

# Autoimmune hepatitis

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# Spectrum of autoimmune liver disease



- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
  
- Outlier syndromes
  - Autoimmune cholangitis
  
- Overlap syndromes
  - simultaneous
  - consecutive ('crossover')

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# Autoimmune hepatitis: a brief history in time



- 1950: Waldenstrom - chronic hepatitis in young females
- 1956: Mackay - link to other autoimmune diseases: 'lupoid hepatitis'
- 1970s/80s: 'Autoimmune chronic active hepatitis'
- 1972/3 reports of dramatic response to steroids +/- azathioprine
- 1990s and beyond: 'Autoimmune hepatitis'
- 1992 (revised 1999): Diagnostic criteria agreed by International group
- 2004: International consensus on antibody profiling

# Autoimmune hepatitis: key features



- Clinical presentation variable
- More common in females
- May be asymptomatic ( approximately 20%) or present with non-specific symptoms
- Acute presentation: may be fulminant hepatic failure
  - Acute on chronic
  - Recent onset
- Significant proportion cirrhotic ( up to 40%) at presentation
- Bridging and pan-acinar necrosis more likely in those with acute presentation

# Autoimmune hepatitis: key features

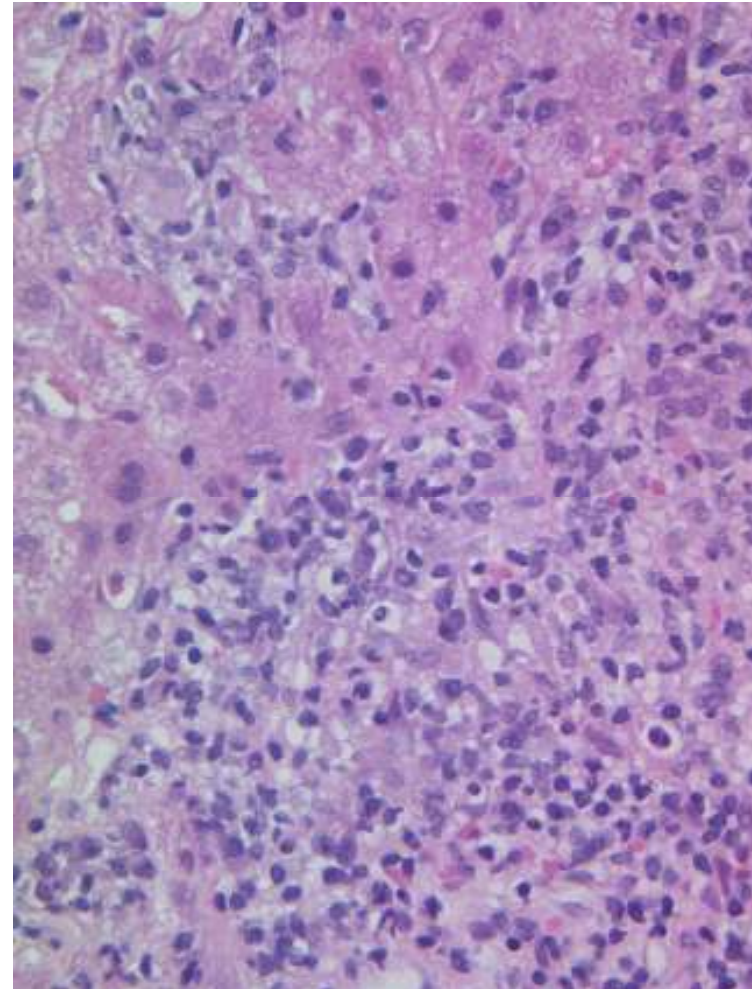


- Necroinflammatory condition: process not specific
- Diagnosis requires exclusion of other mimics
- Loss of tolerance to self antigens expressed by hepatocytes: accompanied by reduction in CD25 suppressor cells
- ? Viral trigger (HAV; EBV; HSV)
- Associated with other autoimmune diseases and specific class II alleles (DR3 and DR4)
- Recent genome wide scan identified markers on chromosomes 11 and 18
- Novel NTx/PD1 KO mouse model



# Asymptomatic AIH

- More often older patients
- Prognosis no different to symptomatic (excluding acute presentation)
- Some are burnt out cirrhotics





# Clinical diagnosis of AIH

- **Positive features**

Female

ALT rise/Low ALP

Raised Igs (esp IgG)

Autoantibody+/AMA-

Seroneg for viruses

No drugs/alcohol

**Interface hepatitis**

Other immunologic disorders  
(incl family)

Compatible HLA markers

Response to steroids

- **Negative features**

High ALP

AMA seronegative

Viral serology –ve

Drug/alcohol history

**Morphological changes  
suggestive of other aetiology**

**Pretreatment score**

**Definite: > 15**

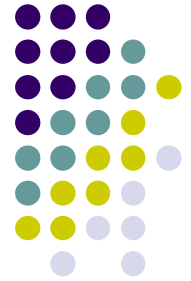
**Probable: 10 – 15**

**Posttreatment score**

**Definite: > 17**

**Probable: 12 -17**

# Simplified criteria for diagnosis of AIH



ANA or SMA > 1:40	1
ANA or SMA > 1:80	
Or LKM > 1:40	
Or SLA positive	2
Histology consistent	1
Histology typical	2
Absence of viral hepatitis	2

**Score of 6: probable AIH**  
**Score of 7 or 8: definite AIH**



# Autoantibodies in AIH

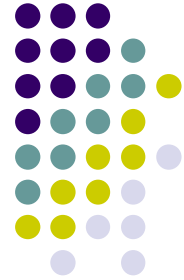
- Anti-nuclear
- Smooth muscle
- Liver kidney microsomal (LKM1; LKM2; LKM3)
- pANCA
- LM (CYP 1A2 and CYP 2A6)
- LC-1
- SLA/LP
- ASGPR
- Chromatin
- Cardiolipin
- ASCA



