

Chronic Hepatitis

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Autoimmune Hepatitis

- Annual incidence 1.9/100 000 in N Europe
- Prevalence 16.9/100 000
- ~5% all liver transplants
- Female preponderance (4:1)
- All ages and ethnic groups
- Type 2 (LKM1 positive) more common in Europe

Scoring system

Table 2. Simplified Scoring System of the International Autoimmune Hepatitis Group*

Component	Result	Points
Autoantibodies		
ANA or SMA	$\geq 1:40$	+1
ANA or SMA	$\geq 1:80$	+2
Antibodies to liver kidney microsome type 1	$\geq 1:40$	+2
Antibodies to soluble liver antigen	Positive	+2
Absent autoantibodies	None	0
Immunoglobulin level		
Immunoglobulin G	>UNL	+1
	>1.1 ULN	+2
	Normal	0
Histological Findings		
Morphological features of AIH	Compatible	+1
	Typical	+2
	Incompatible	0
Viral Disease		
Absence of viral hepatitis	No viral markers	+2
	Viral markers present	0
Pretreatment Aggregate Score: Definite diagnosis		≥ 7
Probable diagnosis		6

Treatment

- Oral prednisolone 40-60 mg
 - taper as ALT improves
- Azathioprine 50-150 mg
 - depending on weight and response
- Rapid response: decreased disease progression
 - no symptoms, ALT < 2 x ULN, normalised IgG
- ~50% develop cirrhosis
 - prognosis still good (10% mortality in 15 years)

Biopsy

- Diagnosis – part of scoring system
- Staging- need for surveillance
- Monitor response – slow responders, possible additional diagnoses
- Stopping treatment

Case 1

- Sept 2017: 17 year old male presents to GP with 4-6 weeks of malaise
- GP notes mild jaundice on examination
 - Bilirubin 64 micromol/l
 - ALT 866 U/l
 - Alk phos 154 U/l
 - GGT 396 U/l

- Referred to infectious diseases unit
- Further history -
 - Occasional right upper pain, rash 2 weeks previously, 4 kg weight loss, 2 days diarrhoea
- PMH Football injuries, dermatitis
- Social Gym 4-5 times per week, non-drinker and non-smoker
- Diagnosis of probable viral hepatitis

Investigations

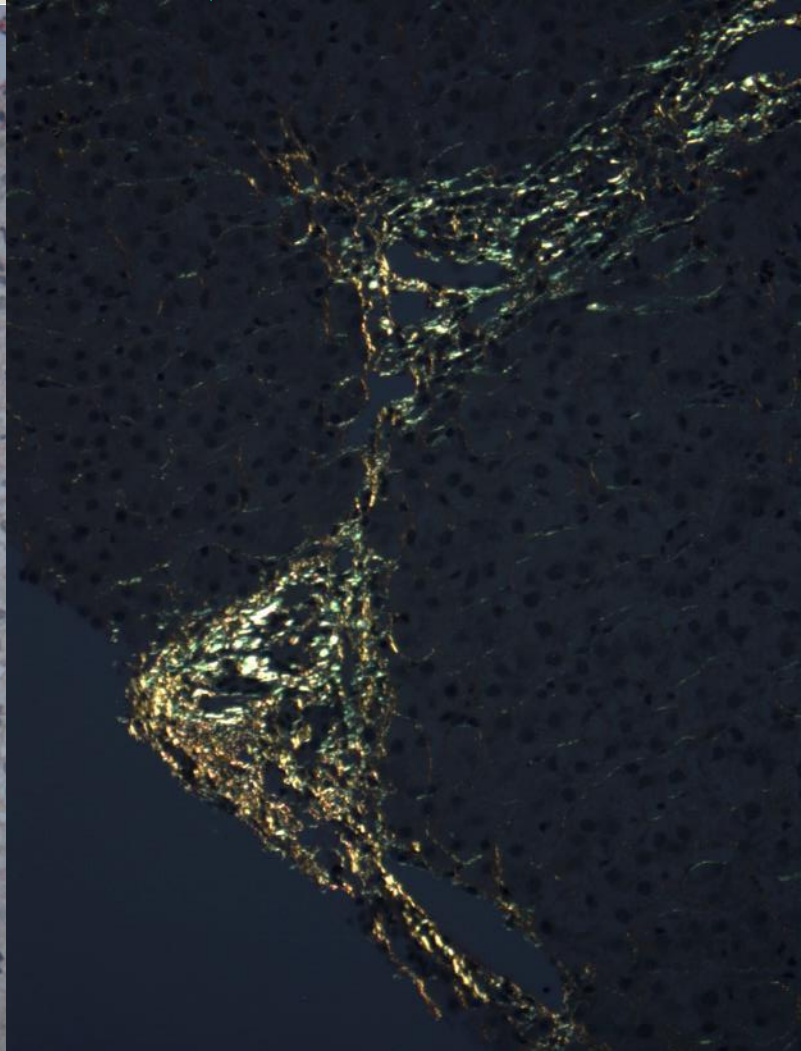
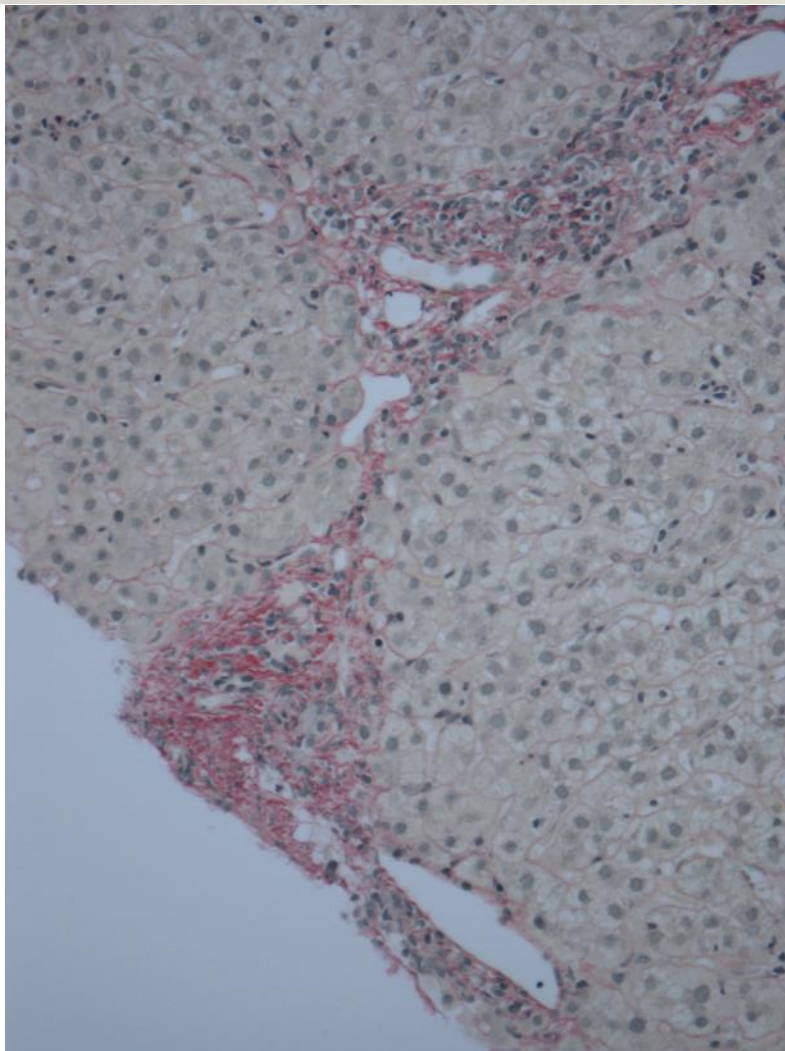
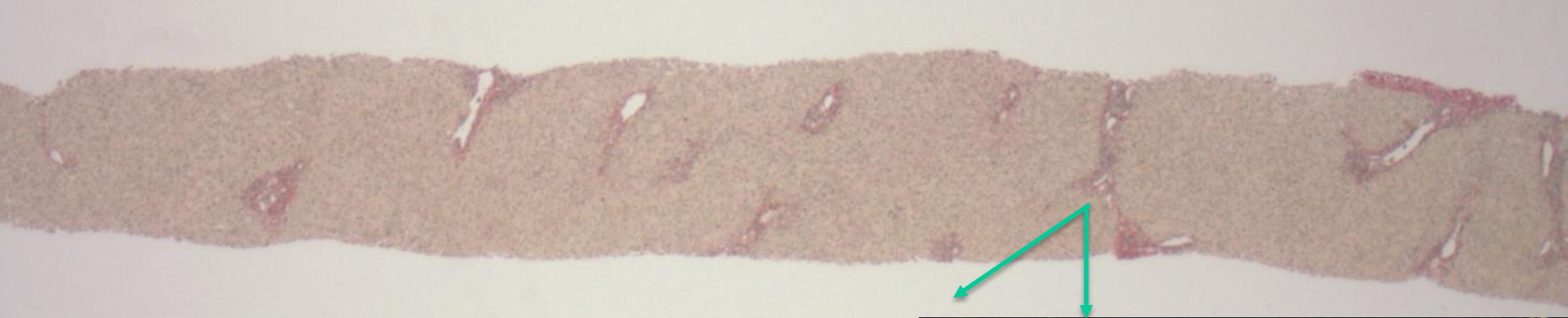
- Hepatitis A,B,C and E negative
- CMV,EBV negative
- Ferritin 813
- Caeruloplasmin 0.27 g/l (normal)

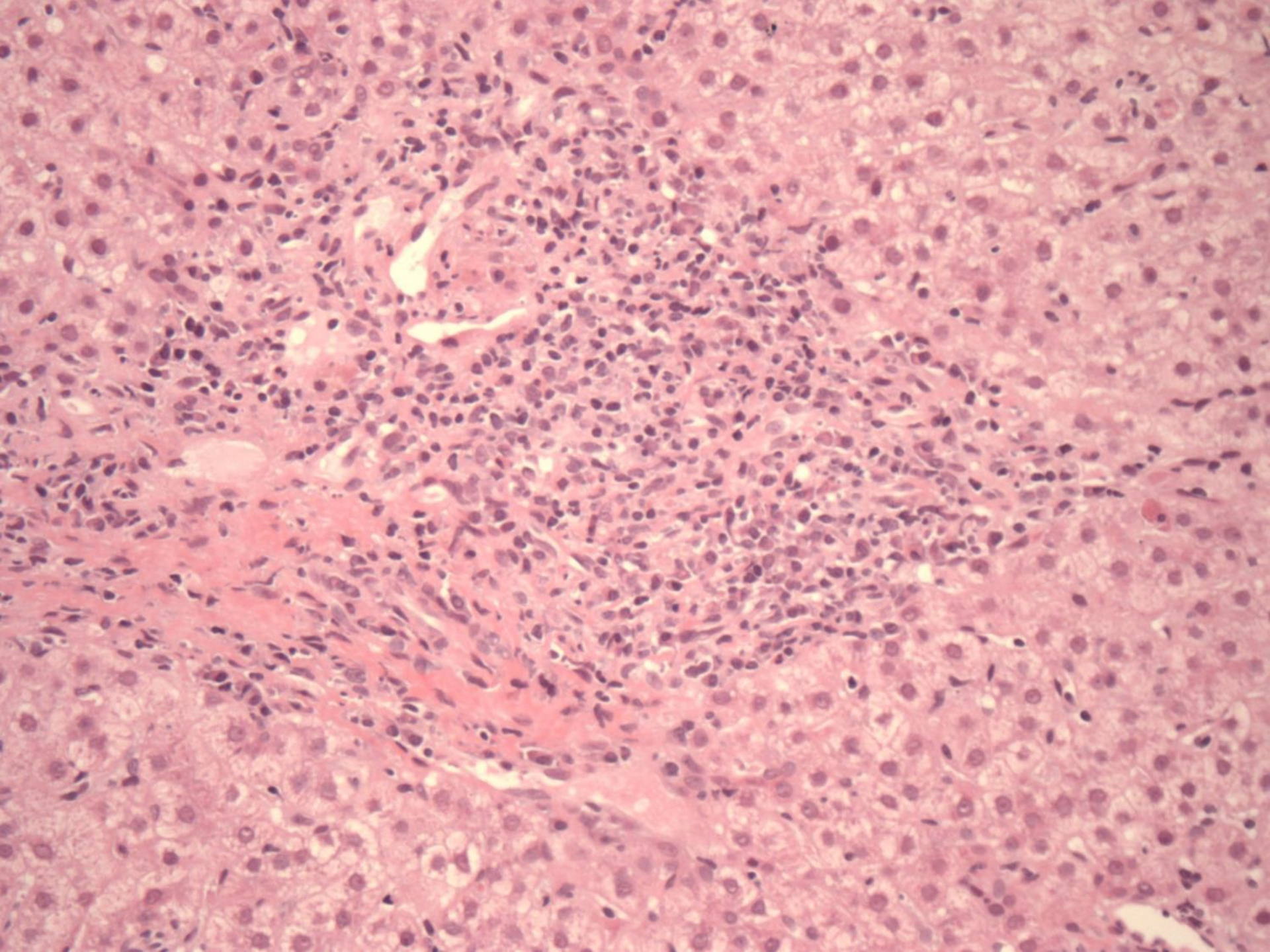
Hepatology referral

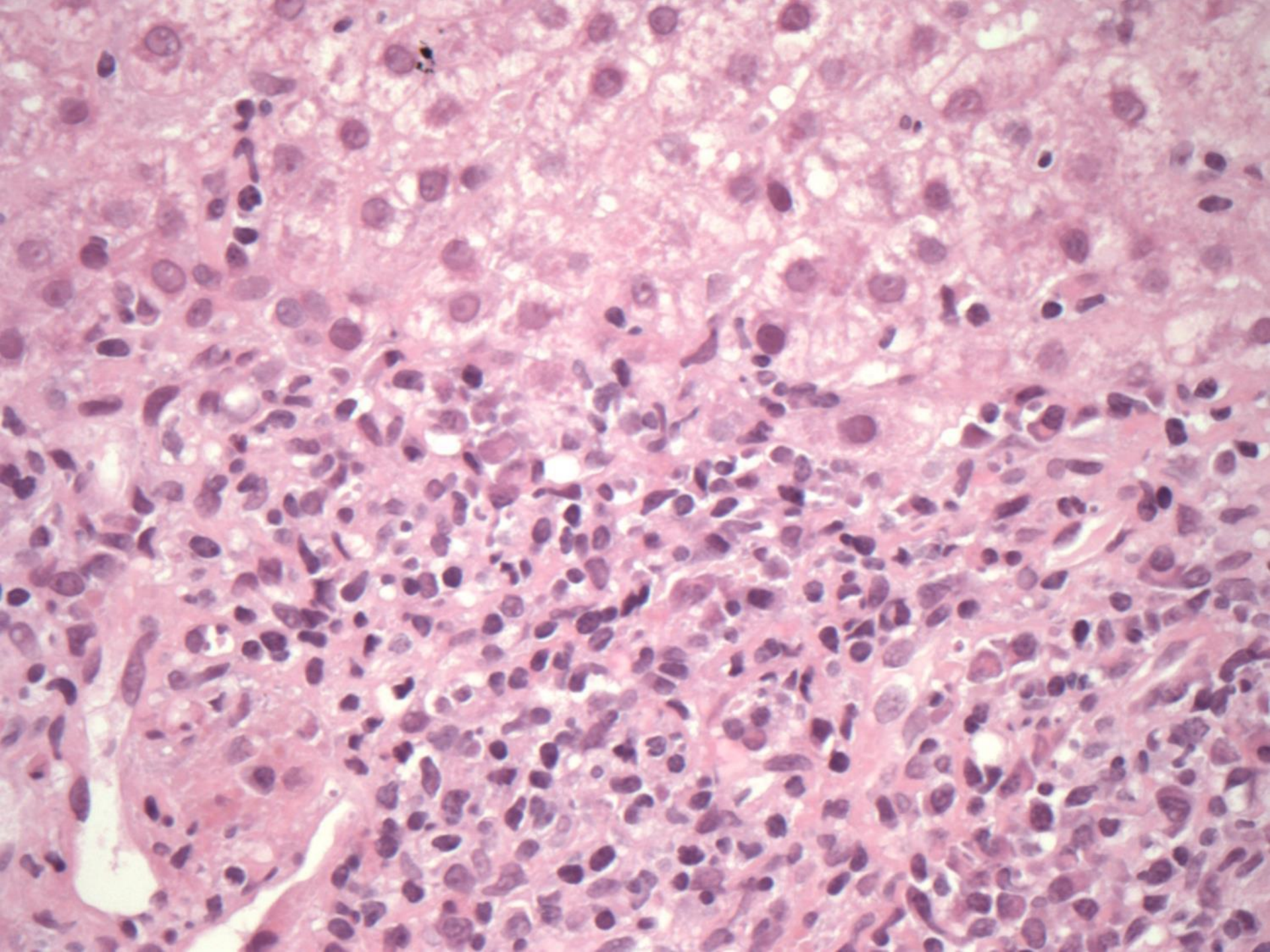
- Reviewed by registrar on 17/9
- History revisited -
 - taking supplements for muscle bulking
 - My protein- alpha man
 - My protein- Vit D3
 - My protein BCAA- Vit B6,leu,isle
- Bili 71
 ALT 895
 ALP 153
- Immunoglobulins and auto-antibodies requested

