Highlights from Gnomes Meeting
Adelaide, Australia
April 27th – 30th 2016

"Patterns of Acute Liver Injury"
(Host – Alastair Burt)

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Annual Meetings of the International Liver Study Group

- First meeting, July 1968, University of Zürich (Martin Schmid)
- Currently 14 circulating members (7 Europe, 5 North America, 2 Australia)

- Cases circulated prior to meeting (2-3/ person) to cover particular theme
- Suggested diagnoses submitted prior to meeting and collated by local organiser

- Cases presented and discussed further at meeting (2 days)
- Aim to reach consensus and provide summary/guidelines
  - Usually a 2 year cycle – 2nd year focuses on specific areas of interest
  - **2015 – "acute hepatitis & acute liver failure"**
  - **2016 – "patterns of acute liver injury"**

Feedback from Liver Update Meeting, Harrogate, December 2015

international speakers
quality assurance in UK (including no-specialist pathologists)
presentations should be focussed rather than general
teaching sessions to incorporate cases sent for eqa
master classes to be presented with powerpoint and uploaded to website
bigger venue
acute hepatitis/chronic distinction
HCA made easy
herbal and unconventional side effects
copper defects and significance
bit slower presentation, may be 3 days
deadline for registration so all people that want to come are able to
AIH - chronic v.acute fibrosis
Biliary pathology
similar variety of topics
develop key points for reporting biopsies
nomenclature
AIH - chronic v.acute fibrosis
transpant pathology
WHO classification of tumours
definitions/diagnosis of acute/chronic hepatitis
grade/prognostic factors HCC
discussion of fibrosis scoring in SH
focussed discussion on chronic v. acute hepatitis
sufficient size venue to accommodate all who wish to attend

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Plan of Talk

1. Role of liver biopsy in the distinction between acute and chronic hepatitis

2. Presentation of selected cases from Gnomes 2016

Acute and Chronic Hepatitis - Definition

1. **Duration of disease**
   - Acute < 6 months
   - Chronic > 6months

2. **Histological Findings**
   - pattern of inflammation
   - presence of cholestatic features
   - presence of fibrosis

- Areas of overlap exist for duration and histology
- Most of the common causes of acute hepatitis can also cause chronic hepatitis
  - ➢ e.g. Viral agents, drugs, autoimmune hepatitis
- Distinction between acute and chronic hepatitis may be difficult

Patterns of Inflammation in the Liver

- Portal Inflammation
  - Most chronic liver diseases (e.g. viral, autoimmune)
  - Also seen in acute hepatitis
- Lobular Inflammation
  - Main pattern in acute hepatitis
  - Varying degrees of lobular inflammation also commonly present in chronic viral and autoimmune hepatitis
  - Predominant pattern in some chronic liver diseases (e.g. fatty liver disease)
- Mixed portal and lobular inflammation

Pattern of inflammation cannot reliably distinguish acute from chronic hepatitis

- Clinical context
- Assessment of fibrosis

Acute versus Chronic Hepatitis - Histological Findings

	Acute	Chronic
Pattern of inflammation	Mixed portal/lobular (mainly lobular)	Mainly portal/periportal (but may sometimes involve lobules)
Cholestatic features (e.g. bilirubinostasis, ductular reaction)	Common	Less common (except in progressive disease – associated with fibrosis)
Fibrosis	Mild (e.g. portal expansion, zone 3 collapse - reversible)	Variable (may progress to cirrhosis)

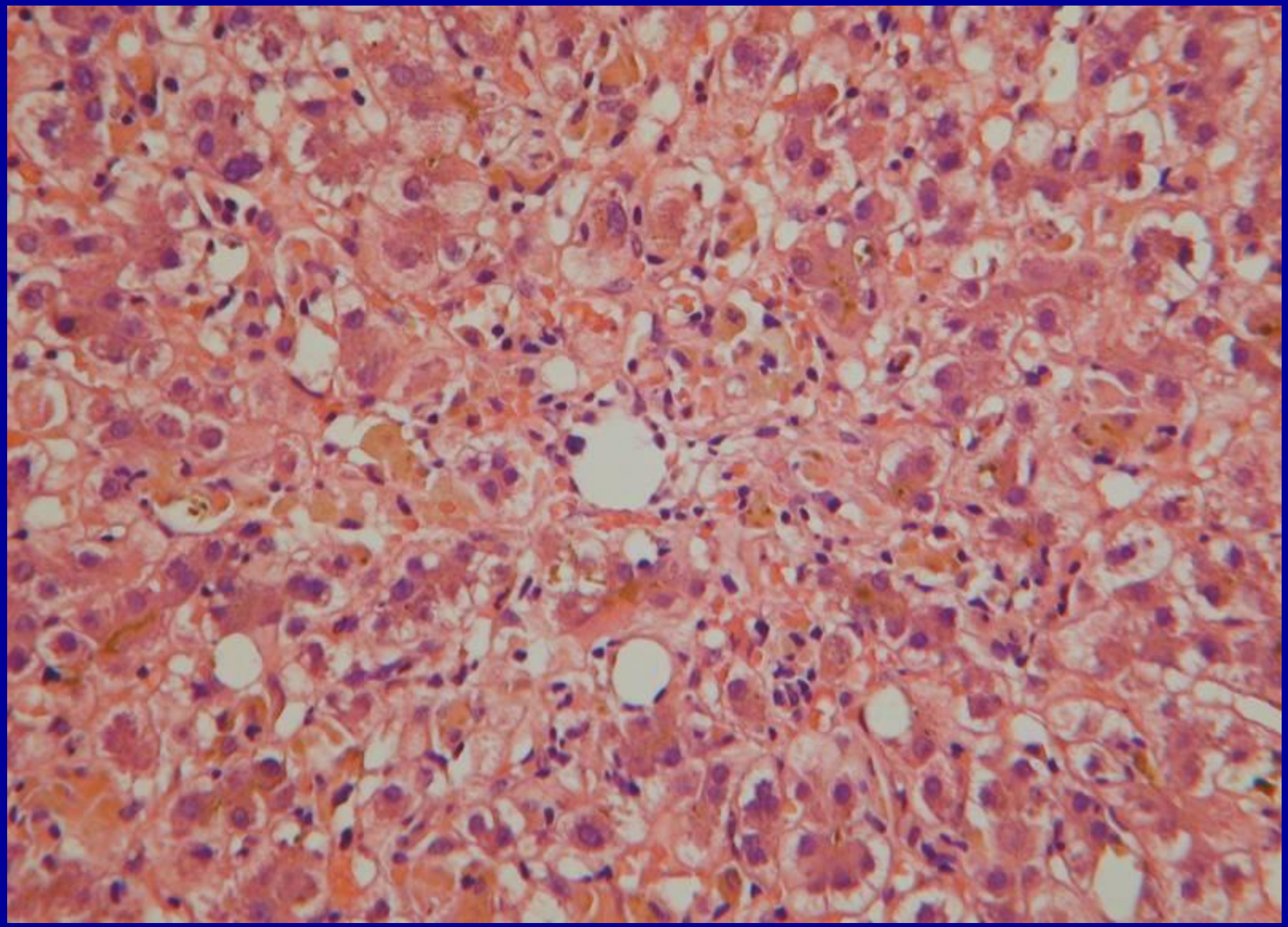
Acute Lobular Hepatitis
Histological Findings in Liver Parenchyma

1. **Inflammatory Infiltration**
   - mainly lymphocytes (T cells >> B cells)
   - plasma cells (esp in AIH)
   - neutrophils (esp in alcoholic hepatitis)
   - eosinophils (esp in drug reactions)

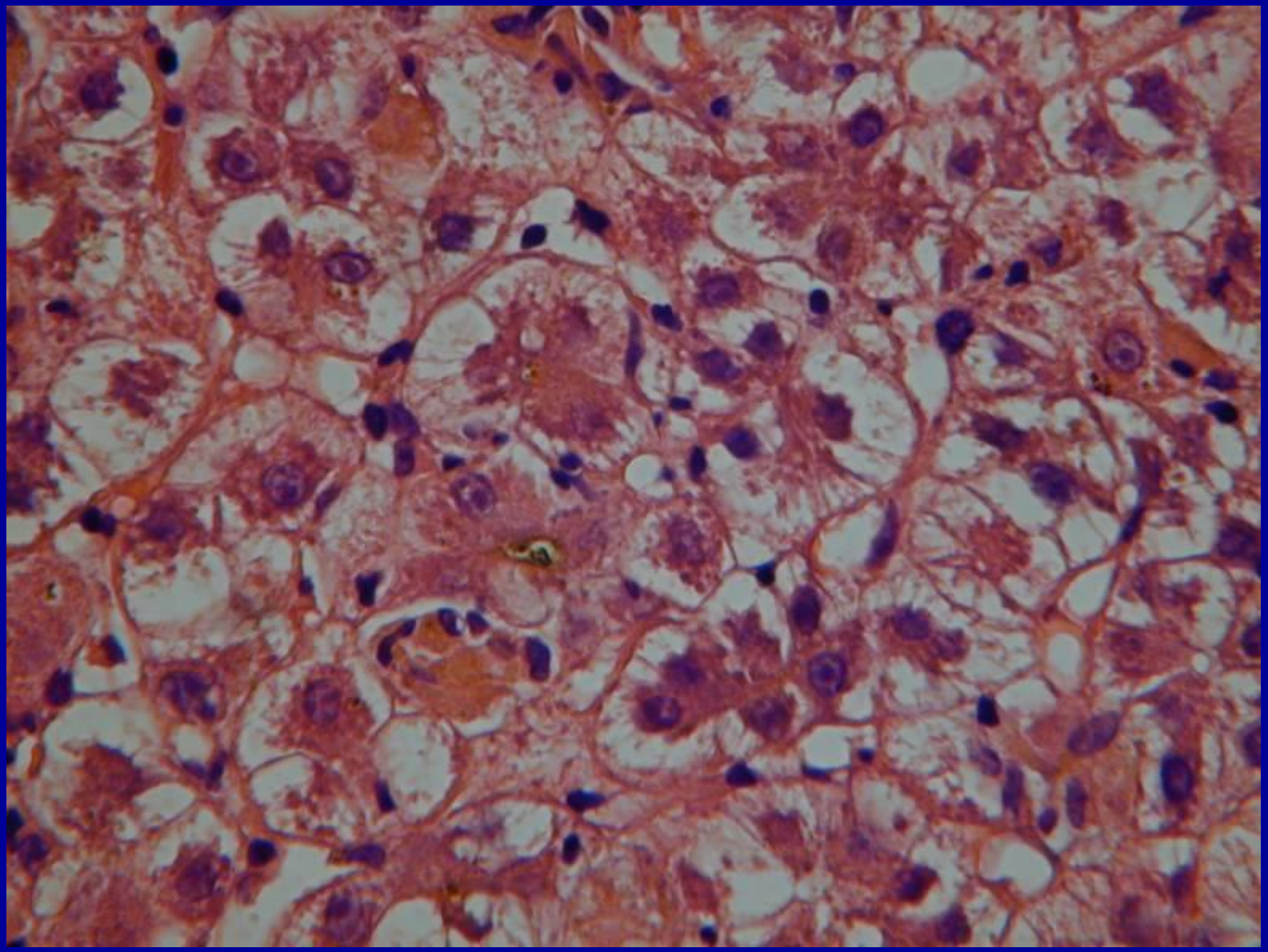
2. **Hepatocellular Damage**
   - ballooning
   - bile pigment accumulation (bilirubinostasis)
   - lobular disarray (may persist after inflammation subsides)
   - cell death (apoptosis and/or necrosis)

Changes tend to be most marked in perivenular regions (zone 3)

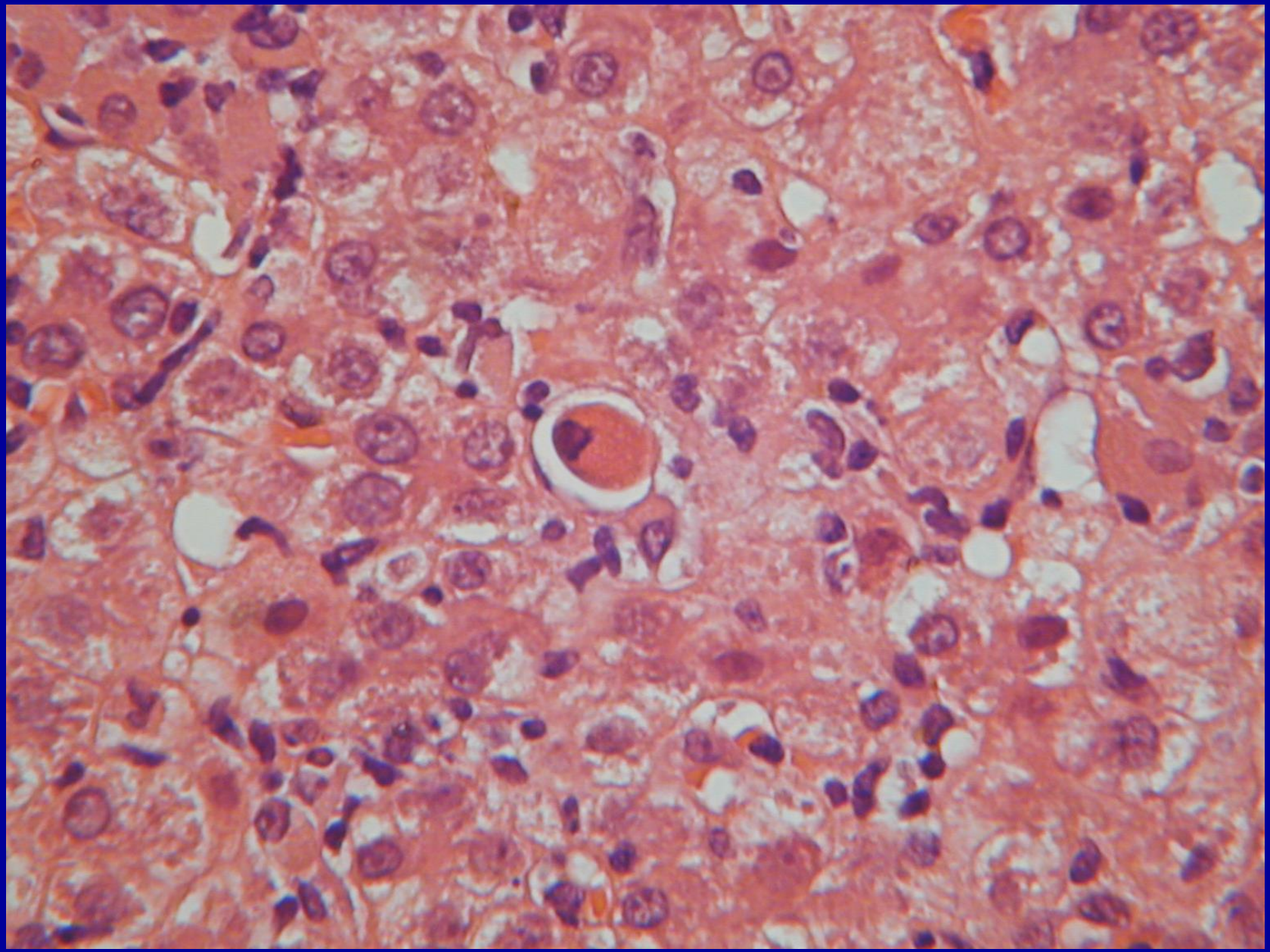
Acute Hepatitis – Spotty Inflammation & Lobular Disarray



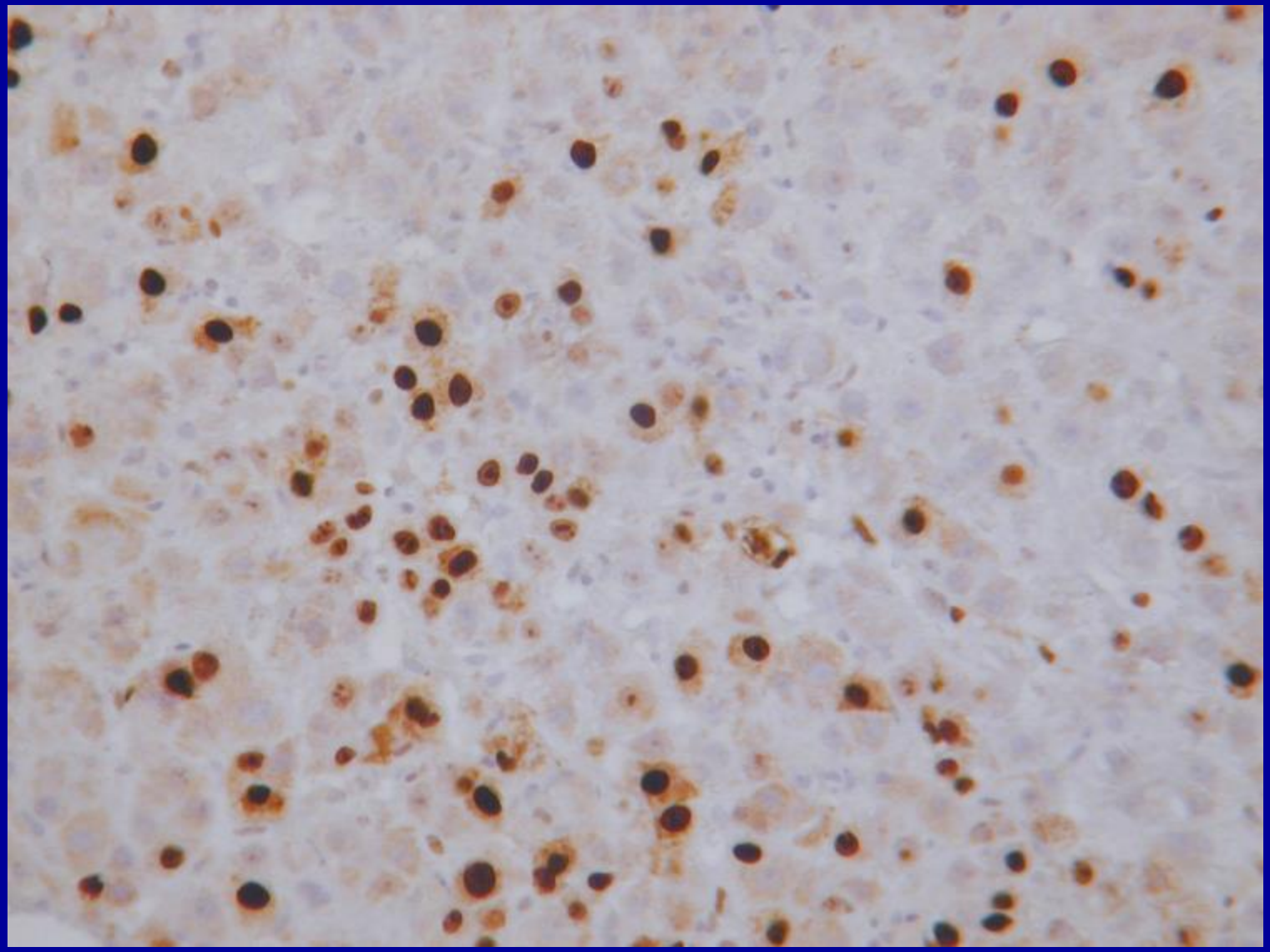
Acute Hepatitis - Ballooning & Bilirubinostasis



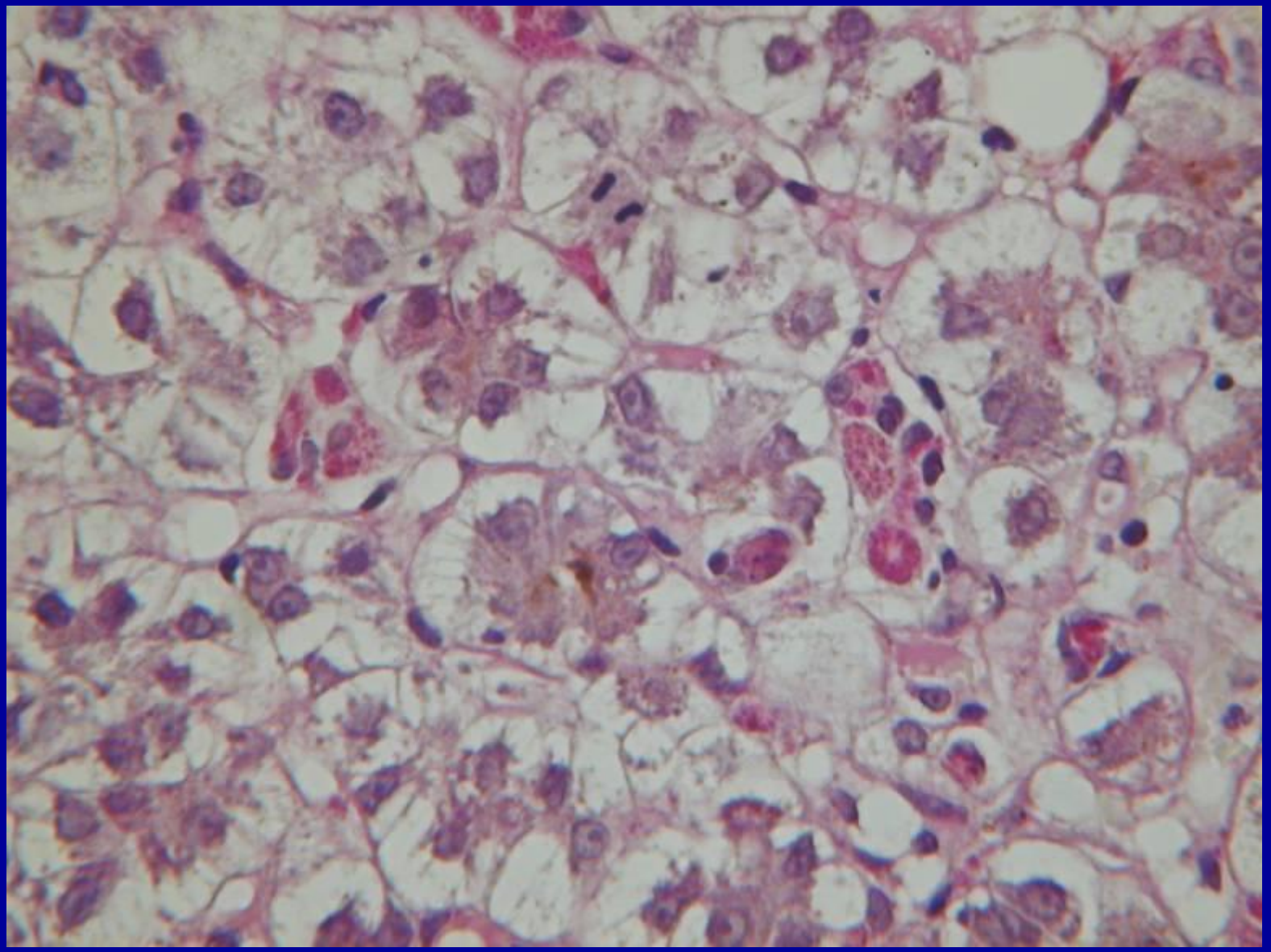
Acute Hepatitis – Acidophil body



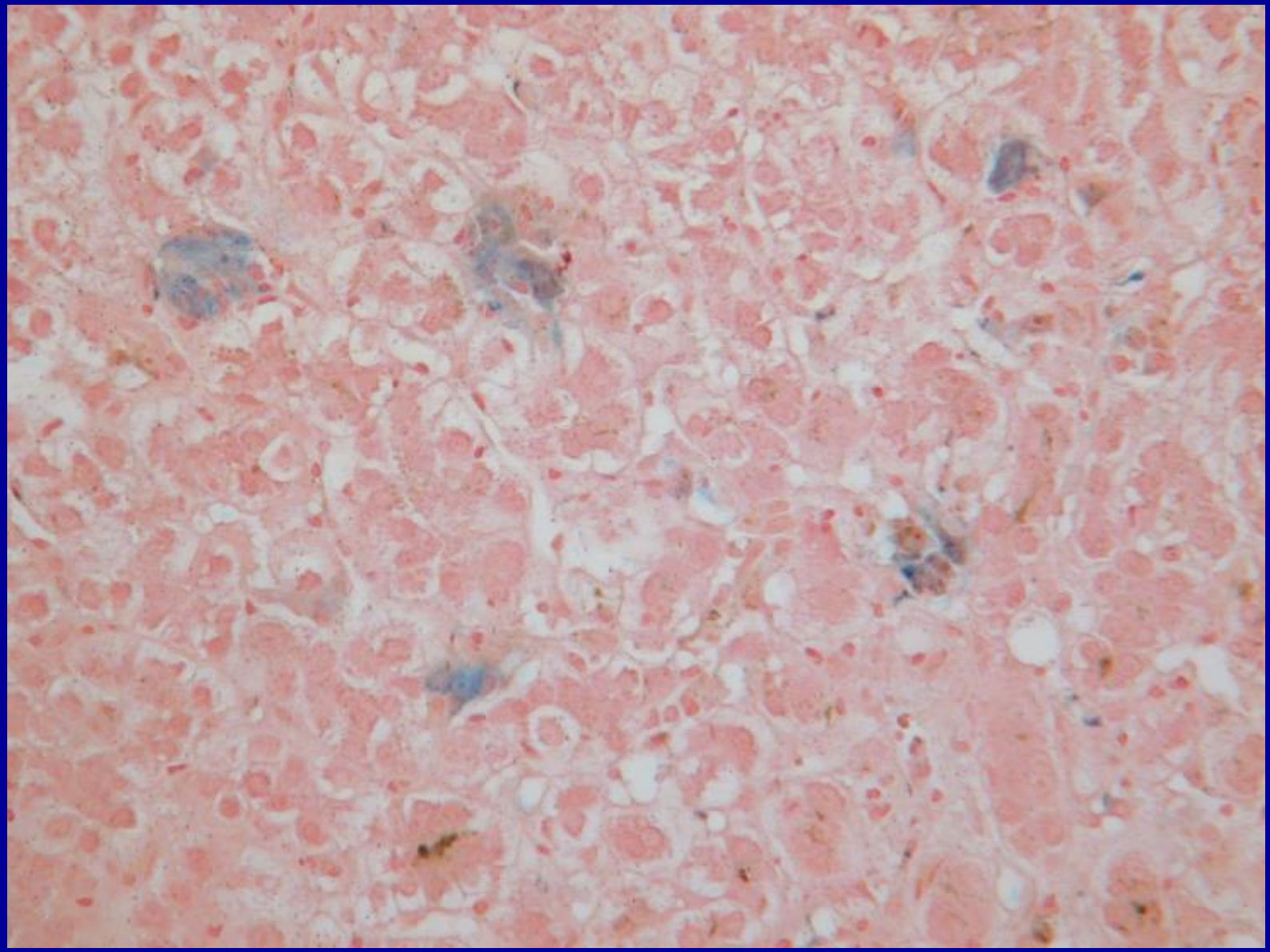
Acute Hepatitis
Hepatocyte Proliferation (Ki 67 immunostaining)



Acute Hepatitis - Ceroid-laden Kupffer cells (PAS-diastase)



