DILI PATHOLOGY

PHILIP KAYE

November 2017

BSG Pathology
Winter Meeting

Outline

- General
- Mechanisms
- Role of Liver Biopsy
- Kleiner Categories
- Pathology!
- Differentials
- Severity
- Finally

Drugs and the liver

Drugs/Toxins may cause almost any pattern of liver injury

No pattern of liver injury is only caused by a drug

There are however some typical patterns

Clinical history, serology and course is paramount in ascribing aetiology

Common differentials:

AIH, LDO, Viral Hepatitis, Alcohol, NASH.

Mechanisms

- **Idiosyncratic**

Unpredictable Genetic predisposition

a) Hypersensitivity – fever, rash shortly after exposure

b) Metabolic/idiosyncratic - - latent period, no systemic features

- **Predictable - Direct toxicity or metabolites**

Substance directly injurious to liver

Genetic component sometimes operative

- **Consequences of Immunosuppression**

Infective and neoplastic

Role of Liver Biopsy

Not mandatory for diagnosis

May help confirm DILI

May provide pointers to consider DILI where DILI was not suspected clinically

Identifying underlying/coexistent liver disease

Identify prognostic features

Kleiner Categories

Pattern Name	Code	Abbreviated Description
Acute Hepatitic	1	Lobular predominant inflammation and apoptosis with lobular disarray in more severe cases. Areas of confluent necrosis allowed. If visible cholestasis present, case was classified as “Cholestatic-Hepatitic”.
Chronic Hepatitic	2	Portal predominant inflammation with generally mild to moderate lobular inflammation. Fibrosis not required. If visible cholestasis present, case was classified as “Cholestatic-Hepatitic”.
Acute Cholestatic	3	Hepatocellular or canalicular bile with little to no portal or lobular inflammation
Chronic Cholestatic	4	Definite cholatestasis or copper accumulation associated with a chronic hepatitic pattern of inflammation and bile duct injury or loss
Cholestatic-Hepatitic	5	Combination pattern with visible hepatocellular or canalicular bile (any degree) with inflammation that was more than minimal. Bile duct injury or loss could be present, but chronic cholestatic changes not yet seen.
Granulomatous	6	Inflammation dominated by non-necrotizing epithelioid granulomas
Macrovesicular Steatotic	7	Moderate to marked macrovesicular steatosis without significant inflammation, cholestasis or features that would allow classification into a separate pattern. Steatosis was a frequent finding in other patterns of injury and did not alter the classification
Microvesicular Steatotic	8	Diffuse microvesicular steatosis as the dominant histological finding
Steatohepatitic	9	Steatohepatitis without other injury types, such as cholestasis, vascular injury or necrosis.
Zonal necrosis	10	Zonal (usually zone 3 predominant) confluent or coagulative necrosis, without significant inflammation that would suggest an acute hepatitis or chronic hepatitis pattern
Non-zonal necrosis	11	Irregular (but not massive) areas of confluent or coagulative necrosis.
Vascular Injury	12	Any vascular injury except NRH, including sinusoidal obstruction syndrome, pure sinusoidal dilation, hepatoportal sclerosis, as long as the vascular injury was the dominant injury.
Hepatocellular Alteration	13	Diffuse hepatocellular cytoplasmic change without other significant findings, e.g. glycogenosis or ground glass cell changes
Nodular Regenerative Hyperplasia (NRH)	14	NRH without significant inflammation or any visible cholestasis
Mixed or Unclassifiable Injury	15	A combination of more than one major pattern, such as steatohepatitis with cholestasis
Minimal non-specific changes	16	Typically minimal inflammation or steatosis, not classifiable into another pattern
Absolutely normal	17	No histological changes from normal
Massive necrosis	18	Extensive (or complete) confluent necrosis in which the remaining hepatic parenchyma (if any) does not show changes that can be classified as another pattern

Common Patterns

Pattern Name	Code	Abbreviated Description
Acute Hepatitic	1	Lobular predominant inflammation and apoptosis with lobular disarray in more severe cases. Areas of confluent necrosis allowed. If visible cholestasis present, case was classified as “Cholestatic-Hepatitic”.
Chronic Hepatitic	2	Portal predominant inflammation with generally mild to moderate lobular inflammation. Fibrosis not required. If visible cholestasis present, case was classified as “Cholestatic-Hepatitic”.
Acute Cholestatic	3	Hepatocellular or canalicular bile with little to no portal or lobular inflammation
Chronic Cholestatic	4	Definite cholatestasis or copper accumulation associated with a chronic hepatitic pattern of inflammation and bile duct injury or loss
Cholestatic-Hepatitic	5	Combination pattern with visible hepatocellular or canalicular bile (any degree) with inflammation that was more than minimal. Bile duct injury or loss could be present, but chronic cholestatic changes not yet seen.

Problems with this classification

- Too Many Categories
- Categories Overlap a lot
- Potential for confusion of clinical and histological terms

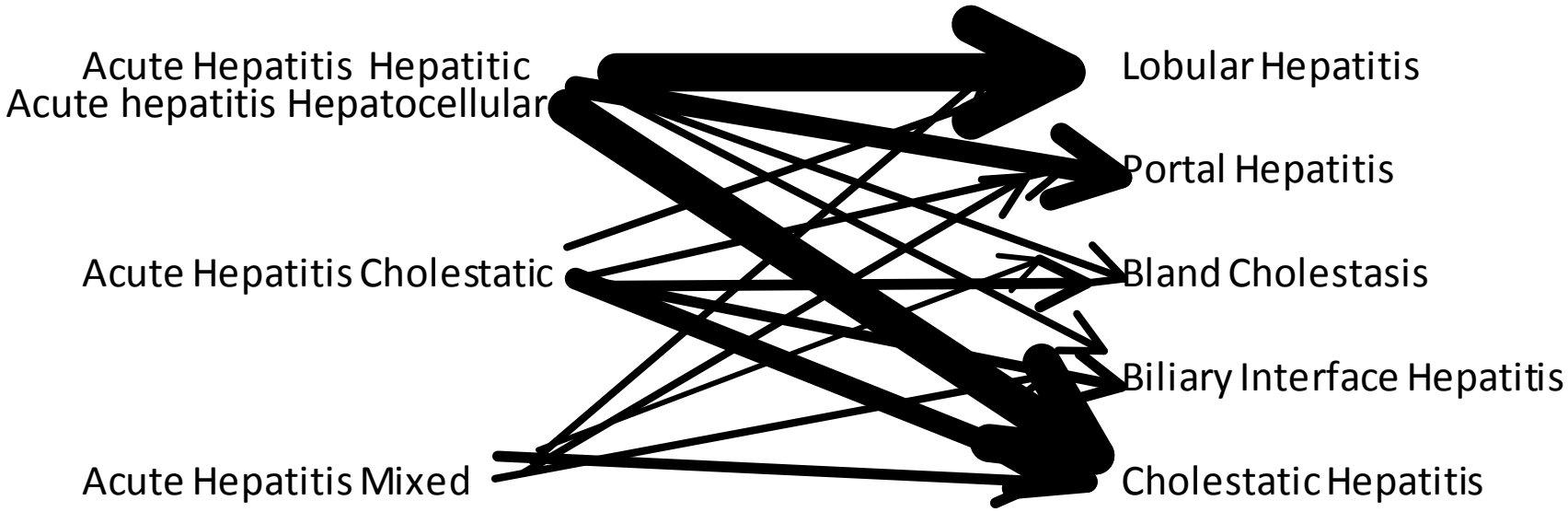
Specific Issues

1. Acute Hepatitis – Lobular Hepatitis may be better term for this
2. Chronic Hepatitis – A very confusing pathological term – should be replaced by Portal hepatitis
3. Acute Cholestatic – should be replaced by what we see, not infer – Bland cholestasis
4. Chronic cholestatic – timing again variable – ? Replace with eg Biliary interface hepatitis
5. Cholestatic Hepatitis – term is OK, but definition needs tightening up as intersects a lot with 1-3. How much cholestasis/inflammation do we need?

Additional Features

- Necrosis – Do we need 3 separate patterns – often seen as part of 1-5.
- Granulomas – frequently seen in 1-5– should this be separate pattern?
- Bile duct injury – in Kleiner's study, it was frequently seen in "acute hepatitis" and was not predictive – How do we define bile duct injury?

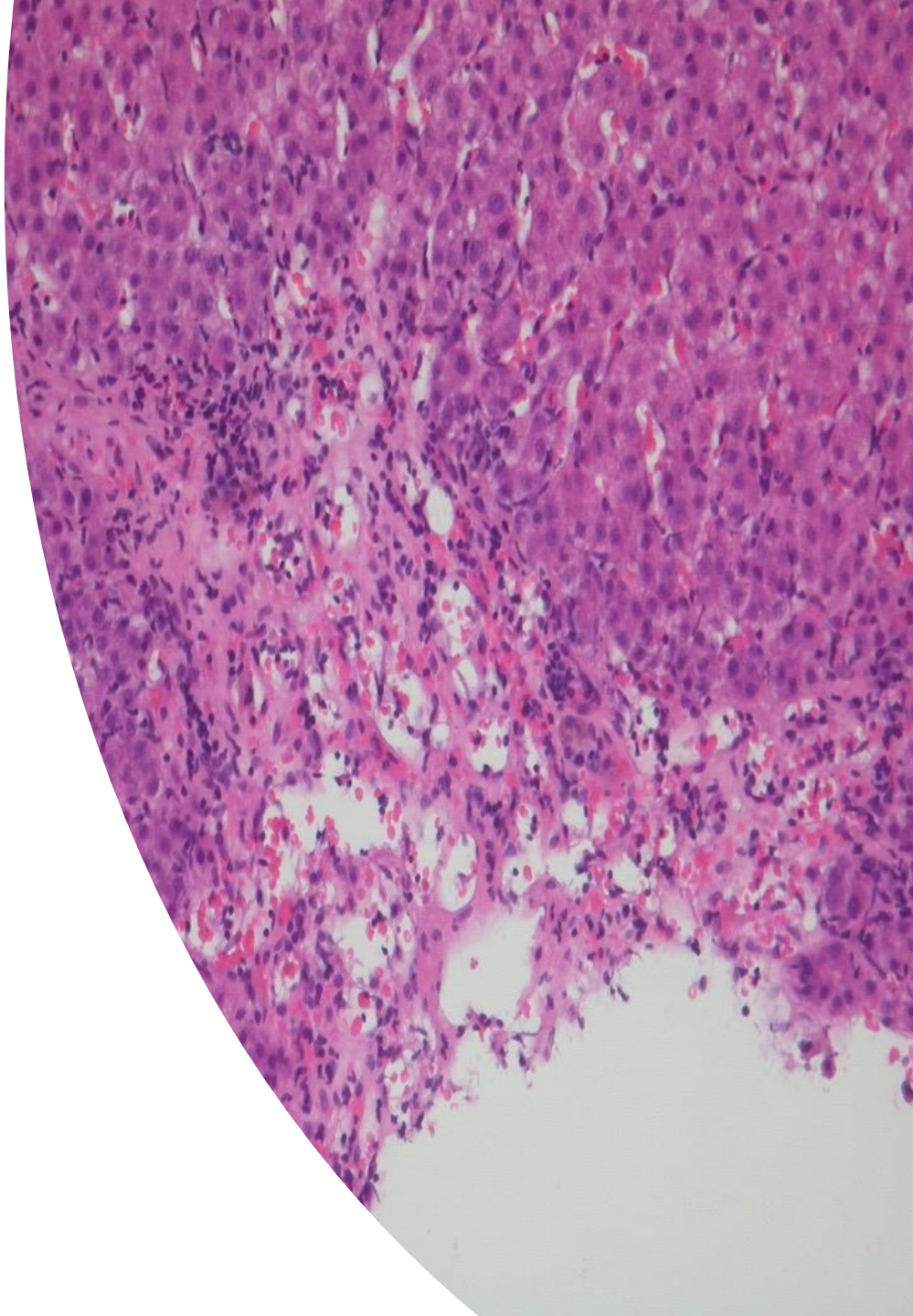
Diagram of clinical and pathological intersects in DILI

