Case 6
Dr JI Wyatt

Problem areas highlighted by Liver EQA scheme

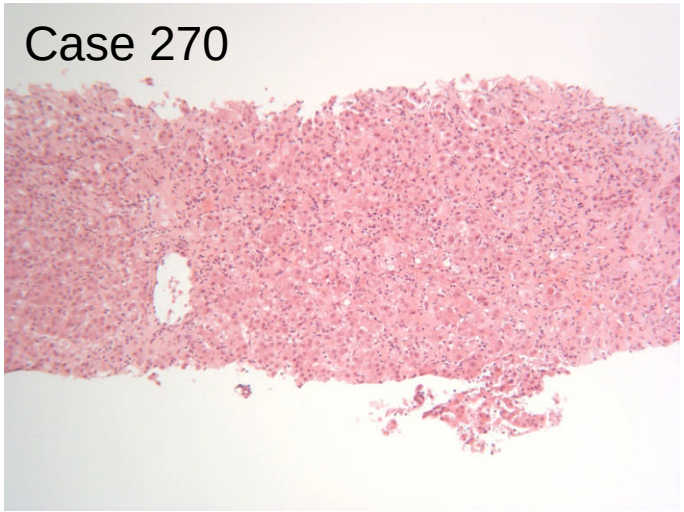
- Circulation V, summer 2007,
  - cases 270,273,276,277

31 acute hepatitis with confluent necrosis, and differential
11 acute hepatitis, no mention of confluent necrosis, with differential

1 acute hepatitis with cholangitis
1 acute viral hepatitis, no differential
1 acute hepatitis, drugs no differential
1 cholestatic hepatitis, ? drugs
1 acute hepatitis with ascending cholangitis, obstruction, secondary biliary cirrhosis
1 cholestatic jaundice, due to sepsis/drugs/LBDO

3 chronic active hepatitis
1 widespread necrosis with chronic active inflammation, ?drug/other
1 ductular reaction with polys etc. ?LBDO
4 acute alcoholic hepatitis
1 veno-occlusive disease
2 description only, no mention of 'hepatitis'

Scoring: A diagnosis of acute hepatitis with appropriate differential of possible causes required for full marks.
The presence of confluent necrosis is important in indicating the severity of the h epatitis, and should be included when reporting such a case (but if required here the case could not be included in scoring).
Responses indicating a single aetiology scored half marks. Other diagnoses scored 0.



