Liver Pathology Symposium - medical livers

Royal College of Pathologists,

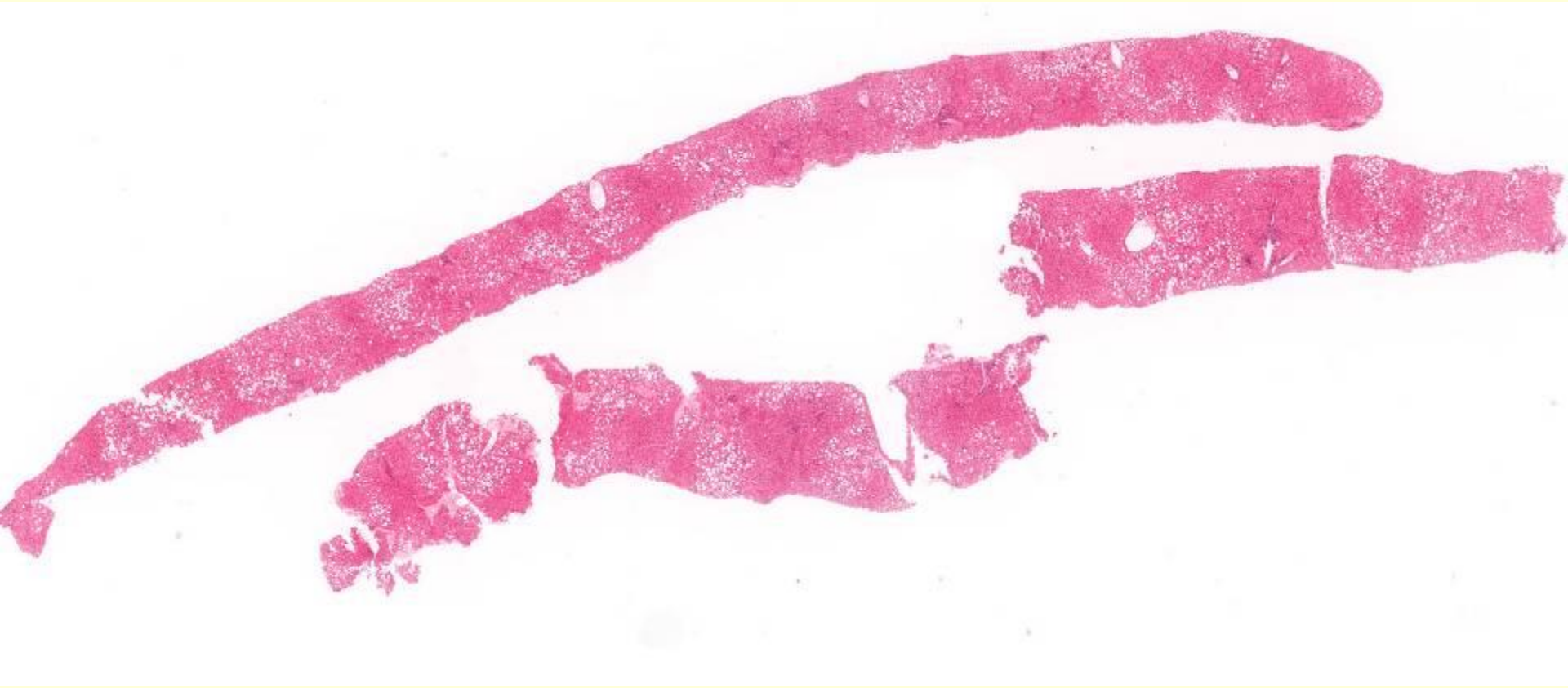
5th April 2019

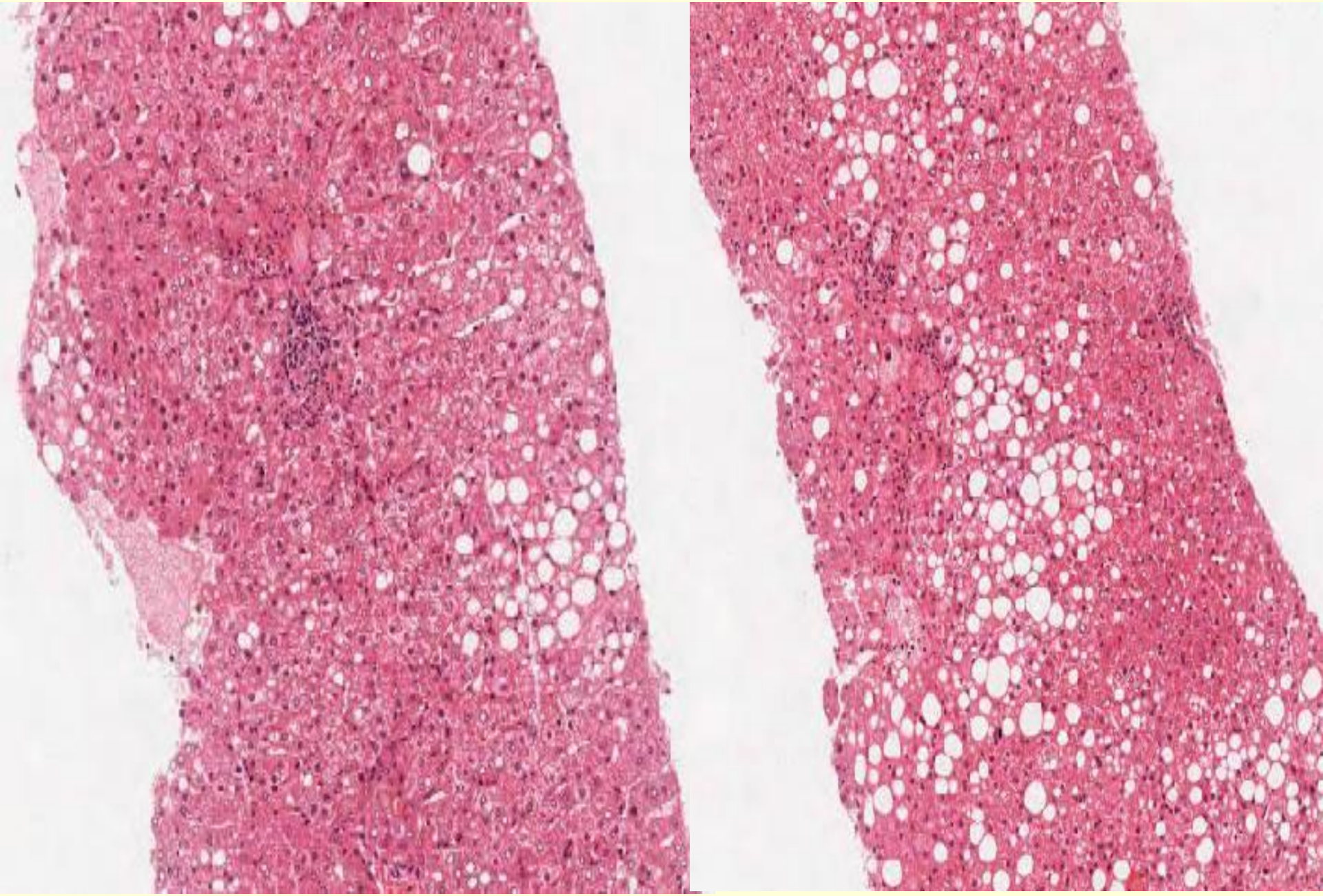
Dr Susan E Davies, Addenbrooke's Hospital,

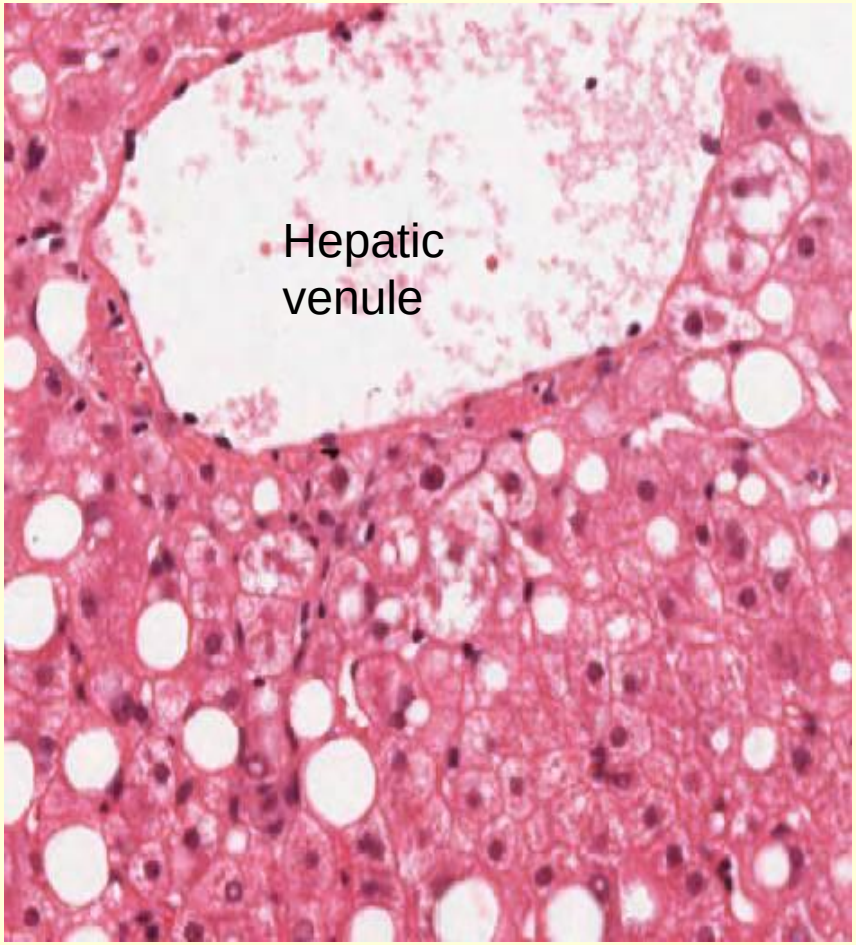
Cambridge University Hospitals NHS
NHS Foundation Trust

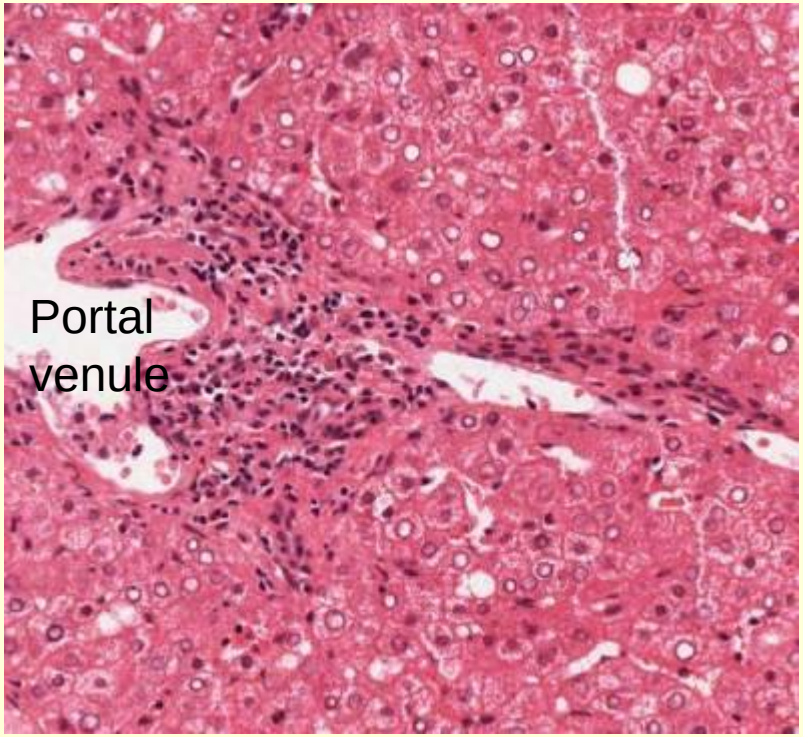
Case 1 SED

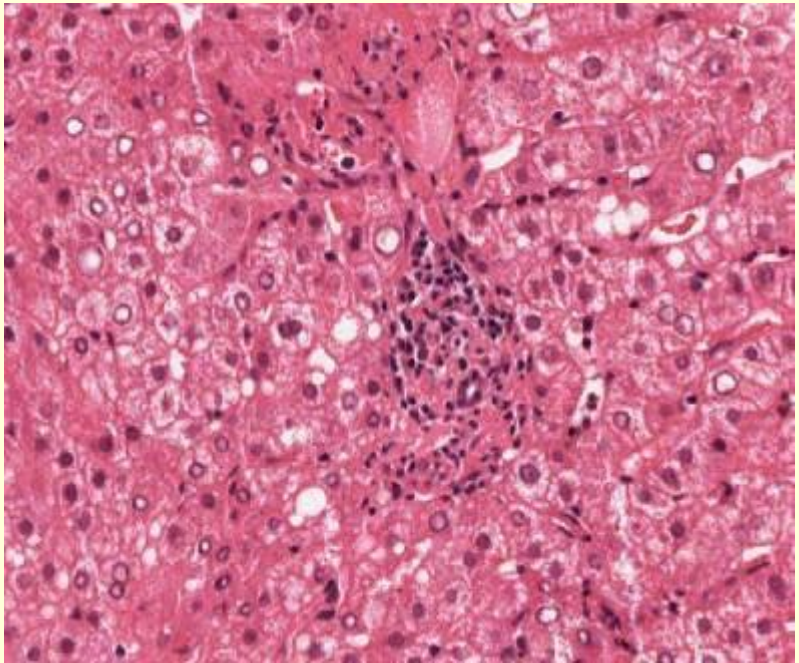
- 65/F Diabetic. Raised ALT , USS fatty. Fibroscan ? cirrhosis
- Reticulin (untoned), CAB



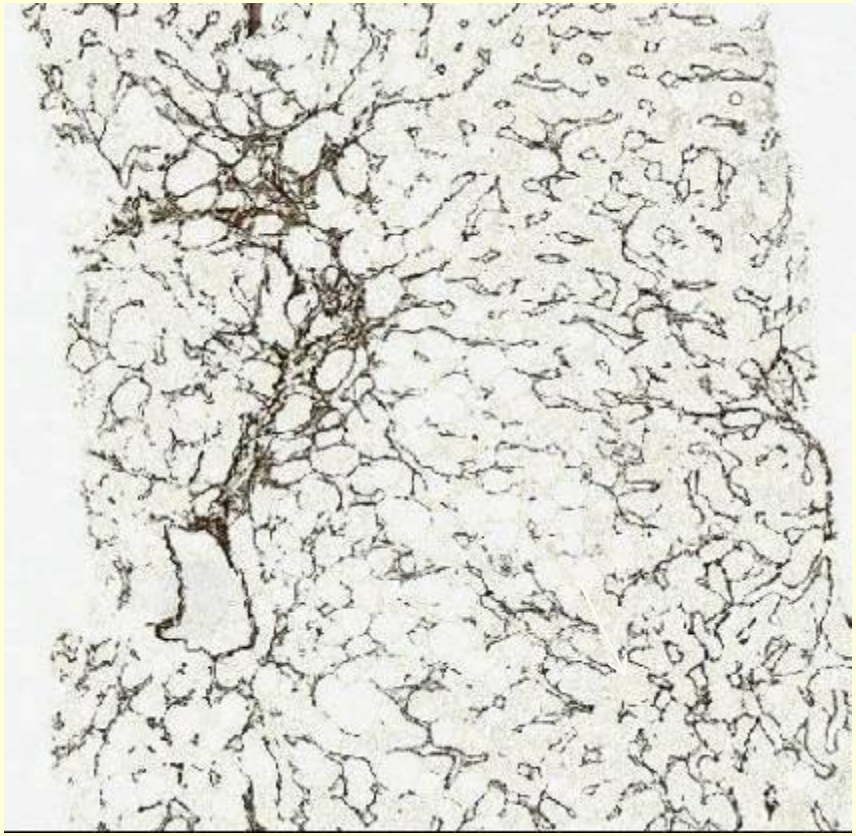


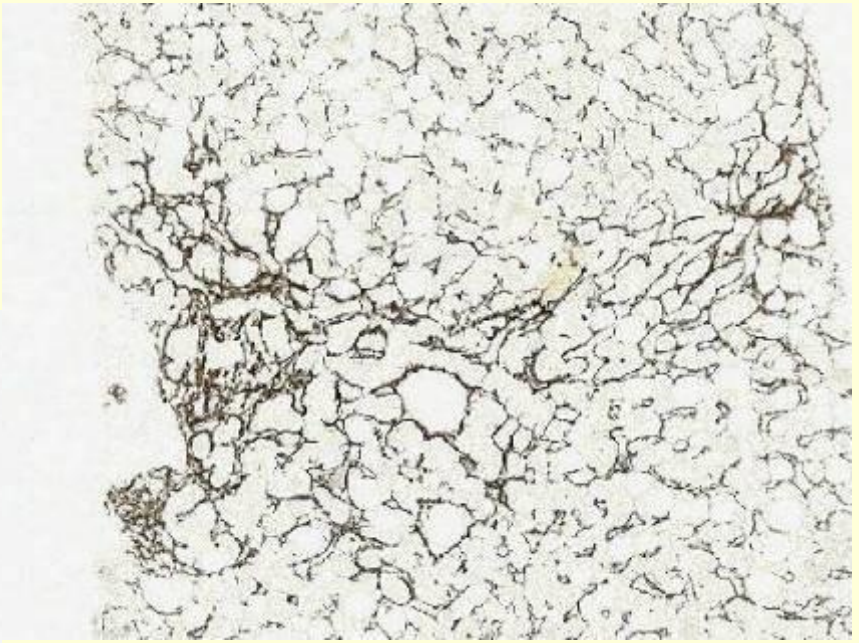

Hepatic
venule

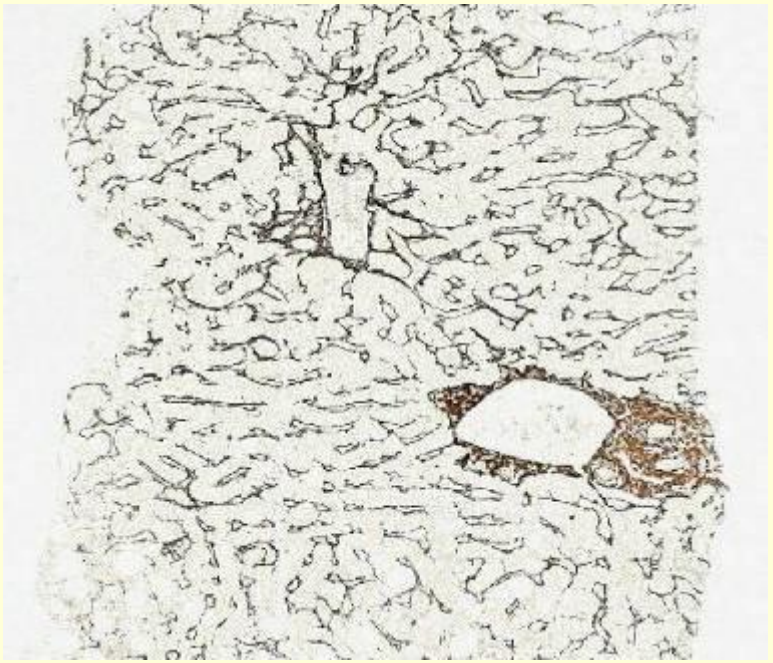

Portal
venule



reticulin

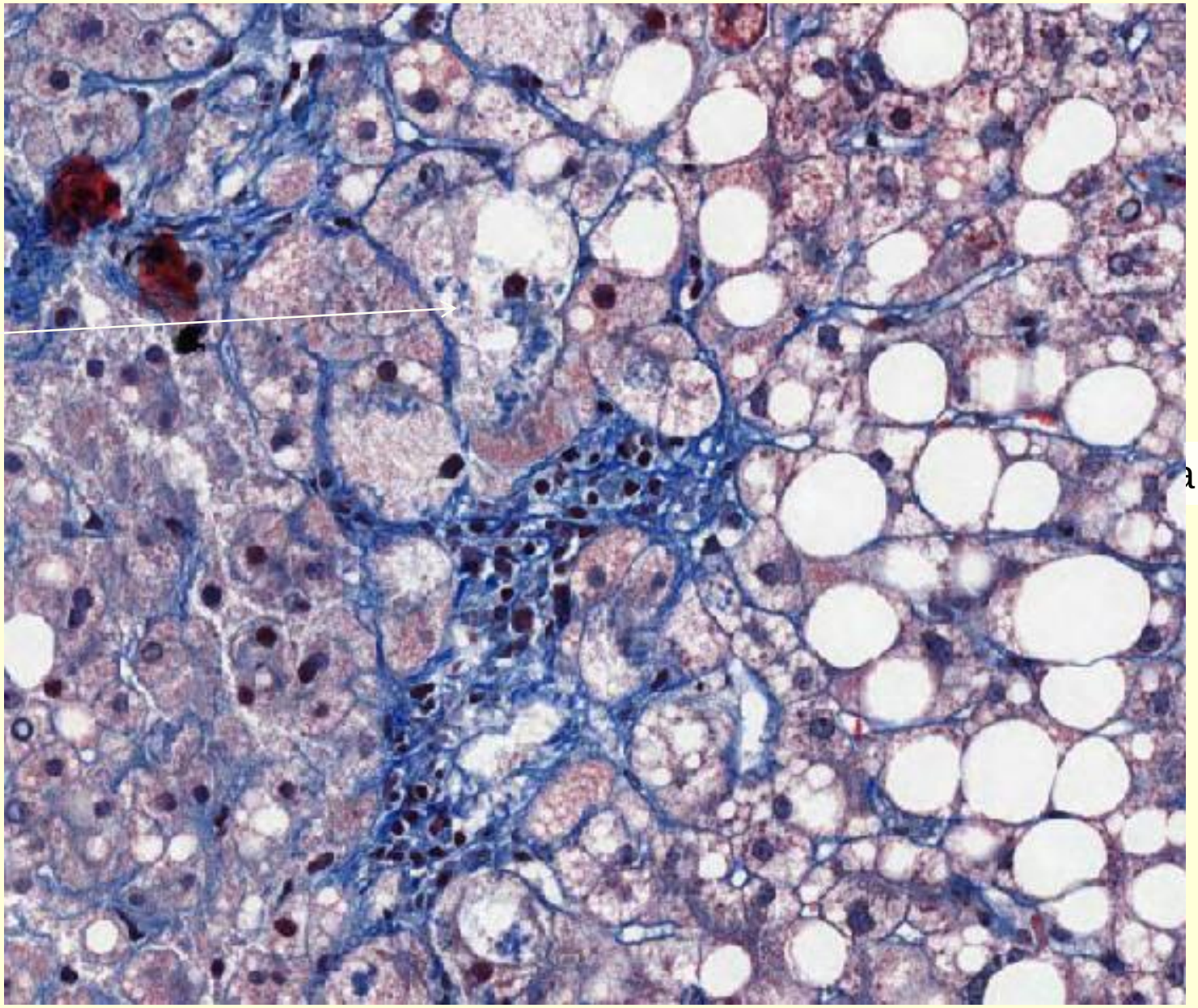






CAB

Mallory Denk bodies



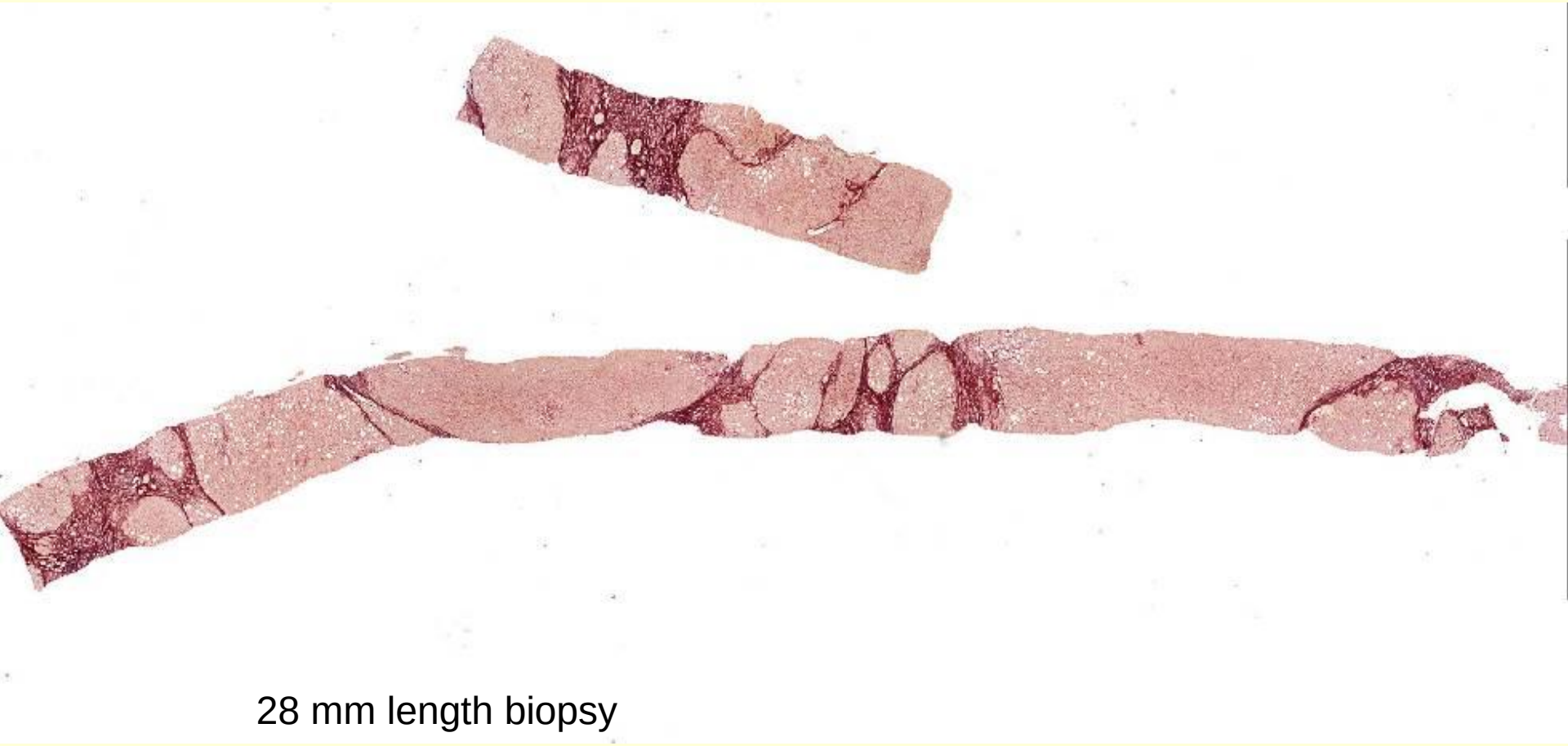
Diagnosis case 1

- Steatohepatitis
- Mild fibrosis
- In keeping with Non-Alcoholic Fatty Liver Disease, ie NASH

Case 2

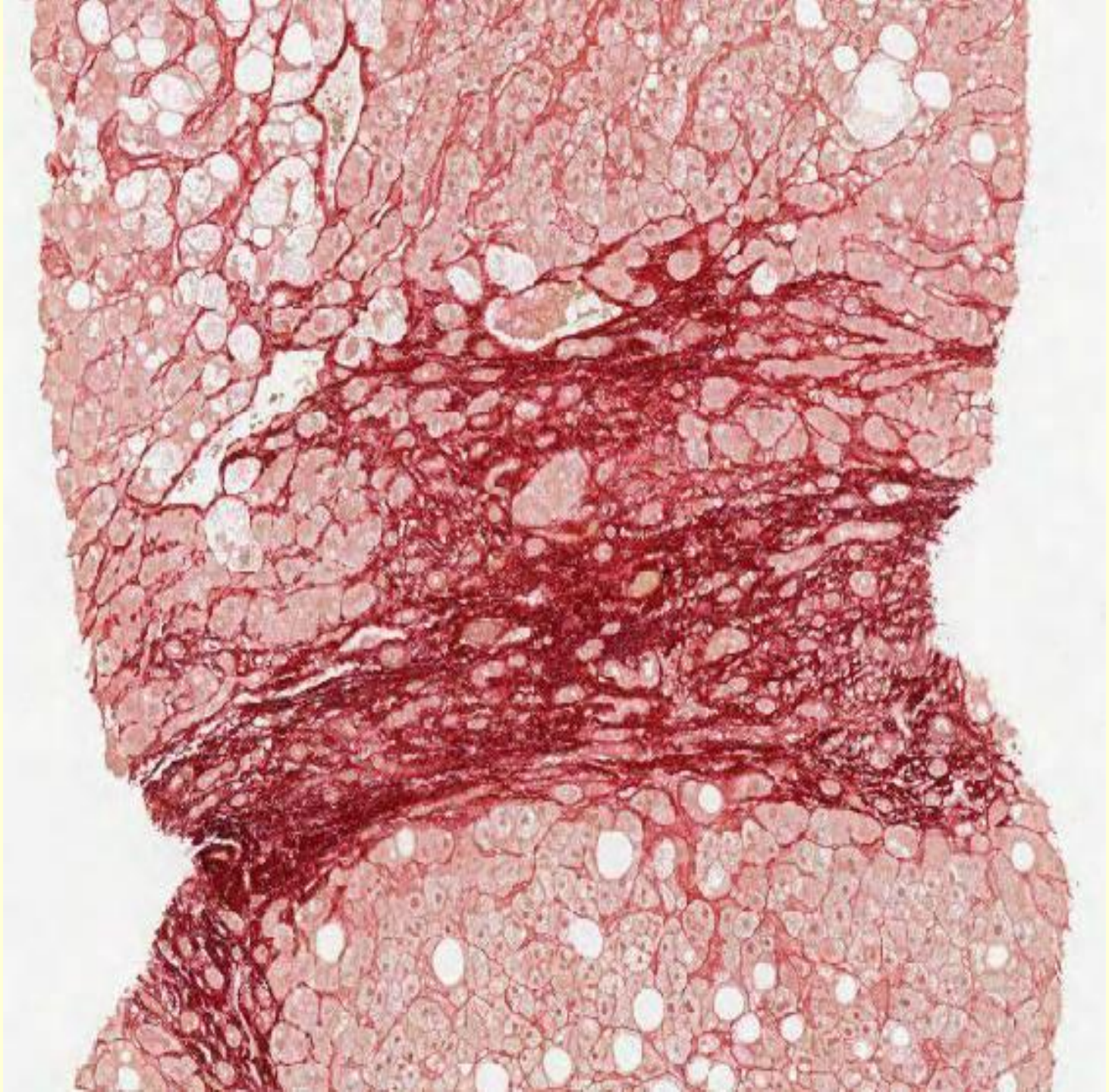
- 52/M Background liver (sic).
- From records; Albumin 35 (35-50 g/L), Bili 12 (0-20 umol/L), Alk Phos 173 (30-130 U/L), ALT 58 (97-40 U/L).
- Reticulin, EPSR, victoria blue

EPSR



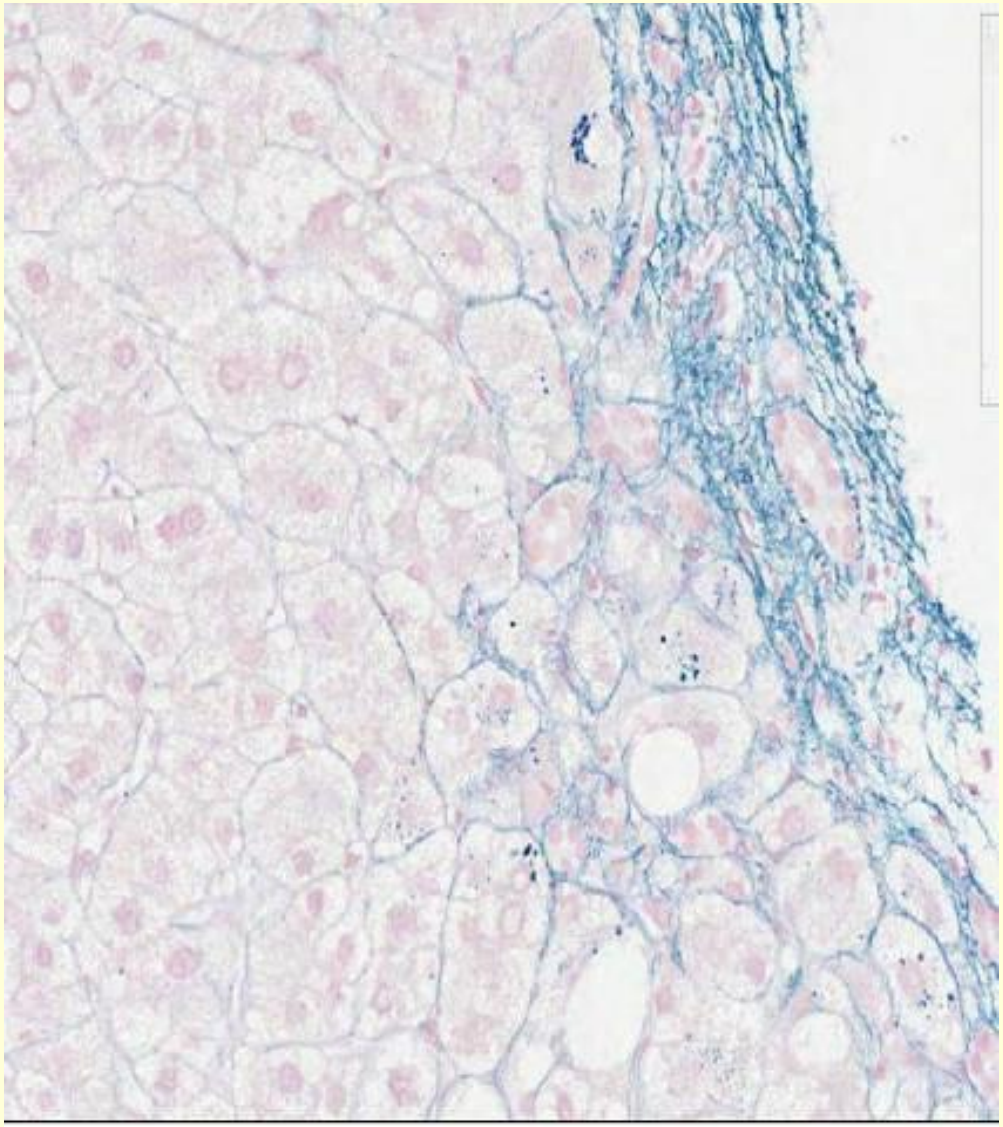
28 mm length biopsy

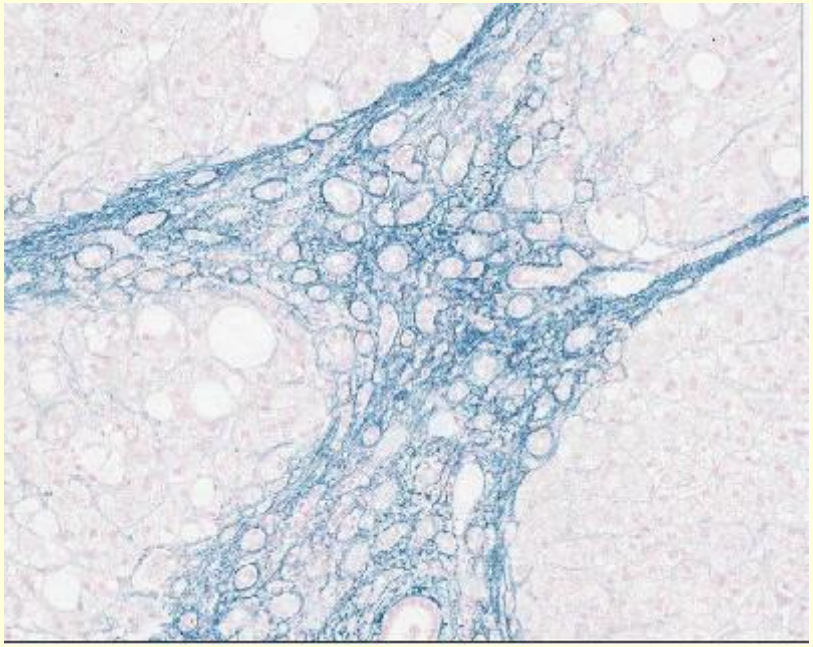
Reticulin

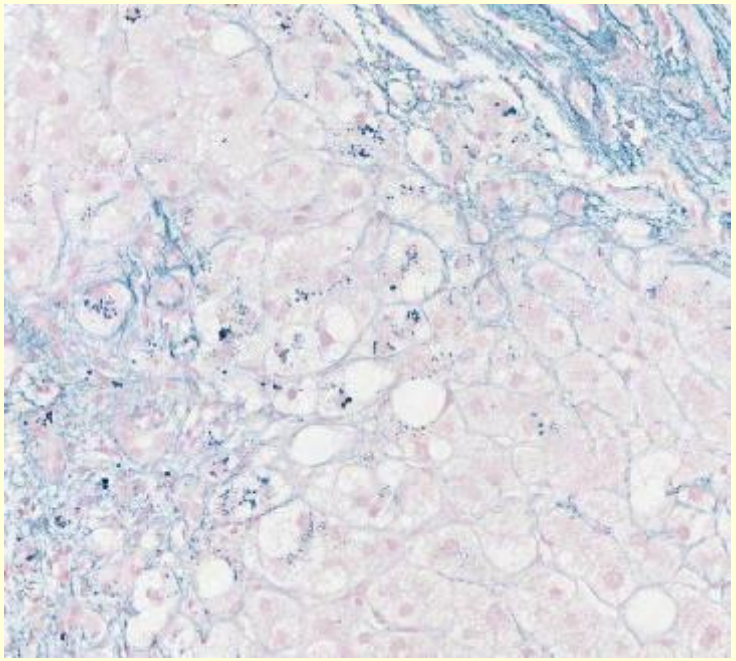


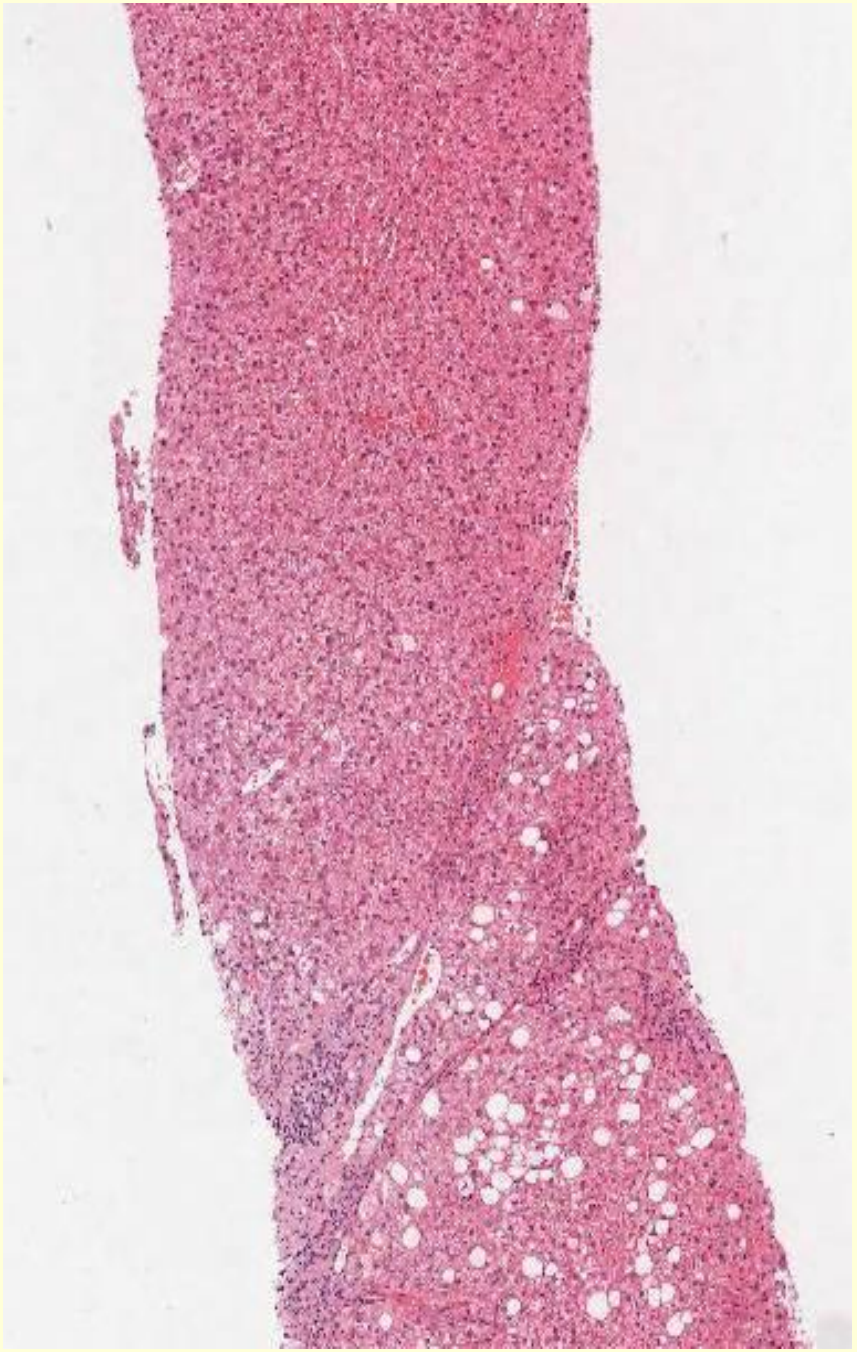
EPSR

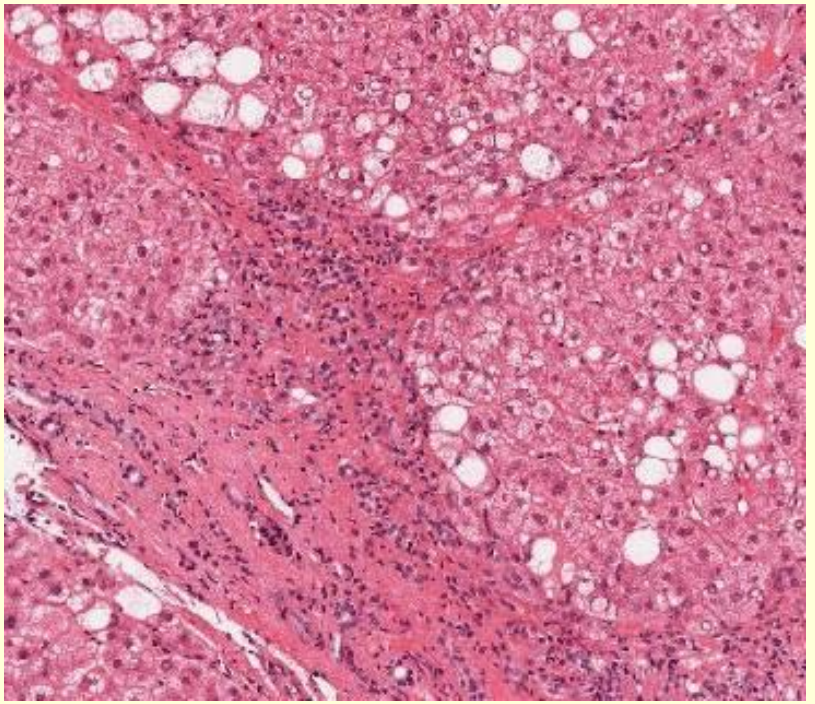
Victoria Blue

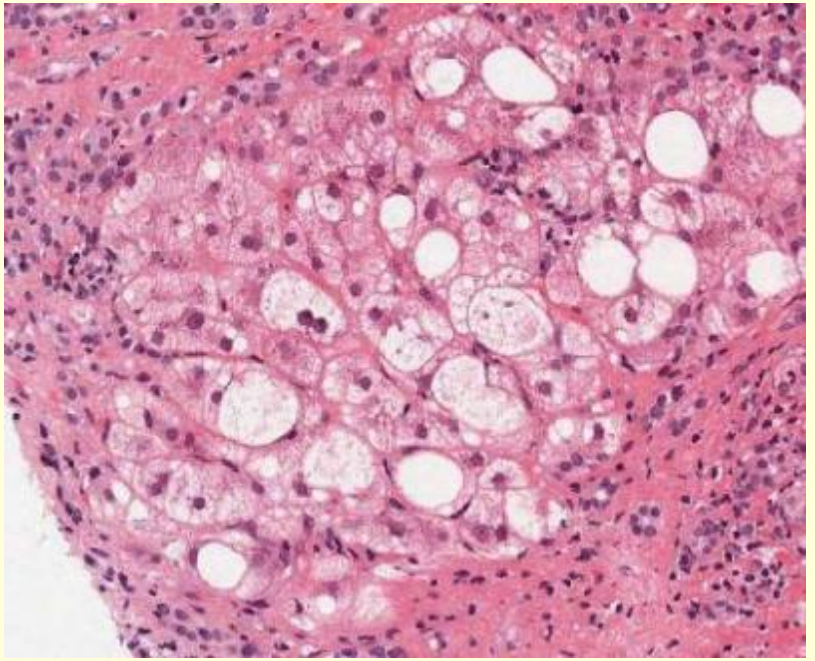












Diagnosis case 2

- Cirrhosis
- Steatohepatitis with minimal steatosis

- Further Info (electronic records) - obese and diabetic
- Consistent with advanced Non-alcoholic fatty liver disease