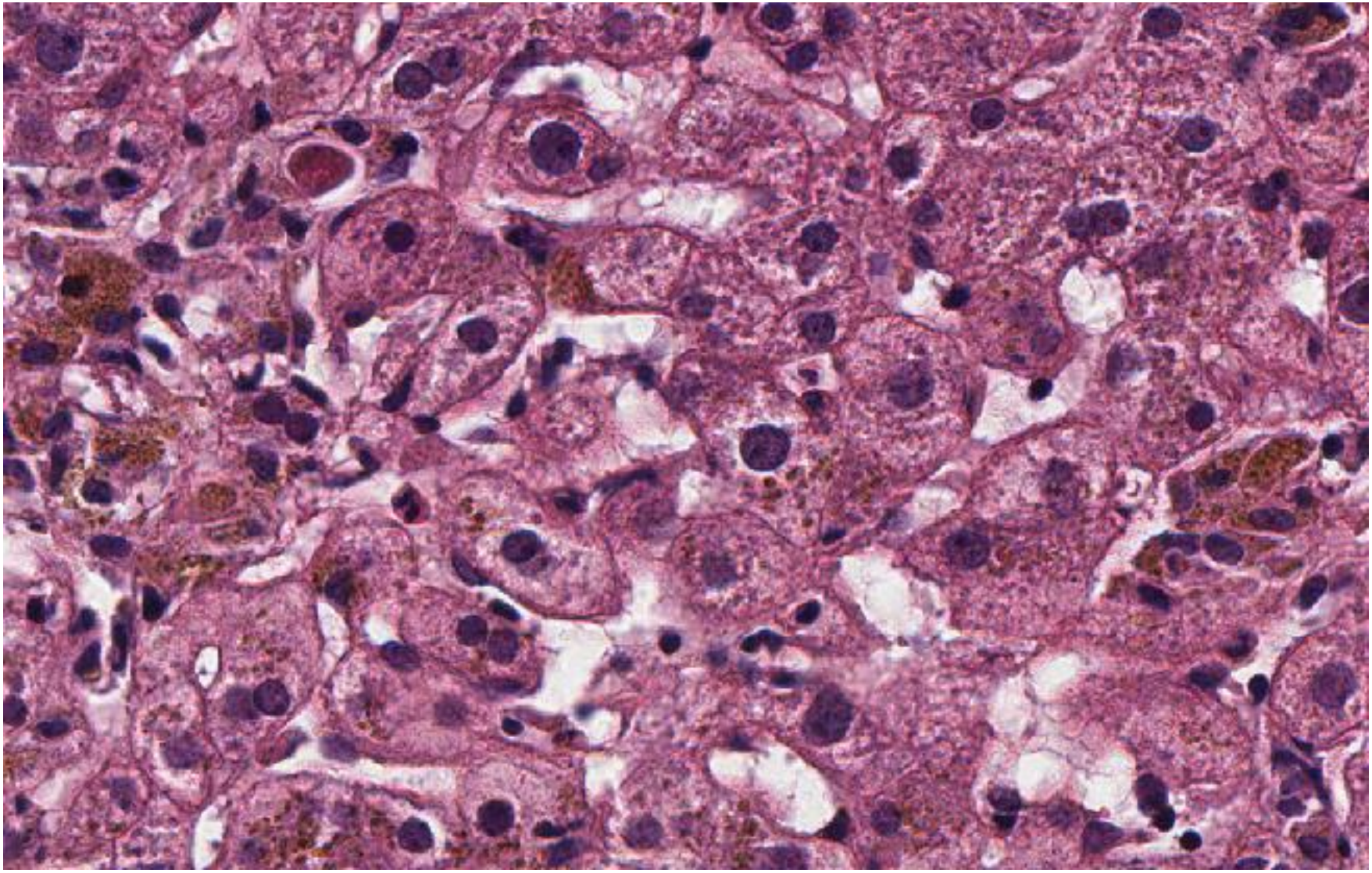


Lobular Hepatitis (Acute Hepatitis)

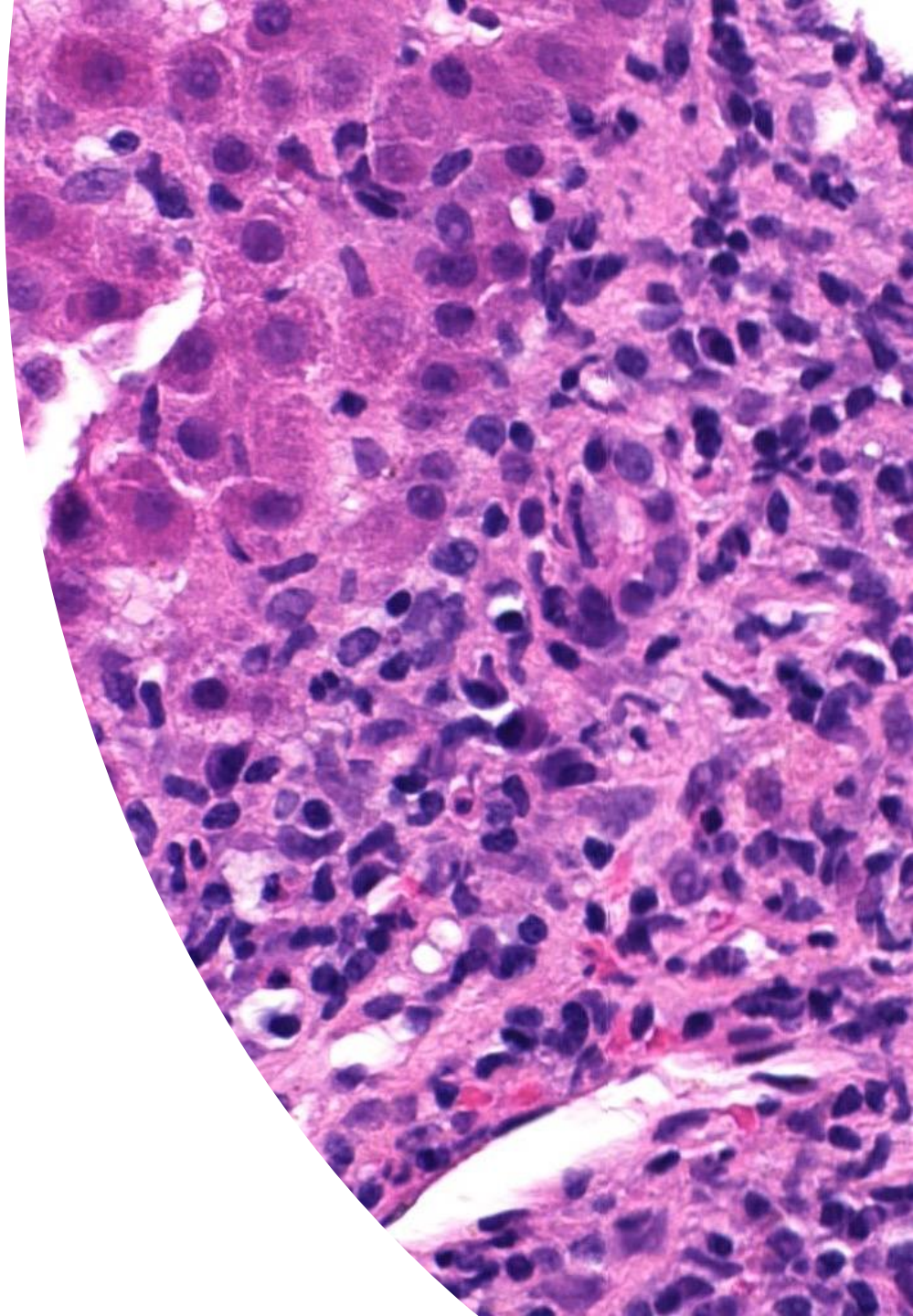
Lobular inflammation
Lobular disarray
Necrosis +-
No cholestasis ?