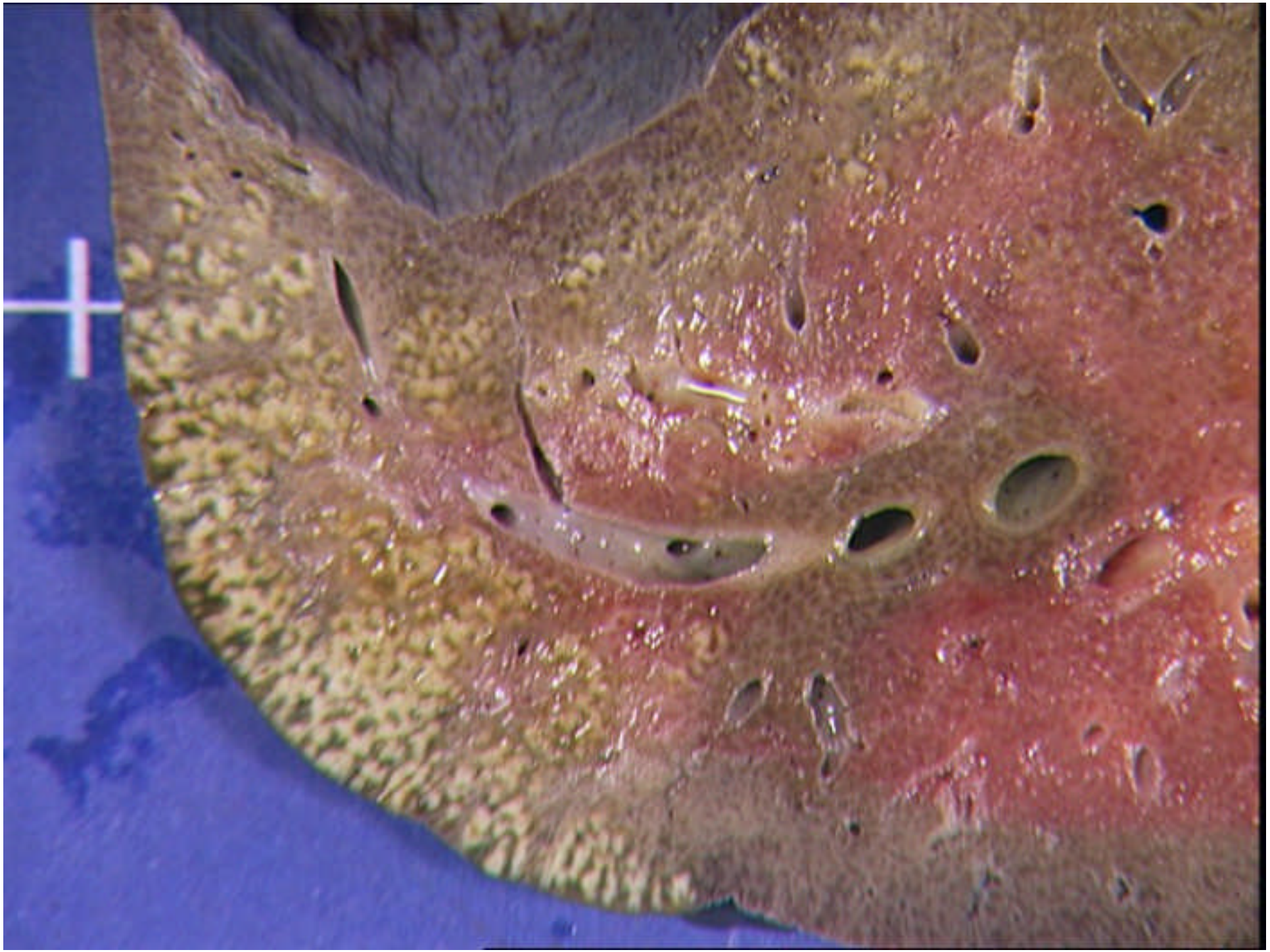
Virtualpathology.leeds.ac.uk

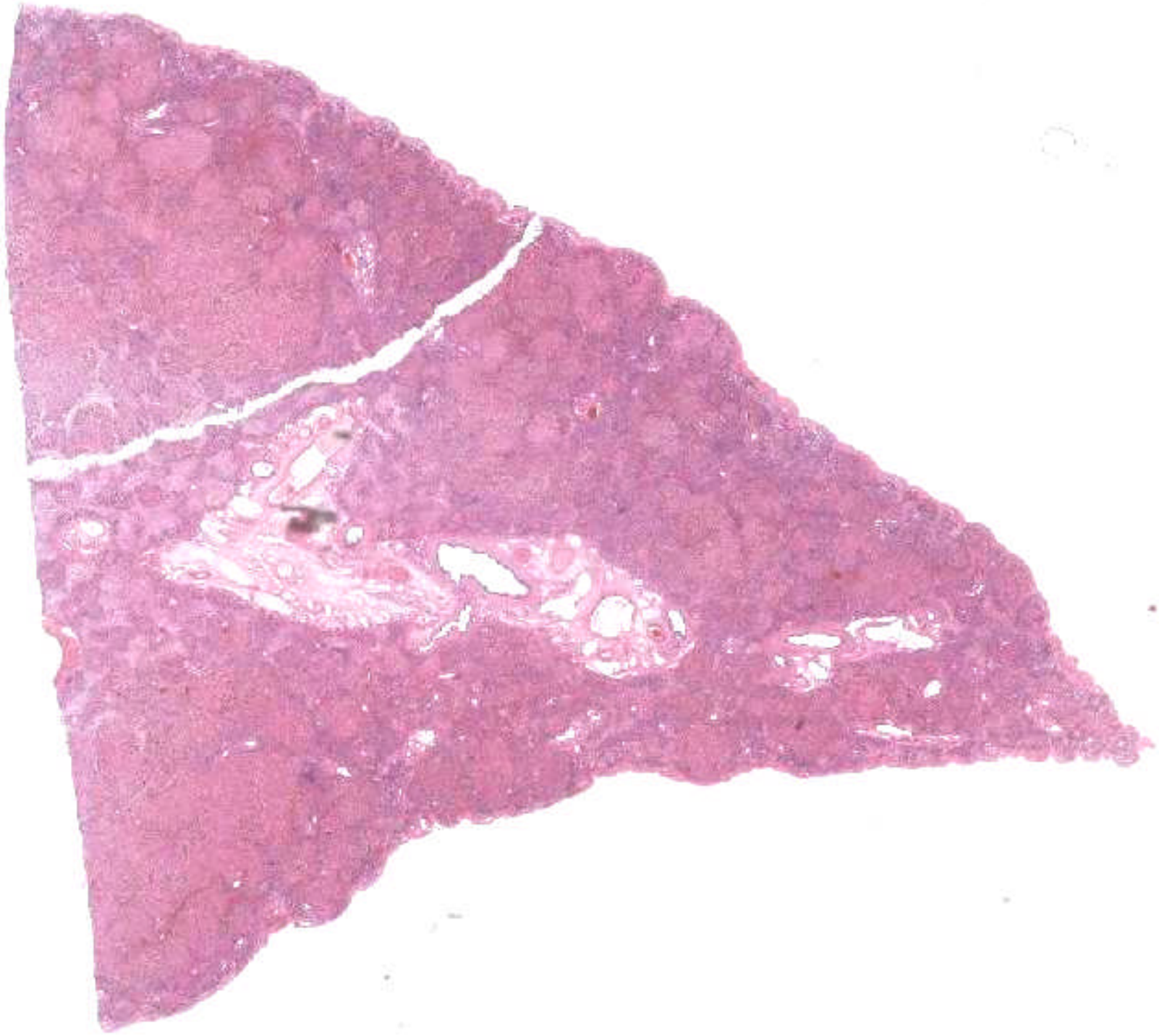
Clinical history

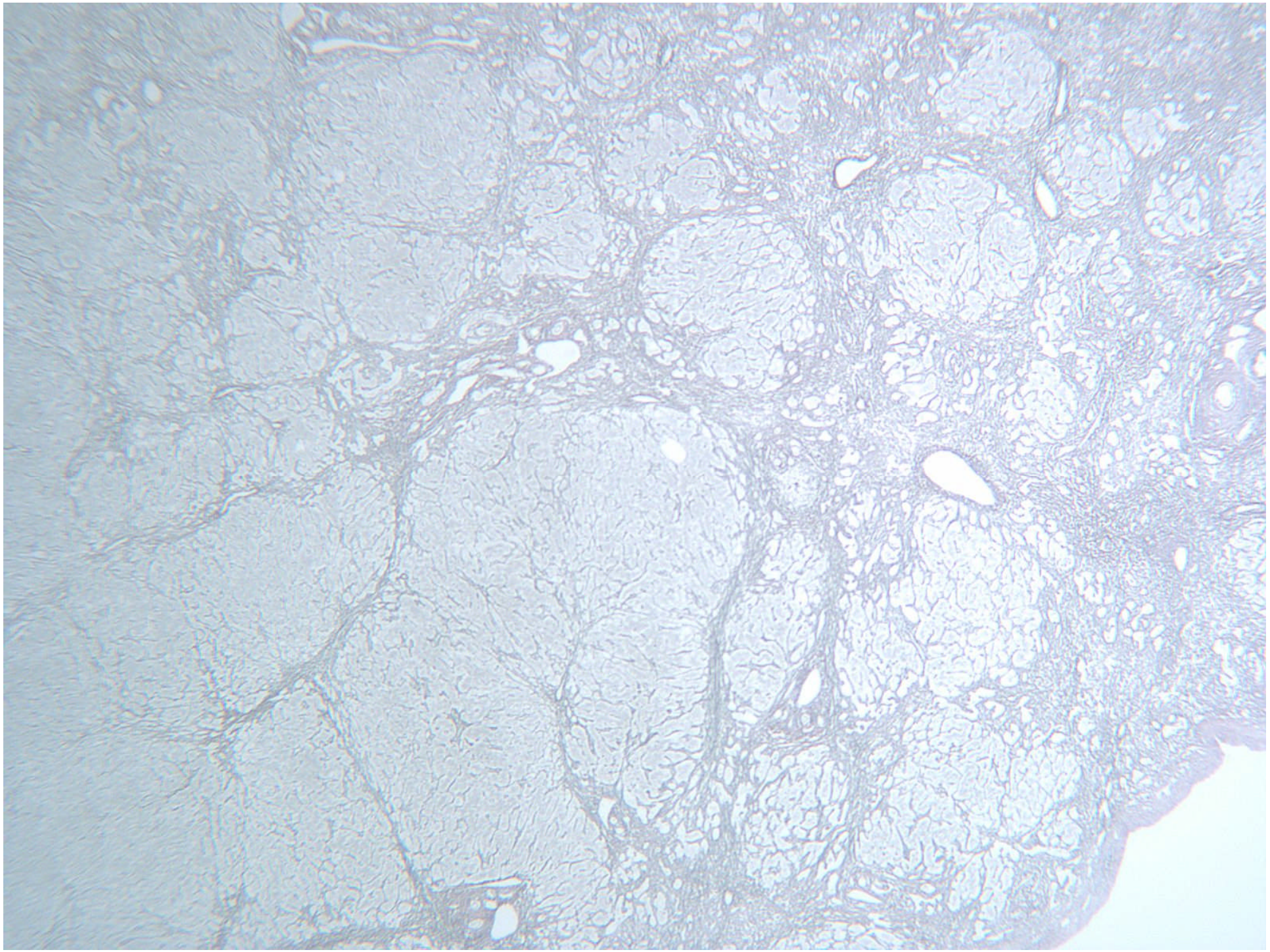
- 48y Philippino, lived in UK since age 16.
- Day 0: flu-like illness in Philippines, diagnosed TB, started ethambutol, rifampicin, pyrazinamide.
- 4 weeks: drugs ran out – stopped
- 8 weeks: back in UK, diagnosis of TB confirmed, commenced quadruple therapy (above + isoniazid)
- 10 weeks: jaundiced, stopped drugs, but went on to develope coagulopathy, ALT 1100, increasing encephalopathy.
- 13 weeks: liver transplant.

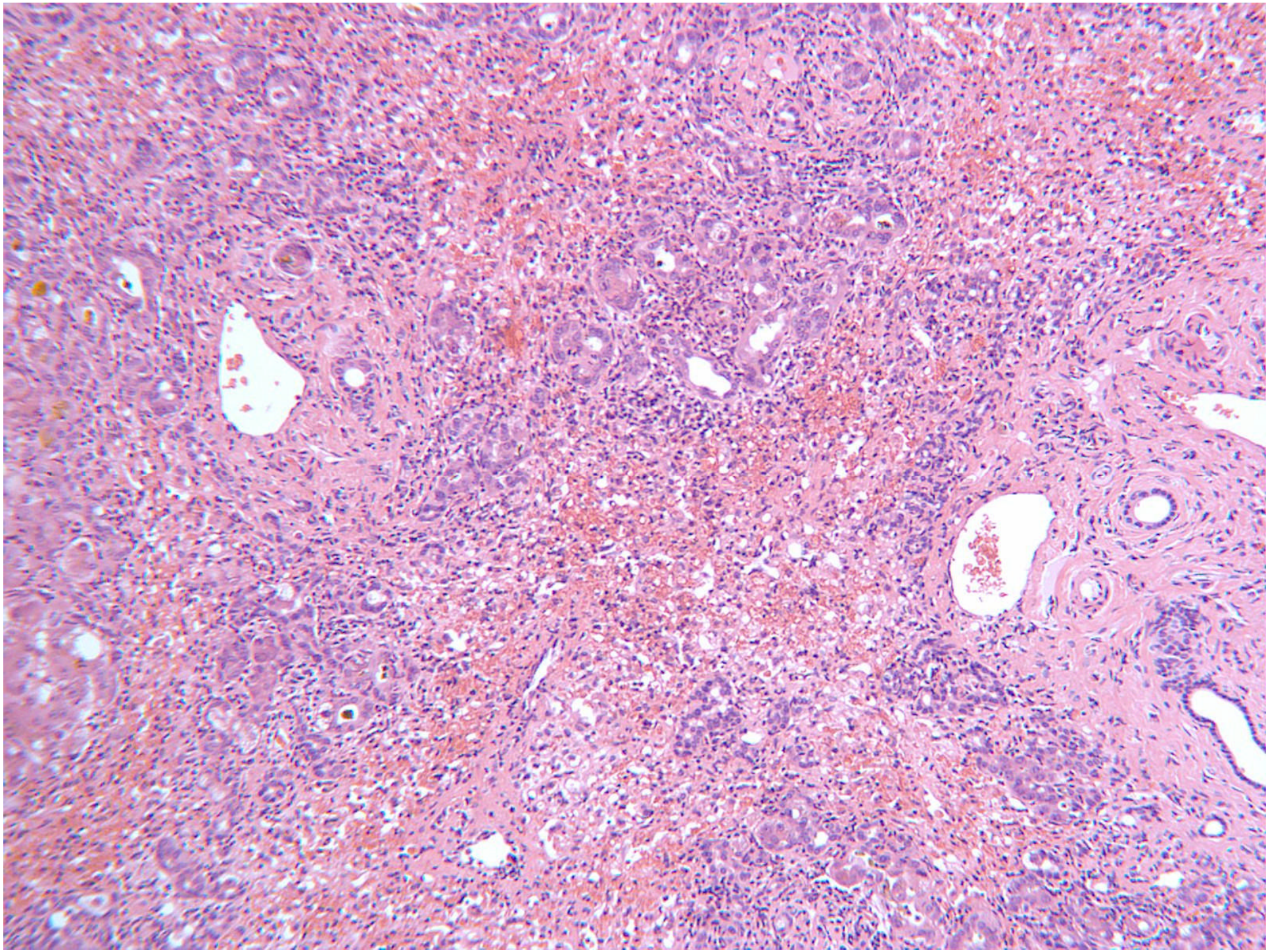
Hepatotoxicity of anti-tuberculous drugs

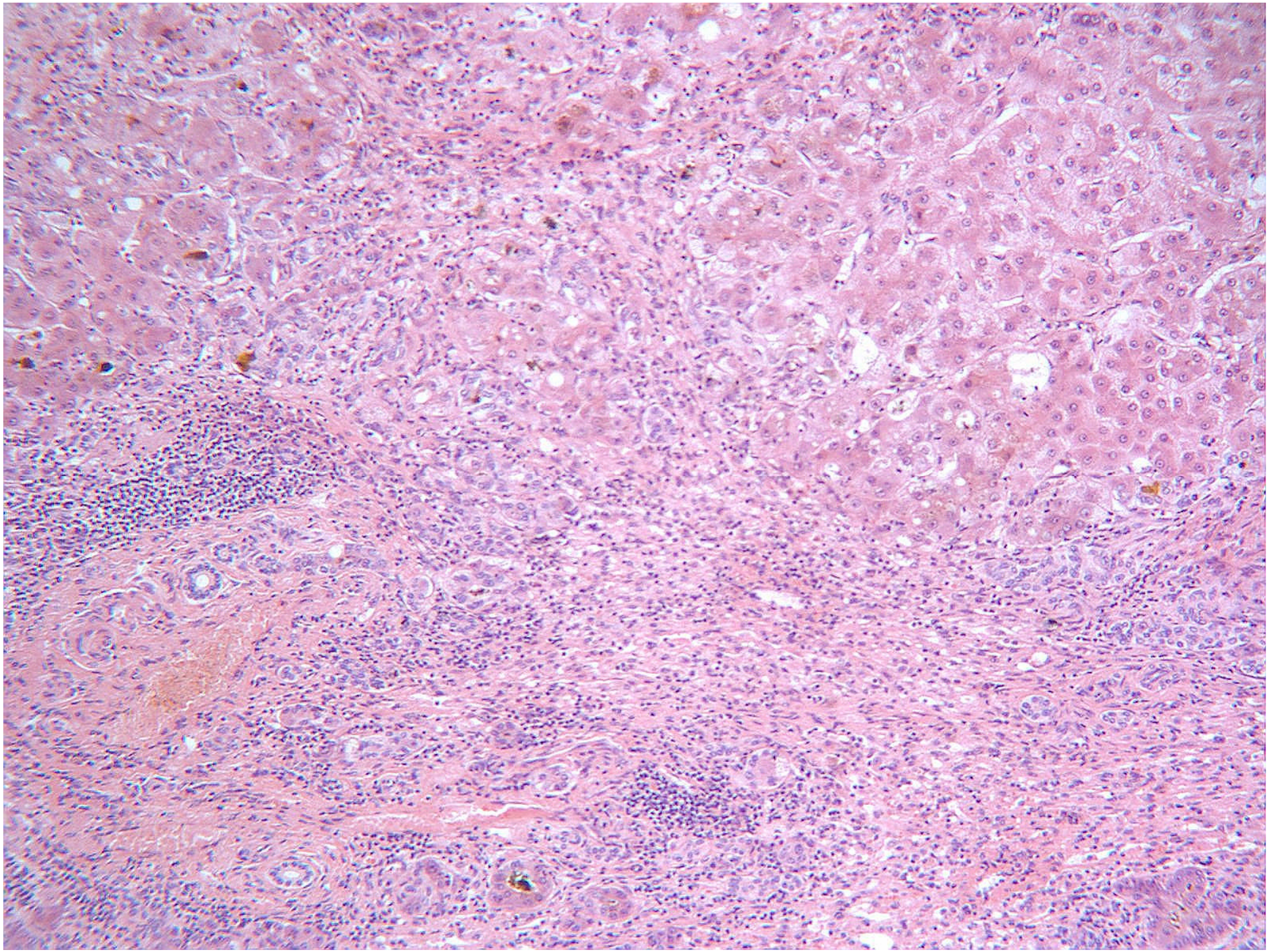
- Rifampicin and isoniazid more than either alone.
- Increases with age, up to 2% in >50s
    - (minor increase LFTs in 10-20%,most do not progress)
- Metabolic idiosyncracy leading to toxic metabolites, rifampicin induces p450
- Jaundice appears during first month
- Pyrizinamide – as for isoniazid, higher frequency of toxicity.

