Autoimmune Liver Diseases

↳ 3 main disease

1. PSC
2. PBC

> Biliary related problems (AP and GGT ↑ > ALT/AST)

3. AH → ALT / AST ↑ , mainly a liver problem.

🧠 Feature	🌿 PSC	🌸 PBC	🔥 AIH
🖼️ Imaging Findings	🧯 Abnormal cholangiogram (beading, strictures), MRCP preferred	✅ Normal cholangiogram	🚫 No diagnostic imaging abnormalities
🔬 Histological Findings	Onion-skin periductal fibrosis	Florid duct lesion (destructive cholangitis)	Interface hepatitis with lymphoplasmacytic infiltrate
👤 Typical Patient Profile	Young/middle-aged men	Middle-aged women	Women of all ages; teens in type 2
🩺 Common Symptoms	Fatigue, pruritus, jaundice, abdominal pain, weight loss, splenomegaly	Fatigue, pruritus, dry eyes/mouth, hepatomegaly, late jaundice	Fatigue, joint pain, jaundice, amenorrhea, hepatomegaly
⚠️ Complications	Cholangiocarcinoma, portal hypertension, cirrhosis, osteoporosis, dominant strictures	Cirrhosis, portal hypertension, osteoporosis, sicca syndrome, hyperlipidemia	Cirrhosis if untreated, portal hypertension, recurrence after transplant
🎗️ Cancer Risk	🧫 High (7–15% cholangiocarcinoma risk)	🎗️ Low direct cancer risk; risk via cirrhosis	⚠️ Moderate (due to cirrhosis)
📋 Diagnosis Approach	Symptoms + abnormal MRCP/ERCP + exclusion of other causes	Positive AMA serology + clinical features ± biopsy	Elevated transaminases + autoantibodies + high IgG + biopsy confirmation
💊 Treatment	No effective cure; ERCP for strictures, manage complications, transplant if needed	UDCA first-line; OCA for non-responders	Corticosteroids (Prednisone) ± Azathioprine
📈 Response to Treatment	Poor; manage only symptoms	Good if started early with UDCA	Excellent if early treatment with steroids
🪨 Need for Biopsy	Rarely needed; only for small-duct PSC	Needed if AMA-negative	Mandatory for diagnosis confirmation
🫃 Portal Hypertension	Common in advanced disease	Develops if cirrhosis occurs	Occurs with untreated disease
🦴 Bone Disease	Osteoporosis common; manage with calcium, vitamin D, bisphosphonates	Osteoporosis common; same management	Steroid-induced osteoporosis risk
😓 Fatigue Importance	Very common and early symptom	Severe fatigue, very disabling	Present but less dominant
🏥 Transplant Indications	Advanced cirrhosis, recurrent cholangitis, liver failure	Cirrhosis, liver decompensation	Failure of medical therapy or cirrhosis
♻️ Recurrence After Transplant	🔁 High (PSC can recur)	Rare	🔁 High relapse rate after transplant
📝 Special Notes	Strong IBD link; cancer surveillance is critical	Long asymptomatic phase; monitor thyroid disease too	Requires close monitoring with scoring systems; HLA-DR3/4 genetic links

Primary Sclerosing Cholangitis

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**

T cell
circulating complex
infections + bacteria

(Bacteria from Gut → Goes to liver through portal circulation)

70–80% from portal coming from SMV + splenic vein

Primary Sclerosing Cholangitis

Clinical Picture

- Cholestasis (elevated alkaline phosphatase) + Gamma GT {in early stages} vs in late stages: ↑ Bilirubin
- Usually in setting of colitis
- May be asymptomatic in early disease. (A patient who has IBD and incidently you find ↑ (AP))
- Abnormal cholangiogram diagnostic

Dx ↵

Primary Sclerosing Cholangitis

Clinical Presentation

Asymptomatic	15 - 44%
Symptomatic	
Fatigue (MC)	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

Advanced in liver cirrhosis.

Primary Sclerosing Cholangitis

Most imp thing to know.