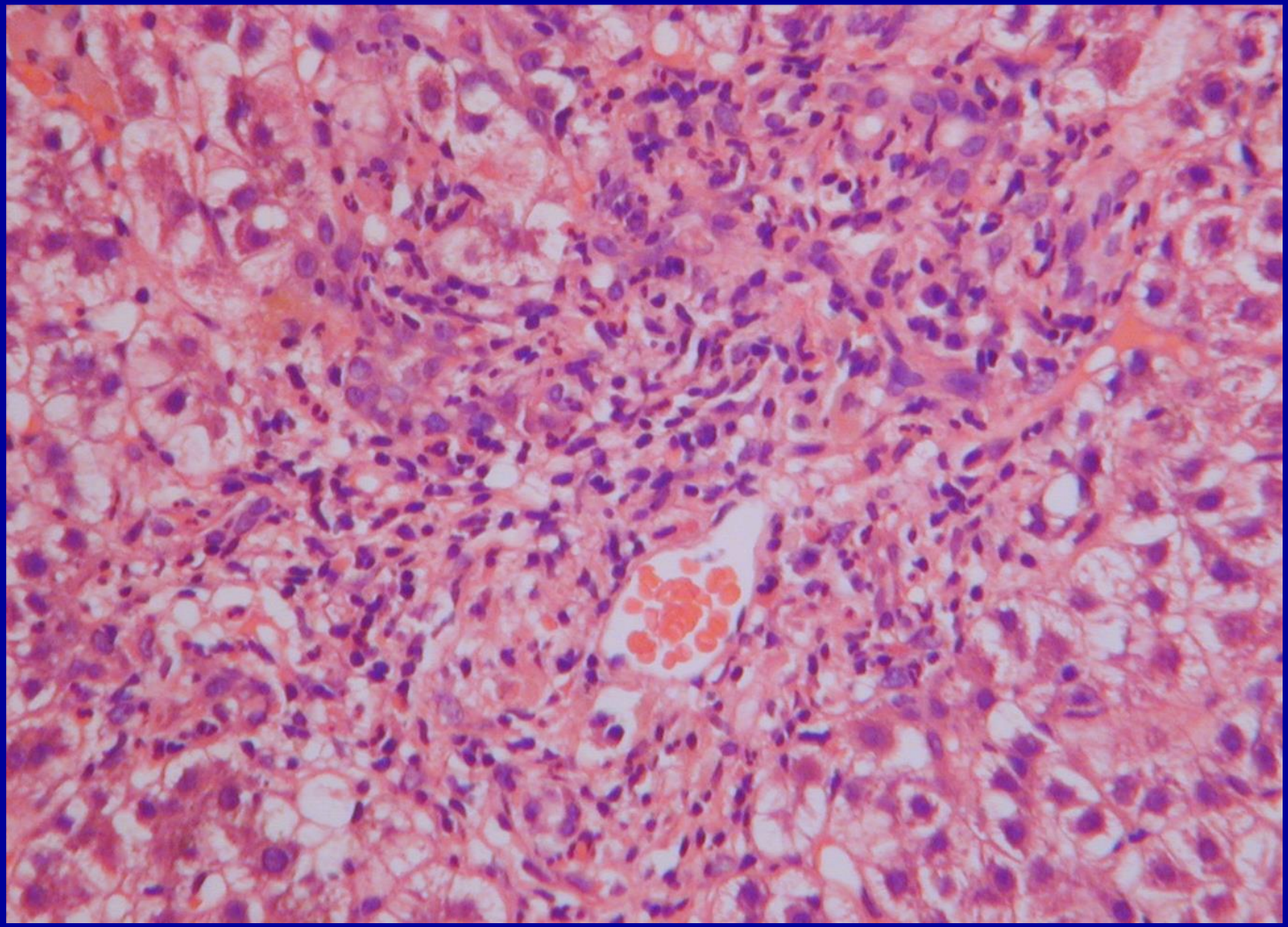
Acute Hepatitis - Haemosiderin-laden Kupffer Cells (Perls)
(also useful for highlighting bile plugs)



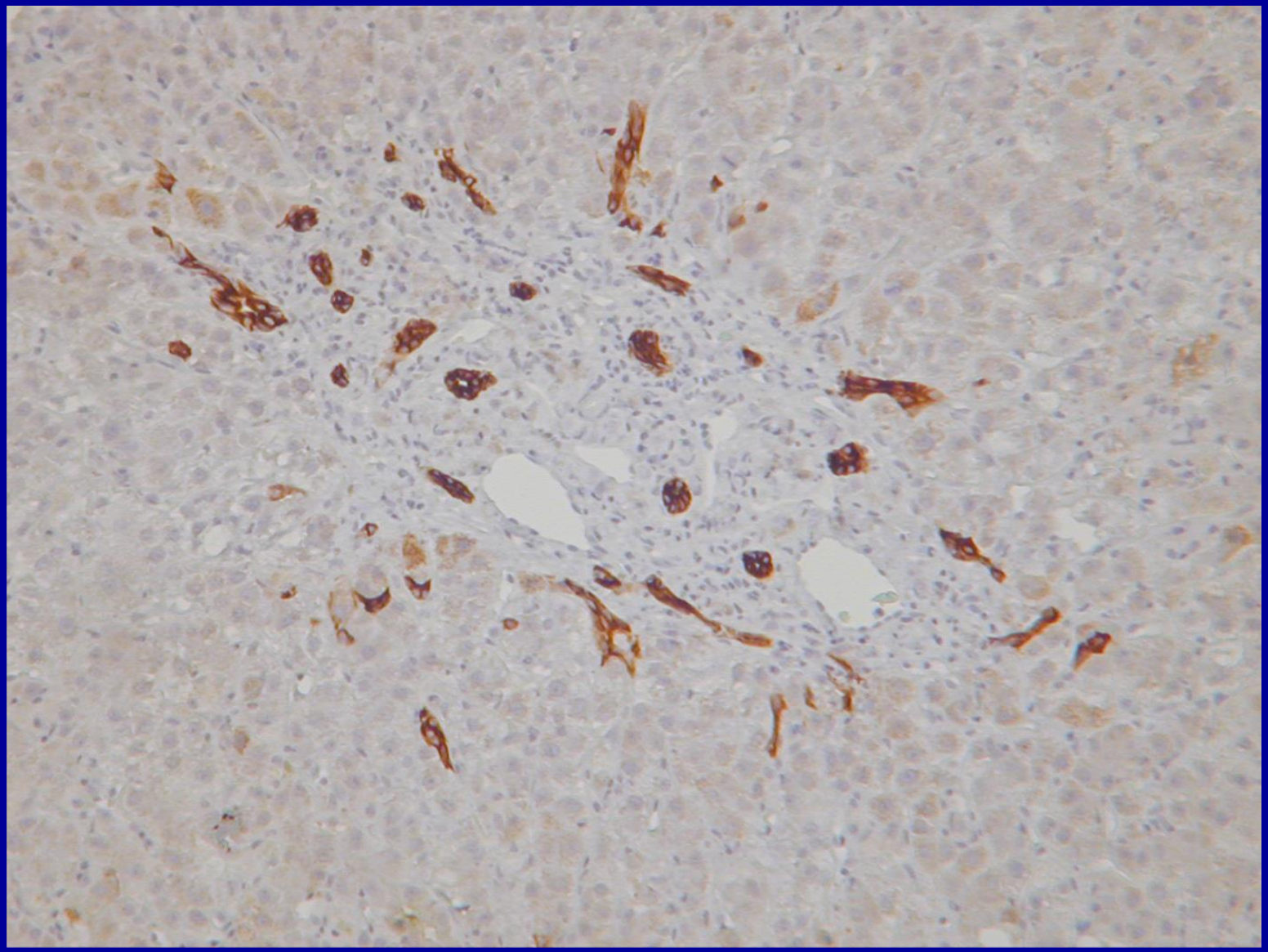
Acute versus Chronic Hepatitis - Portal and Periportal Changes

Histological Feature	Acute hepatitis	Chronic hepatitis
Inflammation	**Mixed** • lymphocytes, macrophages, plasma cells, neutrophils, eosinophils	**Mainly mononuclear** • may include lymphoid follicles – e.g. HCV, AIH • May be associated with periportal extension (“interface hepatitis”)
Ductular reaction	**Common** • associated with severity of cholestasis • May be associated with neutrophils – “cholangiolitis”	**Less common** • associated with severity of fibrosis
Fibrosis	Mild (reversible) portal expansion	Progressive periportal fibrosis, may lead to cirrhosis

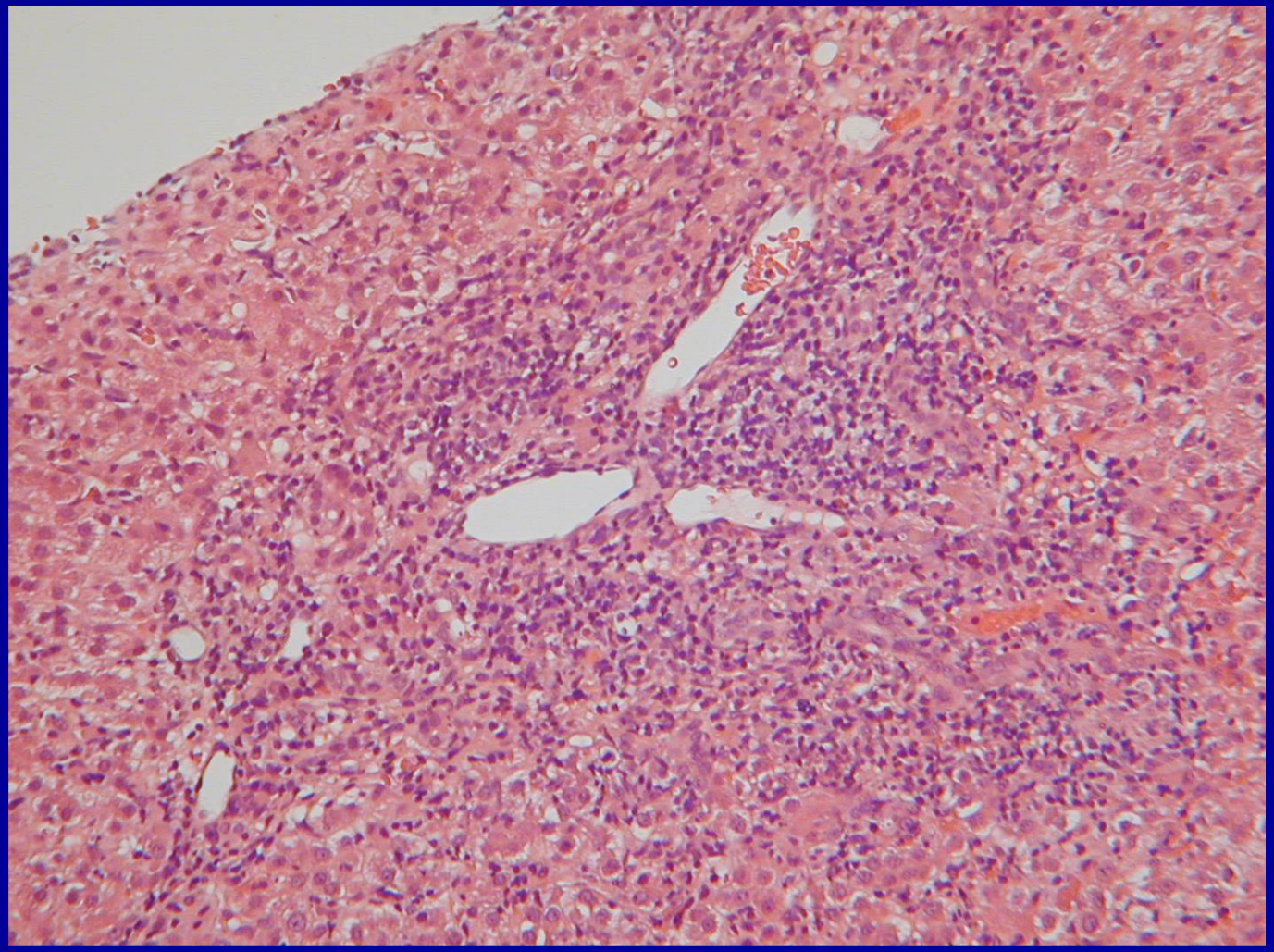
Acute Hepatitis
Portal Inflammation & Ductular Reaction (with neutrophils)



Acute Hepatitis
Ductular Reaction (Keratin 7 Immunohistochemistry)



Acute Hepatitis - Portal Inflammation & Interface Hepatitis ("acute hepatitis with periportal necrosis")

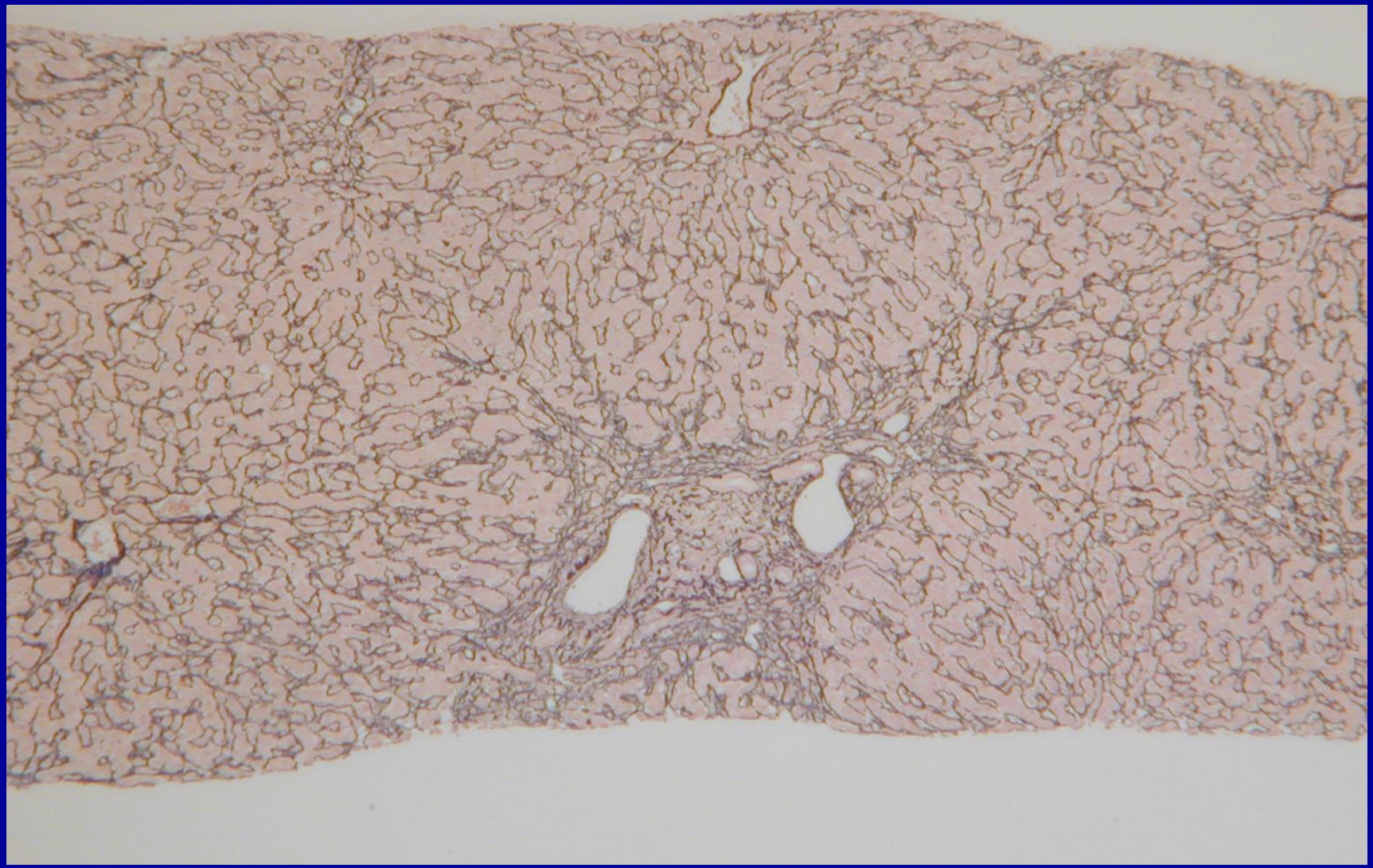


- Changes resemble those seen in chronic hepatitis
- May be seen in hepatitis A, also autoimmune hepatitis

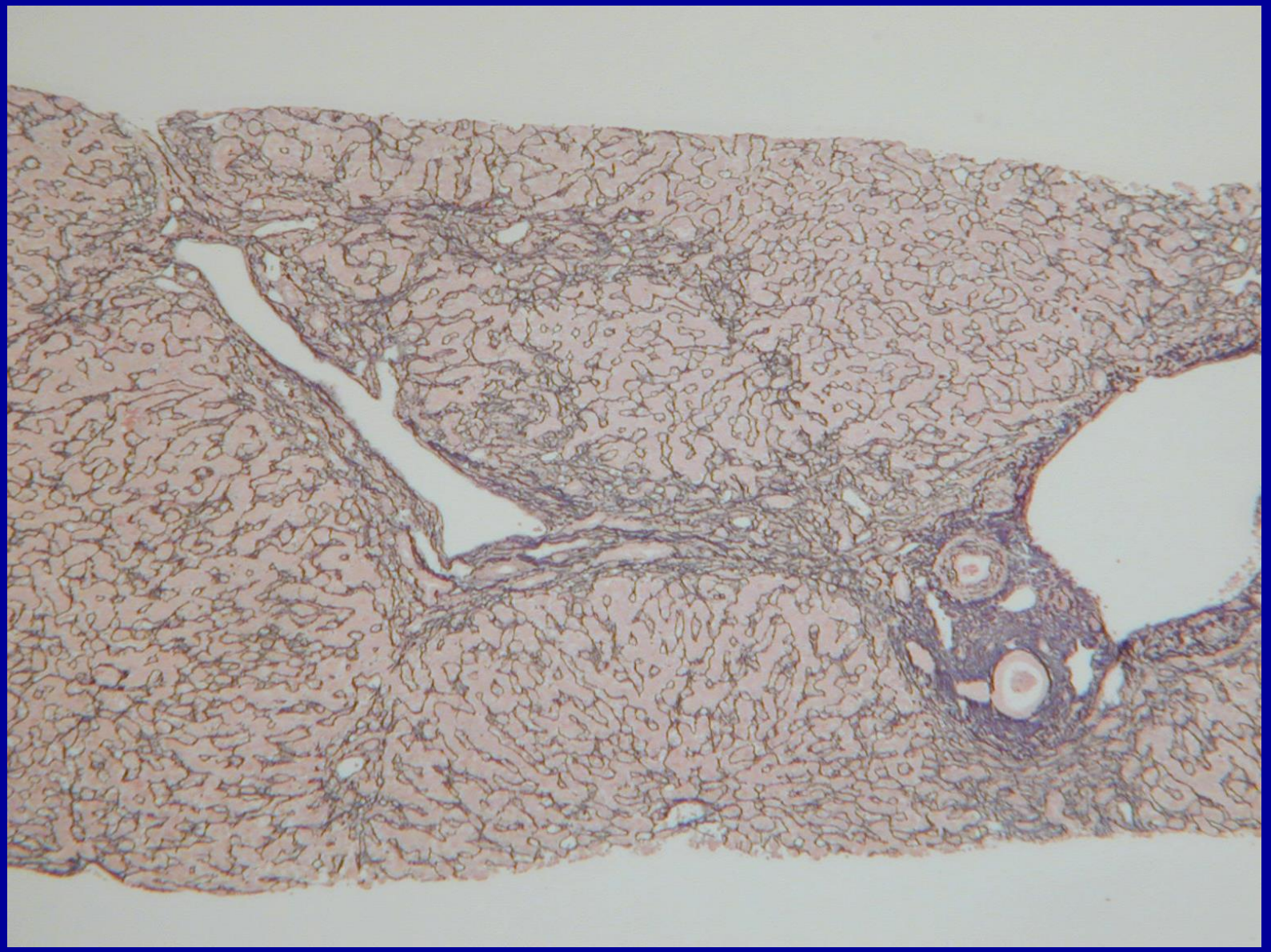
Acute versus Chronic Hepatitis
Distinguishing Recent Injury from Evolving/Longstanding Fibrosis
Use of Connective Tissue Stains

Stain	**Material Demonstrated**	**Distribution In Normal Liver**	**Changes In Liver Disease**
Reticulin	Type III collagen fibres	Portal tracts, hepatic sinusoids	Portal expansion due to portal inflammation Collapse of reticulin framework in areas of recent liver cell necrosis. (few days)
Haematoxylin Van Gieson (or Trichrome)	Type I collagen fibres	Portal tracts, walls of hepatic veins	Increased in hepatic fibrosis (weeks/months)
Orcein	Elastic fibres	Portal tracts, walls of hepatic veins	Found in long-standing fibrosis/cirrhosis (months/years)

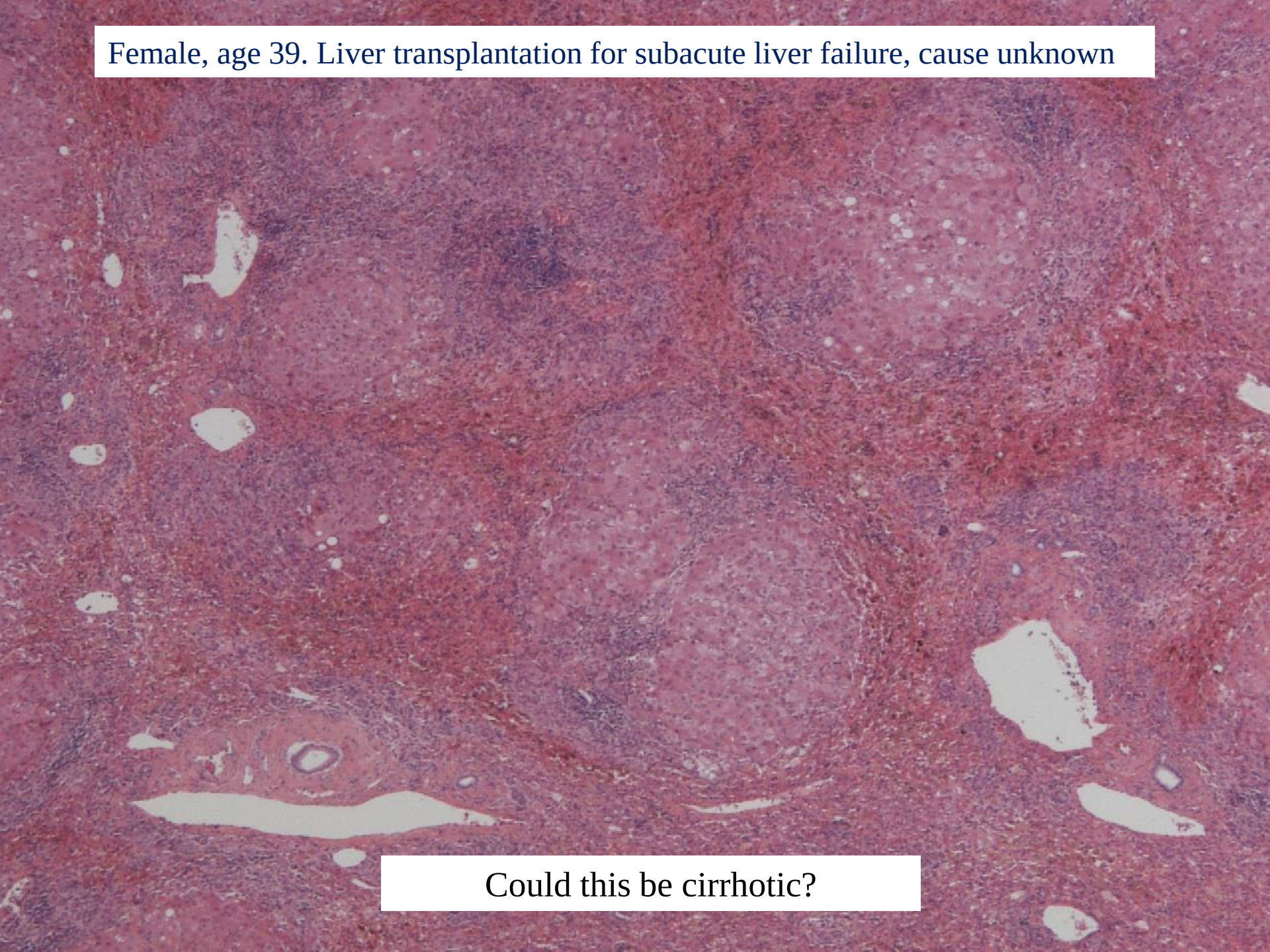
Acute Hepatitis – Mild Periportal Fibrosis (Reticulin)



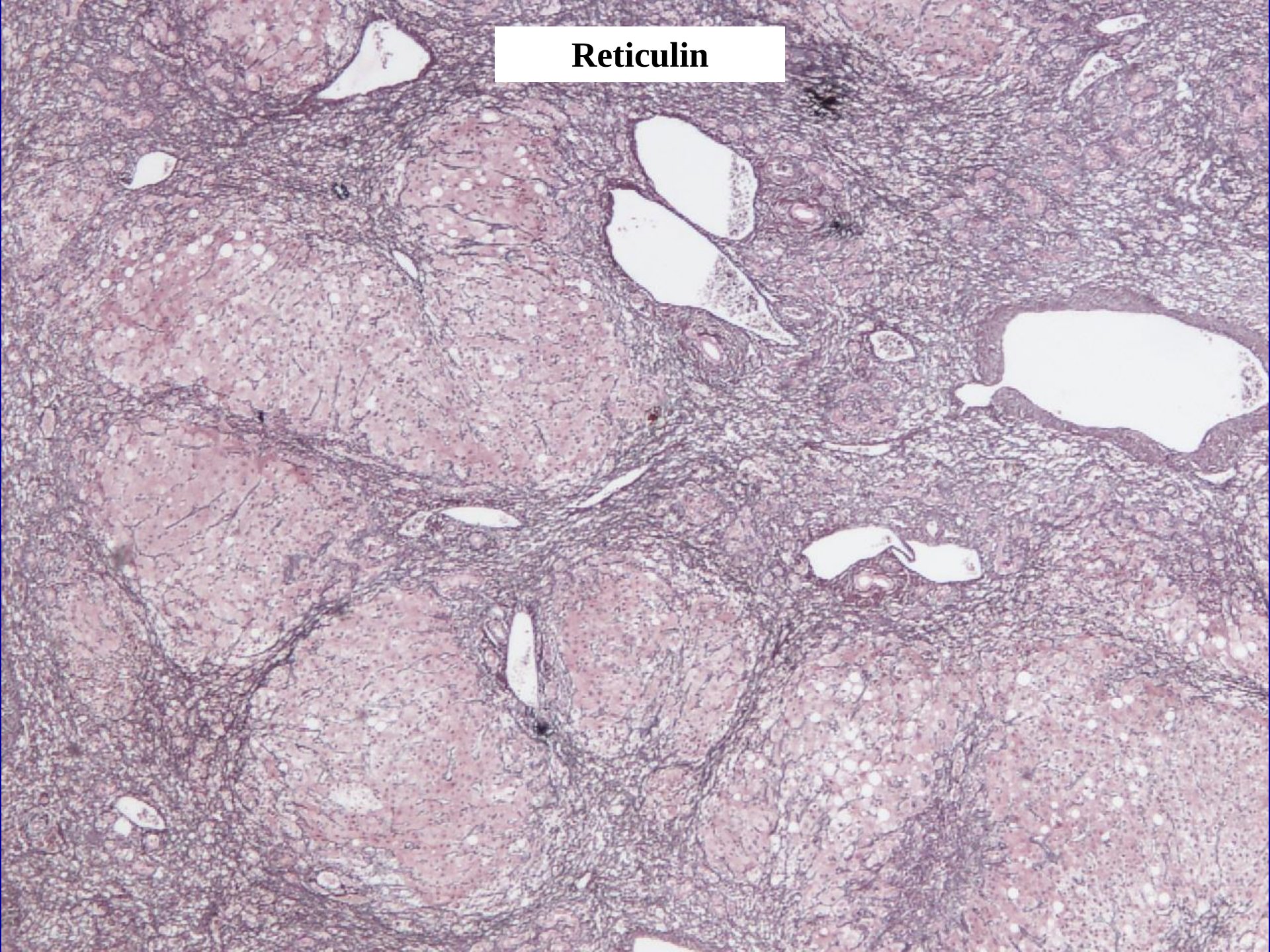
Acute Hepatitis – Periportal & Bridging Fibrosis (Reticulin Collapse)

