National Liver Histopathology EQA Scheme

Circulation J1

Spring 2014

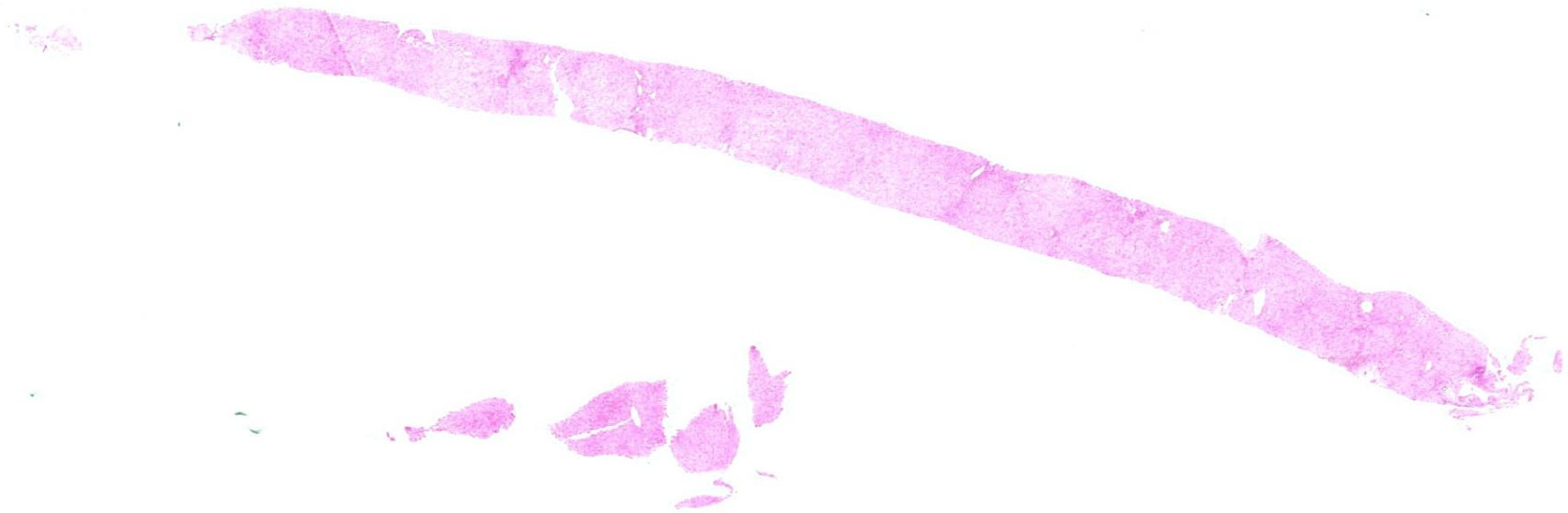
Circulation J1

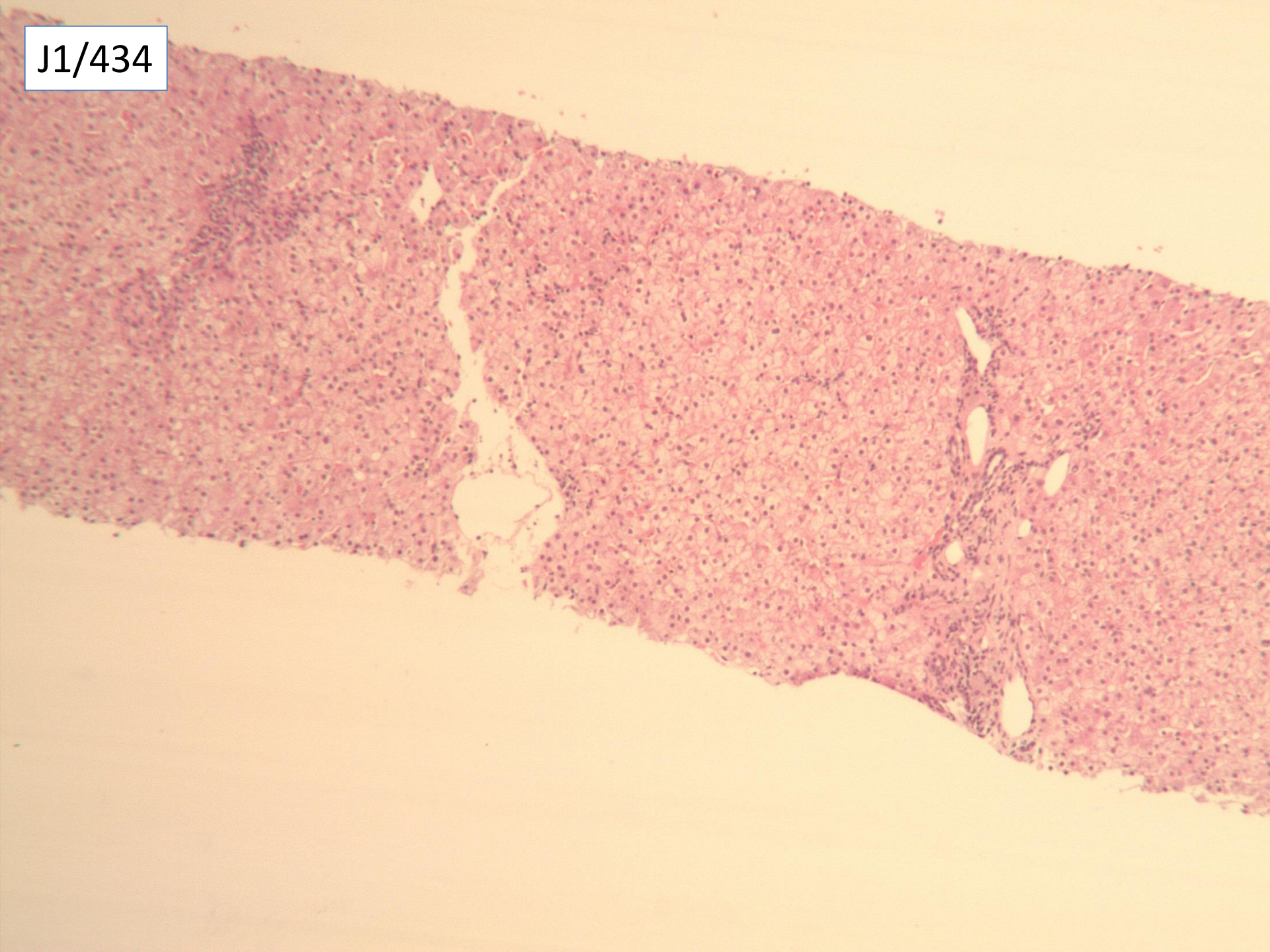
- Spring 2014.
- 82 responses,
- so 80% consensus is 66,
- Not more than 16 alternative diagnosis to be suitable for scoring.
- Collated responses for comment – received from 14 members. These are shown in blue on collated responses.

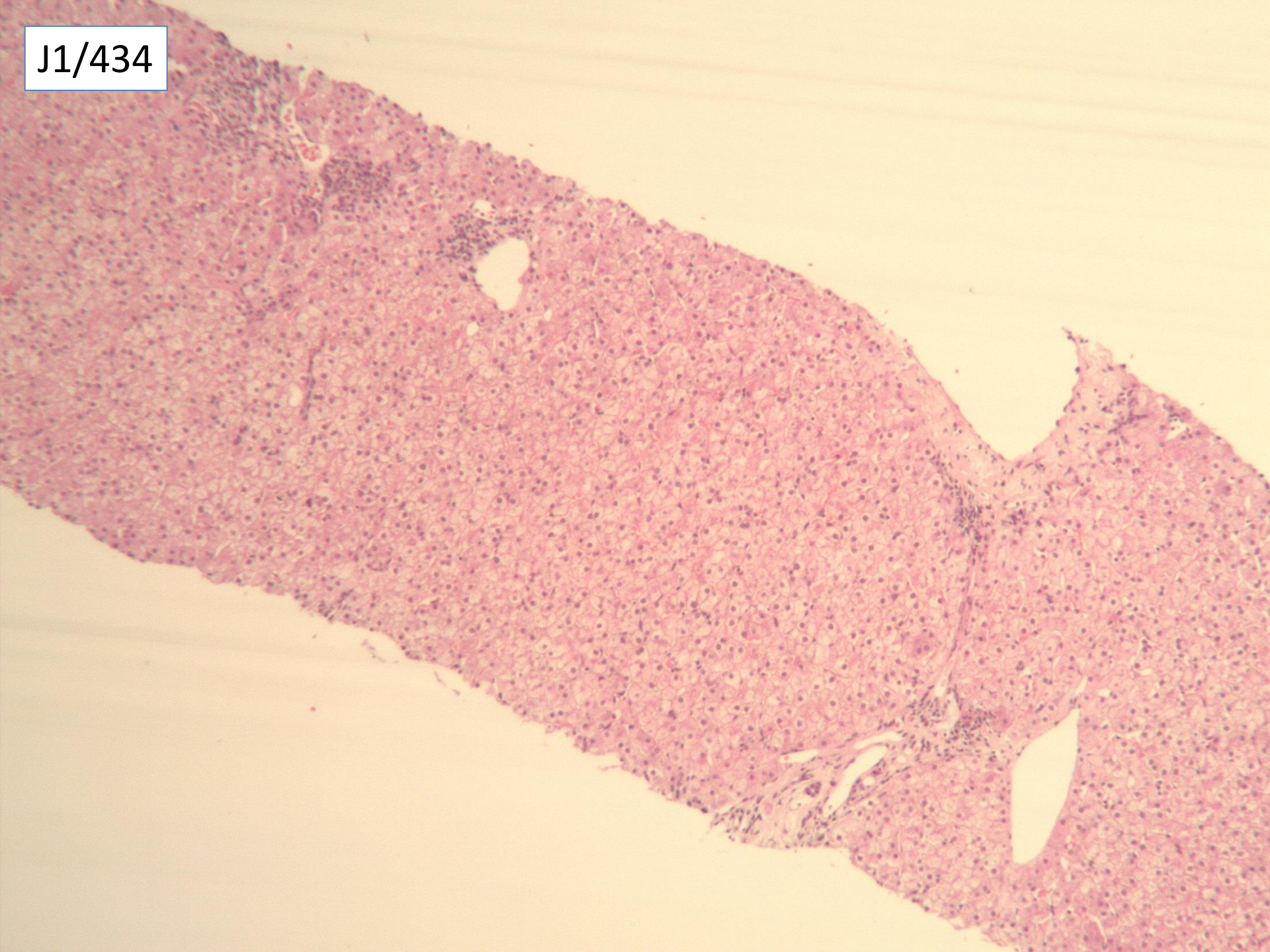
- Open meeting attended by 32 members and 14 guests.

J1/434 Age 53, Female

AID, AMA++ and PBC?




J1/434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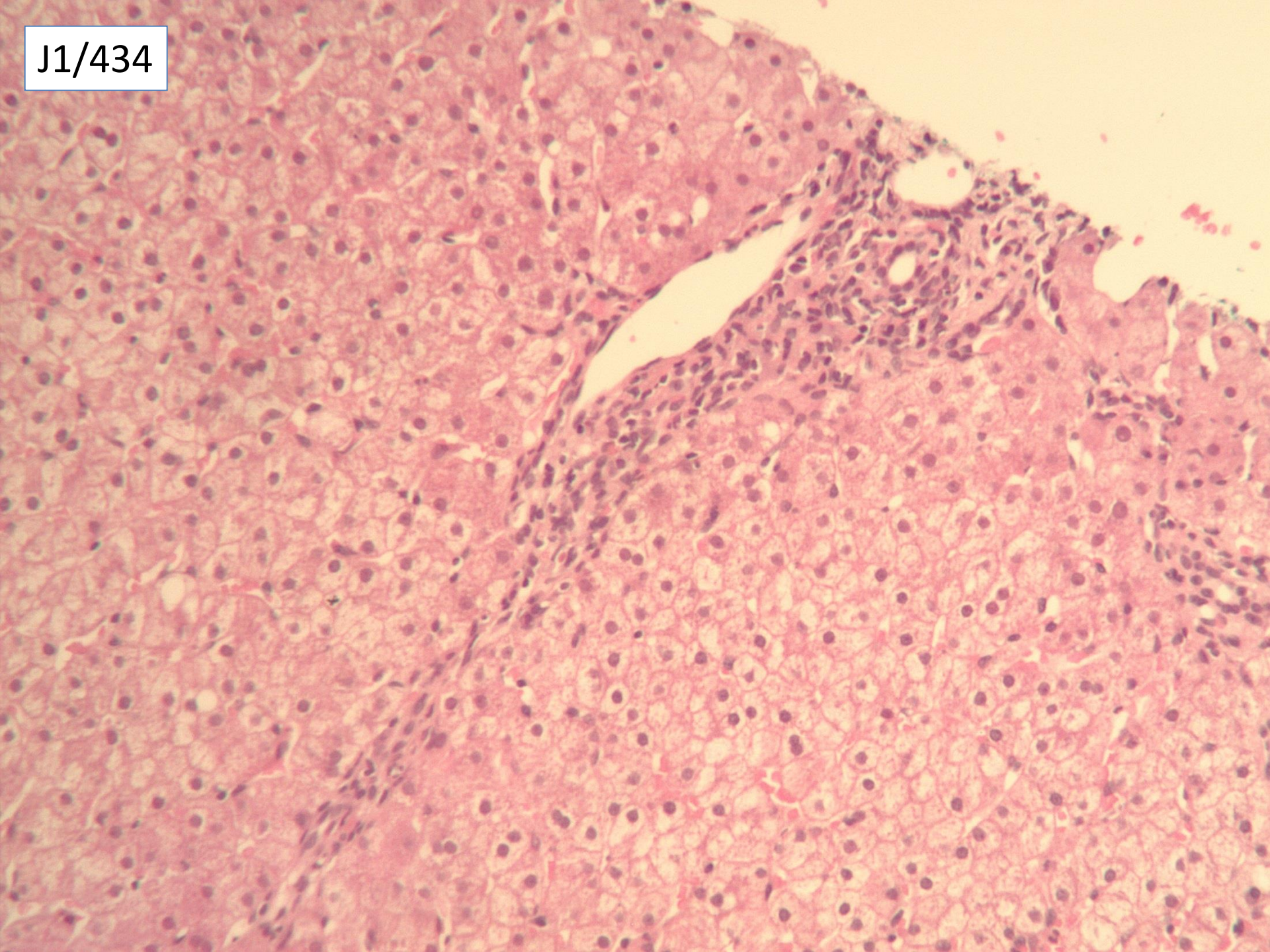
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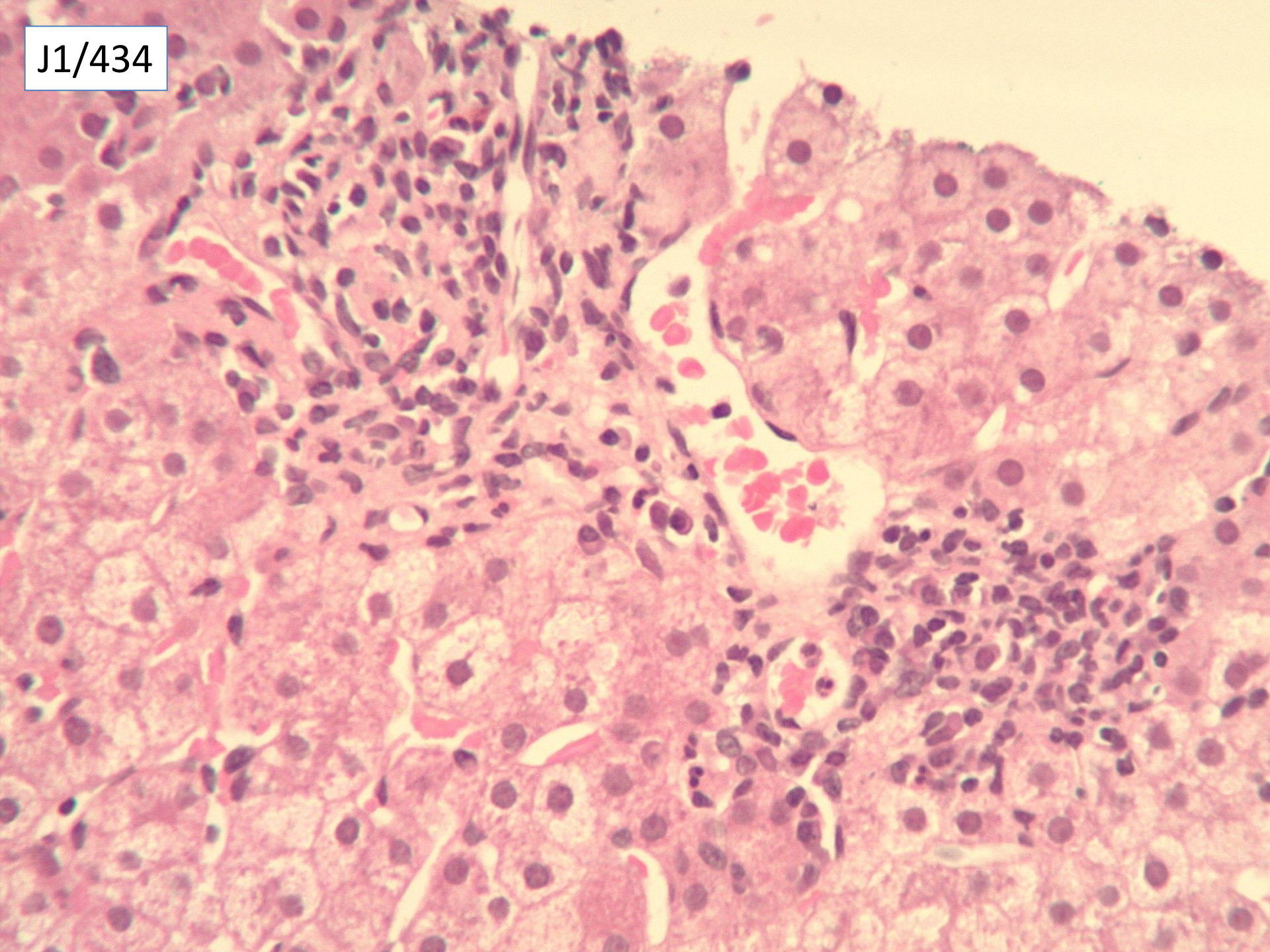
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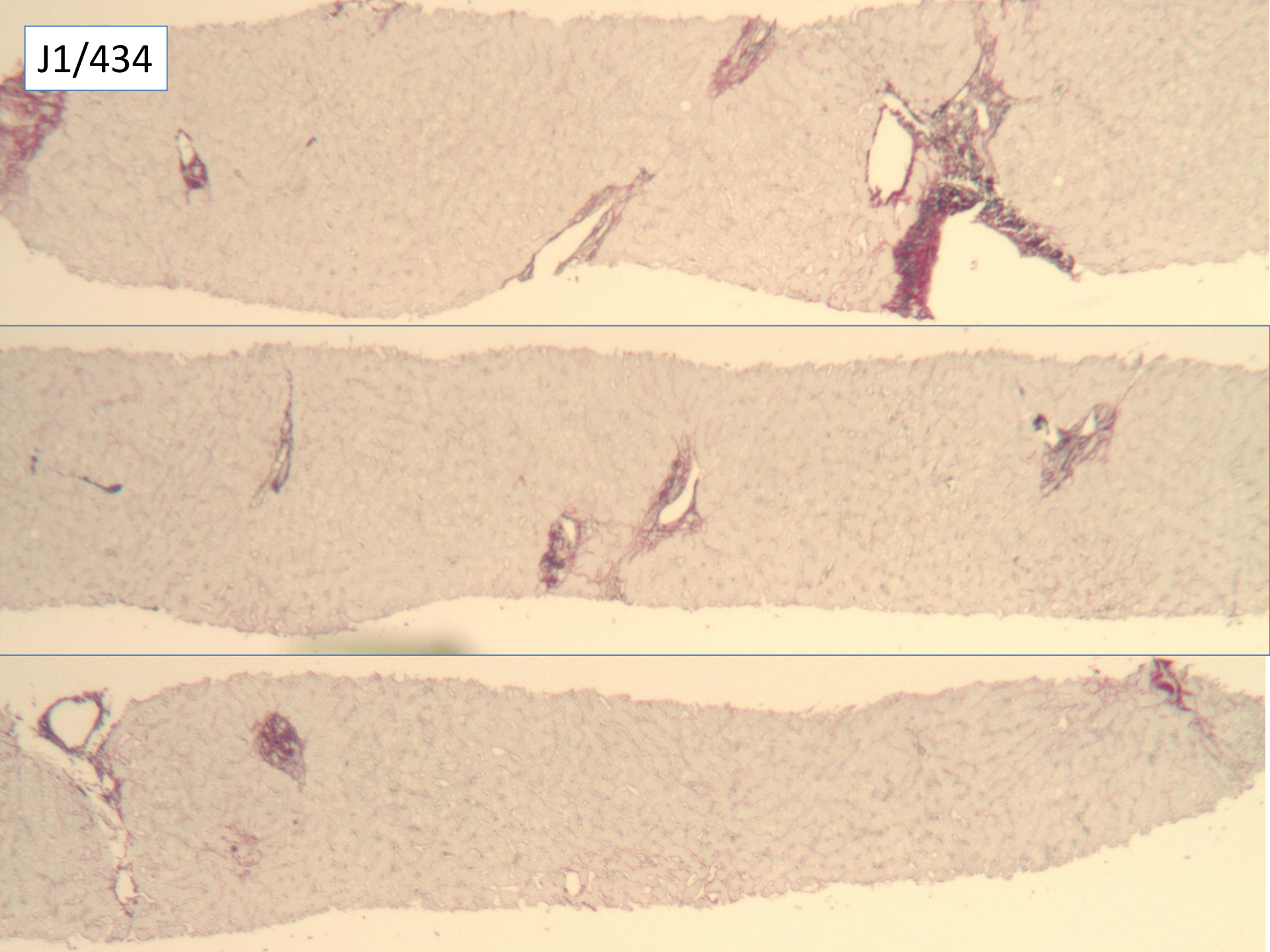

J1/434

J1/434 Age 53, Female

AID,AMA++ and PBC?

