium $\pm$ vitamin D helpful**
- **Bisphosphonates may be helpful**
- **Steroid therapy may worsen bone disease**
- **Calcitonin not helpful**

Primary Sclerosing Cholangitis

Management of Cholestasis

Steatorrhea due to ↓ bile in the gut

- 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**

biopsy if risk of cholangiocarcinoma

Primary Sclerosing Cholangitis

Cancer Risk

Most common
ca. in those pts:

①

Cholangiocarcinoma

MRCP yearly

② Colorectal ca.
Colon ca.

- Lifetime risk 7-15%
- Incidence 0.5 to 1%
- Smoking and IBD may increase risk

Other cancers: pancreatic, liver, and colon

Primary Sclerosing Cholangitis

Liver Transplantation for PSC

Survival

1 year 90-97%

5 years 85-88%

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

Primary Sclerosing Cholangitis

Treatment Recommendations

- **No standard medical therapy** *supportive therapy*
- **Cancer surveillance** *for cholangio.. + colorectal*
- **Hepatitis A & B vaccination**
- **Antibiotics for cholangitis**
- **Screen for varices**
- **Dilate symptomatic strictures** *by ERCP*
- **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**
 - Middle aged females
 - elevated IgM

Primary Biliary Cirrhosis

Natural History: Risk Factors

- Female gender
- Autoimmune thyroid disease & celiac disease
- Prior urinary tract infection
- History of previous tonsillectomy
- Smoking
- Inflammatory skin disease (psoriasis, eczema)
- Genetic predisposition

Primary Biliary Cirrhosis

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Clinical Features at Presentation

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

dryness in mucus
membranes & eyes ←

in advanced
untreated

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 *not highly elevated*
- Bilirubin - usually rises late
- Cholesterol elevated in 85%
- IgM - commonly elevated

Primary Biliary Cirrhosis

Serum Antibodies in PBC

Type	Prevalence
* AMA	++++ +ve > 90% pts.
ANA	+++
ASMA	++
Anti-Centromere	+
Anti-Gp210	++
Anti-Sp100	++
p-ANCA	+

Primary Biliary Cirrhosis

AMA-Negative PBC

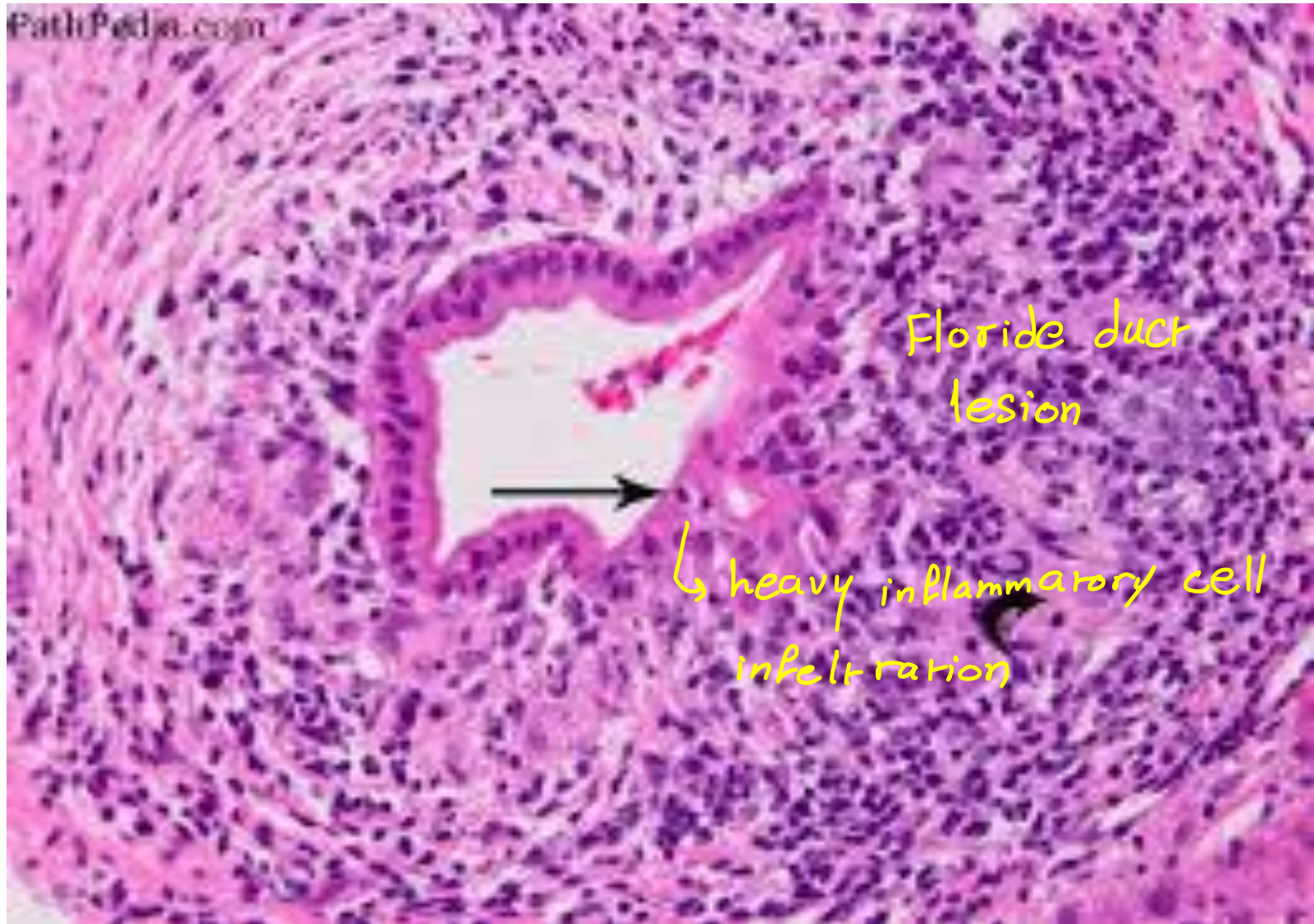
- Occurs in 5%-10% of all cases
- No evidence of extrahepatic biliary obstruction
- No difference in clinical presentation, natural history and prognosis compared to AMA-positive cases
- Response to medical therapy similar to AMA-positive individuals
- High prevalence of serum ANA ^{+ve}

