

Role of liver biopsy in assessing disease severity in autoimmune hepatitis

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Autoimmune hepatitis

- Relapsing and remitting disease process in some, progressive in others.
- Unknown triggers, but sometimes drug-induced.
- Genetic risk associated with HLA type
 - HLA-DRB1*03:01 and HLA-DRB1*04:01
- Female preponderance.
- Diagnosed by scoring the constellation of features (simplified IAHG criteria).

What constitutes severe disease ?

- Clinical or biochemical decompensation.
- High stage fibrosis.
- But only about 10% of patients present with decompensation.
- Histological activity.
- About 40% as a clinically acute hepatitis.
- About 90% will have a liver biopsy.

Drawbacks of liver biopsy

- Complications.
- Invasive procedure.
- Sampling error.
- Intra- and inter-observer variability in interpretation.

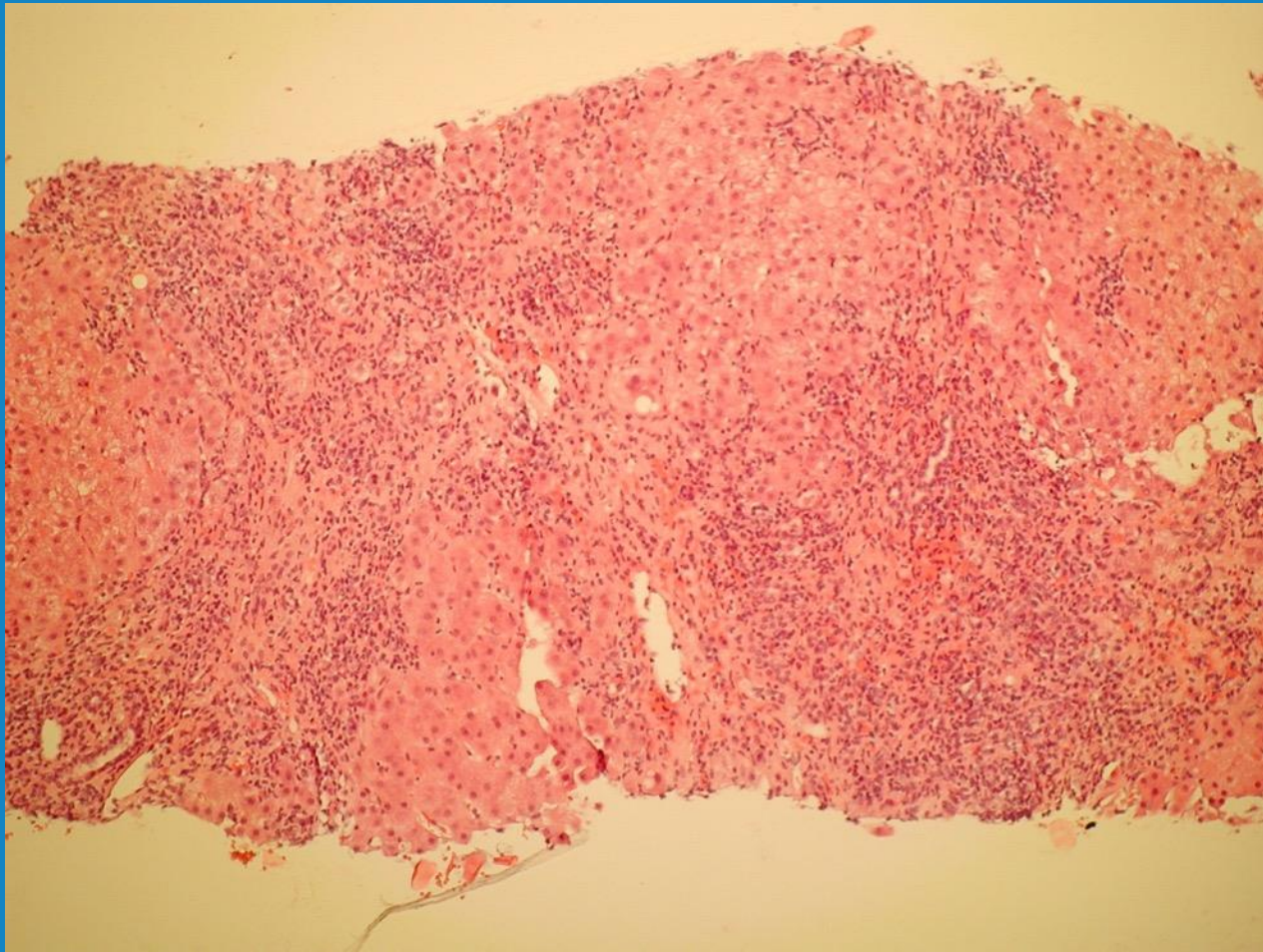
Justification for biopsy

- Presence of ANA or ASMA positivity does not correlate with clinical or histological severity, or predict response to antibody therapy (52 patients). Mehendiratta et al. Clin Gastroenterol Hepatol 2009 7: 98- 103
- Patients presenting with acute hepatitis or atypically (eg. male) may be missed. Miyake et al. Dig Liver Dis 2010 42: 210- 5
- Half with normal serum parameters still showed histological activity HAI 4 or 5, but these were at lower risk of fibrosis progression than those with scores of ≥ 6 . Lüth et al. J Clin Gastroenterol 2008 42: 926- 30

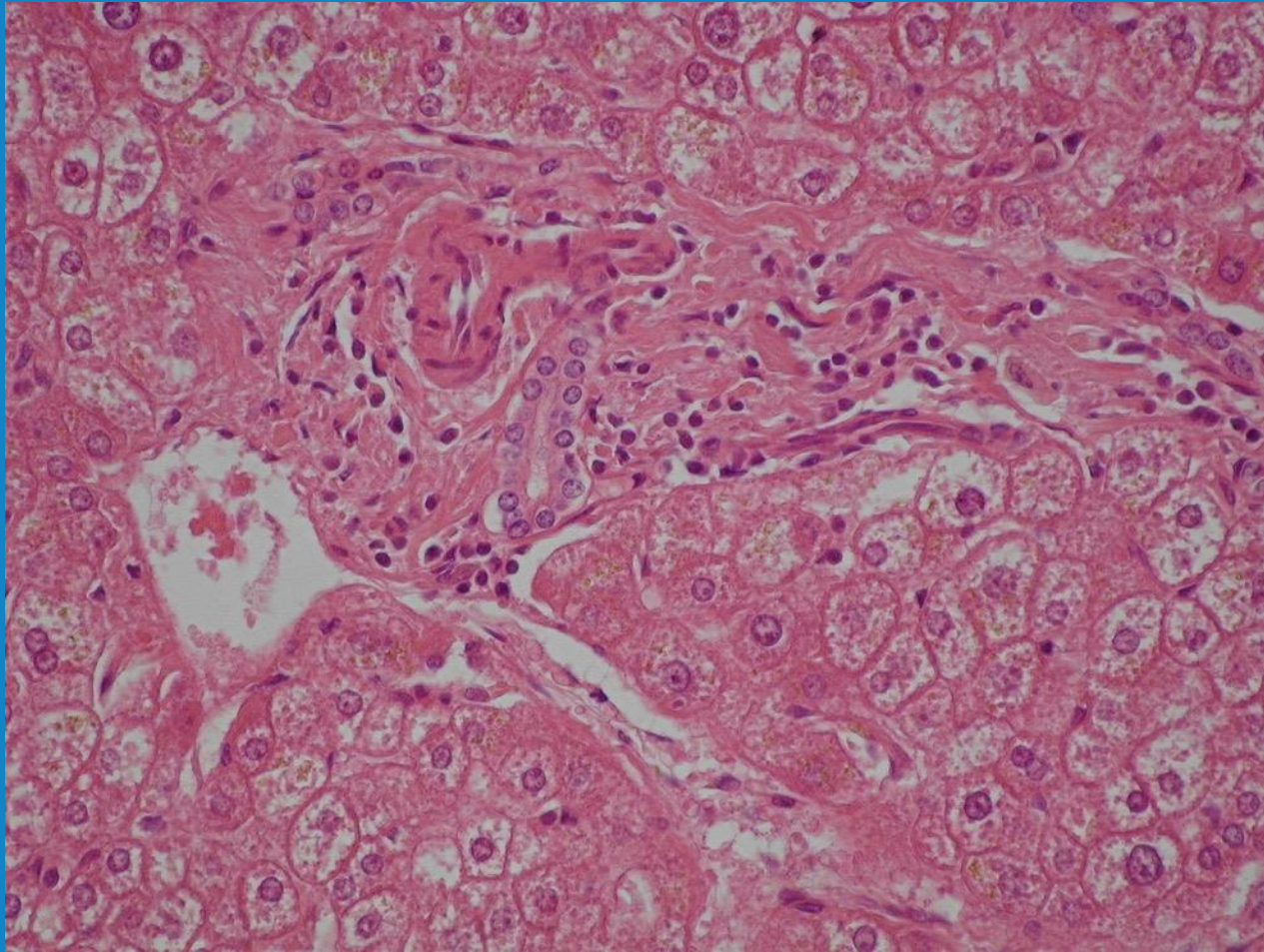
Activity

- Histological activity index.
- Portal inflammation – type and amount
- Interface hepatitis – extent and amount
- Lobular activity
- More extensive necrosis