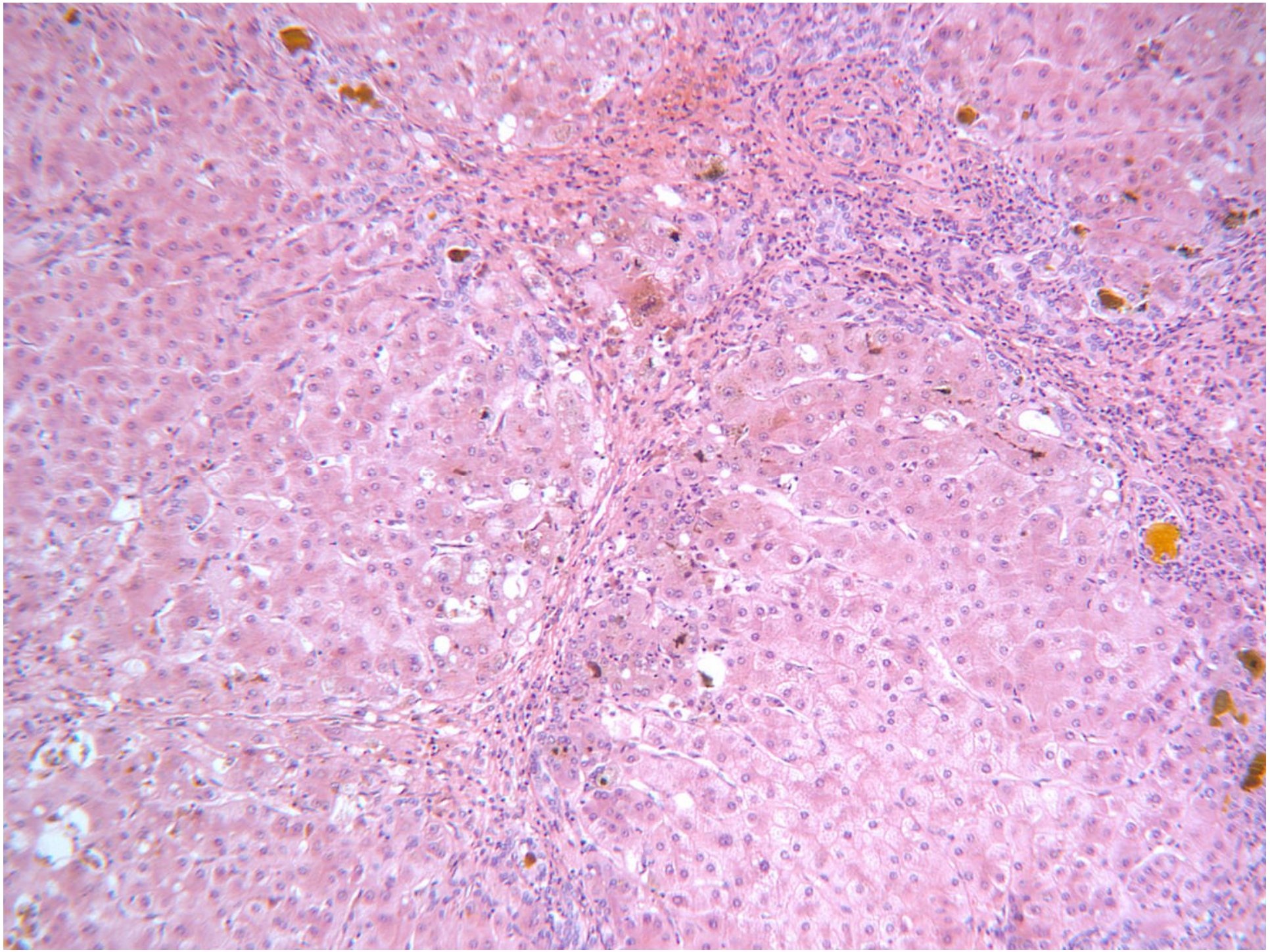


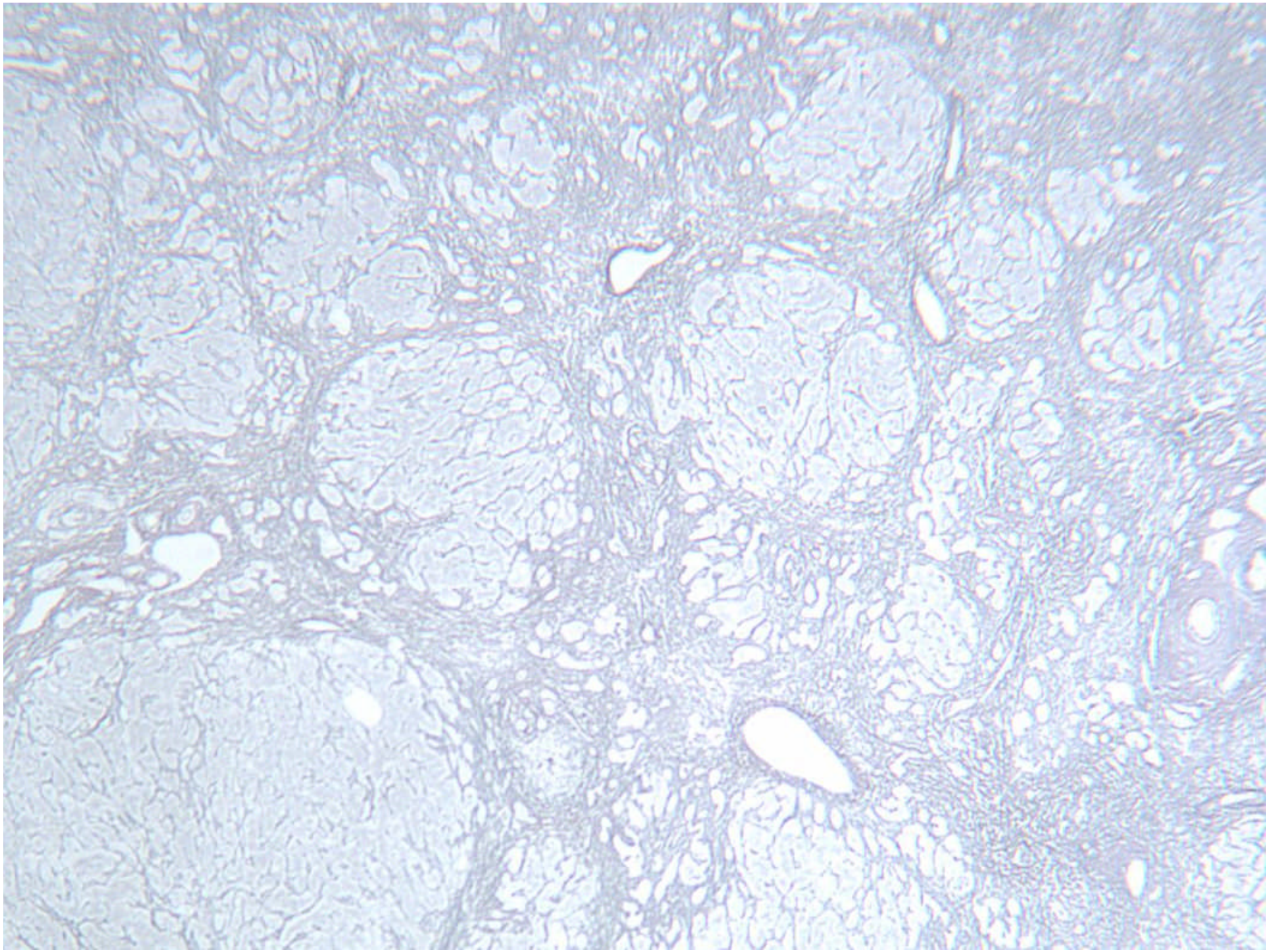


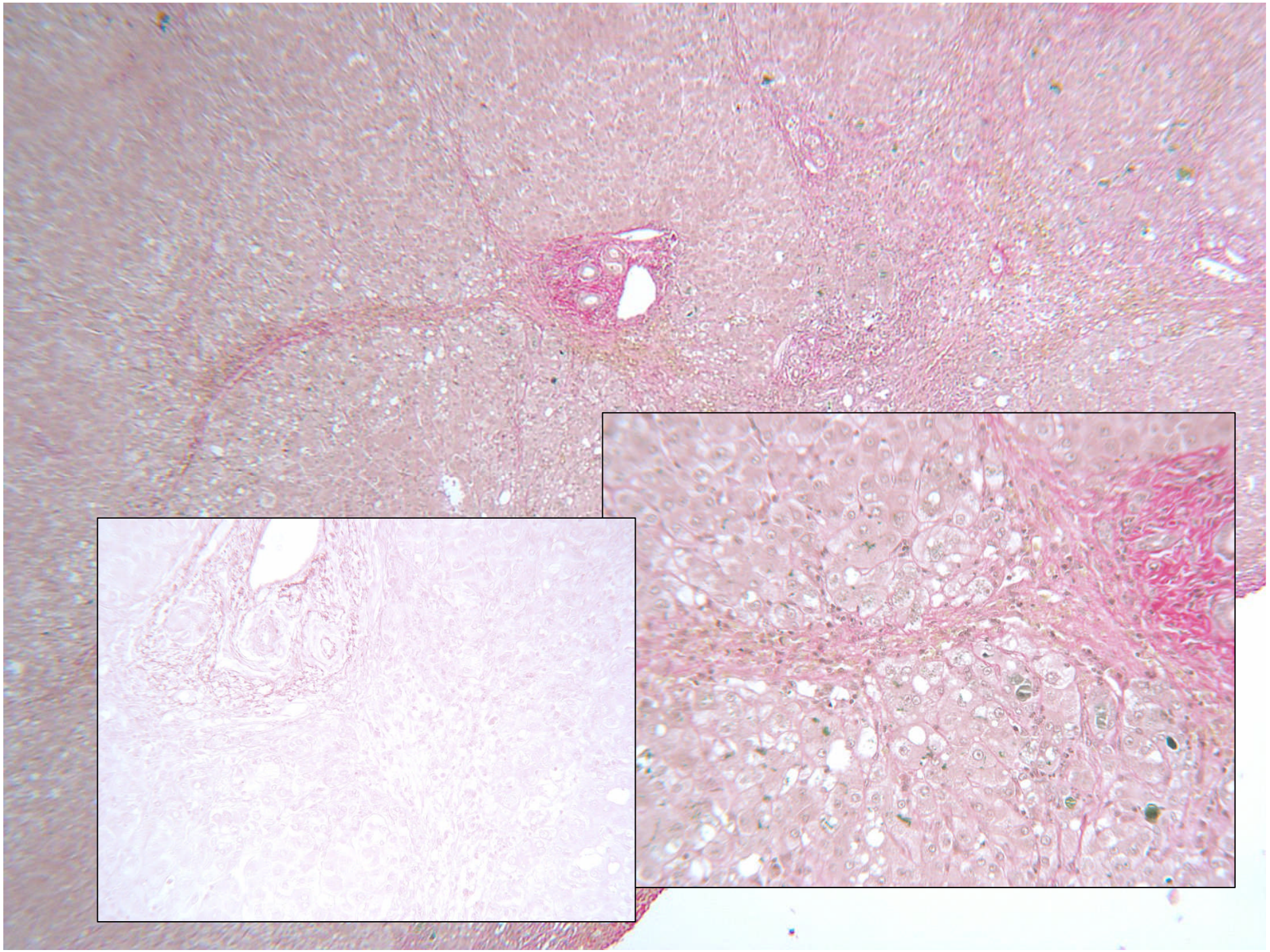


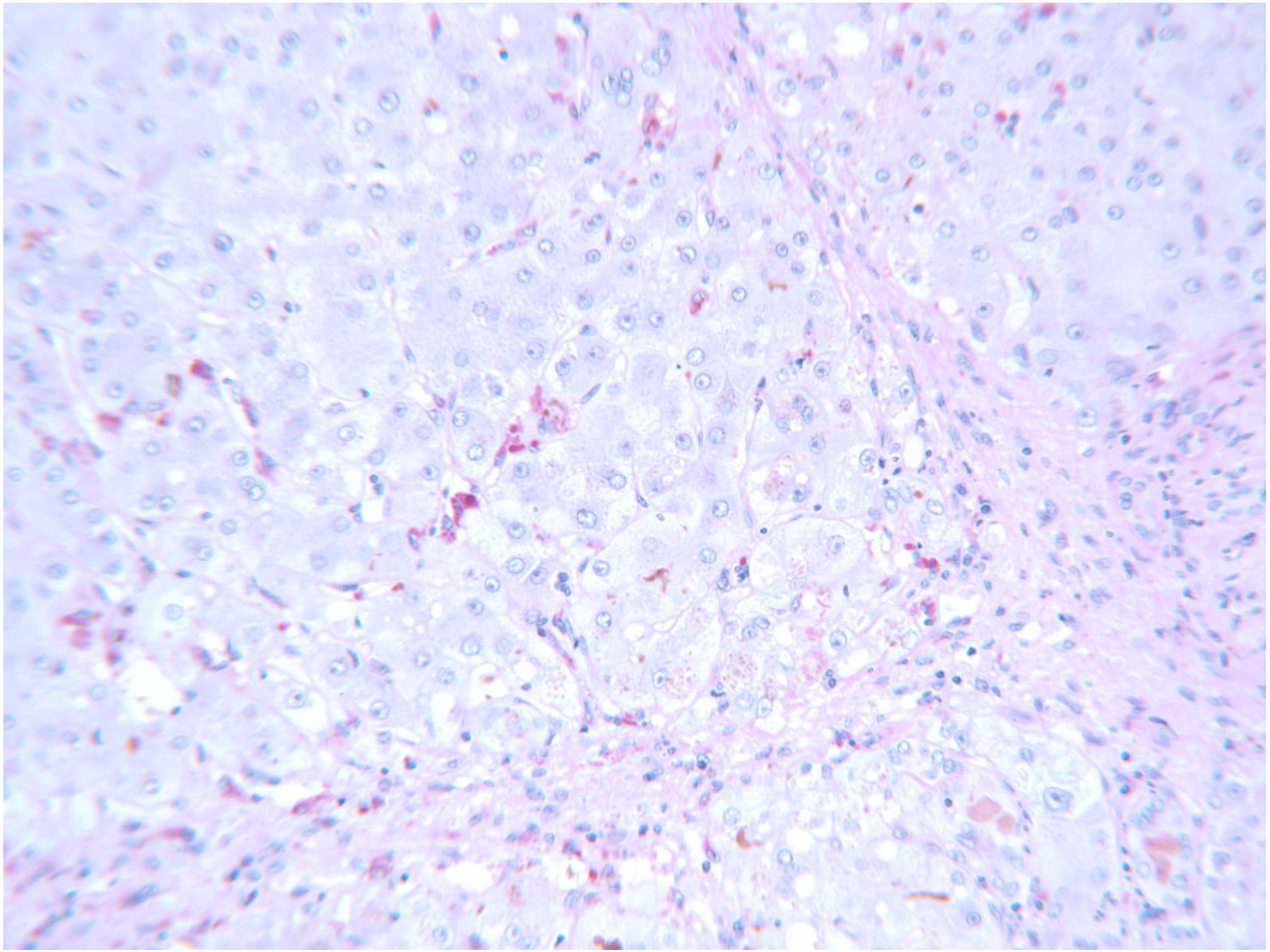


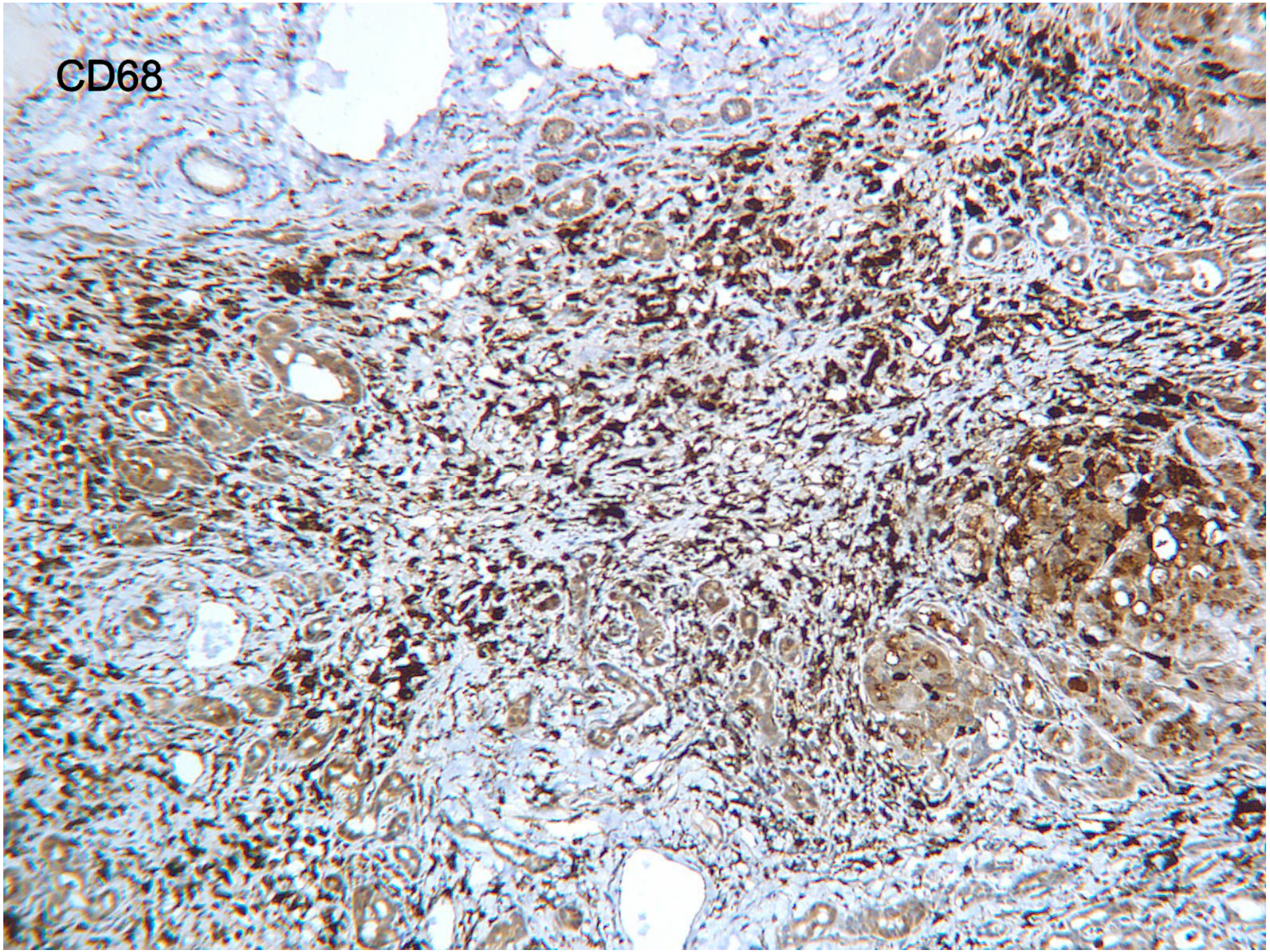


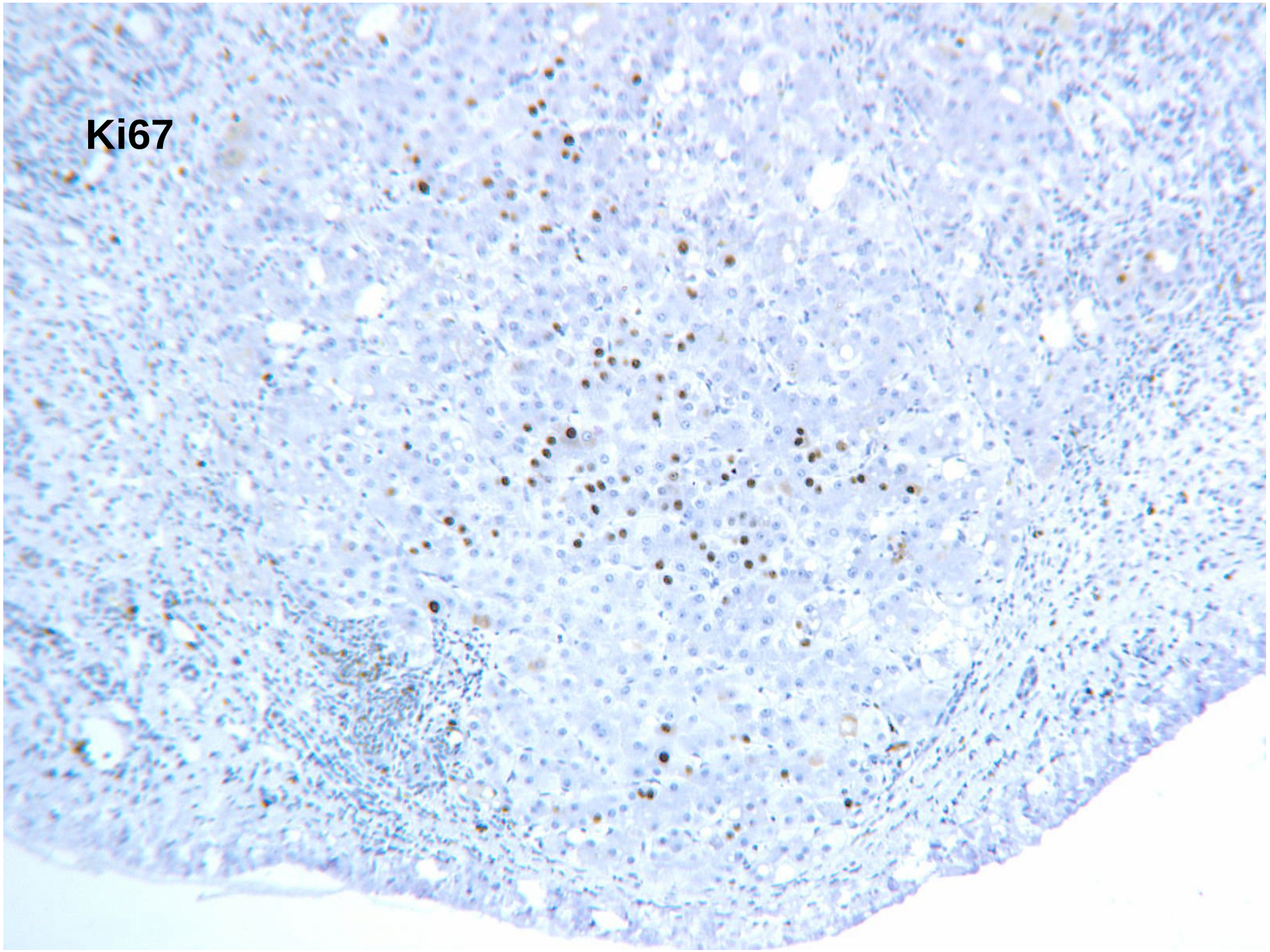


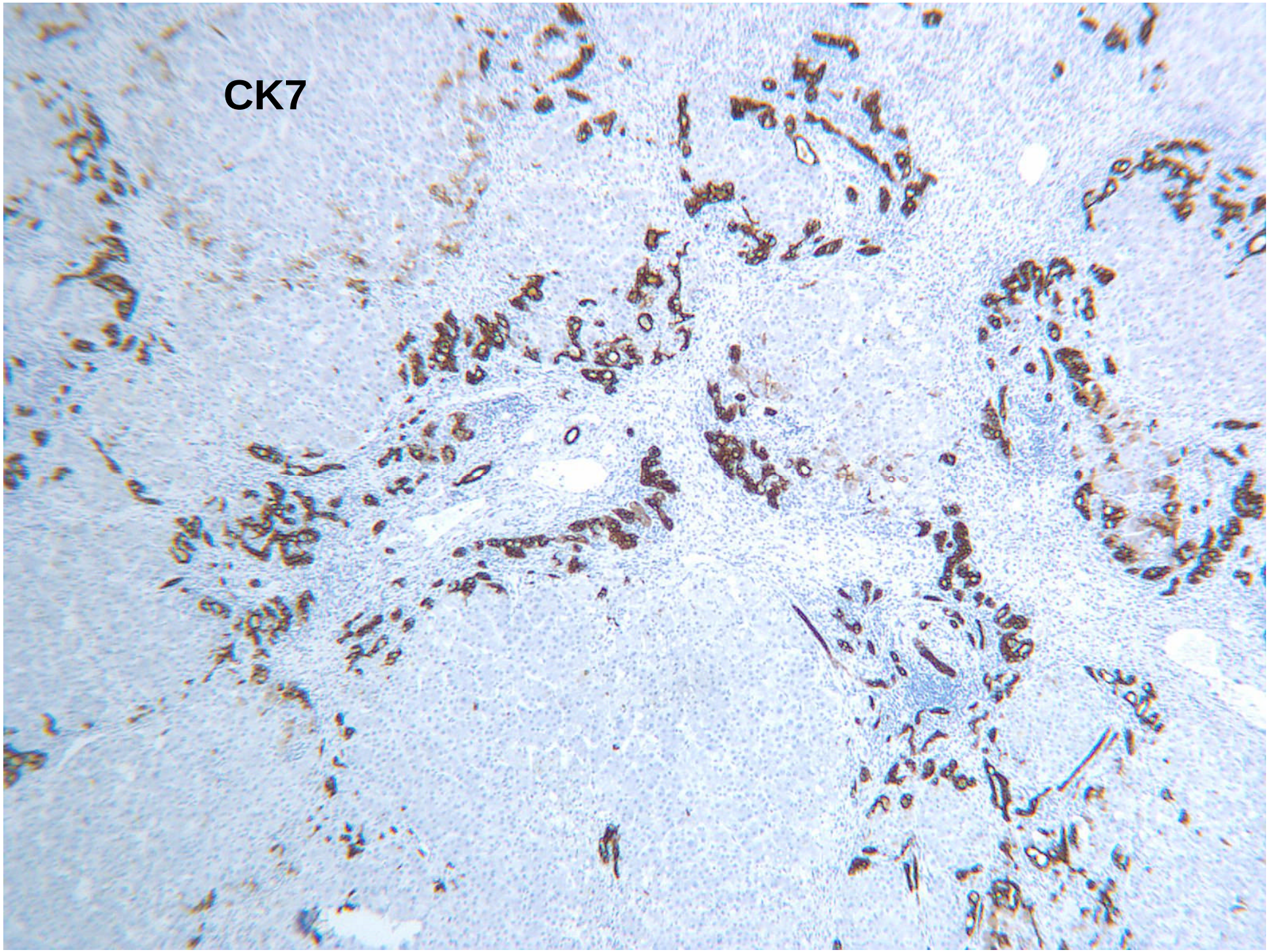




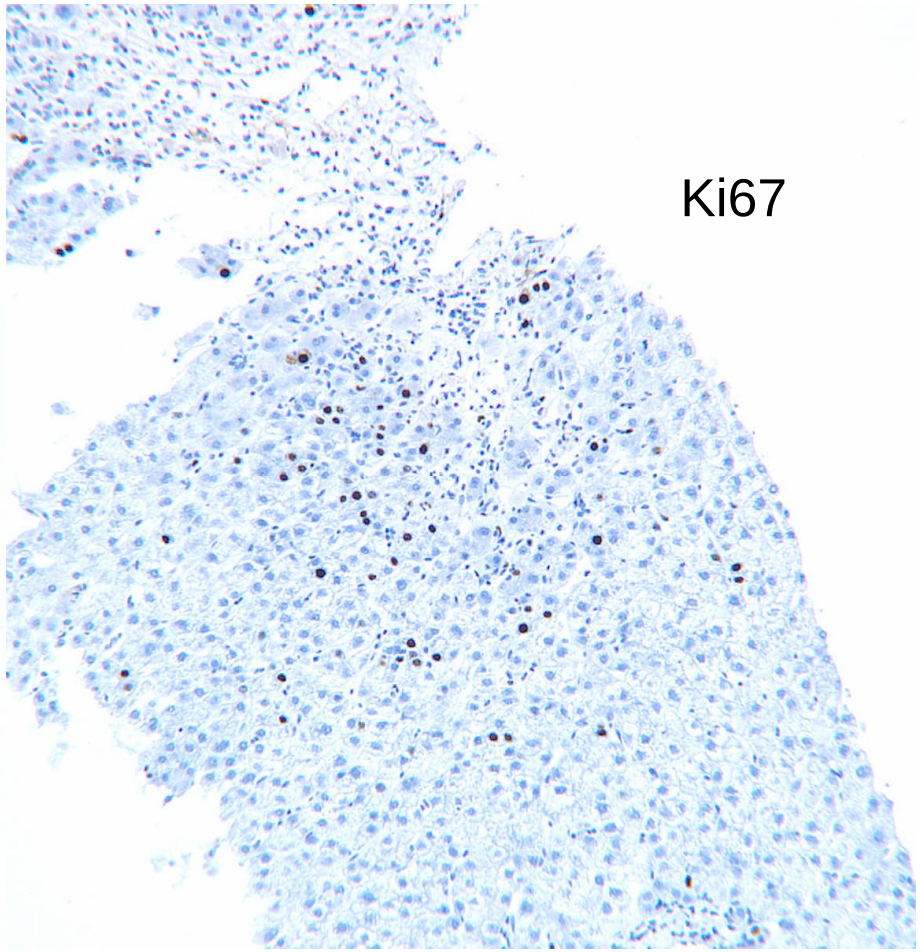


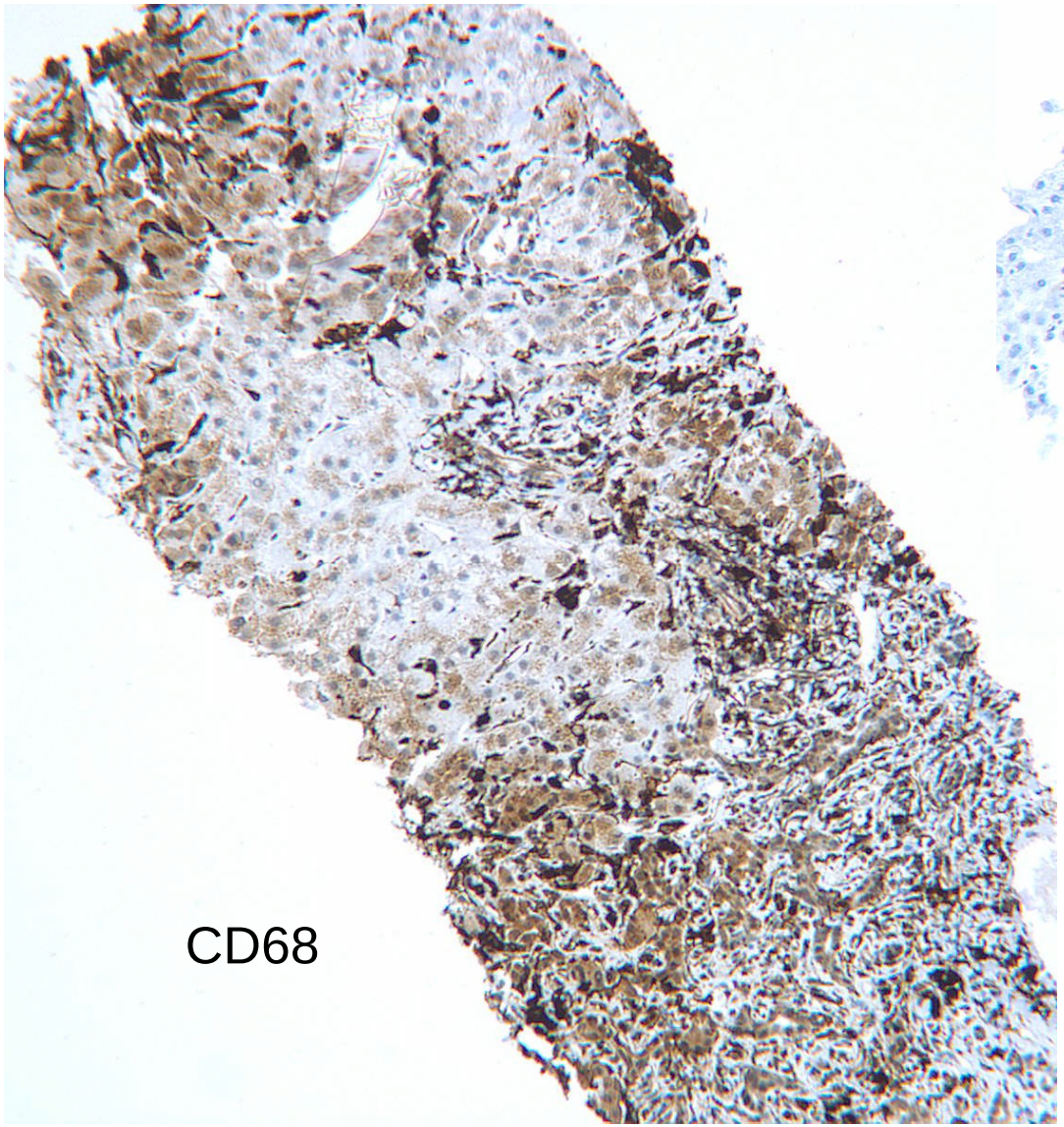

CD68