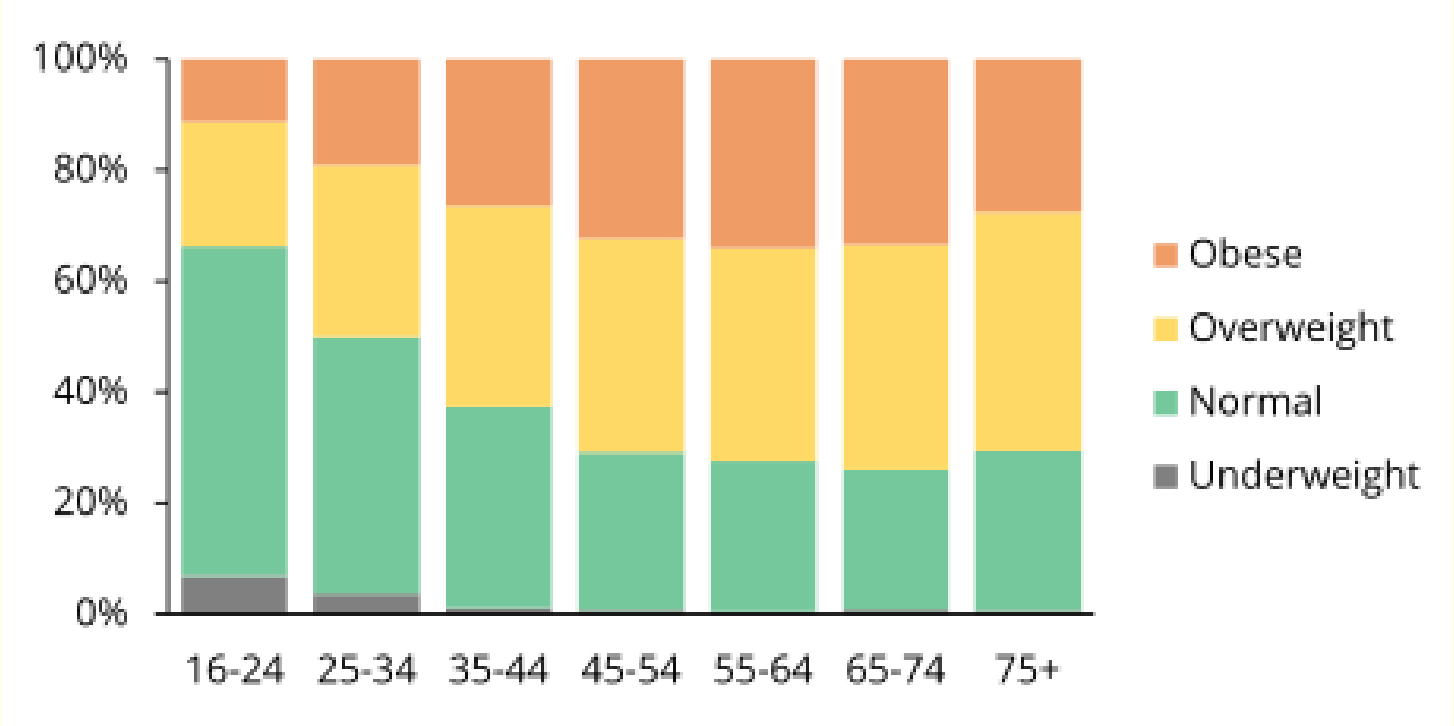
Non Alcoholic Fatty liver Disease

Death by chocolate…

Obesity among adults

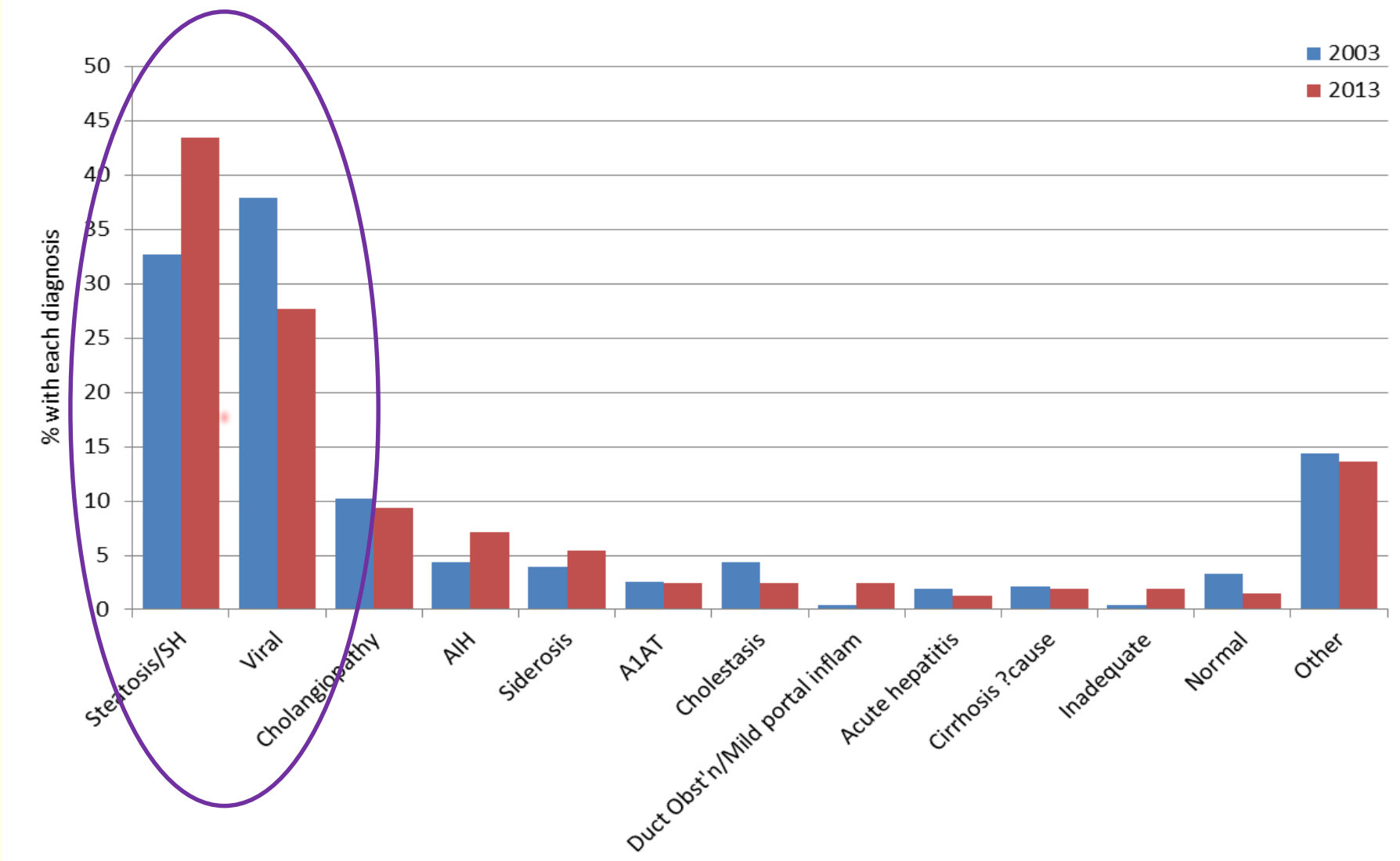
Health Survey for England 2016

Adult (aged 16+) overweight BMI – 25-30; obesity: BMI ≥ 30kg/$m^{2.}$



26% adults obese (men > women)
35% overweight

Pathologies Present (2003 & 2013)



Scoring NASH

First up – *Brunt Am J Gastro 1999*, 0-3 for steatosis, inflammation and fibrosis

Large USA group, *Kleiner Hepatology 2005*, **NAS score**, on 14 categories, with borderline cases. Problems – cries of misuse (*Hepatology 2011*) when tried to be used diagnostically

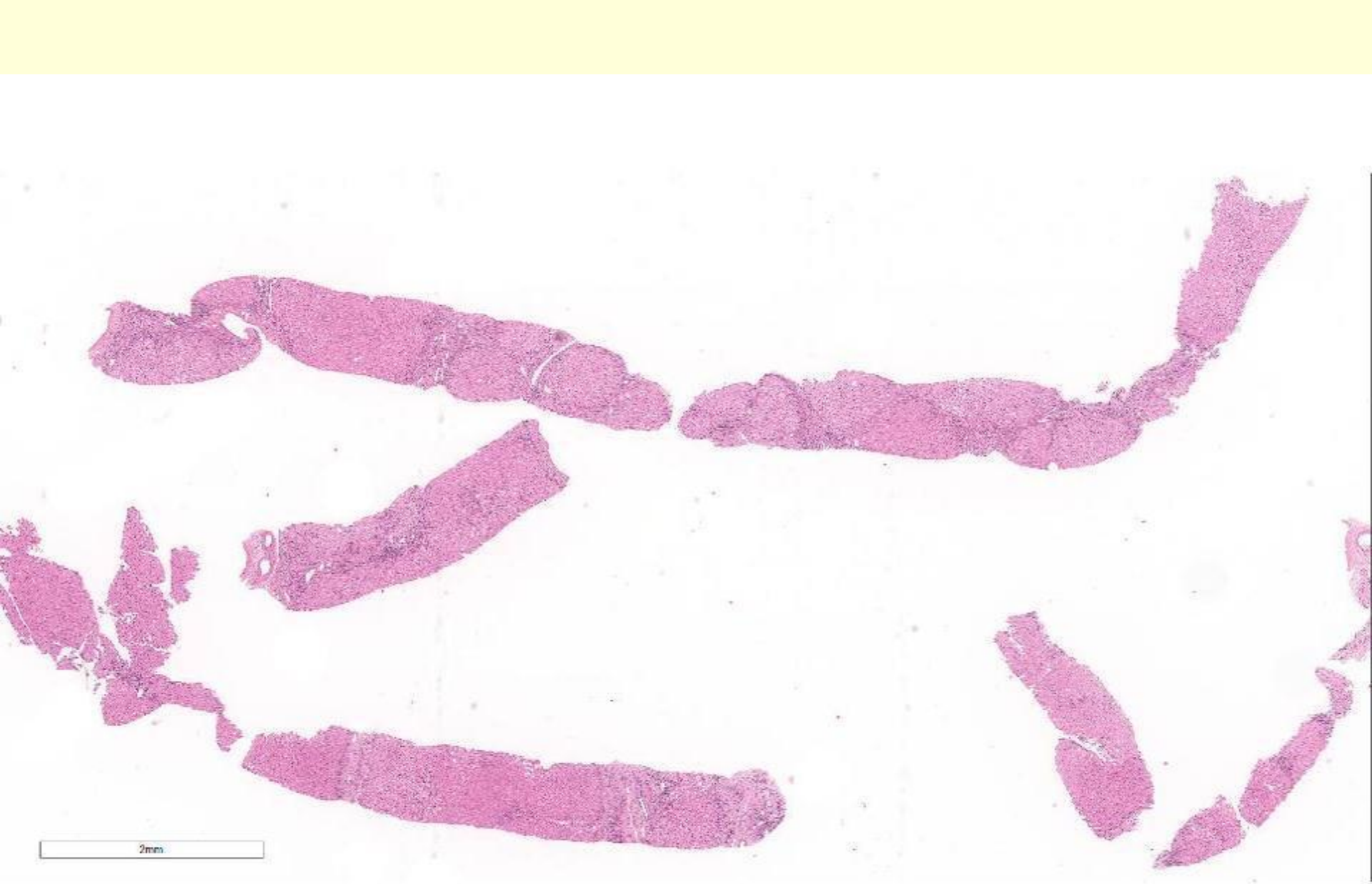
– primarily for t**rails** and long term follow-up of NASH only

Scoring NAFLD

- French group *Bedossa Hepatology 2012*, for **spectrum of NAFLD**, (when >5% steatosis), originated in morbid obesity patients.
- Algorithm to separate normal, NAFLD and NASH; validated in metabolic syndrome
- **SAF score** – steatosis (0-3), activity (0-4; ballooning & inflammation), fibrosis (0-4)
- Correlated with diagnosis of NASH (activity >2) and ALT levels

Case 4

- 42/F HCV. Clinically cirrhotic. Tissue confirmation please.
- EPSR, orcein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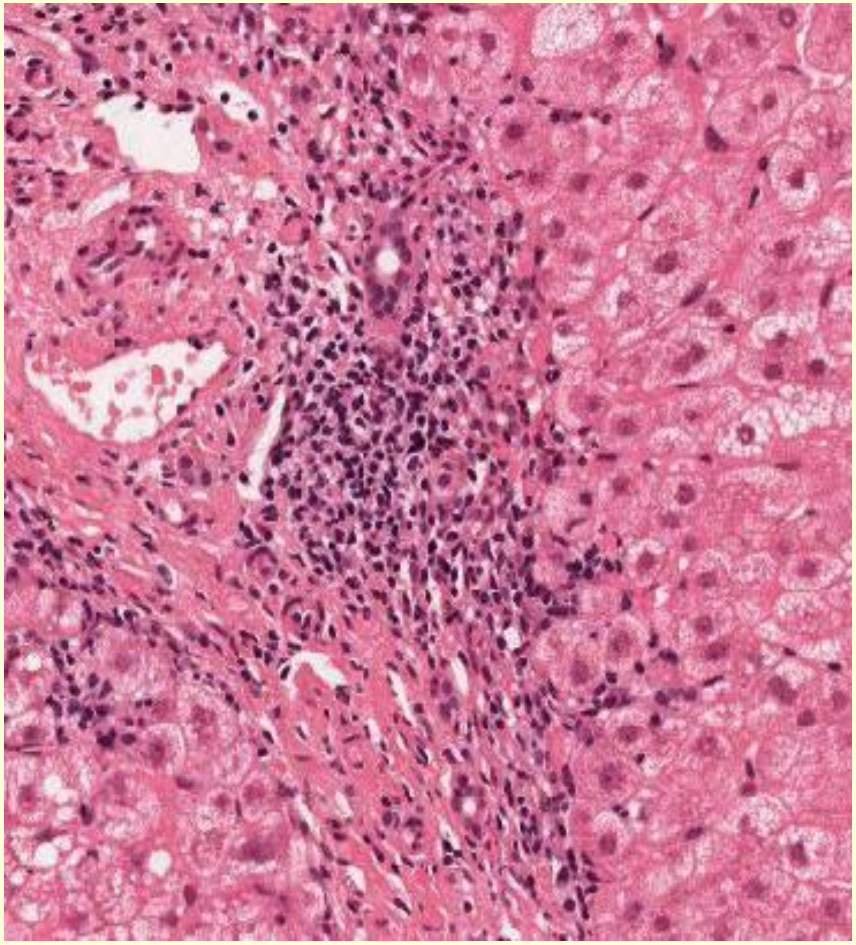
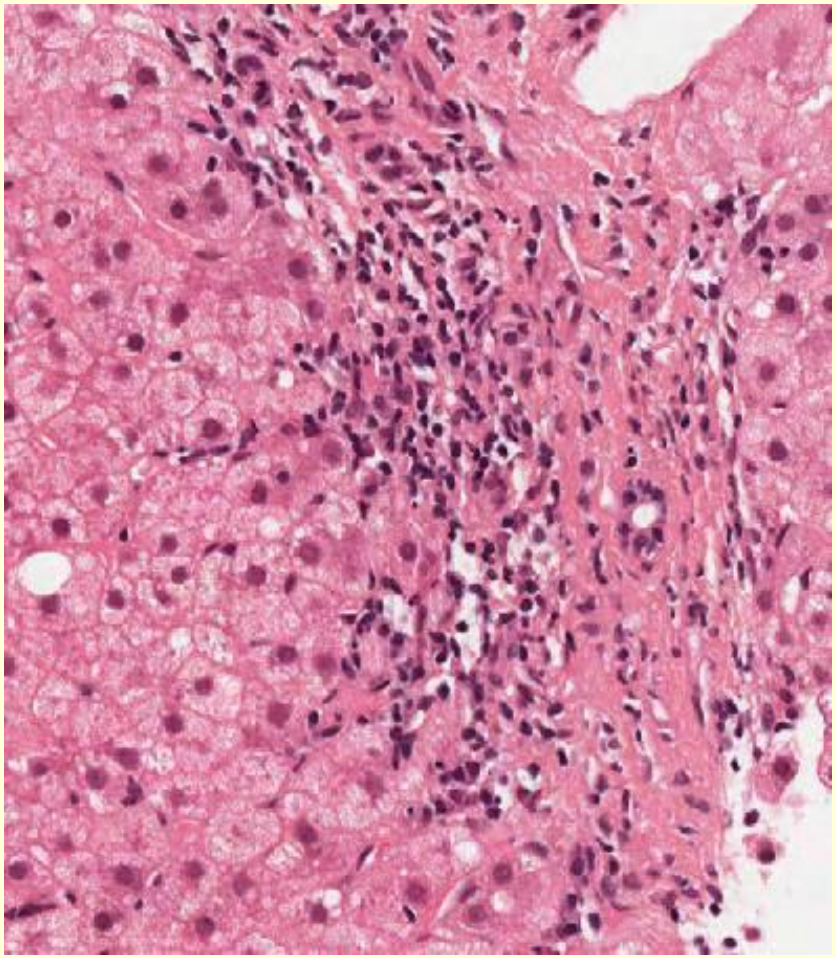
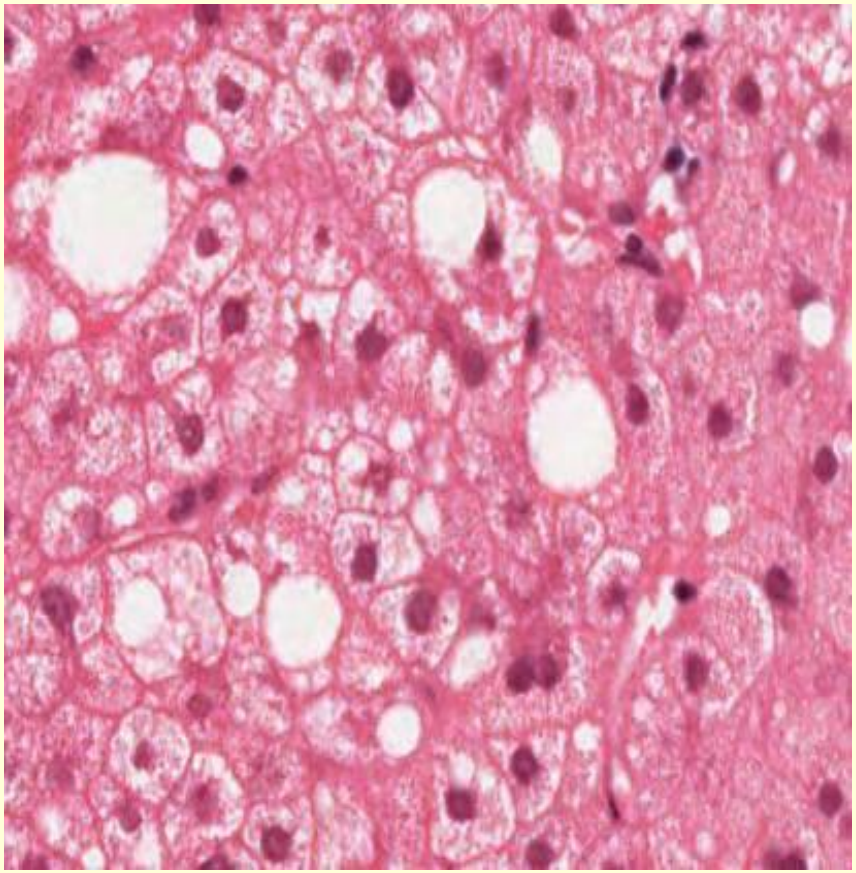
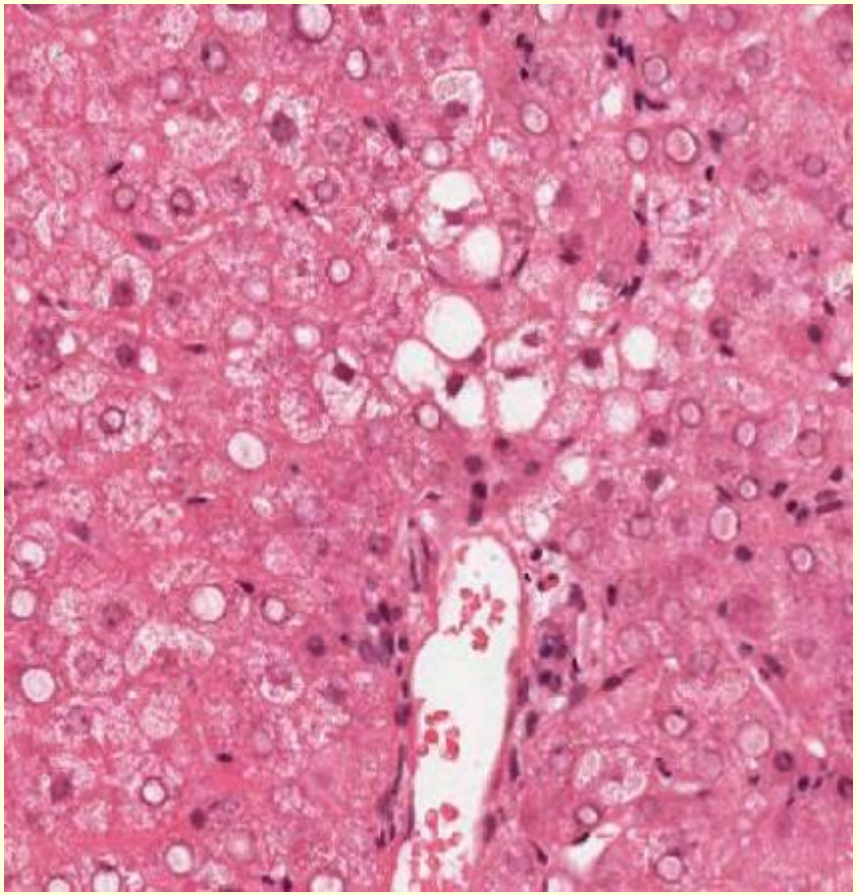
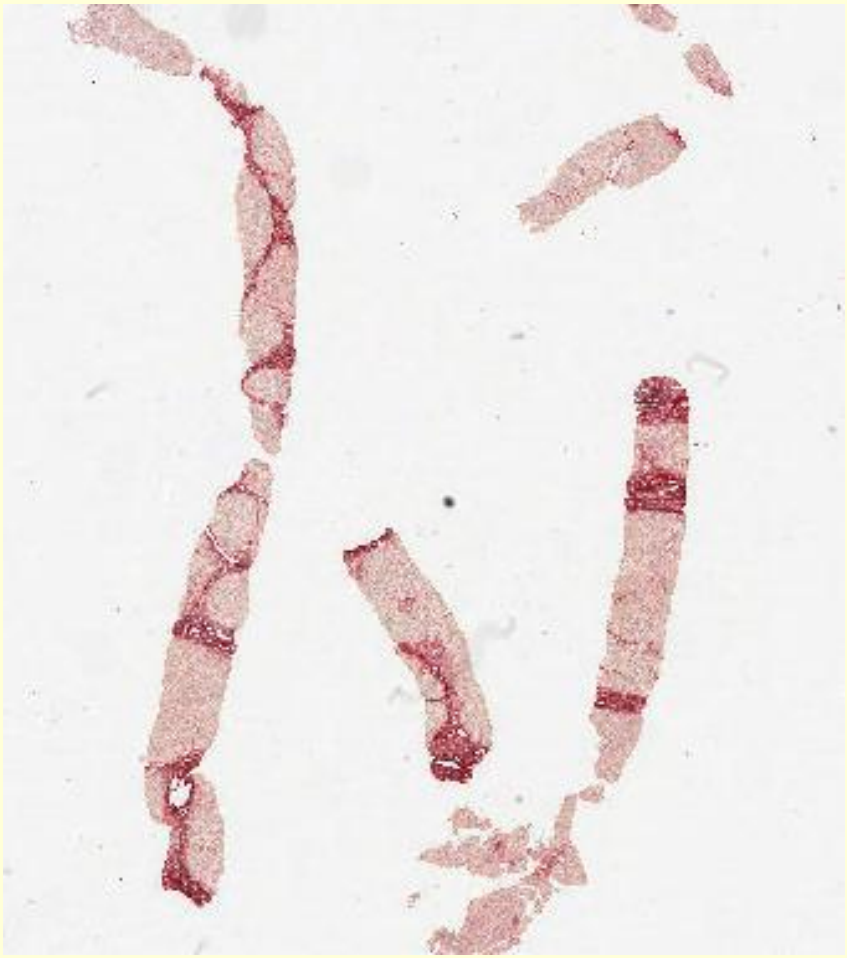
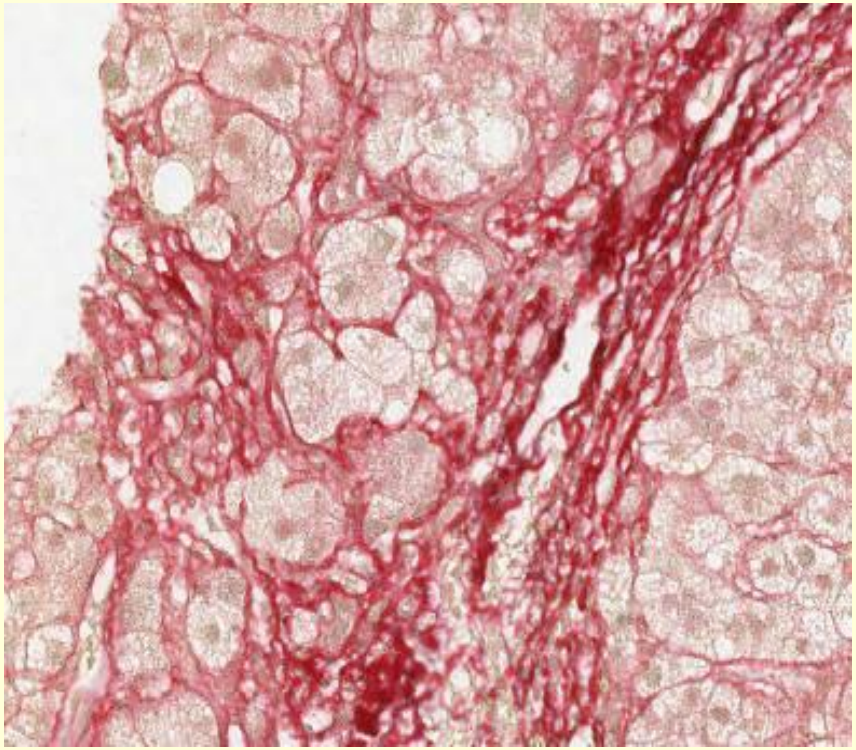




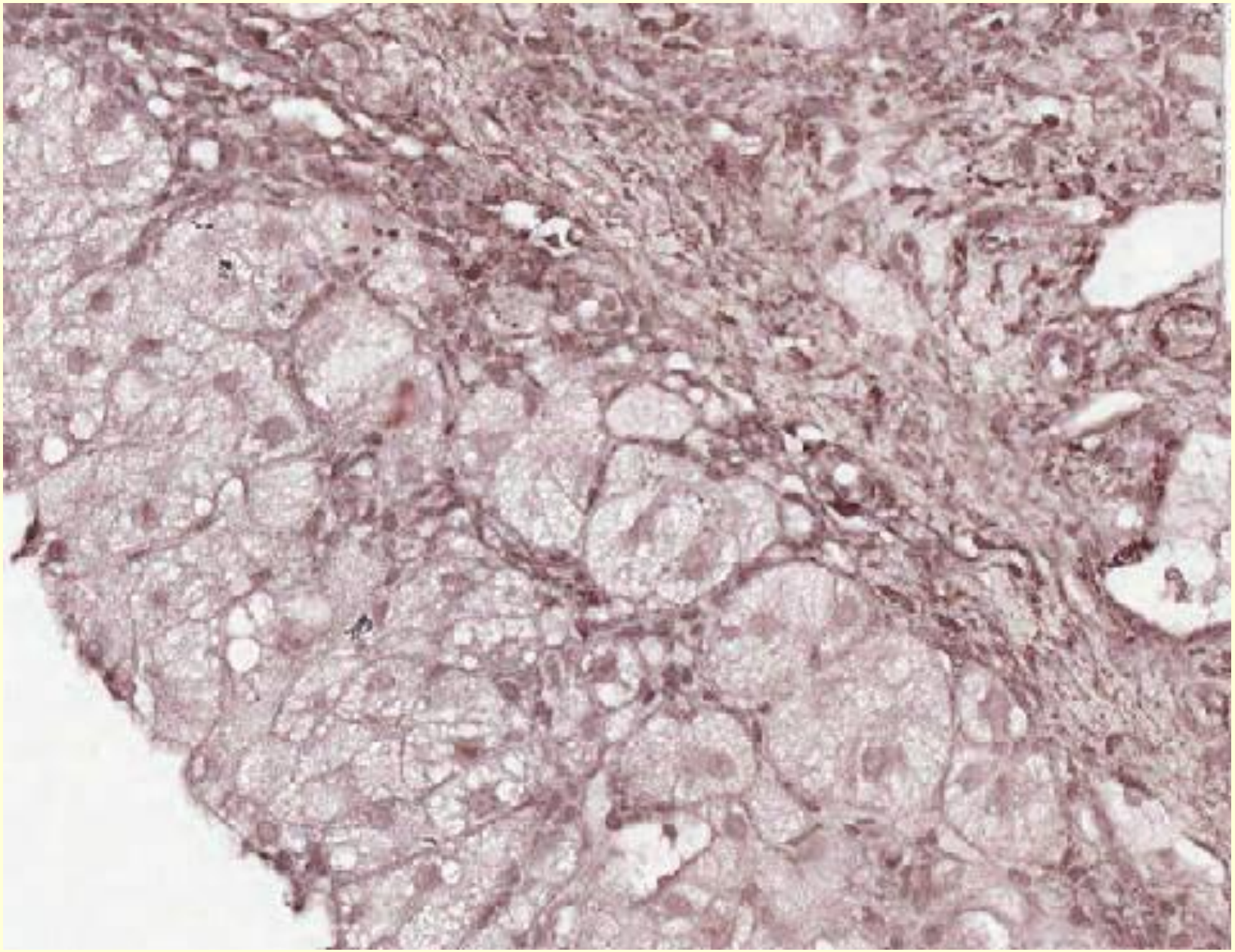








EPSR



Orcein

Diagnosis case 4

- Cirrhosis
- Overall mild chronic hepatitic activity in keeping with chronic HCV infection
- With mild steatohepatitis
- F/I – patient also diabetic

Is it a real issue? CUH study on Dual Pathology

2003, of 480 consecutive medical liver biopsies

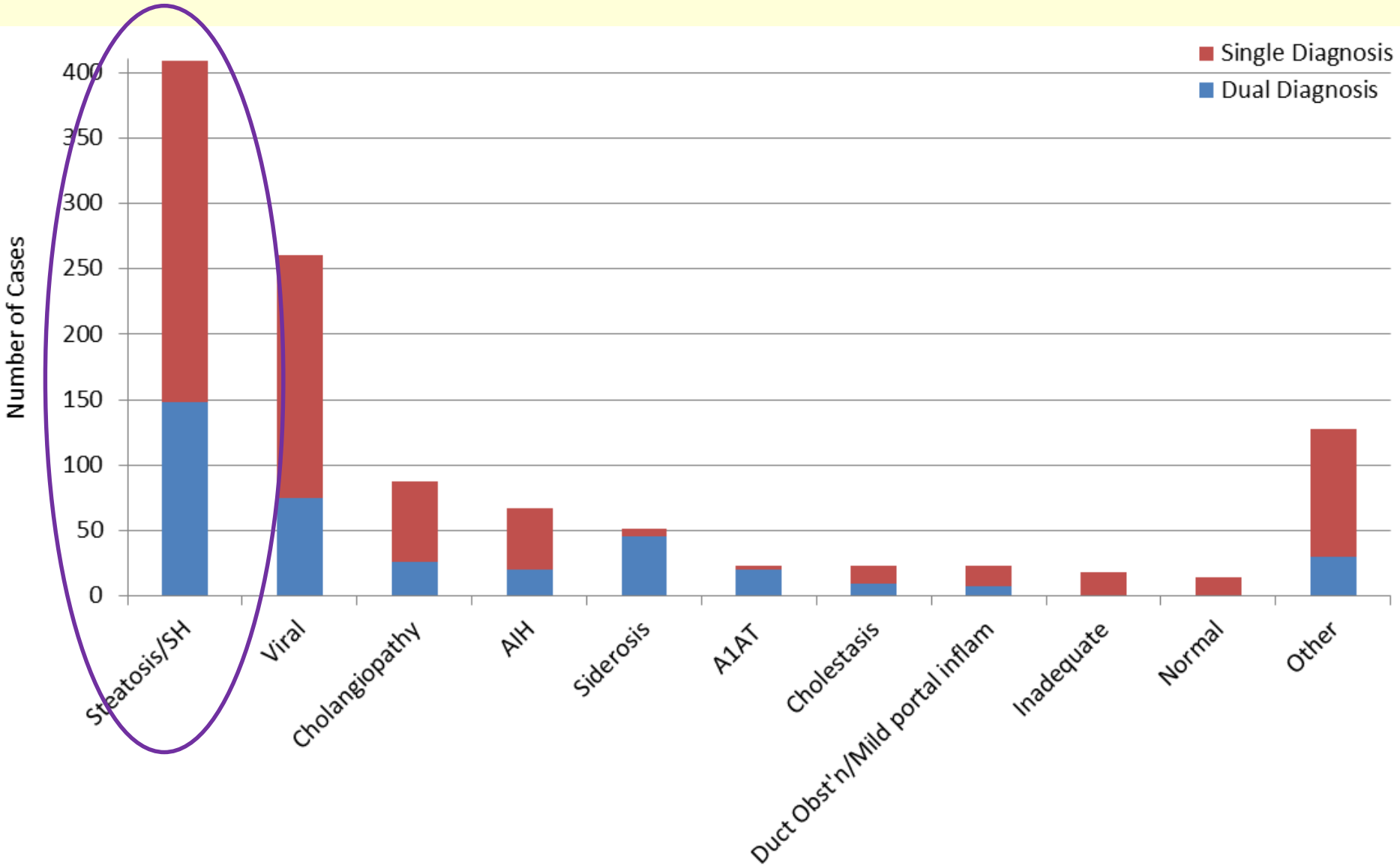
- 85 (18%) >= two significant pathologies
- 4 (1%) three pathologies

2013, of 941 consecutive liver biopsies

- 189 (21%) >= two pathologies
- 9 (1%) three pathologies

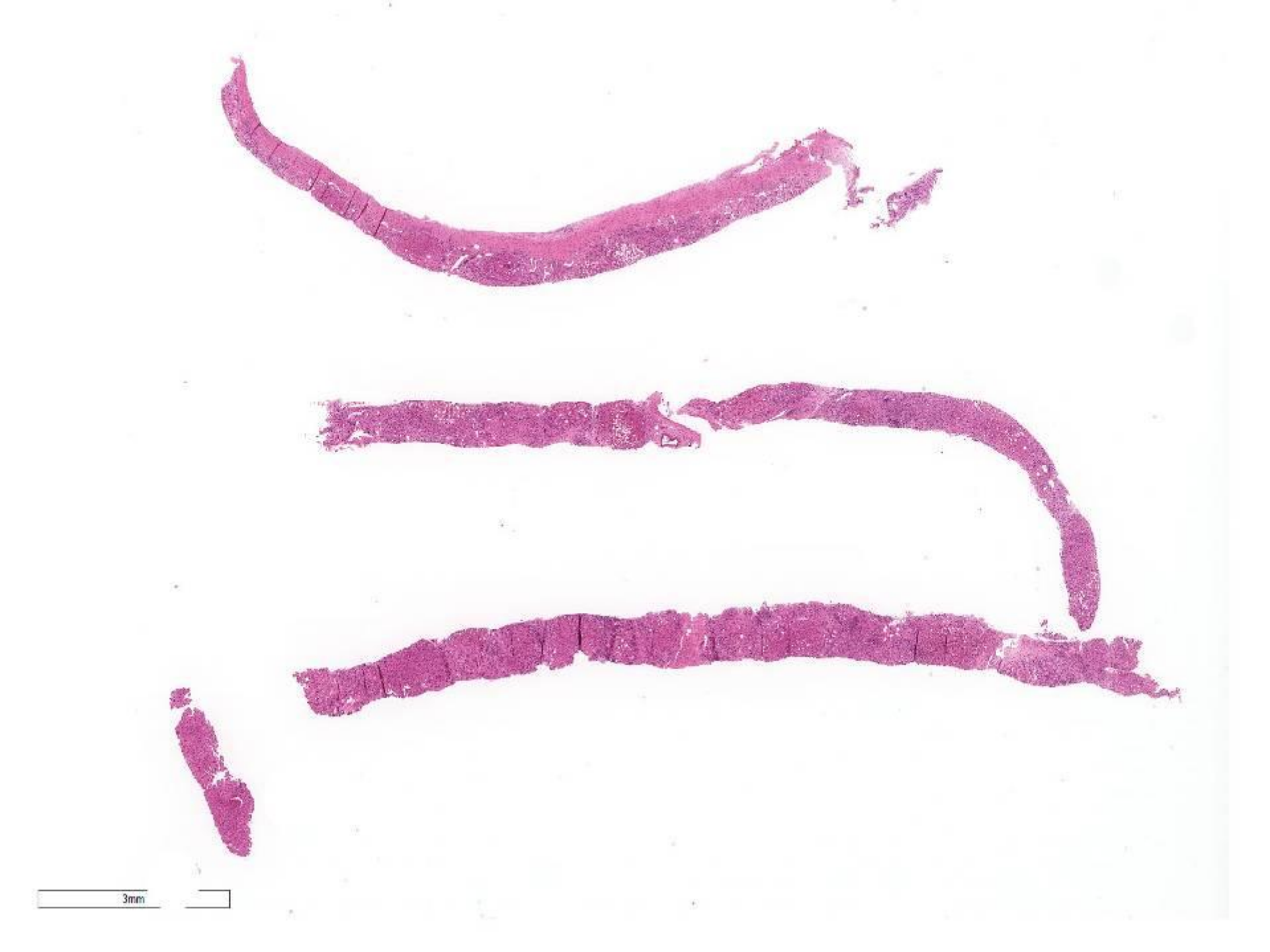
Dual Pathology (2013)

Number of cases with each pathology; including the number that are present as part of a dual pathology. Pathology present based on microscopy not the clinical impression.