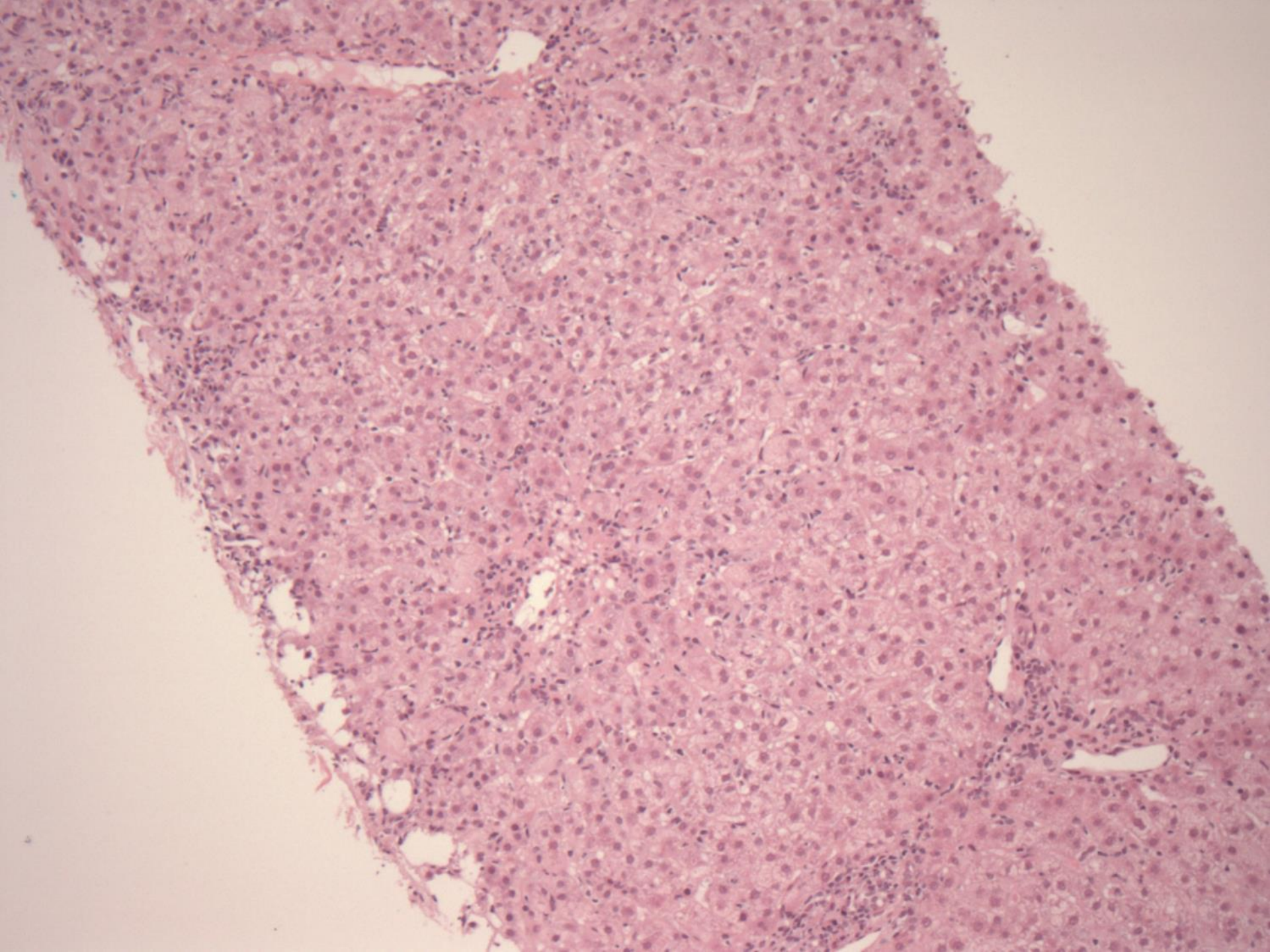
Admitted for biopsy

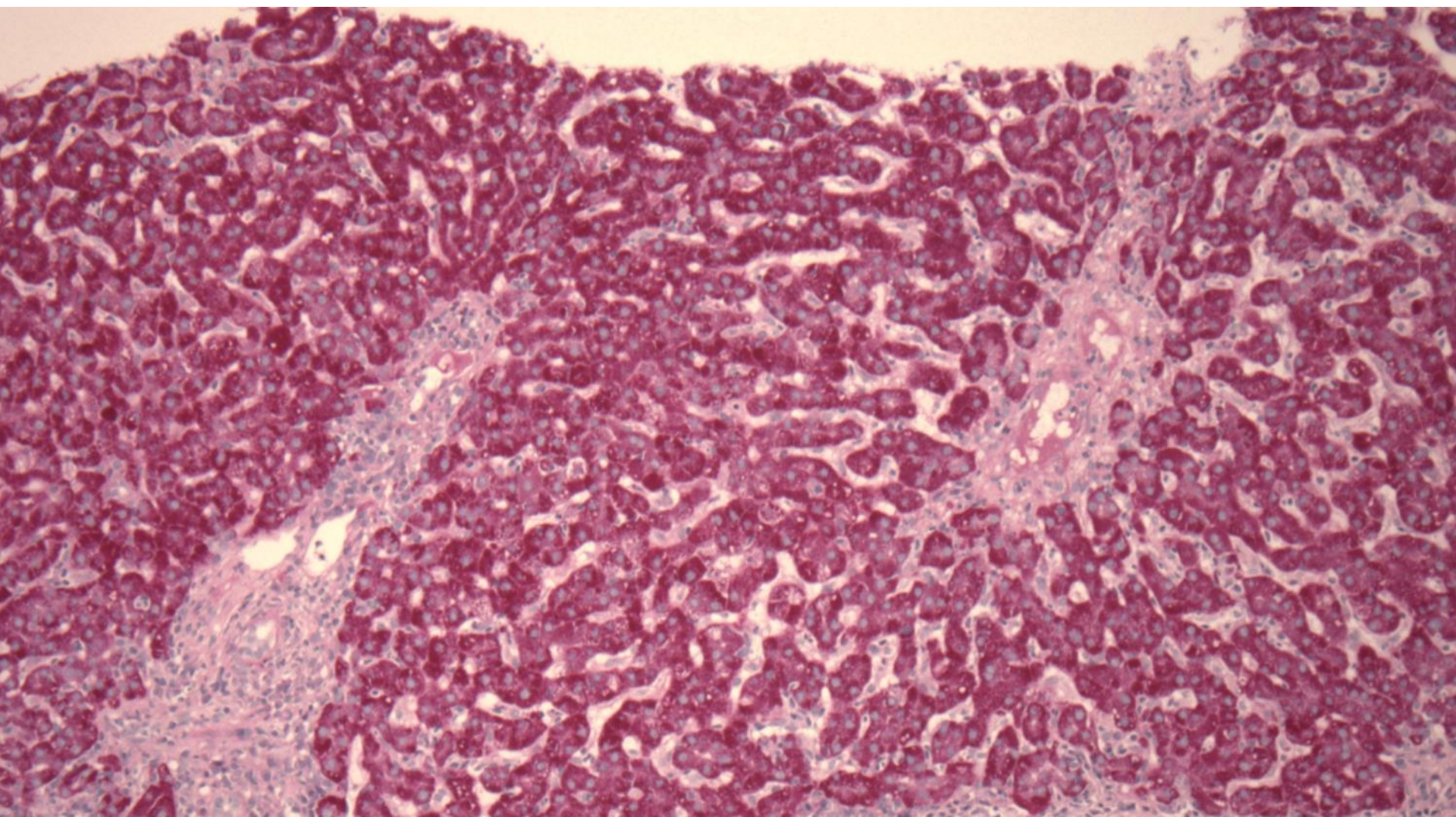
- Bili 43, ALT 995
- **History revisited** – aunt and maternal grandmother both had rheumatoid arthritis