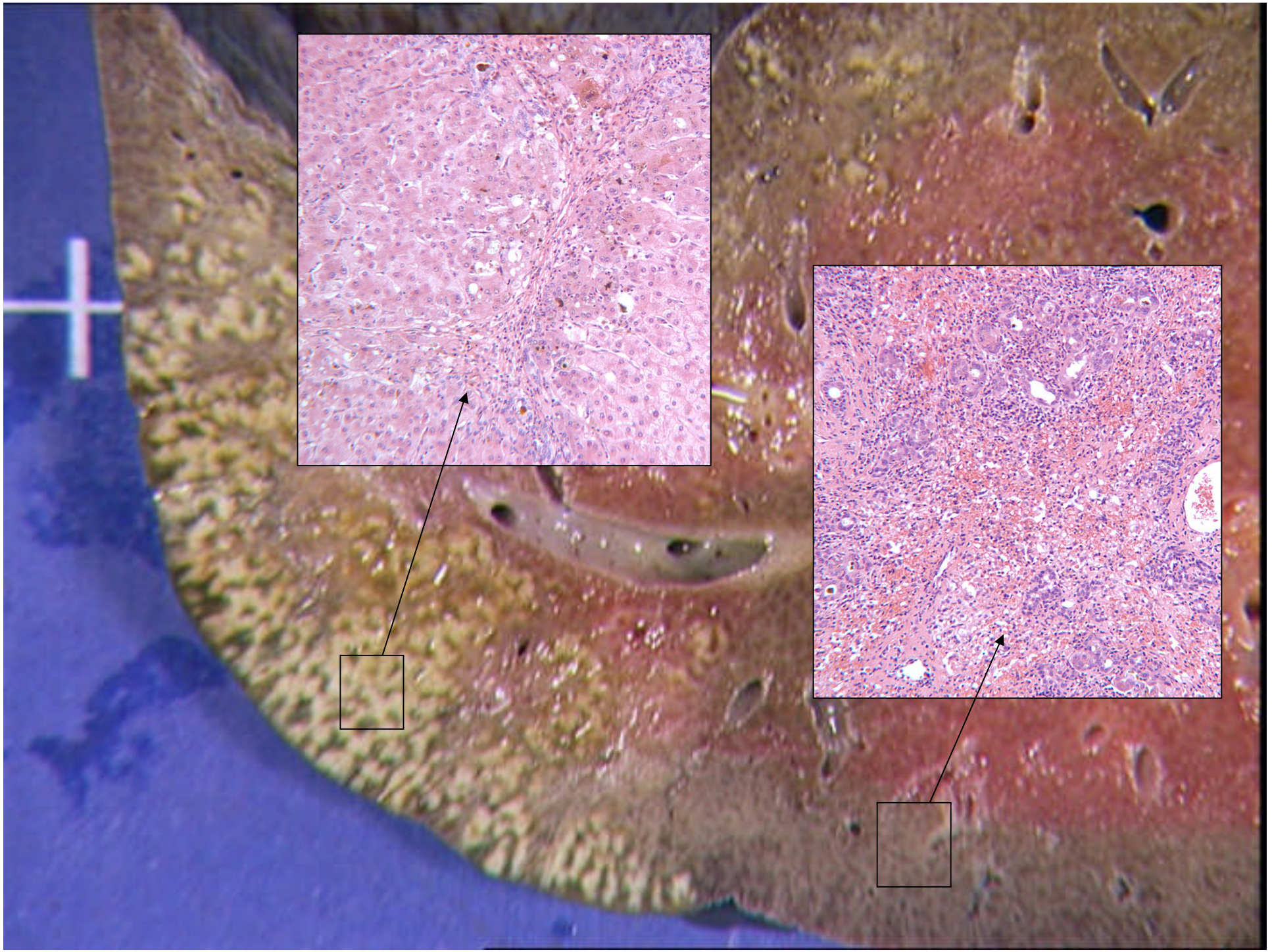

Ki67


CK7

Referred liver biopsy:
Original diagnosis = cirrhosis







92 Patients listed for super-urgent transplant, Leeds 2002-2007 (data from UK Transplant)

Diagnosis	number
Acute hepatitis, cause unknown	33
Acute hepatitis – drug (non-paracetamol)	5
Acute viral hepatitis	3
Paracetamol toxicity	27
Acute Wilson's disease	11
Budd Chiari Syndrome	6
Other/unknown to database	7