3 PBC definite

55 consistent with PBC

4 not diagnostic of / not obviously PBC, no alternatives suggested

6 not typical of PBC, suggests other alternatives that are favoured, but needs more information

10 non-specific inflammation/chronic hepatitis, not histological features of PBC

5 PBC not mentioned anywhere

17 no ductopenia

6 possible ductopenia

16 probable ductopenia

Rest - ductopenia not mentioned

35 need copper associated protein

24 need CK7

14 both

37 neither

Suggested scoring: Wide range of comments – not suitable for scoring

– or accept if possibility of PBC mentioned anywhere in the report?

– non-specific responses usually had discussion about further information needed etc.

8/15 agree, 3 unsuitable

J1/434 Age 53, Female
AID, AMA++ and PBC?

Original diagnosis: Autoimmune hepatitis.

Discussion – very little diagnostic material in this biopsy.

Discussion over whether it is appropriate to score this case – show of hands favoured scoring.

The responses score 10 if there is a mention of the extent to which PBC is likely, 5 if biliary disease PBC not mentioned, 0 if no mention of PBC or biliary disease.

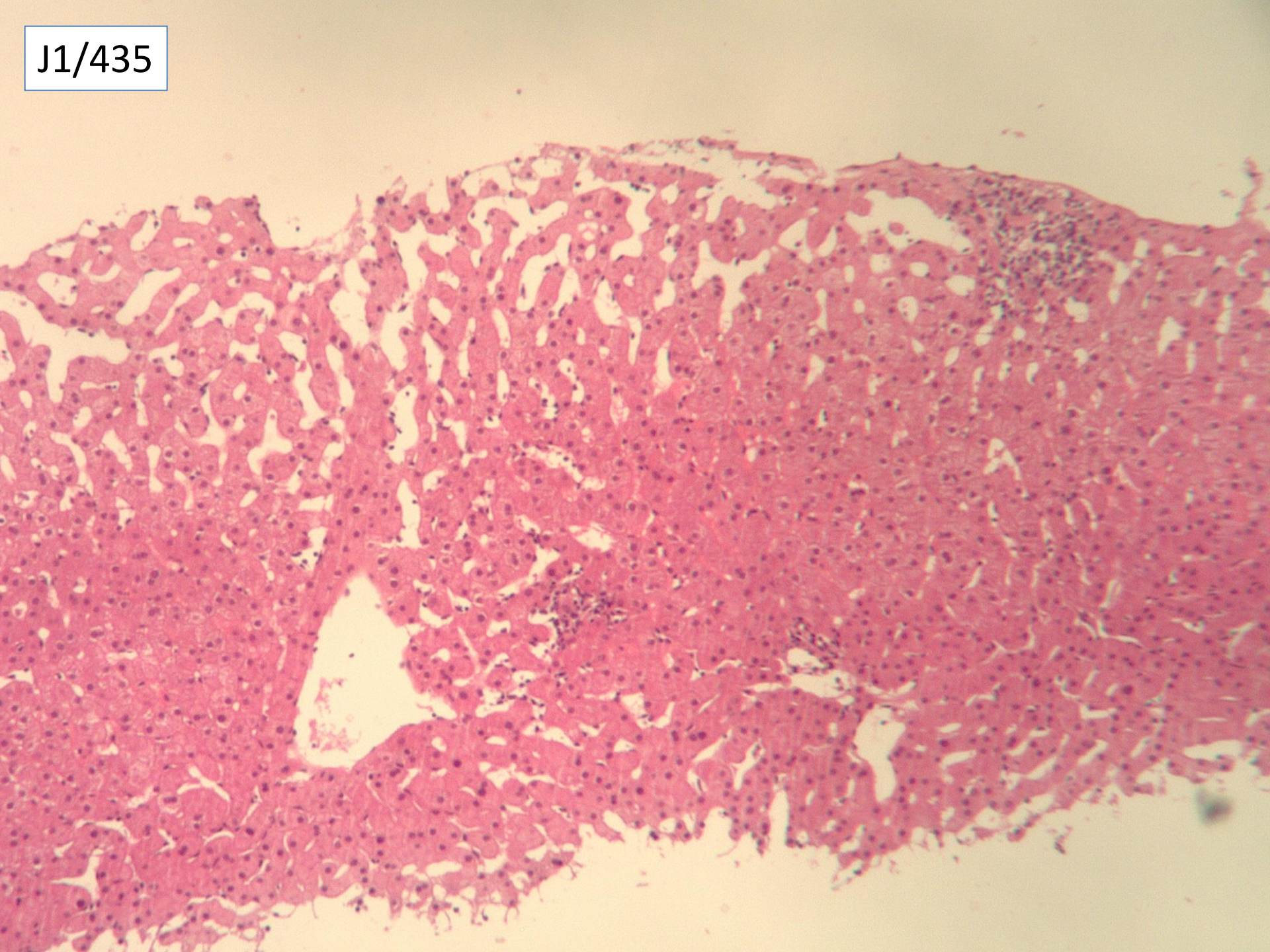
Comment: The reason for the biopsy is not clearly indicated.
Positive antimitochondrial antibodies and any evidence of chronic liver disease is sufficient for supportive diagnosis of PBC, even though there are not diagnostic features here. In practice, this biopsy would not be reported without a Shikata stain and further clinical information.

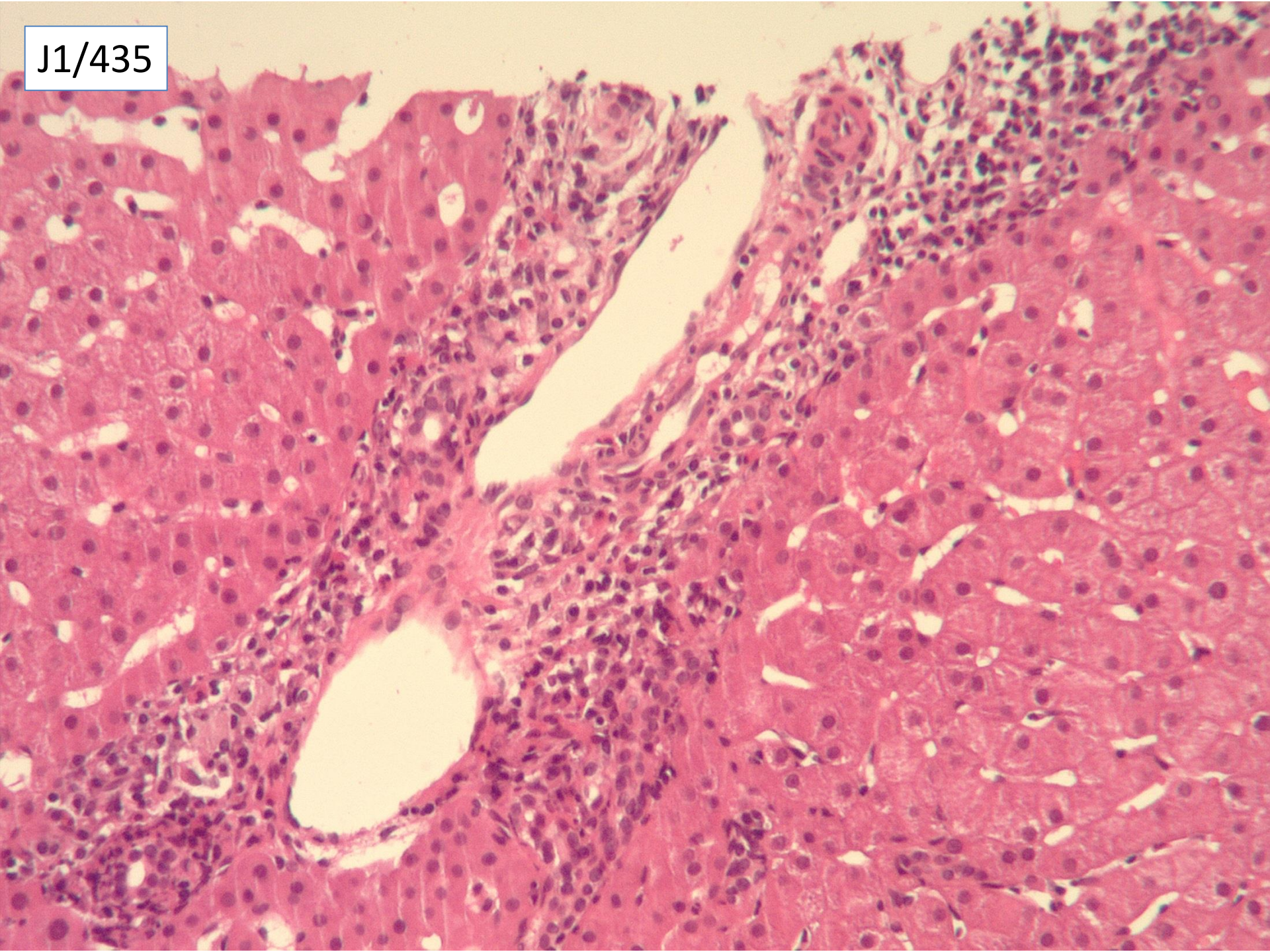
J1/435 Age 21, Female

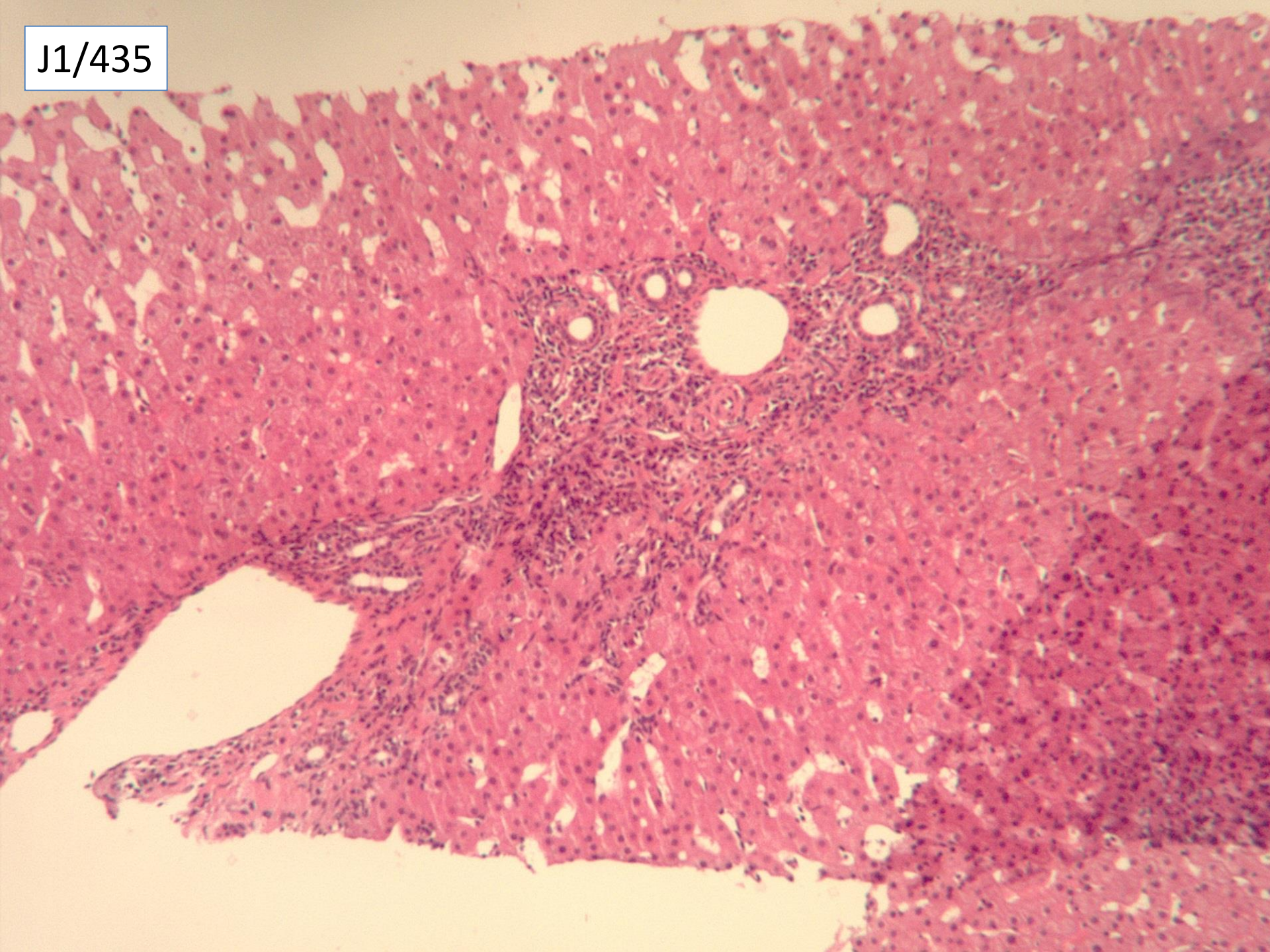
ANA positive 1:80 ASM positive; AMA negative.

IgG elevated = 37, IgM mild increase 2.8

J1/435




J1/435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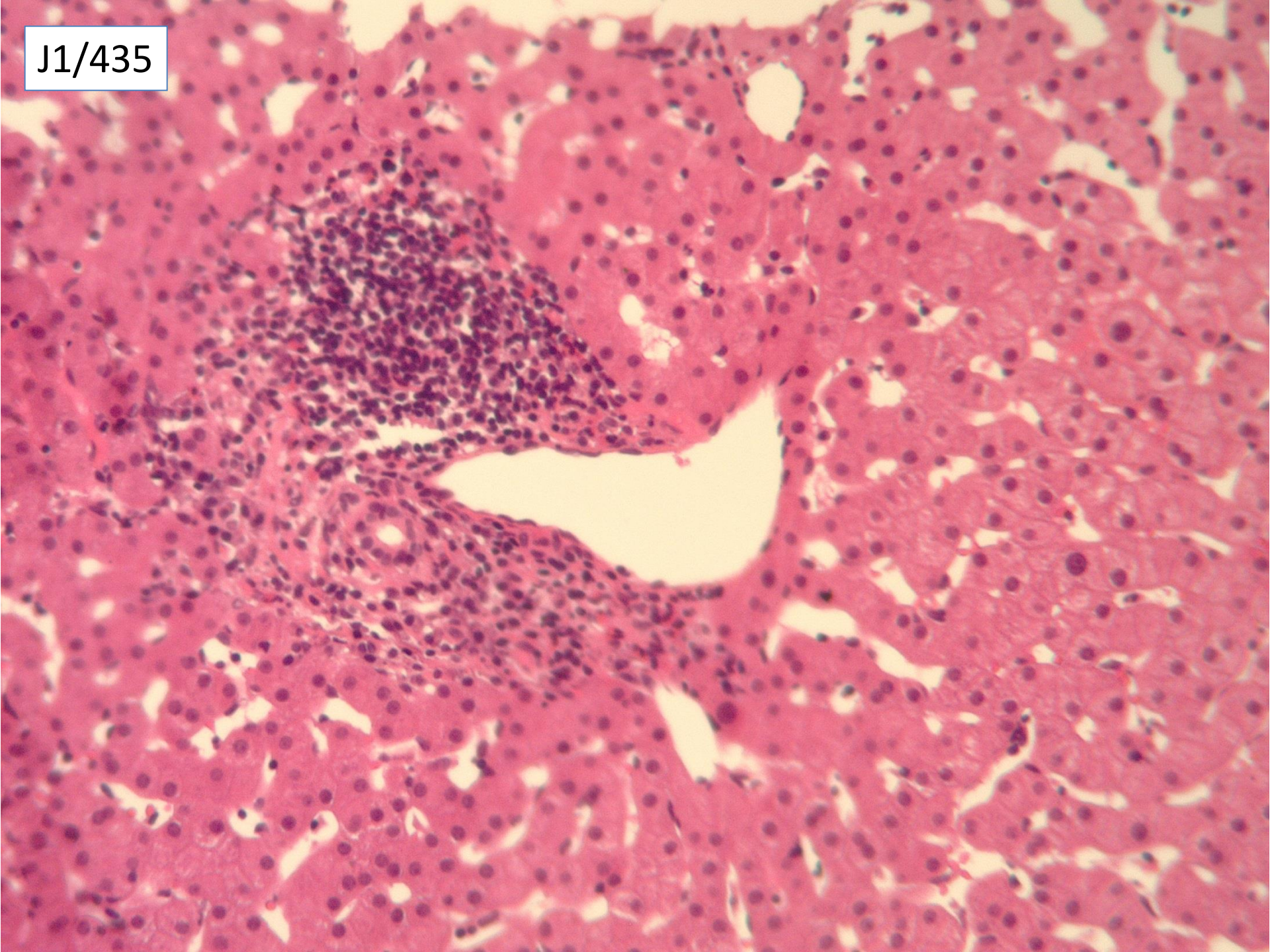
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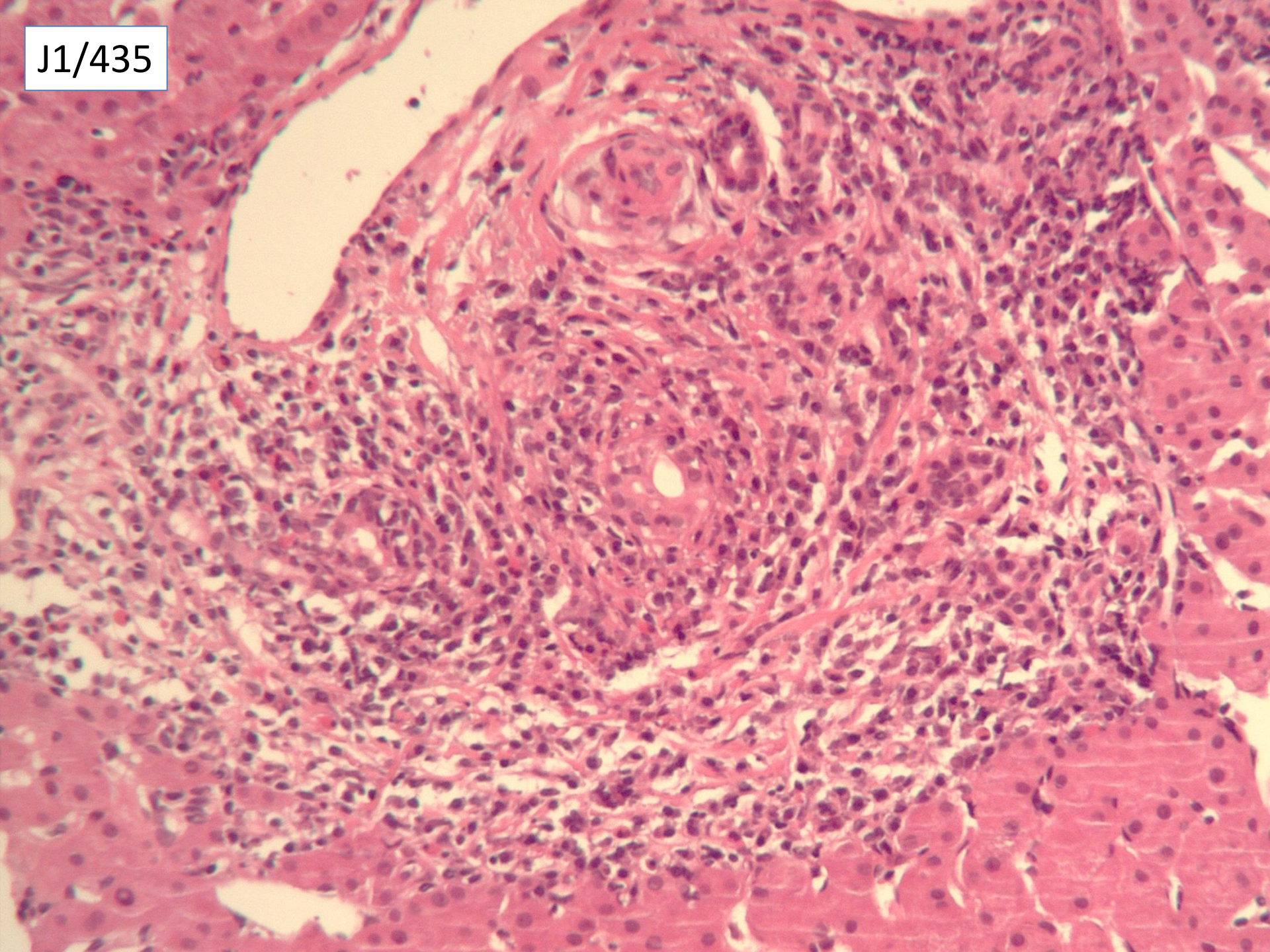

J1/435

J1/435 Age 21, Female

ANA positive 1:80 ASM positive; AMA negative.