Primary Biliary Cirrhosis

Role of Liver Biopsy in Diagnosis

- Positive predictive value for PBC is 98% when
 - Alk Phos > 1.5x normal
 - AST < 5x normal
- Biopsy needed when
 - AMA is negative
 - ? AIH-PBC overlap
 - Staging desired





Primary Biliary Cirrhosis

Persistent itching pt. → do liver enzymes

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 *symptomatic treatment*
 - increased fluid intake
 - oral sialogogues
 - artificial tears
 - vaginal lubricants

Primary Biliary Cirrhosis

Xanthomata

due to high HDL levels

↳ protective against
cardiovascular
diseases

- 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

↳ ursodeoxycholic acid
ursodiol

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**

Xenobiotic is a term used to describe chemical substances that are foreign to animal life and thus includes such examples as plant constituents, drugs, pesticides, cosmetics, flavorings, fragrances, food additives, industrial chemicals and environmental pollutants.
- **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
calcinosis	sclerodactyly
Raynaud's	Telangiectasias
Esophageal dysfunction	

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

Dexa scan every 2 yrs

Primary Biliary Cirrhosis

Management of Metabolic Bone Disease

Osteoporosis much more common than osteomalacia

- **Hormone replacement in women**
- **Calcium $\pm$ 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 *bas at risk of thyroiditis*

Lipid profile

Yearly

Bone density

Diagnosis, 2 years

Vitamin levels

If total bilirubin elevated

obstruction → ↓ vitamin absorption

Primary Biliary Cirrhosis

Medical Management

← not used ↓ Unsuccessful	Questionable	Useful
penicillamine	steroids	*UDCA*
cyclosporine	colchicine	polyretic & anti-inflammatory
azathioprine	methotrexate	Obeticholic acid OCA
thalidomide		Fibrates
malotilate		} seconde line
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

Respond to steroids

Autoimmune Hepatitis

Autoimmune Hepatitis

Intermittently progressive inflammatory liver disease of presumed autoimmune etiology

- High gamma globulins, autoantibodies *IgG*
- Predominately periportal hepatitis
- Usually responds favorably to corticosteroids
- *ANA*
- *ASMA*

