UK Liver Histopathology EQA Scheme

Circulation LV.

Summer 2020

UK National Liver Histopathology EQA Scheme 2020

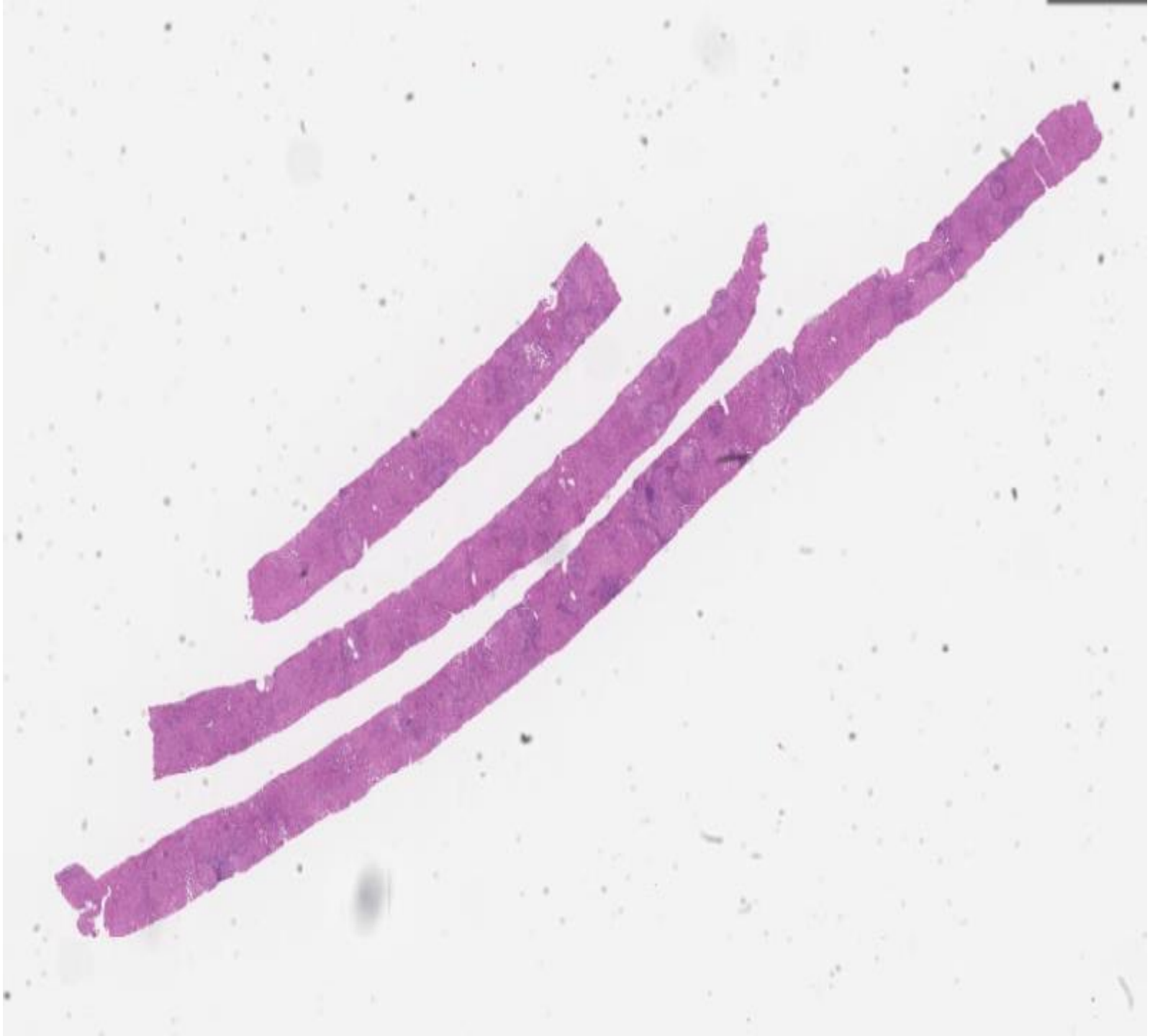
LV1, LV2, LV3

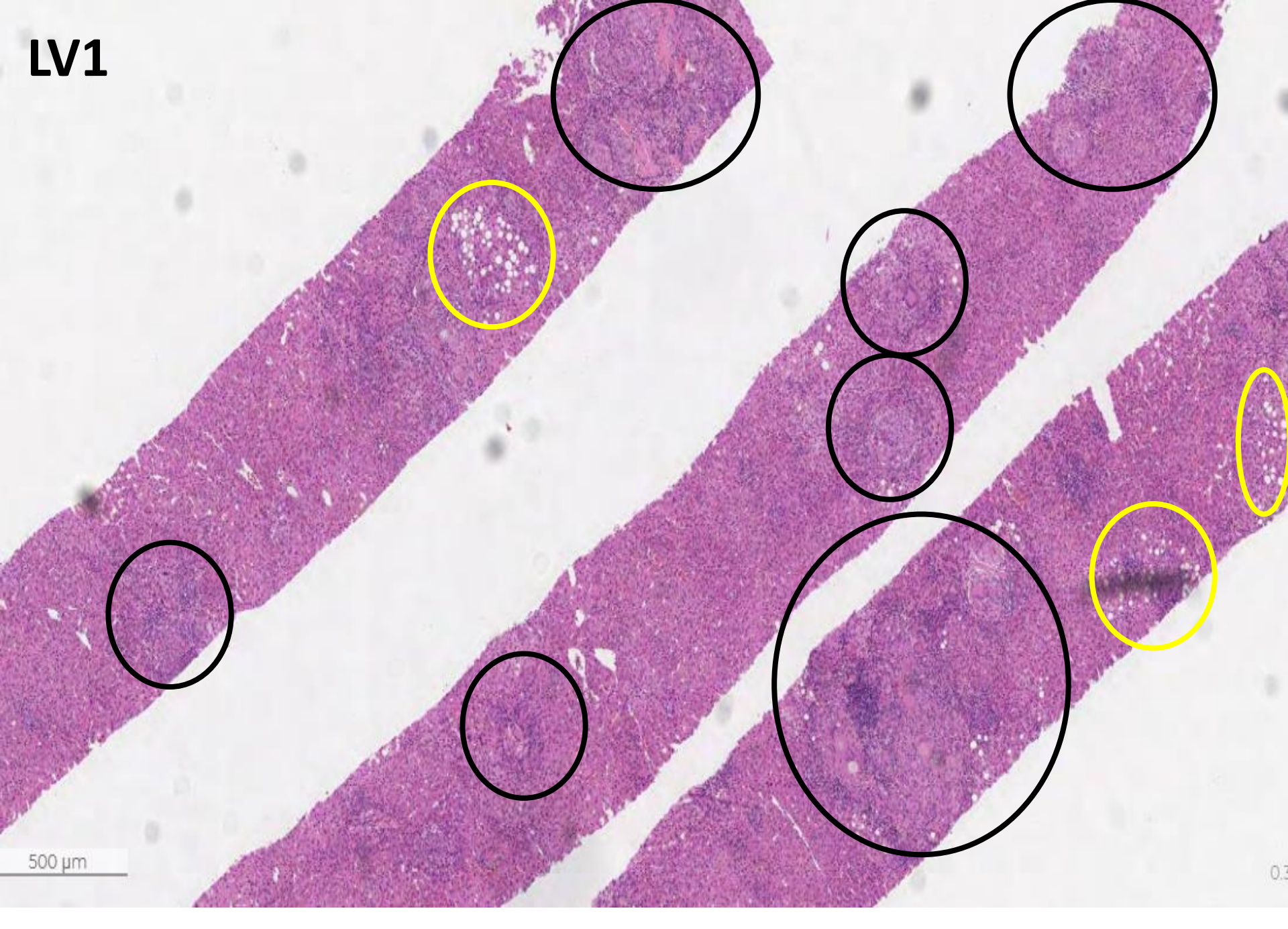
Dr Rosa Miquel

LV
Case 1

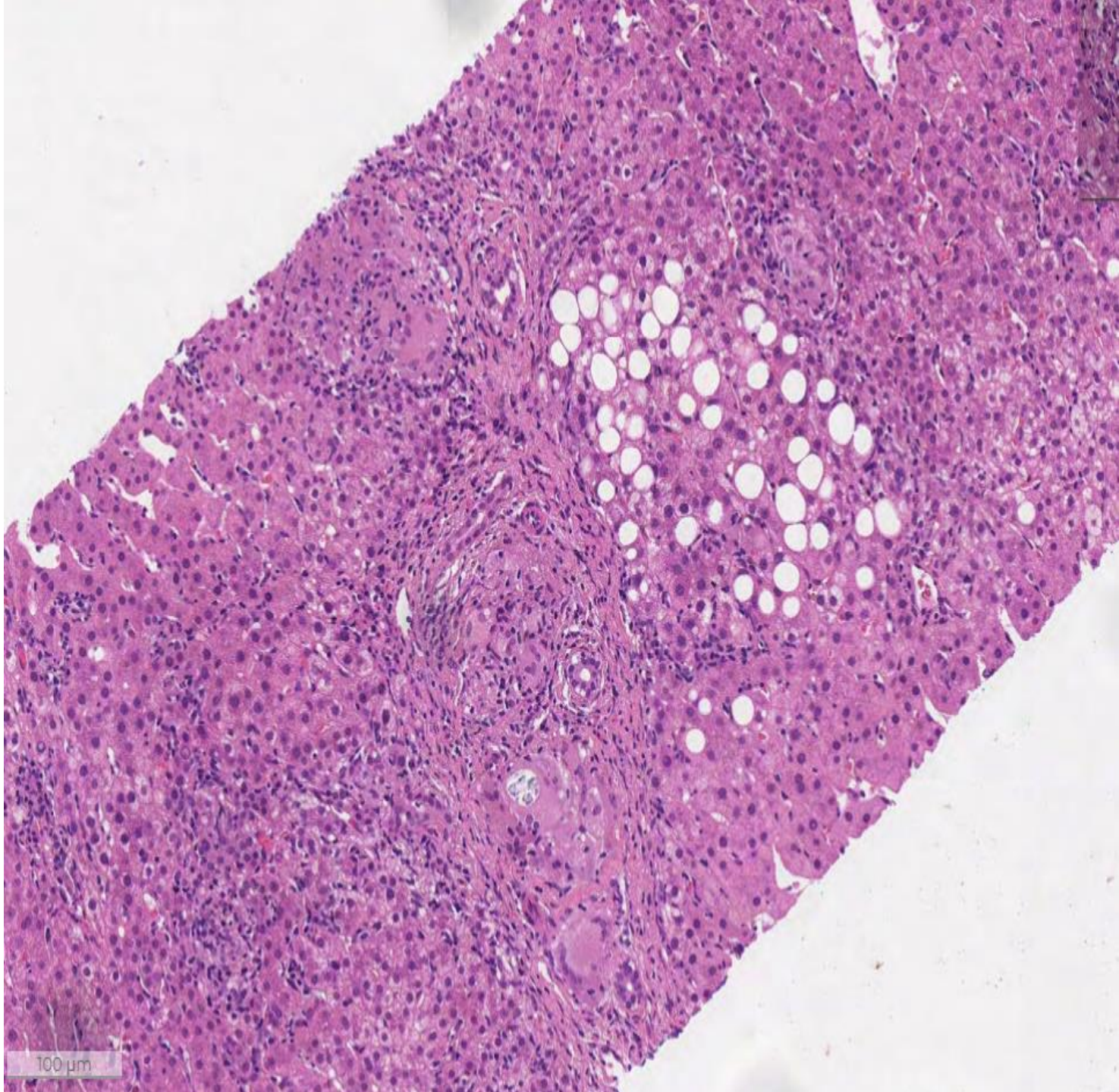
Case number:	LV1
Clinical Information:	Sarcoid diagnosed 2008. Subsequent Methotrexate, now stopped. GGT 137 iu/L, Alk Phos 258 iu/L, br 10 umol/L, ALT 16 iu/L. Normal Immunoglobulins. Autoimmune liver profile negative. Overweight. Splenomegaly.
Specimen:	liver biopsy
Age:	51
Sex:	Female
Macroscopic description: Immunohistochemistry:	Two fine pale brown cores each 19mm Special stains - fungal and mycobacterial stains are negative. Focal deposition of copper associated protein noted.

LV1

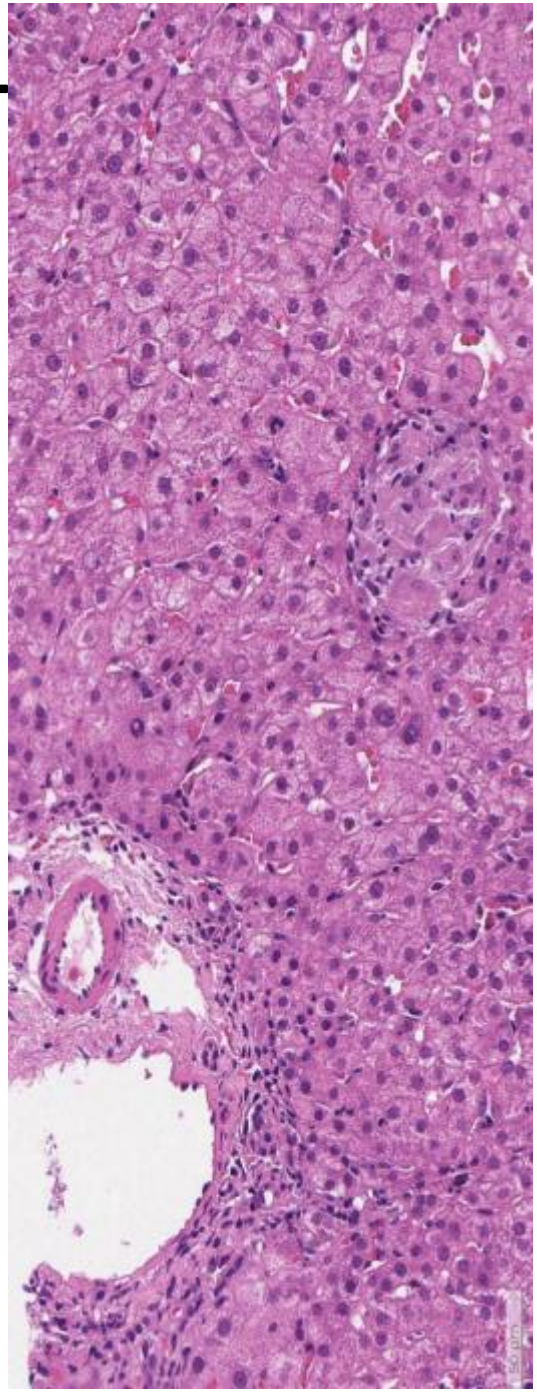


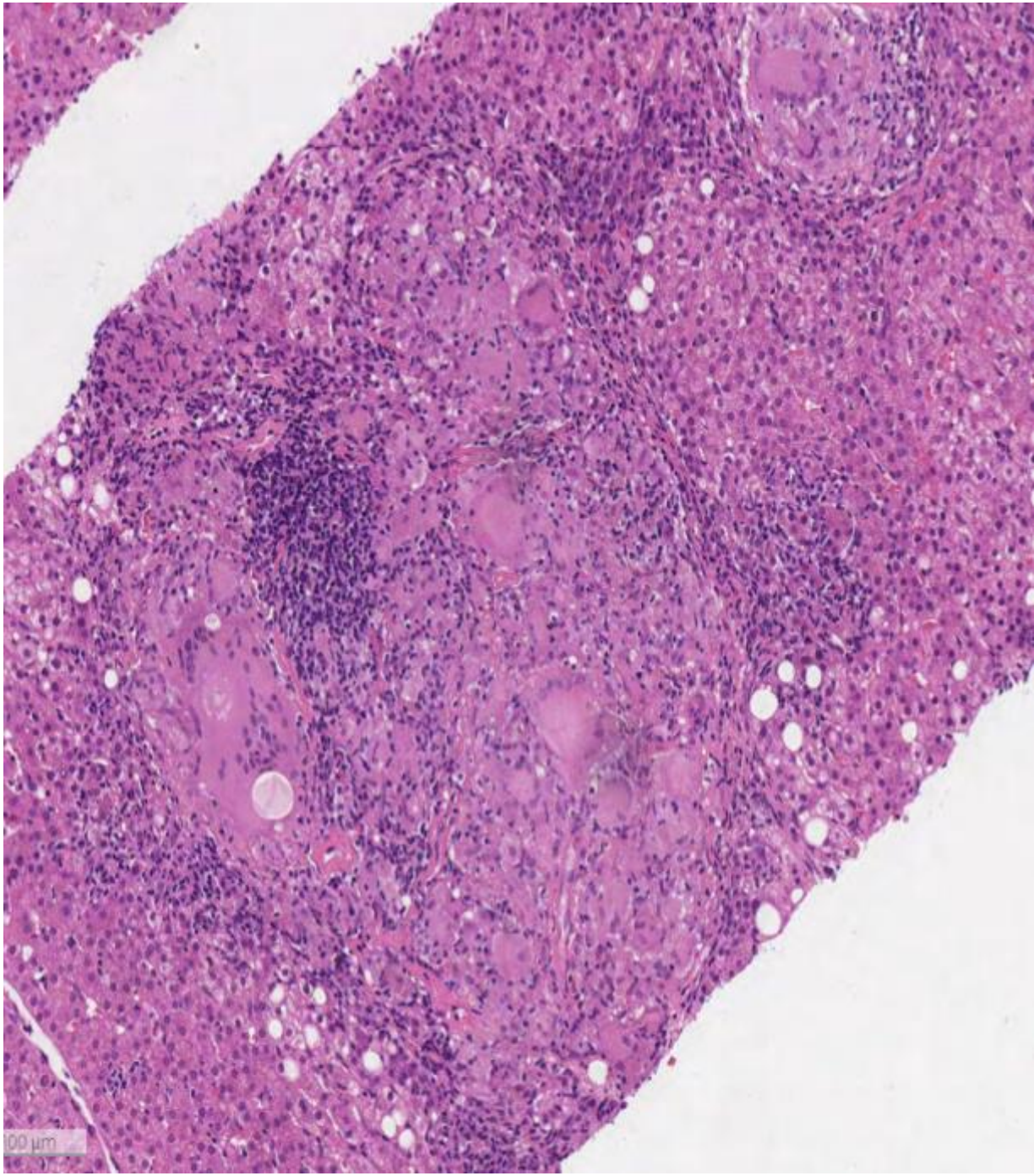

LV1
500 µm

LV1

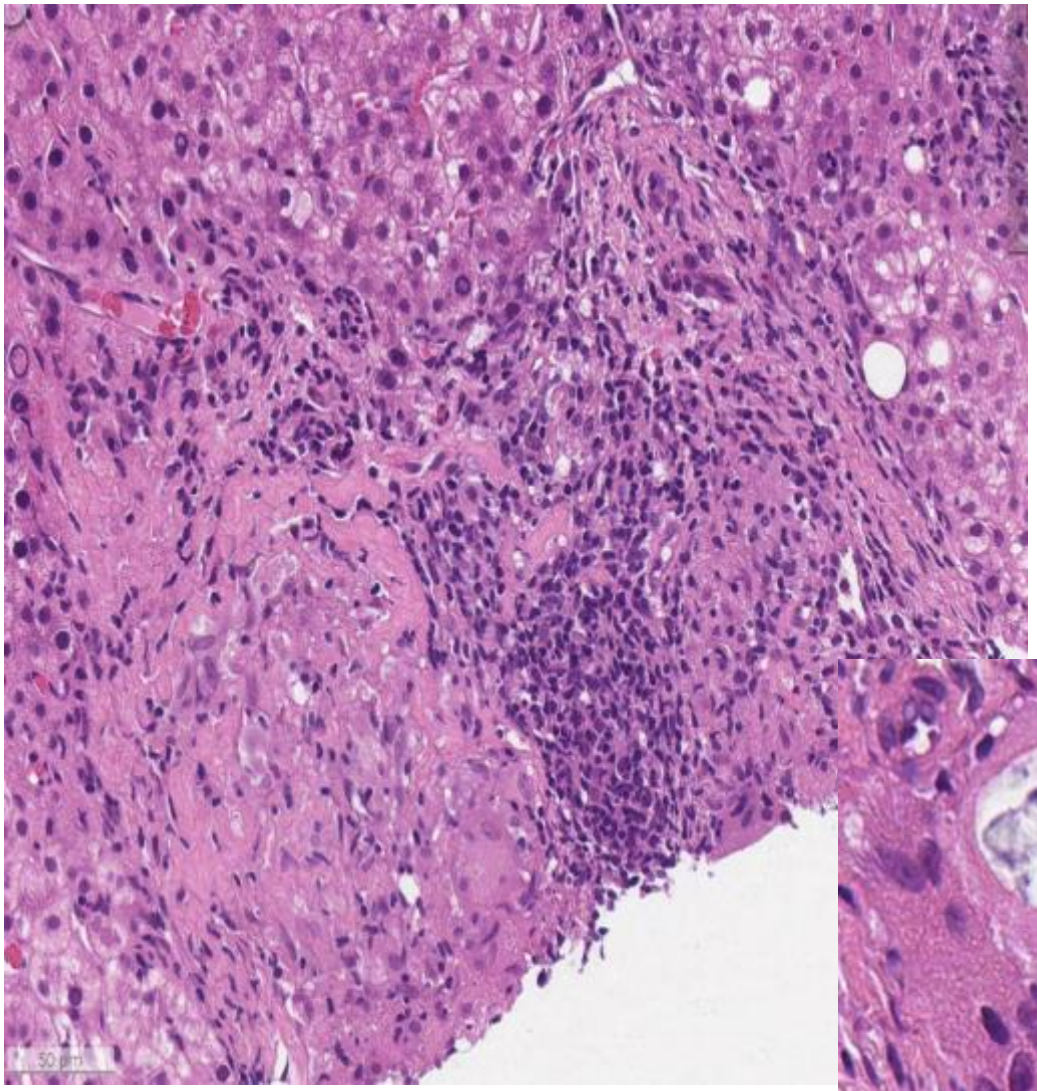


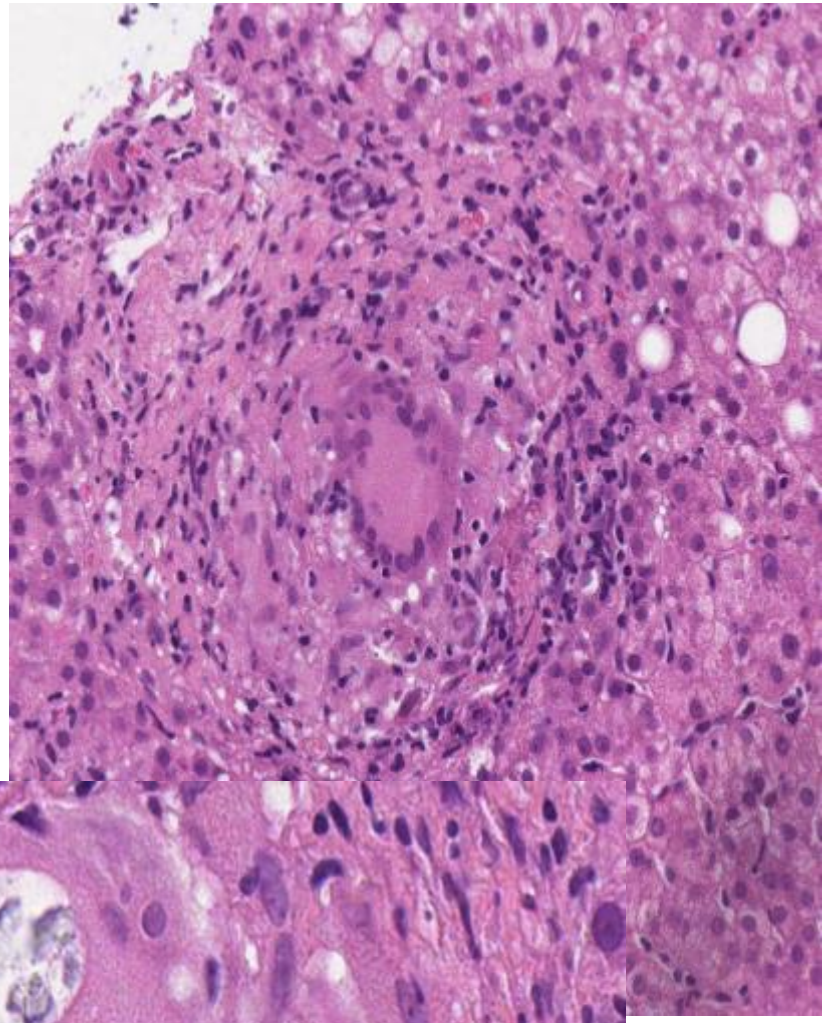
LV1

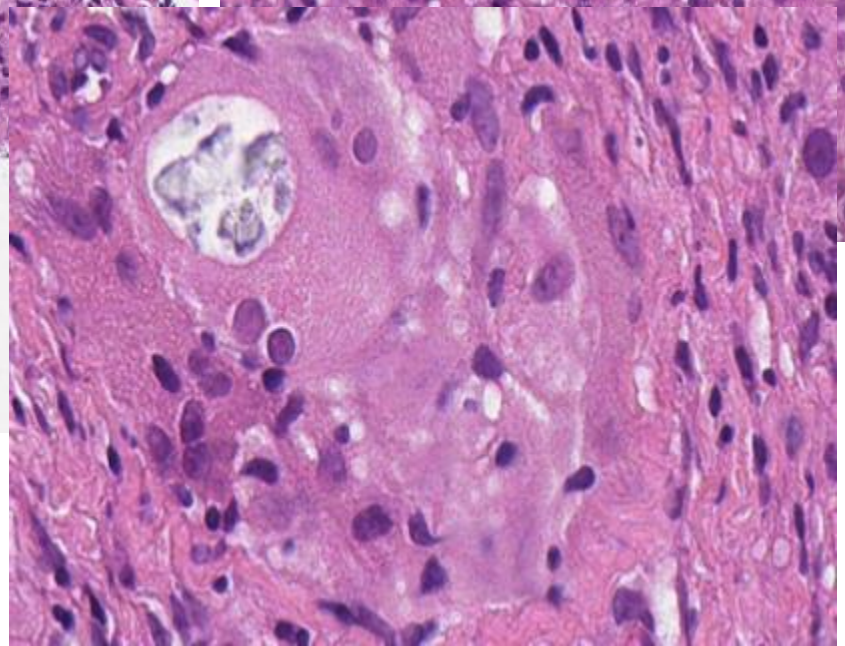




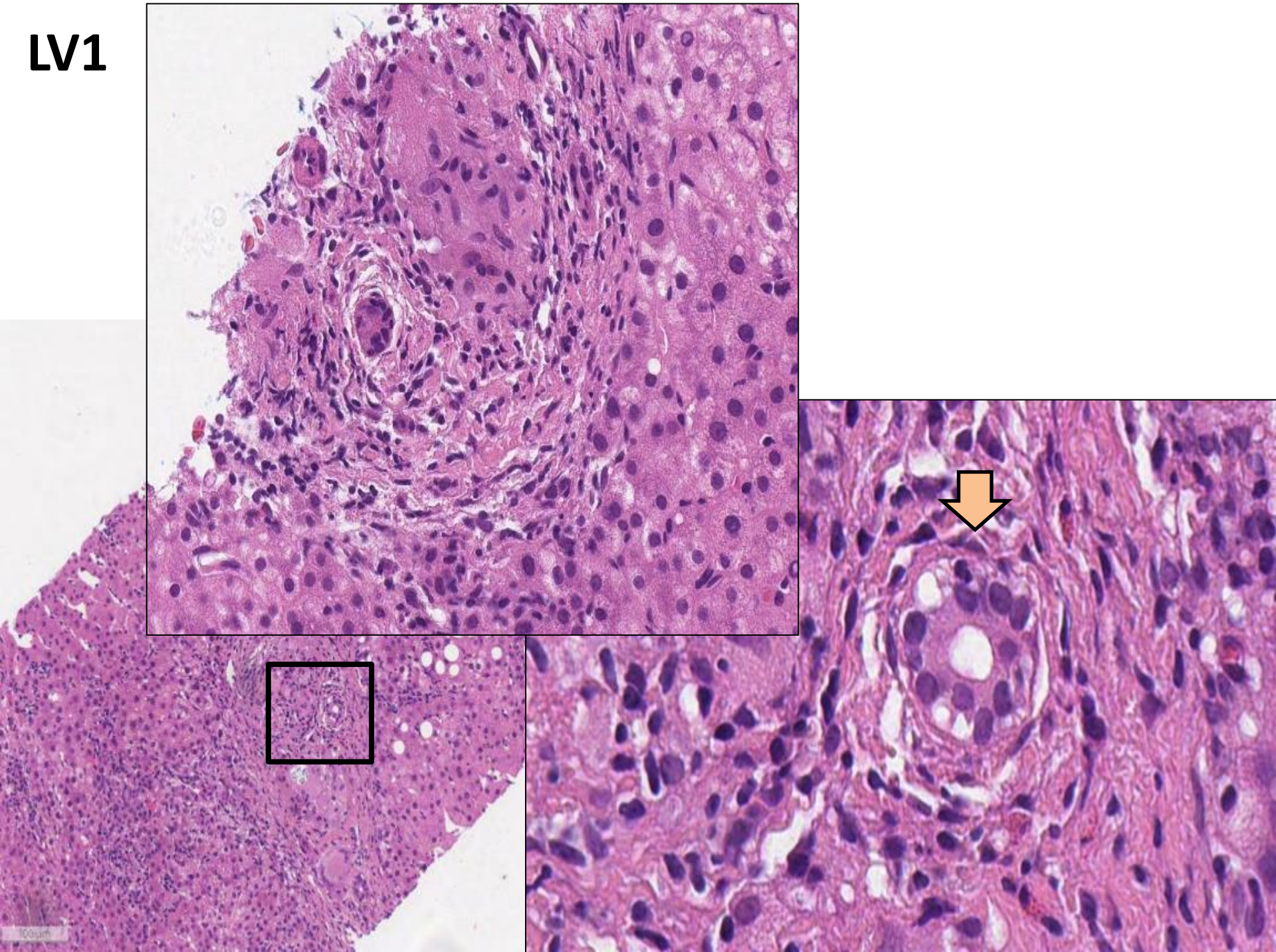
LV1



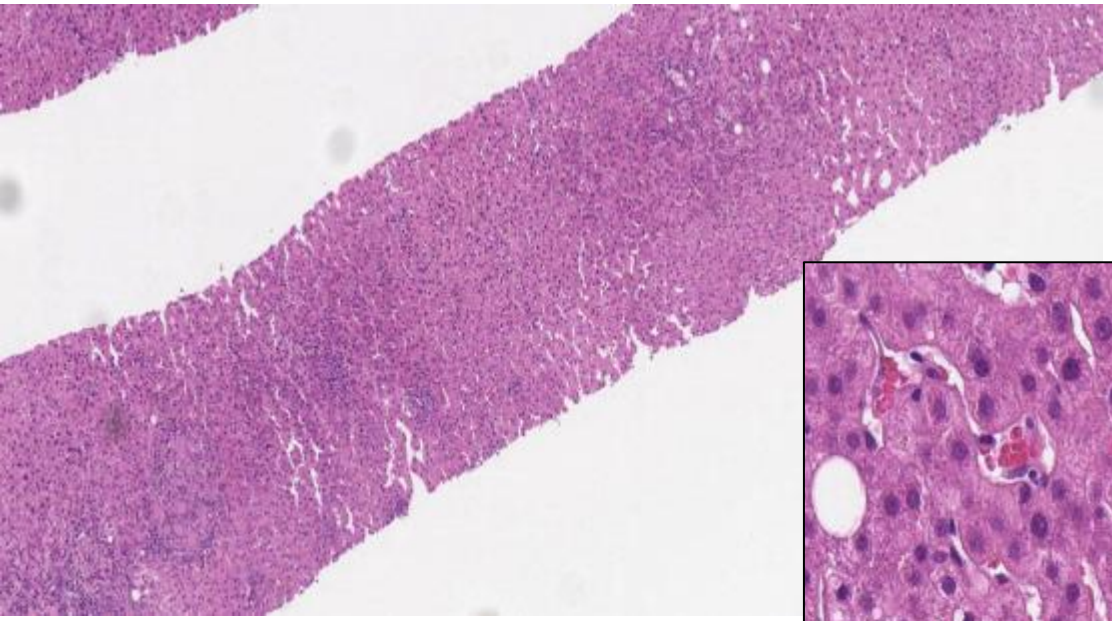


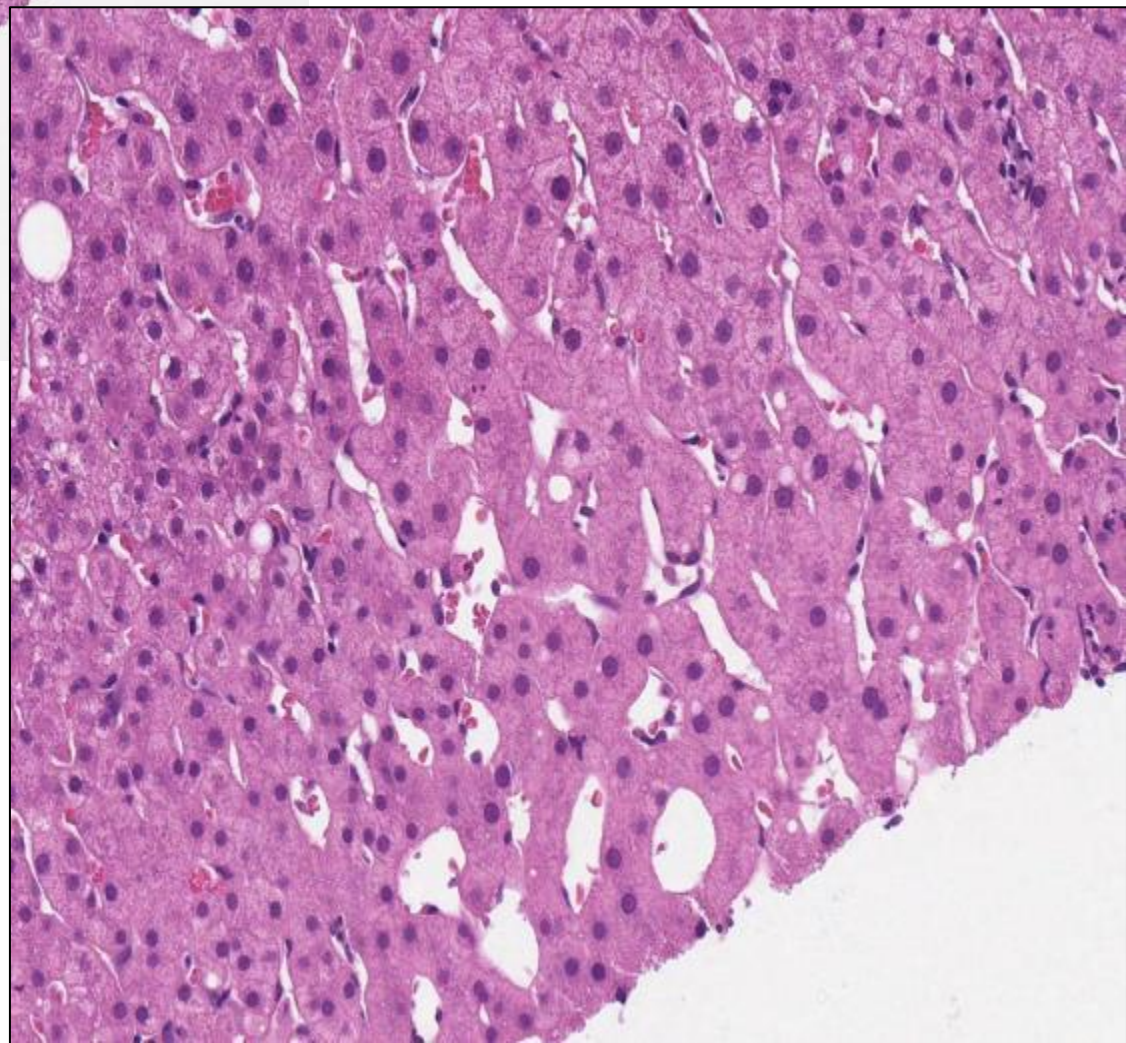


LV1

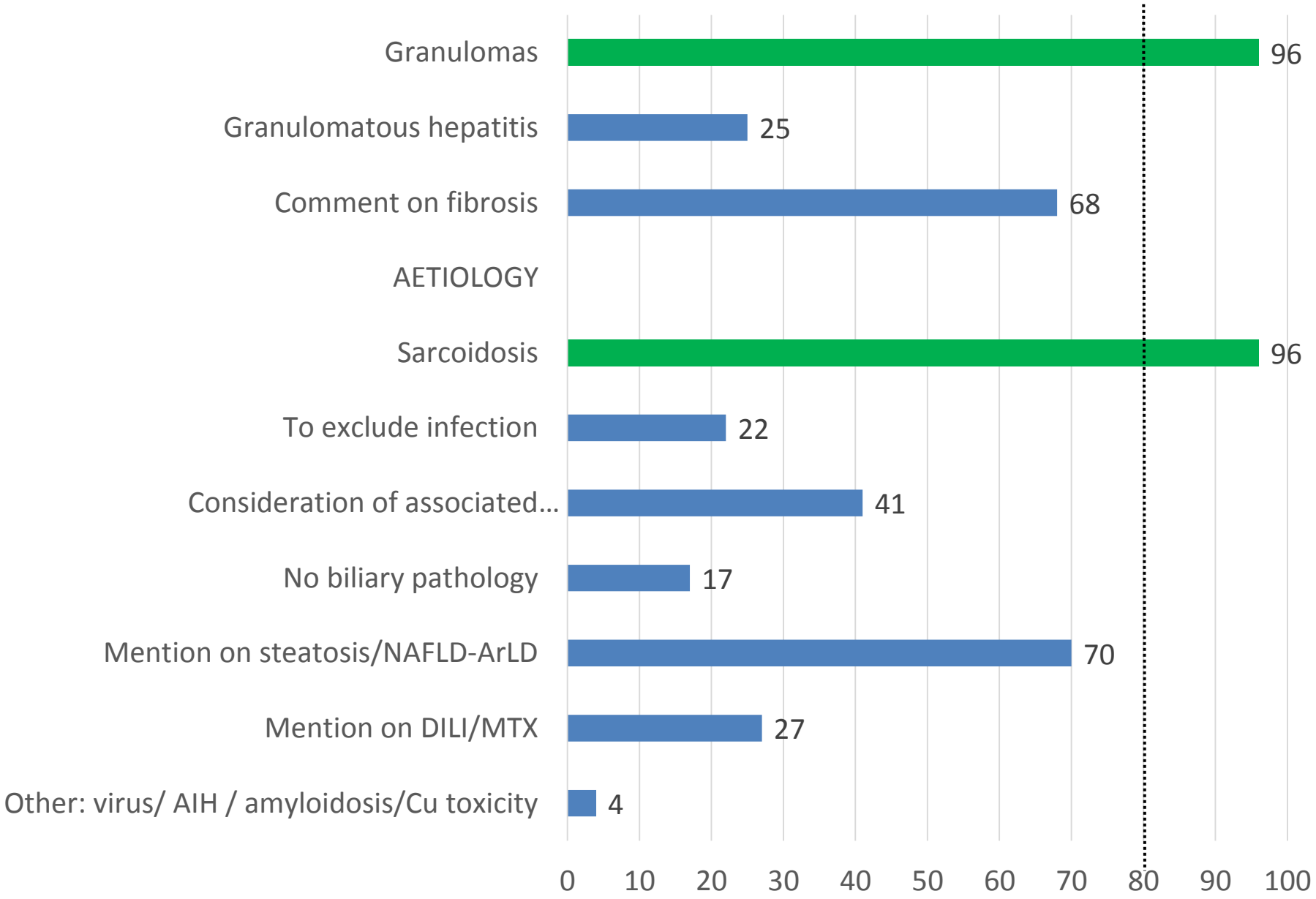


LV1





LV1 - Chart of responses



Consensus complete responses would include reference to the main lesion, **granulomas** and aetiology, **sarcoidosis**. Other diagnostic considerations or differential diagnosis did not reach consensus and consequently are not included. Many responses attempted to give an approximation of fibrosis but did not reach consensus, and, special stains for collagen deposition were not provided to assess properly this feature.

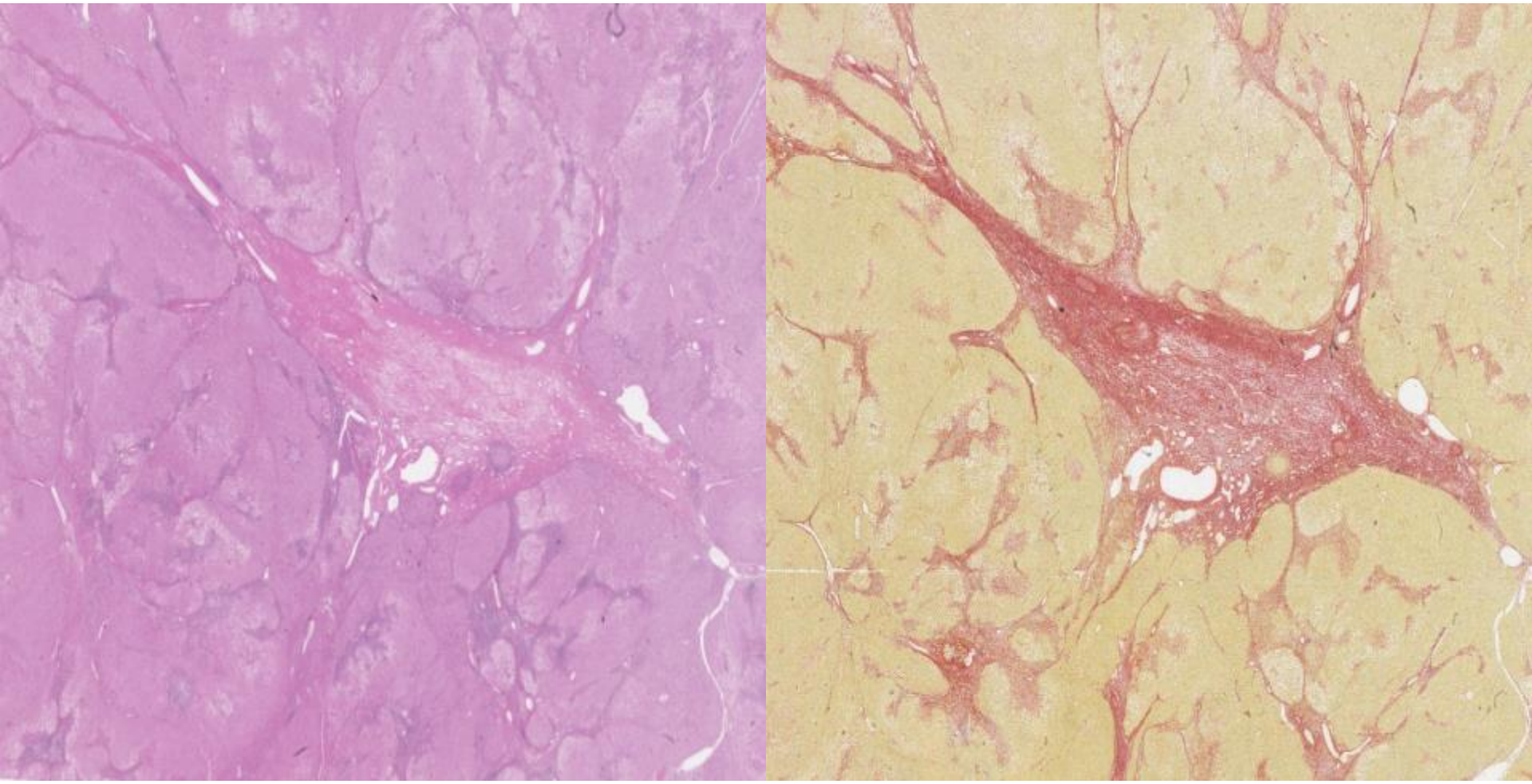
Suggested scoring: for 10 points include Granuloma and Sarcoidosis Agreed
Lose 5 marks if -
Lose 10 marks (score 0) if -

Discussion points:
- Granulomas / Granulomatous hepatitis correct nomenclature?
- Sarcoidosis and cholangiopathy association 41 mentioned biliary features 17 'no biliary features'

LV
Case 2

Case number:	**LV2**
Clinical Information:	Liver mass on imaging
Specimen:	Liver resection segment 3
Age:	32
Sex:	Female
Macroscopic description:	Wedge of liver 90 x 60 x 50mm, central fibrous scar
Immunohistochemistry:	PSR

LV2



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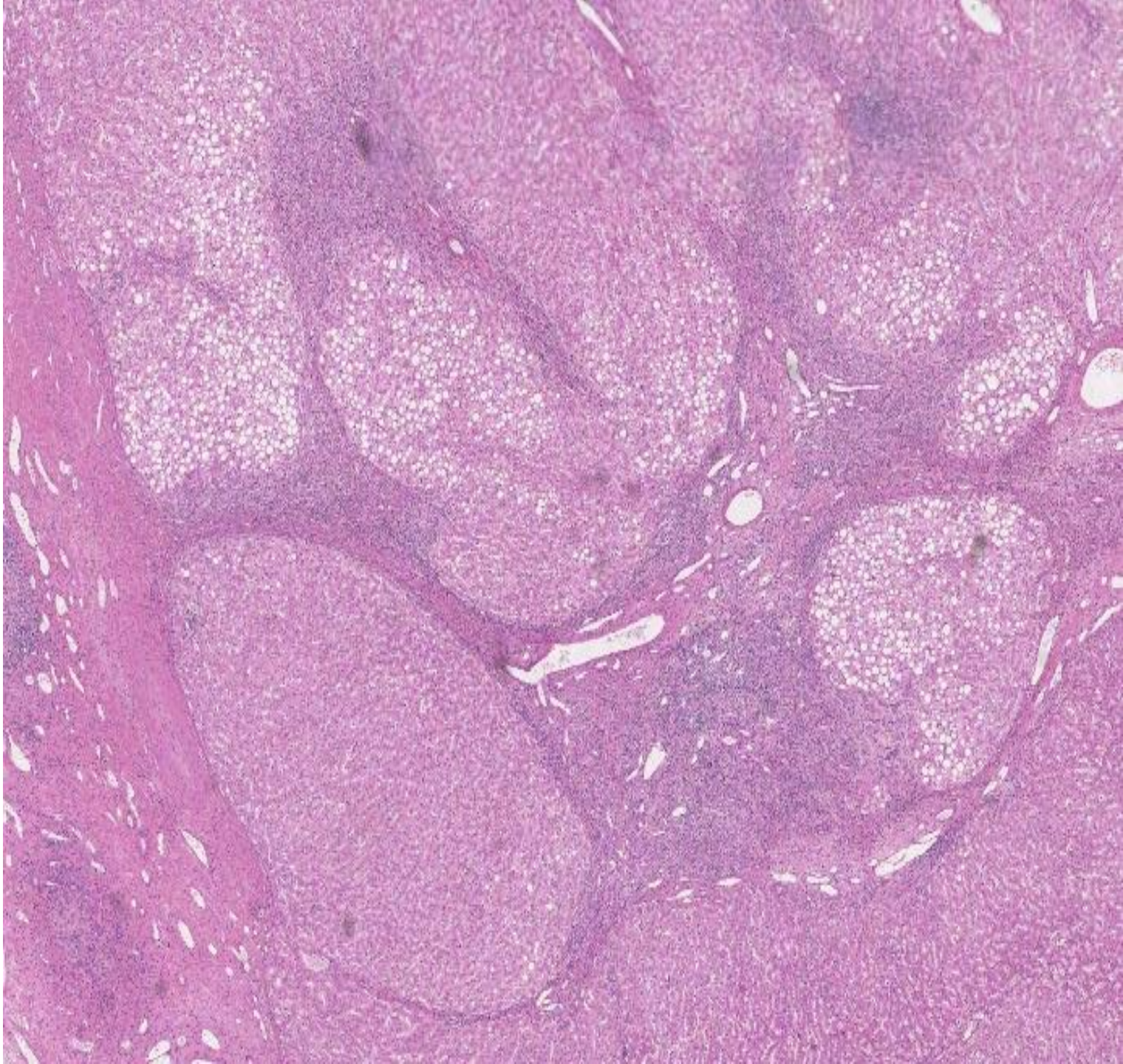

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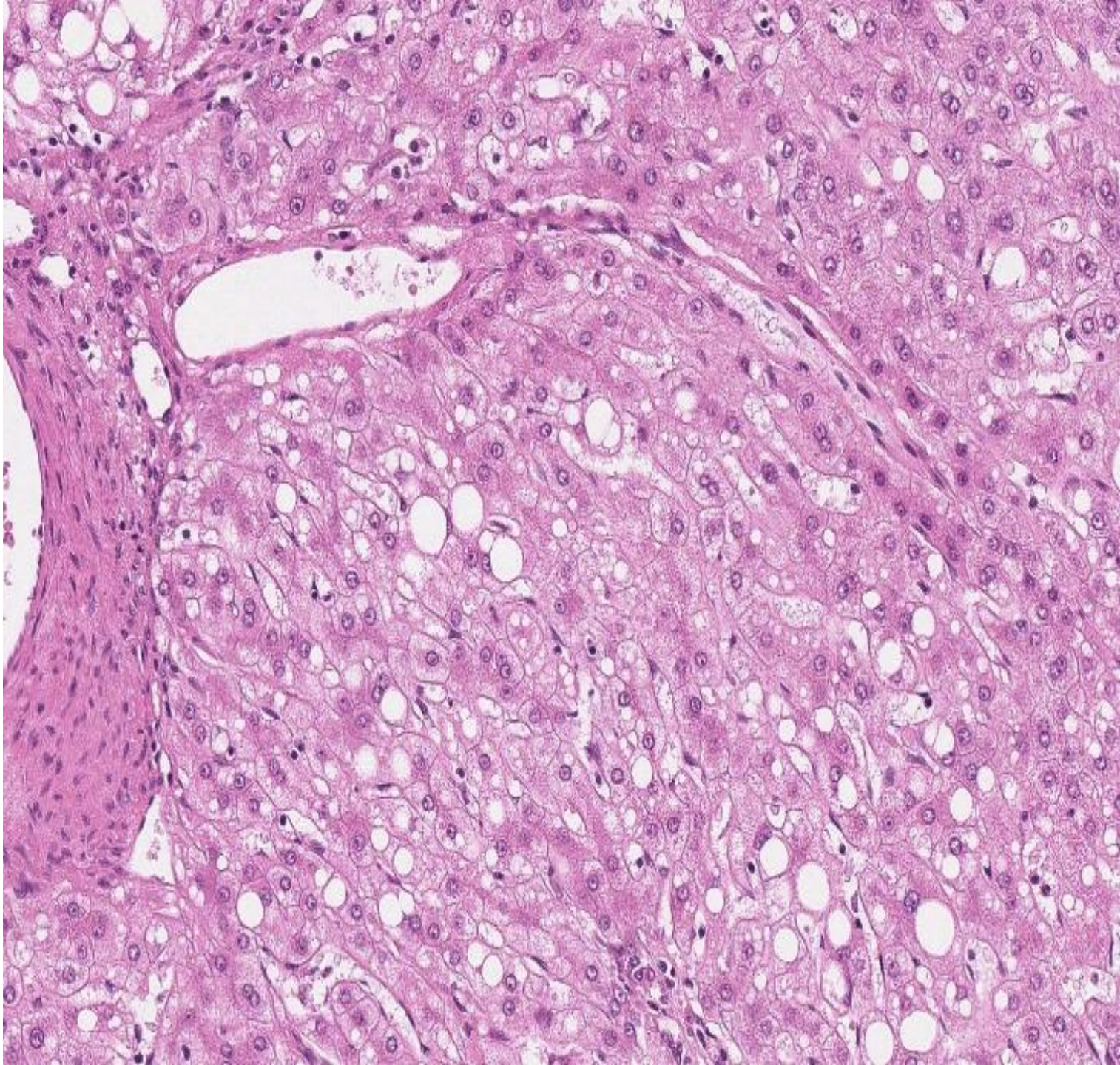

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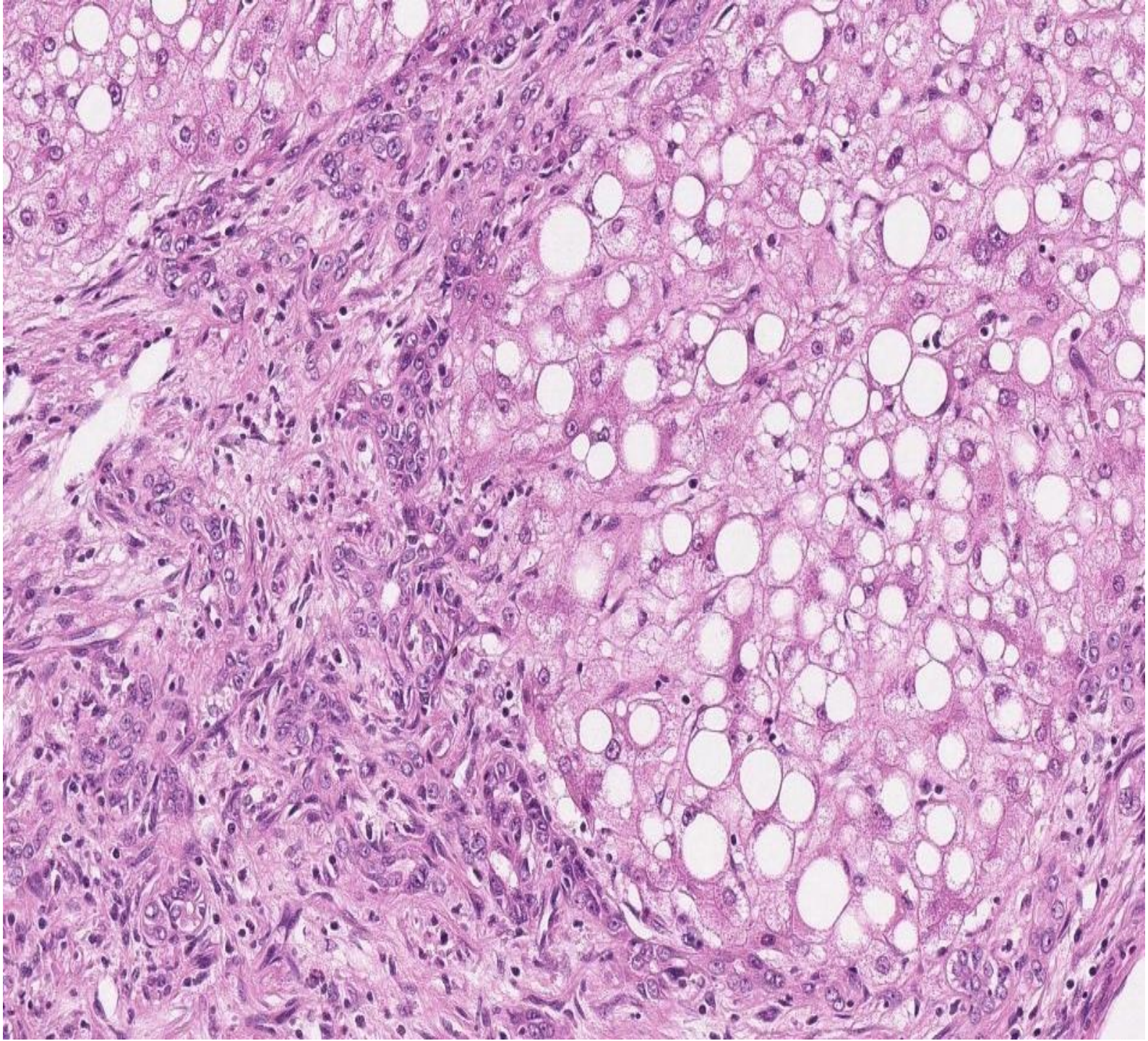

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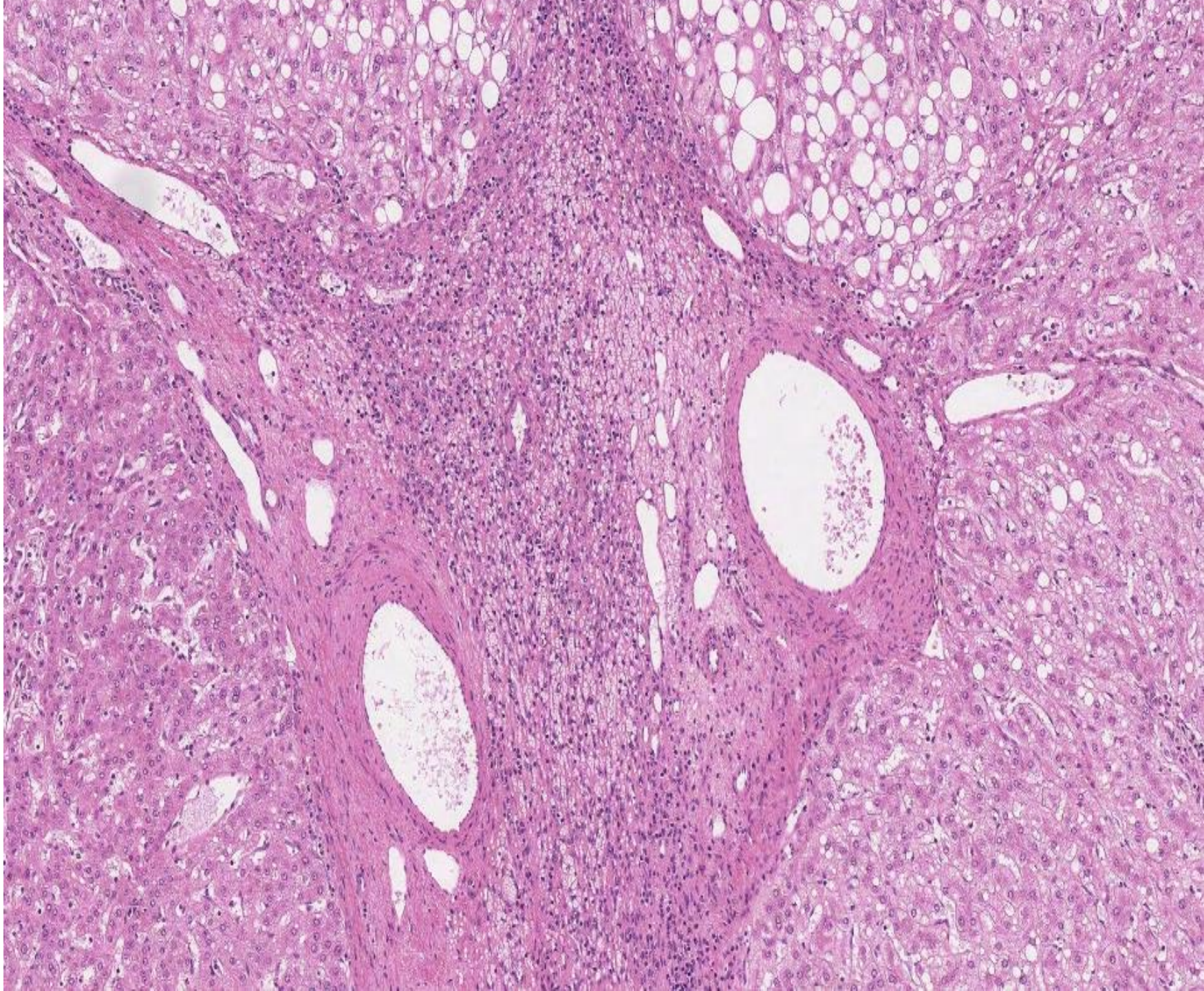
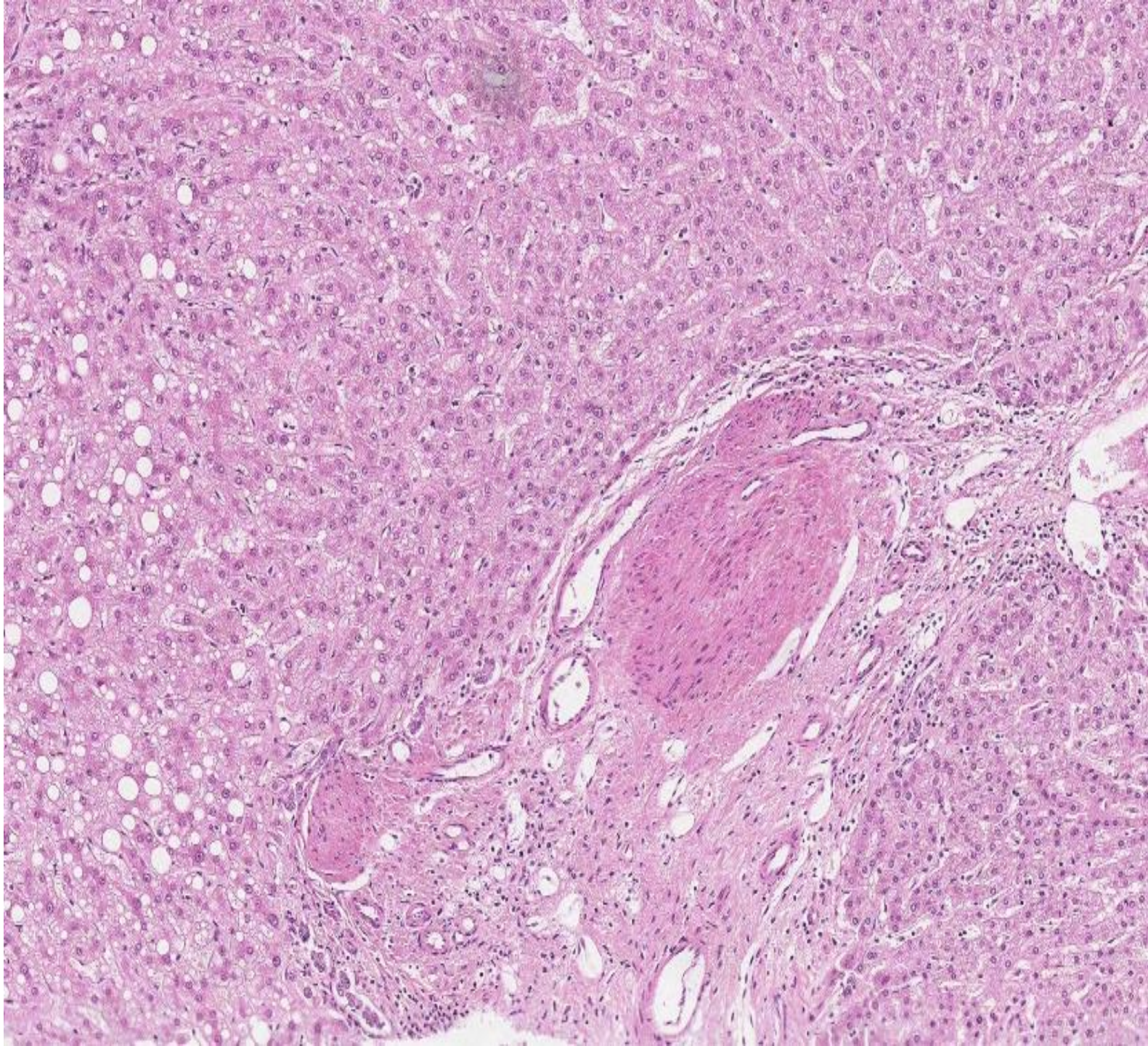
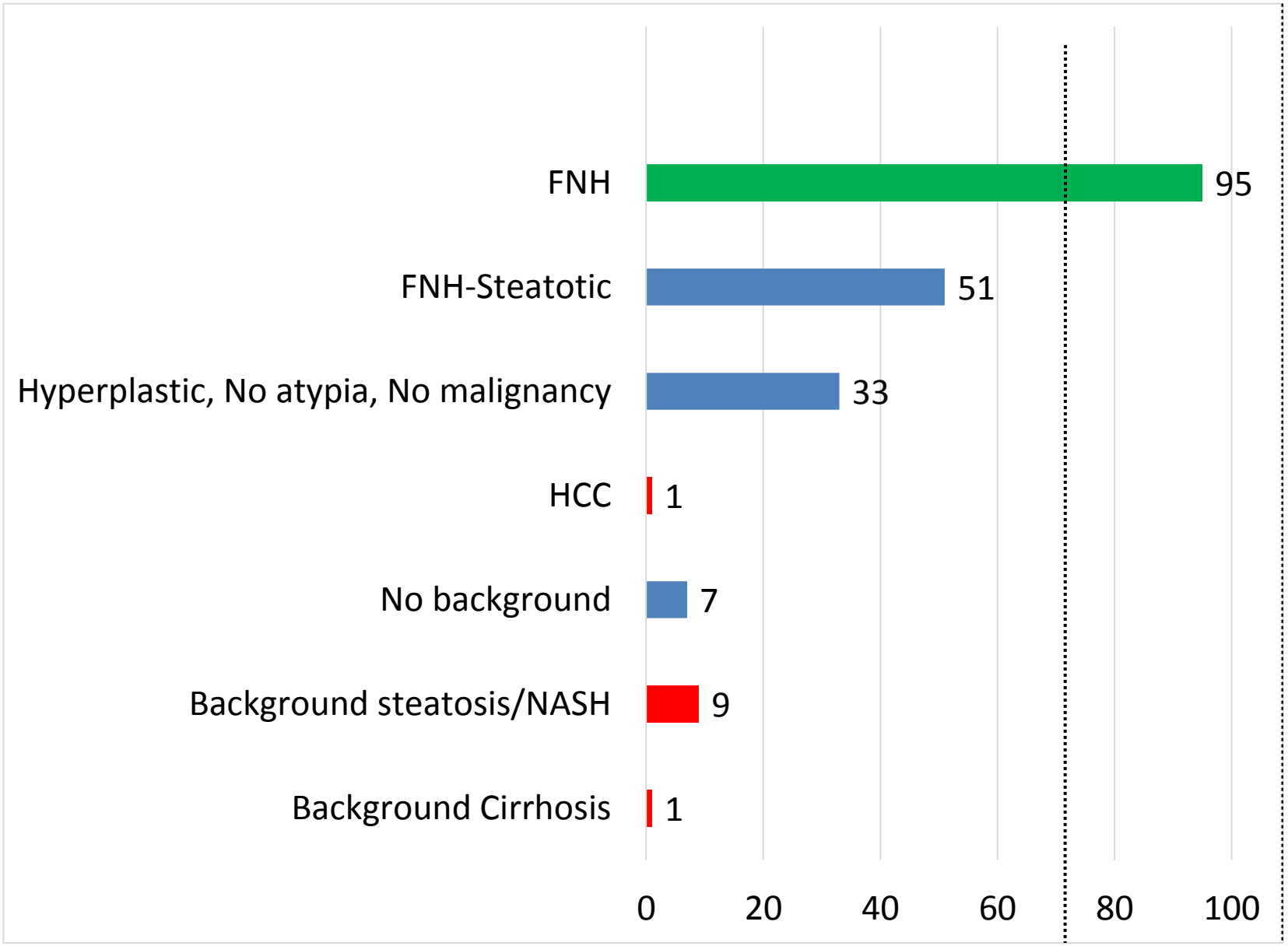


LV2



LV2 – Chart of responses



LV2 Consensus complete responses would include: Focal nodular hyperplasia.