IgG elevated = 37, IgM mild increase 2.8

82 autoimmune liver disease of some kind

40 autoimmune hepatitis, of which
- 25 commented on duct damage,
- 5 commented no duct damage

15 PBC/autoimmune cholangitis/AMA-ve PBC,
- of which 5 had differential of overlap

25 overlap autoimmune hepatitis/PBC likely or to be considered

2 sclerosing cholangitis – with overlap

4 consider IgG4 disease

2 ? vascular component

13 eosinophils so consider drugs – as main diagnosis – many more mentioned in differential

Duct granulomas commented by 22 – 12 not present, 10 present

14 need copper associated protein

5 do CK7

8/14 agree, 2 unsuitable

Suggested scoring: no consensus, unsuitable for scoring – or 10 points for any response indicating autoimmune liver disease with discussion of diagnosis. (all but one response accepted on this basis

J1/435 Age 21, Female

ANA positive 1:80 ASM positive; AMA negative.

IgG elevated = 37, IgM mild increase 2.8

Original diagnosis: Features of destructive cholangiopathy as well as some AIH Features.

Follow up – Reported as possible AIH/autoimmune cholangitis overlap

Alk p'ase 237. IgM raised at 4.2. Polycystic ovaries

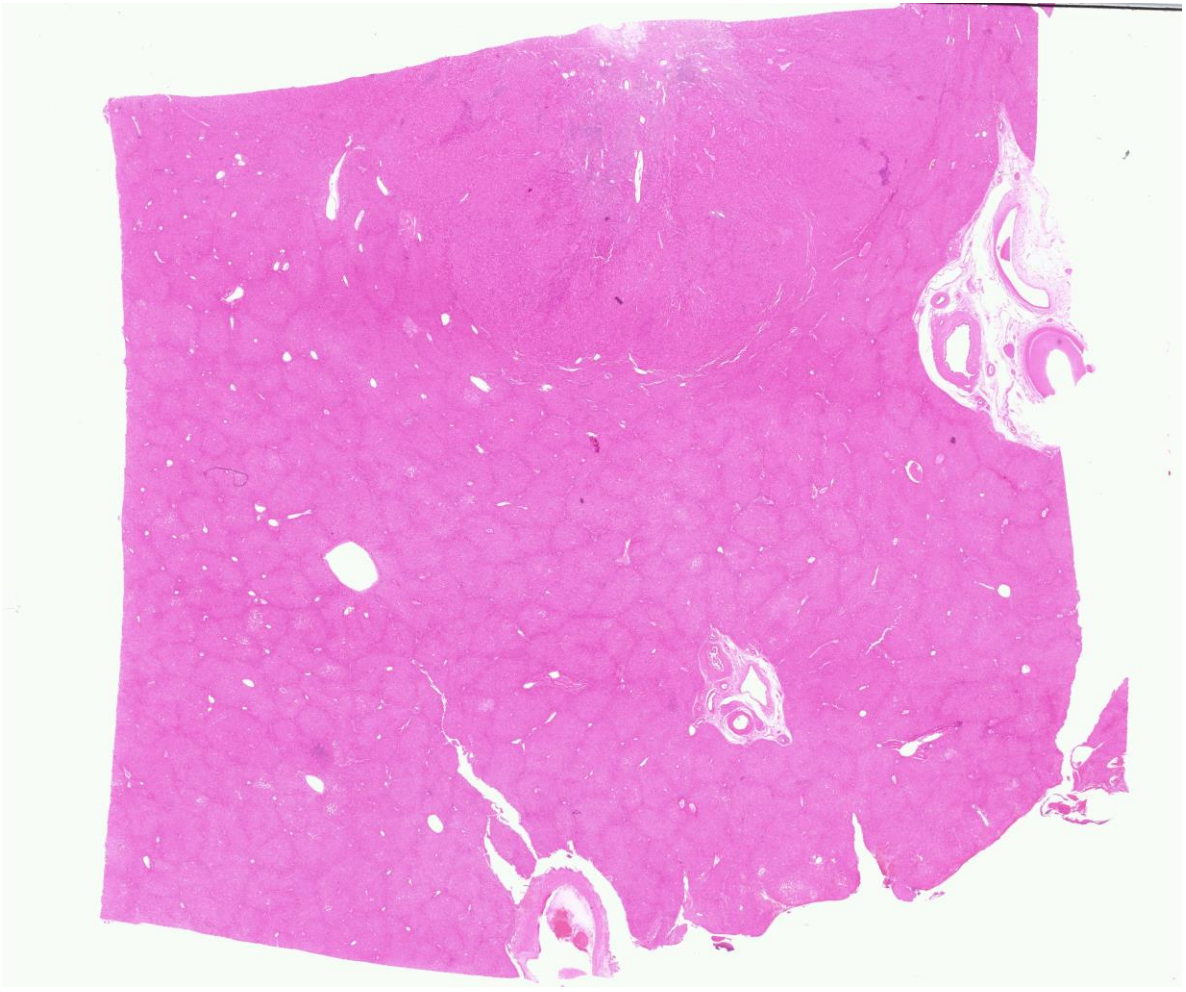
Treatment steroids and ursodeoxycholate. IgG and enzymes decreasing

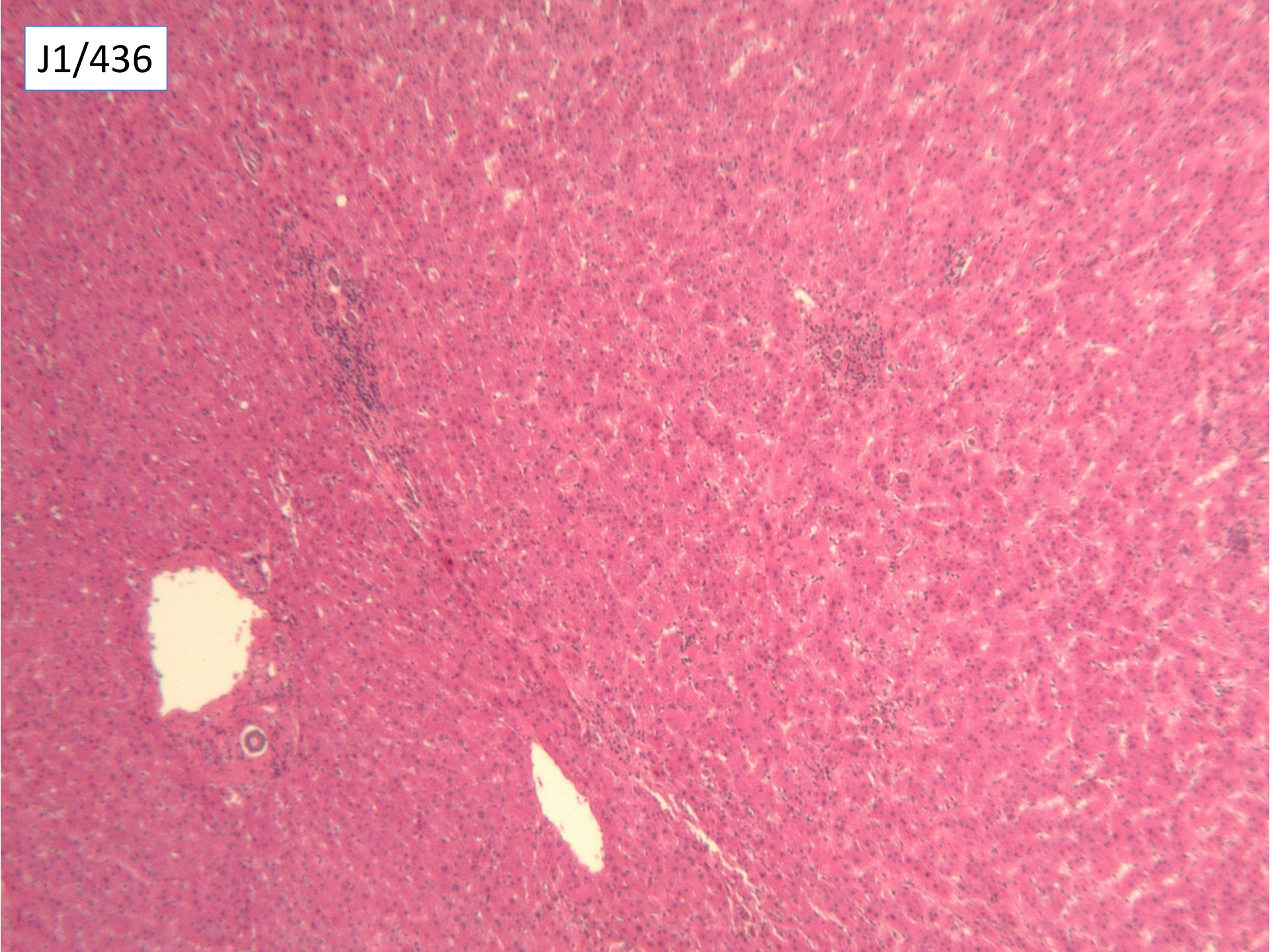
Discussion: one portal tract with marked inflammation and bile duct lesion. ? Is this sufficient to suggest overlap with primary biliary cirrhosis. This requires clinical information (? raised Alk phos) and Shikata stain or CK7, insufficient evidence on the slide provided.

See case J1/441 for masterclass discussion of atypical features in autoimmune hepatitis.

Case J1/436 Age 68, Female

Right Hemihepatectomy and gallbladder Hemihepatectomy weighing 613g and M 15 x 9 x 10 cm. Slicing reveals a well circumscribed yellow nodule with a multilobular contour measuring 2.8 x 2 x 1.5cm. Uninvolved liver has a normal cut surface.

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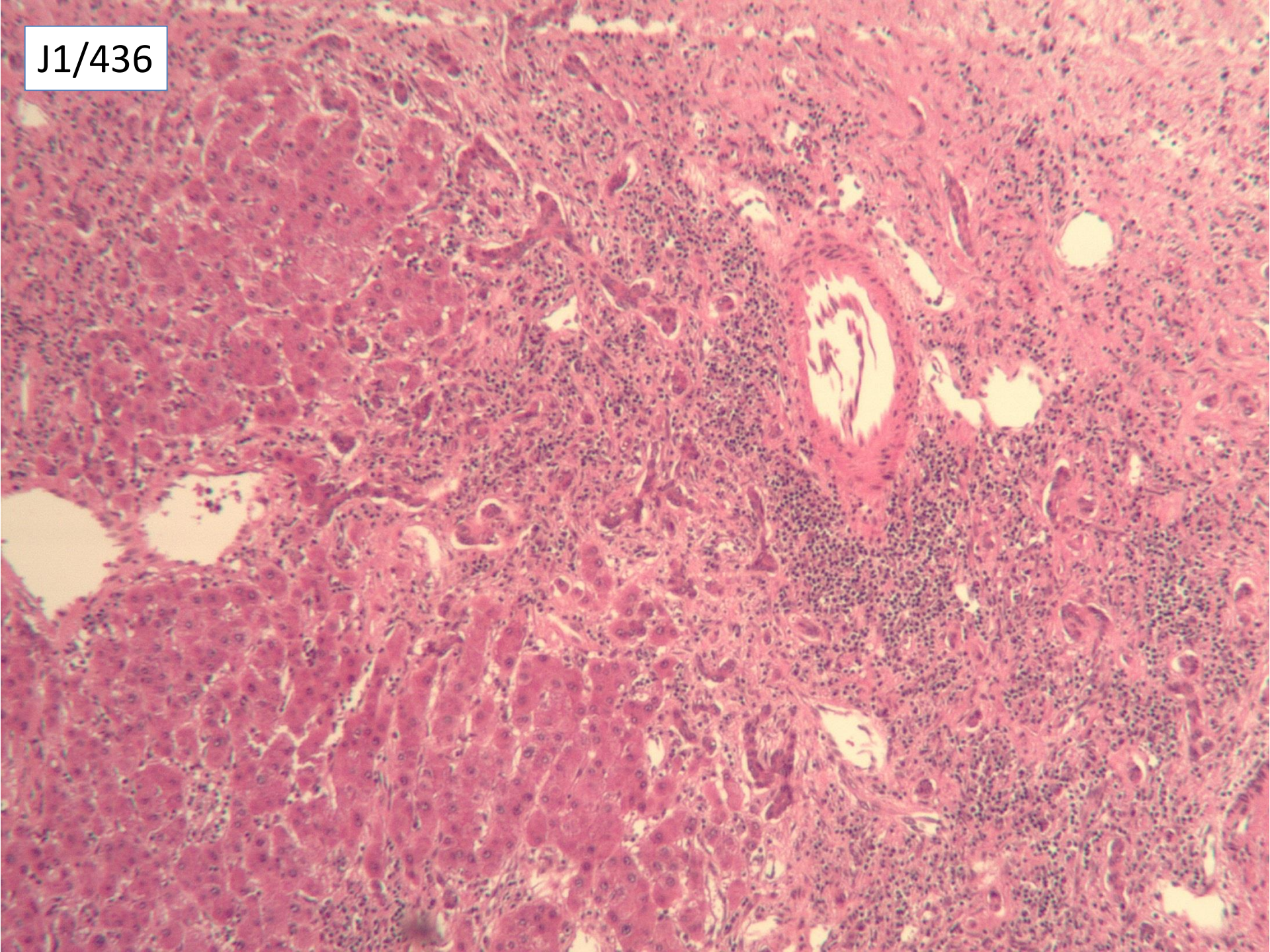
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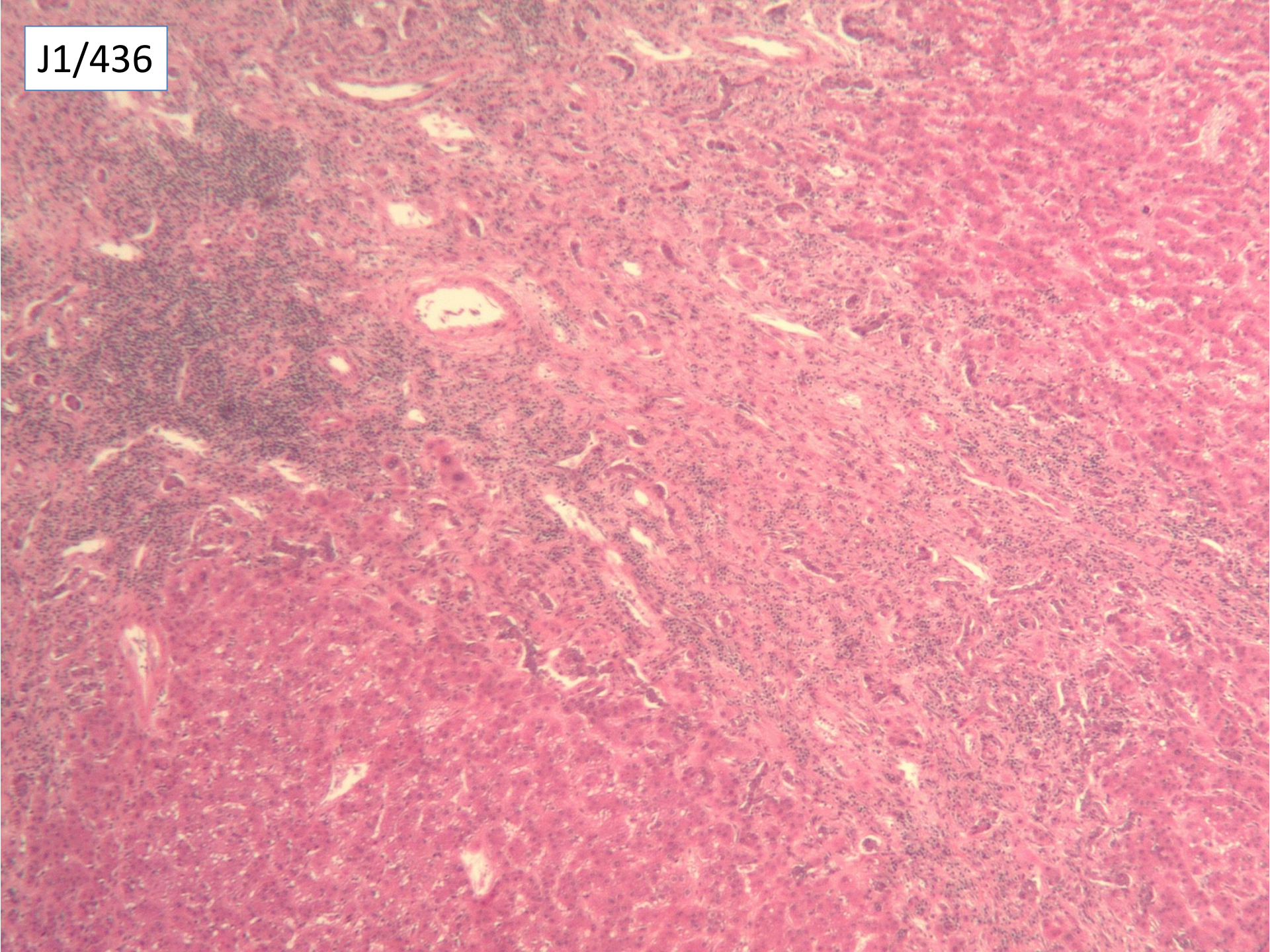
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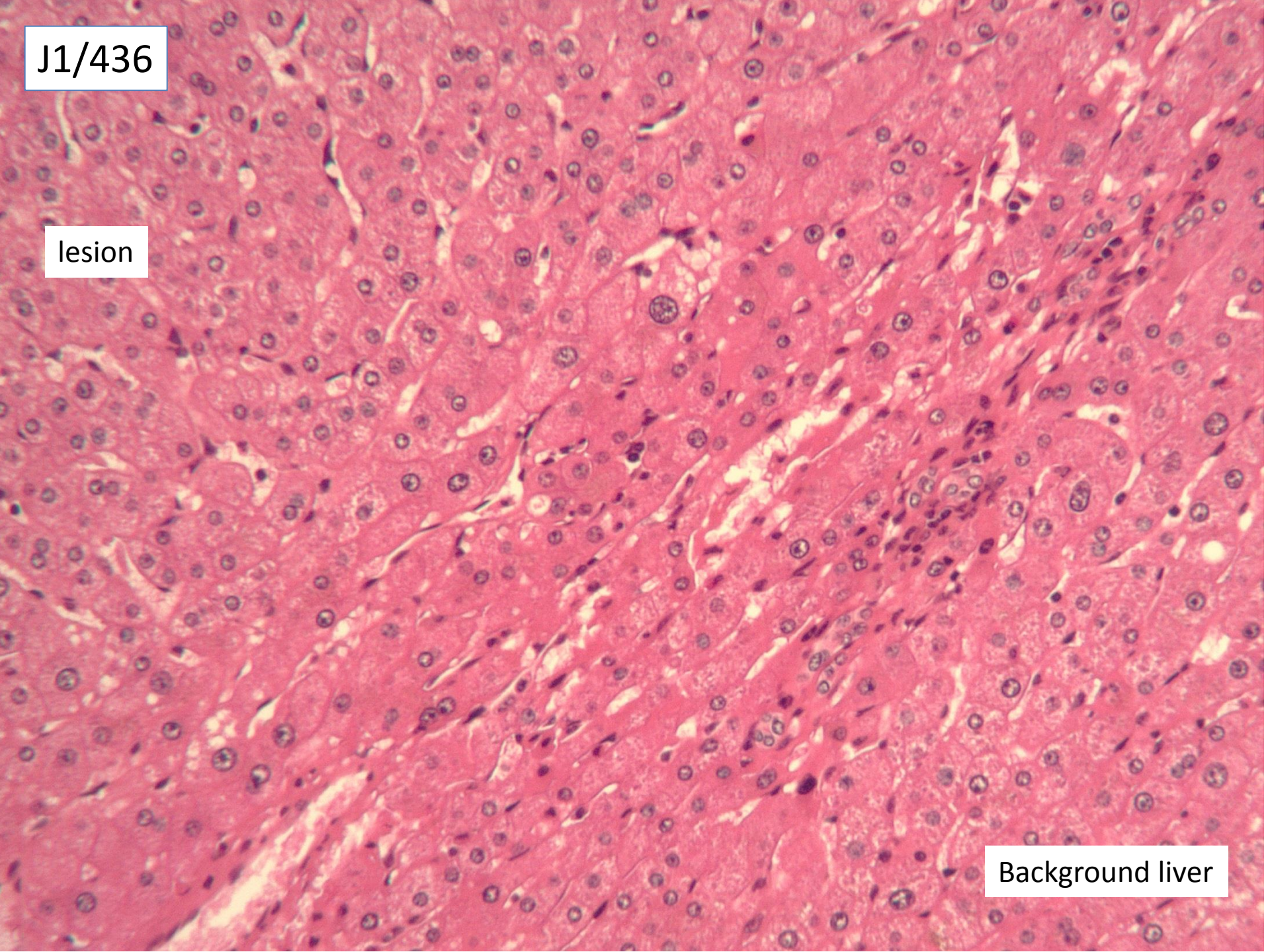
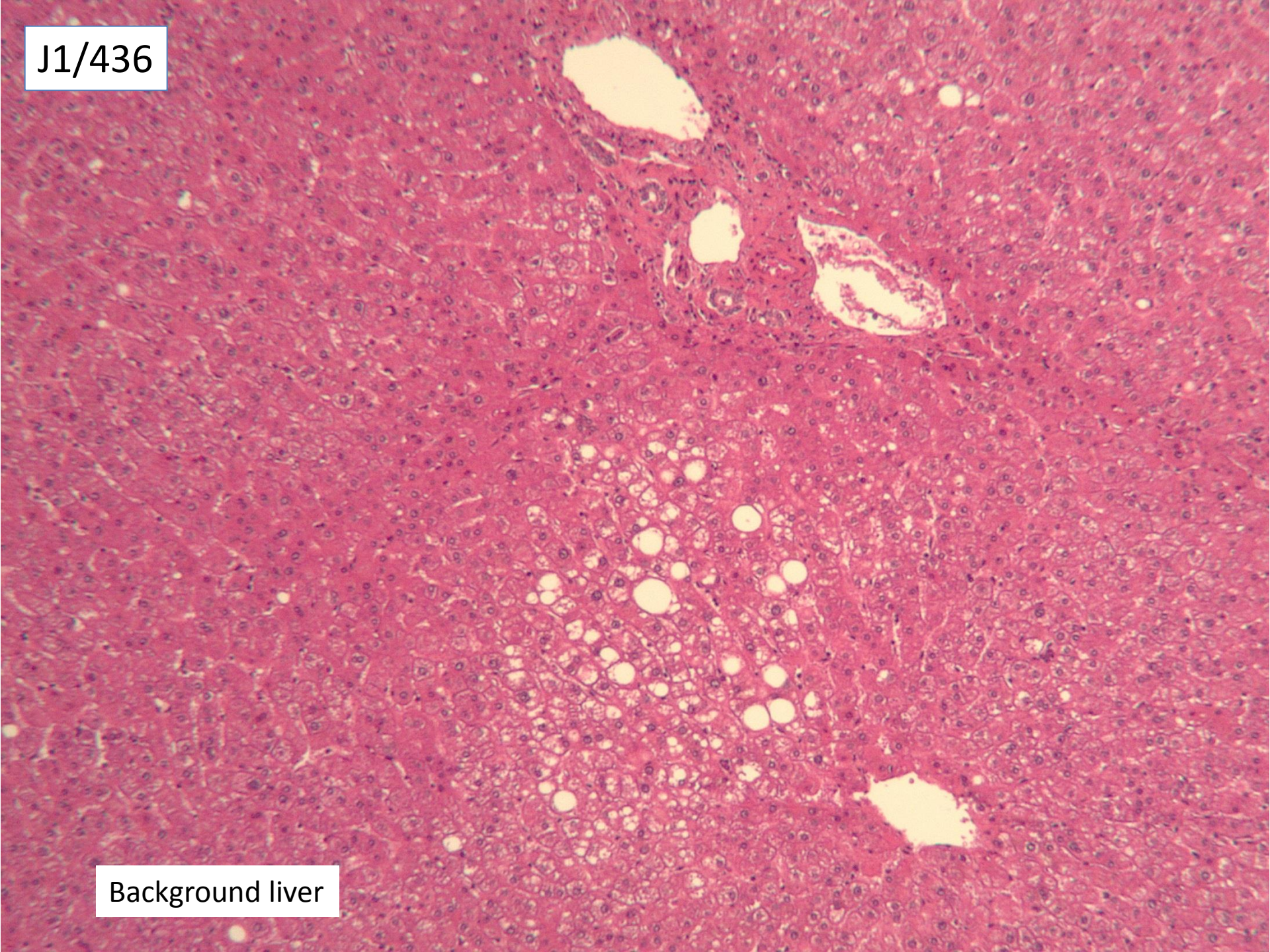
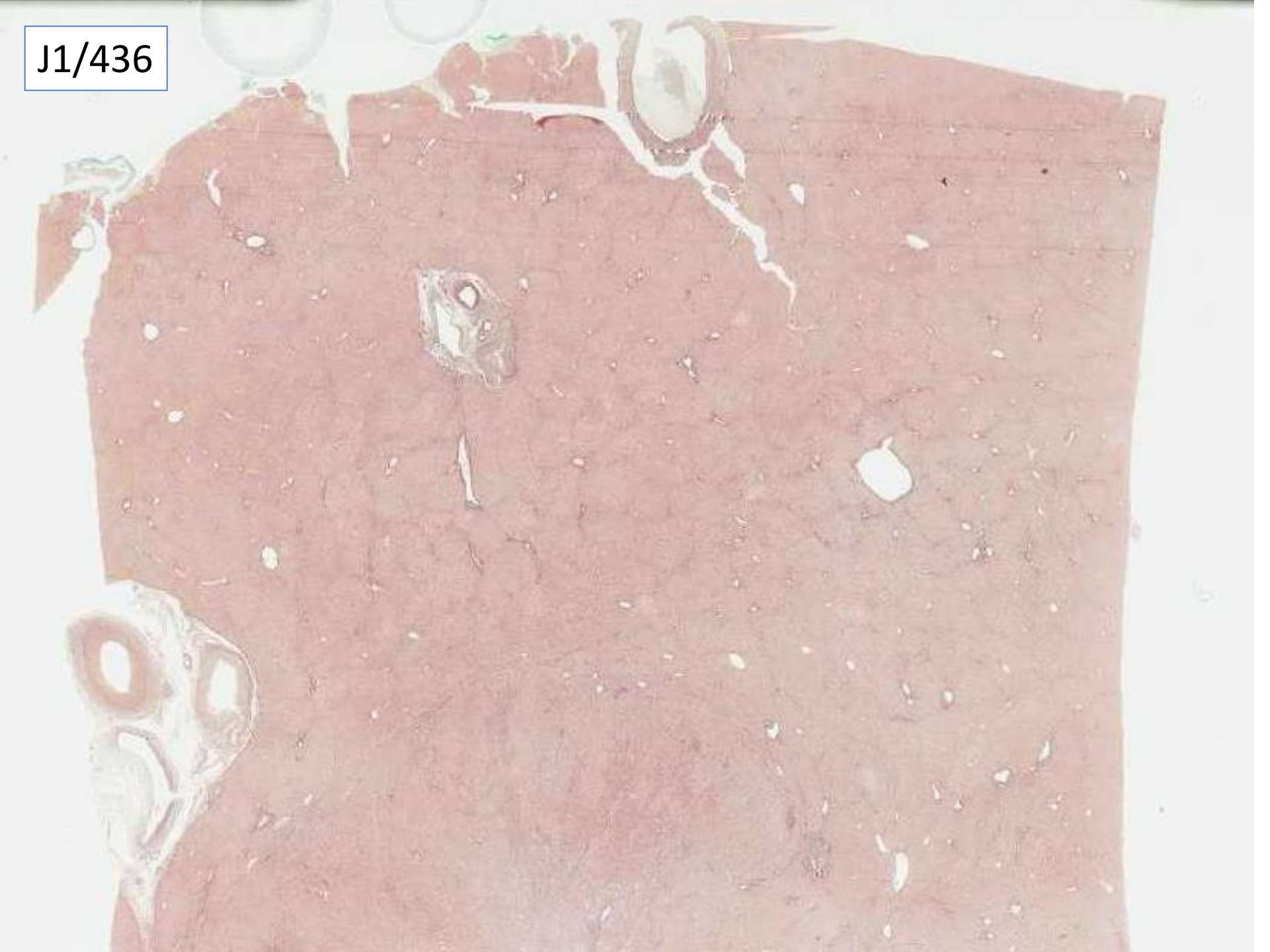
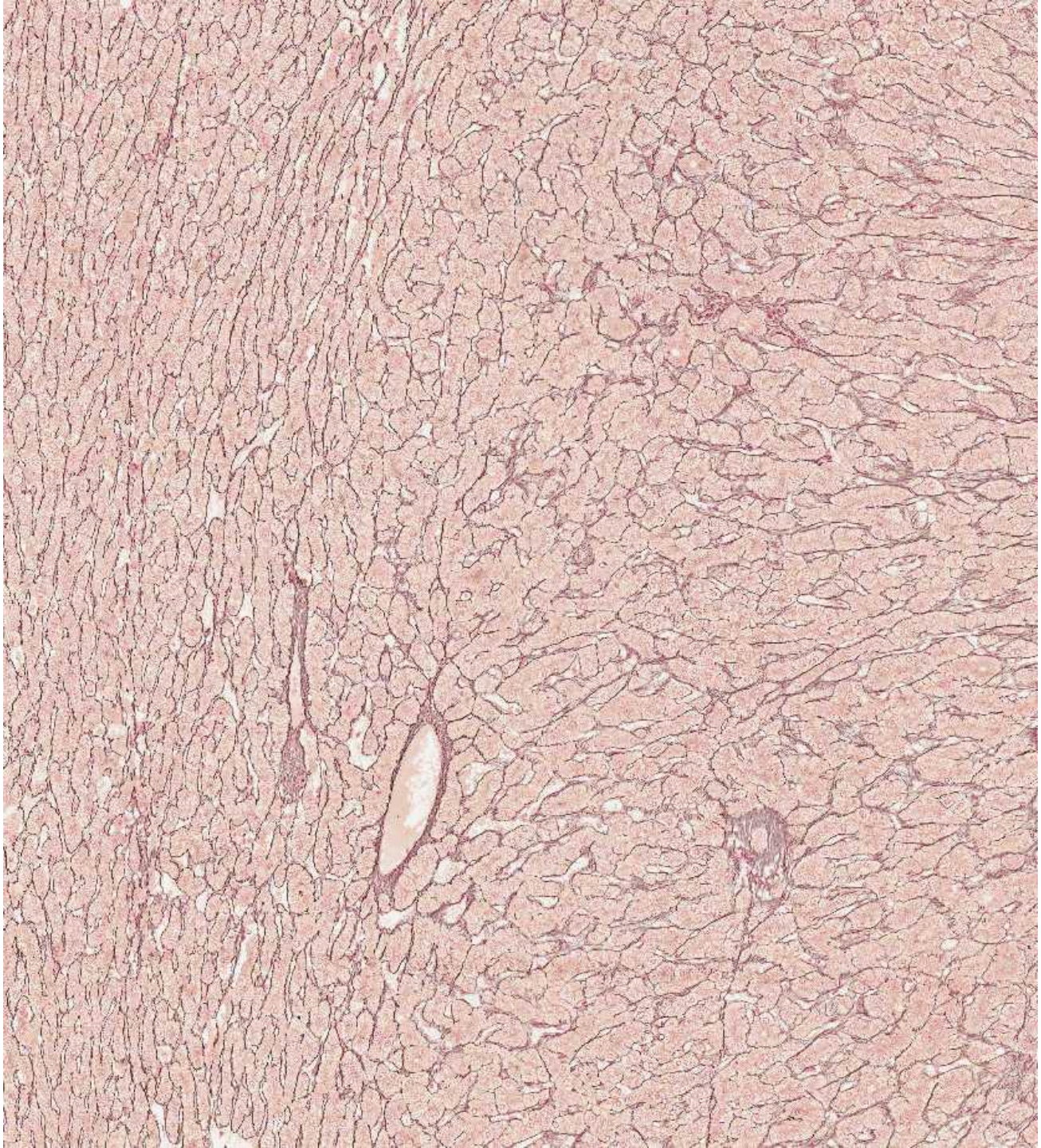