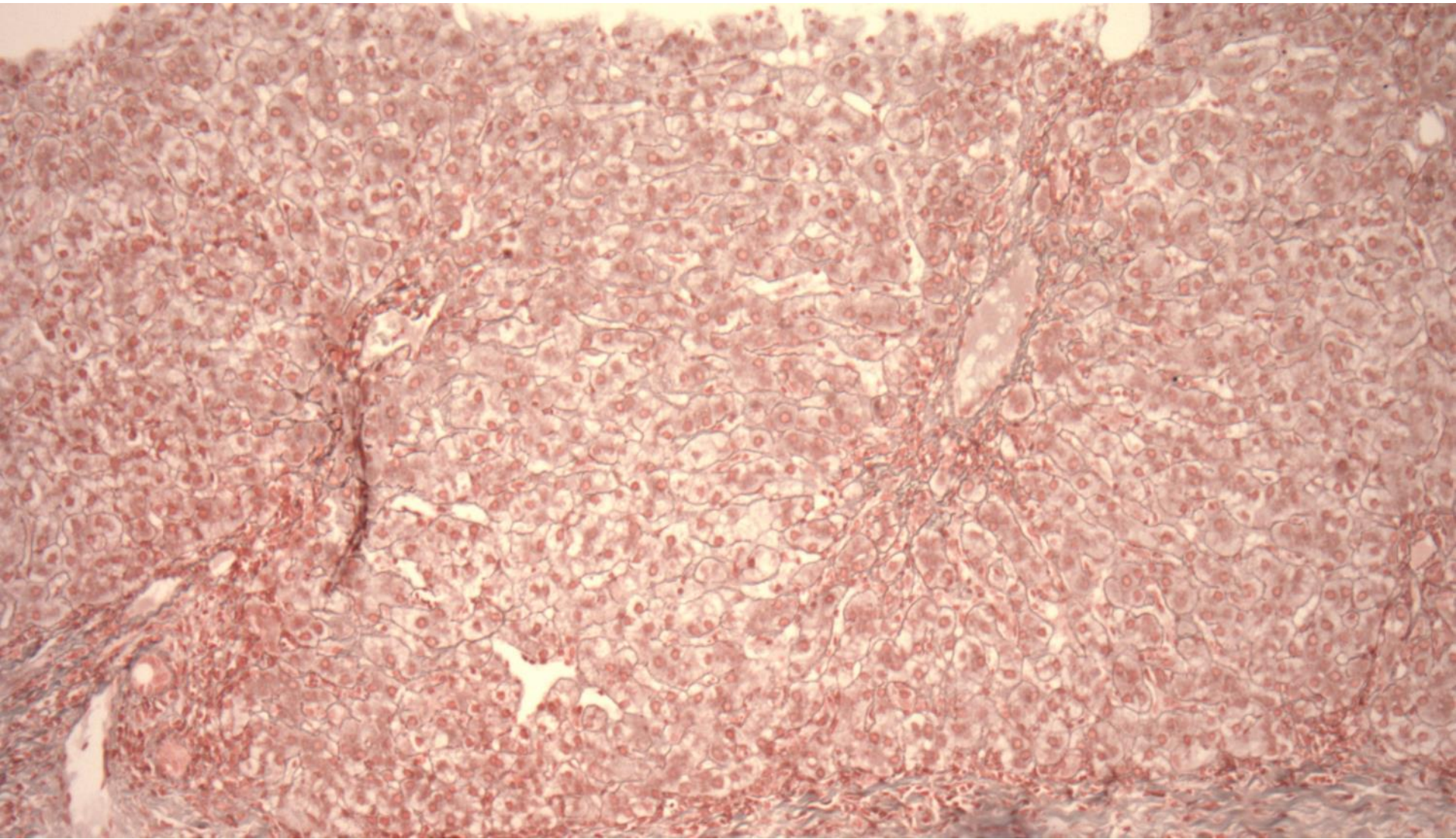




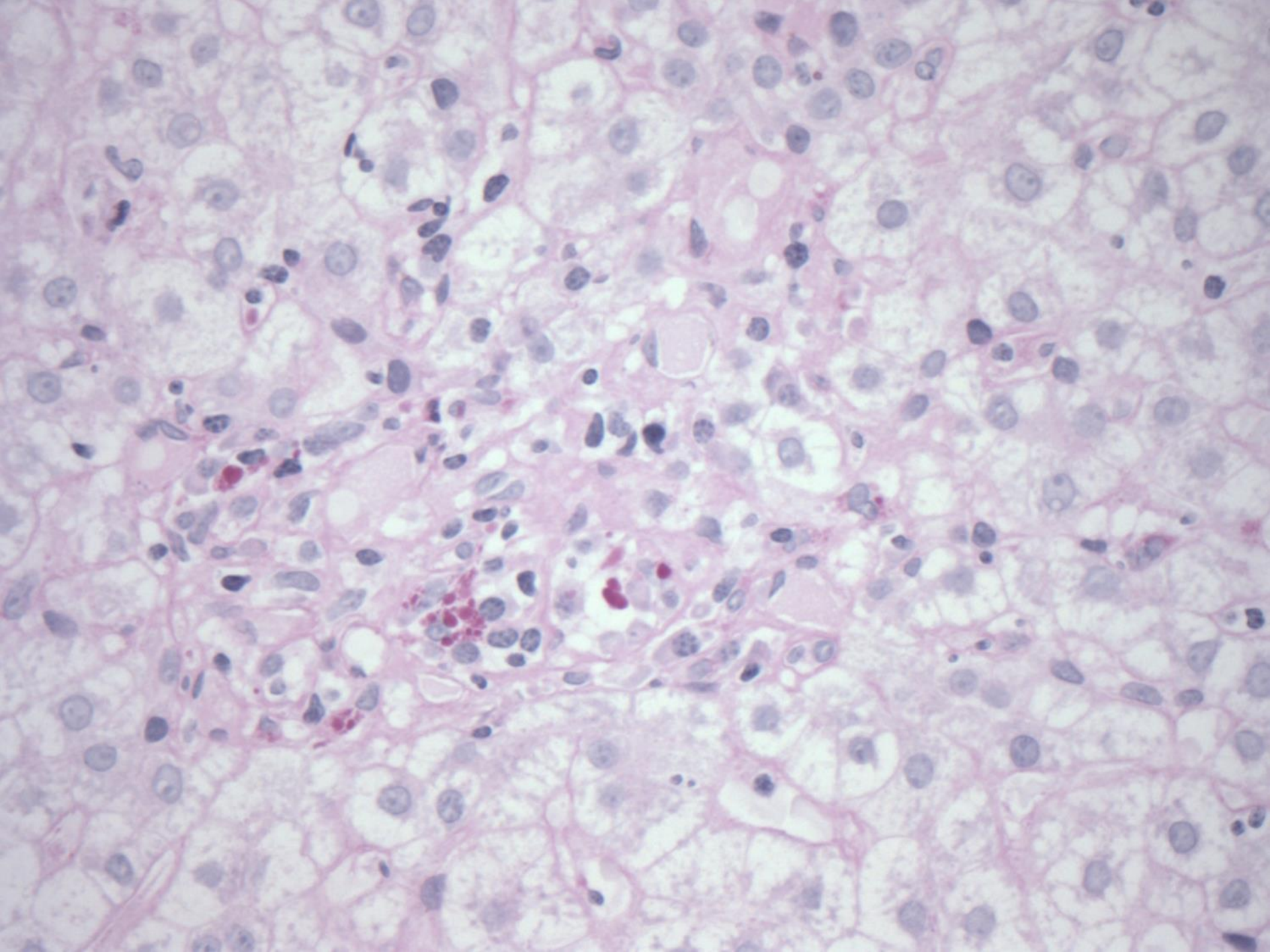


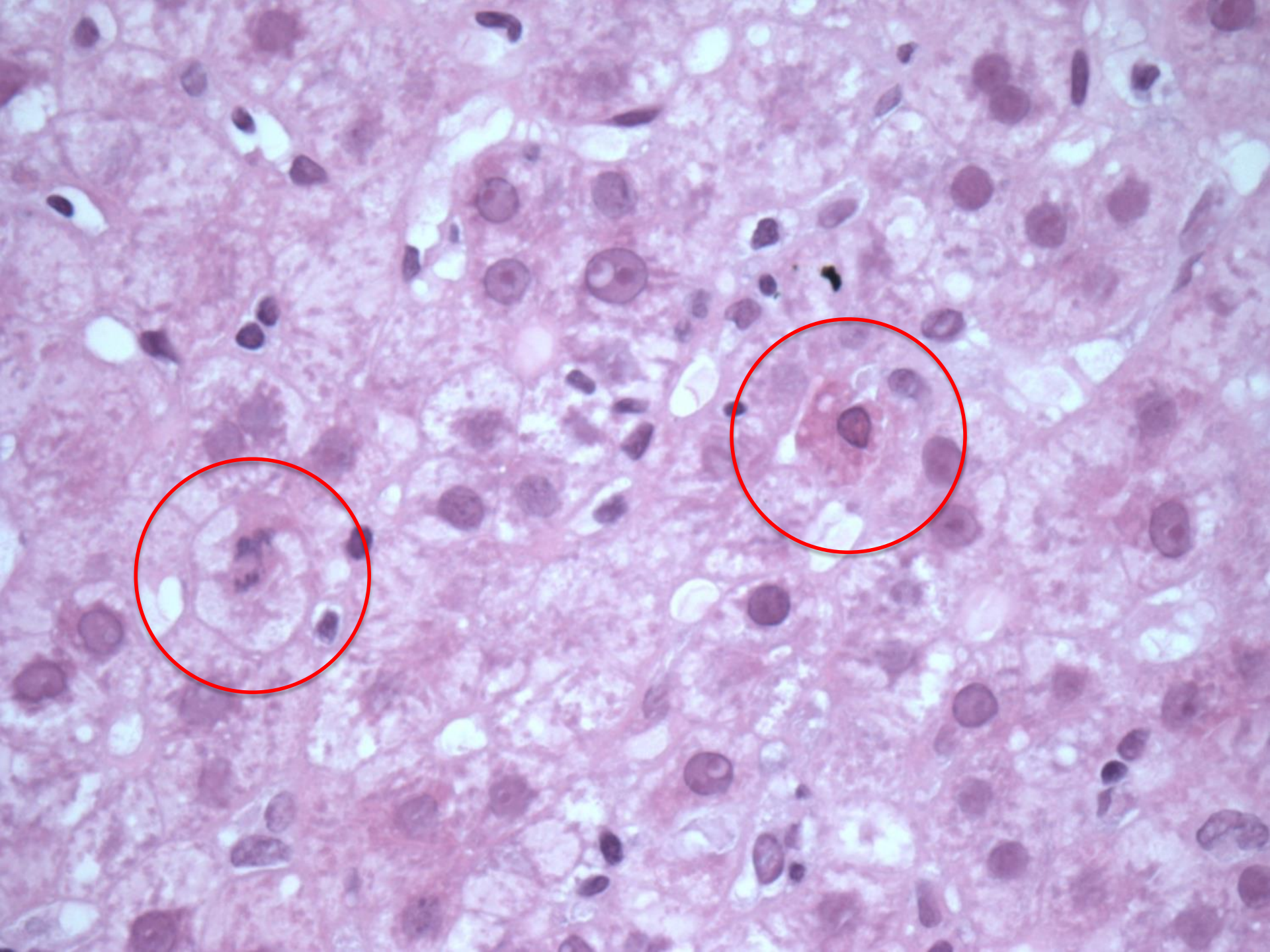


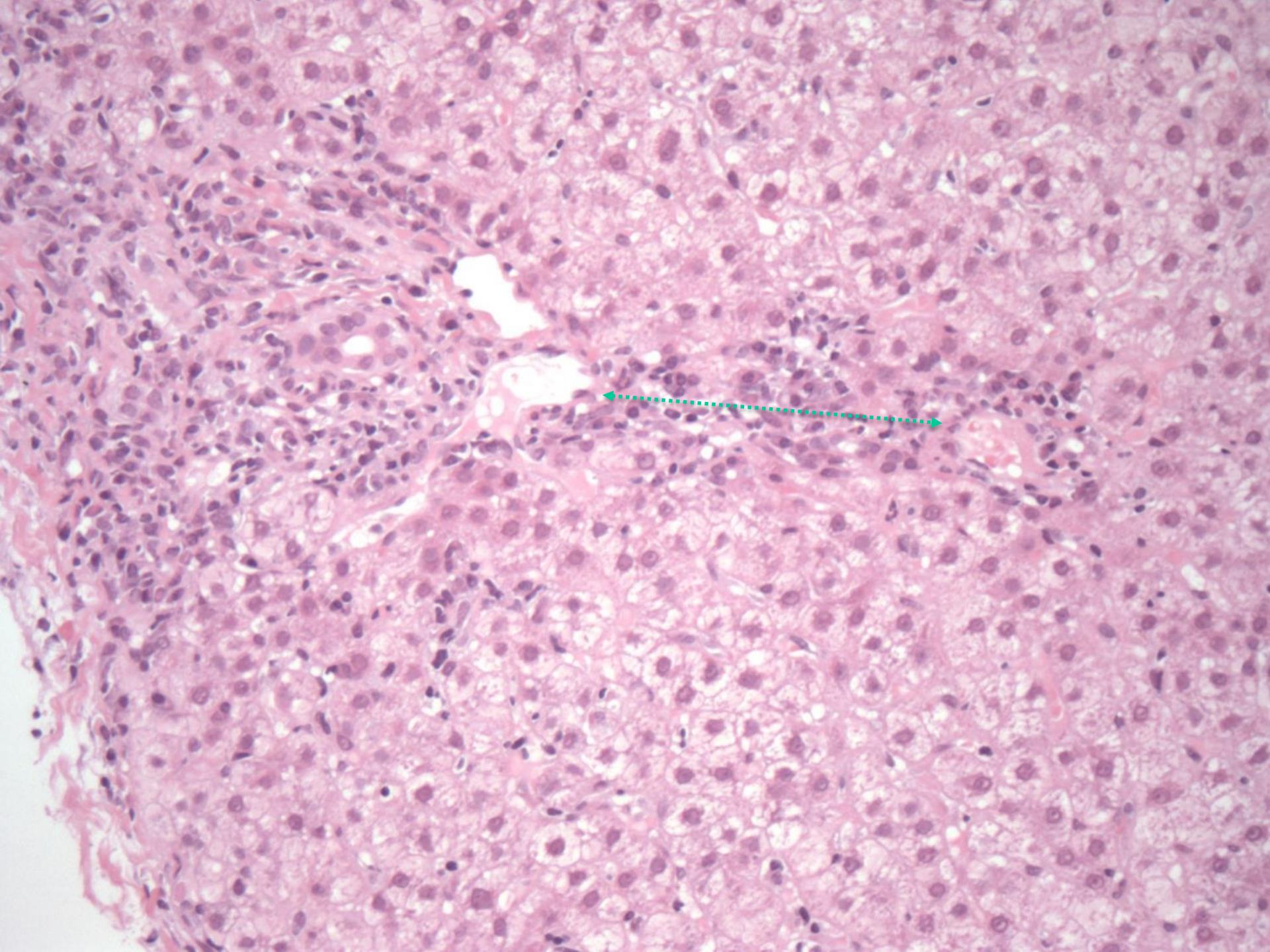


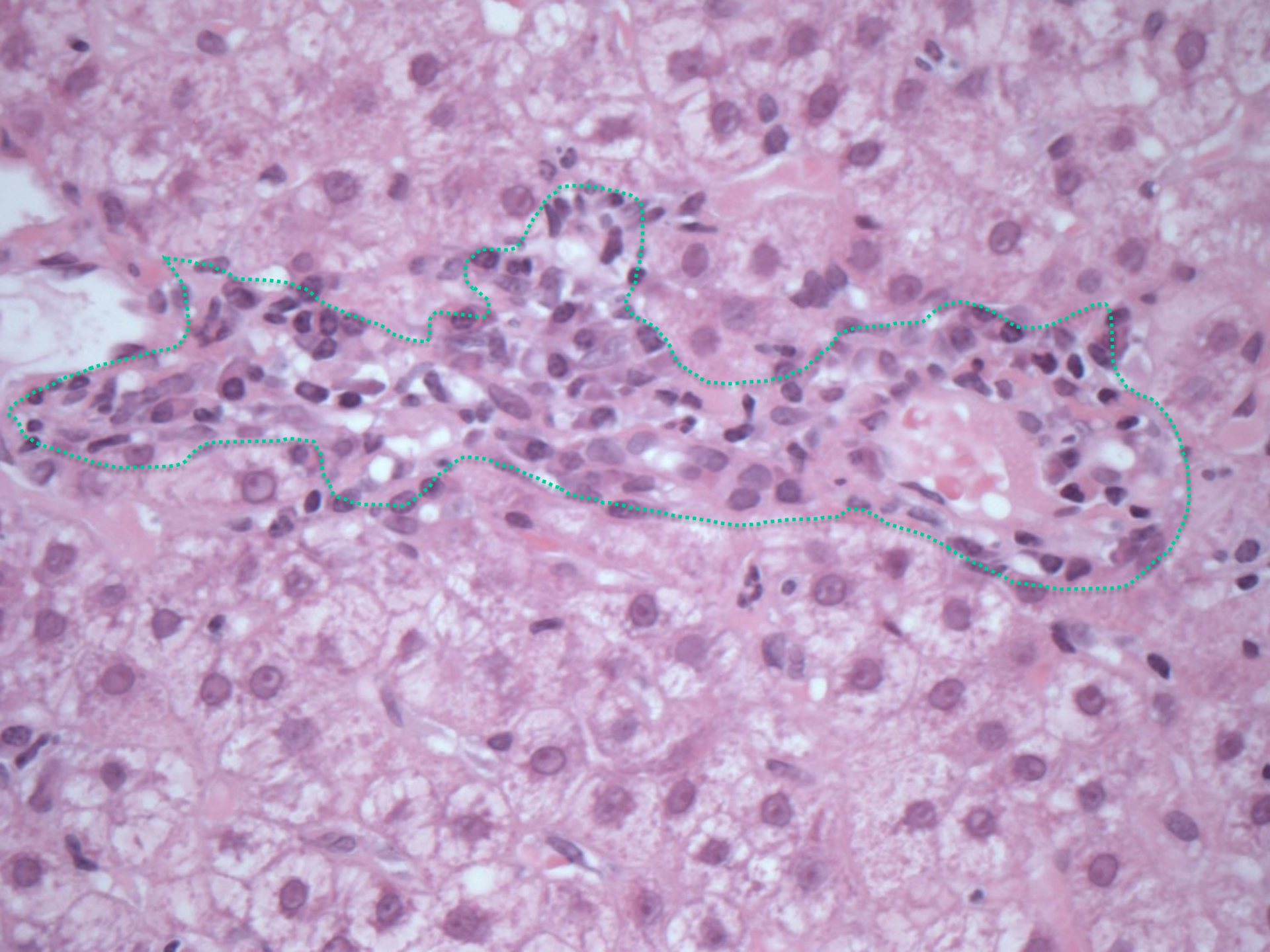


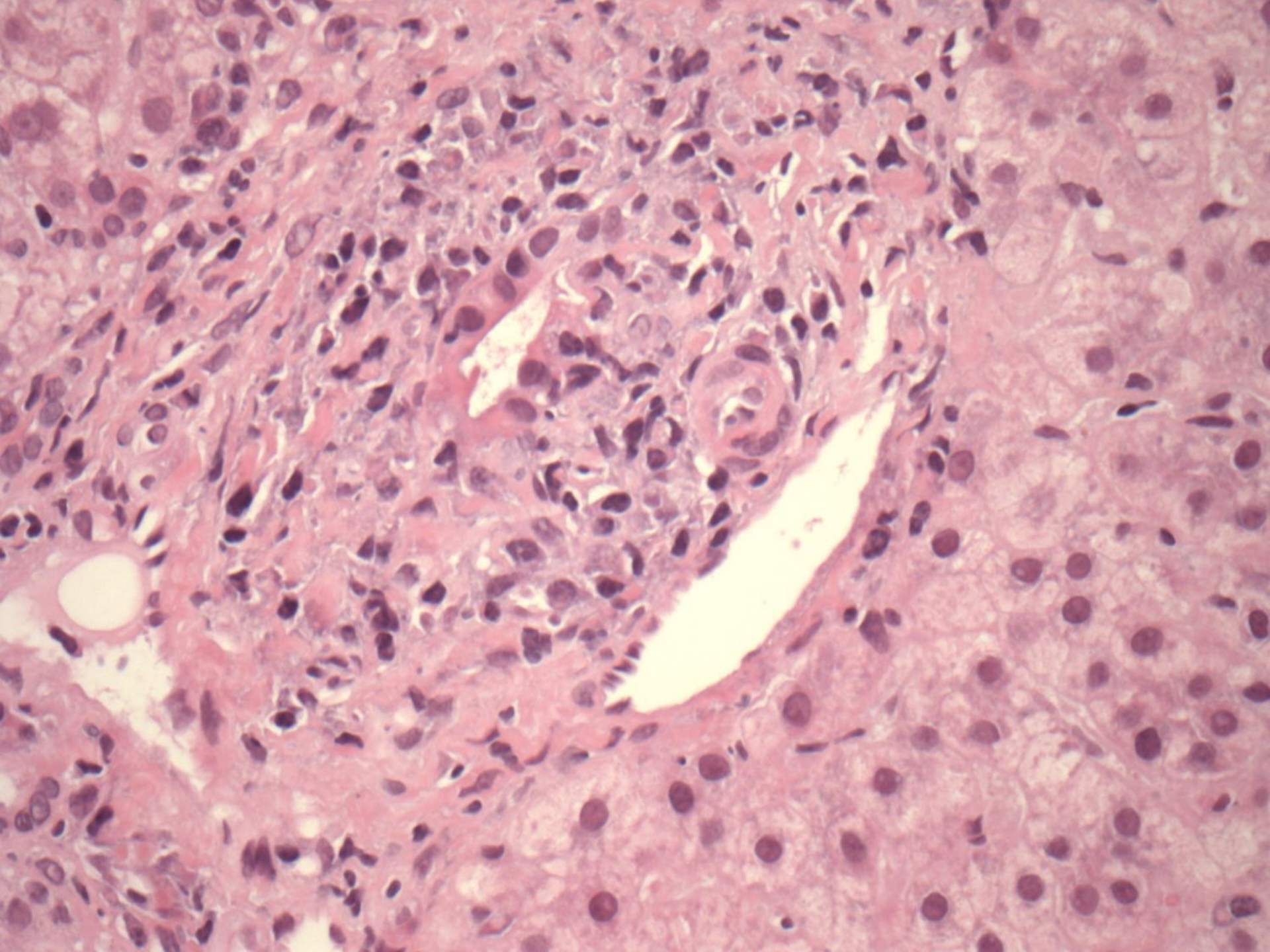


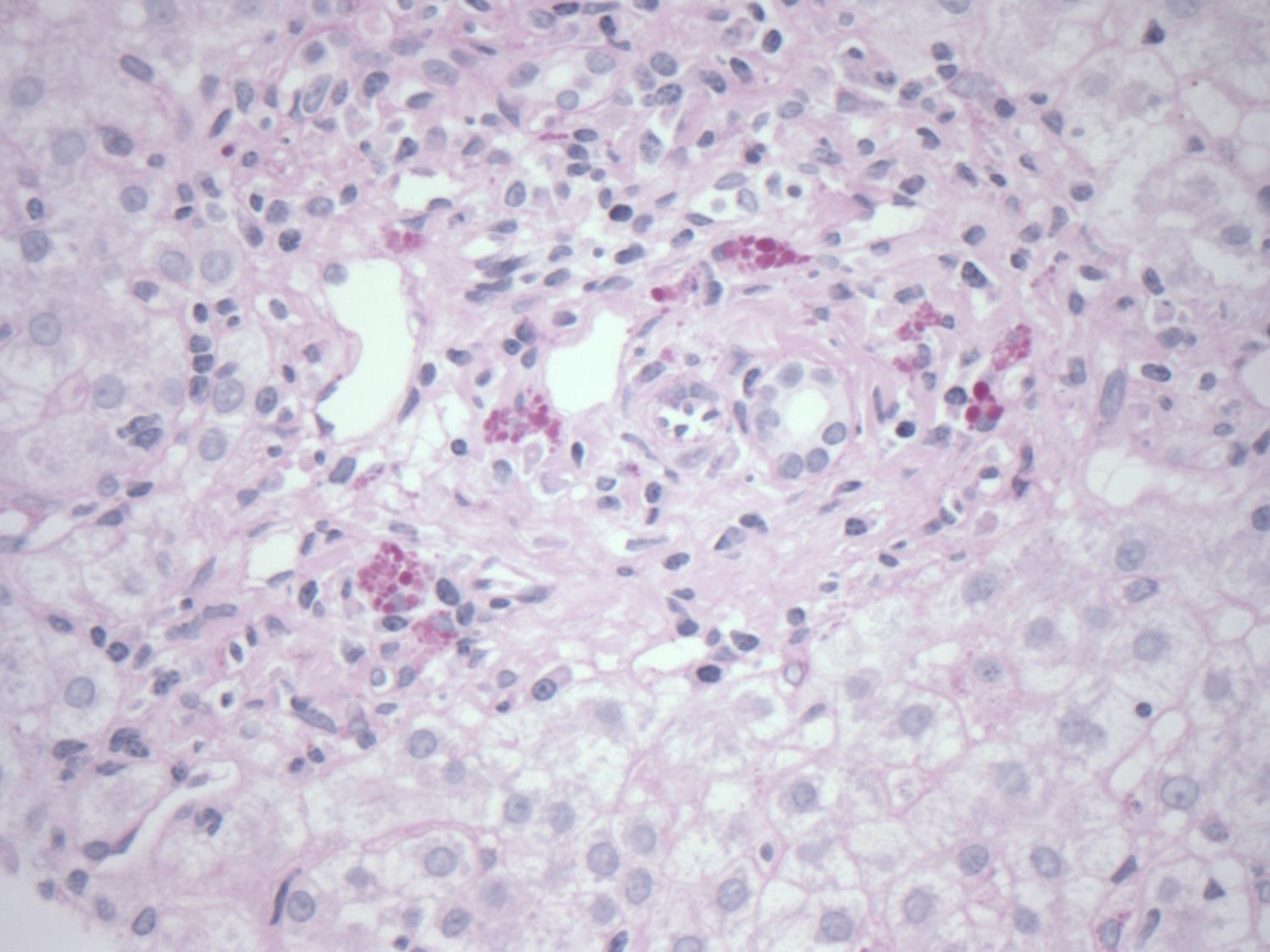


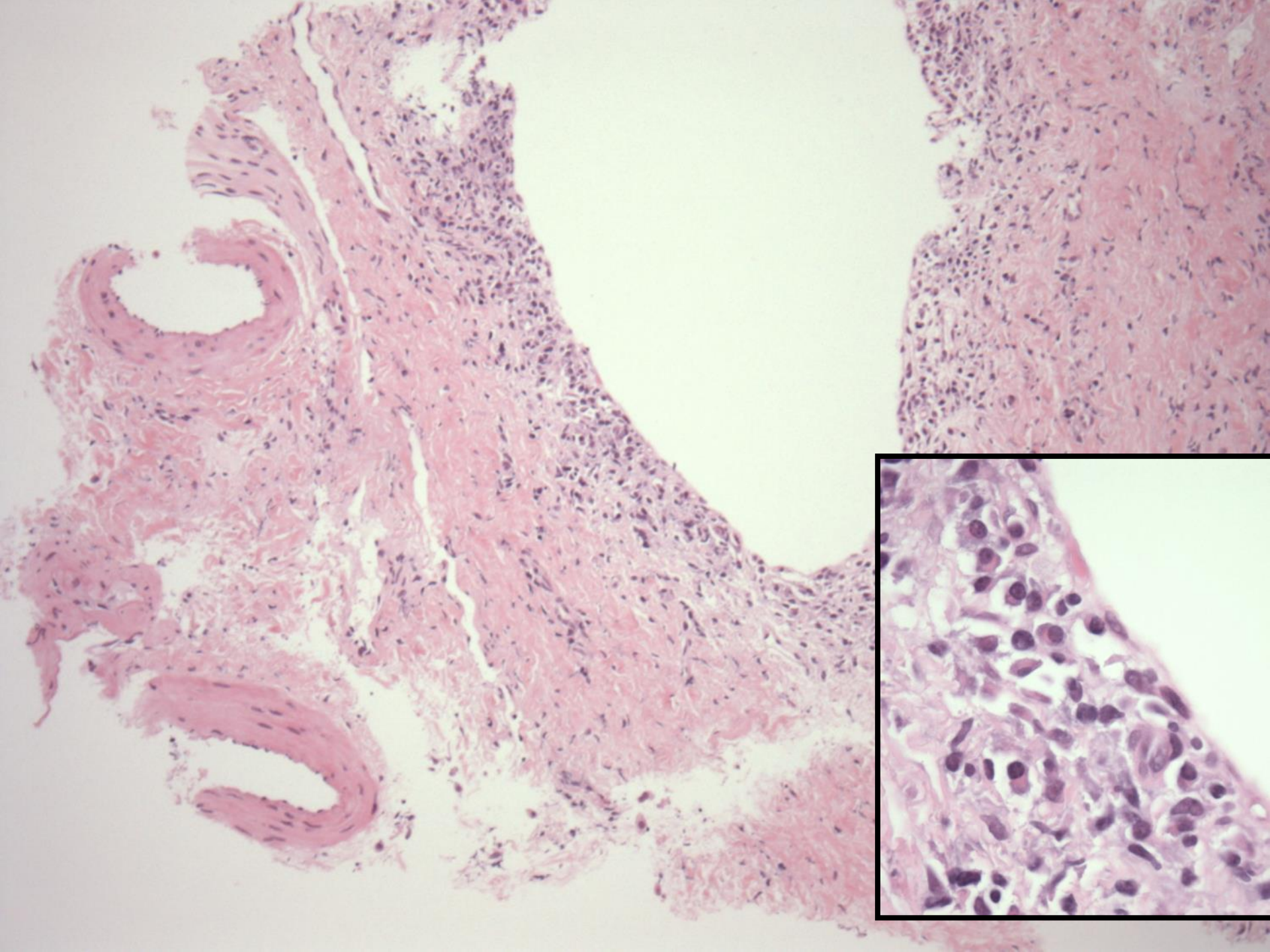












Biopsy findings

- severely active lymphoplasmacytic hepatitis
- mild fibrosis
- in this setting: c/w recent flare of autoimmune hepatitis with only incipient fibrosis

Treatment

- Started 40mg prednisolone and discharged
- 12.10 (1 week later) bili 24
ALT 443
ALP 133
- 19.10 – autoantibodies- AMA negative, LKM1 negative, anti-nuclear antibody positive 1/640, anti-ds DNA 32.6 (ULN 20), smooth muscle antibody borderline positive

Follow- up

- 08.11.17 Reduced prednisolone, commenced azathioprine at 50 mg
bili 20
ALT 110
ALP 94
- 19.12.17 Prednisolone reducing
bili 7
ALT 38
ALP 97

- 31/01/18 Seen in clinic well. Pred 10mg,
increased azathioprine to 75 mg

bili 25

ALT 236

ALP 295

Prednisolone increased to 20mg

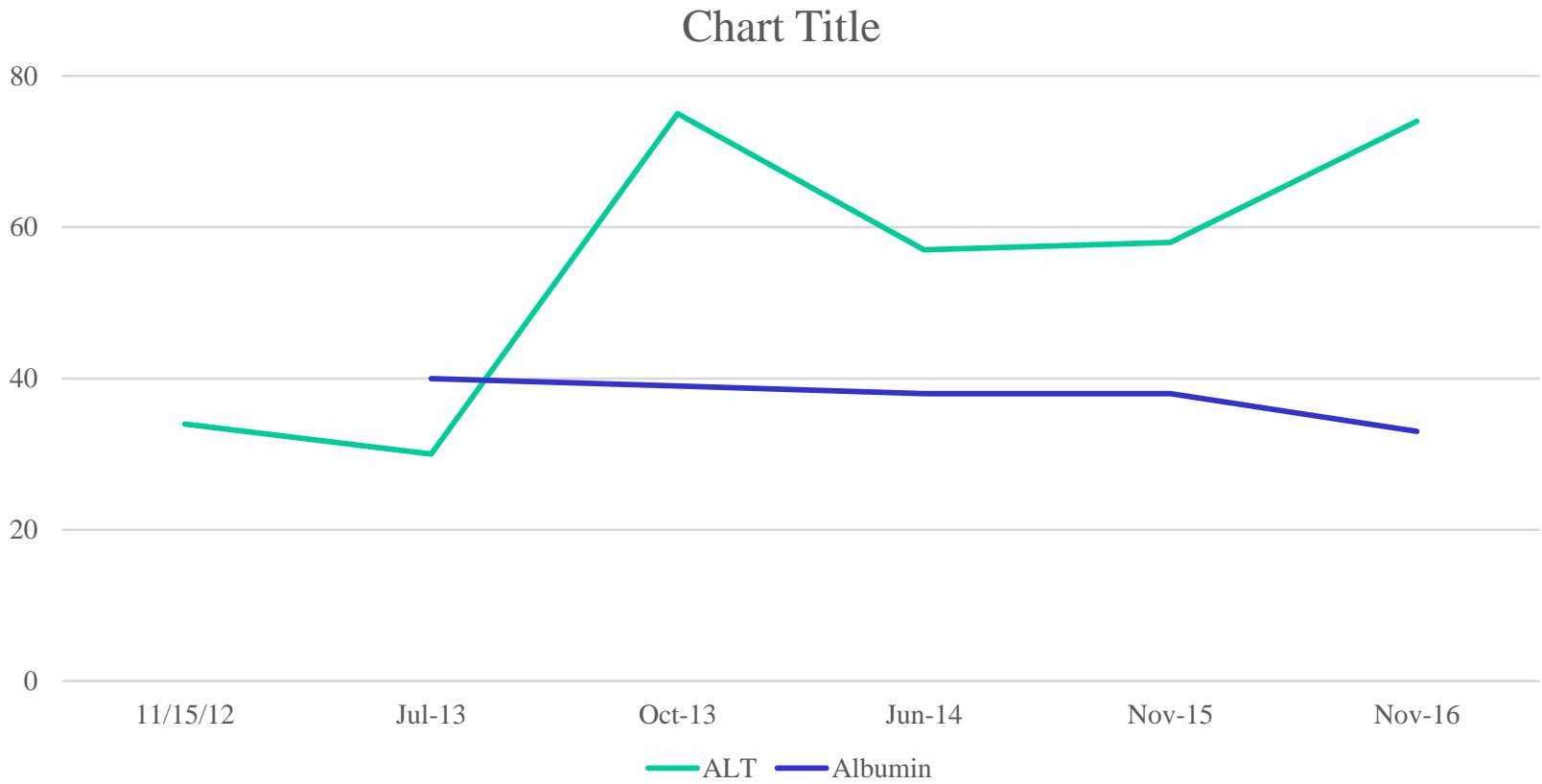
- 13.02.18 bili 20
ALT 180
ALP 266

- Apr 18 ALT reduced to 67 , prednisolone dropped to 15mg
- Dec 18 ALT 54 – acne an issue switched to budesonide
- Jan 19 ALT 134- trial of advagraf (not tolerated)
- Mar 19 ALT 130- Budesonide increased, Azathioprine increased to 125mg