Differential
Acute Viral
AIH

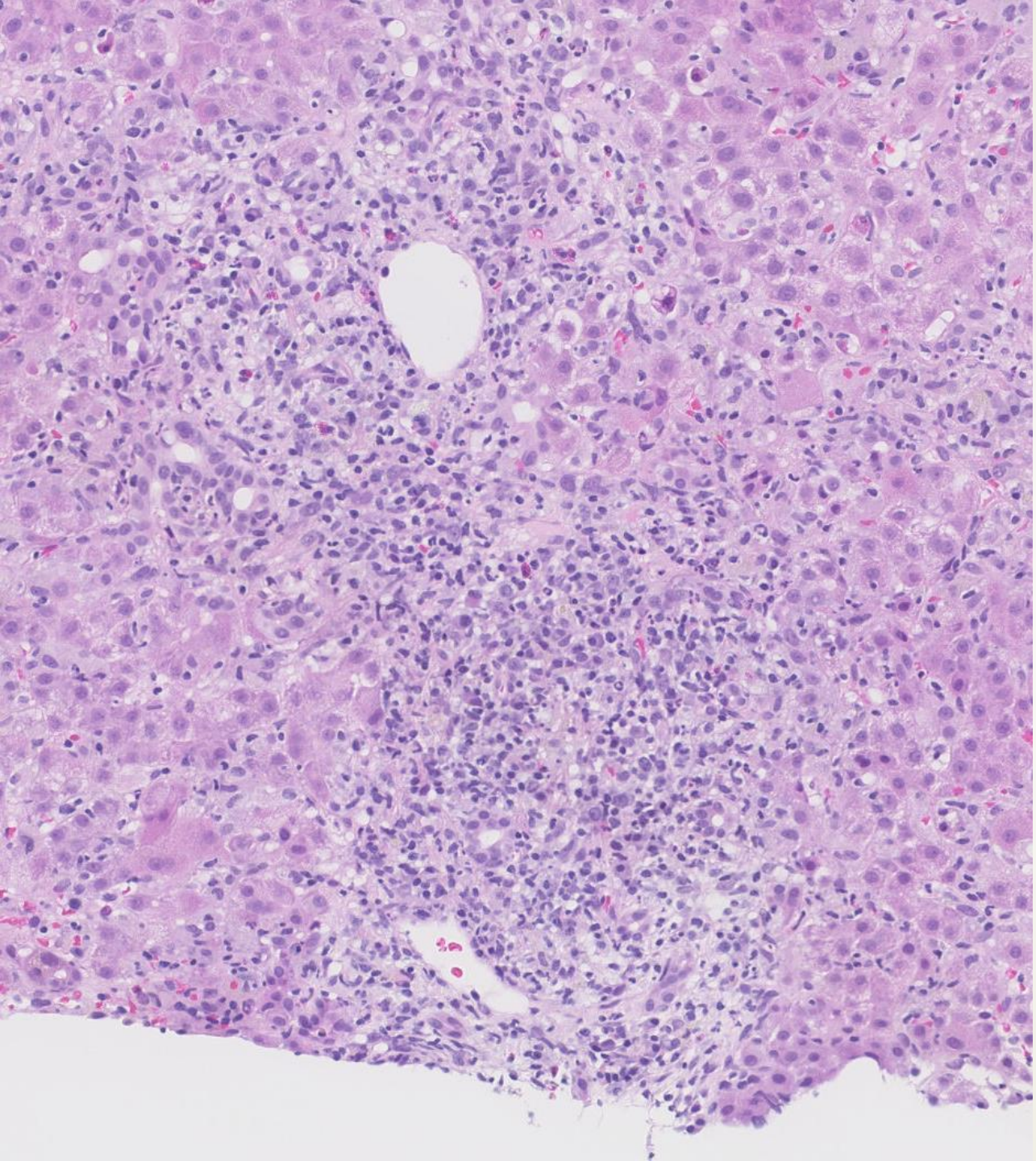




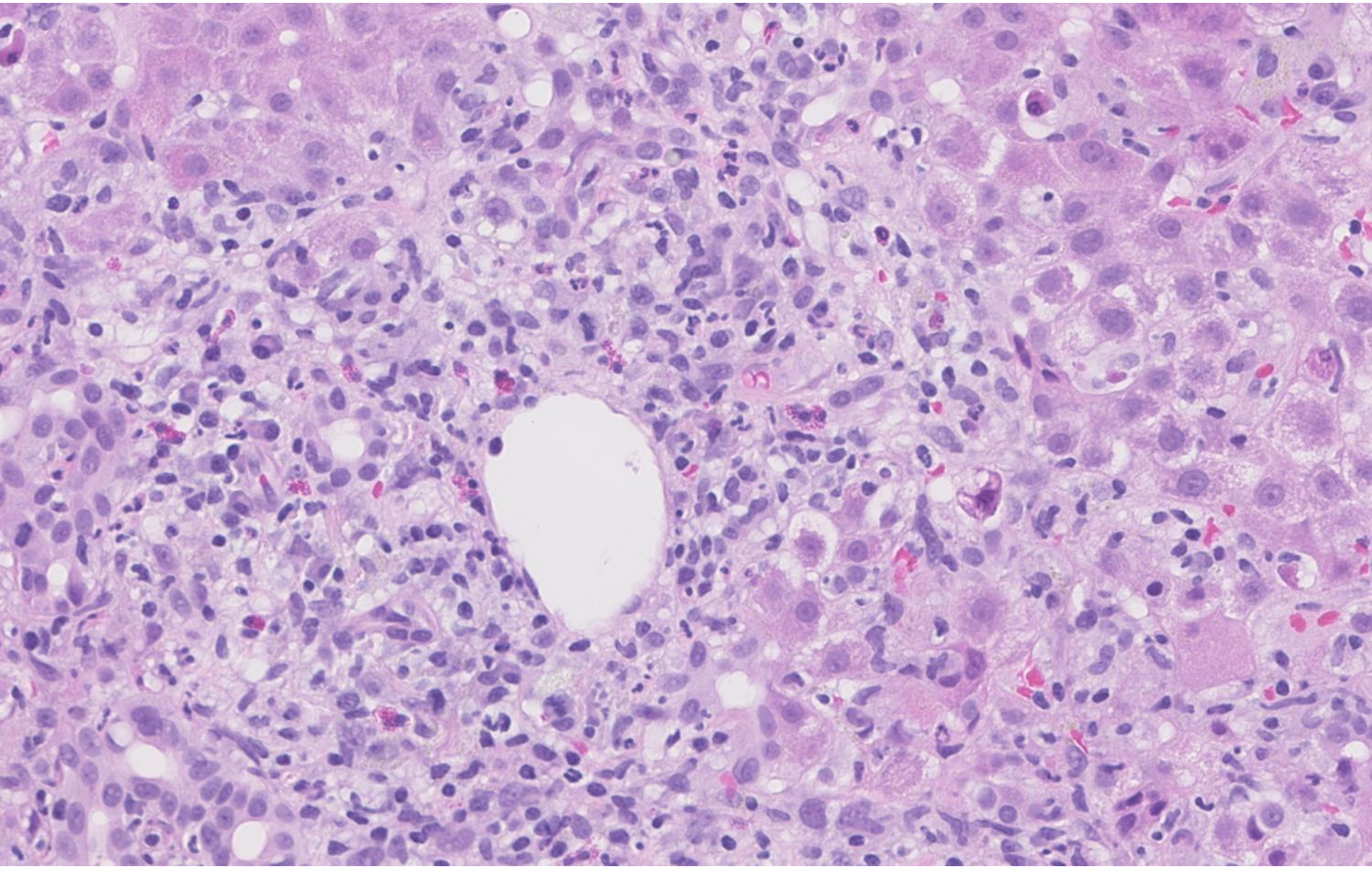
Portal Hepatitis (Chronic hepatitis)

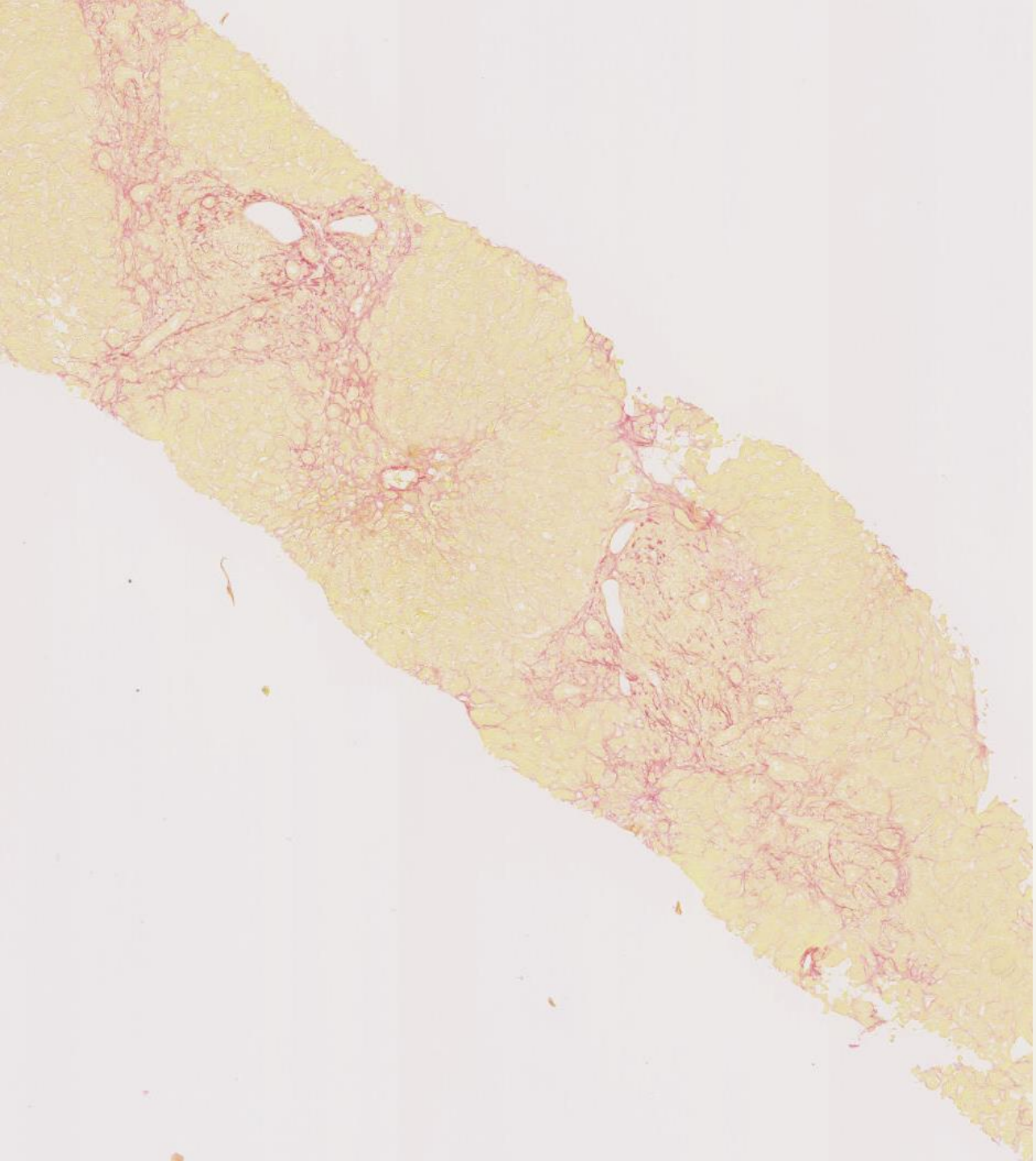


Portal Predominant
Interface hepatitis
Lobular mild/moderate
+- fibrosis
No cholestasis ??
May be very similar to AIH
Plasma cells, rosettes etc
Positive serology in DI AIH
? Role for lymphocyte typing



Heavy portal inflammation



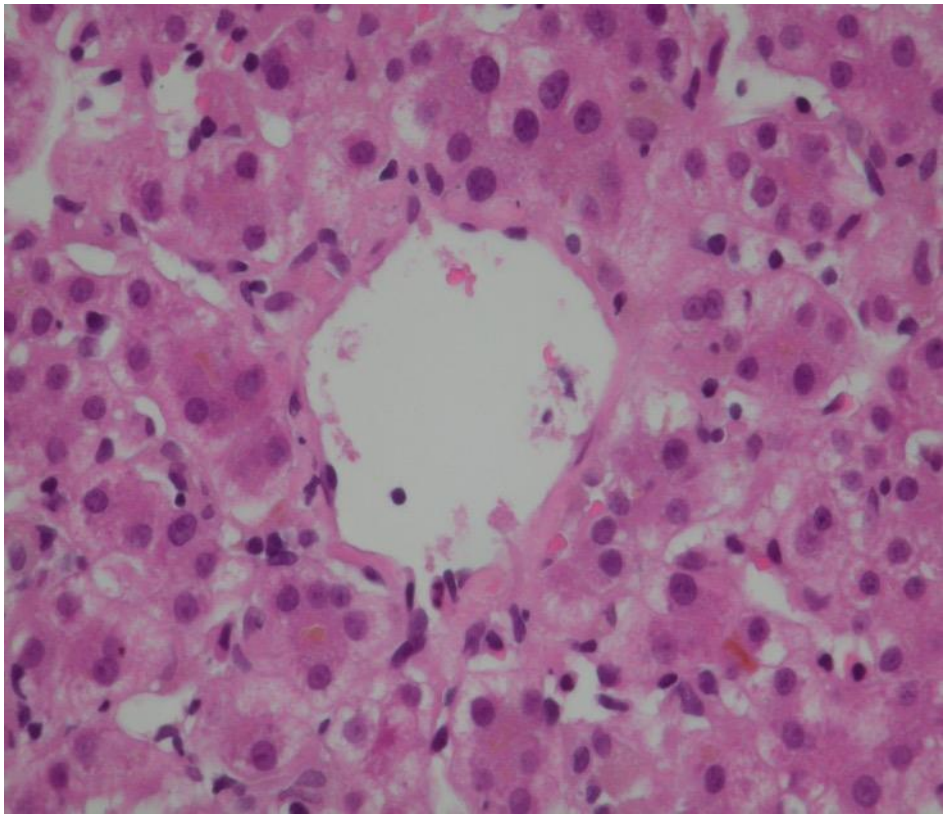


Collapse

Bland Cholestasis (acute cholestasis)

