# GI Grand Rounds

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# History of Present Illness

Chief Complaint: Referral for NASH

HPI:

- 60 y/o WF evaluated and diagnosed at Cleveland GI clinic for NASH. Moved to Louisville and needs a GI Doc.
- Abnormal LFT since 5/2004
- Complain of RUQ pain, intermittent, stabbing in consistency, 4/10 intensity, no precipitating factors
- 20 lb weight gain since last 3 months
- On a herbal medication – “Simeri” for reducing LFT’s
- No other complaints

# PMH

- Meds: celebrex 200mg QD, atenolol 25mg QD, hyzaar 100/25, fexofenadine 180mg QD, reglan 10mg QD, prevacid sol tab 30mg QD, actonel, nasonex, vitamin E, fish oil, simera herbal medication
- NKDA
- Medical Problems: OA, HTN, GERD, Vocal cord polyp resected in 2003, enrolled in the Trental Sudy for NASH at Cleveland Clinic

# PMH (con't)

- Endoscopic procedures: EGD & Colonscopy June 2006 – esophageal erosions, small hiatal hernia, mild sigmoid diverticulosis, internal hemorrhoids

  Prior C-scopy June (1998) & Flex Sigmoidoscopy: Normal

- SH: Not smoker, occasional ETOH, no recreational drugs, no blood transfusions

- FH: Lived in multiple countries including Hong Kong 1991 – 1994, Paris 1994 – 1996, Avon Ohio since 1996

ROS: + RUQ pain, all other systems were negative

Physical Examination:

BP: 134/83 P: 61 RR:18 T-97.1

weight 183 lbs height 5’ 3”, BMI – 32

Gen appearance: obese

HEENT, CVS, Resp, Neuro: Normal

Skin: No spider angiomas or palmer erythema

Abd: soft, BS +, No HSM

# Labs from Cleveland Clinic

- 10/2006 CBC, BMP, Iron, TIBC, Transferrin Sat, Ferritin – Normal
- Alpha 1 antitrypsin – Normal
- ANA – Negative
- Smooth muscle antibody – Negative
- AMA – Positive
- Hepatitis A, B , C Profile – Negative
- Cholesterol – 230, TG – 96, LDL -142

| | AST | ALT | Alk Phos | TB | Alb | PT/ INR |
|---|---|---|---|---|---|---|
| 8/2002 | 29 | 26 | *167* | 0.3 | 3.8 | |
| 12/2002 | 22 | 21 | *142* | 0.3 | 4.2 | |
| 5/2003 | 3 | 41 | 112 | 0.4 | 4.3 | |
| 5/2004 | *47* | *57* | 93 | 0.4 | 4.4 | |
| 12/2005 | *44* | *67* | 119 | 0.4 | 4.3 | |
| 5/2006 | *136* | *204* | 119 | 0.4 | 4.1 | |
| 10/2006 | *198* | *197* | 94 | 0.7 | 4.1 | 11 / 1 |
| 3/2007 | *159* | *142* | 111 | 0.3 | 4.0 | |

- Liver USG: increase echogenicity of liver parenchyma suggestive of fatty liver

- Liver Bx: 11/2006: inflammatory activity is marked, interlobular bile ducts appear intact, Interface hepatitis / piecemeal necrosis, extensive bridging fibrosis, lobular hepatocytes remarkable for extensive necroinflammatory change. No fatty change

# Initial Consult on 10/2007

- Plan: Basic labs with work-up for other causes of hepatic Steatosis.
- Started Zinc 220mg QD

# ROUND 1
# McClain vs McCollough

# Clinic Follow Up

| | AST | ALT | Alk Phos | TB | Alb | PT/ INR |
|---|---|---|---|---|---|---|
| 3/2007 | ***159*** | ***142*** | 111 | 0.3 | 4.0 | |
| 10/2007<br><br>DHC | ***210*** | ***229*** | 102 | 0.5 | 4.0 | 10.7/ 1.1 |