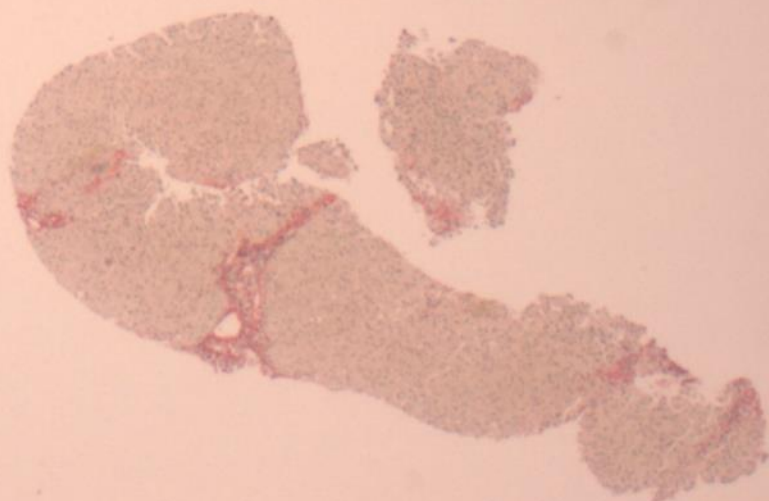
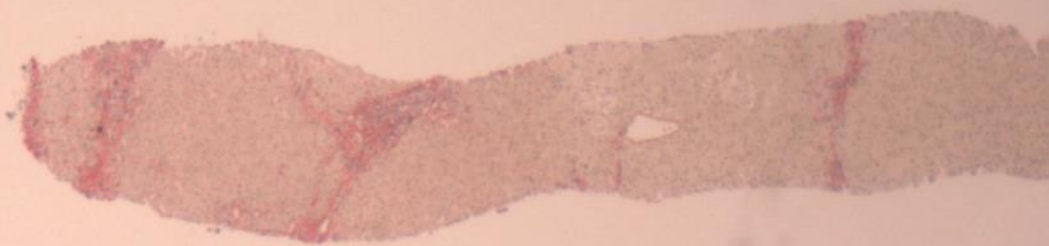
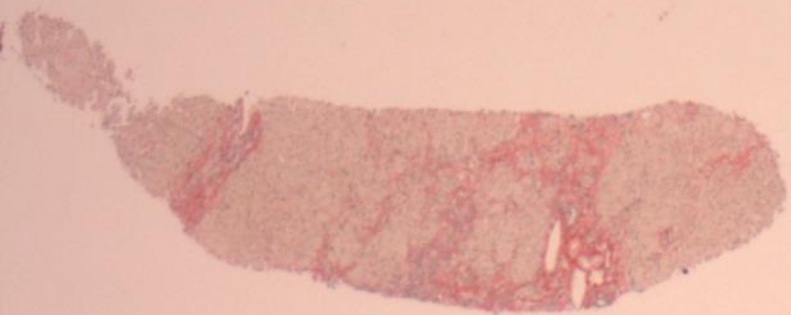
Case 2

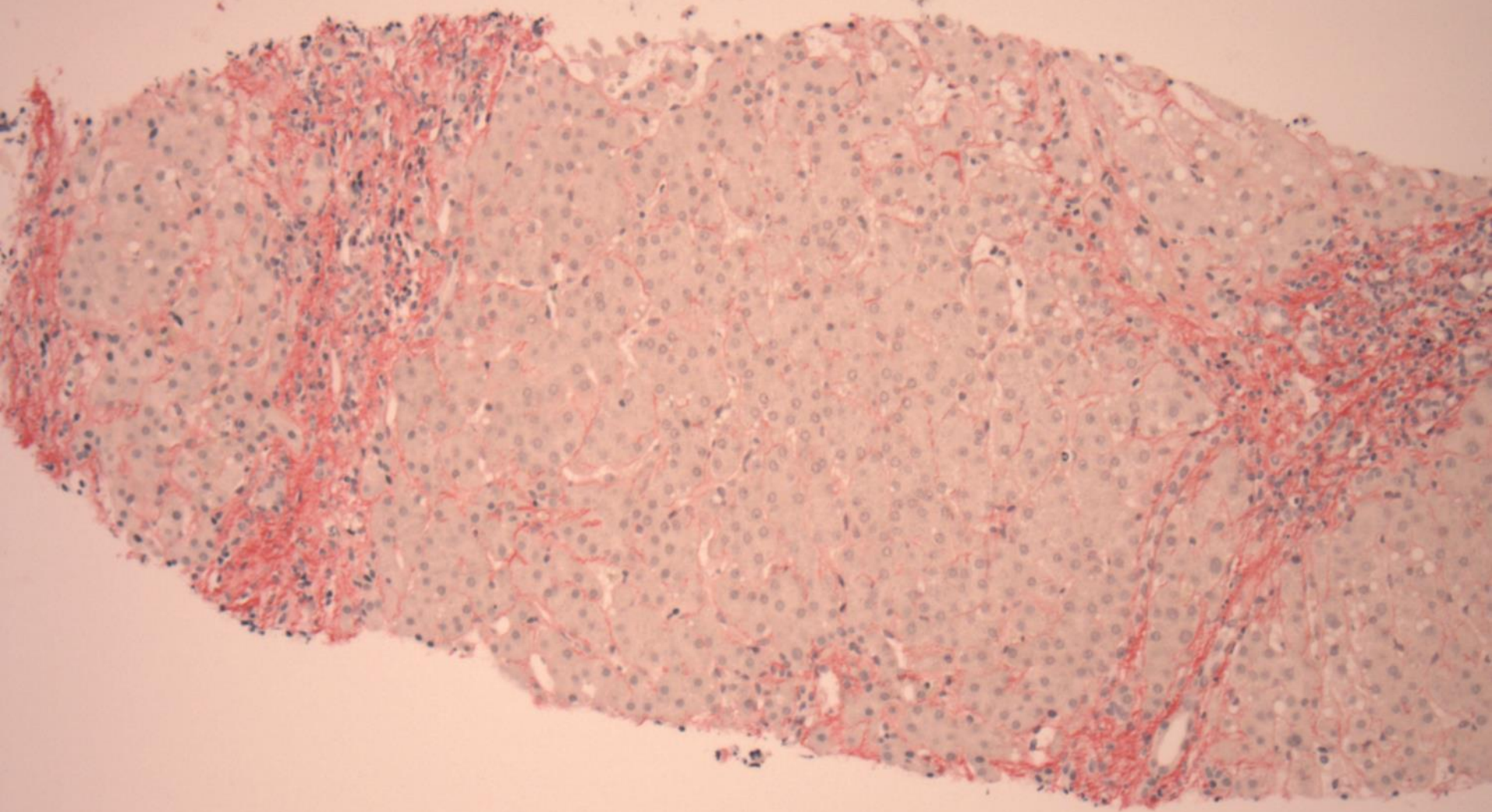
- 2007 Hypertension, endstage renal disease
Commences haemodialysis
- 2011 Renal transplantation
- Immunosuppression- once-daily tacrolimus,
mycophenolate mofetil, prednisolone
- Good kidney graft function
- Working full-time
- AF, hypertension
- Warfarin, nifedipine, atorvastatin, lansoprazole

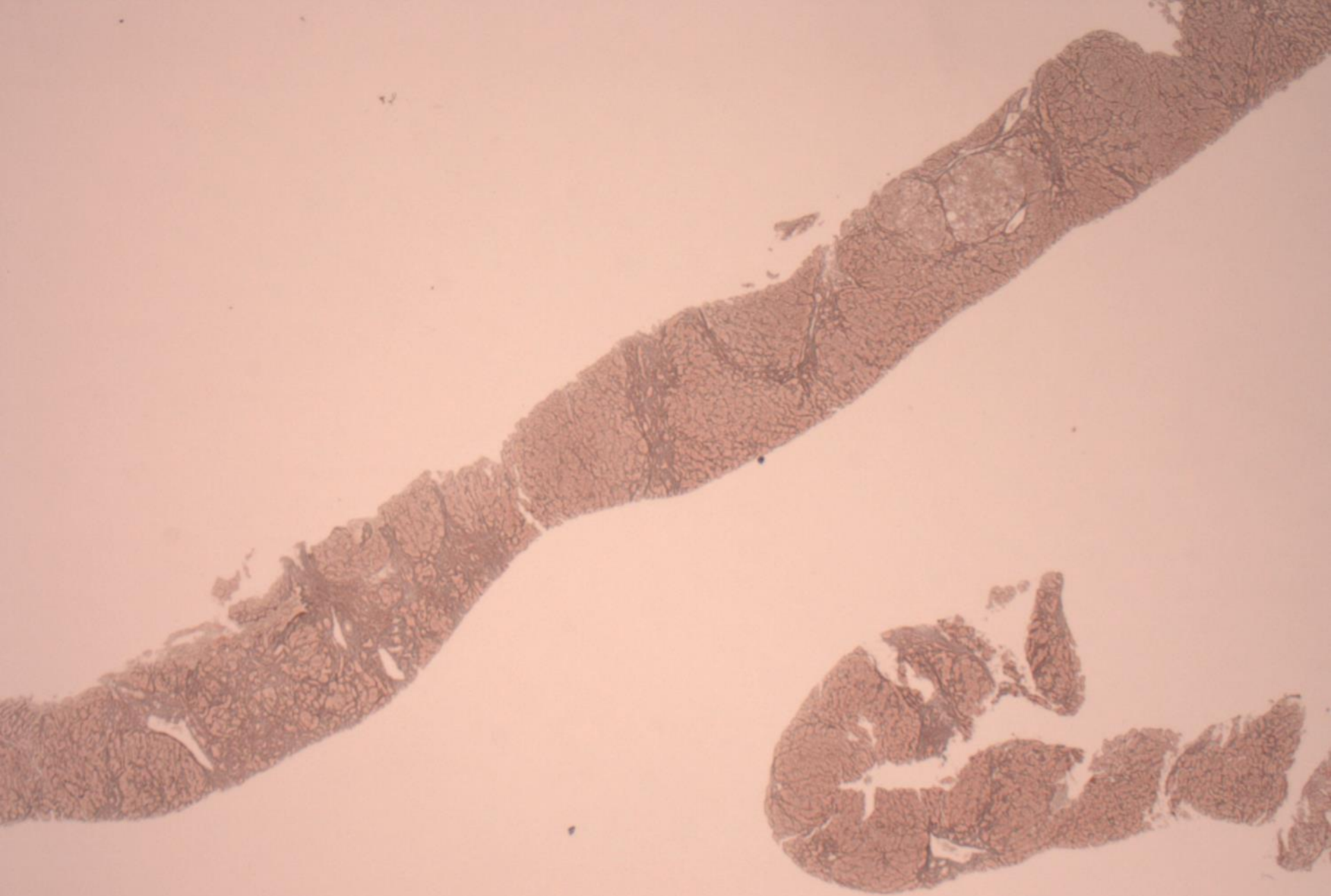
Liver tests

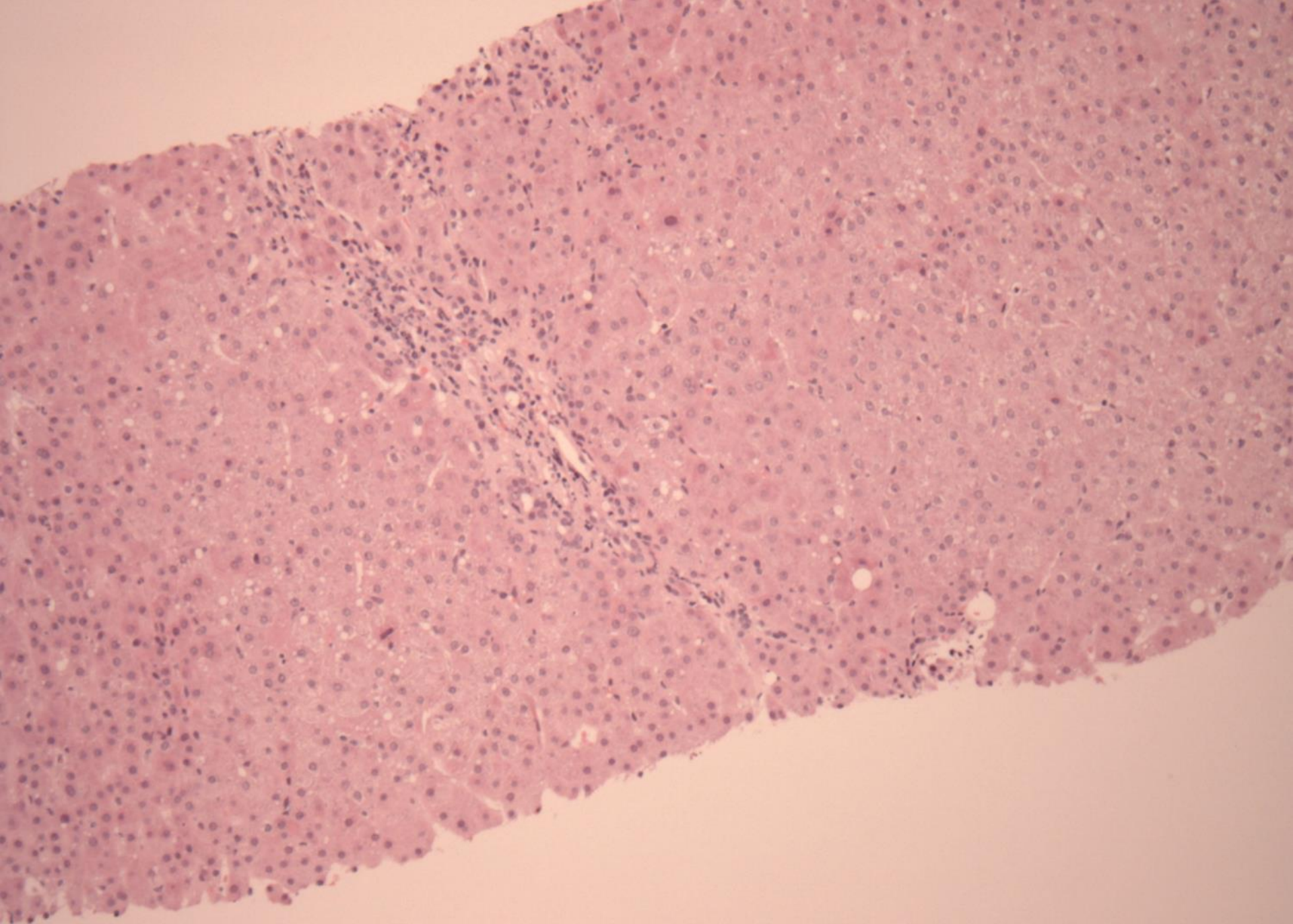


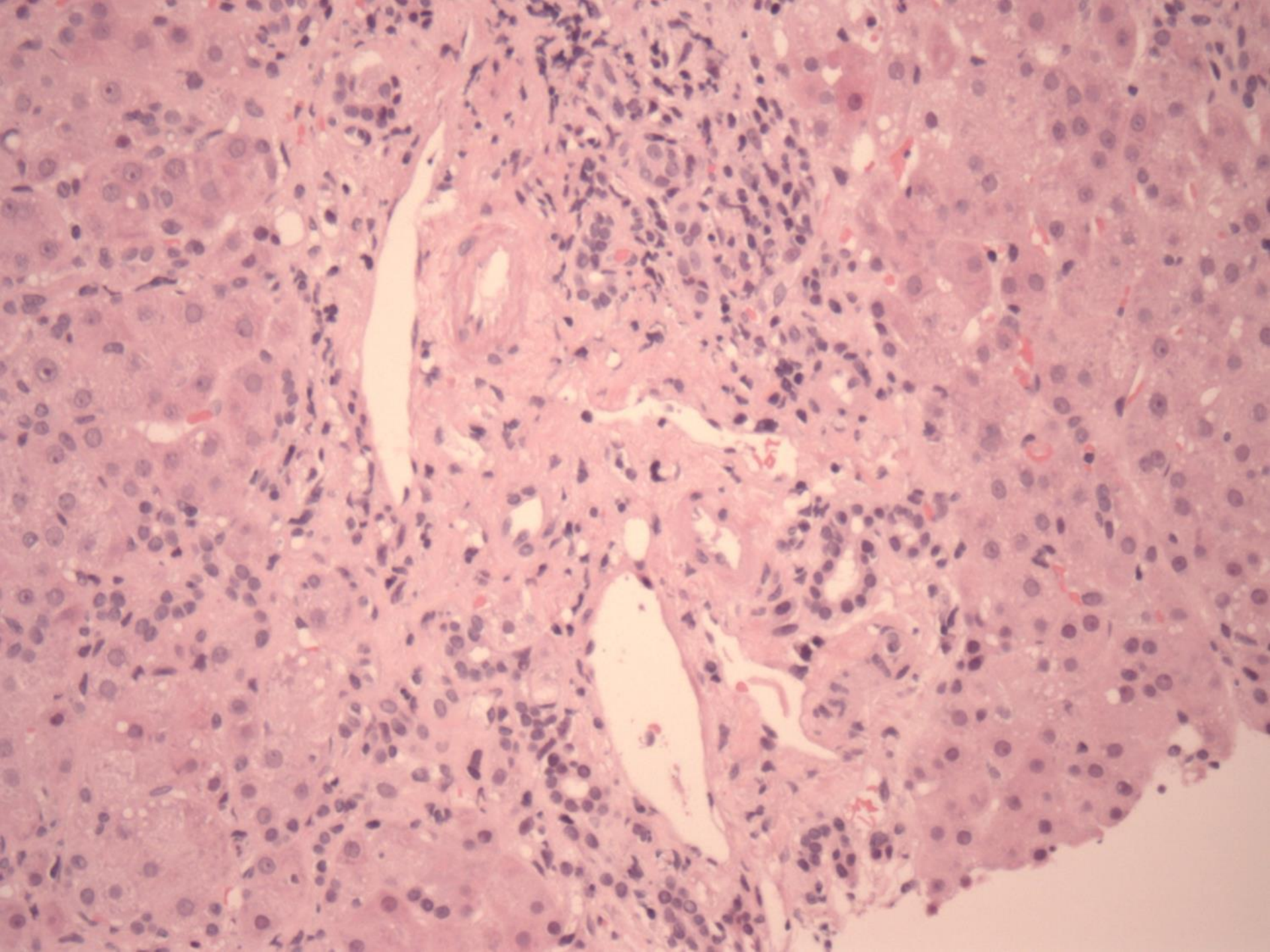
- May 2017: admitted with ascites, peripheral oedema
- Liver screening tests negative
- Hepatitis E antibody positive
- HEV pcr positive – retrospective positive too
- Mycophenolate stopped
- Liver biopsy- transjugular