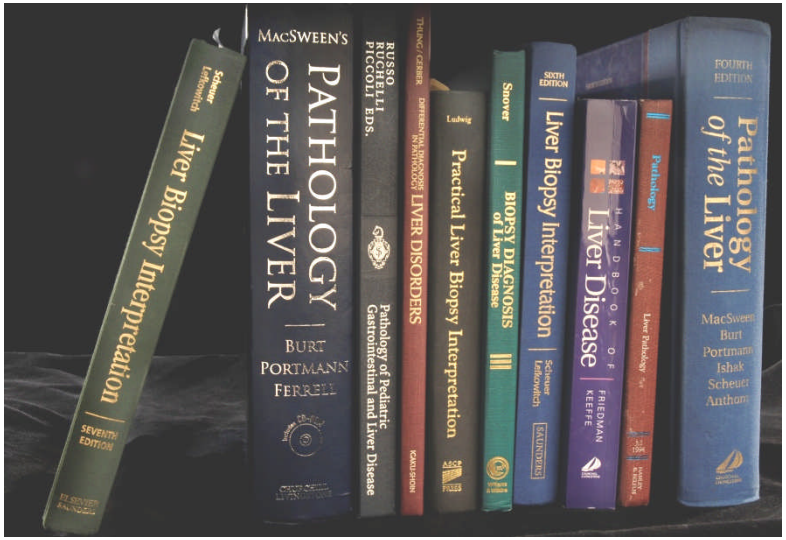
Geographical variation in the aetiology of acute liver failure

	UK	US	France	India	Japan
paracetamol	54	40	2	-	-
Drug reaction	7	12	15	5	-
Seronegative	17	17	18	24	45
Hepatitis A/B	14	12	49	33	55
Hepatitis E	-	-	-	38	-
Other causes	8	19	16	-	-

O'Grady. Acute Liver Failure
Postgrad Med J 2005;81;148-154

What is seronegative hepatitis?

- Not in the index!