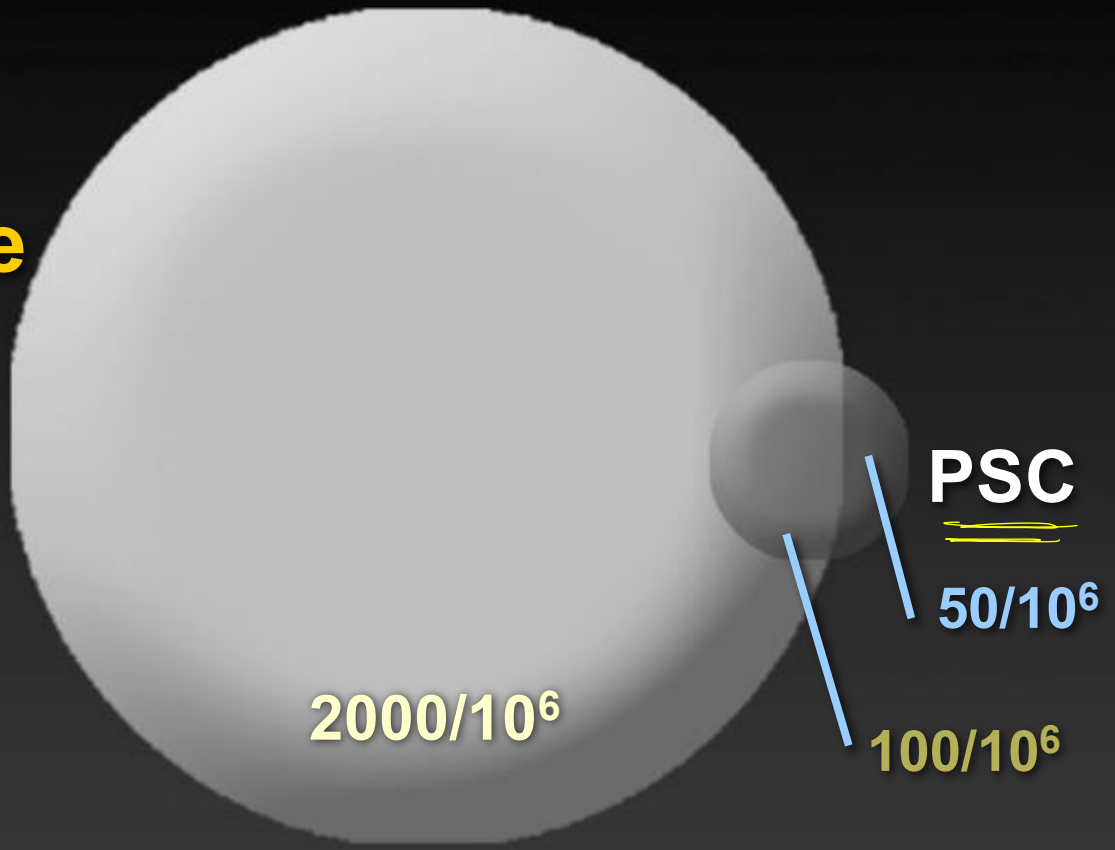
Relationship to Inflammatory Bowel Disease

- 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

imp but 80% in the opposite case.

Primary Sclerosing Cholangitis in Colitis

Chronic ulcerative colitis



(Estimated prevalence)

* PSC can precede the UC

Diagnostic Criteria

- **Typical cholangiographic abnormalities involving any part of the biliary tree**
  - narrowing / stricture and dilatation → beaded appearance
  - ⇒ inflx / fibrosis / narrowing
  - في المسرة
- **Compatible clinical and biochemical findings**
  - **History of IBD, cholestatic symptoms**
  - **Two- to three-fold increase in serum alkaline phosphatase level > 6 mos.** (not transient)

Primary Sclerosing Cholangitis

Diagnostic Criteria

Exclude: (other causes) → cause above in the slides & for primary but 2nd)

- **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 progression ⟶ ⇈

Primary Sclerosing Cholangitis

Prevalence of Autoantibodies in PSC

not very beneficial in diagnosis. ⟹ we mainly depend on Hx, abnormal cholangiography, cholestasis (↑ AP).

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

NO Dx criteria they only guide you.

تنظير

=

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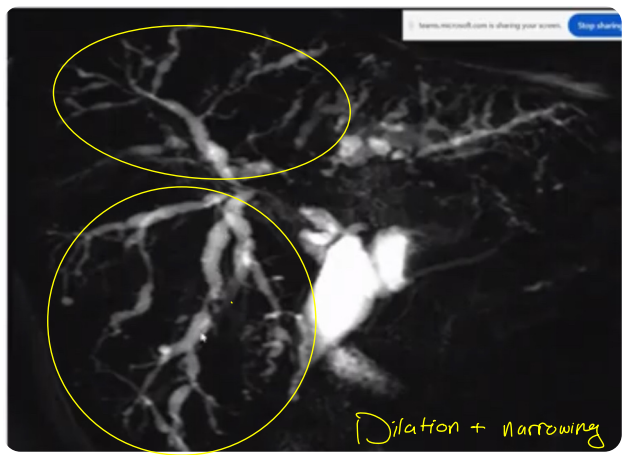
if you suspect
↳ you do this

→ complications
(↑ risk of cholangitis).