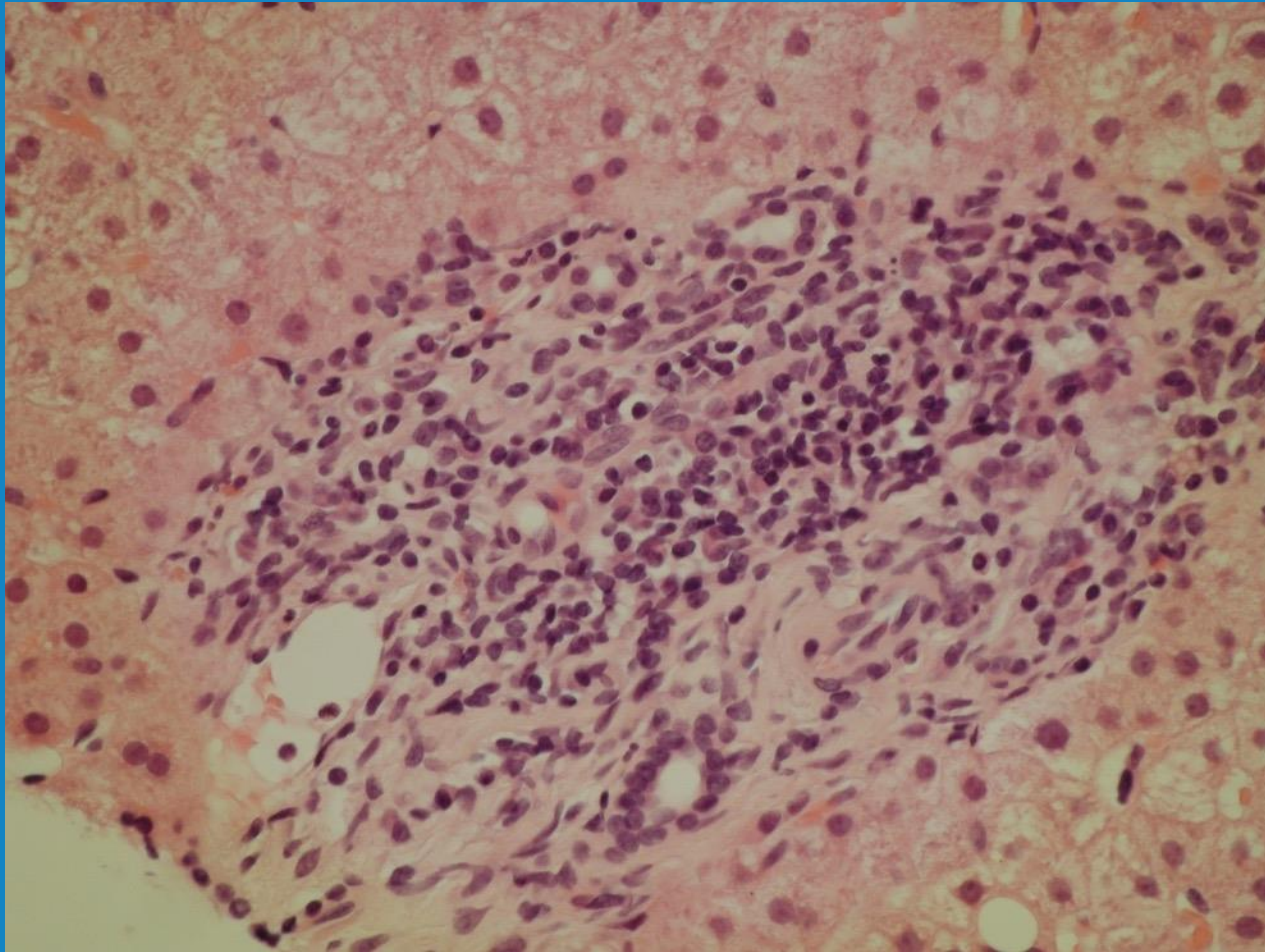
Acute hepatitic presentation



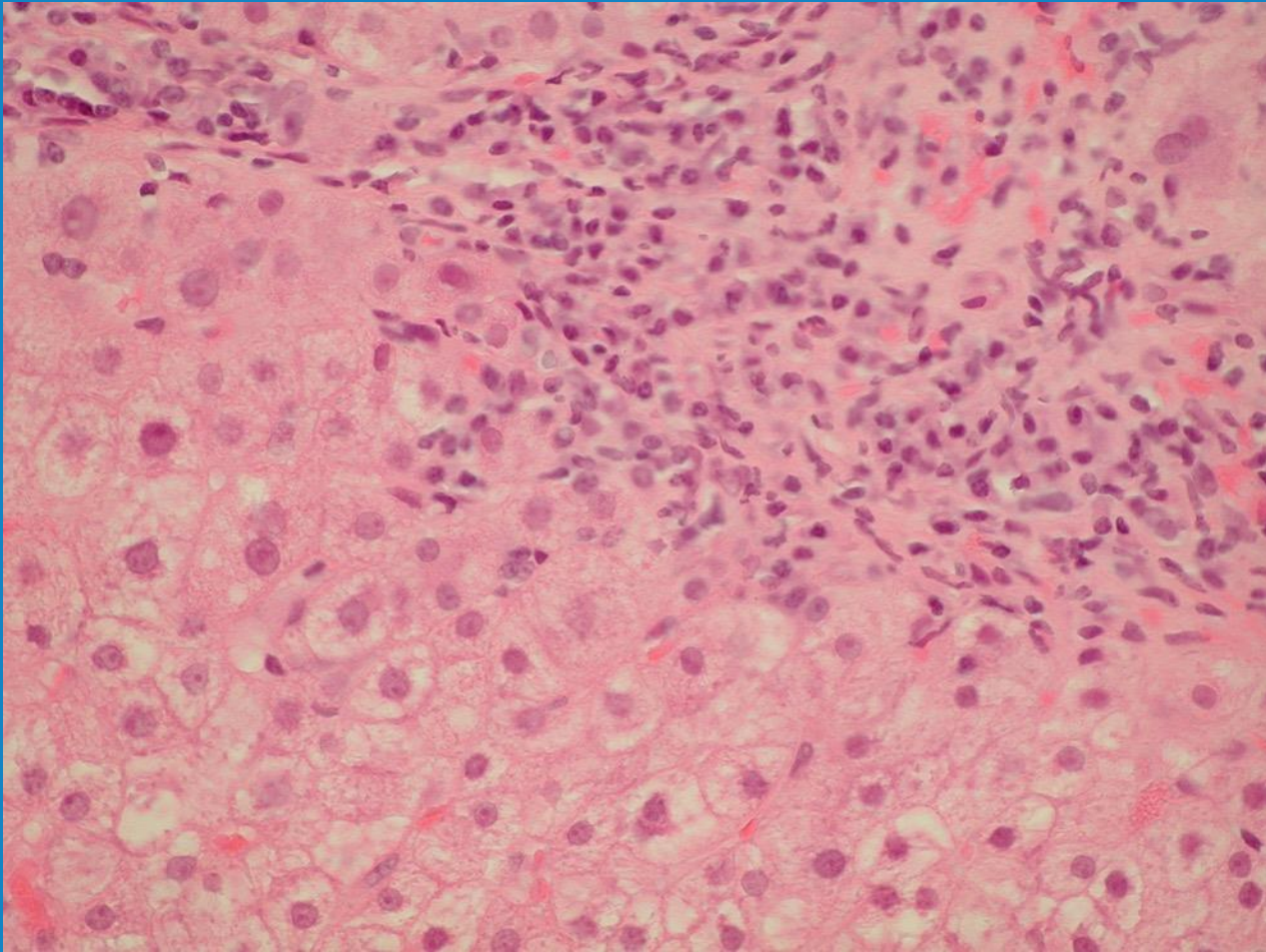
Normal portal area



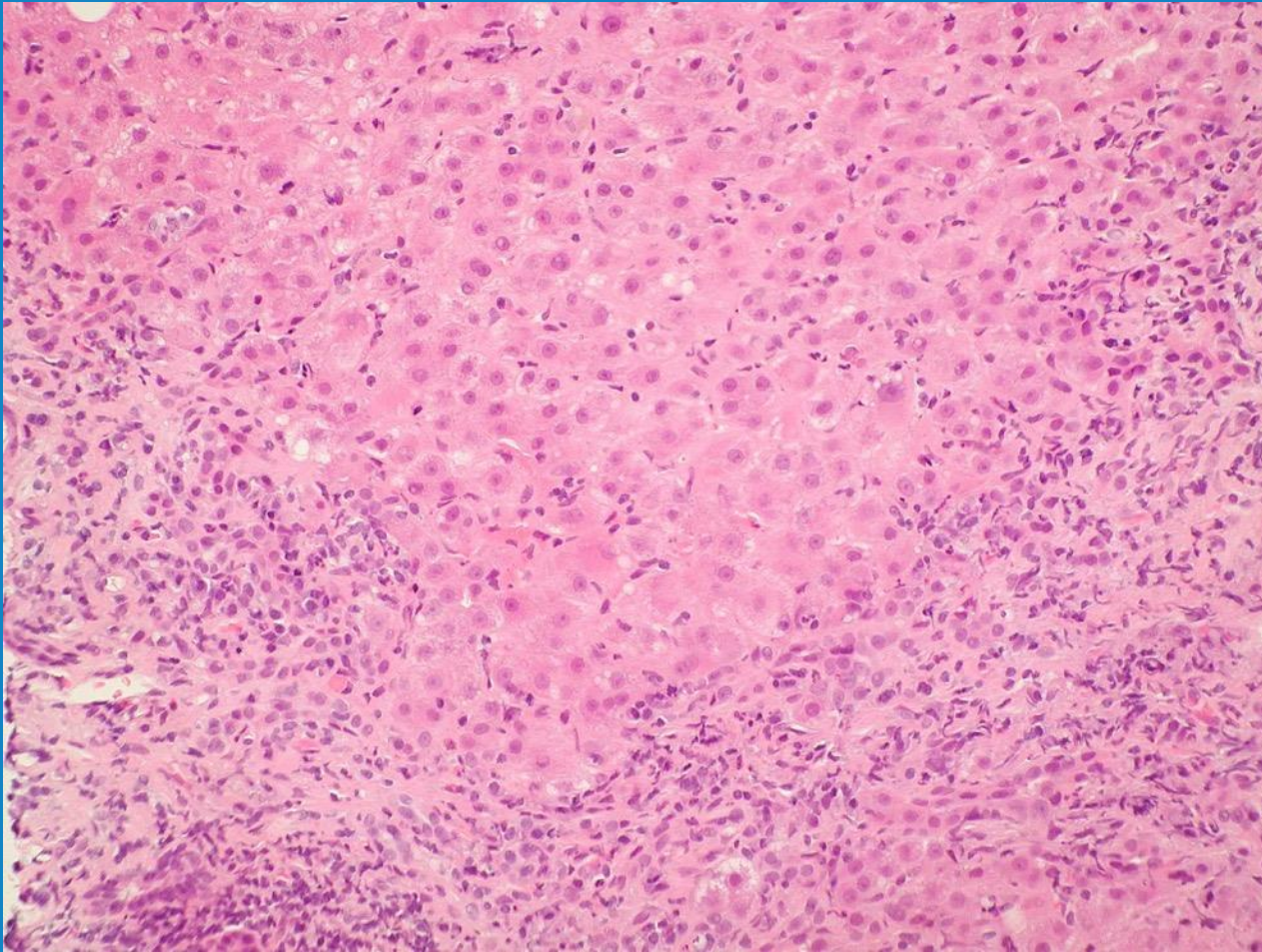
Portal inflammation



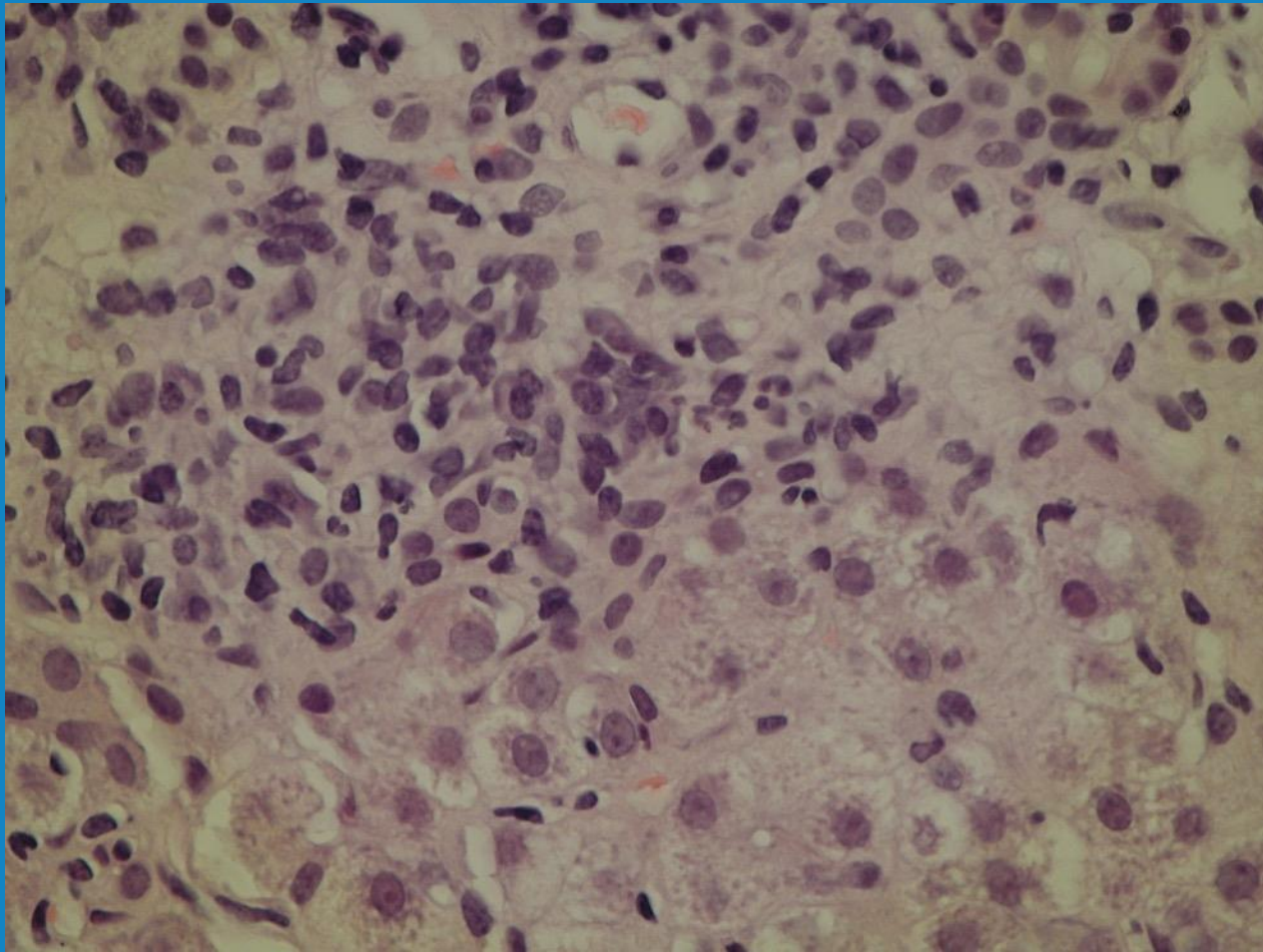
Interface hepatitis



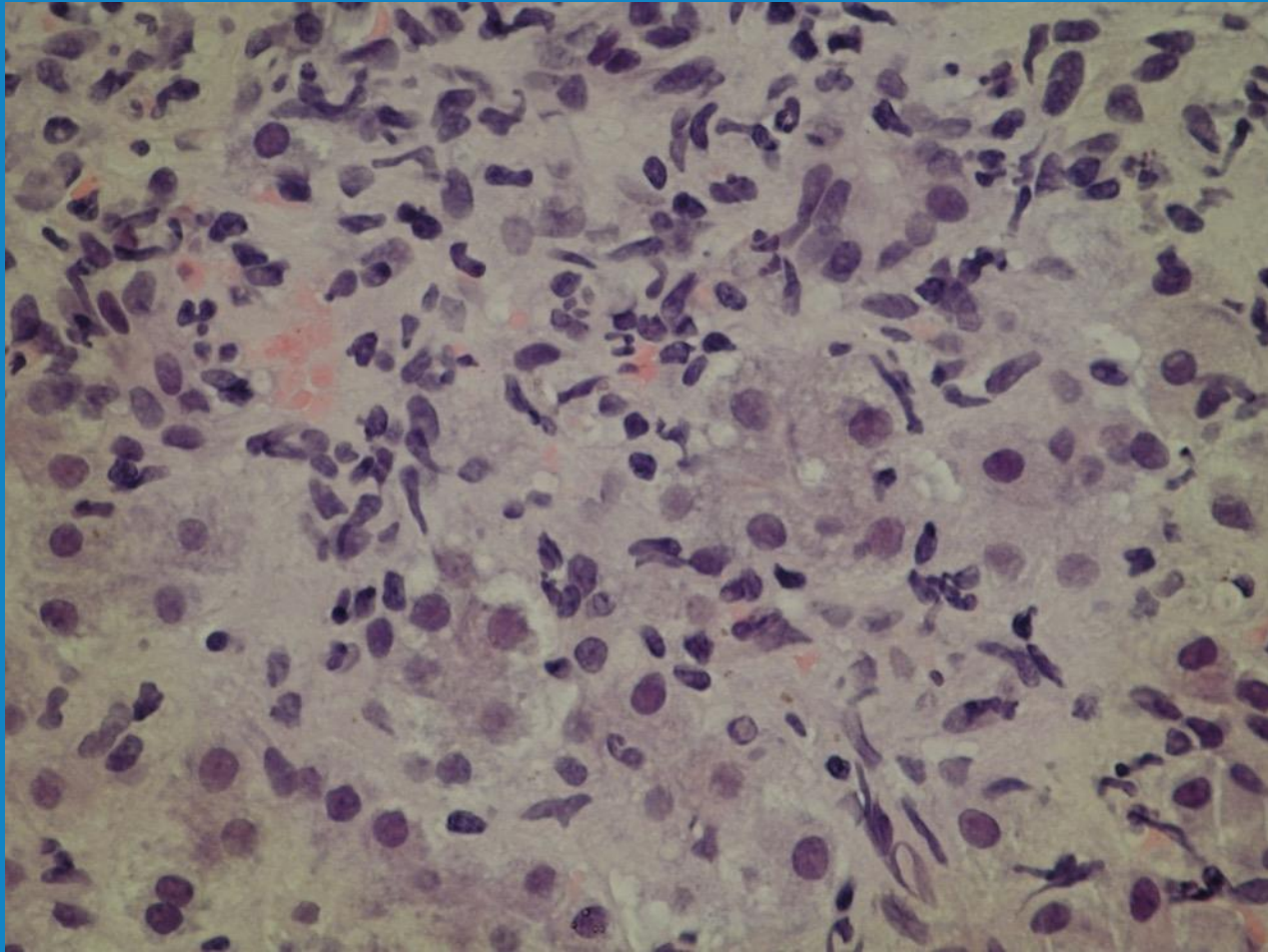