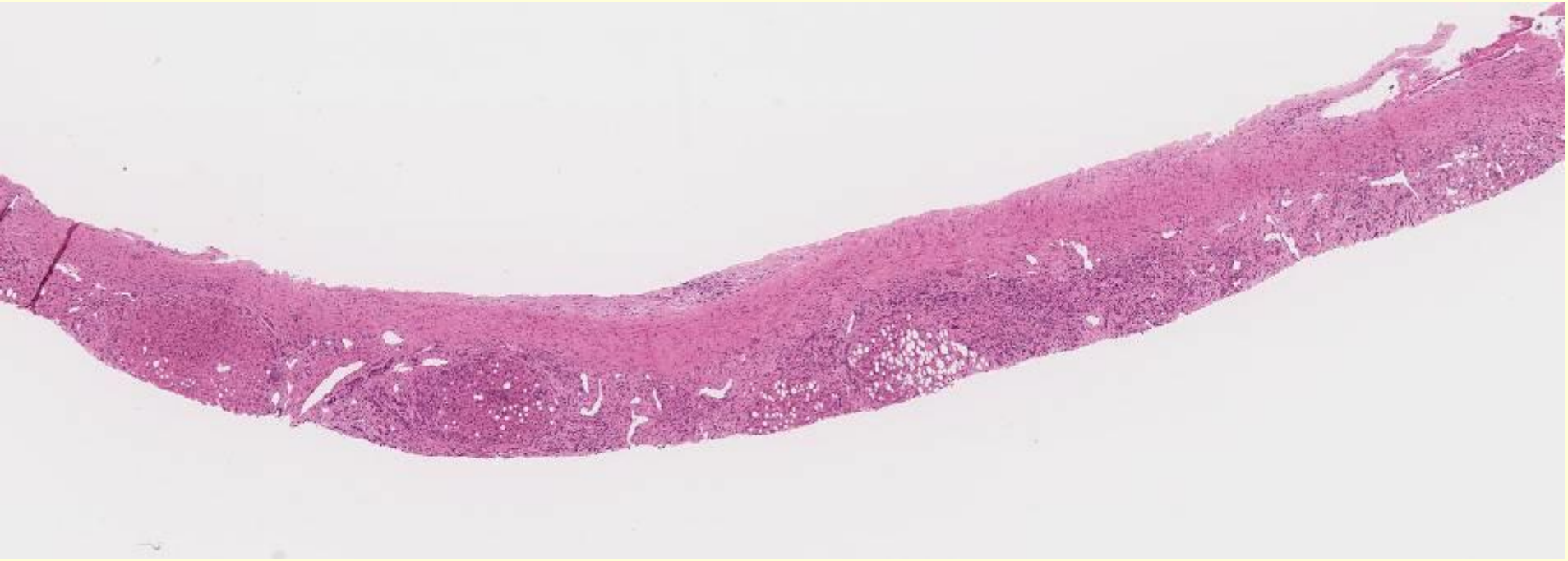


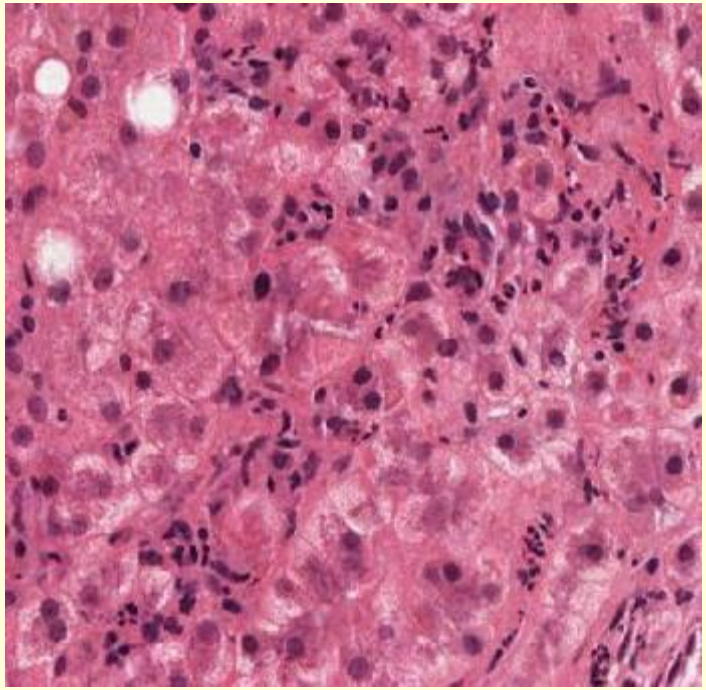
Case 3

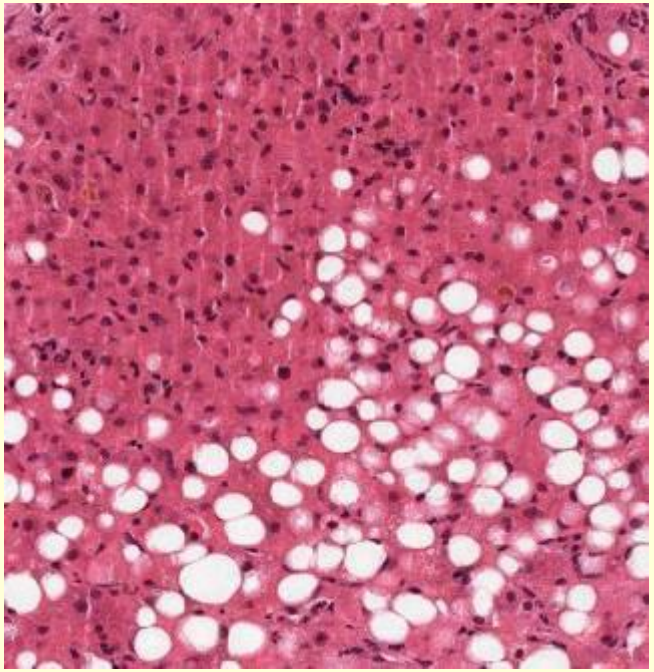
- 53/M Jaundiced 2-3 weeks, ascites, bilirubin 354 (0-20 umol/L). TJ biopsy.
- CAB, orcein, PASD, Retic

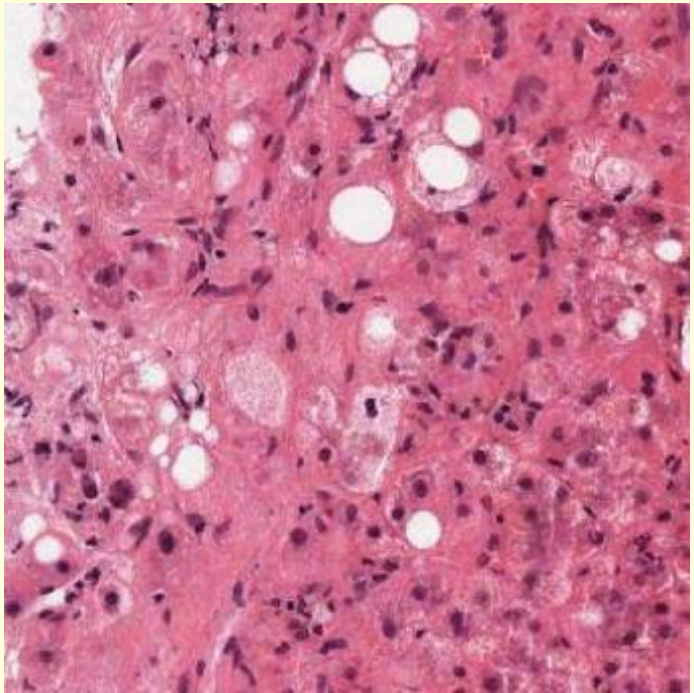

3mm

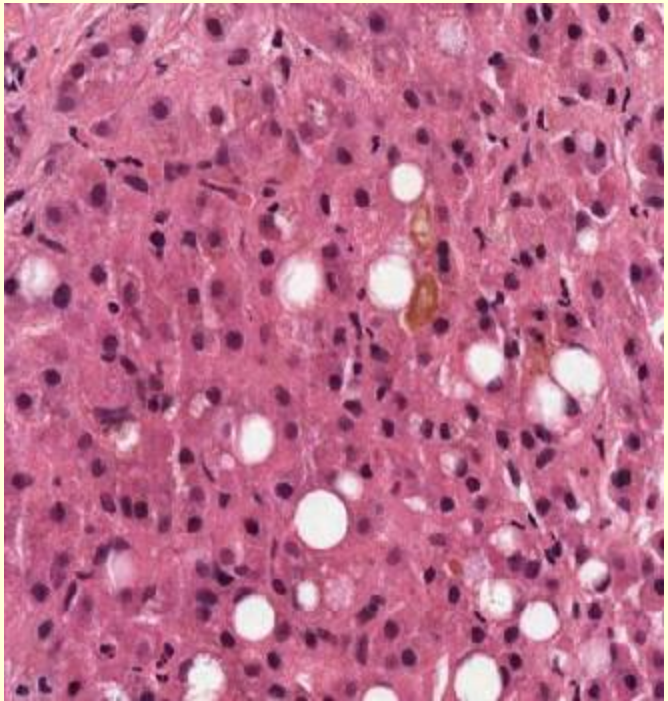
reticulin

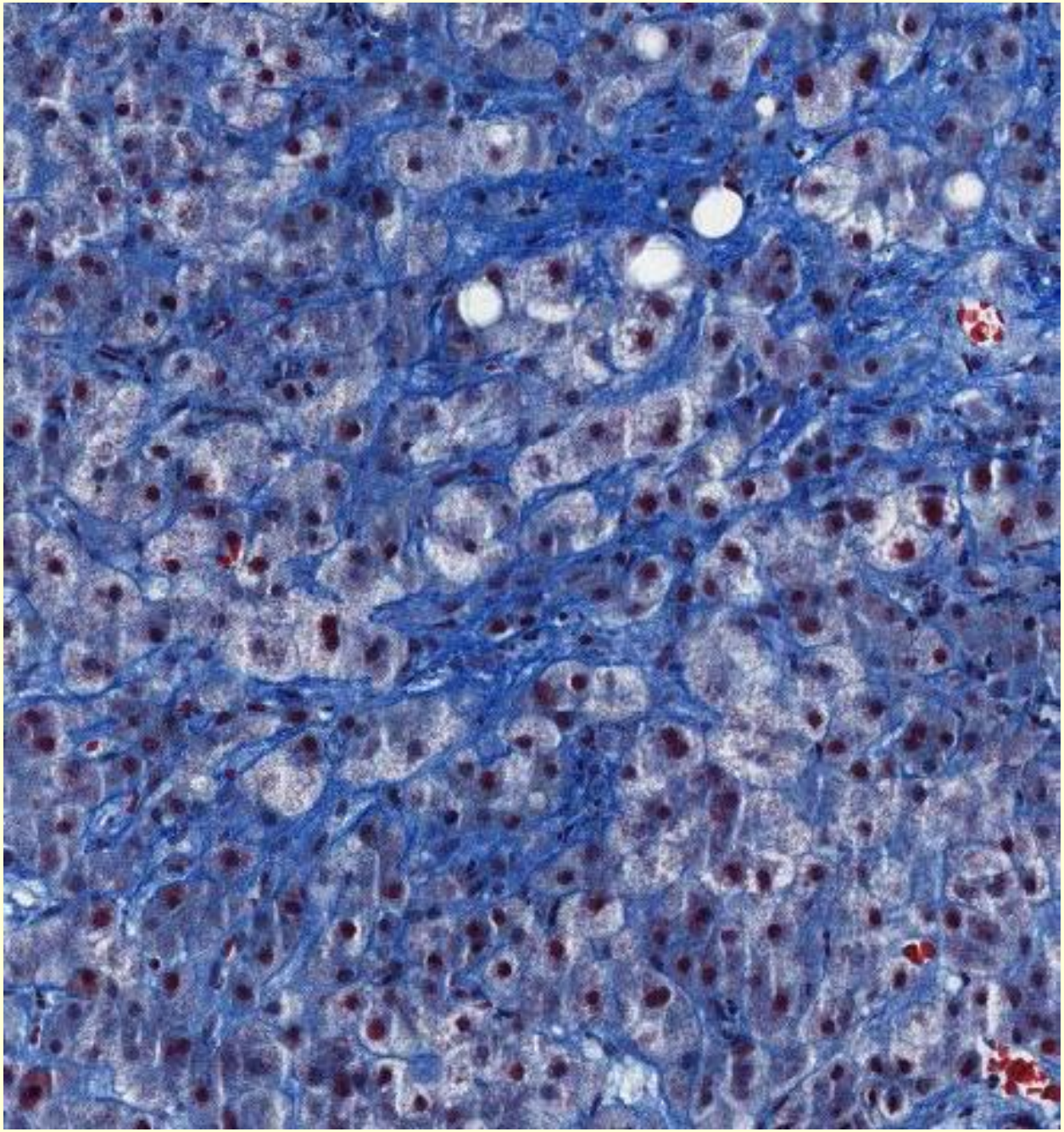




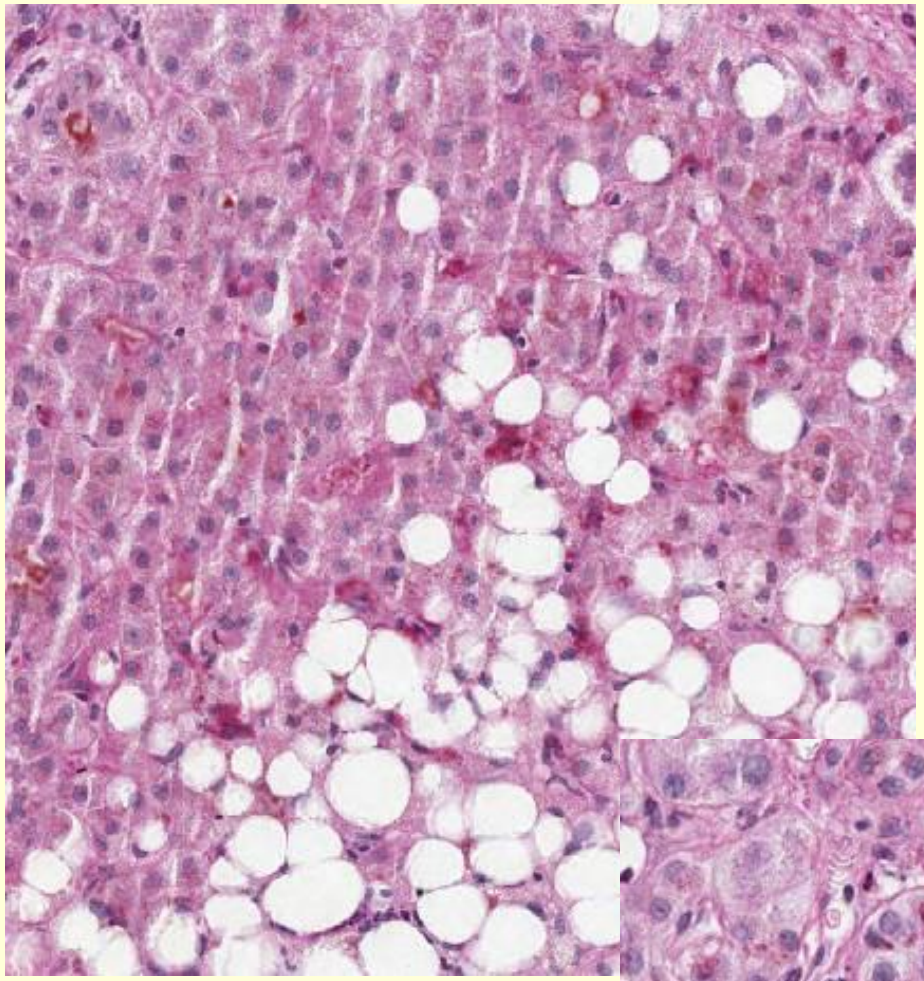




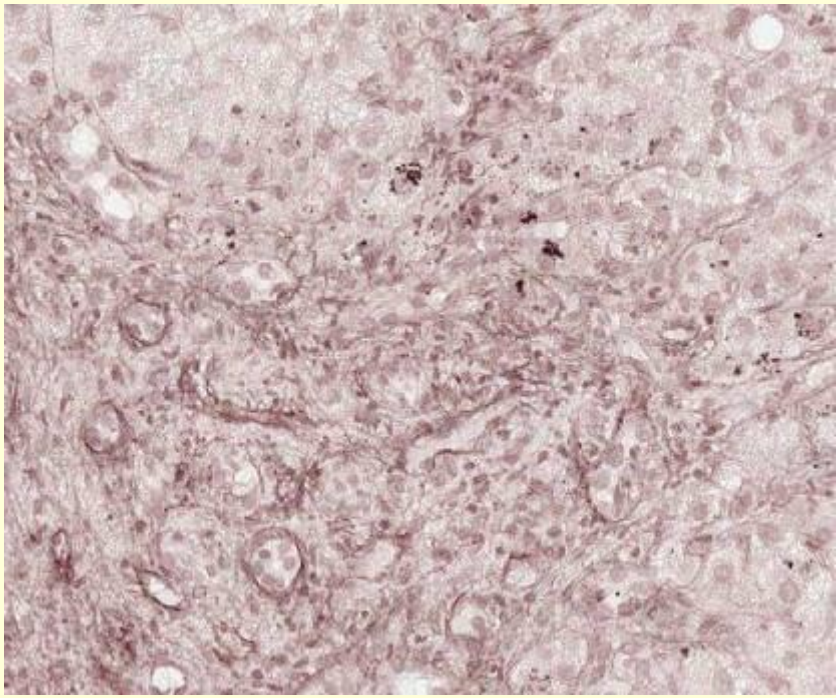




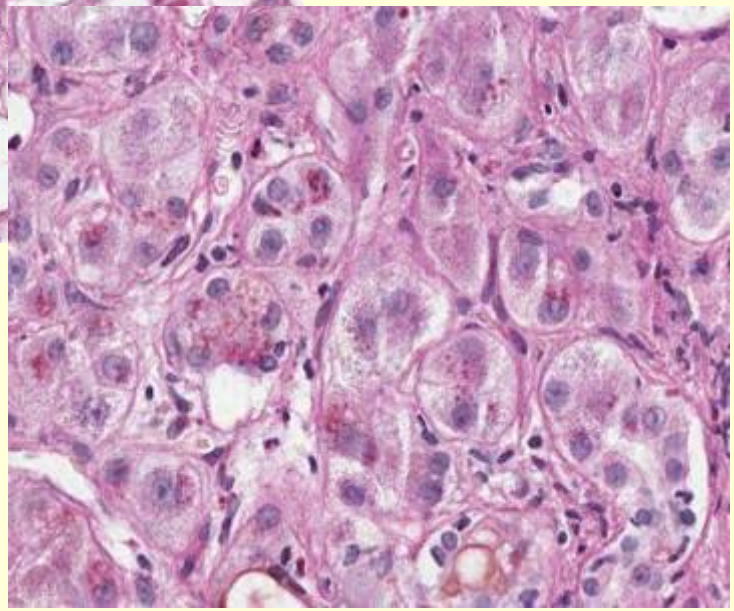
CAB



PASD



Orcein

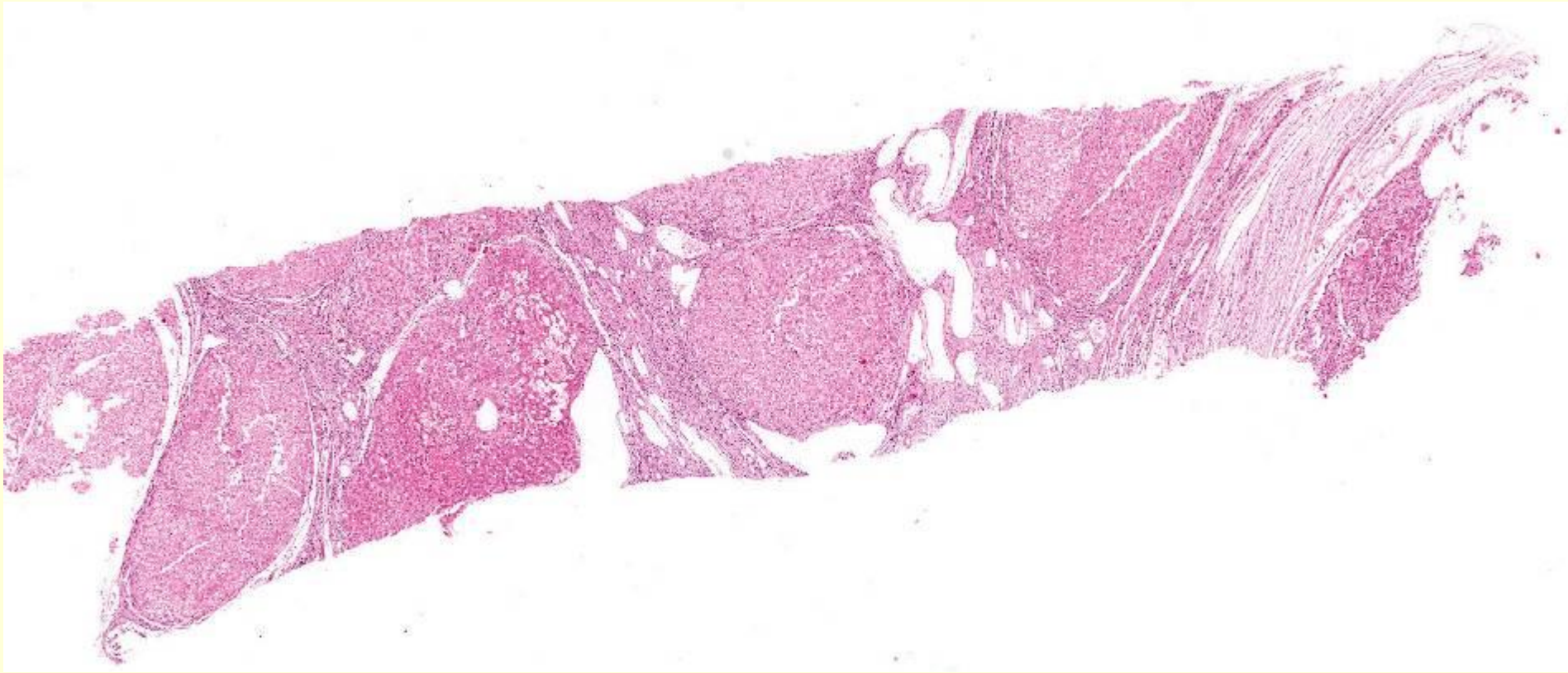


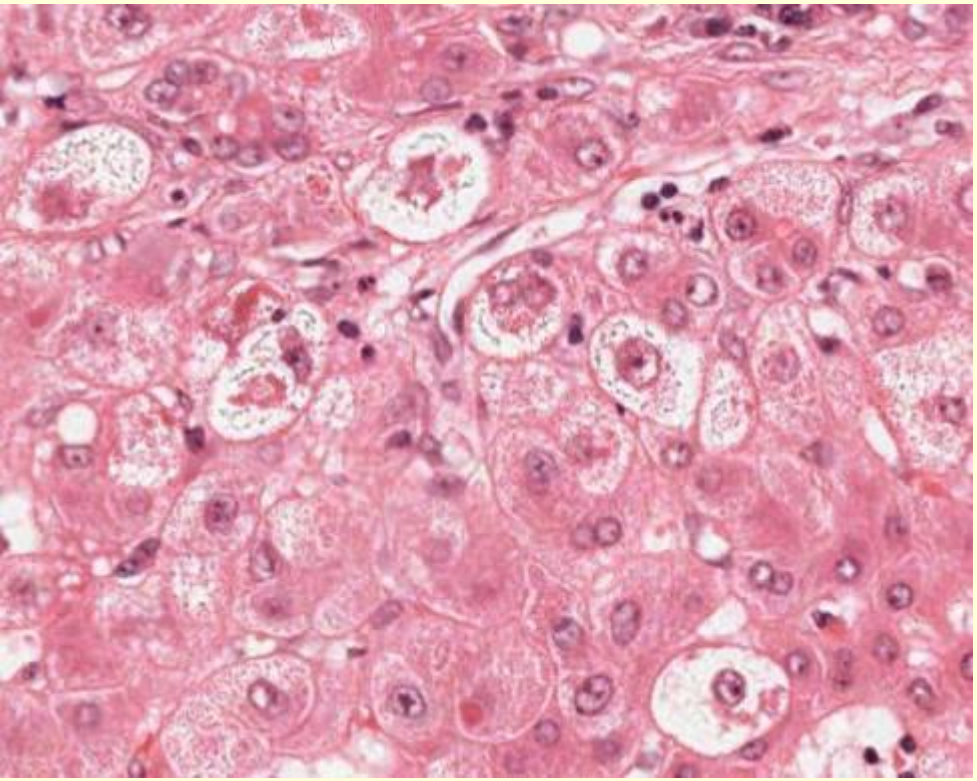
Diagnosis case 3

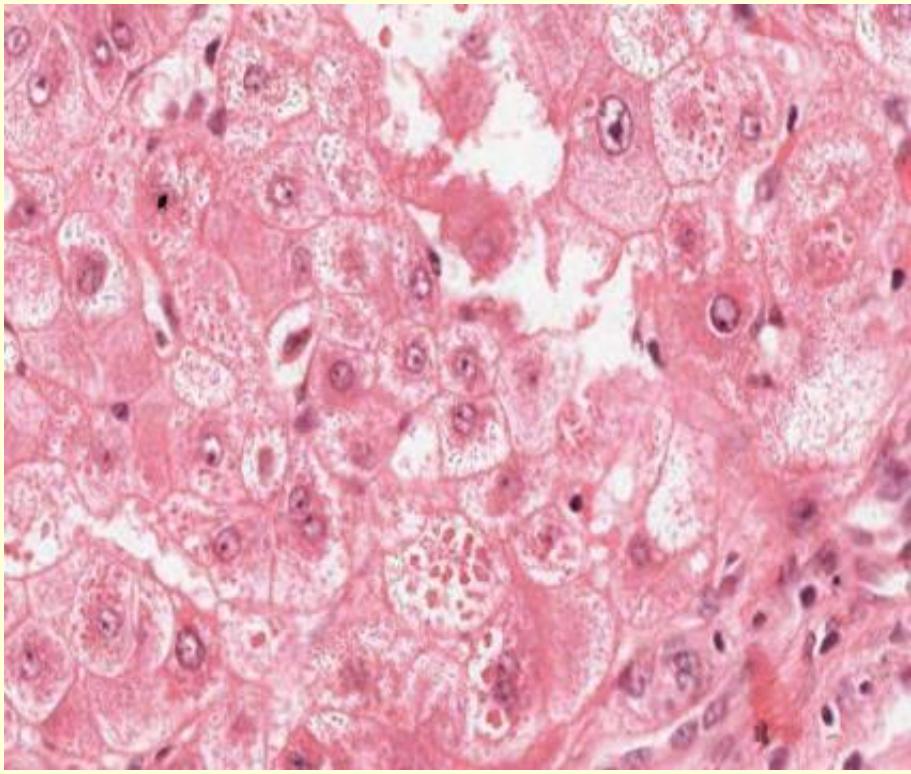
- Cirrhosis
- Steatohepatitis, cholestasis, regeneration (6 weeks abstinence)
- First presentation of Alcoholic liver disease with decompensation.

Case 5

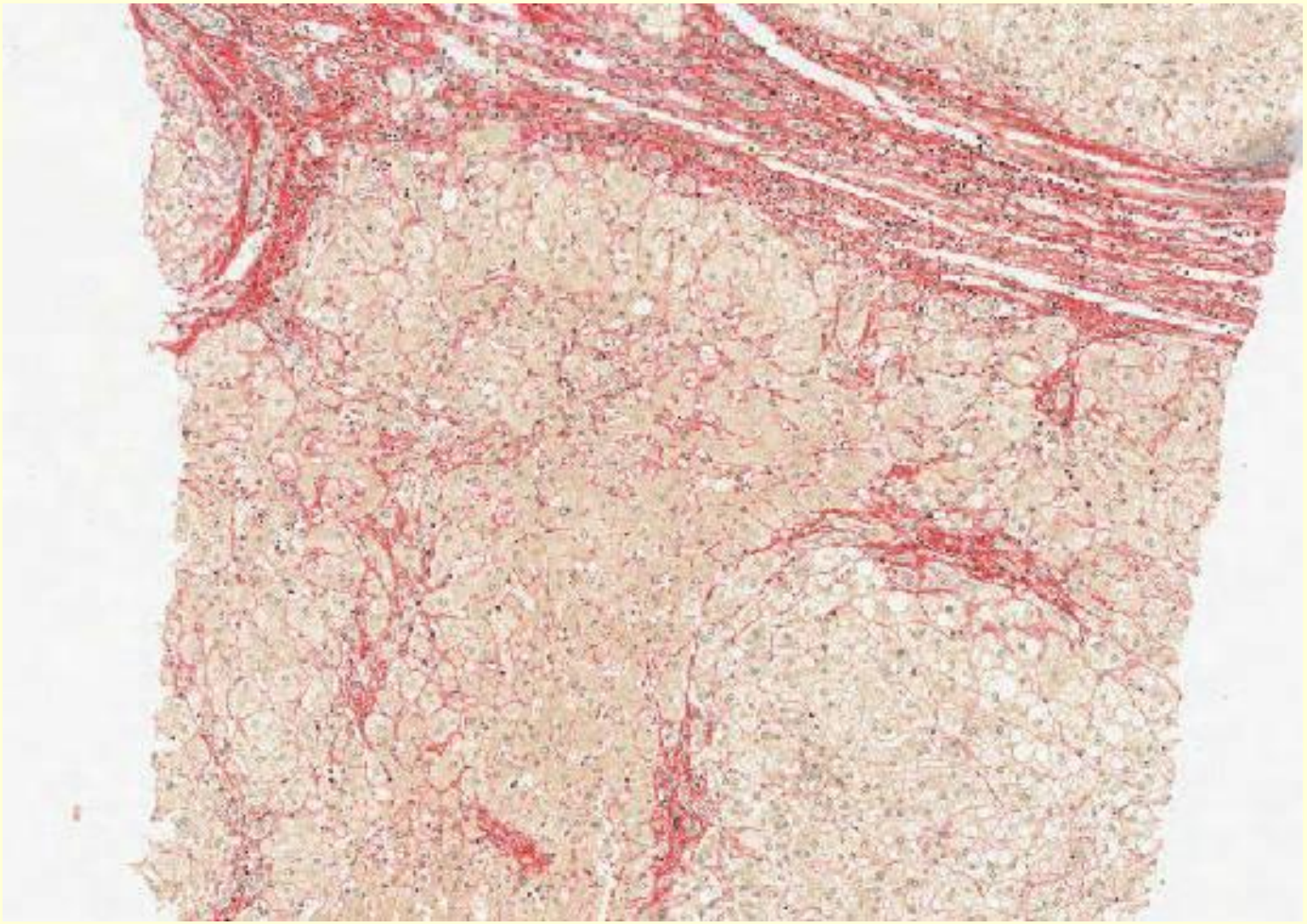
- 65/M Cryptogenic cirrhosis
- All stains – apart from Perls



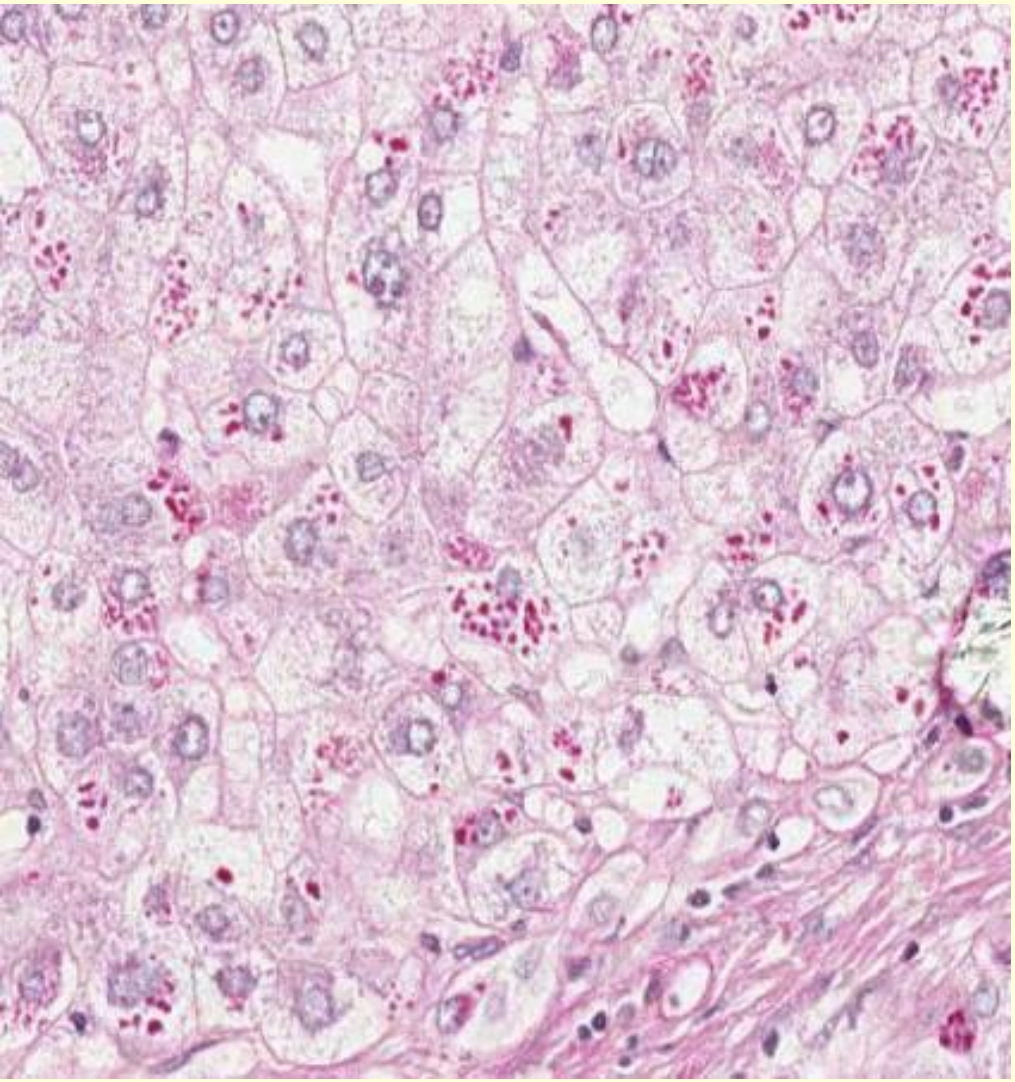




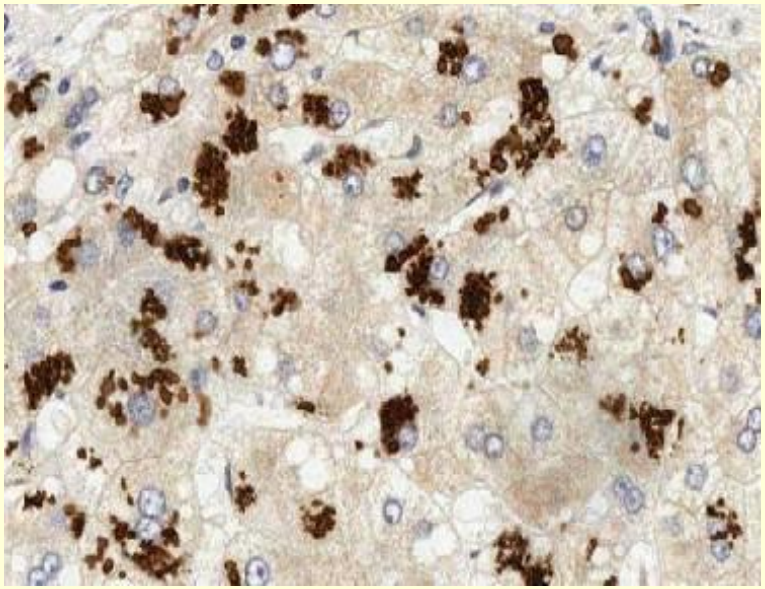
Special stains…



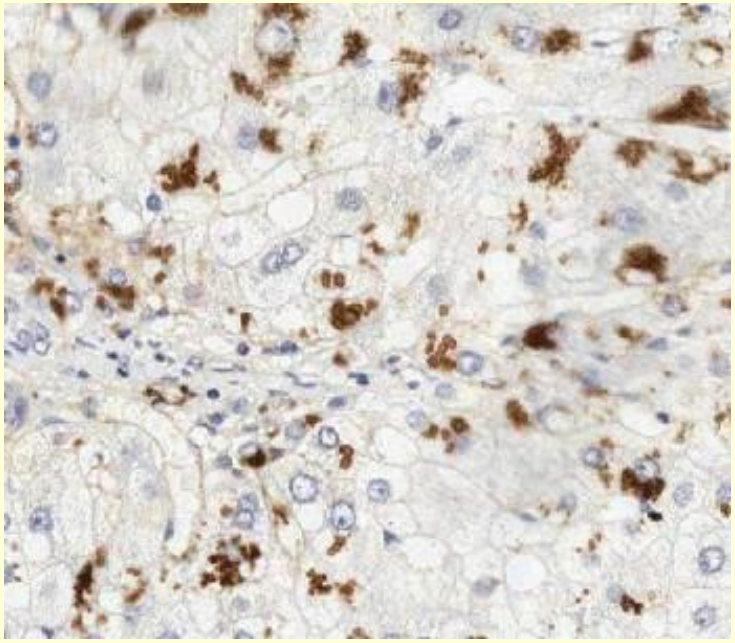
EPSR



PASD



Alpha-1 antitrypsin



PiZ antigen

Diagnosis case 5

- Cirrhosis
- Steatohepatitis, presumed NAFLD
- Abnormal phenotype for Alpha-1-antitrypsin (serum level in normal range)

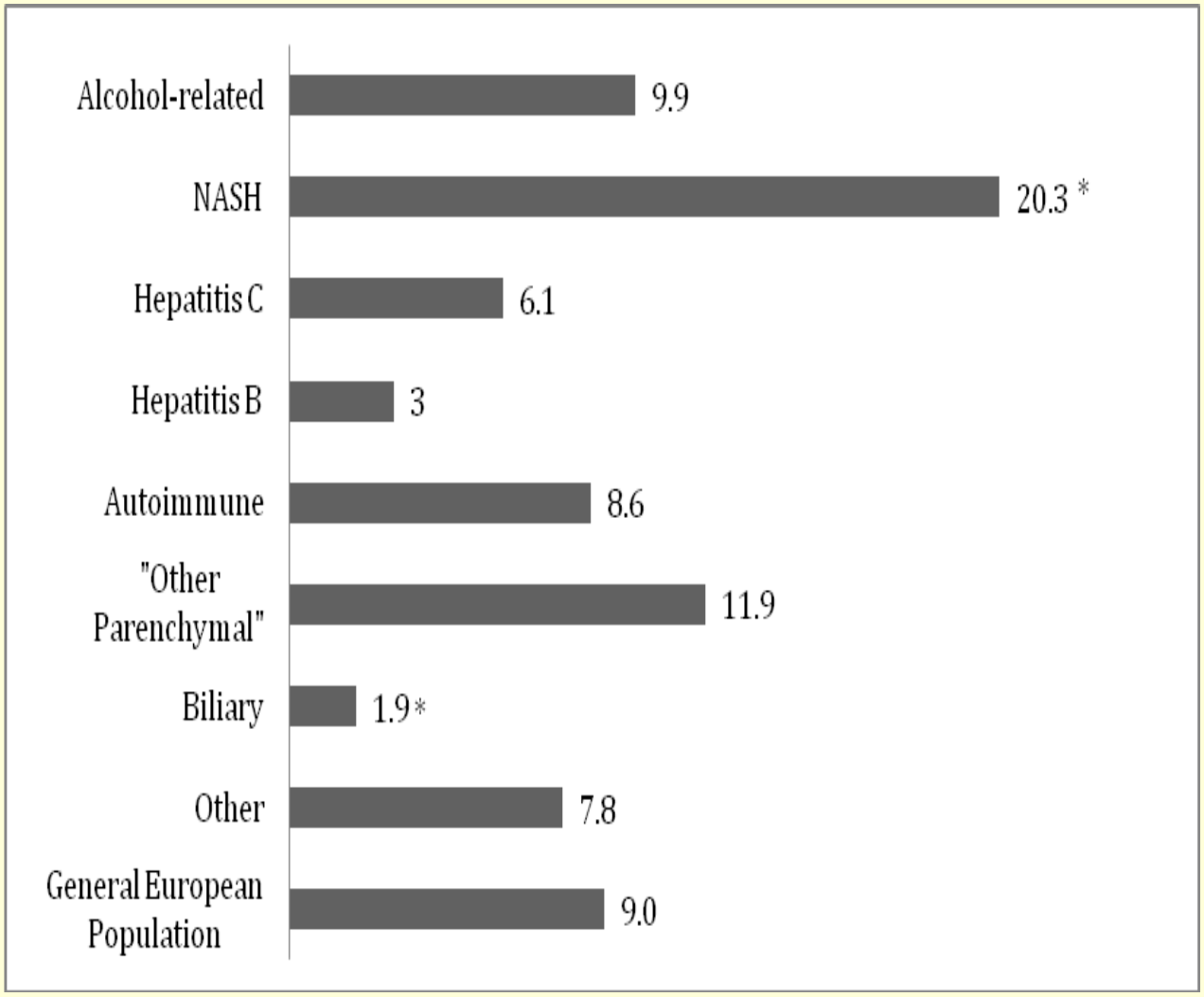
Alpha-1-Antitrypsin

- Two main variants; S (60% of wild type) ~ 6.2% prevalence, Z (10% activity) ~ 2.7%
- Homozygous PiZZ – clear disorder with emphysema and cirrhosis

  ? Role of Heterozygous in chronic liver disease
- CUH study >1000 pts OLT assessment
  - IsoElectricFocusing and/or histology (PASD & IHC PiZ)

Cacciotolo, Eu J Gas &Hep, 2014

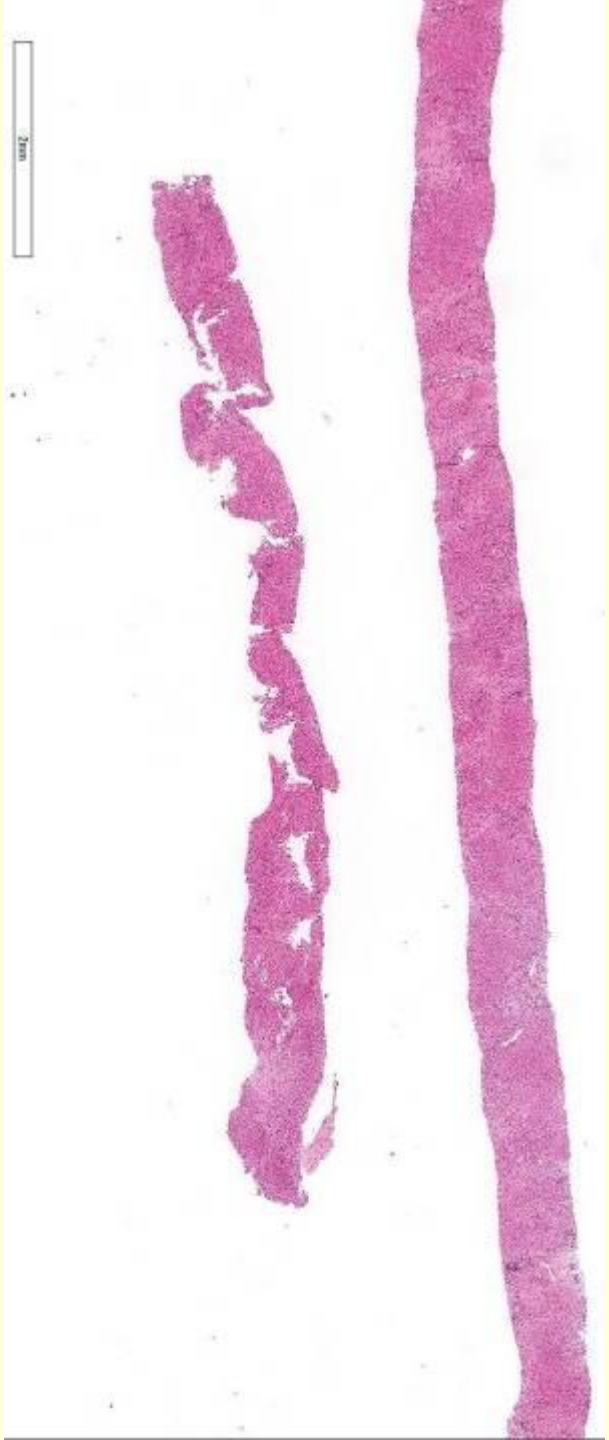
Results

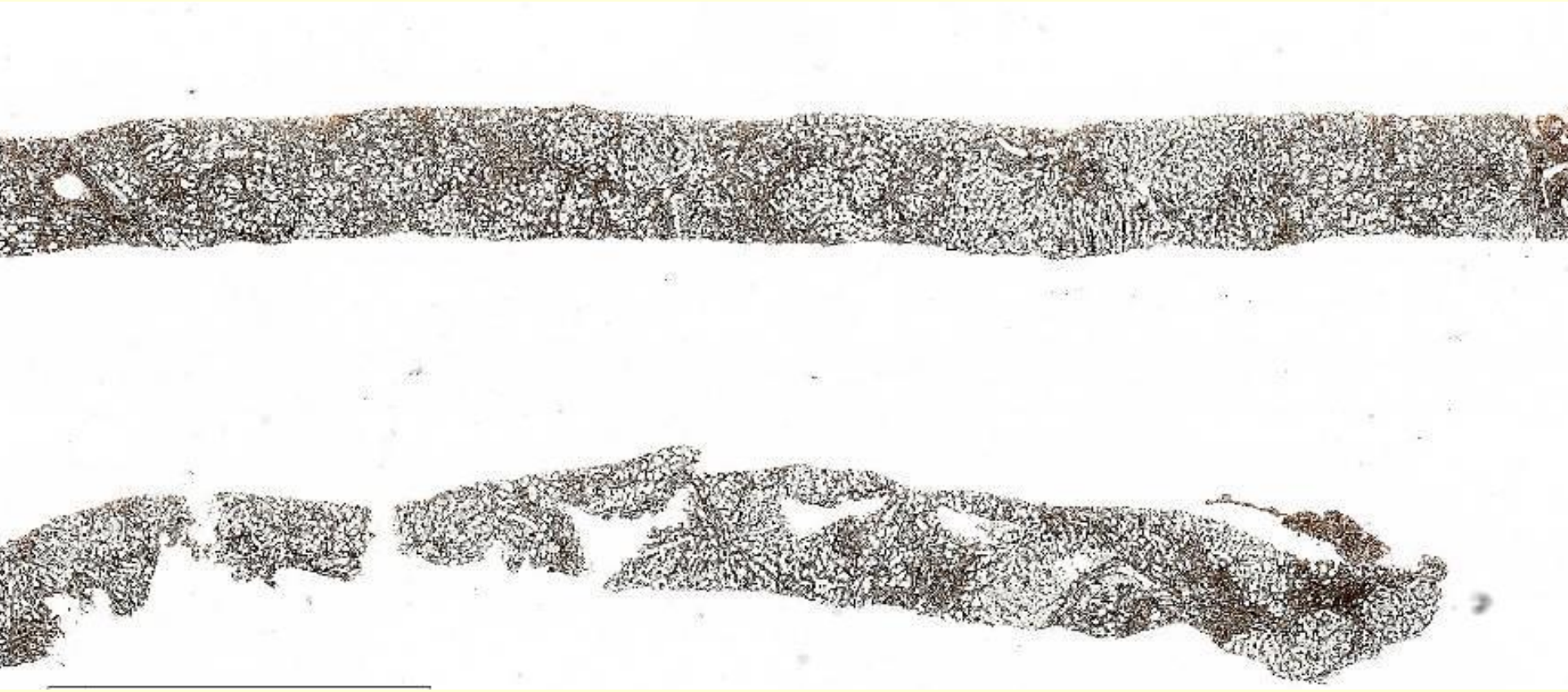


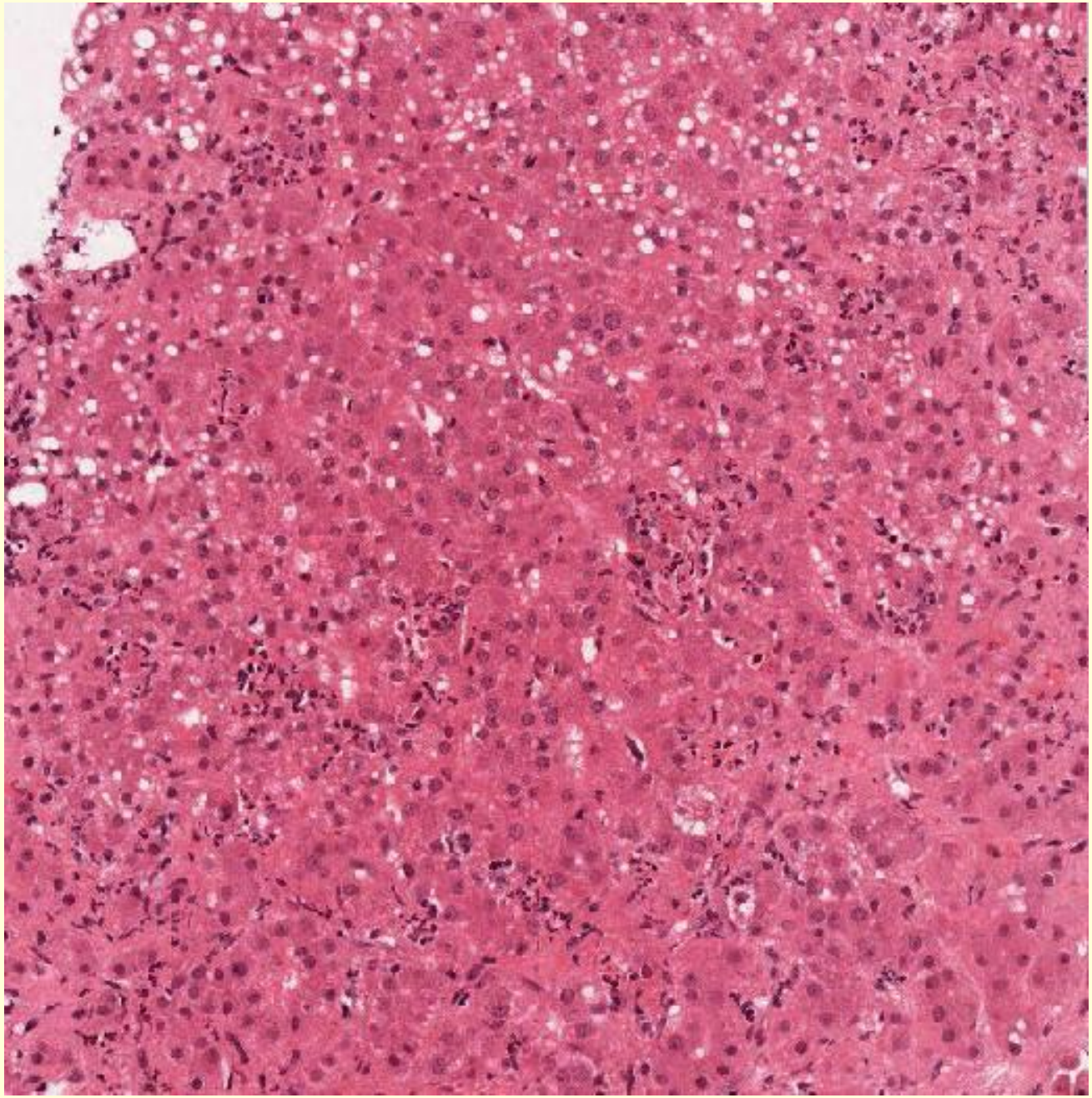
Mean Prevalence of Pi*Z Allele Carriers by disease group