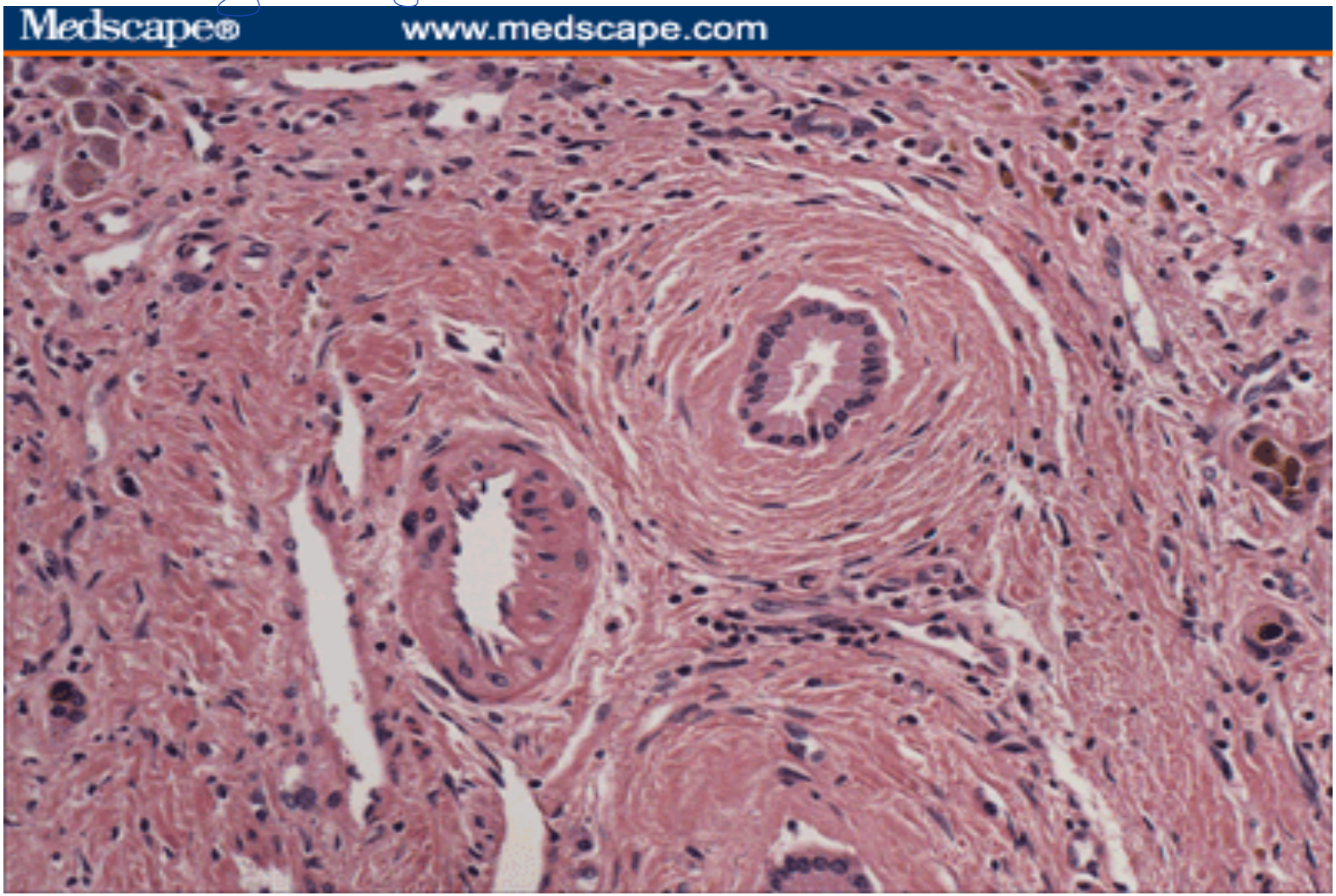
(MRCP)



Concentric Fibrosis in PSC

→ you see onion skin appearance.

Biopsy is rarely needed, unless you have Small Duct PSC.