# Clinic Follow - Up (10/2007)

- Iron 136, TIBC 319, Iron Sat 43%, Ferritin 268
- Mitochondrial Antibody 51.9 (>25)
- Antinuclear Antibody 578 (>120)
- Actin (Smooth Muscle) Antibody – 128 (>30)

# Clinic Follow Up 12/11/2007

- + ANA, + ASMA, + AMA : Autoimmune Hepatitis with PBC overlap
- Urso 500mg BID
- Basic labs
- Vaccinated for Pneumovax, Hepatitis A and B
- RTC 3 months

| | AST | ALT | Alk Phos | TB | Alb | PT / INR |
|---|---|---|---|---|---|---|
| 3/2007 | ***159*** | ***142*** | 111 | 0.3 | 4.0 | |
| 10/2007 | ***210*** | ***229*** | 102 | 0.5 | 4.0 | 10.7/1.1 |
| 12/11/2007 | ***146*** | ***158*** | 72 | 0.5 | 3.9 | 10.8/ 1.1 |

# Clinic Follow Up 3/11/2008

- Doing better
- LFT trending down
- Discussed risks & benefits of steriods & imuran
- Prednisone 10mg QD & Imuran 50mg QD
- Basic Labs today and recheck LFT in 2 wks, 1 month, and 2 months later

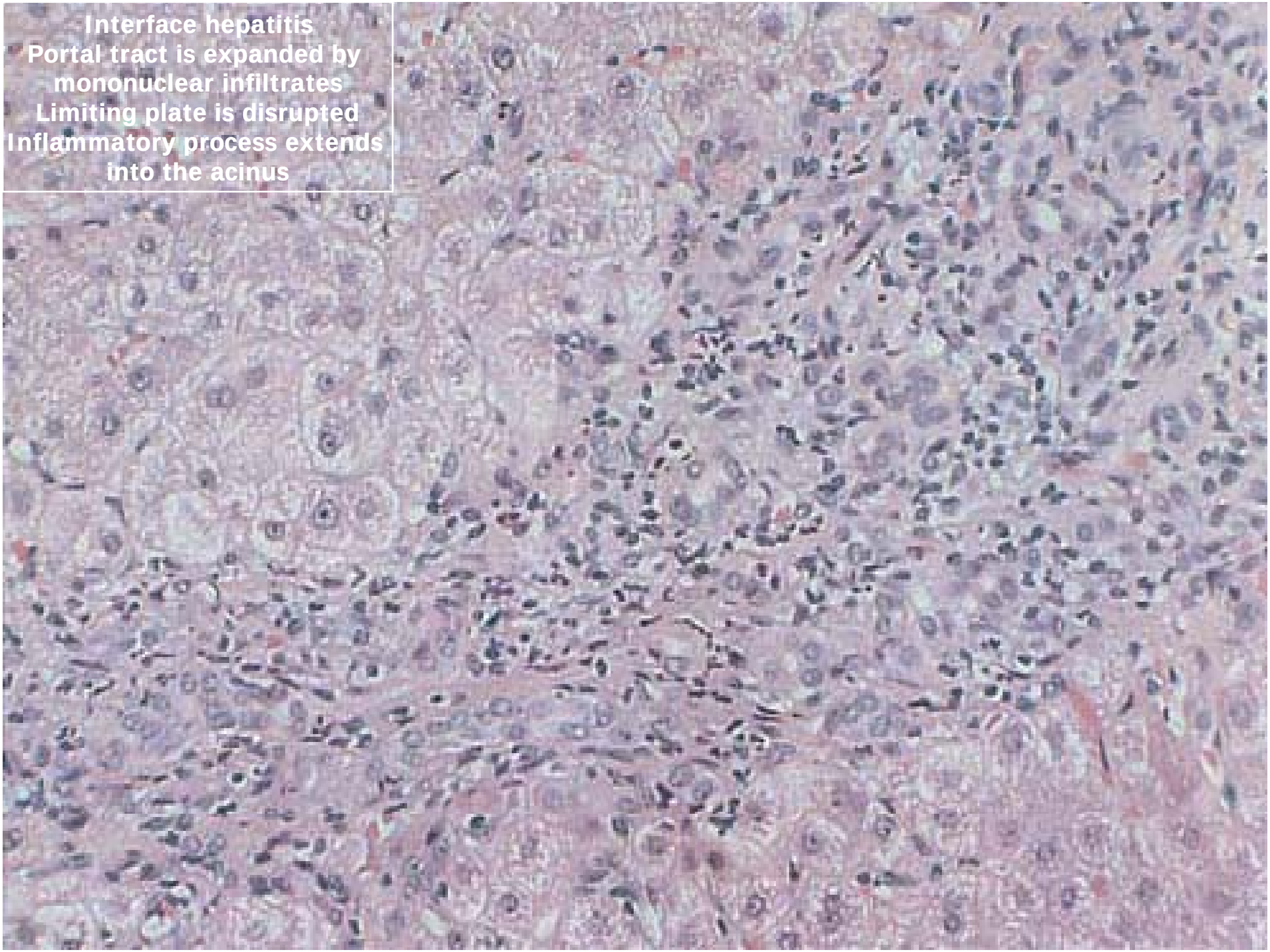
| | AST | ALT | Alk Phos | TB | Alb | PT/ INR |
|---|---|---|---|---|---|---|
| 3/2007 | 159 | 142 | 111 | 0.3 | 4.0 | |
| 10/2007 | 210 | 229 | 102 | 0.5 | 4.0 | 10.7/1.1 |
| 12/11/2007 | 146 | 158 | 72 | 0.5 | 3.9 | 10.8/ 1.1 |
| 3/11/2008 | 81 | 83 | 81 | 0.5 | 4.3 | |
| 3/25/2008 | 30 | 21 | 66 | 0.6 | 4.1 | |
| 4/09/2008 | 34 | 15 | 67 | 0.8 | 4.4 | |