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

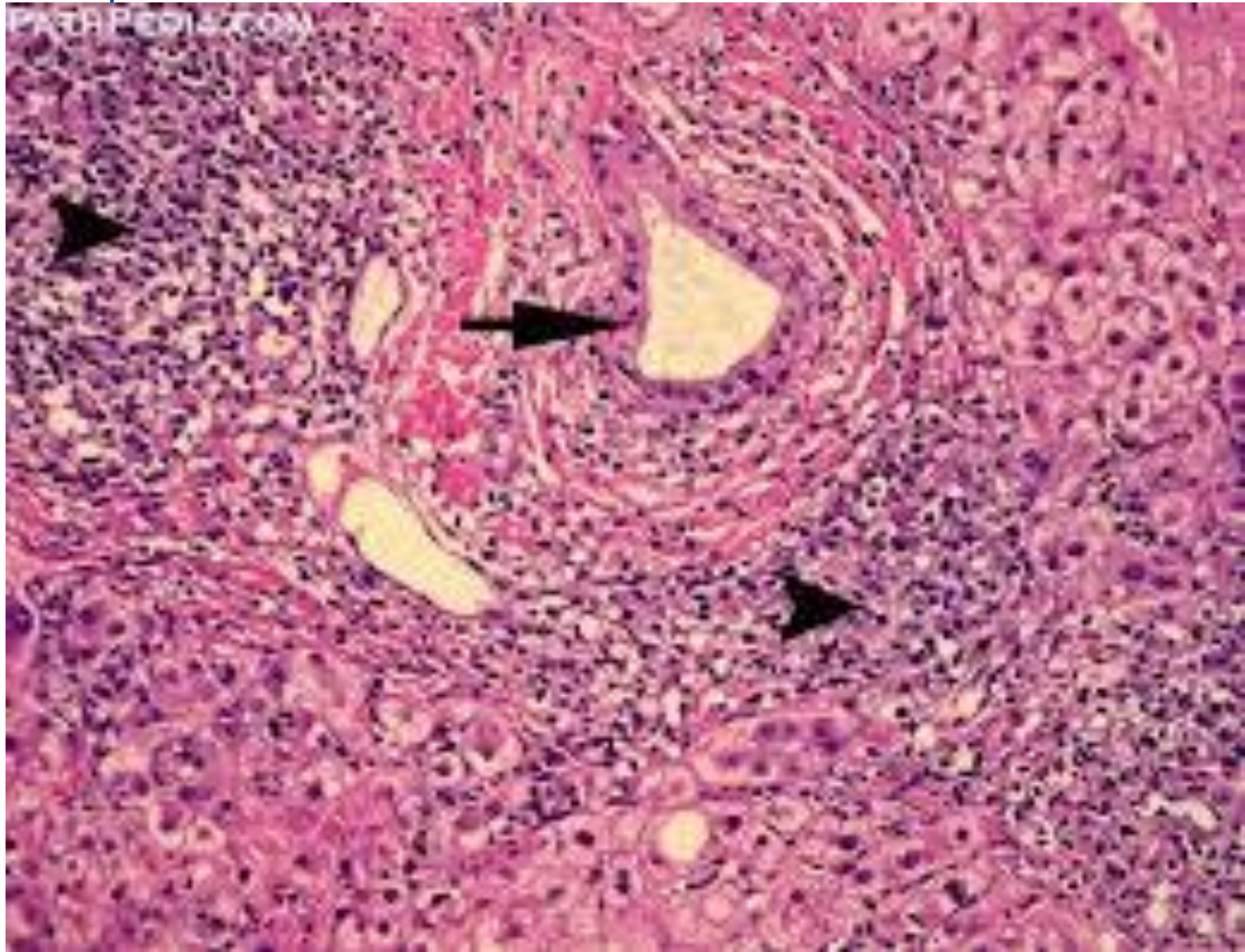
Auto-Antibodies in AIH

	Antibody	Target Antigens	Prevalence	Other Disease
Type I	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
Type II in Kids & young females More aggressive	LKM-1 Liver Kidney microsomal	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 <i>Adults</i>	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%

lymphoblastic cell infiltration with interphase hepatitis



Recognition and Diagnosis of AIH

- Should be considered in patient with elevated AST/ALT or cirrhosis of uncertain etiology
↳ in thousands
- 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-globulins)	Upper normal limit	1
	>1.10 times normal limit	2
Liver histology*	Compatible with ALH	1
	Typical for ALH	2
Absence of viral hepatitis	Yes	2
	No	0

Autoimmune Hepatitis

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)

Autoimmune Hepatitis

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)

Autoimmune Hepatitis

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)

Autoimmune Hepatitis

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

Autoimmune Hepatitis

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

Autoimmune Hepatitis - Criteria

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

Autoimmune Hepatitis

Indications for Treatment

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

start treatment

burned out liver
↳ no need to
treat

Autoimmune Hepatitis

Therapy in Adults

Interval	Monotherapy	Combination Therapy	
	^{Steroid} Prednisone mg/d	Prednisone mg/d	^{Imuran} Azathioprine 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

سنين مثلاً

لـ بعمل Liver biopsy وبتشوف إذا في inflammation بتكمل العلاج

Autoimmune Hepatitis

Reasons for Selecting Treatment Regimens

Prednisone Monotherapy

- Severe cytopenia → side effect of aza
- TPMT deficiency → enzyme of aza metabolism
- Prior Aza intolerance
- Pregnancy
- Malignancy high risk

Thiopurine
methyltransferase

Combination (Pred+Aza)

Aza له بسلش فيه كد ما يتحسس بقطي

↳ have hepato-
toxicity
effect in
some pts.

- 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**