Cholestasis

Minimal inflammation



- Differential

BRIC, PFIC

Lymphoma

Sepsis

LDO

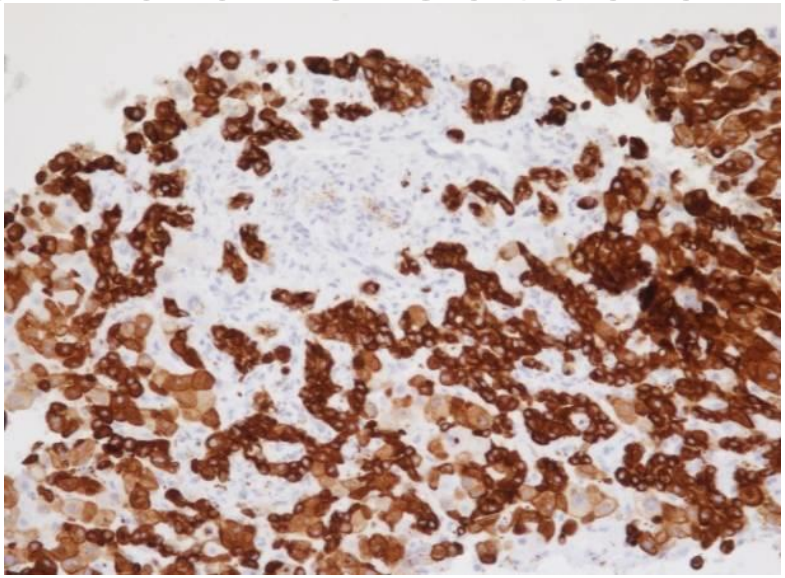
Biliary Interface/chronic cholestasis

Bile duct injury/loss

Portal inflammation

Ductular reaction

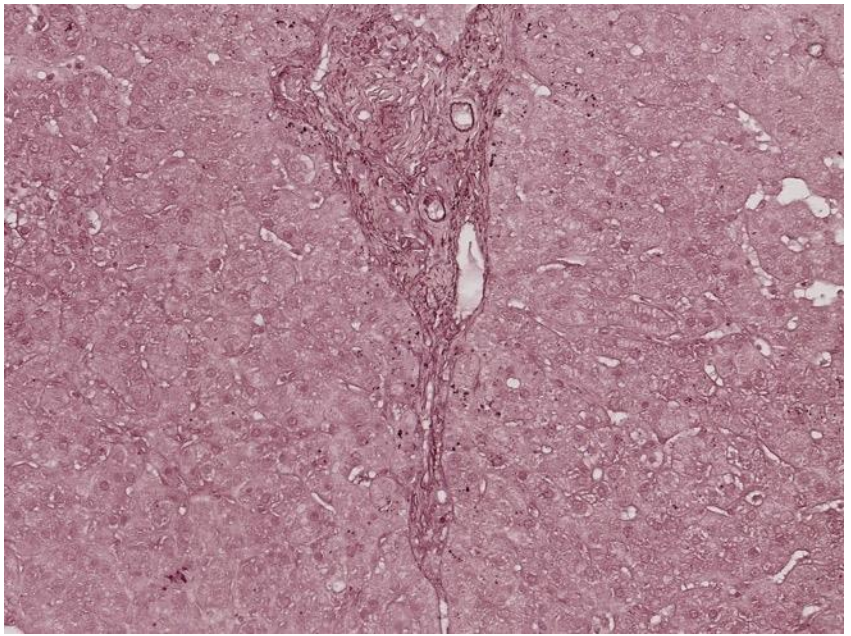
Cholate stasis/copper



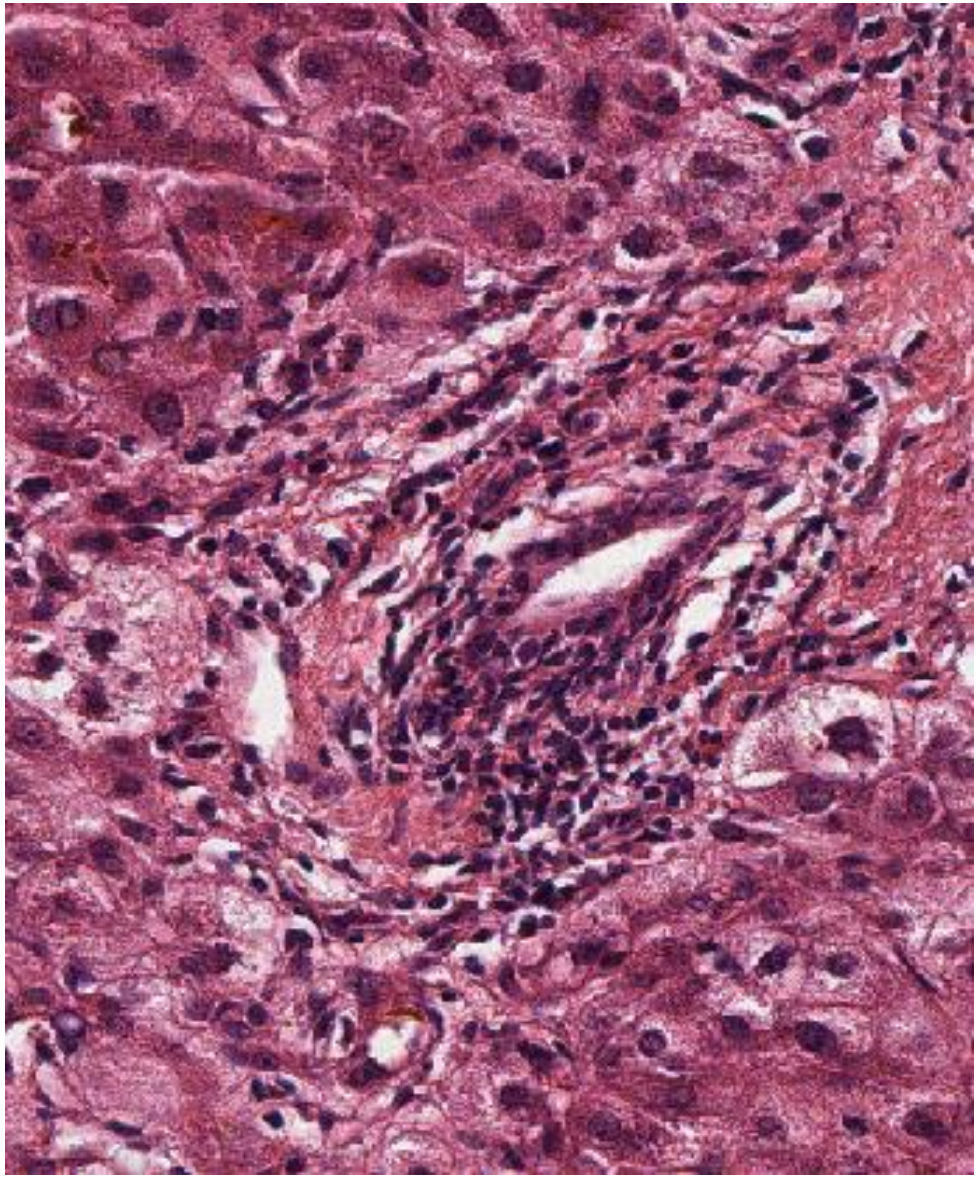
Differential

PBC, PSC

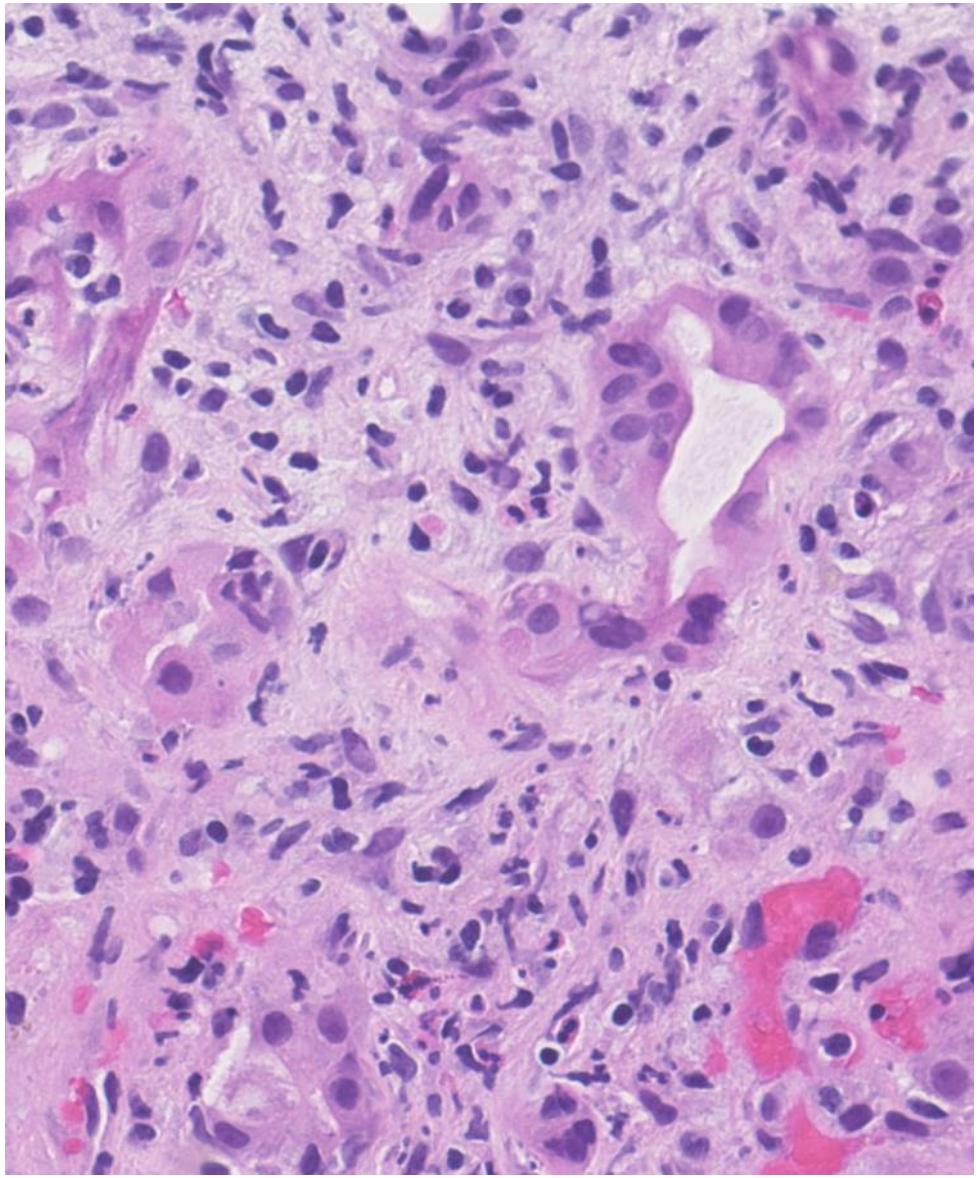
May be reversible



Cholate Stasis



Ductular reaction



Cholestatic Hepatitis

Cholestasis (any amount)