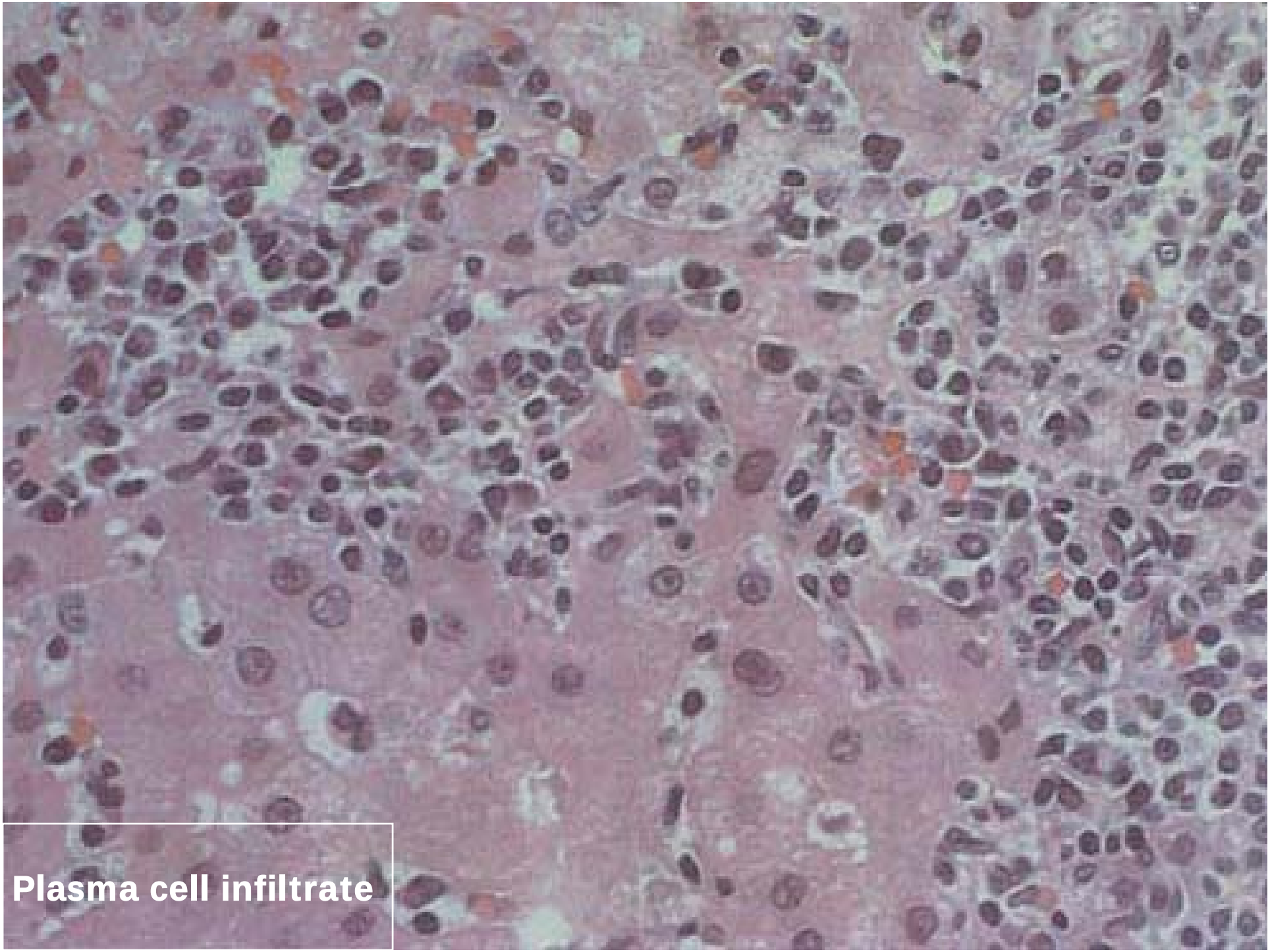
# Autoimmune Hepatitis

- Definition: unresolving inflammation of the liver of unknown cause. Characterized by the presence of interface hepatitis and portal plasma cell infiltration, hypergammaglobulinemia, and autoantibodies.
- Incidence: 1.9 per 100,000
- 2.6% of Liver Transplantations in the US
- 40% of patients with untreated severe disease die within 6 months of diagnosis

| Requisites | Definite | Probable |
|---|---|---|
| **NO genetic Liver Disease** | Normal alpha 1 antitrypsin phenotype<br><br>Normal serum ceruloplasmin, FE, & Ferritin | Normal alpha 1 antitrypsin phenotype<br><br>Nonspecific copper, ceruloplasmin, FE, & Ferritin abnormalities |
| **No Active Viral Replication** | NO current markers of infection with Hepatitis A, B, C | NO current markers of infection with Hepatitis A, B, C |
| **NO toxic or ETOH ingestion** | ETOH <25g/day or recent use of hepatotoxic drugs | ETOH <50g/day or recent use of hepatotoxic drugs |

| | | |
|---|---|---|
| **Lab Features** | Predominant serum aminotransferase Abnormality<br><br>Globulin, Gamma Globulin or IgG >1.5 x normal | Predominant serum aminotransferase Abnormality<br><br>Predominant Hypergammaglobulinemia, of any degree |
| **Autoantibodies** | ANA, SMA, or anti-LKM1 >1:80 in adults & >1:20 in children, NO AMA | ANA, SMA, or anti-LKM1 >1:40 or autoantibodies |
| **Histological** | Interface Hepatitis<br><br>No biliary lesions, granulomas, or prominent changes suggestive of another disease | Interface Hepatitis<br><br>No biliary lesions, granulomas, or prominent changes suggestive of another disease |


Interface hepatitis
Portal tract is expanded by mononuclear infiltrates
Limiting plate is disrupted
Inflammatory process extends into the acinus