J1/436
lesion
Background liver


J1/436
Background liver


J1/436

J1/436



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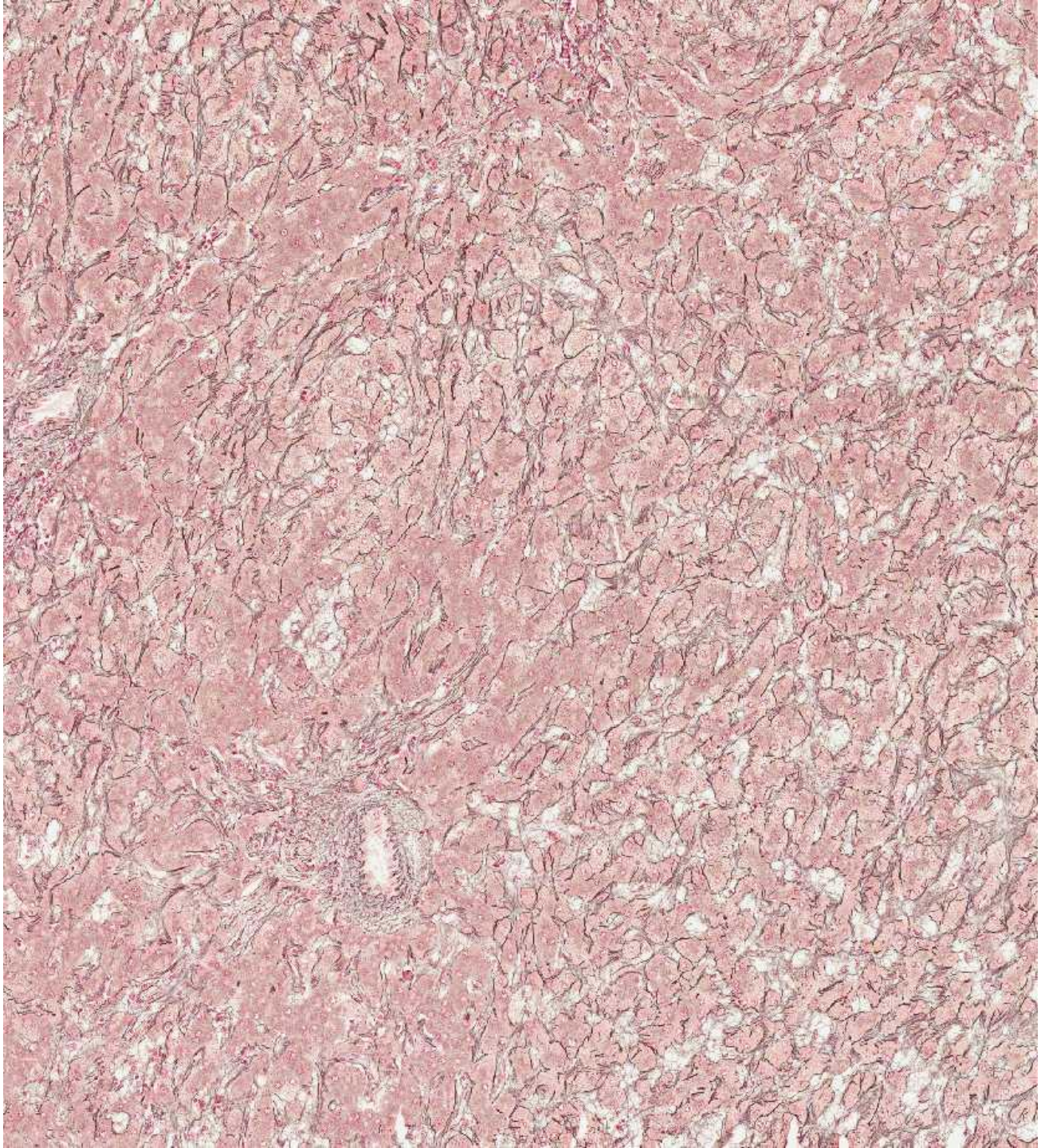


Case J1/436 Age 68, Female

Right Hemihepatectomy and gallbladder Well circumscribed yellow nodule with a multilobular contour measuring 2.8 max

66 focal nodular hyperplasia

9 most likely focal nodular hyperplasia, differential

2 liver cell adenoma

1 FNH or other benign lesion

1 variant of FNH/NRH

1 differential between inflammatory adenoma and FNH – immunos

1 differential between FNH and fibrolamellar carcinoma – favour FNH

1 ?mixed cholangio and well differentiated HCC

50 background not mentioned or just 'non-cirrhotic'

11 mild or minimal steatosis

1 steatohepatitis

5 normal

5 do glutamine synthetase

7 immunohistochemistry to exclude inflammatory adenoma – SAA etc.

Comment: Score 10 points for FNH as only or favoured diagnosis. No points for malignant or definite diagnosis of adenoma. 5 points for unclear diagnosis or malignant differential.

11/14 agree, 0 unsuitable

Case J1/436 Age 68, Female

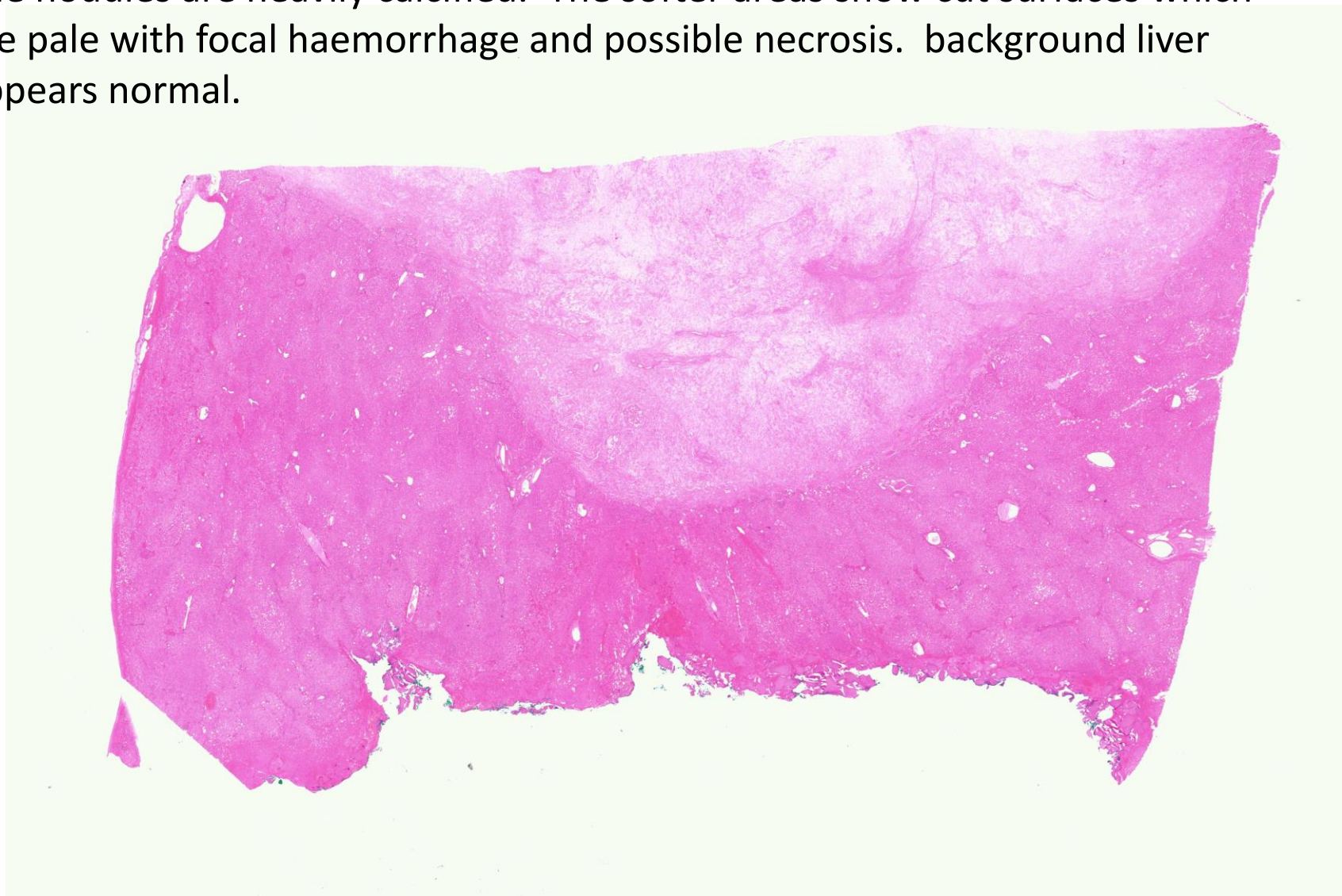
Right Hemihepatectomy and gallbladder Well circumscribed yellow nodule with a multilobular contour measuring 2.8 max

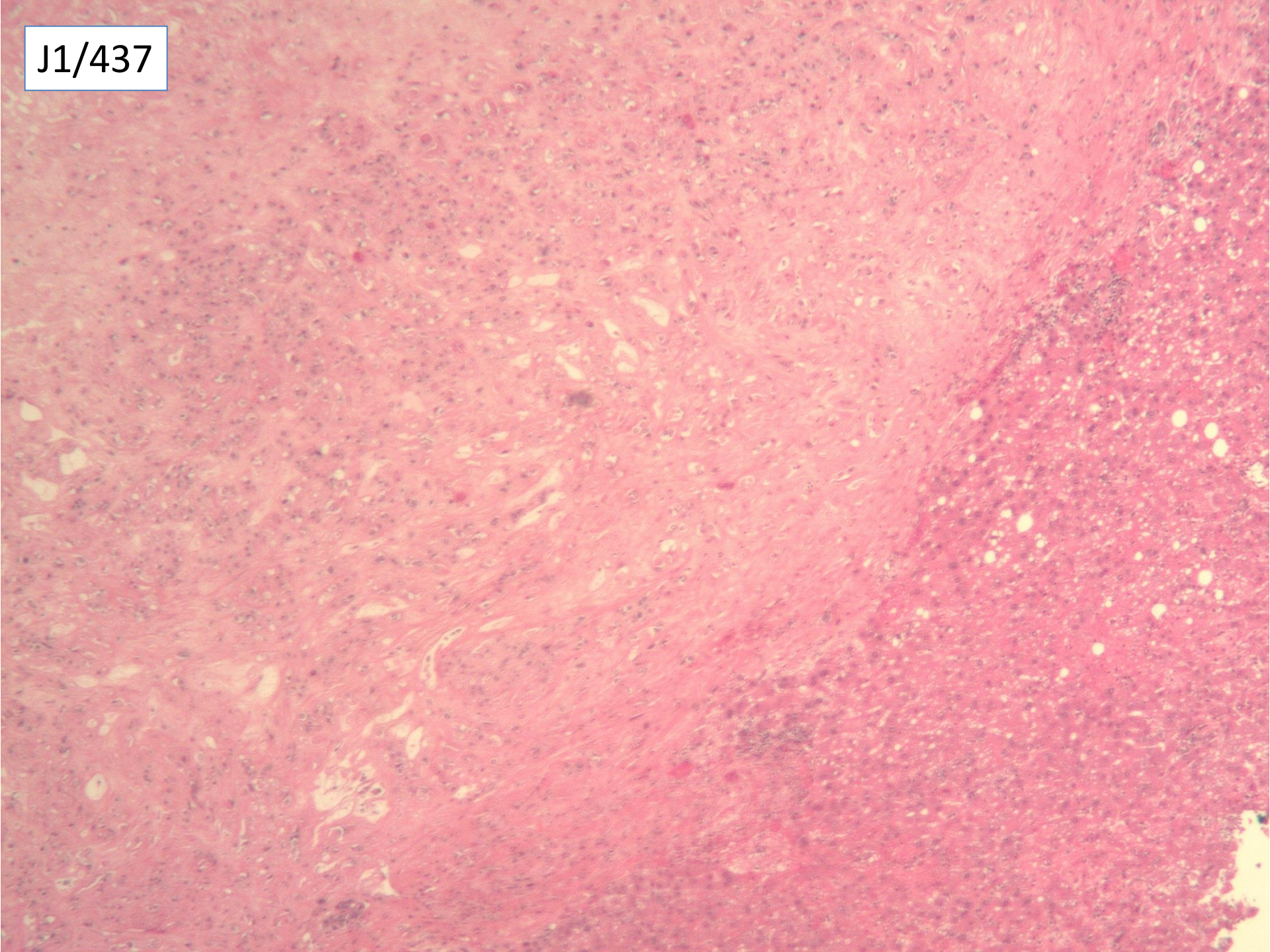
- Original diagnosis: focal nodular hyperplasia.
- Comment: characteristic features of FNH, considered sufficient for diagnosis on H&E in this case.