Small-Duct PSC

- 5% of PSC
- Normal cholangiogram but biopsy showing PSC
- Can progress to classic PSC
- May exist with or without colitis

Primary Sclerosing Cholangitis

Differentiating PSC from PBC

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

IMP

not included

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

Primary Sclerosing Cholangitis

no tx, you just manage the complications.

Disease Specific Therapy

- Surgical therapy seldom used (Rare)
- Dilation for dominant strictures (Balloon.) → by ERCP (only for tx but never for dx).
- No proven medical therapy

Primary Sclerosing Cholangitis

Management of Cholestasis

complications

Vitamin Deficiency

A	40%
D	14%
E	2%
K	Unknown

Primary Sclerosing Cholangitis

Management of Cholestasis

Metabolic Bone Disease

Vit D deficiency

complication

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

complications.

- 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

Primary Sclerosing Cholangitis

Cancer Risk

Cholangiocarcinoma

Always think about it.

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

Other cancers: pancreatic, liver, and colon

Annual colonoscopy

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 (AMA +ve)
- Non-suppurative destructive cholangitis on liver histology → (cholangiogram is normal)

Primary Biliary Cirrhosis

Natural History: Risk Factors

* classical:
Middle aged F/
Hx of itching / Fatigue /
AMA + / cholestasis.
↳ PBC until proven other wise → no need for bx.

- Female gender (Middle age).
- Autoimmune thyroid disease
- Prior urinary tract infection (1)
- History of previous tonsillectomy (2)
- Smoking (3)
- Inflammatory skin disease (4)
  (psoriasis, eczema)
- Genetic predisposition (5)

Primary Biliary Cirrhosis

Clinical Features at Presentation

Asymptomatic	40-60%
Fatigue	+++
Pruritus	++
Sicca symptoms (Dryness).	+++
Hepatomegaly	+
Splenomegaly	+
Jaundice	uncommon
Xanthelasma	uncommon

Advanced stages.

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**

(only these too)

- May progress to liver cirrhosis and the patient doesn't know their

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

imp

Pruritus → persistant

- Frequency between 20-60% of cases
- Insidious onset
- May be intractable
- No association with age, sex, histological stage, and Mayo Risk score
- Etiology unknown
- needs multiple treatement (not easy).

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

imp

Due to high cholesterol but HDL not LDL

no ↑ risk of atherosclerosis

- 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

Biochemical Features of PBC

→ if no AP → not PBC.

- Alkaline Phosphatase almost always elevated (generally 3-4x normal)
  → vs PSC (2-3x).
- 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	+