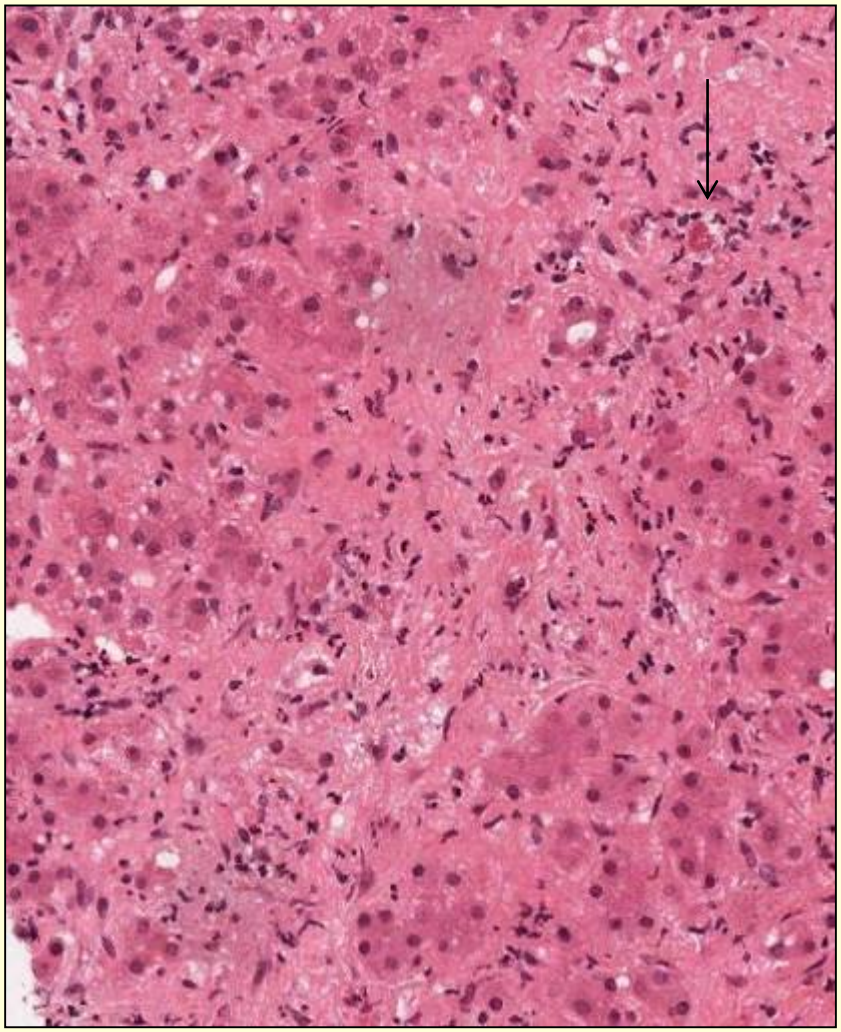
Case 6

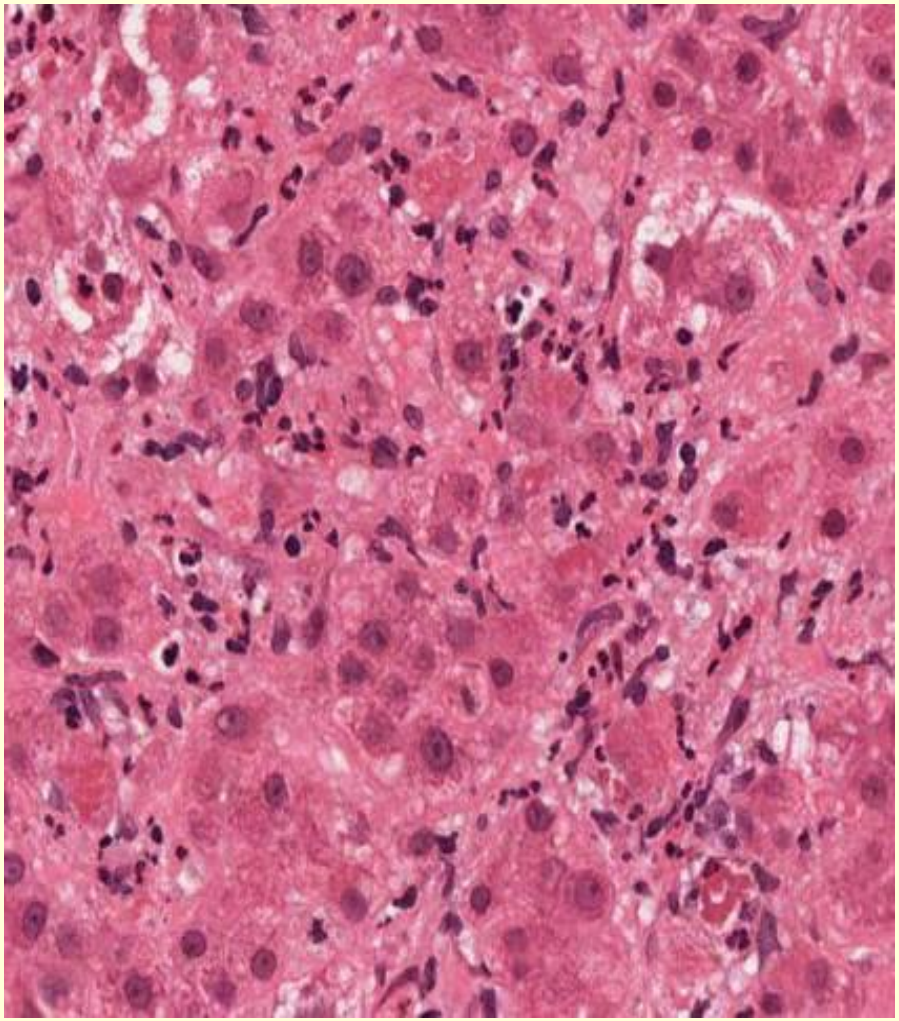
- 42/F known ALD ? AIH .
- Retic , orcein, EVG, EPSR

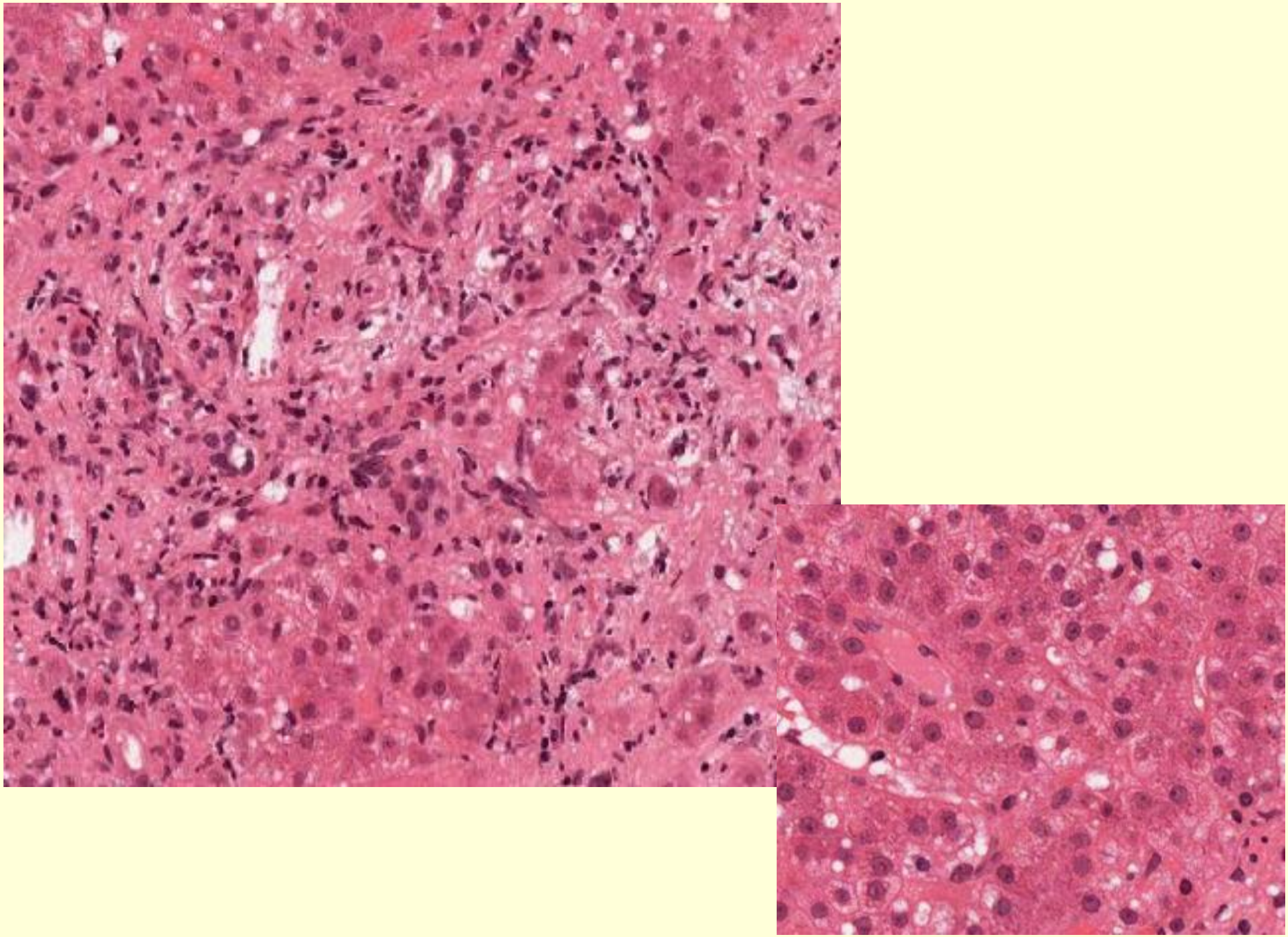

2mm

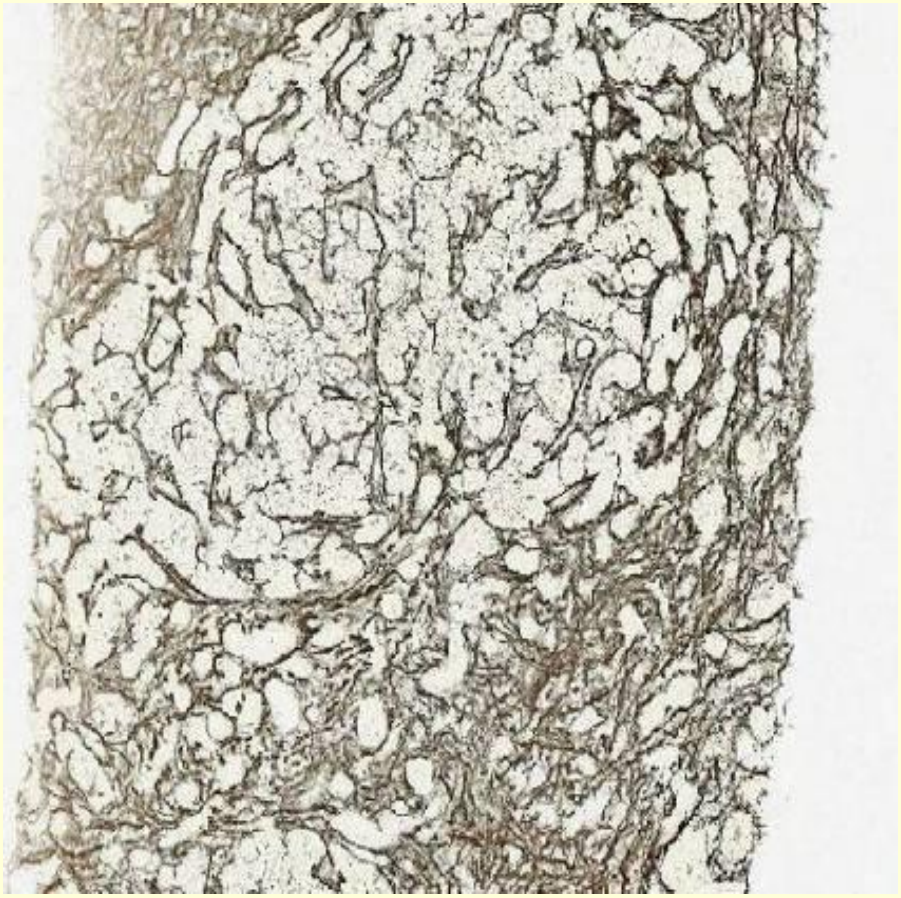




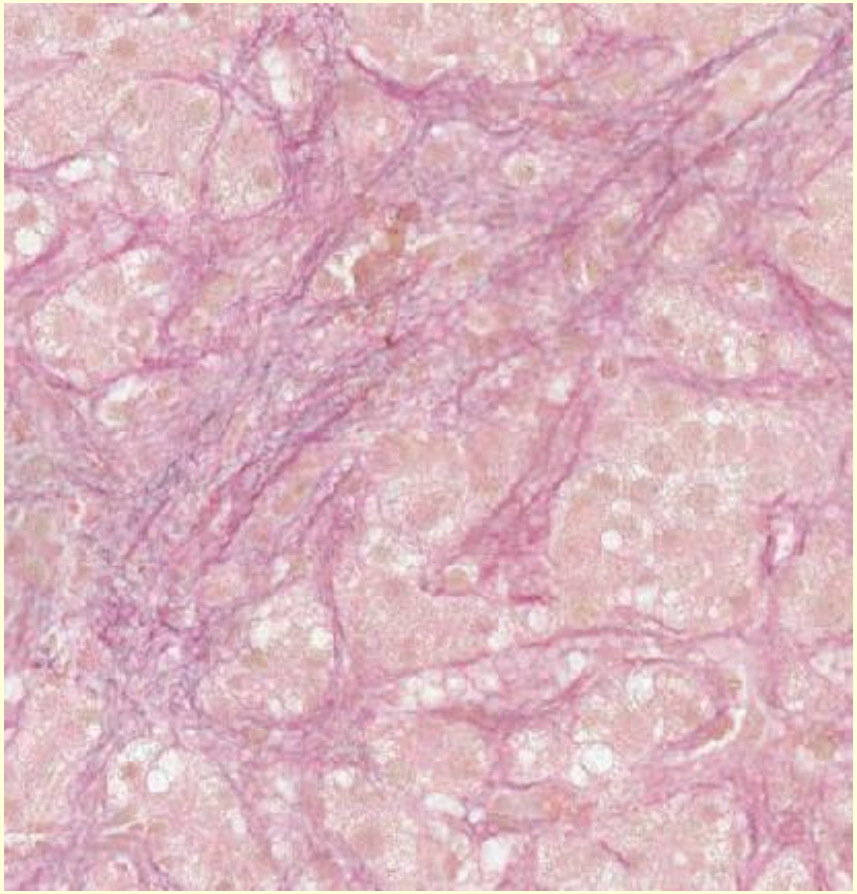








reticulin



EVG

Diagnosis case 6

- Severe fibrosis, central hyaline sclerosis, regeneration
- Florid Steatohepatitis, with little steatosis
- Alcoholic liver disease
- No features of AIH

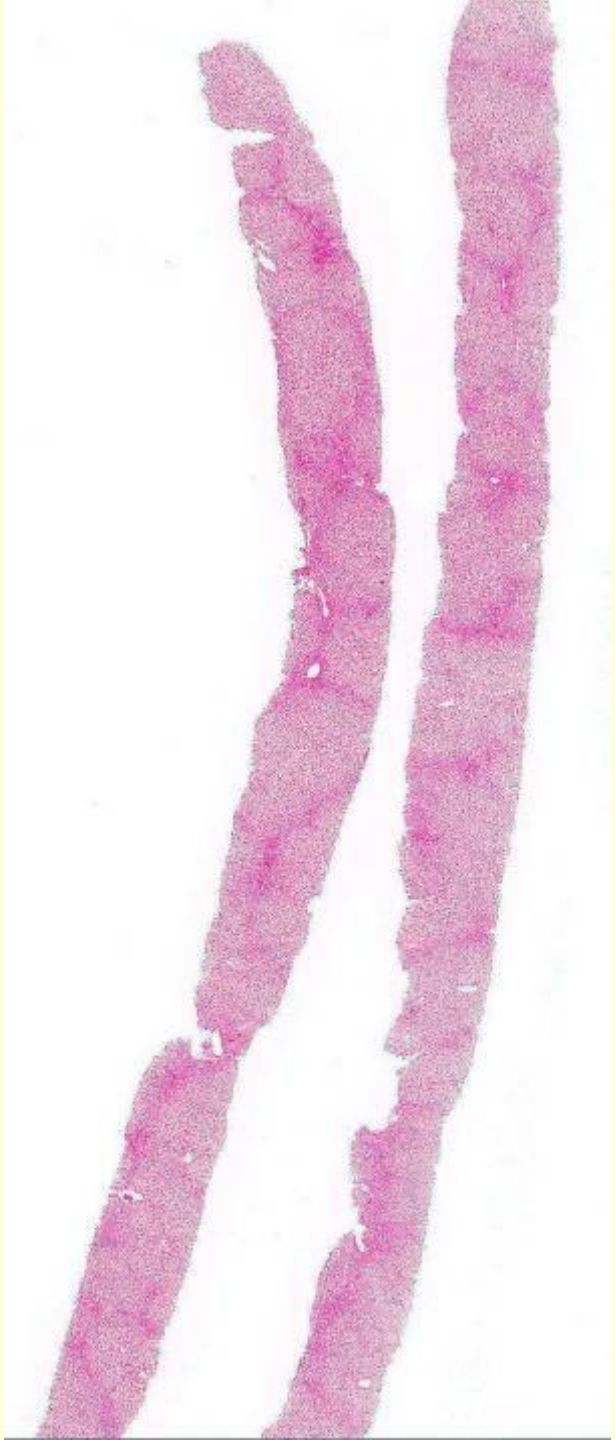
- F/I - IgG 14.2 (6.0-13.0g/l), IgA 4.4 (0.8-3.7g/l), IgM 1.1 (0.4-2.2g/l)
- ANA +ve weak, ANCA, SMA, AMA neg

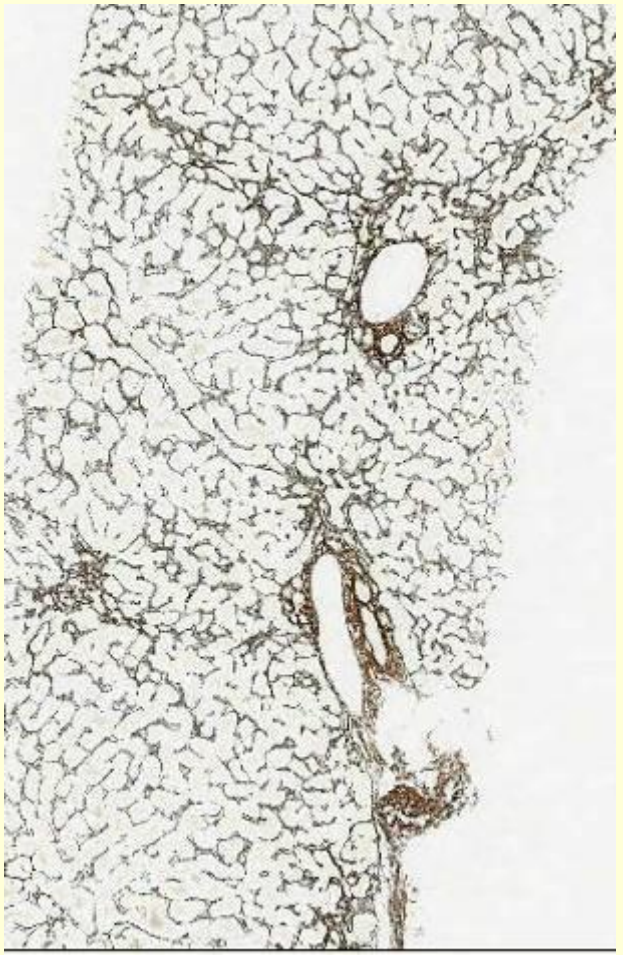
Assessment of ASH

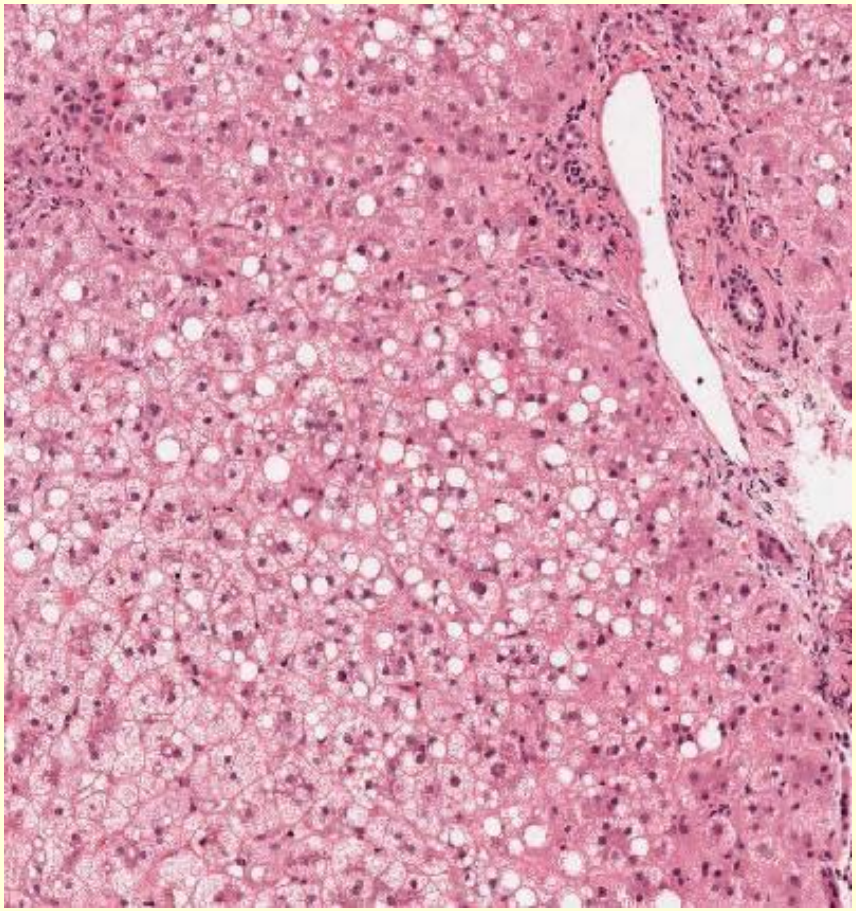
- Histology score to predict short term mortality *Altamarino Gastroenterology 2014*
- Fibrosis (bridging/cirrhotic), bile in hepatocytes, cannaliculae and ductules - poorer outcome
- steatosis, MDB and ballooning – no effect
- prominent PMNs and megamitochondria – positive effect on outcome.

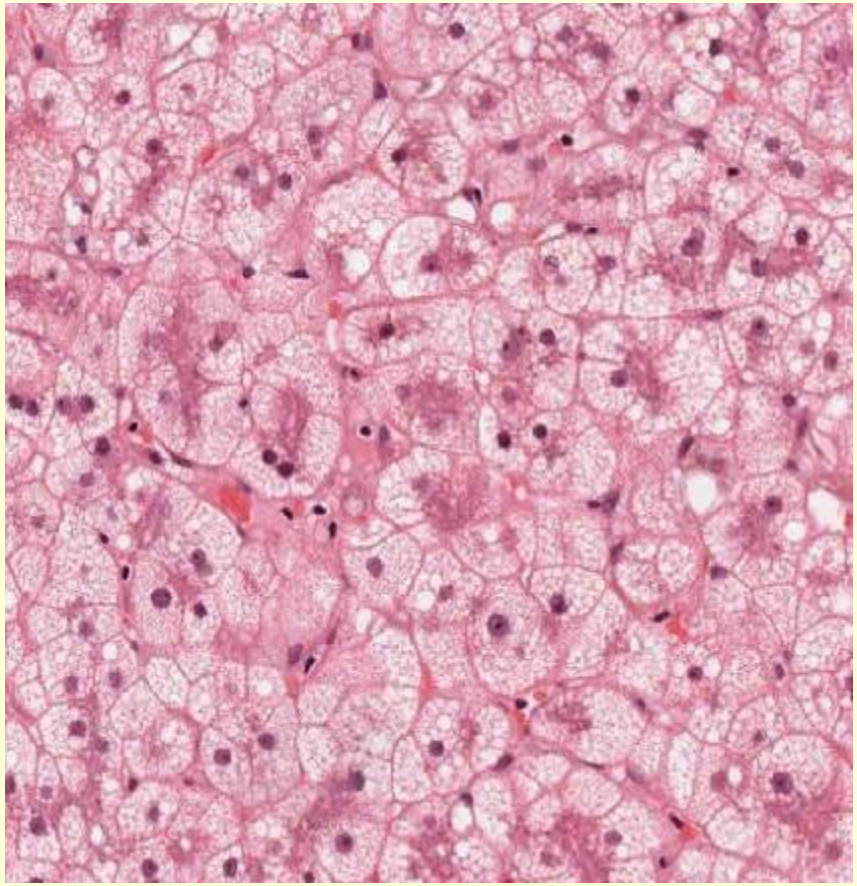
Case 7

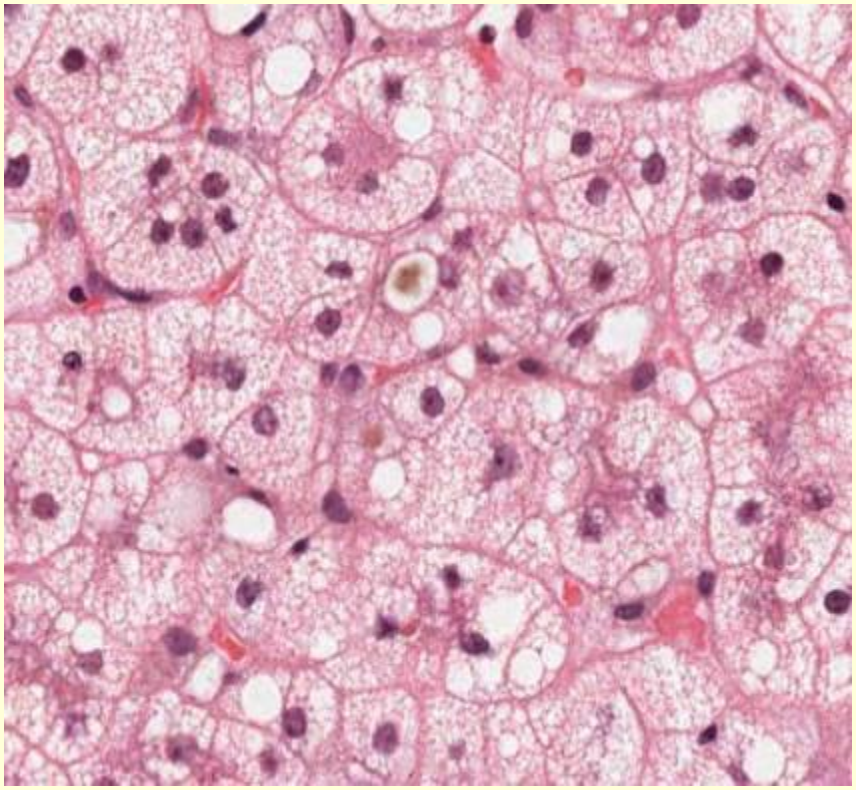
- 32/M Deranged LFT's. Hx of ETOH abuse, however more hepatitic picutre. CLD screen -ve. Hx of anabolic steroid use.
- Retic, CAB, PASD

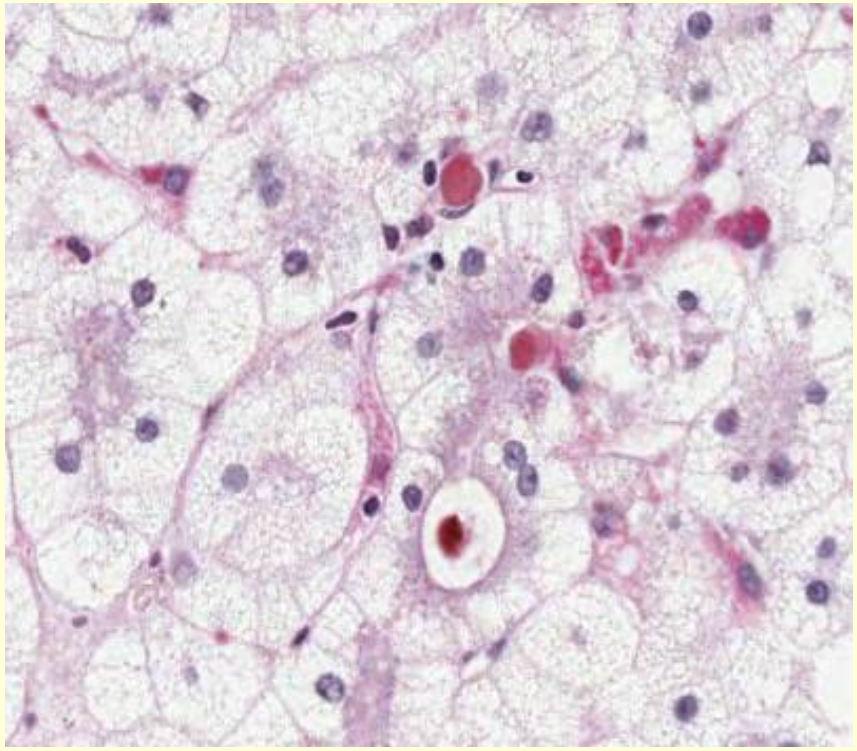












PASD

Diagnosis case 7

- Microvesicular steatosis, probably alcohol
- Cholestasis, probably drug.

- F/I – seizures with acute detox 3yrs later

Alcohol related Liver Disease

Why biopsy in ALD?

- Anything to treat? Possible 2nd diagnosis – not all jaundice in xs alcohol intake is ArLD
- ASH or decompensation or sepsis or drug reaction?
- ? Evidence of drinking in transplant setting

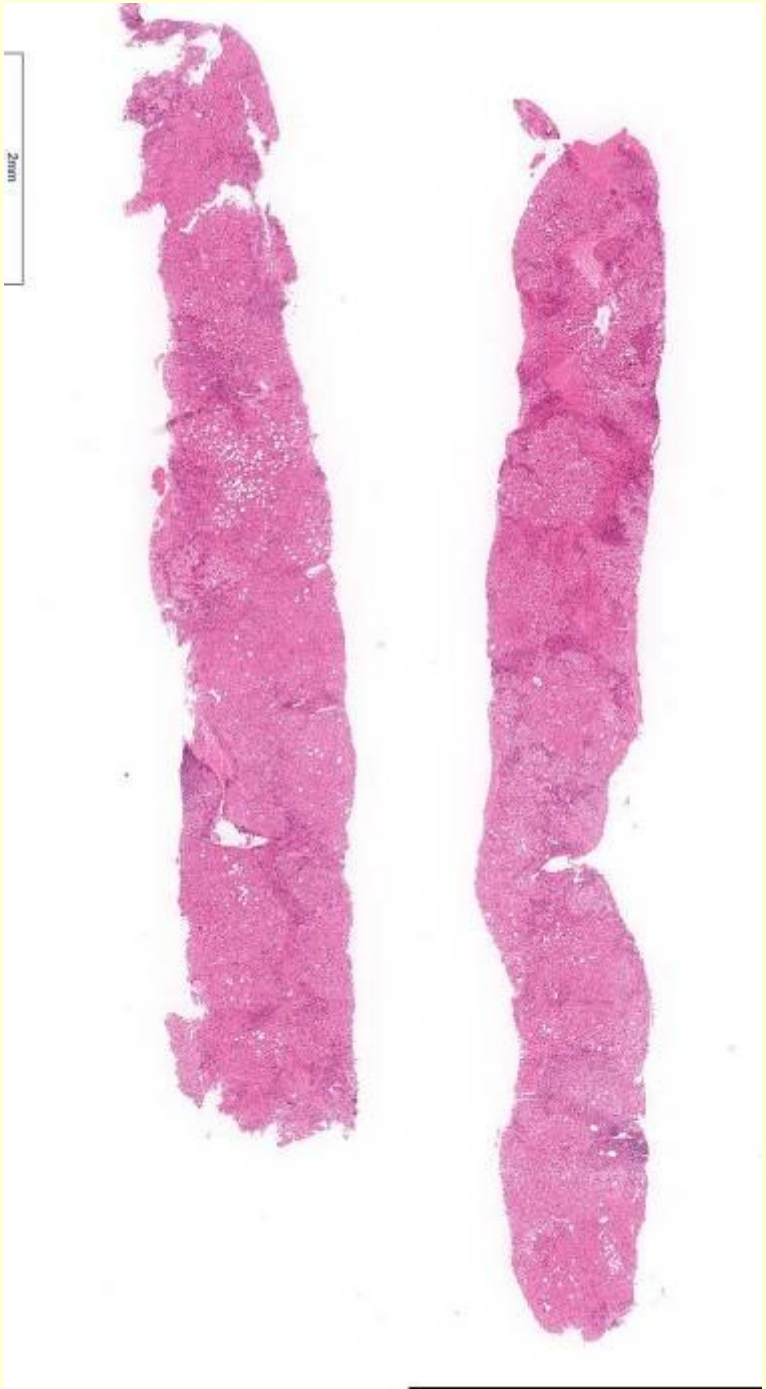
AND Lunch…

NO alcohol

Possible NAFLD factors?

Case 8

- 61/M Abnormal LFTs. Recently on Methotrexate, for rheumatoid arthritis. ??PBC.
- EPSR, orcein, perls, PASD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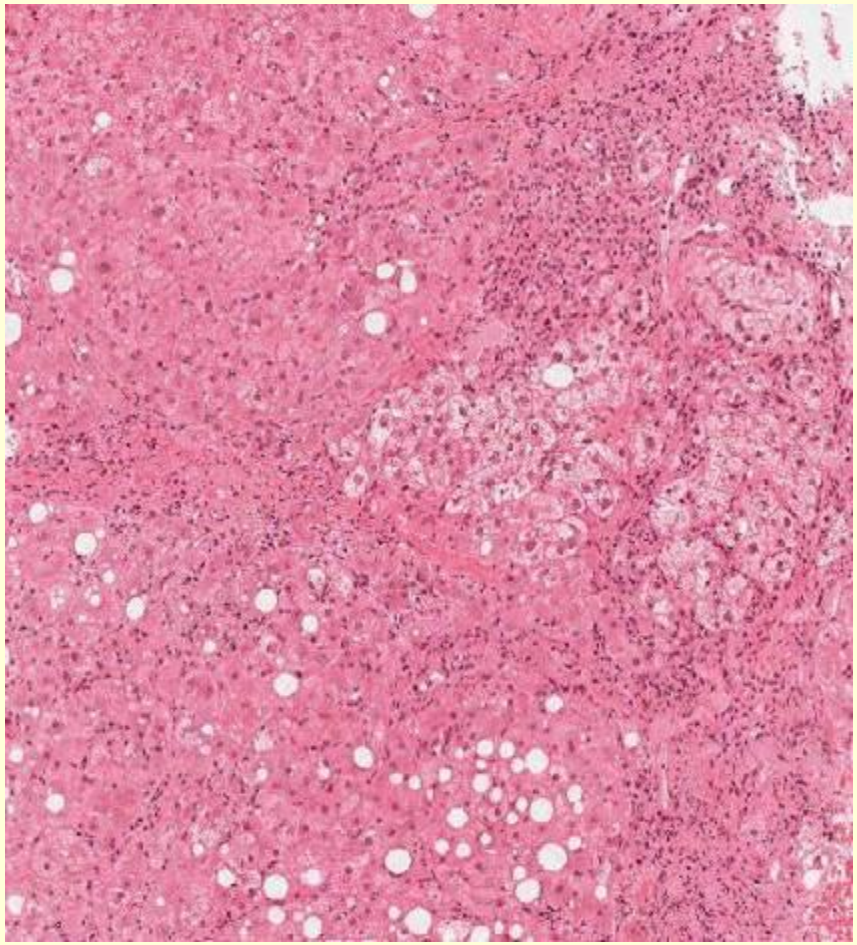

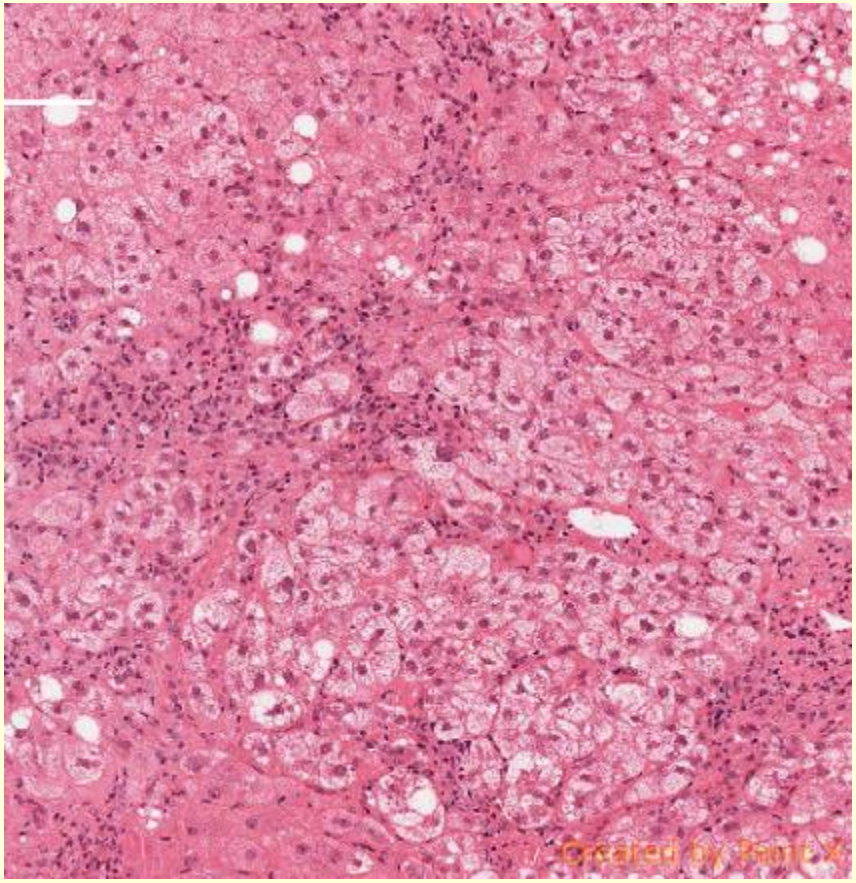
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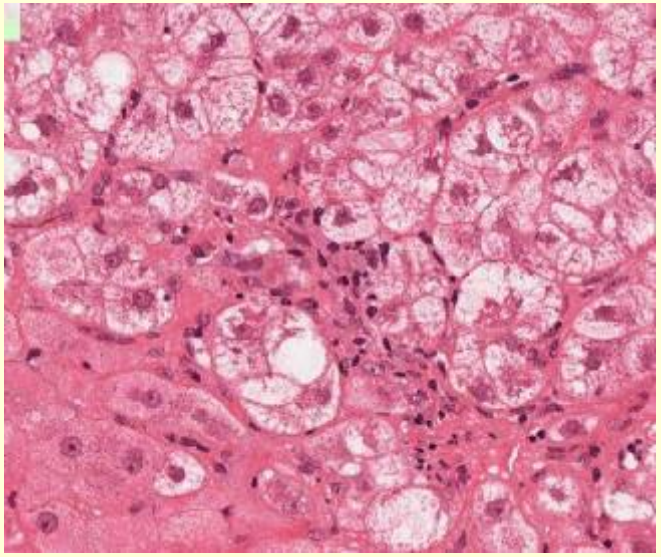
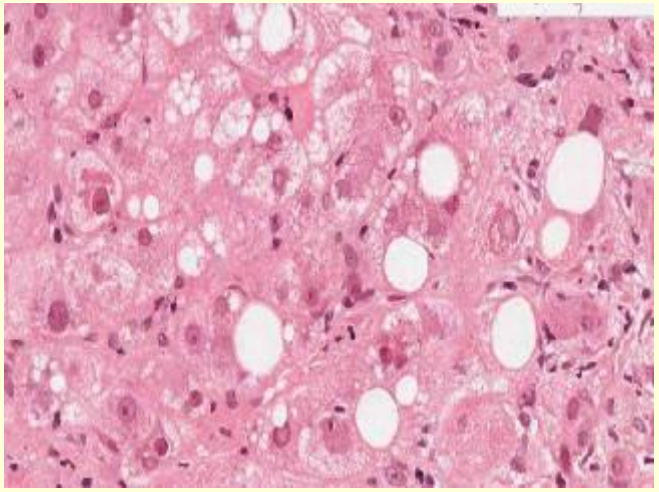
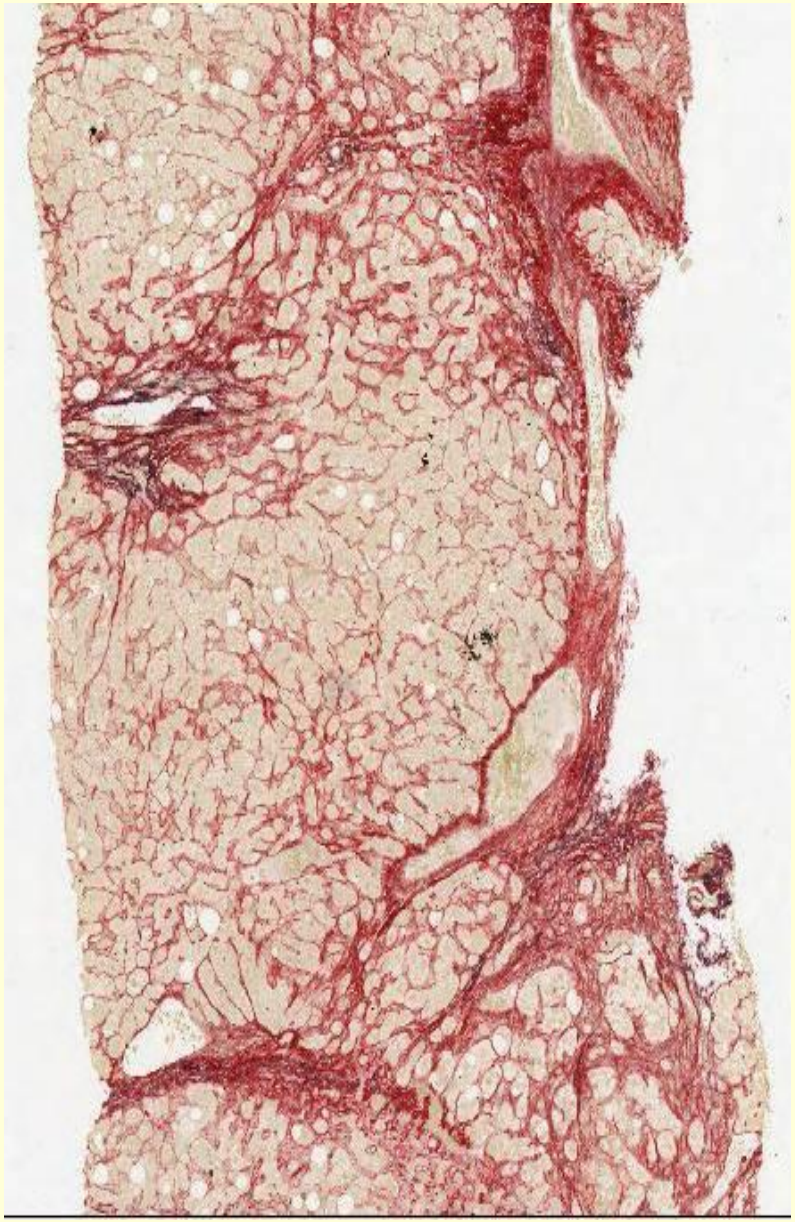
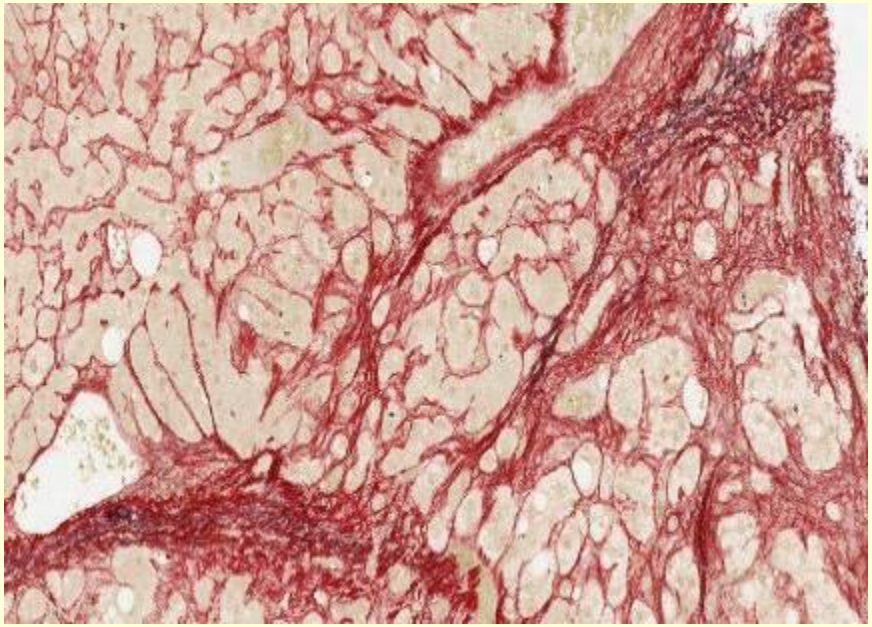
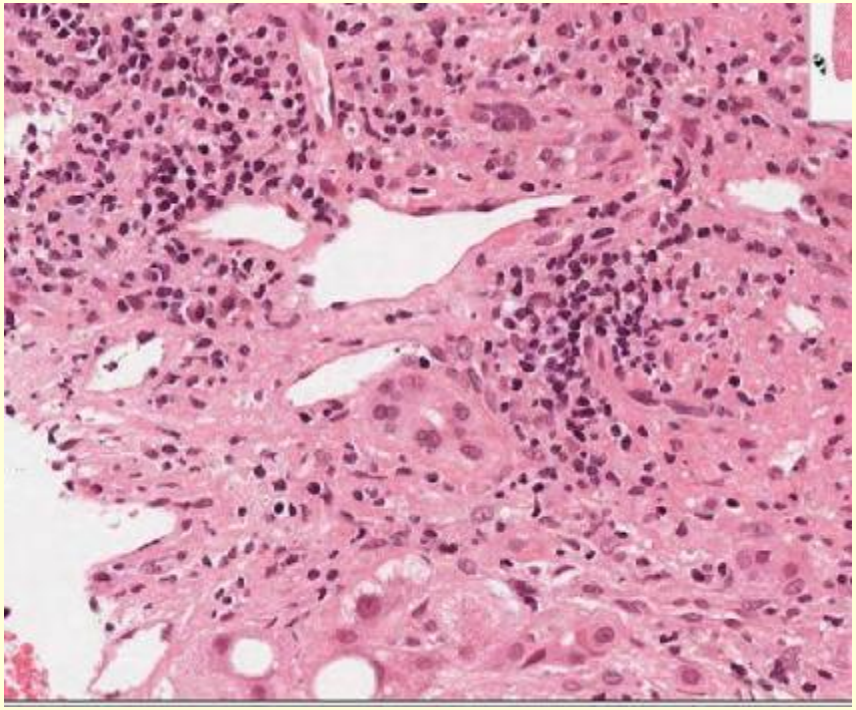