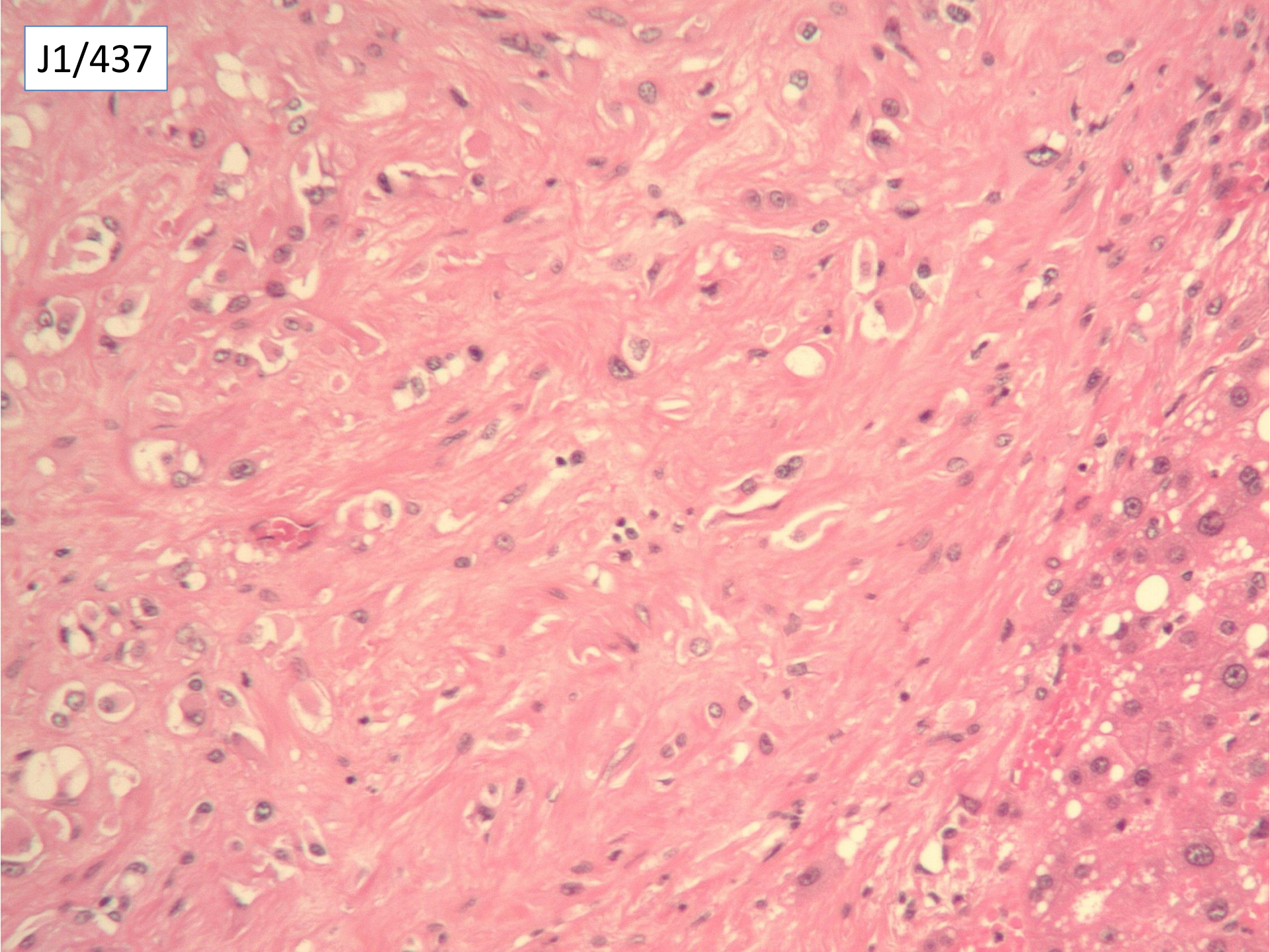
Case J1/437 Age 64, Female

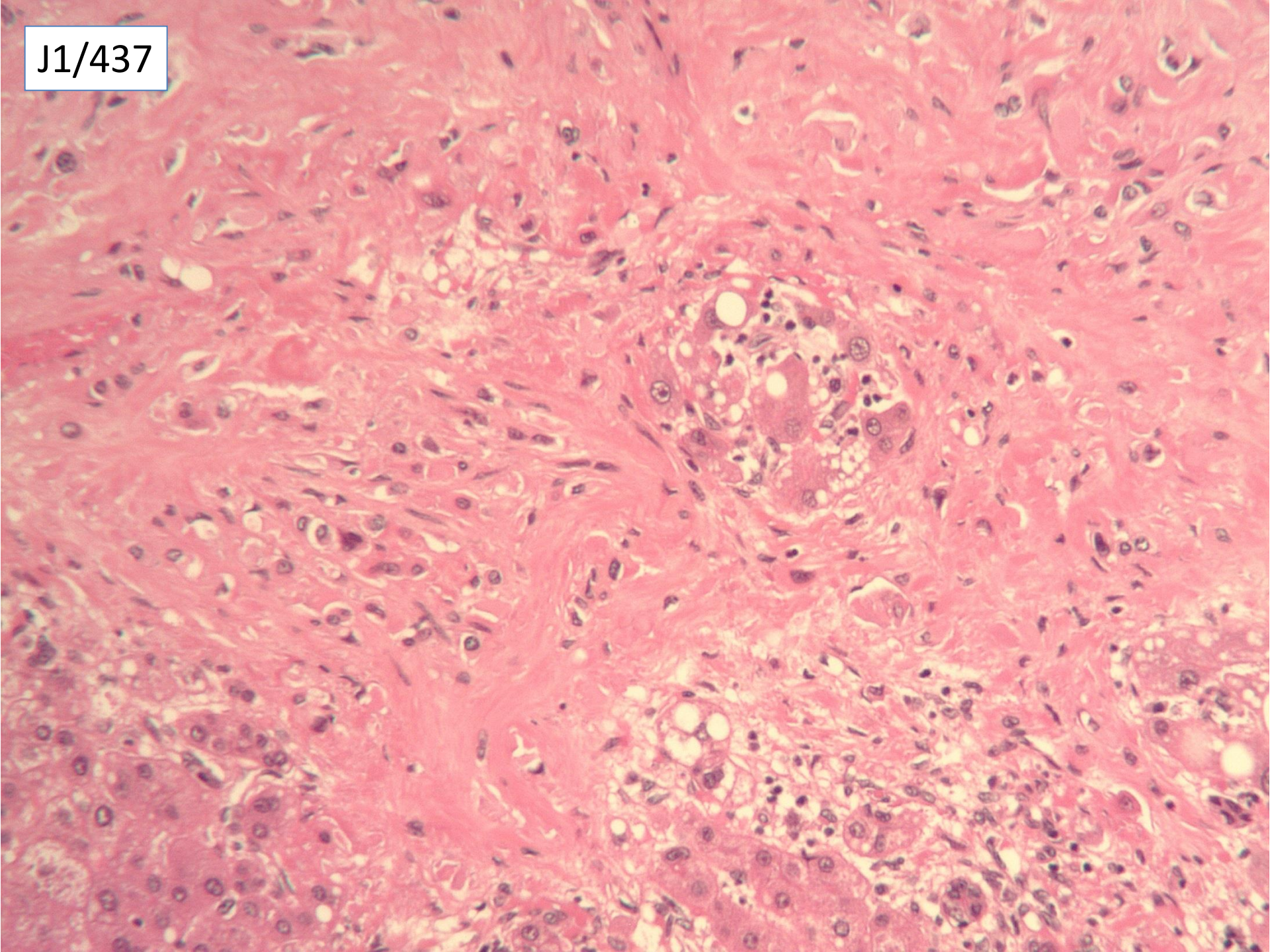
Colorectal liver mets?? Previous colectomy Right hepatectomy.

On slicing the liver contains 3 separate nodules 1.5, 2.7 and 6.8cm across. The nodules are heavily calcified. The softer areas show cut surfaces which are pale with focal haemorrhage and possible necrosis. background liver appears normal.




J1/437


J1/437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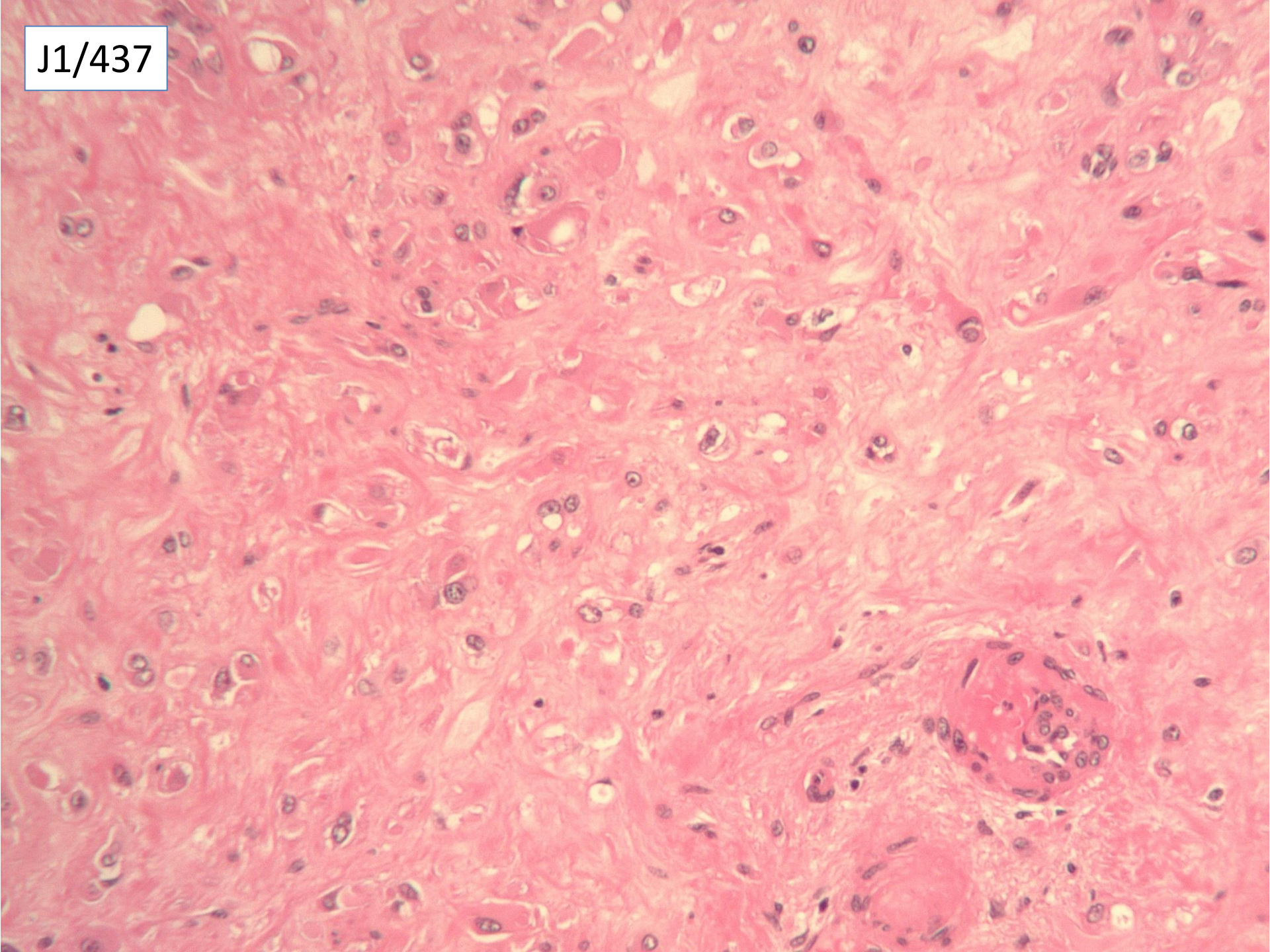
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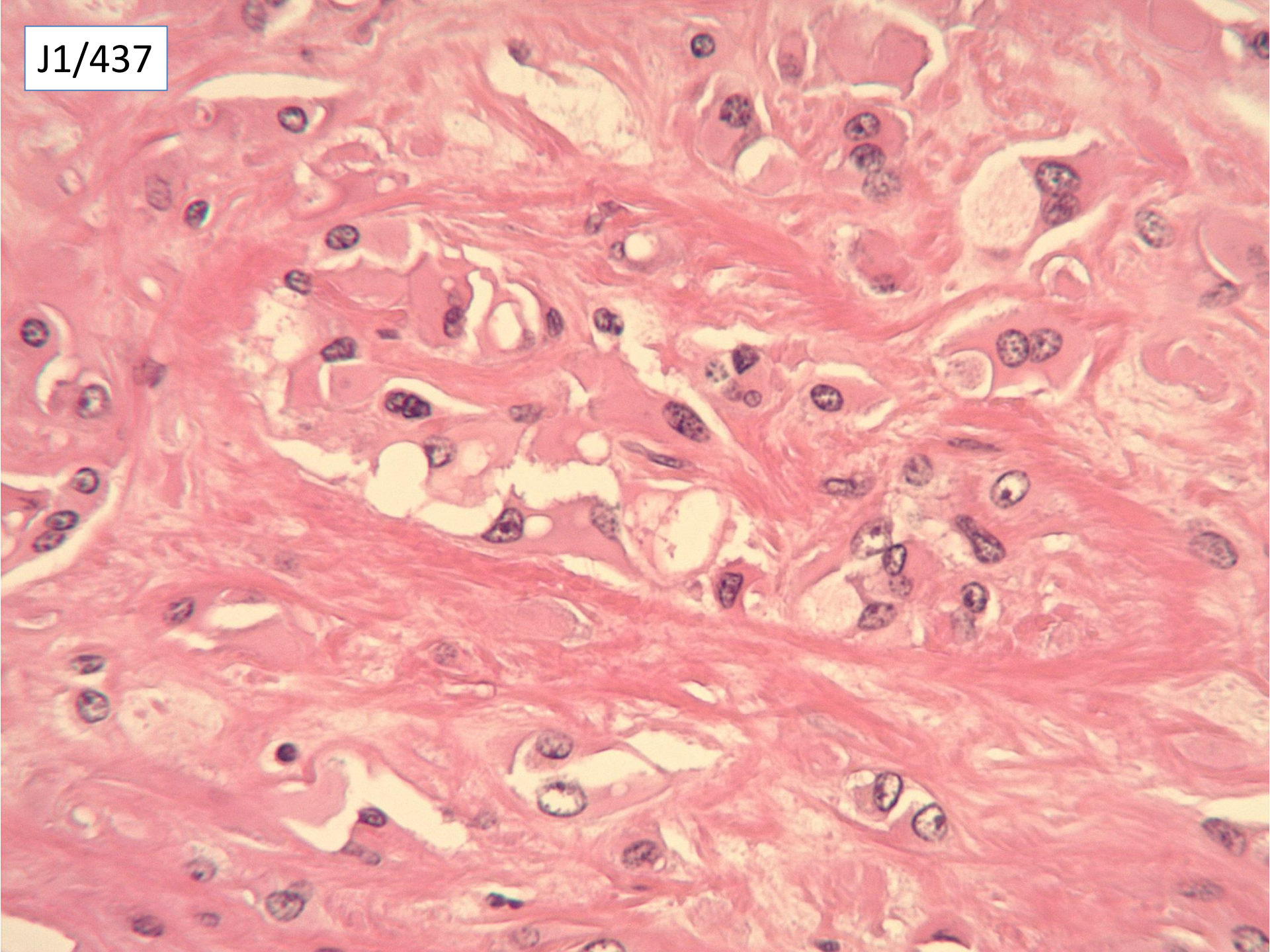
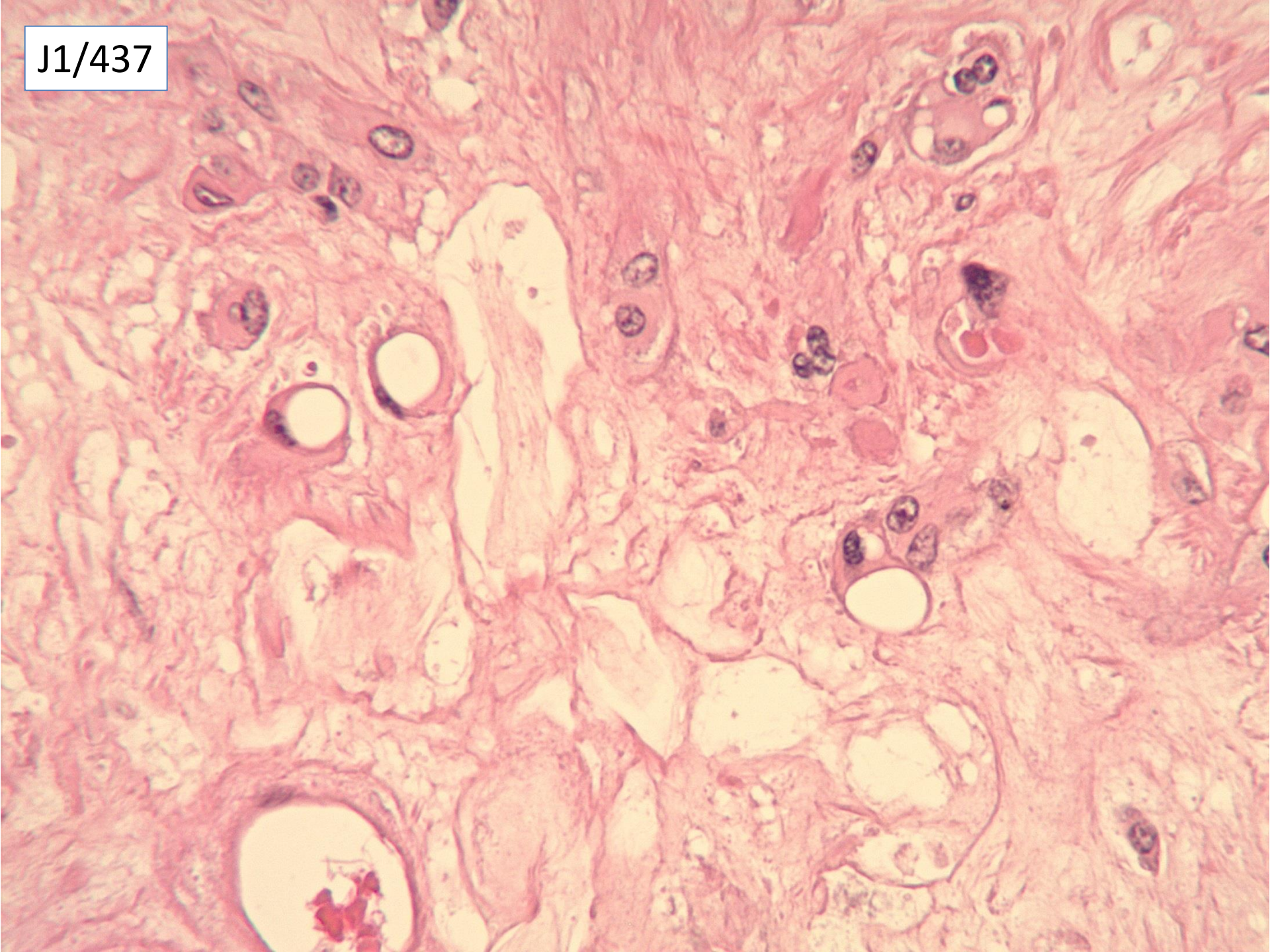

J1/437


J1/437

Case J1/437 Age 64, Female

Colorectal liver mets?? Previous colectomy Right hepatectomy.