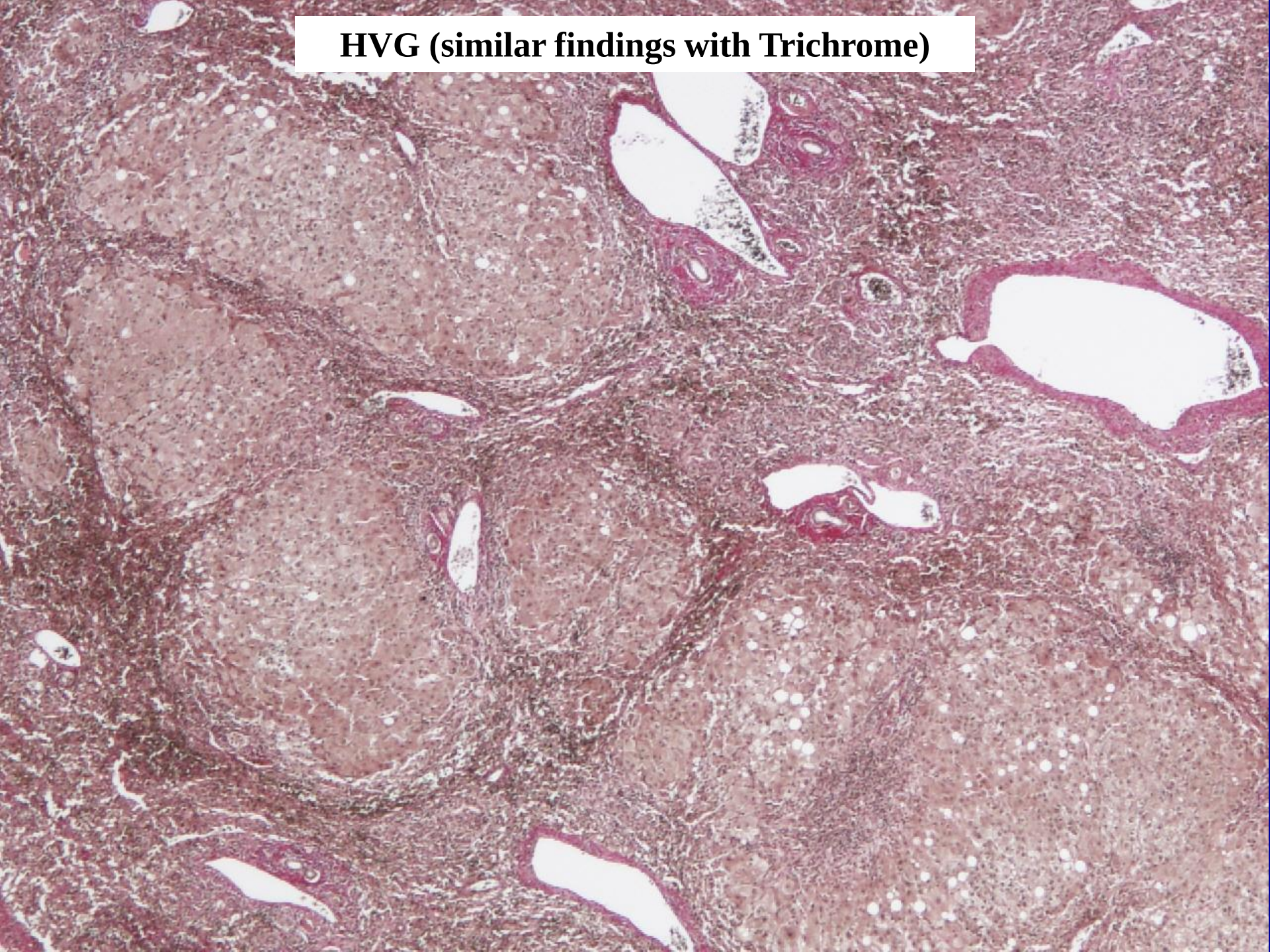


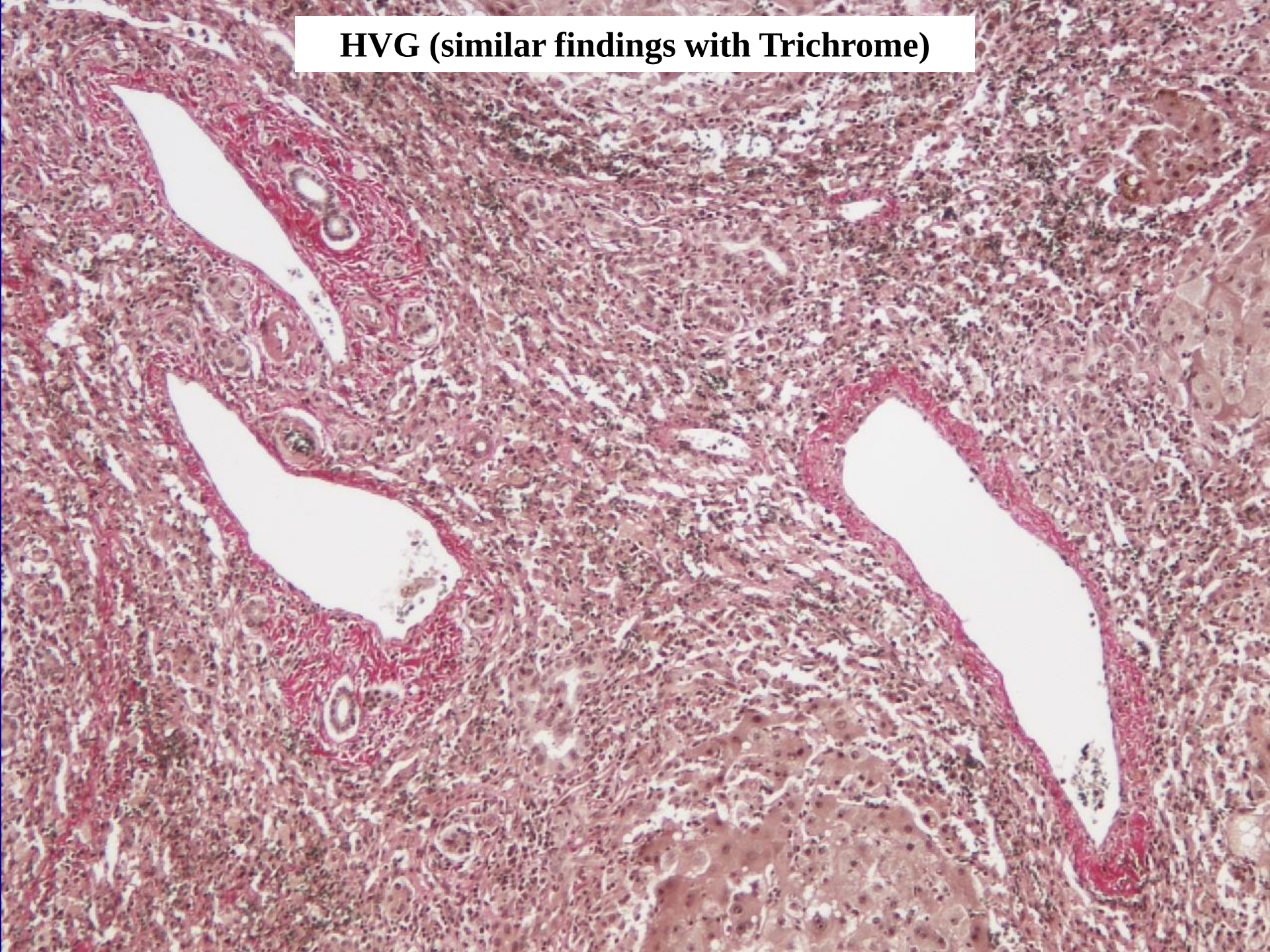
Female, age 39. Liver transplantation for subacute liver failure, cause unknown



Could this be cirrhotic?


Reticulin


HVG (similar findings with Trichrome)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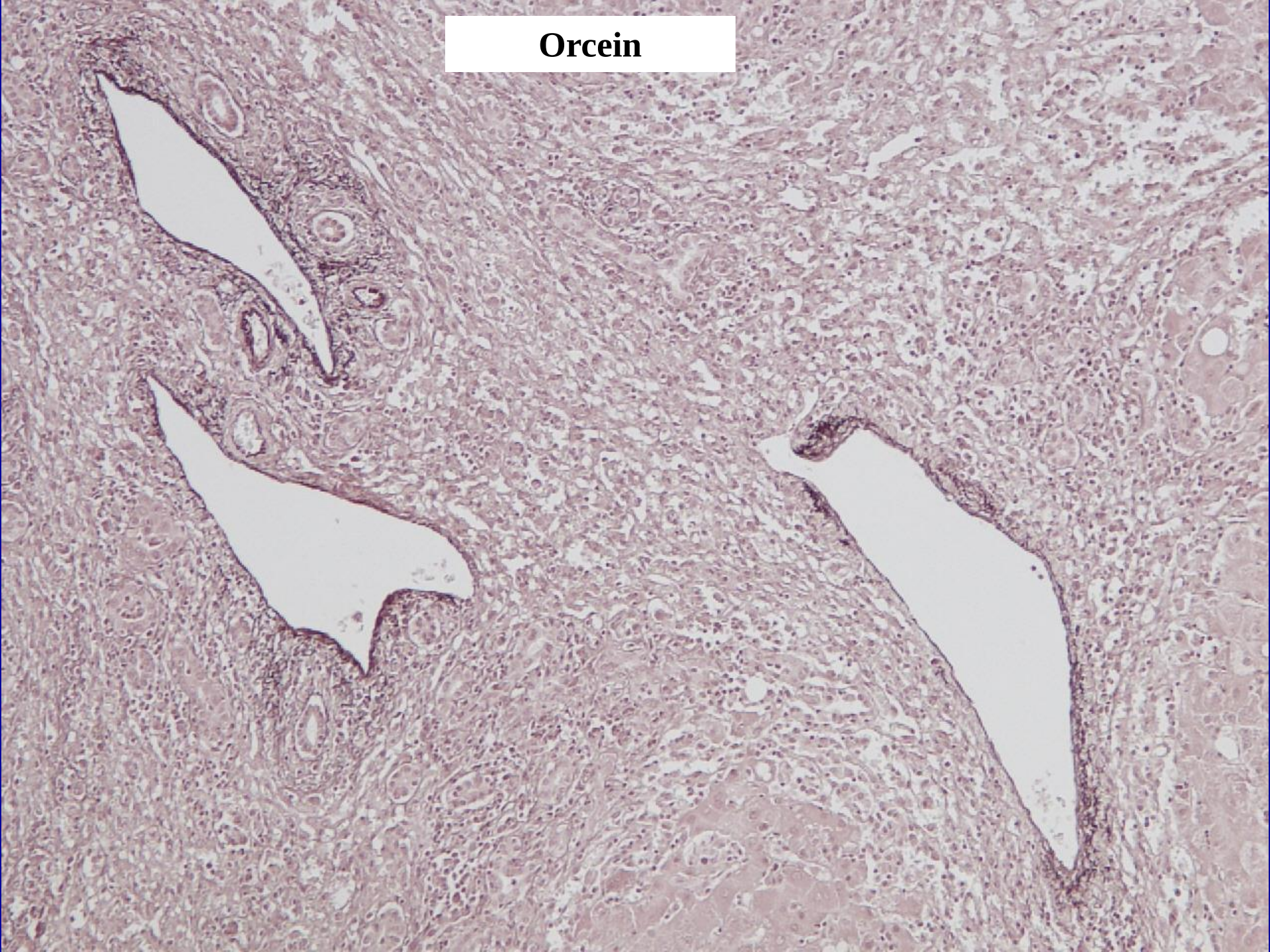

Orcein

Cases of Hepatitis Difficult to Classify as Acute or Chronic

1. **Acute exacerbation of chronic liver injury (not decompensated cirrhosis)**

Examples

- Acute HAV/HEV infection superimposed on cirrhosis
  - Most frequently described in India, associated with high mortality
  - Histological features (other than cirrhosis) not well described

- "Acute" presentation of chronic autoimmune hepatitis
  - 14-35% have features of chronic hepatitis (Fujiwara 2011, Yasui 2011)
  - 10-95% have bridging fibrosis or cirrhosis (Nikias 1994, Burgart 1995, Miyake 2010, Fujiwara 2011)

Diagnostic Features

- Use of connective tissue stains important to demonstrate longstanding fibrosis/cirrhosis (versus recent post-necrotic collapse)

Cases of Hepatitis Difficult to Classify as Acute or Chronic

2. **Acute hepatitis evolving to chronic liver injury ("acute-on-chronic hepatitis")**

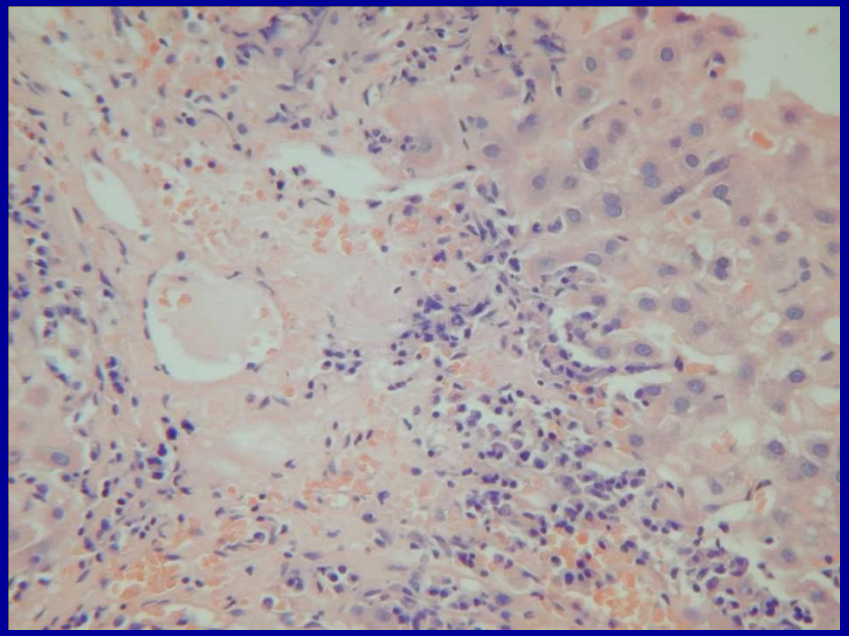
Examples

- Viral hepatitis - HBV, HCV, HEV (in immunocompromised people)
  - Acute phase rarely symptomatic and uncommonly biopsied
- Autoimmune hepatitis
- Drug-induced liver injury

Diagnostic Features

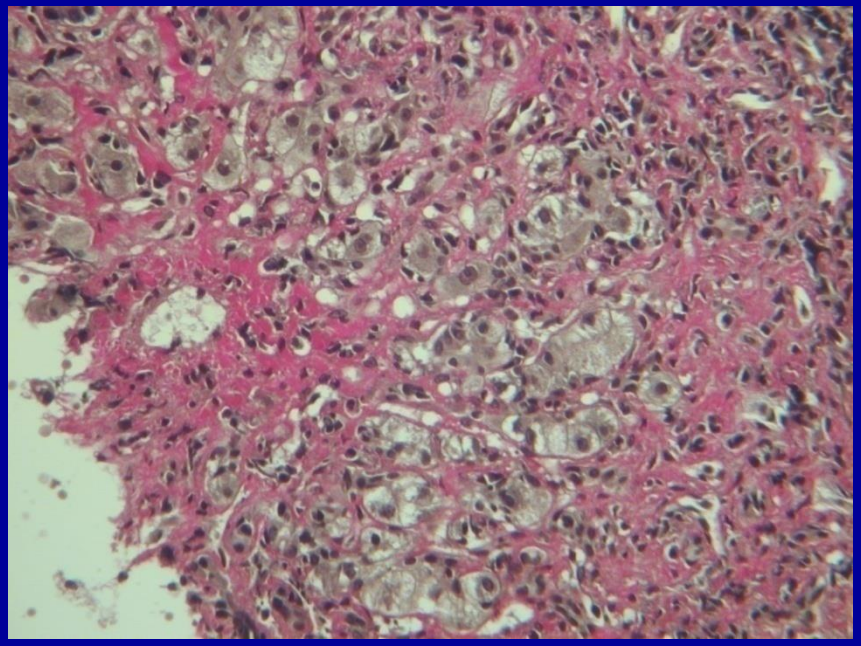
- Transition from lobular to portal inflammation
- Connective tissue stains helpful in identifying evolving fibrosis

Autoimmune Hepatitis - Acute-on-Chronic Liver Injury



Lobular Hepatitis

- Plasma cell rich
- Centrilobular accentuation with zone 3 necrosis (“central perivenulitis”)



Evolving Fibrosis (HVG)

- Periportal and perivenular fibrosis
- Lobular dissection by delicate septa, hepatocyte rosettes
- Normal vascular relationships retained
- No elastic fibres

Cases Presented at Gnomes Meeting
Adelaide, April 2016

27-30 April 2016

Newcastle 1 (Dina Tiniakos)

Case History 1

- 53-year-old woman
- Previous medical history:

  Urinary tract infection

  No history of liver disease

- Clinical presentation

  - **urgent admission with acute hepatitis**

Case History 1

On admission:

- ALT 1378 U/L, AST 970 U/L
- bilirubin 183 µmol/L
- ALP 454 U/L
- CRP 13 mg/L
- prolonged prothrombin time 15 sec
- Viral screen negative (HAV, HBV, HCV, HEV, HIV, CMV)

  Evidence of previous EBV infection

- serum ceruloplasmin, α1-antitrypsin normal

Case History 1

On admission:

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- bilirubin 183 µmol/L
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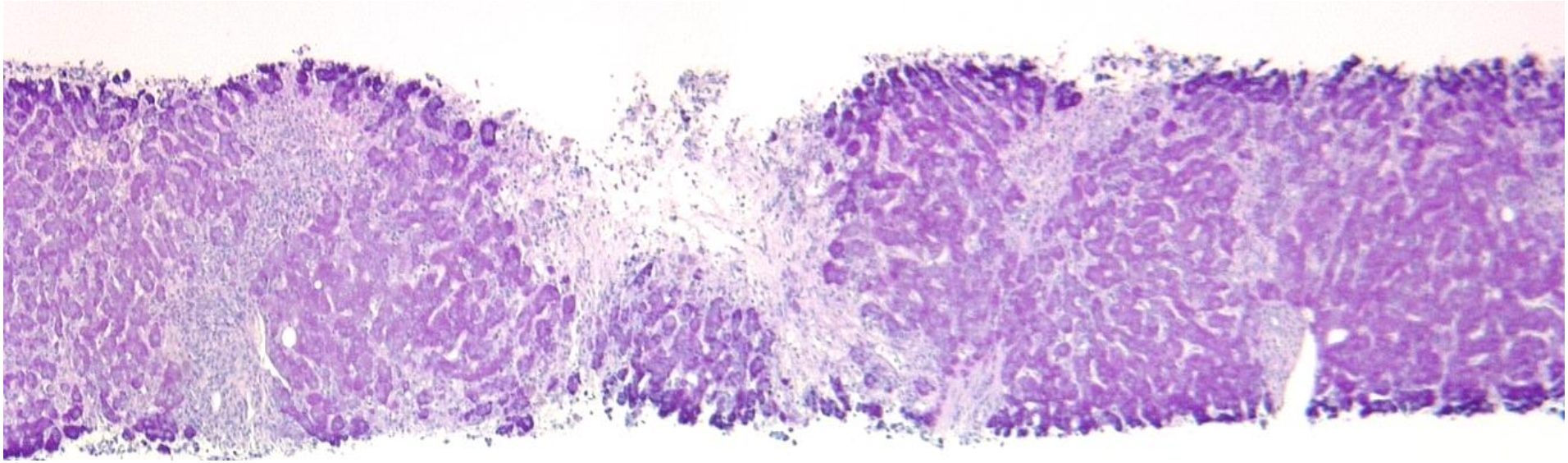
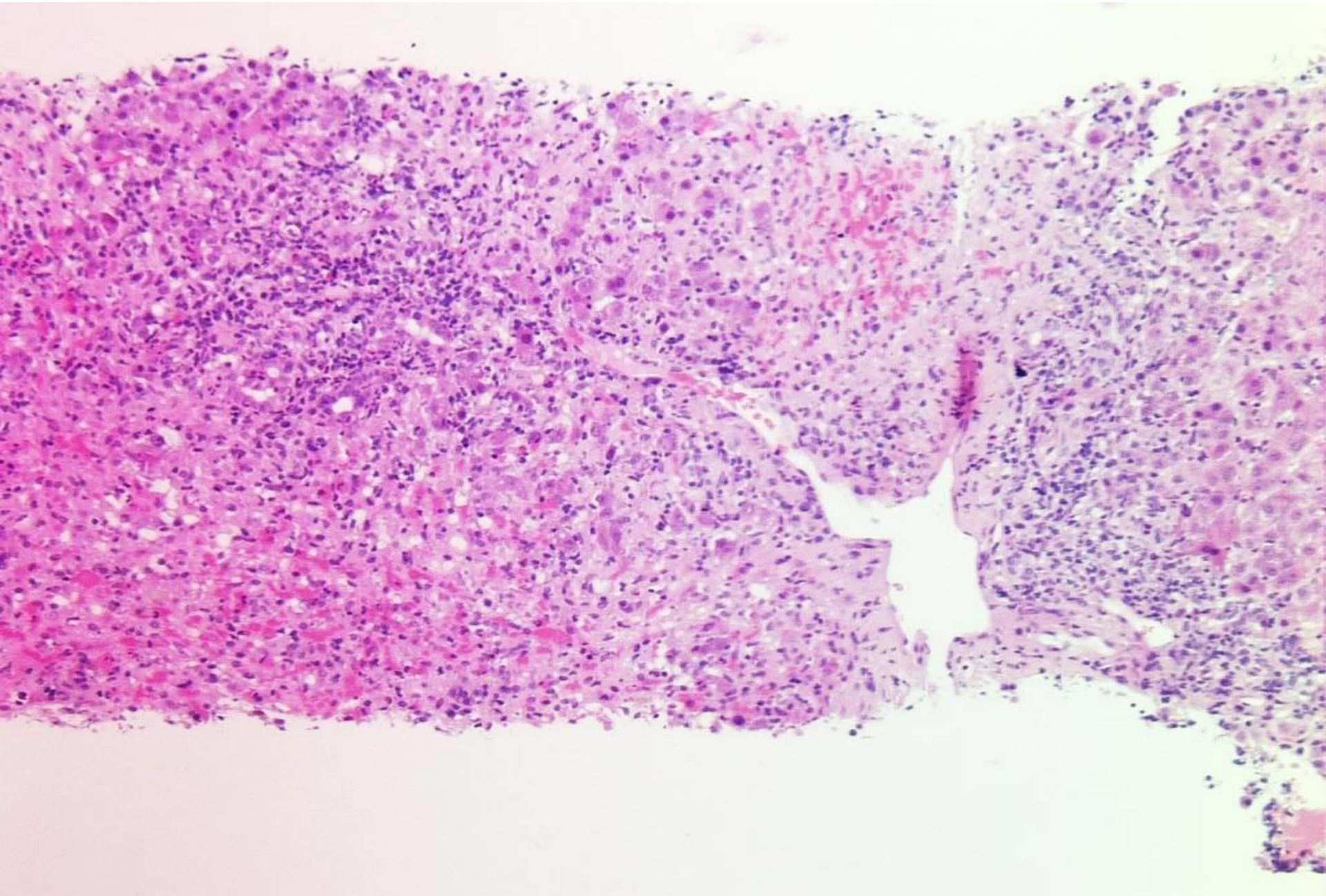
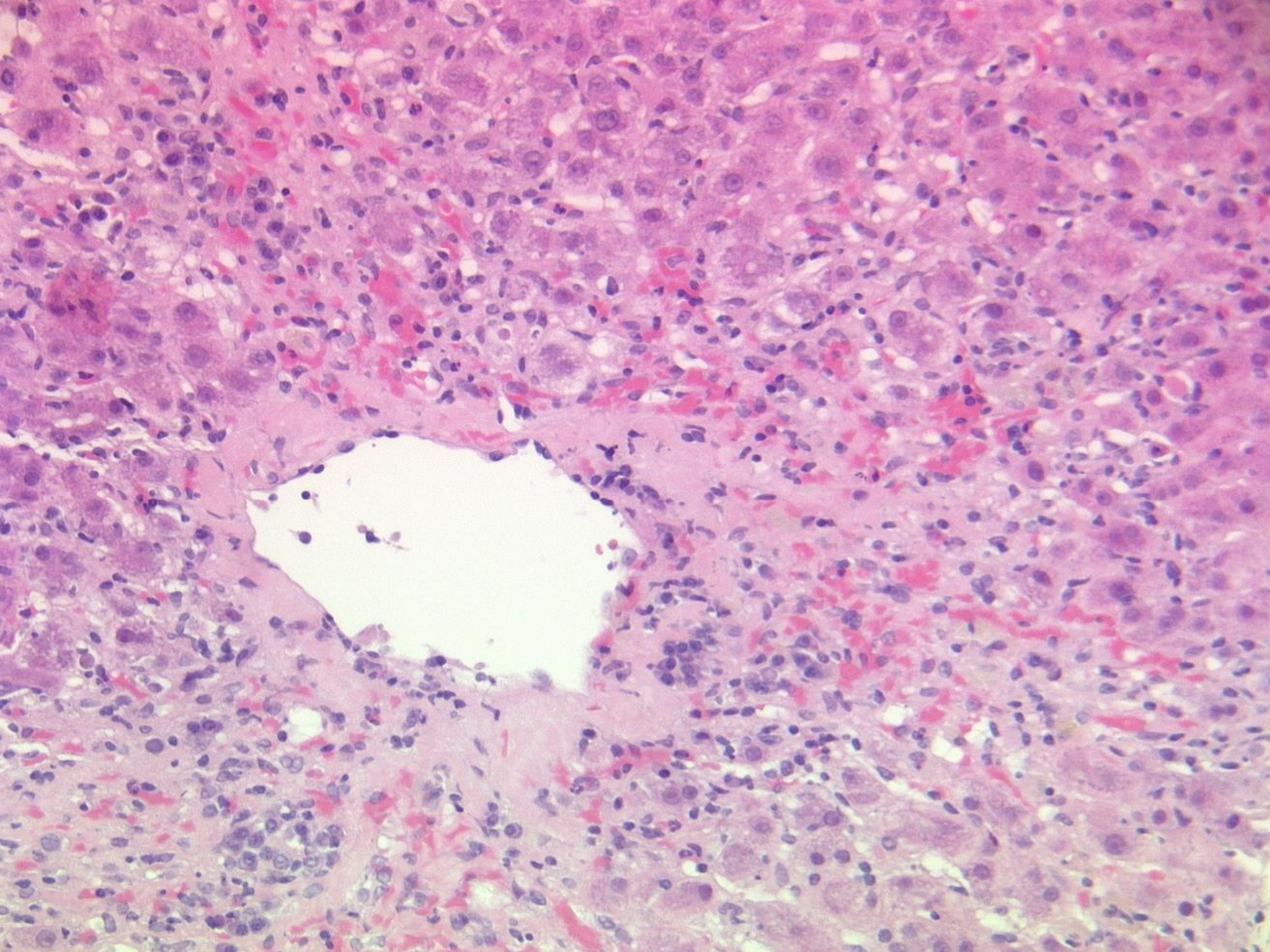
- CRP 13 mg/L
- prolonged prothrombin time 15 sec
- Viral screen negative (HAV, HBV, HCV, HEV, HIV, CMV)