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# Subtypes of AIH

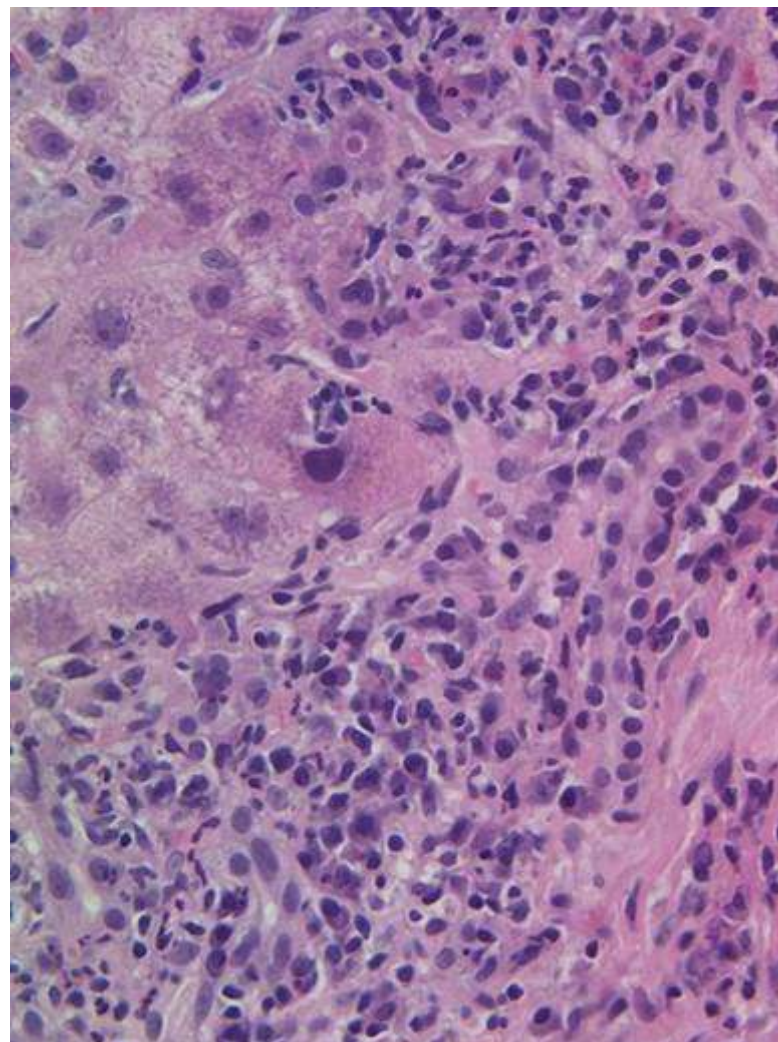


	Type 1	Type 2	Type 3 (?)
Autoab	SMA/ANF	LKM	SLA/ANF
Age	10-20; 45-70	2-24	30-50
Female	78%	89%	90%
Ig elevation	+++	+	++
Steroid response	+++	+	++
Cirrhosis	45%	82%	75%



# Histological features of AIH

- Interface hepatitis
  - ++ plasma cells
- Portal inflammation
- Spotty necrosis: apoptotic bodies
- Confluent necrosis
- Bridging necrosis
- Panacinar necrosis

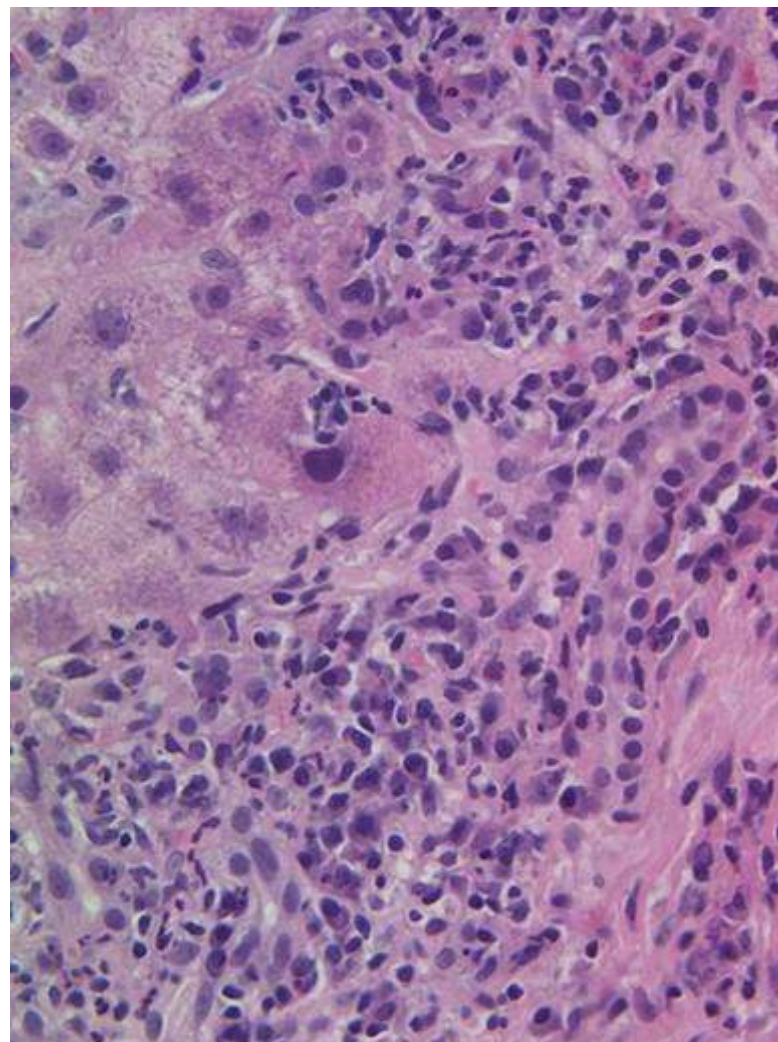




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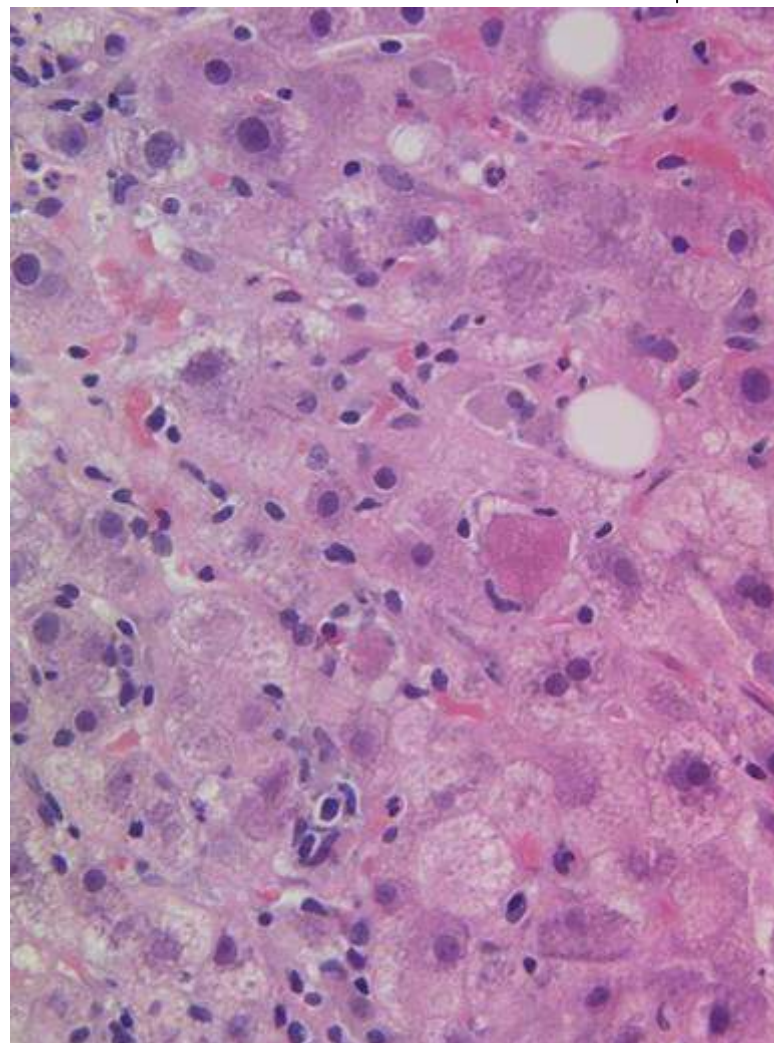
Predominantly IgG containing  
plasma cells