48 haemangioendothelioma – as only or most likely neoplastic diagnosis

9 differential diagnosis that includes haemangioendothelioma

13 metastatic colorectal cancer with complete response to therapy (?chemo, embolization)

3 suggests complete response but odd – do immunos

1 angiosarcoma

1 angiomyolipoma, needs immunos

1 HCC – fibrolamellar

1 sarcoma

3 wide differential diagnosis of malignant lesions not including EHE

2 ? embolization material in background liver

1 "cannot do this with the available information – don't want it to be scored"

1 "I don't see resections, please disregard for scoring"

5/14 agree, 6 unsuitable

Comment: consensus response is haemangioendothelioma, but insufficient for 80% majority so this is unsuitable for scoring. Alternatively – score 0 for definite diagnosis of metastatic CRC with complete response to therapy or fibrolamellar HCC. Discussion – score 5 for angiomyolipoma with immunos. Discussion – majority voted to score this case

Case J1/437 Age 64, Female

Colorectal liver mets?? Previous colectomy Right hepatectomy. 3 separate nodules up to 6.8cm, heavily calcified. The softer areas are pale with focal haemorrhage

Original diagnosis: Epithelioid haemangioendothelioma (immuno: AE1/AE3 highlights entrapped hepatocytes, hepar1 - unsatisfactory as section has partially washed off. CD31 strongly, diffusely positive in stronmal cells, CD34 - patchy positivity, s100 - weak patchy cytoplasmic positivity)

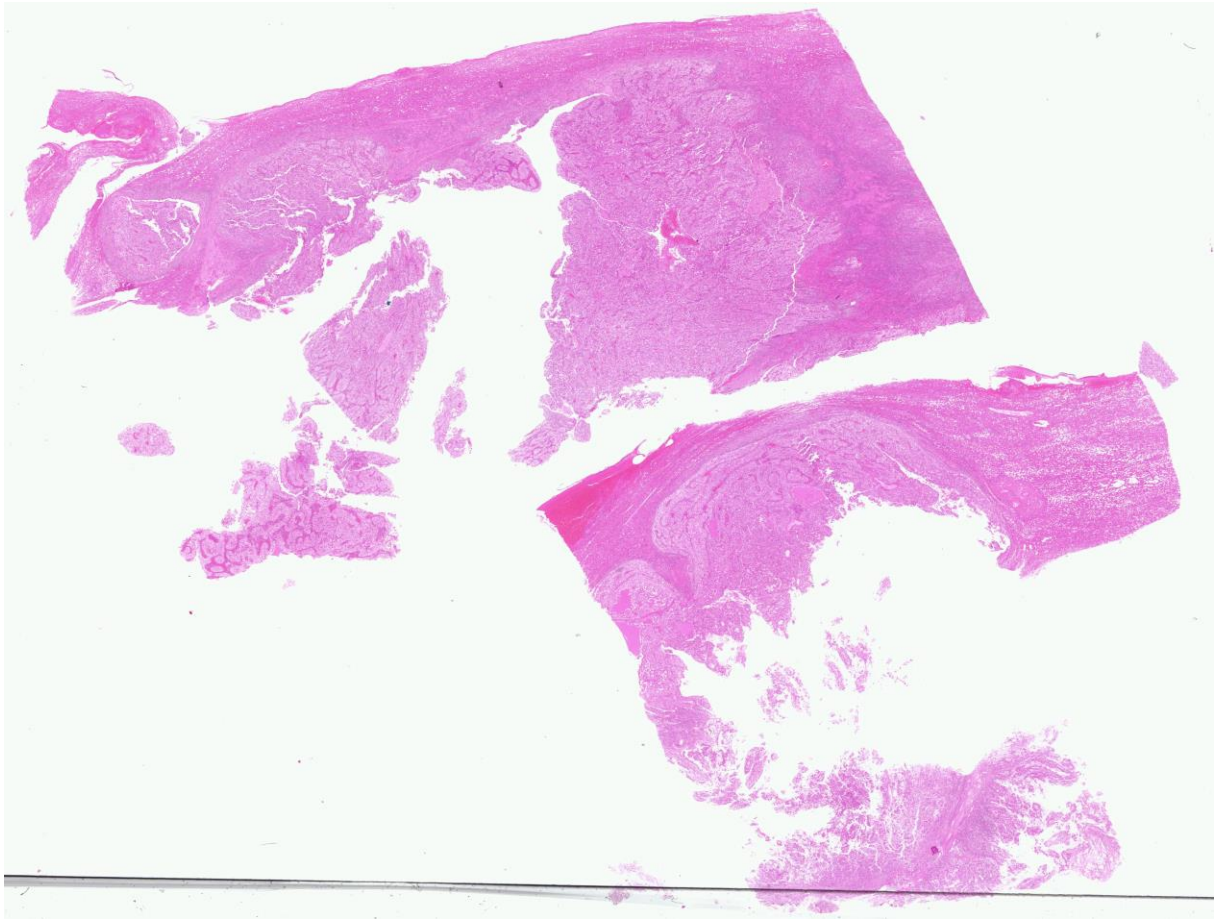
Follow up - scans scheduled, no further information available.

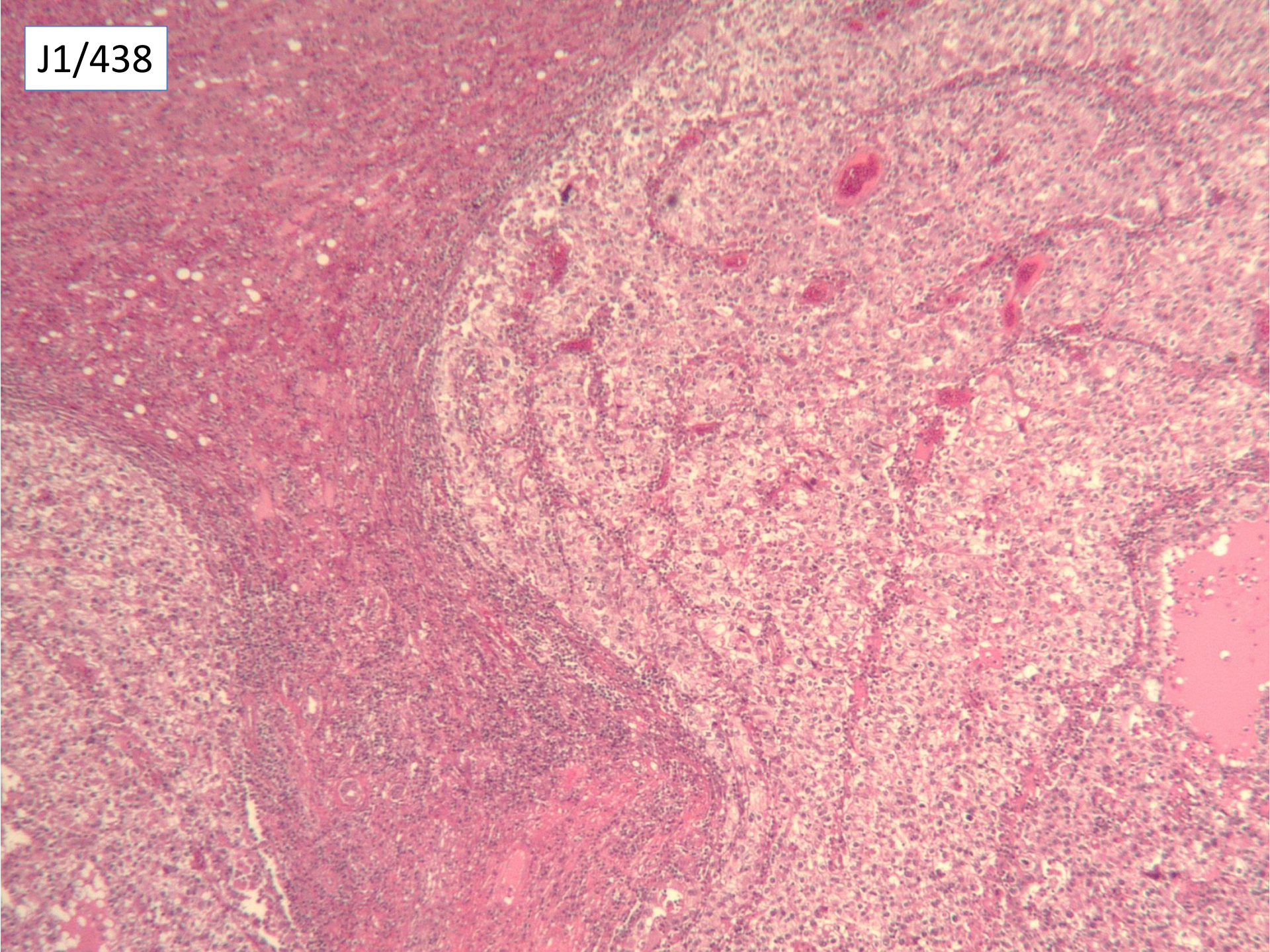
Discussion – debate about whether to score – considered that histology is not suggestive of metastatic CRC altered due to treatment, and sufficient consensus to allow scoring on this point.

CaseJ1/438 Age 49, Female

Liver Ovarian mets Partial hepatectomy measuring 21x15x5cm. Slicing reveals a single tumour 8x8x10cm. The tumour has a pale surface. No other lesions identified. The background liver appears normal.

TAH + BSO in 2004 – clear cell carcinoma of left ovary.

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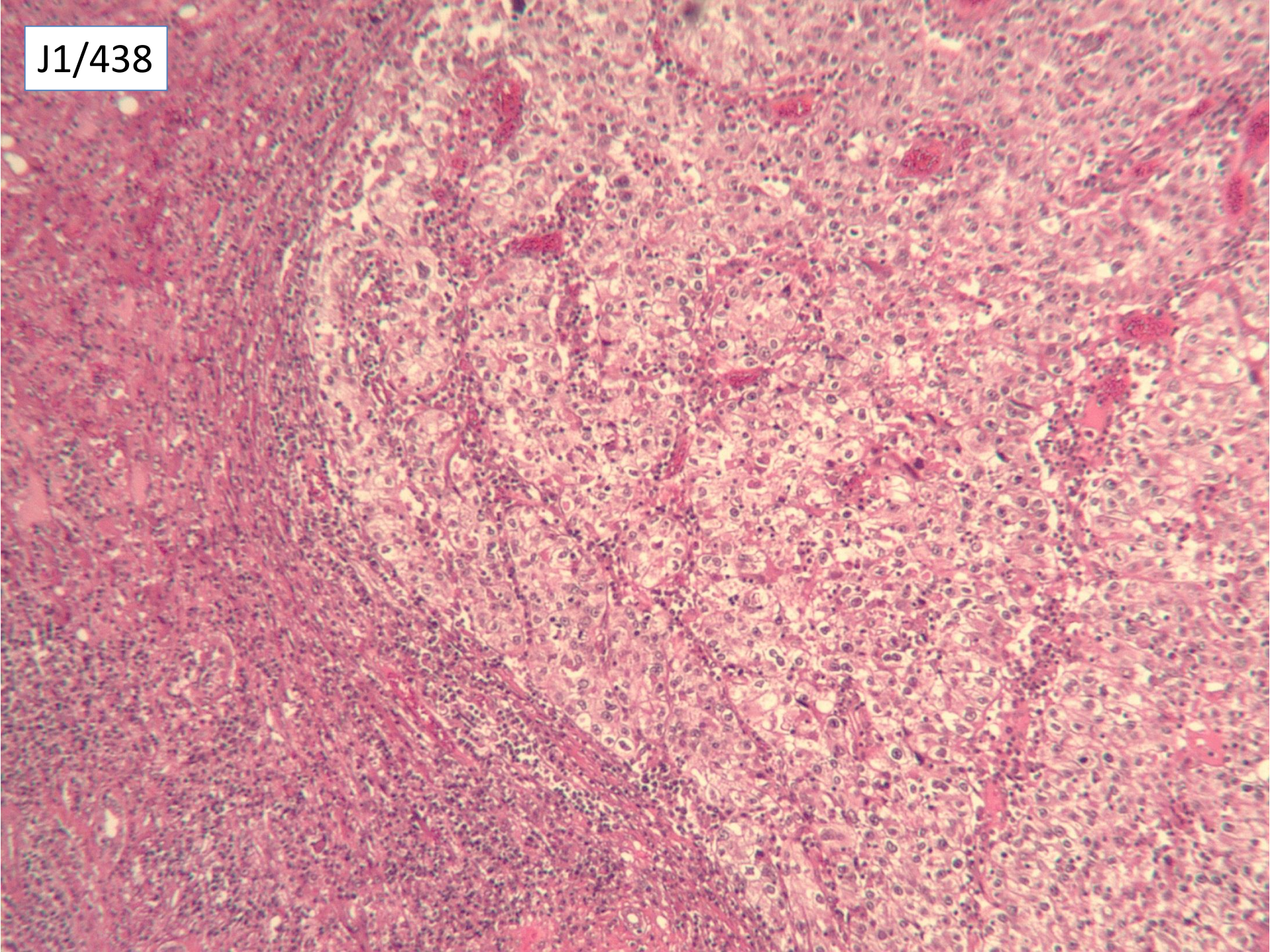
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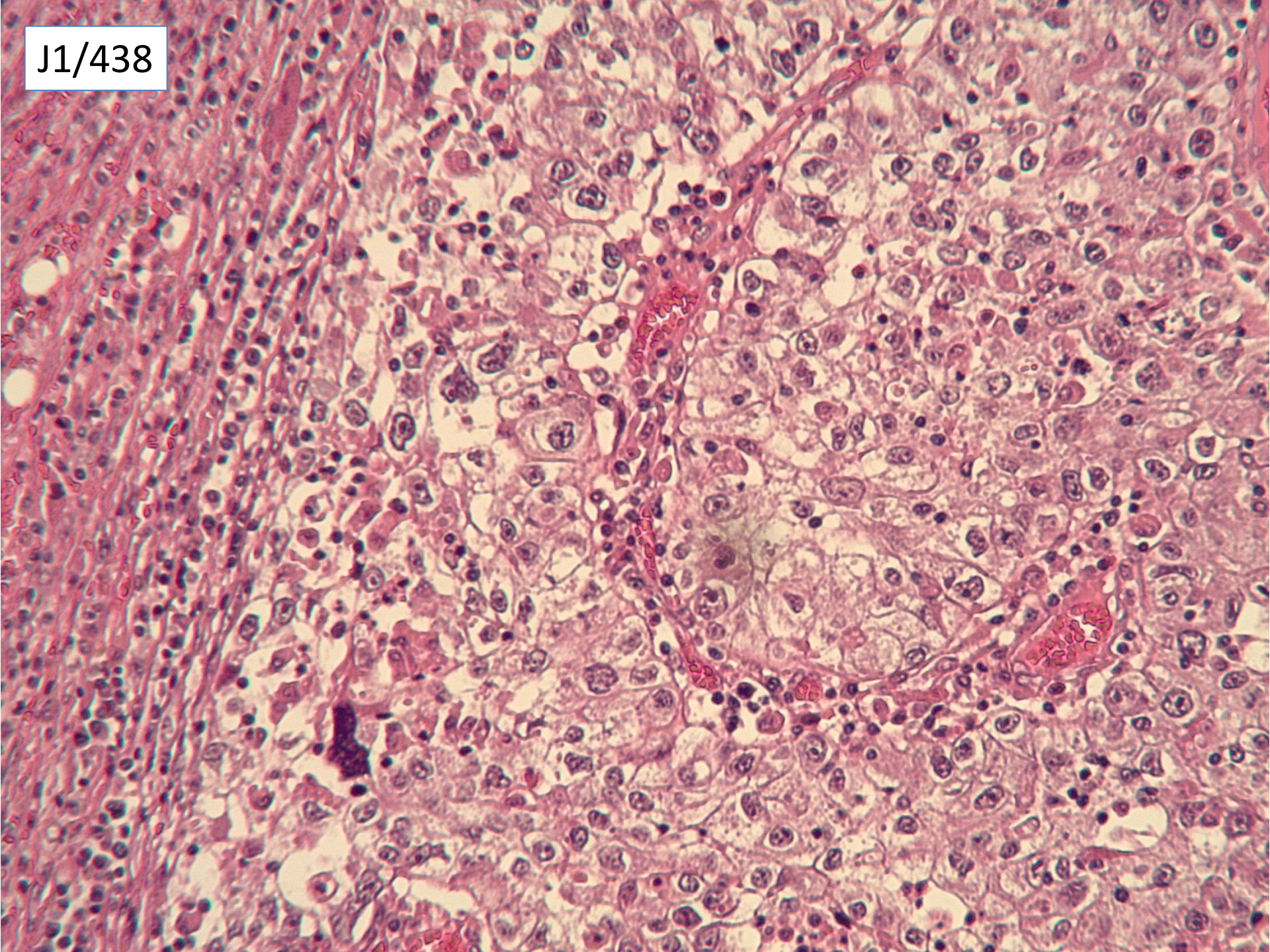
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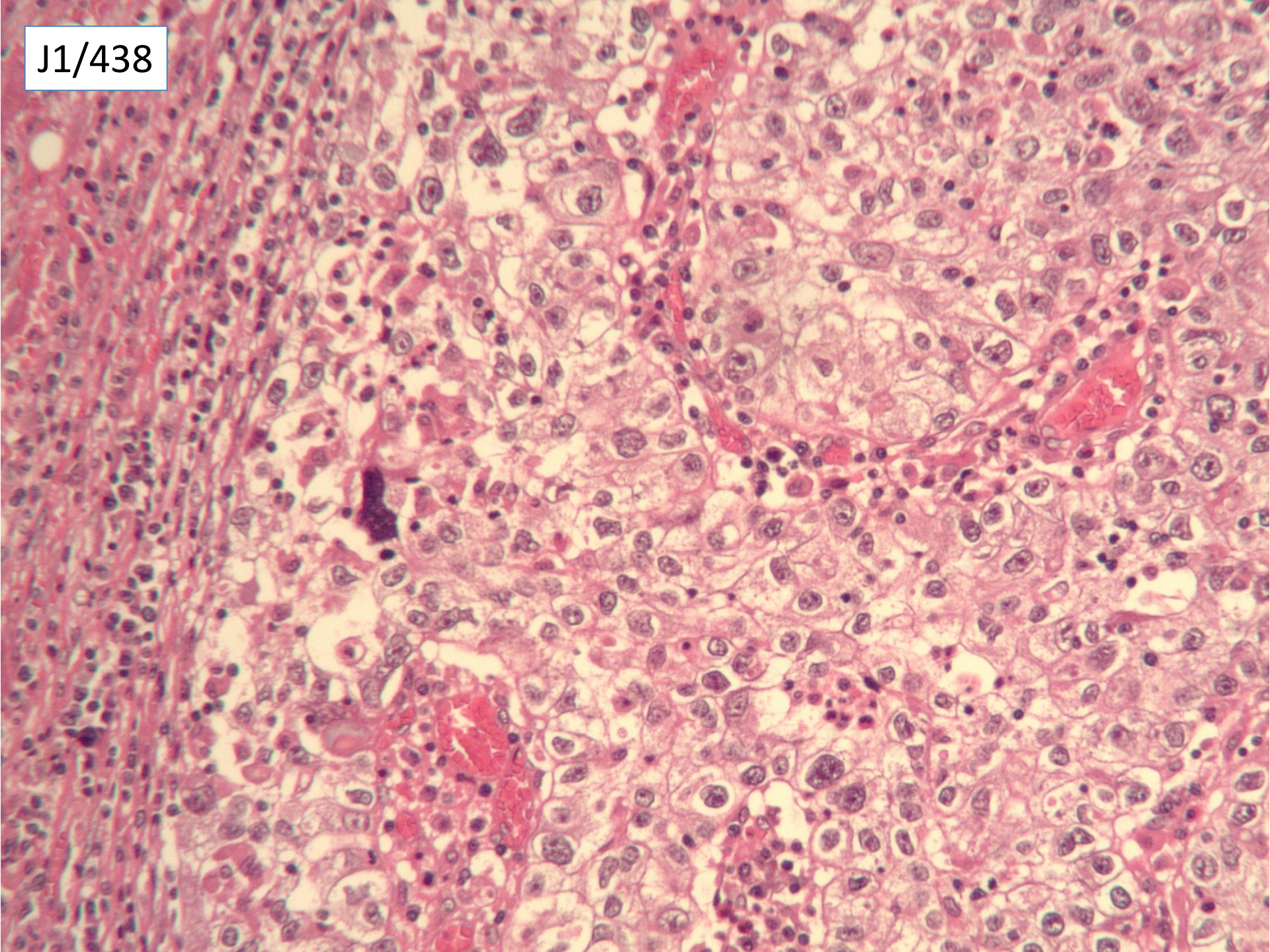
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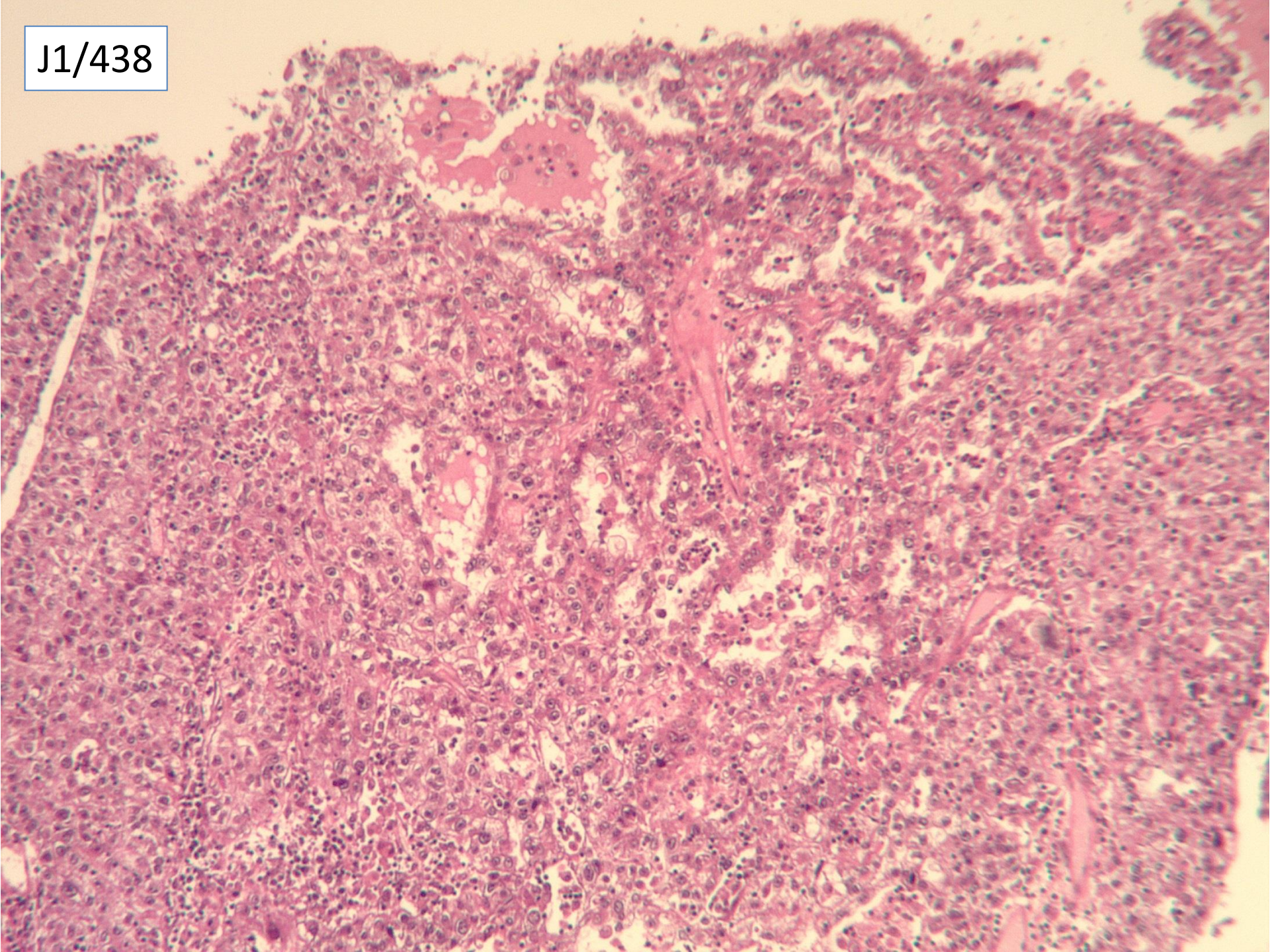