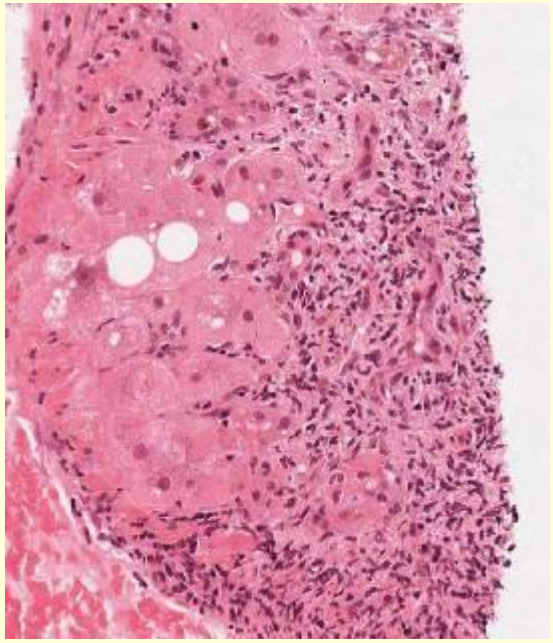


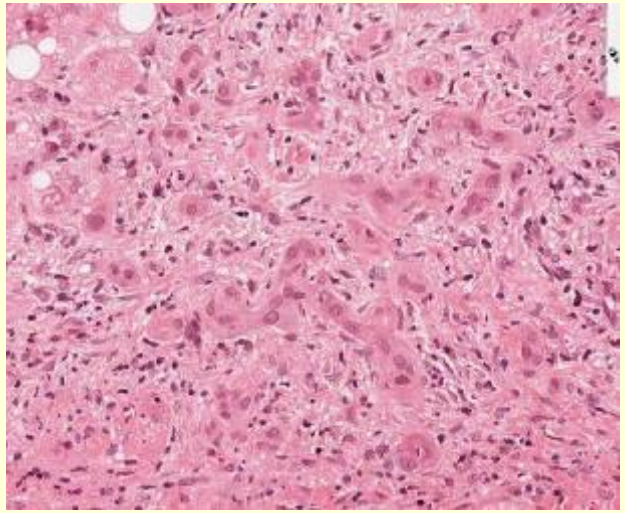


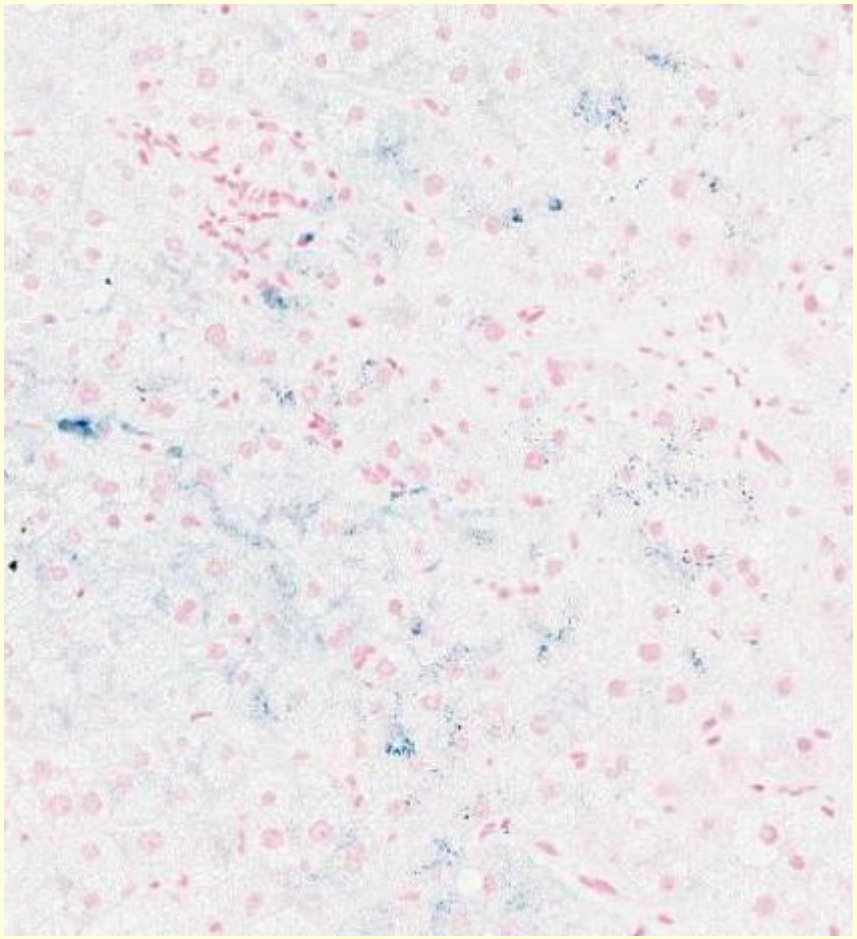


EPSR

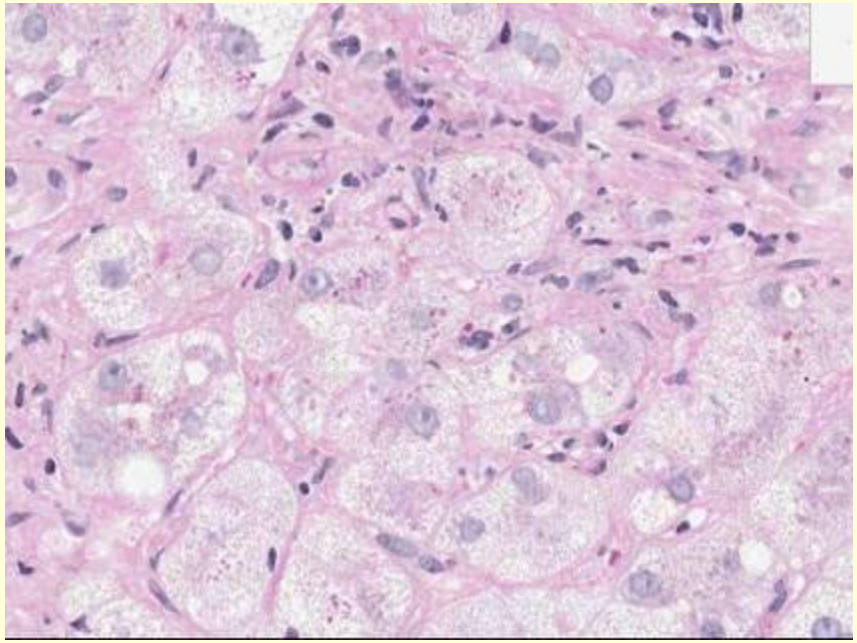




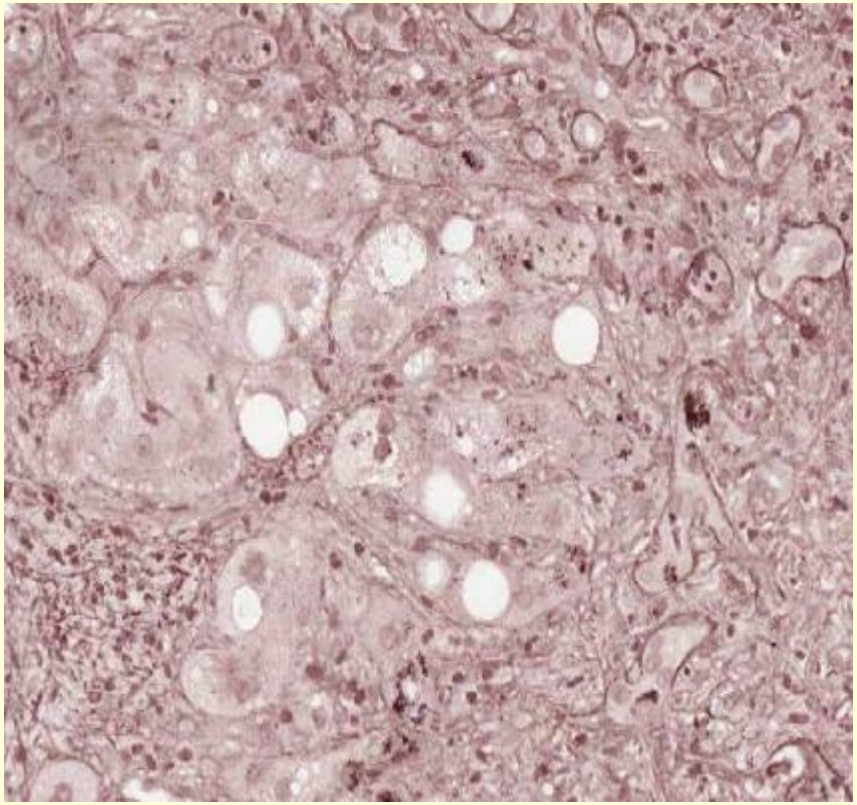


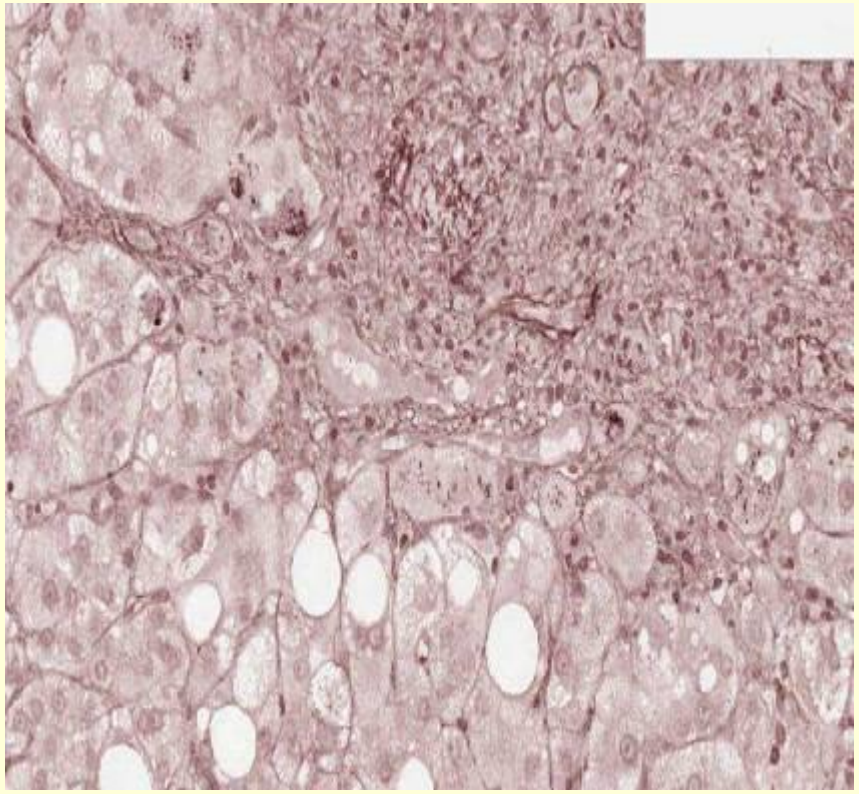


Perls



PASD





orcein

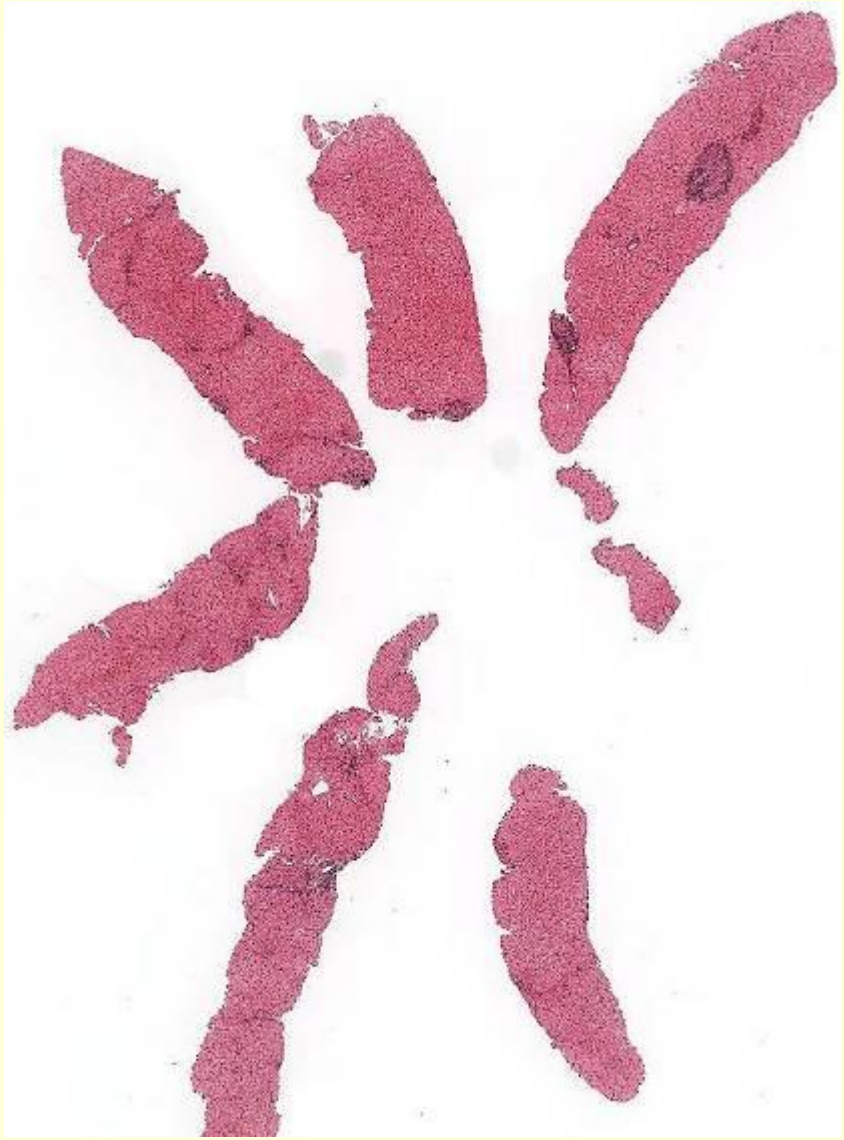
Diagnosis case 8

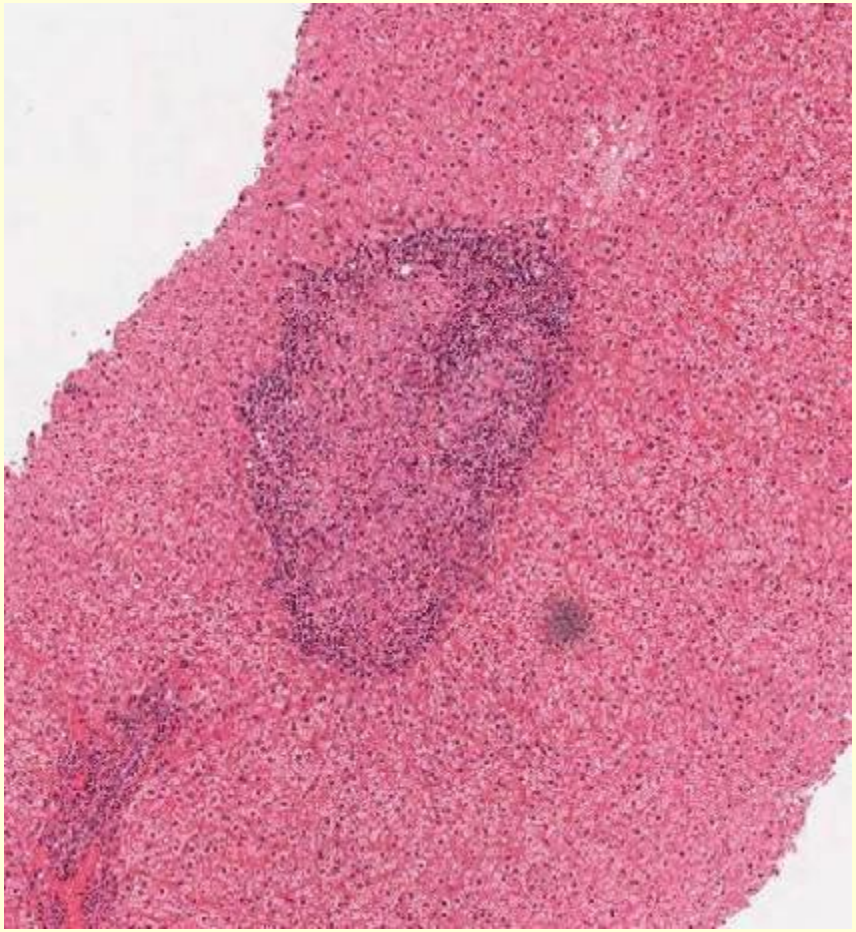
- Incipient cirrhosis, with little fat but on-going steatohepatitis – possible alcohol or NAFLD
- Focal biliary features ? risk factors

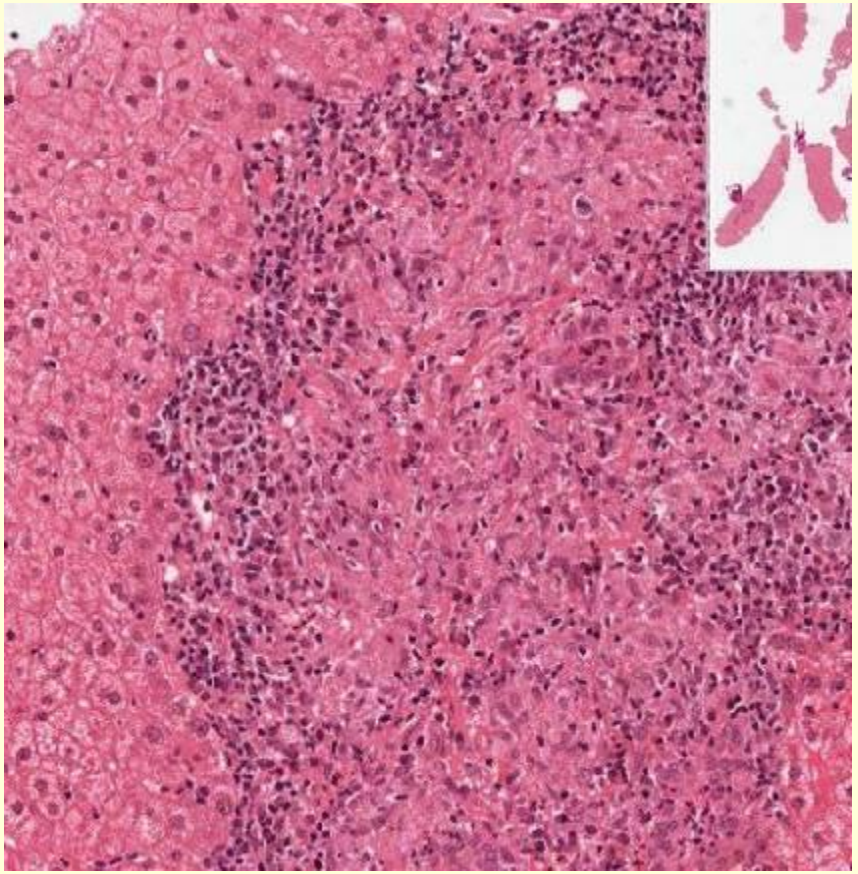
- F/I – Alk phos 225 (30-130 U/L), ALT 31 (97-40 U/L). ; denies alcohol, hi BMI, AMA pos, IgG, IgA & IgM raised.
- Bx taken as USS fatty but AMA positive!
- ?dual diagnosis

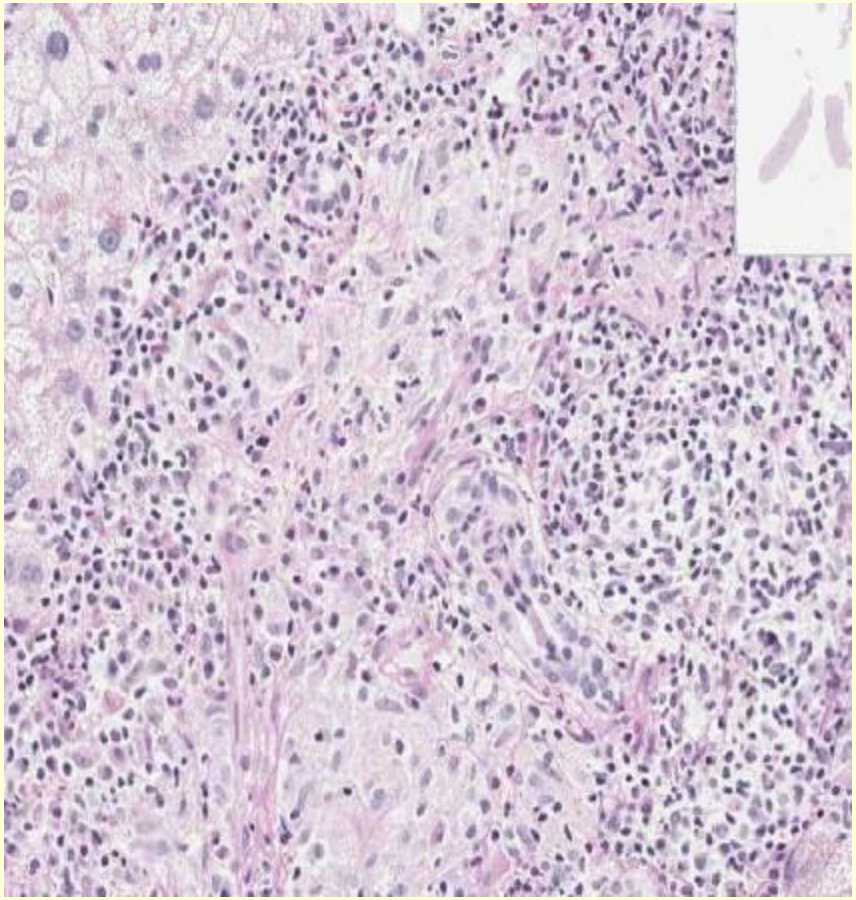
Case 9

- 67/M Deranged LFTs. ?NAFLD, heterogenous liver on US. Raised Alk phos.
- Retic, CAB, PASD, orcein









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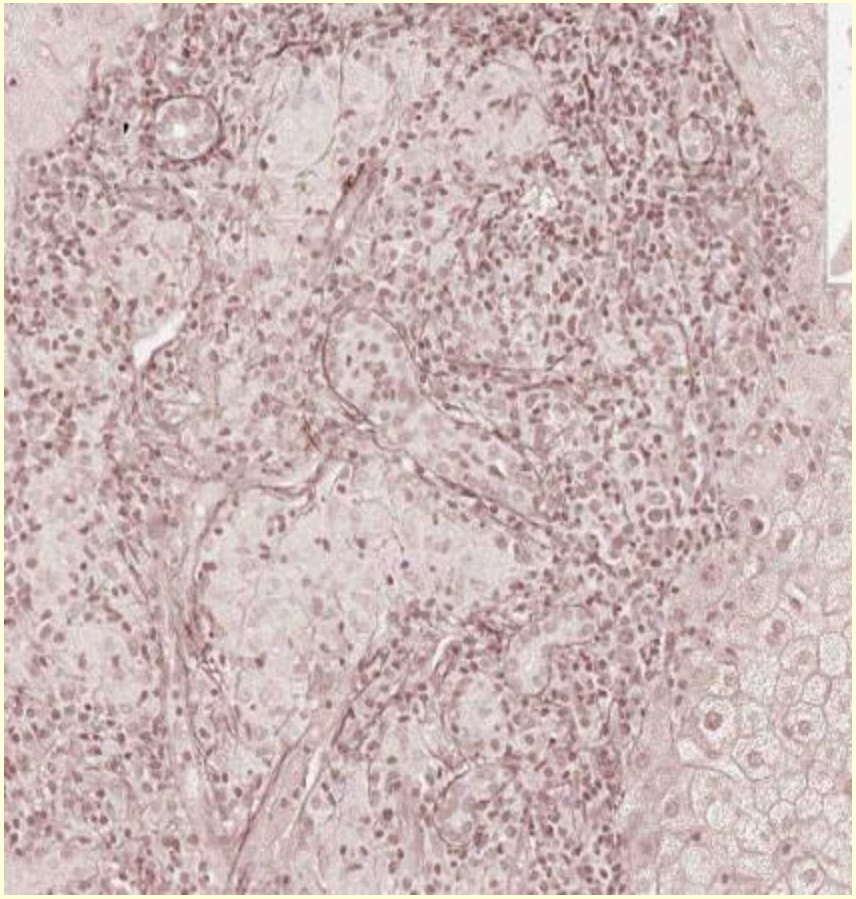
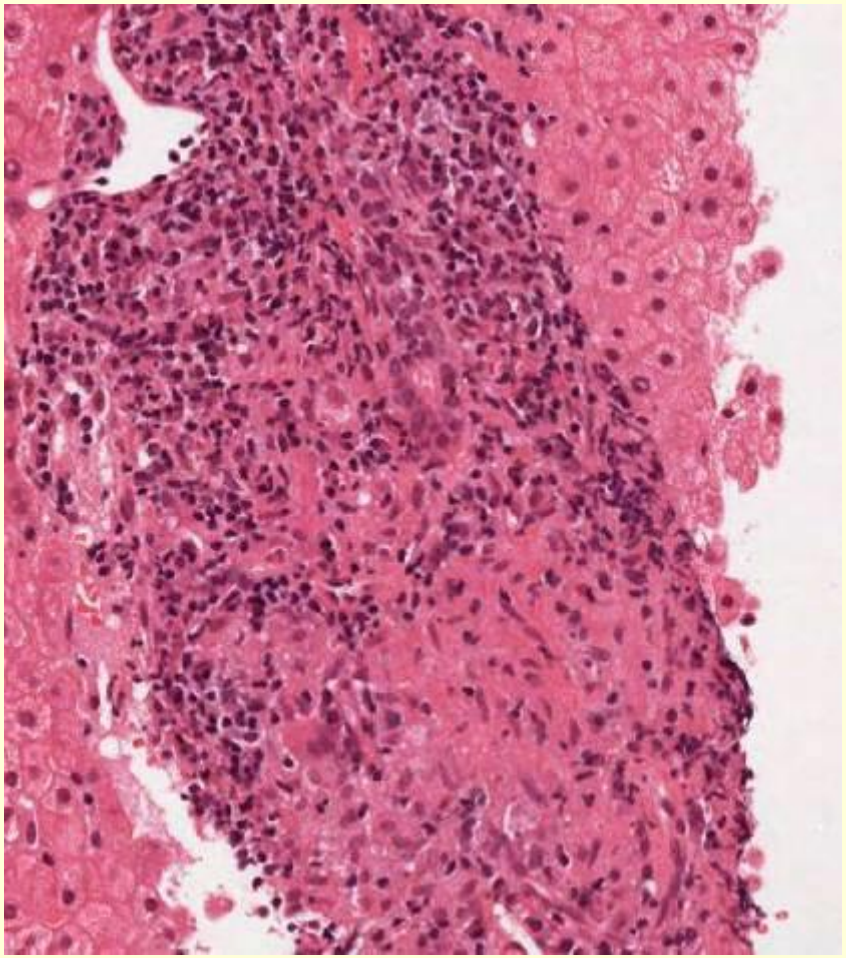
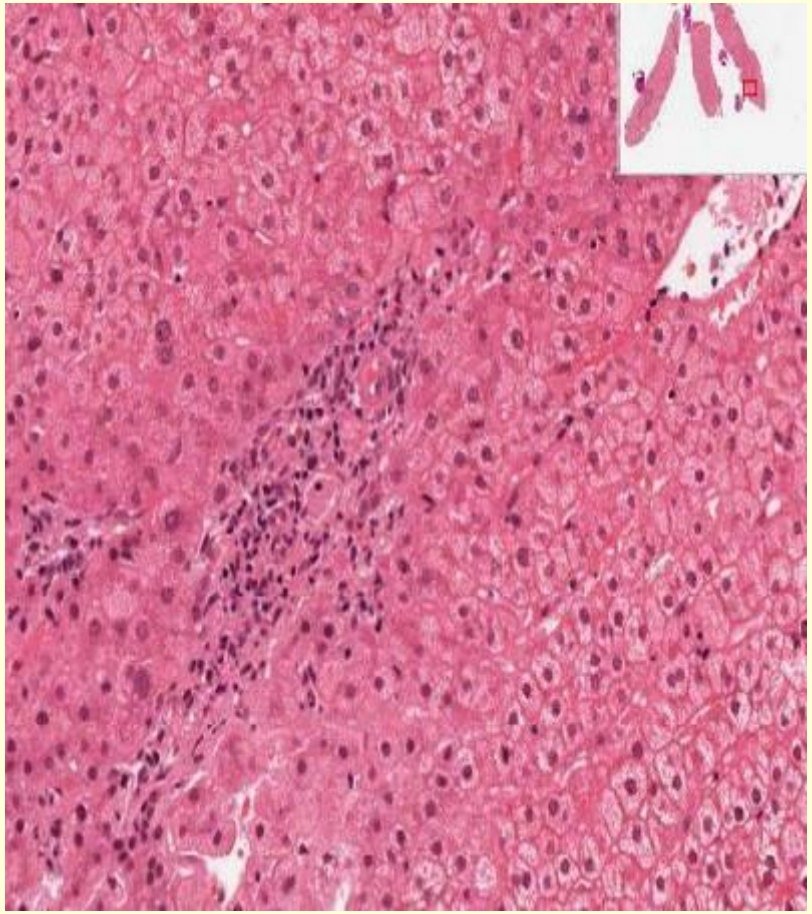


orcein





Diagnosis case 9

- Granulomatous cholangiopathy – probable Primary Biliary Cholangitis (PBC)
- No sig NAFLD features
- AMA negative

- AP 385 (30-130 U/L) Alt 95 (97-40 U/L) , IgM 3.4 (0.4-2.2g/l), IgG 13.6 (6.0-13.0g/l), ACE Normal

AMA negative PBC

- Overall natural history is similar to AMA pos
- AMA +ve >90%, with specificity of 95% and non-specific ANA ~30% PBC
- Second order serology may be helpful if AMA -ve, nuclear and envelope antigens - anti-Sp100 and anti-gp210

Staging of PBC

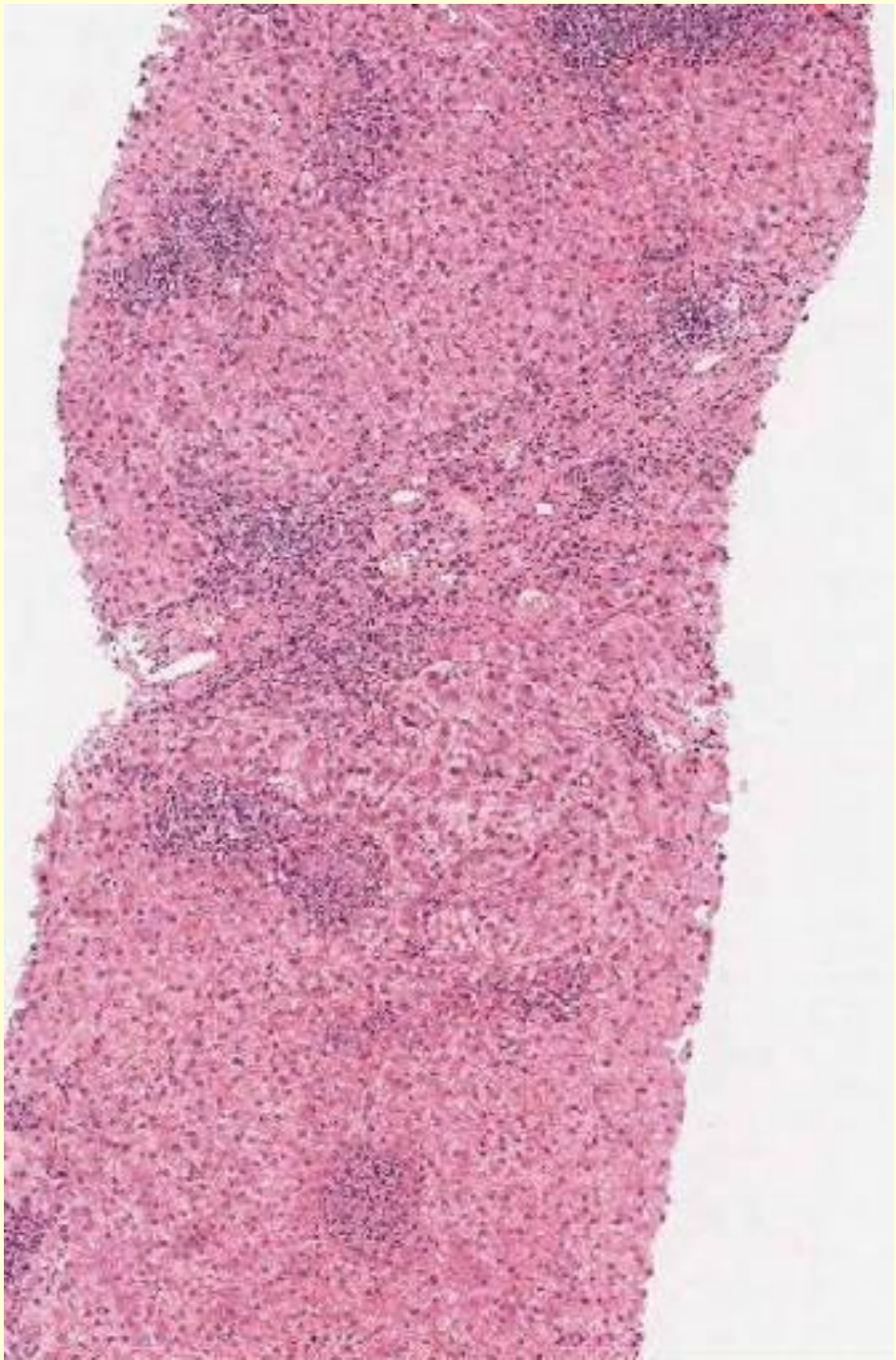
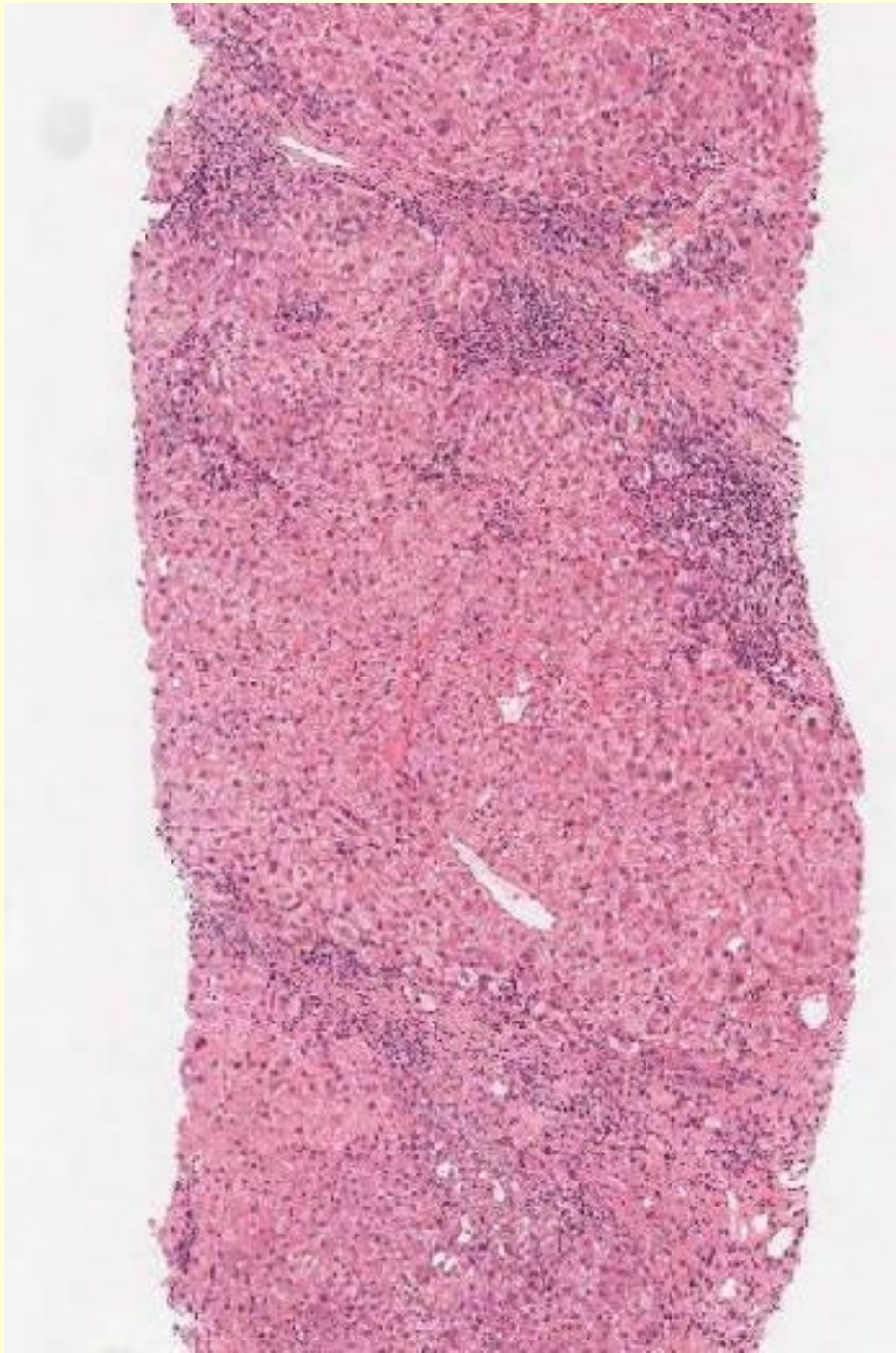
- Related to ducts and fibrosis – *Scheuer 1976, Ludwig 1978*
- But biliary disease very irregular – staging not appropriate
- More recent Japanese proposal (also grade) *Nakanuma senior author Pathol Int 2010, Histopathology 2006 & 2014*
  - Bile duct loss, 0-3
  - Fibrosis, 0-3
  - Copper associated protein *, 0-3

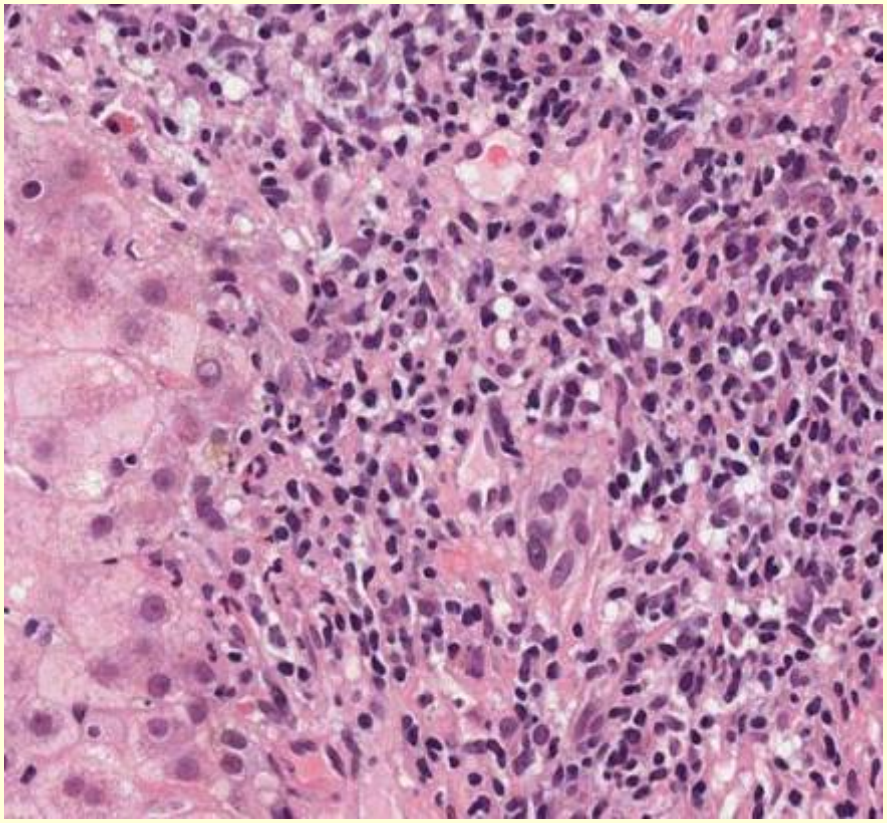
Case 10

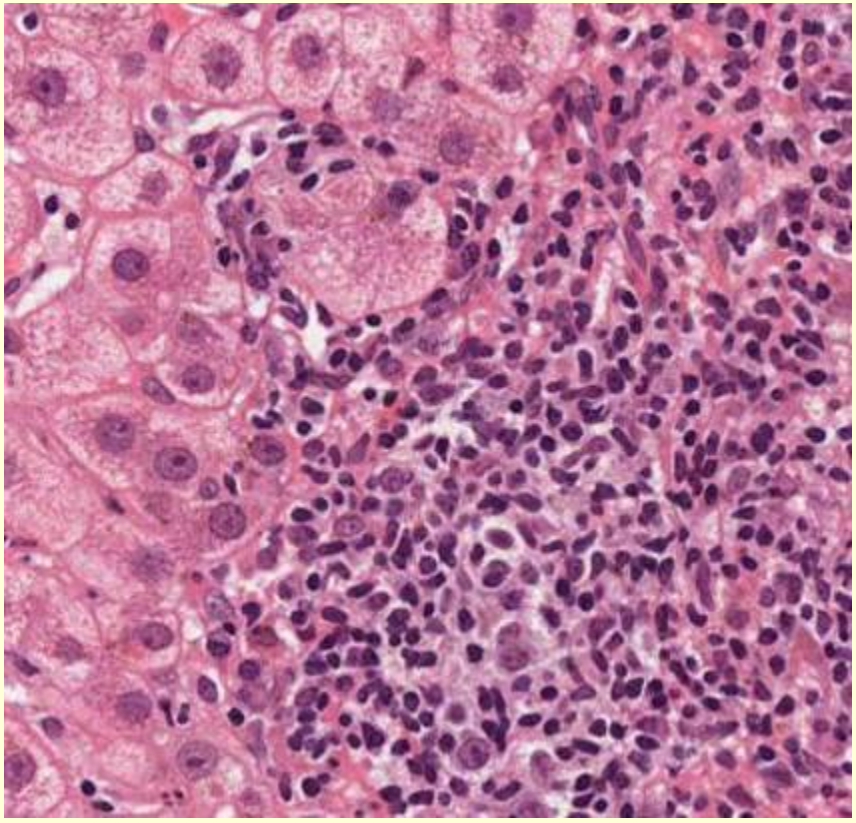
- 66/F Abnormal LFTs Bili 25 (0-20 umol/L), Alk Phos 574(30-130 U/L), ALT 148 (97-40 U/L), AMA weakly +ve, SMA -ve

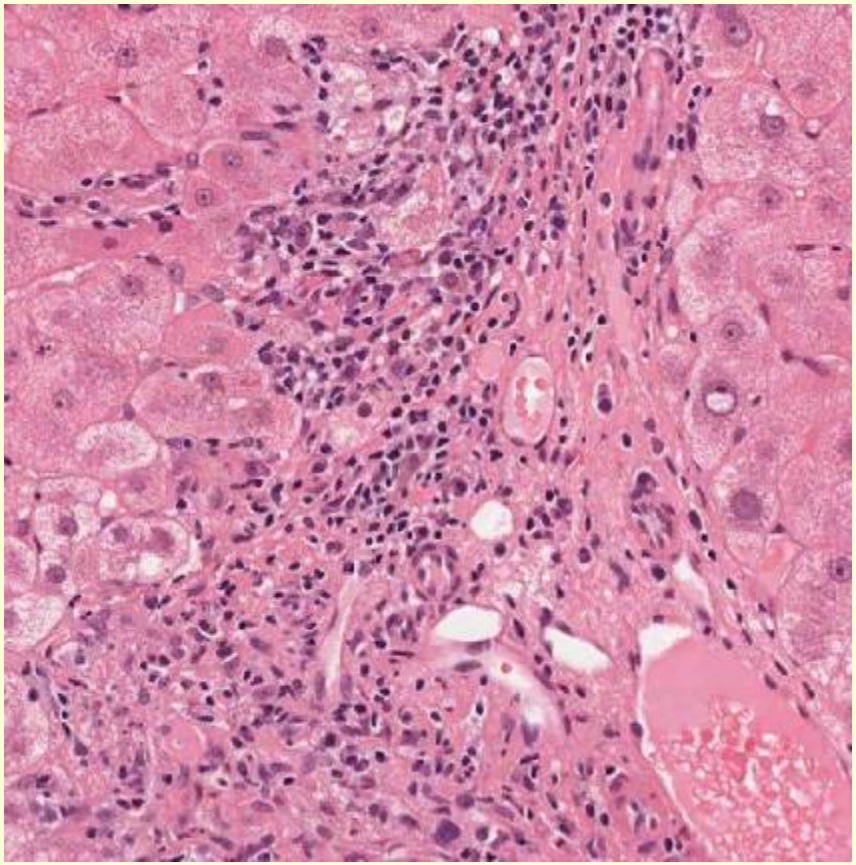
  PBC diagnosed 20yrs ago elsewhere.