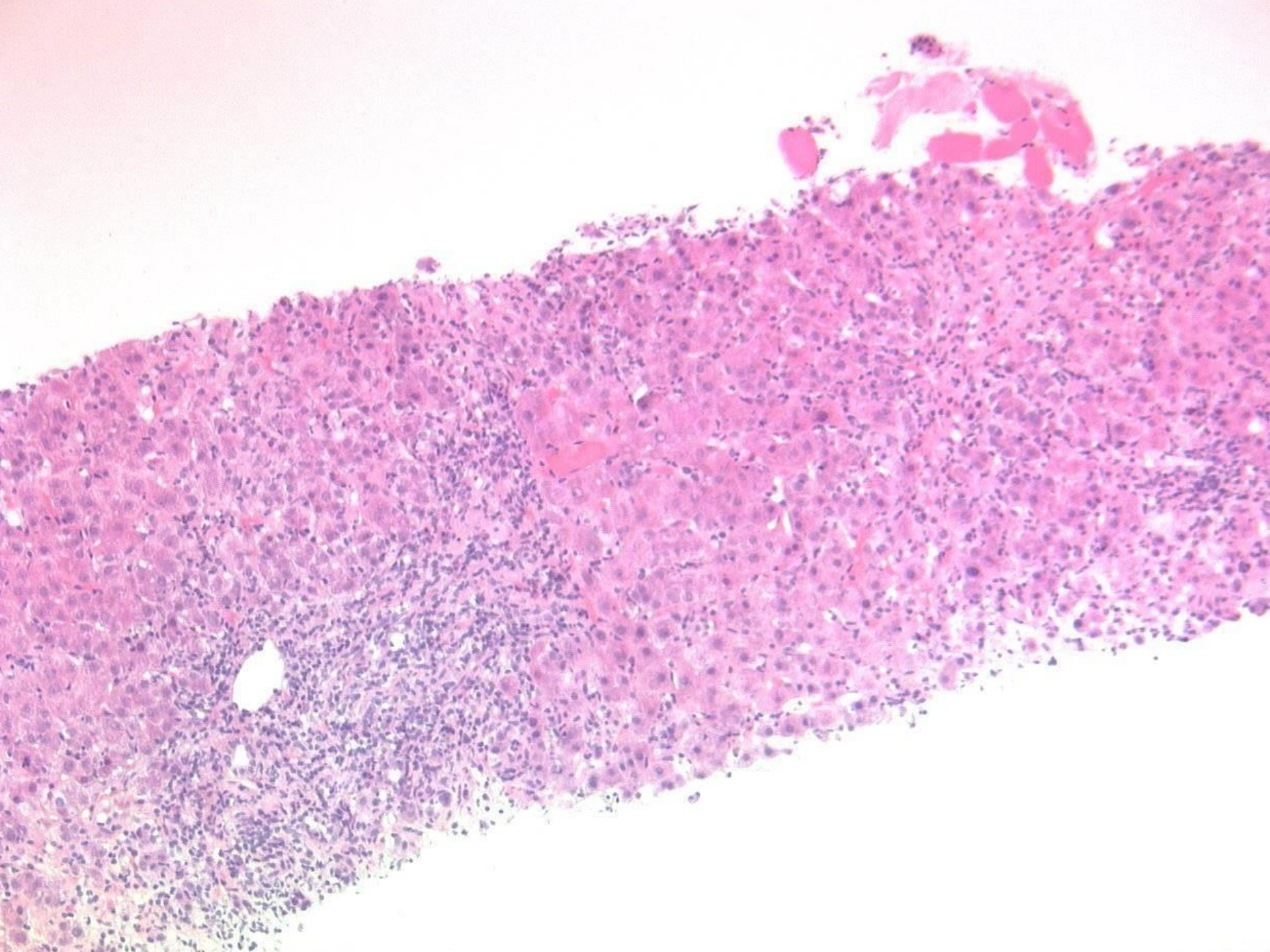
  Evidence of previous EBV infection

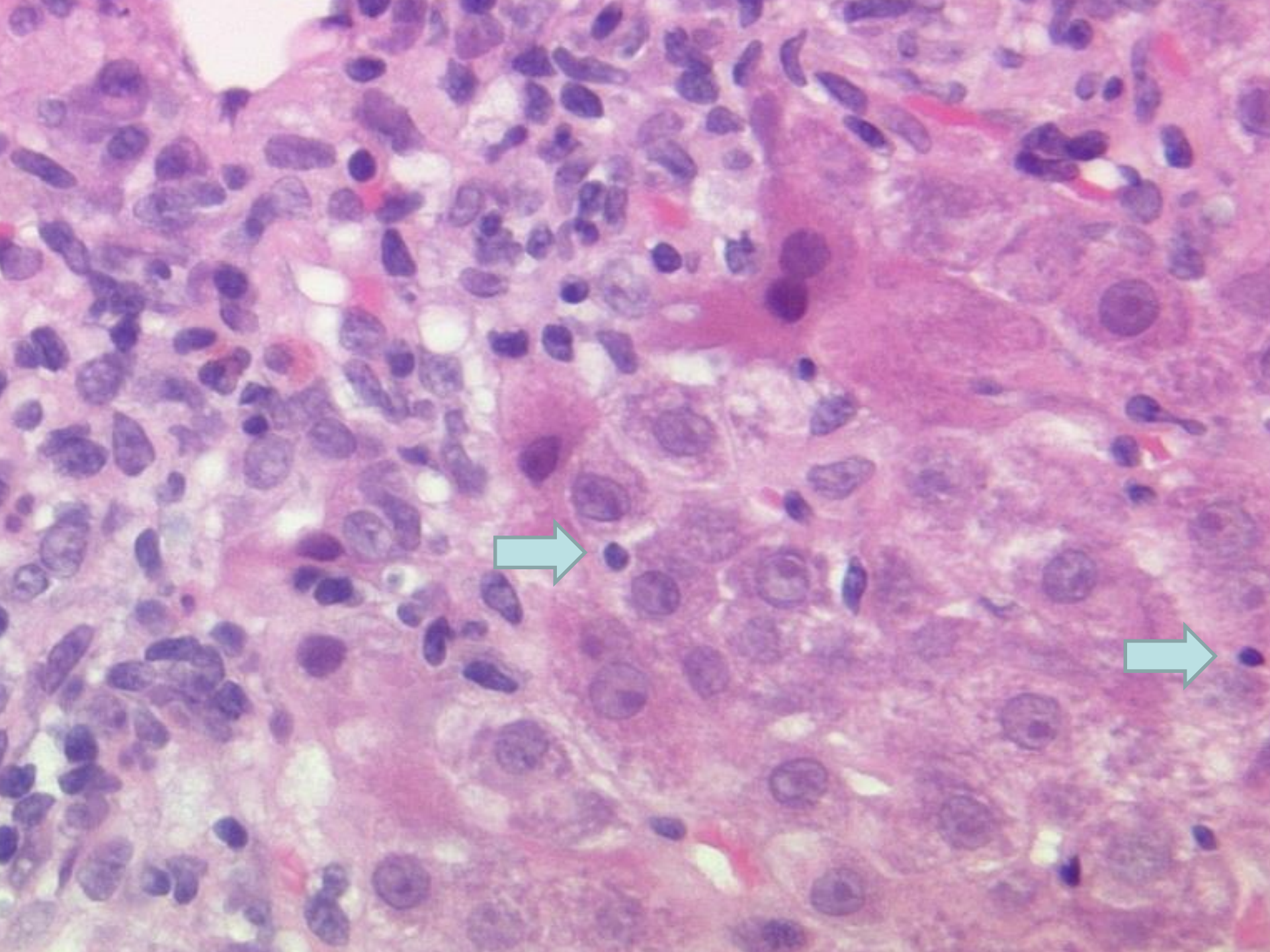
- White cell count 13.5x10^9/L, neutrophils 11.2x10^9/L
- Urine culture positive for E. *coli*

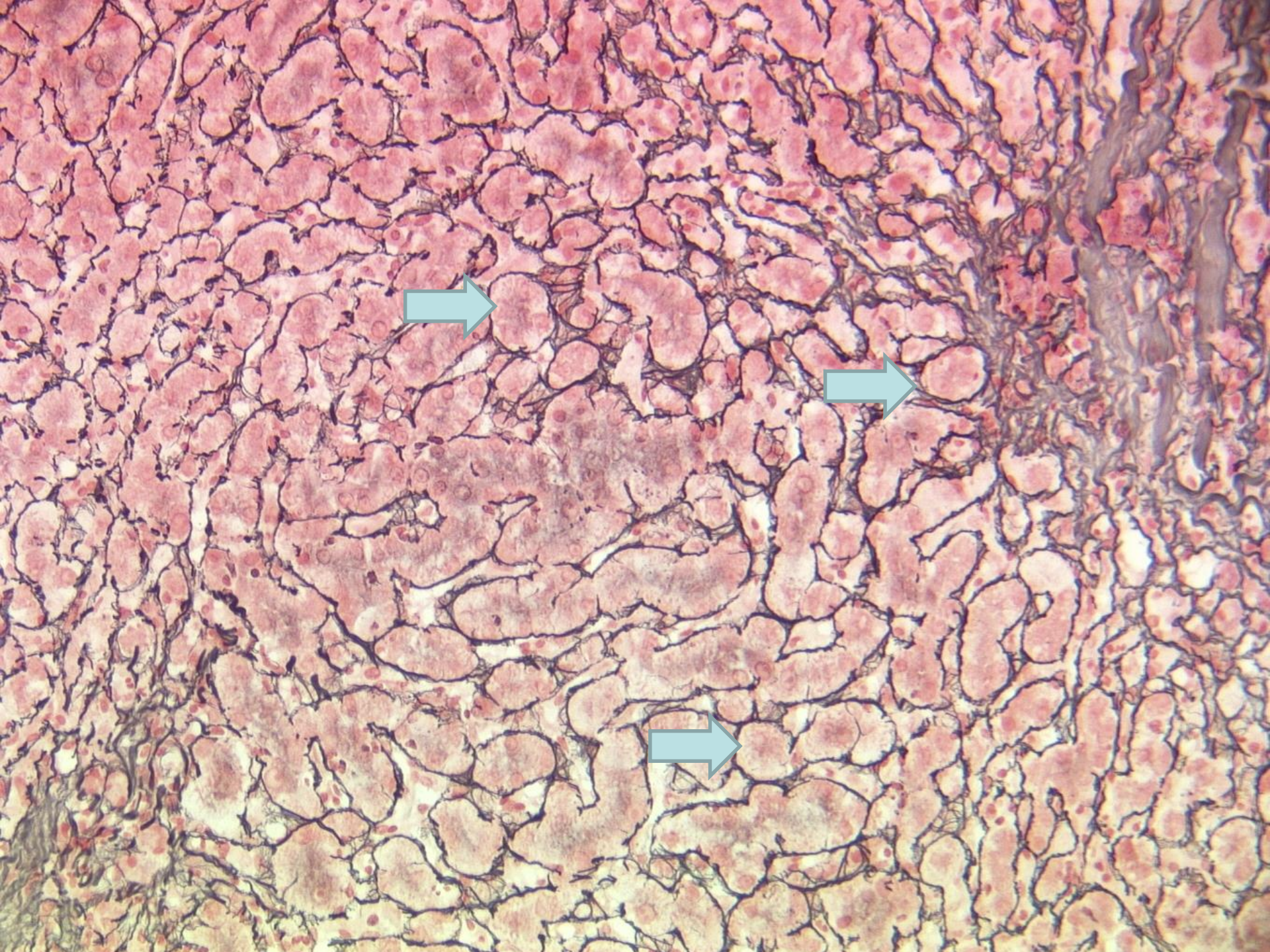


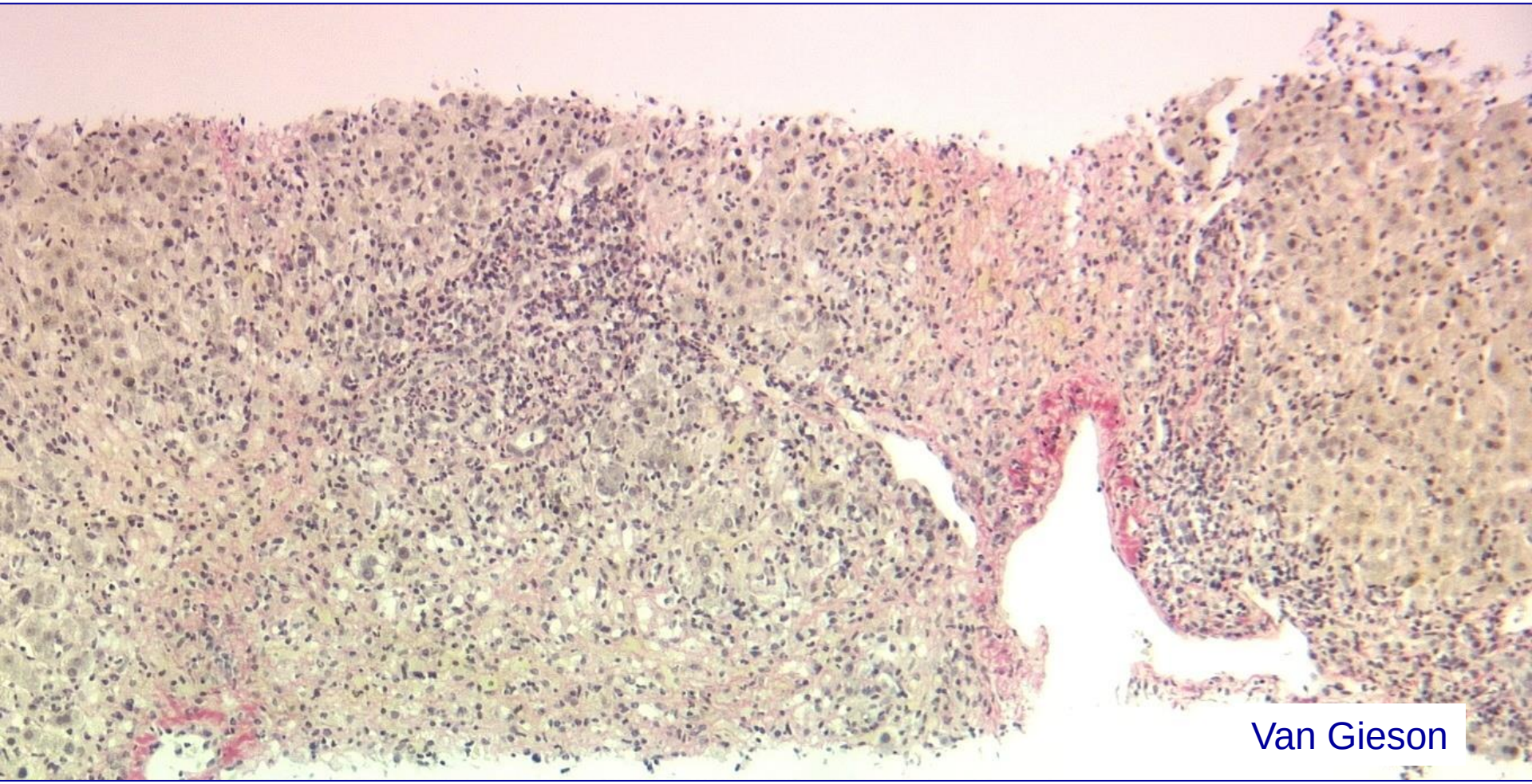


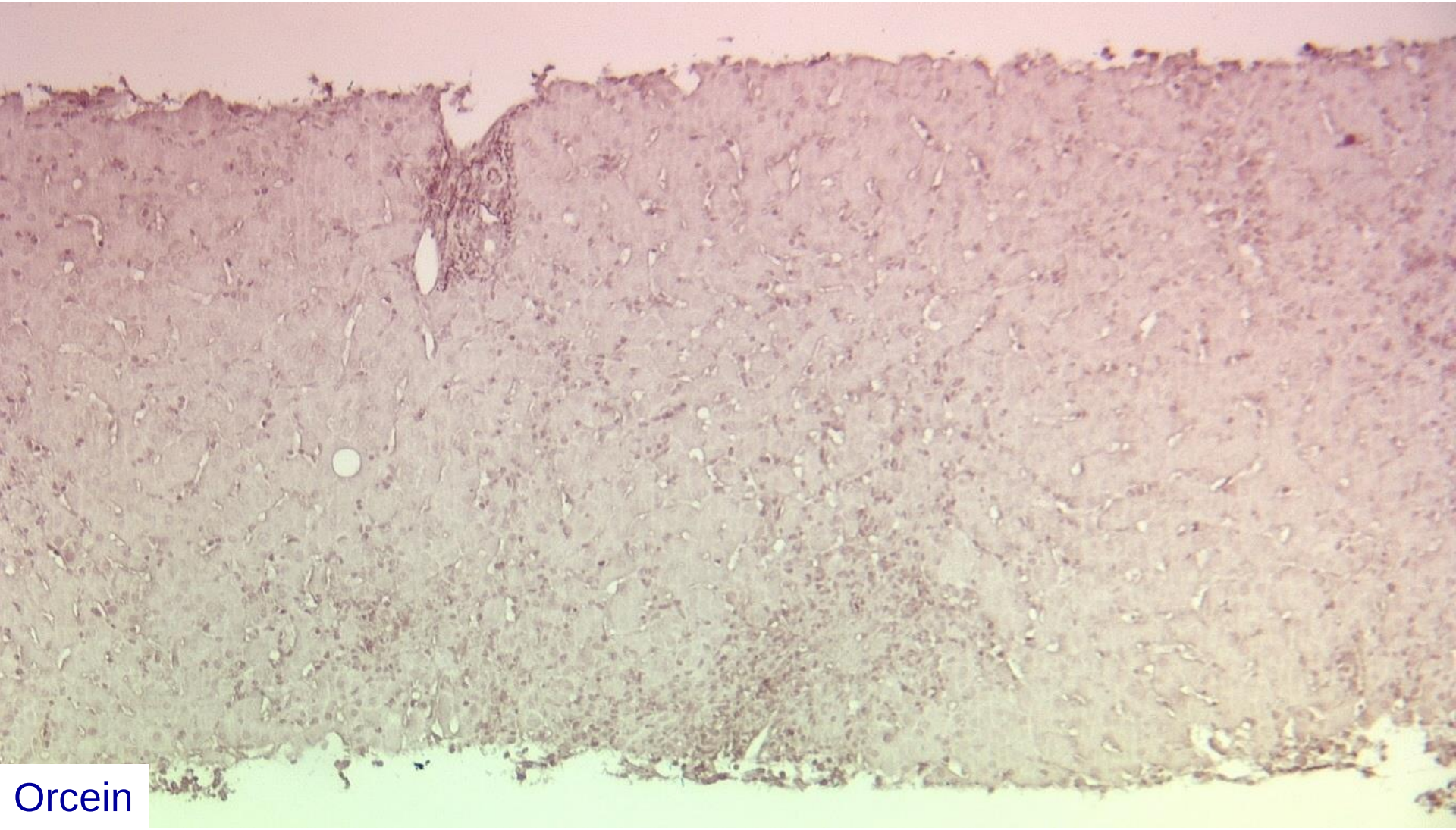









Van Gieson


Orcein

Newcastle 1

Severe acute hepatitis

(no pre-existing fibrosis)

On admission: ANA >1:640, ↑ IgG 15.4 g/L, ↑ IgA 5.04 g/L

Typical features of autoimmune hepatitis

(IAHG Group - Hennes 2008)

- lymphoplasmacytic portal infiltrate + interface hepatitis
- emperipolesis
- hepatocyte rosettes

Newcastle 1

Severe acute hepatitis, autoimmune aetiology

On nitrofurantoin for 2 years
for recurrent urinary tract infections

Newcastle 1

Nitrofurantoin-triggered autoimmune hepatitis

Follow-up:

- Responded well to prednizolone and azathioprine (AZT)
- 4 months post-diagnosis: - ALT 24 U/L, ALP 57 U/L (30-130)
  - bilirubin 12 µmol/L (0-21)
  - autoantibodies negative, Ig normal
- Now on reducing doses of prednizolone and long term AZT

Drug-induced Autoimmune Hepatitis

- Biochemical, serological and histological features closely resembling classical autoimmune hepatitis
  - Mostly type 1 AIH (ANA, SMA positive)
  - Less commonly type 2 AIH (LKM positive)

- At least 15 drugs implicated – common examples include methyldopa, minocycline, nitrofurantoin
  - 24/261 (9%) of patients with AIH at Mayo Clinic = drug-induced (Bjornsson 2010)
  - 11 nitrofurantoin, 11 minocycline

- Liver injury may only become apparent after years of use

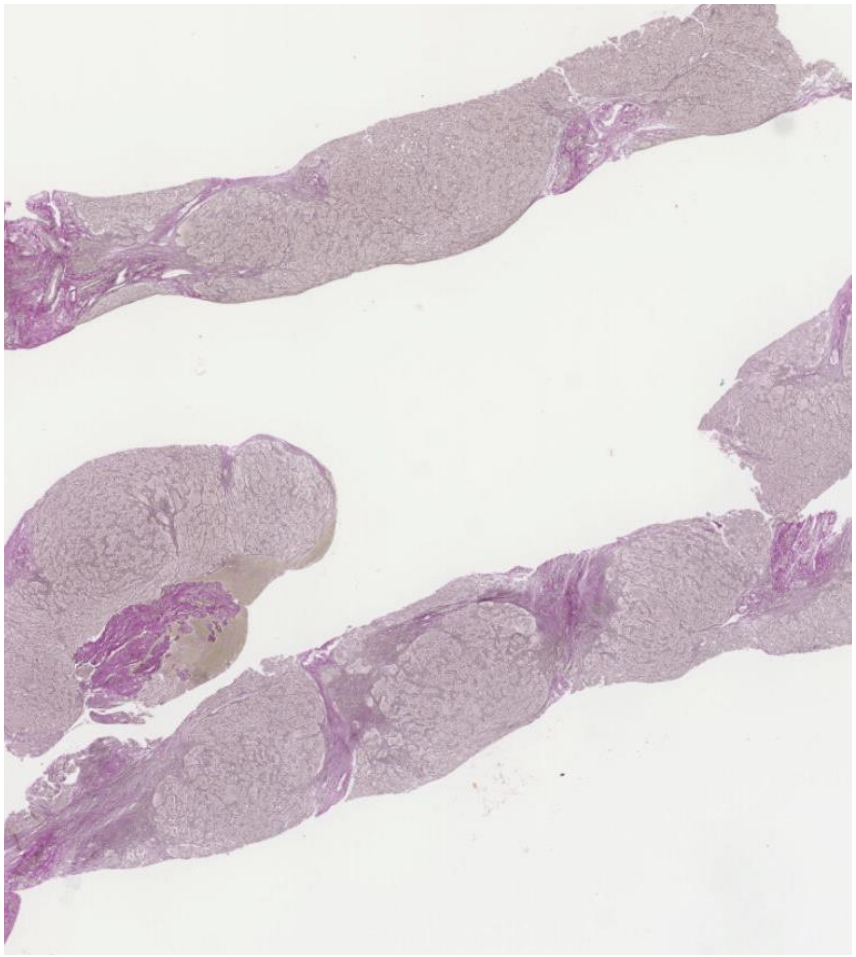
- Response to treatment similar to AIH
  - No relapse after treatment withdrawn (up to 65% in AIH)

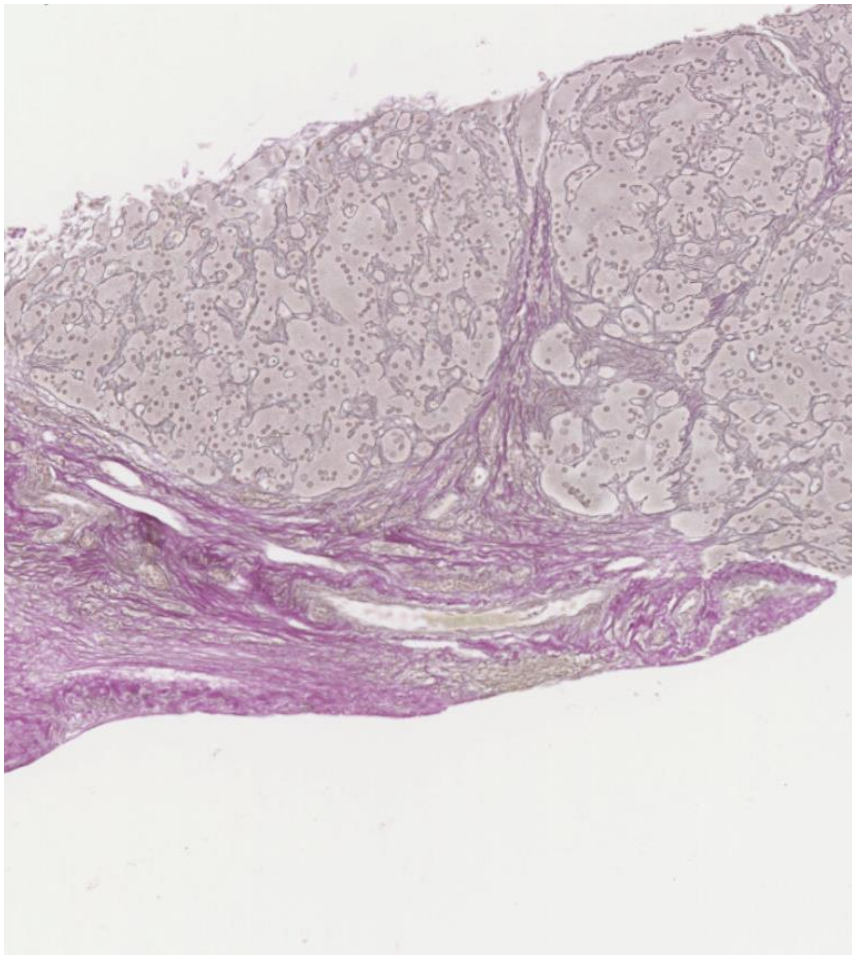
Adelaide B
(Alastair Burt)

Adelaide B

- 15 year old female
- Seen initially with fatigue
- Biochemical tests showed mildly elevated transaminases which persisted
- No FH of note
- No drug history or herbals
- Autoantibody screen normal
- HBV and HCV negative
- Normal peripheral blood parameters
- Normal caeruloplasmin
- Recent severe fatigue and onset of jaundice: no encephalopathy and synthetic function preserved

Adelaide B





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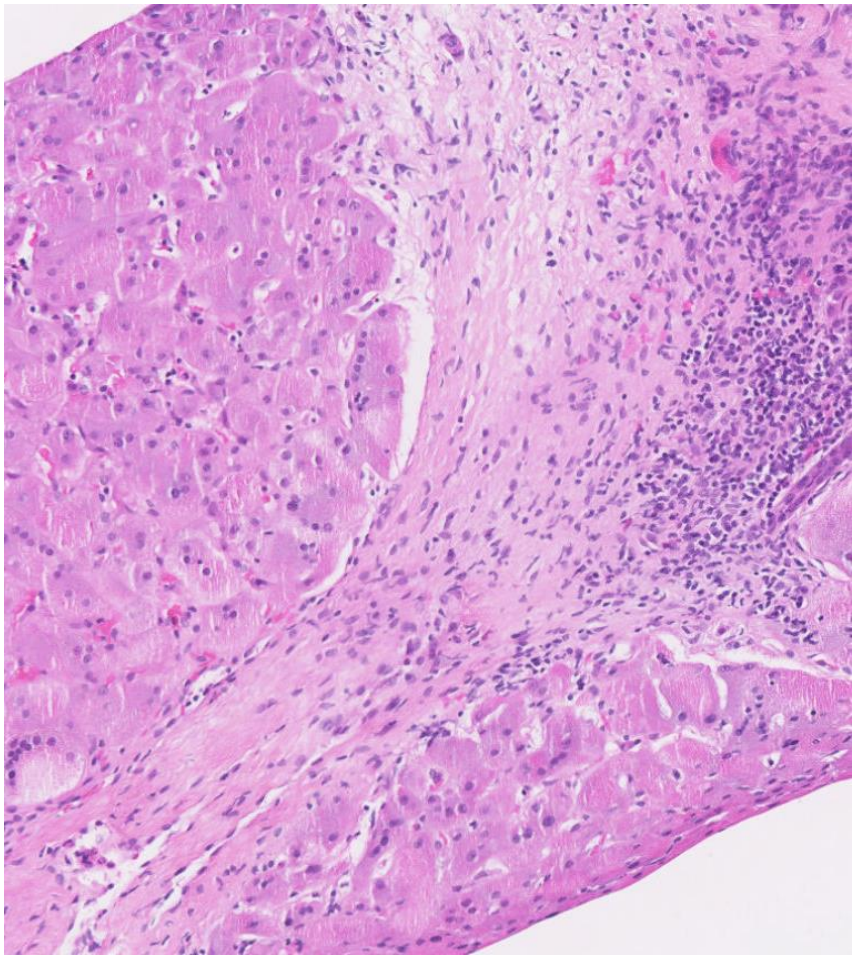

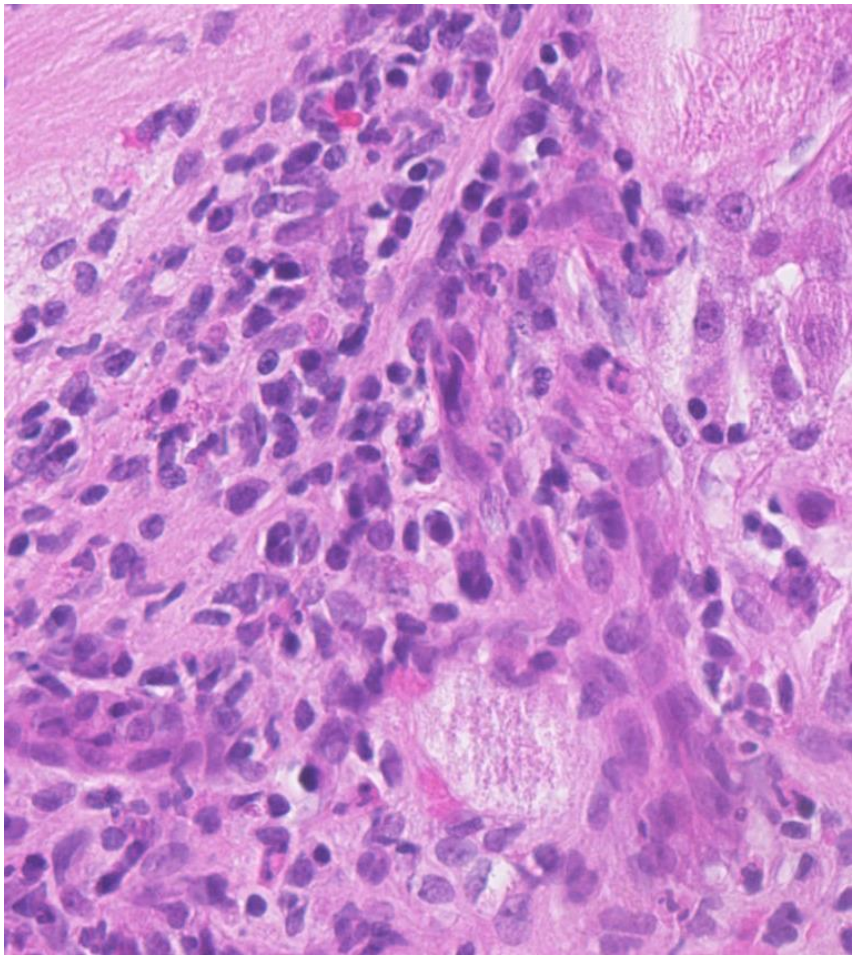

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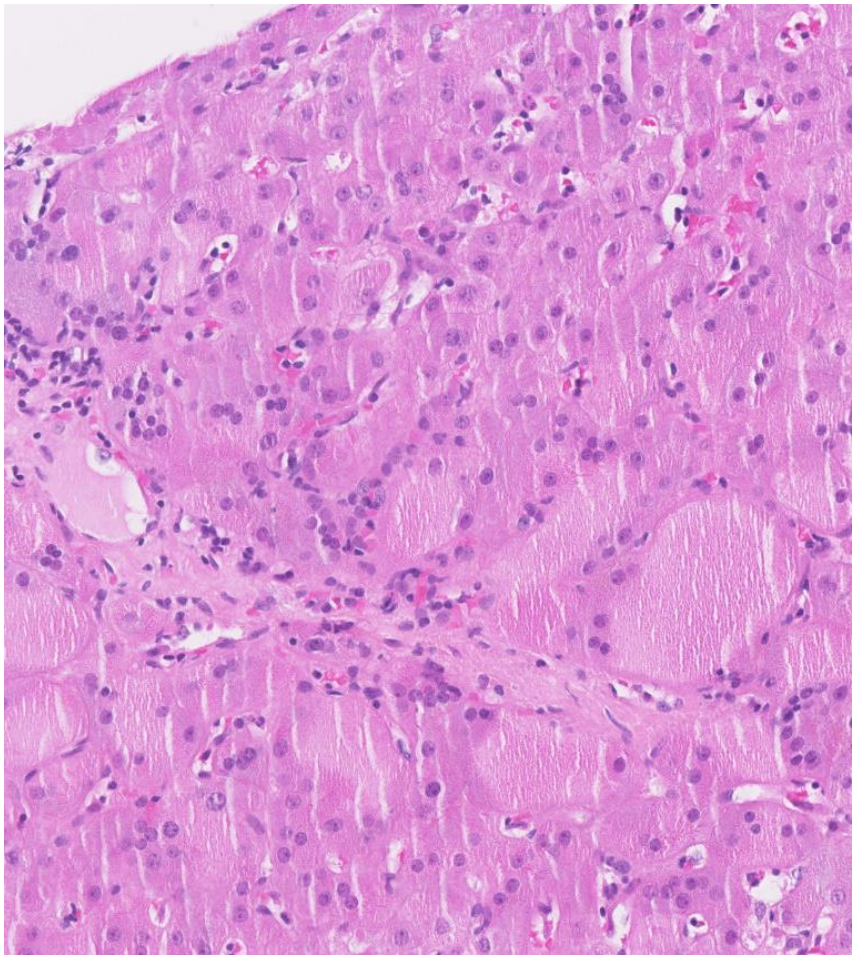