Interface hepatitis



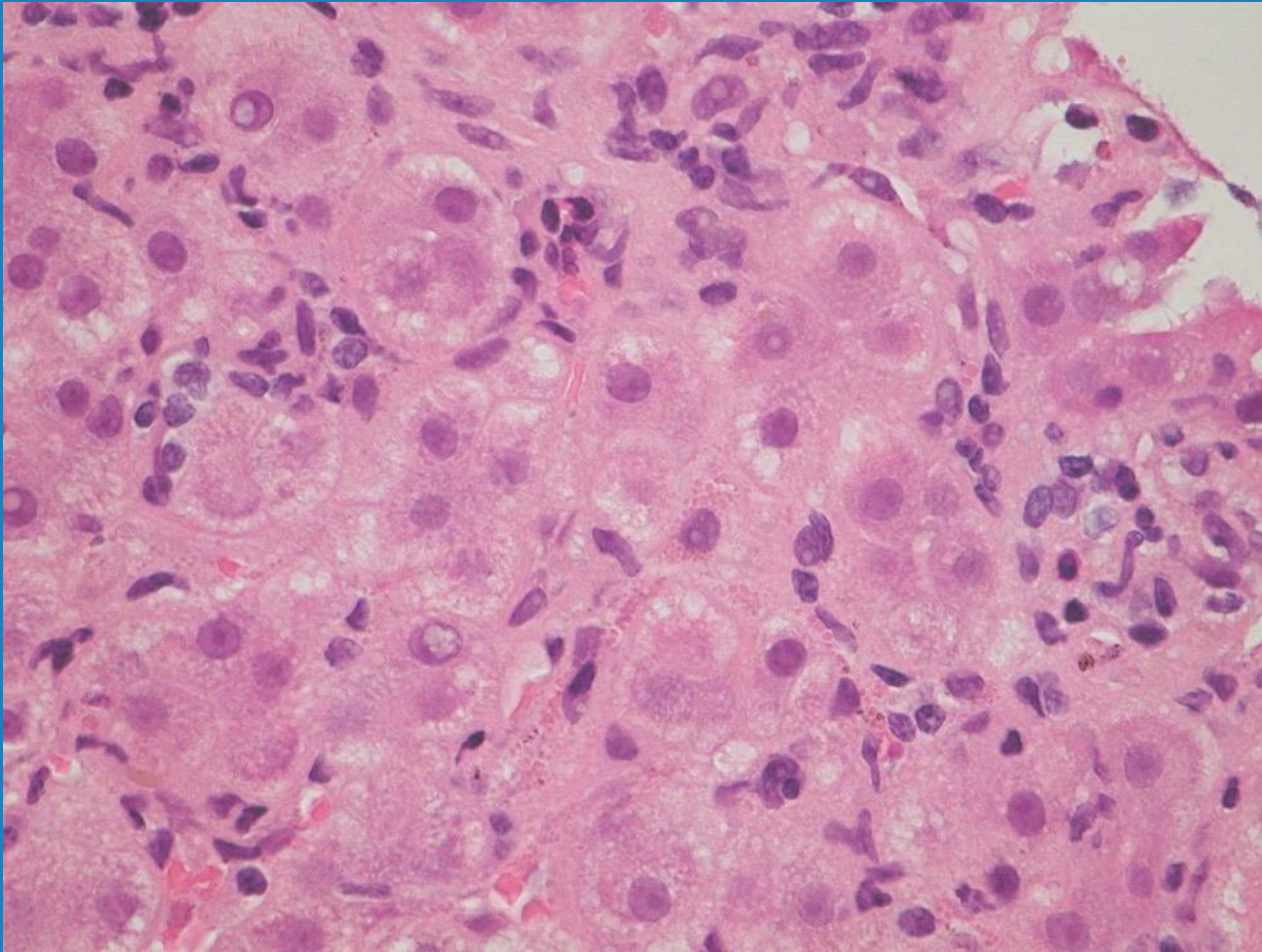
Interface hepatitis



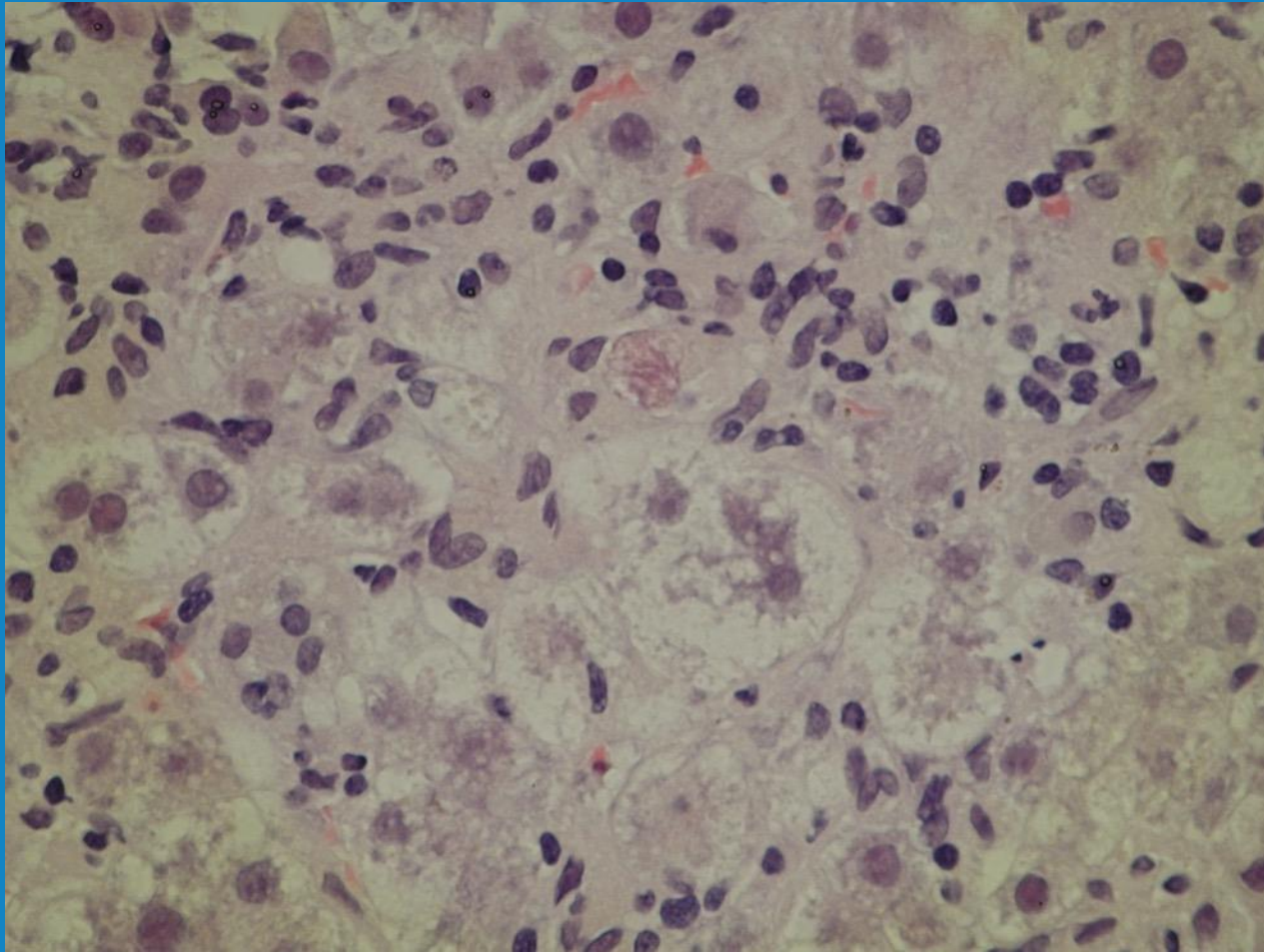
Other interface findings



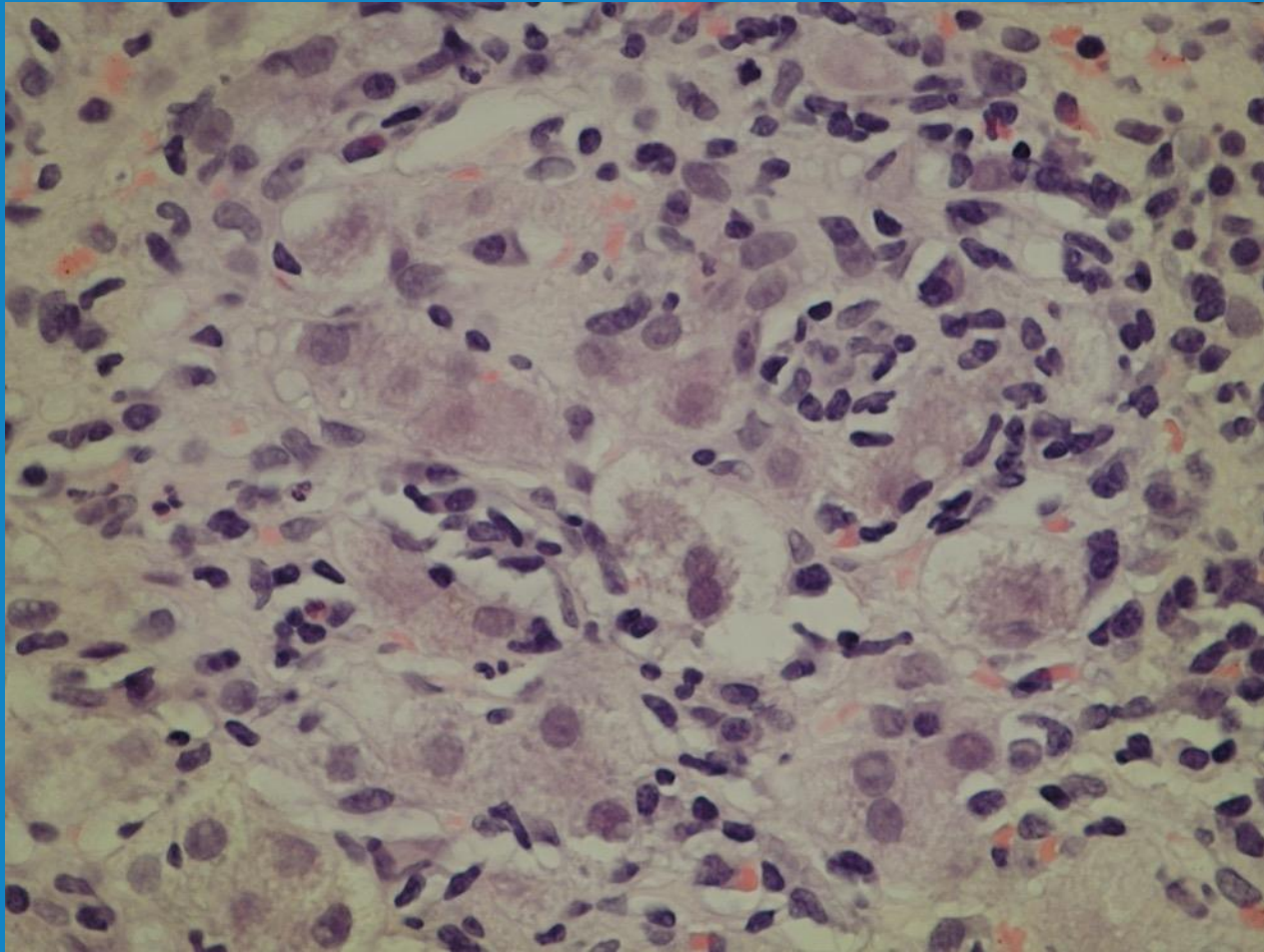
Hepatocyte rosettes



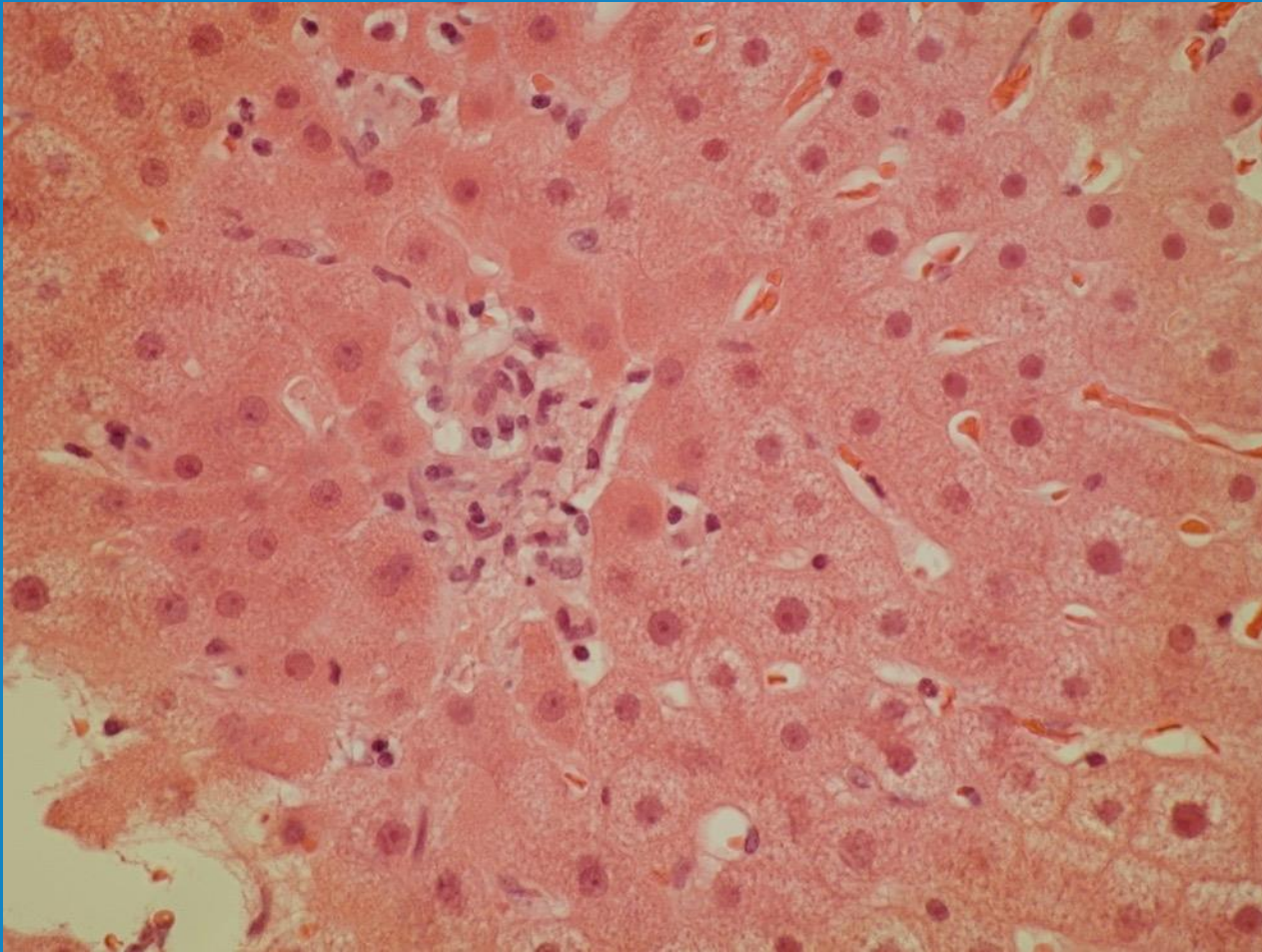