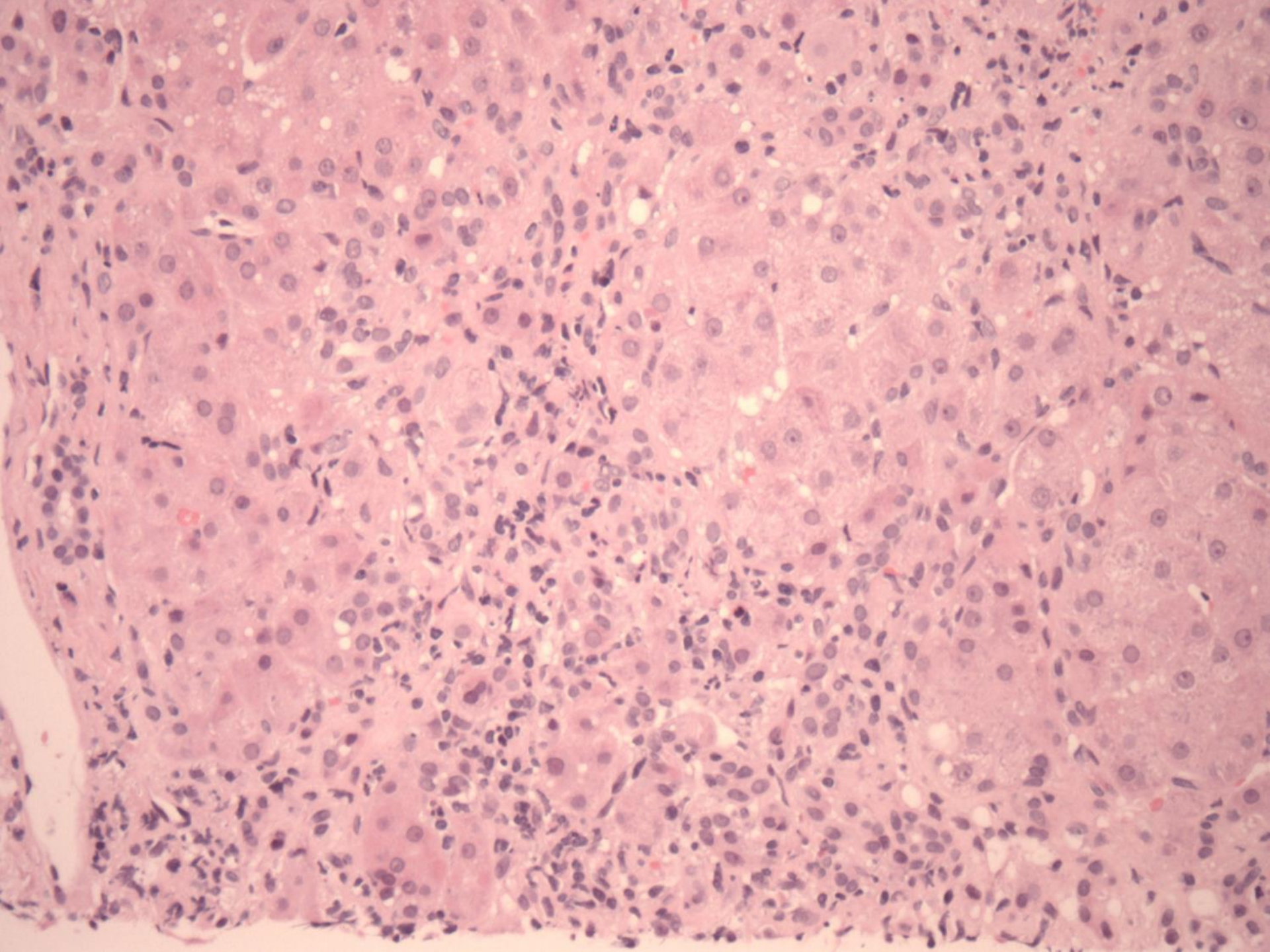


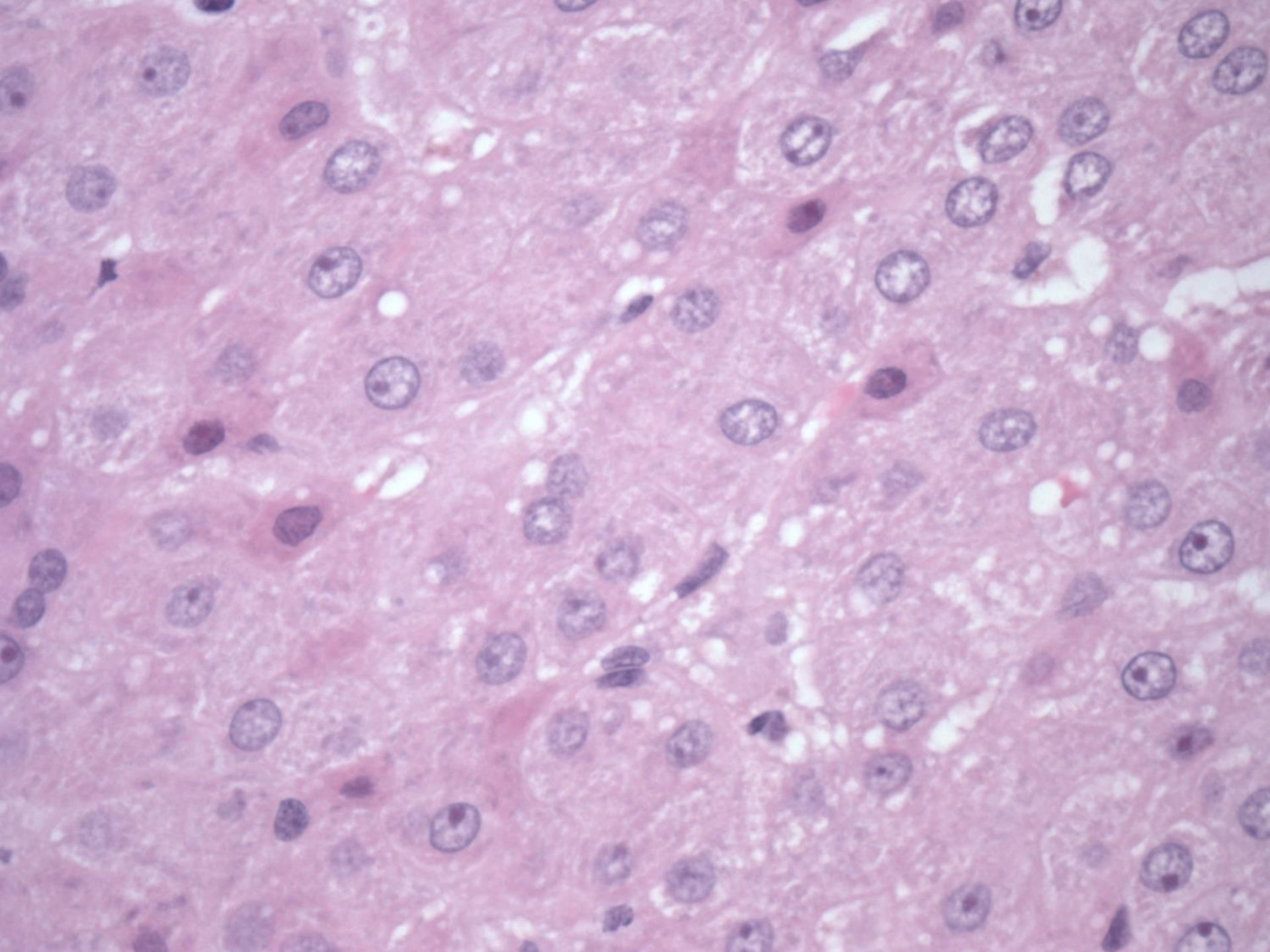












Biopsy findings

- Severe fibrosis & loss of vascular relationships
 - c/w cirrhosis
- Minimal lymphocytic hepatitis with hepatocyte single cell death
 - not diagnostic but c/w chronic HEV
 - no other disease pattern evident

Management

- Advagraf reduced to 1.5mg daily, pred 5 mg
- Commenced ribavirin 400mg bd
- ALT 32
- Repeated HEV RNA every 6 weeks
- 20.12.17 HEV RNA negative in blood
- 15.02.18 HEV RNA negative in blood and stool. Ribavirin stopped.

- June 2018 ALT increased to 268, Bili 30
HEV RNA positive again
Recommenced ribavirin
- Aug 18 ALT 13
- Sept 18 E. coli septicaemia- died

Chronic hepatitis E

- Solid organ transplantation
- Haematological malignancy Tamura2007, Tavitian2010
 - stem cell transplantation Peron2006
 - including reactivation
- Pauci-immune vasculitis
- SLE on treatment Grewal2014
- HIV with low CD4 count Dalton2009, Kaba2011
- CD4 T cell defect HonerZuSiederdisen2014

Geographic distribution of human cases of Hepatitis E

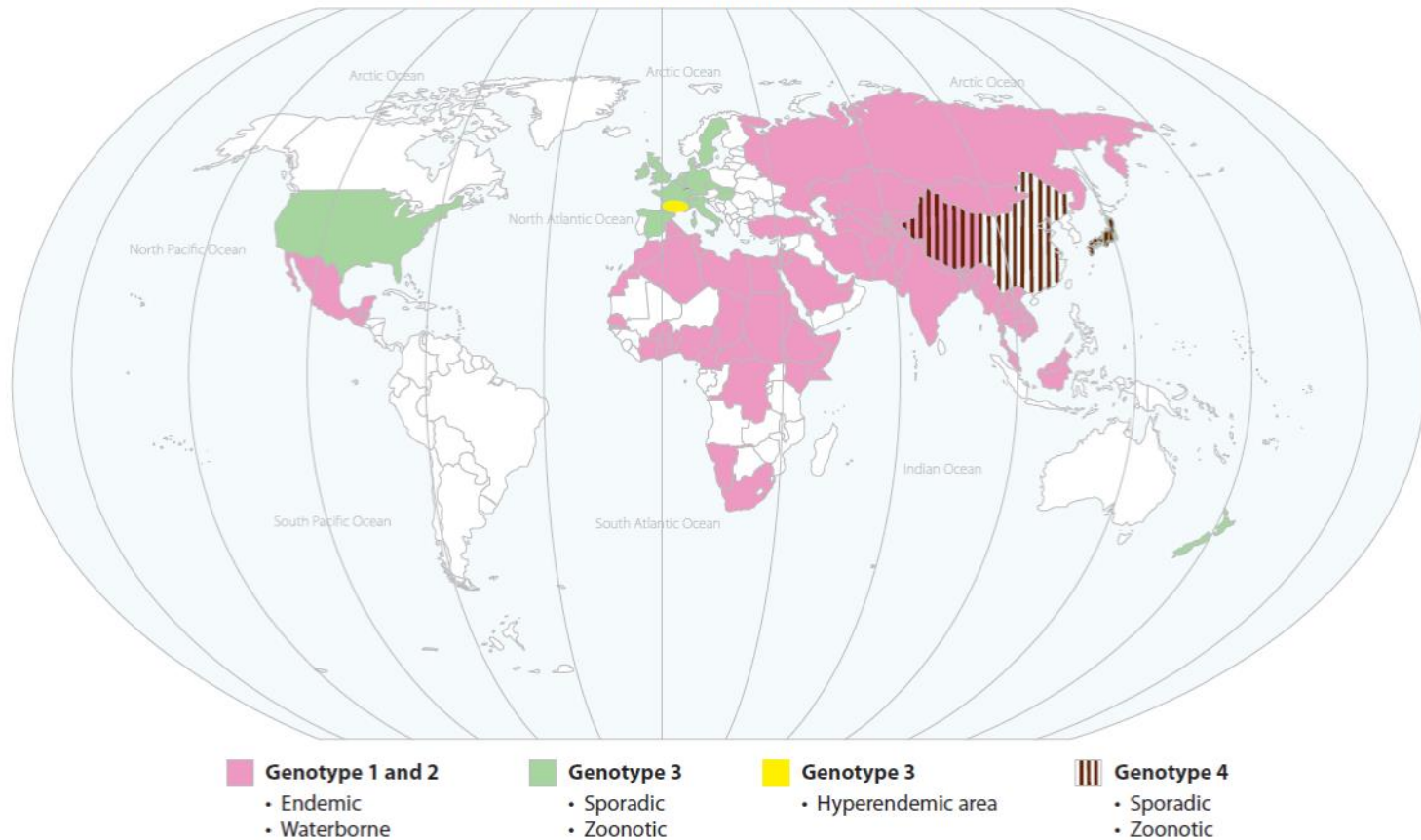
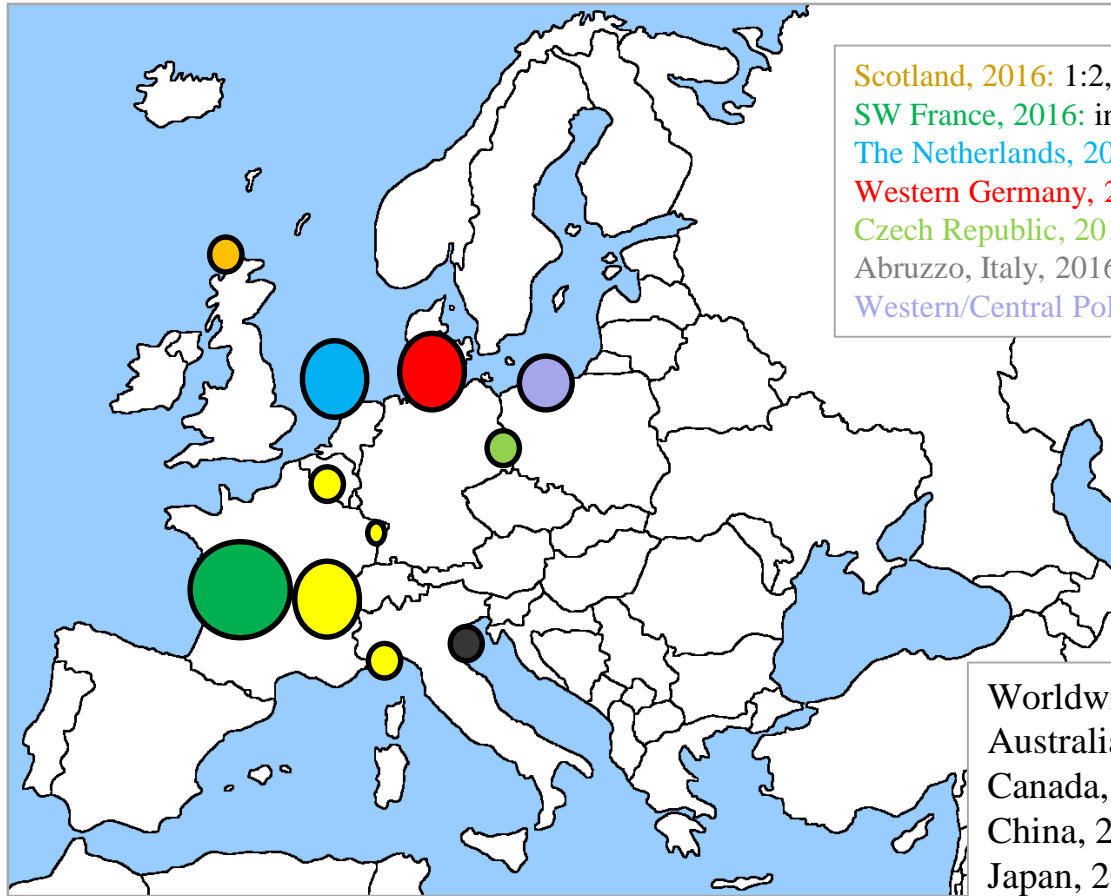


Fig. 1 Worldwide distribution of hepatitis E virus (HEV) by genotype. Areas left blank are those with no or little data. From Kamar *et al.* [3]. Copyright permission granted by Elsevier.



HEV ‘hot spots’ in Europe



Scotland, 2016: 1:2,481 donors viraemic¹
SW France, 2016: incidence 3–4%²
The Netherlands, 2014: 1:600 donors viraemic³
Western Germany, 2015: 1:616 donors viraemic⁴
Czech Republic, 2015: 400 lab-confirmed cases⁵
Abruzzo, Italy, 2016: seroprevalence 49%⁶
Western/Central Poland, 2018: seroprevalence 50%⁷

Worldwide HEV viraemia in blood donors
Australia, 2015: 1:14,799–74,131^{8,9}
Canada, 2017: 1:13,993¹⁰
China, 2016: 1:1,000¹¹
Japan, 2011: 1:8,173–15,075^{12,13}
USA, 2016: 1:9,500¹⁴

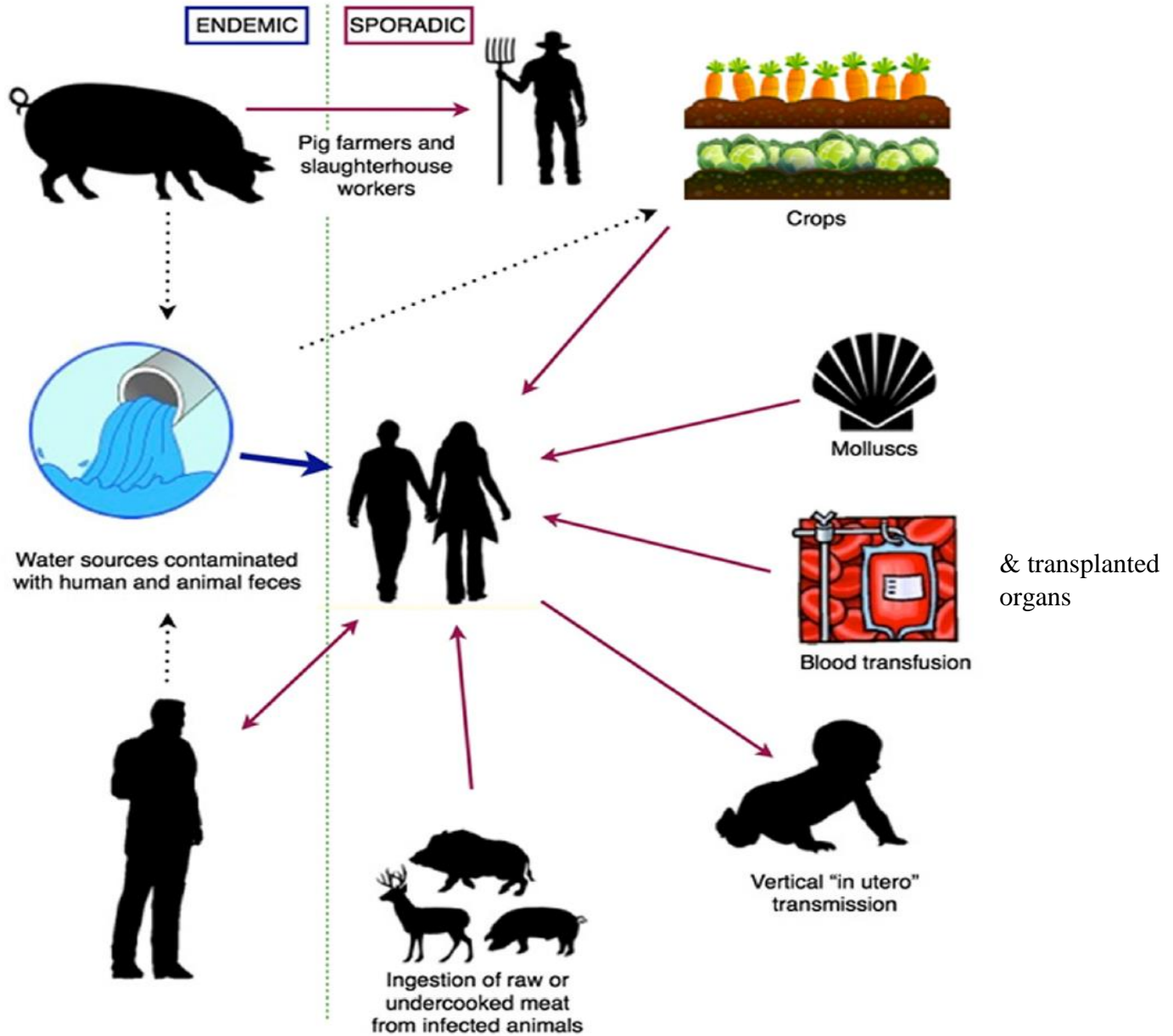


Fig. 5. Transmission routes of HEV.