Suggested scoring: for 10 points include Focal nodular hyperplasia

Lose 5 marks if there is description of the background liver (only lesional tissue is represented) responses saying background cirrhosis should lose 5 marks as a diagnosis of cirrhosis has significant implications for the patient leading to wrong management pathway. Implying a background of fatty liver disease less clinically relevant, don't lose marks – could put this to members.

Lose 10 marks (score 0) if diagnosis of malignancy, HCC agreed

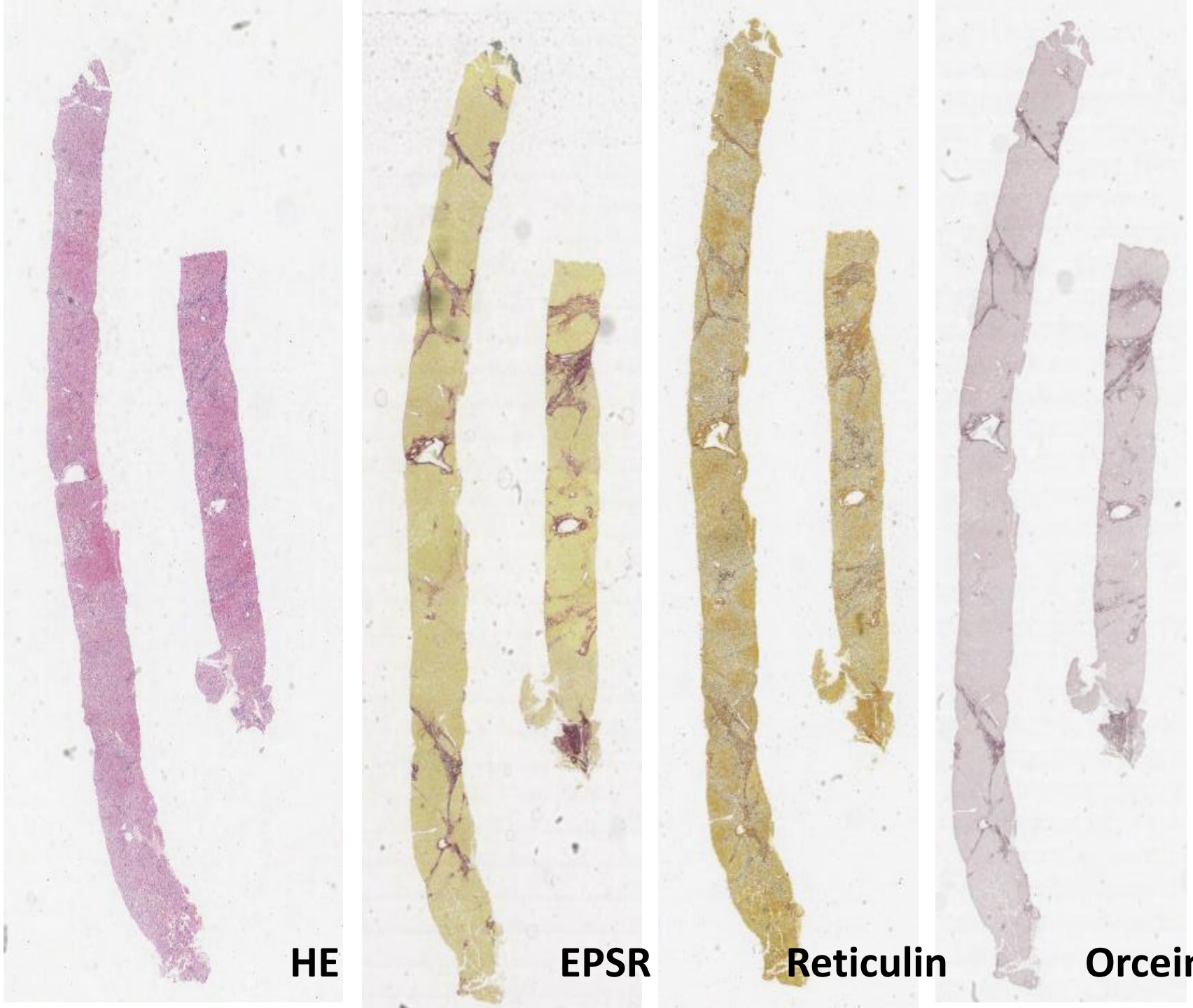
Discussion points

- Steatosis in FNH
- "Cirrhotic" architecture in FNH

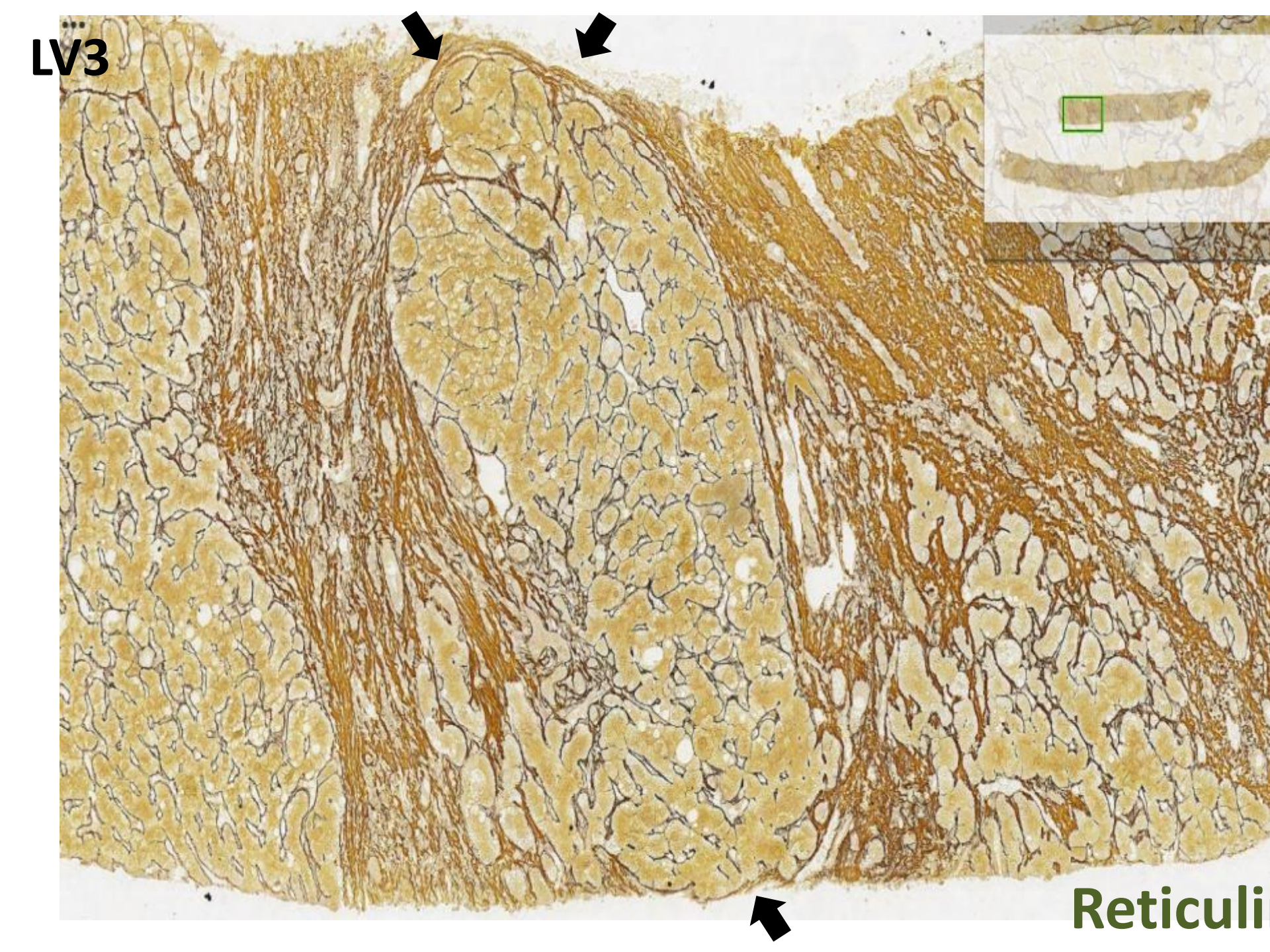
LV
Case 3

Case number:	LV3
Clinical Information:	He has an active hepatitis C. He is now within the window period where he can now be transplanted (downstaged). Background liver biopsy to establish cirrhosis or not (as this would determine eligibility if cirrhotic).
Specimen:	liver core biopsy
Age:	69
Sex:	Male
Macroscopic description: Immunohistochemistry:	Liver biopsy background: Core of tissue 2.4cm in length bisected at 1.7cm special stains EPSR, Perls, Reticulin, PASD, orcein

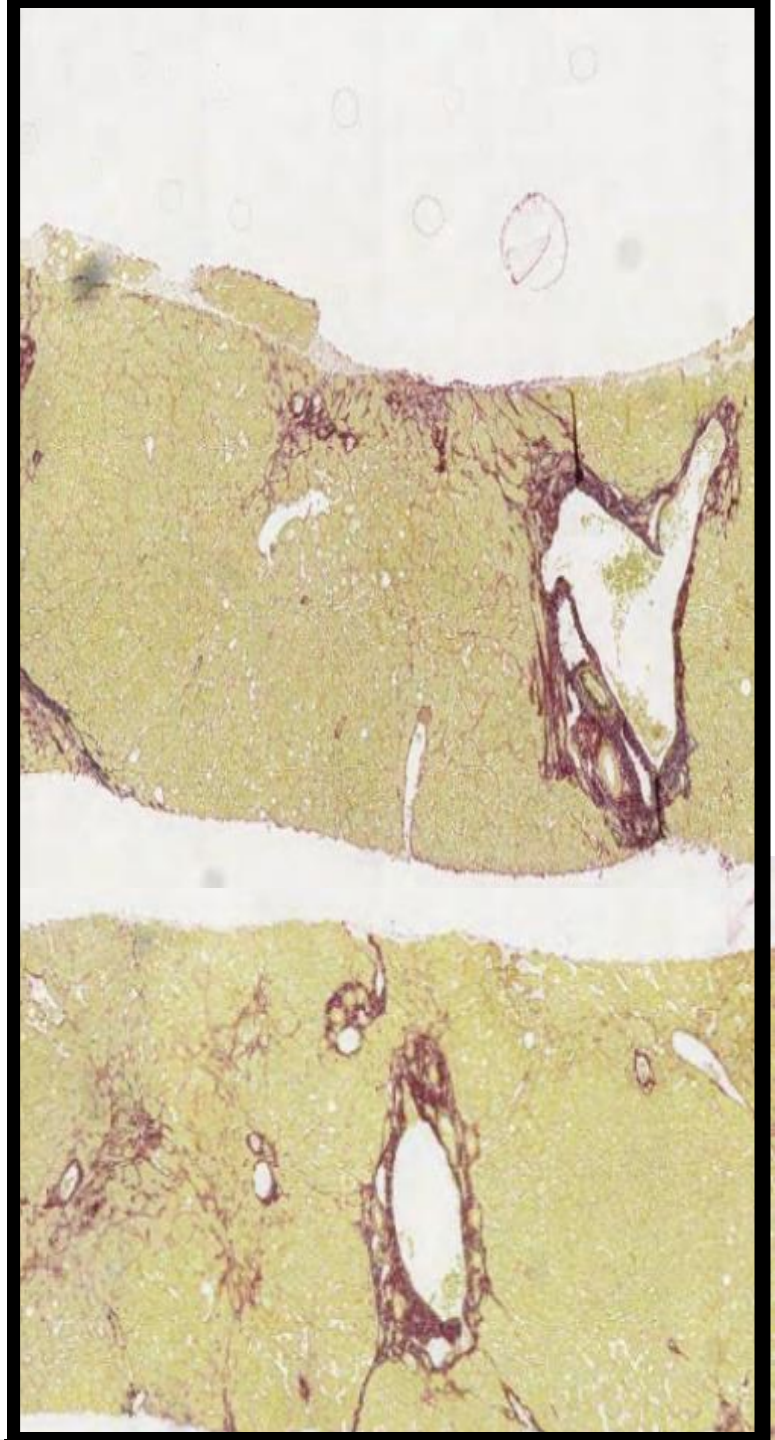
LV3

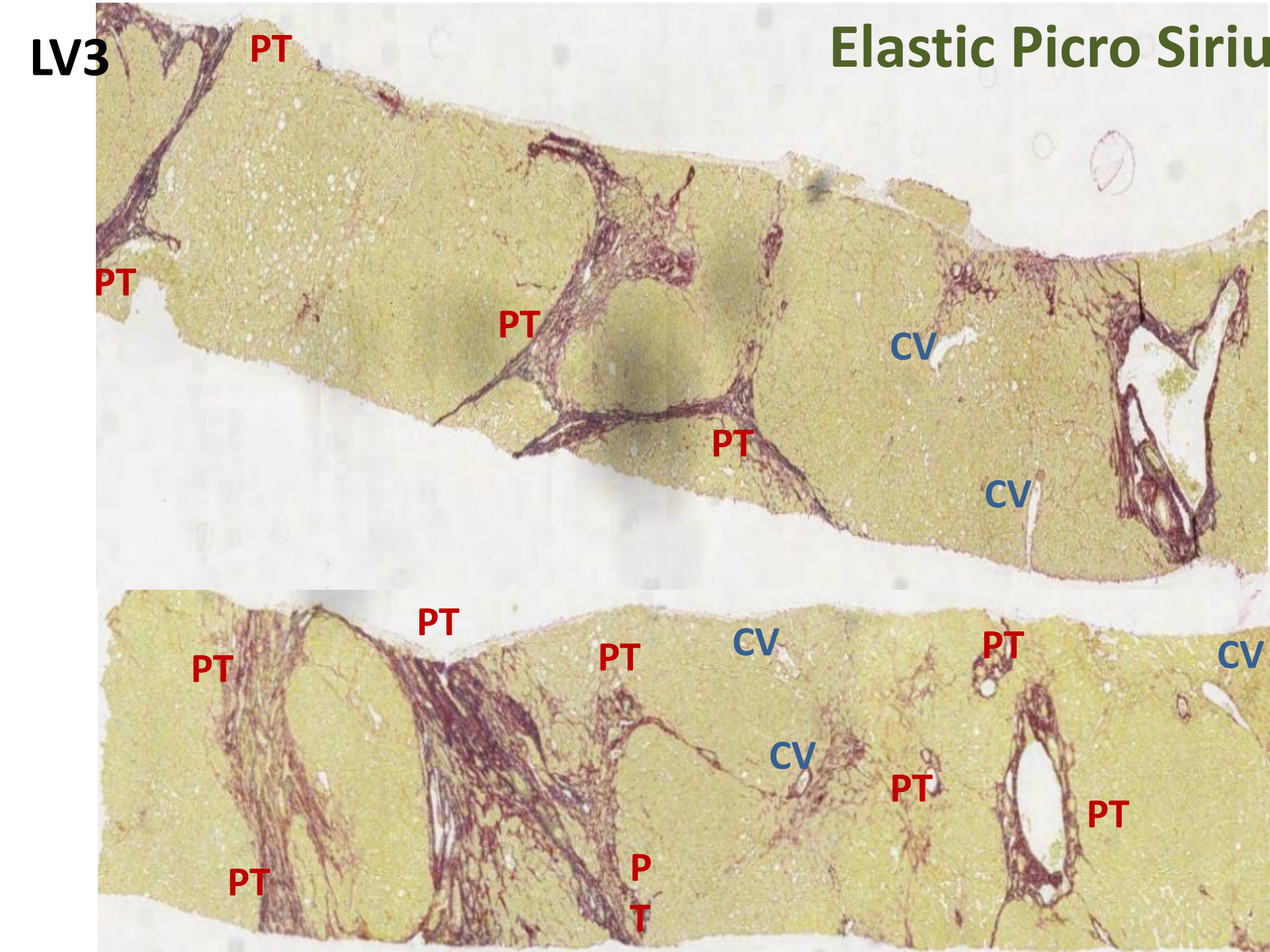


LV3


LV3
Reticuli

LV3

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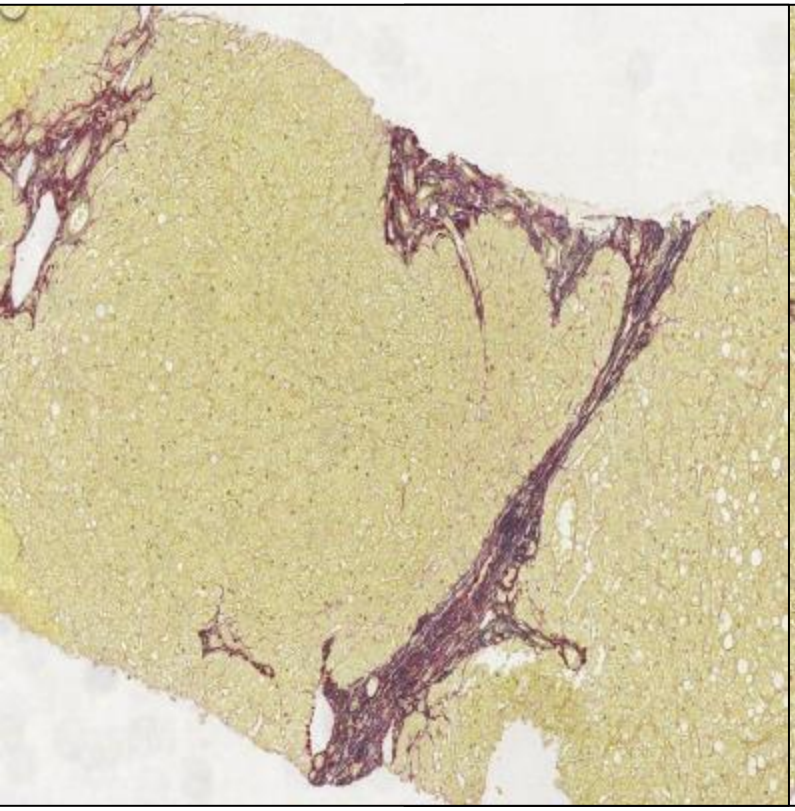
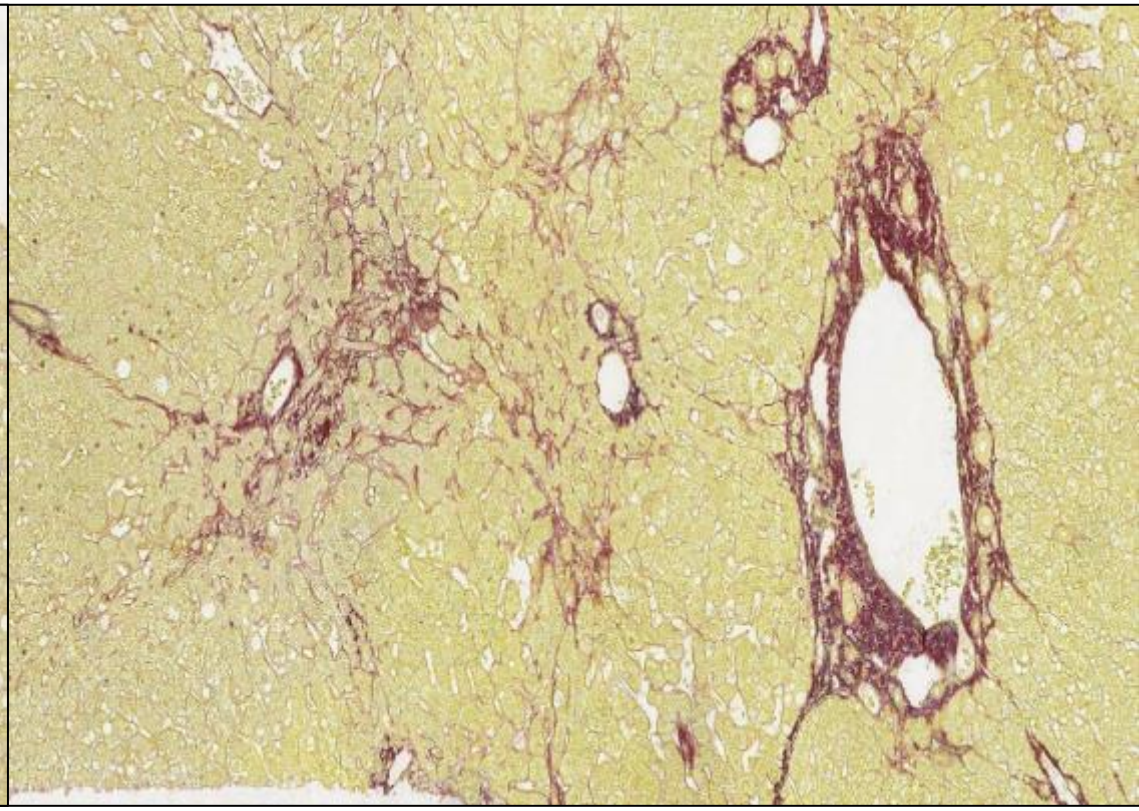
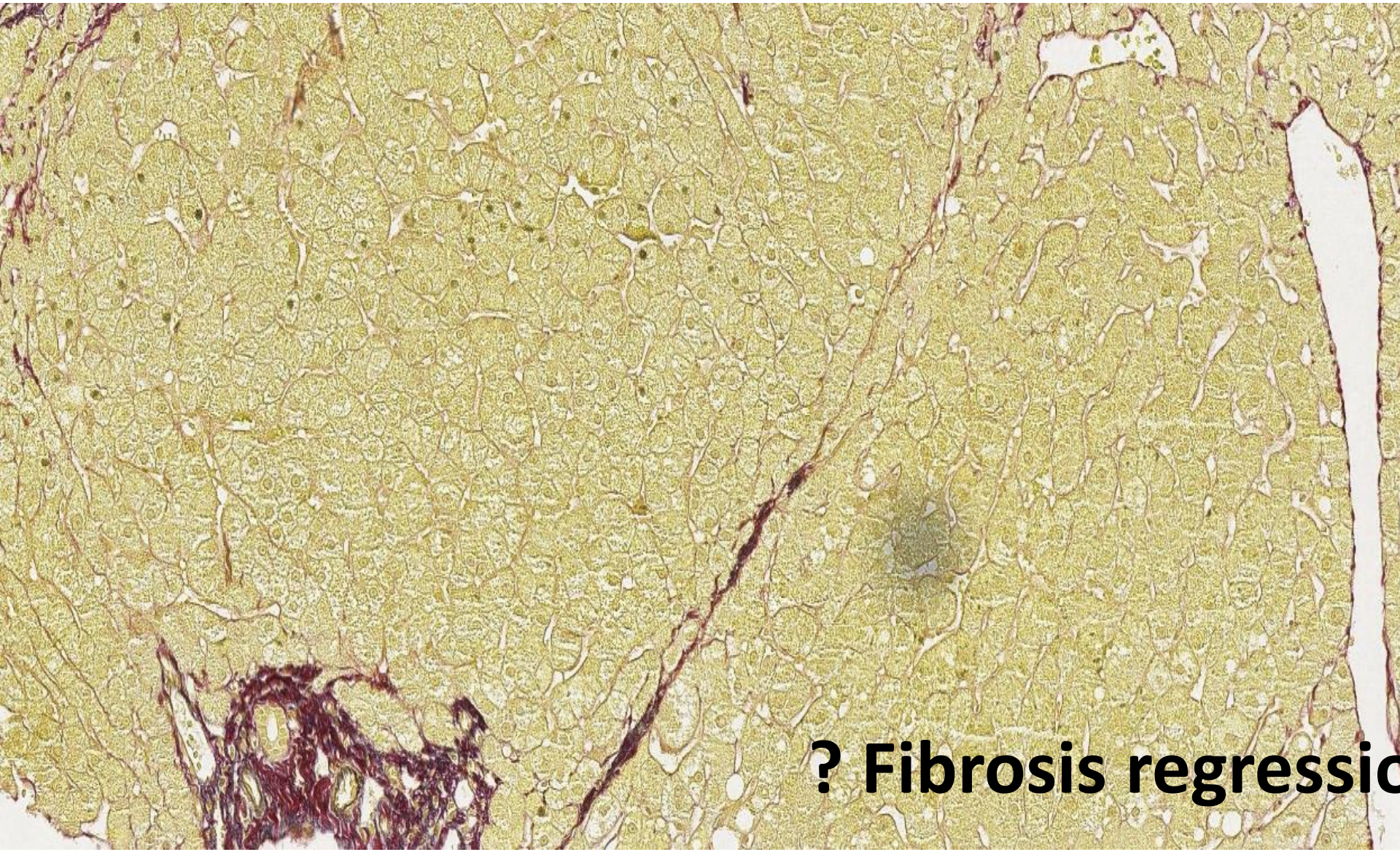


Portal-based fibrosis

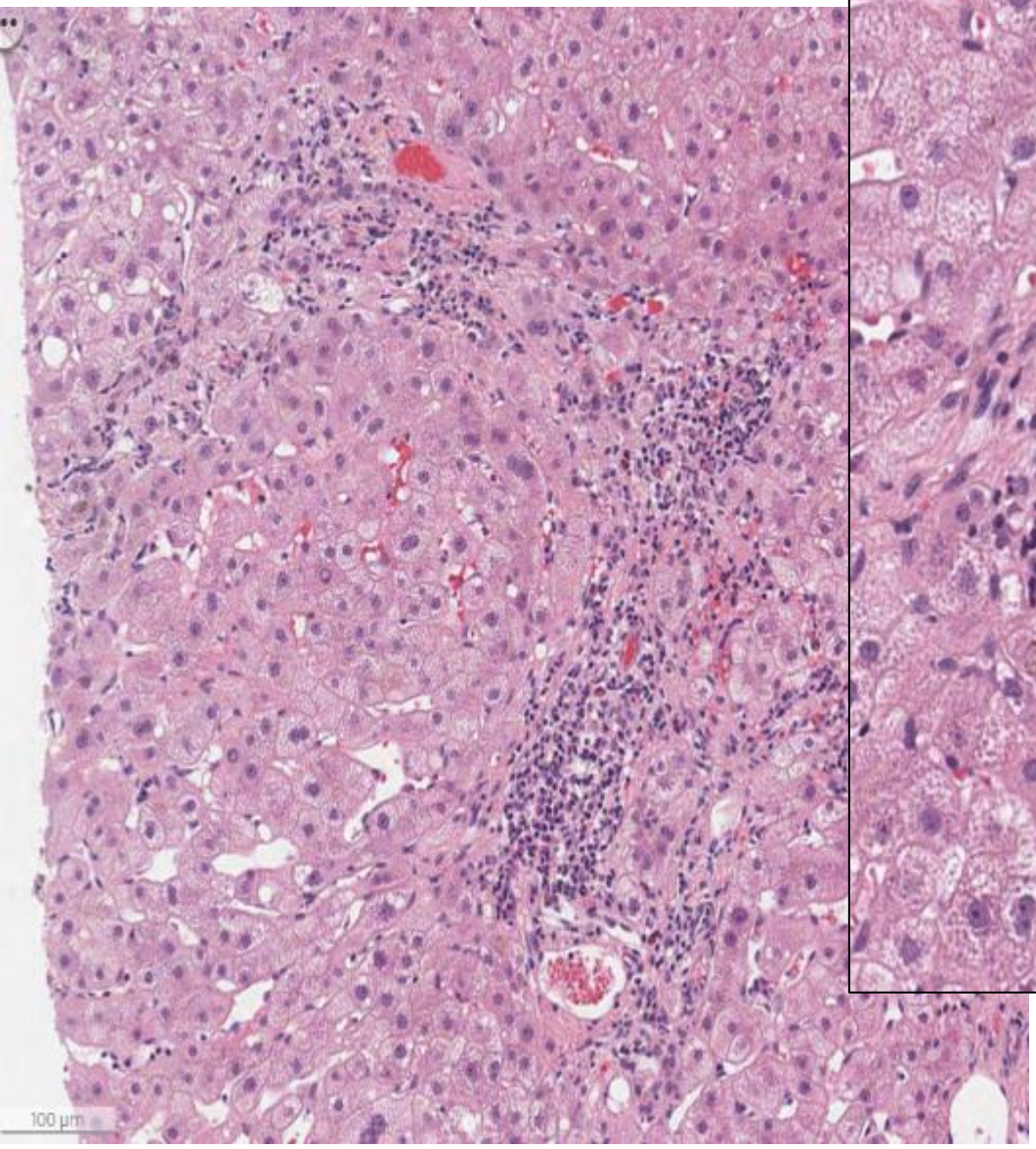


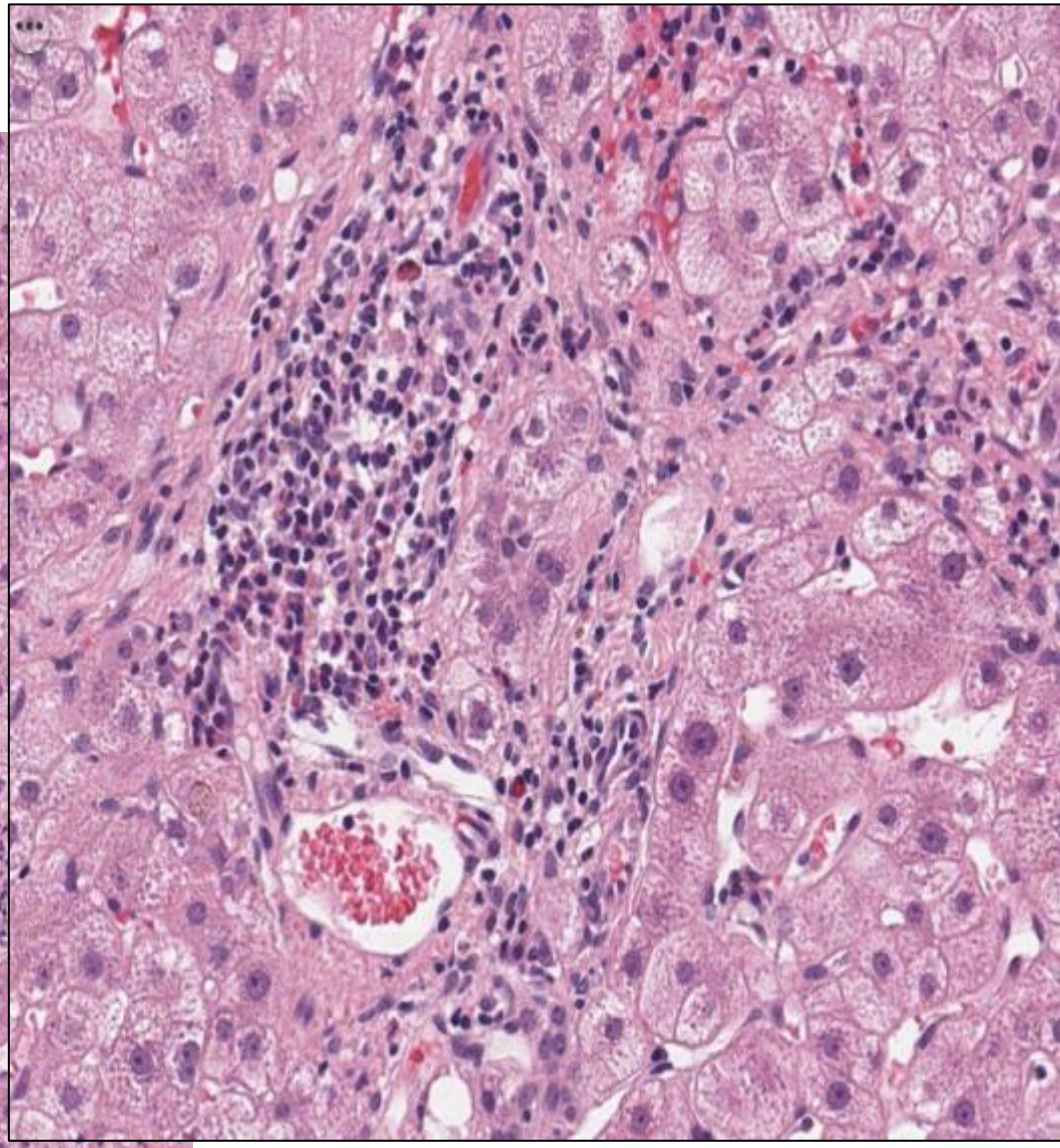
Subsinusoidal fibrosis

LV3

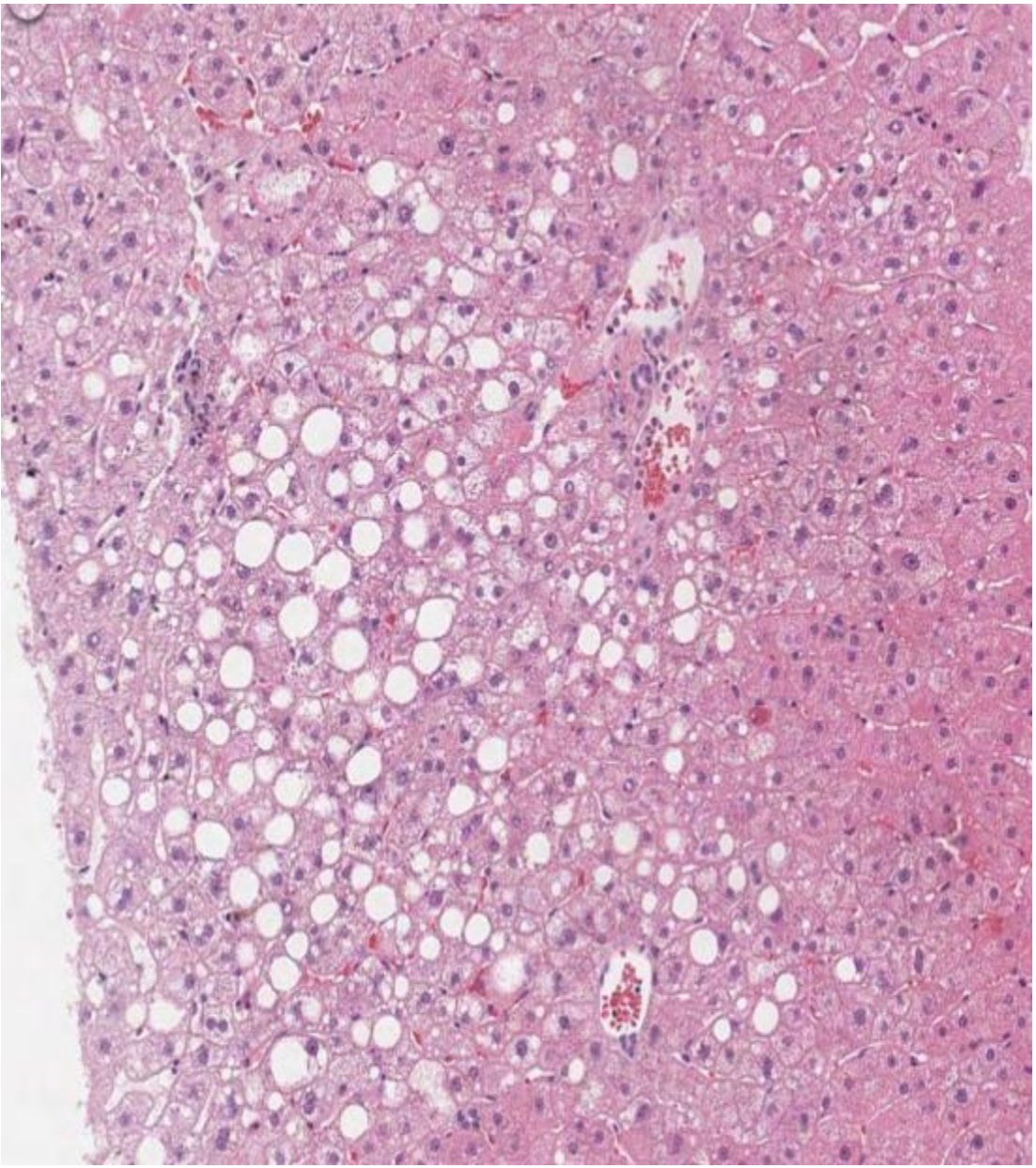


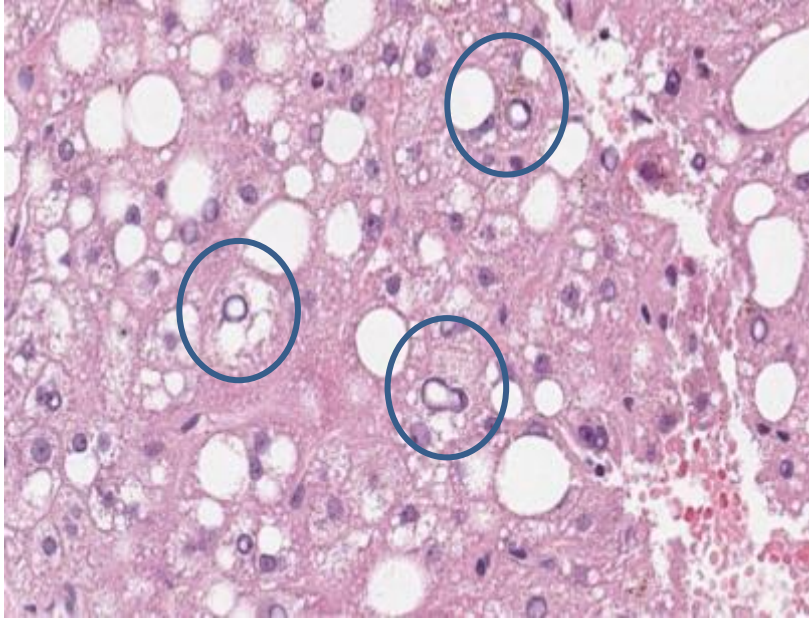
LV3

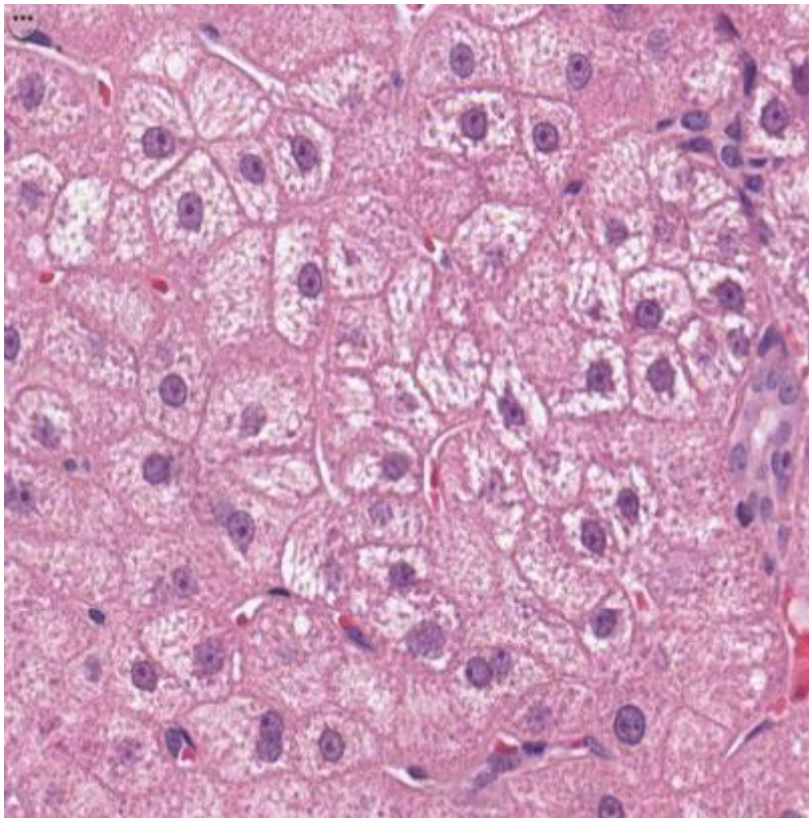




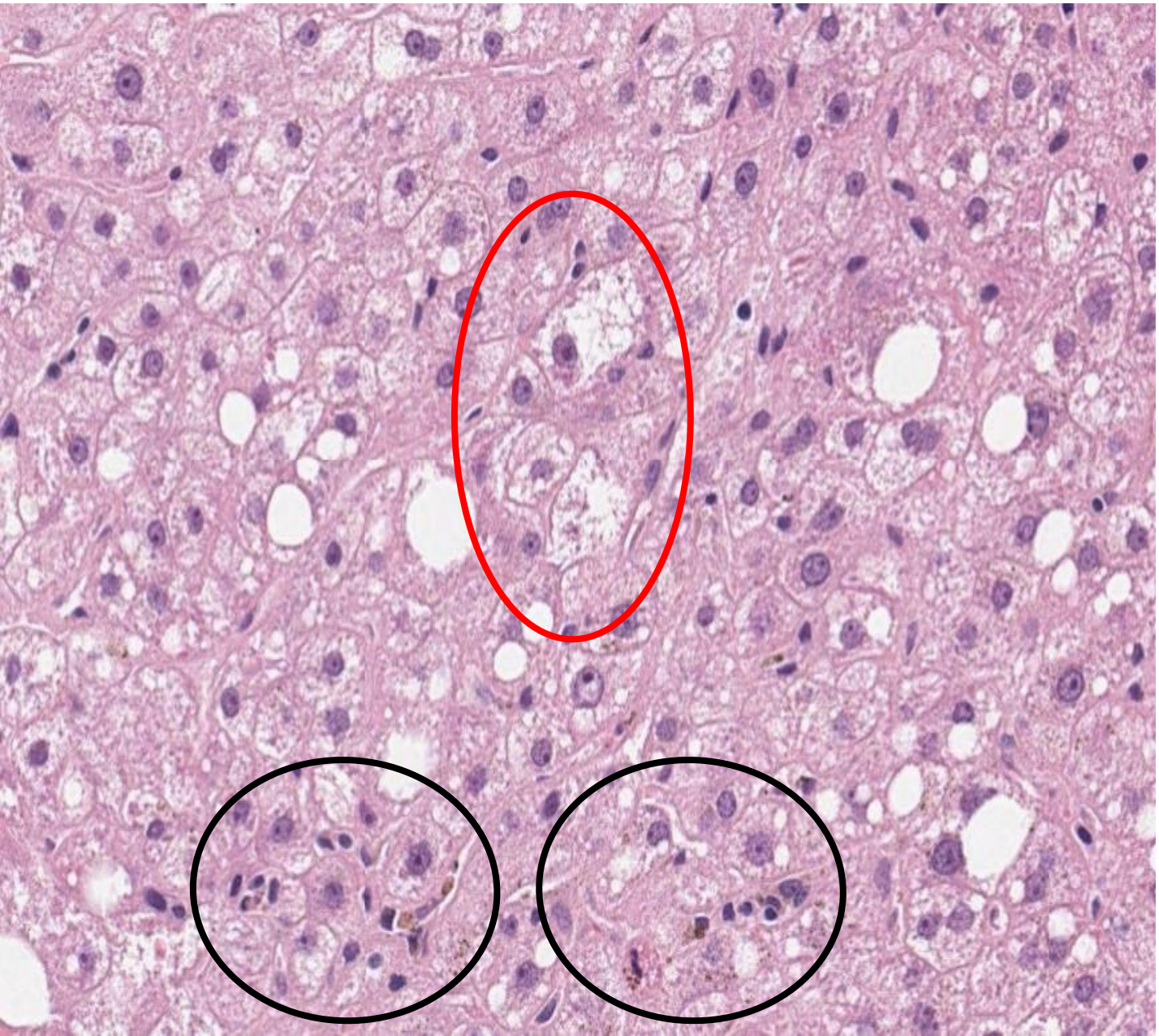
LV3







LV3



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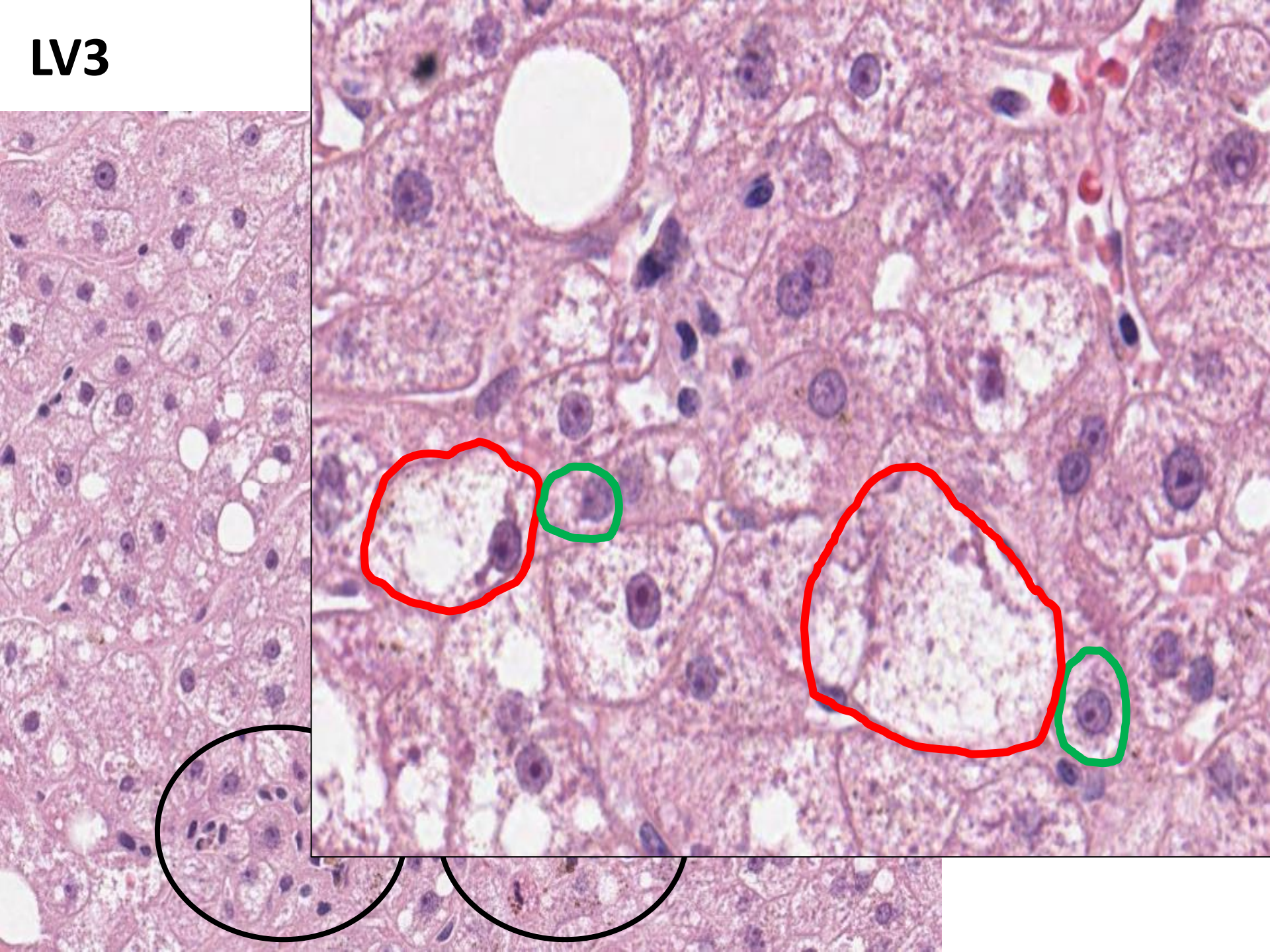
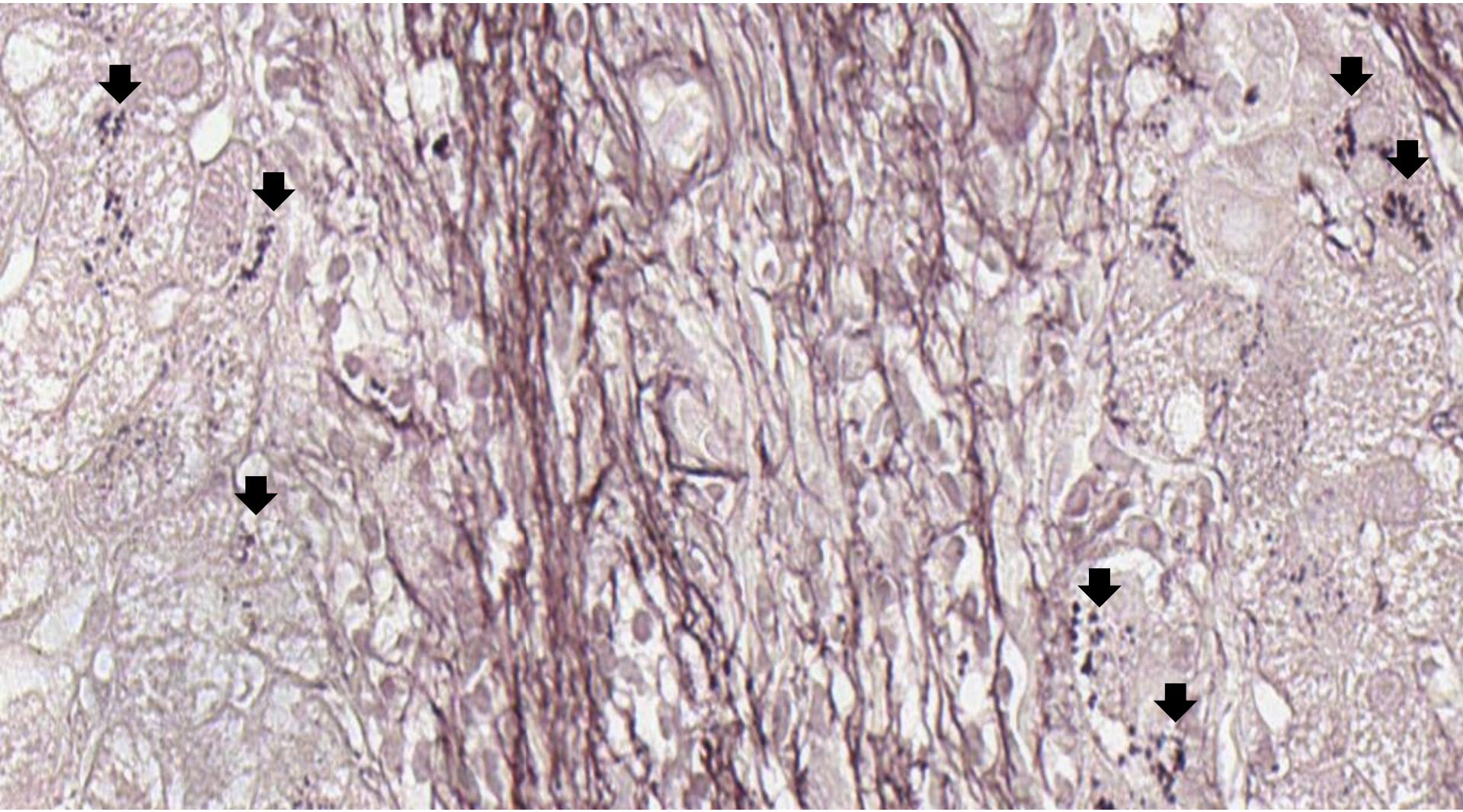
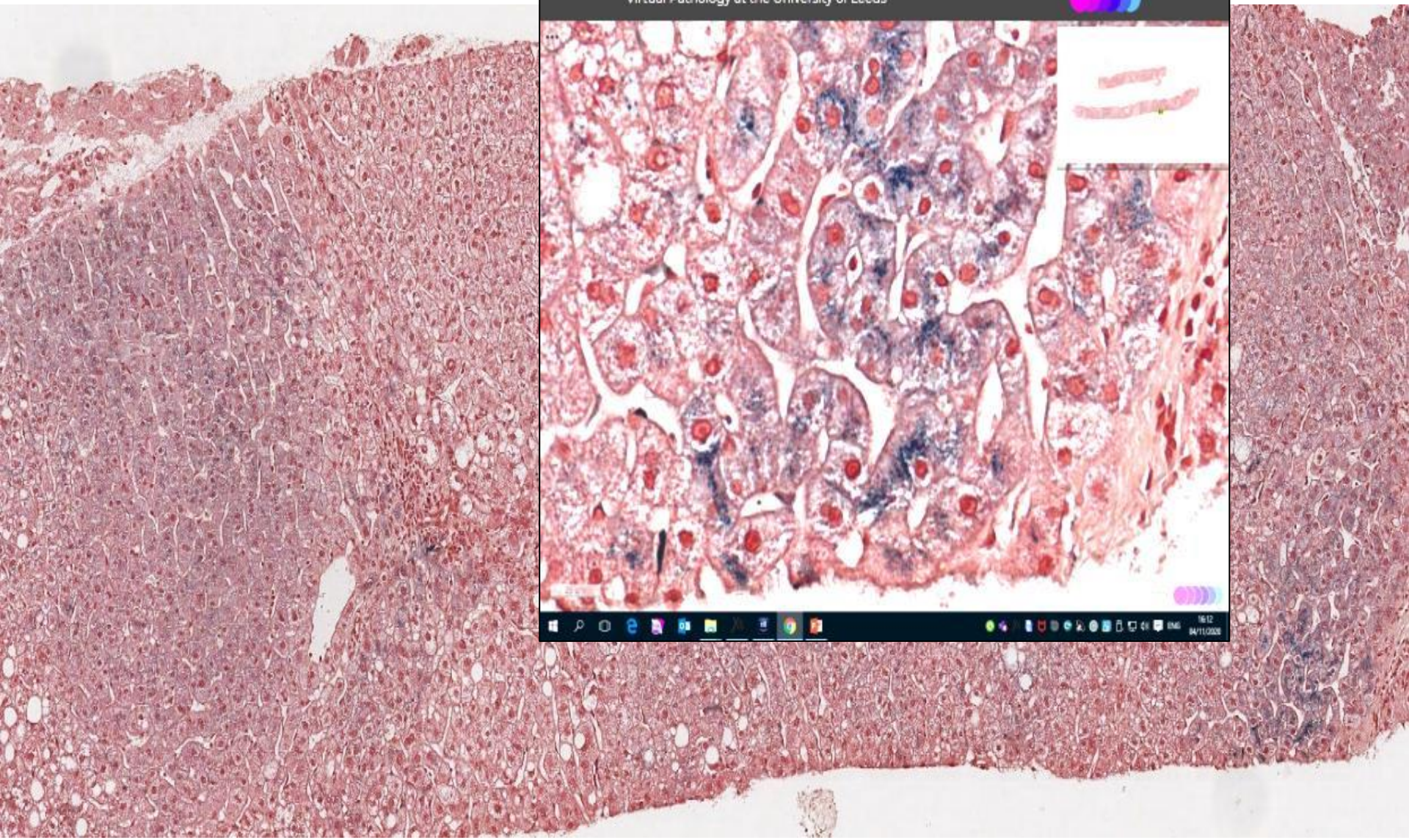