Lobular hepatitis



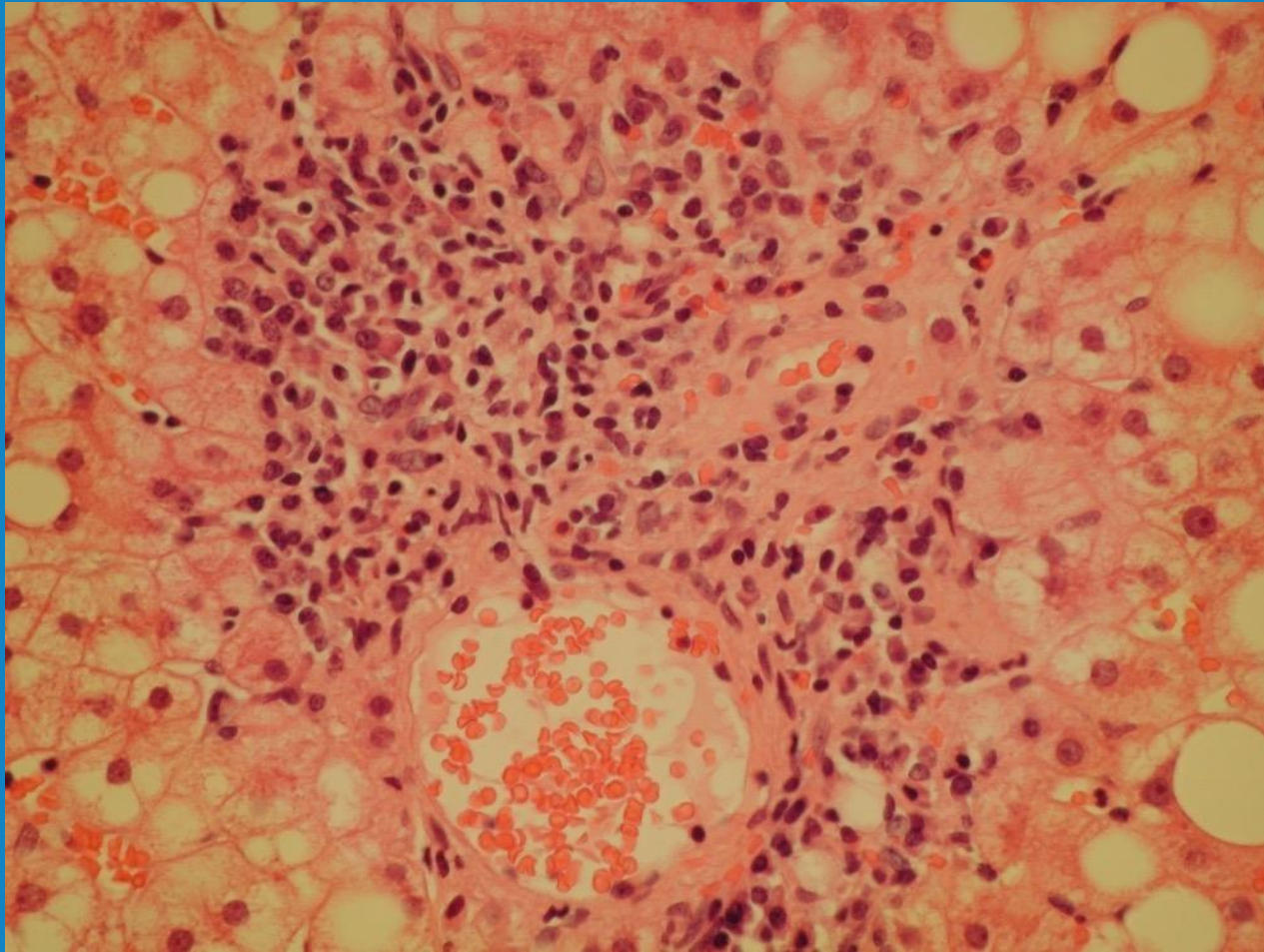
Lobular hepatitis



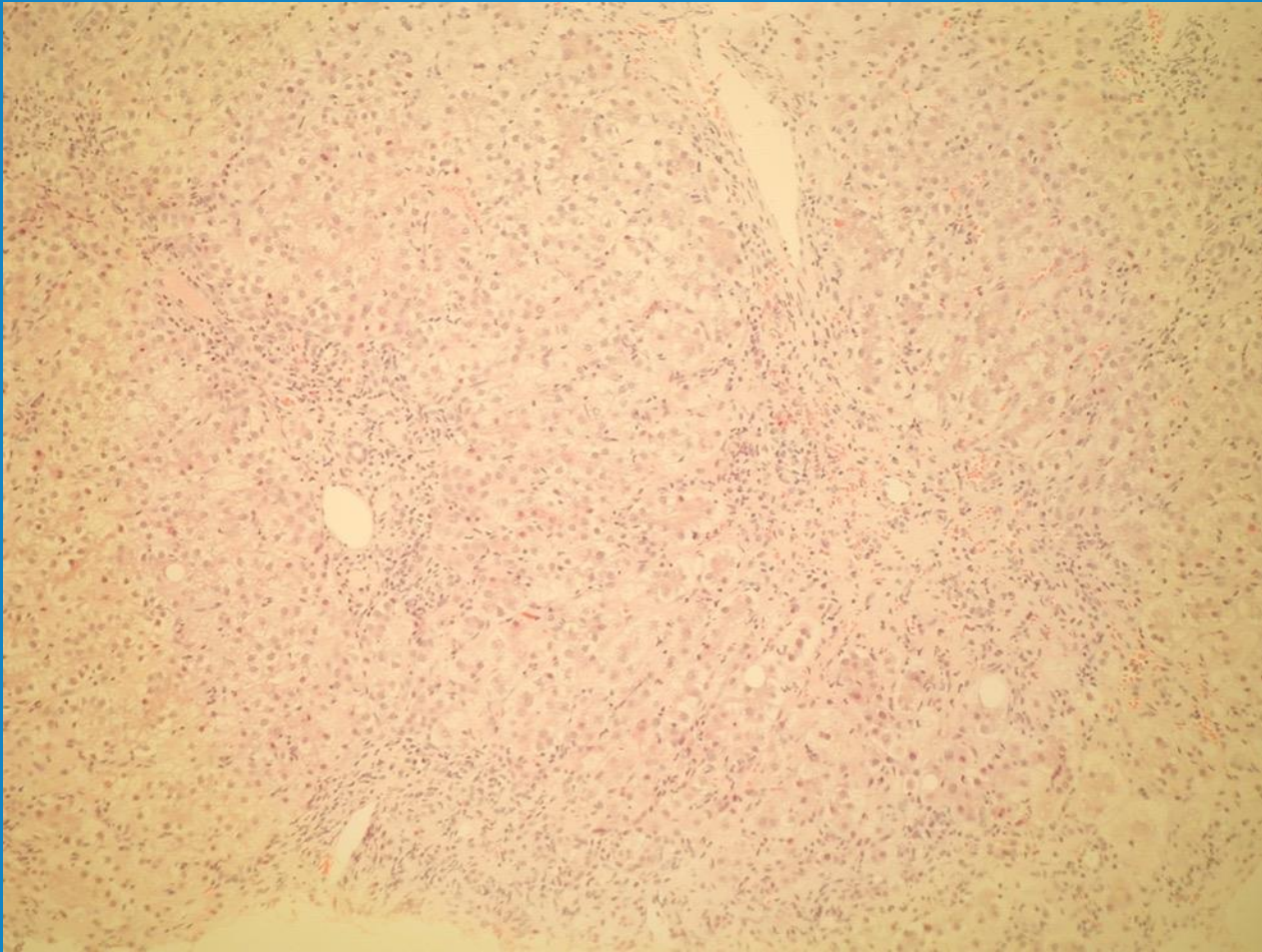
Lobular hepatitis



Confluent necrosis



Bridging necrosis



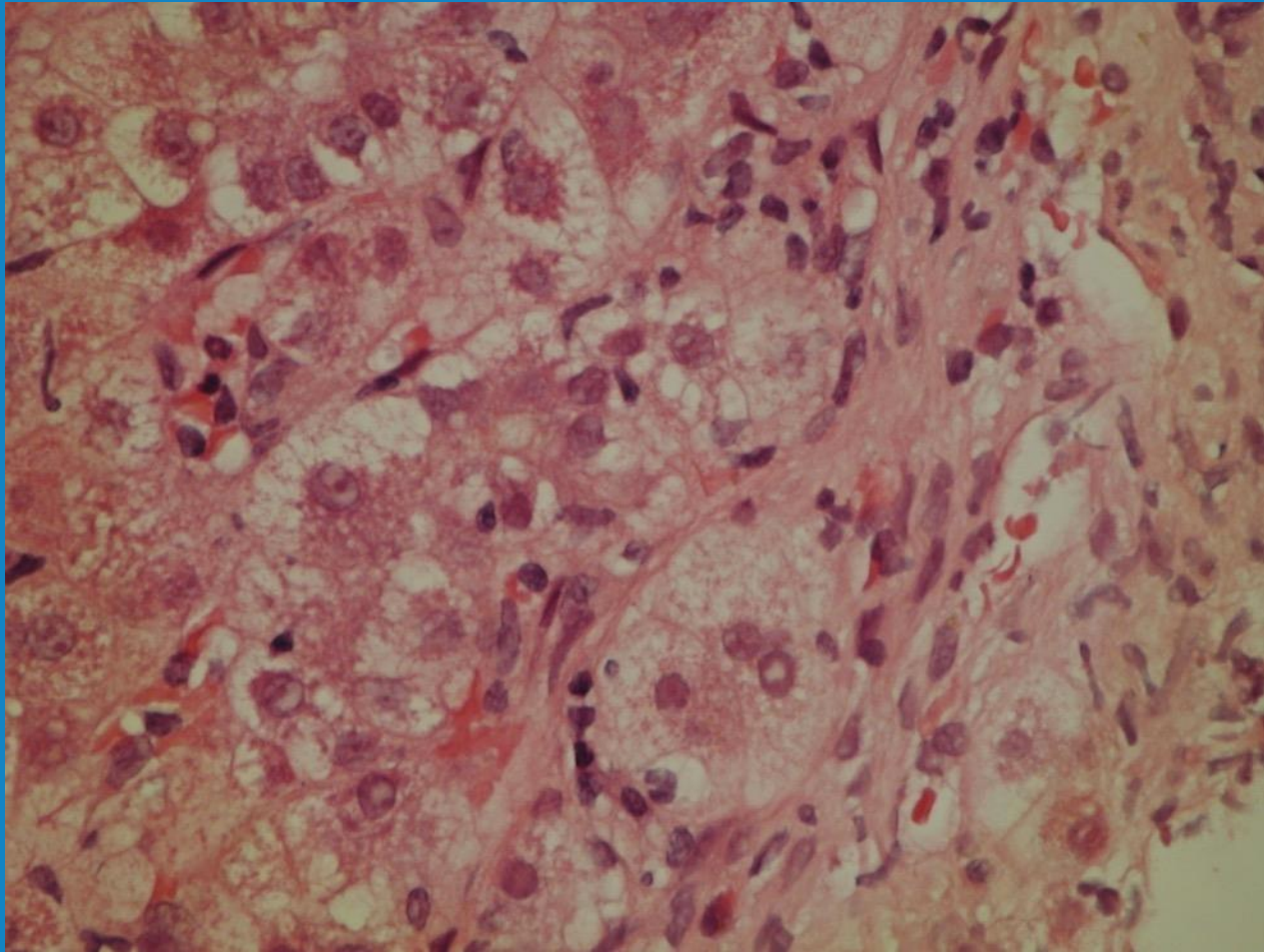
Emperipolesis

- More recently recognised as a feature.
- 65.3% of 101 patients with AIH vs. 17.9% PBC, 14.9% chronic hepatitis and 25.6% DILI. Miao et al. Clin Rev Allergy Immunol 2015 48: 226- 35
- Where present, significantly higher transaminases, more severe necroinflammatory features and more advanced fibrosis.
- CD8+ lymphocytes in hepatocytes.