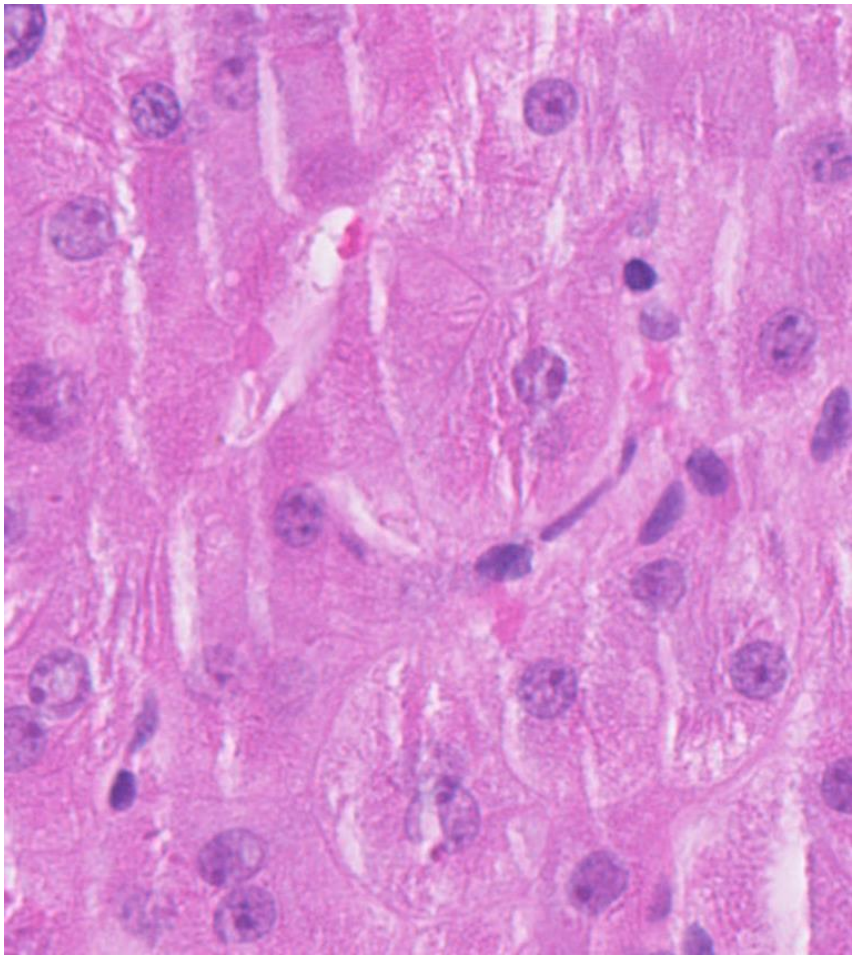

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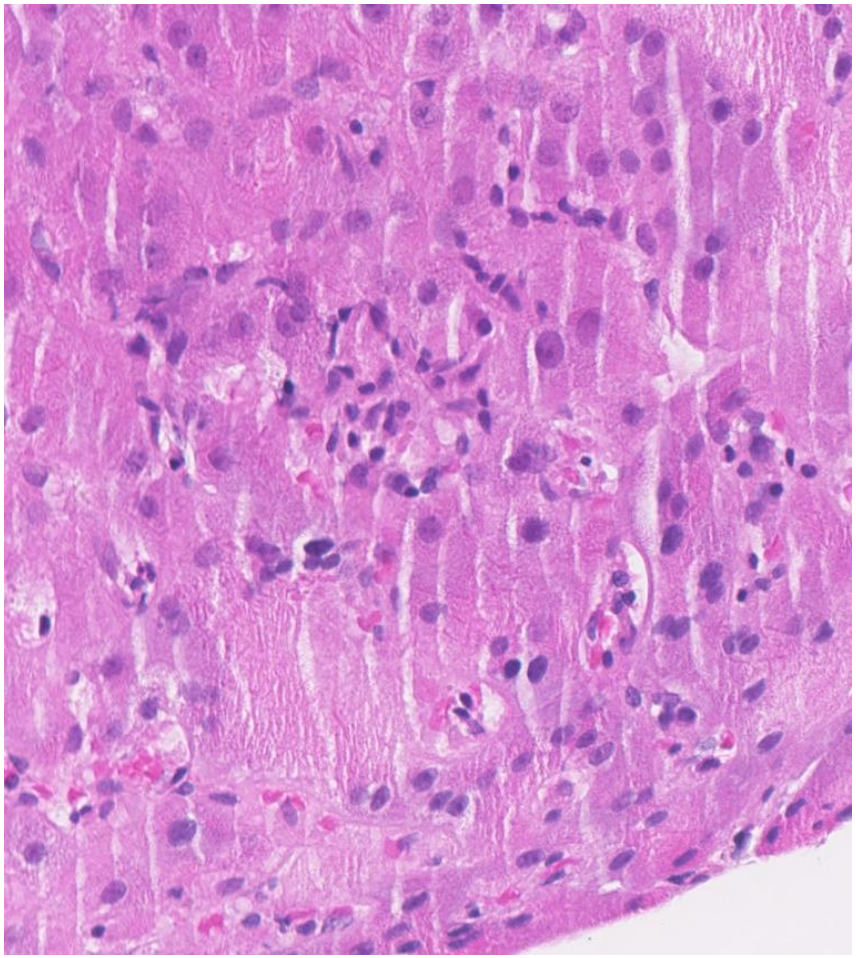

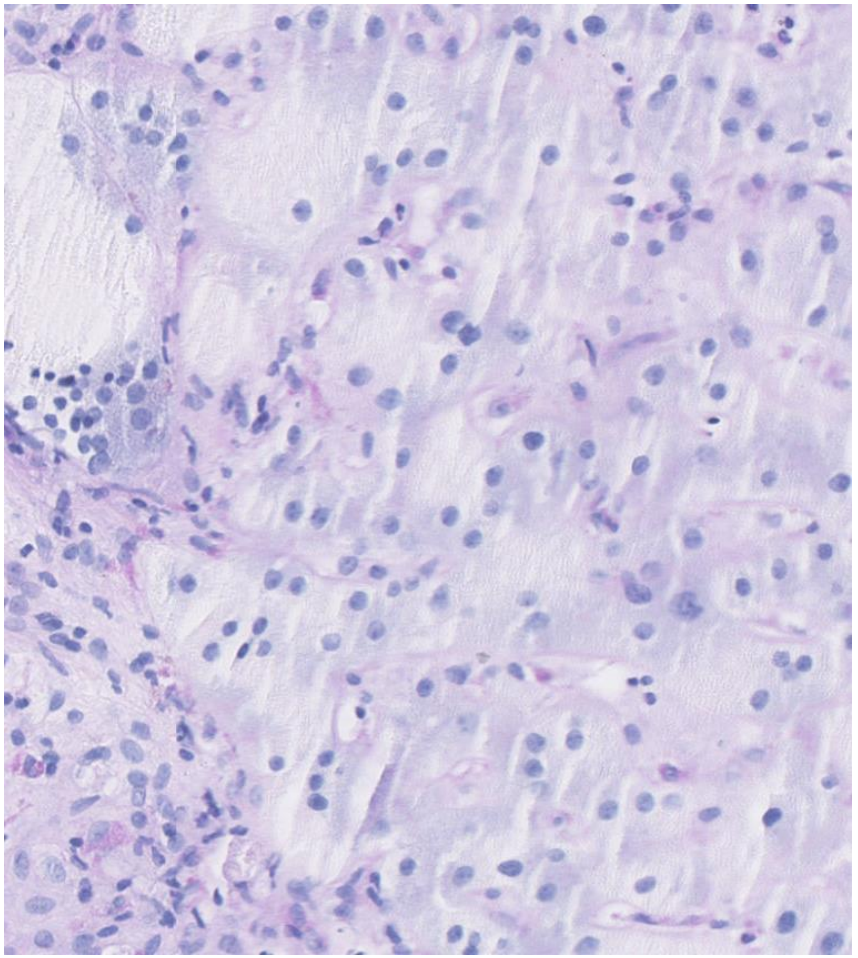

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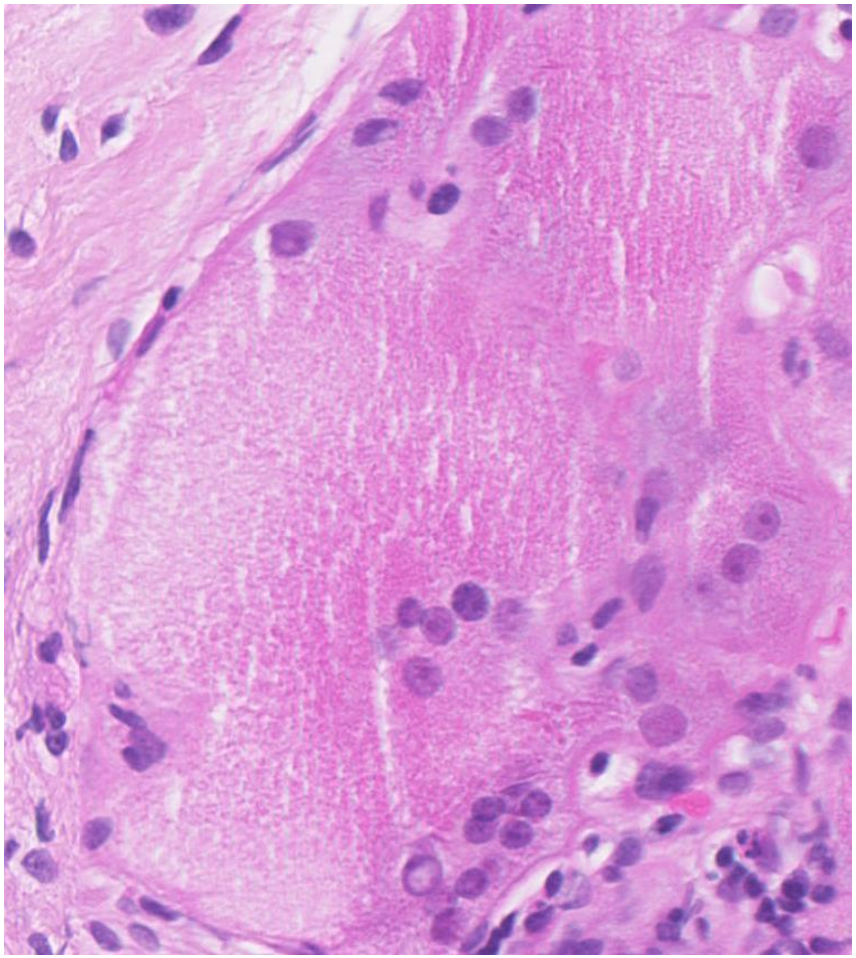
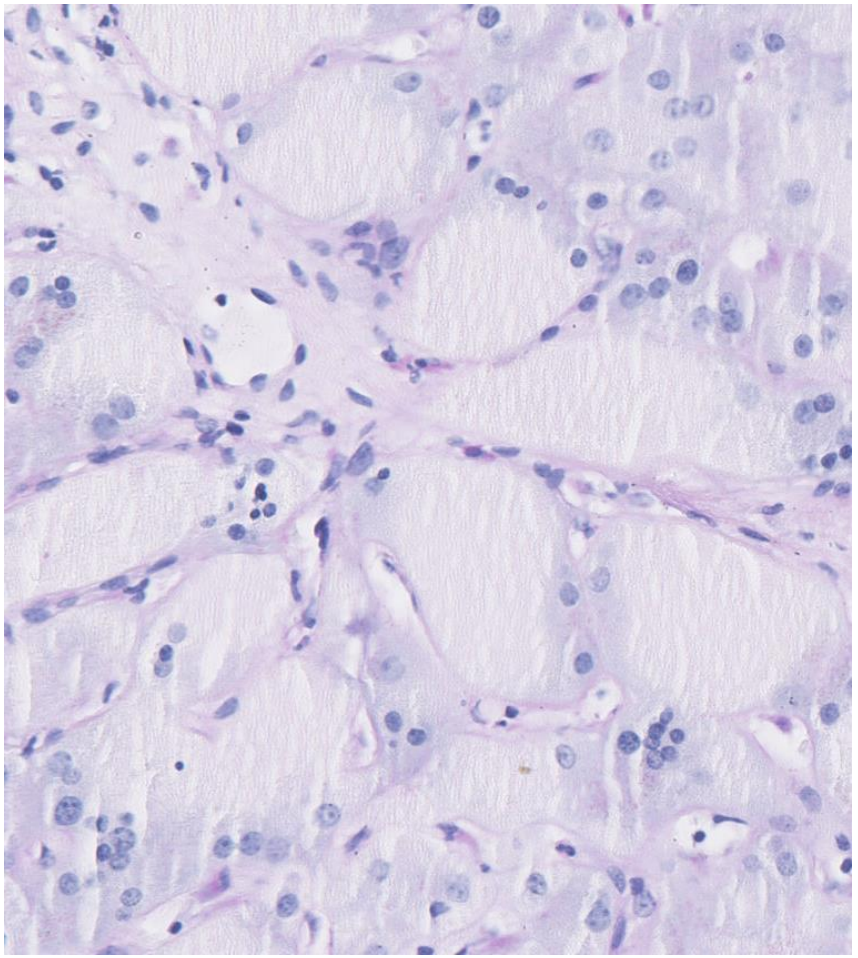




Adelaide B

- Post-infantile giant cell hepatitis: cirrhotic
- Acute on chronic or simply decompensating?
- Significance of inclusions?
- EM: enlarged mitochondria but no other inclusions

Post infantile giant cell hepatitis

TABLE 1: Various etiological agents of post infantile giant cell hepatitis.

Drugs and medication	Methotrexate, clometacin, 6-mercaptapurine, p-aminosalicylic acid, vinyl chloride, amitriptyline, chlordiazepoxide, and chlorpromazine and herbal medicine
Autoimmune diseases	Systemic lupus erythematosus, rheumatoid arthritis, polyarthritis, ulcerative colitis, autoimmune hemolytic anemia, primary sclerosing cholangitis, and autoimmune hepatitis (AIH), polyarteritis nodosa, and primary biliary cirrhosis
Viral causes	Hepatitis A, B, C, E Epstein-Barr virus (EBV), HIV, paramyxo-like virus. herpesvirus 6A infection, and human papillomavirus.
Miscellaneous	Hypereosinophilia, chronic lymphocytic leukaemia, lymphoma, sarcoidosis, Kugelberg-Welander syndrome, hypoparathyroidism, Sickle cell anaemia, and post transplant

Bihari et al, Hepatitis Research and Treatment, 2013

Post-Infantile Giant Cell Hepatitis

Possible mechanisms of giant cell formation:

- Fusion of neighbouring hepatocytes
- Nuclear division not accompanied by cell division

Histological appearances of giant cells (typical cases)

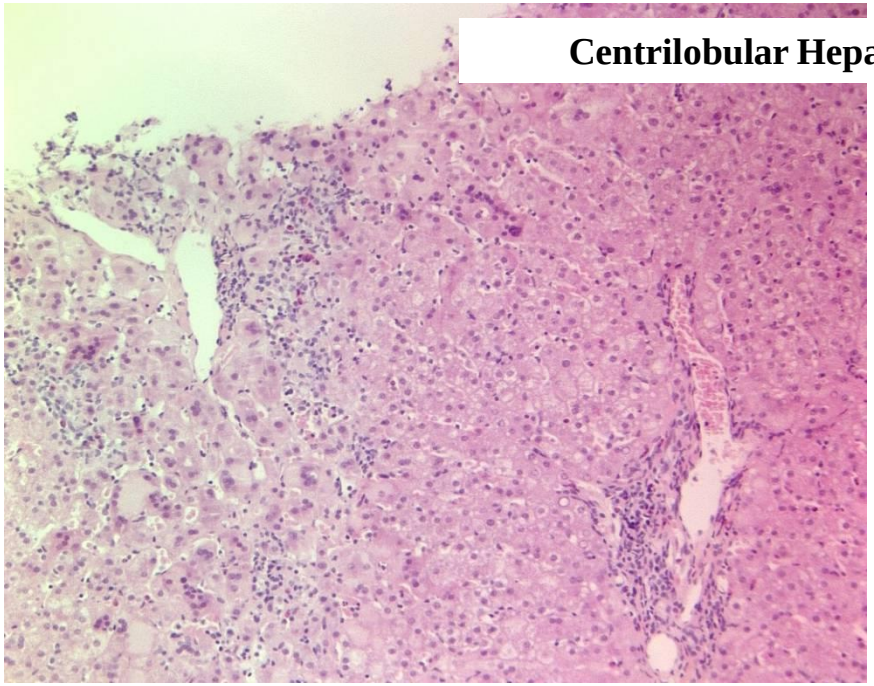
- 4-20 nuclei
- > 2/3rds of liver parenchyma
- More pronounced in zone 3

Patterns of liver injury

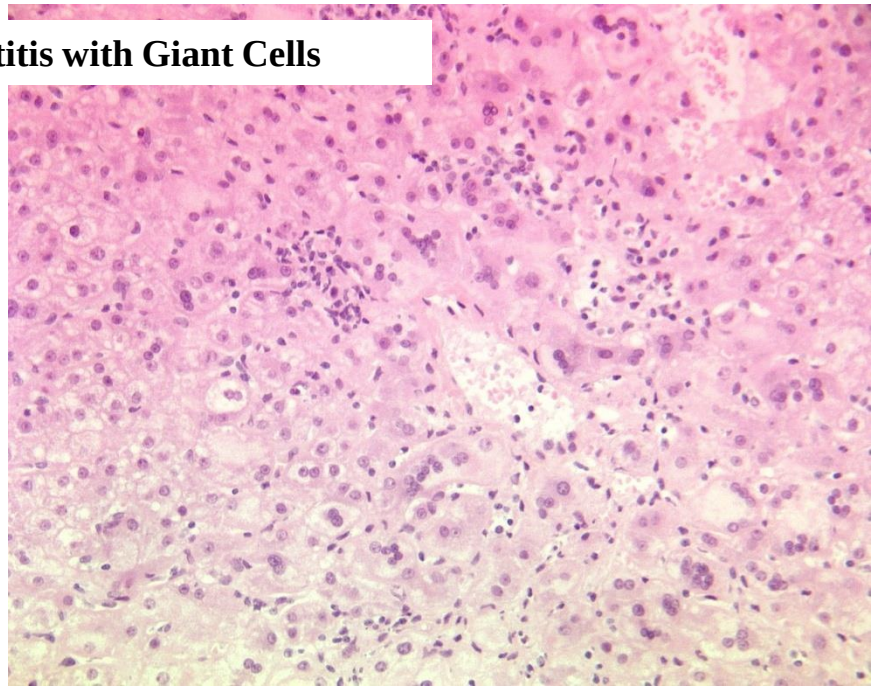
- Acute/subacute hepatitis (severe cases may present as liver failure)
- Chronic hepatitis (may progress to cirrhosis)

Post-Infantile Giant Cell Hepatitis – Two Other Cases Presented

1. **Newcastle B**
   - Female, age 7
   - Autoimmune PolyEndocrinopathy-Candidiasis-Ectodermal Dystrophy syndrome (APECED/APS-1 syndrome)
     - autosomal recessive disease characterised by the triad of the 'major' components hypoparathyroidism, primary adrenocortical insufficiency and chronic mucocutaneous candidosis



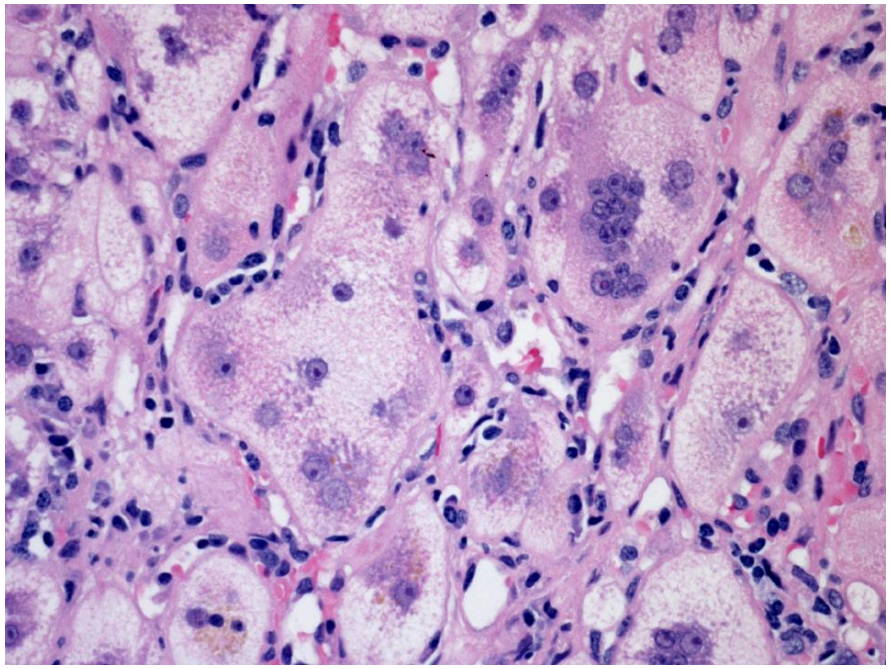
Centrilobular Hepatitis with Giant Cells

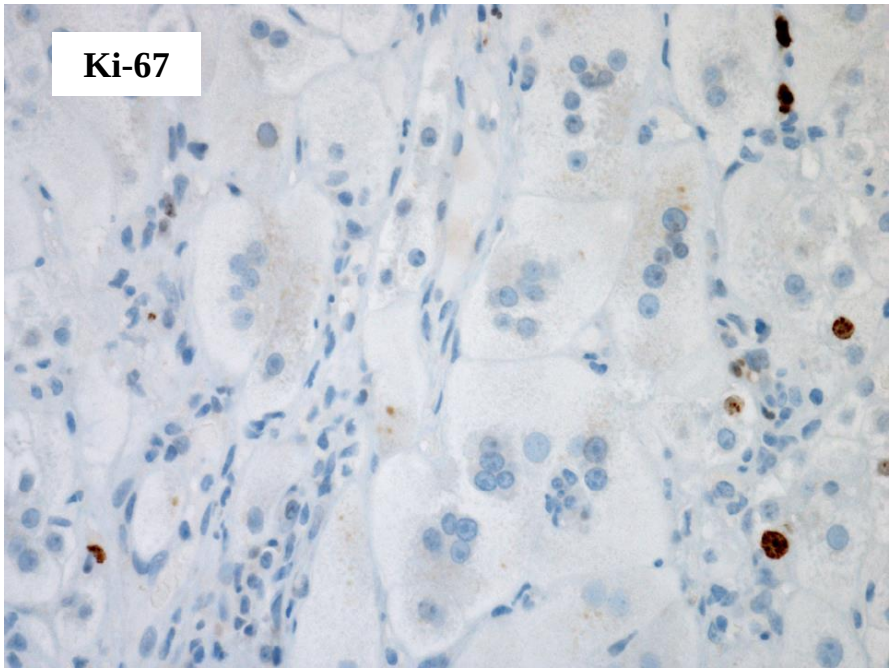


Post-Infantile Giant Cell Hepatitis – Two Other Cases Presented

2. Washington B

- Female, age 19
- Acute presentation
- Features of autoimmune hepatitis
  - ANA 1:160, actin ab 116 (ref 0-19)





The shape of things to come?

Rochester Case A

(Michael Torbenson)

History

A 60 year old woman

- Normal health until 6 days prior to admission
  - Presents with lethargy, malaise, hypoglycemia, jaundice
  - Coagulopathy
  - Elevated transaminases
    - AST of 11,500
    - ALT of 12,200
    - Total bilirubin of 6

- Past medical history:
  - No foreign travel; Vacation 2 weeks prior to illness—frequent eating out
  - Hypothyroidism
  - Remote history of breast carcinoma (20+ years ago; in remission)

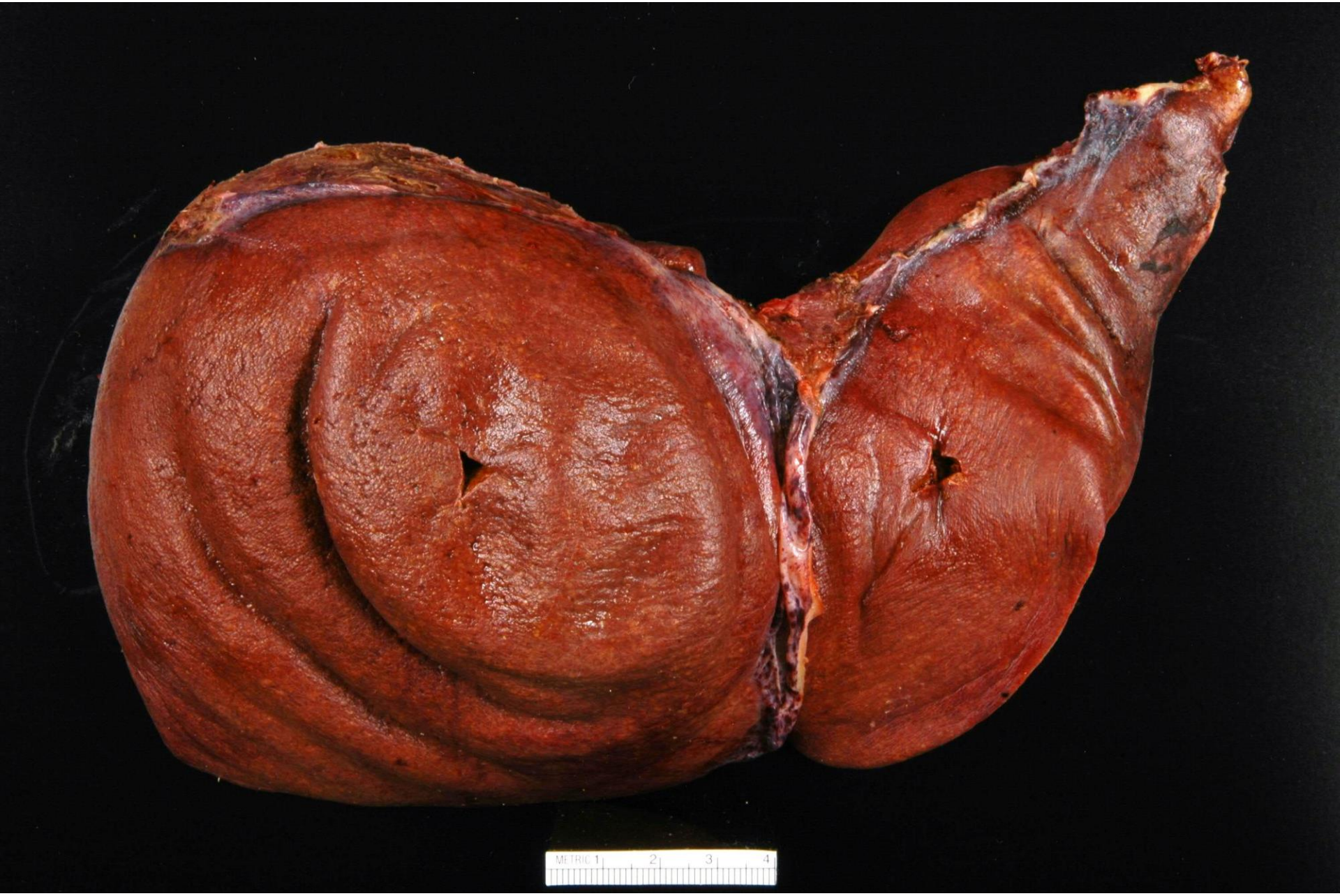
History

Day 2

- AST and ALT have dropped to 2100 and 4200
- Coag studies and mental status worsening
- Imaging studies:
  - Essentially normal
    - Distended gallbladder
    - Removed laparoscopically in an uneventful procedure.