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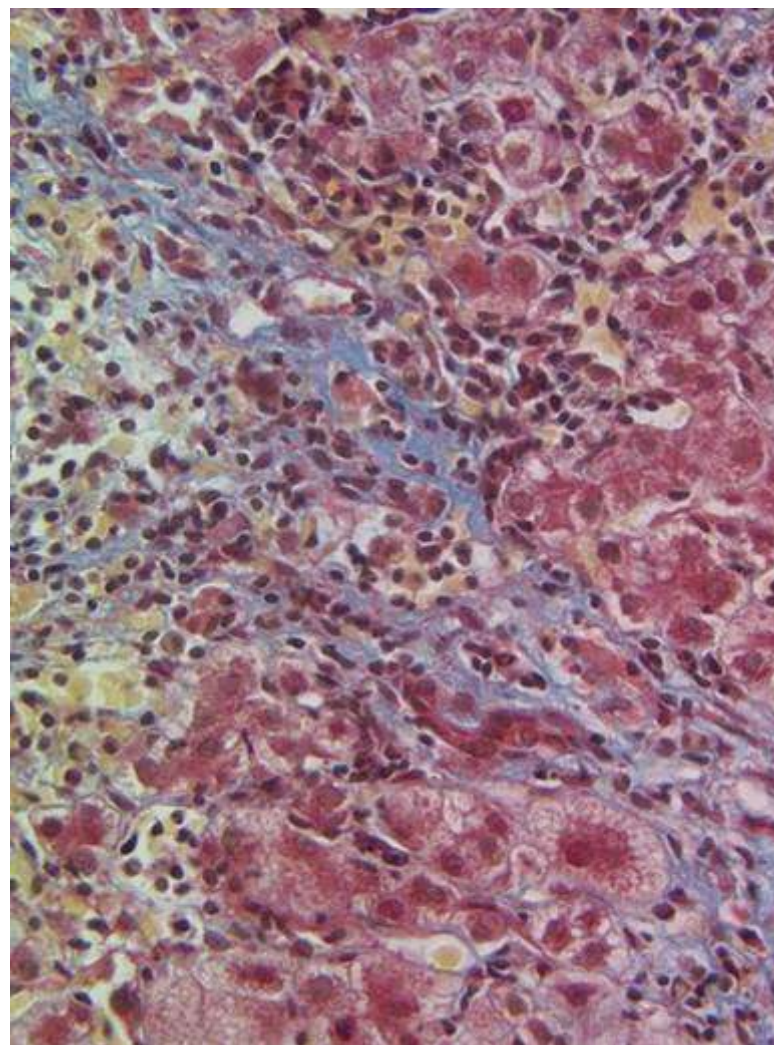
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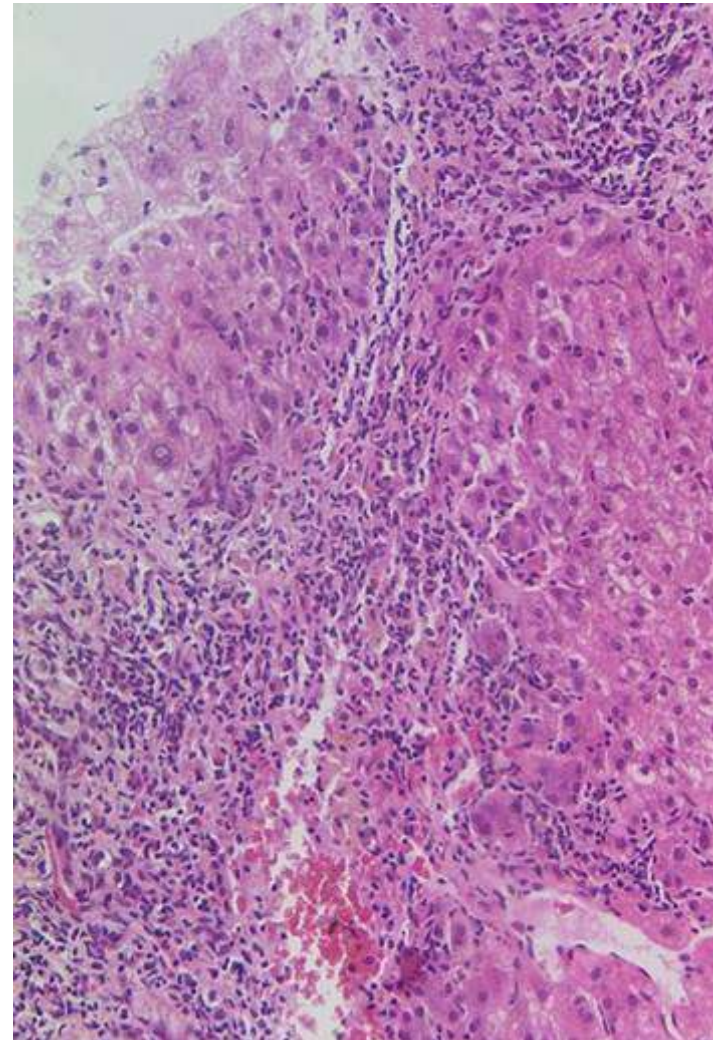
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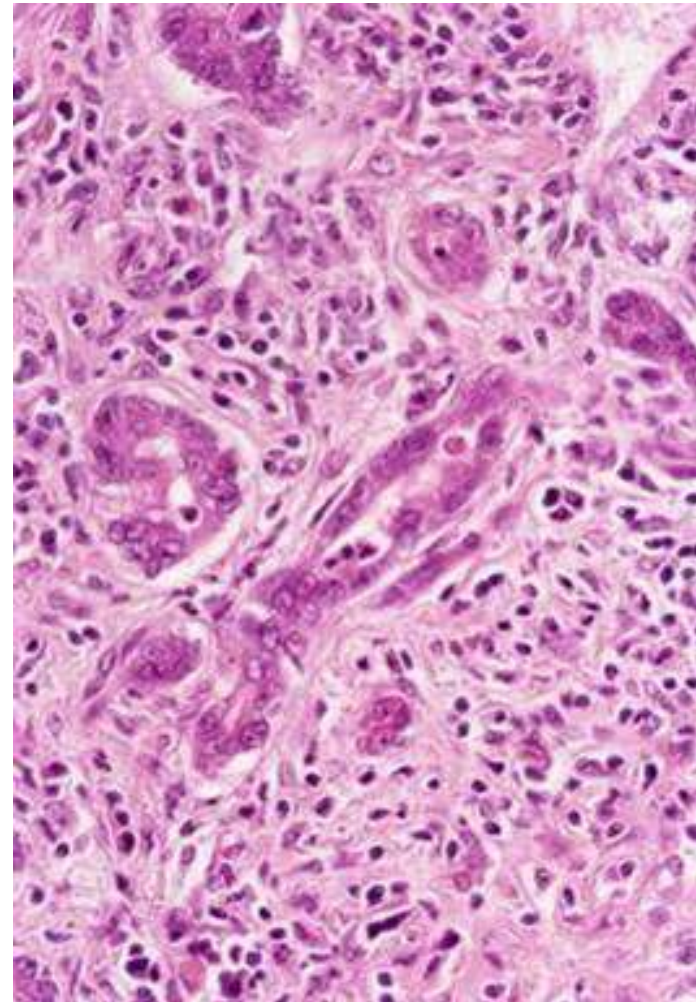
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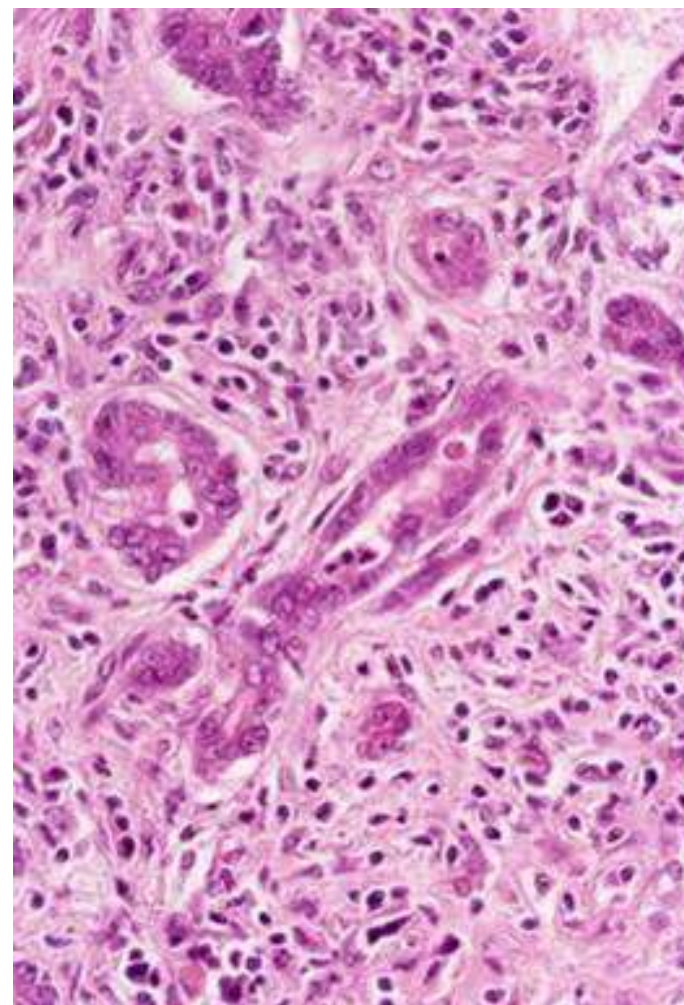