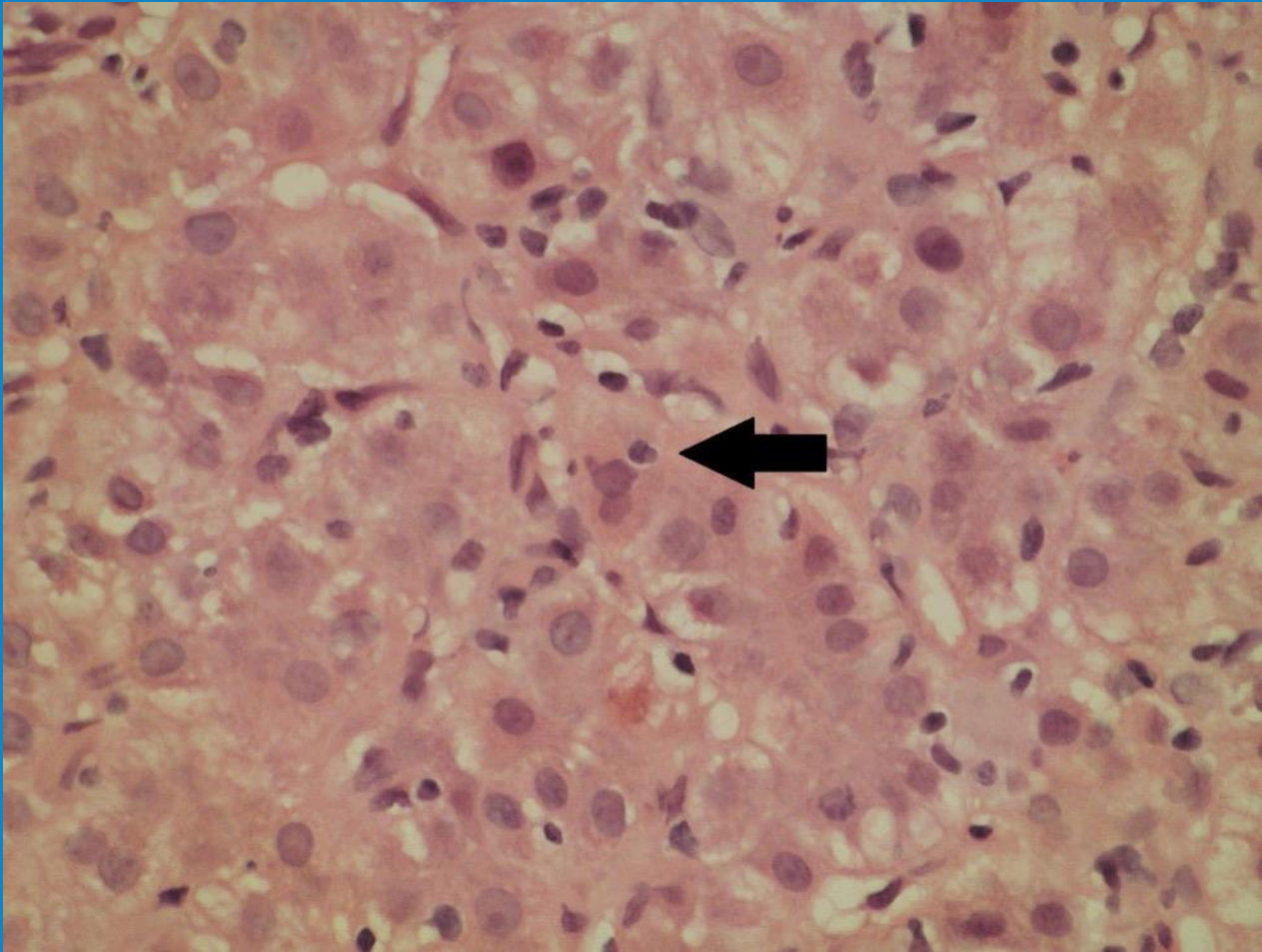
Emperipolesis

- We looked at first AIH biopsies for emperipolesis.
- Graded as None, Rare (1- 4 in 15hpf), Few (5- 10 in 15hpf or many >10 in 15 hpf)
- Present in 83 of 84 biopsies. All had lymphocytes in hepatocytes, but also occasional plasma cells or neutrophils involved. 30% had lymphocytes in biliary epithelial cells.
- 40% Many and 39% Few.
- Grade positively correlated with portal tract number, necroinflammatory score and presenting serum IgG.

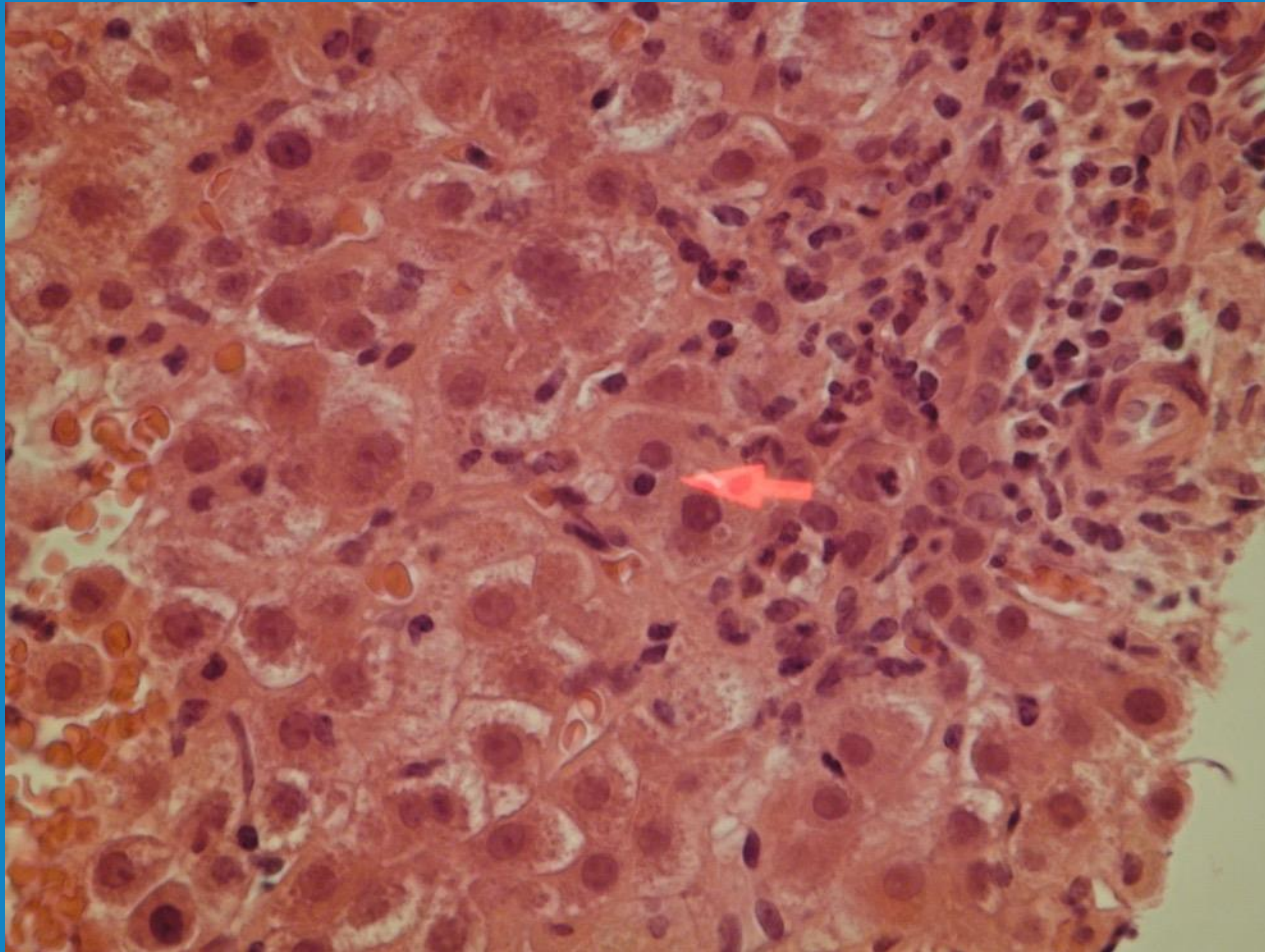
Emperipolesis



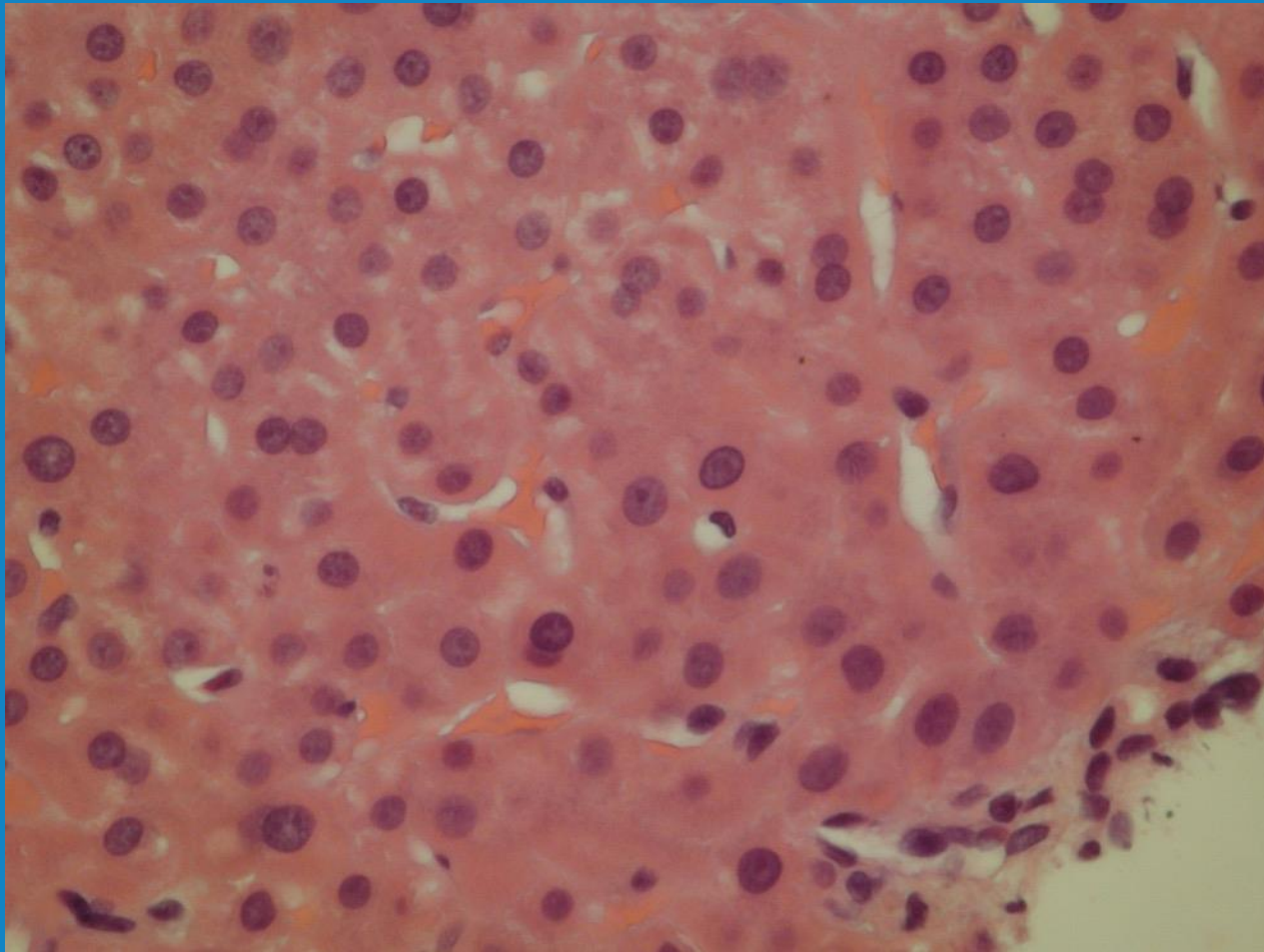
Emperipolesis



Emperipolesis



Not emperipolesis



Cholestasis

- Can be seen in acute presentation cases.
- Found by some to be more indicative of drug-induced injury.

Differential diagnosis – drug-induced liver injury

- Includes patients who have ALH already and in whom an exacerbation is triggered by a drug/ herbal medication.
- Includes patients whom the drug/ herbal medication triggers ALH in those with a predisposition to developing it.
- Some patients will develop progressive disease if not treated.

Is biopsy severity important ?

- Half with normal serum parameters still showed histological activity HAI 4 or 5, but these were at lower risk of fibrosis progression than those with scores of ≥ 6 . Lüth et al. J Clin Gastroenterol 2008 42: 926- 30
- Compared outcome of histological remission with HAI 0- 3 with HAI 4- 5. Latter less likely to achieve fibrosis regression (27% vs 60%).
- Liver-related death and transplant independently associated with persisting histological activity (HR 9.7).

Dhaliwal et al. Am J Gastroenterol 2015 110: 993- 9

Non-invasive assessment of inflammation

- Inflammatory score =
 $17.0 + 0.0049 \text{ AST [U/L]} - 3.40 \text{ total albumin [g/dl]} + - 0.4128 \text{ total bilirubin [mg/dl]} + 0.2527 \text{ CRP [mg/L]}$
- ≥ 3.57 differentiates HAI >4 from <4 .
- Sensitivity 100%, specificity 85%.
- Gutkowski et al. Liver Int 2013 33: 1370- 7

Non-invasive assessment of inflammation - drawbacks

- Training and validation sets – small numbers.
- Mixed active/ remission groups in differing proportions.
- CRP not specific for type of inflammation, so not suitable if co-morbidity.
- Remains to see if it will catch on and if it is good enough.

Prediction of relapse ?

- Only the presence of portal plasma cells in the biopsy prior to withdrawal was associated with relapse (31% vs 7%). PPV 92%.