Day 5

- Clinical status deteriorates even more and a liver transplant was performed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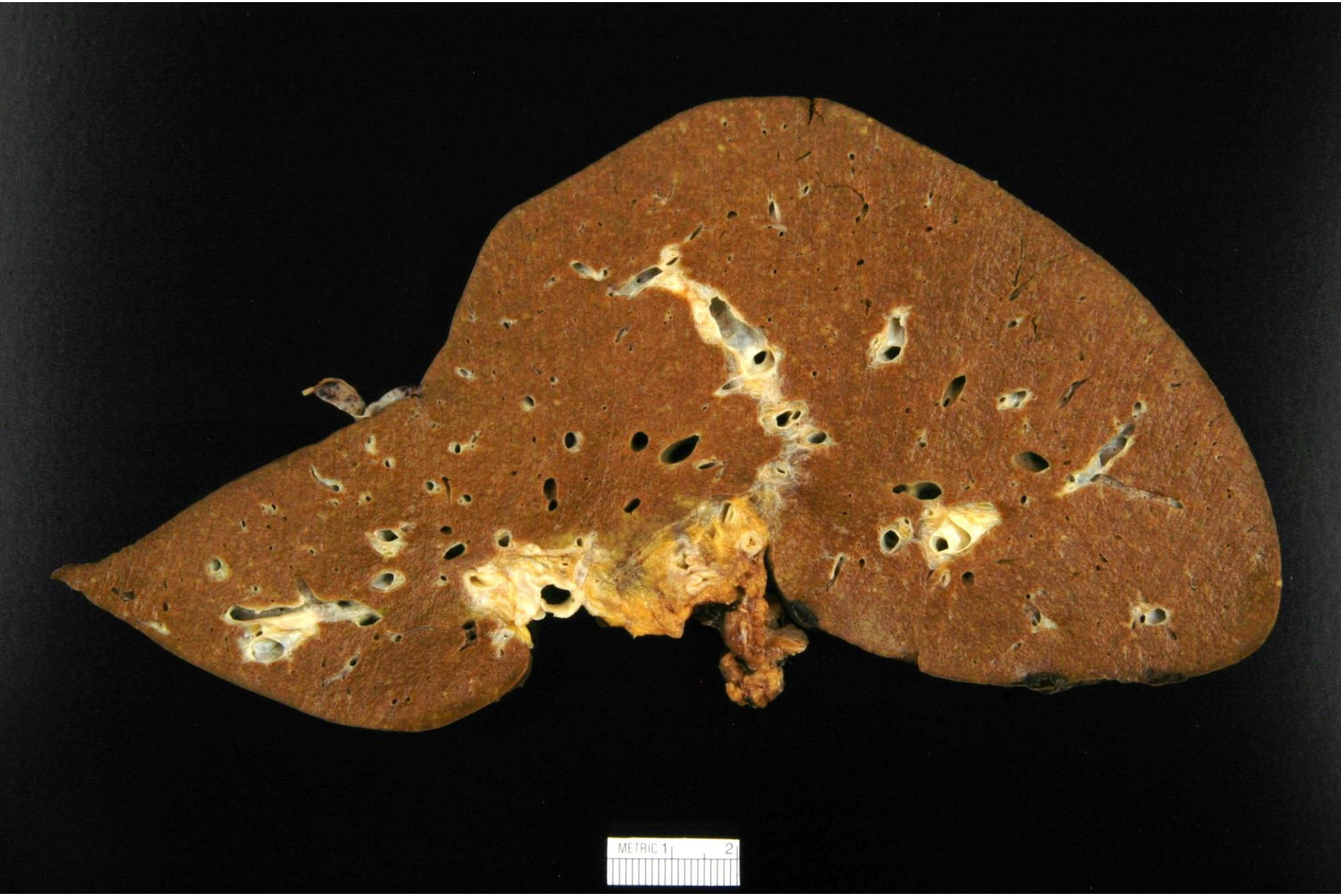
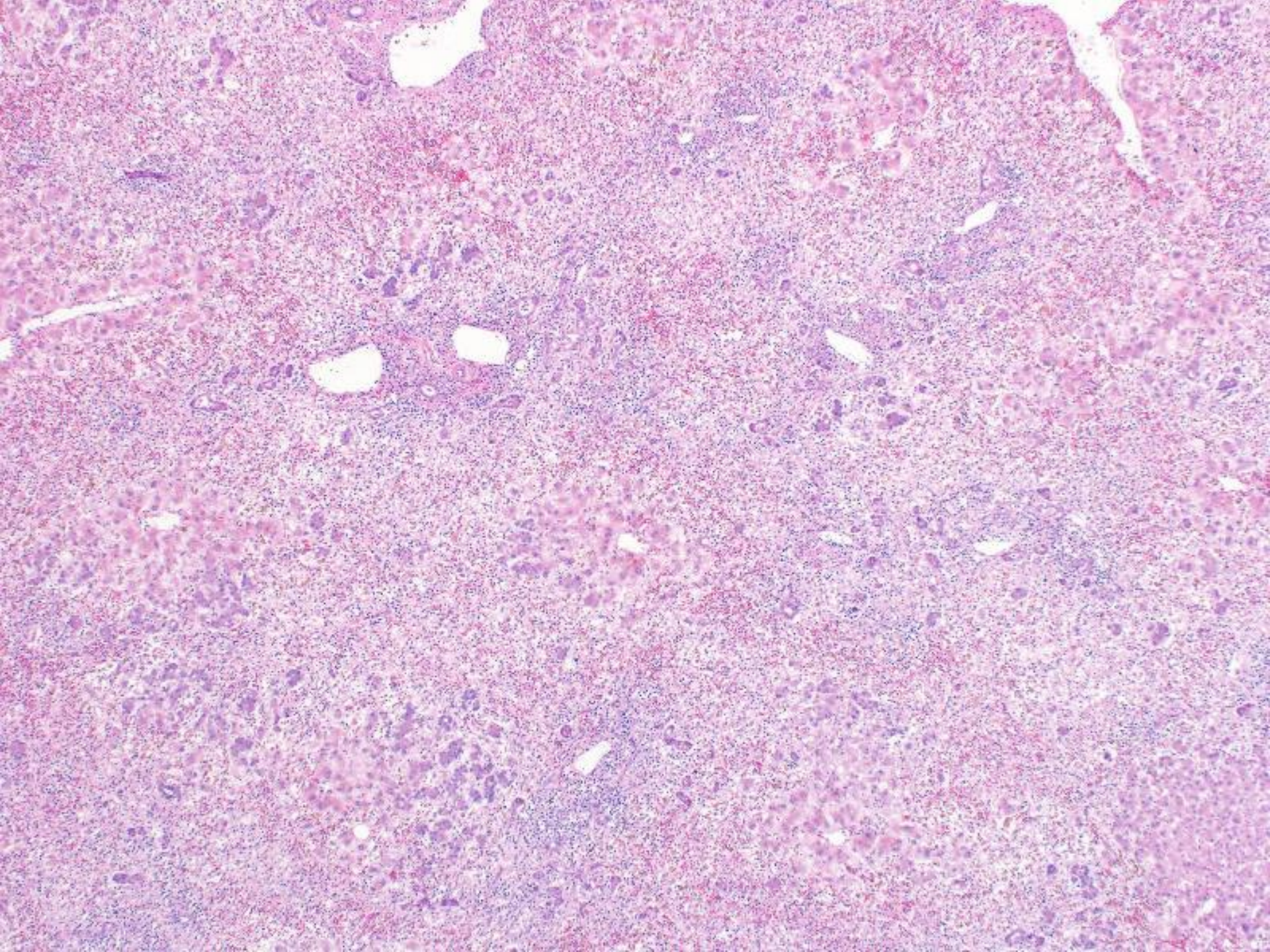
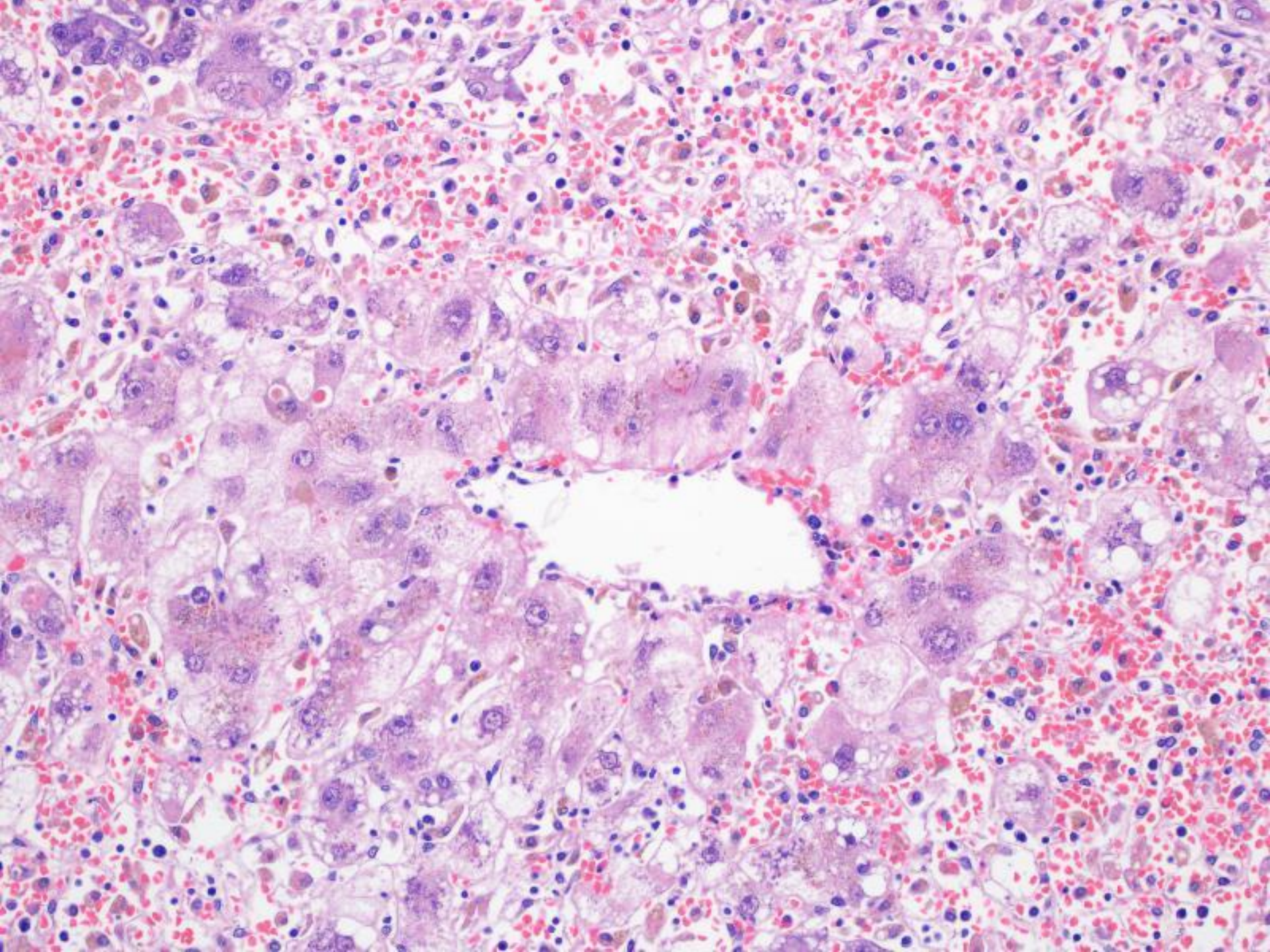

METRIC 1
2





Final Diagnosis

One more lab result

Final Diagnosis

HAV IgM positive

Hepatitis A

- Acute hepatitis A (~85%)
- Fulminant hepatitis A (~1%)
- Relapsing hepatitis A (~15%)
- Prolonged cholestatic hepatitis A (~2%)

- No convincing reports of chronic hepatitis

Acute Hepatitis A

- Biopsies rarely performed in acute hepatitis A
  - diagnosis made by serological studies
- Reported histological findings
  - Plasma cell rich hepatitis
  - Portal inflammation can be more striking than lobular inflammation
  - Lobular inflammation may have a zone 3 predominance
  - Fibrin ring granulomas have been reported

Fulminant Hepatitis A

- Up to 3% of cases of fulminant hepatitis in some studies
  - Increased risk in people with chronic liver disease (e.g chronic HBV or HCV infection)
- Massive liver necrosis
- Variable inflammation and cholestasis
- Nothing specific to suggest HAV

Necrosis pattern

- Preservation of zone 3 hepatocytes!

Necrosis pattern

Recognized causes of Zone 1 or Zone 1/2 necrosis

- Eclampsia
- DIC
- Halothane toxicity (more commonly causes zone 3 necrosis)
- Ferrous iron toxicity
- White phosphorous toxicity
- Endotoxin release from *proteus vulgaris*
- Some industrial chemicals such as allyl alcohol

Necrosis pattern

- Zone 1 necrosis pattern and HAV?

Necrosis pattern

- Zone 1 necrosis pattern and HAV?

"The one exception among the examples of hepatitis A was in case 9, biopsied 20 days after the onset of illness. In this patient, there were prominent periportal liver cell alterations (Fig. 3A), but ***centrilobular liver cell swelling and necrosis were sparse*** (Fig. 3B). (Okuno et al, 1984; 6695857)

Necrosis pattern

- Zone 1 necrosis pattern and HAV?

"Hepatitis type A was characterized by conspicuous, mononuclear inflammatory cell infiltration of the portal tract with frequent disruption of the limiting plate, and periportal hepatocyte focal necrosis ***with virtual sparing of parenchyma about the central vein tributary*** (Abe et al, 1982; 6174391)

Necrosis pattern

- Zone 1 necrosis pattern and HAV?

YES

HAV can rarely show relative sparing of zone 3

Basel – Case A

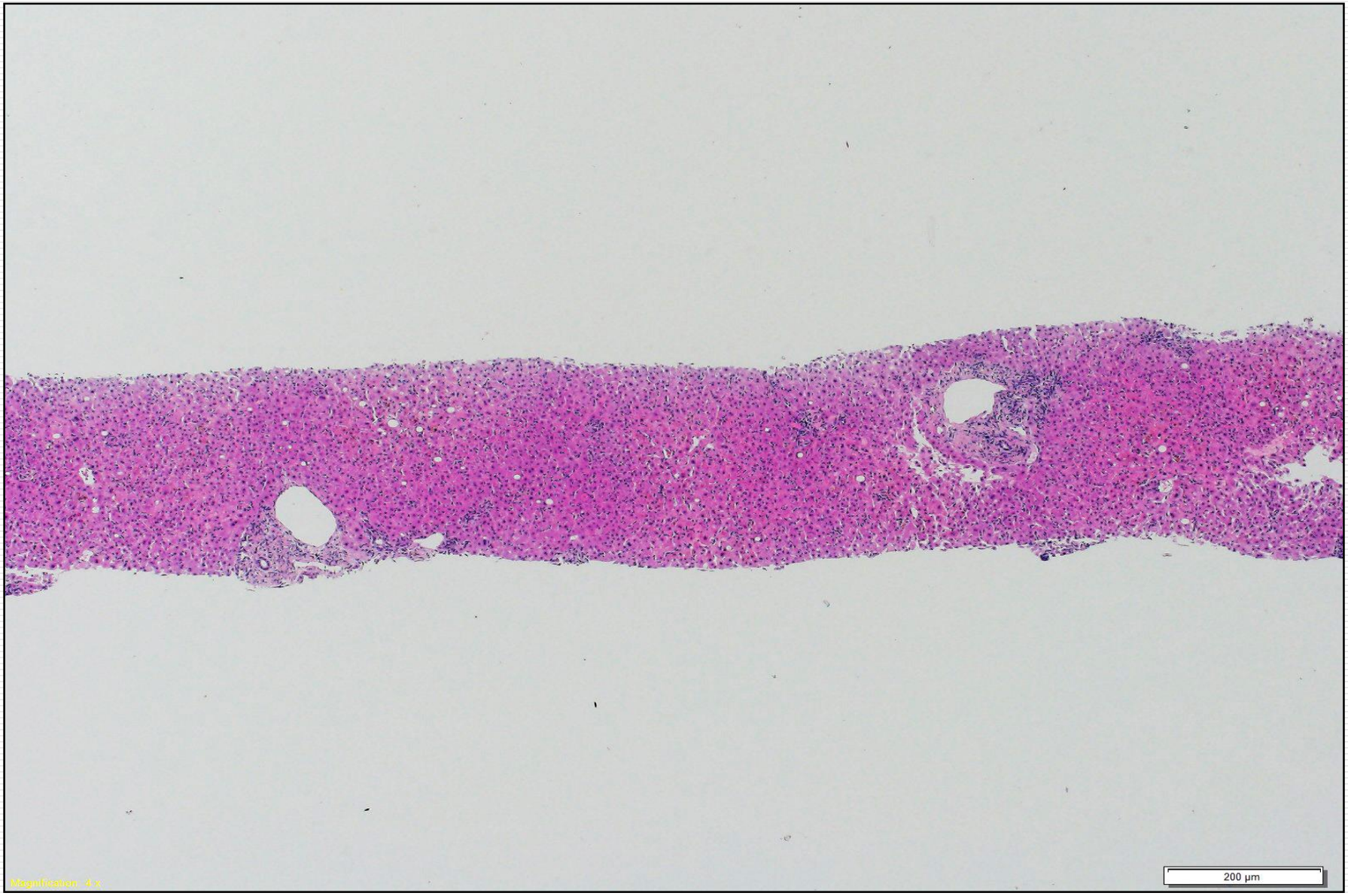
(Luigi Terracciano)

Clinical history I

- A 52- year-old man was admitted to our hospital because of fatigue, icterus, dark urine and marked increase of cholestatic parameters and transaminases.
- At ultrasonography no evidence of mechanical obstruction.
- The patient suffered since 12 years of multiple sclerosis treated with Gilenya (Fingolimid, a sphingosine-1-phosphate receptor modulator).
- The patient did not have any recent travels, or a personal history or risk factors for liver disease

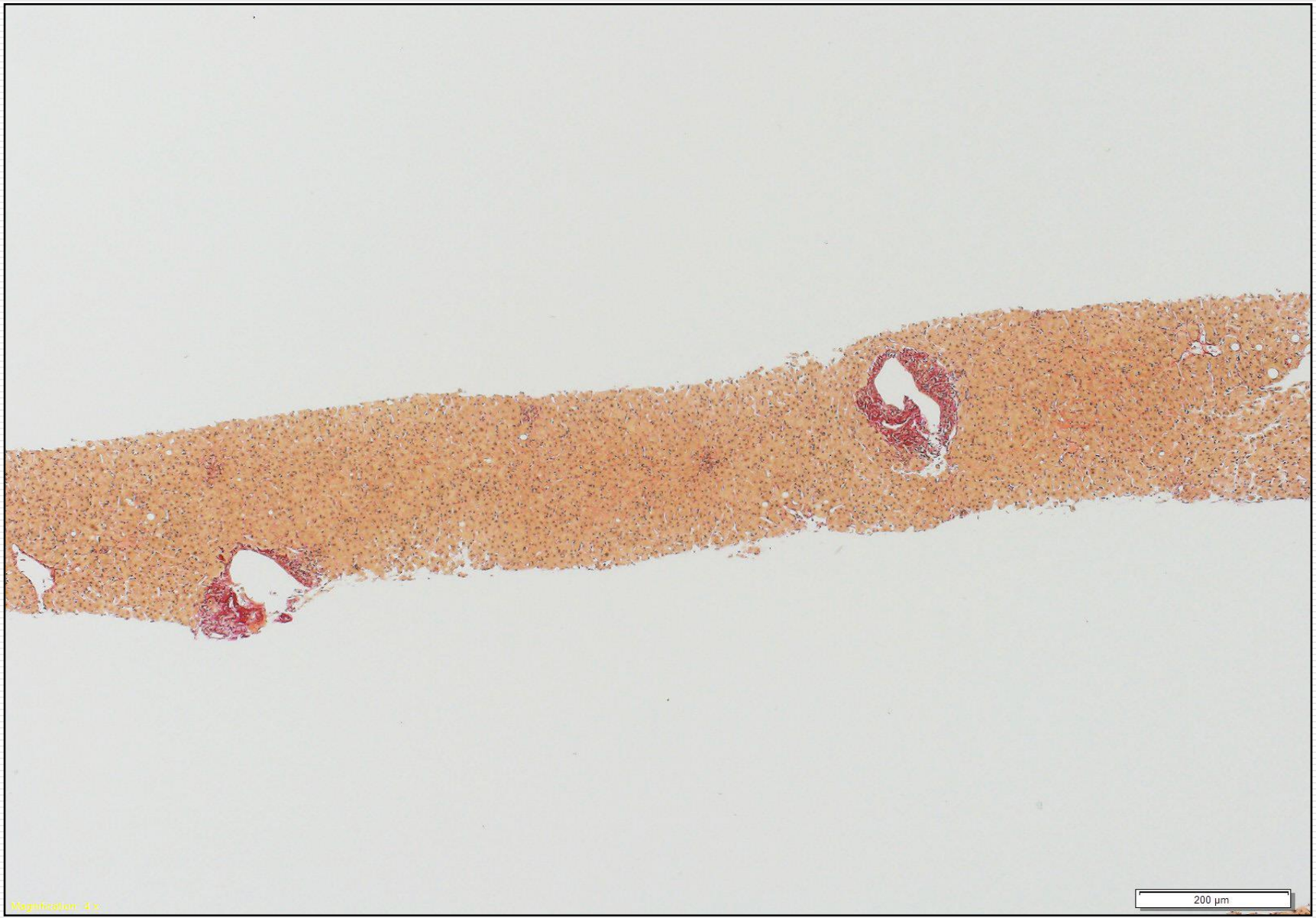
Clinical history II

- Search for causes of liver disease including HAV, HBV, HCV, EBV, HIV, hemochromatosis and autoantibodies, was negative.
- Laboratory test results: ASAT 1410 U/l, ALAT 2522 U/l, gGT 430 U/l, Alk.phos. 250 U/l, ferritin 3144 µg/l
- A liver biospy was performed.



Preserved lobular architecture

B16.952



No increase of fibrosis

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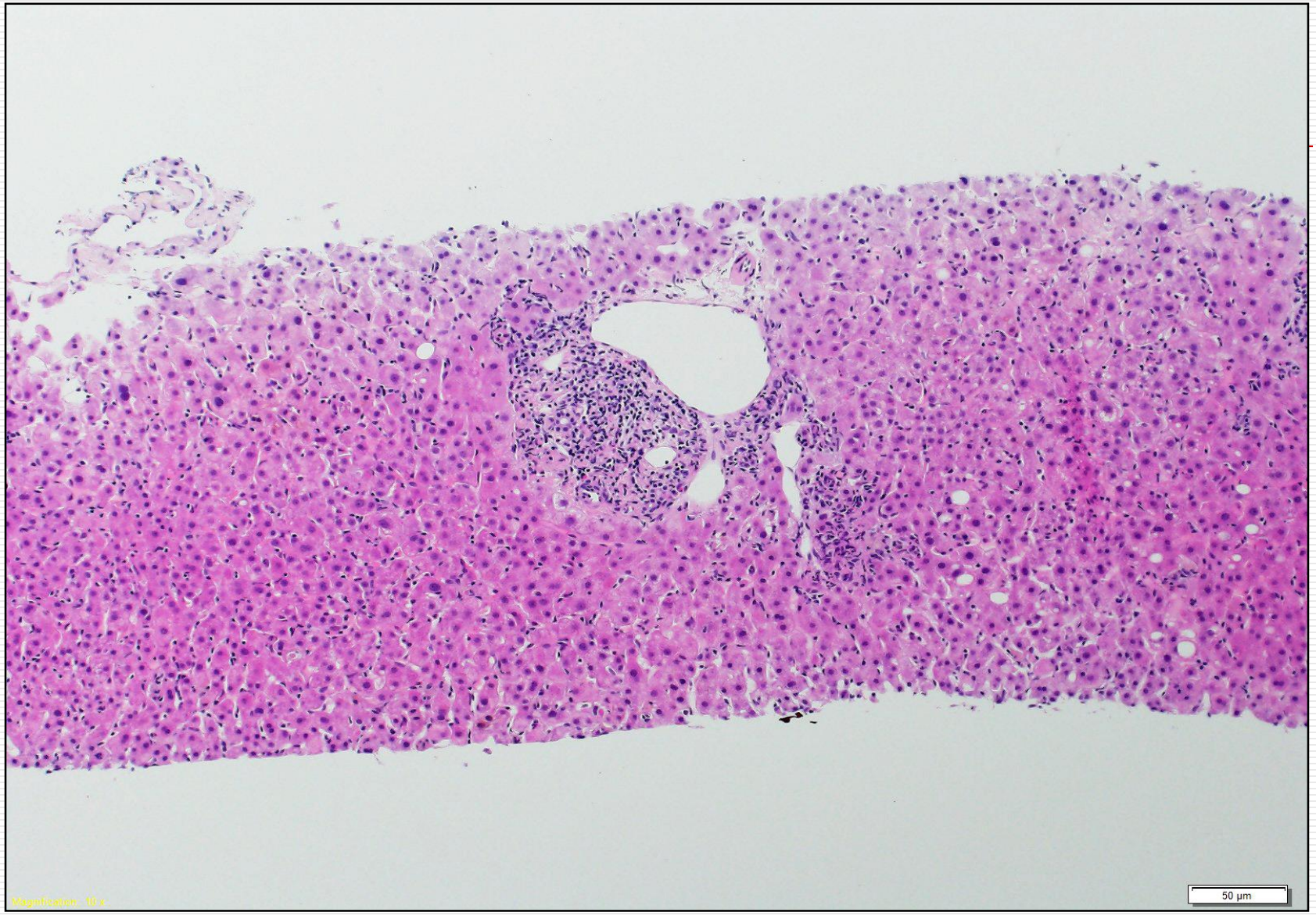

Mild to moderate mononuclear inflammatory infiltrates with scattered neutrophils in some PTs