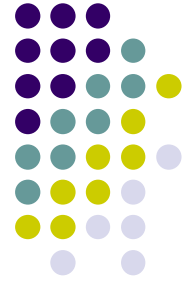


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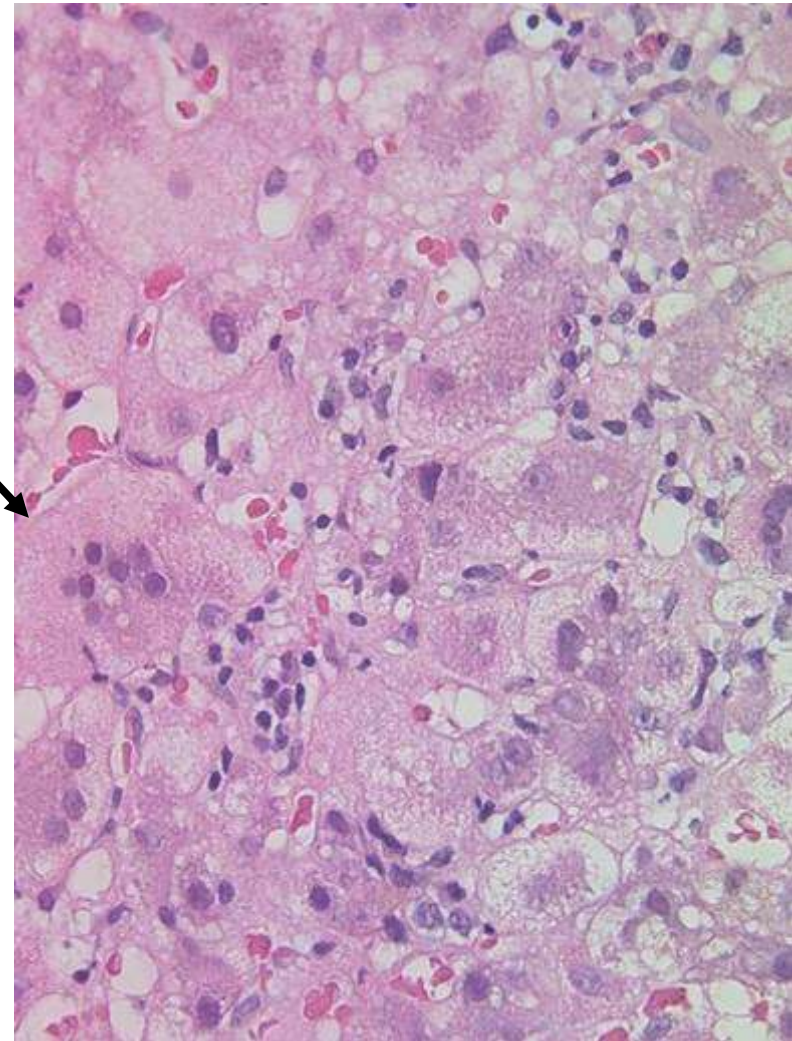
**Biopsy changes provide important prognostic information: degree of necrosis/fibrosis**





# Histological features of AIH

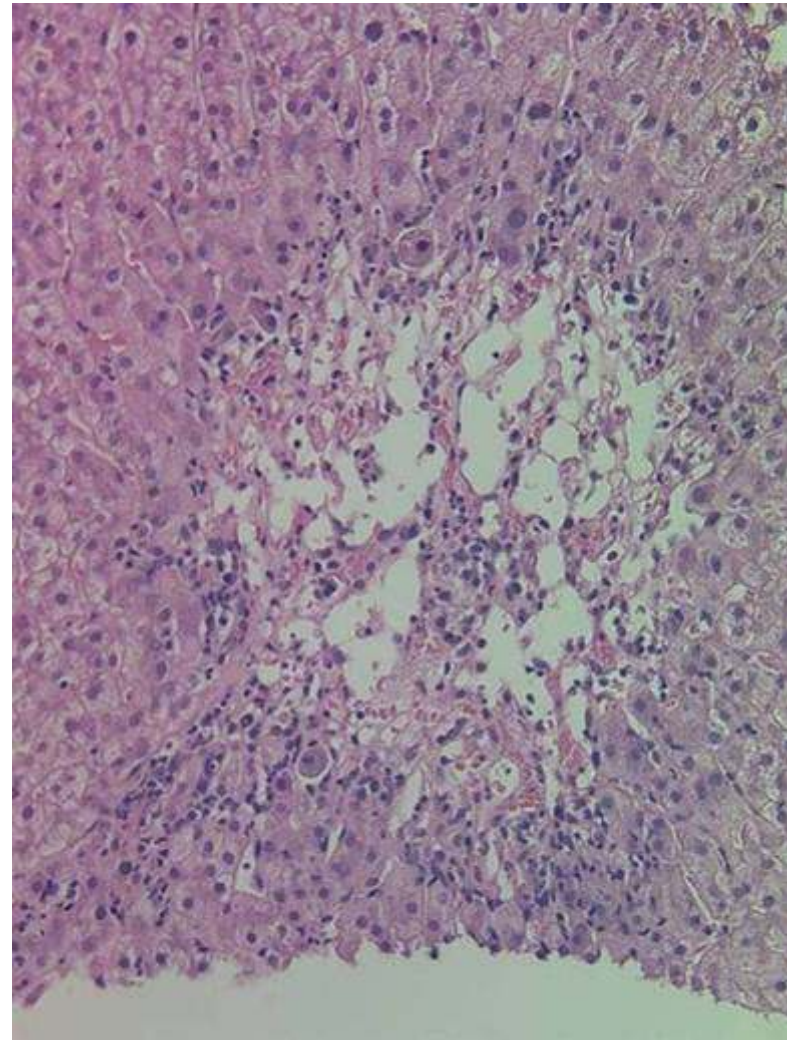
- Multinucleated hepatocytes
- Perivenular changes including endotheliitis
- Rosettes