J1/438

CaseJ1/438 Age 49, Female

Liver Ovarian mets single tumour 8x8x10cm. The tumour has a pale surface. No other lesions identified.

TAH + BSO in 2004 – clear cell carcinoma of left ovary.

78 consistent with metastatic clear cell carcinoma of ovary.

2 favours HCC, differential diagnosis of metastasis from ovary

1 metastatic adenocarcinoma NOS

1 metastatic tumour v. HCC, needs immunos

56 commented needs IHC and/or comparison with previous ovarian histology

26 no suggestions for confirmation offered

55 background not mentioned

25 background steatosis

1 background not fatty

1 background = inflammation and fibrosis

3 evidence of embolization

3 commented on long time since primary was removed.

13/14 agree, 0 unsuitable

Suggested scoring : 10 points – consistent with metastasis from ovary.
5 points – favours HCC, with ovarian metastasis in differential diagnosis.
No points for metastatic tumour that doesn't mention ovary.

CaseJ1/438 Age 49, Female

Liver Ovarian mets single tumour 8x8x10cm. The tumour has a pale surface. No other lesions identified.

TAH + BSO in 2004 – clear cell carcinoma of left ovary (7 years earlier).

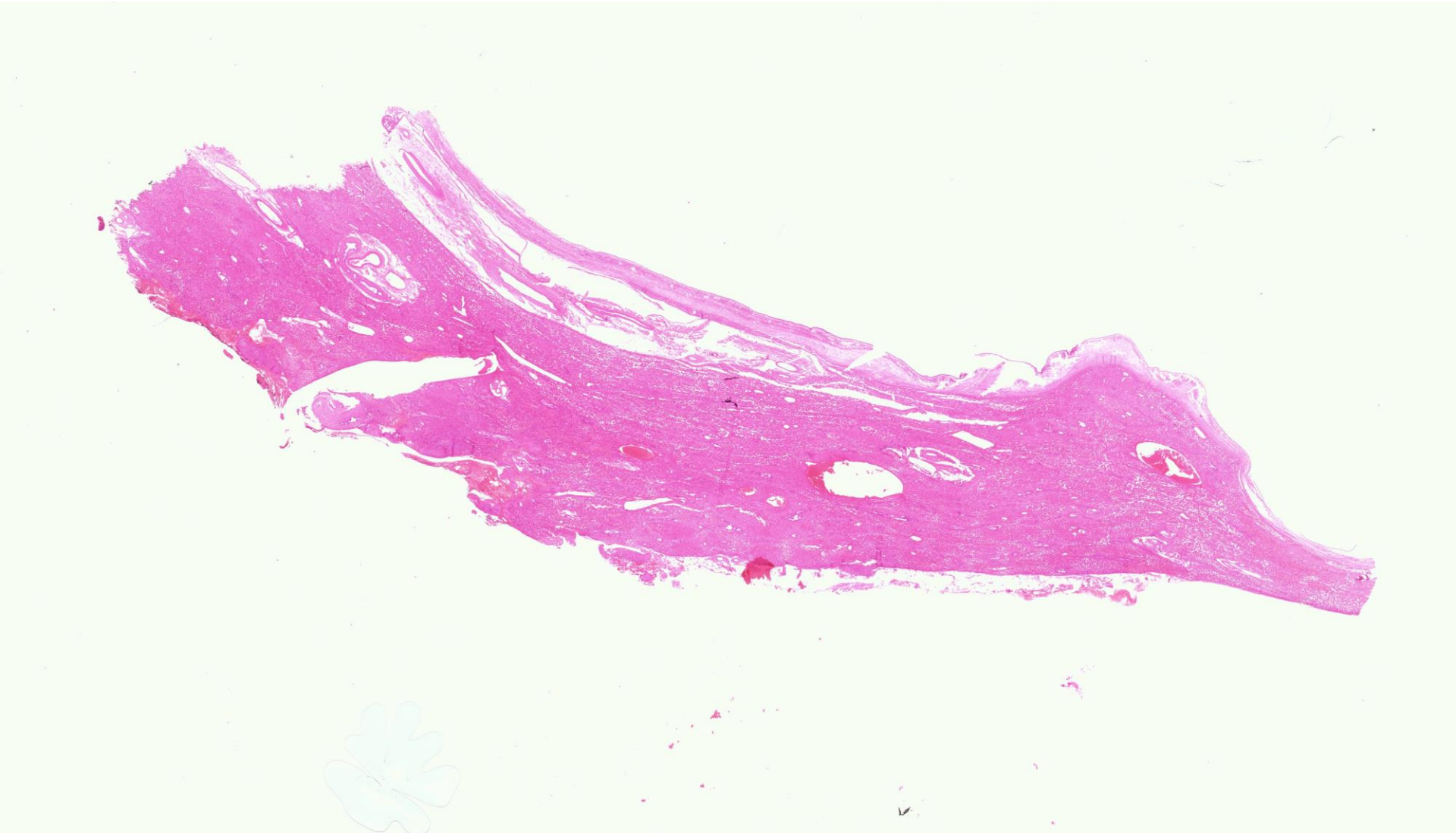
Original diagnosis: metastatic clear cell carcinoma of the ovary

Follow up information: also thought to have extensive lymph node involvement. Ongoing treatment with chemotherapy

Discussion: commented that recurrence >5 years after resection of clear cell carcinoma of ovary would be exceptionally rare. More likely is metastatic renal cell carcinoma – need to exclude a second renal primary.

Case J1/439 Age 27, Female

Lesion in segment 2 septate cyst 145x110x125mm smooth walled, containing serous fluid



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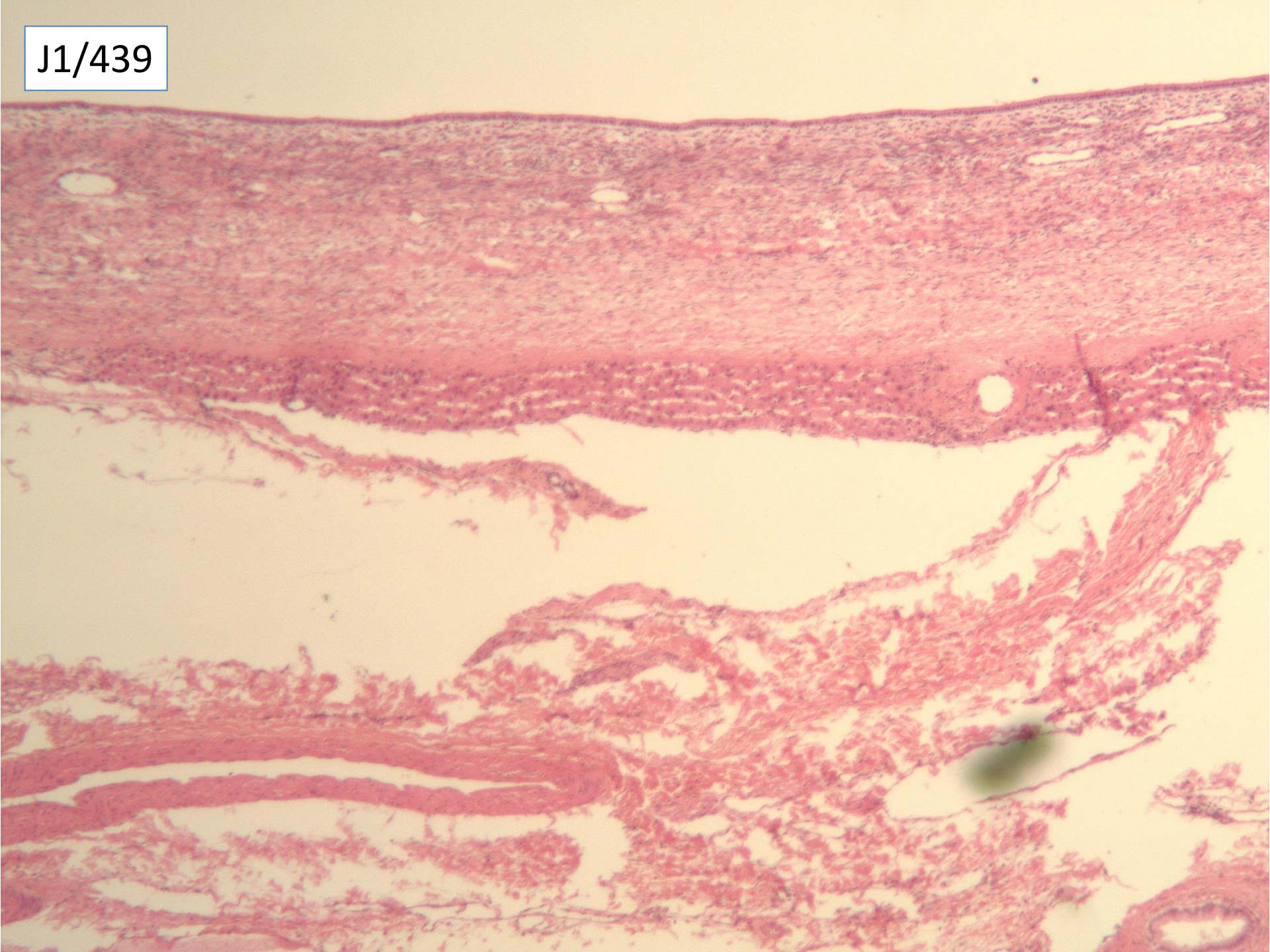

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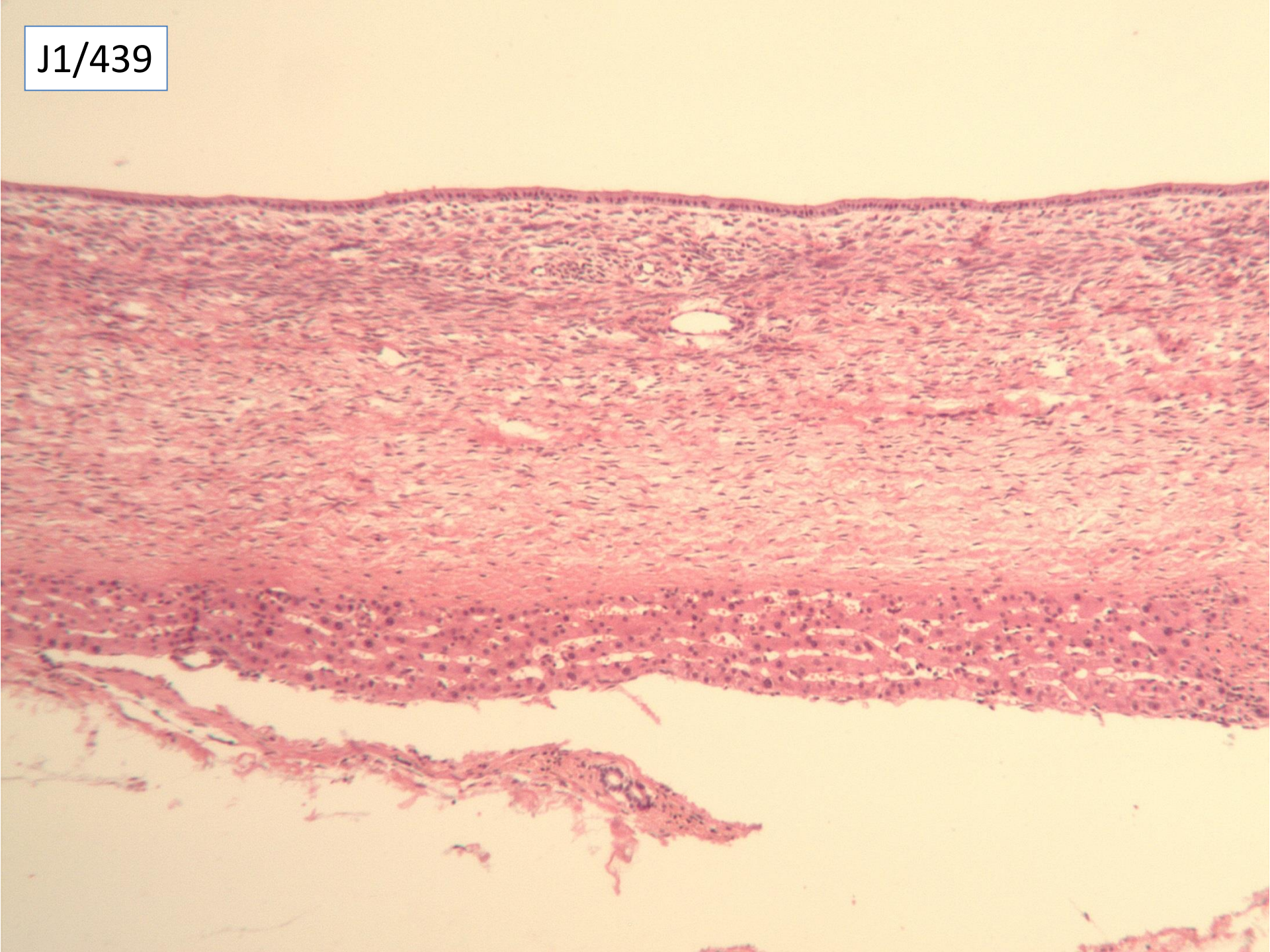
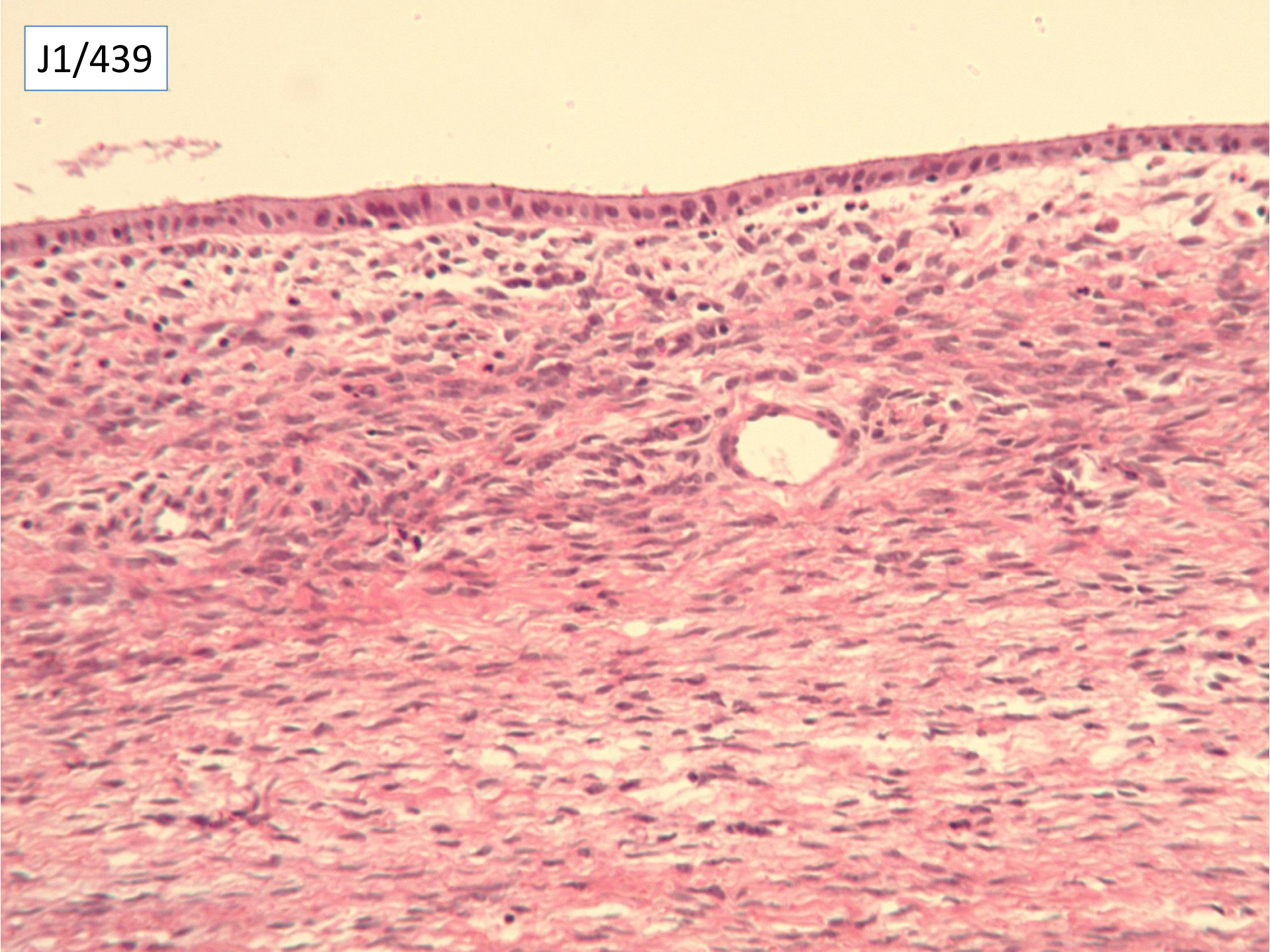
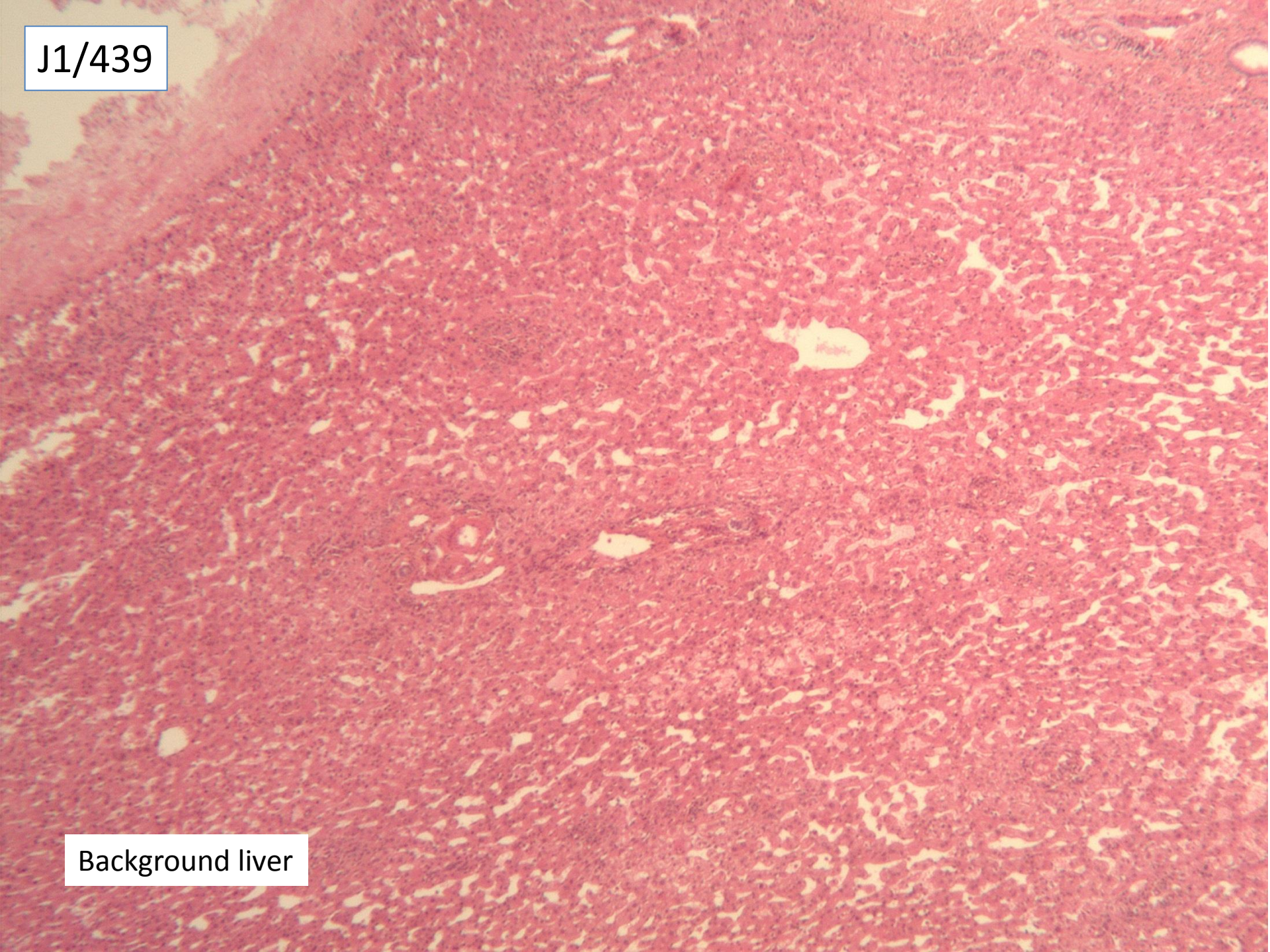