Inflammation > minimal

Lobular and/or portal

+- biliary injury

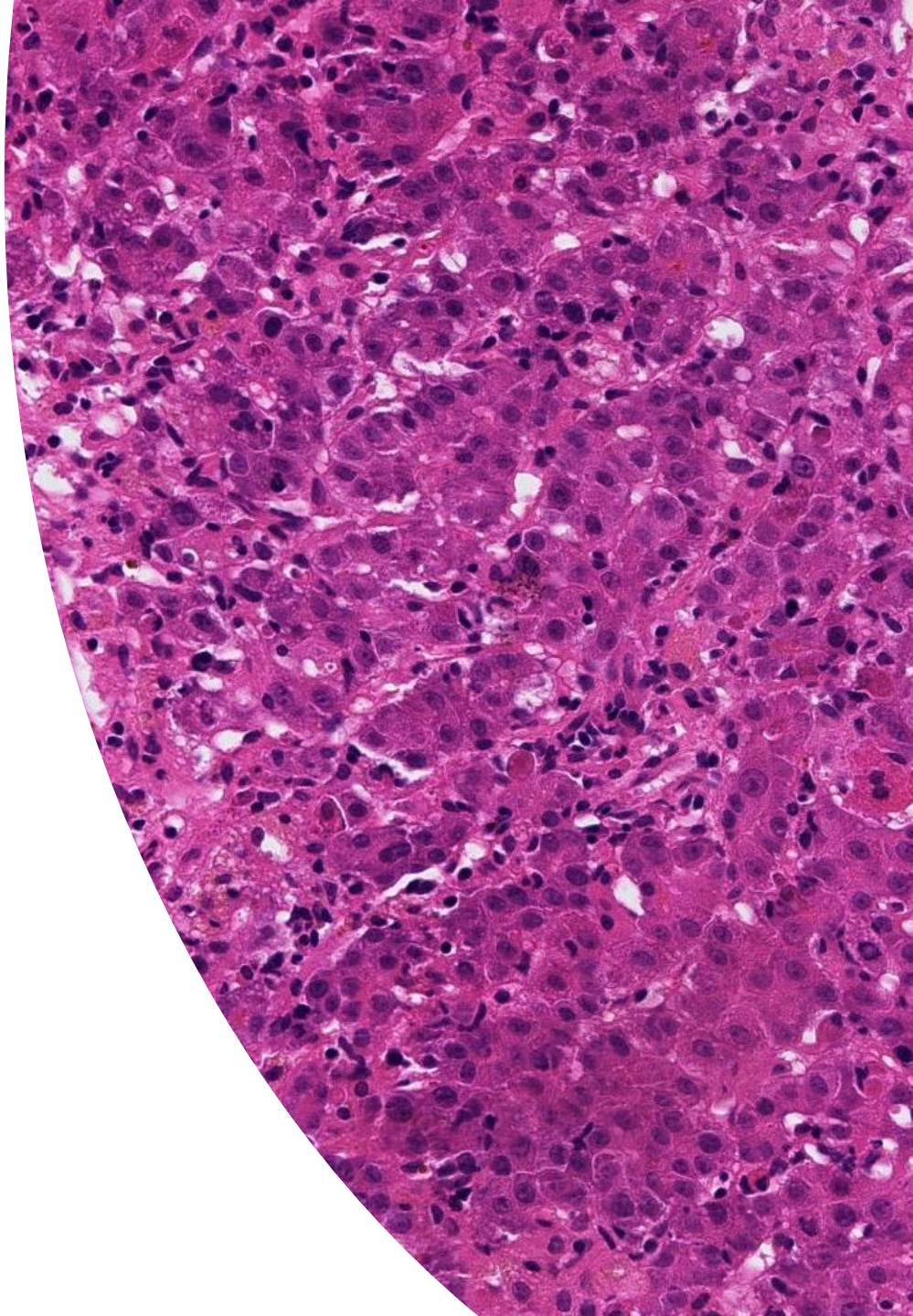
No cholate stasis ?

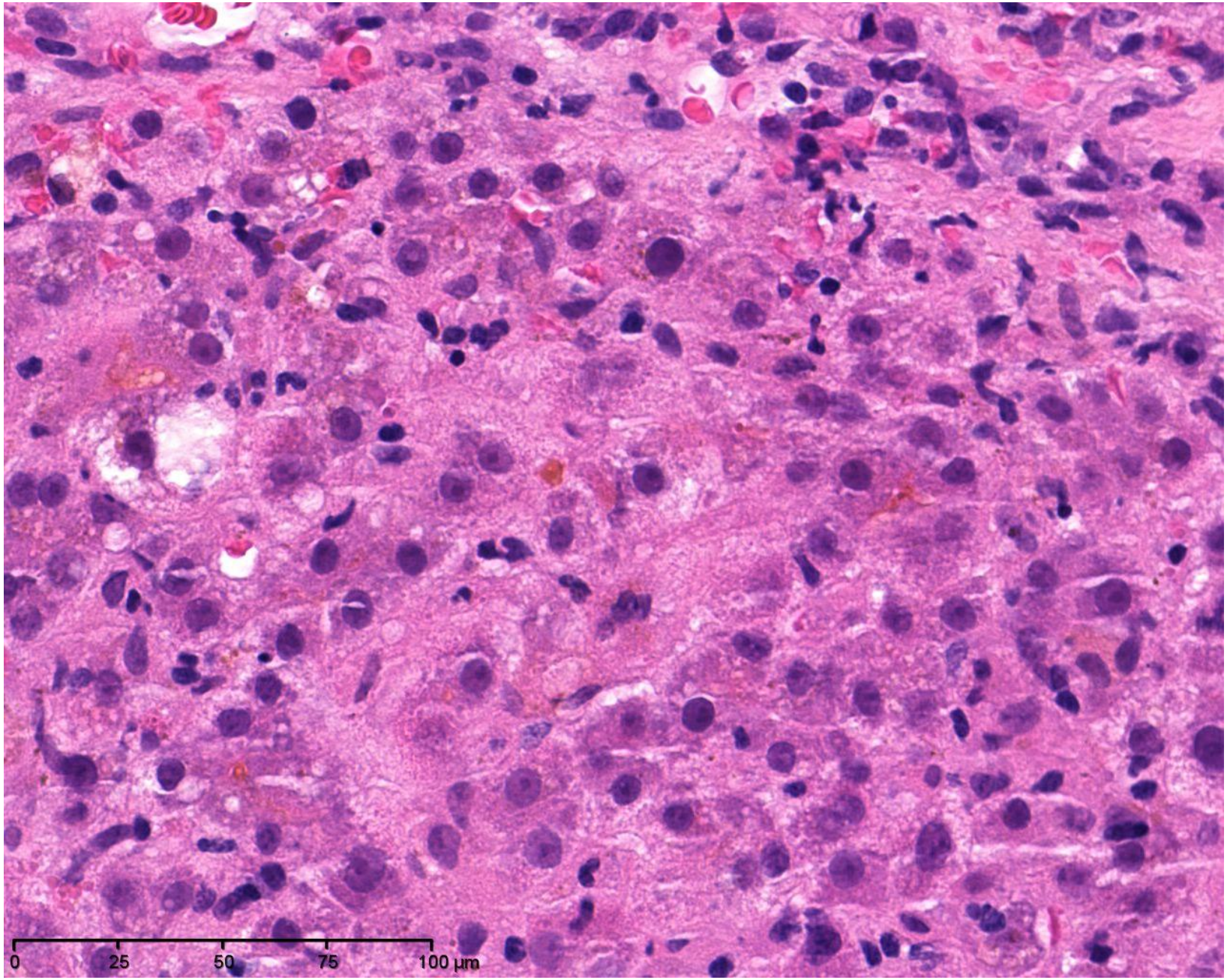
Differential

Autoimmune (if lots of inflam)

Viral hepatitis

LDO (if inflammation mild)