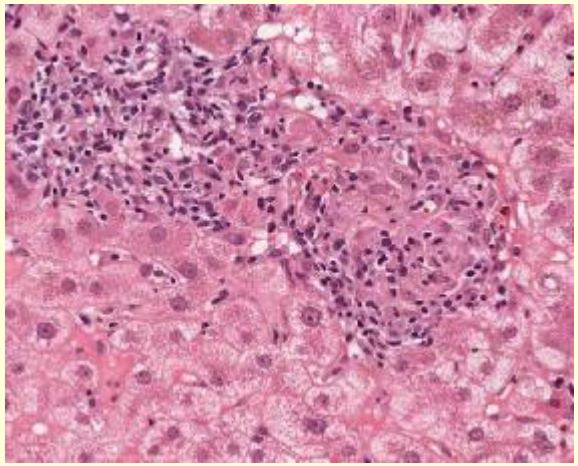
Retic, EPSR, orcein, vic blue, PASD, IHC CK7 CK19

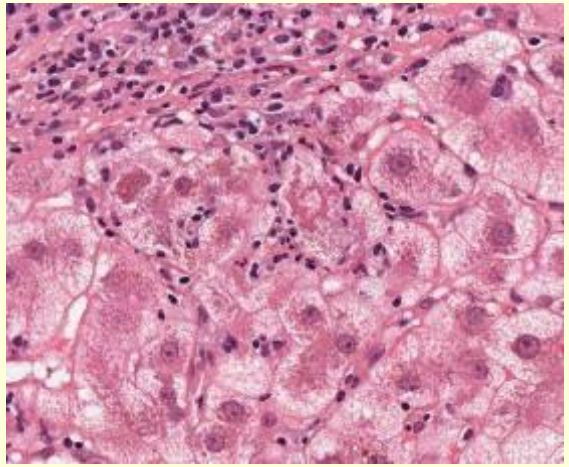



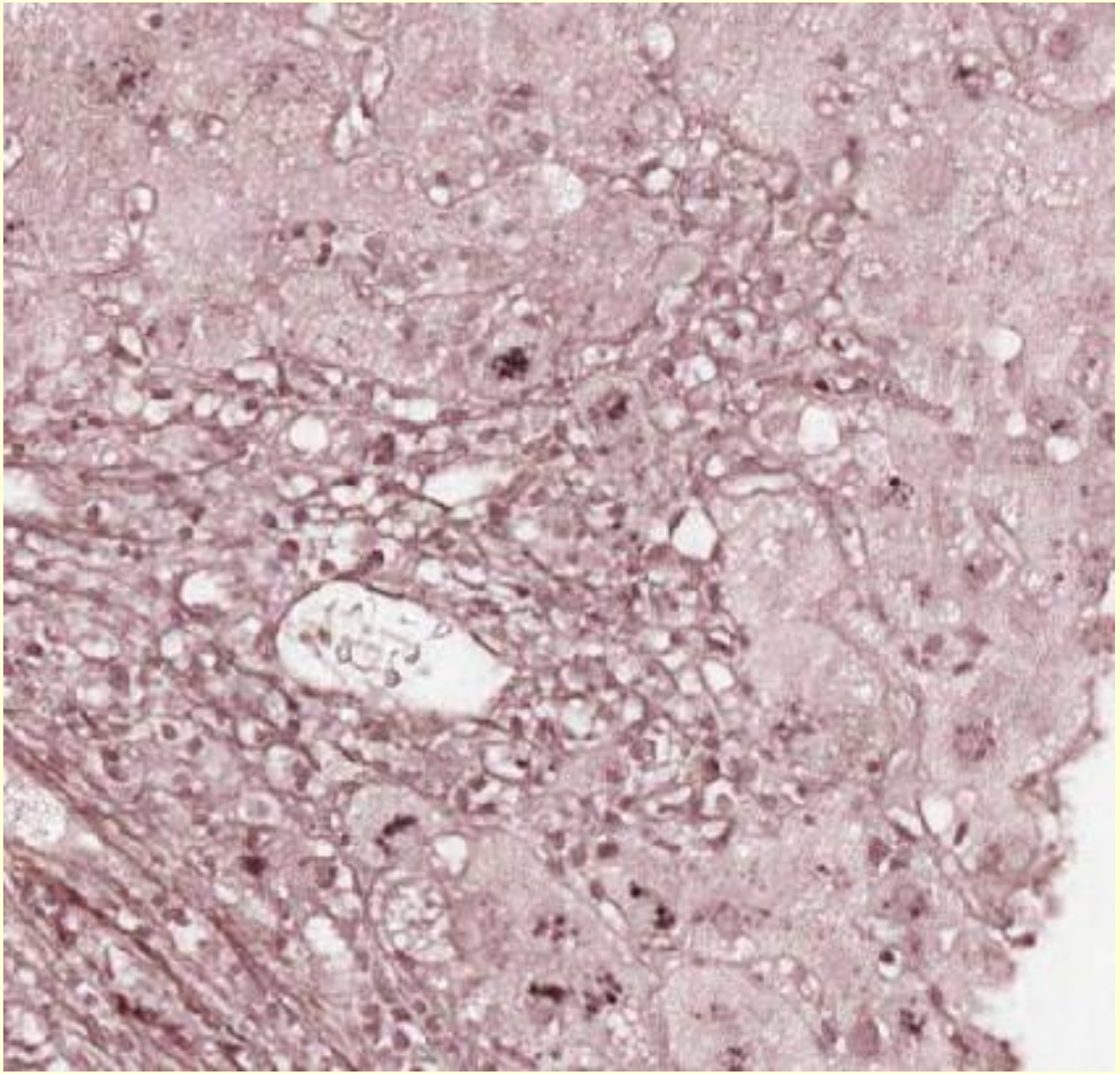




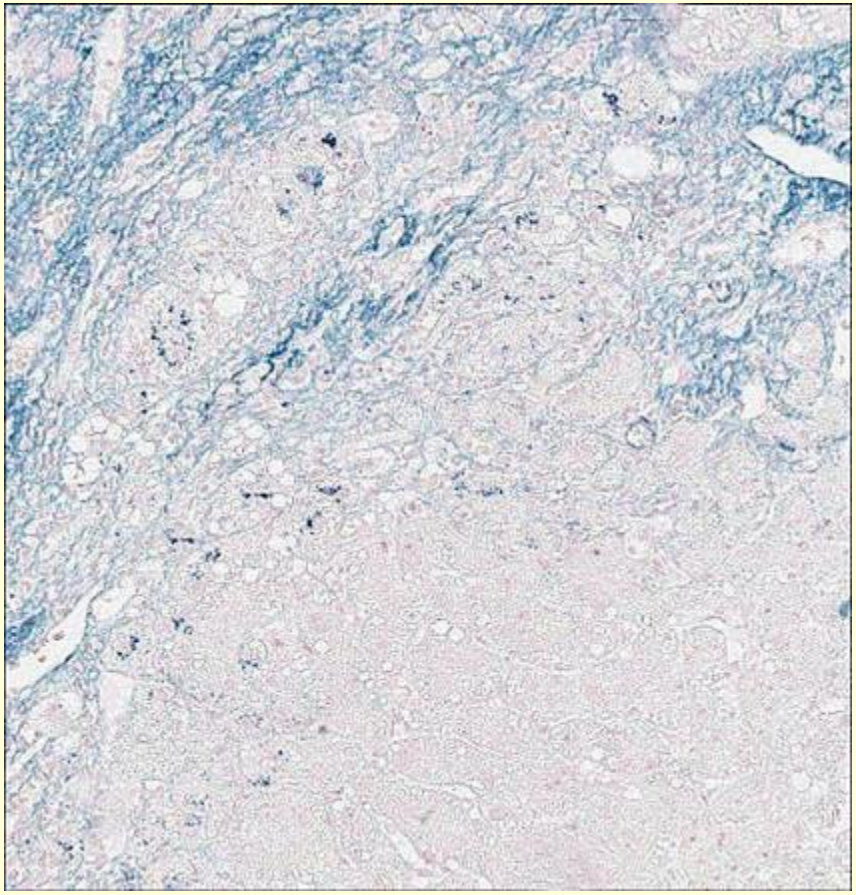




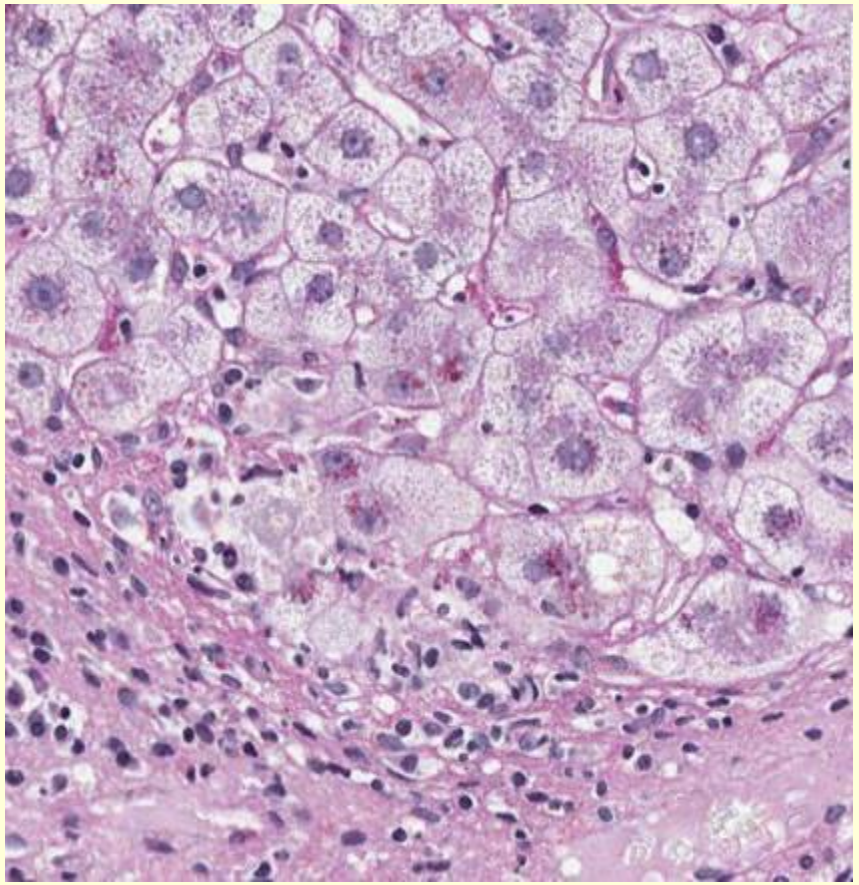




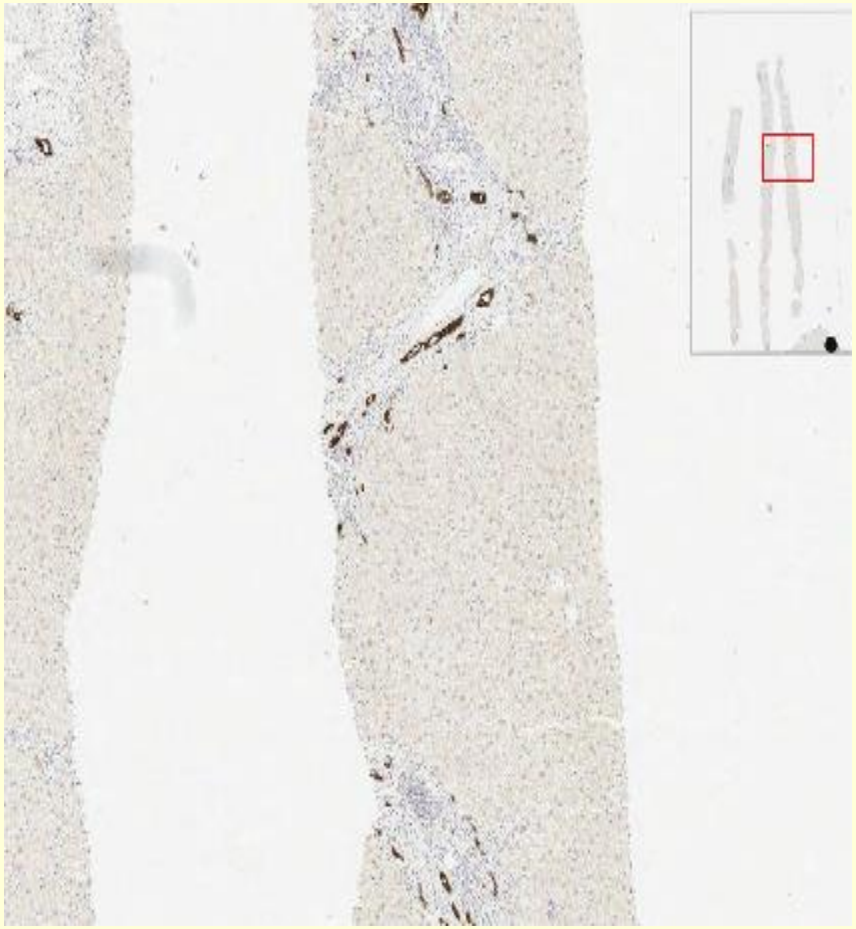
orcein

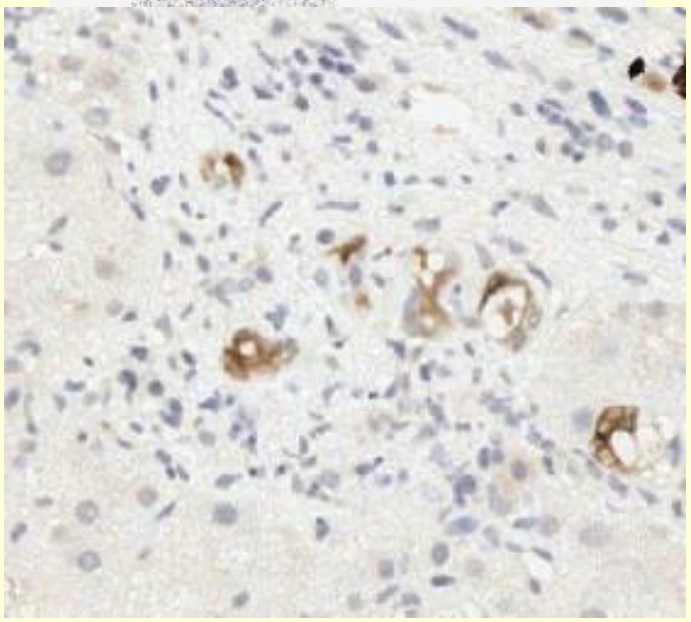


Victoria blue

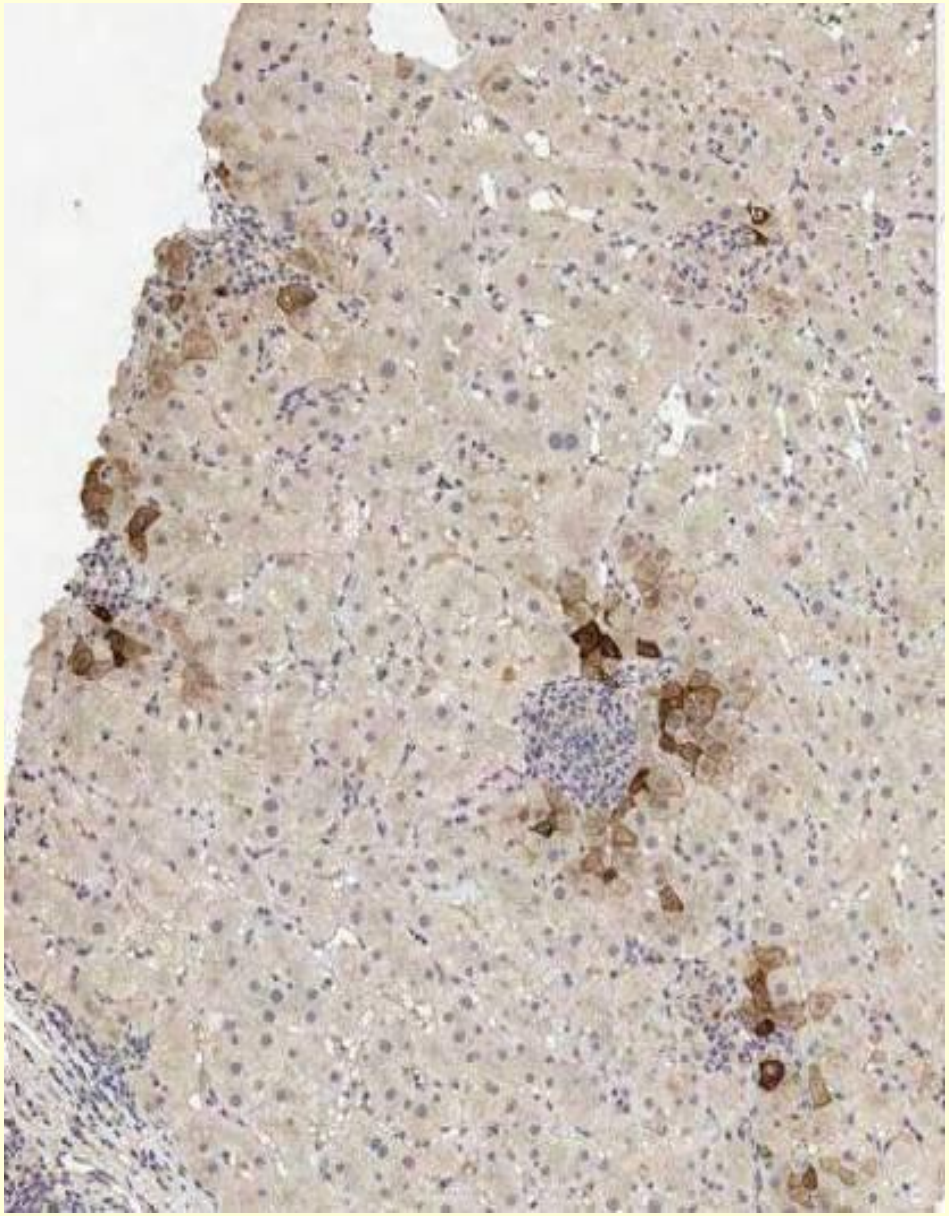


PASD

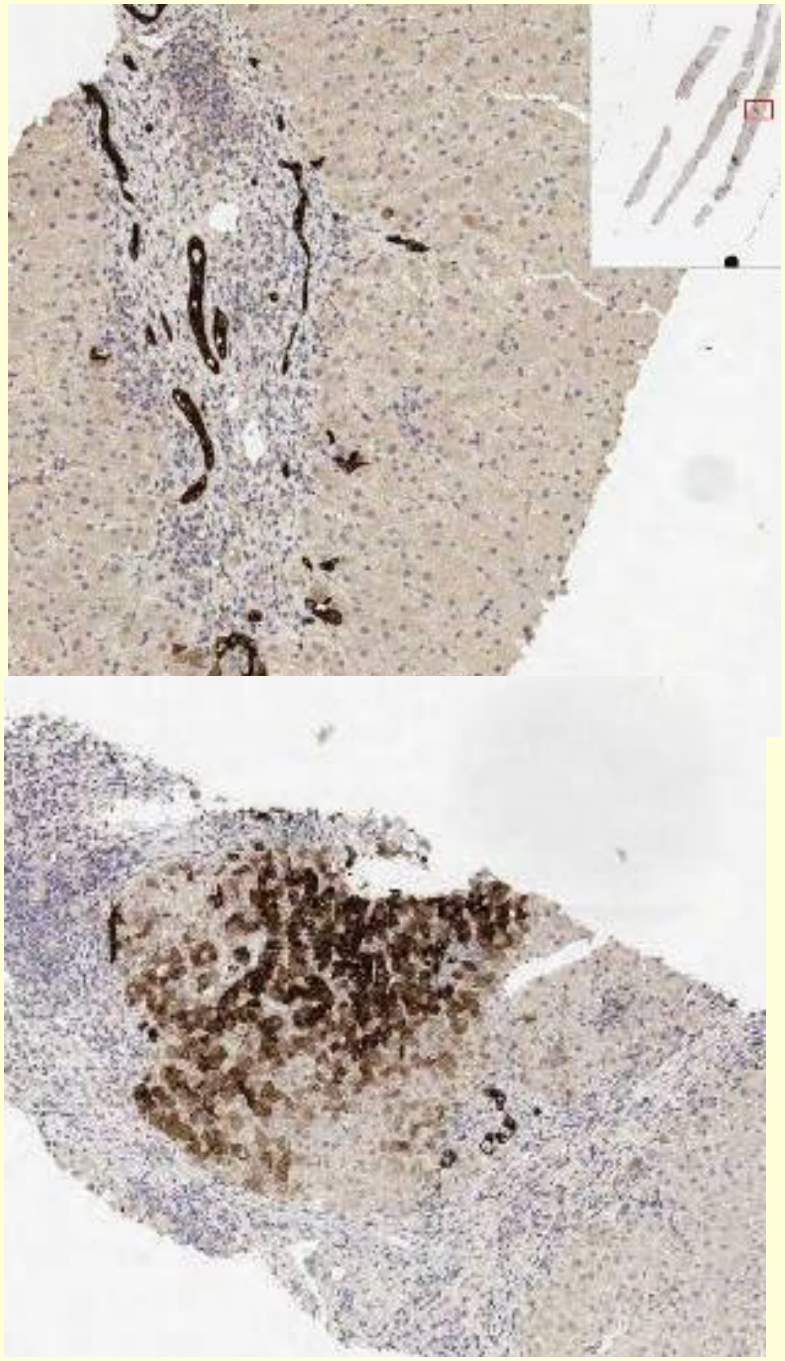




CK 19



CK 7



Diagnosis case 10

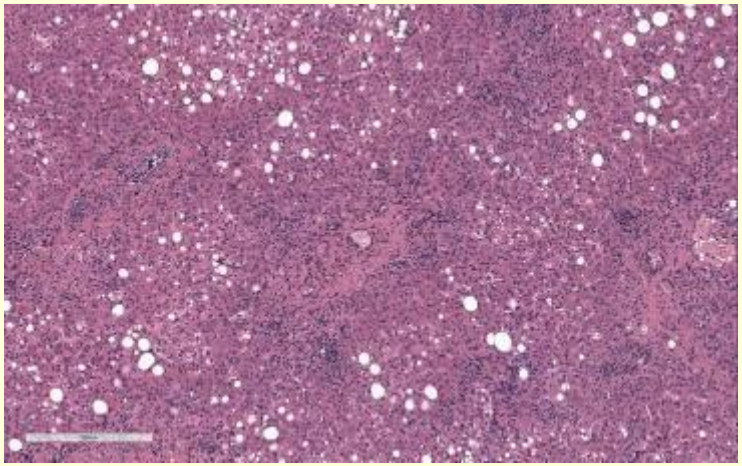
- Primary Biliary Cholangitis/ Autoimmune Hepatitis overlap, with cirrhosis

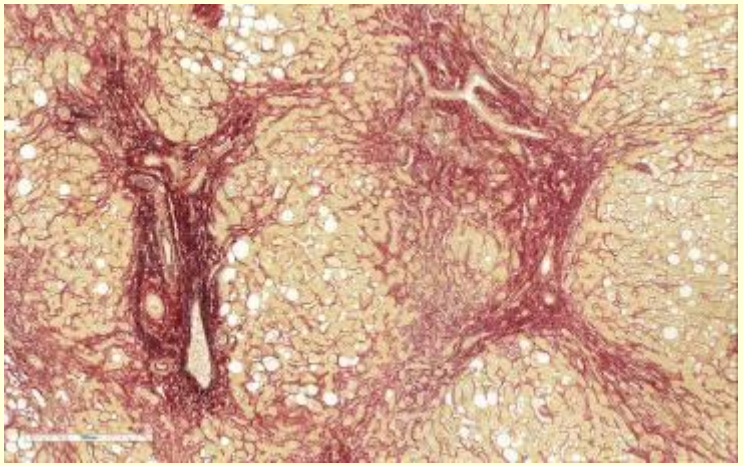
- F/I Had recently felt unwell, weight loss; IgG 29.6 (6.0-13.0g/l). Initial biopsy not available therefore proceeded to this biopsy

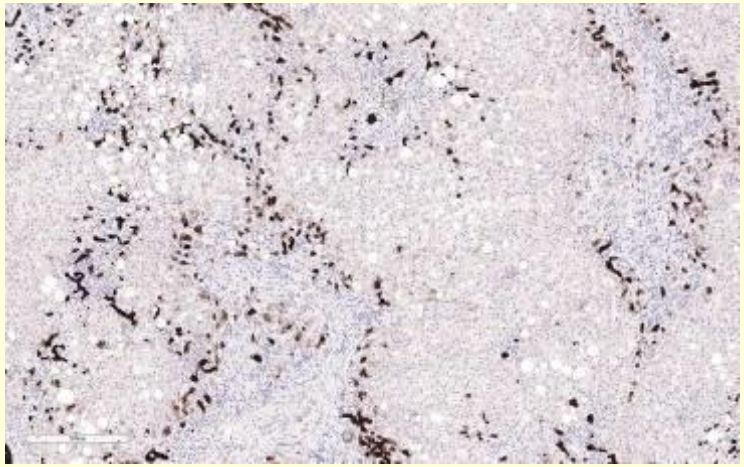
PBC/AIH overlap

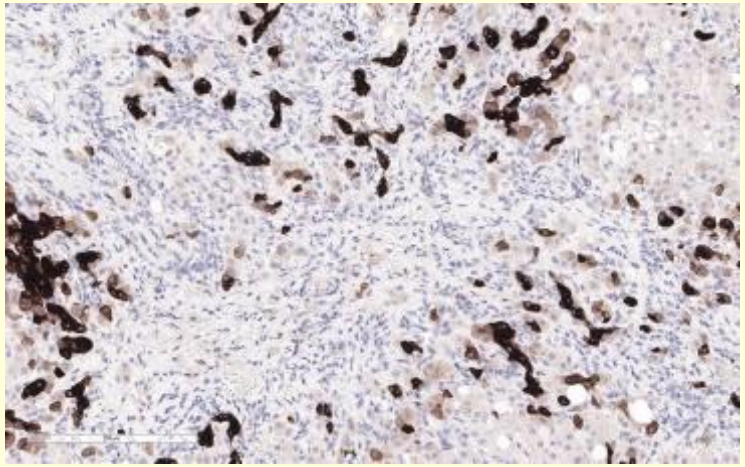
- May be synchronous or metachronous; biochemical, serological and histological diagnosis – uncommon to rare
- Two out of 3 major criteria for both diagnoses need to be present (EASL guidelines)
- Florid interface activity
- Newer guidelines and 2nd order antibodies may help clarify.

CK 7 immunohistochemistry



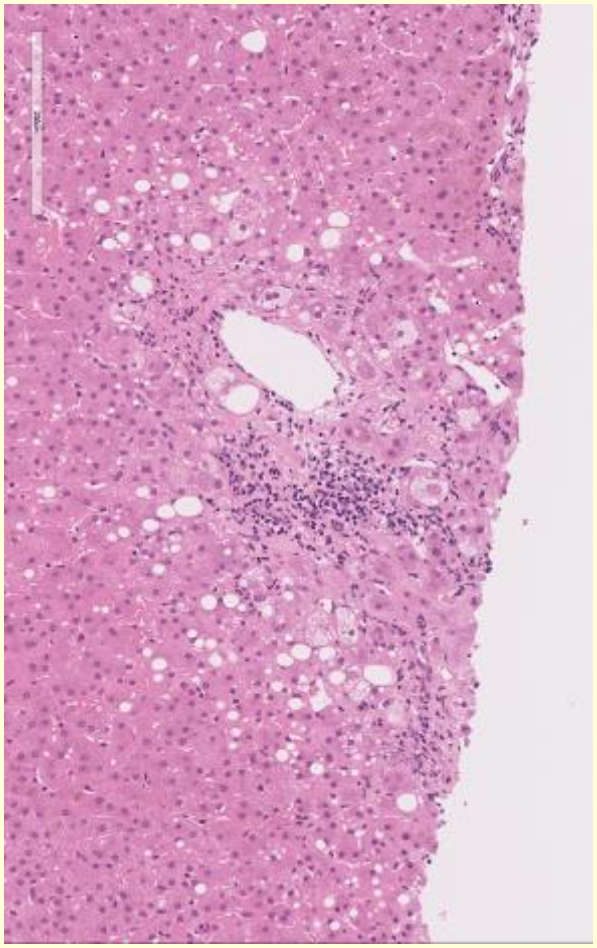


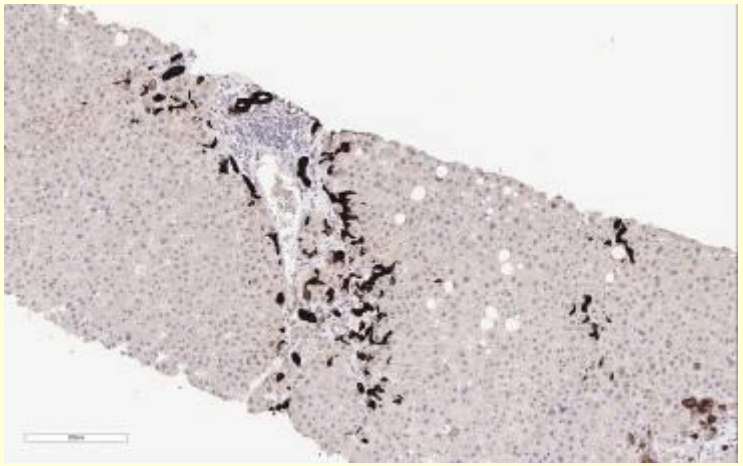


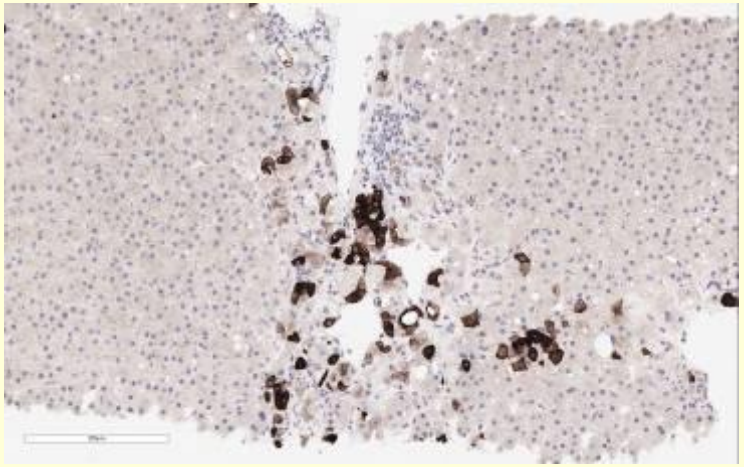


Care with pseudobiliary…

CK 7



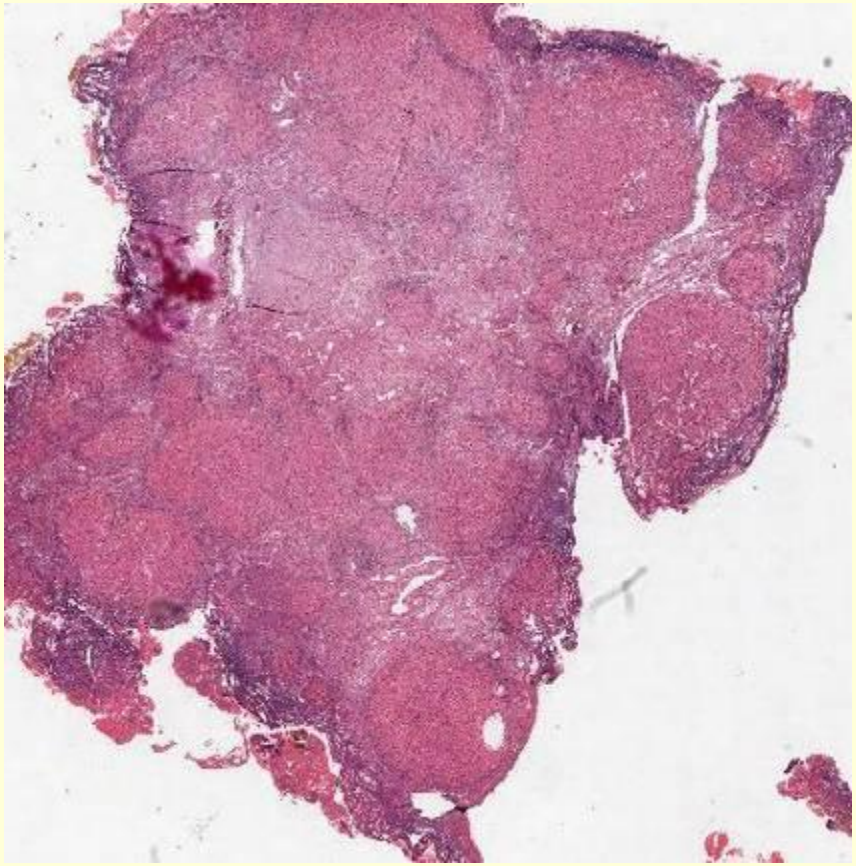


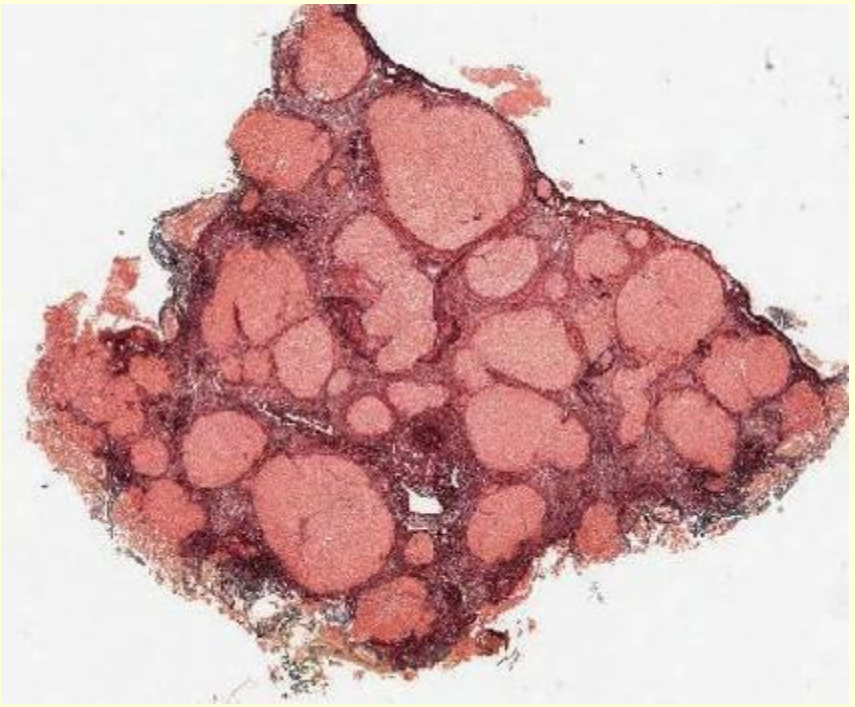


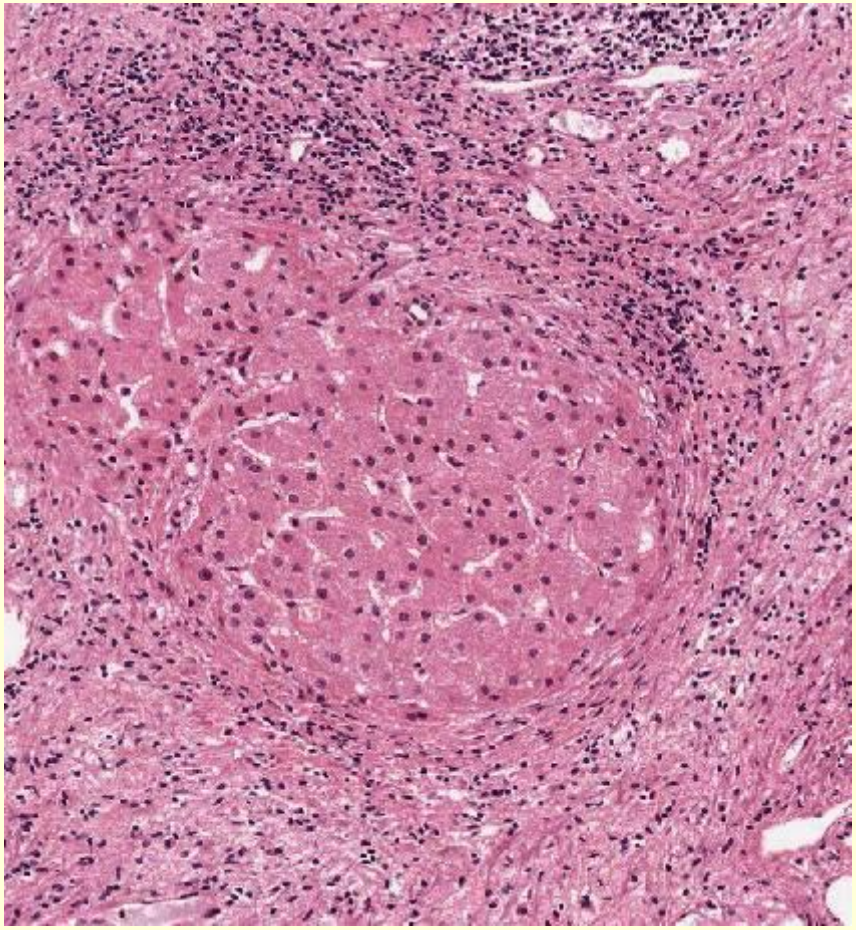
Especially with ischaemia & N/ASH

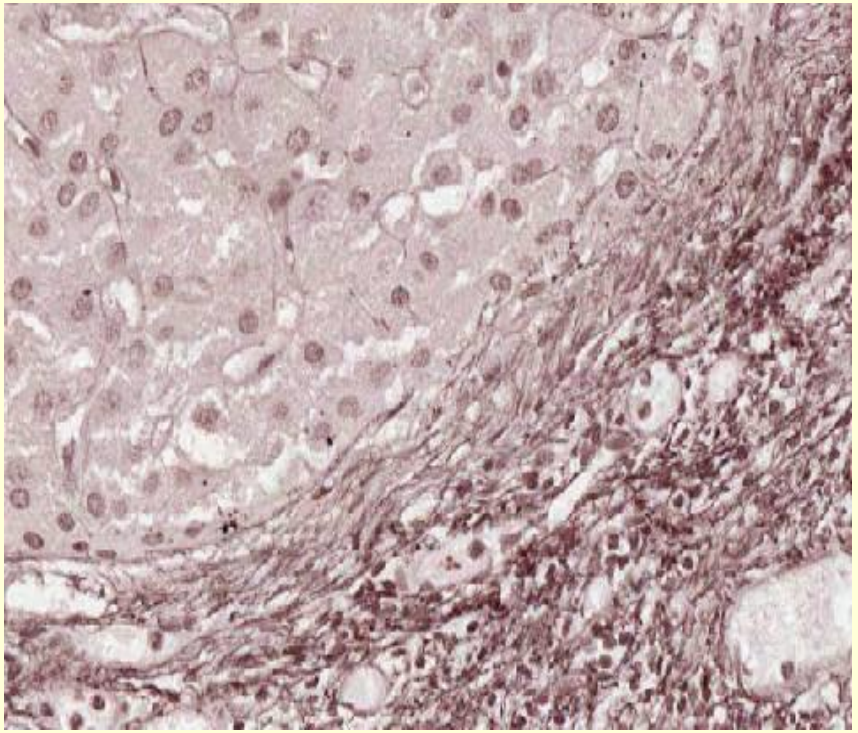
Case 11

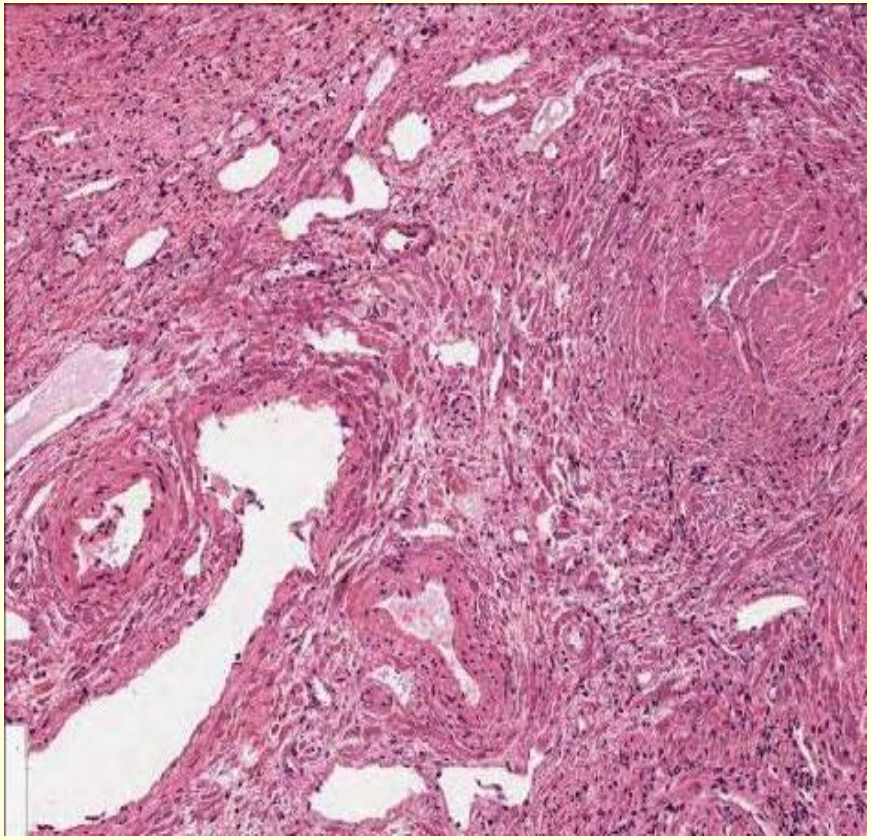
- 32/F Mass in liver ? cholangiocarcinoma. Wedge biopsy of non-lesional liver at time of laparoscopic staging.
- EPSR, orcein vic blue