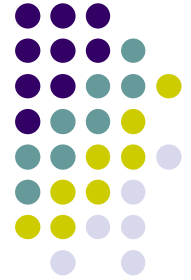




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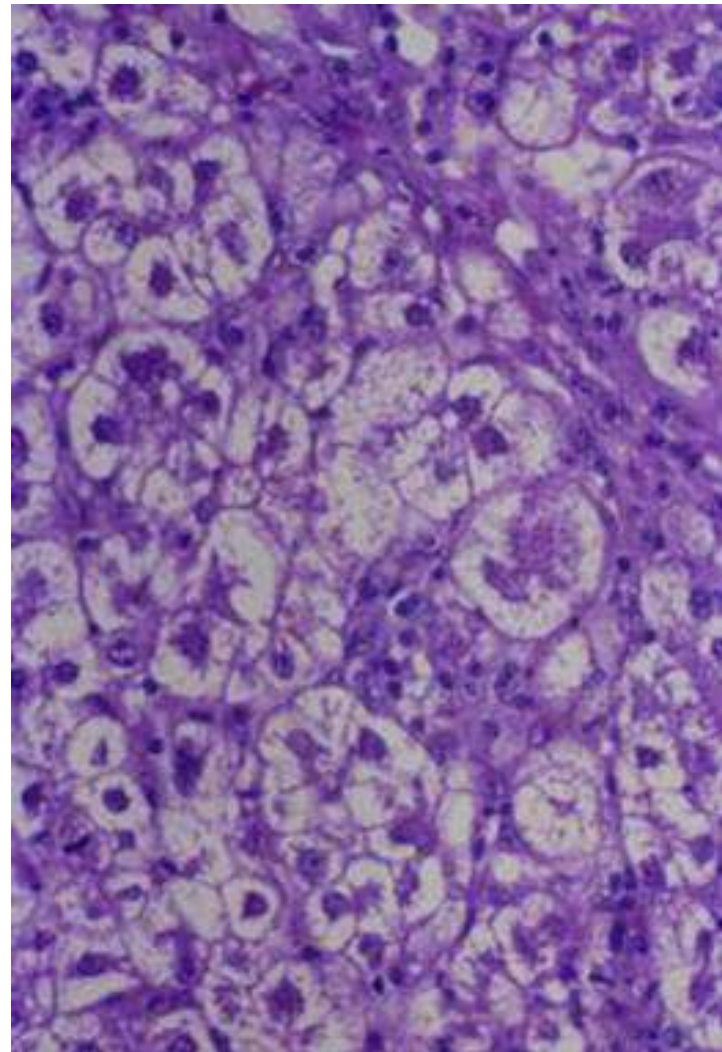
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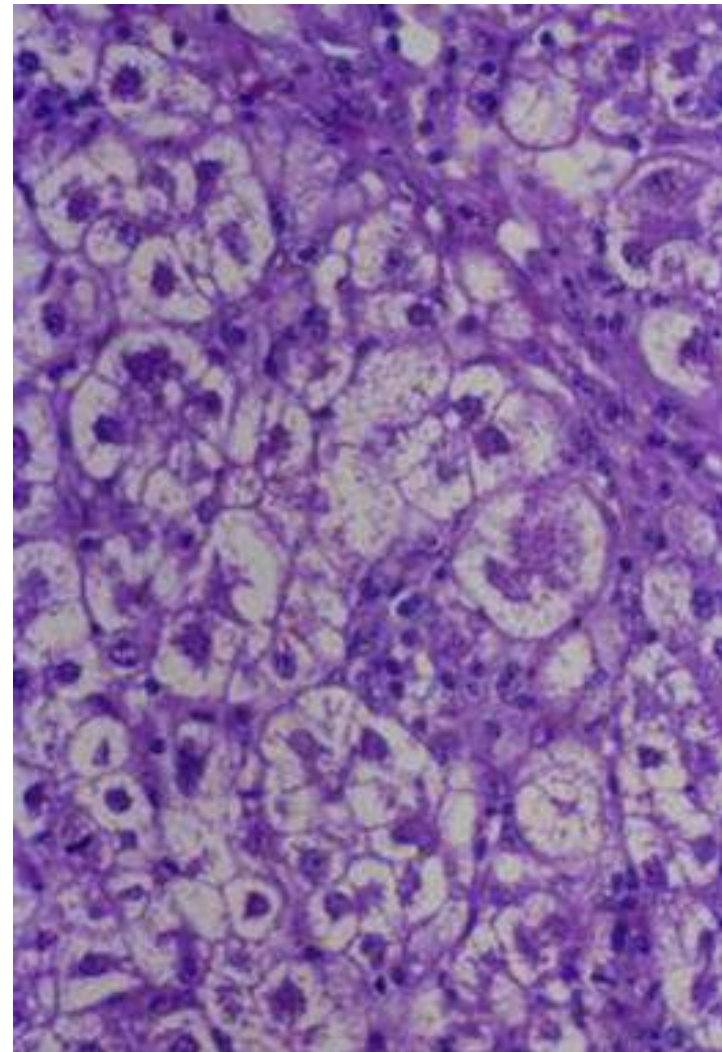




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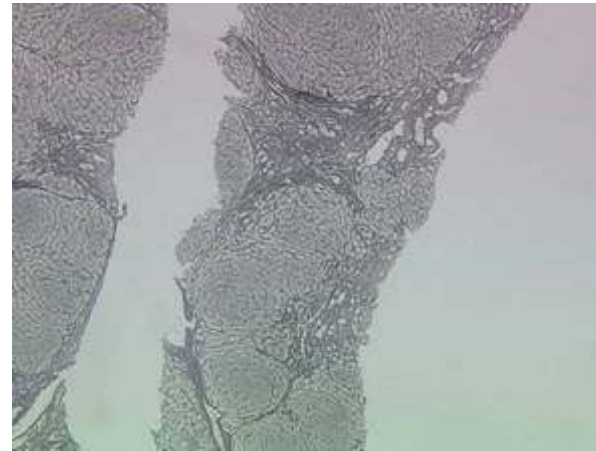
**NOT: steatosis or granulomas**



# Reversibility of hepatic fibrosis in AIH



- 8 patients with good biochemical response
- All scored using Knodell
- Cirrhosis or severe fibrosis present in all patients on initial biopsy
- Resolution in all 8 patients
- Median Knodell score fell from 14 to 1.3