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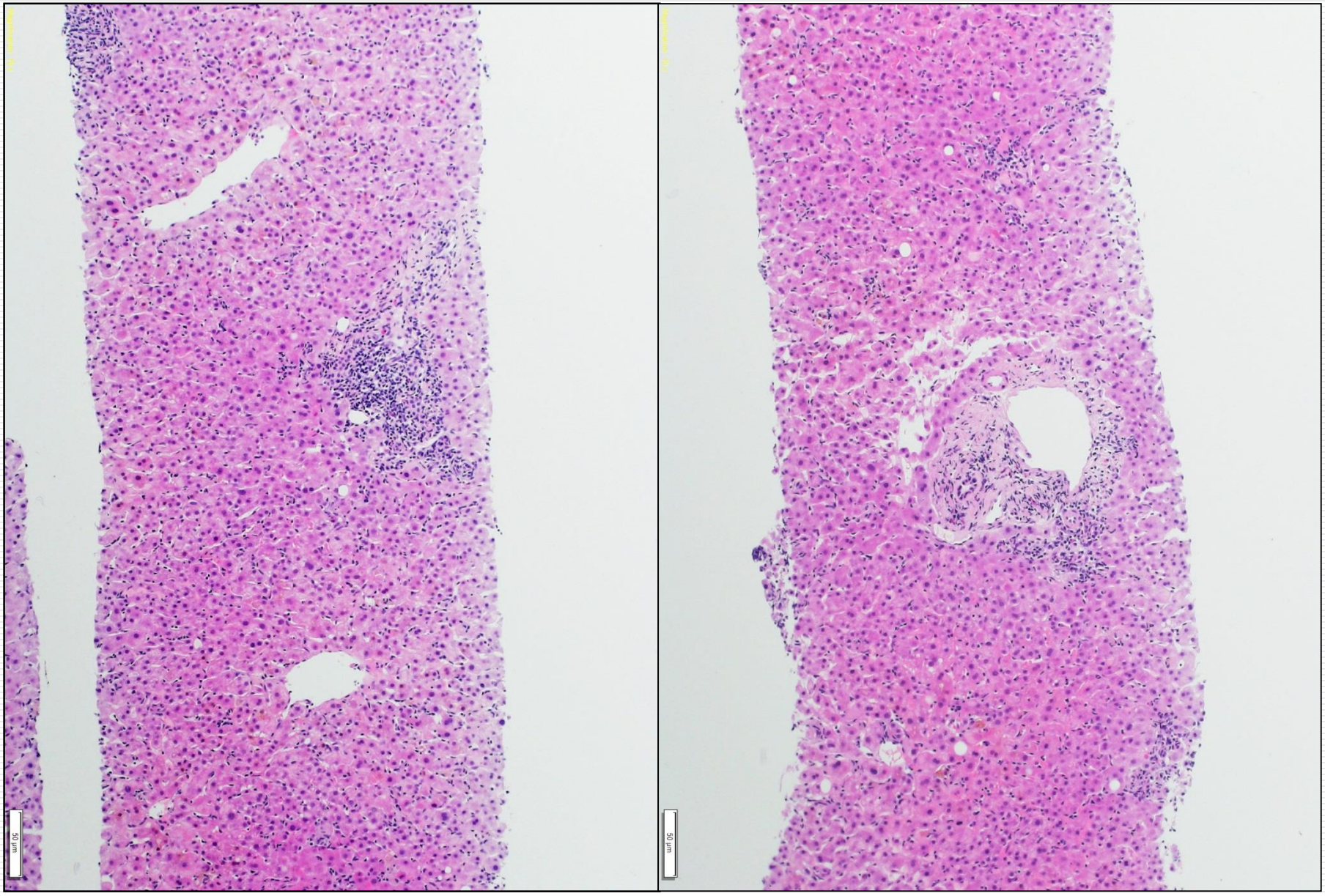
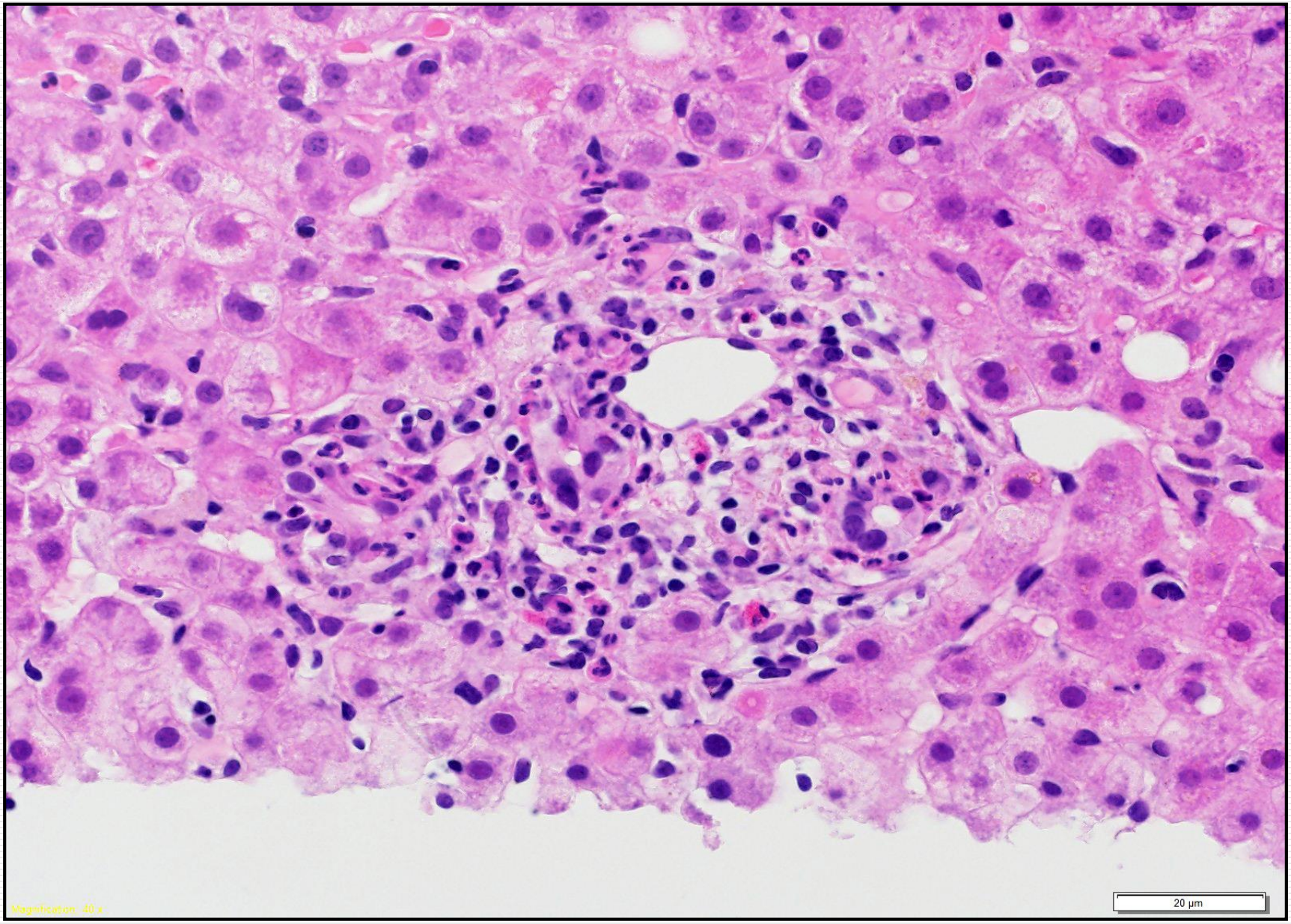
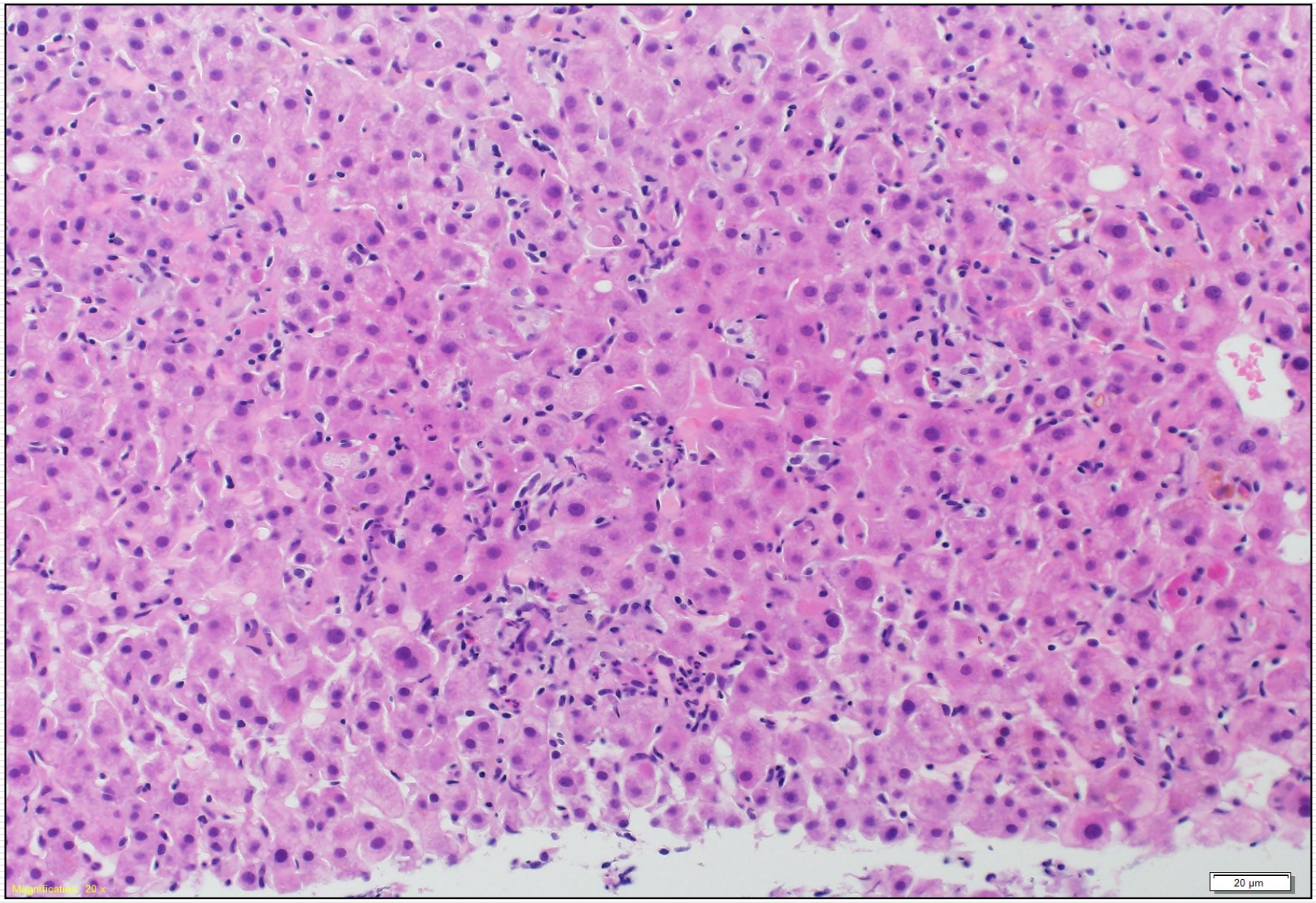


Slight periportal hepatitis, but no trapped periportal hepatocytes B16.952



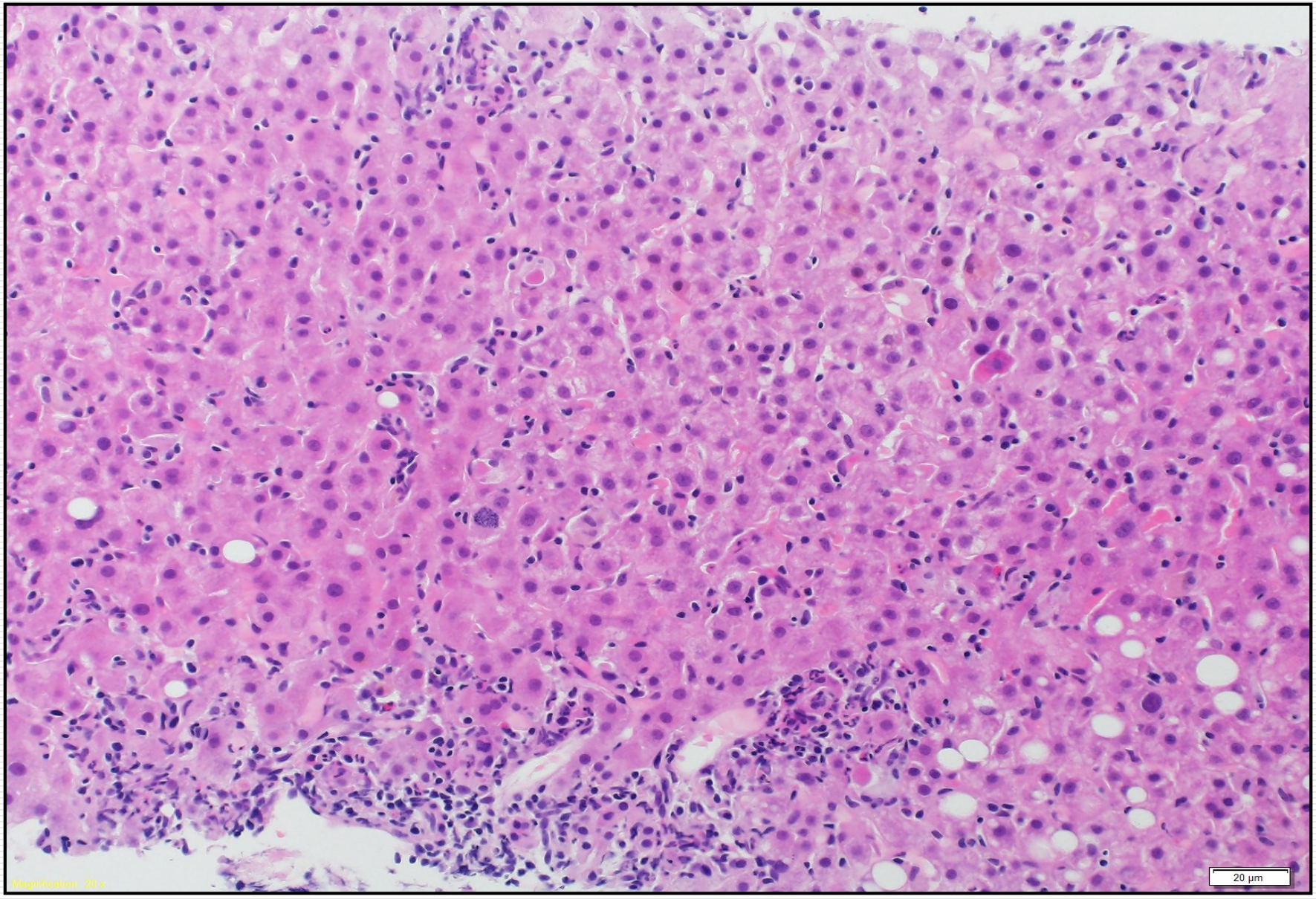
Some portal tracts with mixed inflammatory infiltrates and mild acute cholangitis. Some eosinophils

B16.952



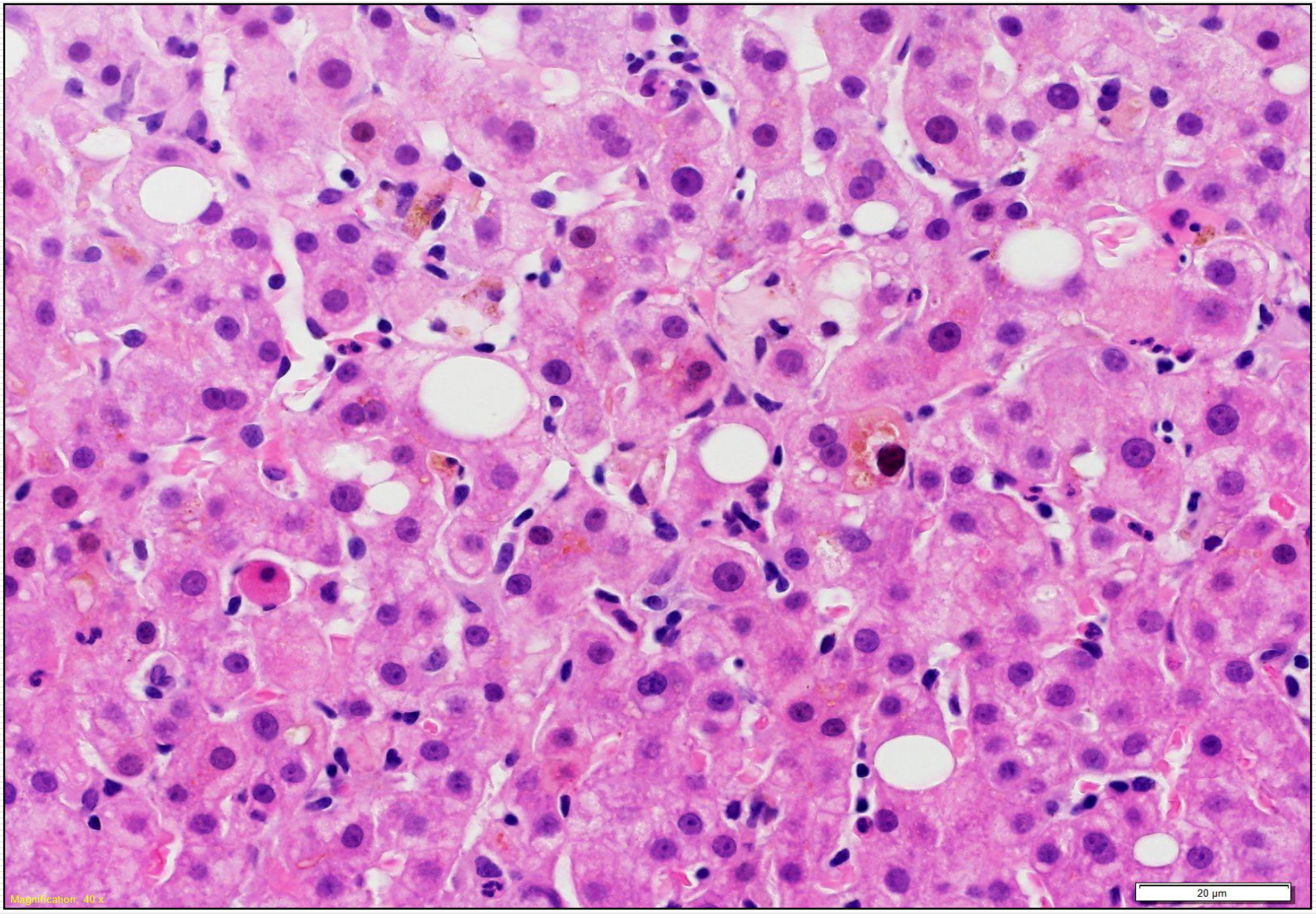
Predominance of lobular lesions: diffuse mononuclear necroinflammation and histiocytic microgranulomas

B16.952



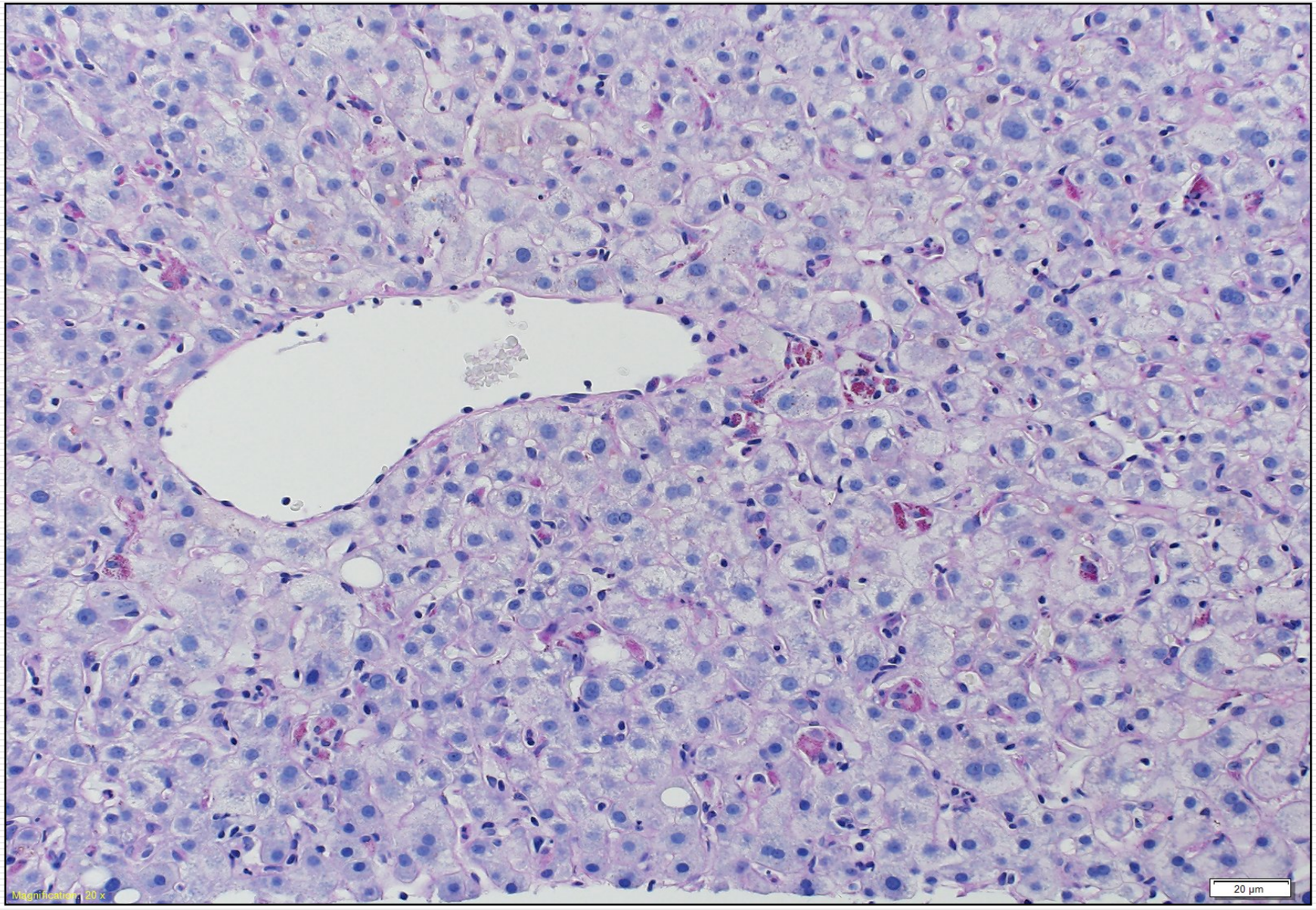
Lobular disarray, spotty necrosis and apoptotic bodies

B16.952



Several sinusoidal monuclear phagocytes, single cell necrosis and bilirubinostasis

B16.952



Several sinusoidal monuclear phagocytes with ceroid pigment

B16.952

Diagnosis

Acute cholestatic hepatitis, possible DILI

Ddx : ? acute HEV

5 days later:

Serology for HEV : strong positivity for HEV IgM (12.2) and IgG (8.8)

Hepatitis E quant. PCR (Virology Lab, University Hospital Zürich):

1400 GEq/mL (21.1.16)
100 GEq/mL (27.1.16)

Final diagnosis

Acute cholestatic HEV hepatitis

? Role of Fingolimid (13 years of therapy!)

Follow-up (1 month later, re-starting therapy with Fingolimid):

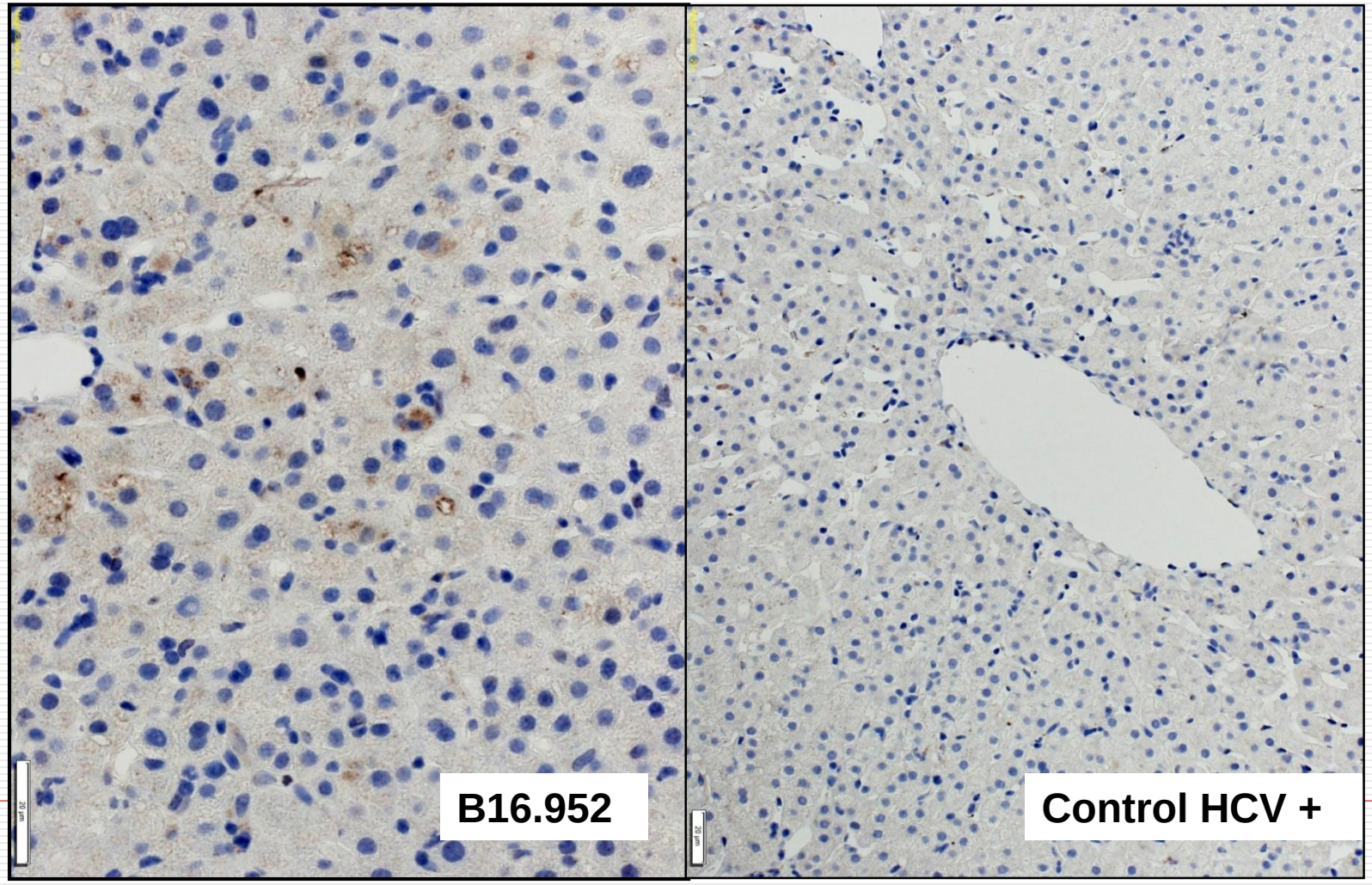
ASAT 28 U/l, ALAT, 25 U/l, GGT 52 U/l, Alk, phos. 70 U/l

HEV RNA not longer detected

A very similar case : Chen YE, Hepatology, 56, 2420-3, 2012

Immunohistochemistry for HEV on FFPE

(? Antibody from Chemicon – mainly intended for Western blotting)



HEV Hepatitis and DILI

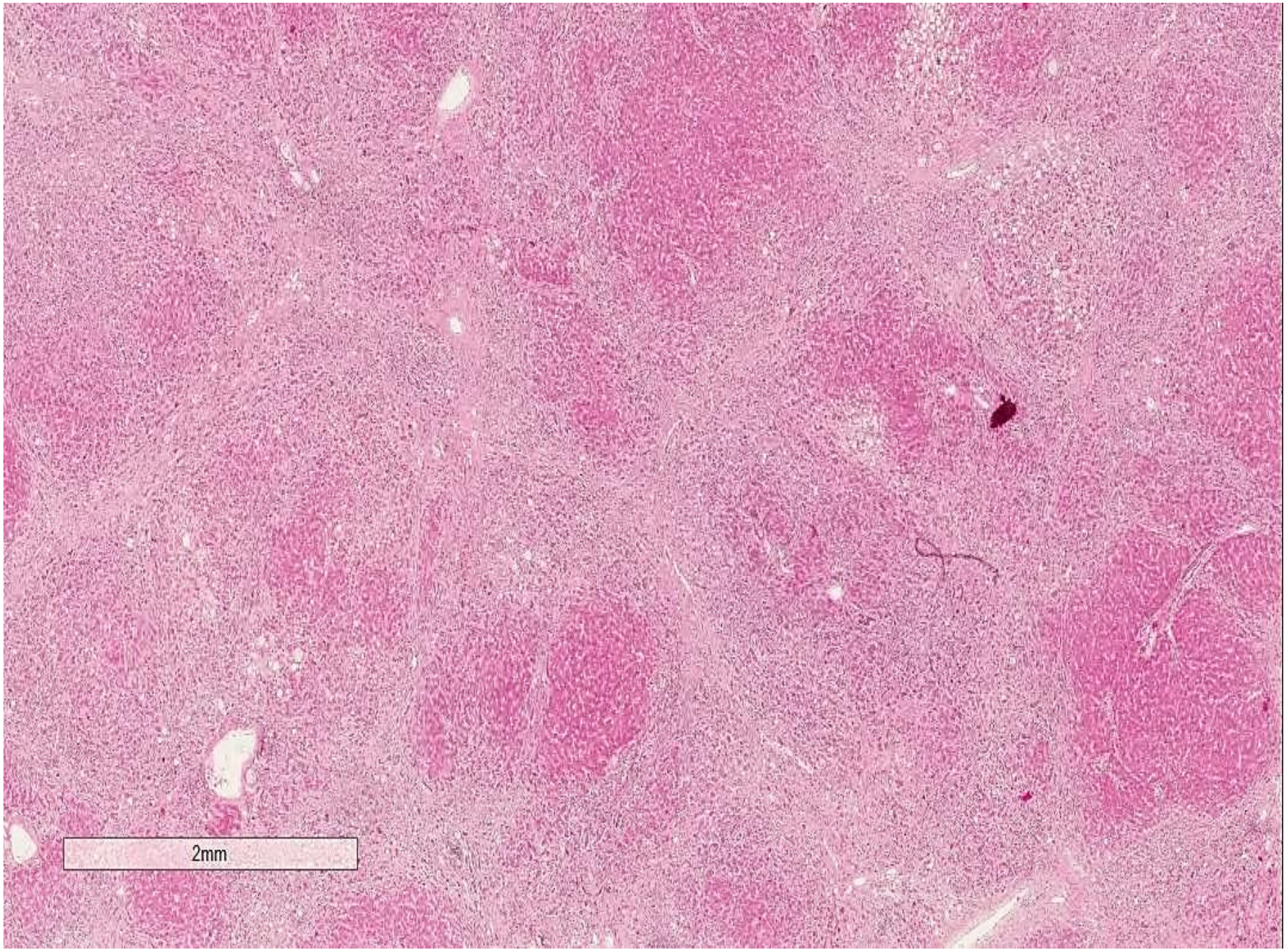
Davern- Gastroenterology 2011, Chijioke - Front Med 2015, Drebber - Front Physiol 2013, Dalton AP&T 2007

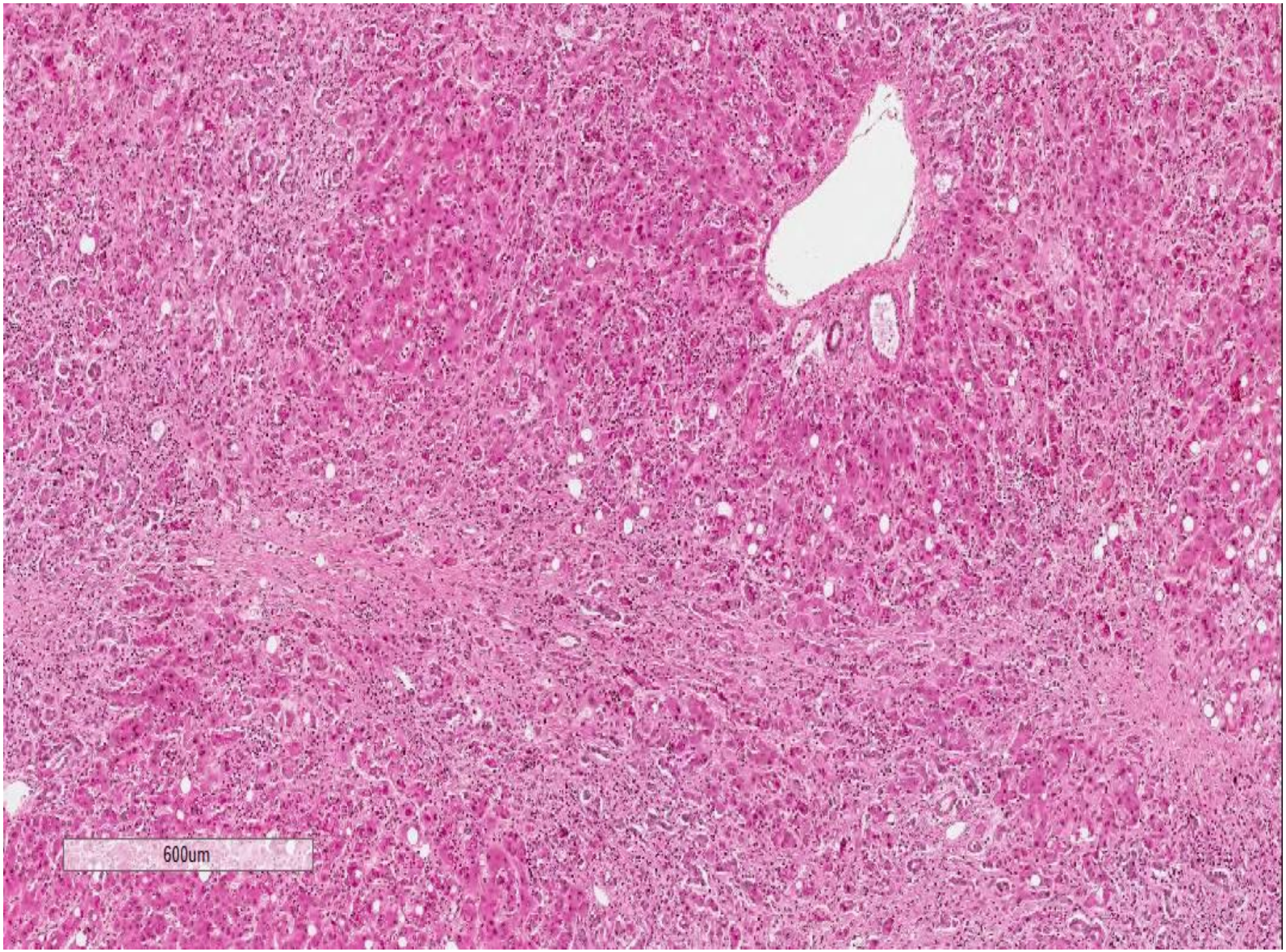
- HEV RNA detectable in 2-21 % of sera from patients with suspected DILI
- 10／45 (22.2%) patients with autochthonous hepatitis E initially diagnosed as DILI (Dalton 2007)
- Absence of any histopathological findings specific or highly characteristic for HEV infection : do we need to test all patients with suspected acute DILI?