Histopathological heterogeneity in fulminant hepatic failure.

(Hanau et al, Hepatology 1995:21:345-351)

38 patients (20 non-ABC), biopsy and/or whole liver.

Acute hepatitis, bridging, submassive, massive necrosis, cirrhosis

No difference in the histology corresponding to different aetiologies

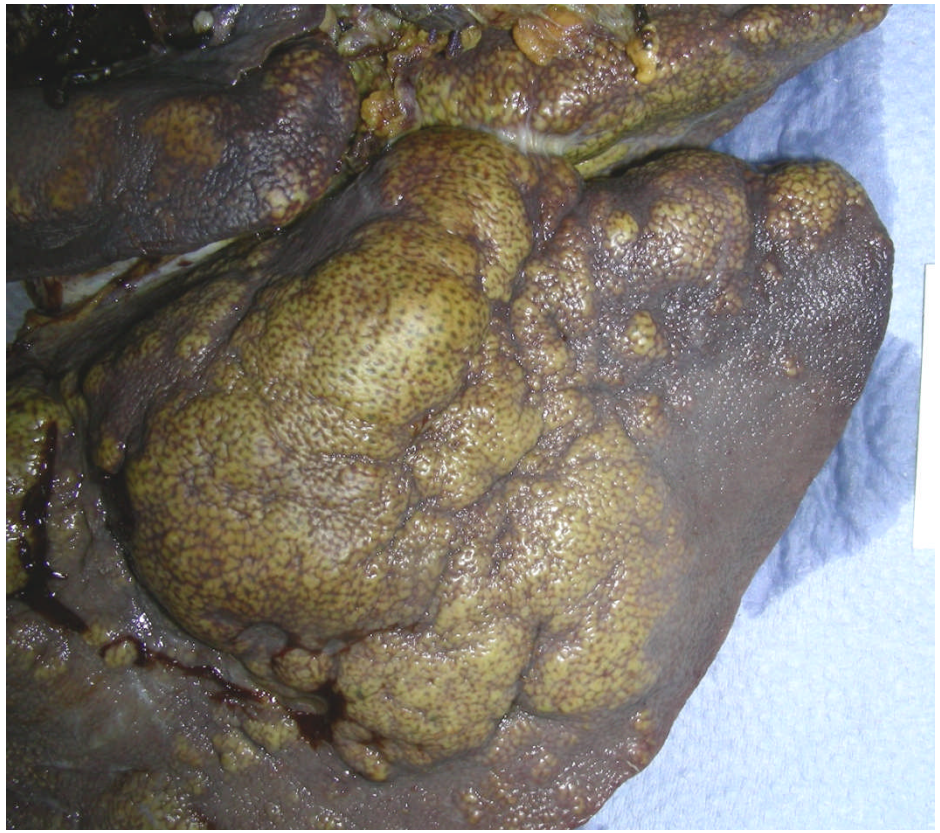
Prognosis depends on age (survivors all <33 years) and encephalopathy.