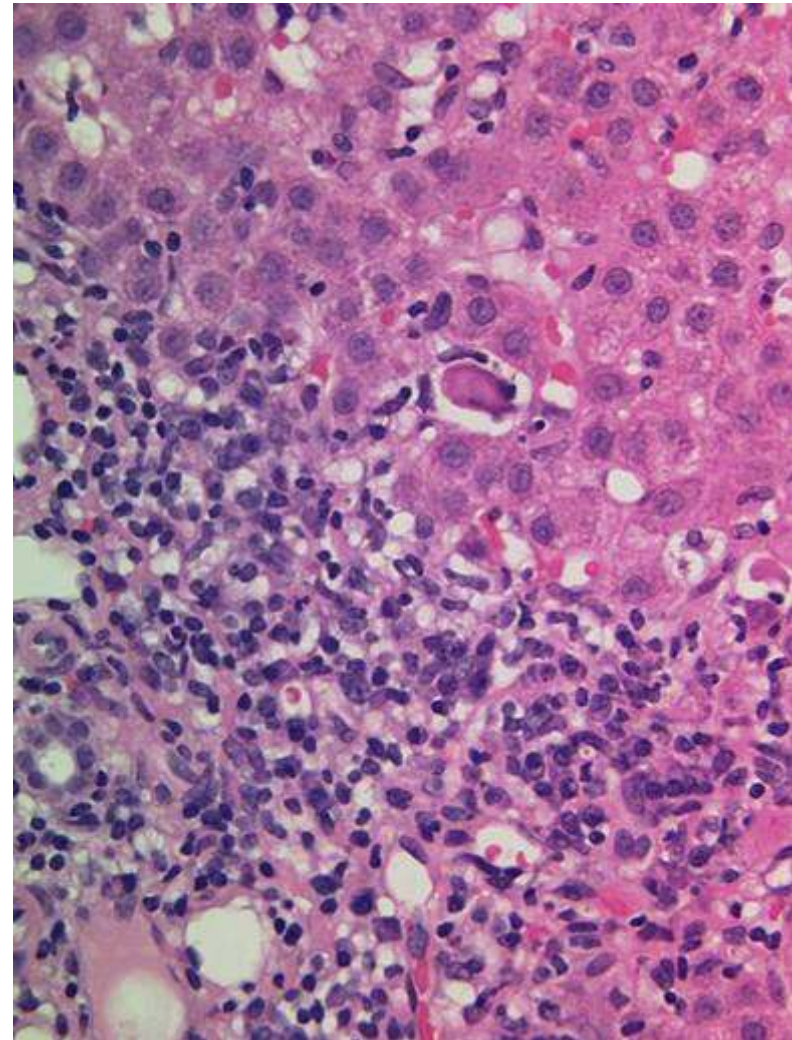
*Dufour et al, (1997)*



# Drugs and AIH

- $\alpha$ -methyl dopa
- Nitrofurantoin
- Ticrynafen
- Minocycline

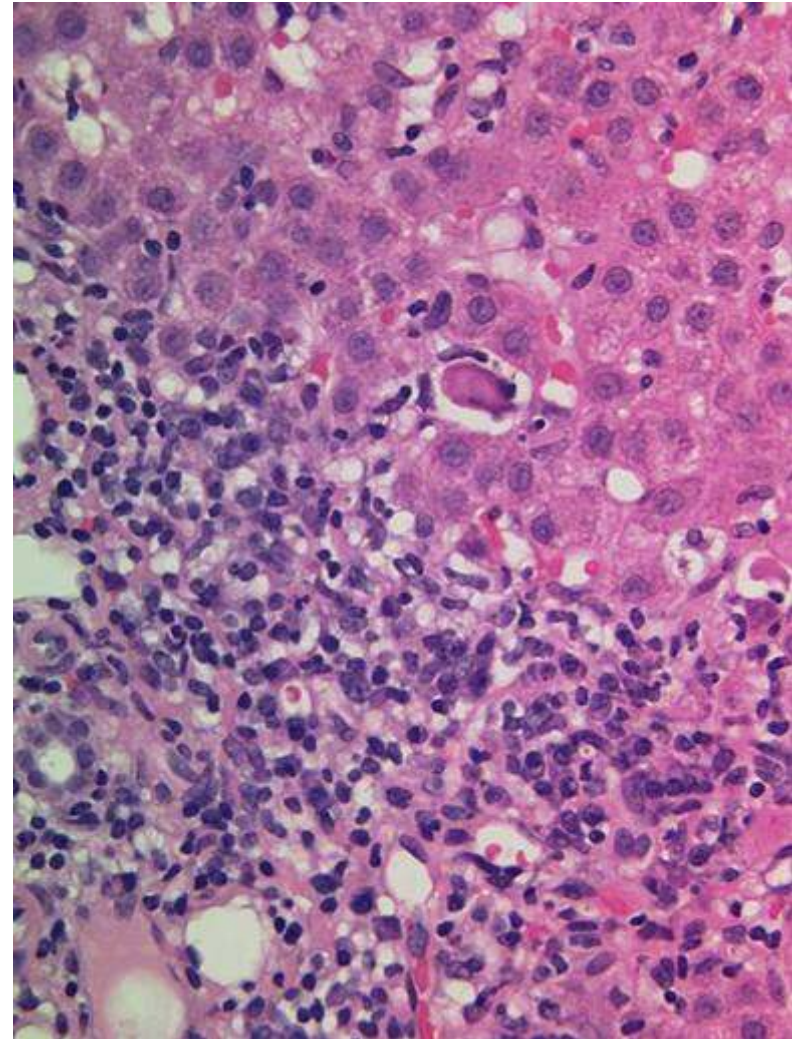
Histological features identical to other AIH; variety of autoantibodies incl LKM and ANF



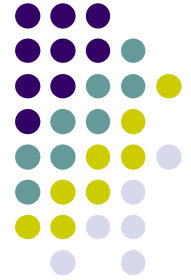
# Drugs and AIH: recent associations



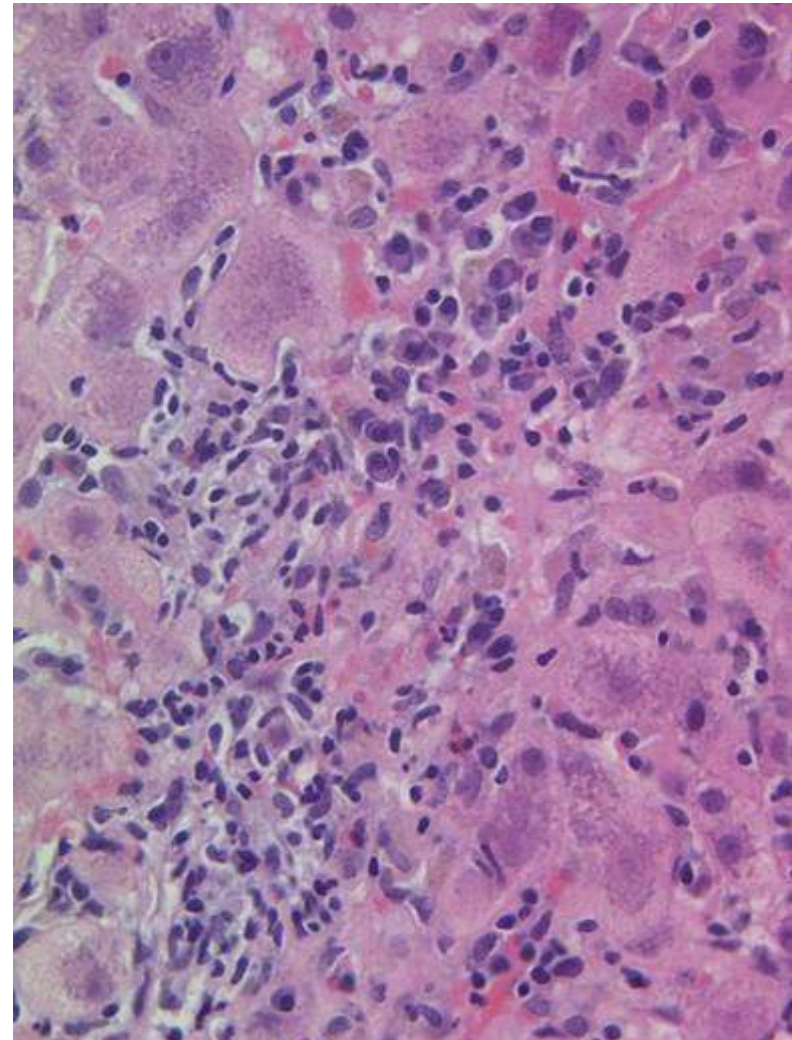
- HAV vaccine
- Interferon
- Terbinafine
- Atomoxetine
- Imatinab
- Infliximab
- Methylphenidate
- Statins
- Kava kava
- St Johns wort
- Respineridone