LV3



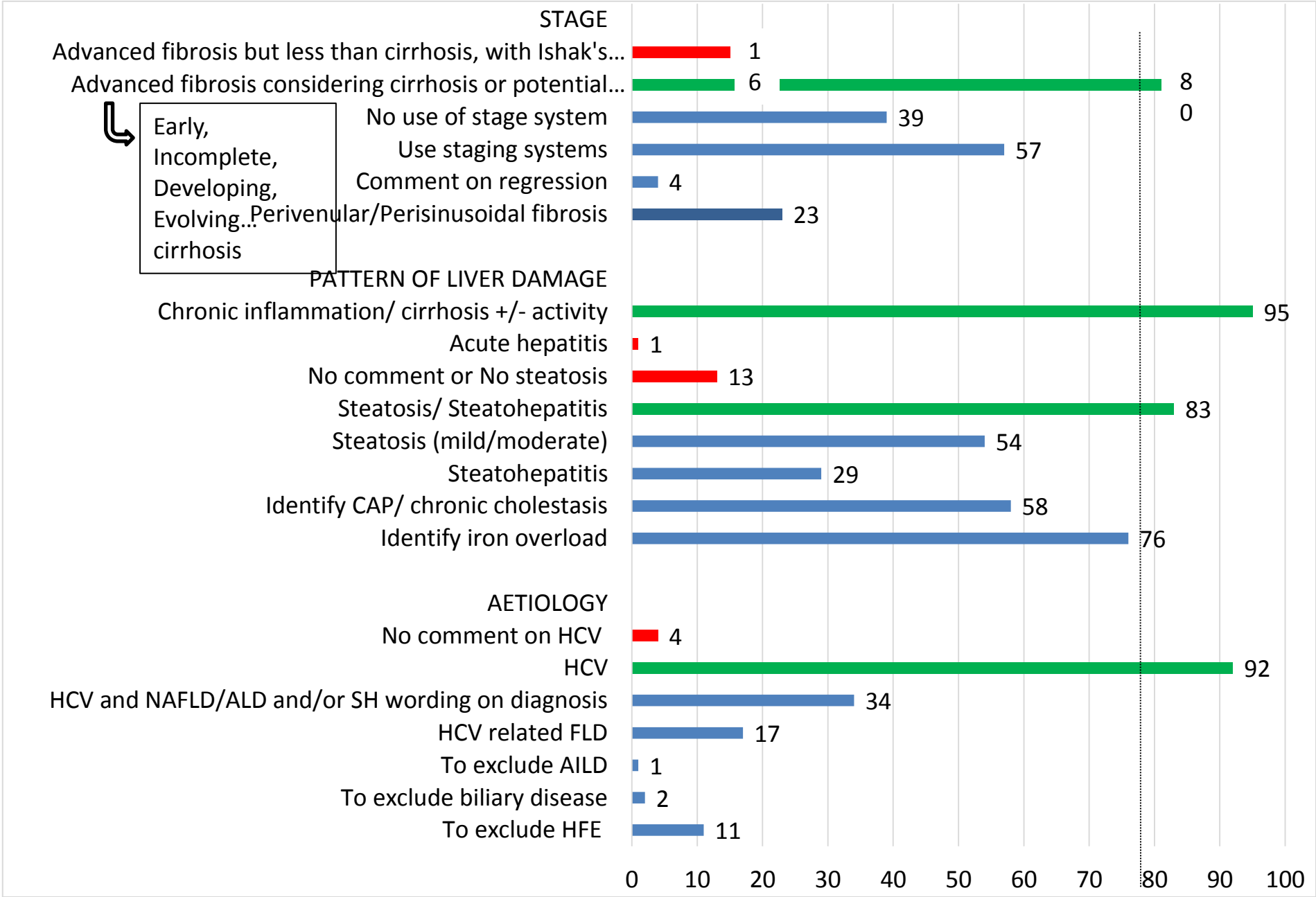
Orcein

LV3

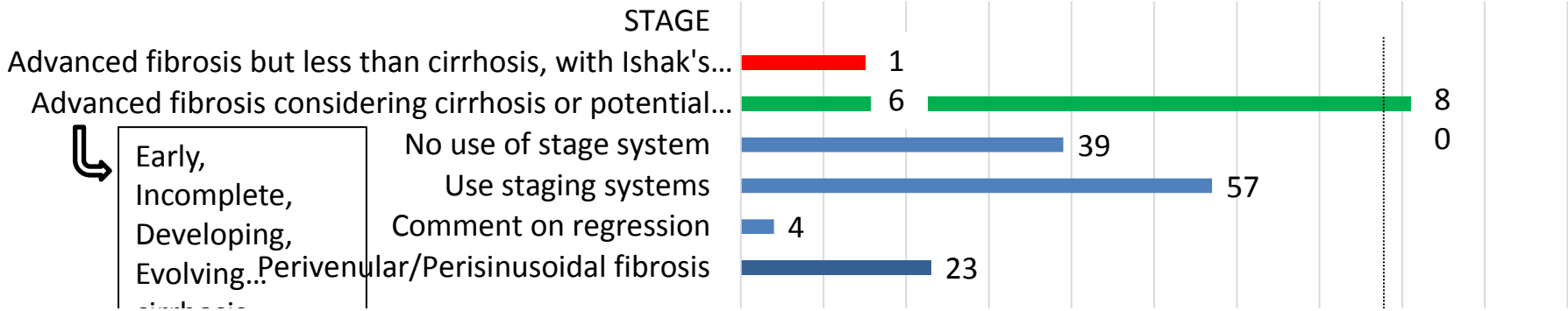


Perls

LV3 – Chart of responses

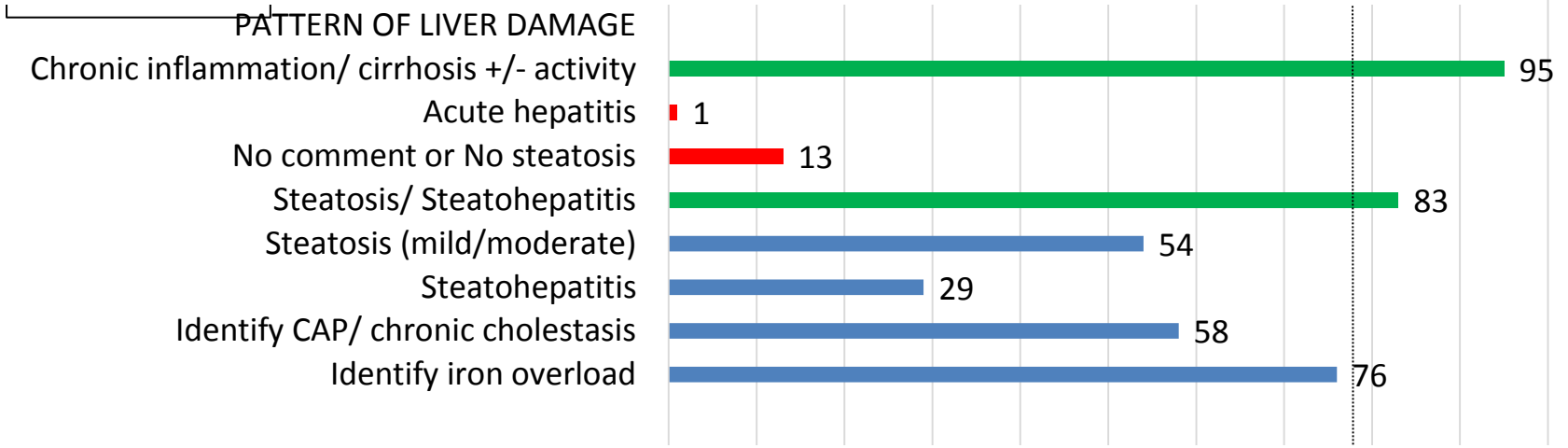


LV3 – Chart of responses



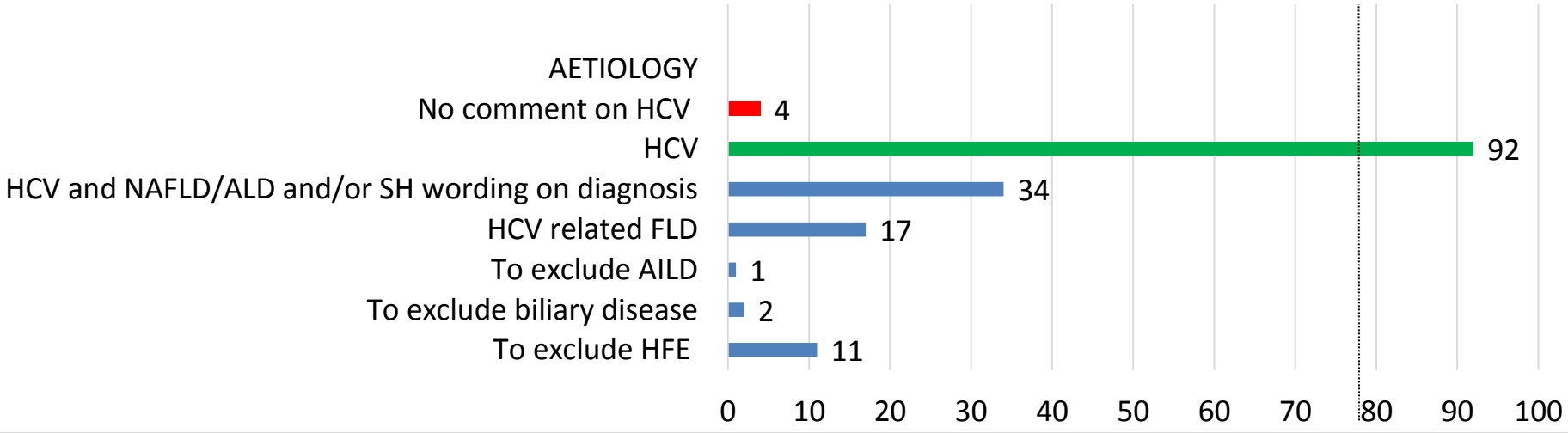
HC\

LV3 – Chart of responses



HCV

LV3 – Chart of responses



LV3: Consensus complete responses would include: Consideration on chronic hepatitis plus steatosis/ steatohepatitis, and HCV aetiology.

Cirrhosis depending on discussion reassess to see if descriptions implying a suitably advanced stage of fibrosis would be communicated by the report. if still no consensus for cirrhosis/advanced fibrosis then any comment on stage sufficient for full marks

– **on reassessment,** if we include any description of cirrhosis, incomplete, developing, incipient, or advanced / late stage, or bridging fibrosis with nodules, Ishak 5 or 6, or Metavir 4 – then this reaches consensus with **80 responses**; bridging fibrosis or Ishak 3-4 = **16 responses**. Should we score for fibrosis stage on this basis?

Suggested scoring: for 10 points include HCV aetiology and histological description on chronic hepatitis and steatosis/steatohepatitis

Lose 5 marks if ? no HCV comment agreed

Lose 5 marks if ? no comment on steatosis/ steatohepatitis agreed

Lose 5 marks if ? response acute hepatitis agreed

UK National Liver Histopathology EQA Scheme 2020

LV4, LV5, LV6

Dr Rachel Brown

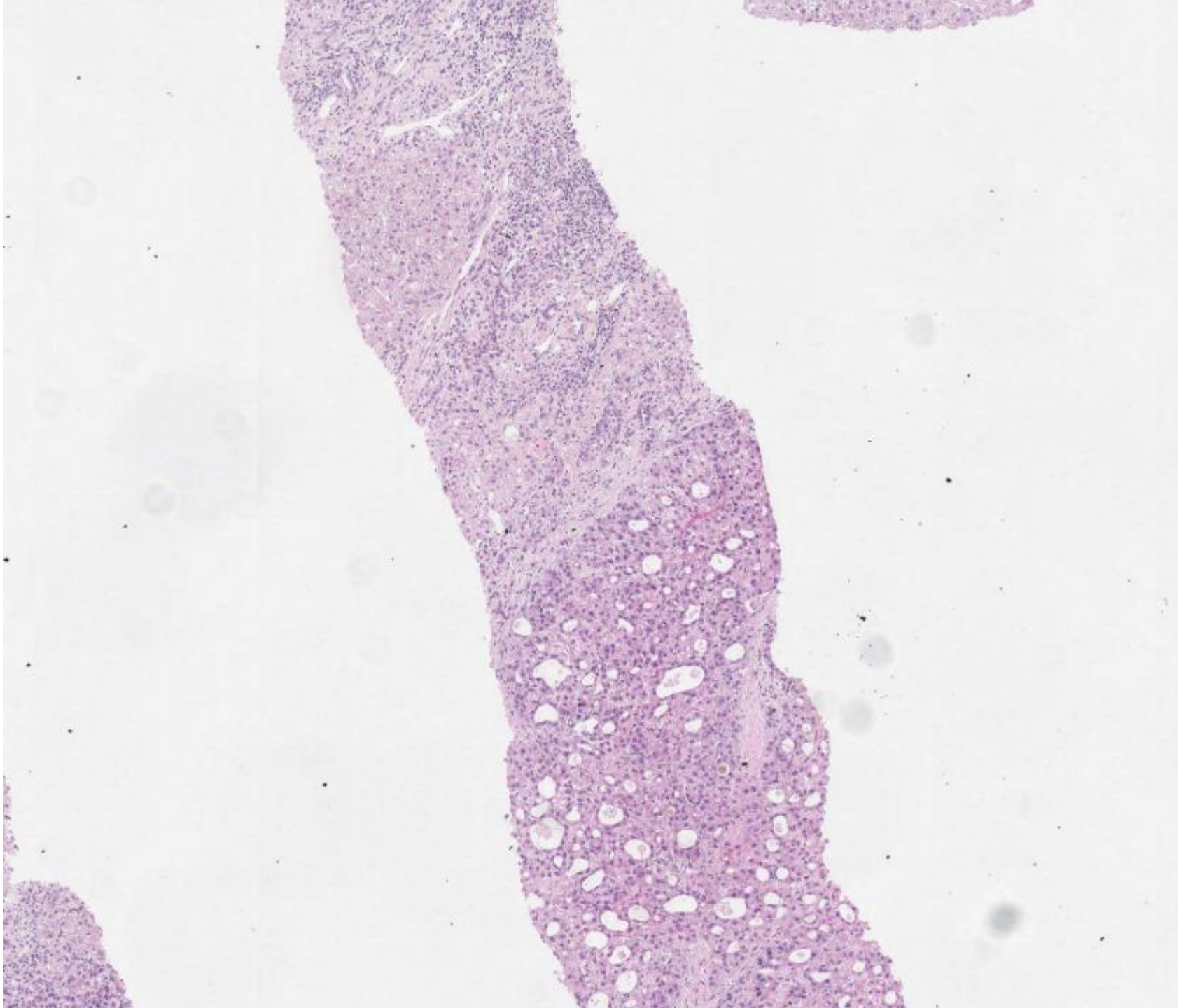
LV4

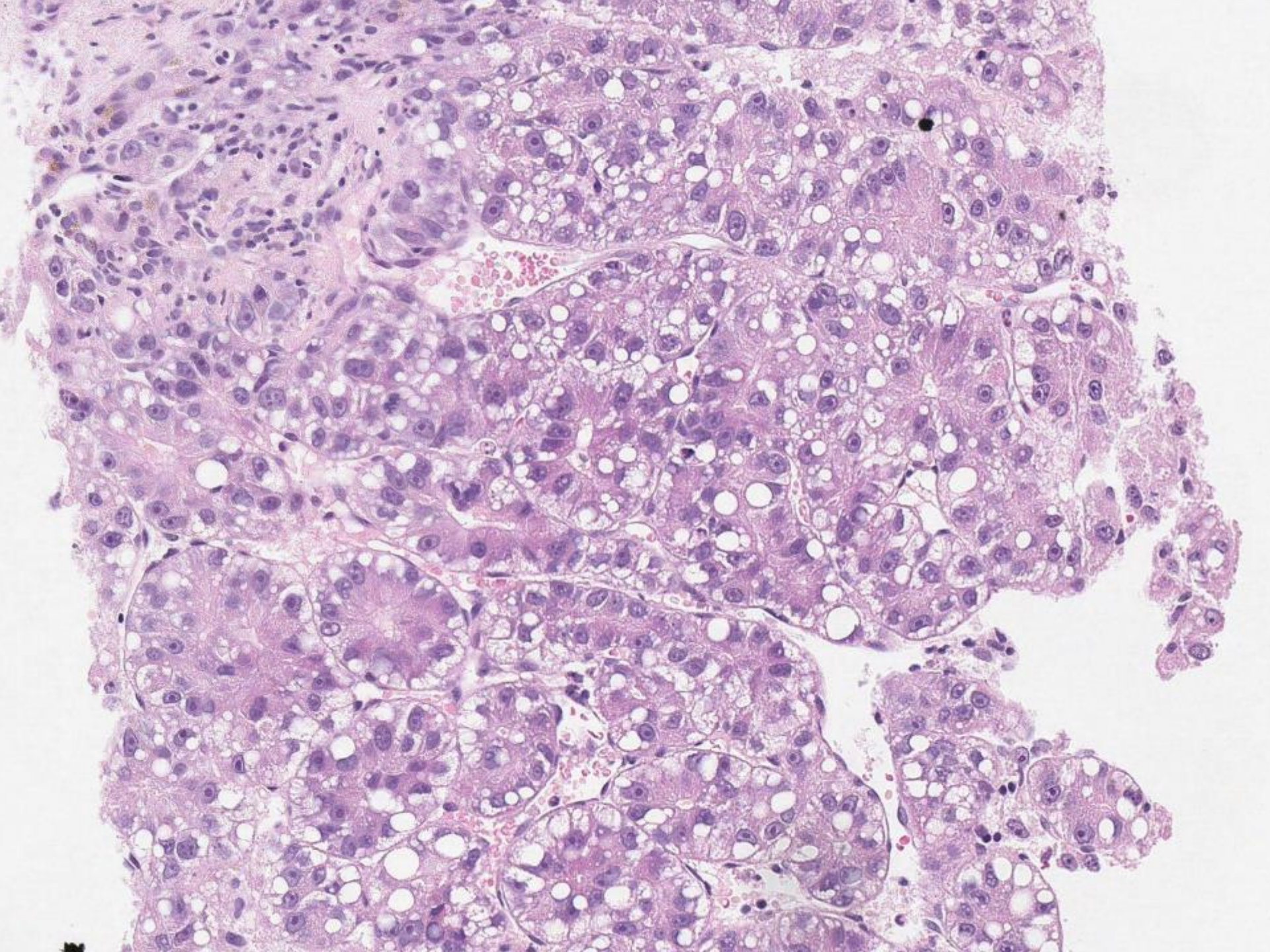
Collation of 96 responses received – number required to reach >80% consensus diagnosis is 77.

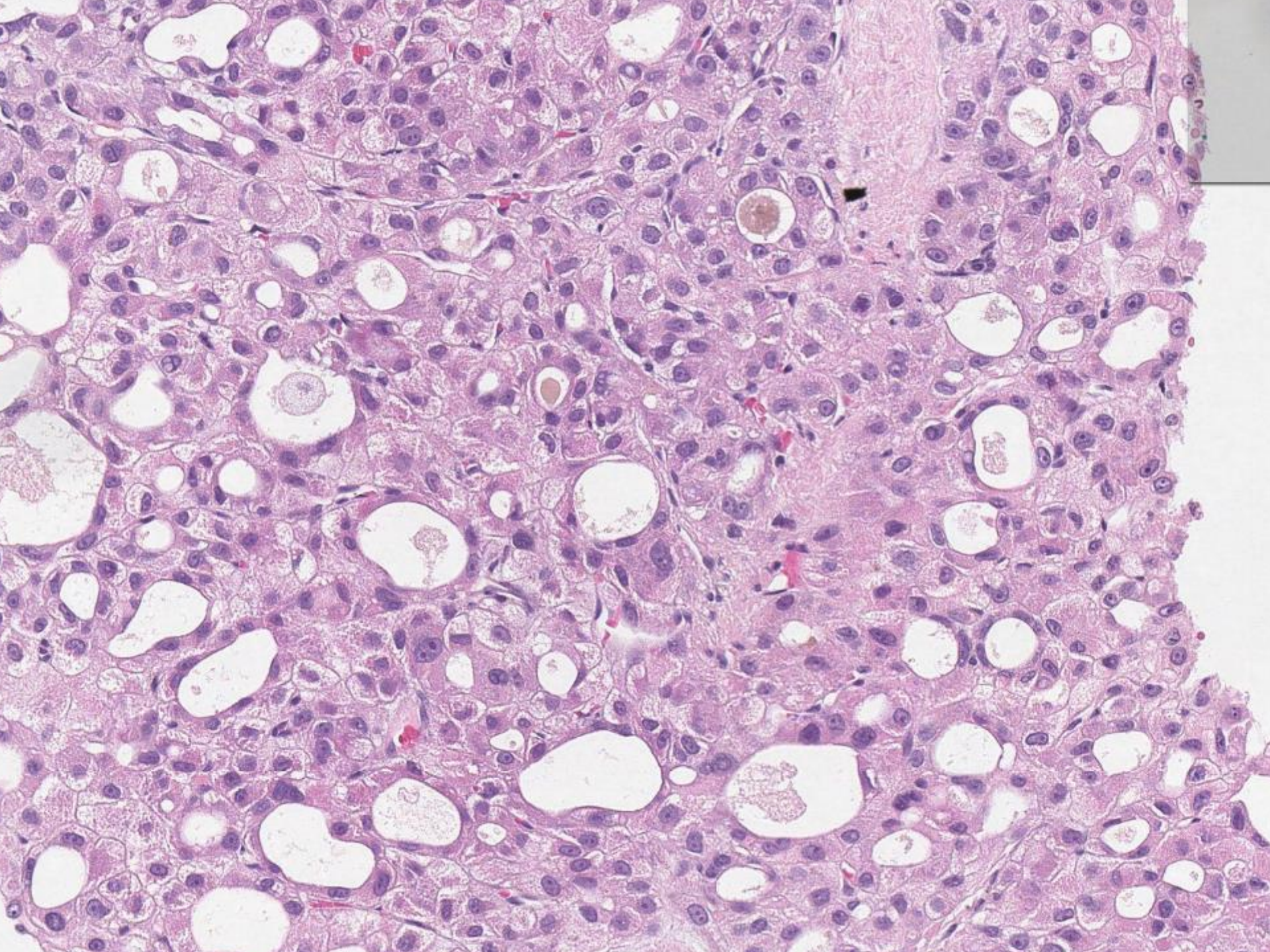
History

Case number:	**LV4**
Clinical Information:	**He has an active HCC same patient as LV3. He is now within the window period where he can now be transplanted (downstaged). Background liver biopsy to establish cirrhosis or not (as this would determine eligibility if cirrhotic). Further lesional biopsy ?HCC or cholangiocarcinoma? Raised CA-19 -9**
Specimen:	**Core biopsy of liver lesion**
Age:	**69**
Sex:	**Male**
Macroscopic description:	**Liver biopsy lesion: 3 cores of tissue 7cm in total length**
Immunohistochemistry:	**reticulin**

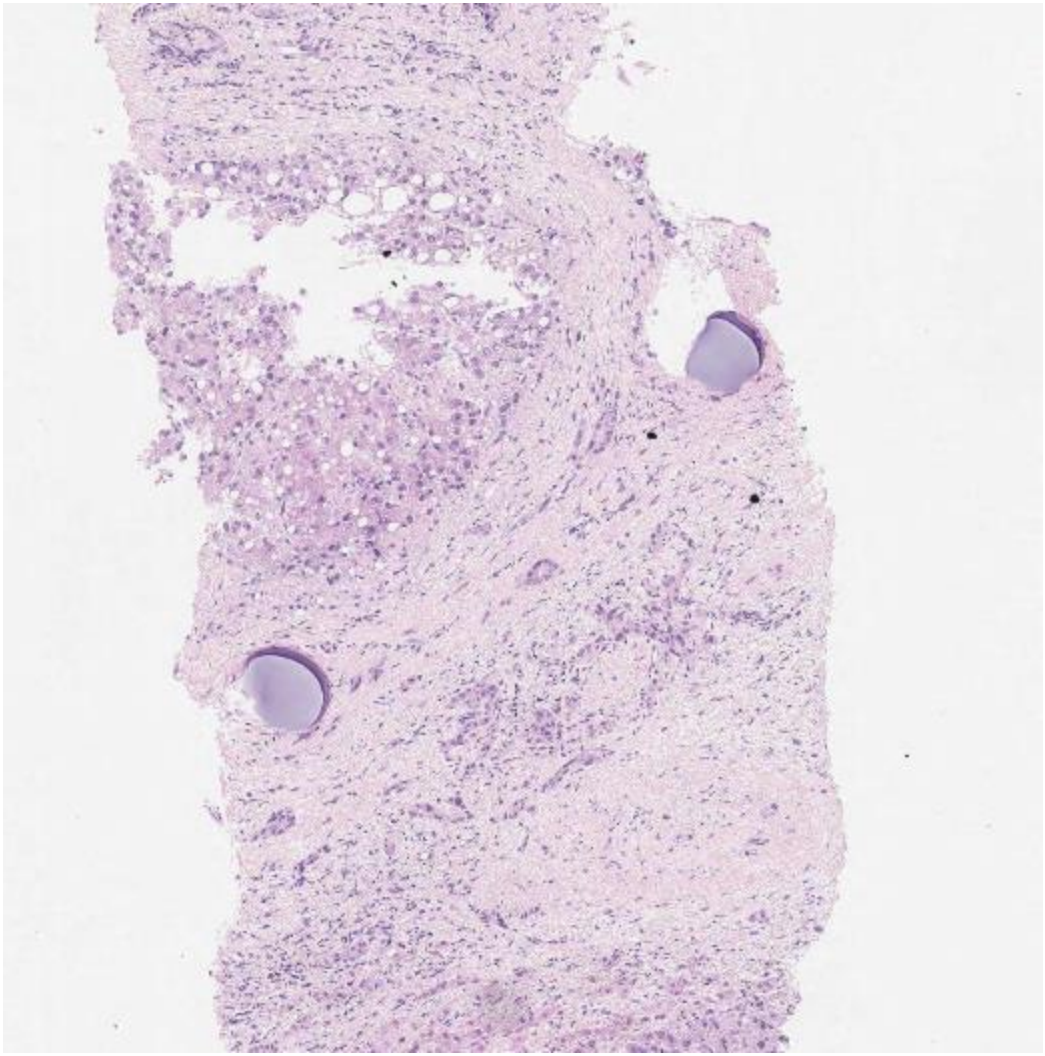
LV4



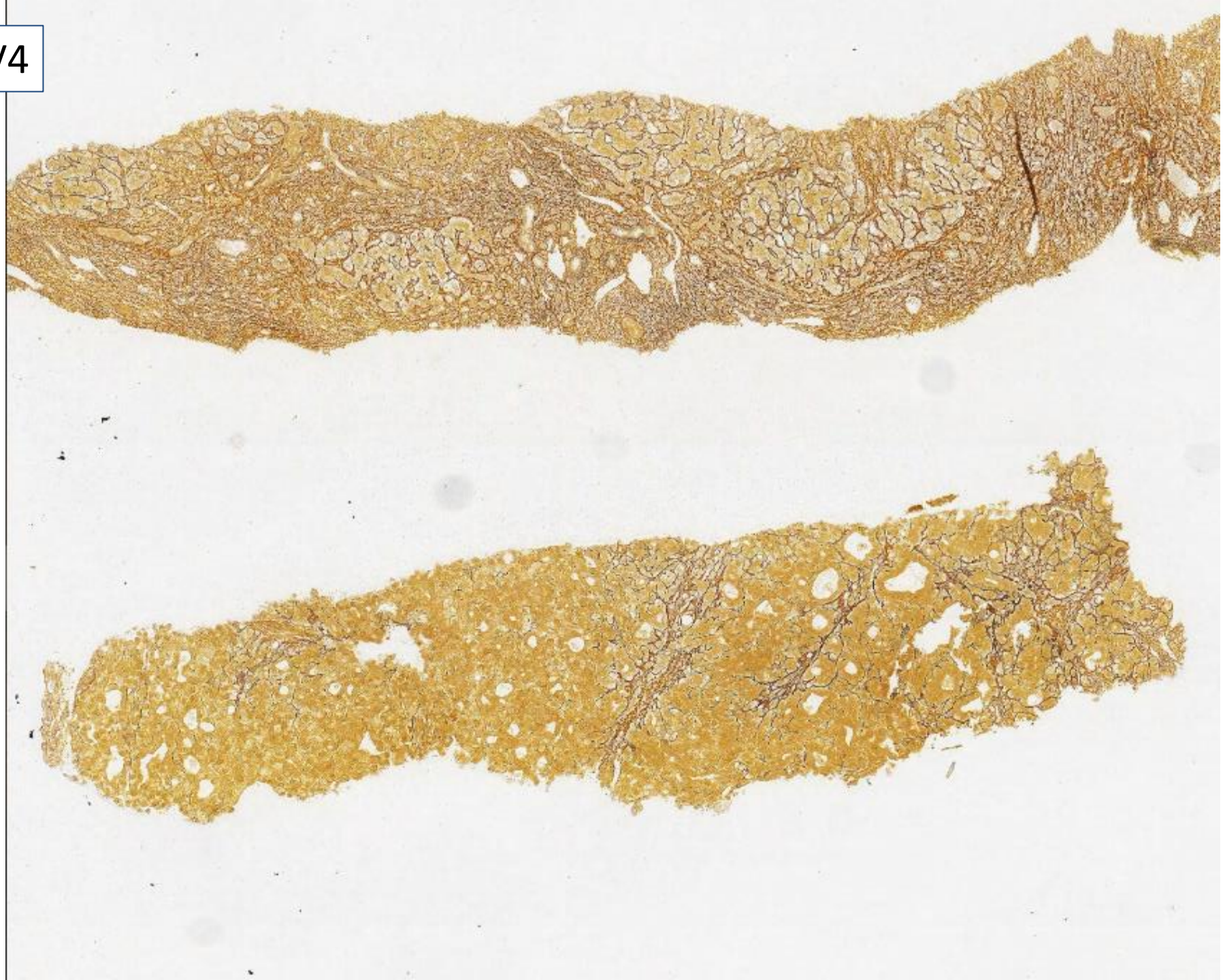




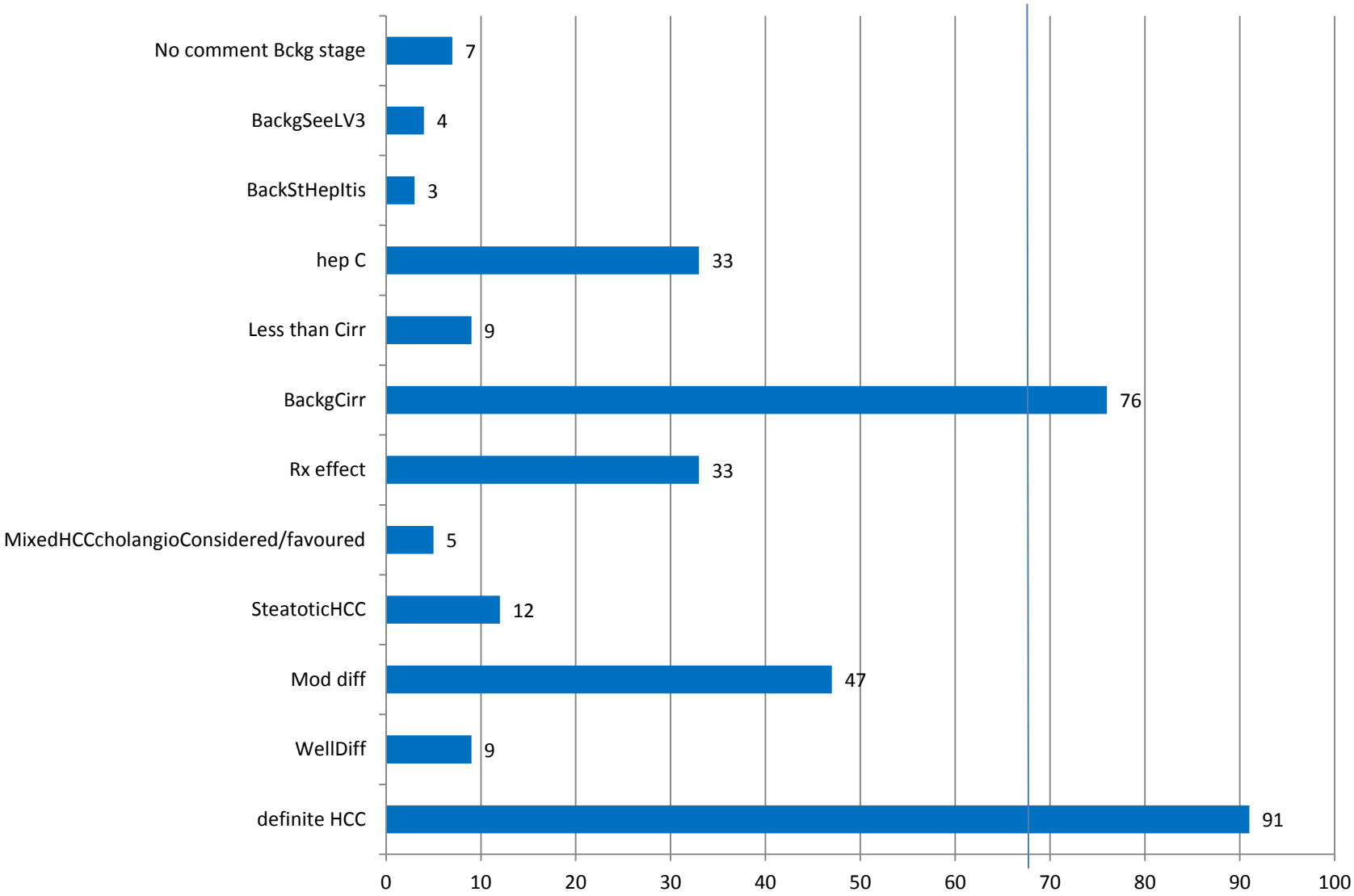
LV4



LV4



LV4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7
BackgSeeLV3
4
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Less than Cirr
9
BackgCirr
76
Rx effect
33
MixedHCCcholangioConsidered/favoured
5
SteatoticHCC
12
Mod diff
47
WellDiff
9
definite HCC
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0
10
20
30
40
50
60
70
80
90
100

LV4

Consensus complete responses would include; definite HCC, some did want immuno but only a few strongly considered or diagnosed combined HCC/cholangio. Comment on background stage (cirrhosis or less than cirrhosis or 'see LV3').

Suggested scoring: for 10 points include; HCC and comment background stage.
Lose 5 marks if no comment background stage (n=7) agreed
Lose 10 marks (score 0) if diagnosis of combined tumour (n=5 or just lose 5? – ask members) agreed that a malignant diagnosis which includes HCC element would score 5 marks – combined HCC-CCa suggested by histology in this biopsy – not just because of raised Ca19.9.

Discussion points; of those who expressed a preference moderately differentiated favoured. 33 noted treatment effects. No consensus background aetiology.

LV5

History

LV5

?Adenoma ?Adenomyolipoma excised. Assume typo angiomyolipoma

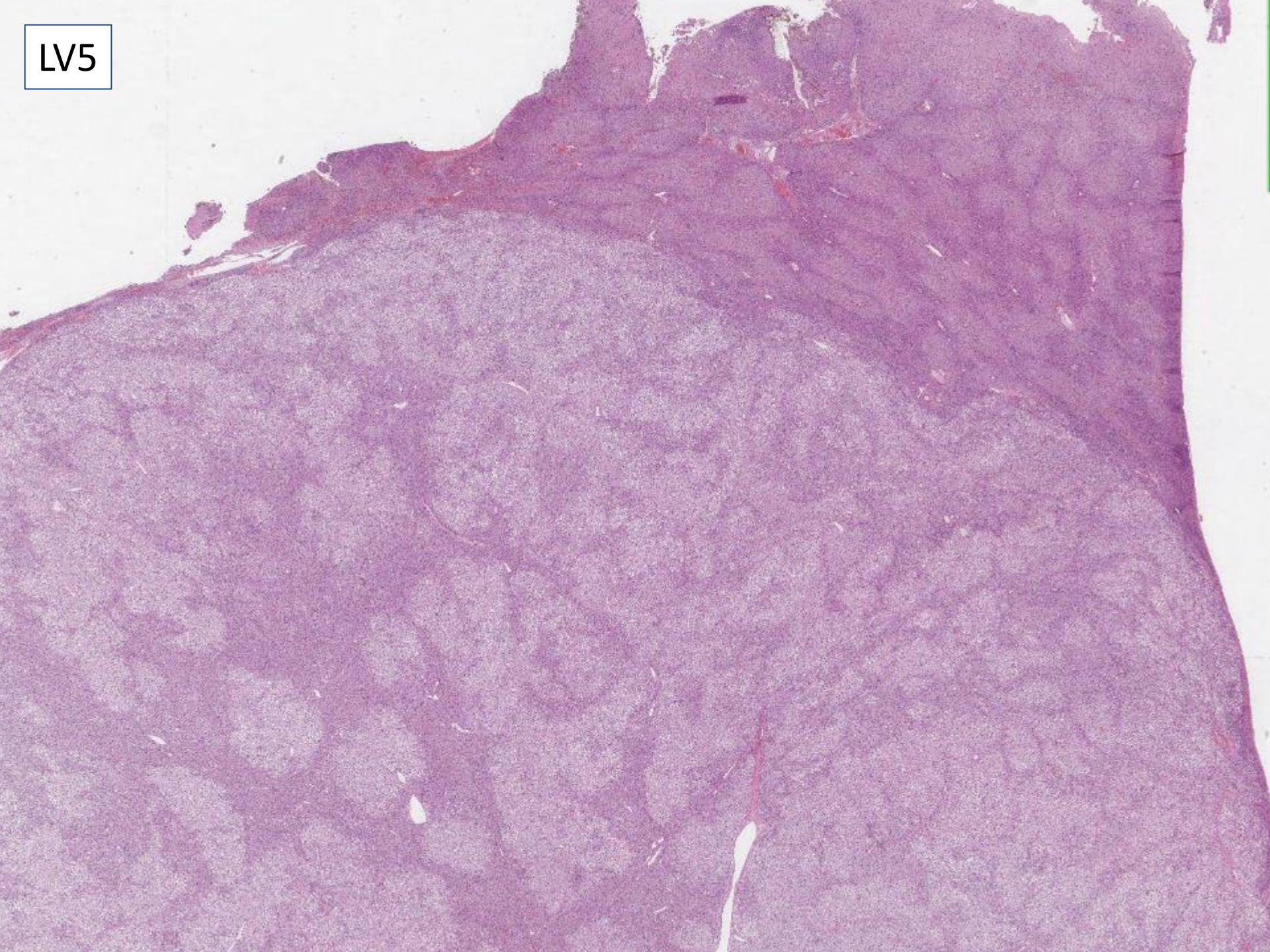
Liver segment 5/8

38

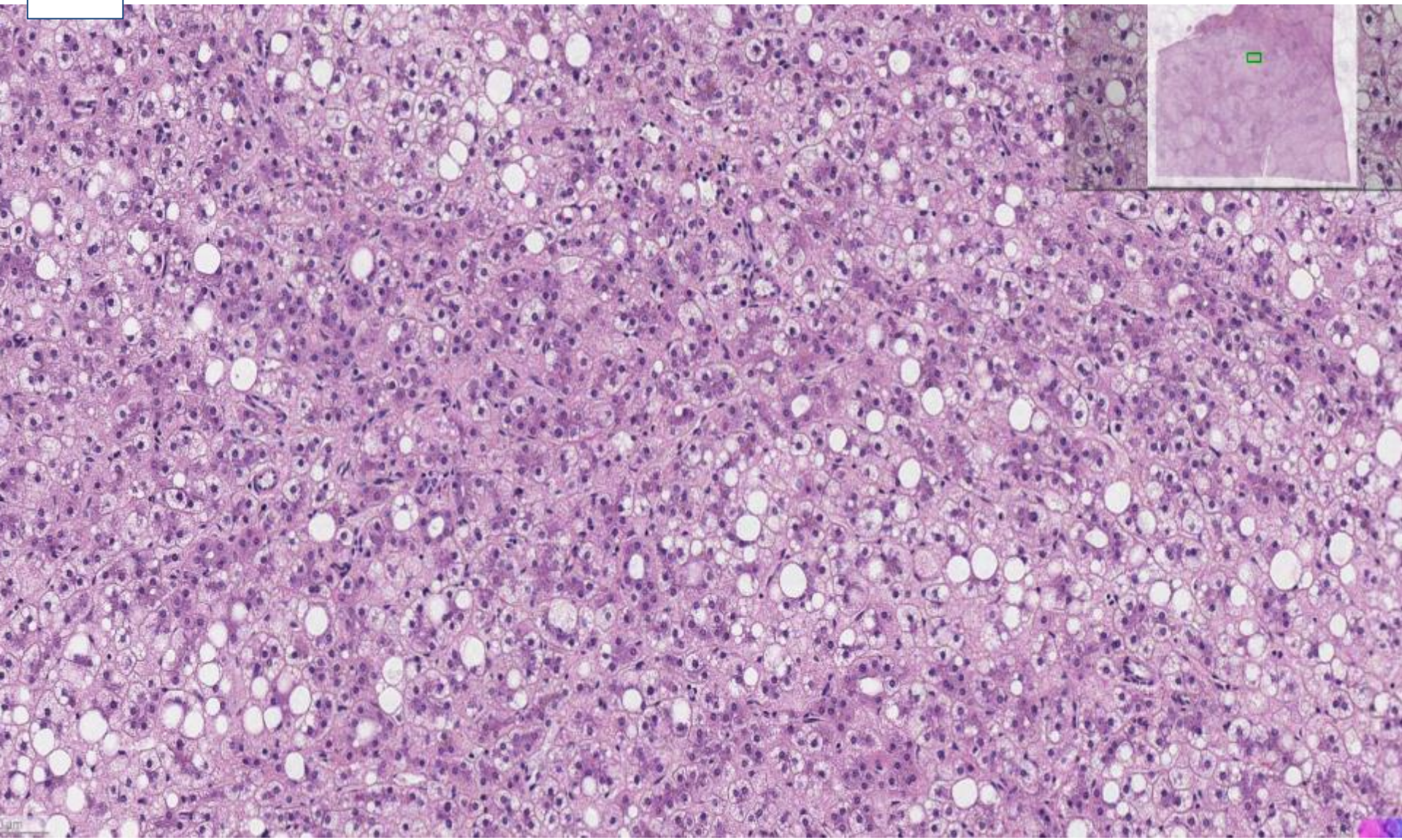
Female

Wedge of liver measuring 80 x 62 x 30mm containing a well demarcated pale tan coloured lesion measuring up to 54mm in maximum dimension & focally abutting the resection margin.

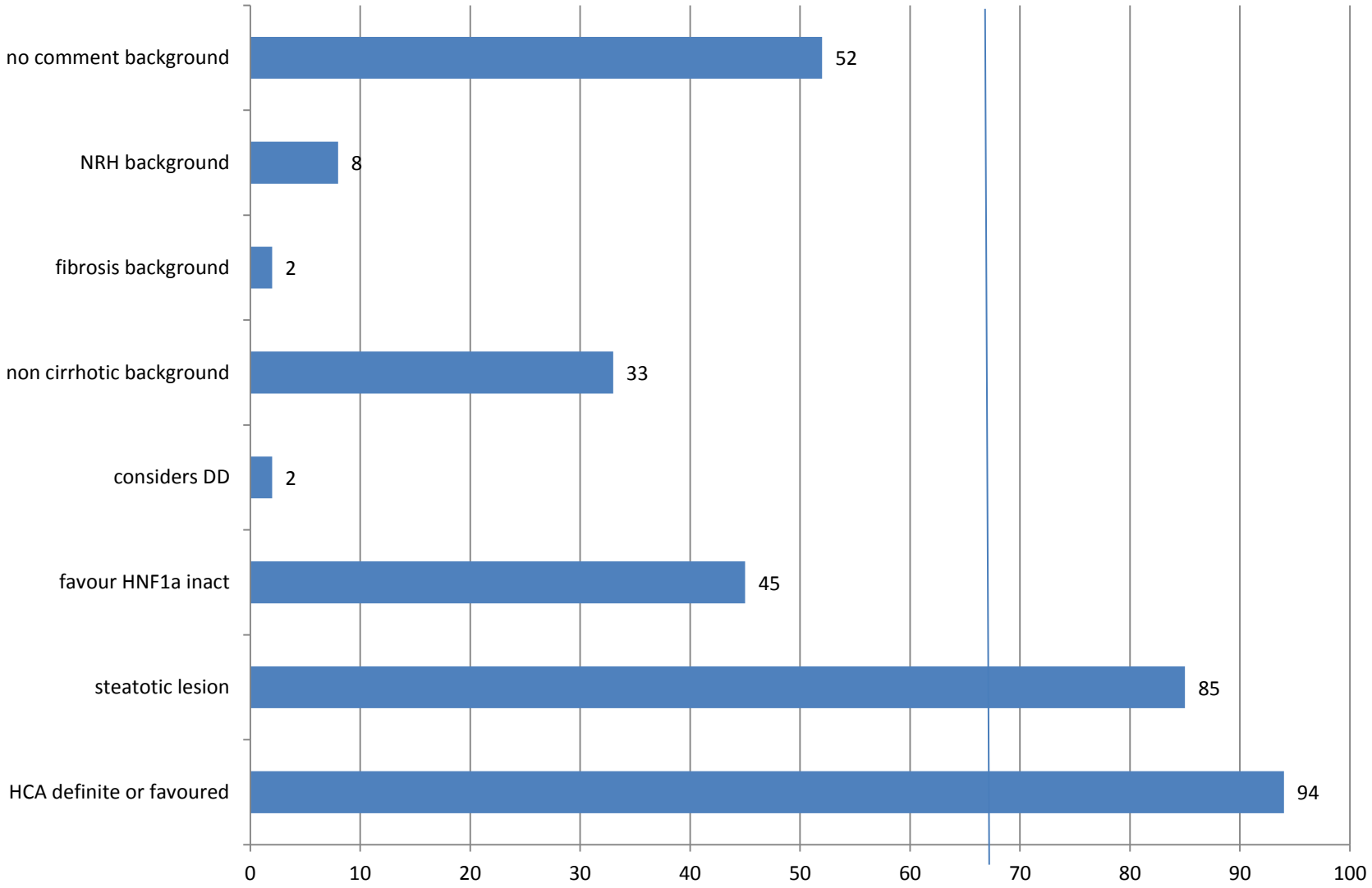
None Just H&E


LV5

LV5



LV5


no comment background
52
NRH background
8
fibrosis background
2
non cirrhotic background
33
considers DD
2
favour HNF1a inact
45
steatotic lesion
85
HCA definite or favoured
94
0
10
20
30
40
50
60
70
80
90
100

LV5

Consensus complete responses would include; strongly favoured hepatocellular adenoma, description of fat in the lesion? (and usually a comment on background liver but here more didn't comment than did!)

Suggested scoring: for 10 points include; adenoma. Some may not have described fat but offered subtyping, not proposing to mark down for not describing fat in the lesion. Agreed

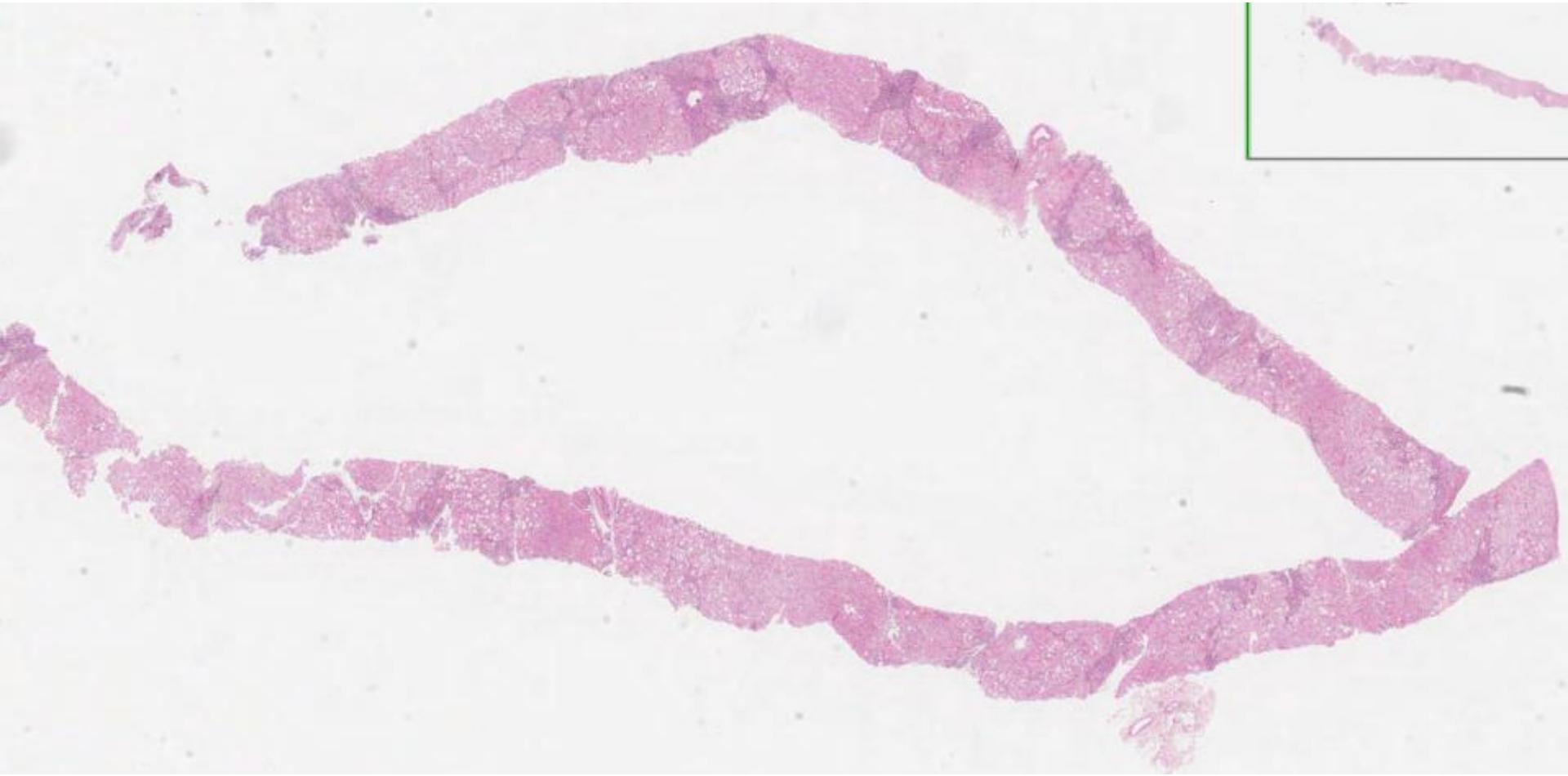
Lose 5 marks if adenoma not favoured but given as differential diagnosis n=2, immuno mentioned leading to diagnosis in both cases so could score full marks? – ask members? Score full marks if immuno would result in adenoma diagnosis (both mention HMB45 which would be –ve) so everyone full marks

Discussion points; 45 willing to offer subtype but most wanted confirmatory immuno.