TABLE 1 Epidemiology and clinical features of HEV infection in developing and developed countries

Feature	Description or value	
	HEV in developing countries	HEV in developed countries
Epidemiology		
Genotypes	1 and 2	3 and 4
Source of infection	Human	Zoonotic; pigs are primary host ^a
Route of infection	Fecal-oral via infected water	Fecal-oral via infected pig meat, direct exposure, infected water
Transfusion-related infection	Yes	Yes
Seroprevalence	Low in children of <15 yr, increases rapidly from ages 15 to 30 yr	Steady increase throughout age groups
Incidence	Variable: 64/1,000 patient-yr, Bangladesh	Variable: 3/100 patient-yr, South of France; 7/1,000 patient-yr, USA
Outbreaks	Yes; can involve thousands of cases	No; occasional small case clusters from a food point source
Attack rate	~1 in 2	67–98% of those infected are asymptomatic
Person-to-person spread	Very limited	No
Seasonality	Yes; outbreaks occur at times of flooding/monsoon	No
Disease in travelers returning from areas of endemicity	Well described	Is beginning to emerge as high-risk areas become defined
Clinical features		
Age at infection (yr)	15–30	>50
Sex (male/female ratio)	2:1	>3:1
Clinical course	Self-limiting hepatitis in most	Self-limiting hepatitis in most
Neurological complications	Yes	Yes
Deaths in pregnant females	Yes; 20–25% in final trimester ^b	No
Outcome in patients with underlying chronic liver disease	Poor	Poor
Chronic infection	No	Yes; genotype 3 only
Burden of disease	3.4 million cases/yr, 70,000 deaths, 3,000 stillbirths ^c	Unknown

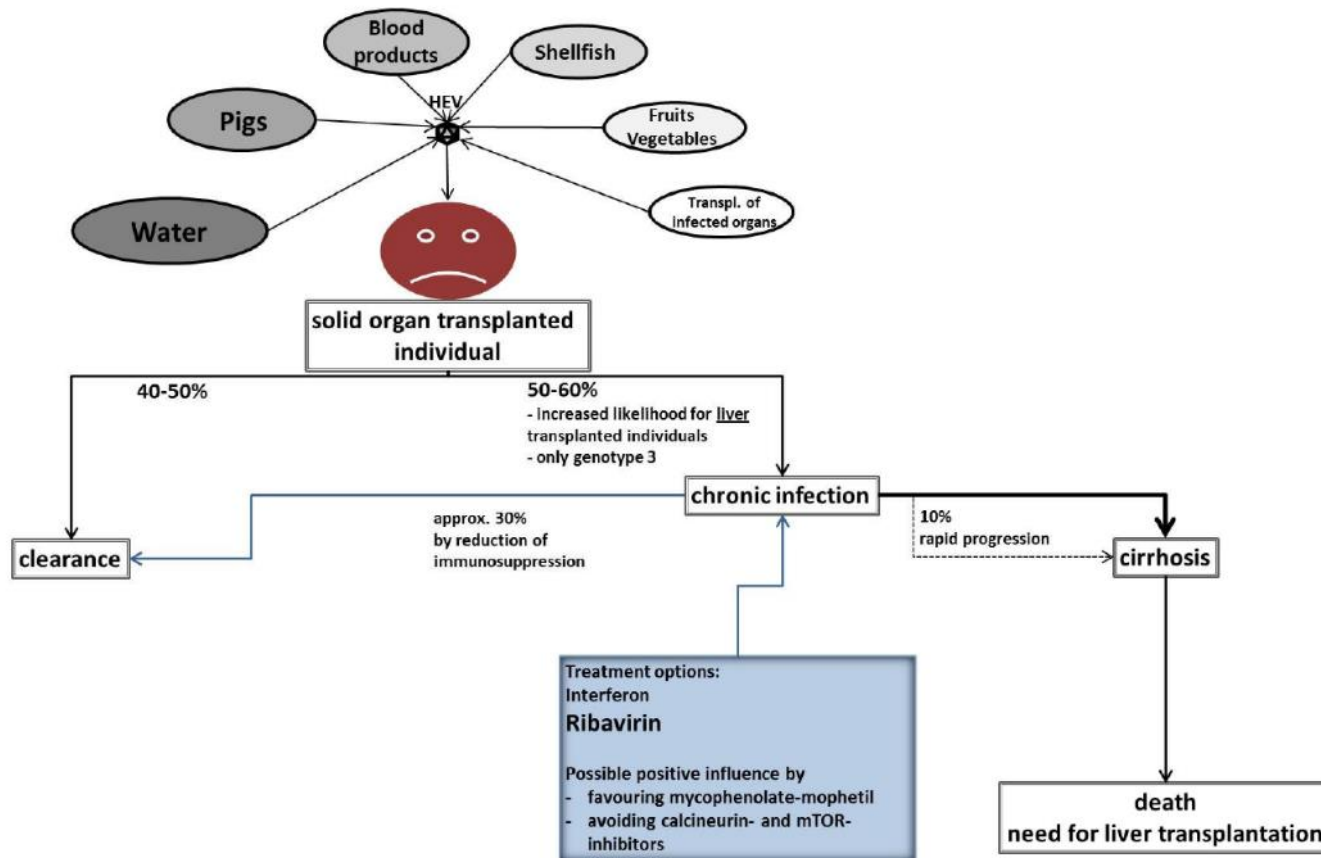
^a HEV genotypes 3 and 4 have also been transmitted from human to human via infected blood products.

^b The epidemiology and clinical course of HEV genotype 1 in Egypt are significantly different from those in other developing countries. In Egypt, the seroprevalence is similar to that of HAV, with nearly universal exposure in childhood, and the risks to pregnant females may be less. The reason for these observations is unknown.

^c Data are for 9 of 21 regions defined for the Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2010 Study), which represent 71% of the world's population.

Chronic HEV management

Fig 1



Case 3

- Dec 2015, GP referral to hepatology: HBsAg +
- March 2016 Clinic appointment
50 year-old male born in Vietnam
UK resident for 30 years
- No family history of hepatitis B
- Past history of treated pulmonary TB
- Ex-smoker, drinks 4 units per day
- 55 kg in weight

Investigations

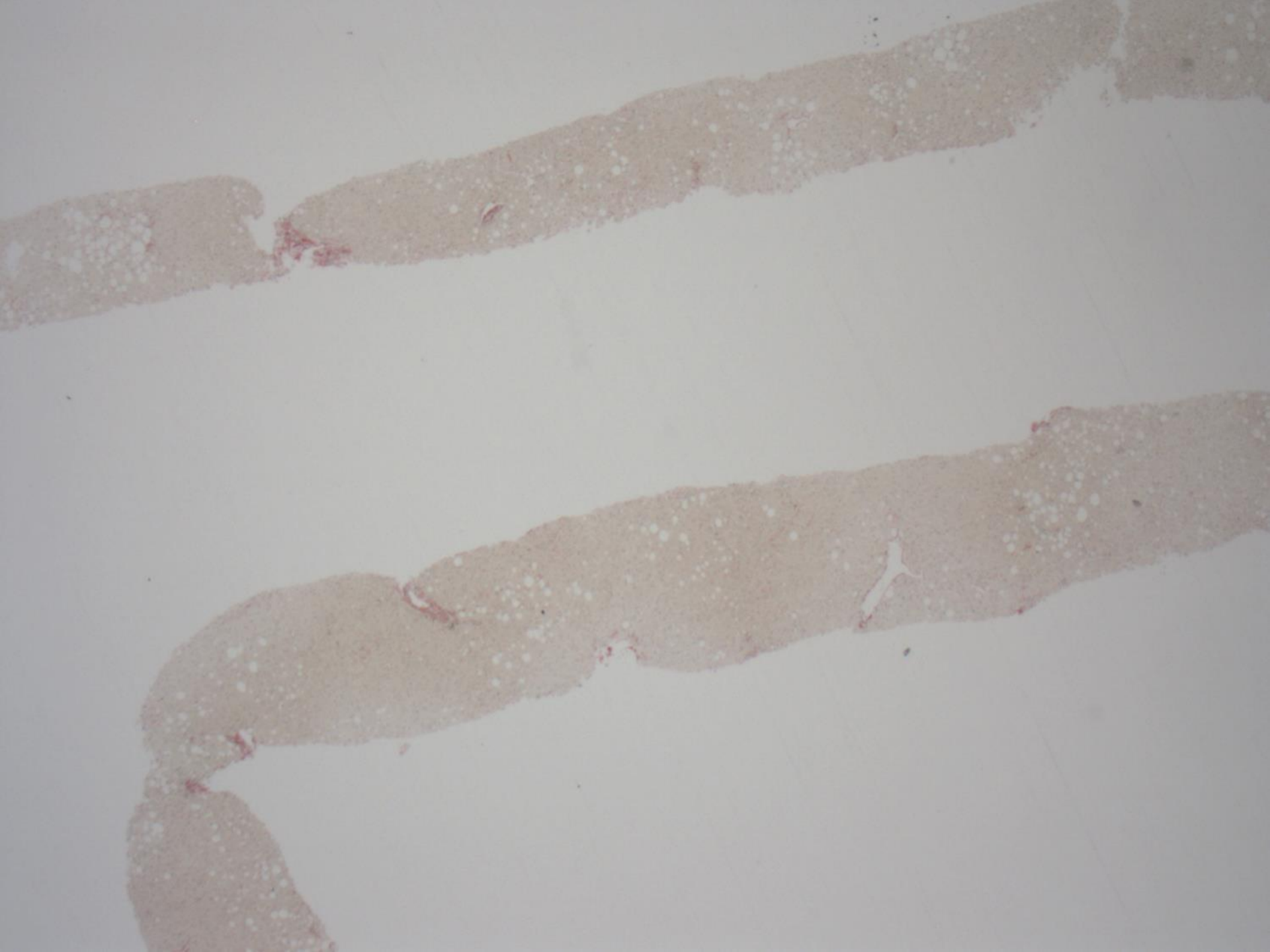
- HBeAg negative, anti-HBe positive
- ALT 64, GGT 404
- Ferritin 1071
- Autoantibodies negative
- HCV/HIV negative
- Hepatitis Delta negative
- Cholesterol 5.5 mmol/l

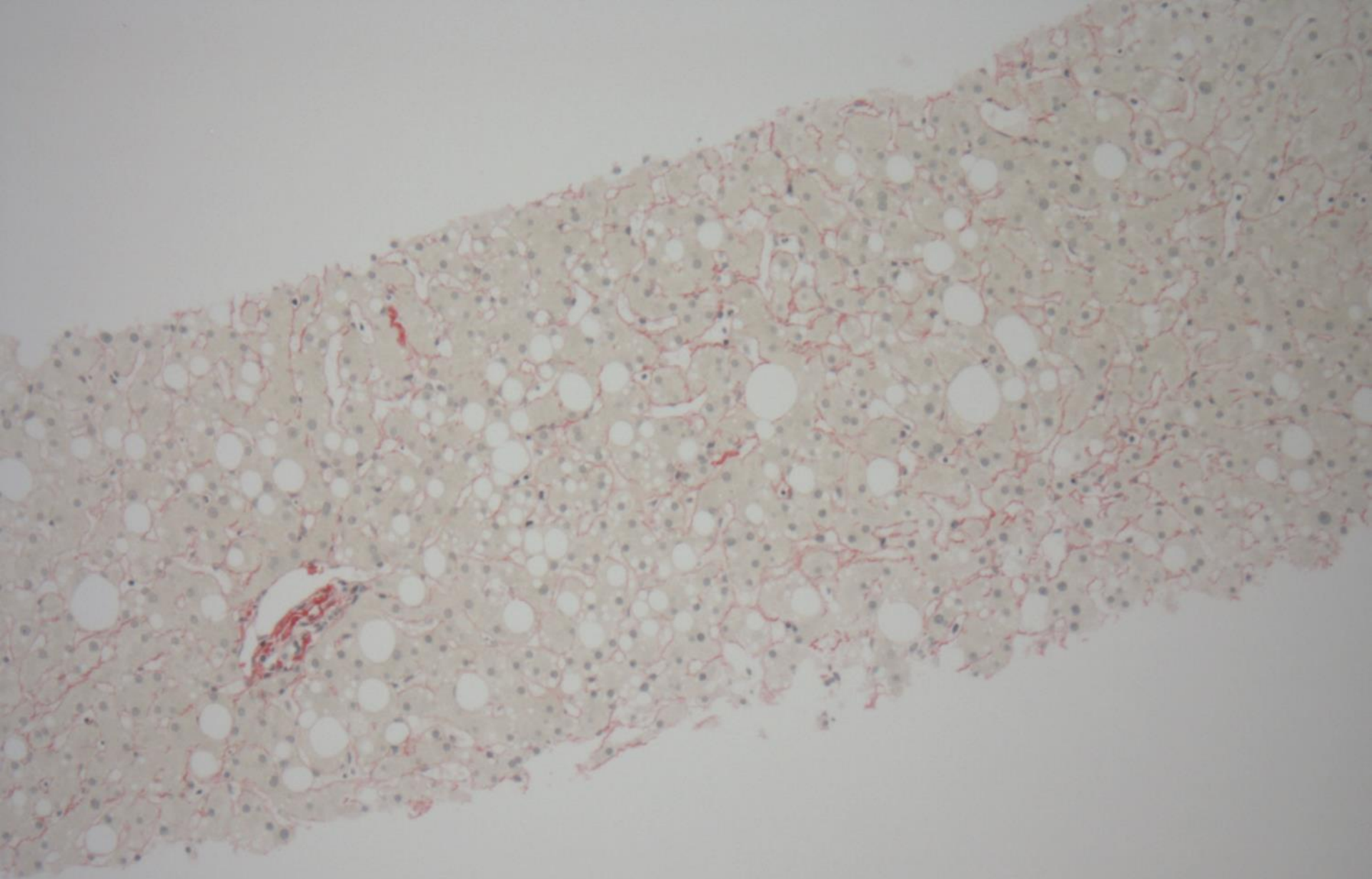
Further assessment

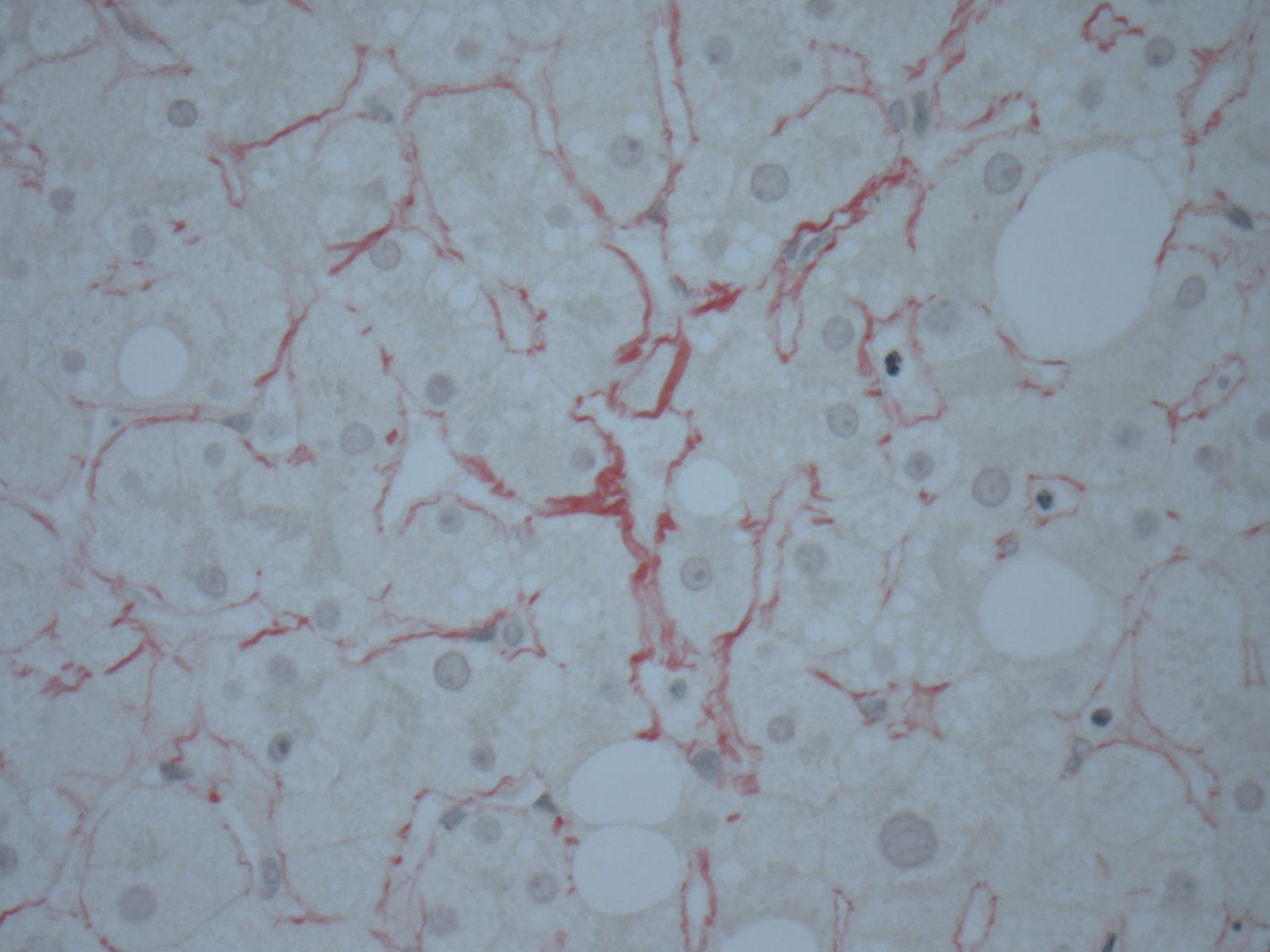
- HBV DNA 40,253 IU/l
- Hyaluronic acid 14.8 ng/l
- Liver stiffness 4 kPa (Fibroscan)