# Cryptogenic chronic hepatitis



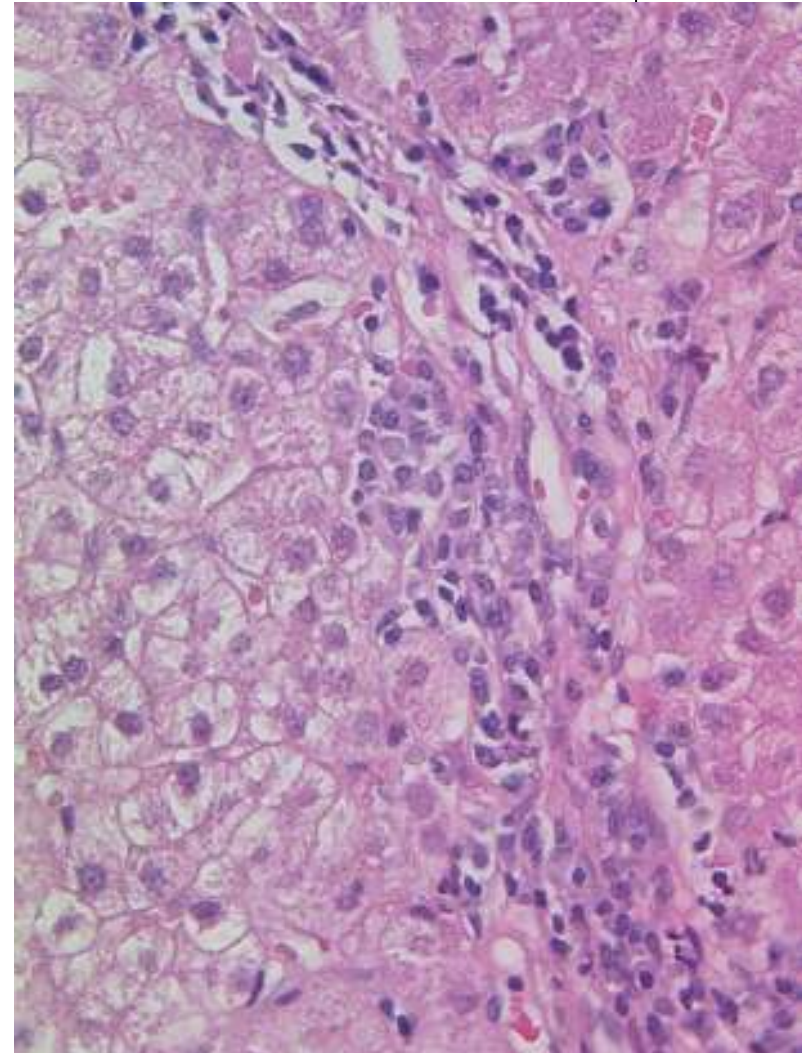
- Cases with biopsy features compatible with AIH which are autoantibody –ve
- ++ perivenular injury
- Less since assays for SLA available
- Hypergammaglobulinaemia
- Raised IgG
- HLA susceptibility factors as for AIH (DR3 and DR4)
- Responds to corticosteroids



# De novo autoimmune hepatitis following orthotopic transplantation



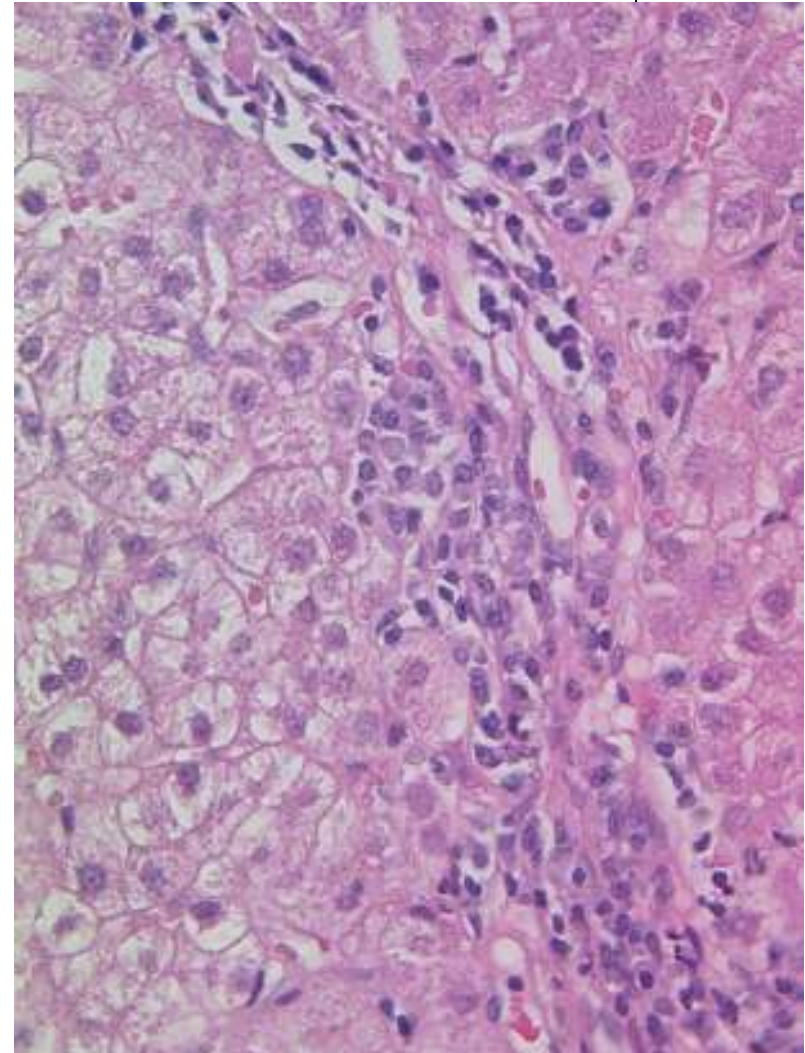
- Resembles AIH in native
- Lobular inflammation with progressive interface activity
- May be confluent and bridging necrosis
- For diagnosis needs:
  - Interface hepatitis with plasma cell/lymphocytic infiltrates
  - > 1:160 ANF, SMA or LKM antibodies
  - Hypergammaglobulinemia
  - Exclusion of other cause of chronic hepatitis