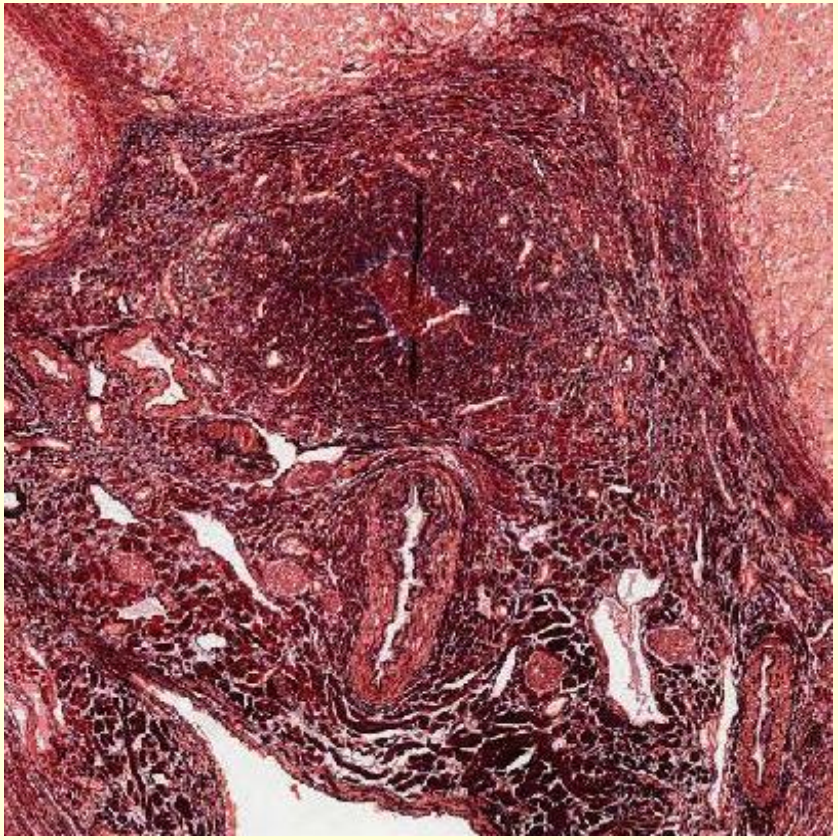












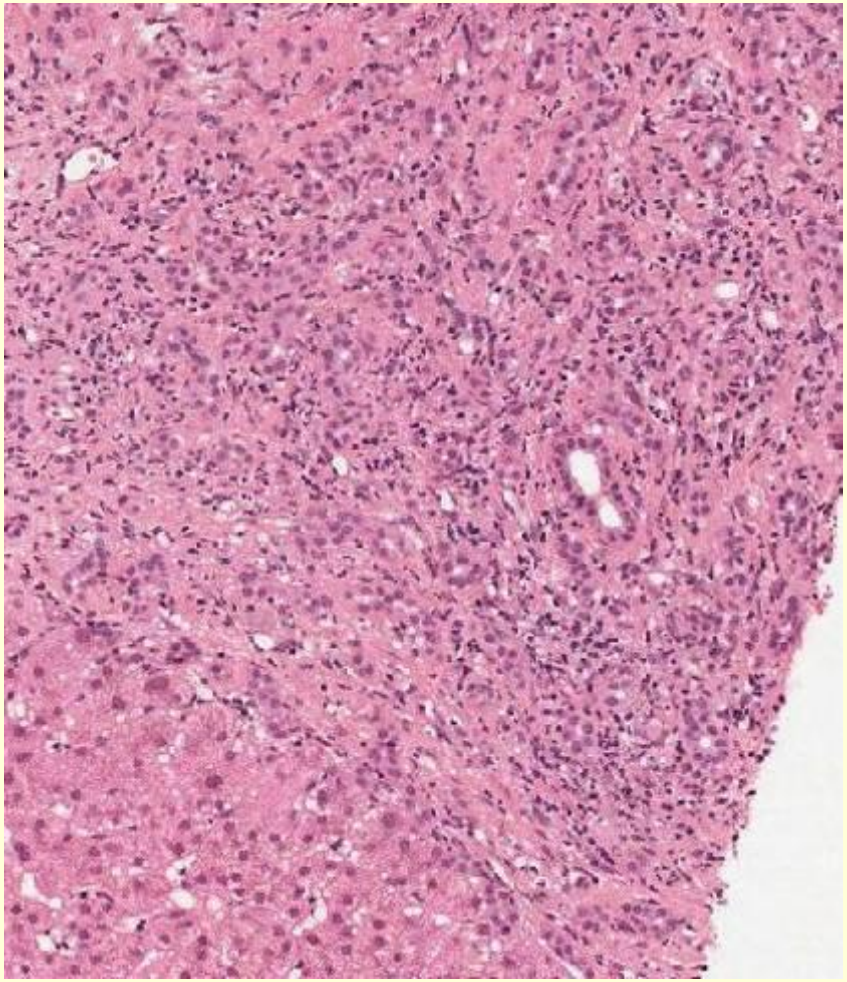
Diagnosis case 11

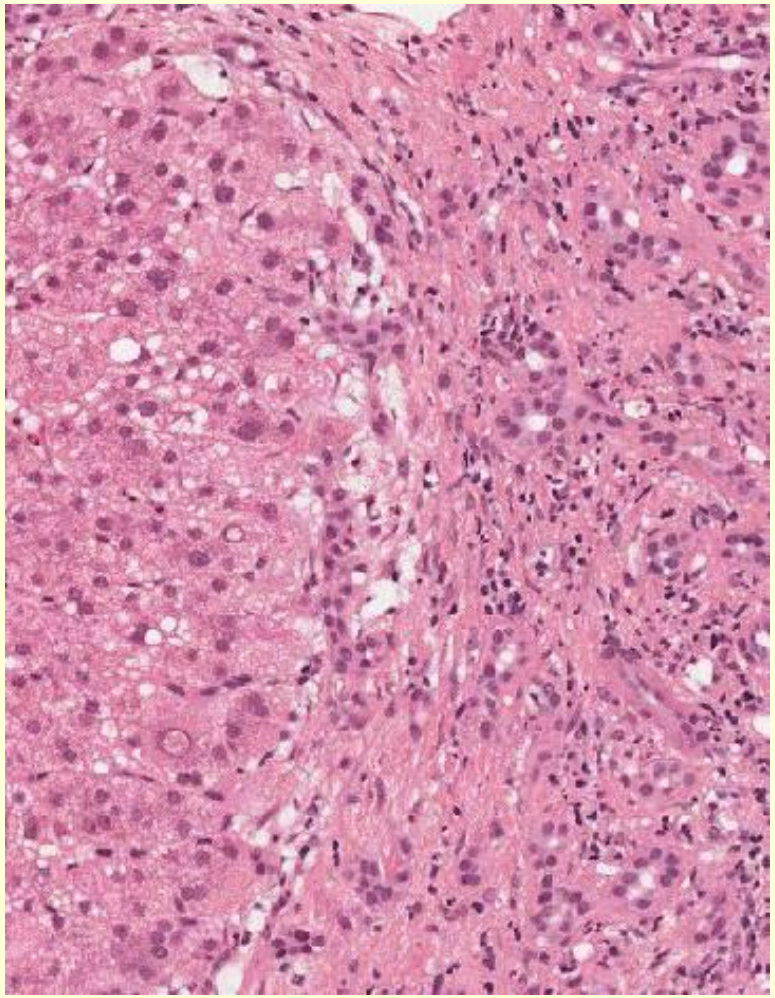
- Primary Sclerosing Cholangitis with large sclerosed ducts

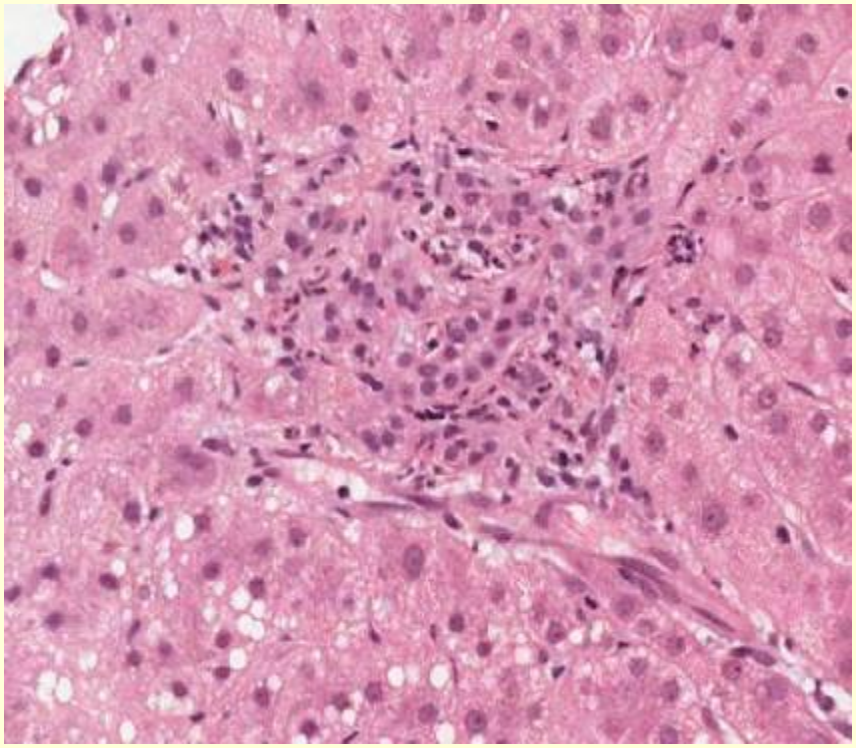
- F/I - Biopsy at time of diagnosis of cholangiocarcinoma near normal.
- Apparent history of PSC diagnosed several years previously but not being followed up...

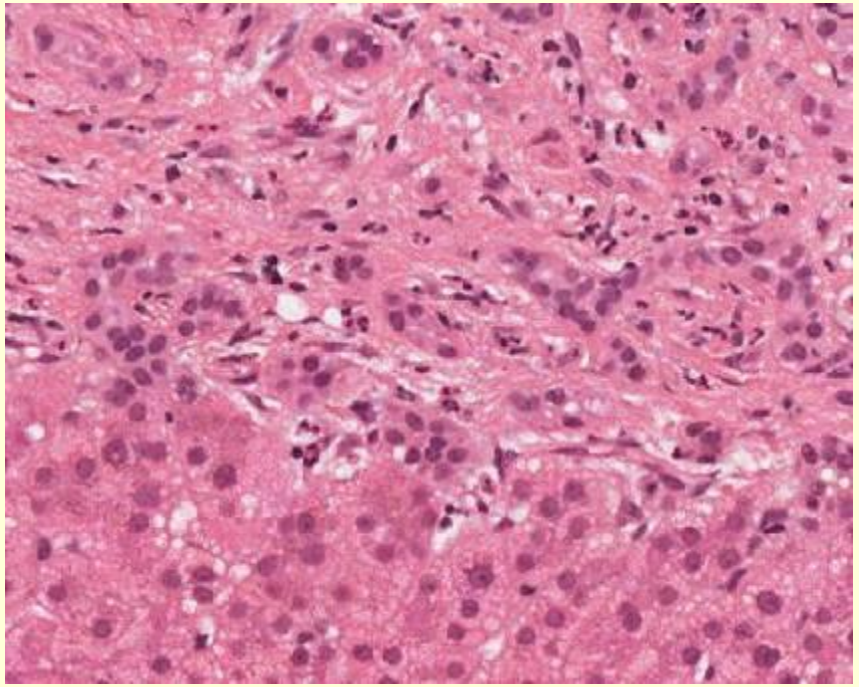
Case 12

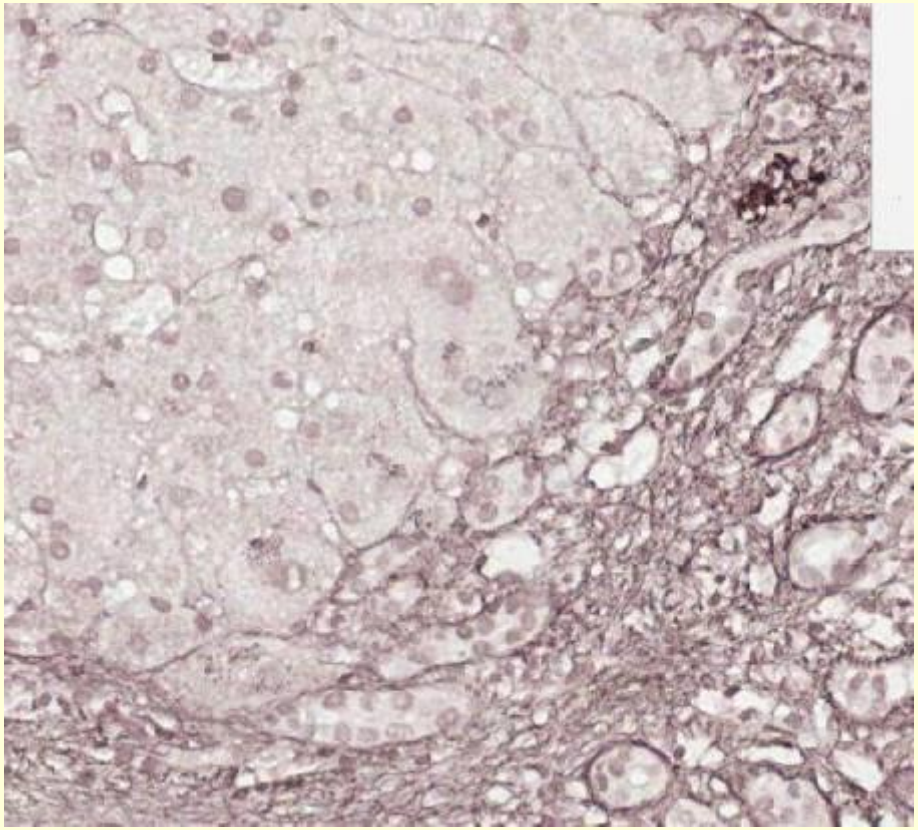
- 56/FAbdo pain, nausea, hepatosplenomegaly, ascites. Previous cholecystitis.
- Retic, CAB, PASD IHC PiZ

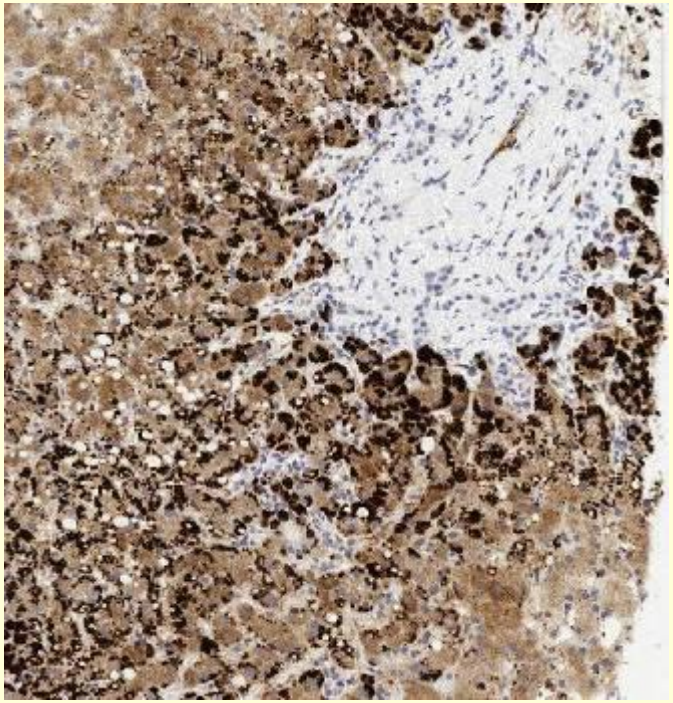




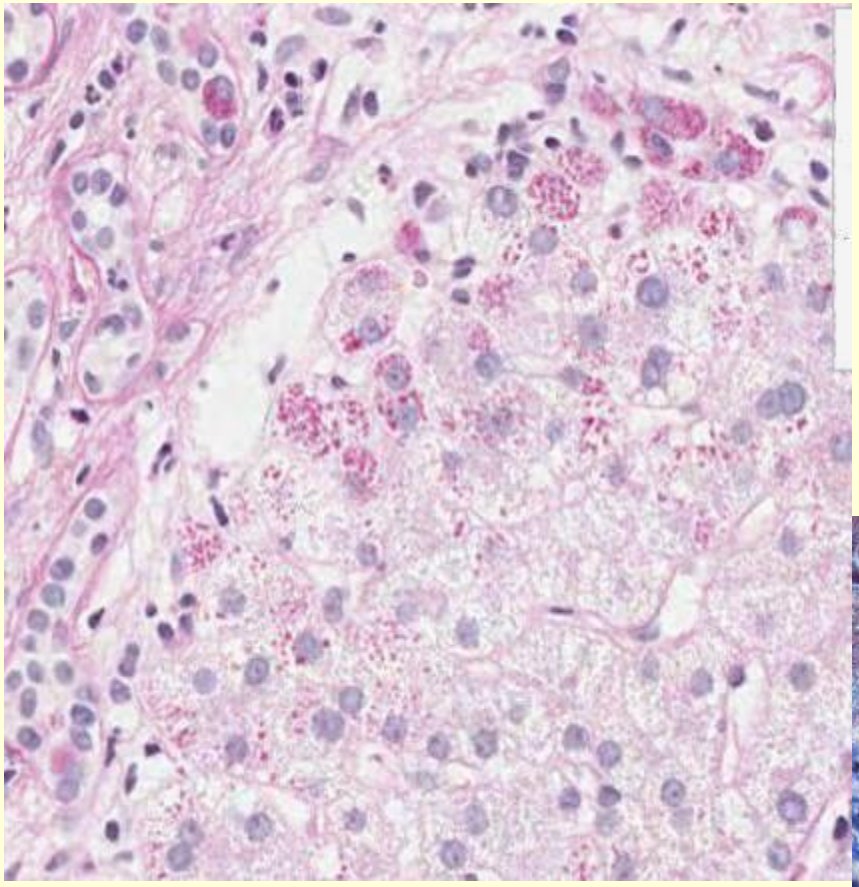




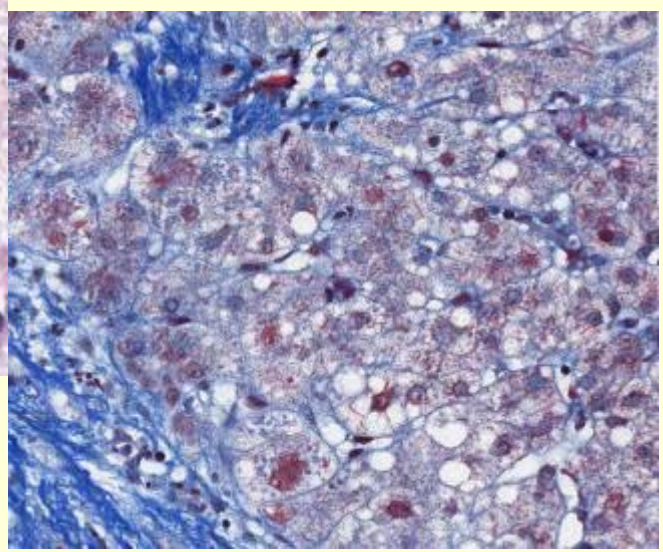




A1AT



PASD



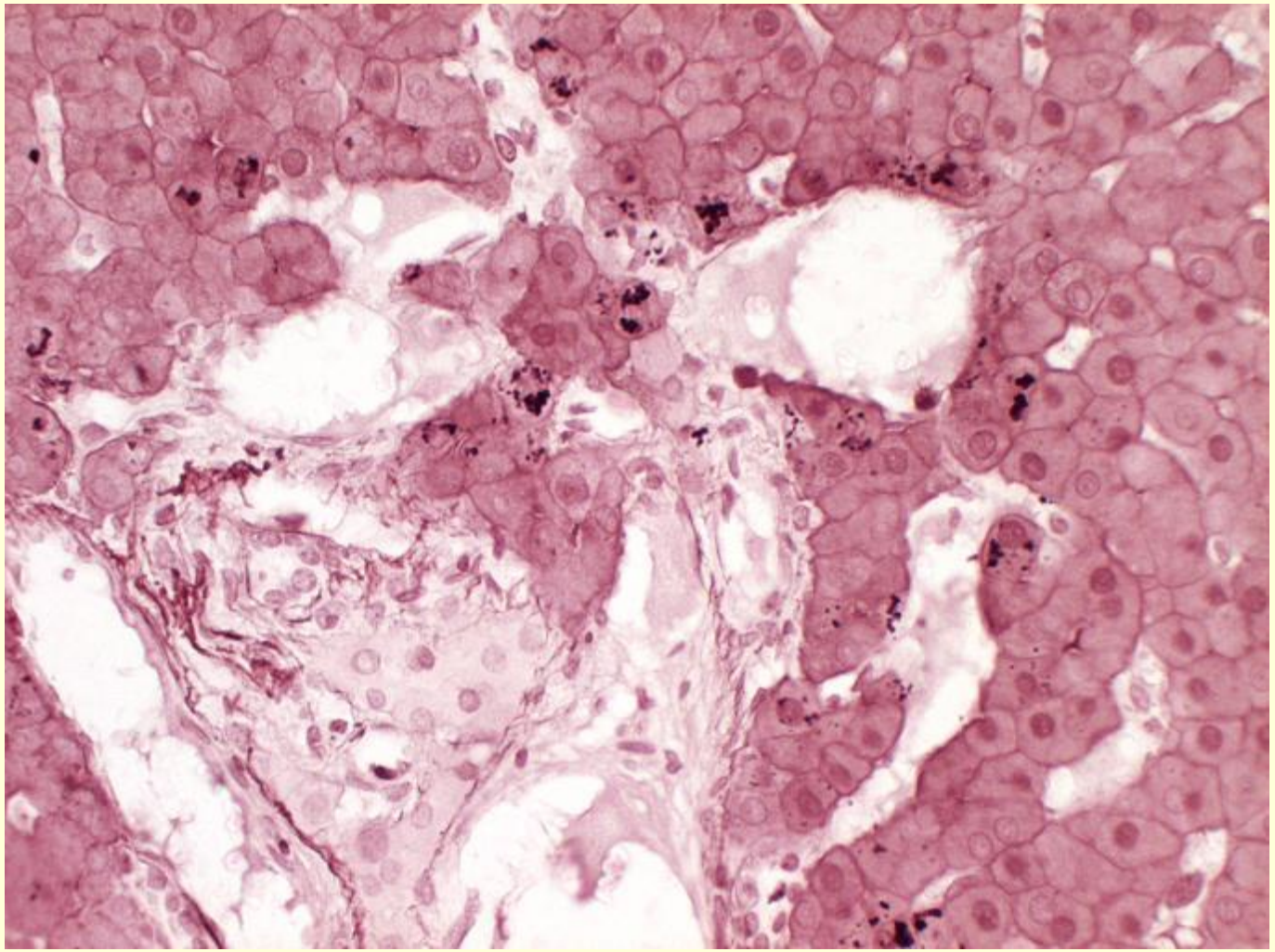
CAB

Diagnosis case 12

- Secondary biliary cirrhosis, with Alpha-1 Antitrypsin abnormal phenotype

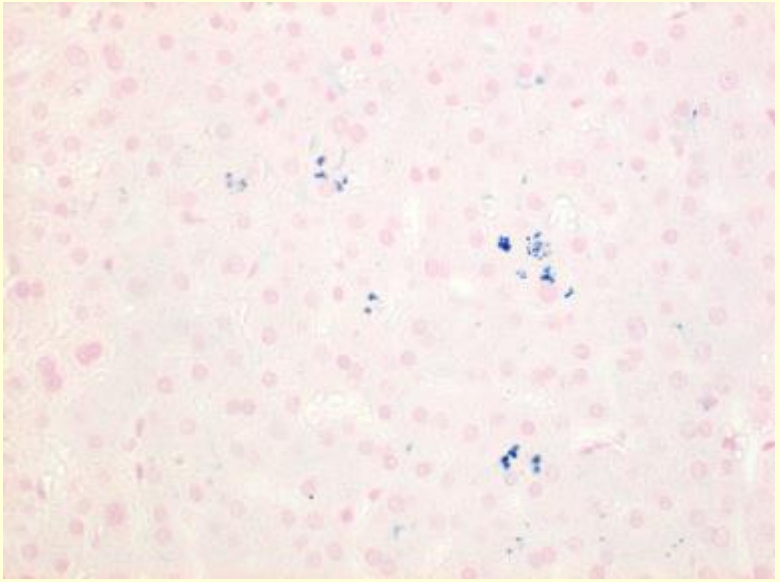
- Cholecystectomy complicated by complex stricturing at 10yrs, with biliary sludge and stones ie an ischaemic cholangiopathy
- MZ phenotype

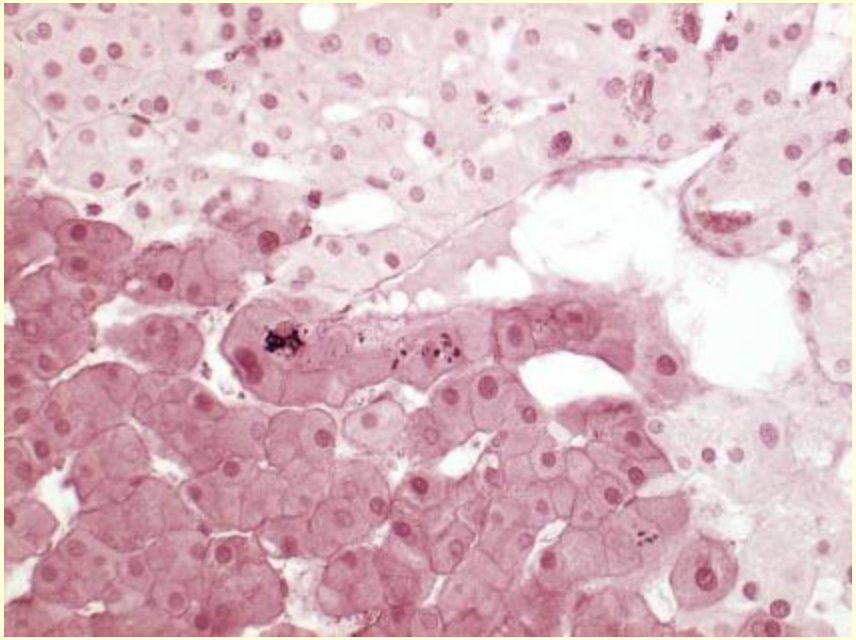
Robustness of CAP assessment…

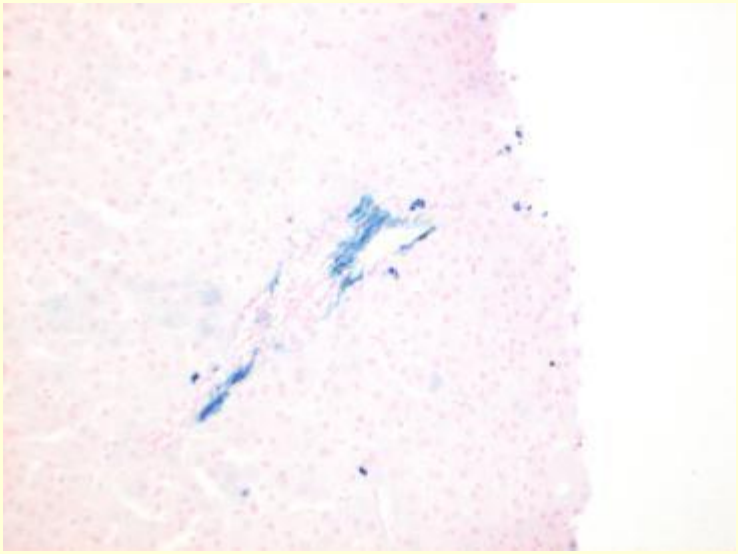


Orcien periportal CAP

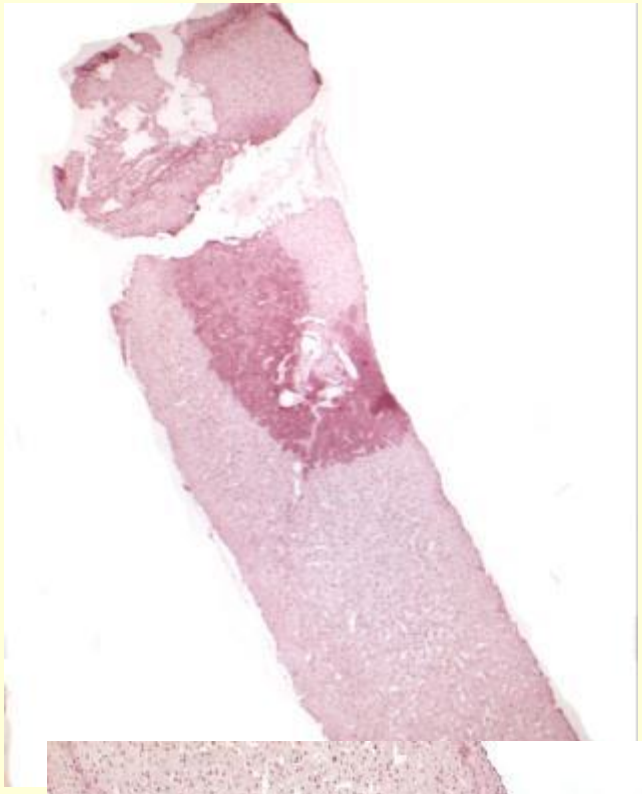
Victoria Blue – the same

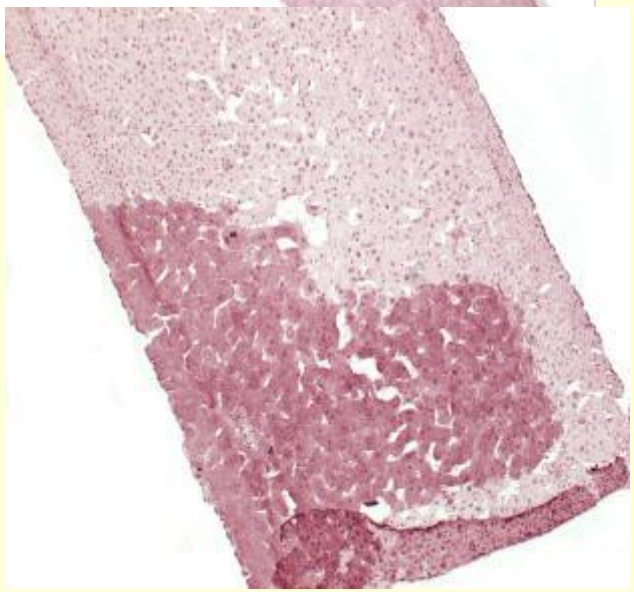


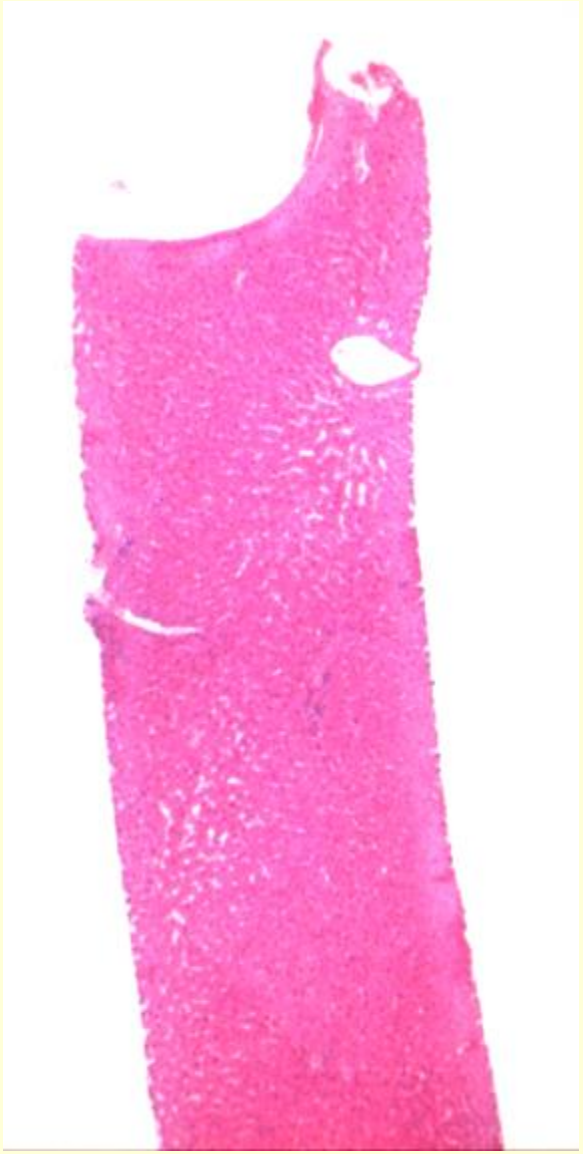




Lobular…



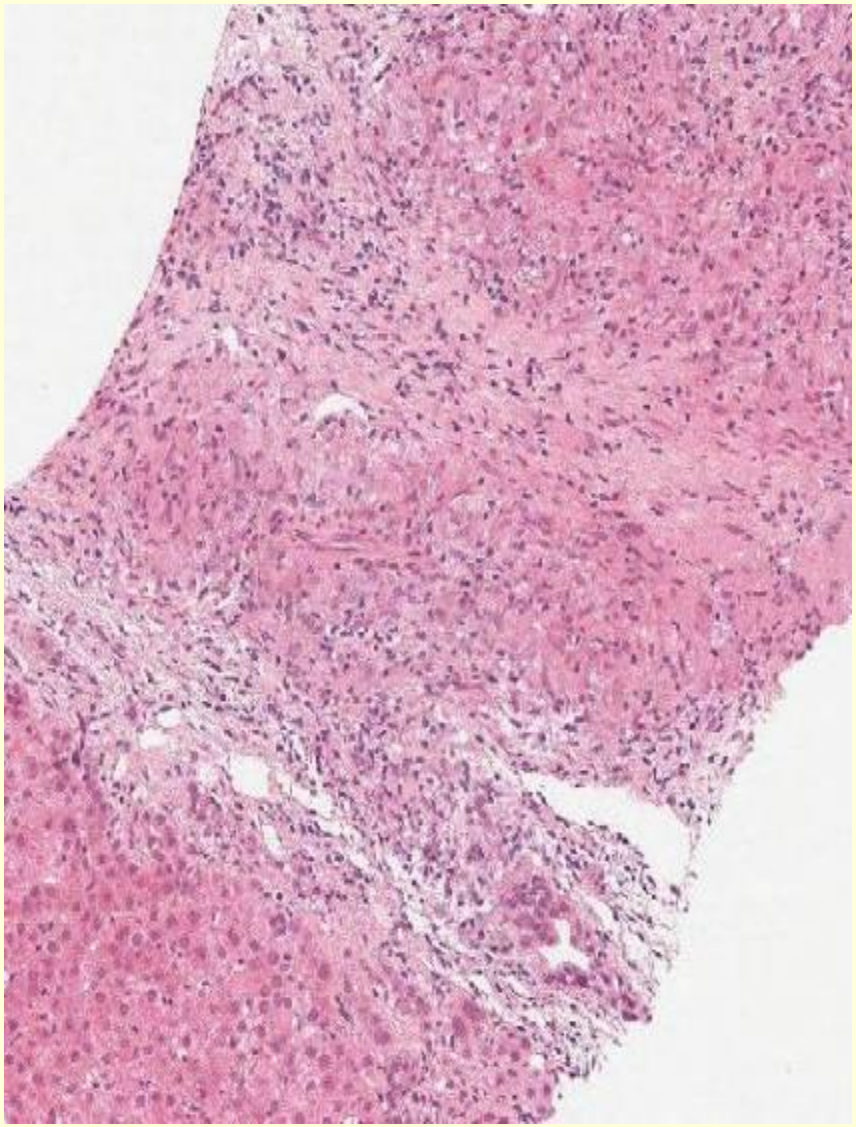


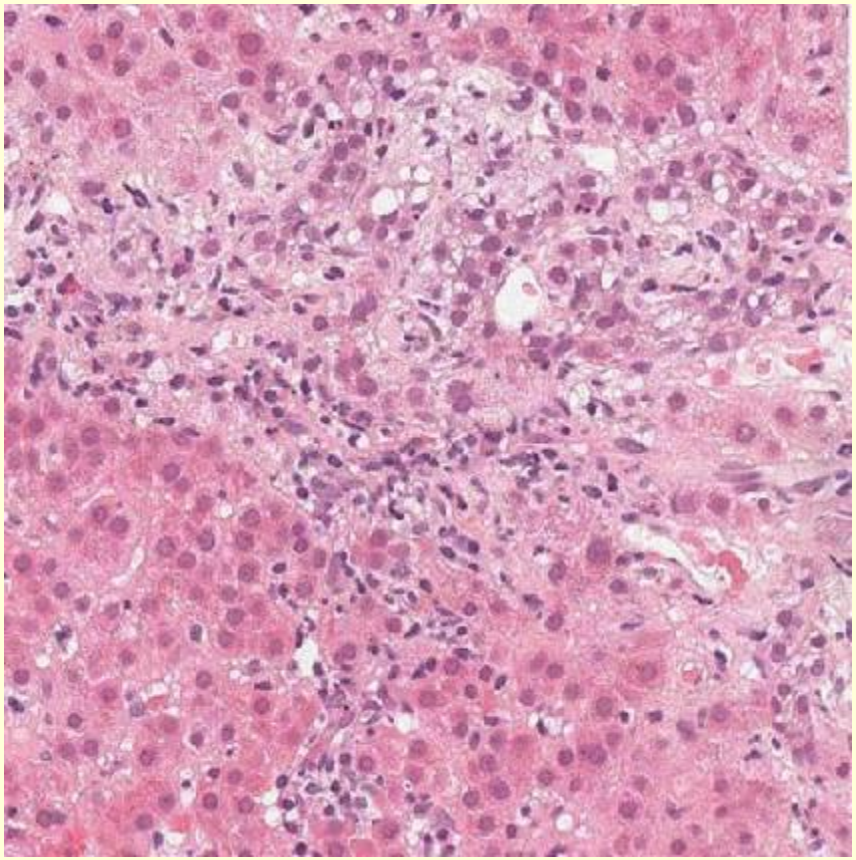


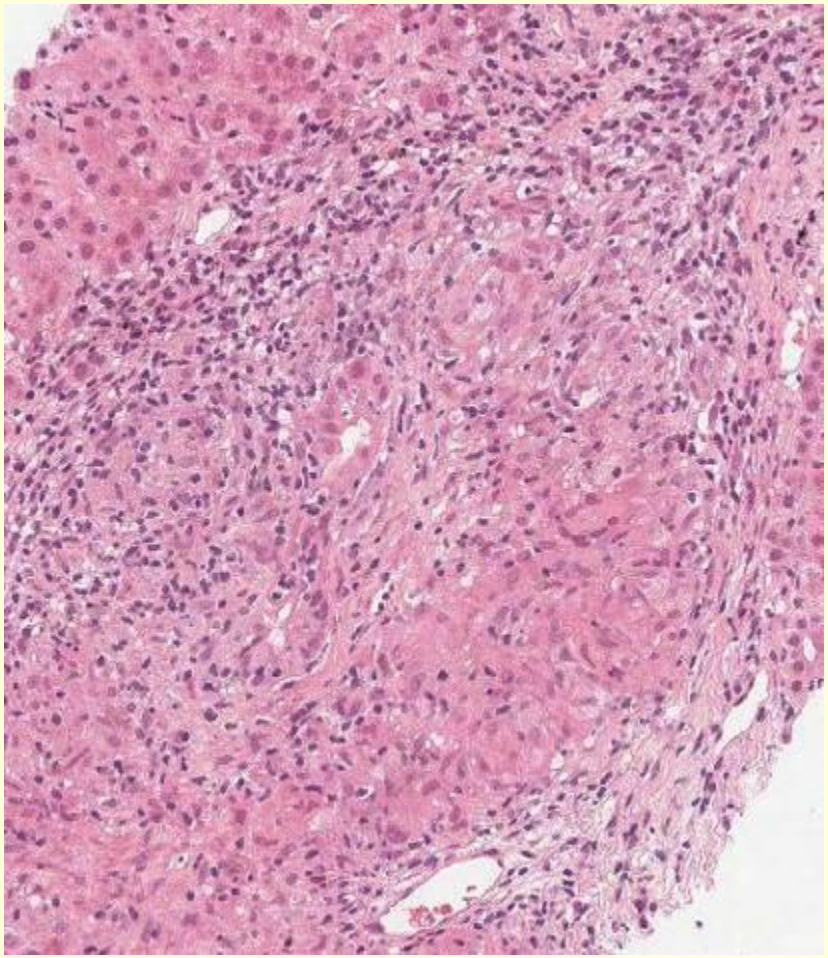
Normal liver…

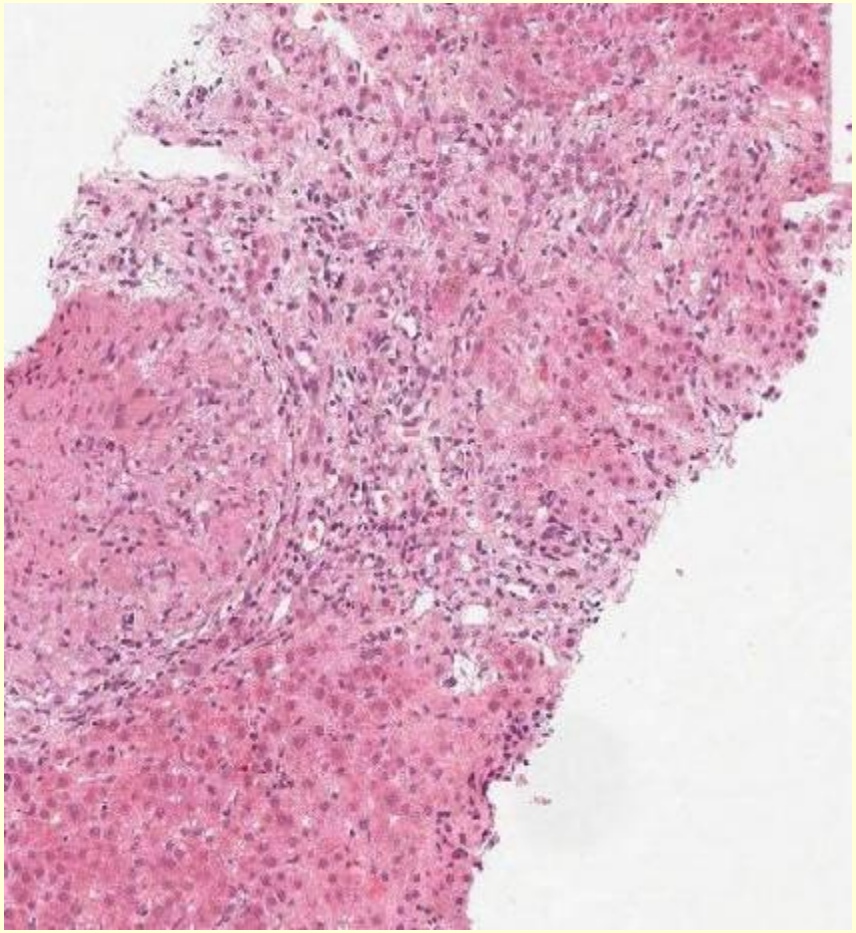
Case 13

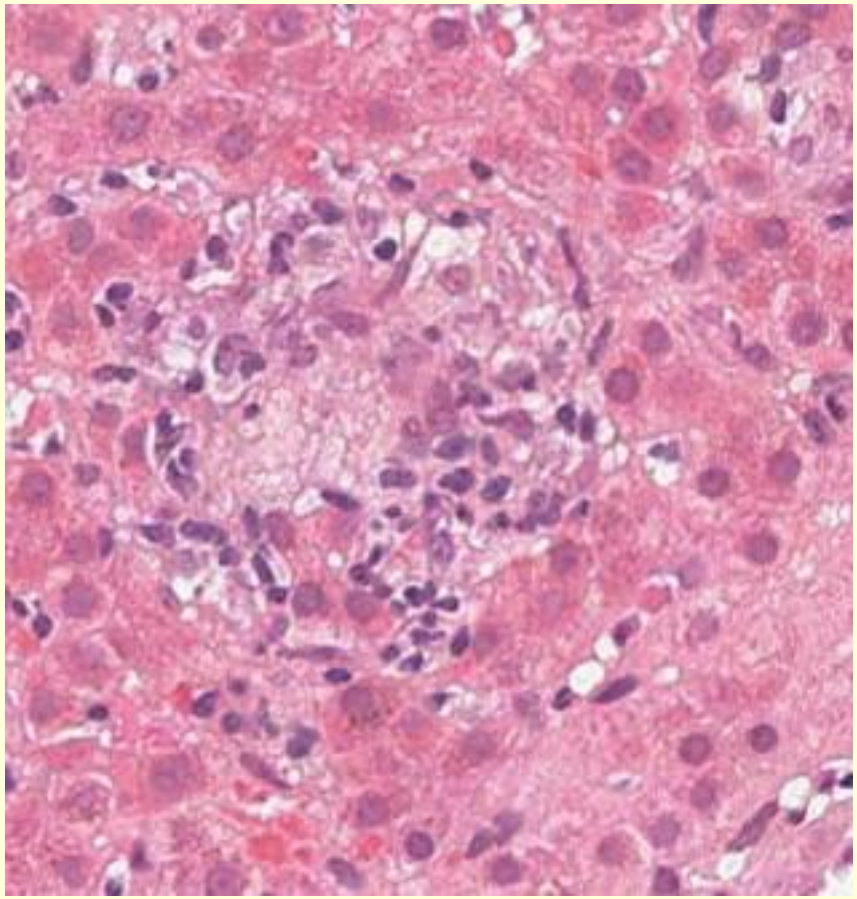
- 30/M previous high alcohol intake, Coeliac disease ?cause of hepatosplenomegaly.
- EPSR, orcein,