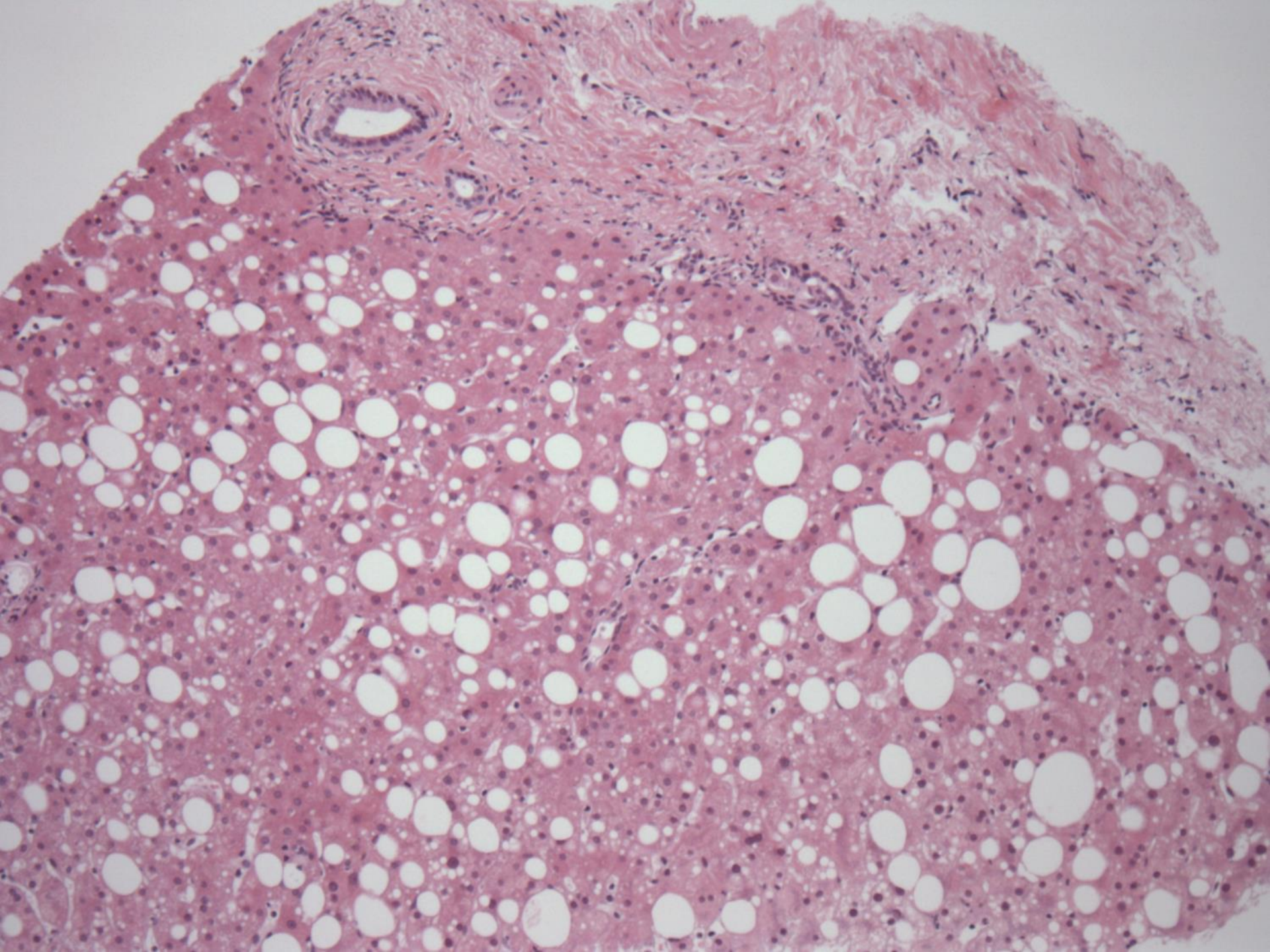
Follow-up

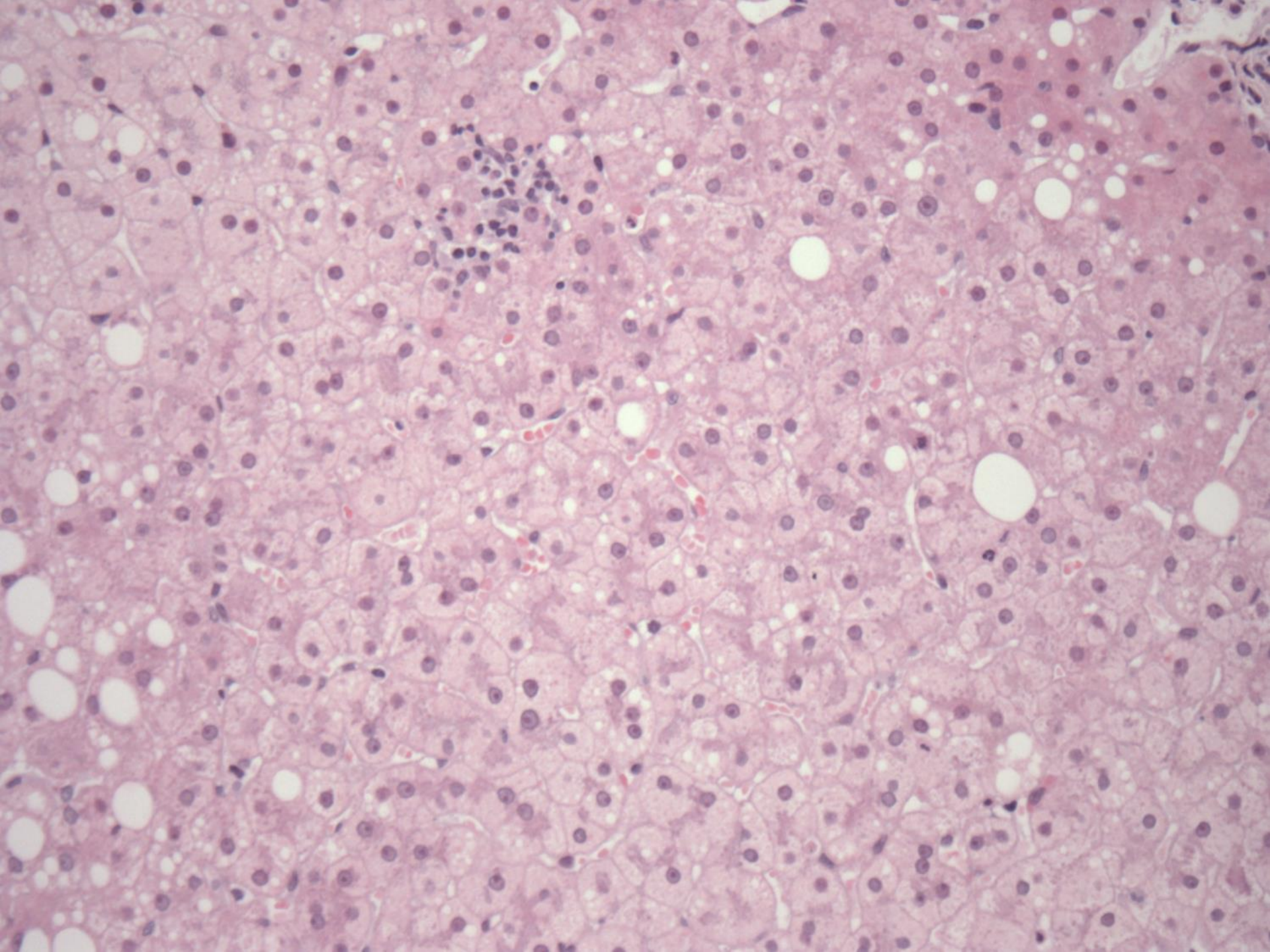
- June 2016 ALT 40 , γ GT 311
ferritin 617
HBV DNA 6,076 IU/l
- Sept 2016 ALT 45
HBV DNA 638
- Jan 2017 Liver biopsy- male over 50, ALT
around ULN variable viral load