most imp

seen more in AI hepatitis

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

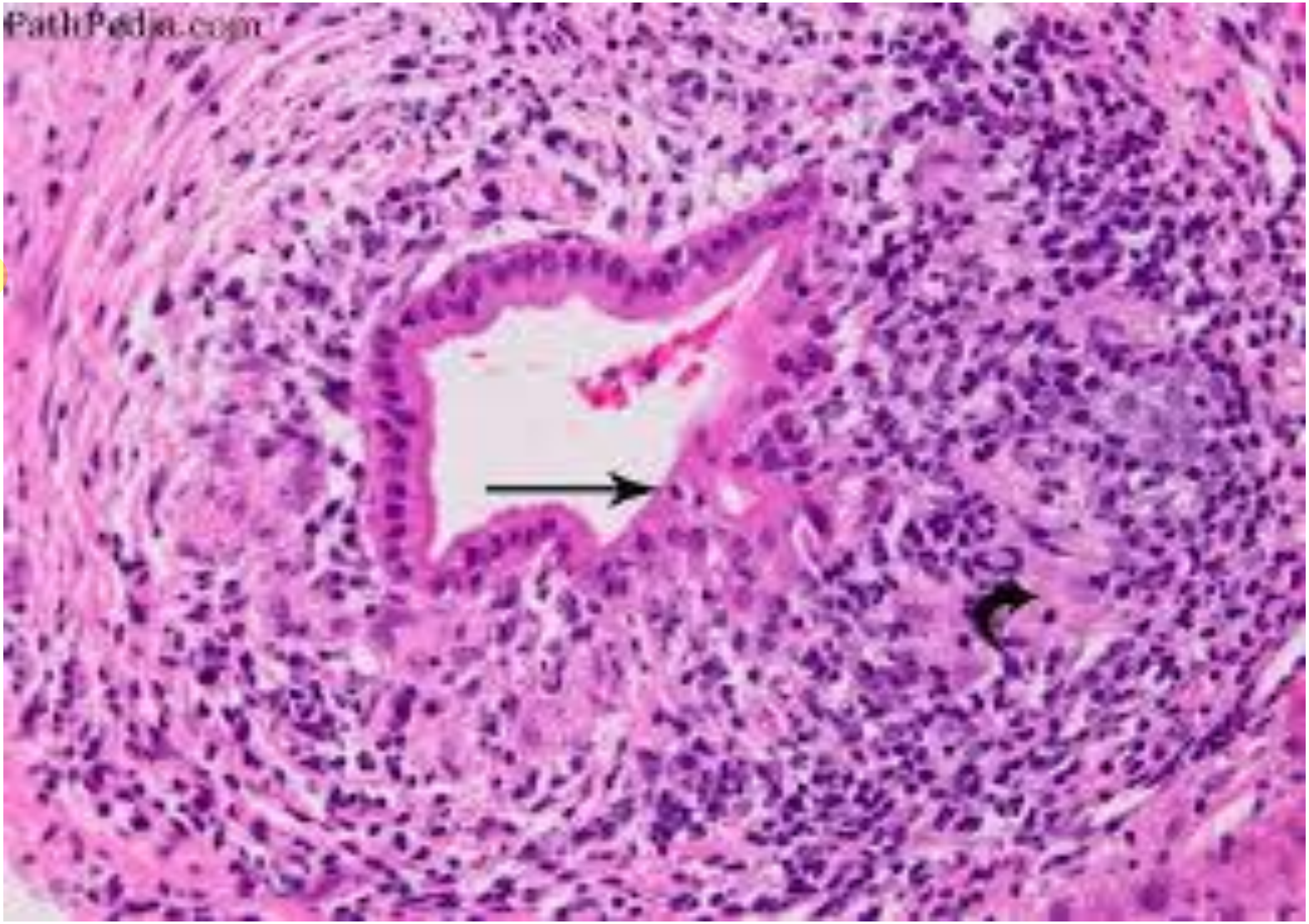
The only difference

- Biopsy to confirm Dx of PBC.

Florid Duct Lesion

- Florrid duct sign due to dense AAB inflammation. (Dense inflammation)

* This is a microscopic disease so only seen on Biopsy but not on MRCP



Potential Mechanisms for the Development of PBC

- Unknown.
- **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

prolonged (cholestasis)

- 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

Same as PSC

- **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

prolonged disease result.

- 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

when the patients reaches the stage of liver cirrhosis, you need to consider transplant.

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	(1) UDCA
cyclosporine	colchicine	Drug of choice
azathioprine	methotrexate	if resistance or no response
thalidomide		(2) OCA
malotilate		(3) Fibrates
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

↳ ALT/AST ↑ >> AP

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

IgG

no response in PSC and PBC

Autoimmune Hepatitis

Clinical Features

- Middle-aged (or teenage) woman, non-drinker without viral hepatitis
- Fatigue (1), arthralgias/myalgias (2), oligomenorrhea (3), jaundice (4)
- Increased ALT, AST, gamma globulins — very imp
- Positive ANA and SMA
- Interface hepatitis with lymphoplasmacytic infiltrate — in liver biopsy
- 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

imp: Seen in type 2

Sub-Types of Autoimmune Hepatitis

Sub-Types of Autoimmune Hepatitis

Difference in Age and type of Auto-Ab.