Czaja & Carpenter Liver Int 2003 23: 116- 23

- Grading of interface hepatitis not significantly associated with relapse. More patients treated with prednisolone only had relapse.

Yokokawa et al. Hepatol Res 2011 41: 641- 6

Prediction of relapse ?

- Compared the outcomes of histological remission HAI 0- 3 with HAI 4- 5. Latter less likely to achieve fibrosis regression (60% vs 27%).
- Persisting histological activity independently associated with liver-related death/ Tx (HR 9.7).

Dhaliwal et al. Am J Gastroenterol 2015 110: 993- 9

- Higher ALT and IgG levels (but within N range) were associated with time to relapse. All patients maintaining remission had ALT < half ULN and IgG <12g/L at the time of withdrawal.

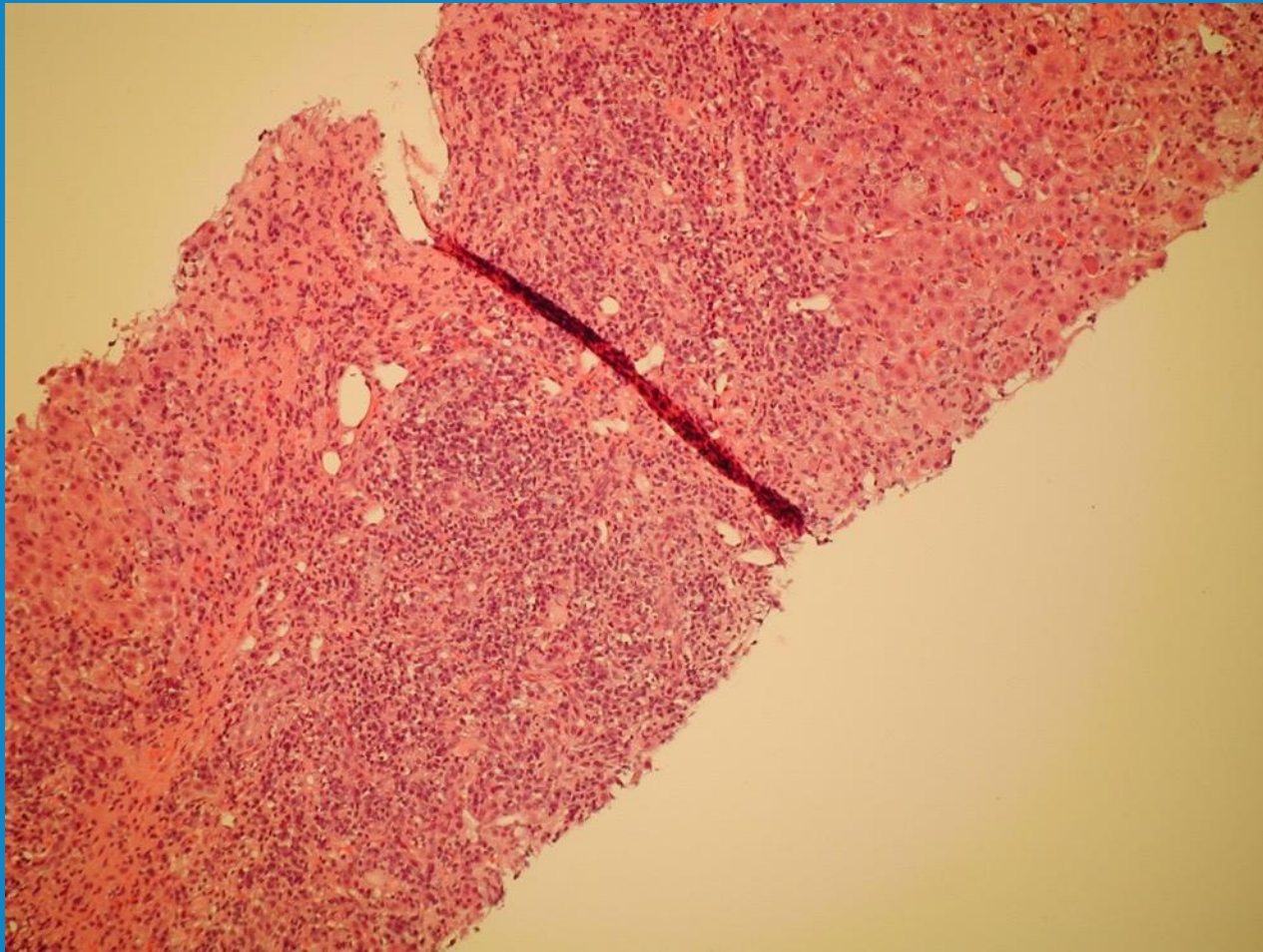
Hartl et al. J Hepatol 2015 62: 642- 6

Prediction of relapse ?

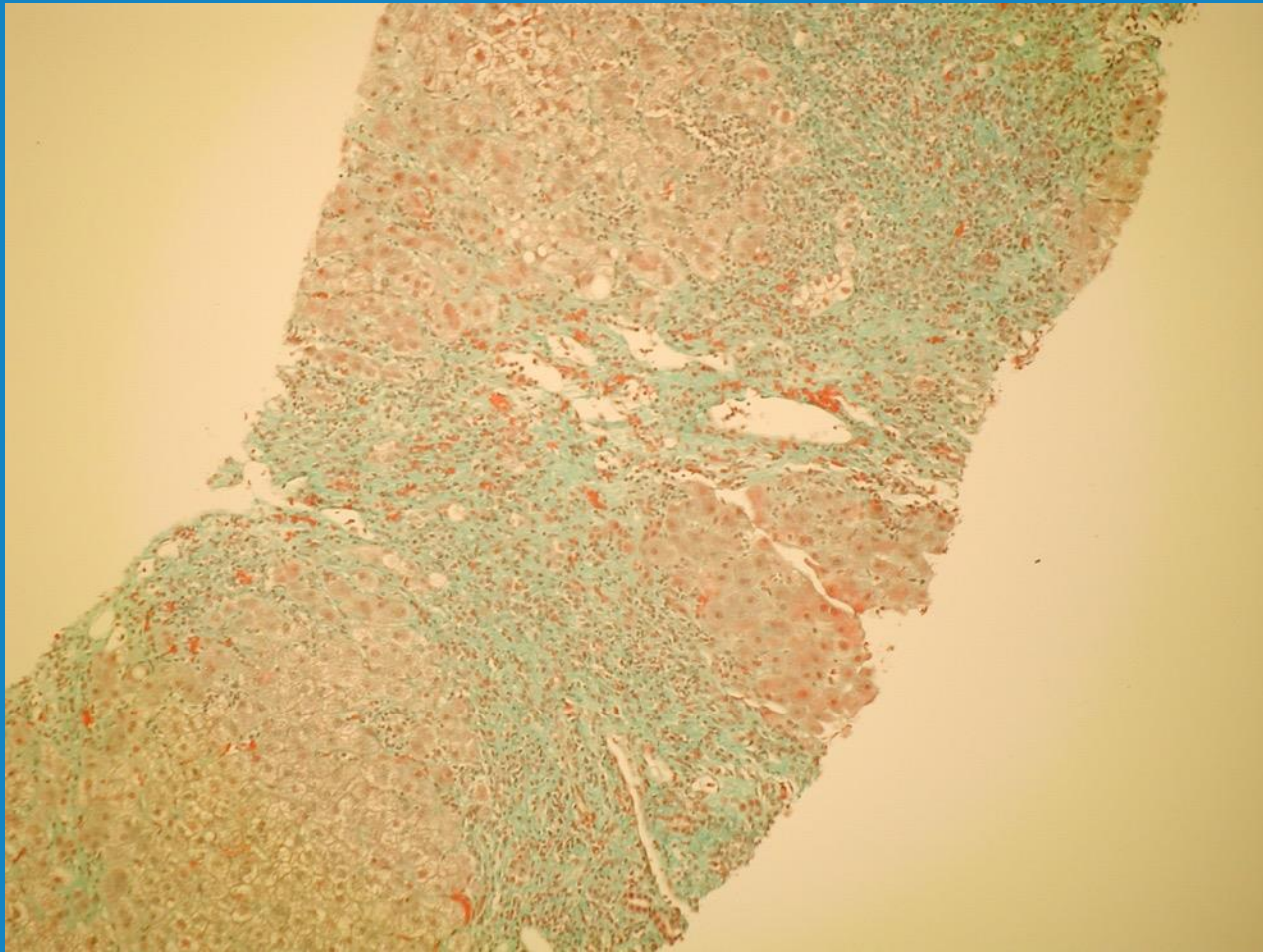
- >90% probability of relapse if time to remission ≥ 5 months, portal plasma cell score ≥ 3 and number of times ALT/AST abnormal per year ≥ 2 (PPV 100%).

Verma et al. Am J Gastroenterol 2004 99: 1510- 6

Is there fibrosis ?



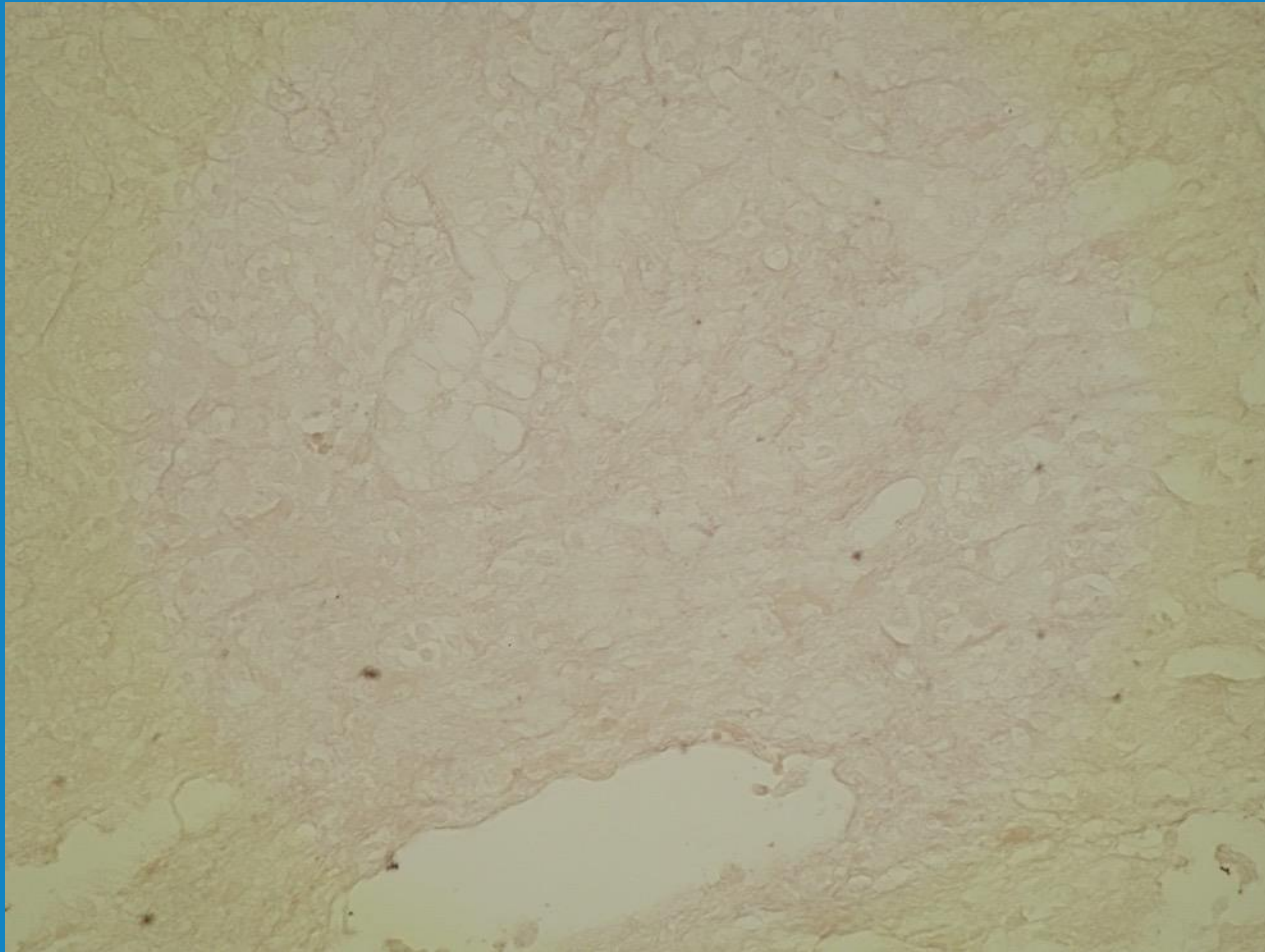
Is there fibrosis ?