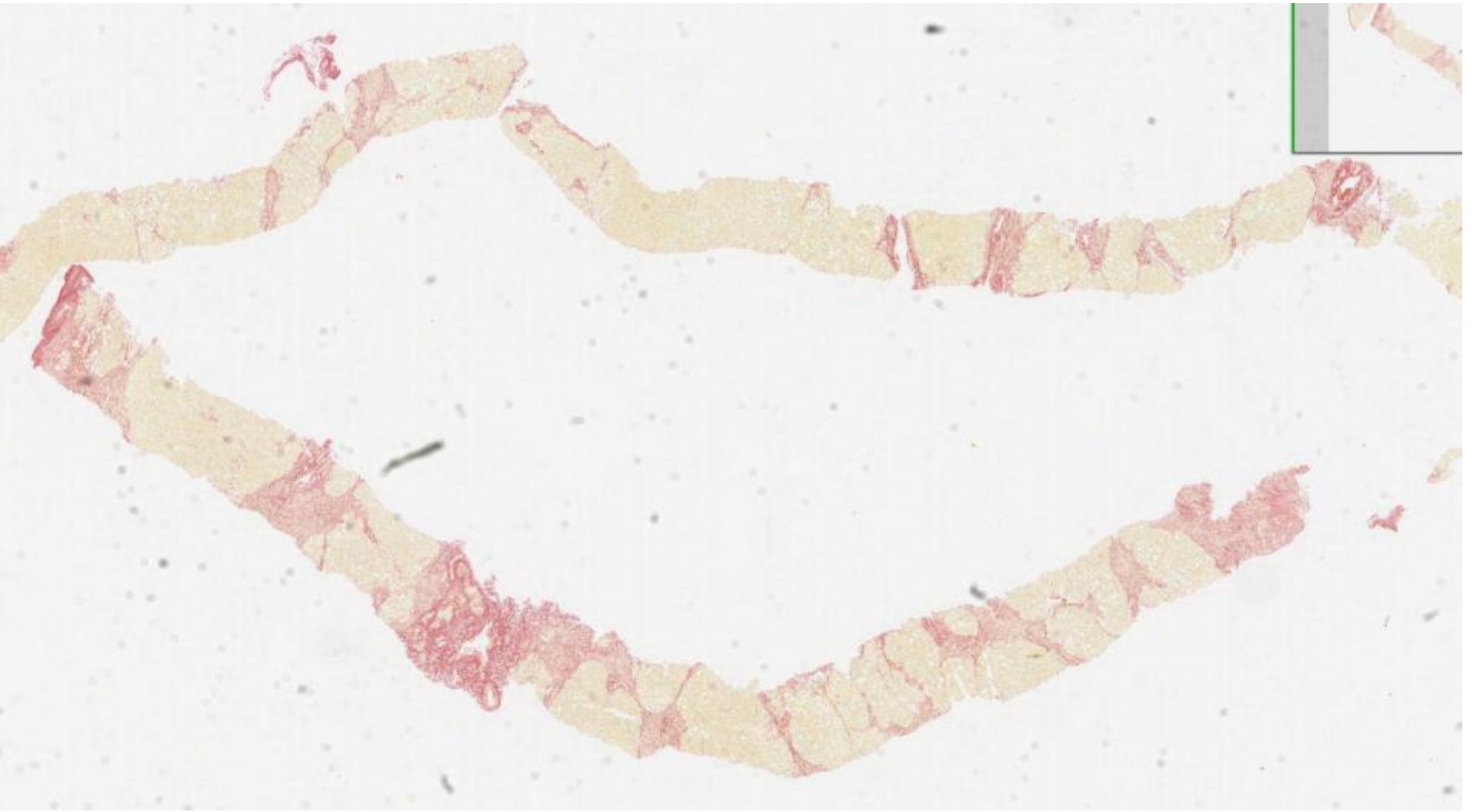
LV6

Case number:	LV6
Clinical Information:	Abnormal LFT's
Specimen:	Liver biopsy
Age:	61
Sex:	Female
Macroscopic description:	Two cores, 18mm and 15mm
Immunohistochemistry:	PSR and reticulin

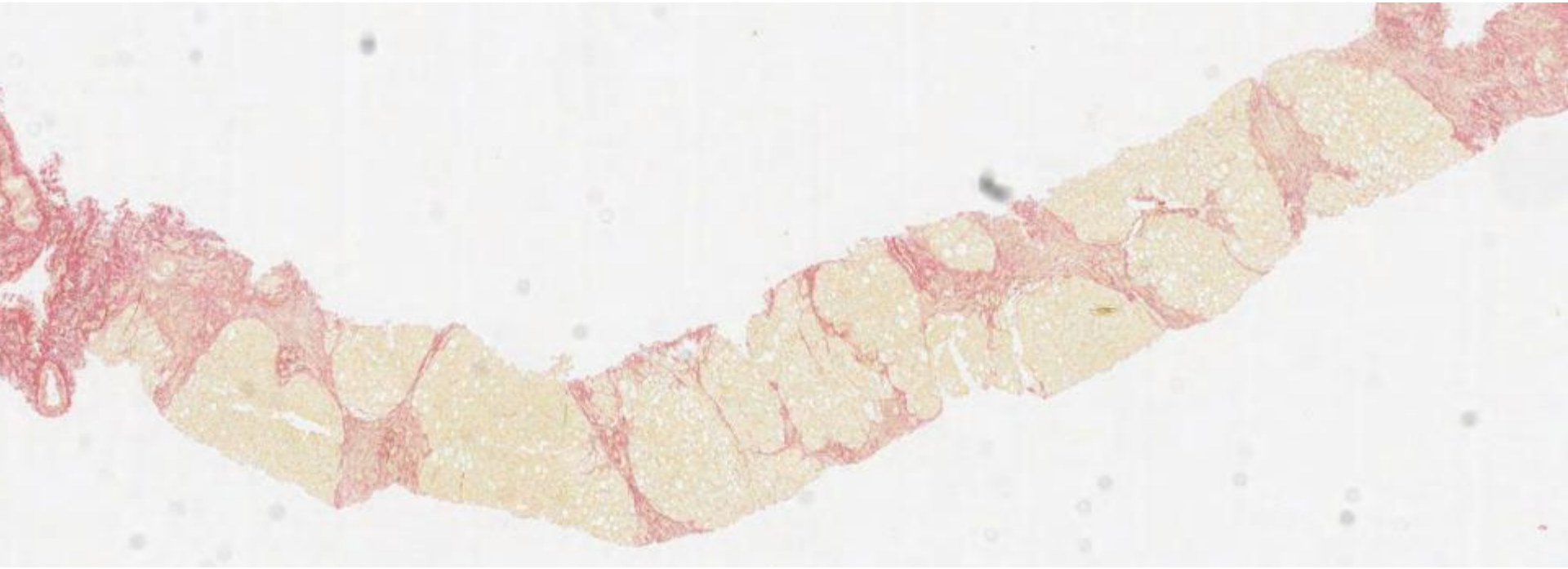
LV6



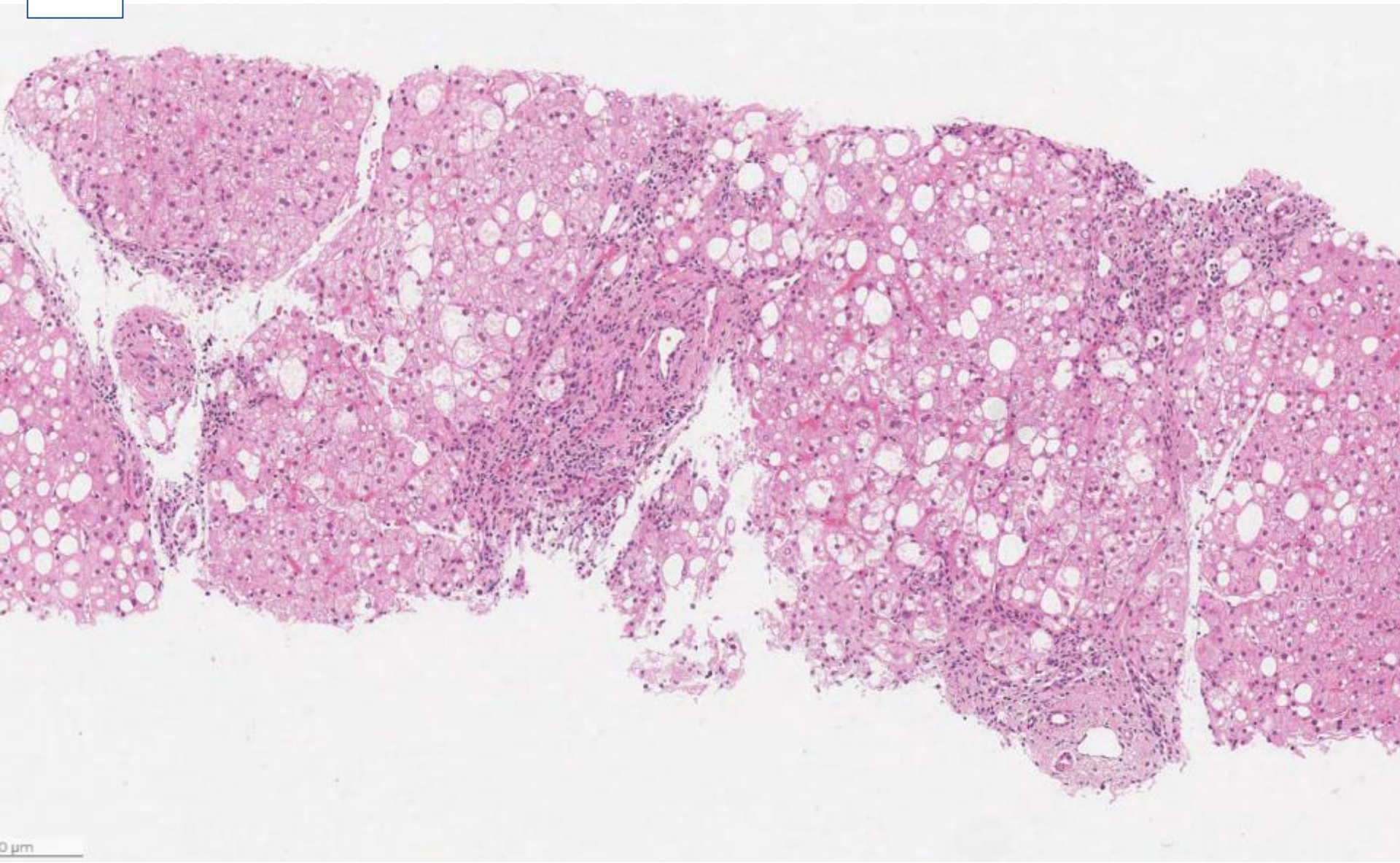
LV6

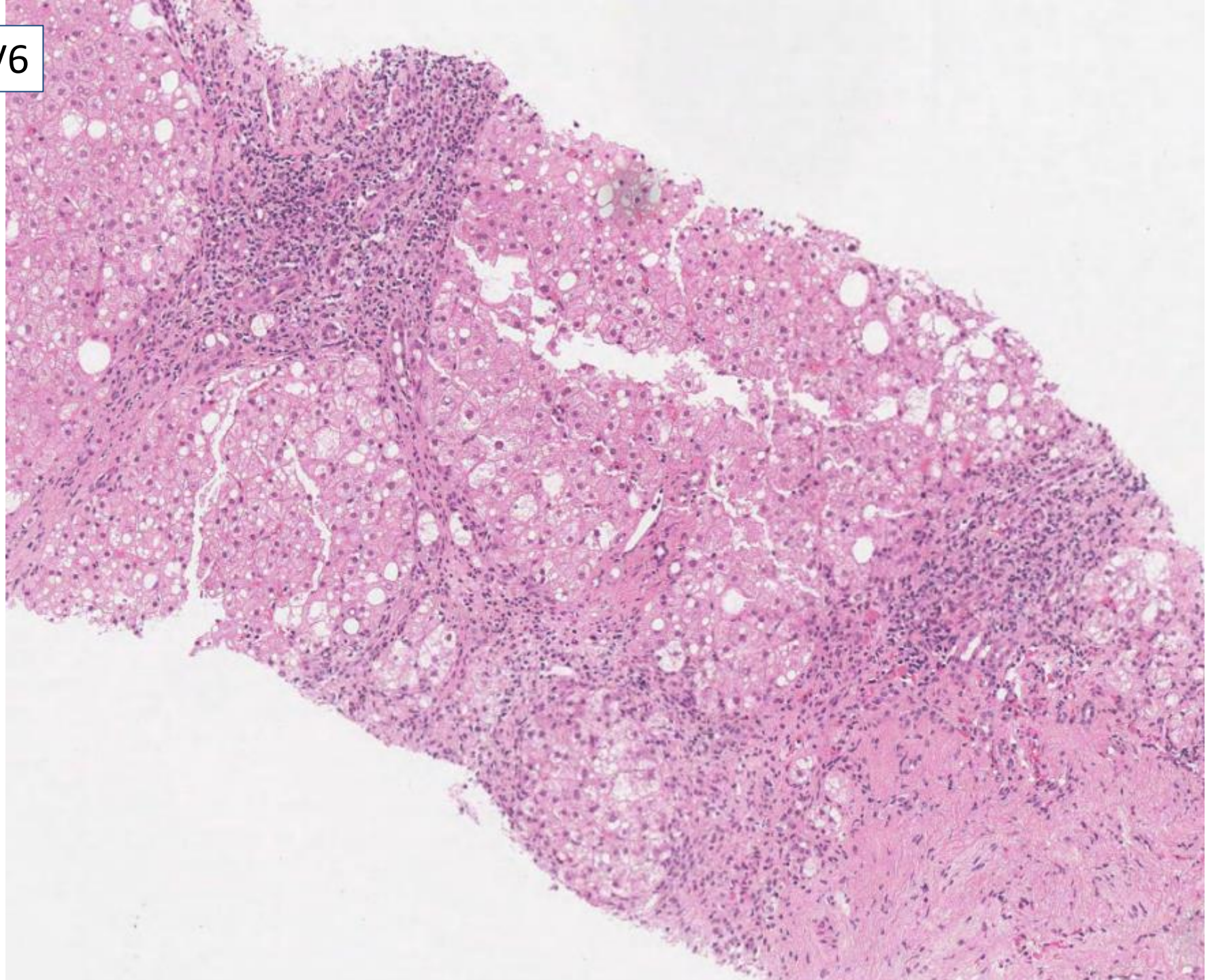


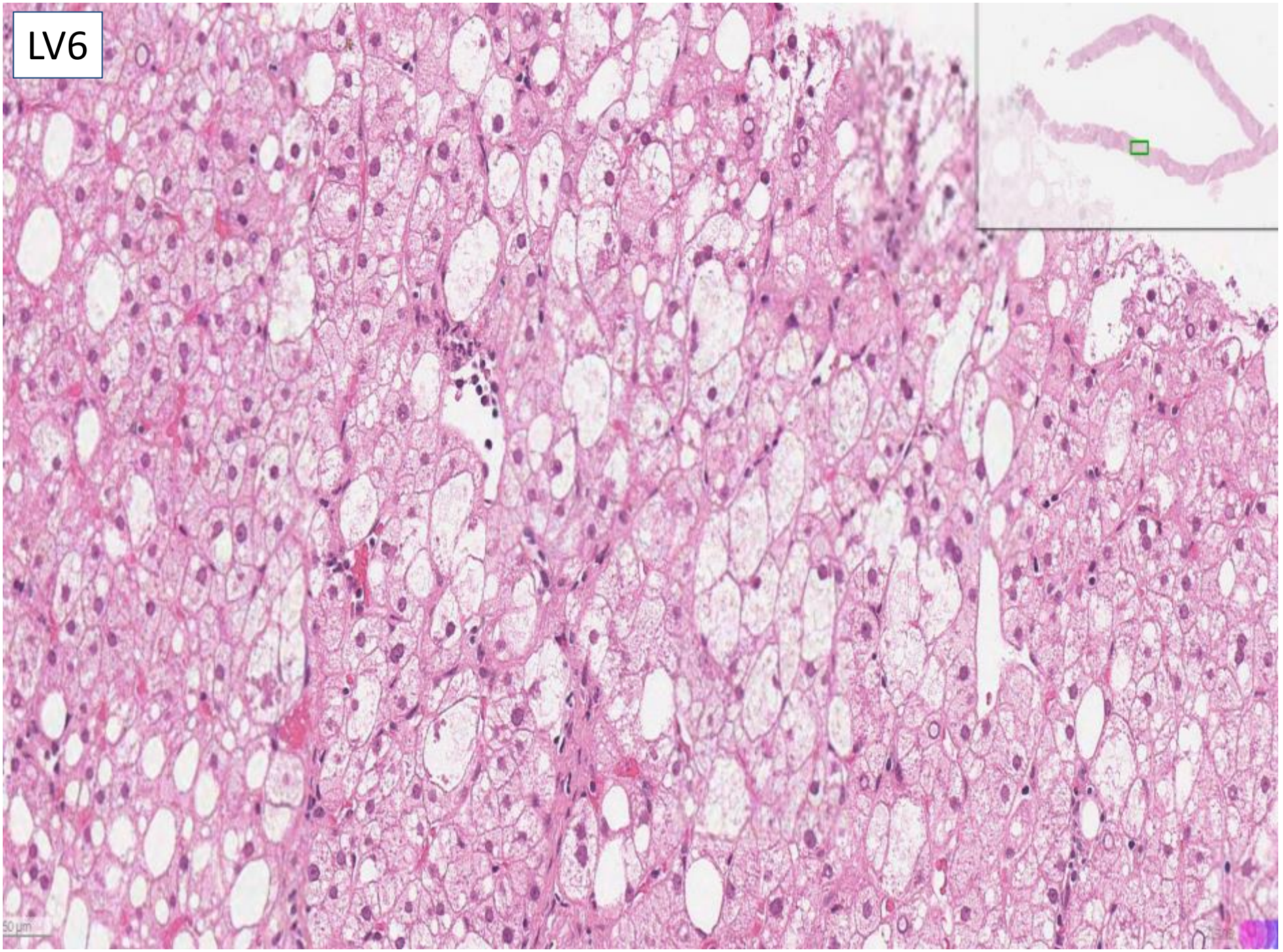
LV6



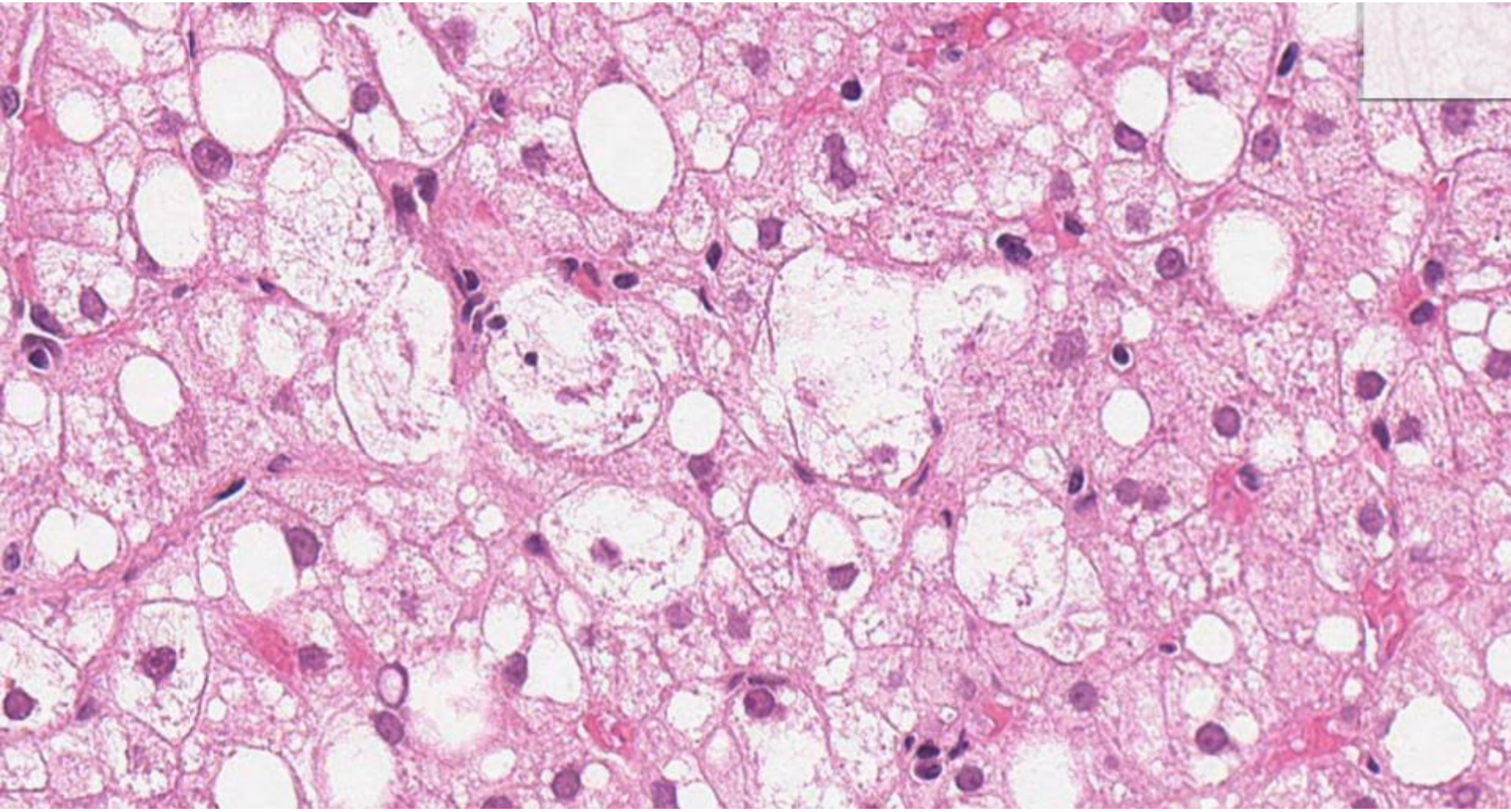
LV6



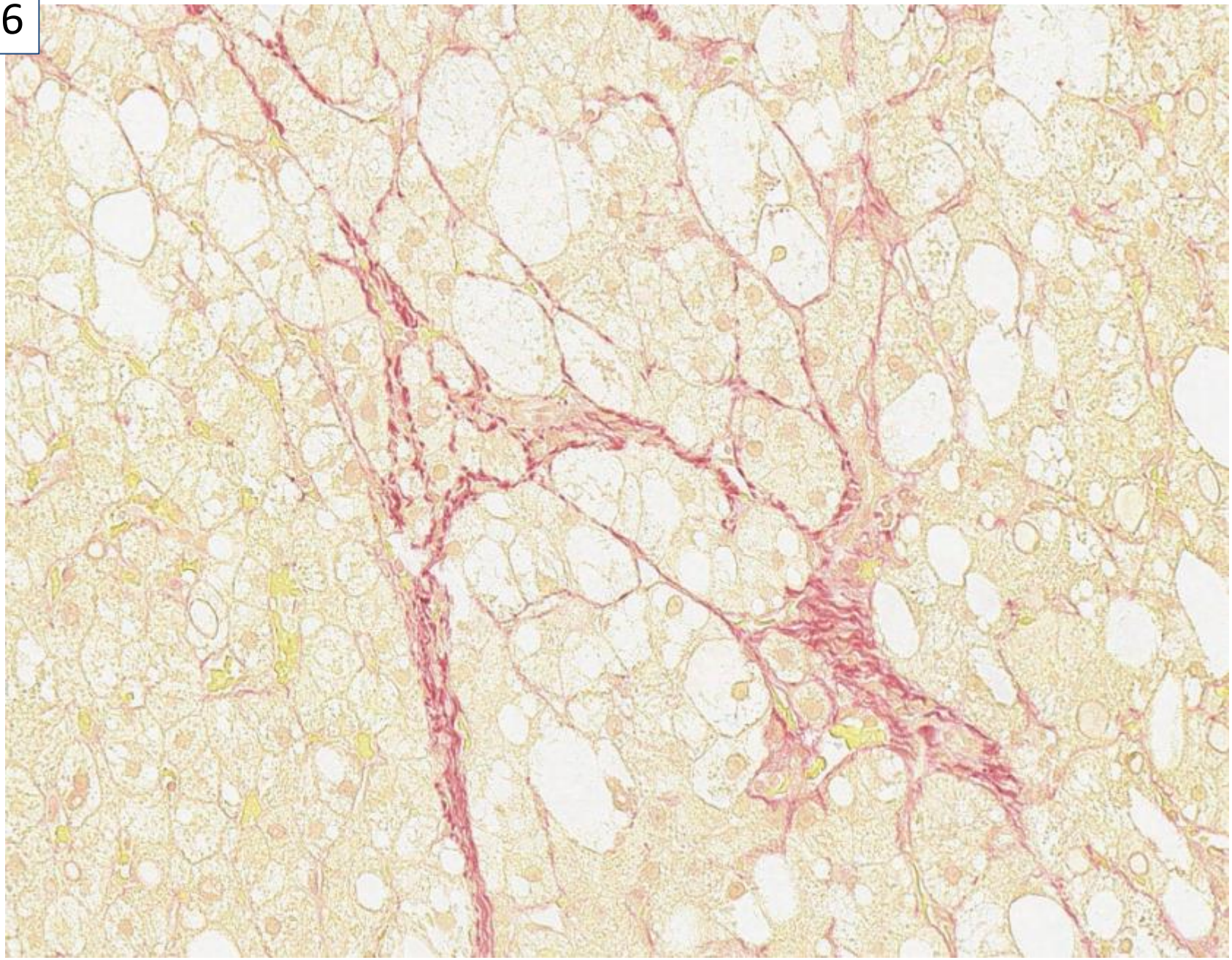

LV6


LV6

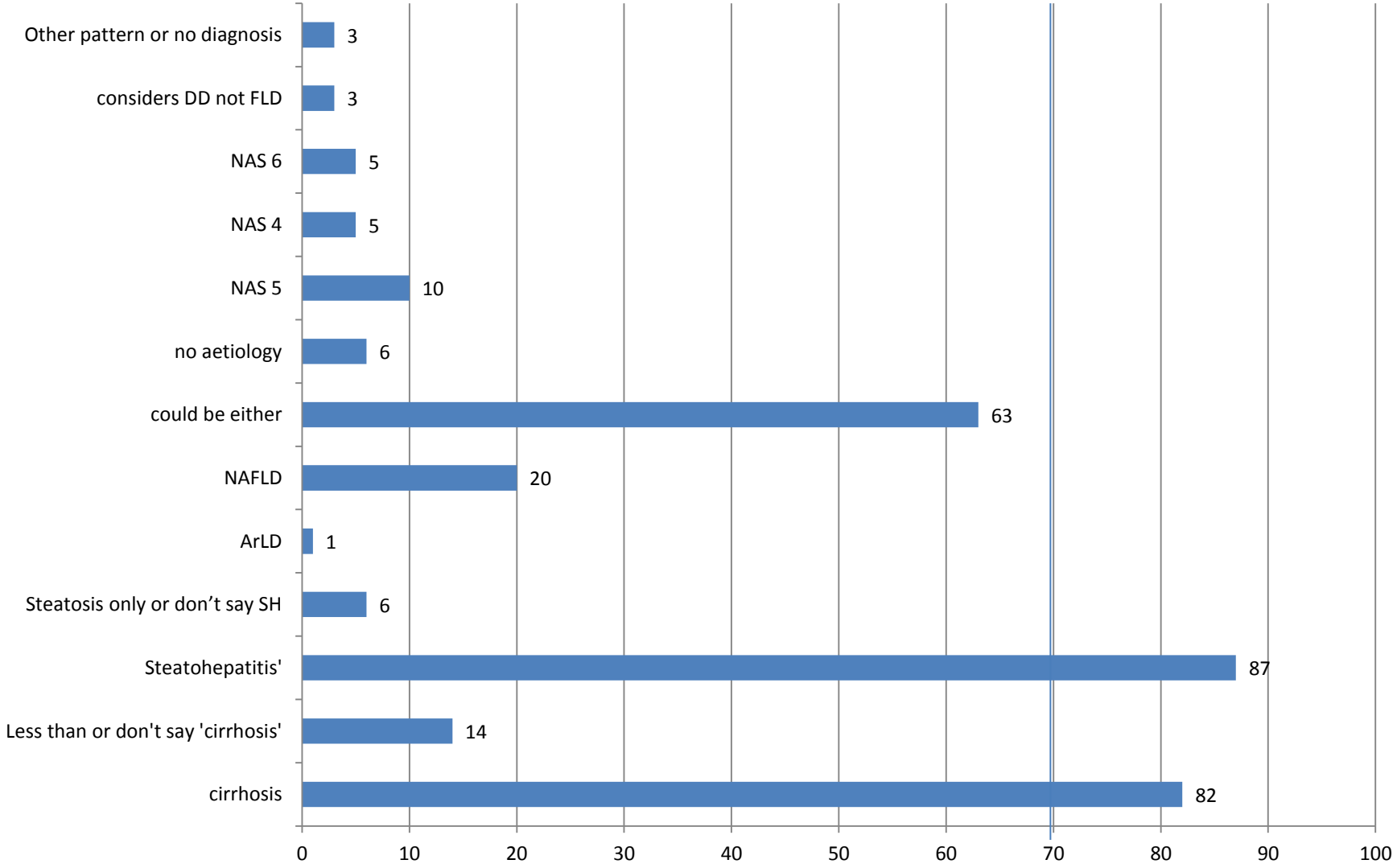
LV6



LV6



LV6


Other pattern or no diagnosis
3
considers DD not FLD
3
NAS 6
5
NAS 4
5
NAS 5
10
no aetiology
6
could be either
63
NAFLD
20
ArLD
1
Steatosis only or don’t say SH
6
Steatohepatitis'
87
Less than or don't say 'cirrhosis'
14
cirrhosis
82
0
10
20
30
40
50
60
70
80
90
100

LV6

Consensus complete responses would include ; cirrhosis and steatohepatitis and differential for aetiology of fatty liver disease either alcohol or non-alcohol favoured or both mentioned (63 + 20 + 1=84).

Suggested scoring: for 10 points include; as above
Lose 5 marks if no aetiology given for fatty liver disease (6) agreed
Lose 5 marks if less than cirrhosis (14) everyone made some comment on stage agreed
Lose 5 marks if don't say 'steatohepatitis' (6) acronyms accepted as steatohepatitits. agreed

Lose 5 marks if alternative differentials considered (3) related to portal/septal inflammation. Not to lose marks if making steatohepatitis diagnosis but considering differentials for an additional chronic hepatitis – all 3 are.

LV6

Lose 5 marks or 10? if no pattern of disease or diagnosis offered beyond cirrhosis? Two examples below score 5

1:

Cirrhosis. Need further clinical information to establish a diagnosis	Established cirrhosis Portal tract chronic inflammation but native bile ducts normal Hepatocyte ballooning and feathery degeneration

2:

Hepatitis with established cirrhosis, cause unknown requires tests as above , consider viral, metabolic , autoimmune, alcohol , drugs.	Cores of liver which have a nodular architecture. Portal tracts are expanded by inflammation and fibrosis. Inflammation mixed with lymphocytes and neutrophils. minimal focal interface and occasional foci of lobular. There is some bile duct proliferation. There is patchy mild steatosis. There is significant fibrosis with bridging and septation PSR and Retic confirm this and on the retic there are well defined nodules. Need to know liver enzymes, IGs, autoantibodies, viral serology. Any imaging. History of drugs, alcohol etc Discussion at MDT.

Lose 10 marks (score 0) if firm diagnosis of something other than fatty liver disease? agreed

Document1

Autoimmune hepatitis with features suggestive of PBC, therefore overlap syndrome cannot be excluded. Ishak fibrosis stage 3 to4 . There is a background of mild steatohepatitis	Expanded portal tracts with inflammatory cells, predominantly plasma cells and lymphocytes. Hepatocyte rosettes and bile duct damage with neoductular regeneration. Parenchyma with steatosis and hepatocyte ballooning with equivocal Mallory bodies.

LV6

Discussion points

Few comments on lymphocytic portal/septal inflammation to say within spectrum of FLD
Scoring, most who did used NAS CRN (Kleiner) couple SAF, couple Ishak.
1 response ‘steatohepatofibrosis’ (included with steatohepatitis)

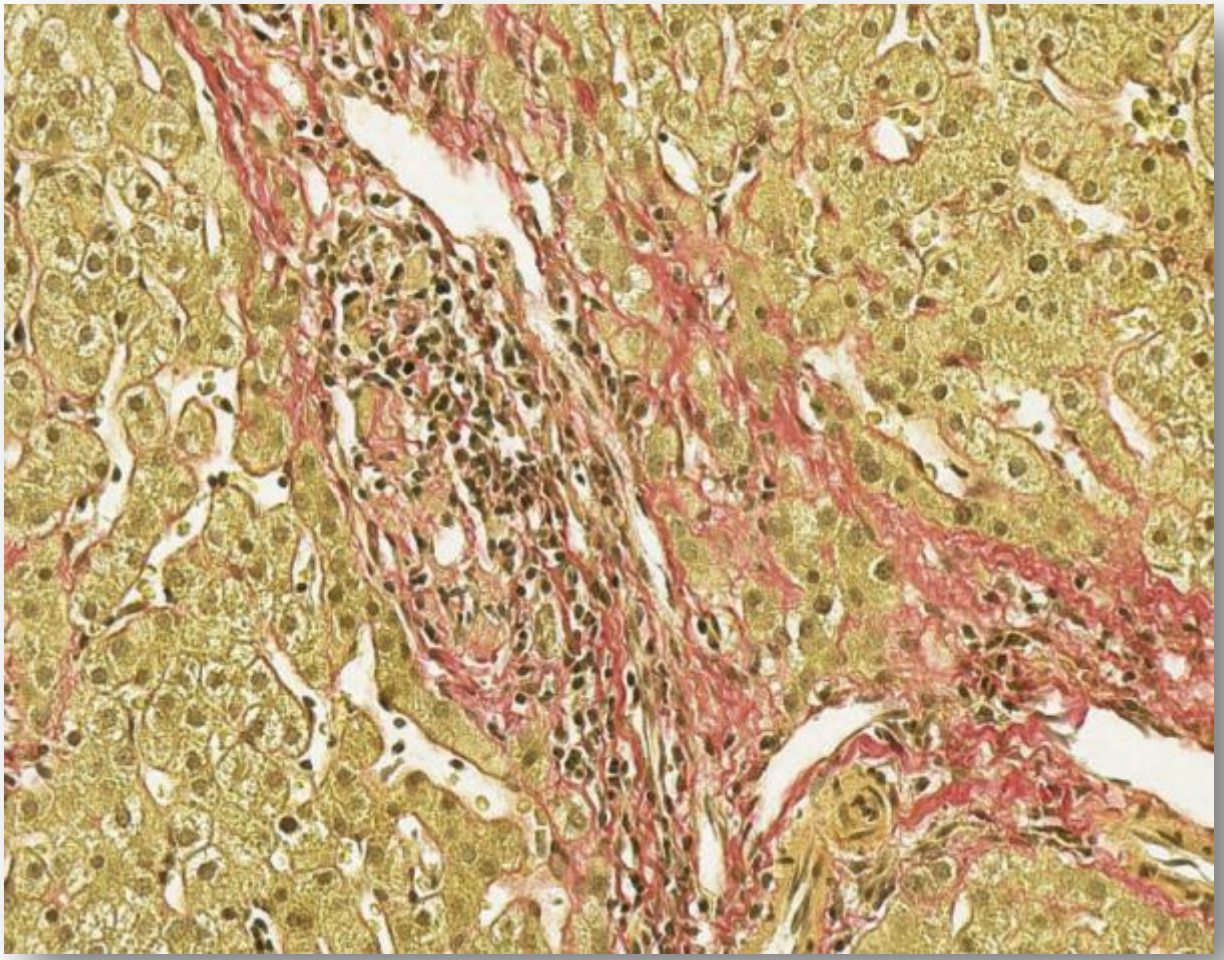
UK National Liver Histopathology EQA Scheme 2020

LV7, LV8, LV9

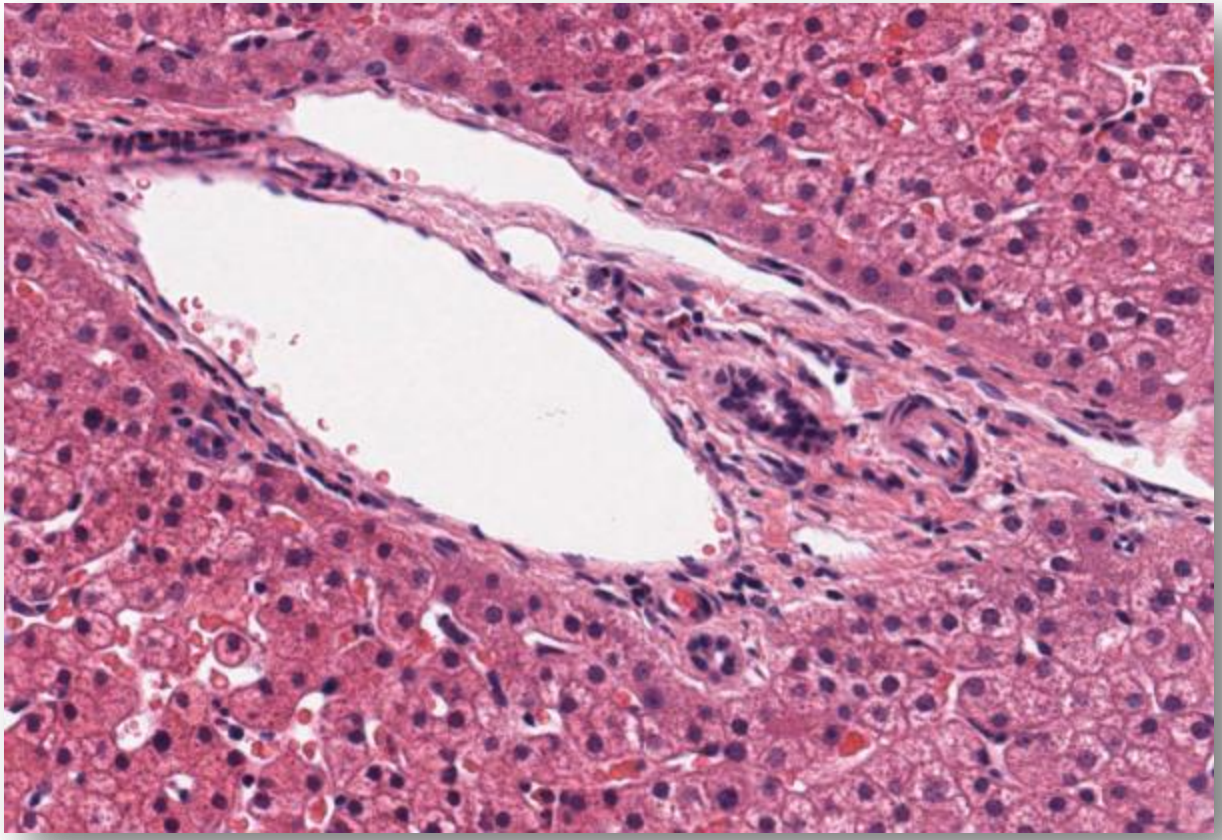
Dr Adrian C. Bateman

Case number:	LV7
Clinical Information:	UC, abnormal LFTs, high ALP 231, ALT back to normal from 58-74. ? Cause of abnormal LFTs.
Specimen:	Liver biopsy
Age:	28
Sex:	Female
Macroscopic description:	One core, 26mm long H&E CK7 shikata VanGieson

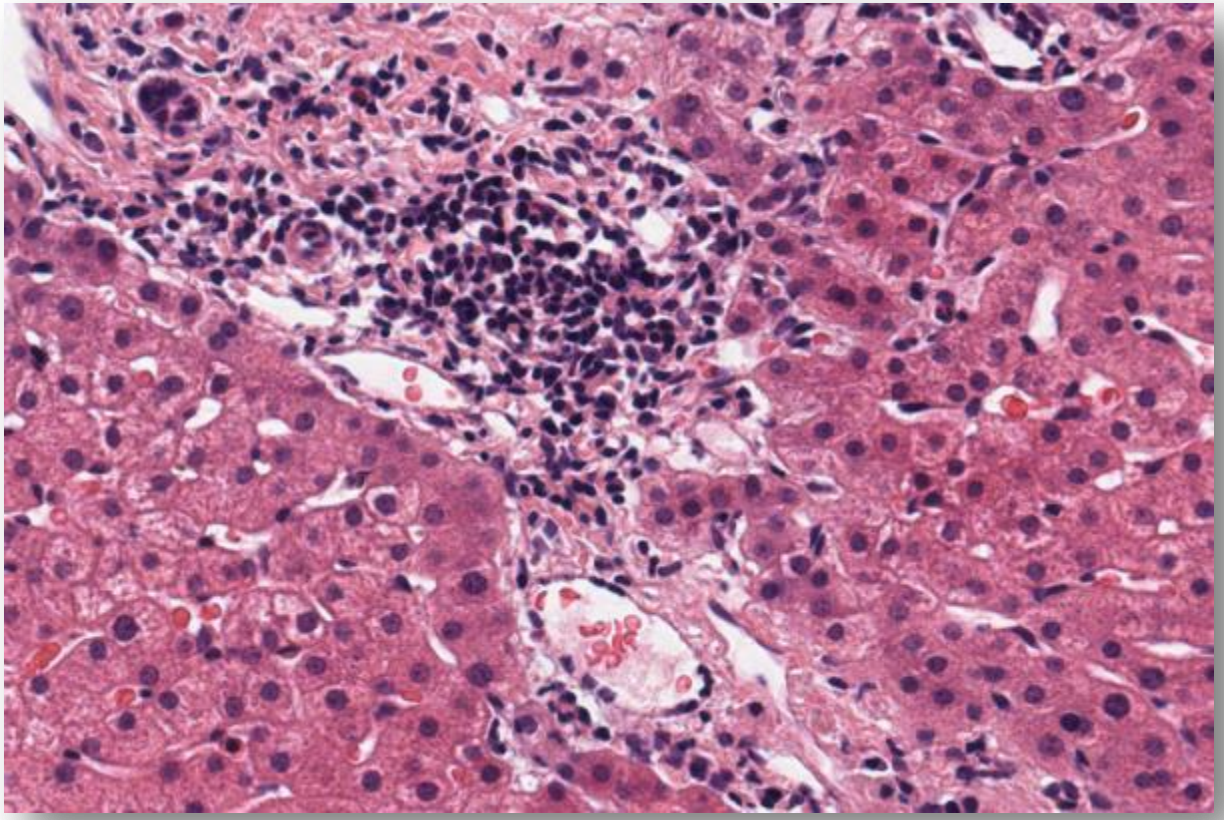
LV7



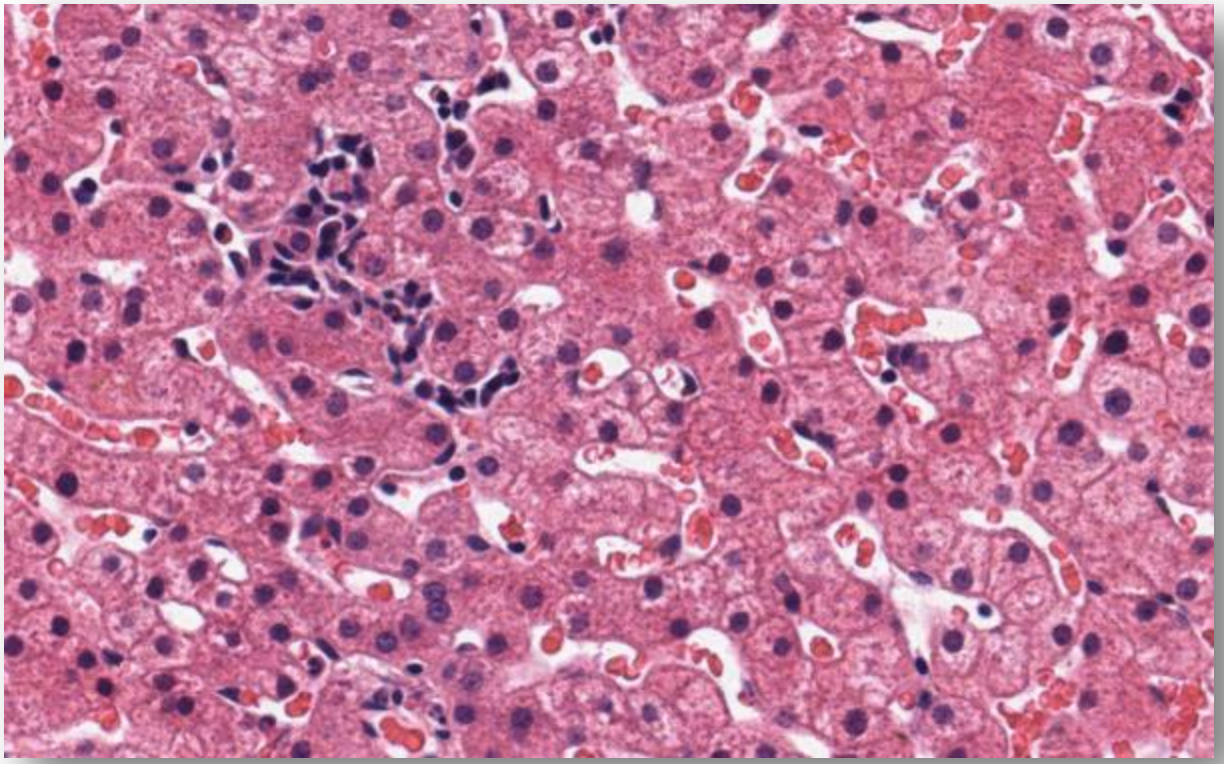
LV7



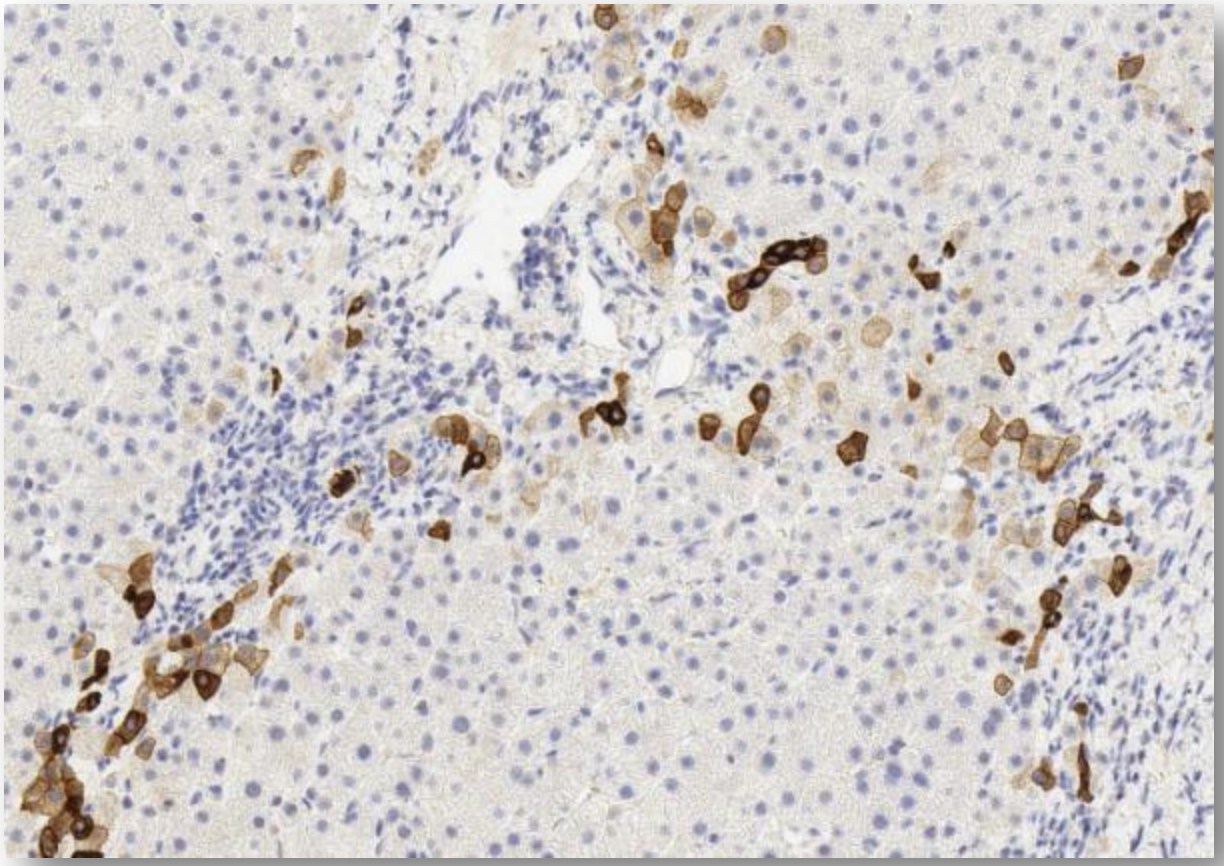
LV7



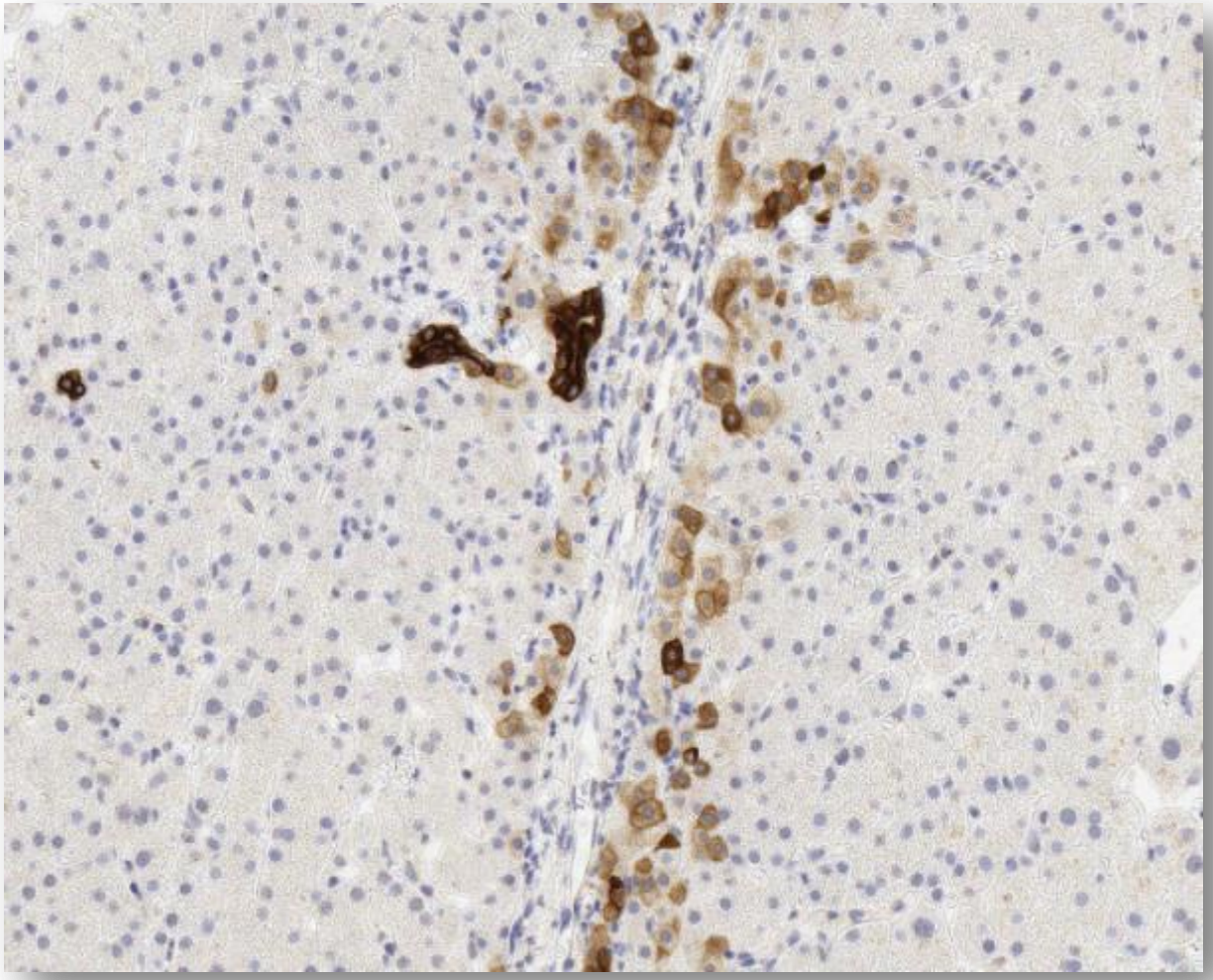
LV7



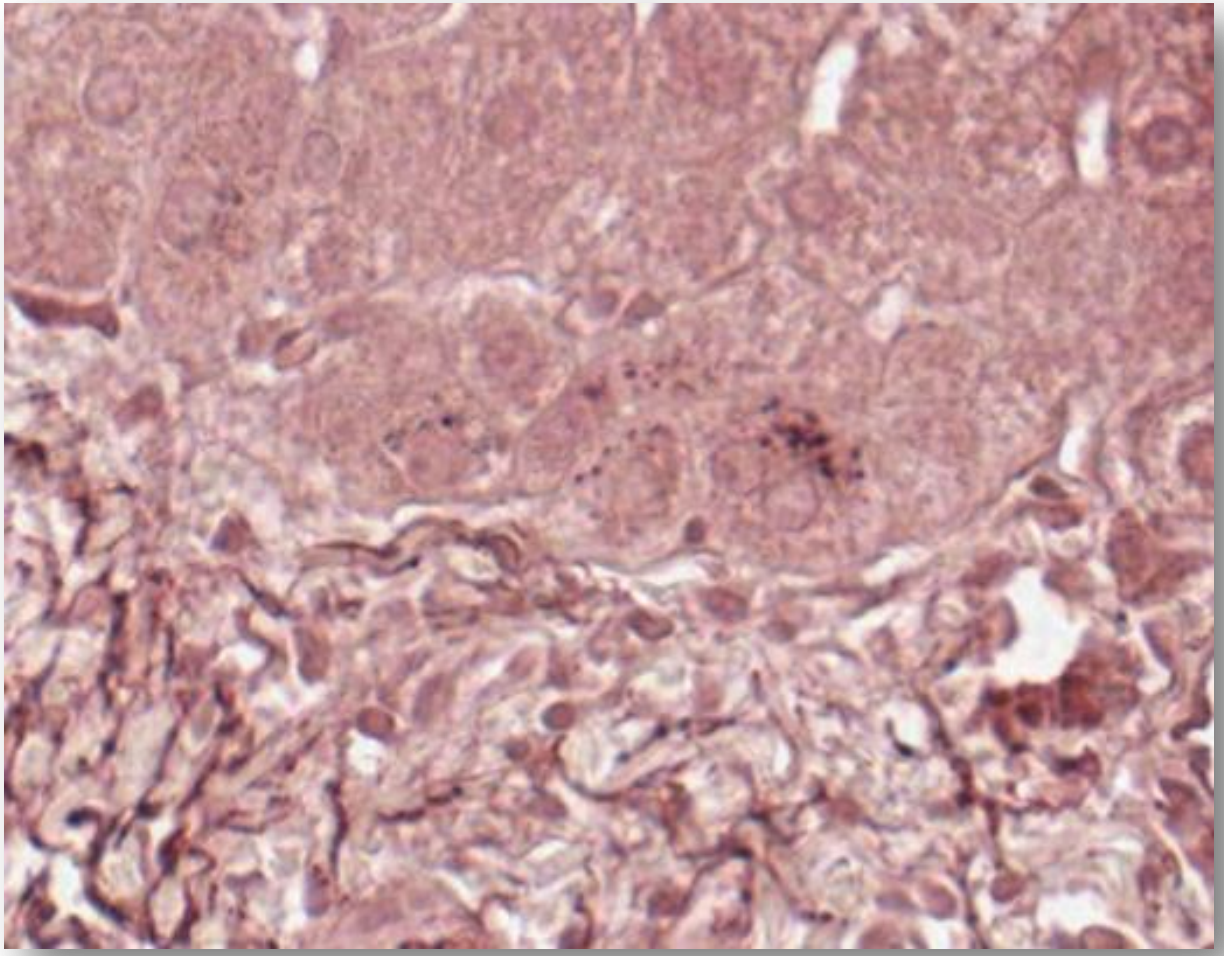
LV7



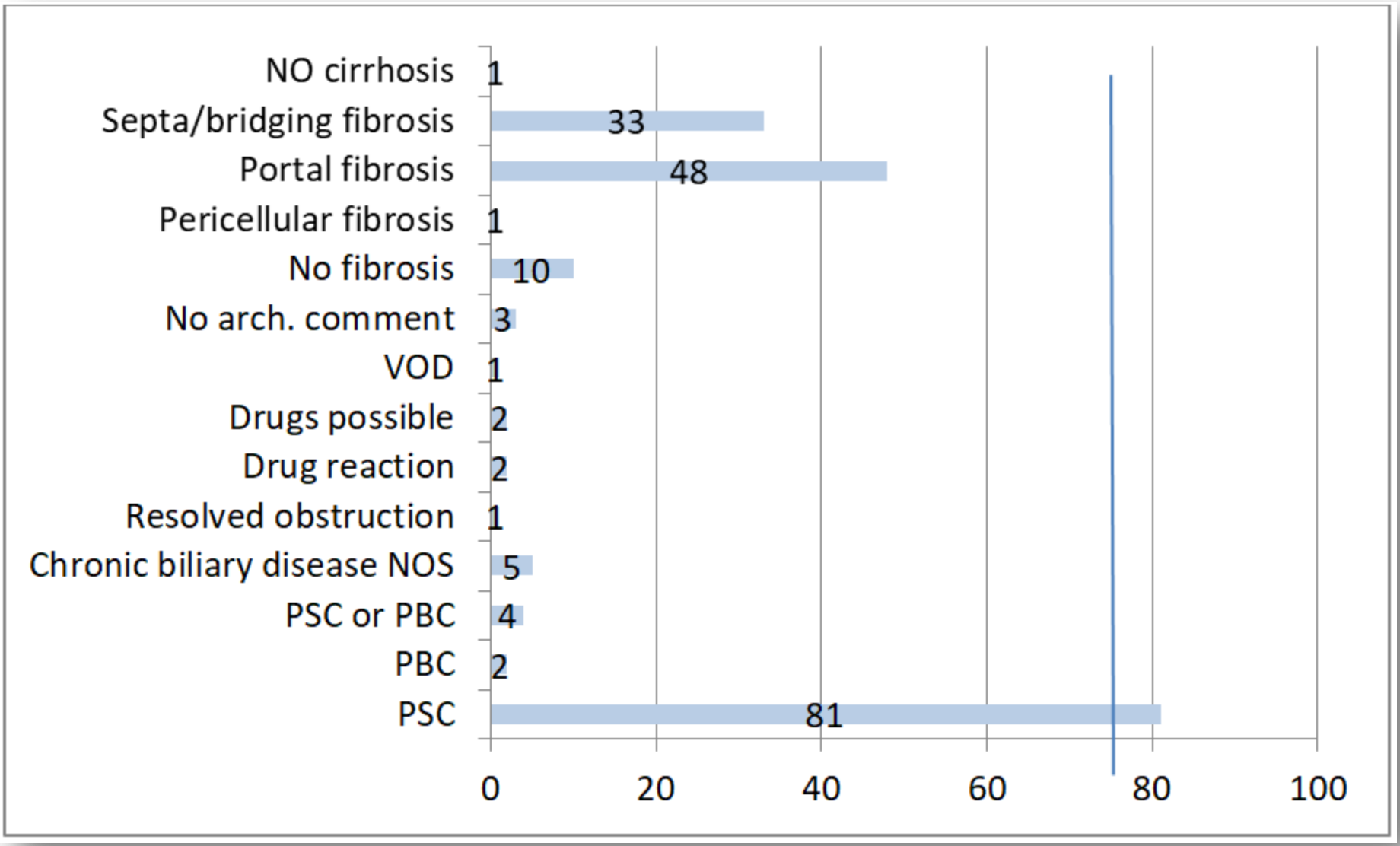
LV7



LV7



LV7


NO cirrhosis
1
Septa/bridging fibrosis
33
Portal fibrosis
48
Pericellular fibrosis
1
No fibrosis
10
No arch. comment
3
VOD
1
Drugs possible
2
Drug reaction
2
Resolved obstruction
1
Chronic biliary disease NOS
5
PSC or PBC
4
PBC
2
PSC
81
0
20
40
60
80
100

LV7

Consensus complete responses would include – mild fibrous portal tract expansion, portal tract chronic inflammation, native bile ducts in all tracts, copper binding protein accumulation seen with orcein staining, CK7 highlights a ductular reaction in portal tracts and CK7-positive periportal hepatocytes. Features consistent with those of chronic biliary tract disease and in this clinical context, favour PSC.

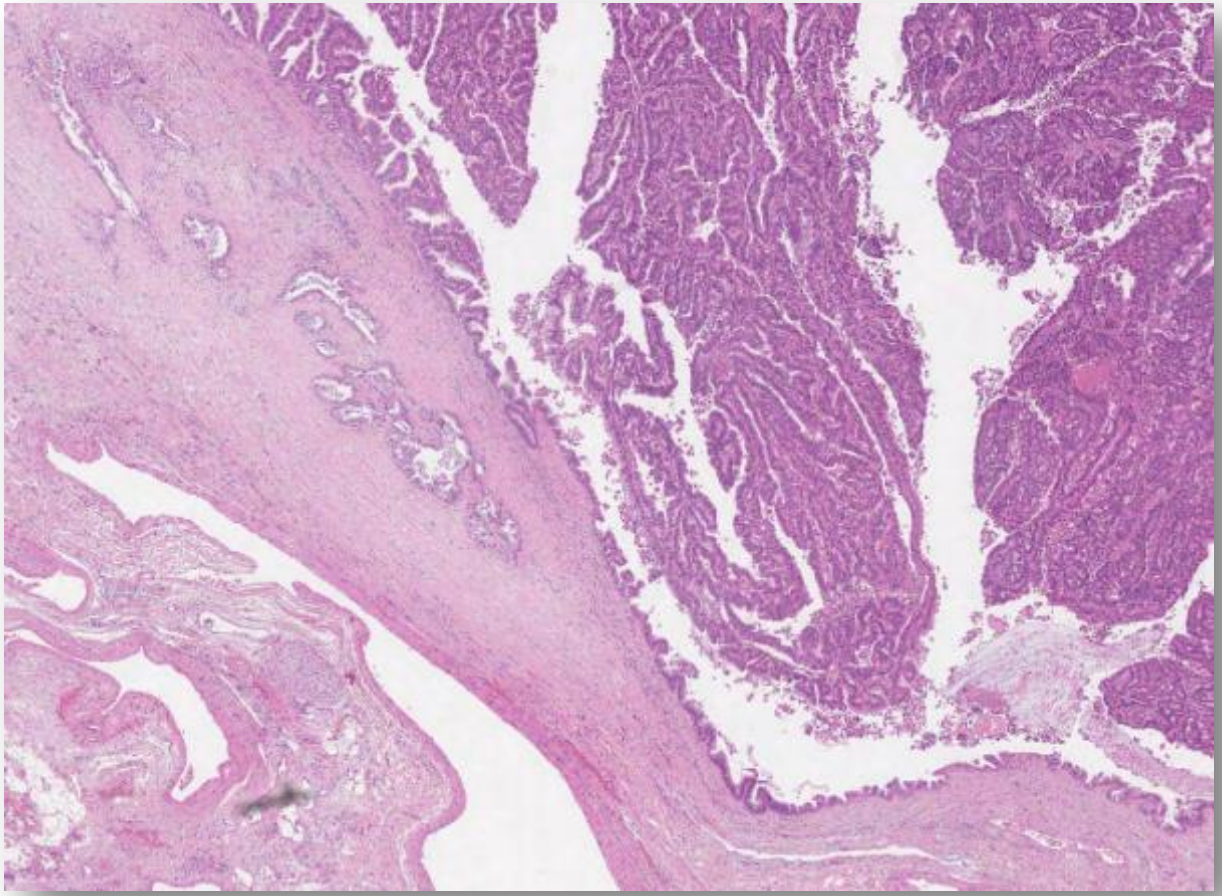
Suggested scoring: for 10 points include – chronic biliary tract disease favouring PSC with comment on architecture.
Lose 5 marks if – mention chronic biliary tract disease but don't favour PSC. agreed
Lose 5 marks if – no comment on architecture. agreed
Lose 10 marks (score 0) if – don't mention chronic biliary tract disease and/or suggest a different aetiology. agreed

Discussion points – most people thought this was chronic biliary tract disease and most (81) favoured PSC. Most people (93) made a comment on architecture, although the severity of fibrosis described was variable. PSC reached consensus.