Plasma cell infiltrate

- **Diagnostic Scoring System for Atypical Autoimmune Hepatitis in Adults** is to assess the strength of the disease and avoid biases & discrepancies.
- Definite diagnosis prior to corticosteriod treatment requires a score of >15 where as the definite diagnosis after corticosteriod treatment requires a score of >17
- Sensitivity of the scoring system: 97 – 100%

# Subclassifications

- 3 types based on differences in their immunoserologic markers
- Type 1: ANA and/or SMA
- Type 2: Anti-LKM1
- Type 3: Anti-SLA / LP

# Treatment

- Clinical judgement is the prinicipal basis for the treatment decision.
- The indications of treatment in children are similar to those in adults. The disease process in children appears to more severe at presentation then in adults perhaps because the delay in diagnosis
- Steroids alone: cytopenia, TPMT def, pregnancy, malignancy, short course <6months
- Combination therapy: Postmenopausal state, osteoporosis, brittle DM, obesity, acne, emotional lability, HTN

| Absolute | Relative |
| --- | --- |
| **Serum AST >10 fold of upper limit of normal** | **Symptoms (arthralgia, fatigue, jaudice)** |
| **Serum AST >5 fold of upper limit of normal & Gamma Globulin level > 2 x normal** | **Serum AST and/or Gamma Globulin less than absolute criteria** |
| **Bridging necrosis or multiacinar necrosis on histological exam** | **Interface hepatitis** |

# Combination

| | Prednisone Only | Prednisone | Azathioprine |
|---|---|---|---|
| **Week 1** | 60 | 30 | 50 |
| **Week 2** | 40 | 20 | 50 |
| **Week 3** | 30 | 15 | 40 |
| **Week 4** | 30 | 15 | 50 |
| **Maintenance until endpoint** | 20 | 10 | 50 |

# Children

| Initial Regimen | Maintenance Regimen | End Point |
|---|---|---|
| Prednisone 2mg/kg (upto 60 mg/day) for 2 weeks either alone or in combination | Predisone taper over 6 – 8 wks to 0.1 – 0.2 mg/kg daily<br><br>Continue Daily prednisone dose with or without azathioprine or switch to alt day prednisone dose adjusted to response with or without azathioprine | Normal LFT for 1-2 years during treatment<br><br>No flare during entire interval<br><br>Liver Bx – no inflammation |