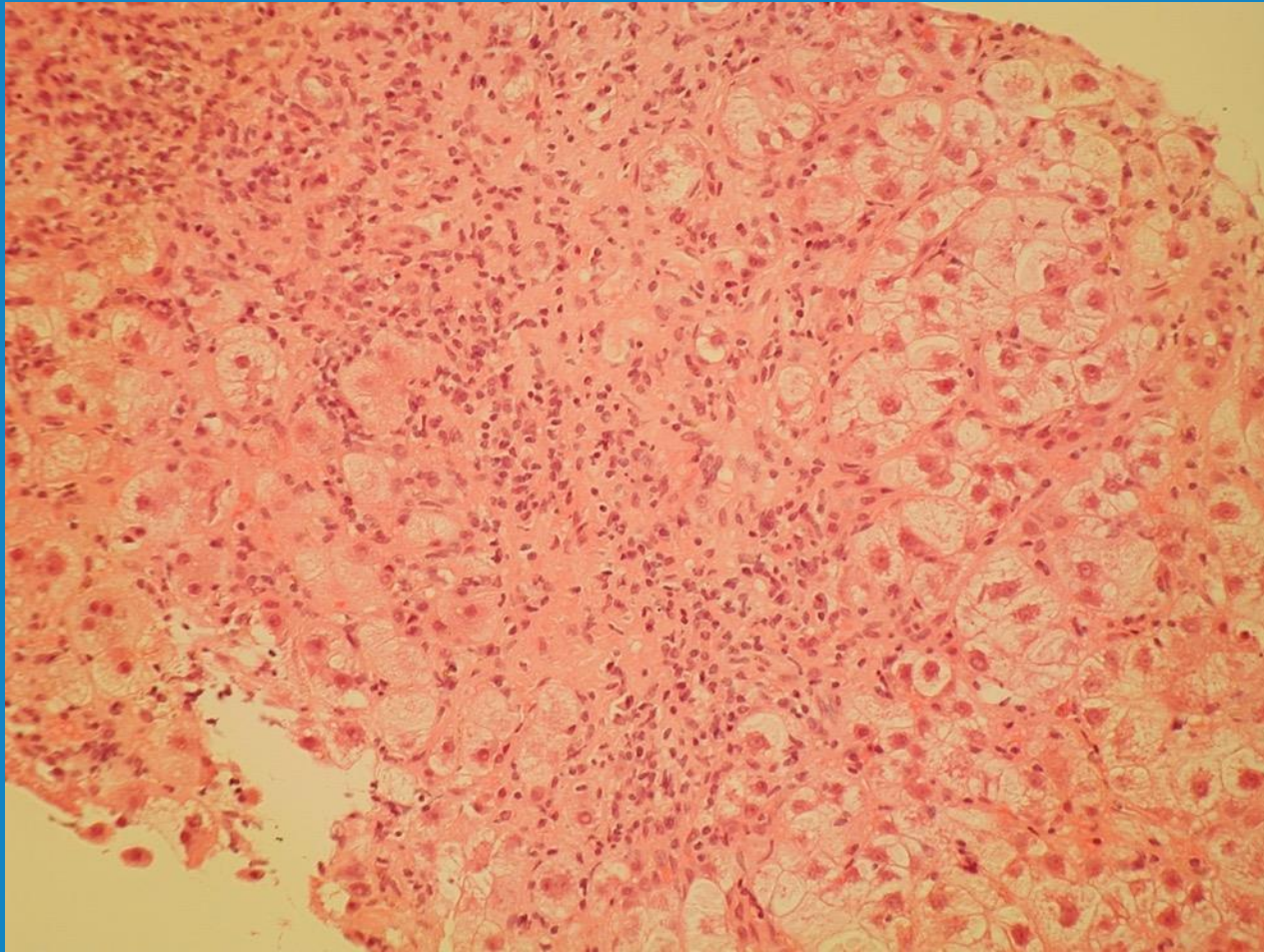
Is there fibrosis ?



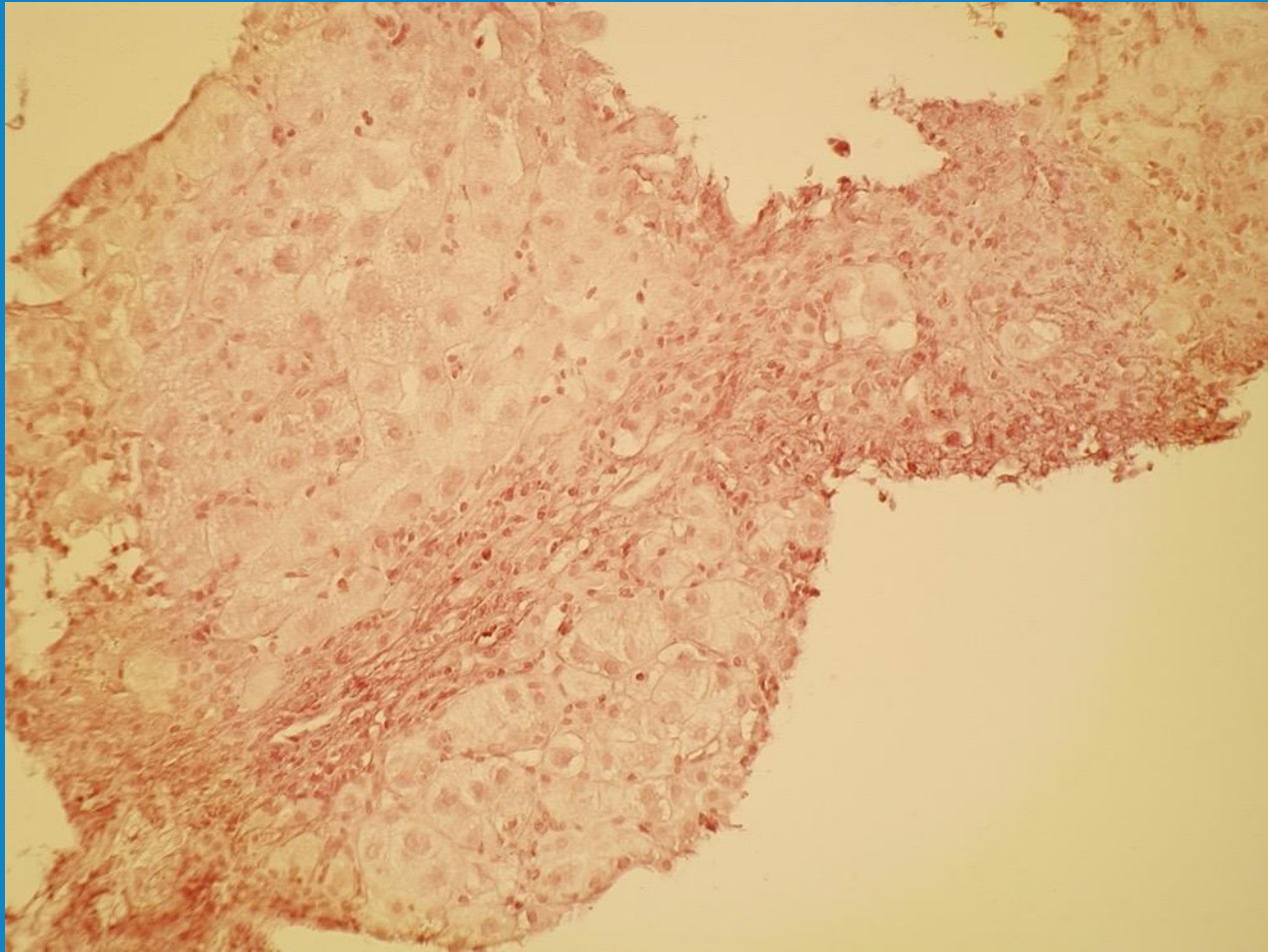
Is there fibrosis ?



Fibrosis ?



Yes



Fibrosis

- Acute loss of hepatocytes causes collapse of the reticulin framework.
- Hepatic stellate cells produce collagen.
- Stimulated by activated kupffer cells and inflammatory cells, including plasma cells.
- Remodelled by collagenases.
- Increased collagen type I in fibrosis and cirrhosis.
- Elastin deposition later than collagen.

Drivers of fibrosis in AIH

- Increased hepatic stellate cell population in AIH, mainly activated phenotype.
- Co-localisation of plasma cells and activated stellate cells.
- Positive correlation between stellate cells, fibrosis scores and number of plasma cells.
- Successful Rx gave reduced numbers of plasma cells, HSCs and fibrosis (those with 2nd bx).

Brandão et al. Pathol Res Pract 2010 206: 800- 4

Non-invasive assessment of fibrosis in autoimmune hepatitis

- Hartl et al. J Hepatol 2016 65: 769- 775
- Diagnosis of cirrhosis optimal cut-off of 16kPa.
- Performance impaired when TE performed within 3 months of start of Rx, where there was correlation with histological grade, but not stage.
- Cut-off excellent in patients treated for 6mths or longer.

Non-invasive assessment of fibrosis

- Fibroscan
- ELF (enhanced liver fibrosis)
- Acoustic radiation force imaging
- Supersonic shear wave imaging
- Other imaging

Non-invasive assessment of fibrosis

- AST-Platelet Ratio Index, APRI=[(AST/upper limit of normal)*100/platelet count]
- Fibrotest – (Fibrosure) alph-2-macroglobulin, haptoglobin, total bilirubin, apolipoprotein-A, GGT, age and gender. 0.0- 1.0.
- FIB4 = $(\text{age} * \text{AST}) / (\text{plts} * \sqrt{\text{ALT}})$
- Fibroindex – plt count , AST and GGT

Non-invasive assessment of fibrosis

- Hyaluronic acid – may correlate with activity and fibrosis
- PIIINP – amino terminal of serum pro-collagen III peptide
- TIMP-1
- YKL-40 – chondrex. Bacterial chitinase family
- ELF – Enhanced Liver Fibrosis – HA, PIIINP, TIMP-1

Conclusions

- The liver biopsy is still important.
- Classical features of AIH occur in an acute setting, but individually are not specific.
- Histological activity illustrates one aspect of severity.
- Degree of fibrosis illustrates another.
- Non-invasive tests remain complementary at present and timing is important.

References

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- HLA types Genes Immun 2015 16: 247- 52
World J Gastroenterol 2006 12: 5513- 6
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References

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- Simplified criteria for diagnosis IAHG Hepatology 2008 48(1):169-76.
- Non-invasive markers of inflammation in AIH (Editorial) Liver Int 2013 33: 1295- 97
- Non-invasive diagnosis of advanced fibrosis/ cirrhosis World J Gastroenterol 2014 20: 16820- 30

Not quite West Bromwich Albion...