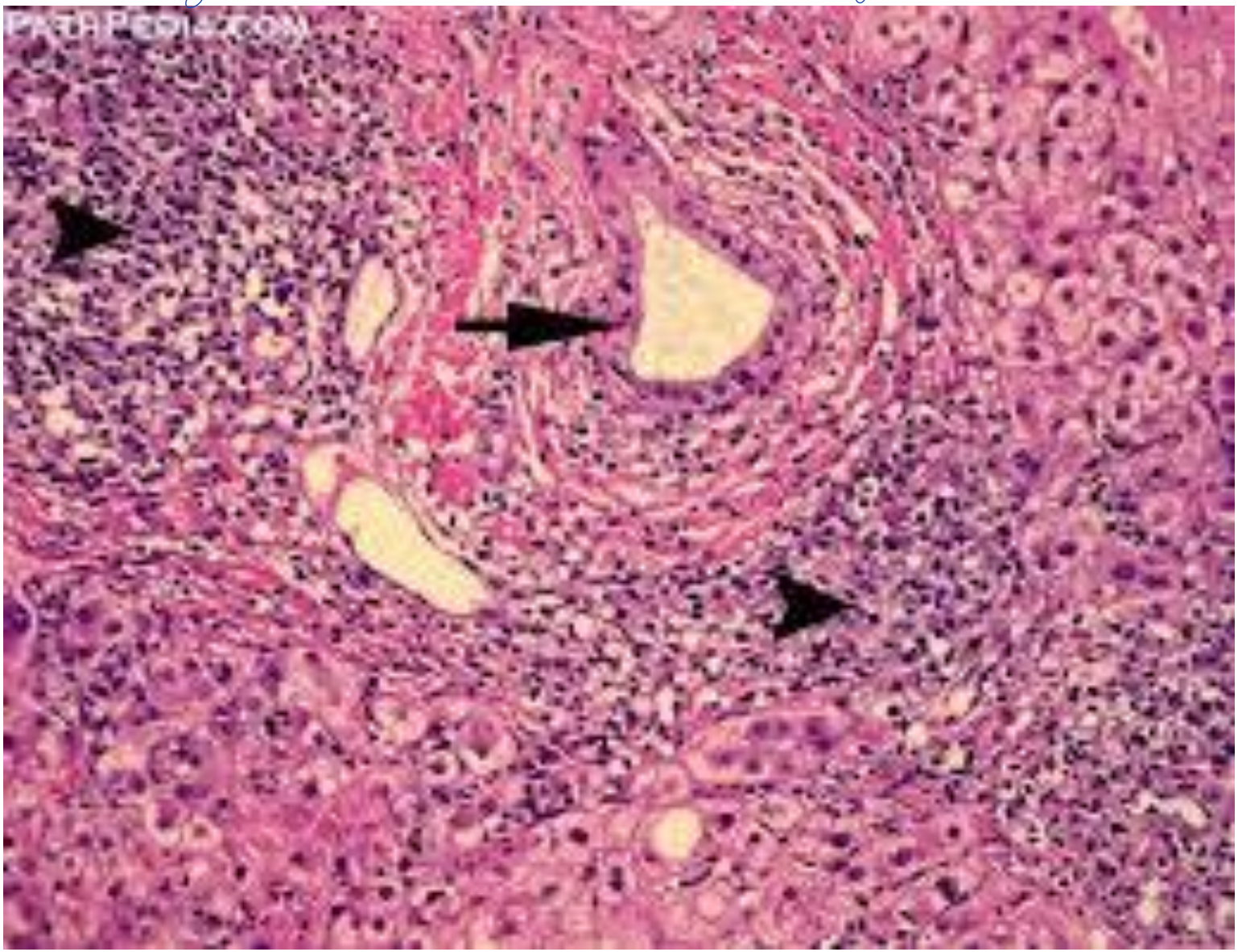
	Type 1	Type 2
Age at Presentation	Any age	Predominantly children
Female:Male	4:1	8:1
Ig G Levels	Elevated IgG	Variable Ig G
Ig A Levels	Normal	+/- Low IgA
Auto-antibodies	ANA, SMA	LKM-1
Cirrhosis at 3 yrs	~ 40%	~ 80%

if left untreated

More Aggressive since it starts at an earlier stage

Biopsy: Multiple features but a single finding that suggest it : so we a scoring system to diagnose Autoimmune hepatitis.

* ما بتساعد كتير ولكن في نقط Suggests ALH



Autoimmune Hepatitis

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"

دايمًا poor لكل الأضداد
ولكن هي بتضيف مساعدة لباقي المعلومات

- The diagnosis of AIH must be based on a constellation of findings

no single way to diagnose you need to add everything up.

- 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)	2
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

More detailed.
الأرقام مو حقائق
اعرف الـ components.

	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

Autoimmune Hepatitis - Criteria

Interpretation of International Autoimmune Hepatitis Group Score

not for memorization.

Score	Interpretation
Pre-therapy:	
>15	Definite AIH
10-15	Probable AIH
Post-therapy:	
use of steroids: Typical for AIH. >17	Definite AIH
12-17	Probable AIH

Autoimmune Hepatitis

Indications for Treatment Based on the results of

we don't treat each patient with 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

Biopsy:

- elevated enzymes + interface hepatitis → yo go for treatement to decrease the progression of liver cirrhosis.

↓ Don't treat.

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

Most used.

Steroid sparing agent.

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 → treated with immunosuppression and steroids
- AIH recurrence in 30-40%
  - Surveillance liver biopsies may be warranted
  - Manage with corticosteroids