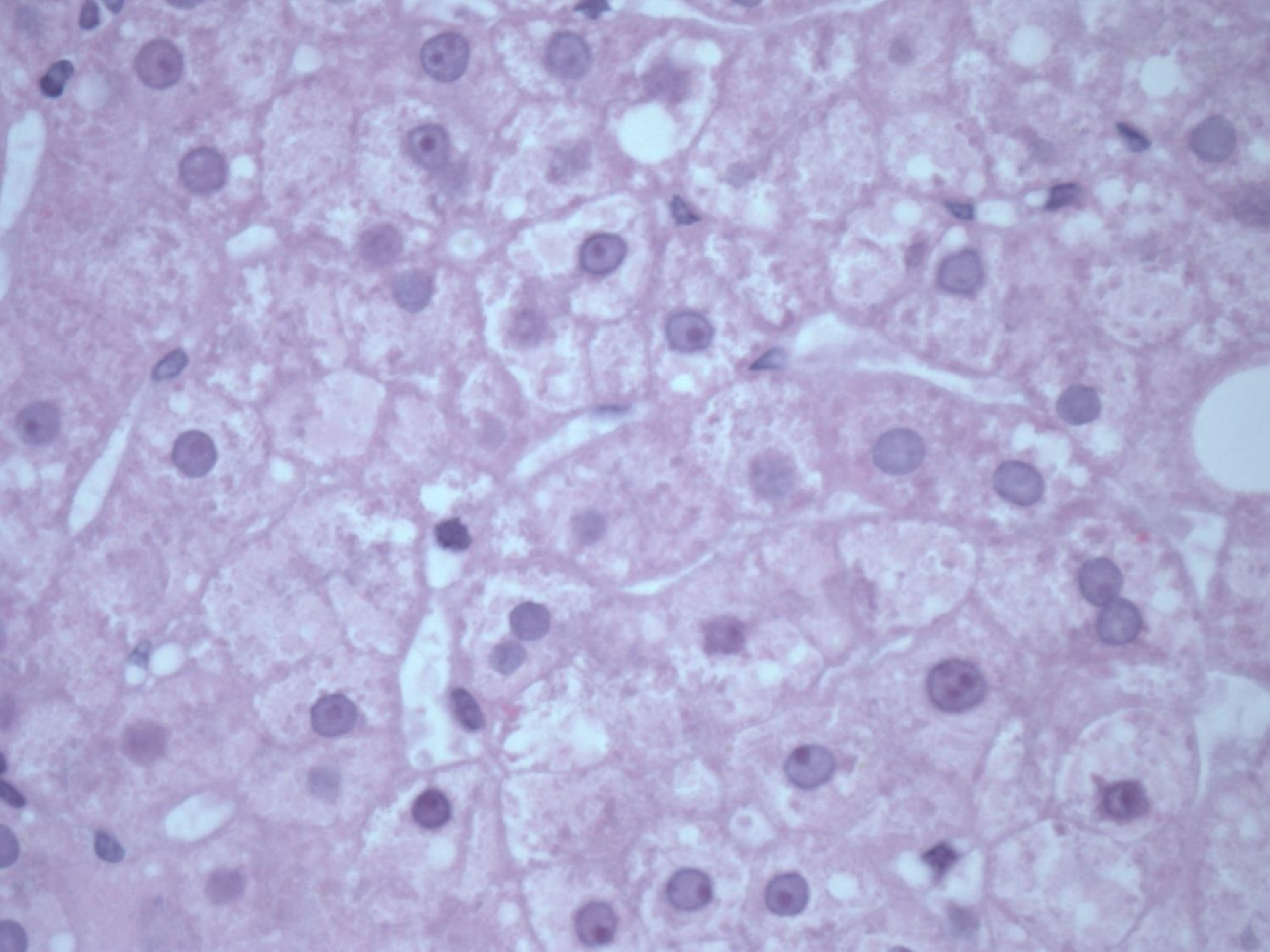


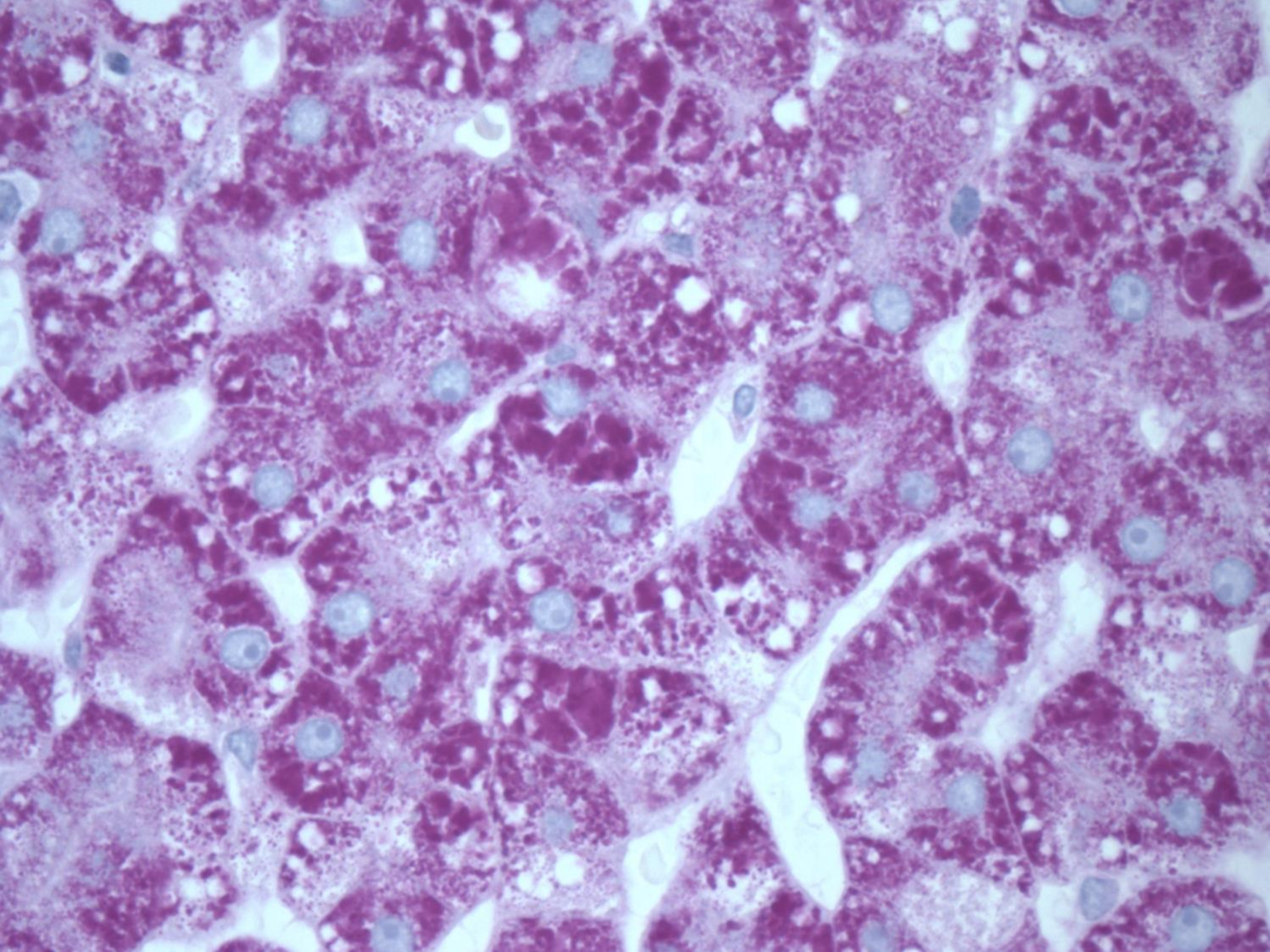


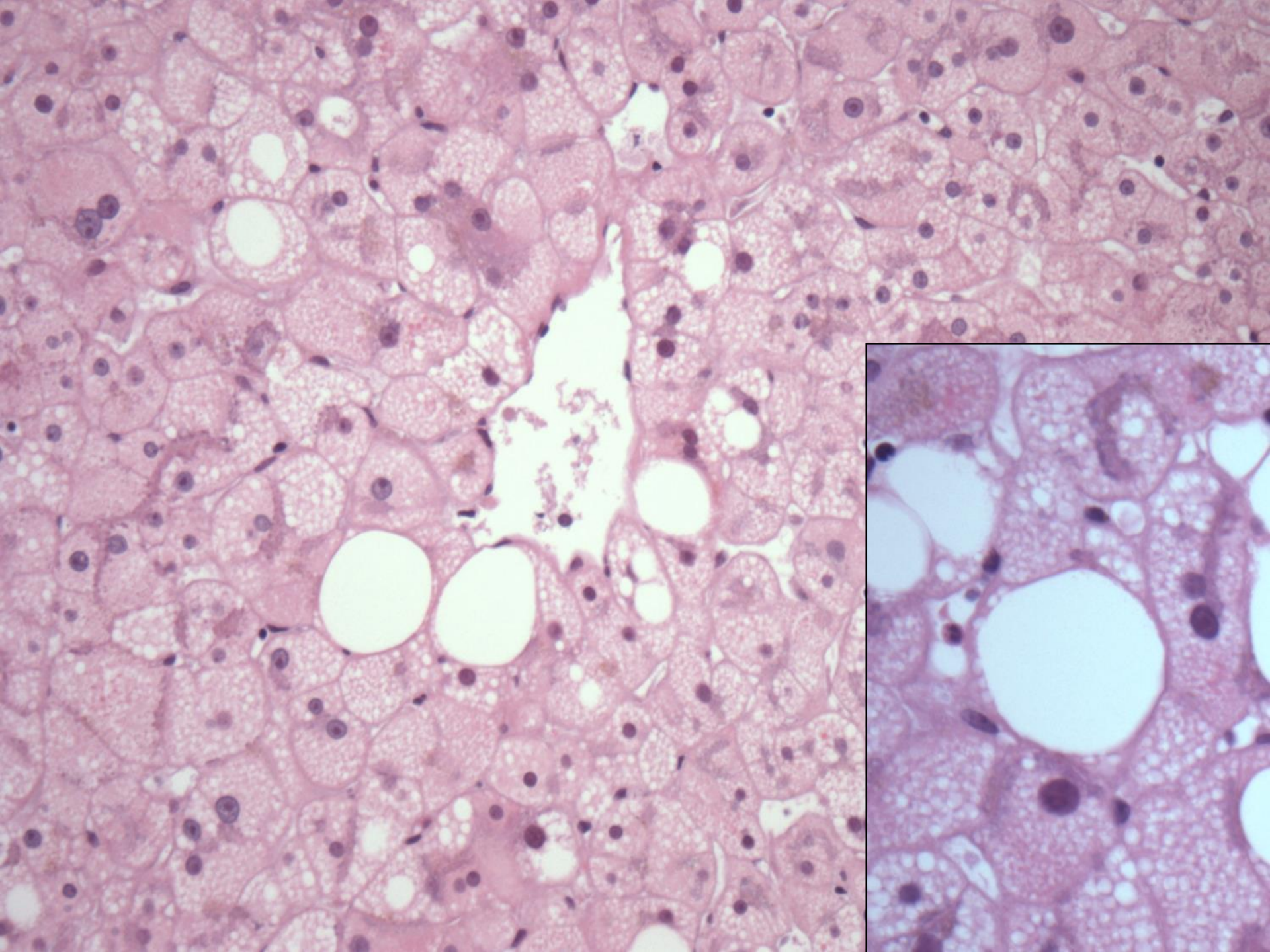


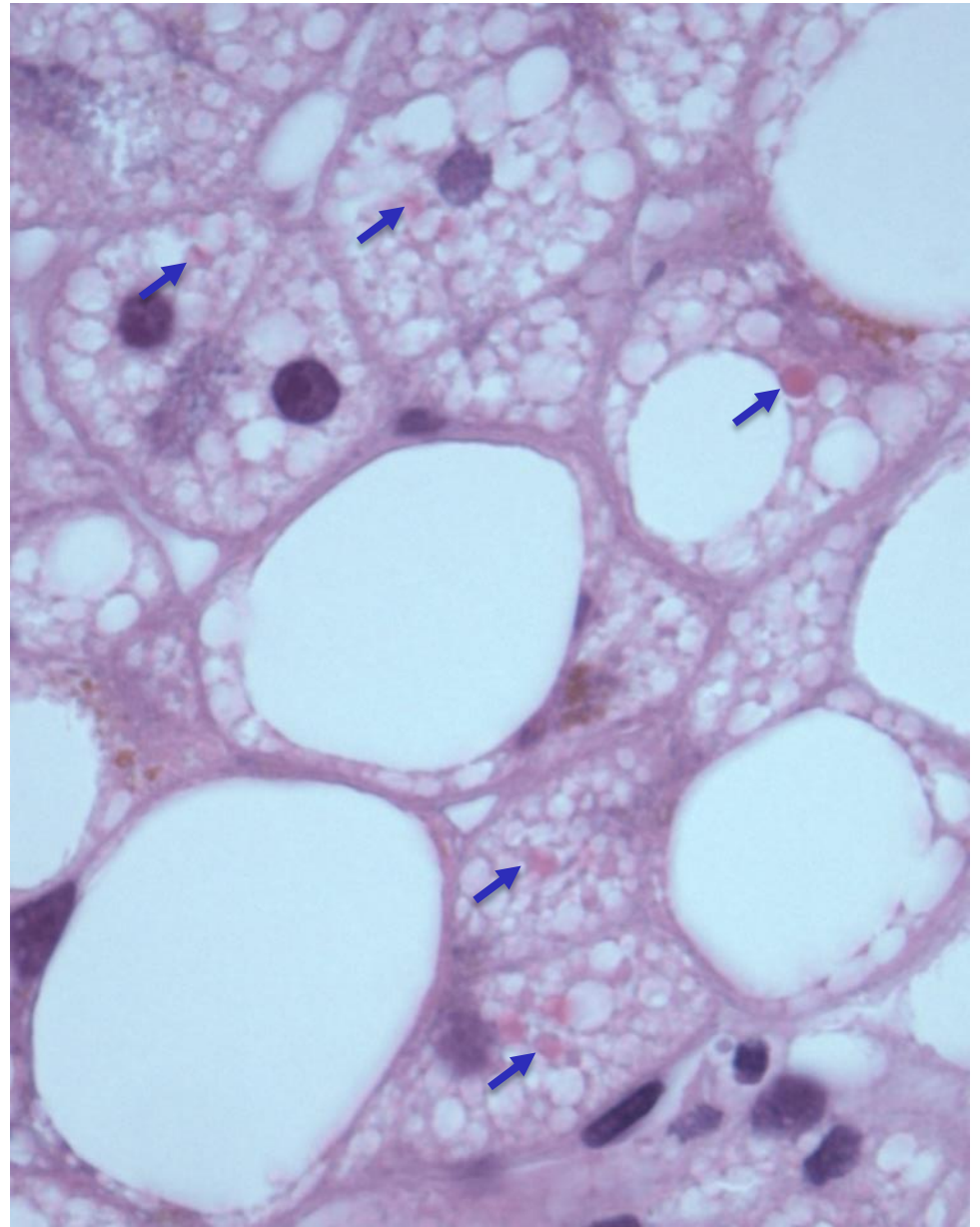
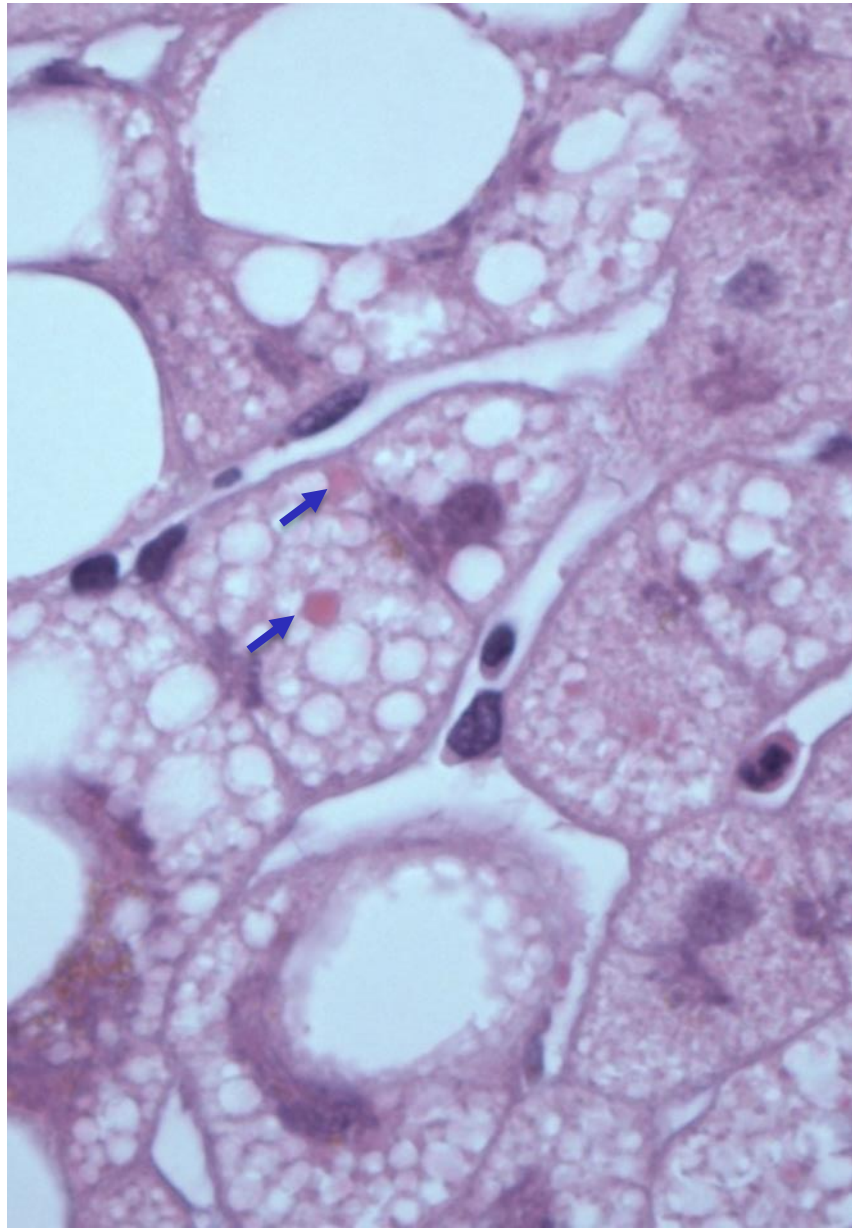


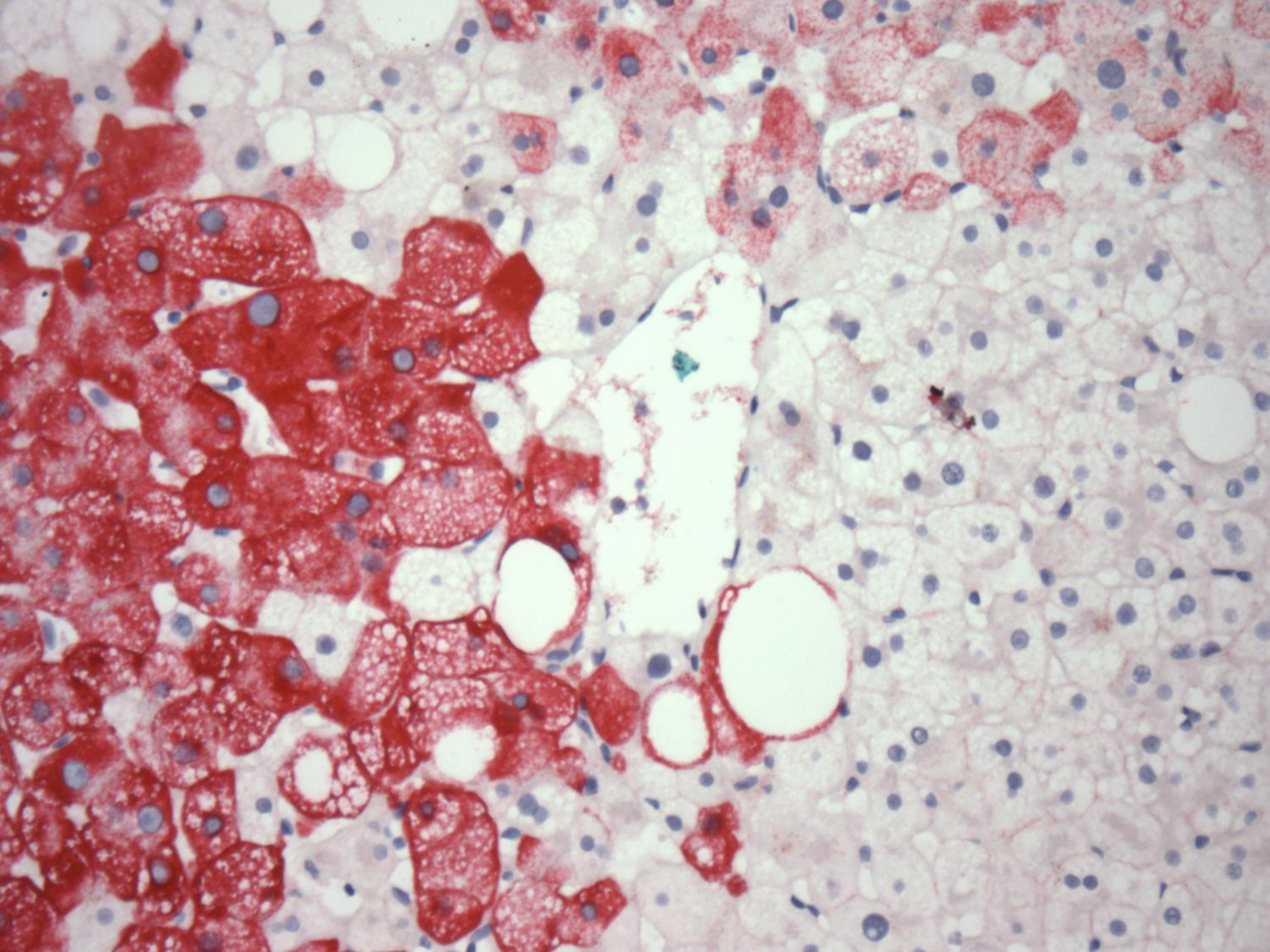


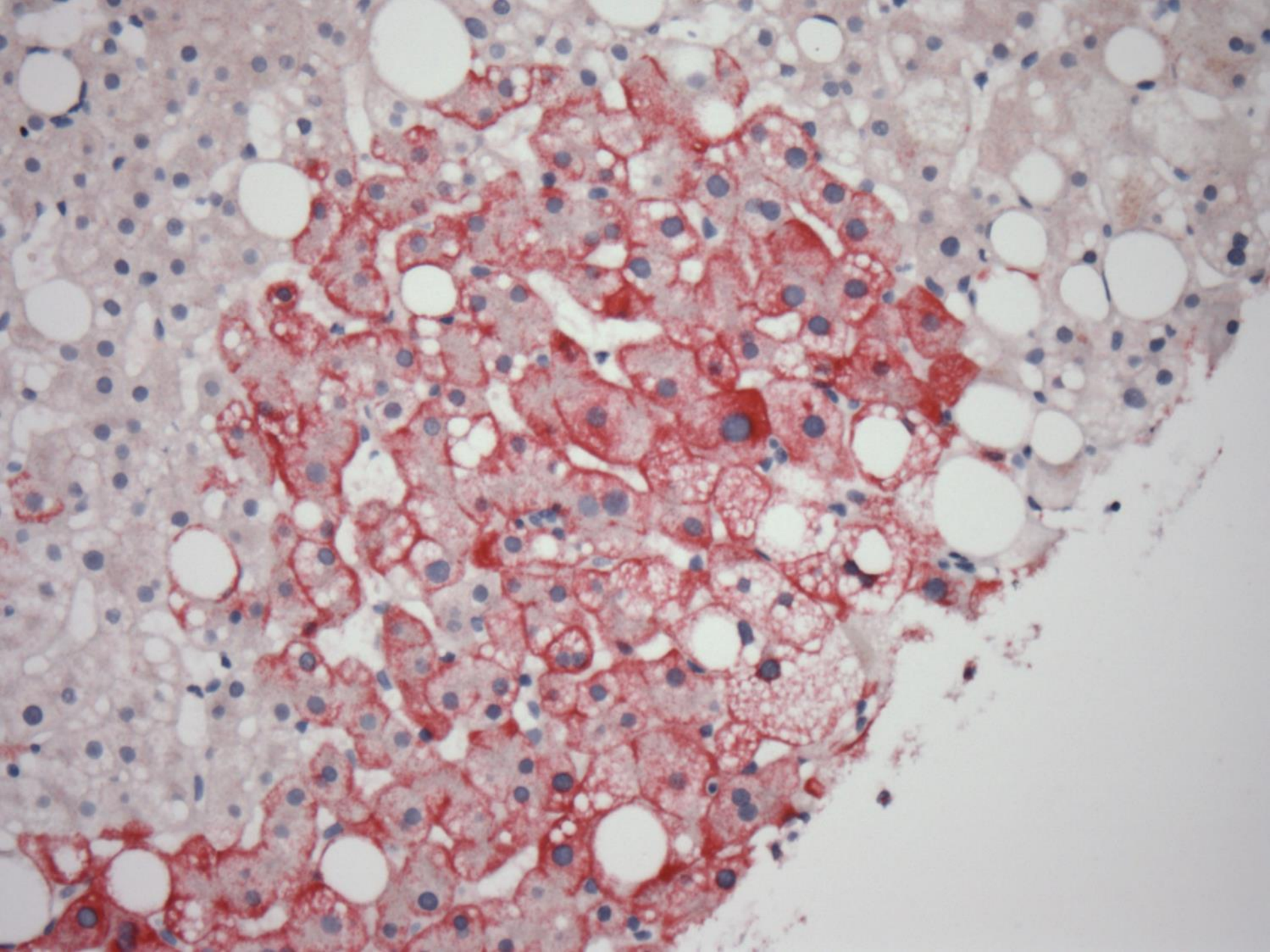












Biopsy findings

- No significant hepatitis or hepatitic fibrosis
 - Abundant HBV sAg+ hepatocytes (cAg-)
 - c/w HBeAg-negative chronic HBV infection
- Steatosis
 - macrovesicular (large, small droplet),
 - minimal peri-sinusoidal fibrosis
 - microvesicular with mega-mitochondria
 - c/w alcohol-associated foamy degeneration

Further management

- No indication to treat chronic HBV
- Advice – reduce alcohol, drink coffee
- Monitor –ALT, HBV DNA

- Fibroscan every 2 years
- No need for HCC surveillance

New nomenclature in chronic HBV

	HBeAg positive Chronic infection	HBeAg positive Chronic hepatitis	HBeAg negative Chronic infection	HBeAg negative Chronic hepatitis
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10E7 IU/mL	10E4-10E7 IU/mL	<2,000 IU/mL ^{°°}	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative Chronic hepatitis

*Persistently or intermittently

^{°°} HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis

When to treat: guidelines

- HBeAg +/-, with HBV DNA $> 2000\text{IU/ml}$, ALT $>\text{ULN}$ (40) and/or at least moderate liver necroinflammation/fibrosis.
- Cirrhosis with any detectable HBV DNA
- HBV DNA $>20,000$ and ALT $>2\text{x ULN}$
 - regardless of fibrosis
- HBeAg positive with persistently normal ALT may be treated if >30 years of age, regardless of fibrosis severity

Chronic HBV assessment

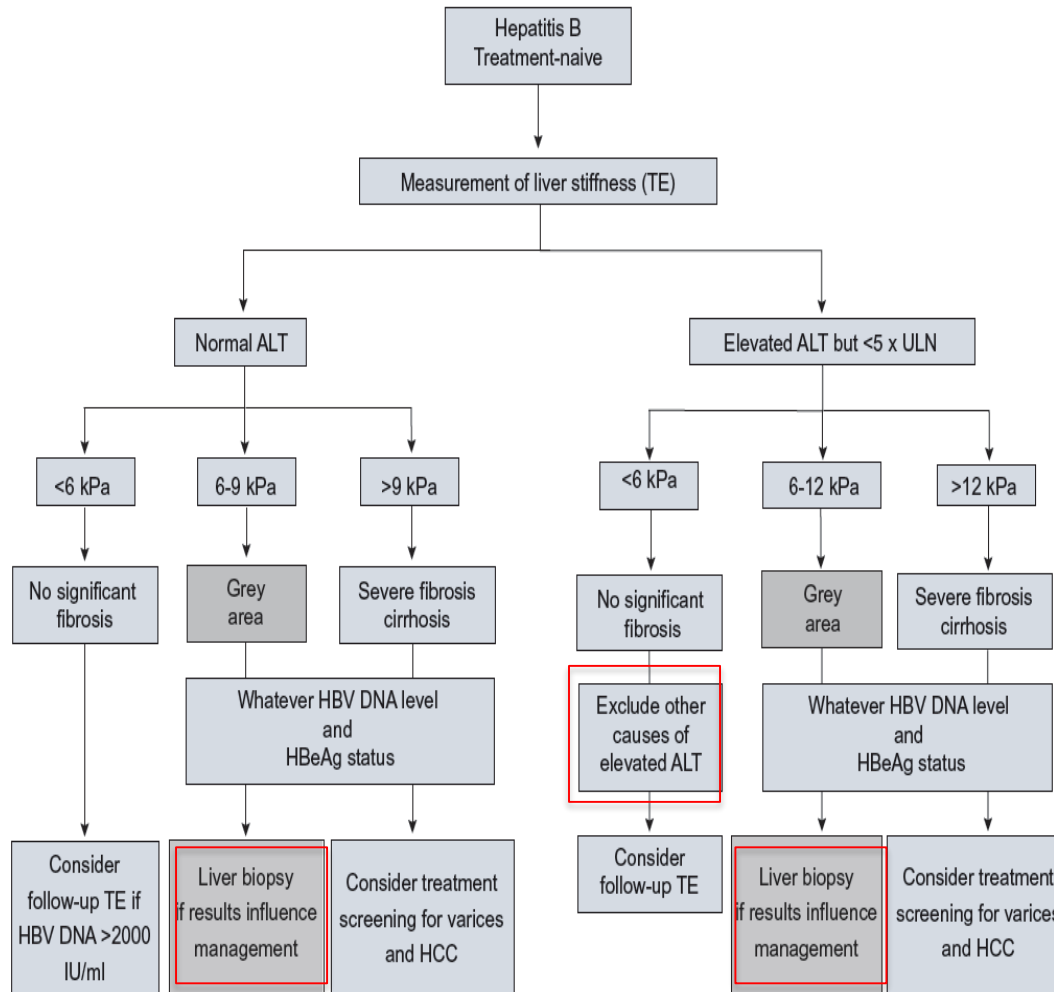


Fig. 2. Proposed algorithm for the use of transient elastography in treatment-naive patients with Hepatitis B.

Treatment options

- Pegylated interferon
 - defined duration for 48 weeks
 - stopping rules at 12 or 24 weeks depending on genotype, HBV DNA and HBsAg levels
- Oral antivirals- tenofovir disoproxil fumarate (TDF), entecavir (ETV) and tenofovir alafenamide (TAF)
 - no dose reduction unless CrCl <15
- Potent minimal (if any resistance)