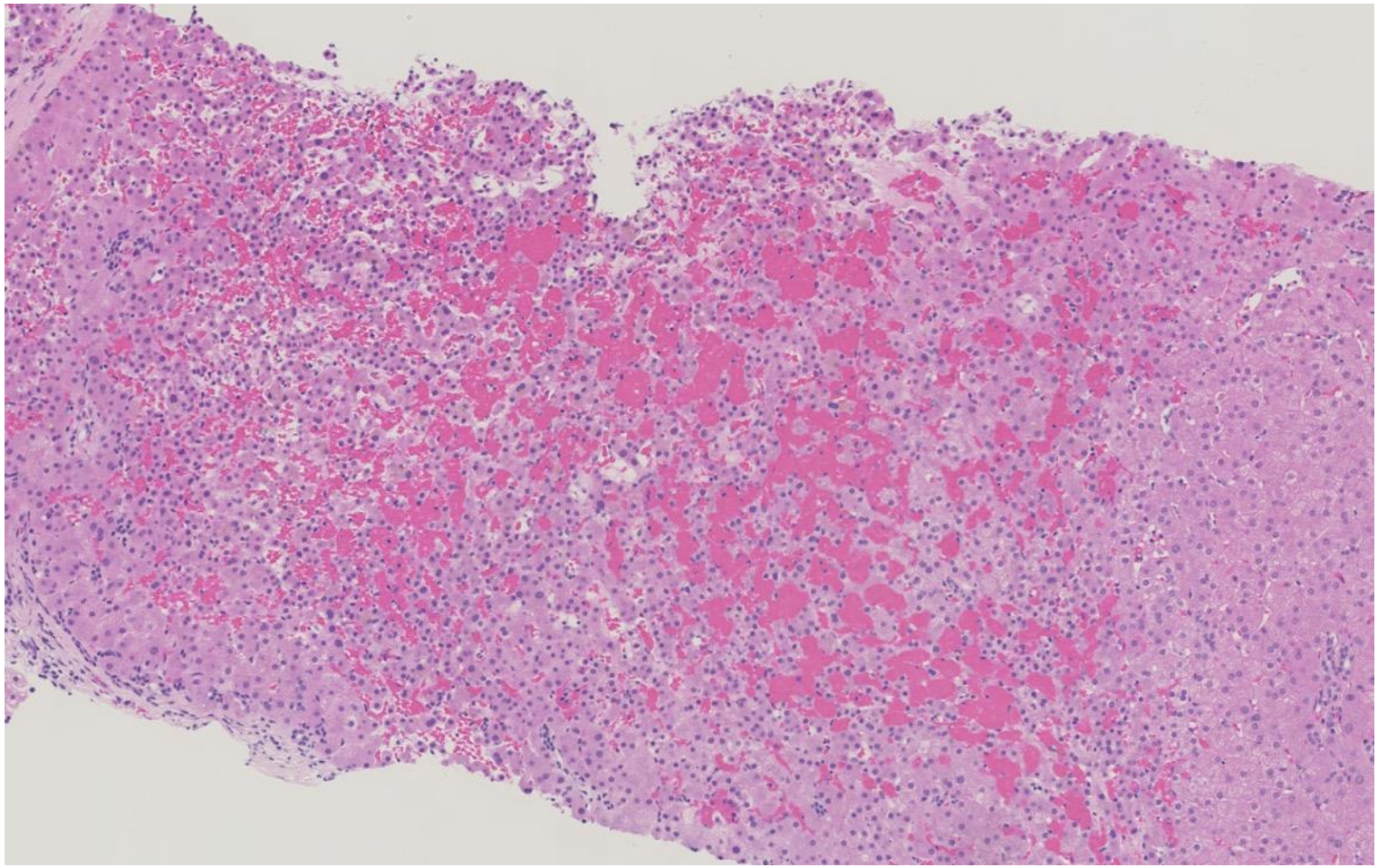


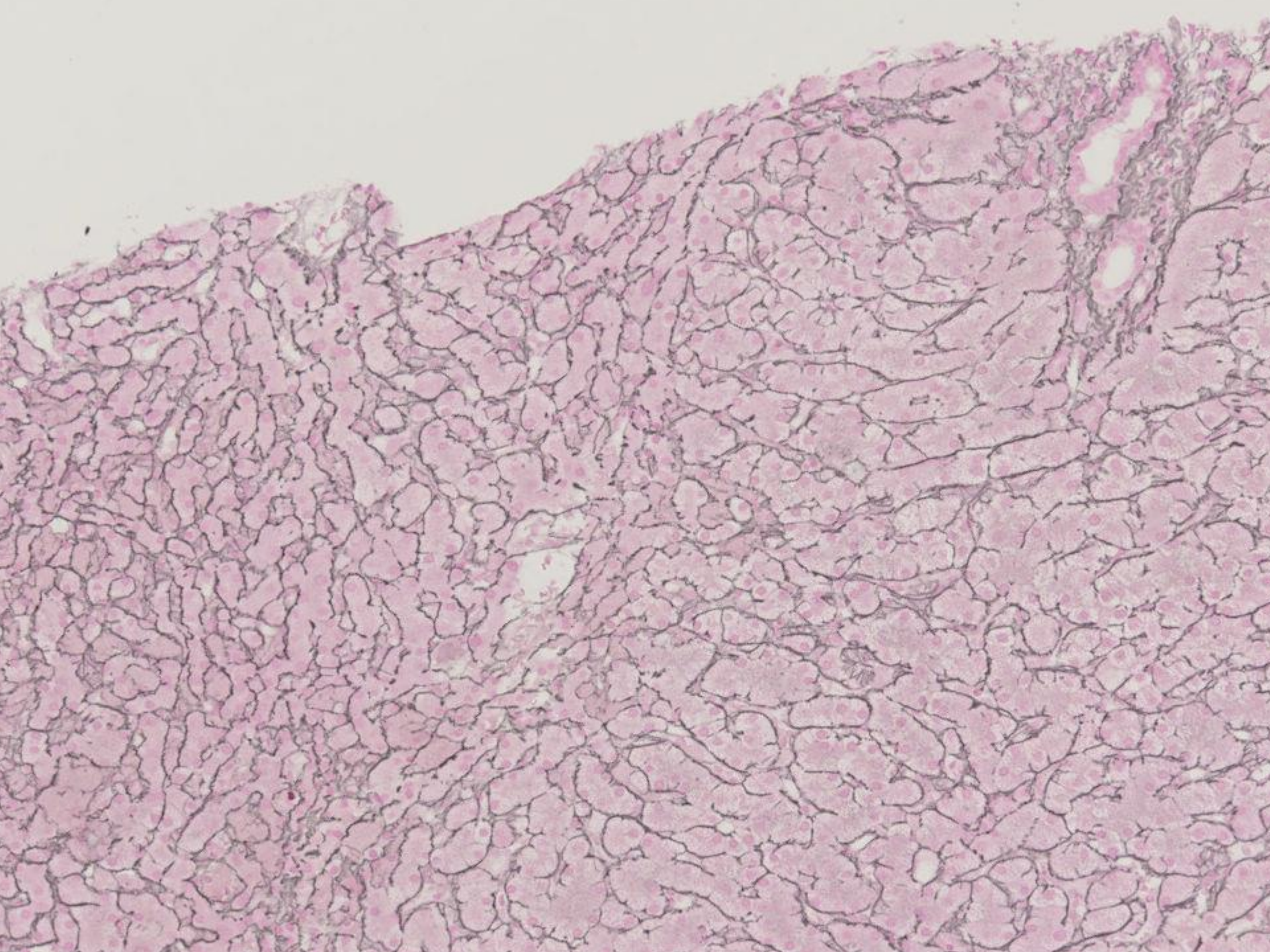

0
25
50
75
100 µm

Vascular Patterns

- Sinusoidal obstruction syndrome and NRH
- Caused by endothelial cell injury
- Variable changes but very common incidental finding in liver resections for CRC mets
- More serious pathology (VOD) seen in haematological patients with BMT conditioning causing Budd-Chiari type clinical syndrome