Common pathway of all severe acute liver injury?

Balance between

confluent necrosis,
no surviving parenchyma
? Due to overwhelming cytokine response to liver injury, preventing hepatocyte regeneration

Groups of surviving regenerating (differentiating?) hepatocytes which quickly grow into regenerative nodules



Survival depends on sufficient regeneration
Poorer in older patients.

What happens to the survivors?

- There isn’t a chronic seronegative hepatitis
- ? Evolves into cryptogenic cirrhosis
  - ‘post necrotic cirrhosis’

- chronic viral hepatitis
- Autoimmune hepatitis

- ? Just some inactive scarring

Acute presentation of autoimmune hepatitis ?

- **Centrilobular necrosis** in AIH – histological features associated with acute clinical presentation: seen in 20/114 patients, 87% with acute presentation. *(J Clin Path 2006:59:241-9)*

- 10/115 patients with AIH had acute presentation:

  necrosis in zone 3 *(Clin Gastroenterol hepatol 2004:2:625-31)*

- **Central necrosis as predominant injury** , mild portal inflammation, steroid responsive, or evolves into chronic hepatitis *(Am J Surg Pathol 2004:28:471-8)*

- Type 1 AIH: acute onset in 40% (Czaja, in: MacSween's Pathology of the Liver, page 494

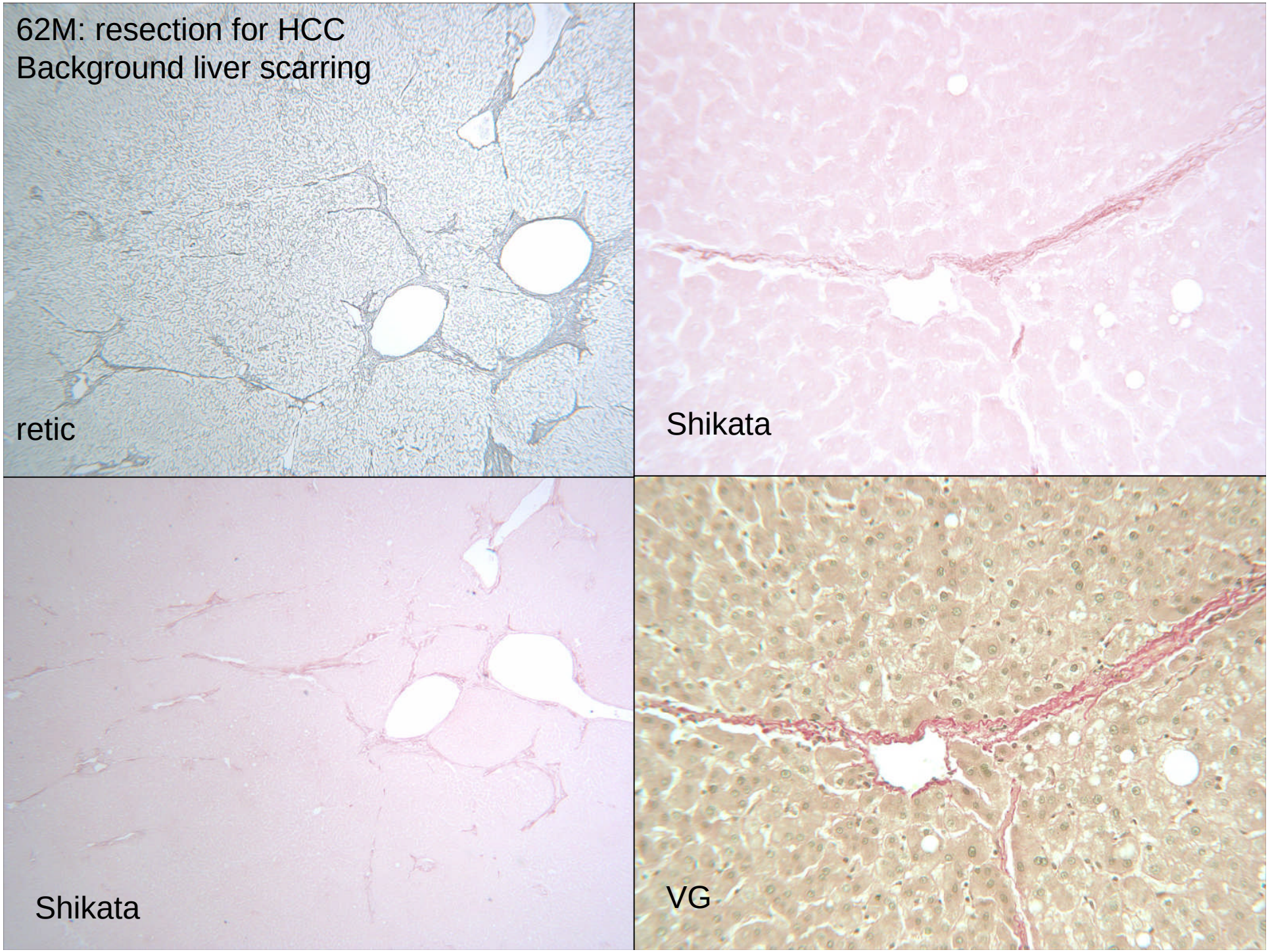
The significance of autoantibodies and immunoglobulins in acute liver failure: a cohort study.

J Hepatol 2007:47:664-670

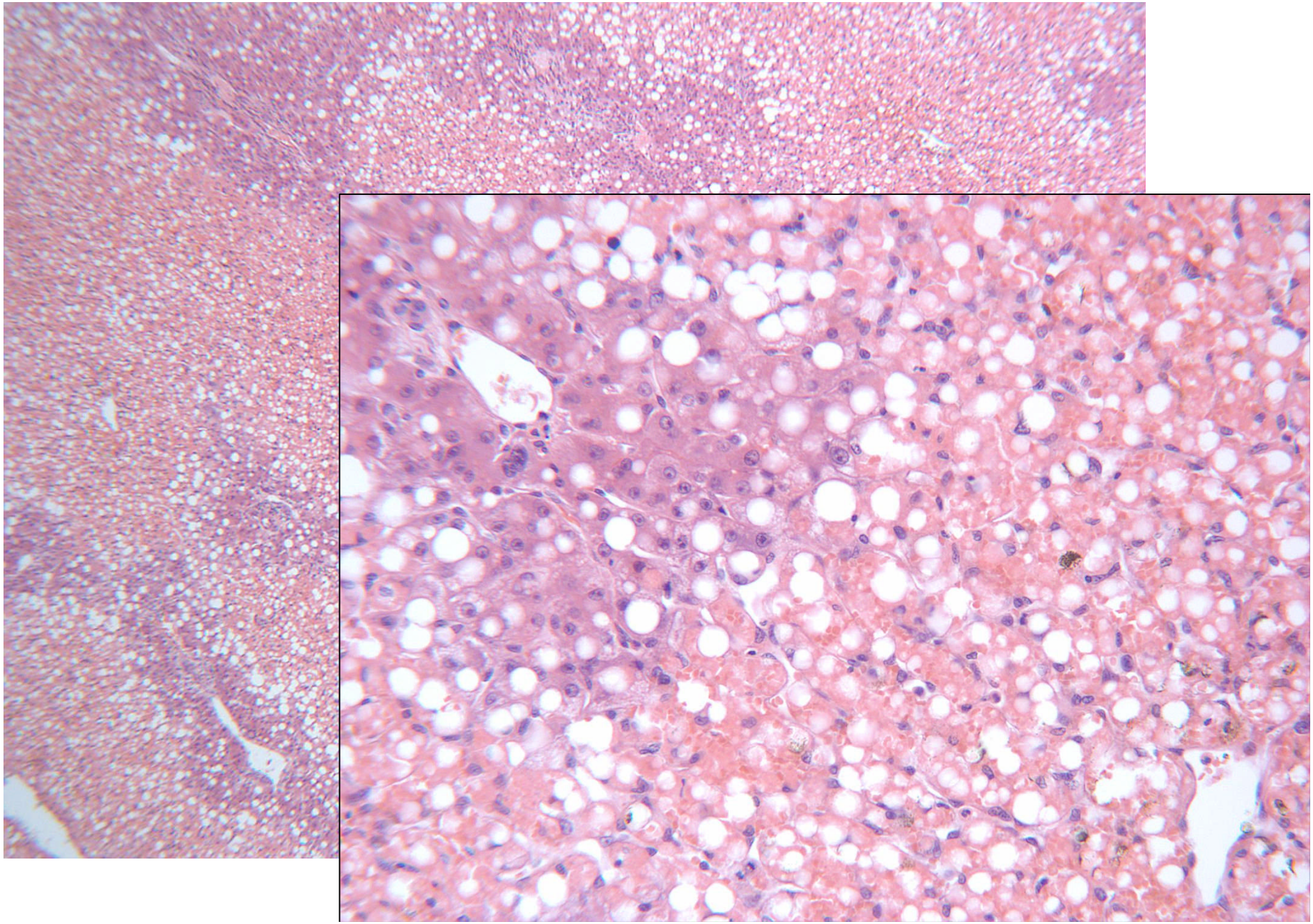
- Autoantibodies present in
  - 23/53 non-paracetamol acute liver failure patients
  - 0/20 paracetamol-related disease