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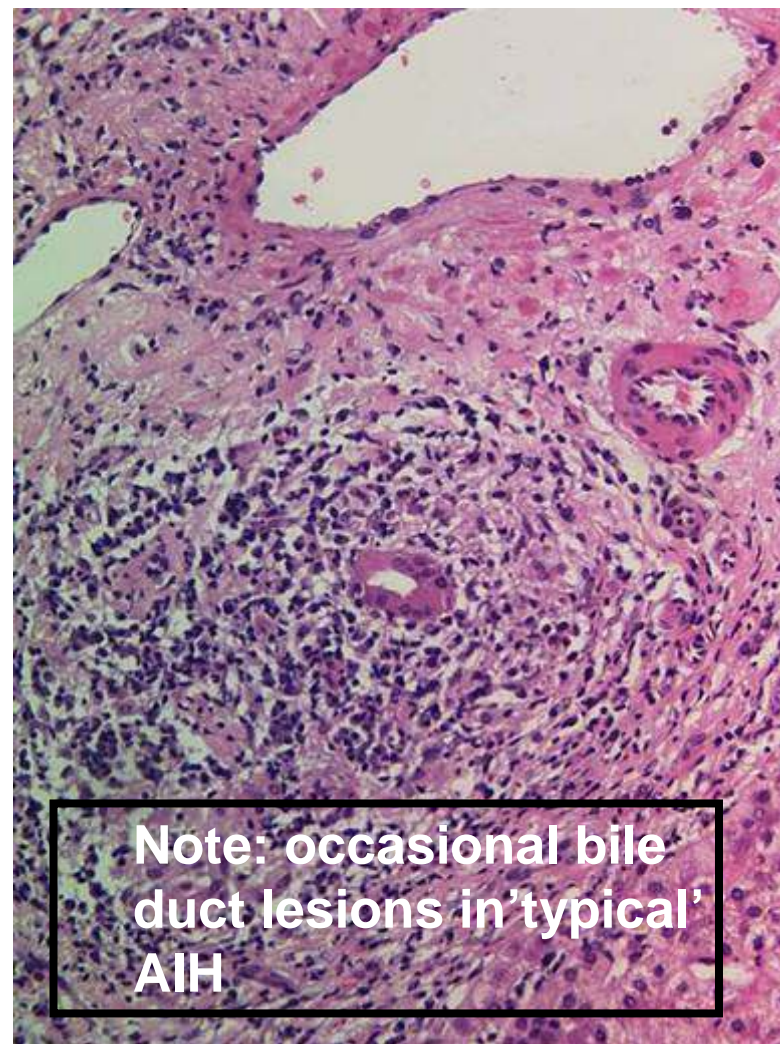
- Alloimmune rather than autoimmune!
- Autoantibodies may be detected in some uncomplicated acute rejection
- ? Form of rejection
- Some may be due to polymorphic expression of glutathione S-transferase
- More common in paediatric transplants: 5-10%





# AIH/PBC overlap

- Co-existence of two conditions presenting simultaneously or developing consecutively
- Blend of PBC-features and AIH
- ALT > 5X normal; SMA+
- Mixed histological picture with marked hepatitic component
- ? Treat with steroids and UDCA
- Mayo clinic: 12% of PBC using revised criteria; 6% with simplified

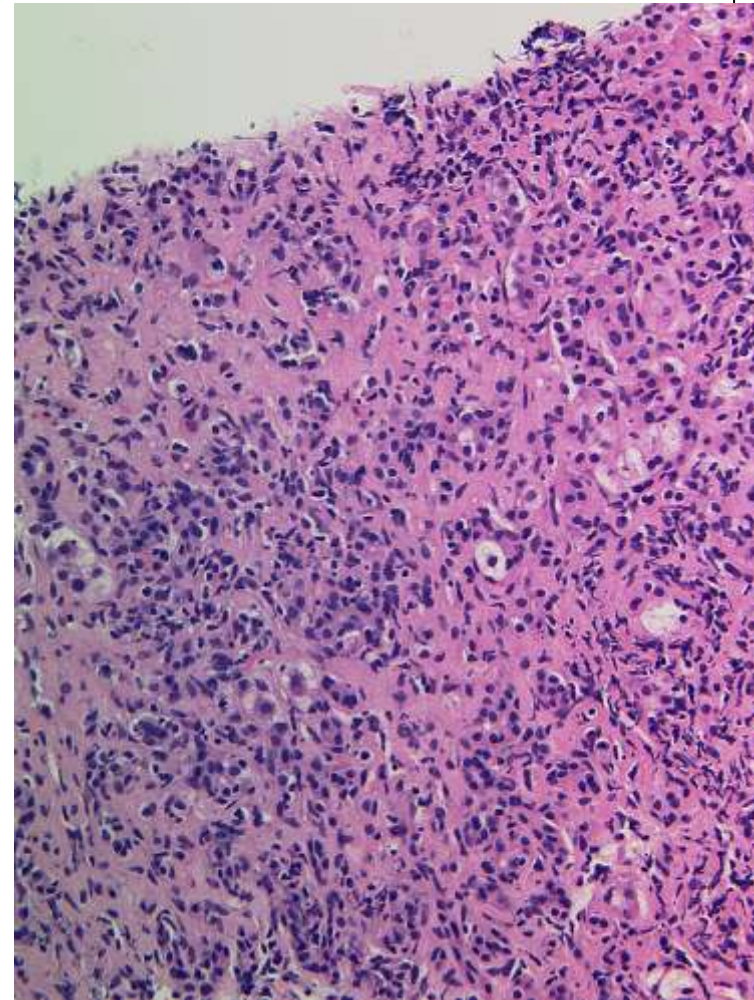


# Hepatitis following treatment with rifampicin for pruritis in PBC



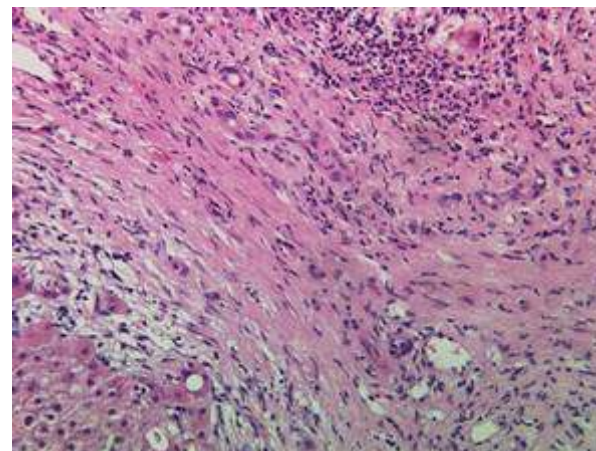
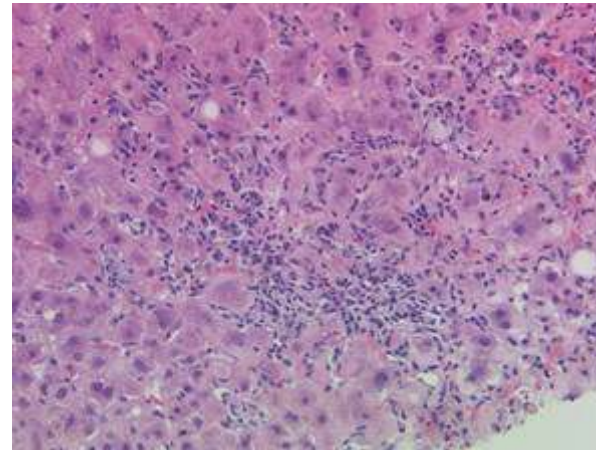
- Three patients with biopsy proven PBC
- Hepatitic pattern of LFTs
- Interface hepatitis and lobular inflammation on biopsy
- Two with impairment of synthetic function (one requiring OLT)
- 7.3% of those treated

*Prince et al, 2002*



# AIH/PSC overlap

- ERCP and histological evidence of sclerosing bile duct lesions (may only be small duct PSC) with significant hepatitic activity
- Particularly noted in children with a crossover phenomenon (AIH to PSC): 'autoimmune sclerosing cholangitis'
- Significant proportion of PSC patients are ANF/SMA +
- Some PSC patients score at least probable on International scoring system



A large, rusted metal sculpture of a cross-like structure on a grassy hill under a blue sky with clouds. The sculpture is made of dark, weathered metal plates and beams, forming a tall, slender vertical post with a long, horizontal arm extending to the right. The background is a clear blue sky with scattered white clouds. The ground is a green grassy hill.

**Histological assessment is likely to continue to contribute to the diagnosis of AIH**

**Biopsies can provide important prognostic information and can be used to assess response to therapy including resolution of fibrosis**

**There is increasing recognition of complex overlap autoimmune liver disease: the pathologist plays a key role in determining the predominant form of injury, directing therapeutic intervention**