Vascular injury





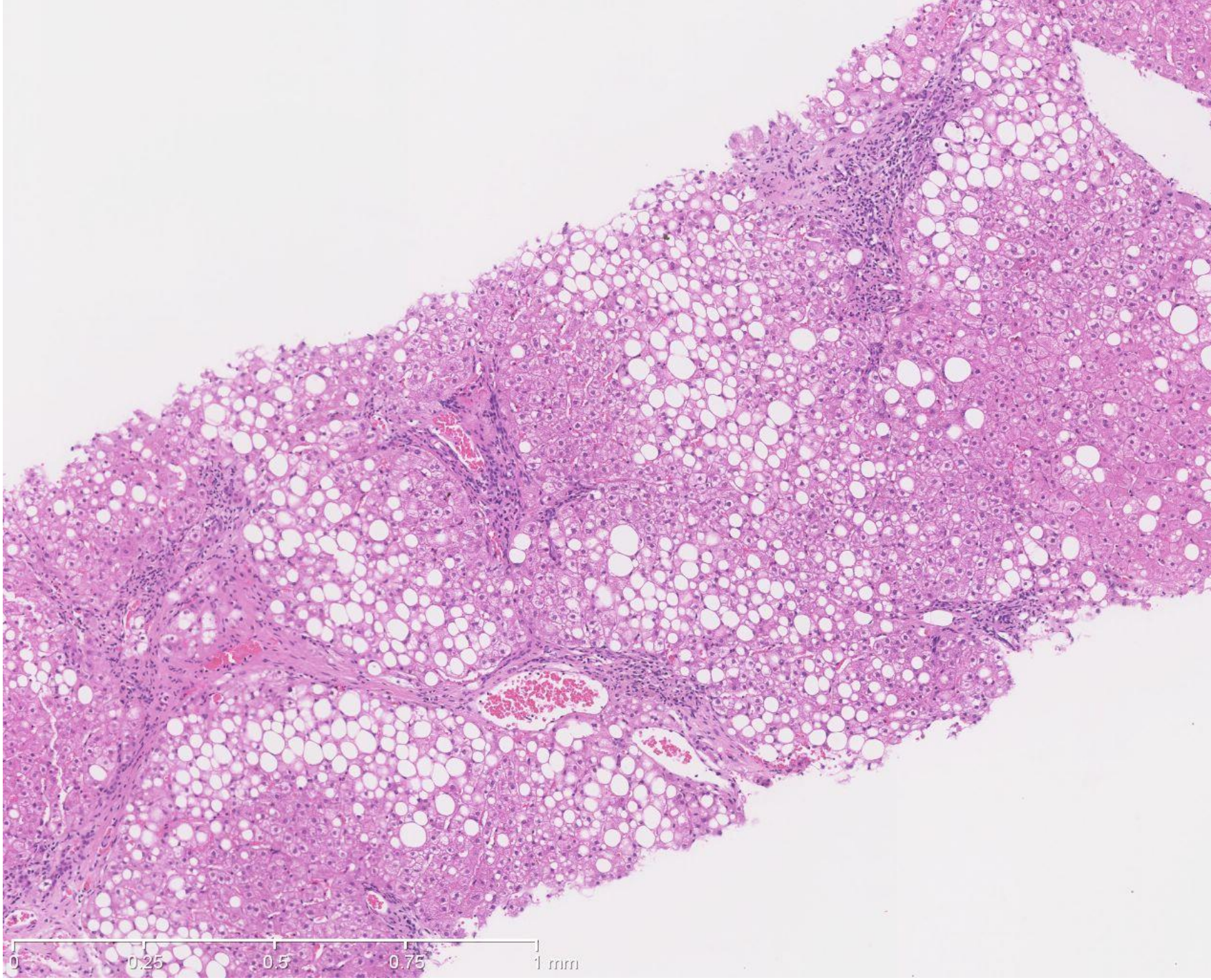
Steatotic patterns

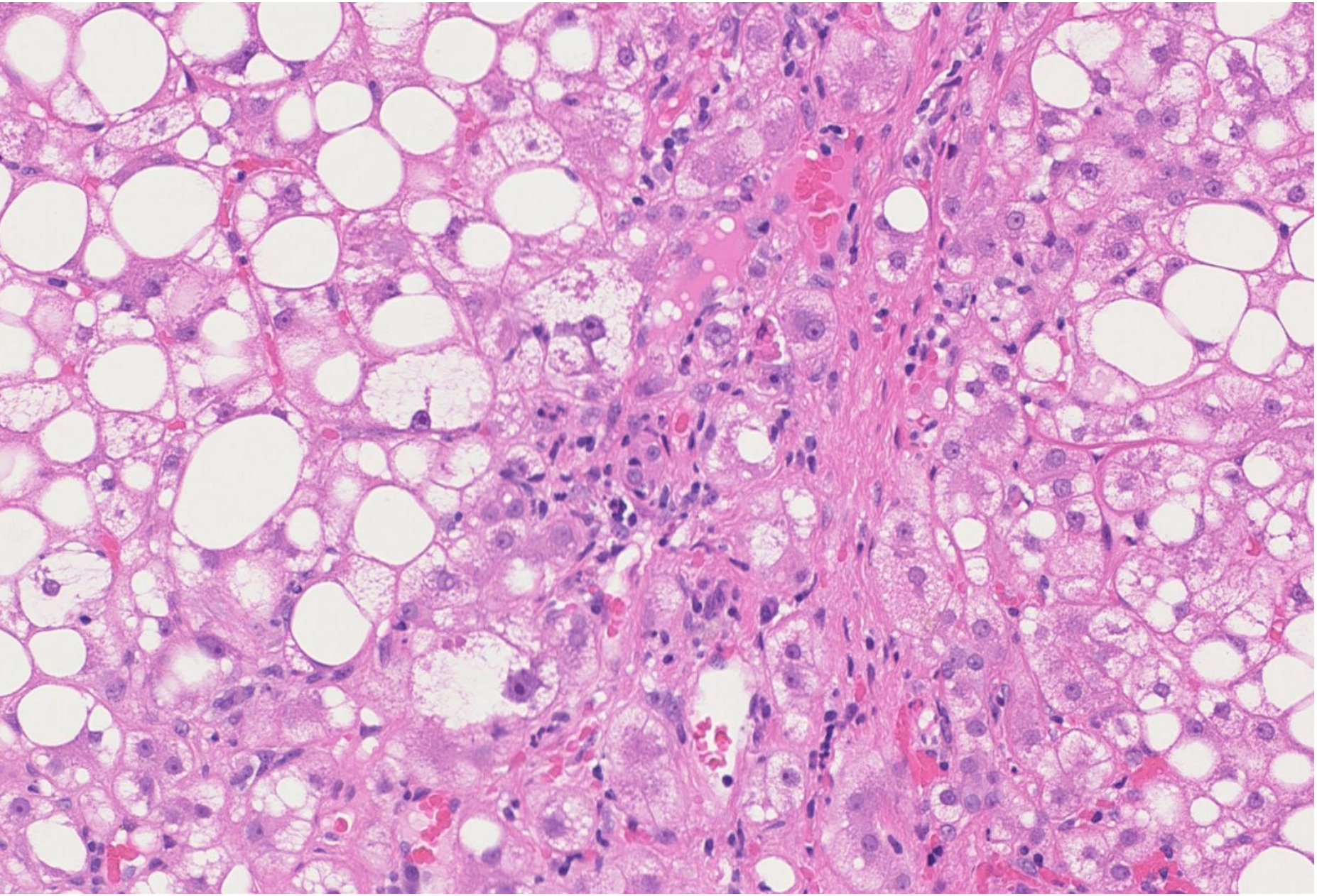
- Fairly uncommon

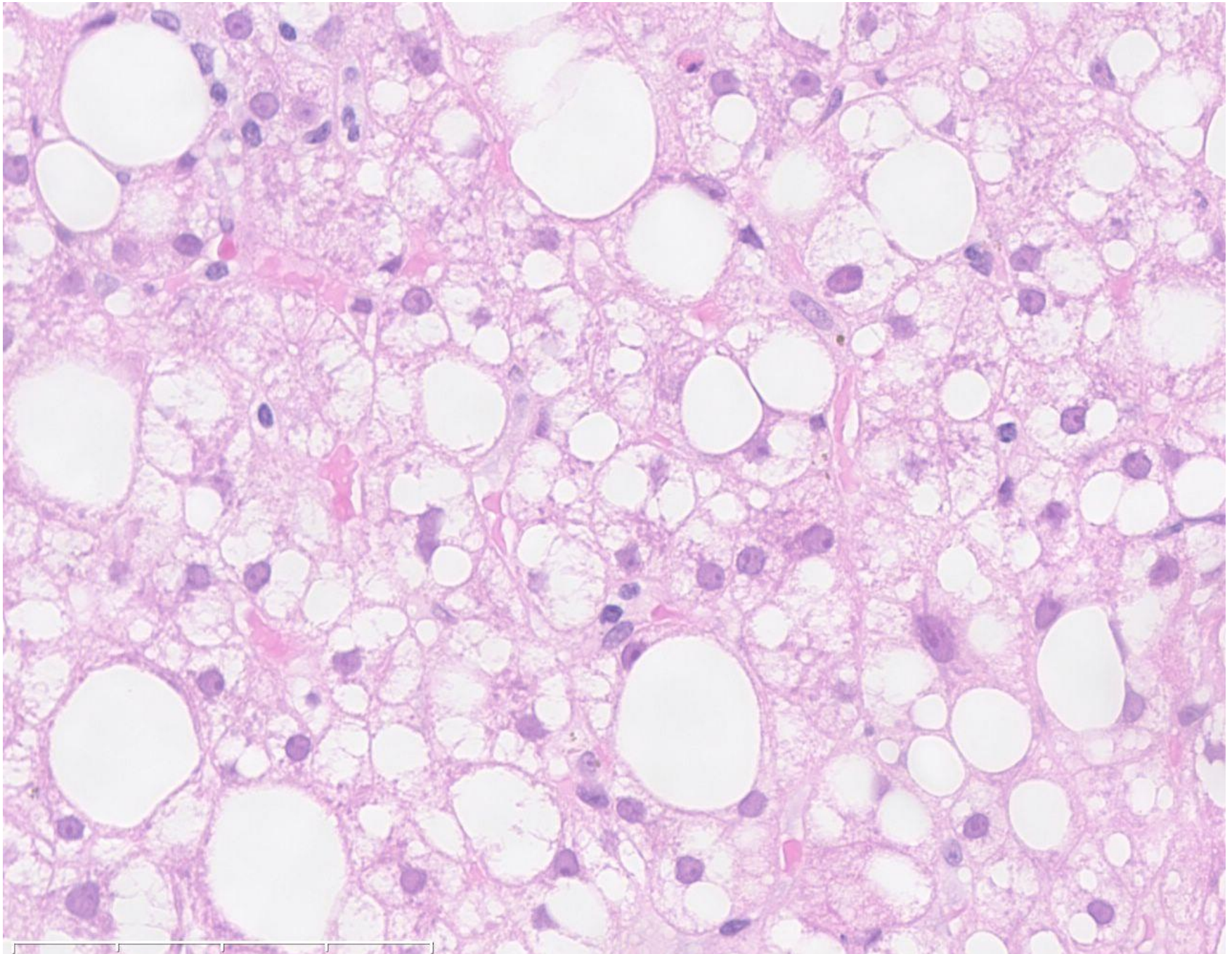
Methotrexate, Tamoxifen, Amiodarone

- Very uncommon – mitochondrial injury causing microvesicular steatosis

Valproic acid, Aspirin, Nucleoside analogs

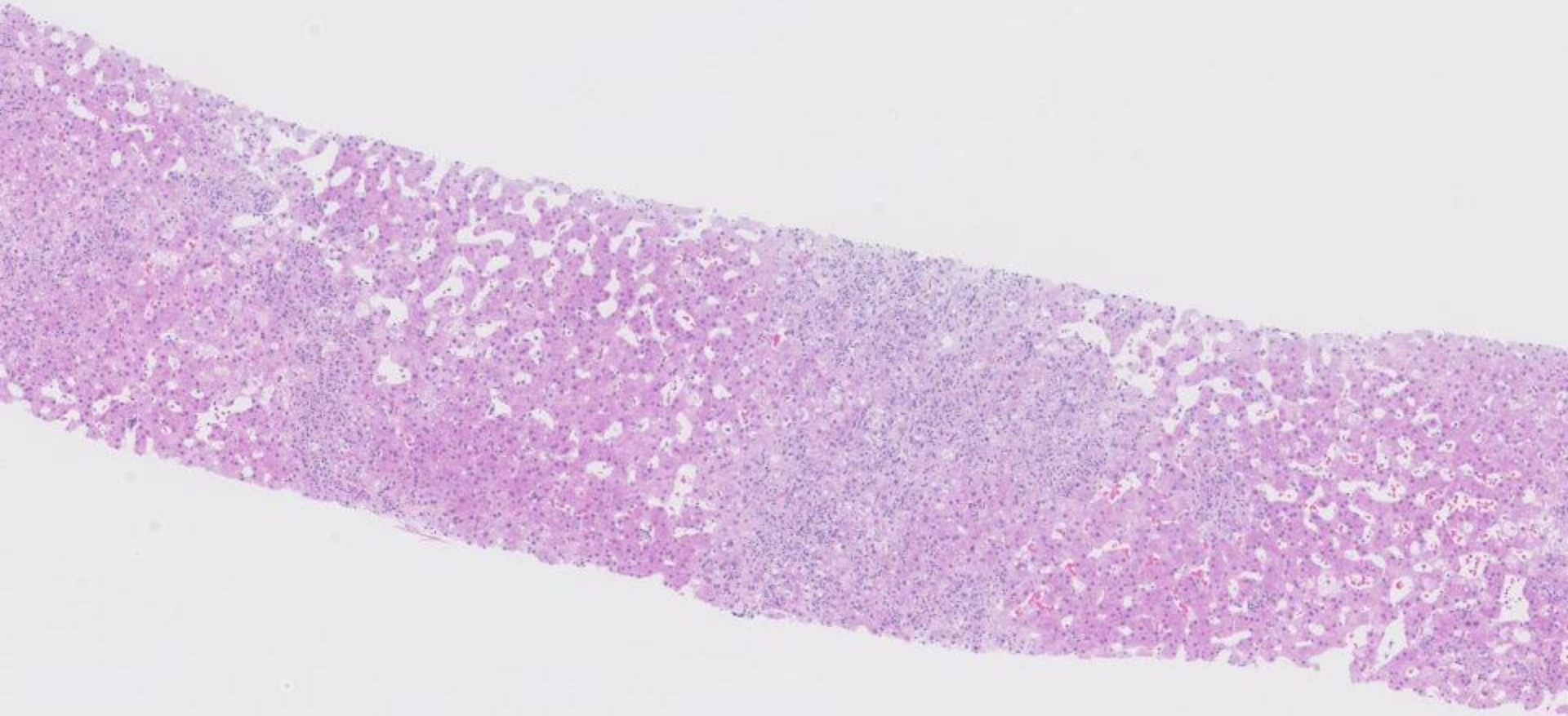

0
0.25
0.5
0.75
1 mm

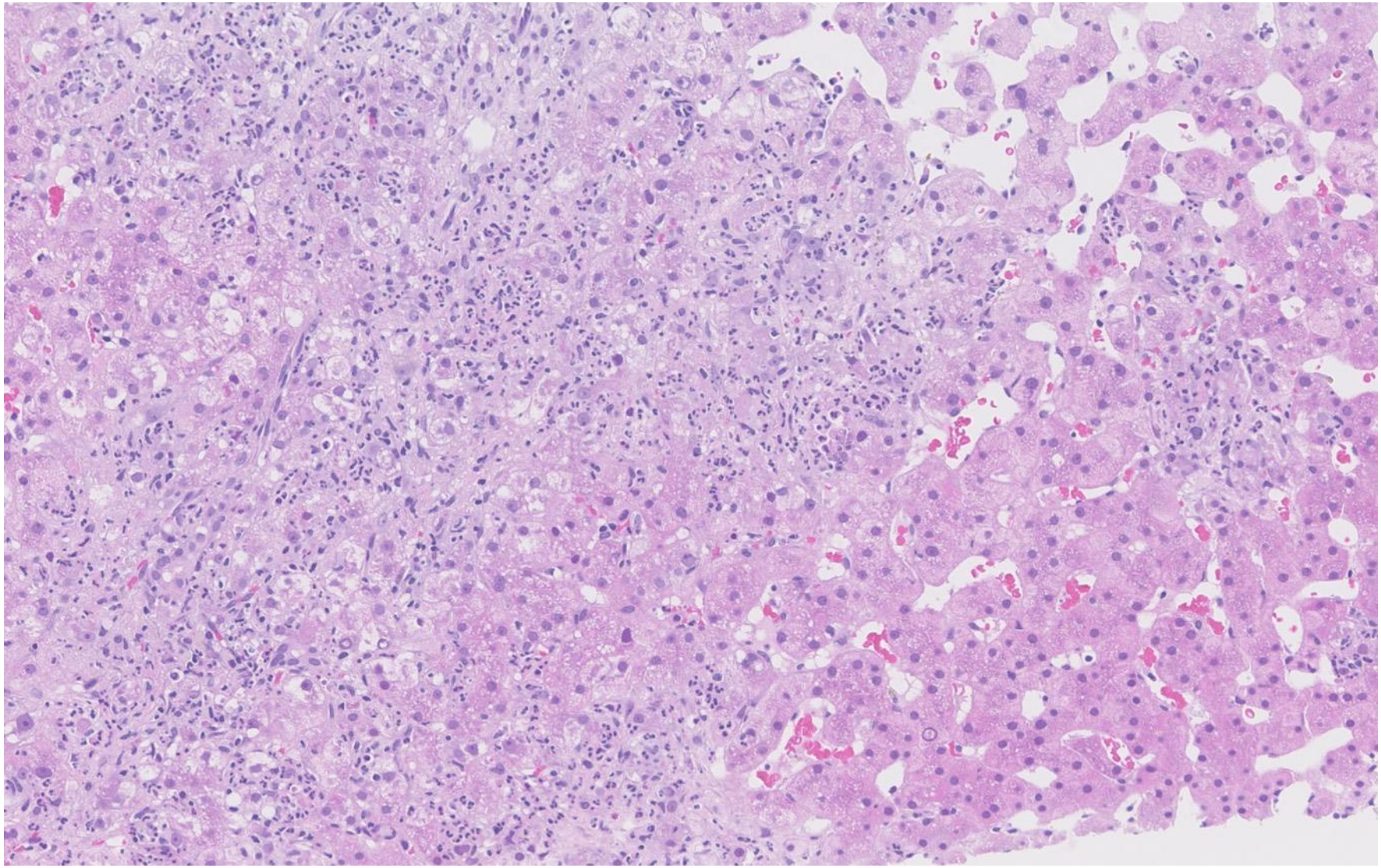


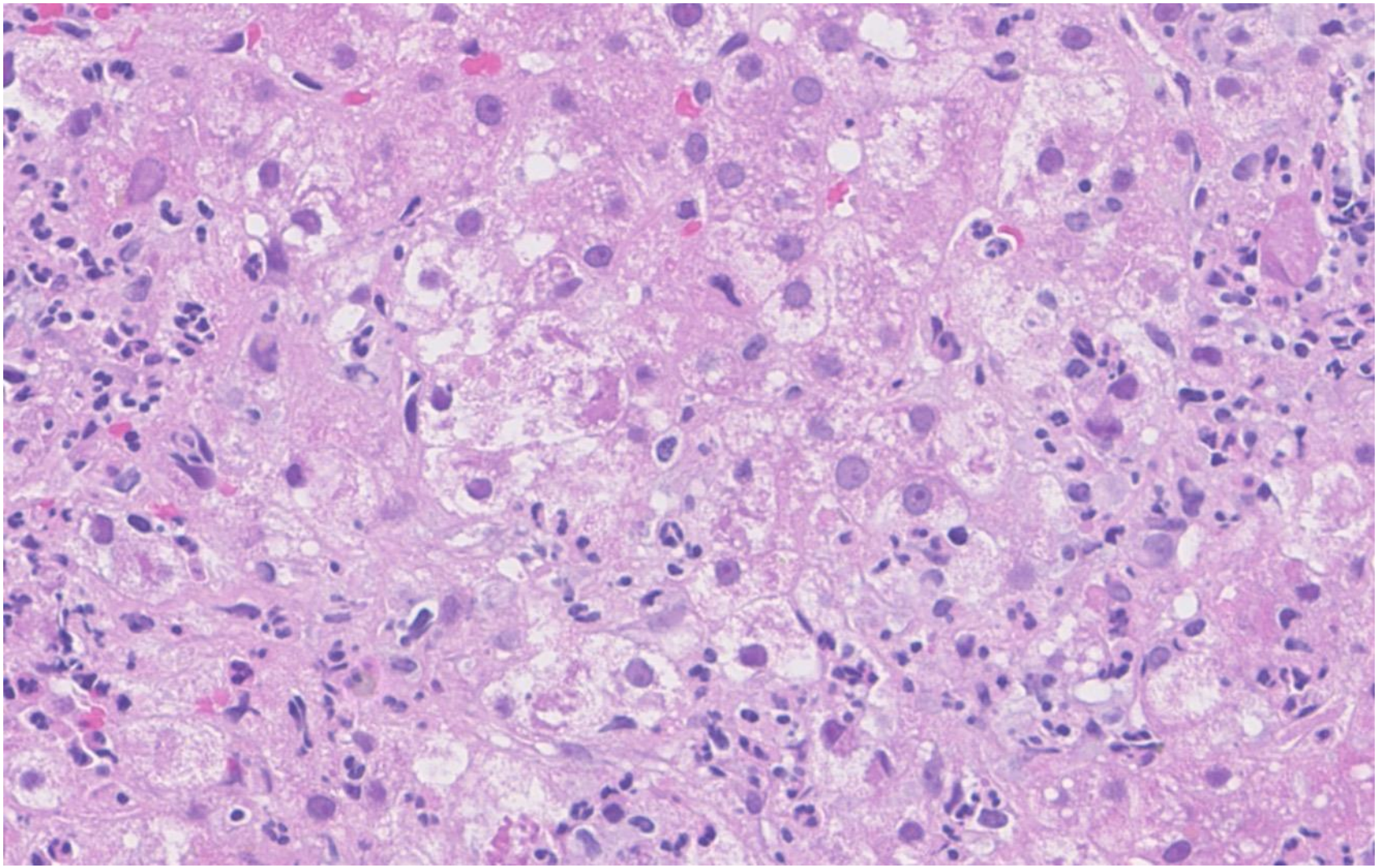


What else can pathology help with

- Prompt clinicians to consider a drug cause
- Diagnose another less likely differential
- Diagnose additional/underlying disease
- Severity of disease







Think Drug If:

- Pattern doesn't fit with clinical expectation
- Features of LDO but ultrasound normal
- Portal hepatitis with prominent cholestasis
- Scattered microgranulomas
- Prominent eosinophils

Less common causes to exclude

Table 3. Uncommon competing causes of liver injury

Feature or pattern of injury	Differential diagnosis
Chronic hepatitis-like or mild non-specific hepatitis	EBV-related hepatitis
	CMV-related hepatitis (mononucleosis pattern)
	Collagen-vascular disease
	Coeliac disease
	Common variable immunodeficiency
Coagulative necrosis	Herpetic hepatitis
	Adenoviral hepatitis
Granulomatous hepatitis	Atypical bacterial infection
	Rickettsial infection
Acute cholestasis	Benign recurrent intrahepatic cholestasis
Chronic cholestasis and ductopenia	Ischaemic cholangitis
	Idiopathic adulthood ductopenia
	Langerhans cell histiocytosis
	IgG4-related systemic sclerosis
	Progressive familial intrahepatic cholestasis
Cholestatic hepatitis	Progressive familial intrahepatic cholestasis

Severity of Injury

Degree of necrosis

Amount of fibrosis

Microvesicular steatosis

+++ neutrophils

+++ ductular reaction

Cholangiolar cholestasis

Eosinophils and granulomas positive feature

Remember

DILI on top of some underlying disease is always a possibility to consider

In particular NASH is so common, that always consider another superimposed cause, if anything doesn't quite fit (eg cholestasis)

Consider timing of drugs and remember supplements

Compare findings to suspect drugs and their published patterns

Common causes of DILI

Table 2 Top ten implicated drugs in three prospective studies on DILI, DILIN study from the USA (Chalasani et al. 2008), a prospective study from Iceland (Björnsson et al. 2013) and Spain (Andrade et al. 2005)

DILIN study	Icelandic study	Spanish registry
Amoxicillin–clavulanate	Amoxicillin–clavulanate	Amoxicillin–clavulanate
Isoniazid	Diclofenac	Isoniazid
Nitrofurantoin	Azathioprine	RIP + INH + PIZ
SMZ/TMP	Infliximab	Flutamide
Minocycline	Nitrofurantoin	Ibuprofen
Azithromycin	Isotretinoin	Ebrotidina[a]
Ciprofloxacin	Atorvastatin	Diclofenac
Diclofenac	Doxycycline	Atorvastatin
Levofloxacin	Herbalife products	Ticlopidine

RIP + INH + PIZ: rifampin, isoniazid and pyrazinamide

SMZ/TMP sulfamethoxazole/trimethoprim

[a] Withdrawn from the Spanish market in 1998 due to hepatotoxicity

Top 50

Drug class	Agent	Histological injury pattern
GI anti-inflammatory	Sulphasalazine	Acute hepatitis, cholestatic hepatitis, granulomas, zonal necrosis
Anti-thrombotic	Ticlopidine	Chronic cholestasis (VBDS), cholestatic hepatitis
Anti-arrhythmic	Quinidine	Cholestatic hepatitis, granulomas, zonal necrosis
	Amiodarone	Steatosis, steatohepatitis, phospholipidosis
Anti-hypertensive	Methyldopa	Acute/chronic hepatitis, zonal necrosis
	Hydralazine	Acute/chronic hepatitis, cholestatic hepatitis, granulomas
Lipid-lowering	Simvastatin	Acute hepatitis, cholestatic hepatitis
	Atorvastatin	
Sex steroids	Oestrogens	Acute cholestasis, sinusoidal dilation, peliosis, Budd–Chiari
	Androgens	Acute cholestasis, Sinusoidal dilation, peliosis, NRH
Anti-thyroidal	Propylthiouracil	Acute/chronic hepatitis, zonal necrosis
Anti-microbials	Minocycline	Chronic hepatitis
	Floxacillin (flucloxacillin)	Acute cholestasis, chronic cholestasis (VBDS)
	Amoxicillin–clavulanate	Cholestatic hepatitis, chronic cholestasis (VBDS)