Paris - Case 2
(Pierre Bedossa)

Paris - Case 2

- 32 years old woman
- Admitted in ICU for hepatic decompensation, encephalopathy, renal failure
- No previous liver investigation
- History of massive alcohol intake (family)
- Transjugular venous biopsy: acute alcoholic hepatitis, no evidence of advanced fibrosis
- A decision of transplantation was taken because of rapid worsening of liver function despite prednisolone therapy (clinical trial in progress)


2mm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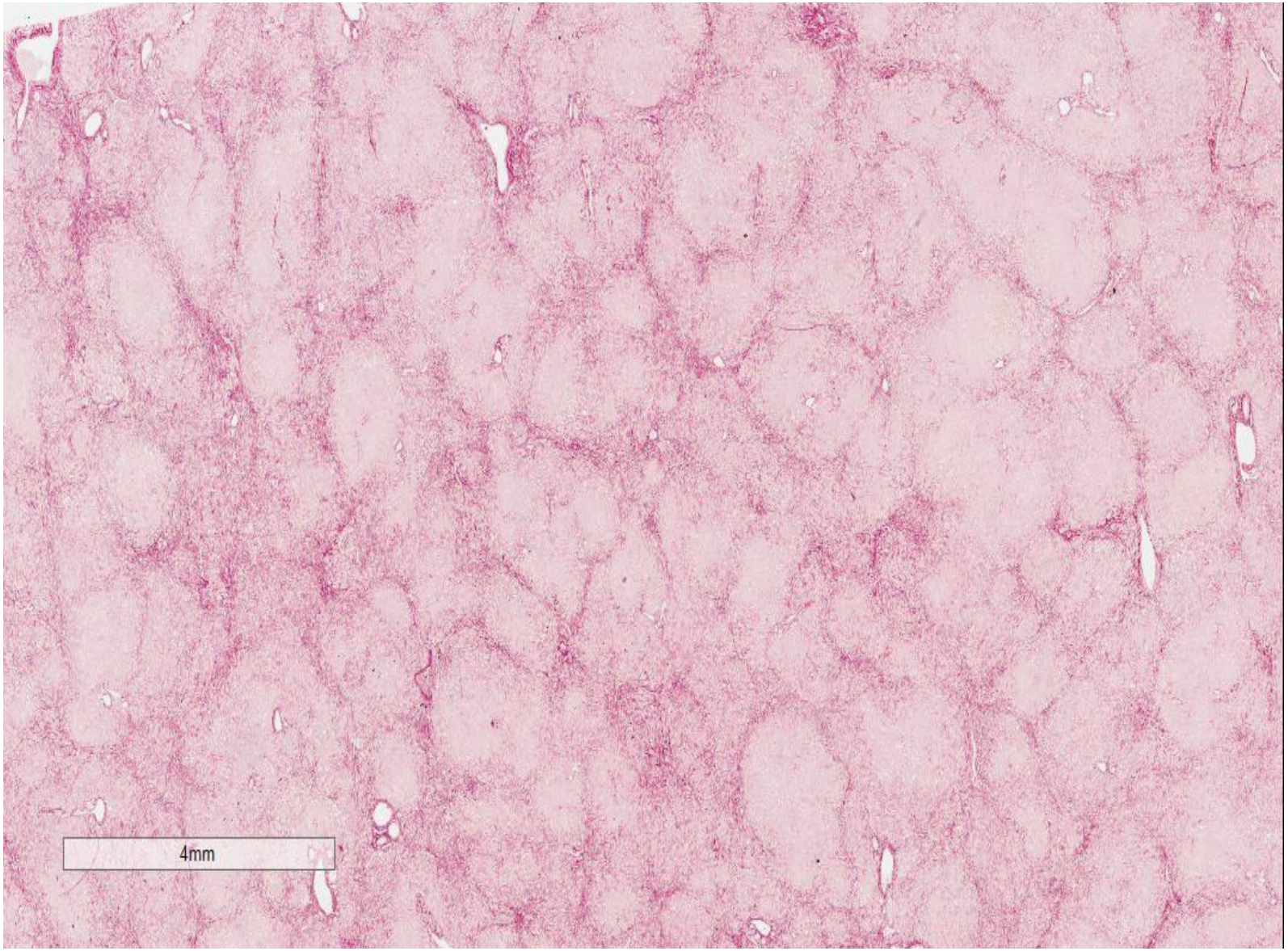
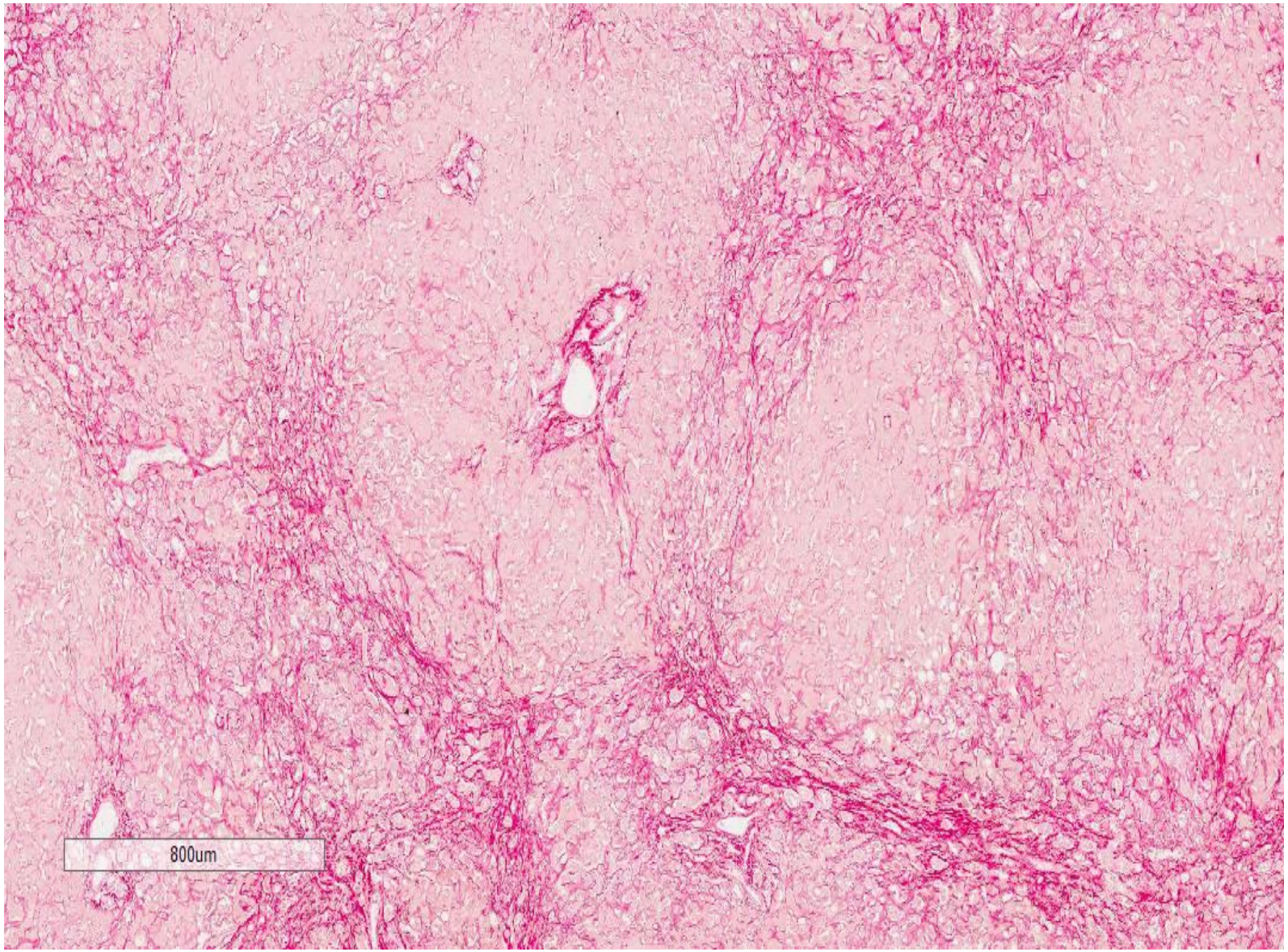
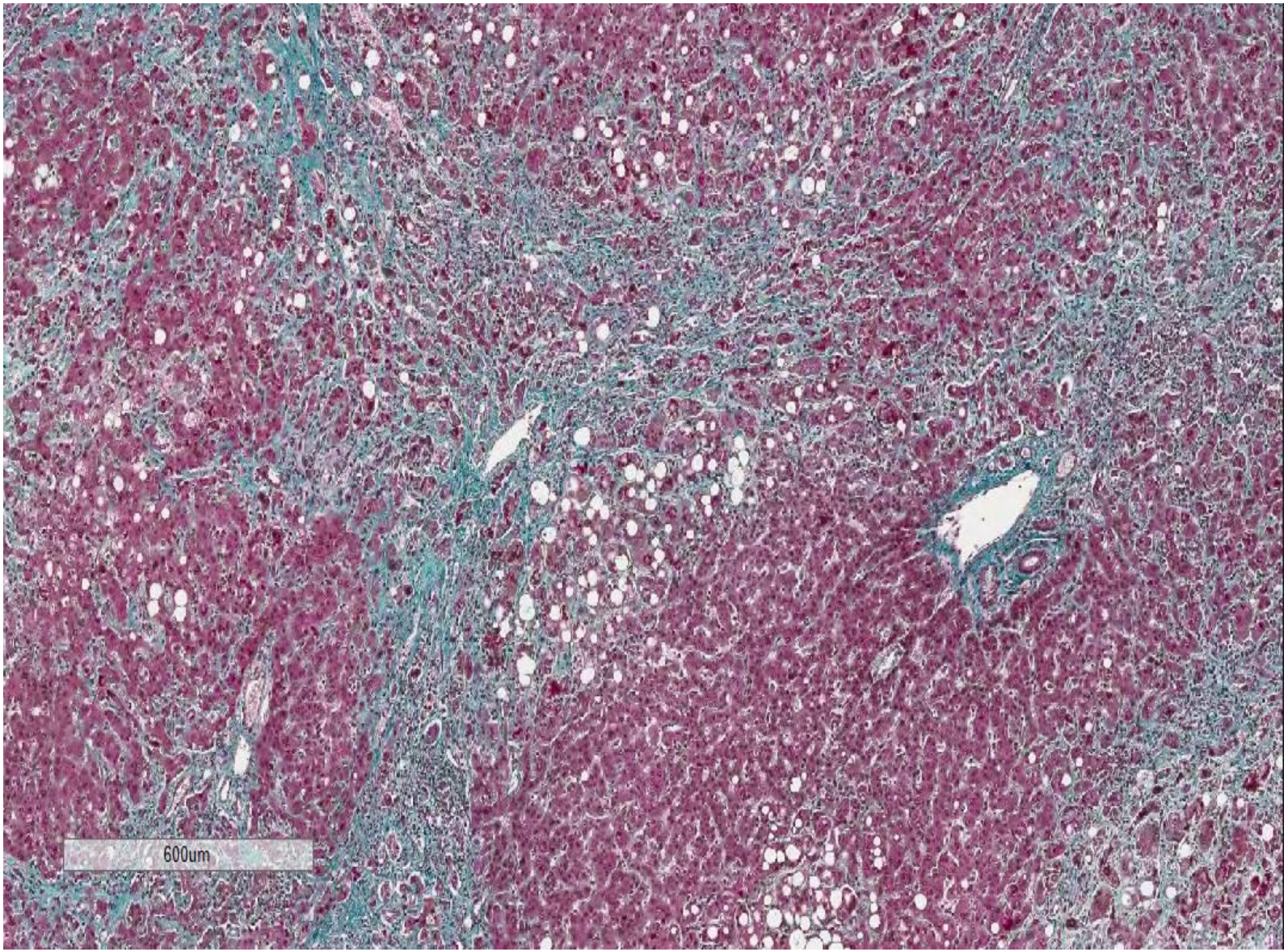


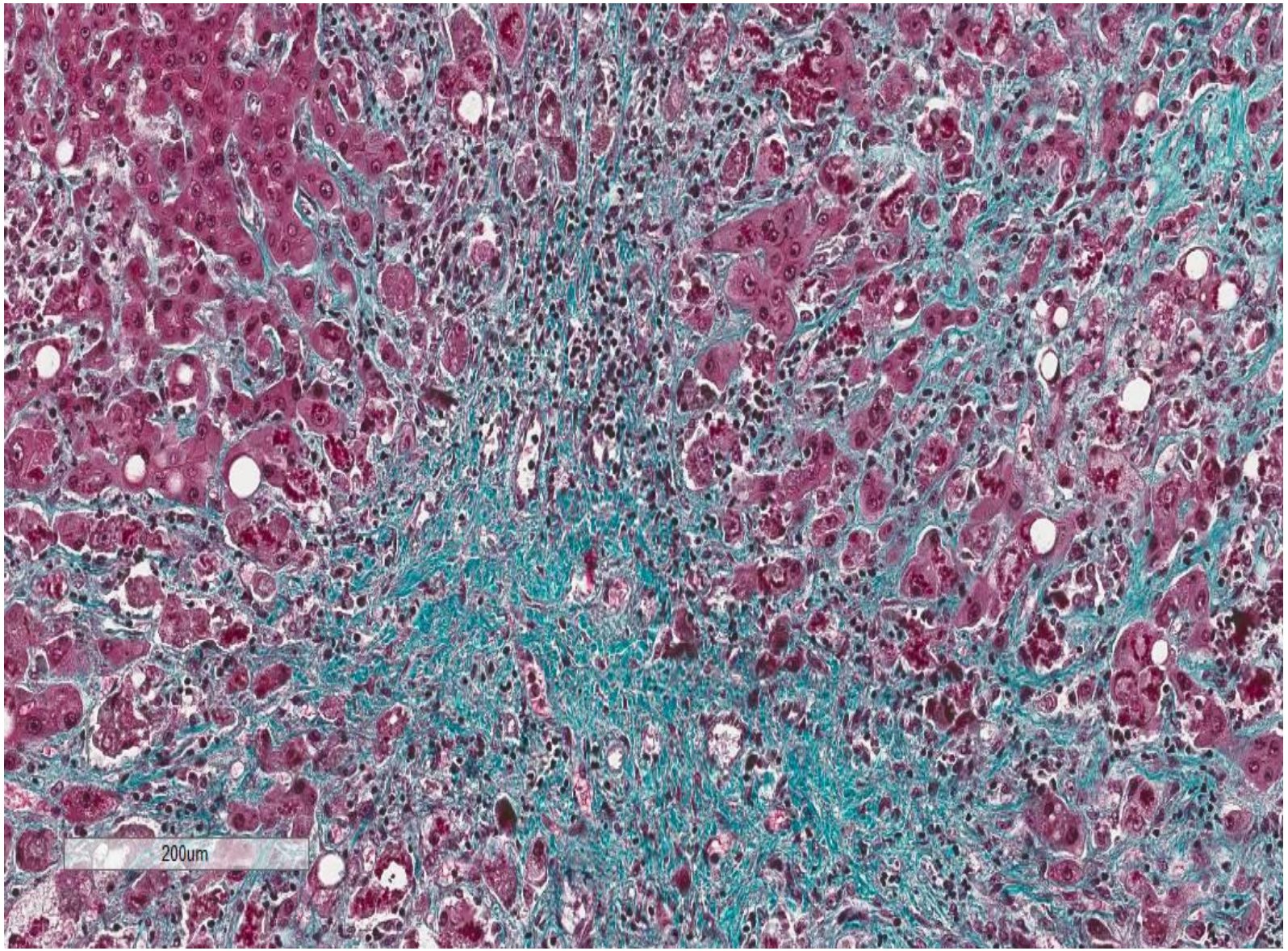
Sirius red staining



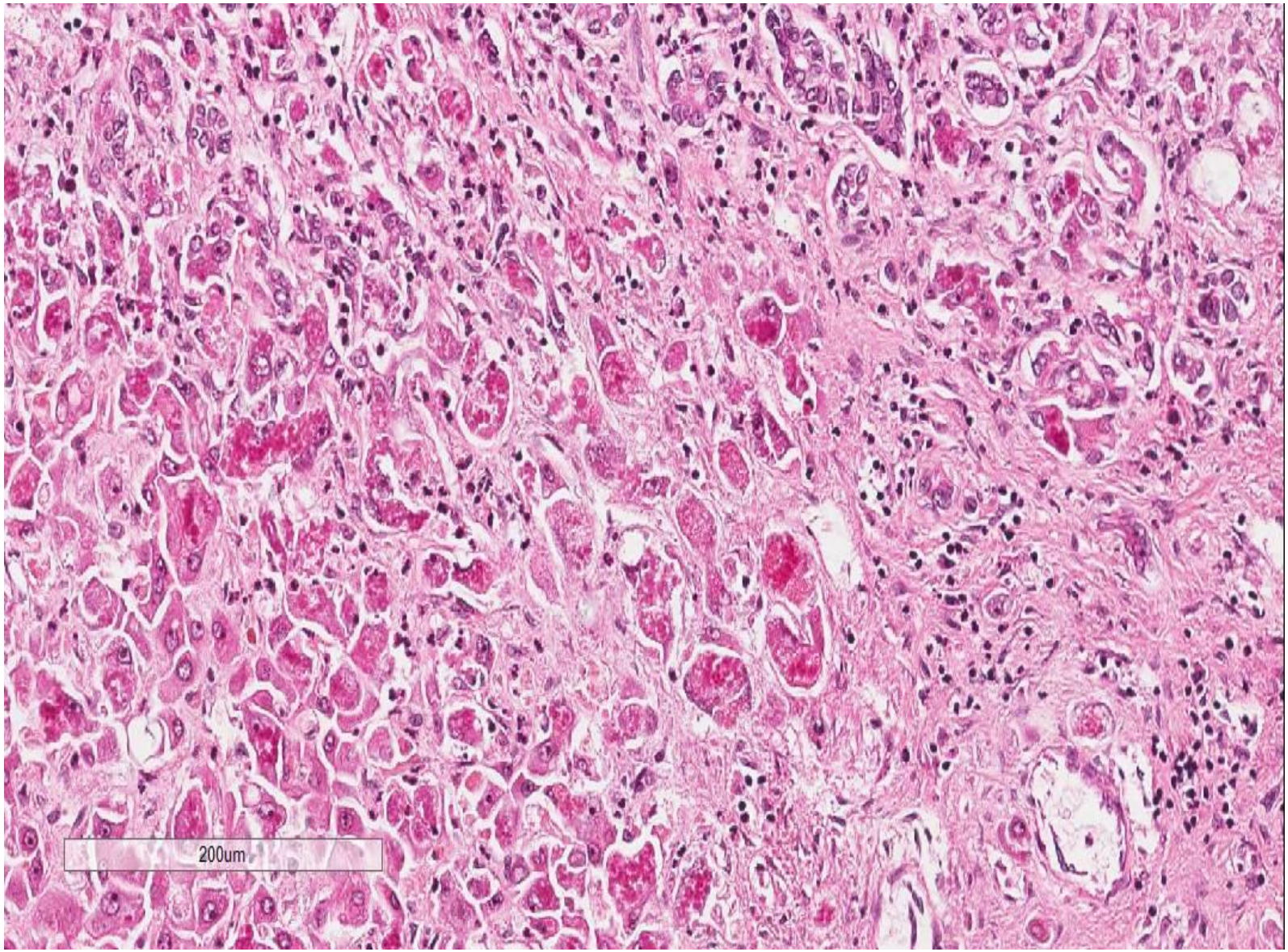
Sirius red staining



Masson’s Trichrome



Masson’s Trichrome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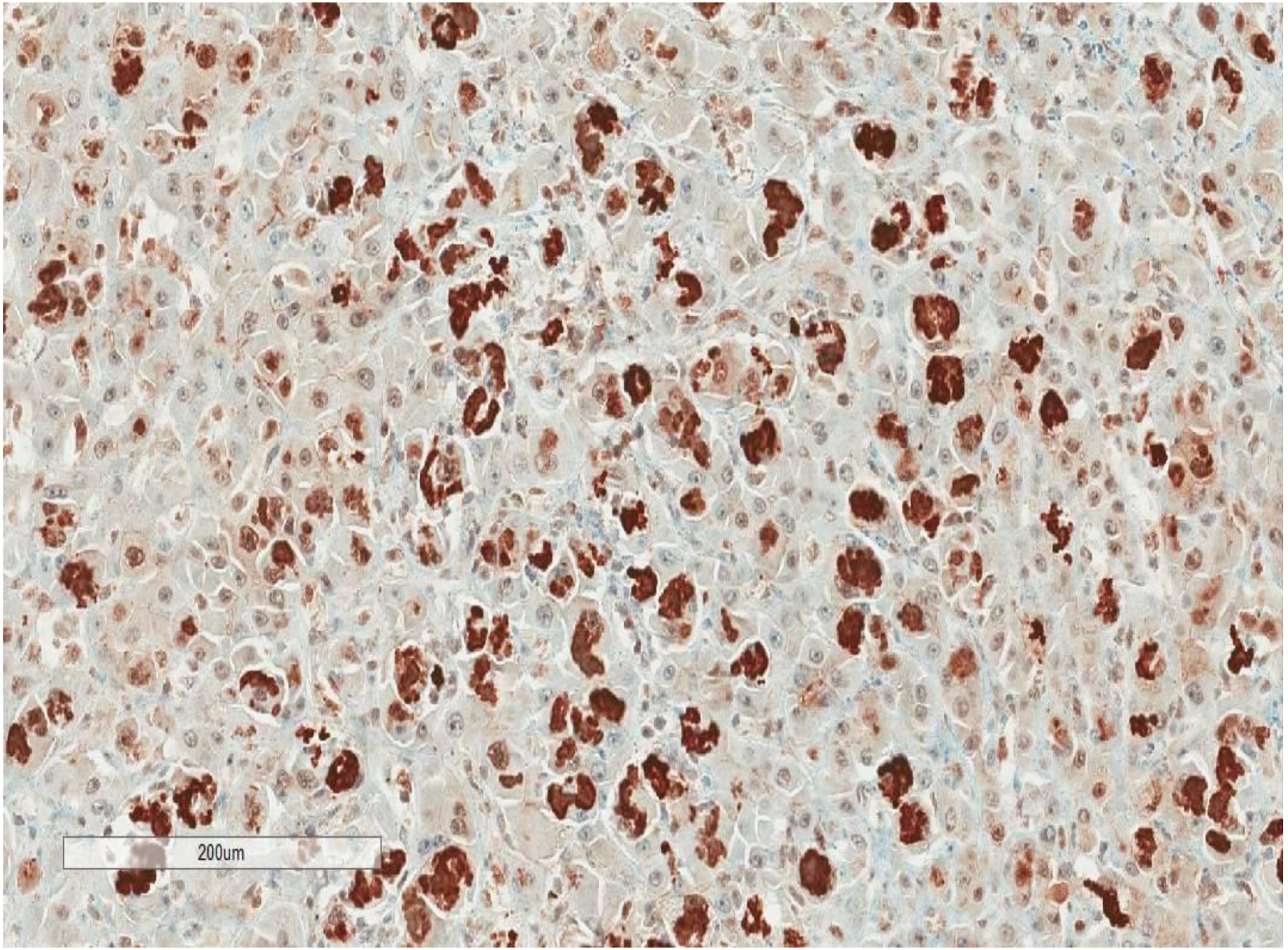

Ubiquitin immunostaining

Severe acute alcoholic hepatitis

No background cirrhosis

Zone 3 fibrosis with central-central bridging

(« acute-on-chronic» injury)

Severe acute alcoholic hepatitis (AH) with liver failure

- AH in end-stage cirrhosis
  - Acute on chronic liver failure (ACLF)
  - The most common form of AH
  - Average age ~ 50 years.
  - Clinical diagnosis (jaundice, liver failure) but biopsy often performed
  - Mainstay treatment: corticosteroids
  - The Lille score predicts responder after 7day corticotherapy

Severe acute alcoholic hepatitis (AH) with liver failure

- Severe AH in non cirrhotic liver :
  - Sclerosing hyaline necrosis (Edmonson's)
  - Veno-occlusive lesions
  - Extensive phlebitis
  - Budd Chiari-like lesions

Case 2 : follow-up

- Surgery and post-operative period were OK
- Discharged from hospital after 15 days
- Close follow-up of immunosuppressive treatment
- Rapid loss of follow-up from the supportive psychotherapy team
- Rehospitalized at 6 months for ↑ transaminases
- No alcohol abstinence
- Liver biopsy : no rejection, acute alcoholic hepatitis
- Die from sepsis and renal failure

A Visit to Jacob's Creek

What Next?

- Aim to produce consensus paper on “patterns of acute liver injury”

- Next meeting in Groningen, Holland, May 10th – 14th 2017 (Chief Gnome – Annette Gouw)
  - Theme – “non-tumoral vascular diseases”