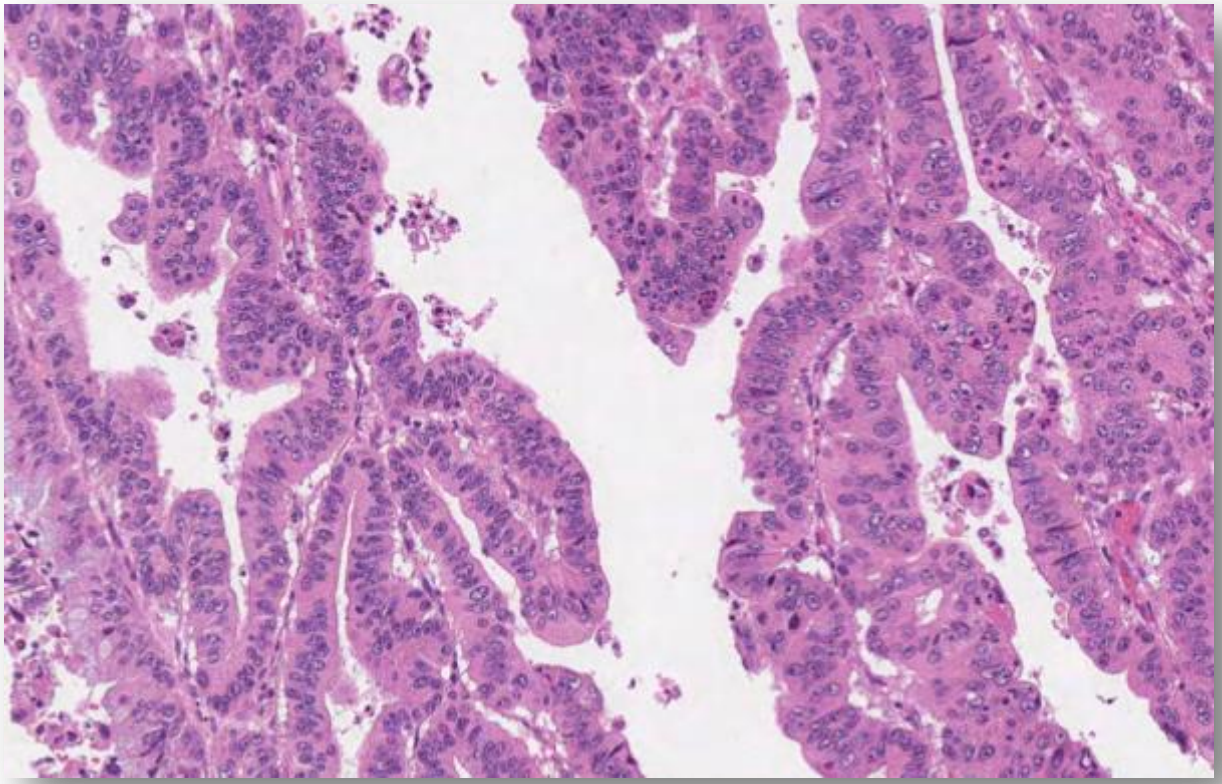
LV8

Case number:	LV8
Clinical Information:	Patient had long history of PSC and underwent liver transplantation. Imaging demonstrated filling defect at the confluence of the intrahepatic ducts and dilatation of the intrahepatic biliary system.
Specimen:	Liver resection.
Age:	63
Sex:	Male
Macroscopic description:	3cm polypoid intraluminal lesion at the confluence of the right and left intrahepatic ducts. Section is from this lesion. Just H&E

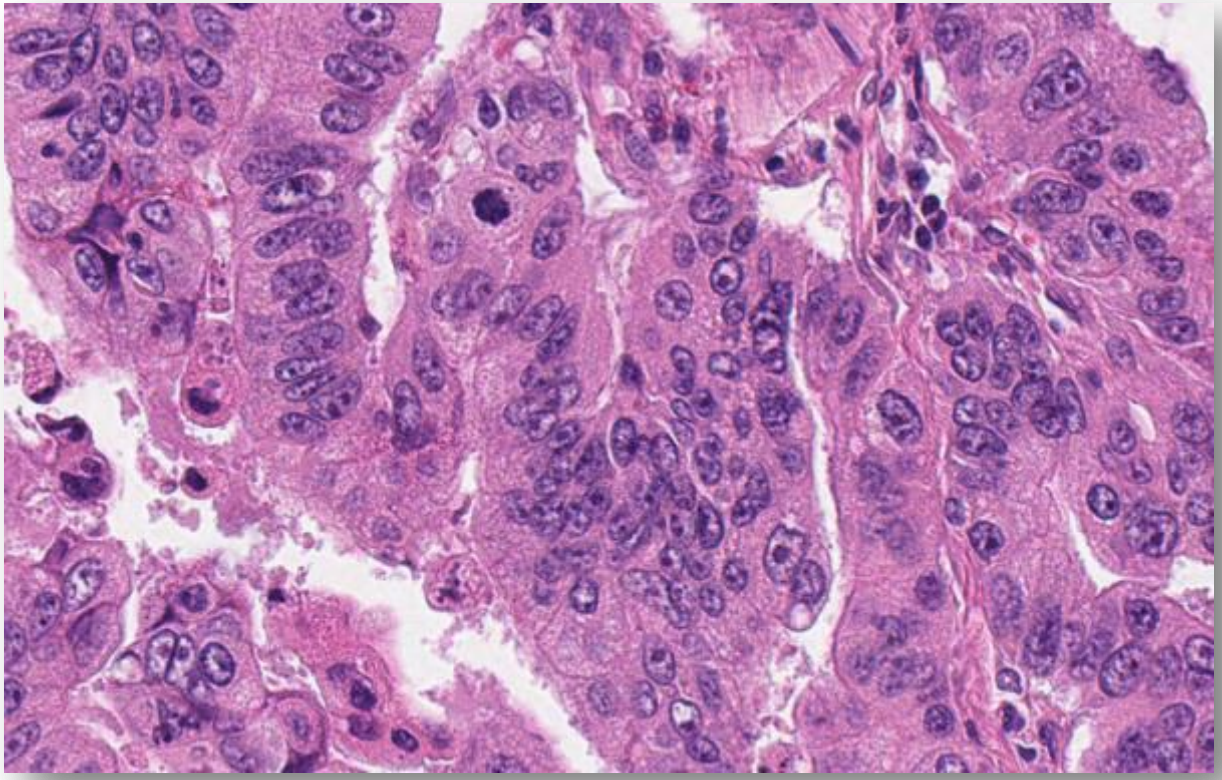
LV8



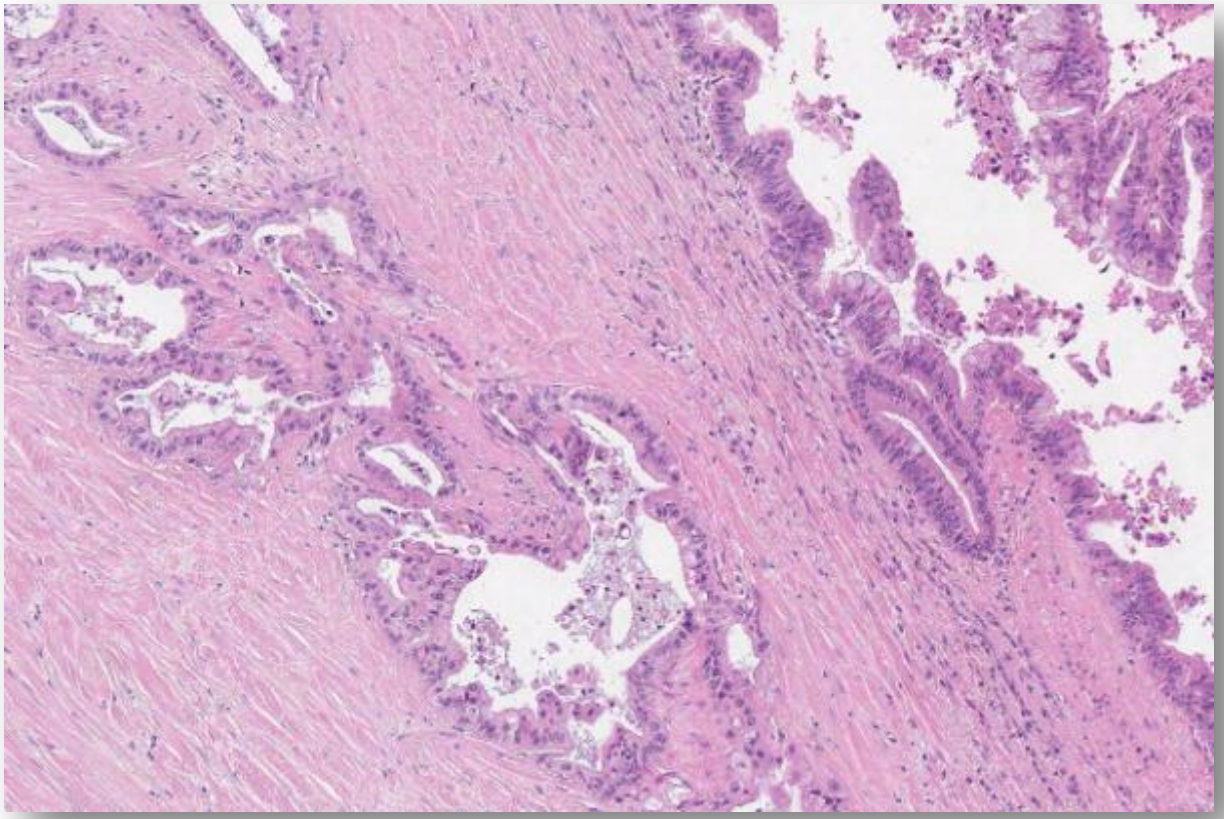
LV8



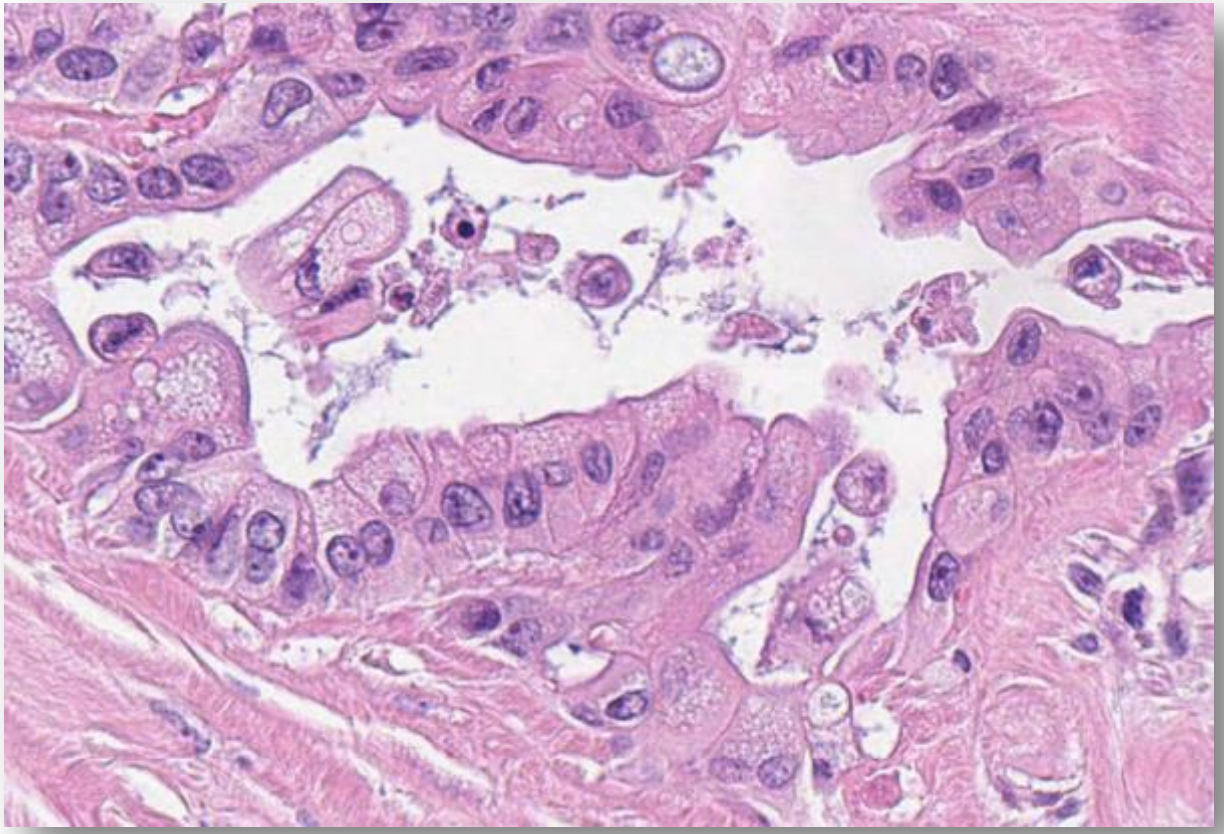
LV8



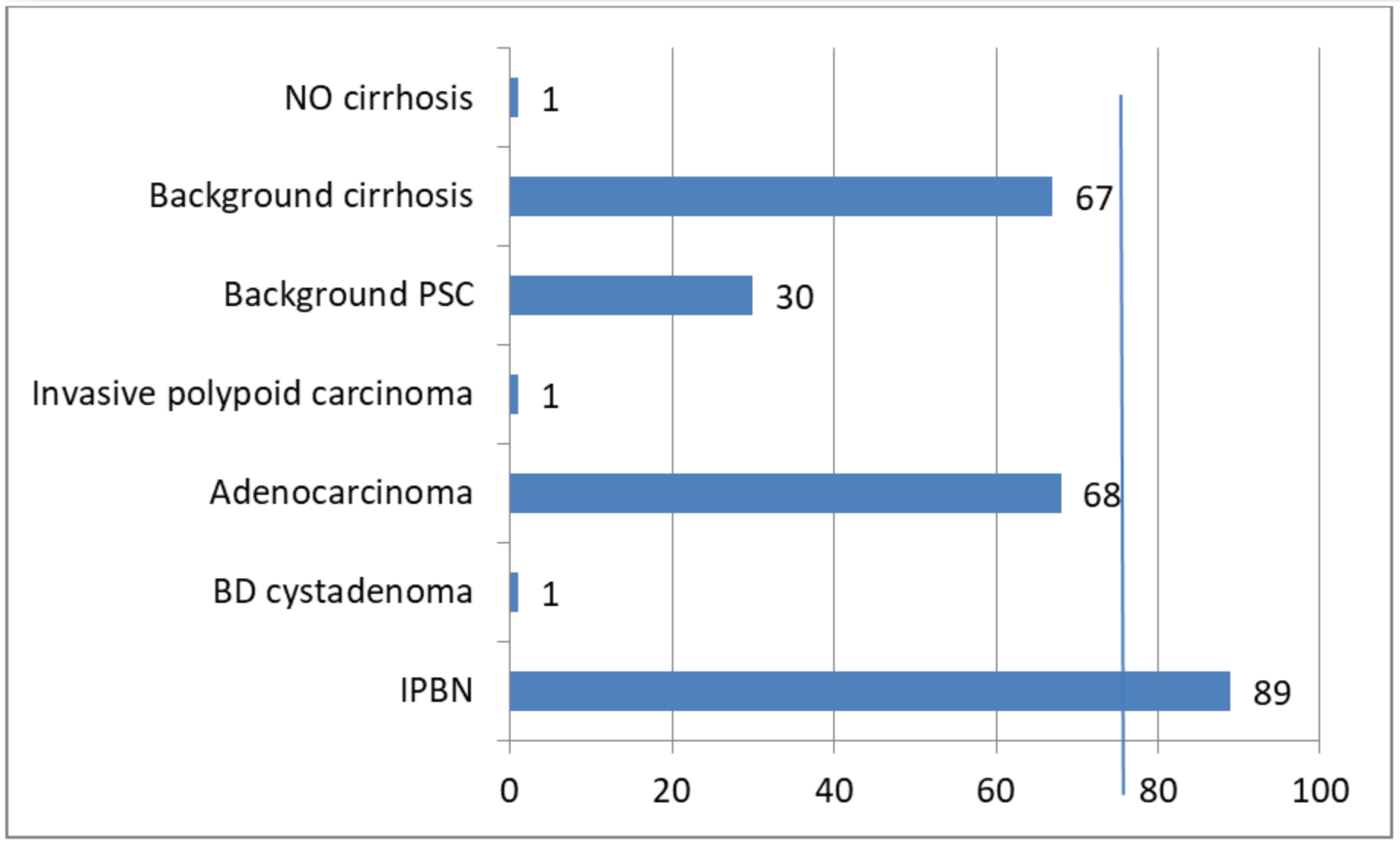
LV8



LV8



LV8


NO cirrhosis
1
Background cirrhosis
67
Background PSC
30
Invasive polypoid carcinoma
1
Adenocarcinoma
68
BD cystadenoma
1
IPBN
89
0
20
40
60
80
100

LV8

As there is a clear diagnosis of malignancy here but this didn't reach consensus not suitable for scoring – include as educational case.

Discussion re glass versus digital assessments

Consensus complete responses would include – an intraduct epithelial lesion is present, with features of IPBN. Adenocarcinoma is also present. The non-lesional liver shows cirrhosis with appearances consistent with a biliary aetiology.

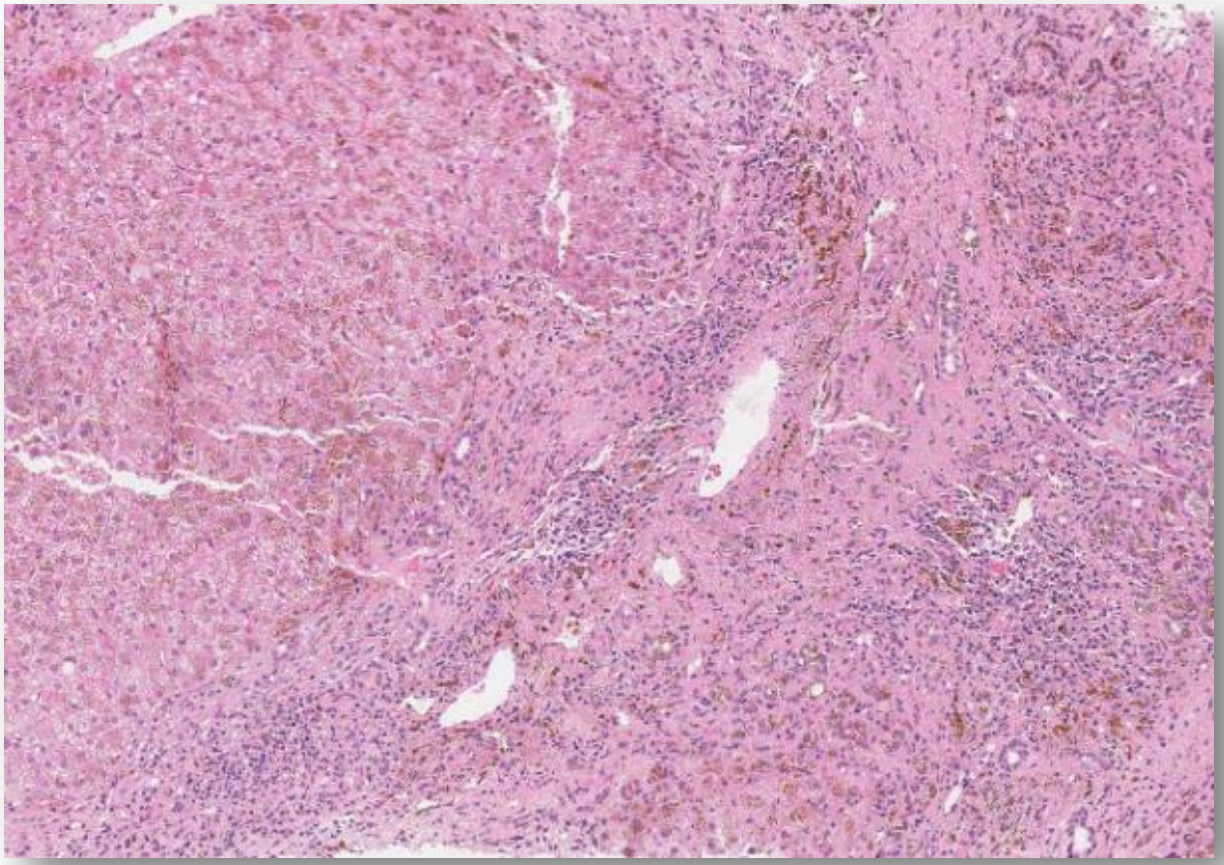
Suggested scoring: for 10 points include – identification of IPBN (some flexibility allowed for precise terminology), identification of co-existent adenocarcinoma. Identification of cirrhosis within non-lesional liver, ideally with a comment that this shows features suggestive of a biliary aetiology.
Lose 5 marks if – no mention of cirrhosis in non-lesional liver or specifically indicate that no cirrhosis was present.
Lose 10 marks (score 0) if – n/a.

Discussion points – most people (89) identified that an IPBN was present, although the terminology used was a little varied. Most but not all of these people (68) indicated that adenocarcinoma was also present. The majority of people (67) recognised that the non-lesional liver showed cirrhosis. IPBN (or very similar term) reached consensus.

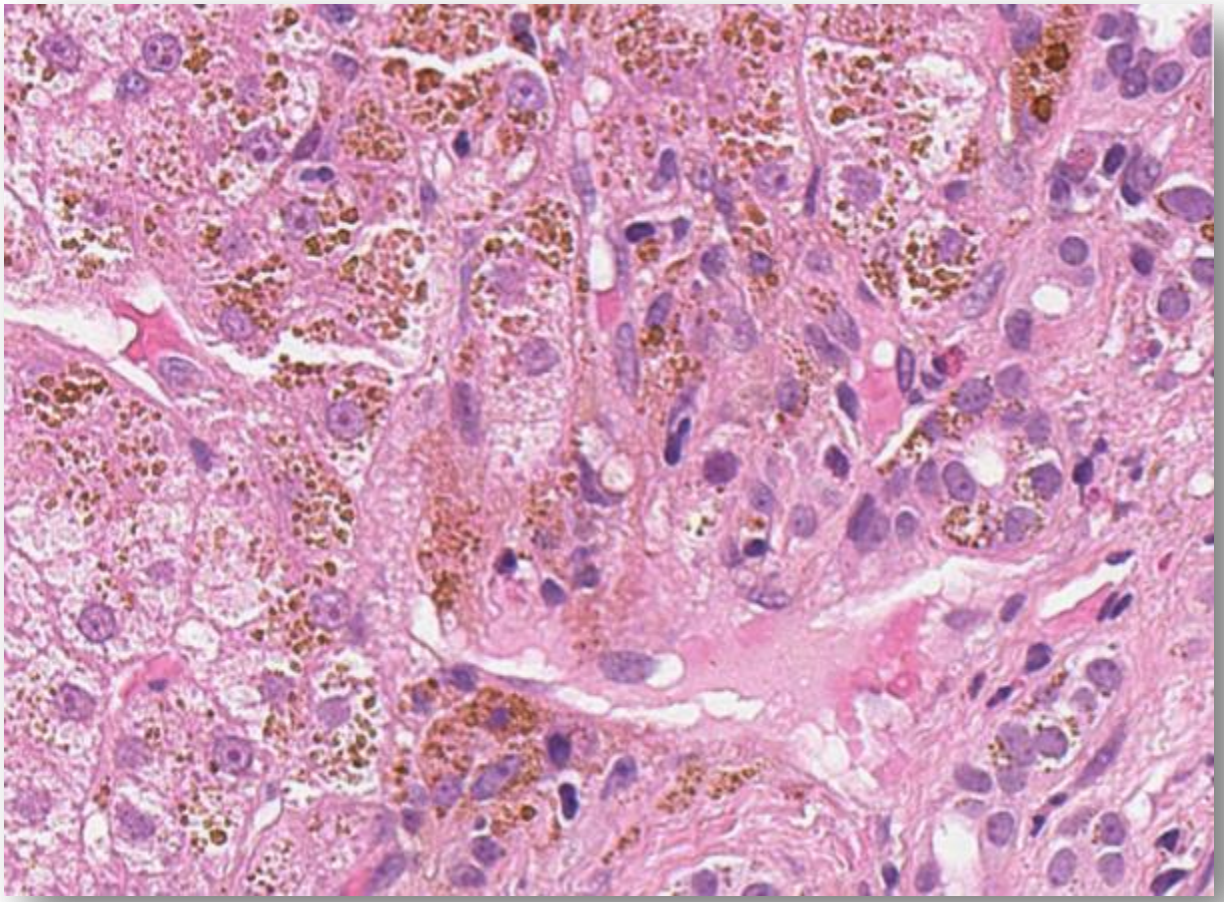
LV9

Case number:	**LV9**
Clinical Information:	Liver disease screen
Specimen:	Liver biopsy
Age:	58
Sex:	Male
Macroscopic description:	Two cores 16mm and 14mm H&E PSR Perls

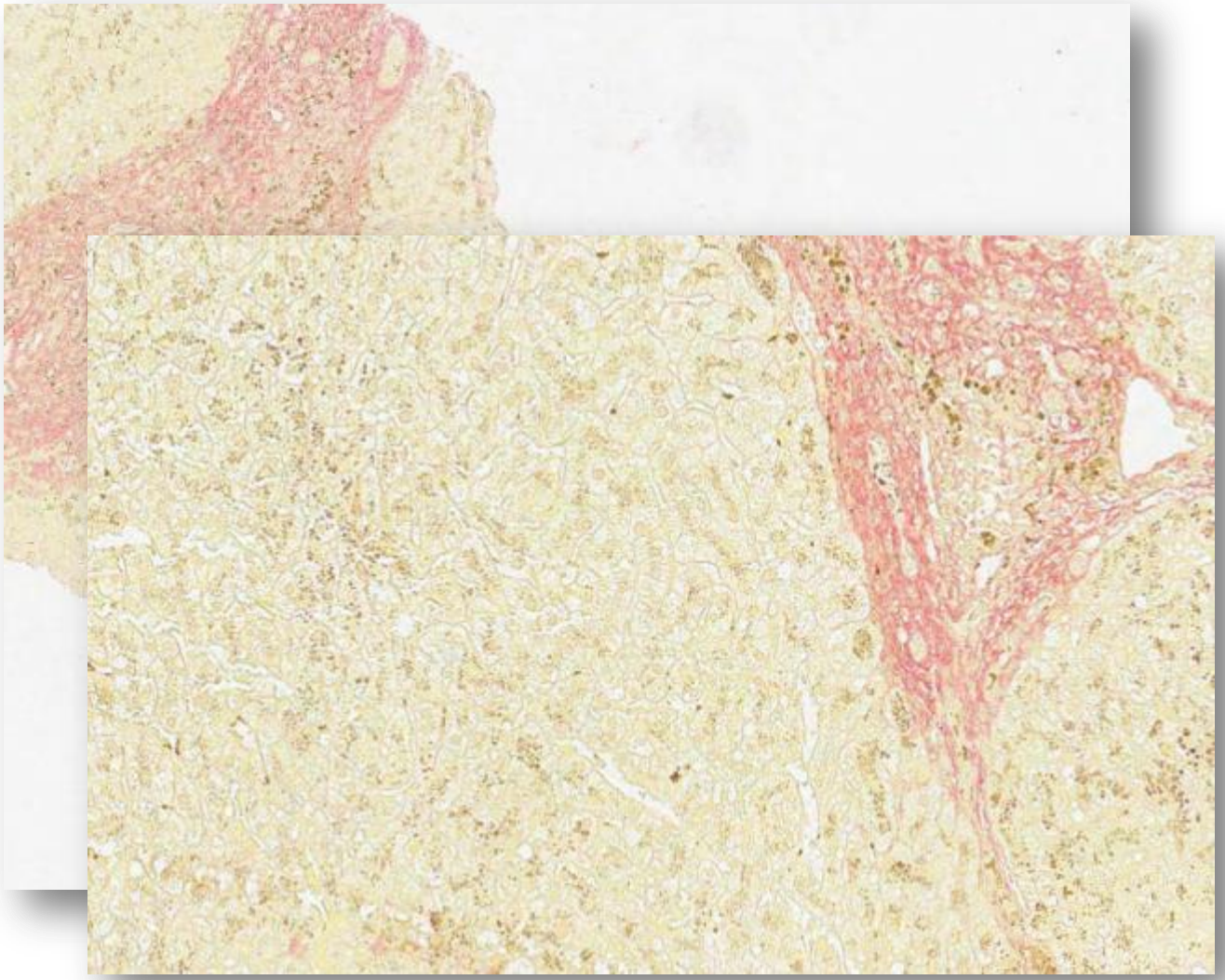
LV9



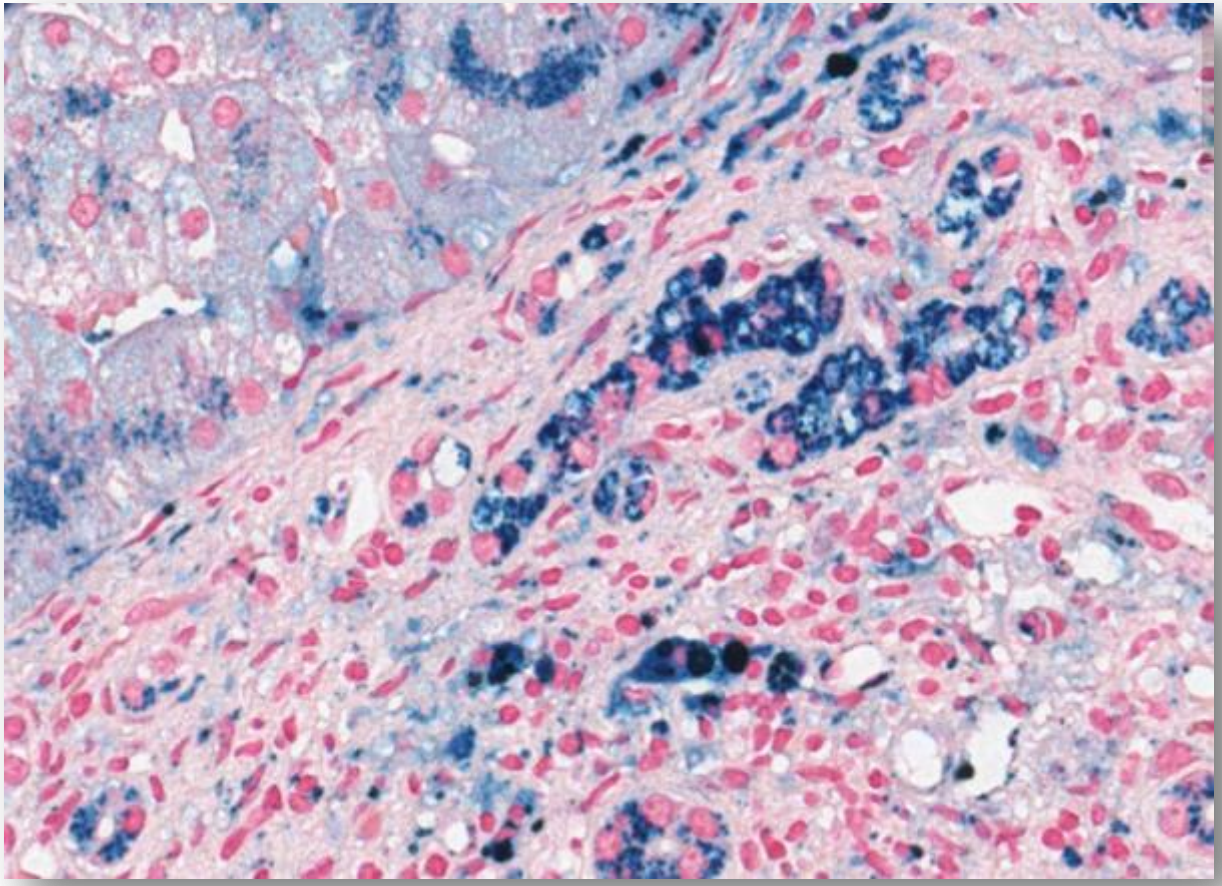
LV9



LV9



LV9



LV9

Severe/bridging fibrosis
2
Cirrhosis
94
Haemochromatosis
96
0
20
40
60
80
100
120

LV9

Consensus complete responses would include – established cirrhosis is present. Marked (grade 4) iron overload is present – highlighted on the Perl's stain. Iron is present mainly within hepatocytes but also within biliary epithelium.

Suggested scoring: for 10 points include – identification of cirrhosis. Identification of marked iron overload. An indication that further testing for genetic haemochromatosis is required.
Lose 5 marks if – didn't indicate that cirrhosis was present. Agreed
Lose 10 marks (score 0) if – n/a.

Discussion points – everyone (96) identified that marked iron overload was present and suggested that this was very likely to represent genetic haemochromatosis. Almost everyone (95) identified that cirrhosis was present. Haemochromatosis and cirrhosis achieved consensus.

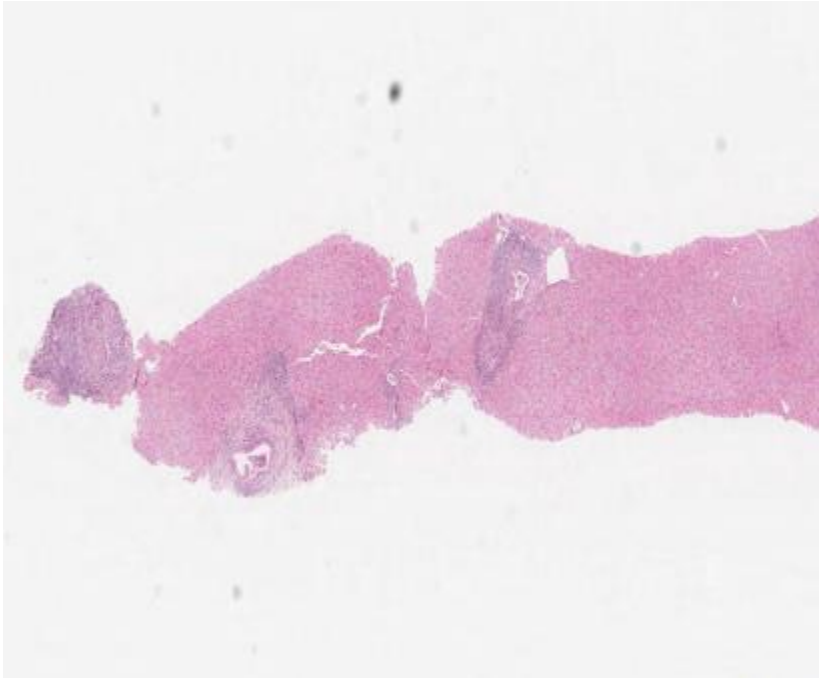
UK National Liver Histopathology EQA Scheme 2020

LV10, LV11, LV12

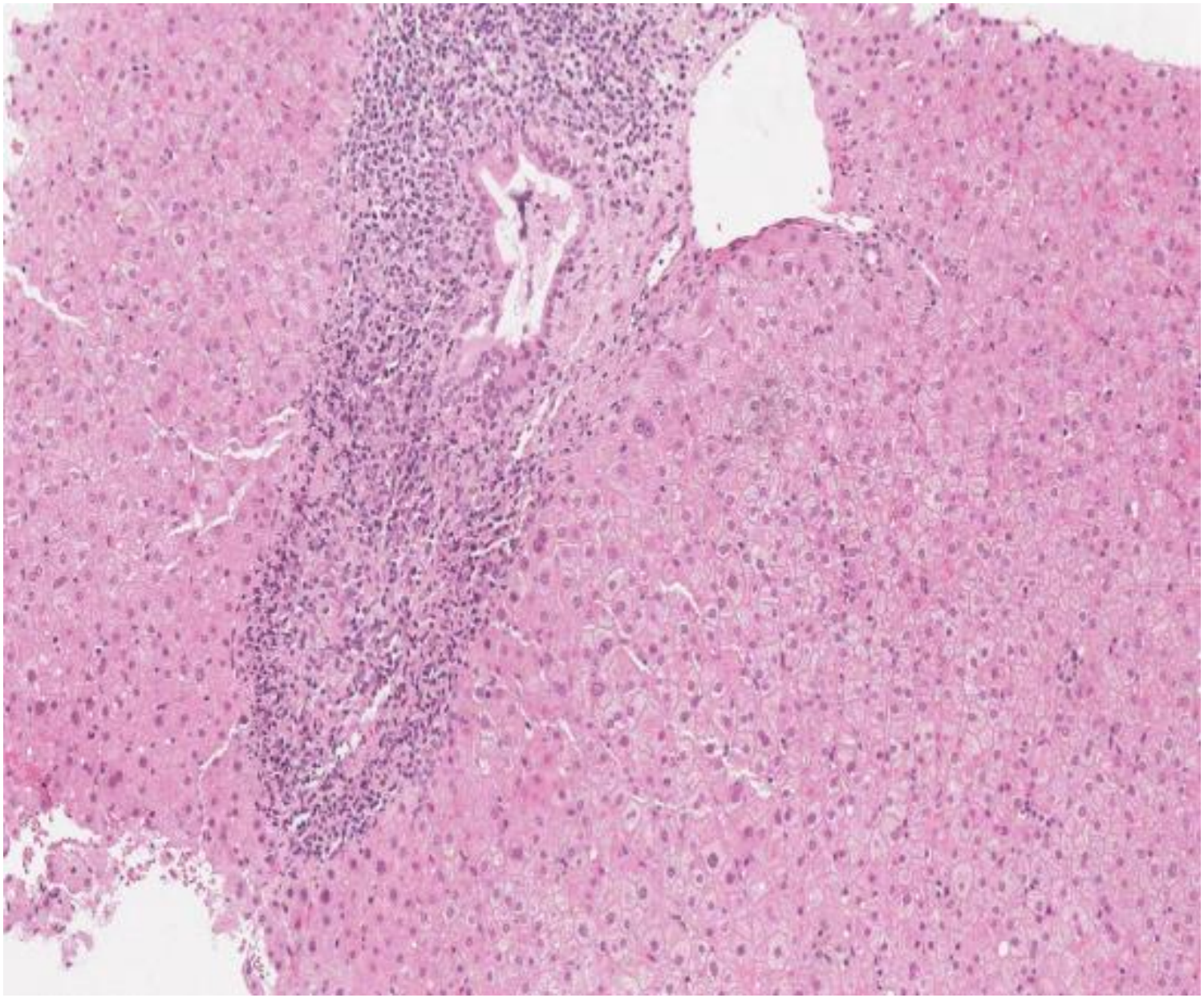
Dr Paul Kelly

LV10

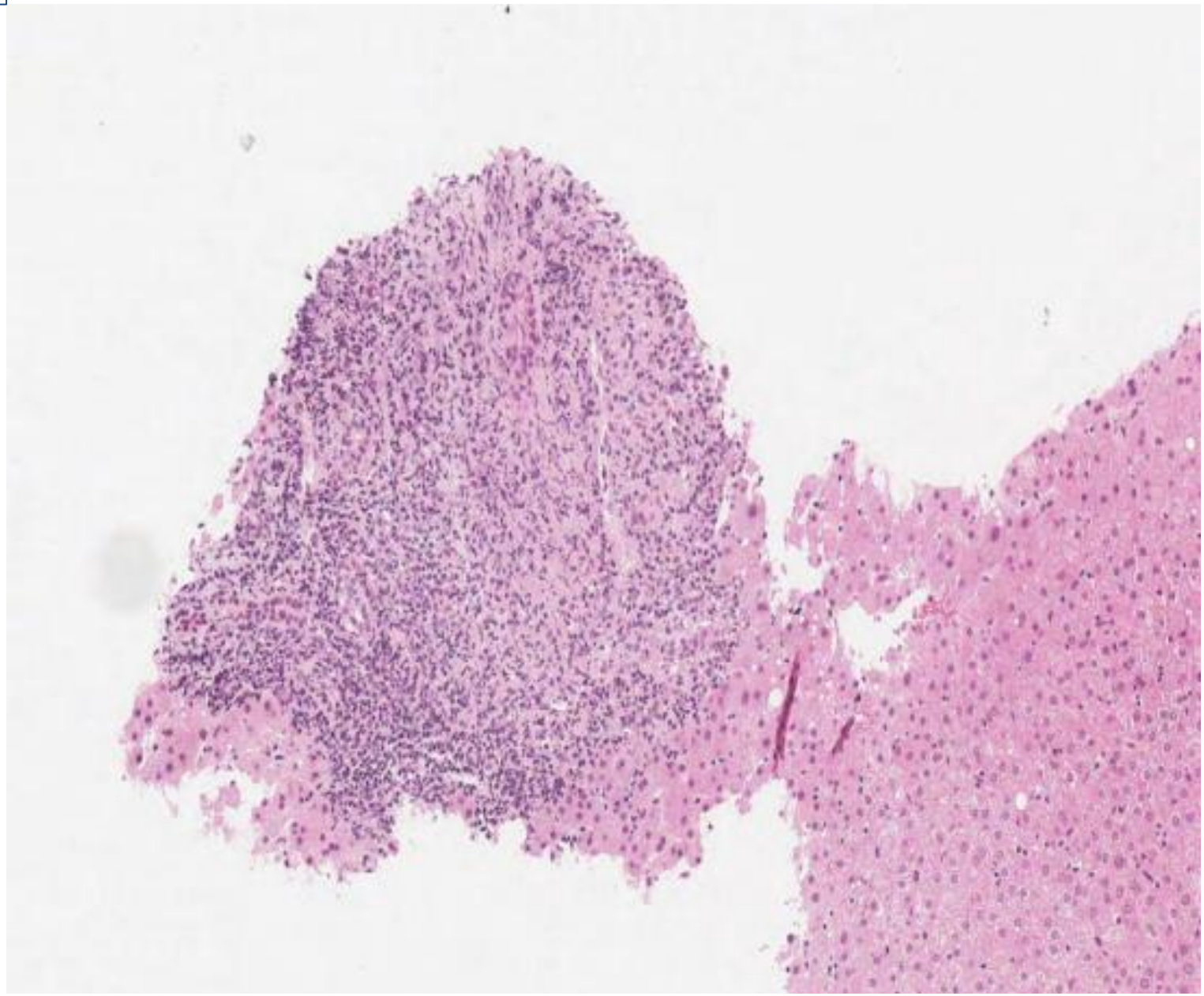
- Male 68 years
- Cholestatic LFT's, +ve AMA.
- Specimen:
- Liver biopsy.
- Macroscopic description:
- 19mm core.
- Immunohistochemistry:
- None.



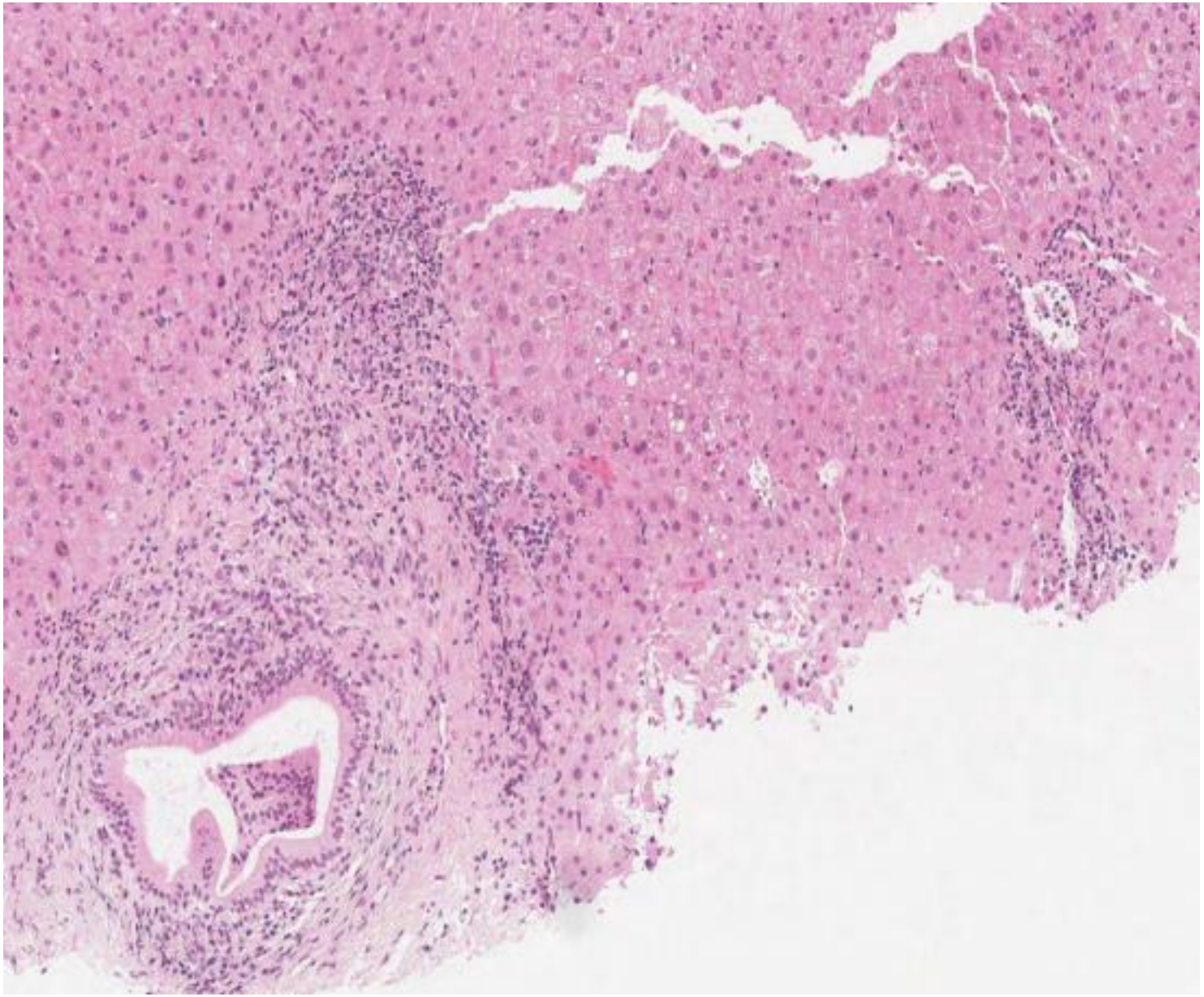
LV10



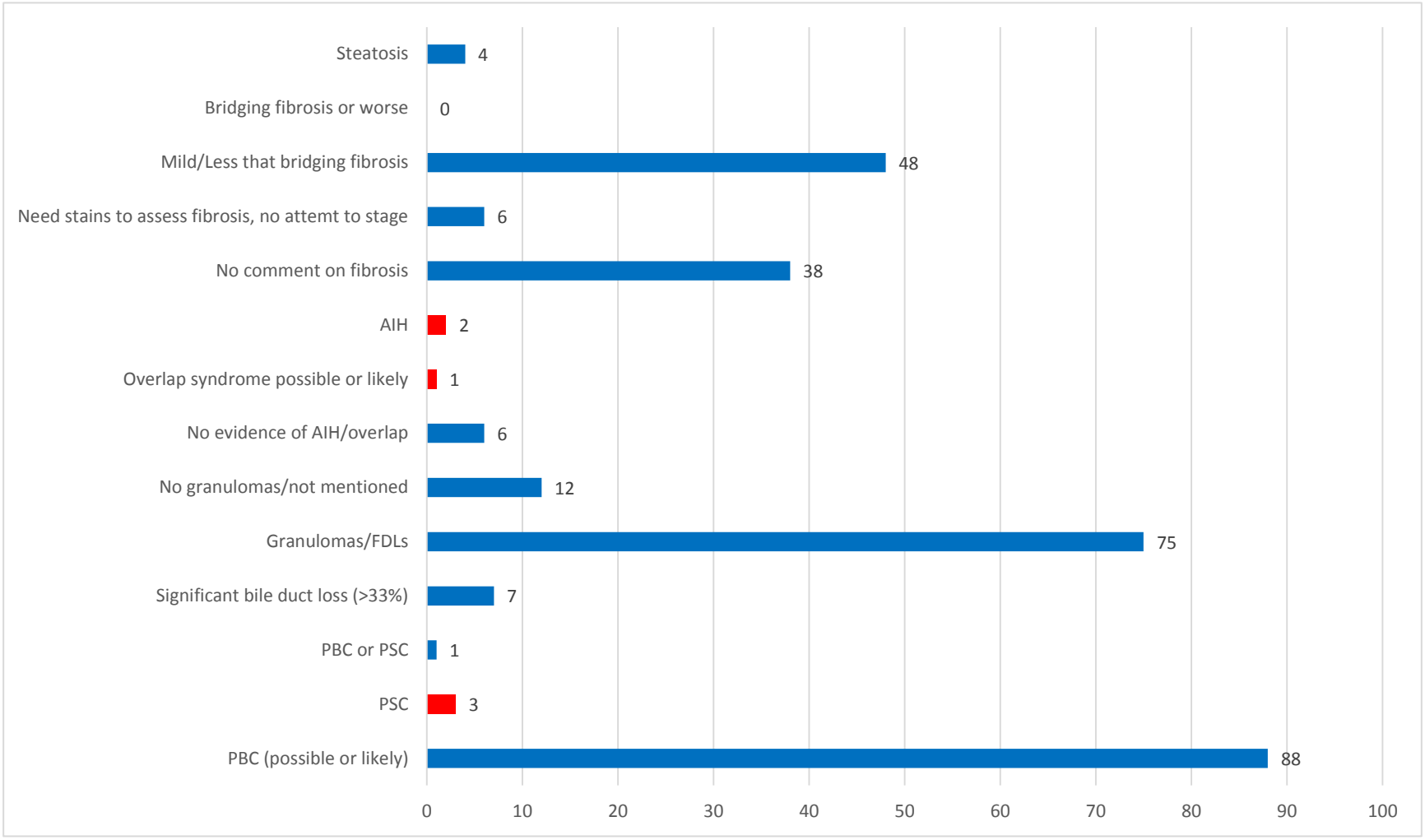
LV10



LV10



LV10


Steatosis
4
Bridging fibrosis or worse
0
Mild/Less that bridging fibrosis
48
Need stains to assess fibrosis, no attemt to stage
6
No comment on fibrosis
38
AIH
2
Overlap syndrome possible or likely
1
No evidence of AIH/overlap
6
No granulomas/not mentioned
12
Granulomas/FDLs
75
Significant bile duct loss (>33%)
7
PBC or PSC
1
PSC
3
PBC (possible or likely)
88
0
10
20
30
40
50
60
70
80
90
100

LV10

- **Consensus complete responses would include**:
- Primary biliary cholangitis. No consensus for fibrosis (no comment provided in 38 responses)

- **Suggested scoring: for 10 points** include Primary biliary cholangitis as likely diagnosis
- **Lose 5 marks** if PSC diagnosed (3) agreed
- **Lose 10 marks (score 0) if** AIH (2) or overlap syndrome (1) diagnosed Lose 5 for overlap lose 10 for AIH

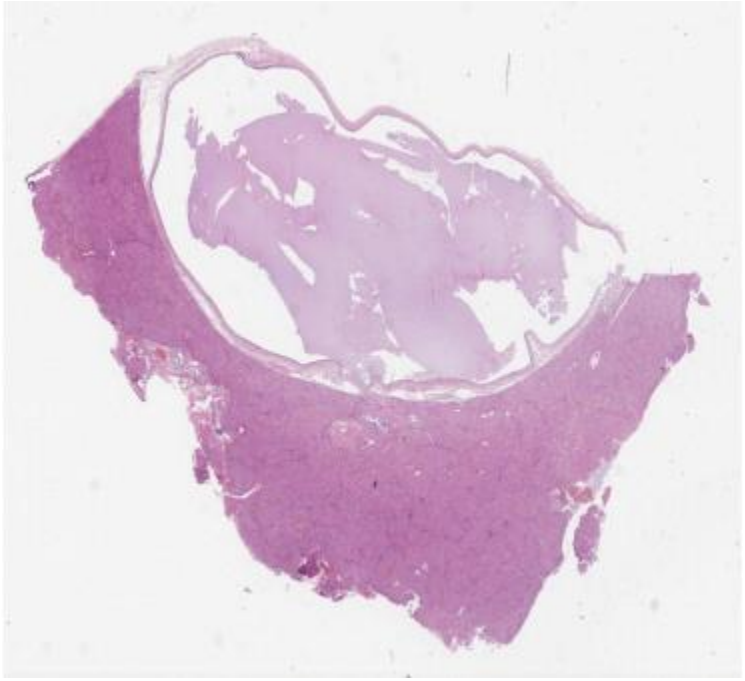
LV10

Discussion points

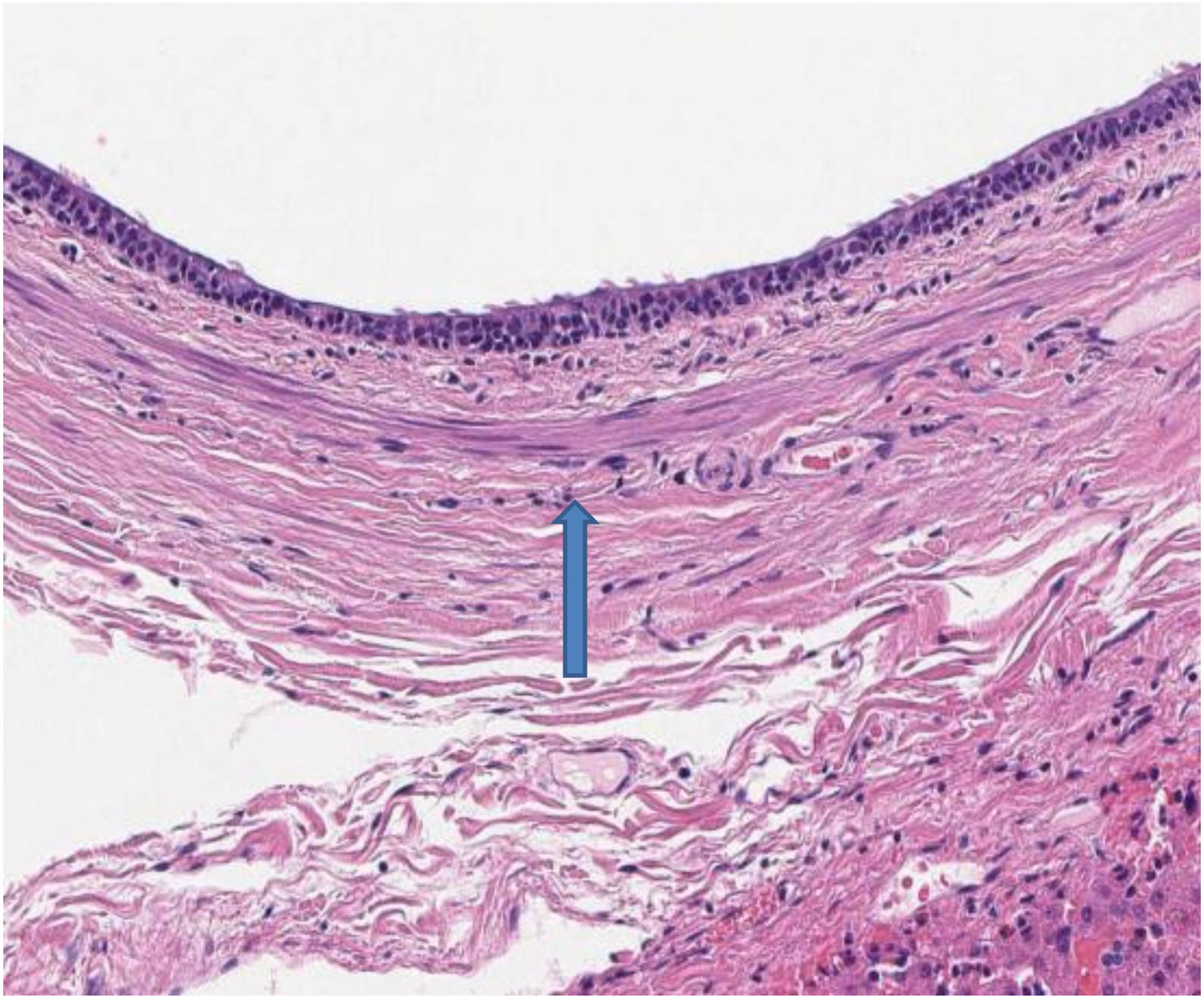
- Several respondents did not refer to, or said need to correlate with AMA serology (AMA mentioned in history as being positive). Titre not specified.
- X 1 respondent described PBC but diagnosis of PSC recorded (??typo) *should lose marks have to go on what is written as for reports*
- Number of portal tracts varied from 8 – 20
- Significant bile duct loss or ductopaenia described by 7 respondents
- Granulomas/FDLs not described by everyone ??present in all sections used
- Two respondents queried IgG4 disease as differential

LV11

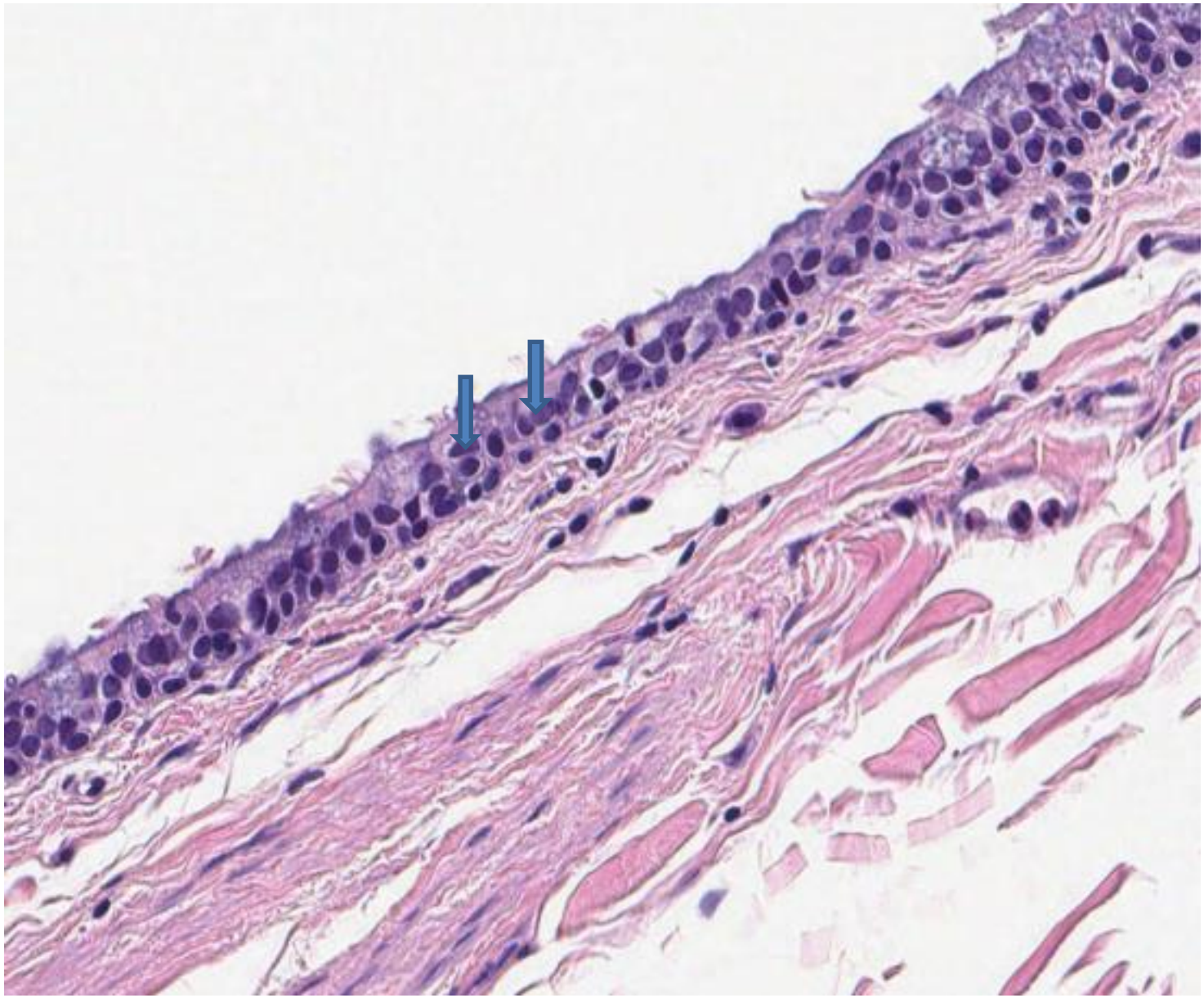
- Female 47 years
- Patient with a cyst segment 4 on CT/MRI looks like a simple cyst.
- Specimen: Liver cyst.
- Macroscopic description:
- a cyst measuring 60 x 40 x 28mm with a rim of liver at the resection margin. Slicing shows a cyst containing off-white mucoid material. The cyst lining is smooth with no solid areas.
- Immunohistochemistry:
- None.