# Primary Biliary Cirrhosis

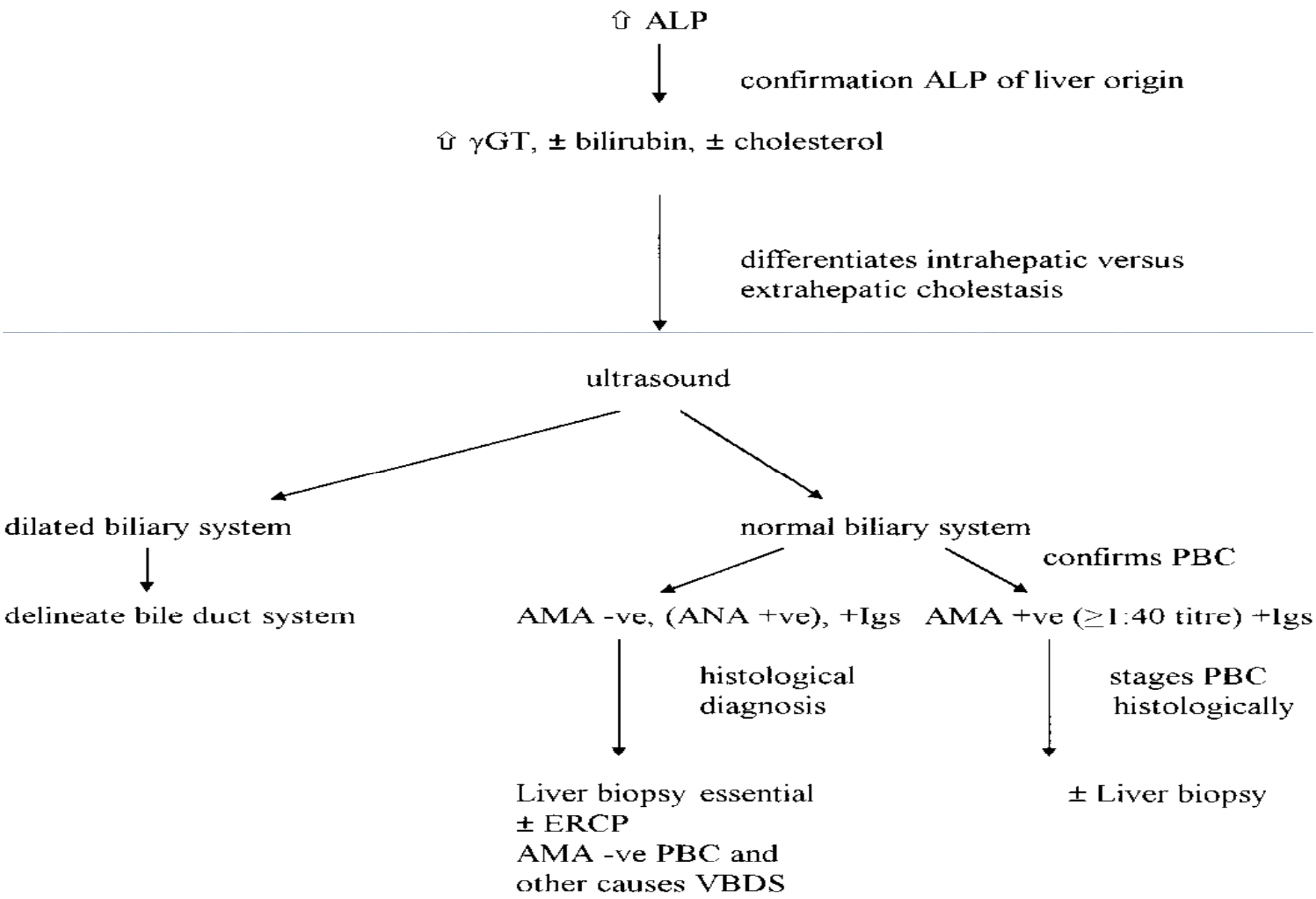
- Autoimmune disease of the liver, which predominantly affects women once over the age of 20 years.
- Caused by the granulomatous destruction of the interlobular bile ducts, which leads to progressive ductopenia
- Slow and progressive cholestasis