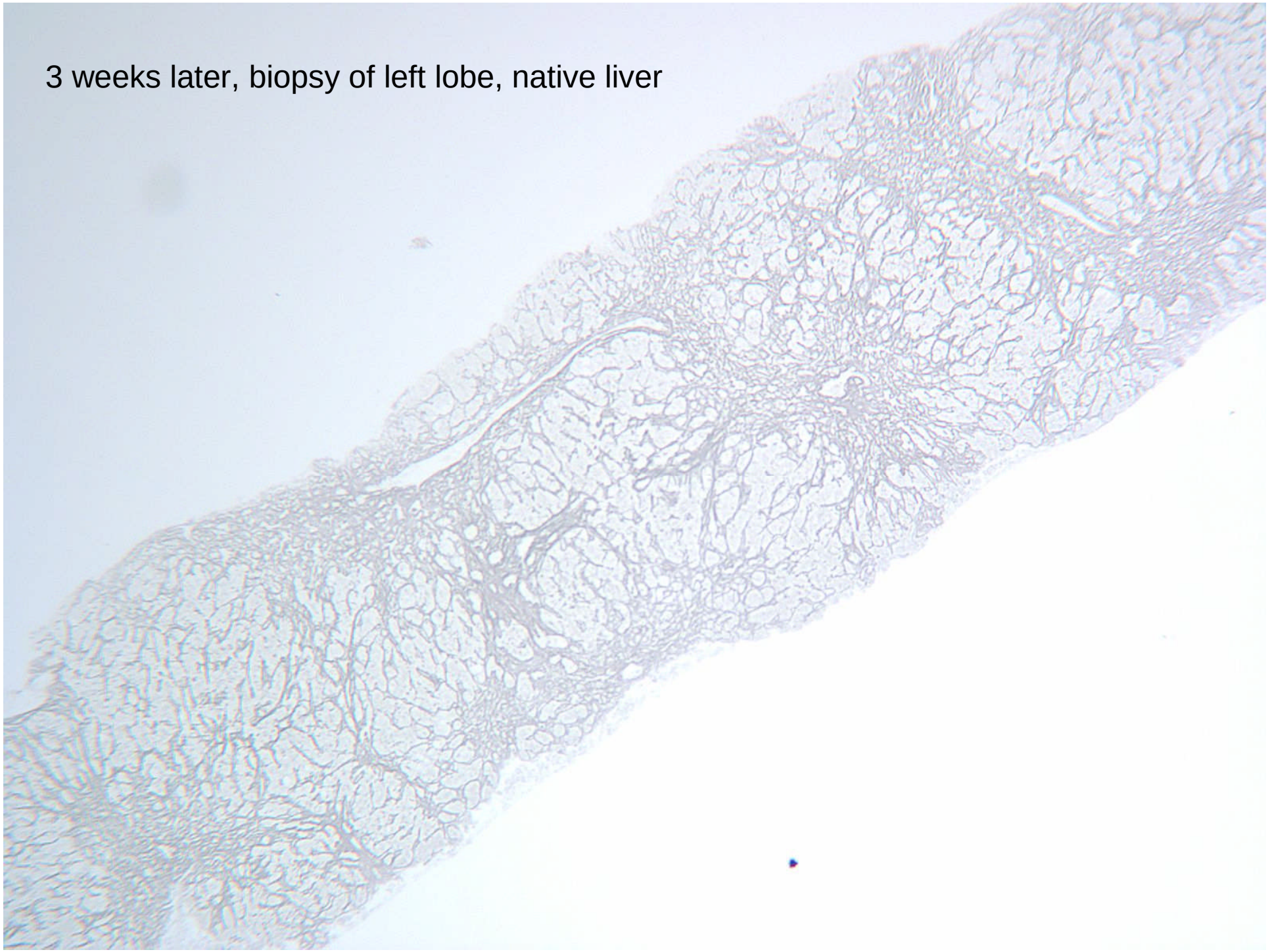
(16 anti-soluble liver antigen, 6 ANA, 4 anti-smooth muscle, 1 AMA)

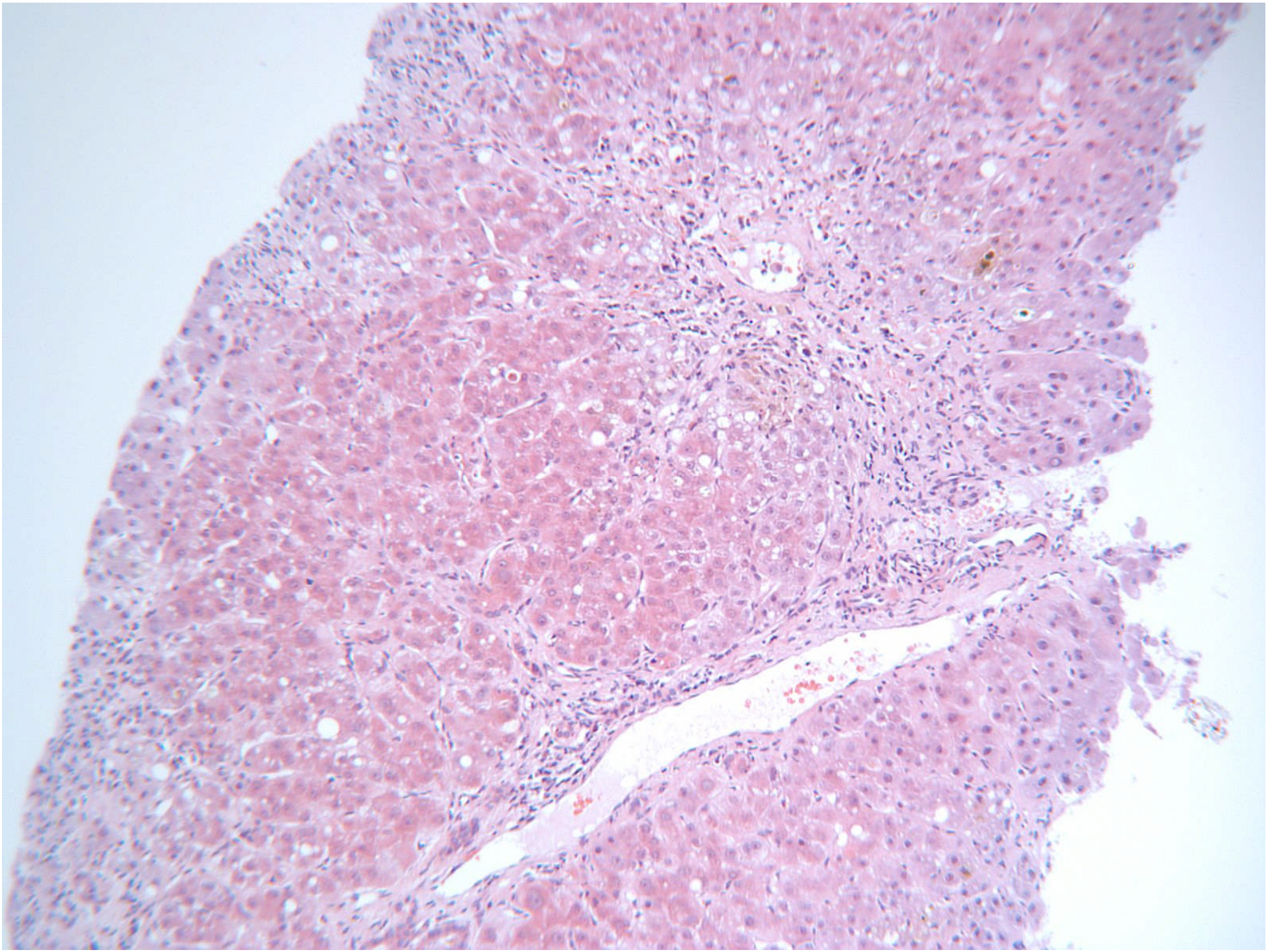
	Any autoantibody	Anti-SLA
Non-paracetamol drug (n=16)	31%	13%
Viral (n=21)	53%	43%
Cryptogenic (n=16)	44%	31%

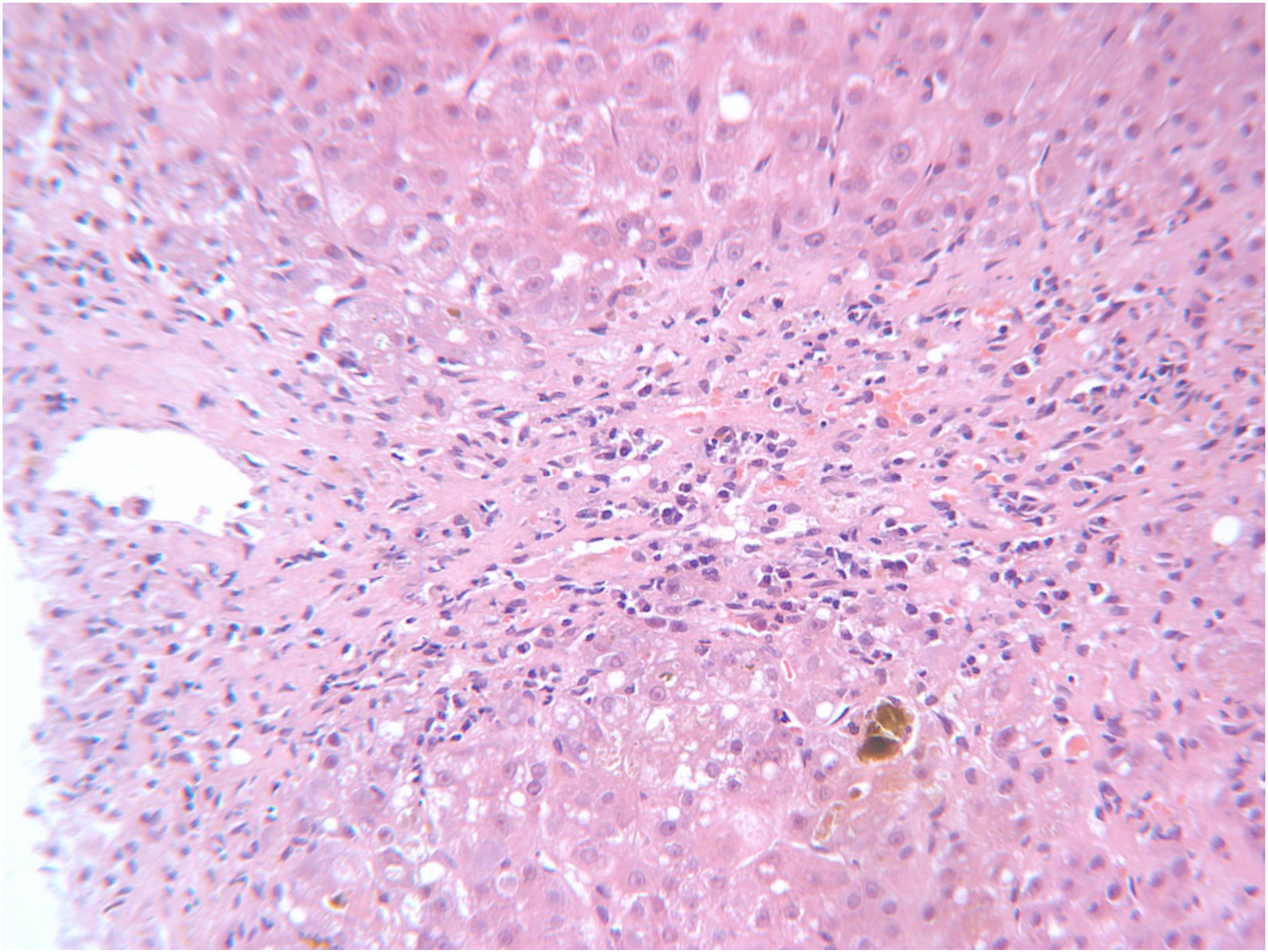

62M: resection for HCC
Background liver scarring
retic
Shikata
Shikata
VG

40M, auxillary transplant for Paracetamol overdose.




3 weeks later, biopsy of left lobe, native liver





Biopsy in acute hepatitis

- Recognise acute hepatitis,

  Zonal, bridging, panacinar necrosis

  Distinguish bridging necrosis from fibrosis in chronic liver disease (PASD, CD68, Ki67)

- Biopsy doesn't indicate the cause or the severity or the prognosis

- Differential diagnosis: drugs, virus, autoimmune, unknown