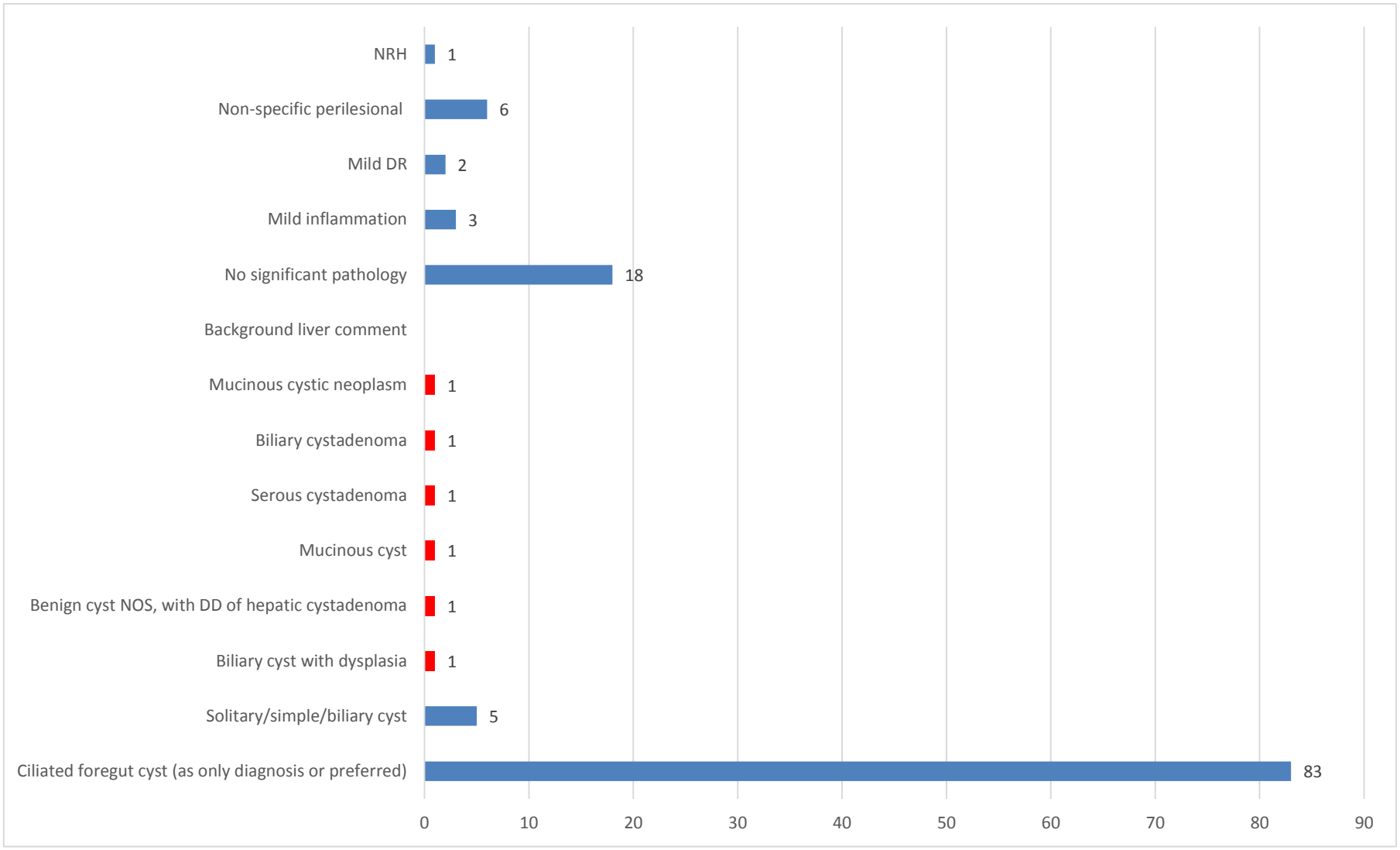
LV11



LV11



LV11


NRH
1
Non-specific perilesional
6
Mild DR
2
Mild inflammation
3
No significant pathology
18
Background liver comment
Mucinous cystic neoplasm
1
Biliary cystadenoma
1
Serous cystadenoma
1
Mucinous cyst
1
Benign cyst NOS, with DD of hepatic cystadenoma
1
Biliary cyst with dysplasia
1
Solitary/simple/biliary cyst
5
Ciliated foregut cyst (as only diagnosis or preferred)
83
0
10
20
30
40
50
60
70
80
90

LV11

- Consensus complete responses would include **ciliated foregut cyst**
- Suggested scoring: for 10 points include ciliated foregut cyst
- Lose 5 marks if solitary/simple/biliary (n=5)
- Lose 10 marks (score 0) if alternative (i.e. not ciliated foregut, or simple benign cyst) diagnosed (n=6) i.e. dysplasia. “cystadenoma”
  - *Management consequences or imply neoplasia – could put this to members*

LV11

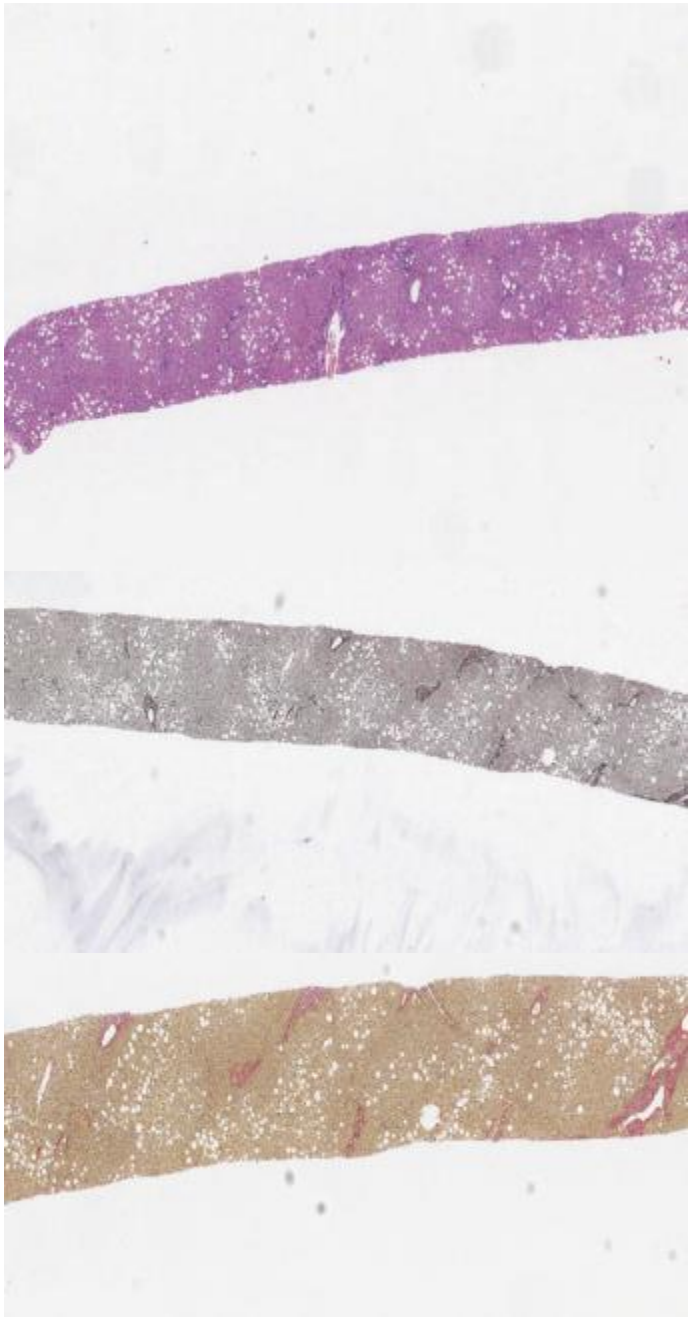
Discussion points

- Continued use of term “cystadenoma” or presence of dysplasia by several respondents. Potential confusion in relation to neoplastic cystic lesions. Implications for future management.

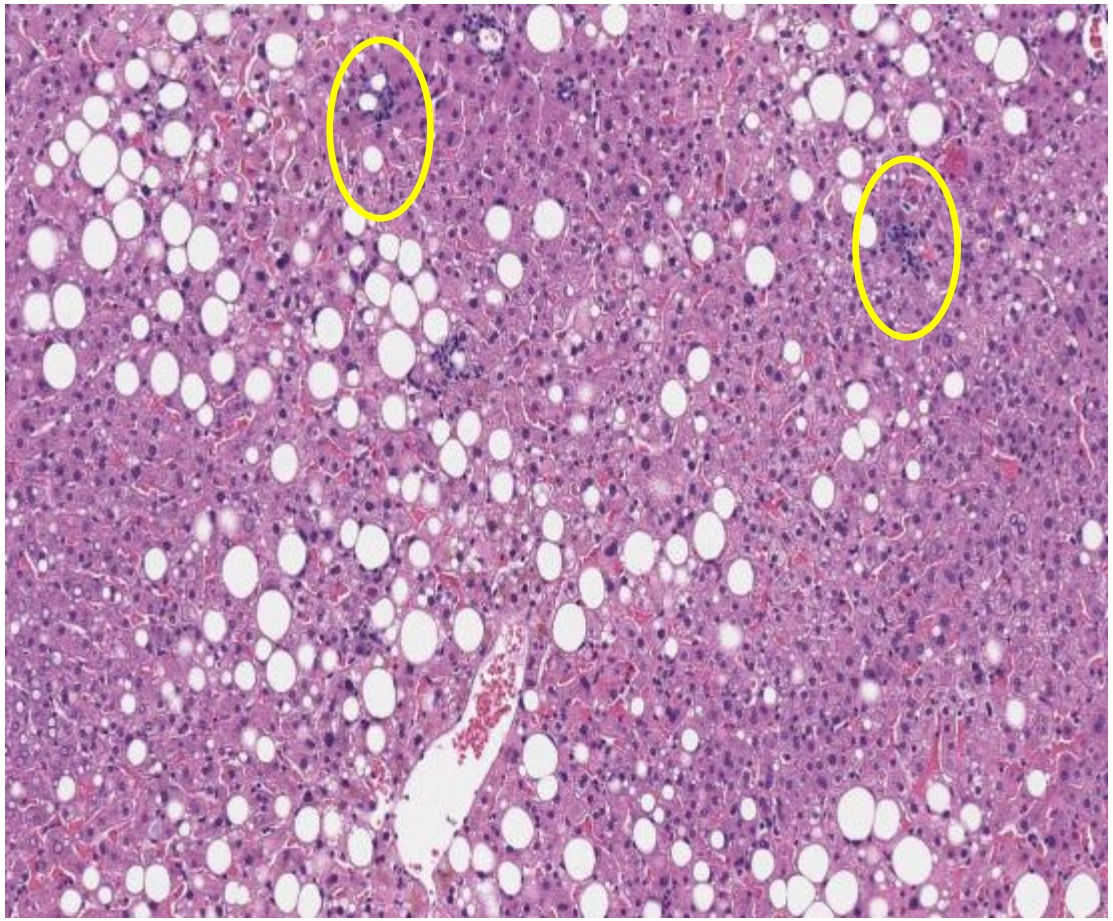
- MCN diagnosis

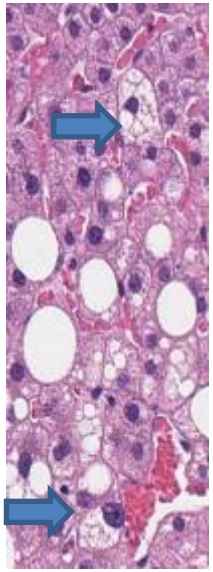
LV12

- Male 48 years
- Transaminitis. NAFLD. methotrexate for ..... Fatty liver.
- Specimen: liver biopsy.
- Macroscopic description:
- one core 30mm long.
- Immunohistochemistry:
- retic, van Gieson.

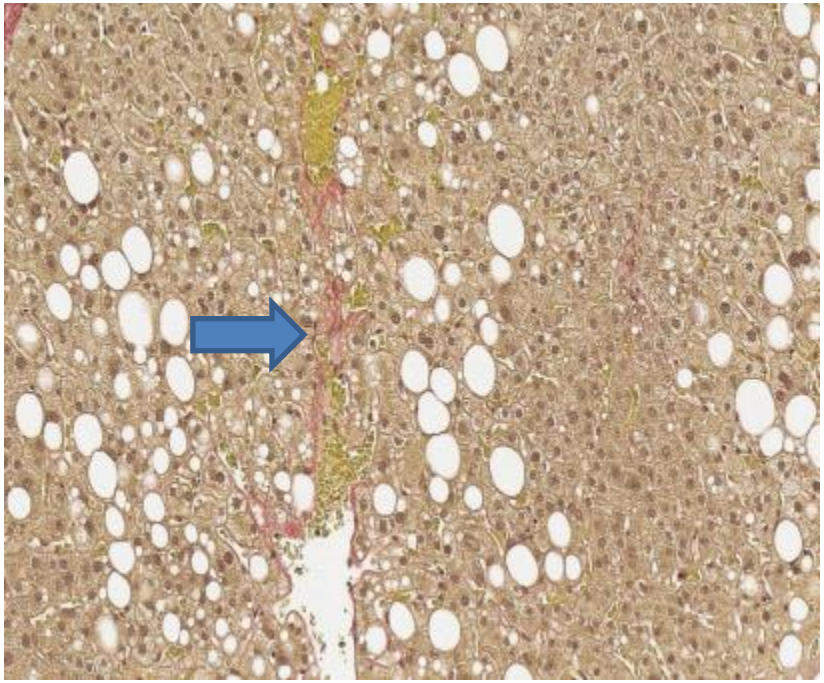


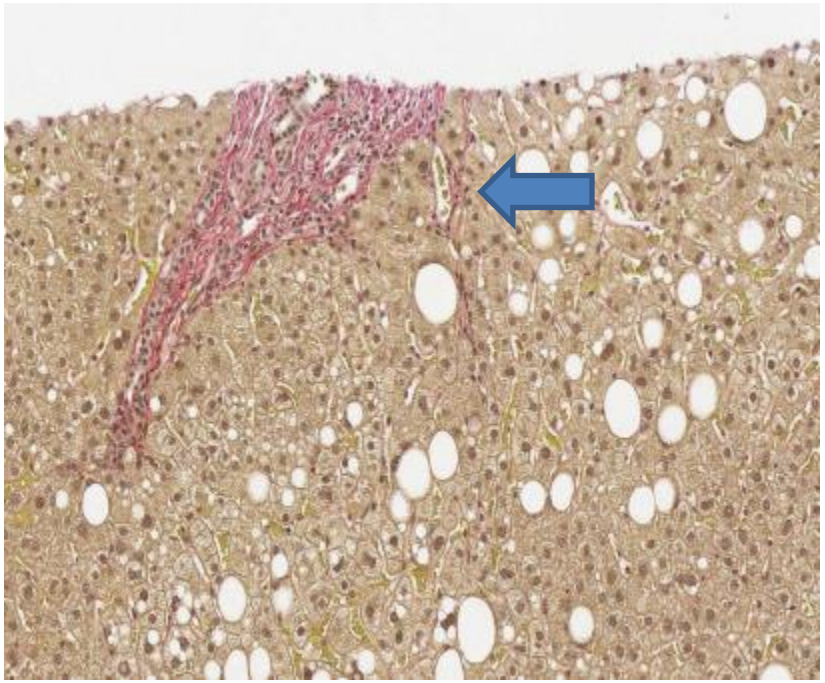
LV12





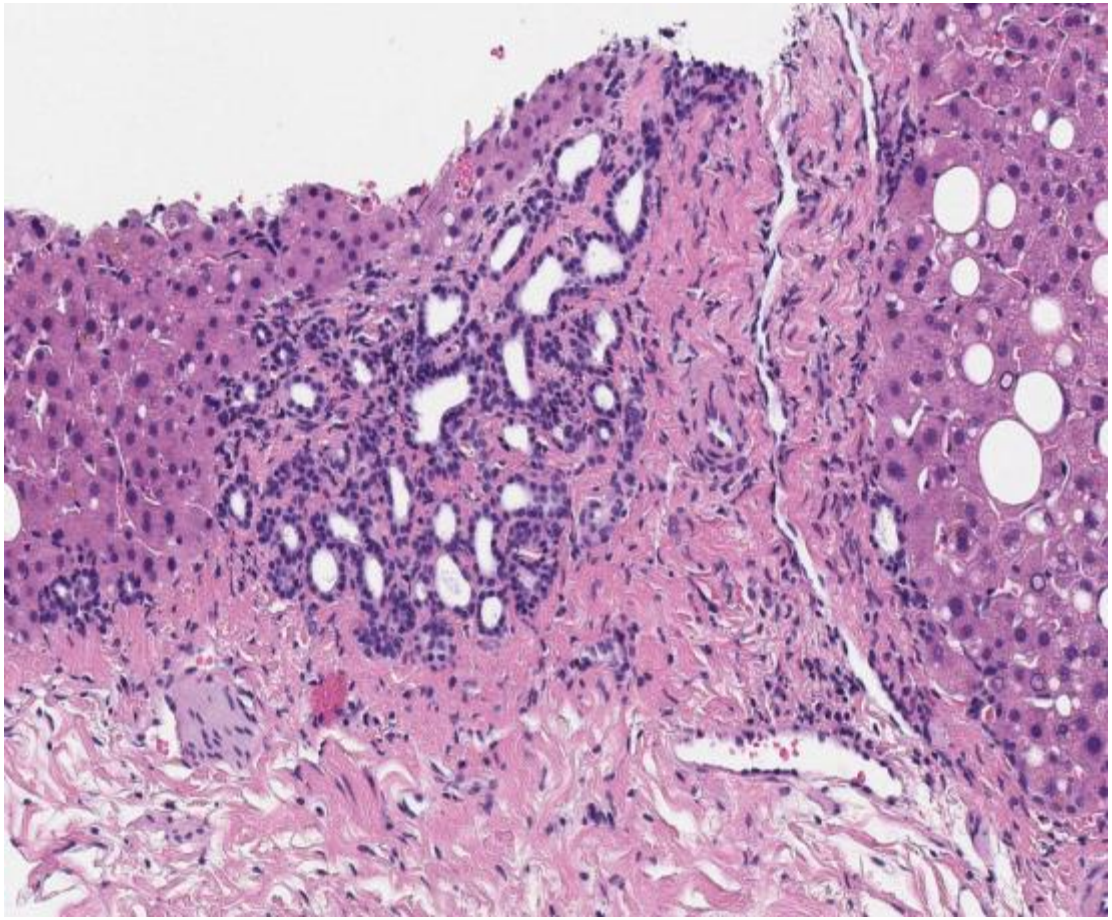
LV12



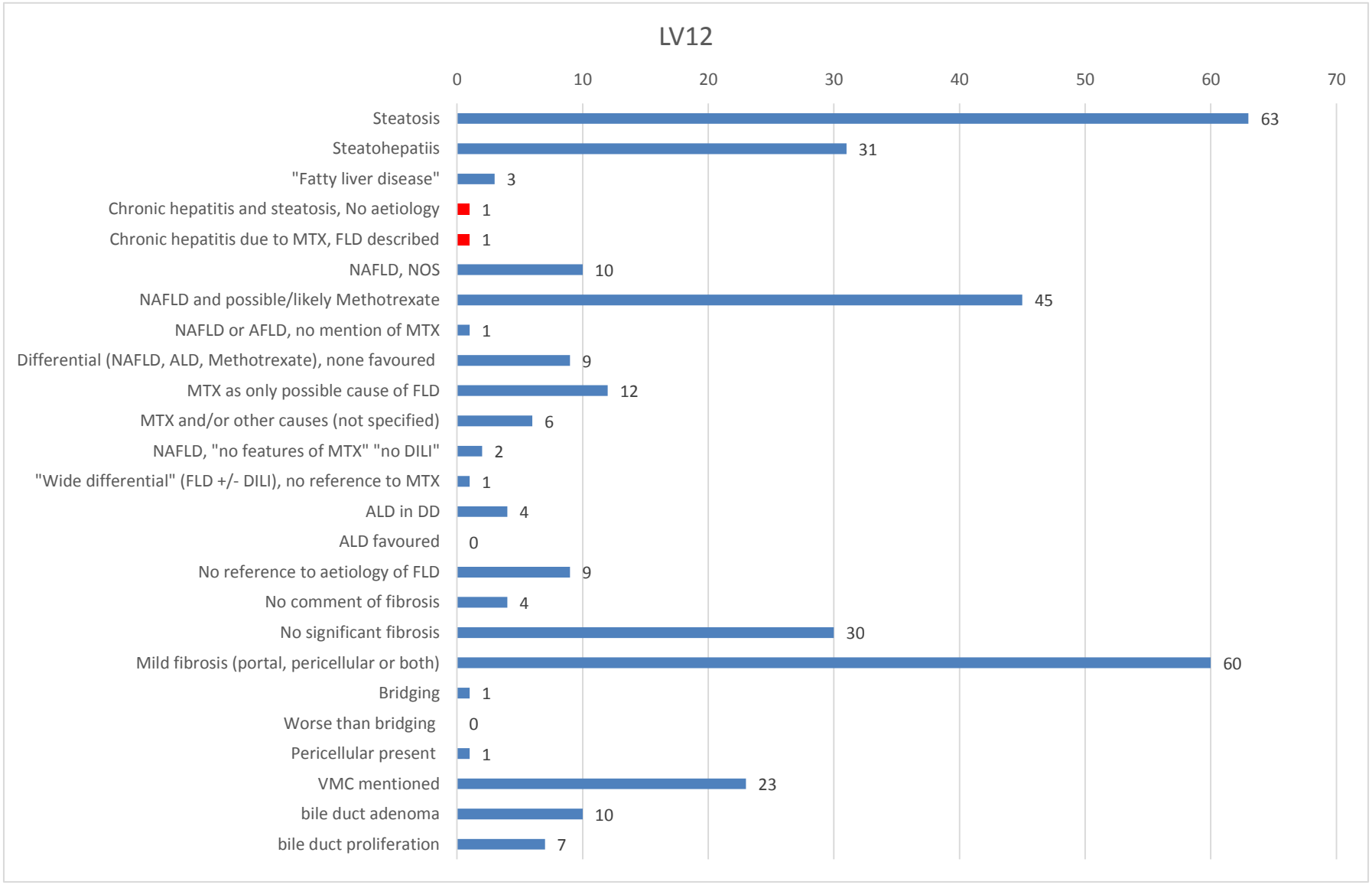


LV12

N = 40



LV12


LV12
0
10
20
30
40
50
60
70
Steatosis
63
Steatohepatiis
31
"Fatty liver disease"
3
Chronic hepatitis and steatosis, No aetiology
1
Chronic hepatitis due to MTX, FLD described
1
NAFLD, NOS
10
NAFLD and possible/likely Methotrexate
45
NAFLD or AFLD, no mention of MTX
1
Differential (NAFLD, ALD, Methotrexate), none favoured
9
MTX as only possible cause of FLD
12
MTX and/or other causes (not specified)
6
NAFLD, "no features of MTX" "no DILI"
2
"Wide differential" (FLD +/- DILI), no reference to MTX
1
ALD in DD
4
ALD favoured
0
No reference to aetiology of FLD
9
No comment of fibrosis
4
No significant fibrosis
30
Mild fibrosis (portal, pericellular or both)
60
Bridging
1
Worse than bridging
0
Pericellular present
1
VMC mentioned
23
bile duct adenoma
10
bile duct proliferation
7

LV12

- Consensus complete responses would include:
- **No outright consensus due to differing views on steatosis versus steatohepatitis.**
- **No consensus on aetiology (NAFLD referenced in 72, MTX in 72, ALD in 14).**
  - NB. Methotrexate and NAFLD specifically mentioned in history

- Suggest (to achieve consensus):
  - Steatosis or steatohepatitis. Comment on presence of no, or, mild fibrosis

LV12

- **Suggested scoring: for 10 points** include. As above

- **Lose 5 marks** if no comment on fibrosis (N = 4) agreed

- **Lose 10 marks (score 0) if** Fatty liver disease not described as main feature/aetiology (regardless of mention of MTX) e.g. chronic hepatitis due to MTX (N = 2) agreed

LV12

Discussion points

- **<u>Mixed aetiology likely.</u> Difficult to establish extent of role of methotrexate in this case, and separate from other cases of FLD (note history alludes to concurrent NAFLD**)
  - Several respondents attributed NAFLD to methotrexate
  - Others stated "NAFLD but no features of MTX"
- Steatosis (mild favoured – 30% v 12% moderate v 2% severe
  - Steatosis c/w…NASH"
- Steatohepatitis (minimal or mild – 62%)
- Definition of steatohepatitis and reference to fibrosis by some to diagnose SH:
  - "Steatosis and mild fibrosis…moderate steatohepatitis"
  - "Insufficient fibrosis for NASH"
- "fatty liver hepatitis"
- Several respondents included comment on appropriateness to continue use of MTX
- "NAFLD but no features of MTX"

EQA Educational case LV13

Rachel Brown Birmingham

LV13

- A good example
- A missed diagnosis……..

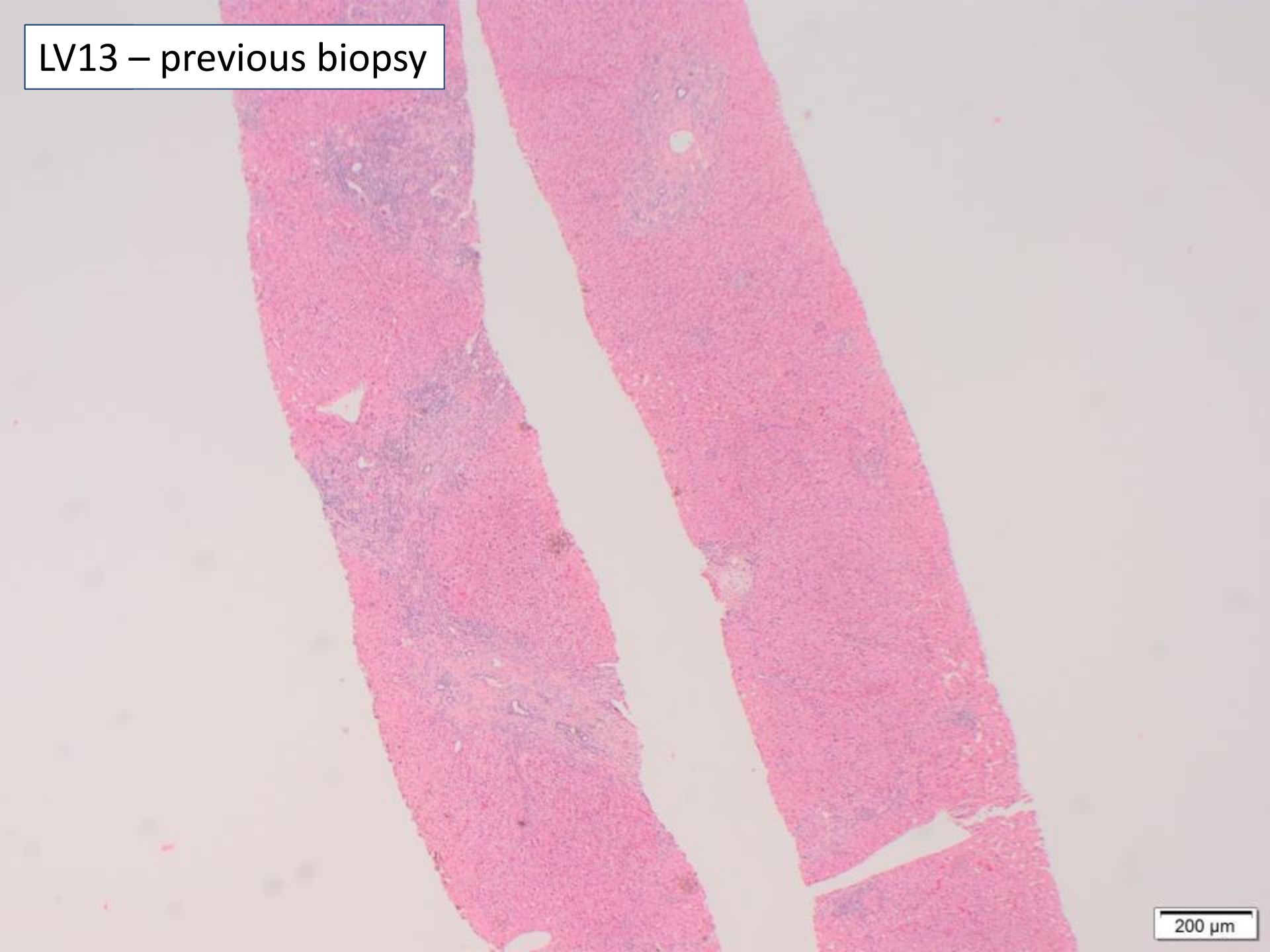
LV13 – previous biopsy

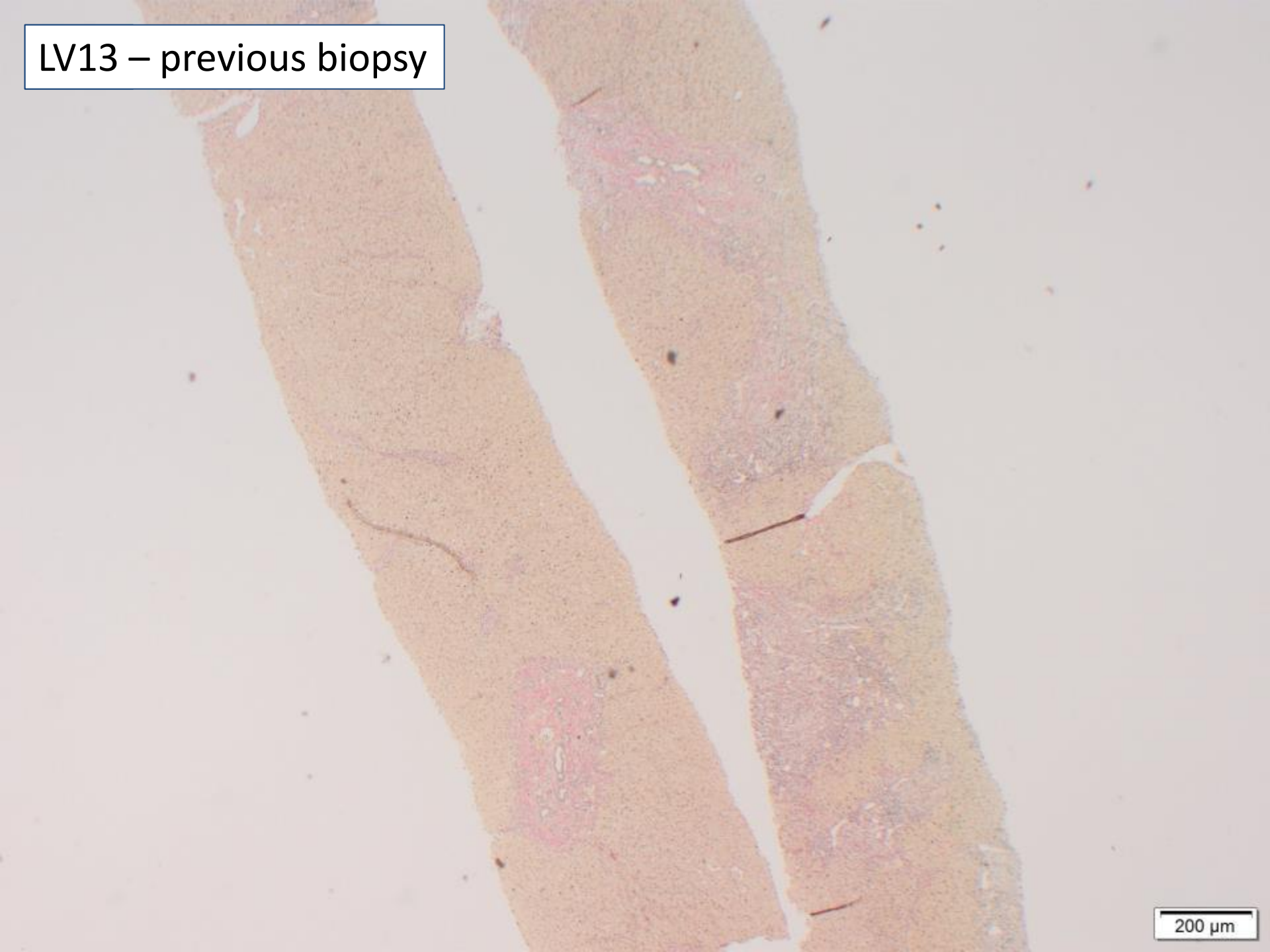
First biopsy (not circulated) 2016

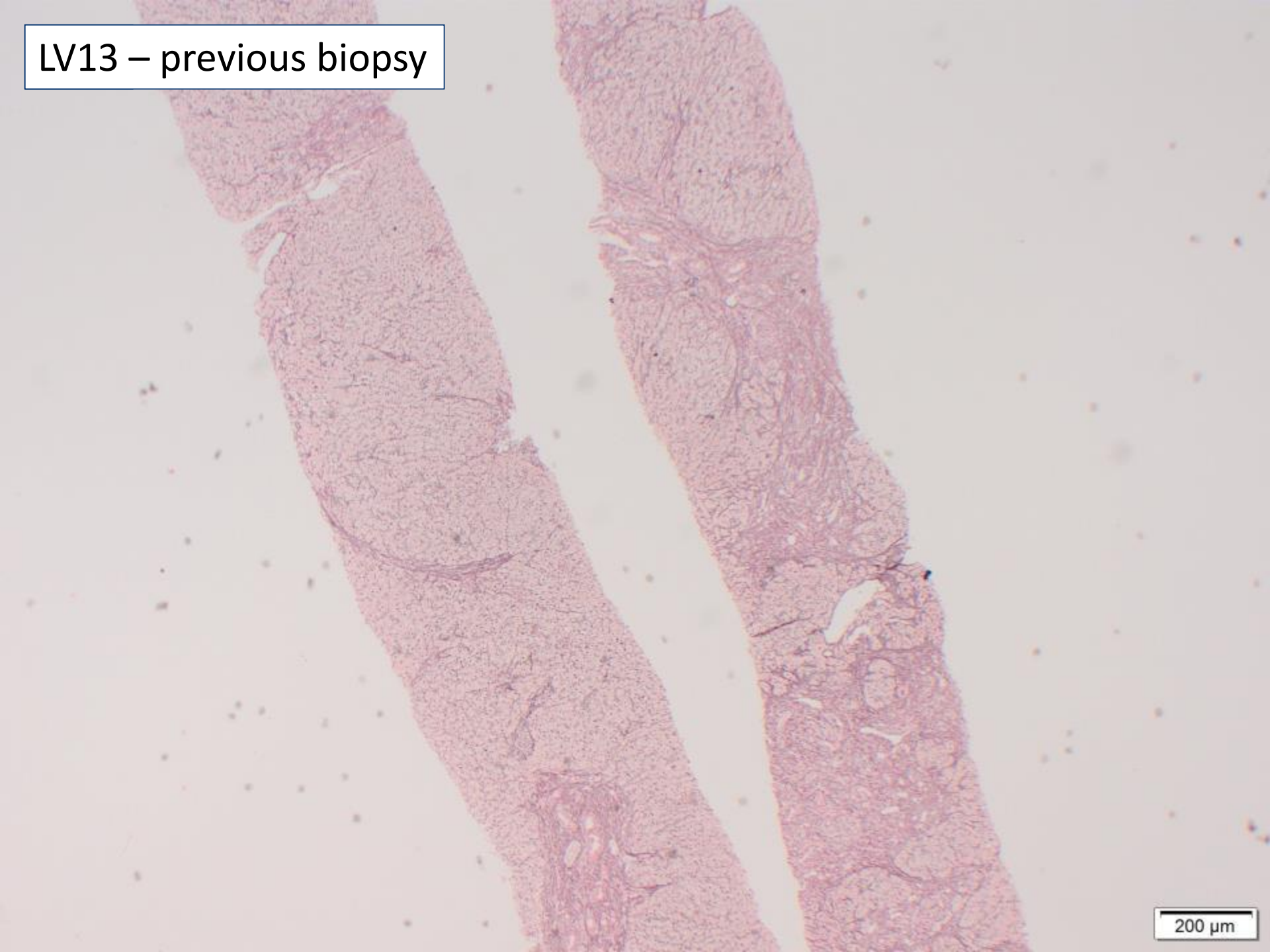
CLINICAL DETAILS:
Awaiting approval to act as live kidney donor to husband.
Unexplained abnormal liver function (ALT 18 ALP 143), high FibroScan (13.8KPa) and coarse liver texture on ultrasound.
Normal MRCP.

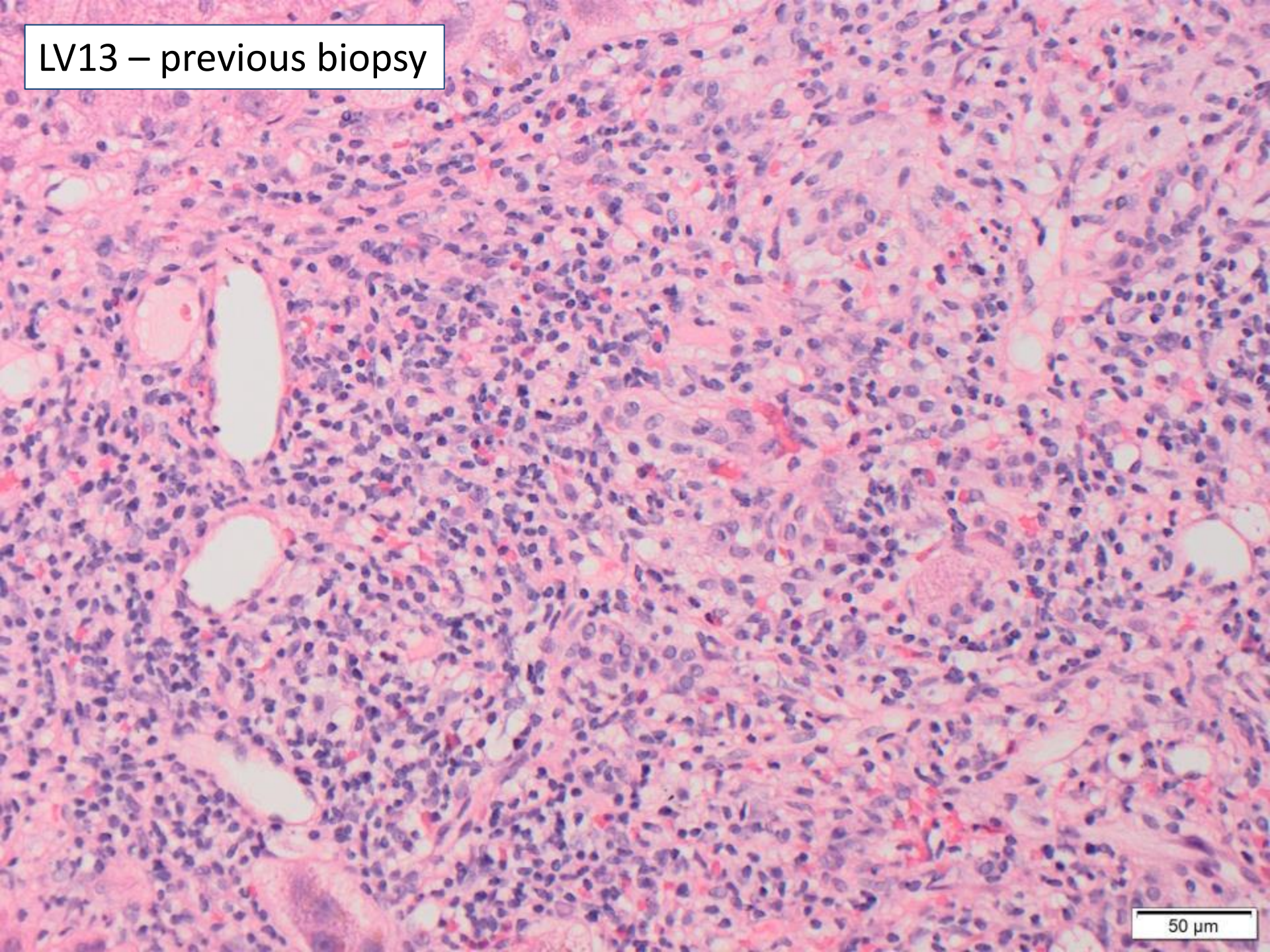
Please biopsy liver to ascertain whether there is underlying liver disease and whether she can act as a live donor.

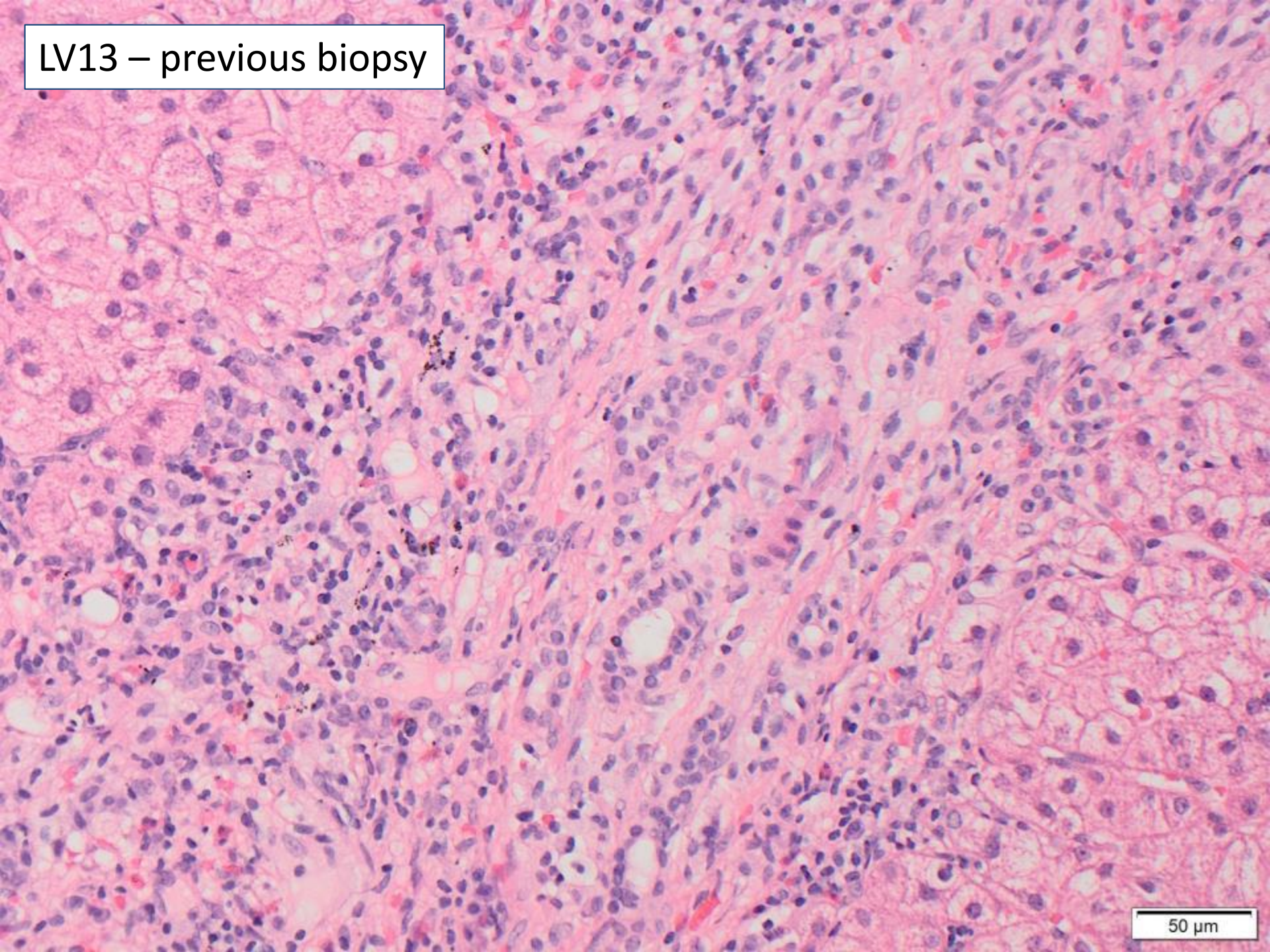
64 years female. 13cm spleen.
Gallstones, mildly dilated intrahepatic bile duct.

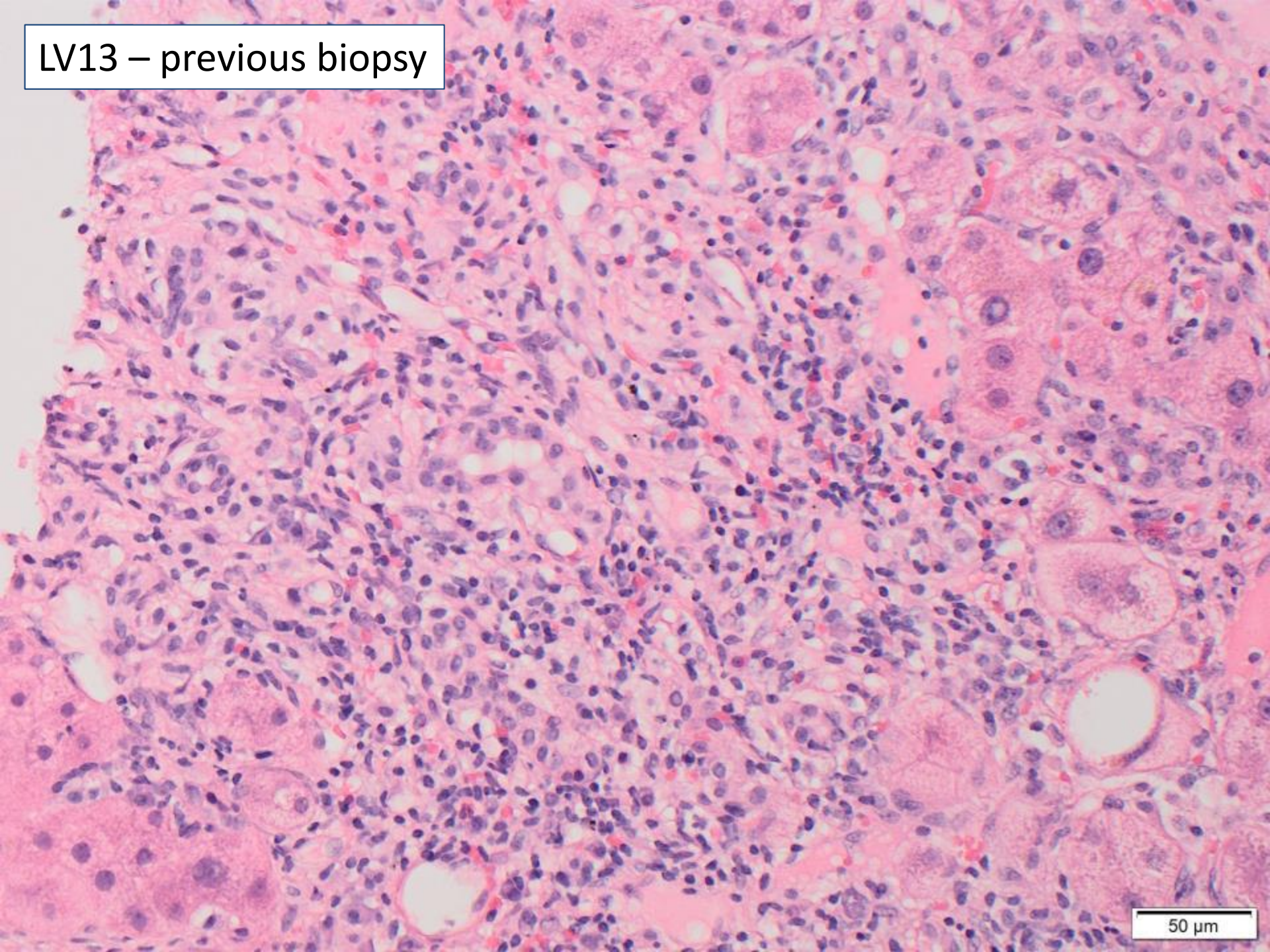

LV13 – previous biopsy
200 µm

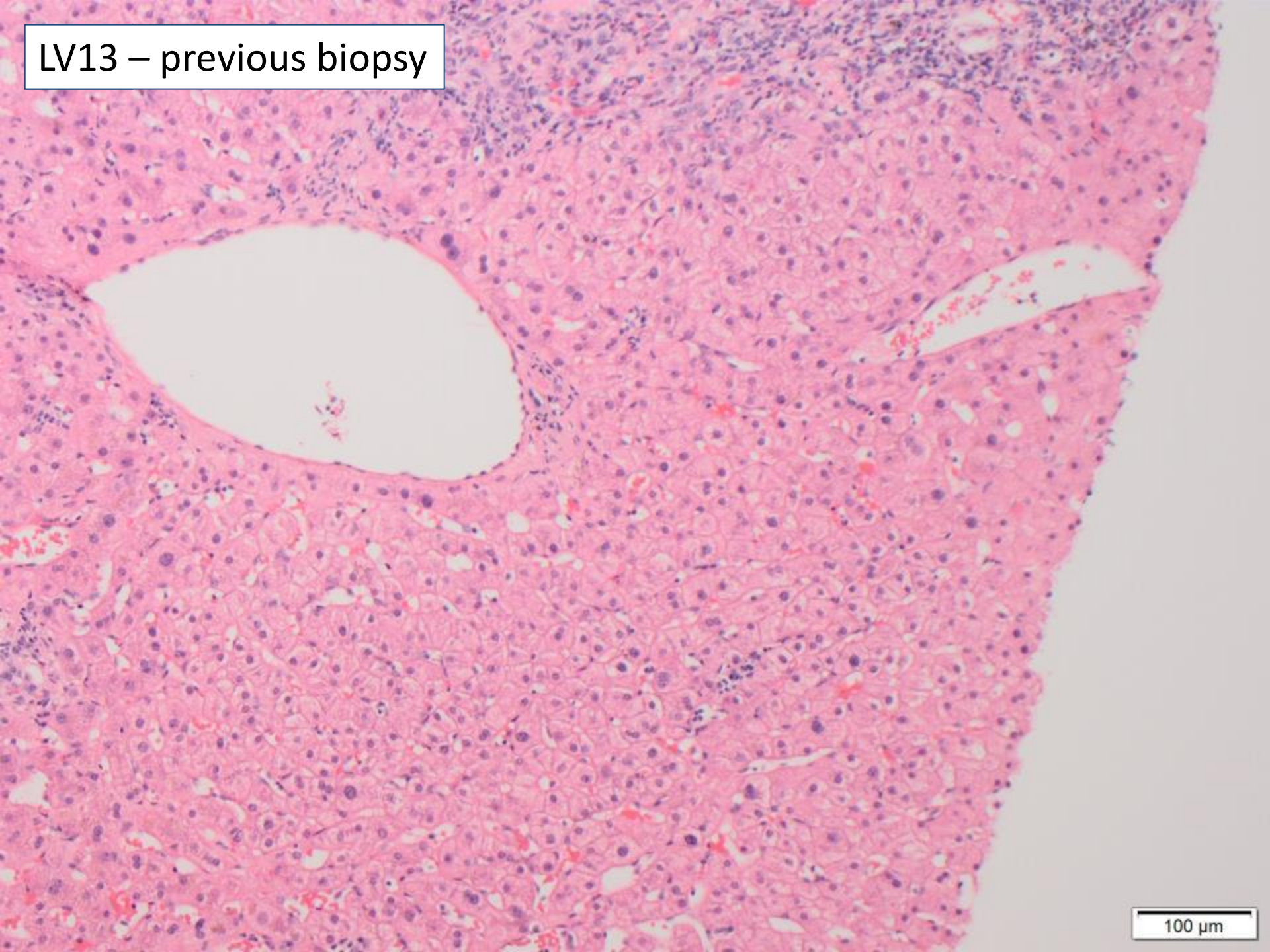

LV13 – previous biopsy
200 µm


LV13 – previous biopsy
200 µm


LV13 – previous biopsy
50 µm


LV13 – previous biopsy
50 µm


LV13 – previous biopsy
50 µm


LV13 – previous biopsy
100 µm

LV13

COMMENT:

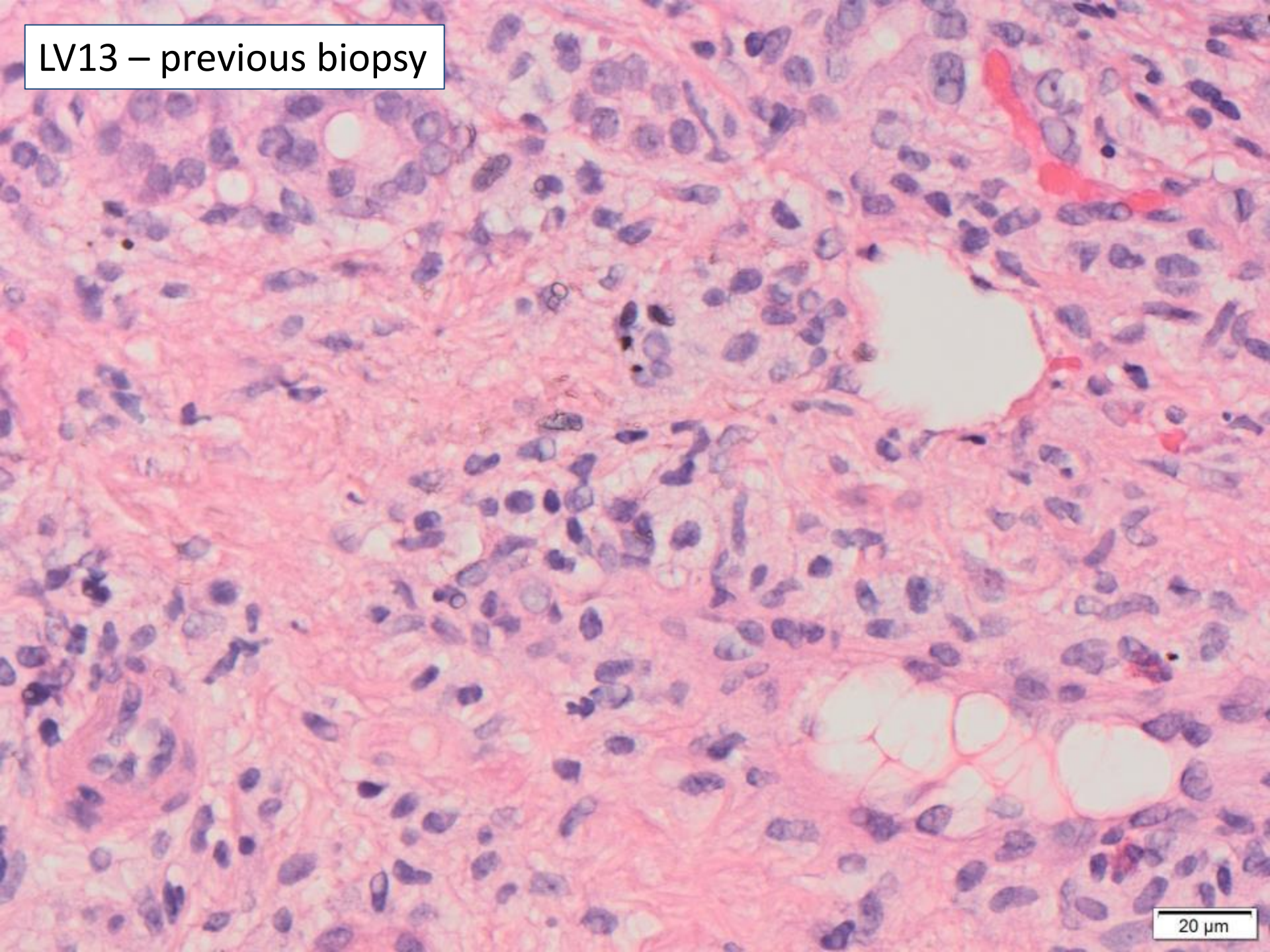
Inflammation (moderate with interface hepatitis) is the dominant lesion histologically here but there are also some biliary features. Fibrosis is moderate (bridging) falling short of established cirrhosis. Whilst drug related and infectious causes might be considered autoimmune liver disease is perhaps most likely morphologically. Primary biliary cholangitis (PBC) can sometimes be accompanied by significant inflammation. It is noted that investigations so far have not been supportive of this (IgG 12.83, ANA, AMA negative).

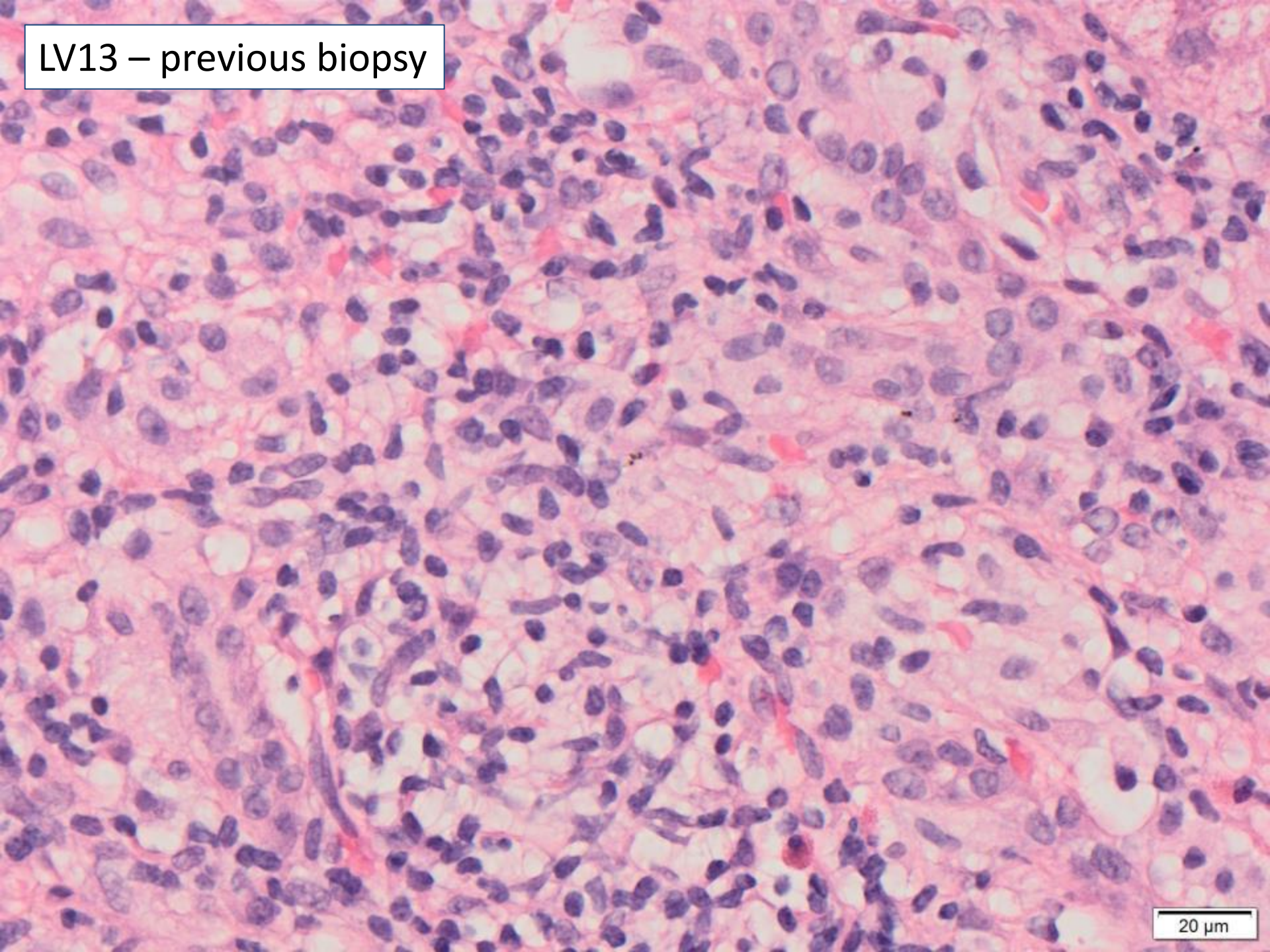
The mild iron deposition is of uncertain significance, it does not have a convincing haemochromatotic pattern.