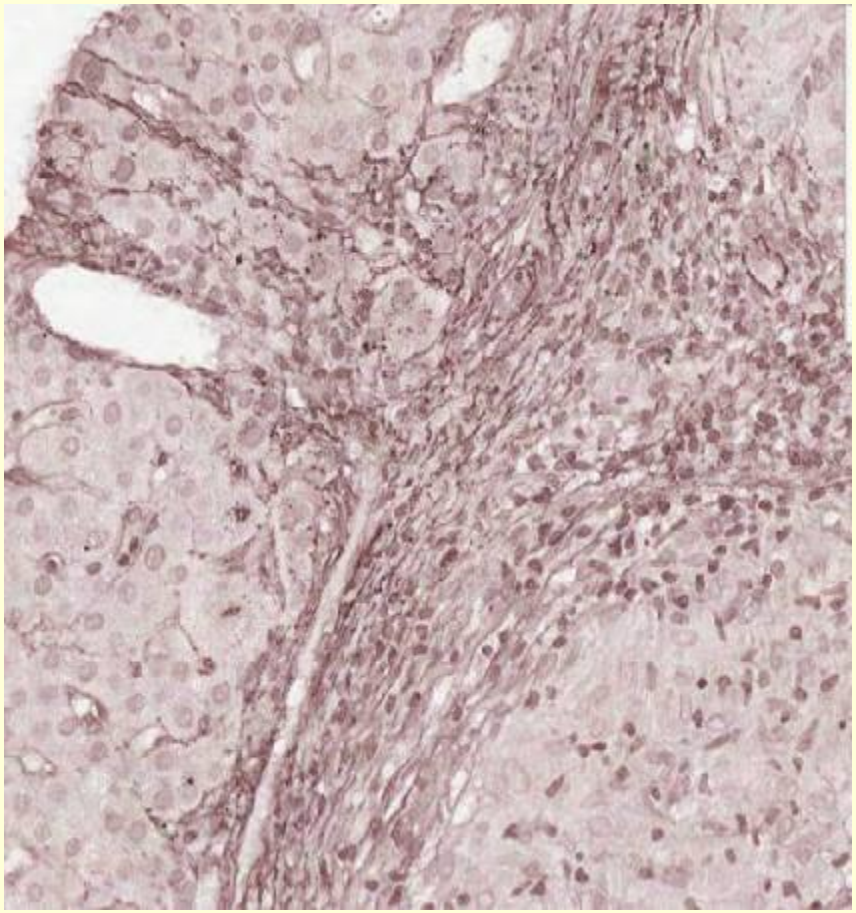




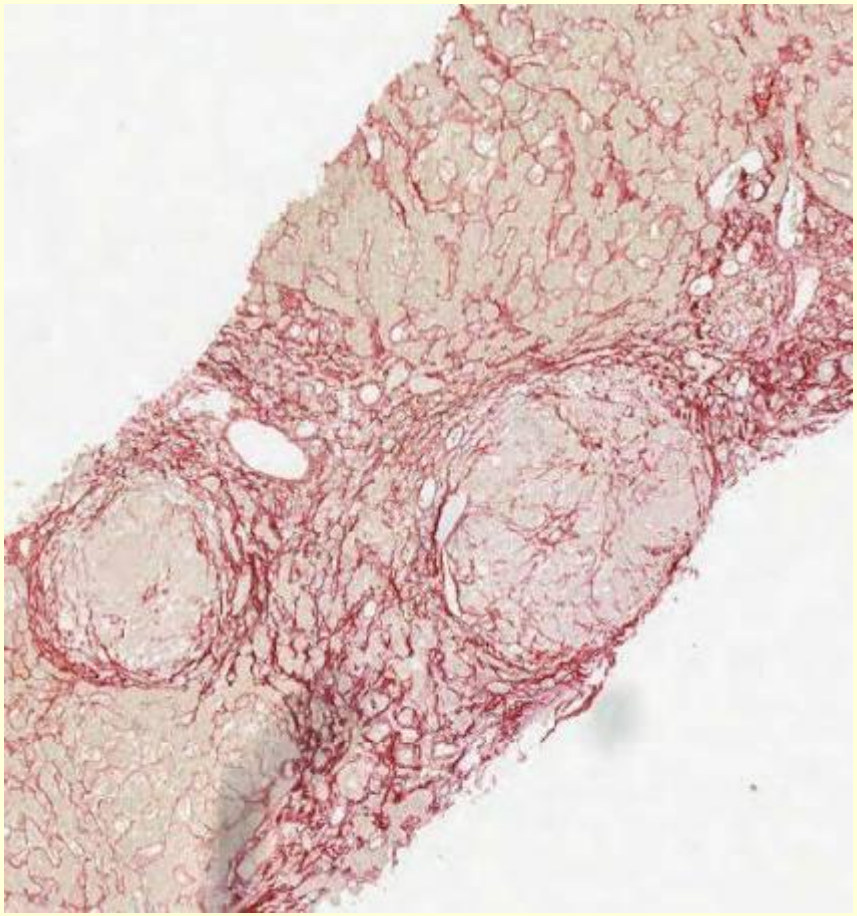








orcein



EPSR

Diagnosis case 13

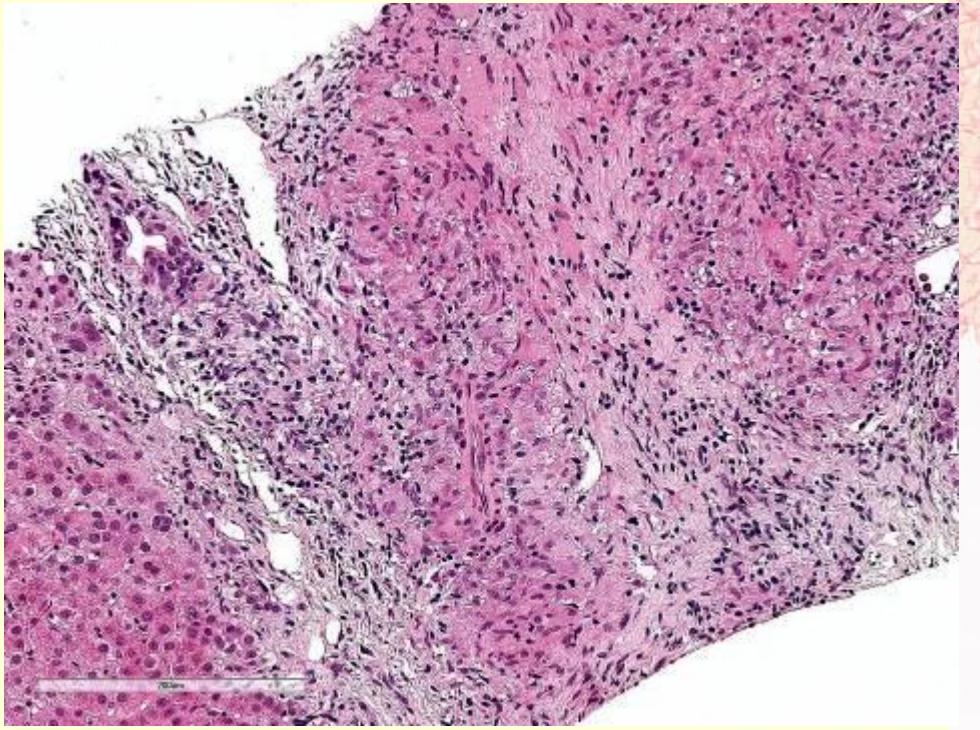
- Granulomatous cholangiopathy – possibly Sarcoidosis

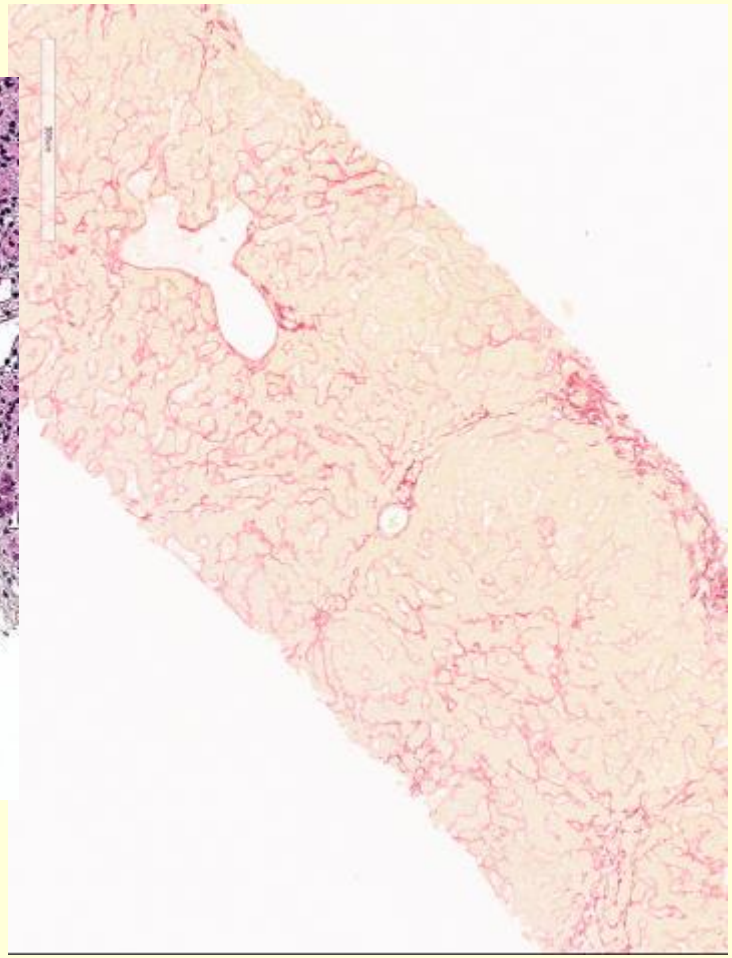
- Coeliac diagnosis – secure; responded to gluten free diet
- Raised Alk Phos and severe pruritis. AMA negative
- *Mediastinal lymphadenopathy*, ACE >120 IU/l (20-70)

Spectrum of sarcoid in liver

- Predominantly portal involvement with fibrosis, +/- lobular granulomata
- Cholestatic – can be PBC like or PSC, about 1/3 with ductopenia (58%)
- Inflammatory – lobular +/- portal (41%)
- Vascular – granulomatous phlebitis portal or hepatic – NRH like, v rare BCS (20%)
- Mass forming – sarcoidoma (6%)

Devaney Am J Surg Pathol 1993





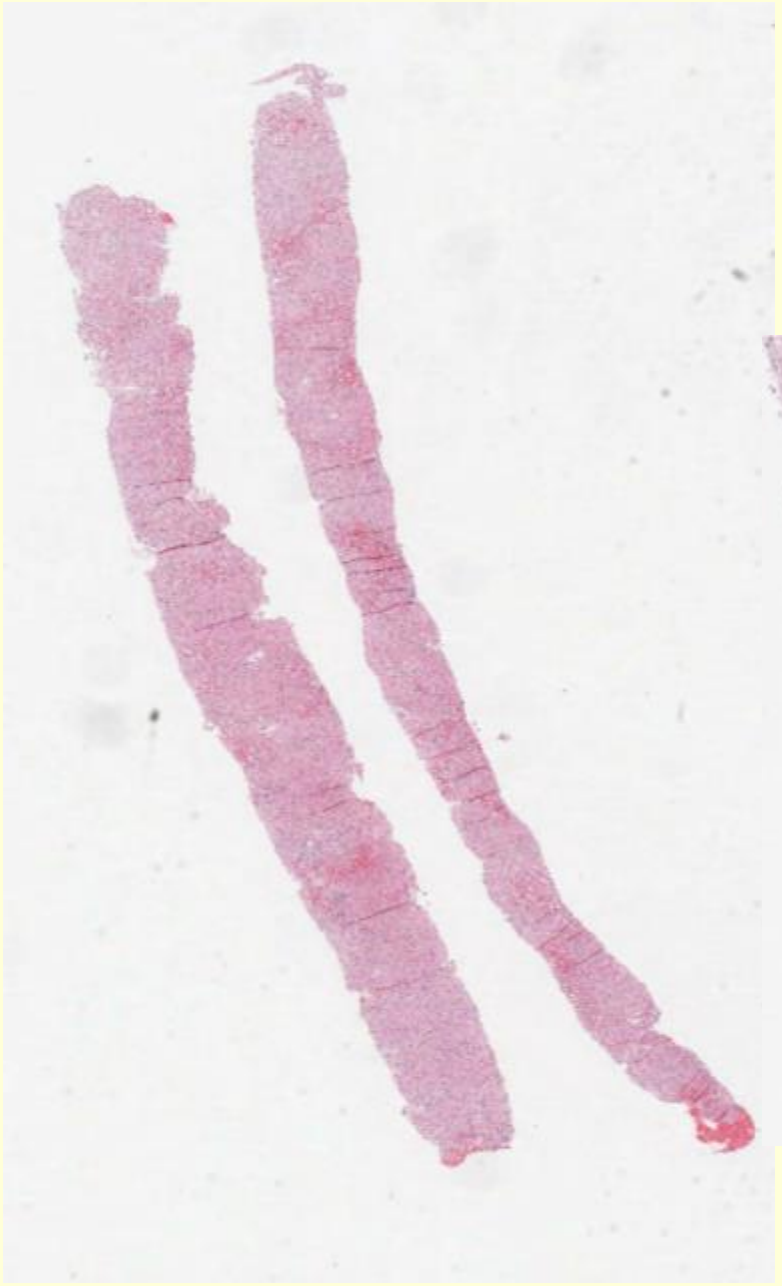
Case 13

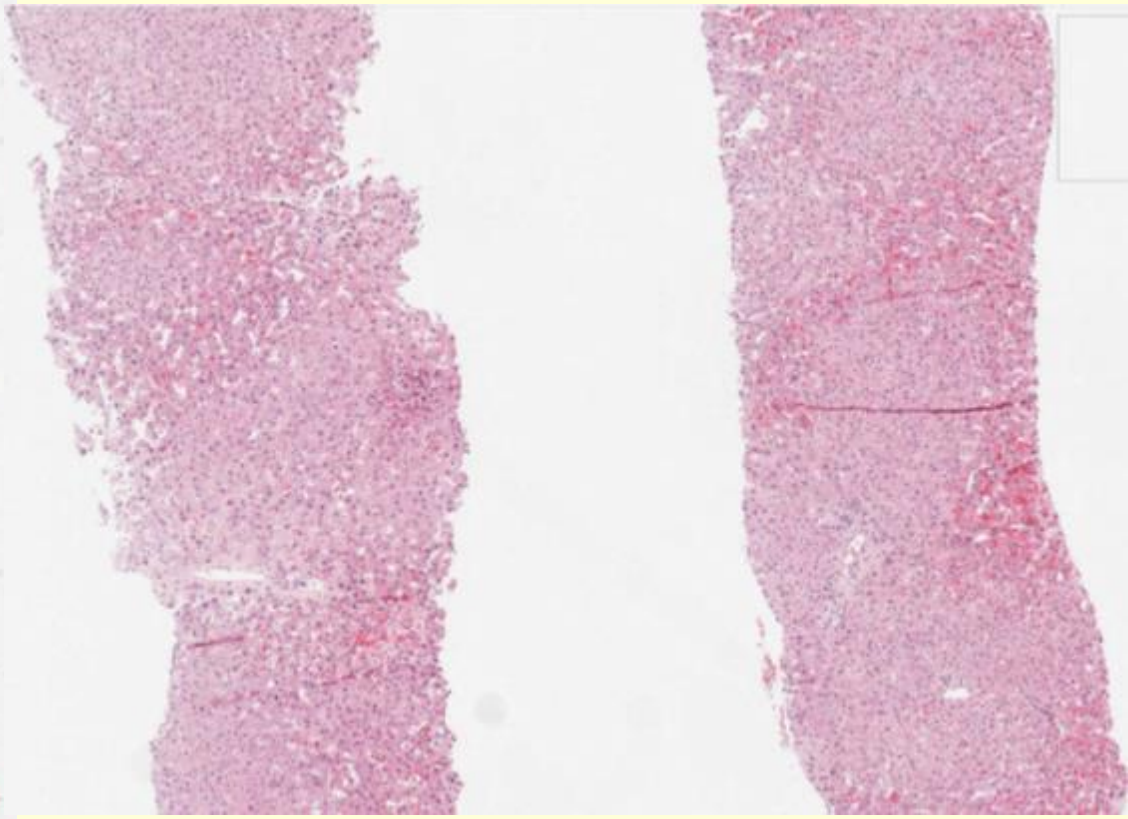
- Possible early developing nodular regenerative hyperplasia
- Very difficult to assess on needle cores
- Subtle architectural and vascular abnormalities often missed

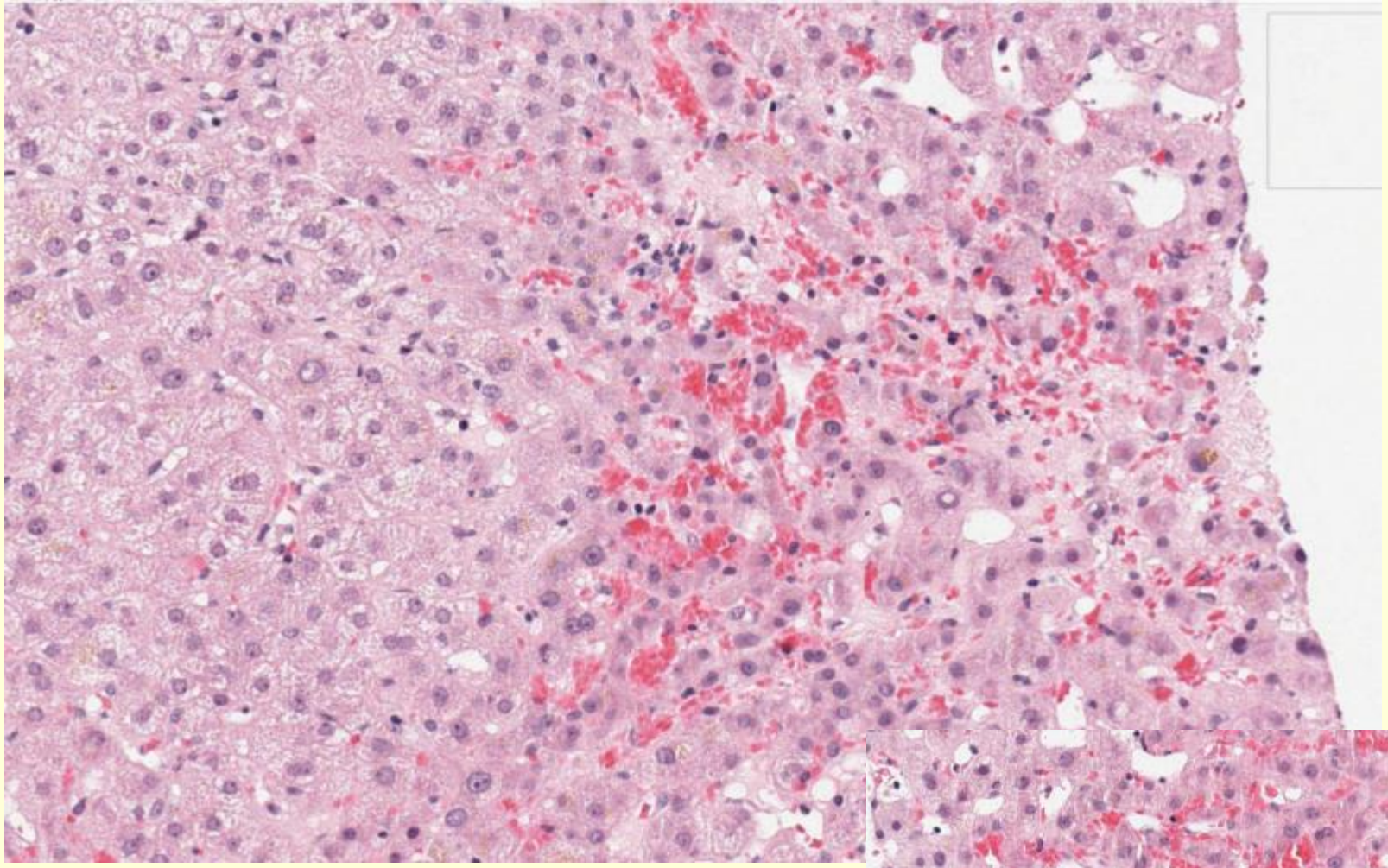
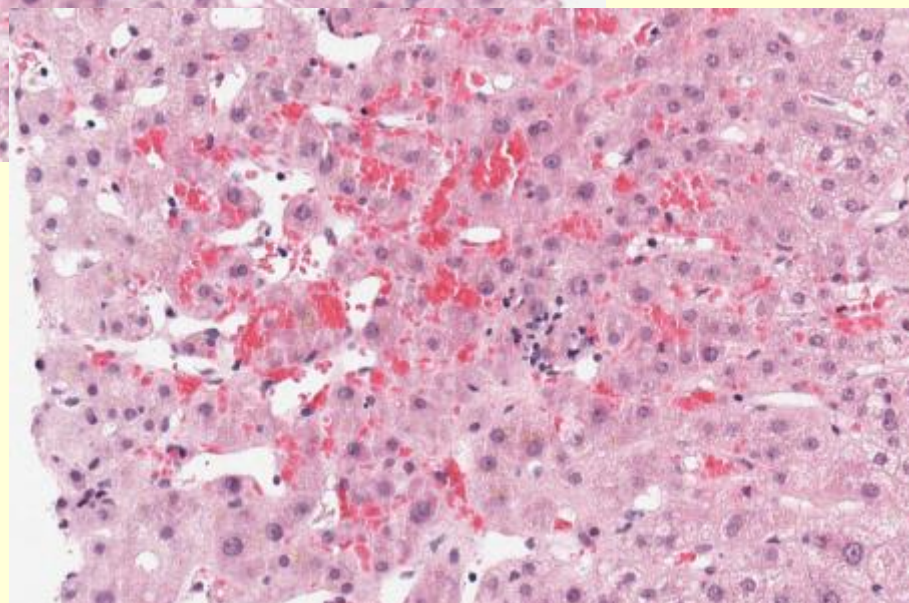
Case 14

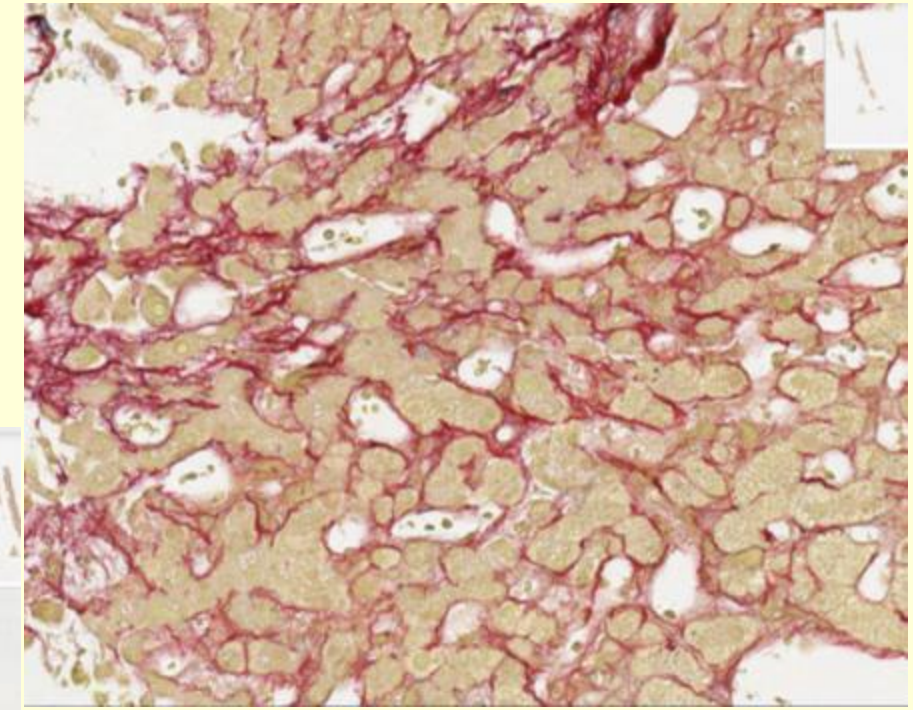
- 78/M Cholestatic LFTs, non-invasive markers suggest cirrhosis ?cirrhotic

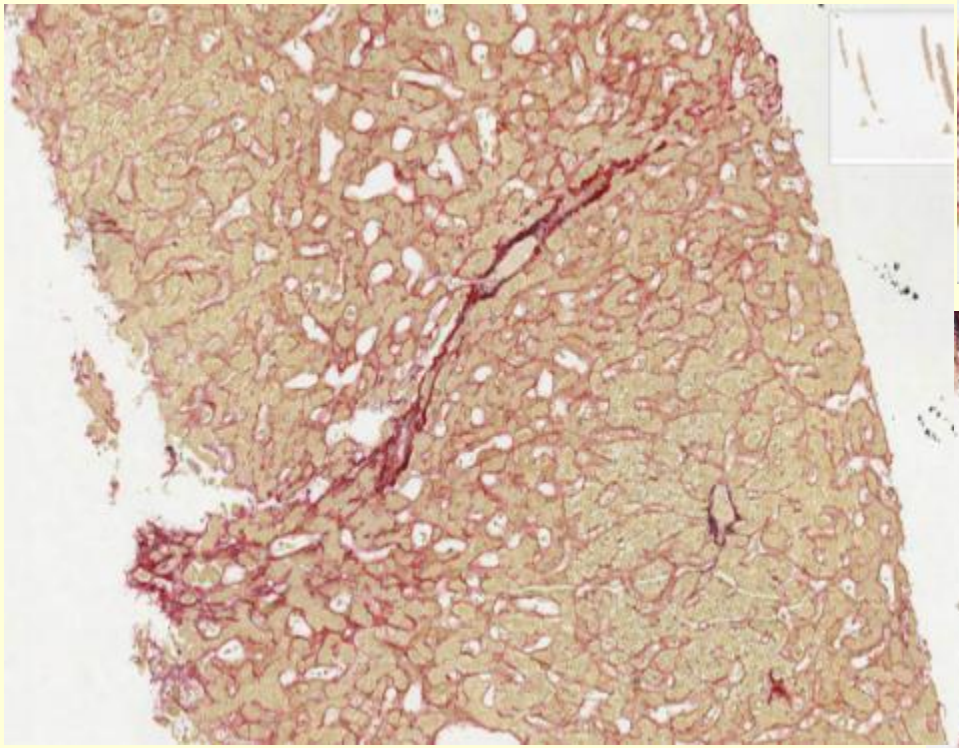
- EPSR, CK7

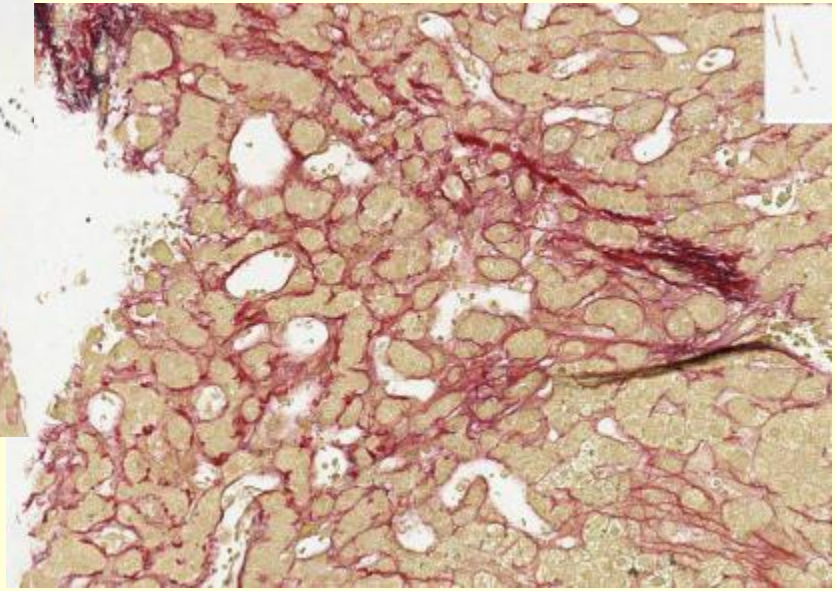




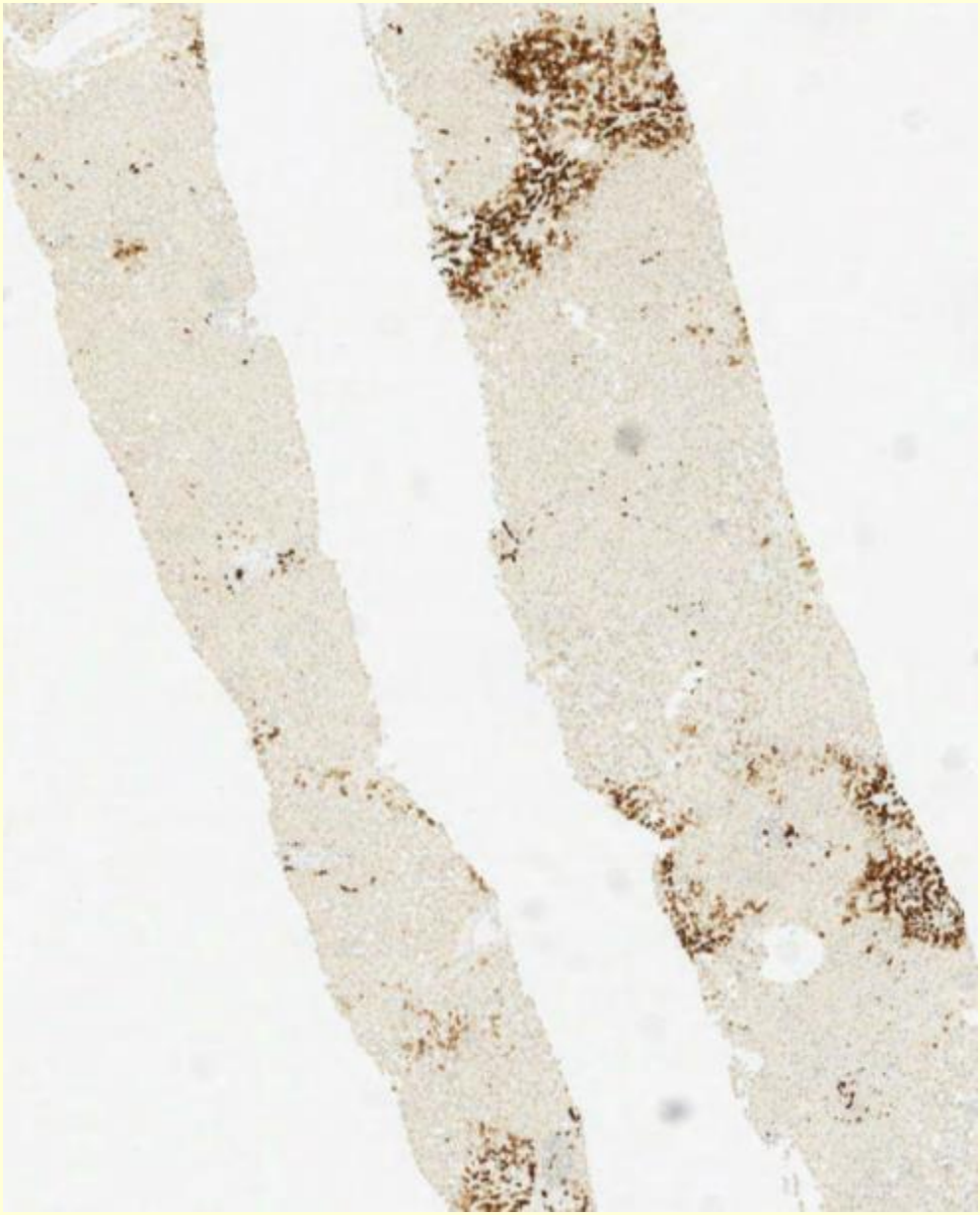



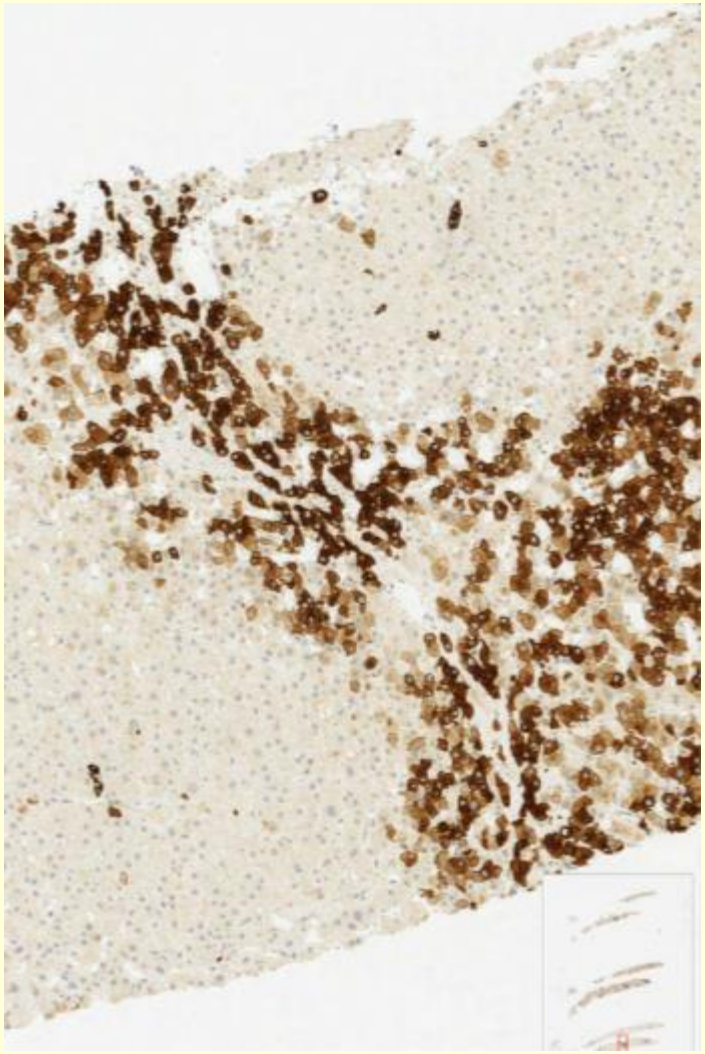




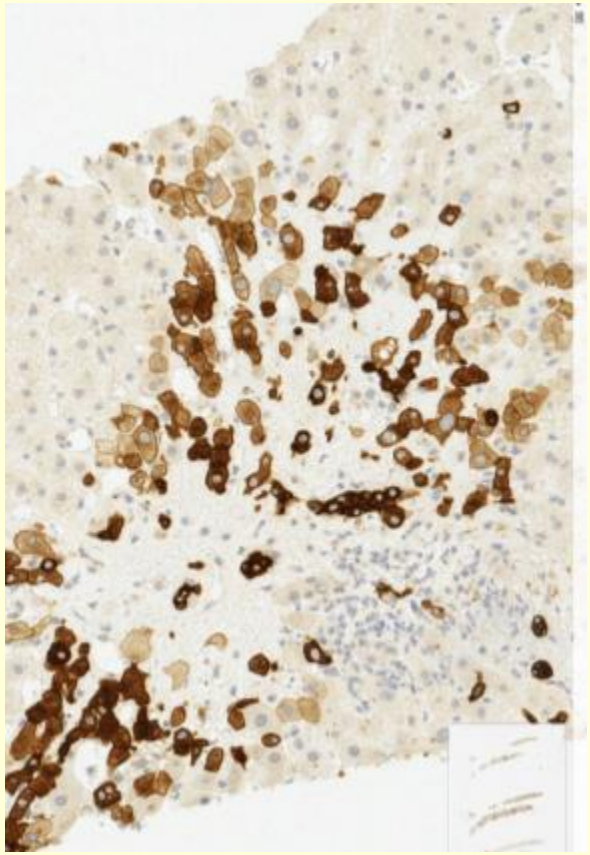


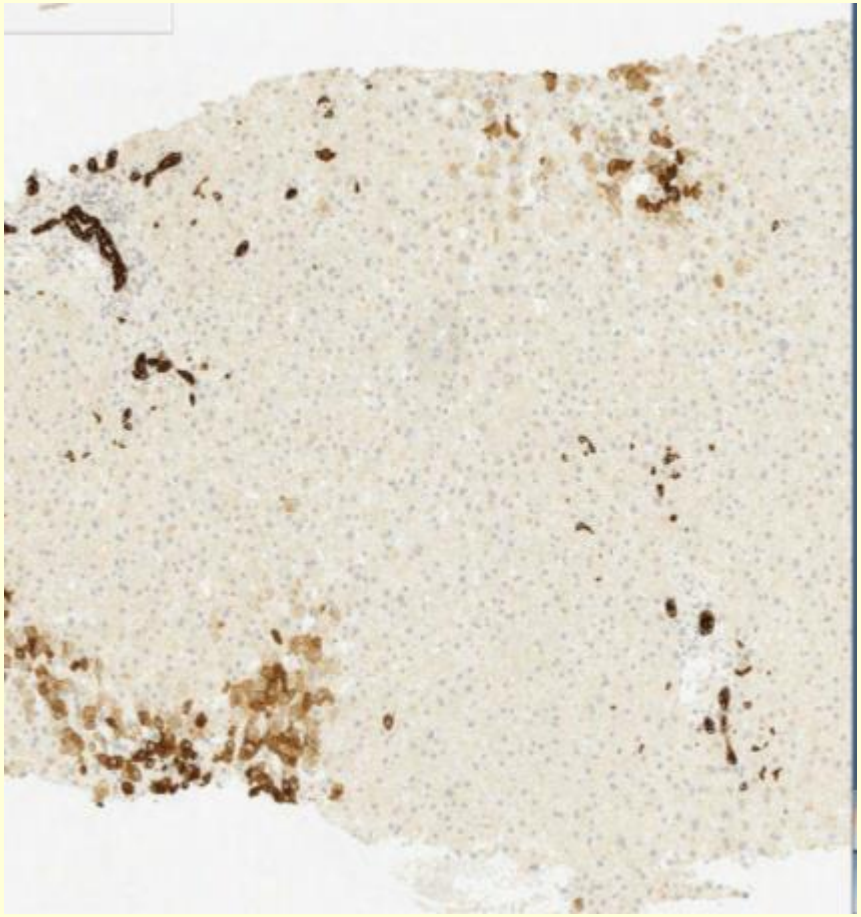
EPSR





CK 7





Diagnosis case 14

- Marked perisinusoidal fibrosis and atrophy of the hepatocytes in perivenular areas with patent venules

- F/I Aortic valve disease with CCF.
  - Chronic venous outflow obstruction / 'Cardiac Sclerosis'

Key Points

- Fatty Liver Disease is common – both alcohol and NAFLD
- Either may be an important secondary, or even primary pathology in patients being investigated for abnormality of liver function
- Liver biopsies may be tricky – are all features explicable by one diagnosis; does your report address the clinical query?

Key Points

- Biliary disease can be subtle, (and is frequently missed), hi Alk Phos and biliary interface are important clues.
- Less typical cases are increasingly being biopsied.
- Vascular abnormalities can be subtle, (and is frequently missed) and ‘cholestatic’
- You need good quality histochemistry and Clinical Information to generate a helpful report.