	Sulphonamides	Cholestatic hepatitis, acute hepatitis, granulomas, chronic cholestasis (VBDS)
	Trimethoprim–sulphamethoxazole	Cholestatic hepatitis, acute hepatitis
	Erythromycin	Acute to chronic cholestasis, acute hepatitis
	Telithromycin	Acute hepatitis, zonal necrosis
	Nitrofurantoin	Acute/chronic hepatitis, zonal necrosis
	Ketoconazole	Cholestatic hepatitis, acute hepatitis, necrosis
Anti-mycobacterial	Rifampin	Acute hepatitis, zonal necrosis, cholestatic hepatitis
	Isoniazid	Acute/chronic hepatitis, fulminant hepatitis
	Pyrazinamide	Acute/chronic hepatitis, necrosis
Anti-viral	Didanosine	Microvesicular steatosis, granulomas
	Nevirapine	Acute/chronic hepatitis, cholestatic hepatitis, zonal necrosis
	Efavirenz	Acute/chronic hepatitis

Immunostimulant	Interferon alpha	Granulomas
	Interferon beta	Acute/chronic hepatitis
Immunosuppressive	Infliximab	Acute/chronic hepatitis, cholestatic hepatitis, acute cholestasis, HBV reactivation
	Azathioprine	Acute cholestasis, cholestatic hepatitis, NRH, sinusoidal dilation, VOD
Anti-inflammatory	Sulindac	Cholestatic hepatitis, acute hepatitis, necrosis, steatosis
	Diclofenac	Acute/chronic hepatitis, cholestatic hepatitis
	Ibuprofen	Acute hepatitis, cholestatic hepatitis, chronic cholestasis (VBDS), necrosis
	Nimesulide	Acute/chronic hepatitis, cholestatic hepatitis, acute cholestasis, necrosis
	Gold	Acute hepatitis, cholestatic hepatitis, chronic cholestasis (VBDS), necrosis
Muscle relaxant	Dantrolene	Acute/chronic hepatitis, cholestatic hepatitis, fibrosis/cirrhosis
Anti-gout	Allopurinol	Cholestatic hepatitis, acute hepatitis, granulomas
Anaesthetic	Halothane	Zonal necrosis, acute/chronic hepatitis, cholestatic hepatitis
Anti-convulsant	Phenytoin	Acute/chronic hepatitis, cholestatic hepatitis, granulomas, chronic cholestasis
	Carbamazepine	Acute/chronic hepatitis, cholestatic hepatitis, granulomas, necrosis
	Valproic acid	Zonal necrosis, cholestatic hepatitis, microvesicular steatosis
Anti-addictive	Disulfiram	Acute hepatitis
Anti-neoplastic	Busulfan	Cholestatic hepatitis, VOD
	Methotrexate	Acute/chronic hepatitis, steatosis, steatohepatitis, fibrosis/cirrhosis
	Mercaptopurine	Cholestatic hepatitis, chronic cholestasis, NRH, sinusoidal dilation, SOS
	Thioguanine	Acute cholestasis, cholestatic hepatitis, NRH, sinusoidal dilation, SOS
	Floxuridine	Cholestatic hepatitis, chronic cholestasis, VOD
Anti-androgen	Flutamide	Cholestatic hepatitis

Pro Euro DILI Registry

REC 15/YH/0294

Coordinating Centres:

Guru Aithal

NIHR Nottingham Digestive Diseases Biomedical Research Unit

Nottingham University Hospitals NHS Trust & the University of Nottingham

Raul Anderade

UGC Ap Digestivo, Biomedical Research Institute of Málaga, Spain

Biorepository: objective

To collect, store and catalogue biological samples and clinical data, to form a large international patient/control cohort available for subsequent detailed analysis by consortium members which can also be used in current and future epidemiologic and mechanistic studies.

270 DILI patients, **270 control** participants, *(& non-DILI symptomatic controls)*

DILI Patients

- **ALT** > 5 xULN or **ALP** > 2 xULN or **ALT** >3 xULN + **TBL** > 2 xULN
- **Exposure** to drugs including any prescription drug, over-the-counter drug, recreational drug, herbal remedies or dietary supplements prior to the DILI onset.
- Absence of other known causes of liver injury after detailed investigations.
- Age over 18 & written consent/consultee

Visit 1 will take place as soon as possible following acute presentation; there may be a time lag of up to 4 weeks between identification of an episode of DILI by the team responsible for the clinical care of the patients and the patient giving consent to take part in the study.

Patient's blood tests must meet the eligibility criteria on the day they are enrolled (Day 0/ visit 1) in order to participate in the study.

References

- Kleiner Histopathology 2017, 70, 81–93
- Kleiner DE, Chalasani NP, Lee WM et al. Hepatology 2014; 59; 661–670.
- Bjornsson ES, Hoofnagle JH. Hepatology 2016; 63; 590–603.