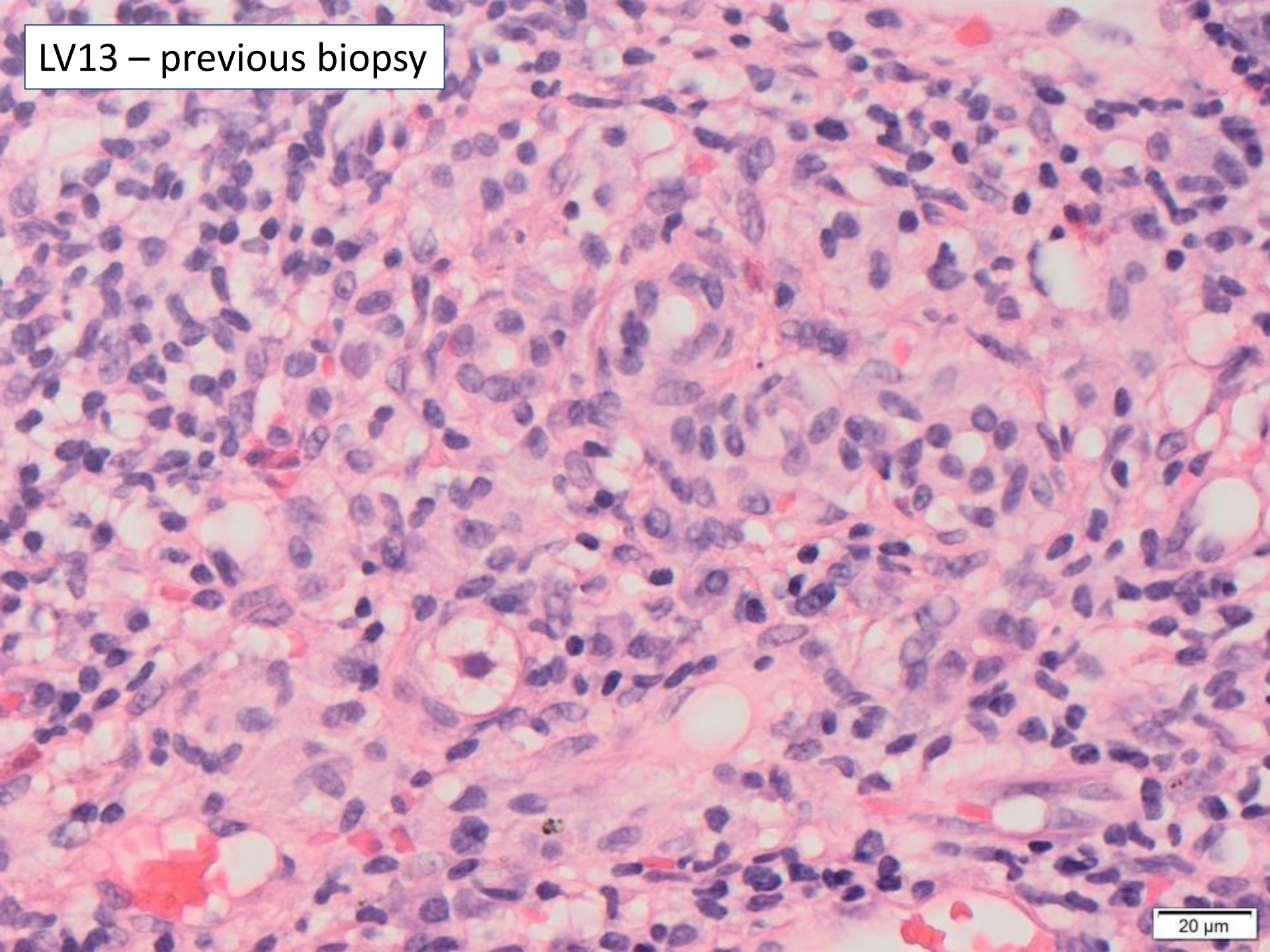
DIAGNOSIS:

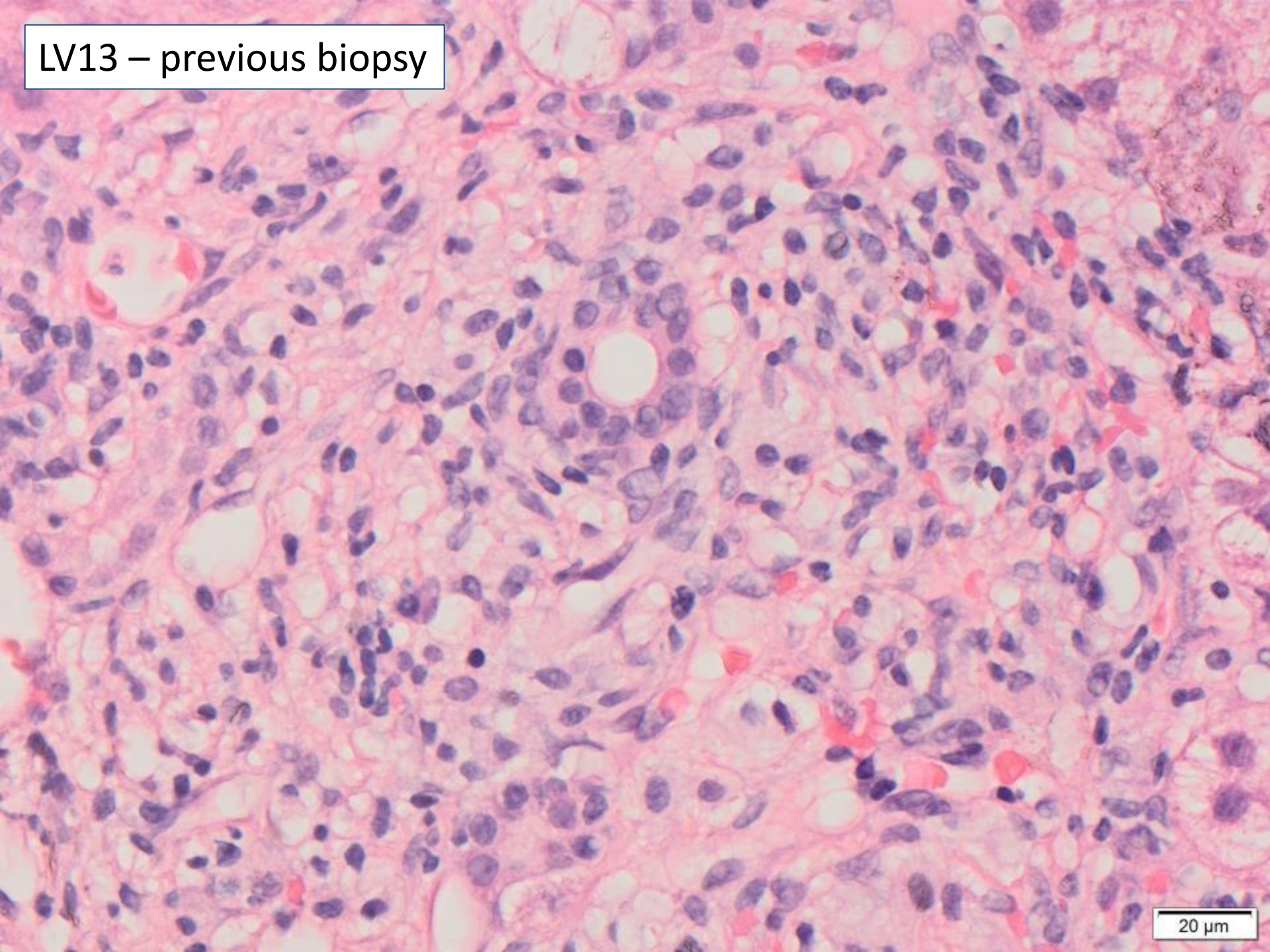
Liver biopsy - chronic hepatitis with biliary features, moderate fibrosis.

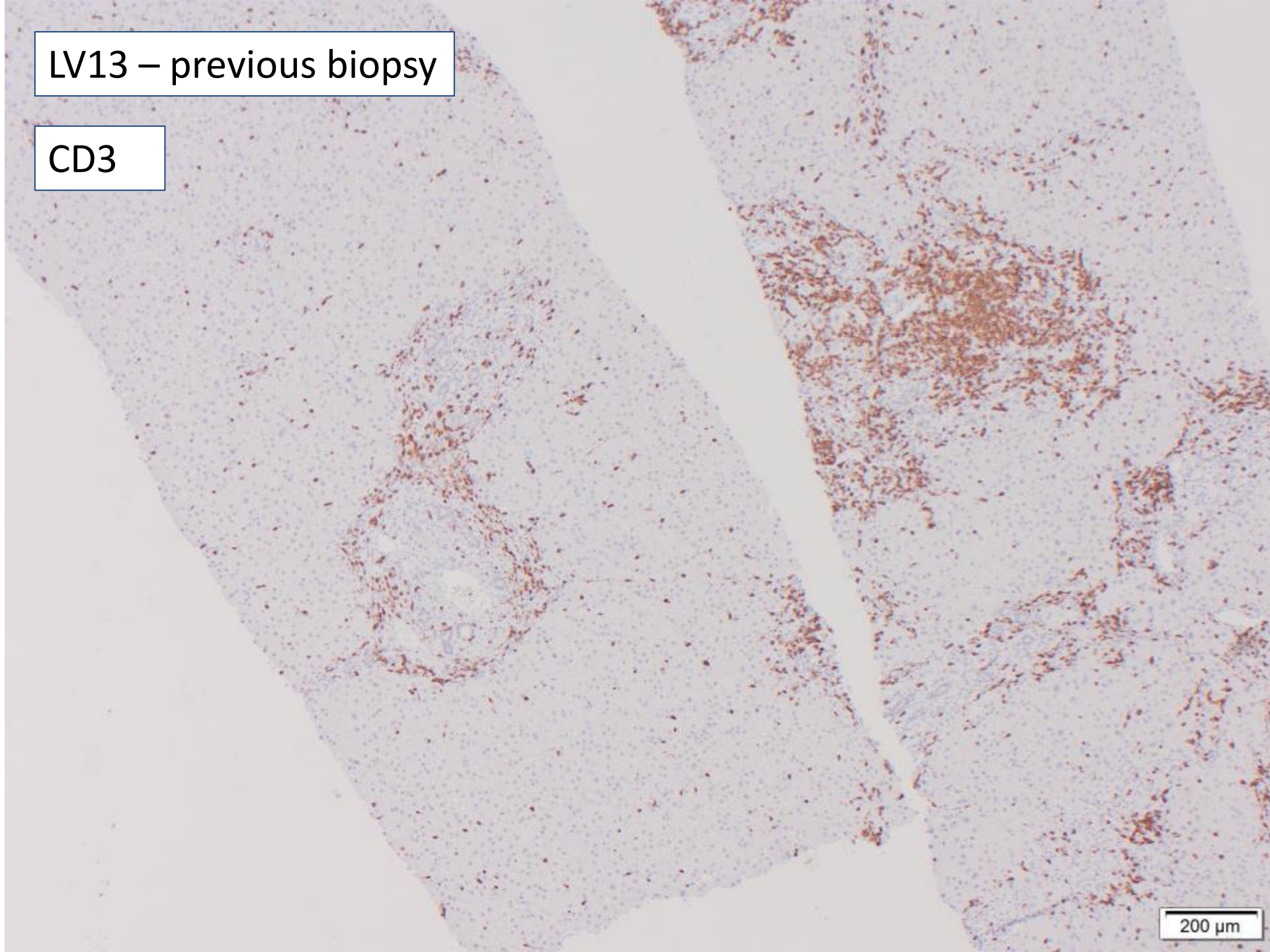
- Followed up in hepatology clinic, ?AMA negative PBC. Started on Urso, some lowering of ALP.
- 2018, mild weight loss, mesenteric and para aortic LNs on imaging, haematology referral, diagnosed with mastocytosis on trephine biopsy ‘surprising’
- Would you have another look at the biopsy?


LV13 – previous biopsy
20 µm


LV13 – previous biopsy
20 µm

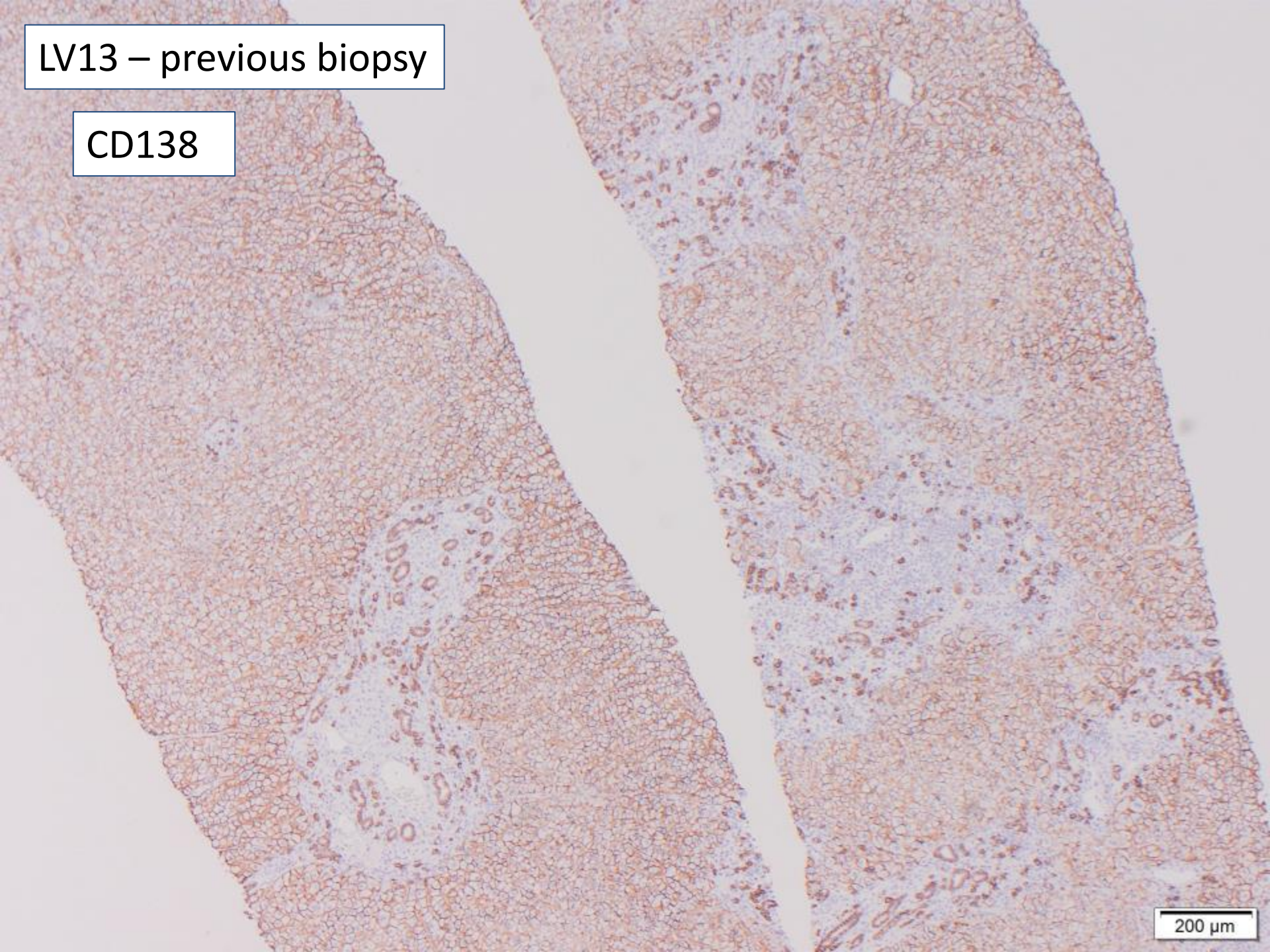

LV13 – previous biopsy
20 µm

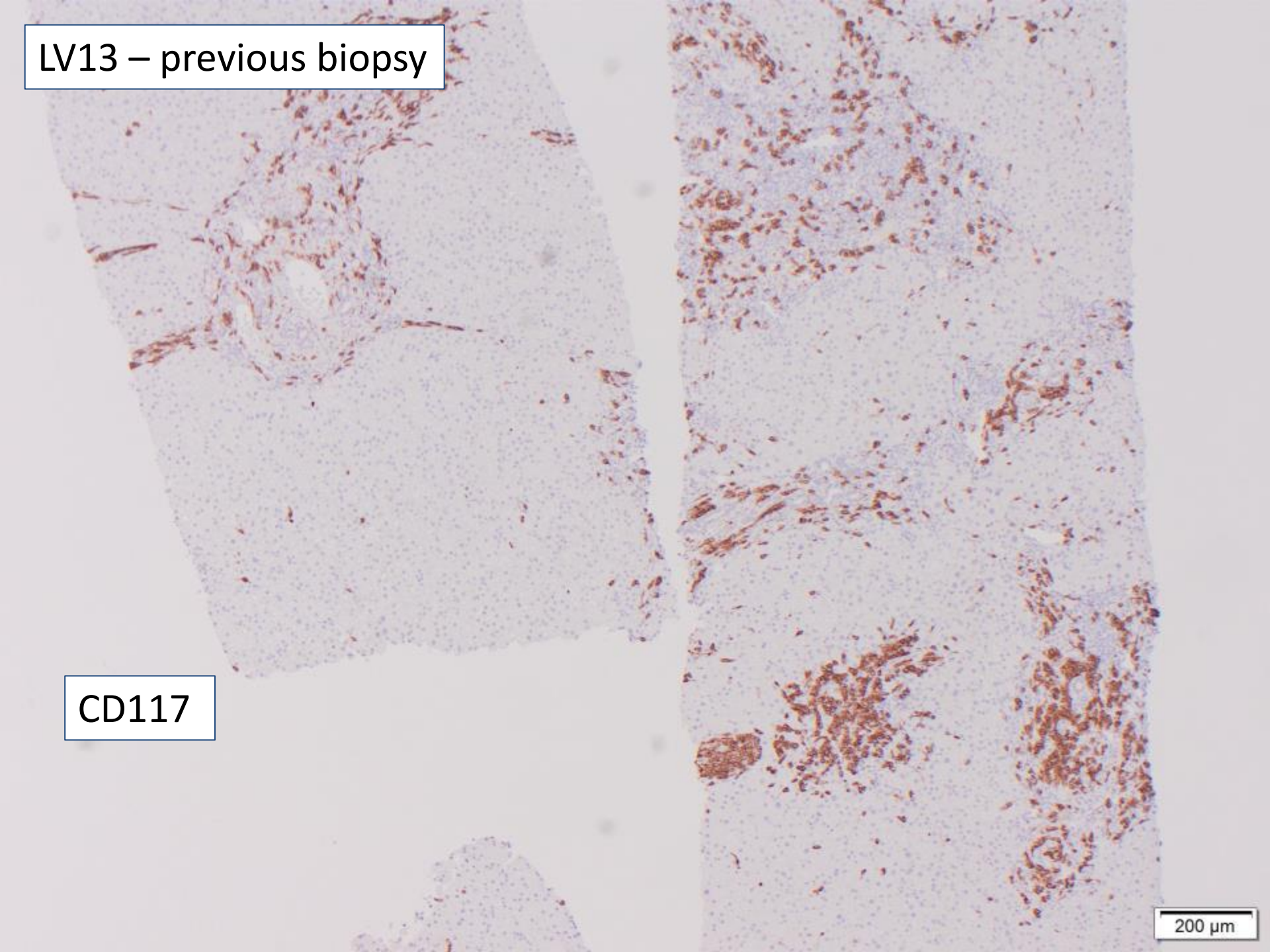

LV13 – previous biopsy
20 µm

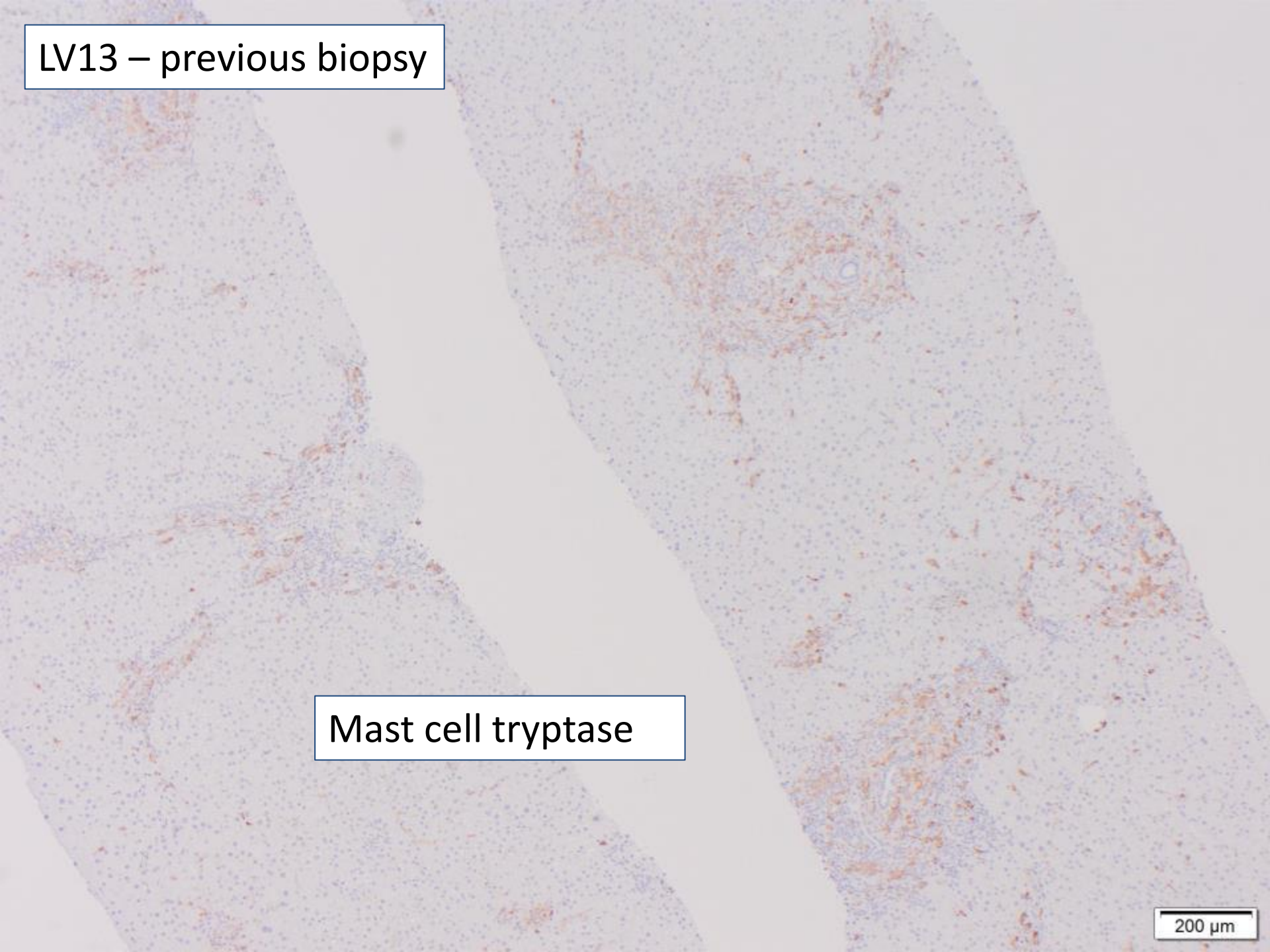

LV13 – previous biopsy
CD3
200 µm

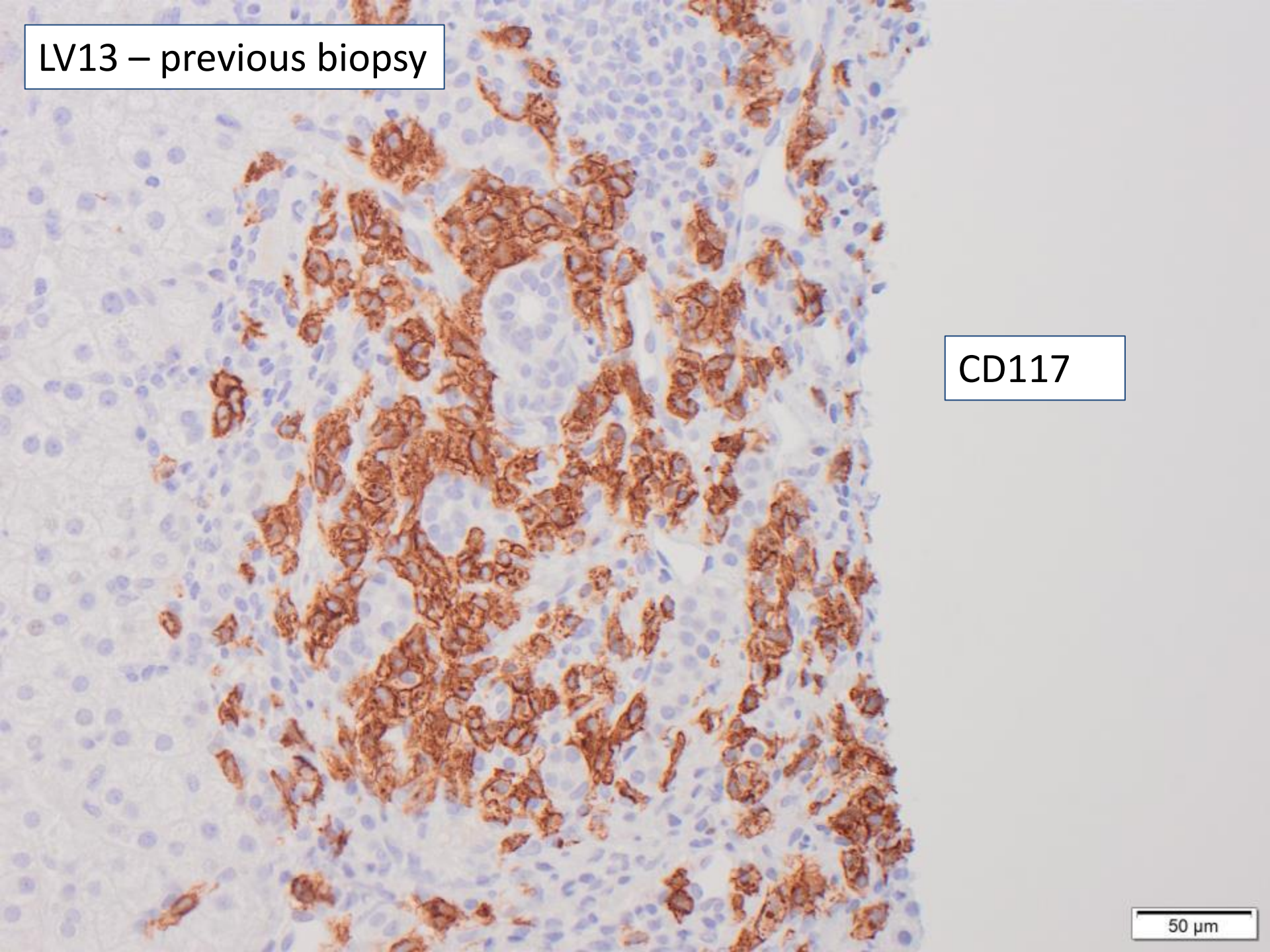
LV13 – previous biopsy

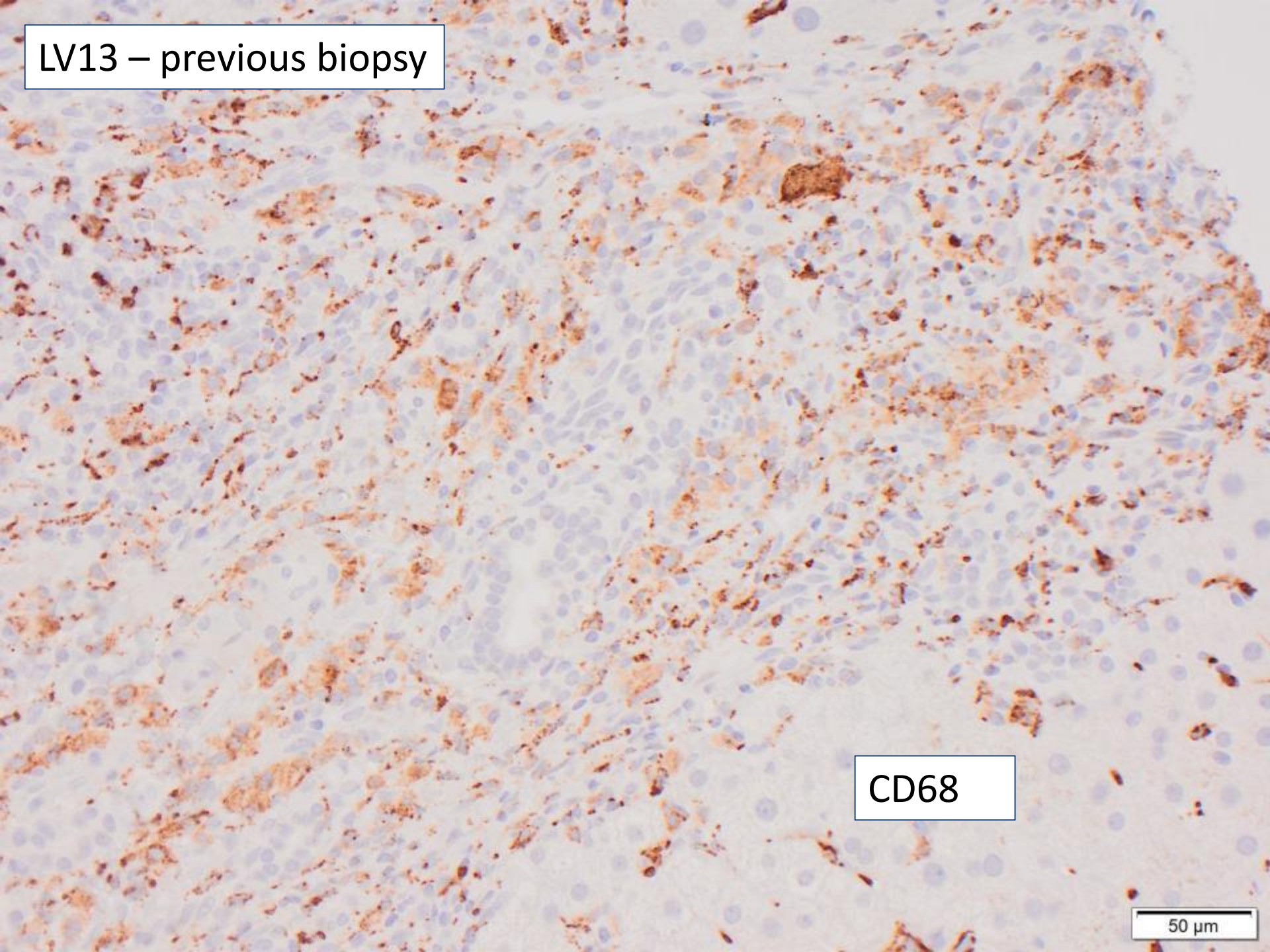
CD20


LV13 – previous biopsy
CD138
200 µm

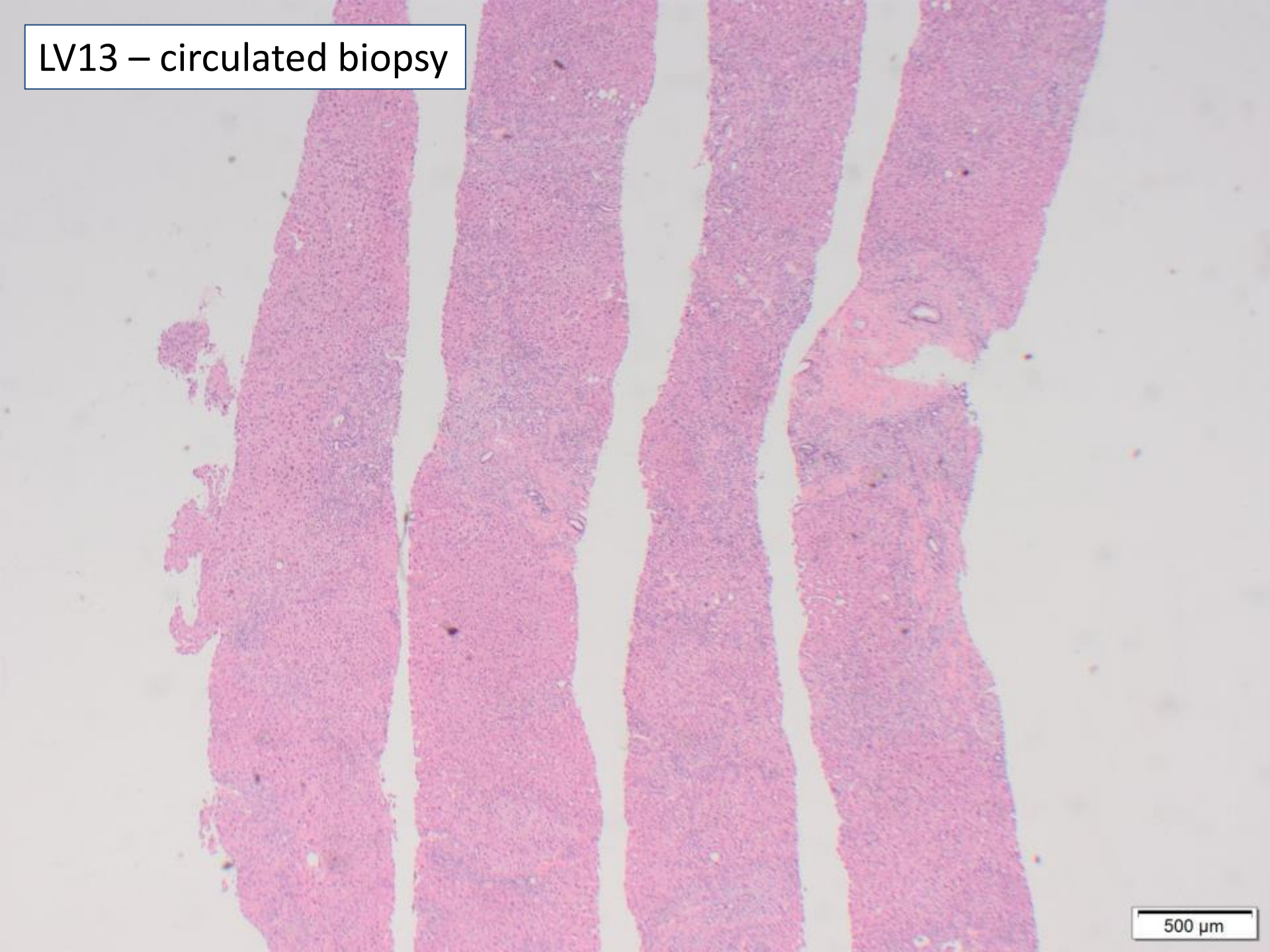

LV13 – previous biopsy
CD117
200 µm

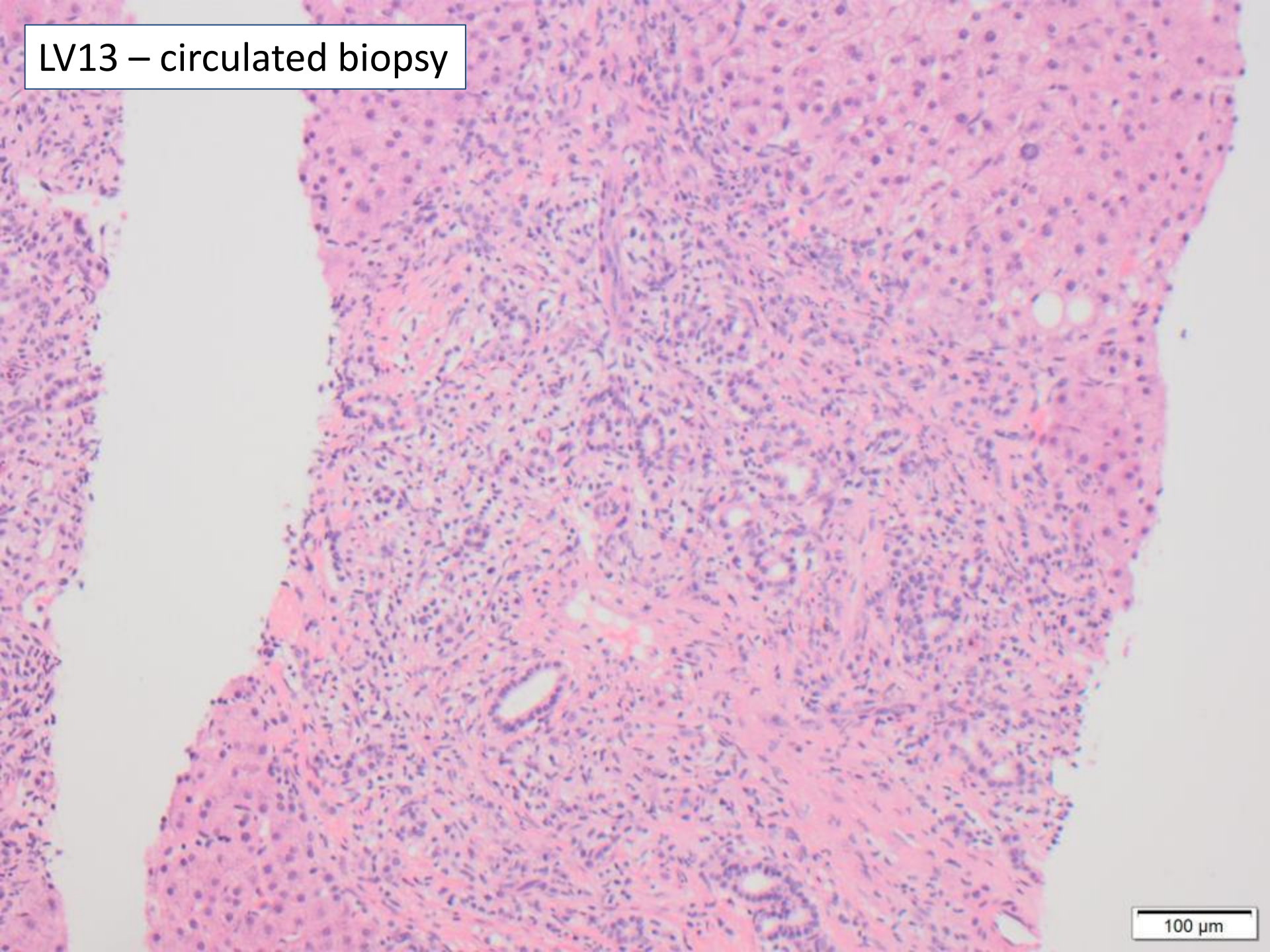

LV13 – previous biopsy
Mast cell tryptase
200 µm

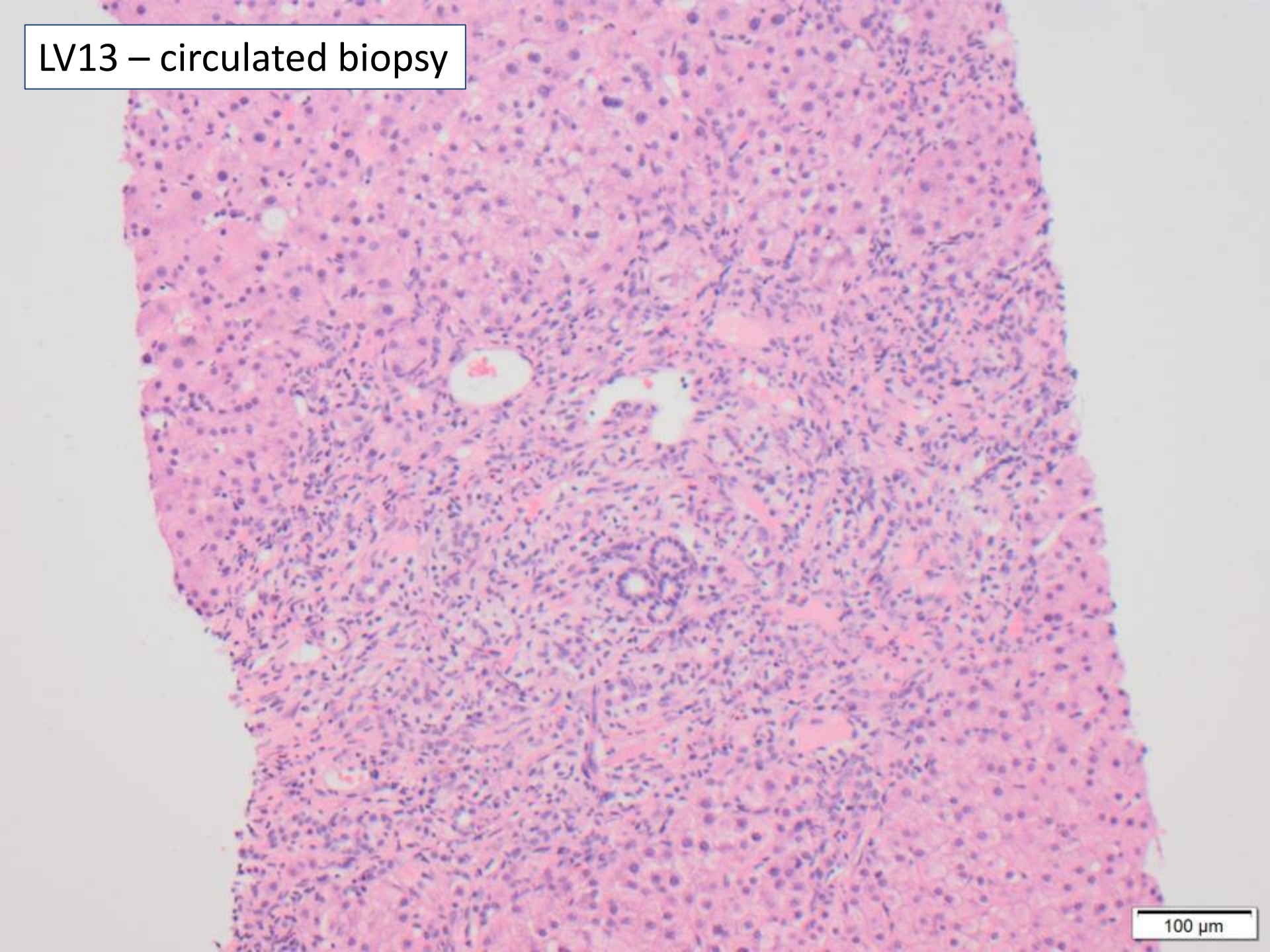

LV13 – previous biopsy
CD117
50 µm

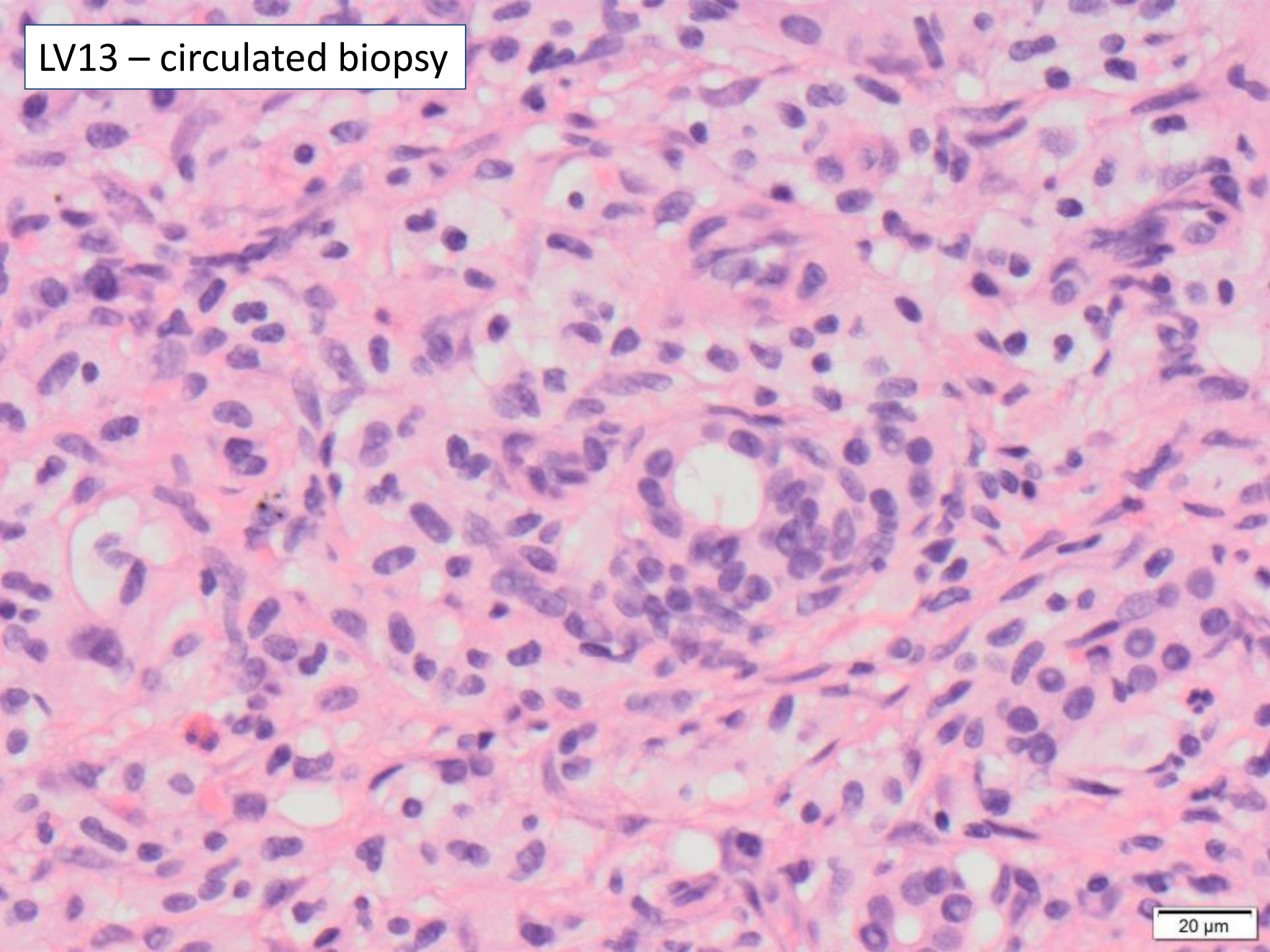

LV13 – previous biopsy
CD68
50 µm

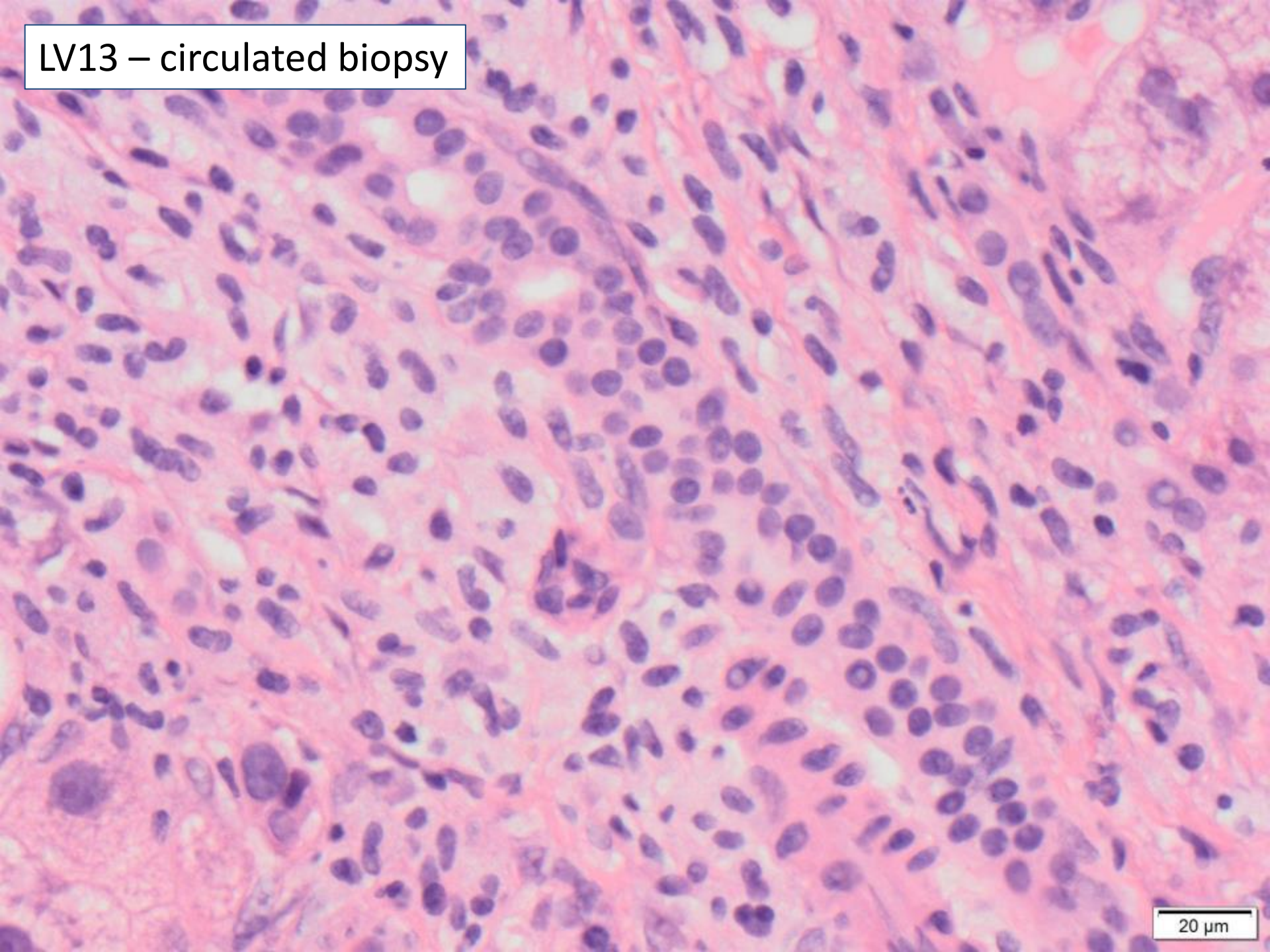
- Haematology follow up. ‘smouldering’ systemic mastocytosis becoming ‘aggressive’ in 2019 (onset of symptoms; fever, diarrhoea) requiring ongoing chemotherapy (trial)
- Re biopsy in 2019 (circulated case) ? Cirrhosis. Clinically ascites.