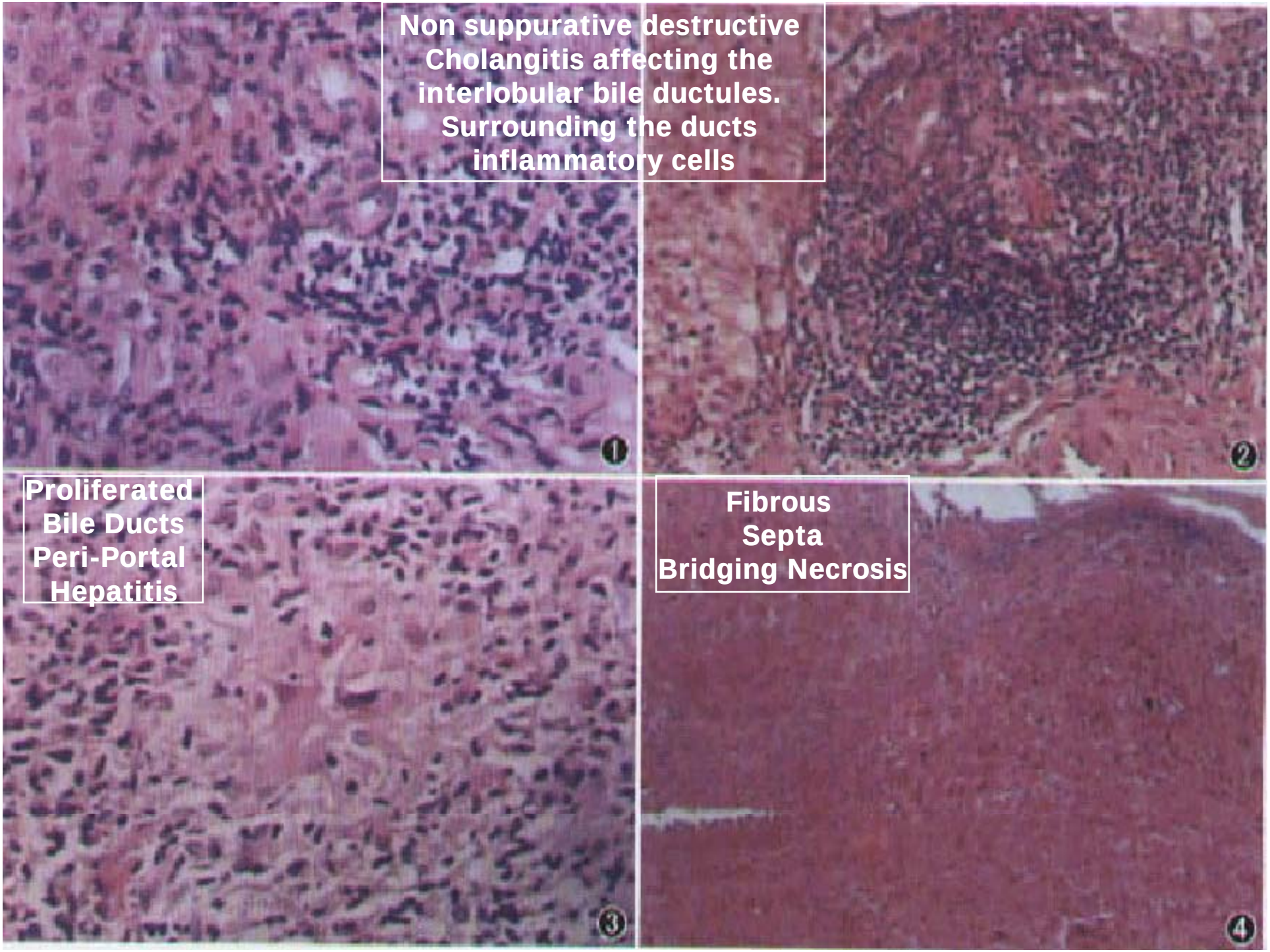
# Diagnosis

- Simplest and most economical test: AMA

  95% sensitivity and specificity
- Elevation of IgM
- AMA titers >1:40, typical symptoms, & biochemistry abnormalities, a liver bx may not be essential

# Diagnosis of PBC




Non suppurative destructive Cholangitis affecting the interlobular bile ductules. Surrounding the ducts inflammatory cells
1
2
Proliferated Bile Ducts Peri-Portal Hepatitis
3
Fibrous Septa Bridging Necrosis
4

# 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

# Treatment

- UDCA (Ursodeoxycholic acid) increases the rate of transport of intracellular bile acids across the liver cell and into the canaliculus
- Reduces intracellular hydrophobic bile acid levels and thereby will have cytoprotective effect on cell membrane
- Dose: 13-15 mg/kg/day
- Insufficient data for immunosuppressive therapy ( AZA, Cyclosporine, or MTX)

# AIH-PBC Overlap

- 2 categories:
- Histologial features of autoimmune hepatitis, but have serological findings of PBC (AMA)
- Histological features of PBC, but are seronegative for AMA, and generally have circulating ANA or ASMA:
  - Immune Cholangiopathy,
  - Autoimmune Cholangiopathy,
  - Immune Cholangitis,
  - Autoimmune Cholangitis.
  - AMA Negative PBC

# AMA Negative PBC

- Immune Cholangitis or Autoimmune Cholangitis
- Similar to autoantibody profile of Autoimmune Hepatitis
- IgG Fraction is increased, less likely to have IgM elevations