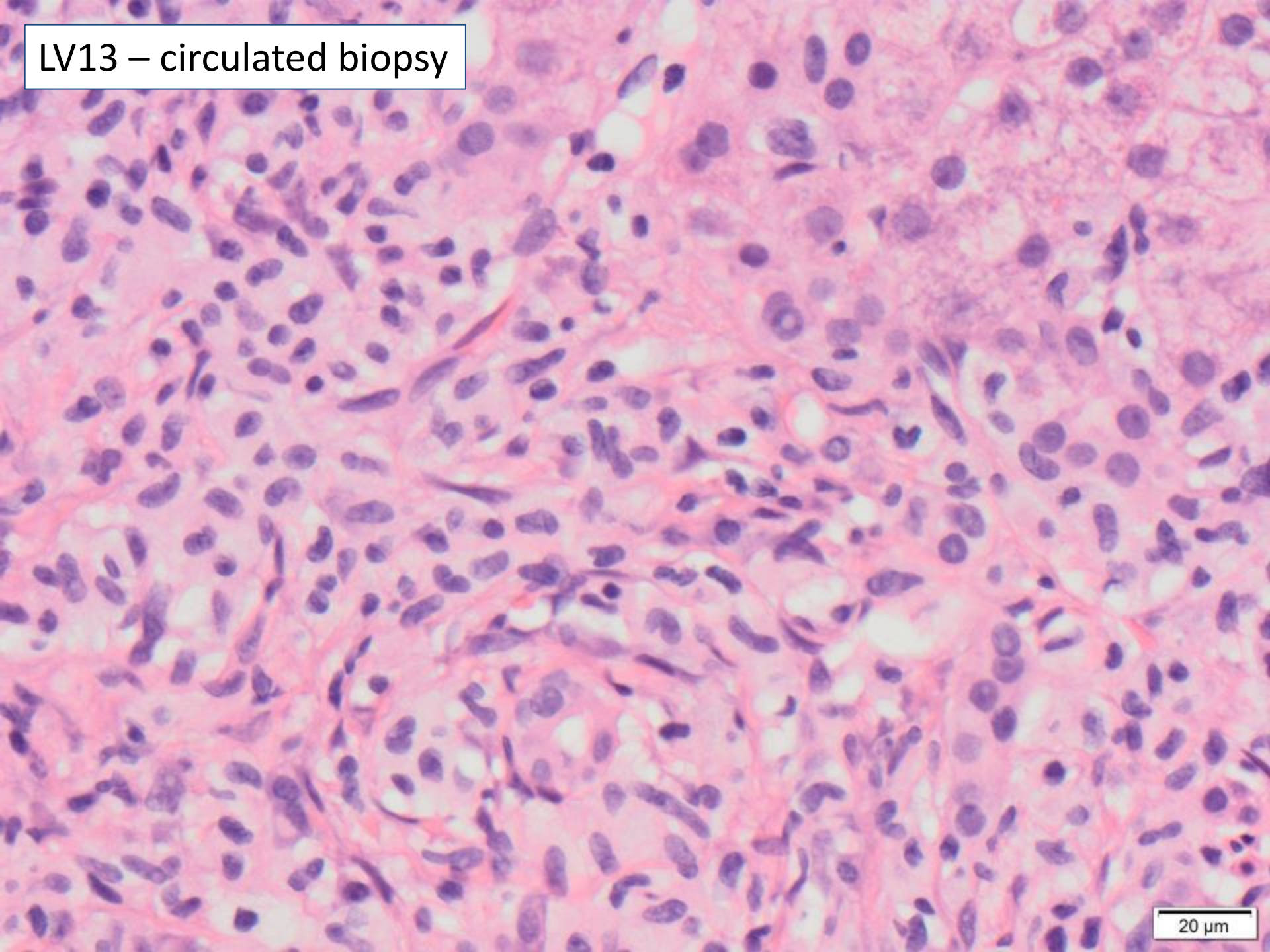

LV13 – circulated biopsy
500 µm

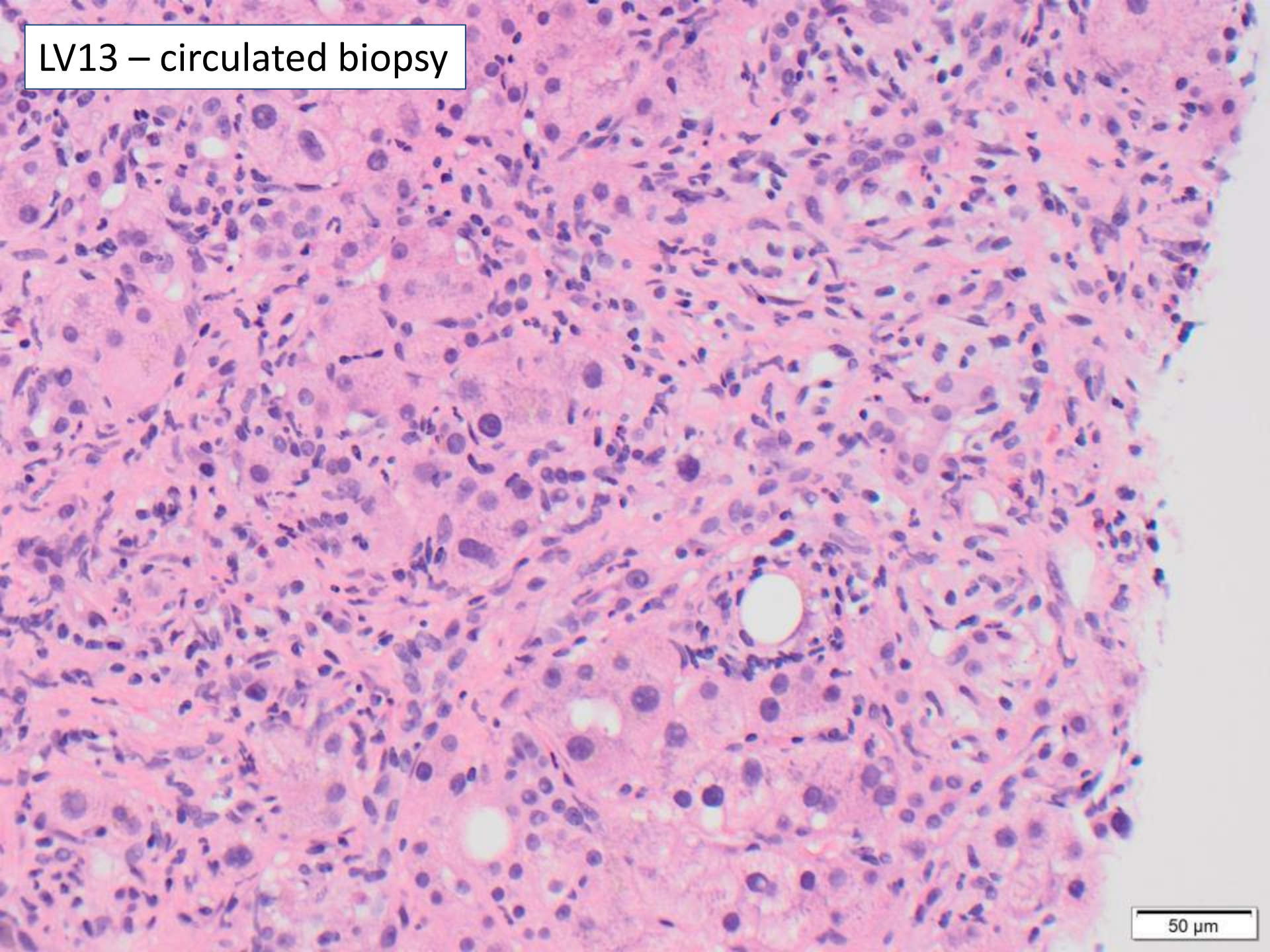

LV13 – circulated biopsy
100 µm

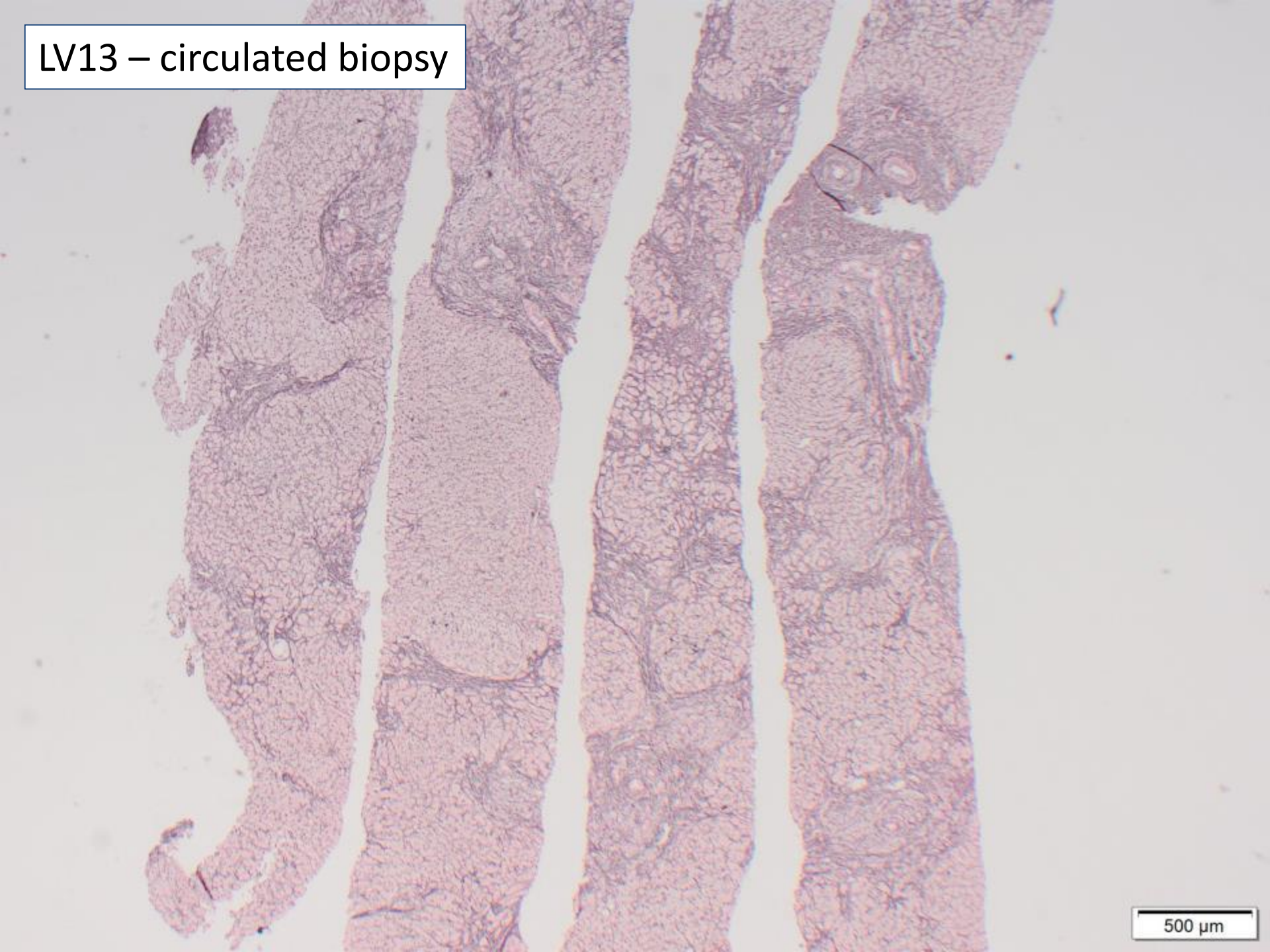

LV13 – circulated biopsy
100 µm


LV13 – circulated biopsy
20 µm


LV13 – circulated biopsy
20 µm

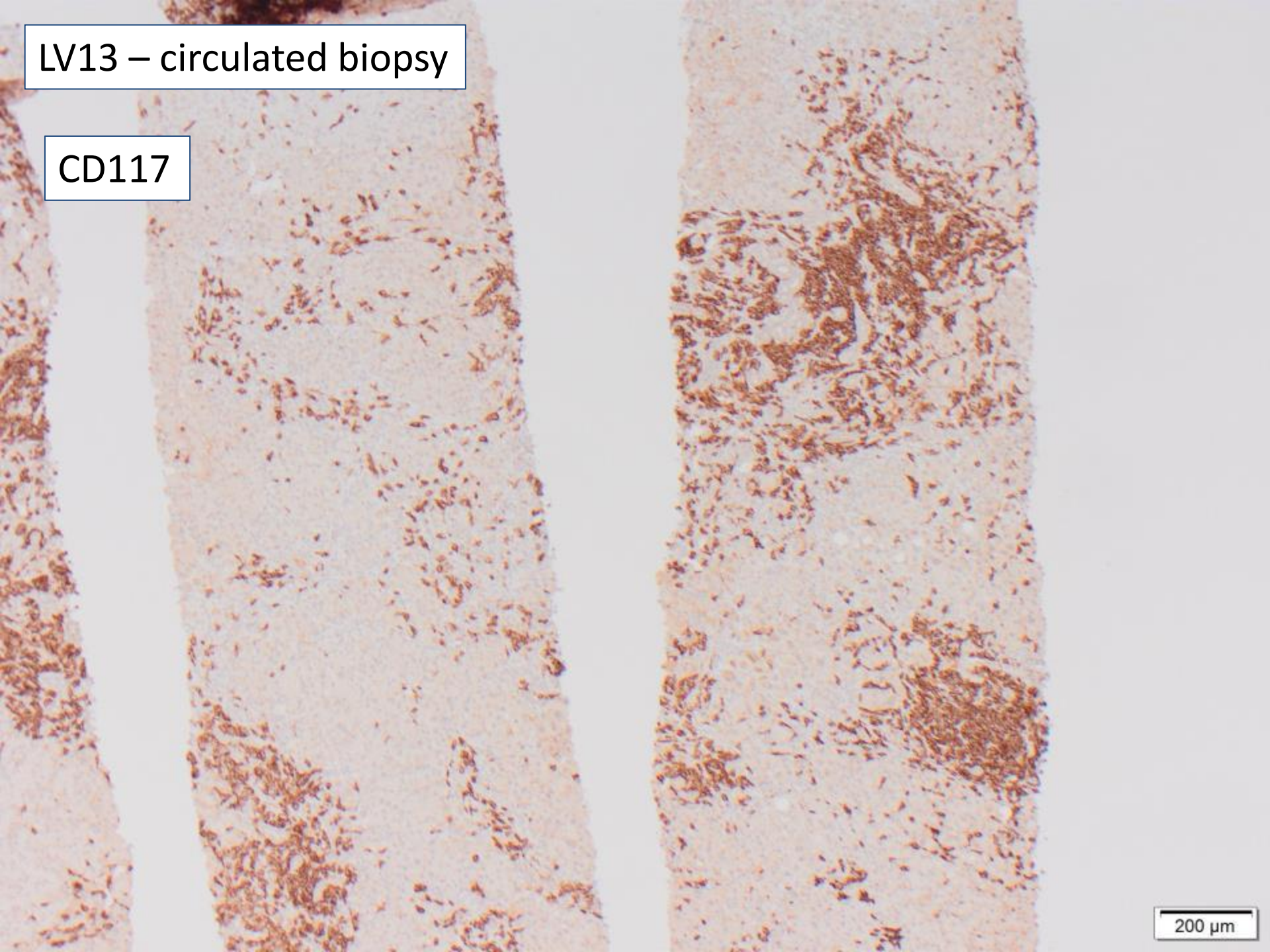

LV13 – circulated biopsy
20 µm

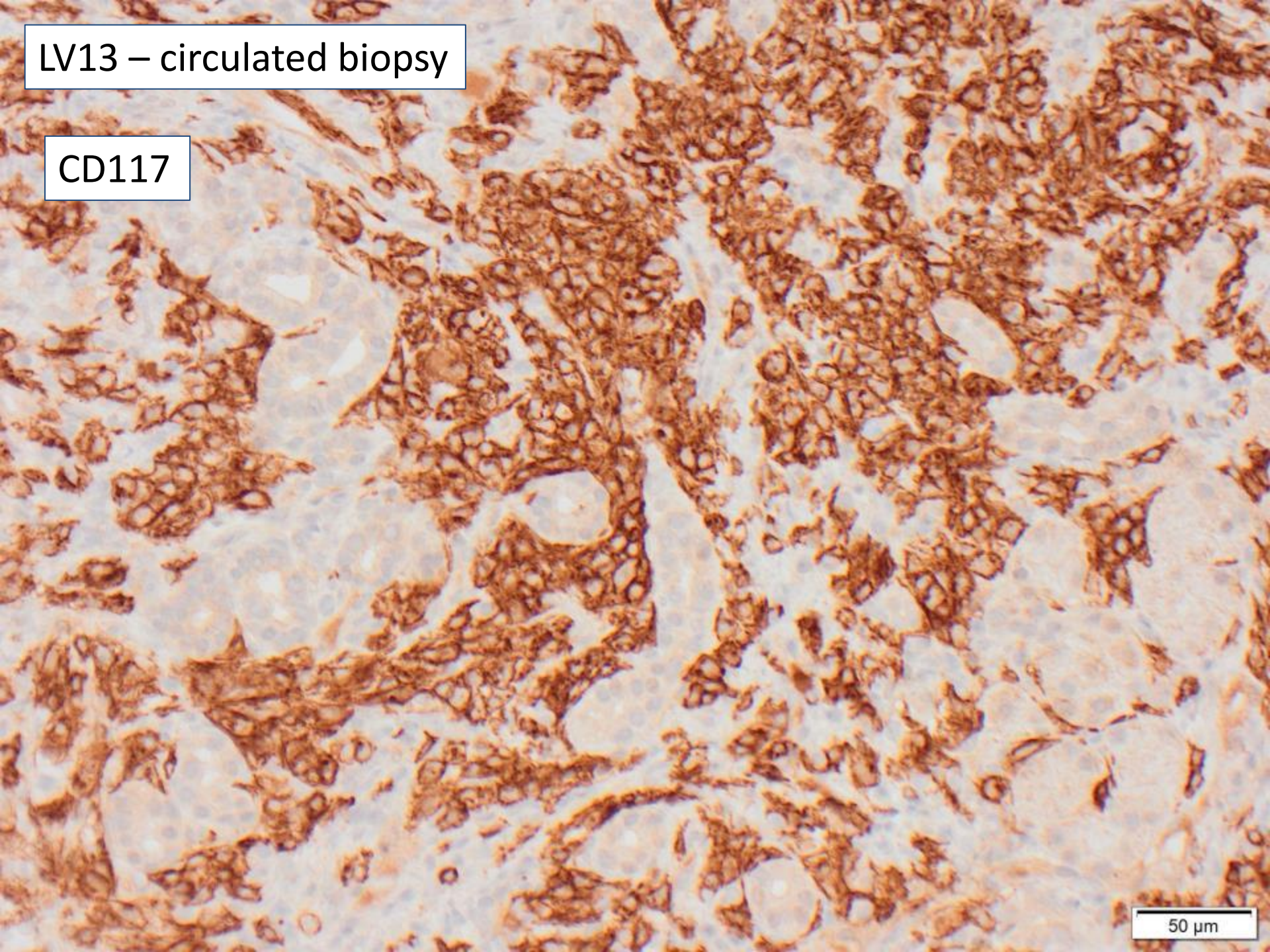

LV13 – circulated biopsy
50 µm

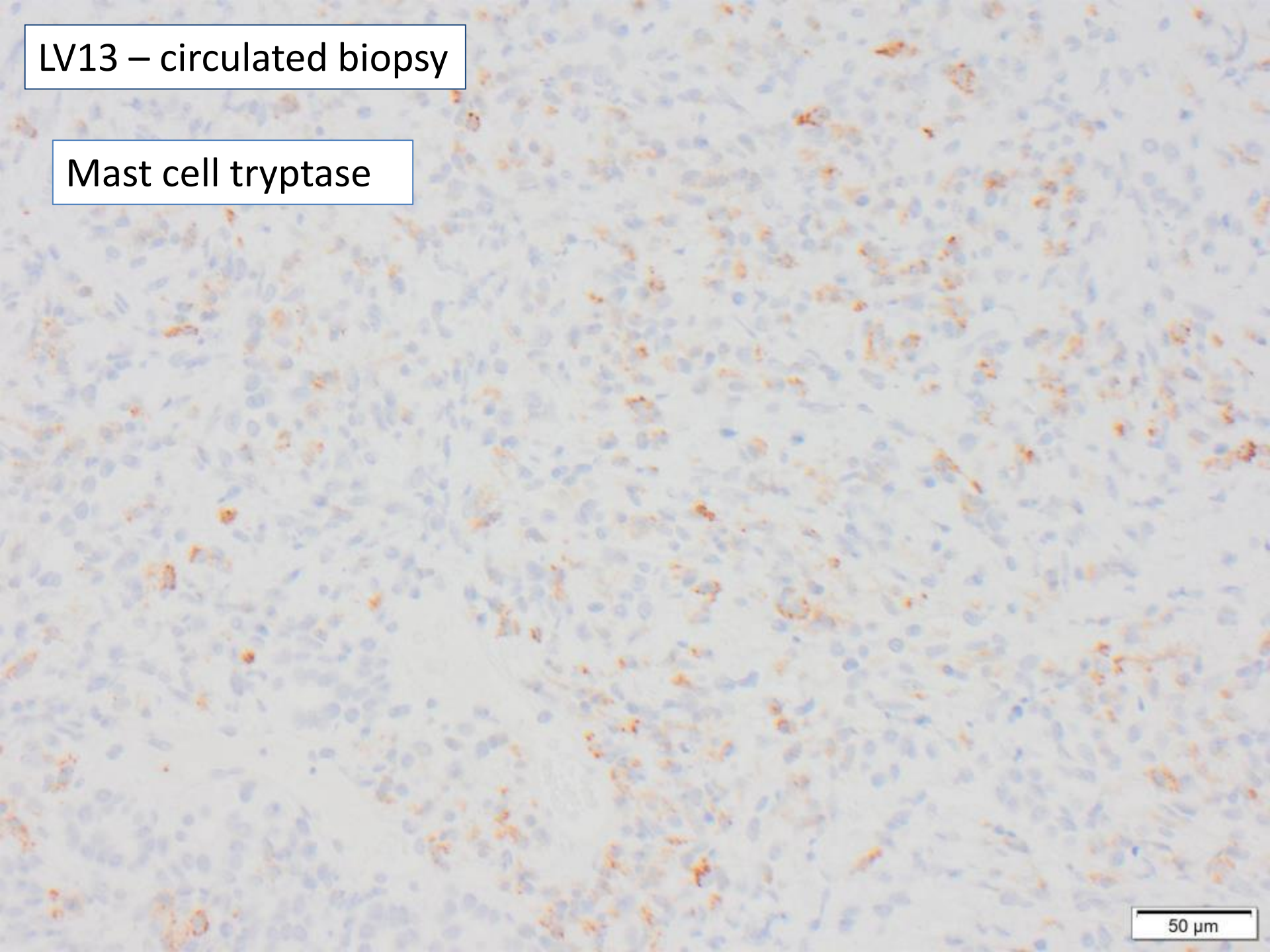

LV13 – circulated biopsy
500 µm


LV13 – circulated biopsy
500 µm


LV13 – circulated biopsy
500 µm


LV13 – circulated biopsy
CD117
200 µm


LV13 – circulated biopsy
CD117
50 µm


LV13 – circulated biopsy
Mast cell tryptase
50 µm

LV13

Mastocytosis

Table 2.

WHO classification of mastocytosis 2016

CM	Cutaneous mastocytosis
MPCM = UP	
DCM	
Mastocytoma of skin (cutaneous mastocytoma)	
SM	
ISM	Systemic mastocytosis Indolent
SSM	Smouldering
SM with AHN*	Additional Haem' neoplasm
ASM	Aggressive
MCL†	Mast cell leukaemia
MC sarcoma	

DCM, diffuse CM; MPCM, maculopapular CM.

*The previous term SM with clonal hematologic non–mast cell-lineage disease and the new abbreviation AHN can be used synonymously.

†Subvariants of MCL are shown in supplemental Table 4.

Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017 Mar 16;129(11):1420-1427. doi: 10.1182/blood-2016-09-731893. Epub 2016 Dec 28.

LV13

Table 1.

SM criteria

Systemic mastocytosis

Major SM criterion	Multifocal dense infiltrates of MCs (≥15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)
Minor SM criteria	a. >25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs
	b. *KIT* point mutation at codon 816 in the BM or another extracutaneous organ
	c. MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25
	d. Baseline serum tryptase level >20 ng/mL (in case of an unrelated myeloid neoplasm, item d is not valid as an SM criterion)
If at least 1 major and 1 minor *or* 3 minor SM criteria are fulfilled, the diagnosis of SM can be established	

SM criteria were defined by the WHO in 2001 and have been confirmed in the WHO updates of 2008 and 2016.

LV13

Mastocytosis in the liver

- Mast cells scanty in normal liver
- Liver involvement in systemic disease common, hepatomegaly, infiltrated portal tracts and sinusoids/endothelium. Fibrosis/cirrhosis also NCPH.
- Biliary picture described:
- Waldburger N, Rupp C, Klinke S, Wieczorek K, Gotthardt D, Kirchner T, Schirmacher P, Straub BK. Aggressive systemic mastocytosis of the liver with cholangitis. Hepat Oncol. 2015 Oct;2(4):343-347. 26 yrs male mimicking PSC
- Kyriakou D, Kouroumalis E, Konsolas J, Oekonomaki H, Tzardi M, Kanavaros P, Manoussos O, Eliopoulos GD. Systemic mastocytosis: a rare cause of noncirrhotic portal hypertension simulating autoimmune cholangitis--report of four cases. Am J Gastroenterol. 1998 Jan;93(1):106-8. 3 of 4 patients bile duct infiltration mimicking 'AMA negative PBC'

LV13

Lessons

- When it doesn't fit think haematolymphoid!
- Investigation of asymptomatic patient may reveal early manifestations of disease

Liver EQA circulation LV
Educational case LV 14

Dr Margaret Sheehan

Galway University Hospital, Ireland

LV 14 clinical information:

- Male aged 53
- On TPN for short gut; recent hemorrhagic pancreatitis; history of alcohol excess;
- Currently jaundiced and rising bilirubin (200-250)
- No biliary obstruction on imaging

- Core biopsies of liver – 4 cores; 42mm; > 40 portal tracts
- Additional stains: reticulin and Mason Trichrome

LV14

Total number of responses =70

69 – final diagnosis (3- without specific morphology description)

66- morphological description

<u>Look at responses under</u>

1. Morphology
2. Final diagnosis/differential (possible aetiology)

1 responder:

“ Sorry the internet speed is to painful”

LV14

4 key morphological features described

- **Cholestasis** (bile plugs/bilirubinostasis)
- **Steatosis** (steatohepatitis; phospholipidosis)
- **Hepatocyte ballooning** (feathery degeneration/swelling/ fibrillary/foamy cytoplasm)
- **Fibrosis** (spectrum from mild/minimal to incomplete nodules)

Concordance on recognising these morphological features – good

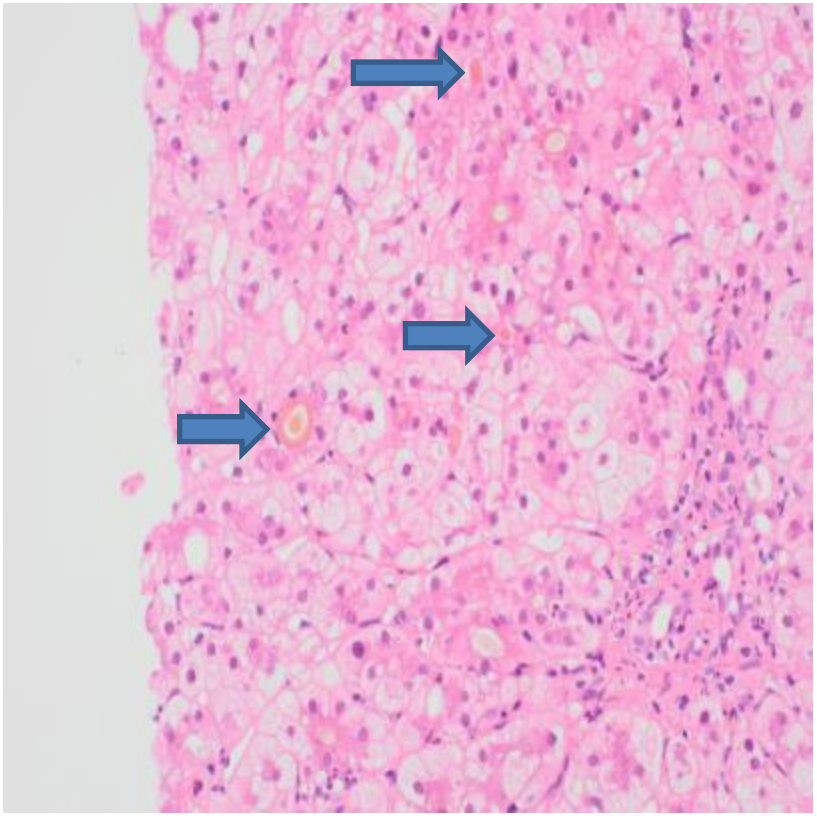
Broad spectrum of responses -interpreting significance re: final likely diagnosis(aetiology)

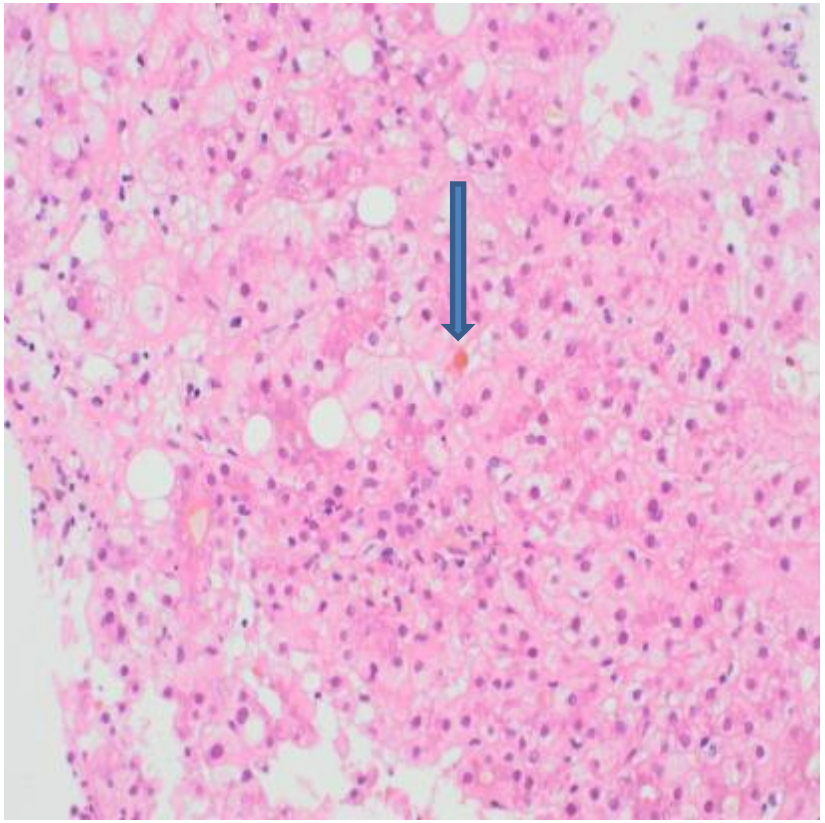
LV14

Feature	Present	Not mentioned	Specifically 'not present'
Cholestasis	**54 (82%)**	**10**	**2**
Steatosis	**51 (77%)**	**11**	**4**
Hepatocyte ballooning	**59 (89%)**	**6**	**1**
Fibrosis	**58 (88%)**	**8**	**0**

LV14

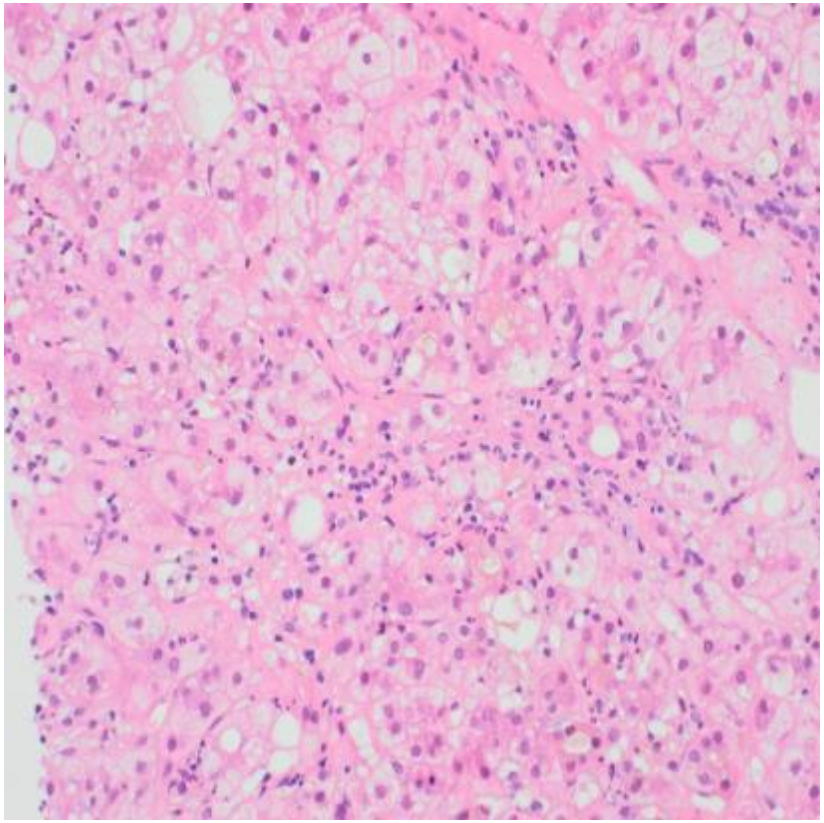
Cholestasis (n=54 ; 82%)

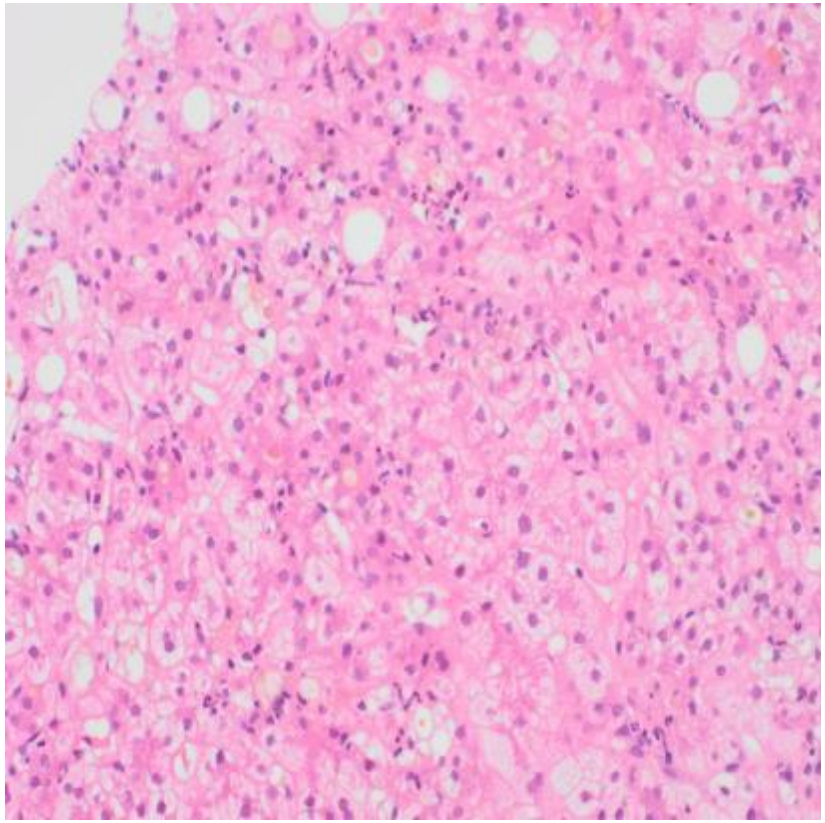




LV14

Steatosis- very mild (n=51;76%)

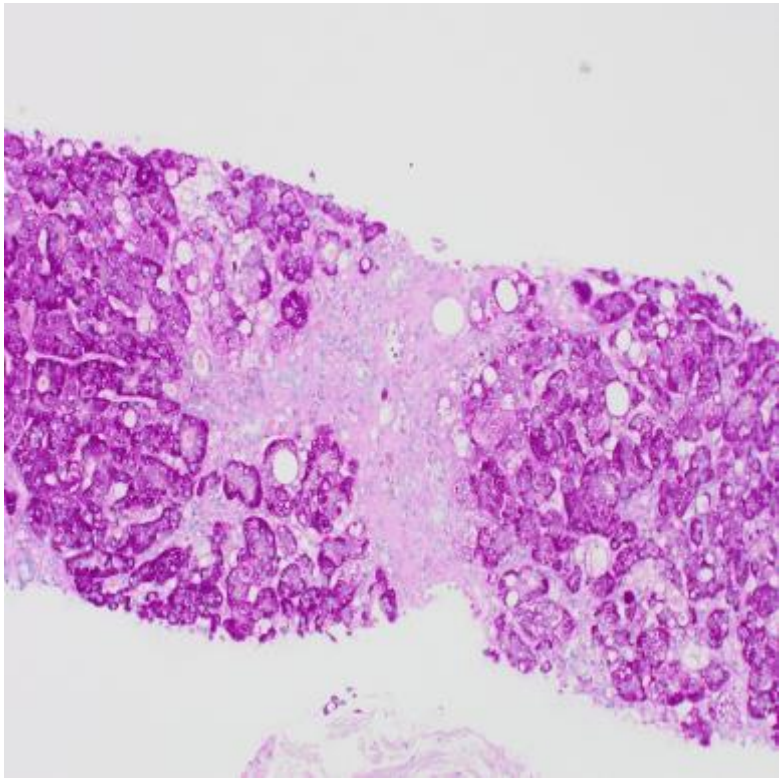




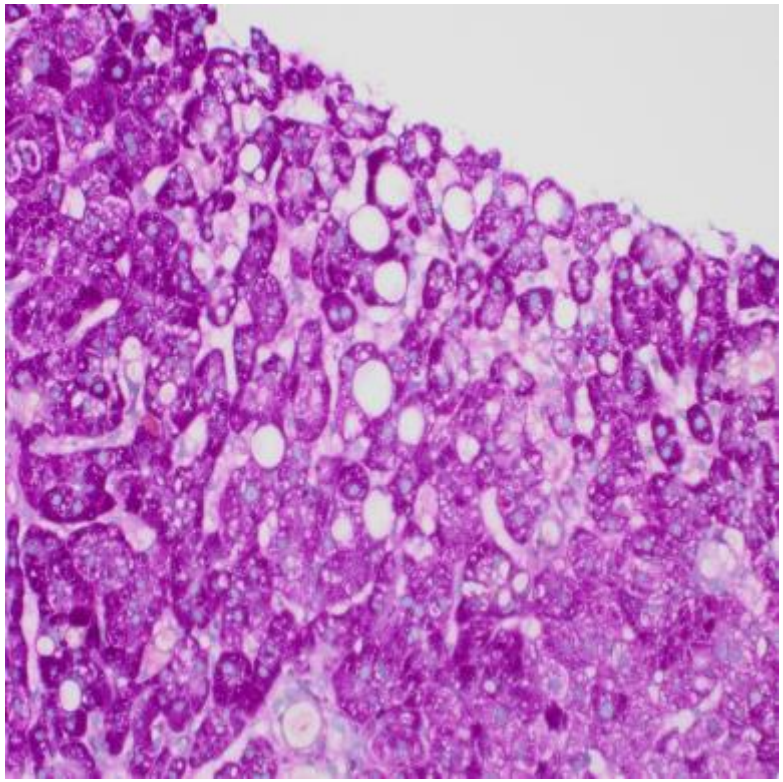
LV14

PAS stain

Loss of parenchyma

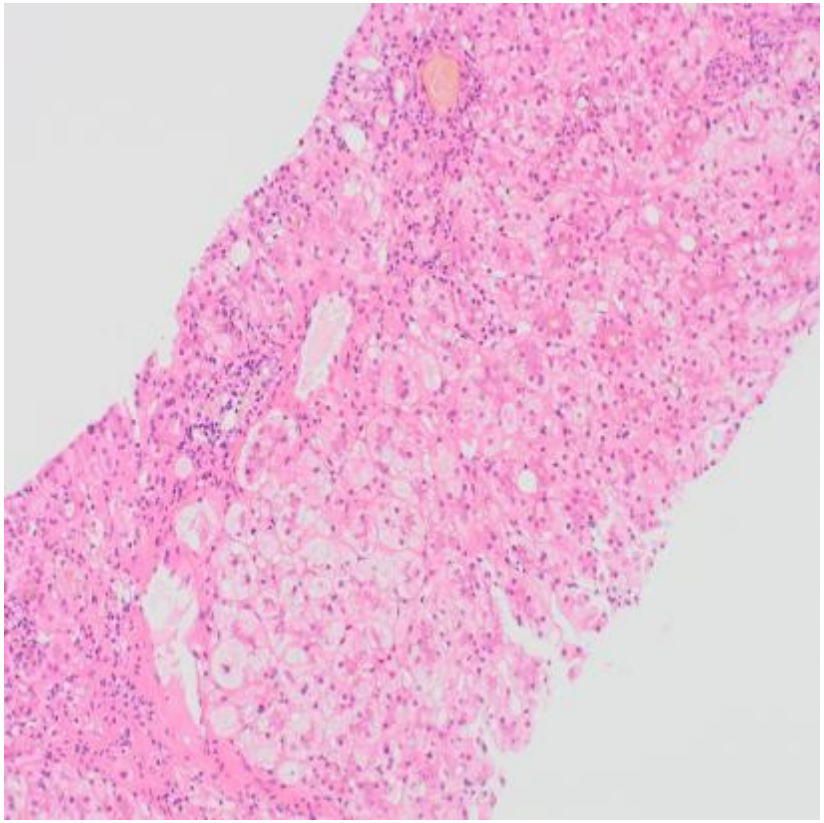


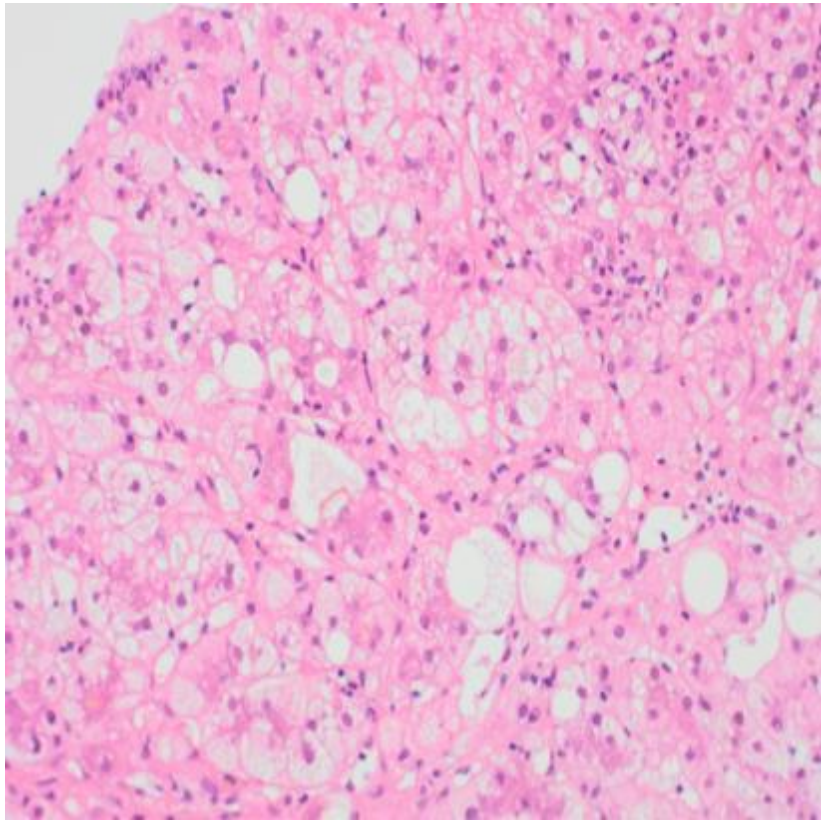
Scattered fat spaces



LV14

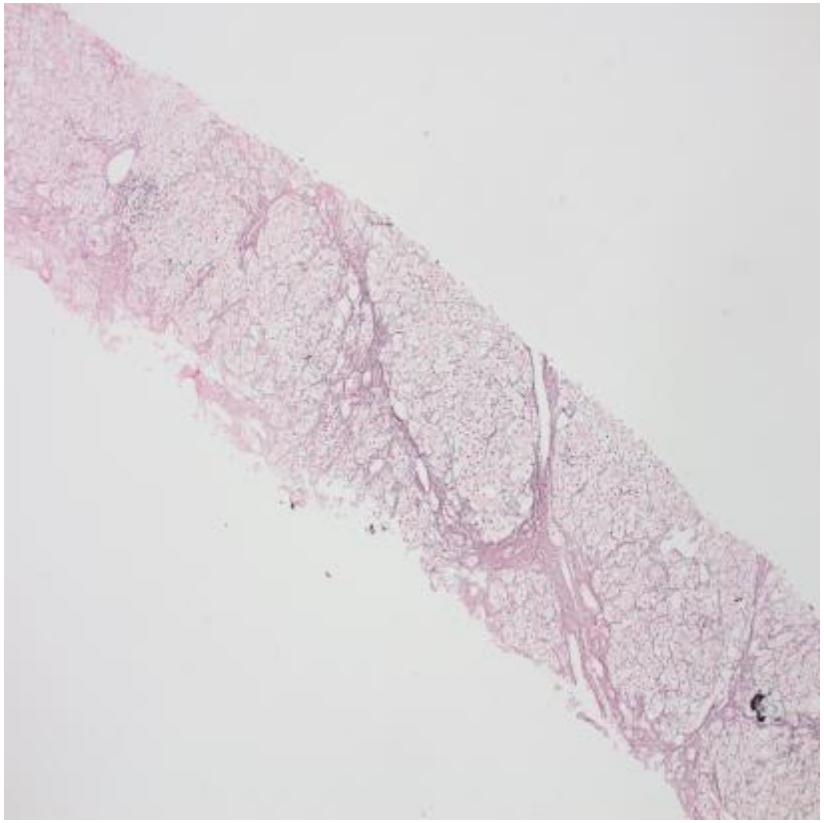
Hepatocyte ballooning (n=59; 89%)

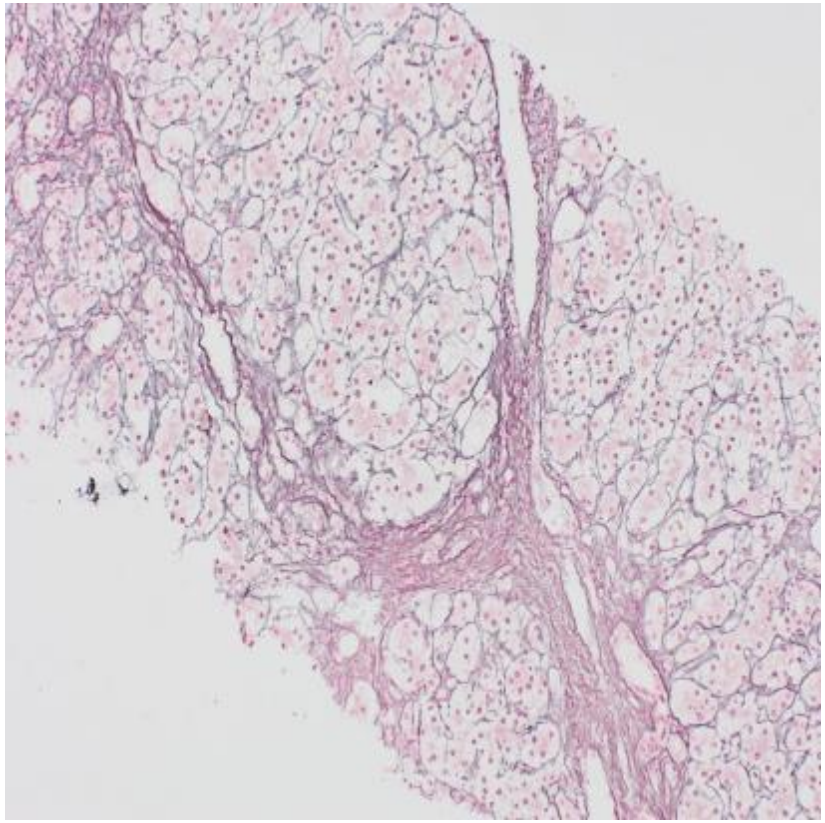




LV14

Architecture-reticulin

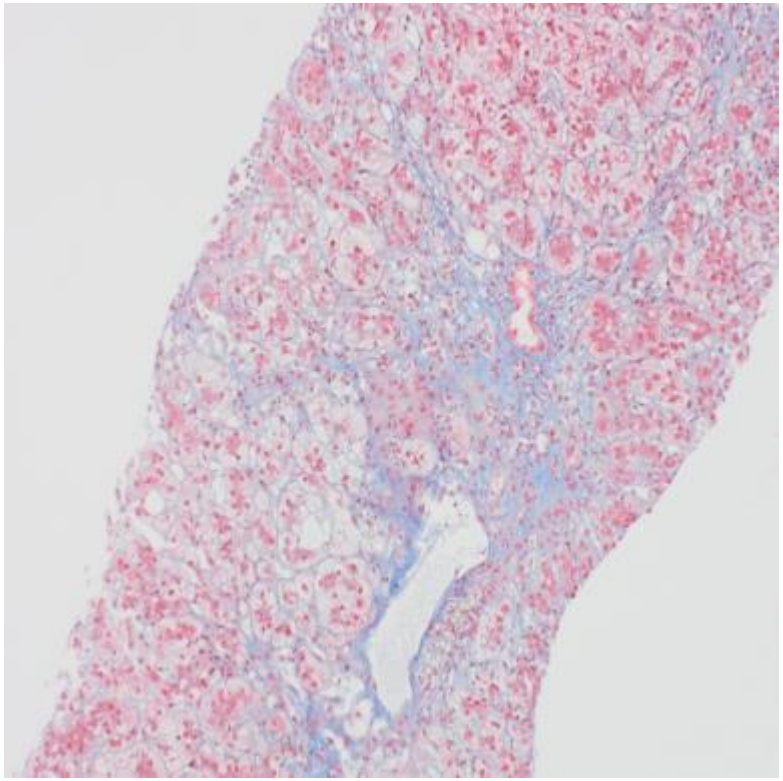




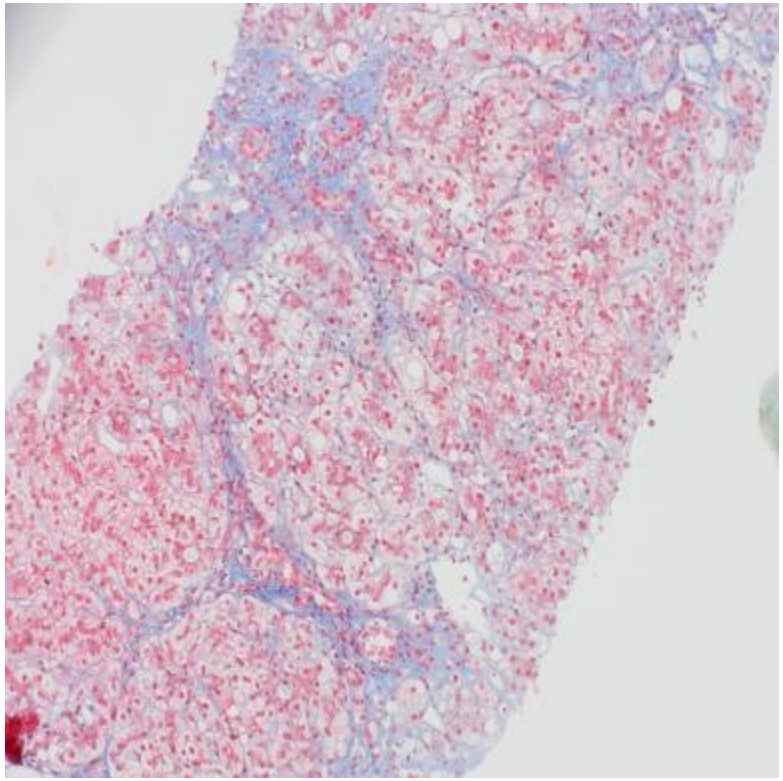
LV14

Fibrosis- Masson Trichrome

Fine pericellular fibrosis



Bridging areas of fibrosis



LV14

Final diagnosis (aetiology) suggested (n=69)

Final aetiological diagnosis (n=69)

- TPN/IFALD only=32 (46.4%)
- TPN and alcohol= 28 (40.6%)
- Alcohol only= 4 (5.8%)
- Cystic fibrosis=1 (1.4%)
- Sepsis (only)=1 (1.4%)
- Drug (not specified)=1 (1.4%)
- No conclusion re aetiology= 2 (2.9%)

Other possible factors

- Pancreatitis as contributor=2
- Sepsis (plus other causes)=1
- HBV as added factor=1
- NASH as factor= 2

LV14

Educational case

AETIOLOGY- DO NOT REACH THRESHOLD FOR CONCORDANCE

LV14

TPN associated liver pathology History and Terminology

- 1960's Long term parenteral nutrition (PN)was introduced by Stanley Dudrick
- 1967: First patient discharged home on PN- extensive carcinomatosis causing intestinal obstruction
- 1968: First patient with Short Bowel Syndrome (SBS) – home on PN; survived 15 years
- Recognised that TPN associated liver disease occurred
- Parenteral nutrition –associated liver disease (**PNALD**)
- Intestinal failure-associated liver disease (**IFALD**)

LV14

Histological changes in liver associated with Parenteral nutrition

- Age of patient and length/duration of therapy
- CHOLESTASIS- more common in infants; commonest finding all age groups
- STEATOSIS/Steatohepatitis- commoner in older children/adults than infants
- Ductopenia- associated with fibrosis; inversely related to length of therapy
- Fibrosis- Perivenular and portal fibrosis – characteristic features

LV14

Parenteral nutrition.... Progressive liver failure

Aetiological mechanisms:

- Intake/metabolism differs- infusions bypass portal circ
- Nutrient deficiencies (choline/ vitamin E)
- Nutrient toxicities
- (bacterial overgrowth)
- Altered bile salt metabolism
- Sepsis- independent risk factor

Potential Therapies

- Decrease dextrose
- Decrease lipid
- Sufficient lipid emulsions
- Cycle TPN infusion
- Encourage oral intake
- Metronidazole/ Urso
- Isolated intestinal transplant
- Combined liver/SB transplant

LV14

Back to our case

LV14

Additional background information: our case

- Workplace accident approx 30 years ago- fell from scaffolding
- Significant small bowel resected; approx 40cm colon left-no ileostomy; on TPN since then
- 2016 acute presentation- multi-organ failure ? Precipitated by an acute pancreatitis, had been drinking heavily before this episode
- Jaundiced with significant impairment of LFT's
- Slow to improve
- LV 14 – liver biopsy taken at that time

LV14

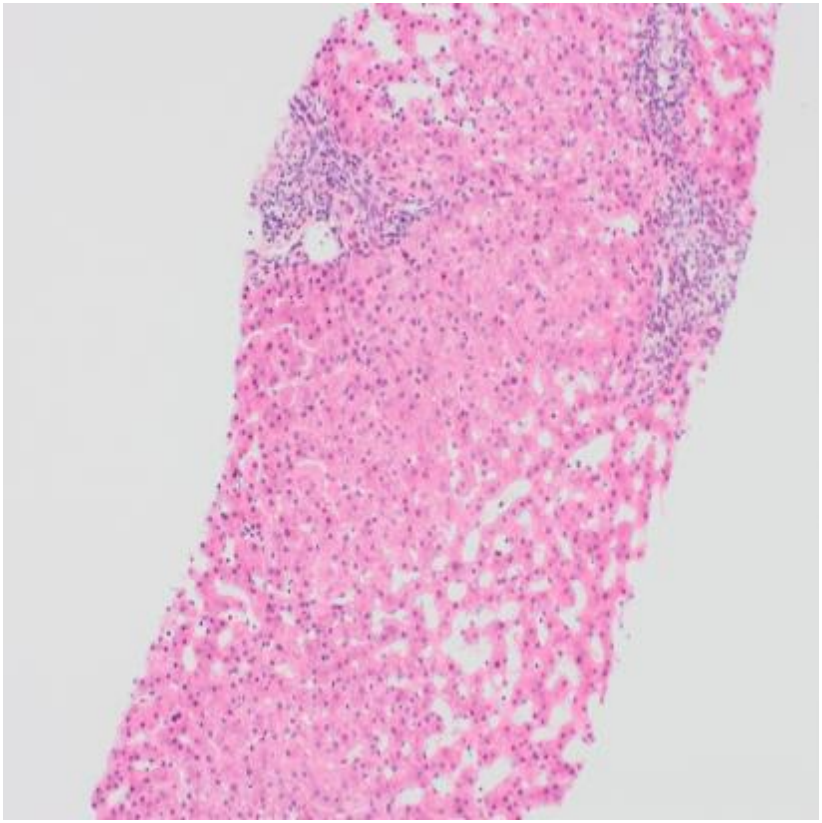
Moving right along.....

- Recovered well
- Stopped drinking ? How much a problem
- TPN modified over the years to reduce fat content
- LFT's continue to vary- modifications to dextrose based kcals when that happens
- Shared medical care with UK
- Repeat bx 3 years later (2019)- primarily to stage given fibrosis in 2016 biopsy

LV14

Repeat biopsy 3 years after first biopsy

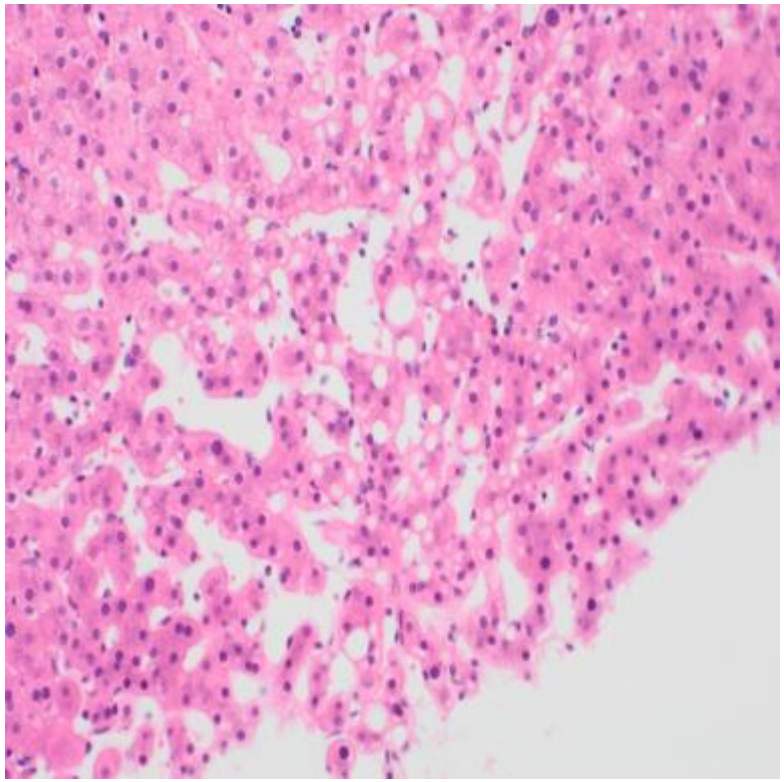
- 2 cores – combined 26mm
- 18 portal tracts
- Scattered fat spaces (<5%)
- Focal sinusoidal dilatation
- Mild portal inflammation
- Occasional portal eosinophil
- NO- cholestasis/ ballooning hepatocytes/fibrosis



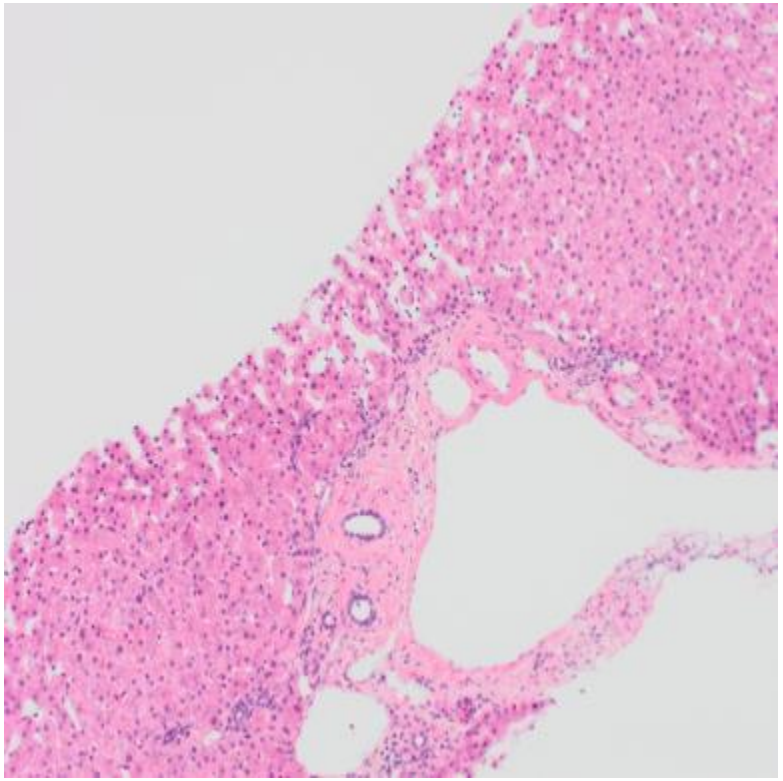
LV14

Repeat Bx 2019

Focal fat spaces



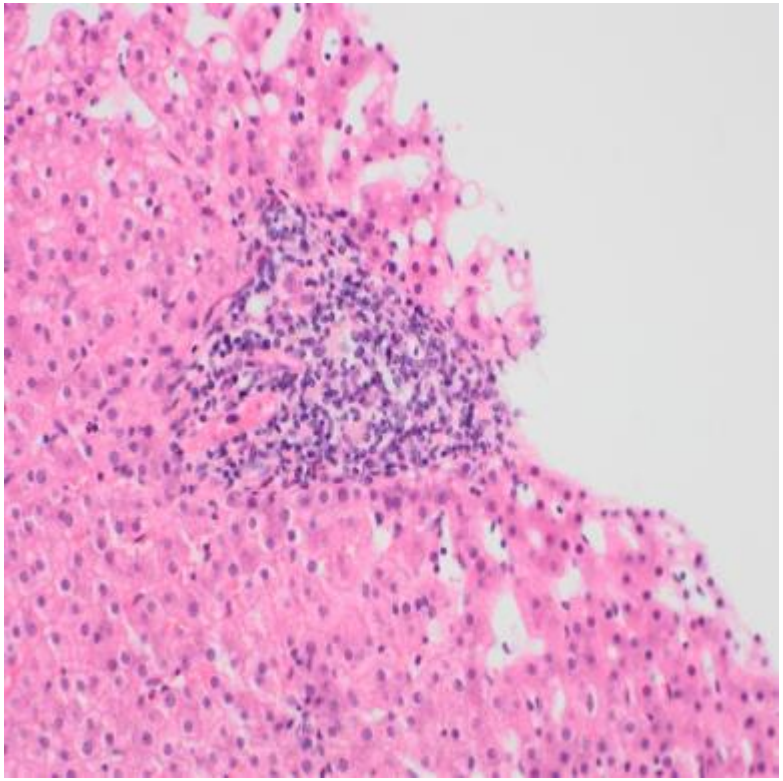
Sinusoidal dilatation



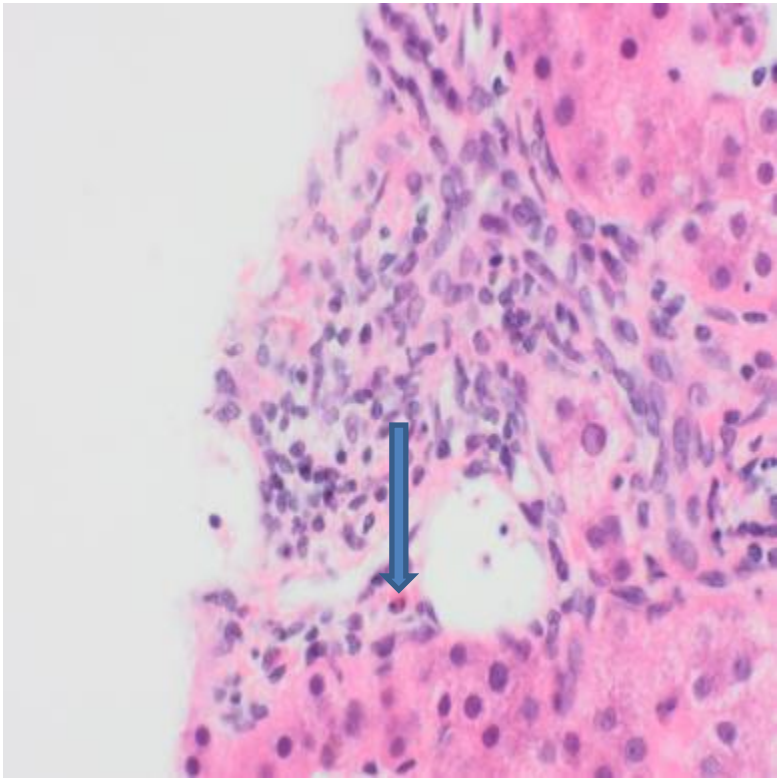
LV14

Repeat Bx 2019

Focal portal/ parenchymal inflammation



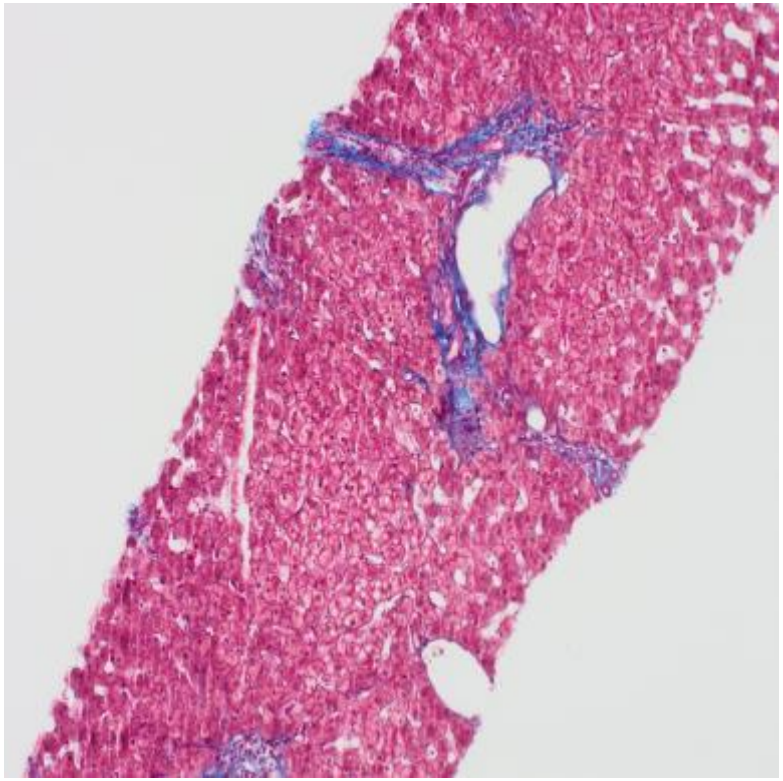
Occasional eosinophils



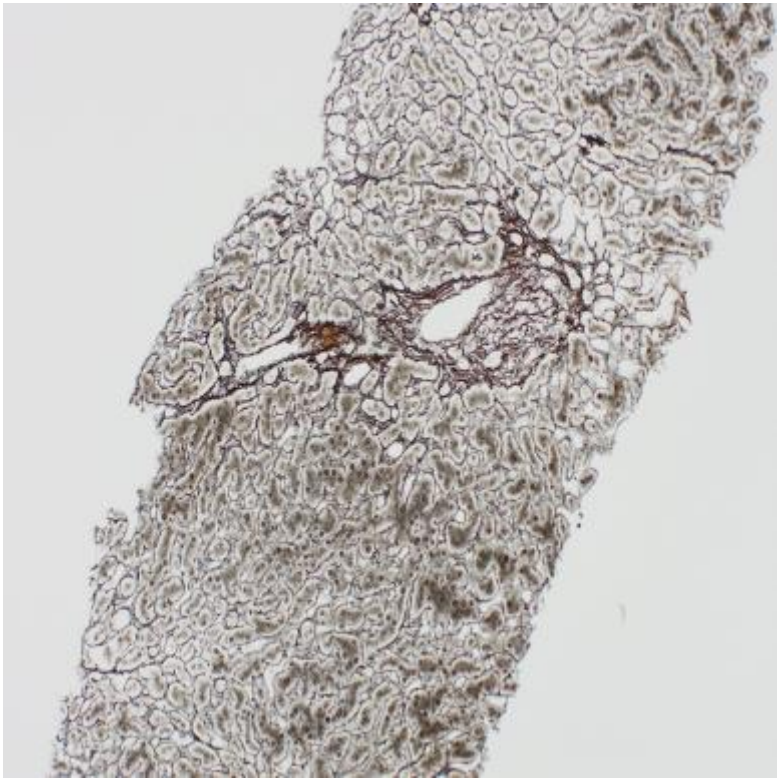
LV14

No significant architectural abnormality

Masson Trichrome



Reticulin



LV14

Overview of this case

2016 biopsy- TPN; alcohol; pancreatitis

- Cholestasis
- Steatosis (minimal)
- Hepatocyte swelling/feathery etc
- Fibrosis

?? Ascribed to TPN/IFALD/ alcohol

(failure to reach threshold concordance in EQA)

2019 Biopsy- TPN ongoing Tx

- NO- cholestasis; hepatocyte swelling etc
- Steatosis (minimal)
- No significant fibrosis

?? Alcohol/pancreatitis now removed as factors

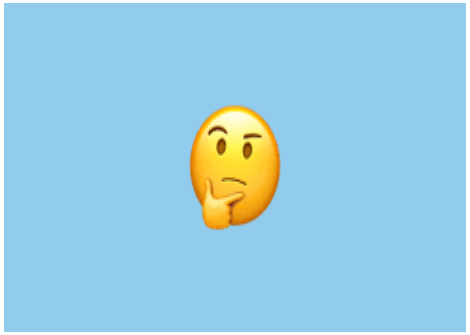
TPN modifications

LV14

Final conclusion re: aetiology

- ? Multi-factorial: alcohol/ TPN
- Absent Mallory Denk bodies/ polymorphs/ minimal steatosis
- Retrospective- alcohol intake not marked/ has decreased+
- Changes in TPN infusions- dextrose kcal content

Balance of probabilities



Open for discussion

Thank you