J1/439


J1/439
Background liver

Case J1/439 Age 27, Female

Lesion in segment 2 septate cyst 145x110x125mm smooth walled, containing serous fluid

31 mucinous cystic neoplasm

36 cystadenoma +/- ovarian like stroma

1 cystadenocarcinoma

1 cystadenofibroma

3 simple hepatic or biliary cyst

1 solitary bile duct cyst or cystadenoma

4 benign hepatobiliary cyst

2 choledochal cyst

9 no mention of ovarian like stroma

Most made no mention of background liver – I stopped counting after a while.

6 need for multiple blocks

11 need to do immunos

Suggested scoring – for 10 points, MCN or cystadenoma.
No points for malignant diagnosis.
Others alternative diagnoses have 5 points

12/14 agree, 0 unsuitable

Case J1/439 Age 27, Female

Lesion in segment 2 septate cyst 145x110x125mm smooth walled, containing serous fluid

Original diagnosis: Intrahepatic cystadenoma

Discussion: whether mention of ovarian-like/mesenchymal stroma is necessary for full marks.

Since this is a necessary feature for hepatobiliary cystadenoma, then considered to be implicit within that diagnosis, and not necessary to specifically include it in the response. Hepatobiliary cystadenoma should not be diagnosed without the stroma present.

Terminology is shifting to mucinous cystic neoplasm, in keeping with the WHO blue book 2010, to match the terminology for pancreatic lesions.

These seem to be larger in the liver and less often complicated by malignancy in comparison with pancreatic MCN (next slide).

Intraductal papillary neoplasms and mucinous cystic neoplasms of the hepatobiliary system:

1. Asian v Western populations – IPNB much commoner in East – stones.
   More often intestinal type v pancreaticobiliary in West. Cancer risk similar.

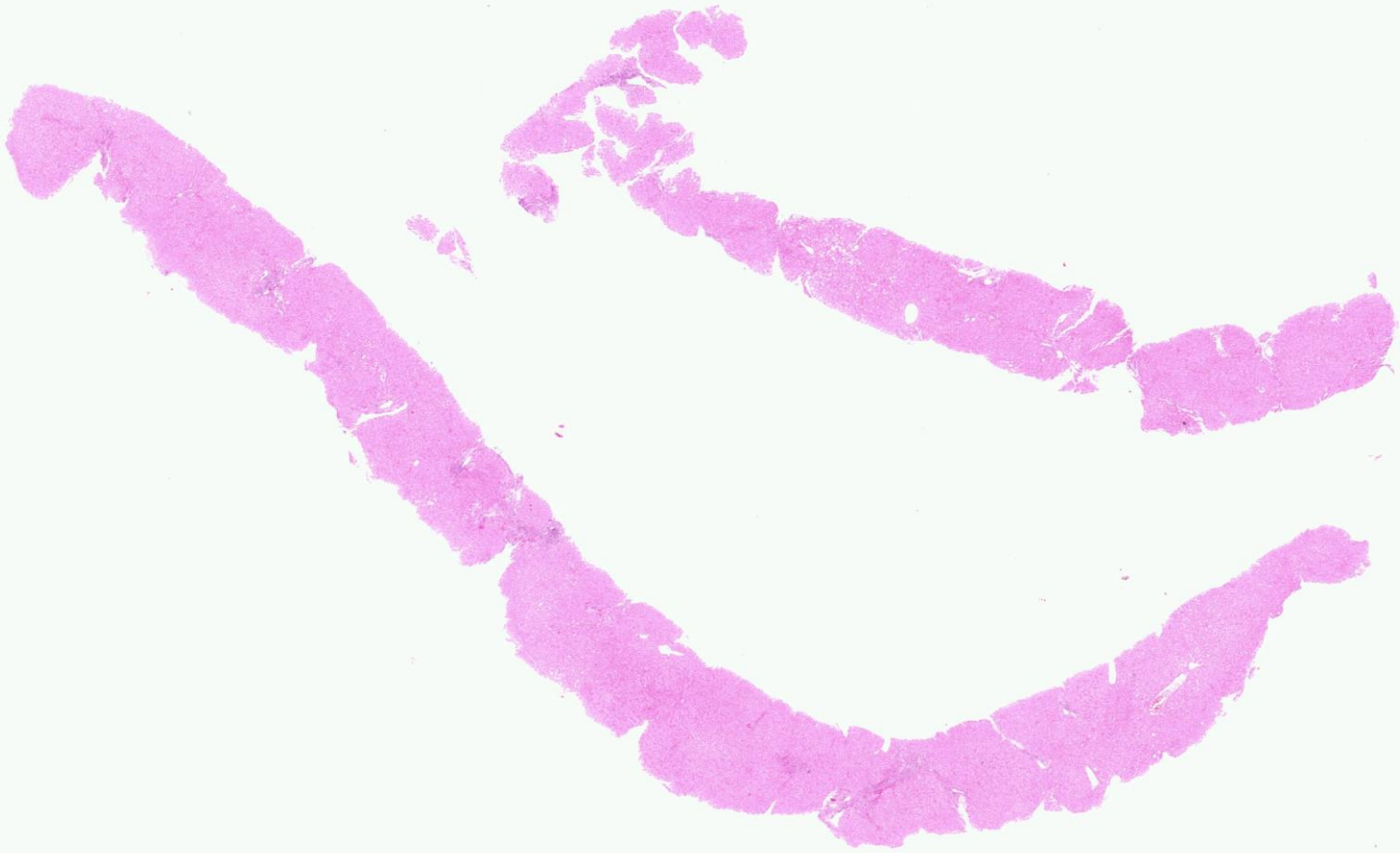
2. Comparison with pancreatic counterparts

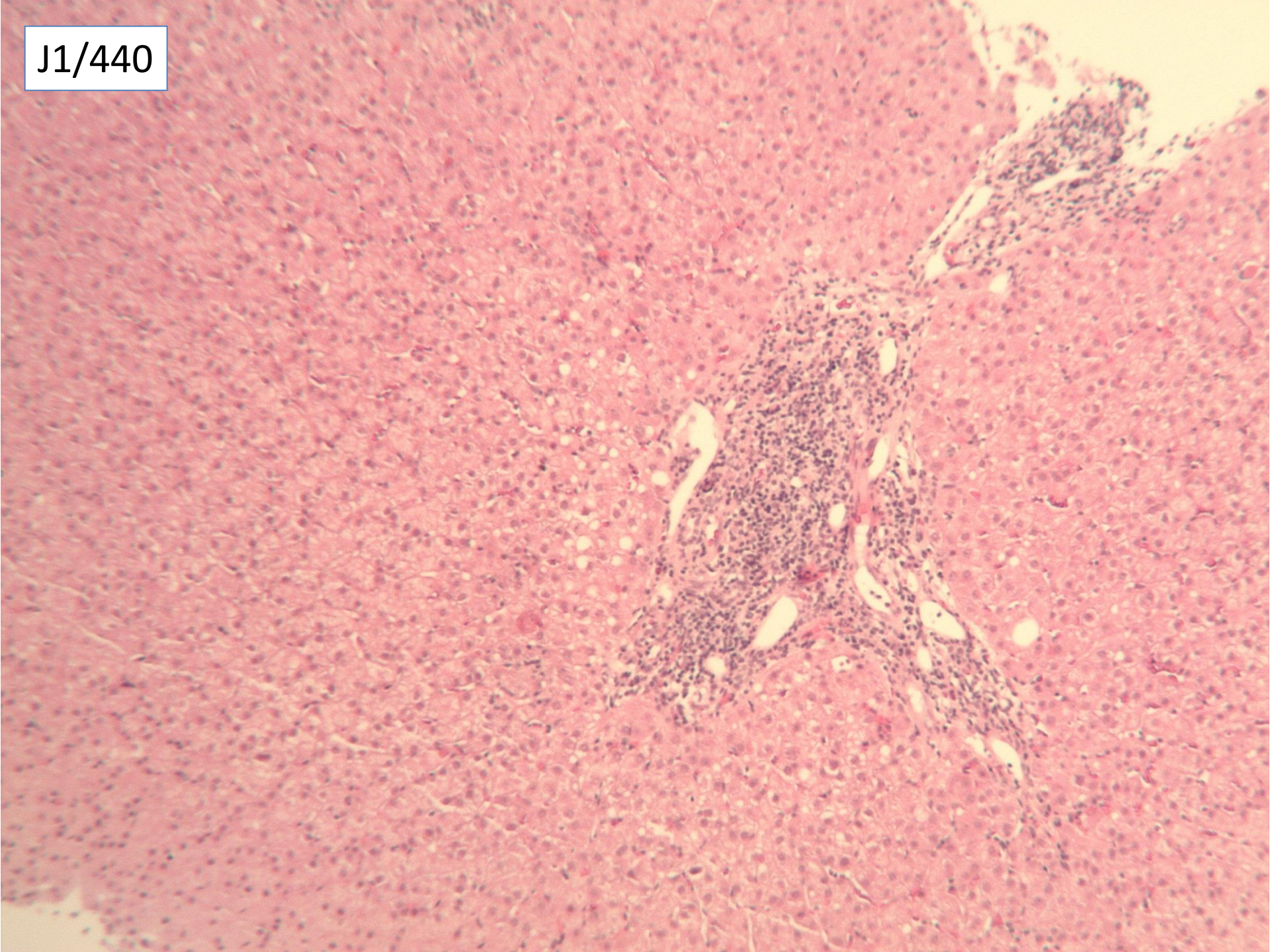
	Liver		Pancreas
For Intraductal papillary neoplasia (IPNB or IPMN-P)			
High grade dysplasia	**39%**	»	7%
Invasive cancer	**49%**	»	26%
Died of cancer	**23%**	»	5%
For Mucinous Cystic Neoplasms (MCN)			
Size (median)	10cm		4.5cm
High grade dysplasia	0%	«	**3%**
Invasive cancer	2%	«	**10%**
Died of cancer	0%	«	**2%**

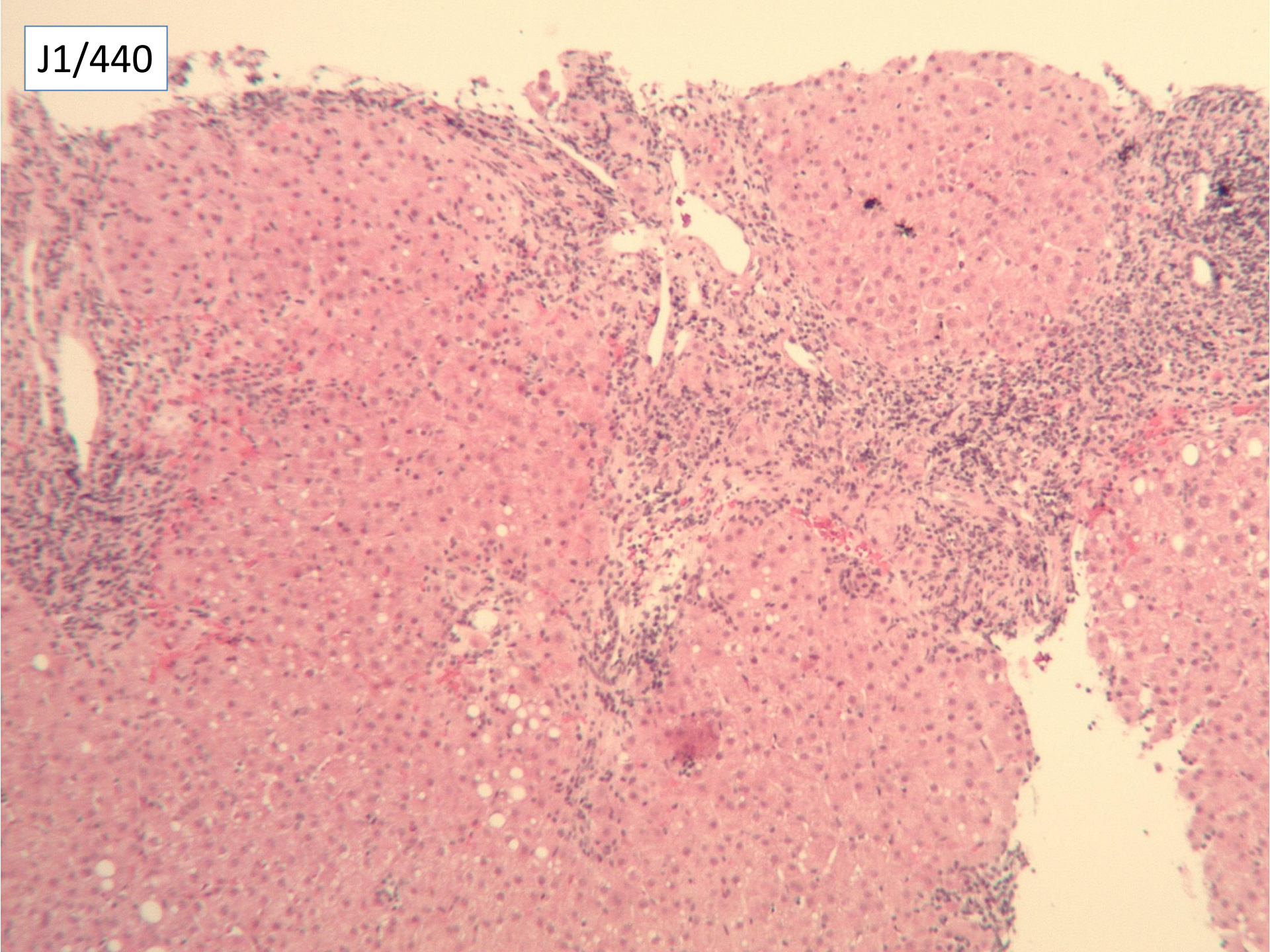
Zen Y *et al.* Histopathology 2014 on line DOI:10.1111/his.12378

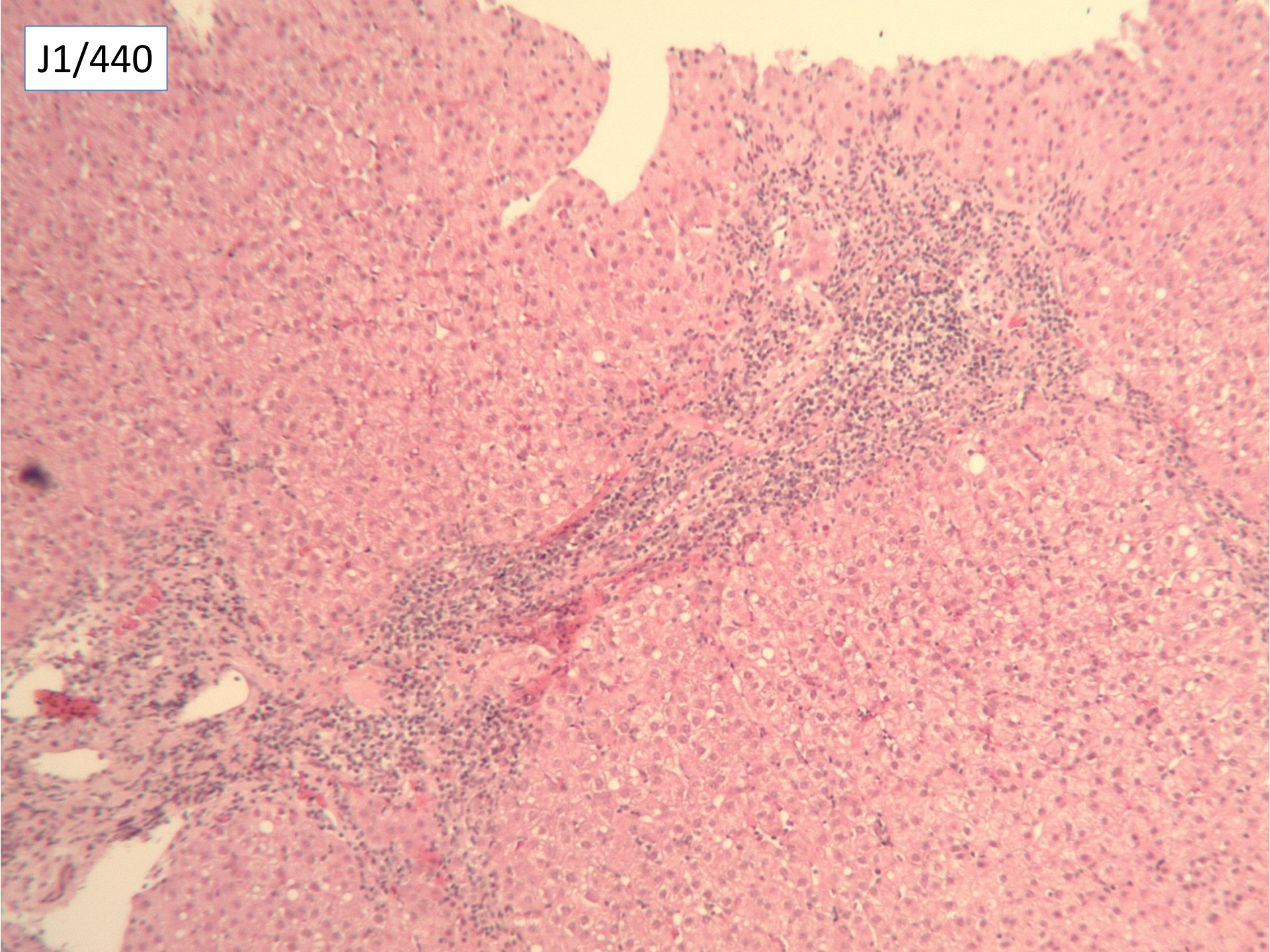
Case J1/440 Age 58, Male

Hepatitis C positive, fibroscan value raised




J1/440


J1/440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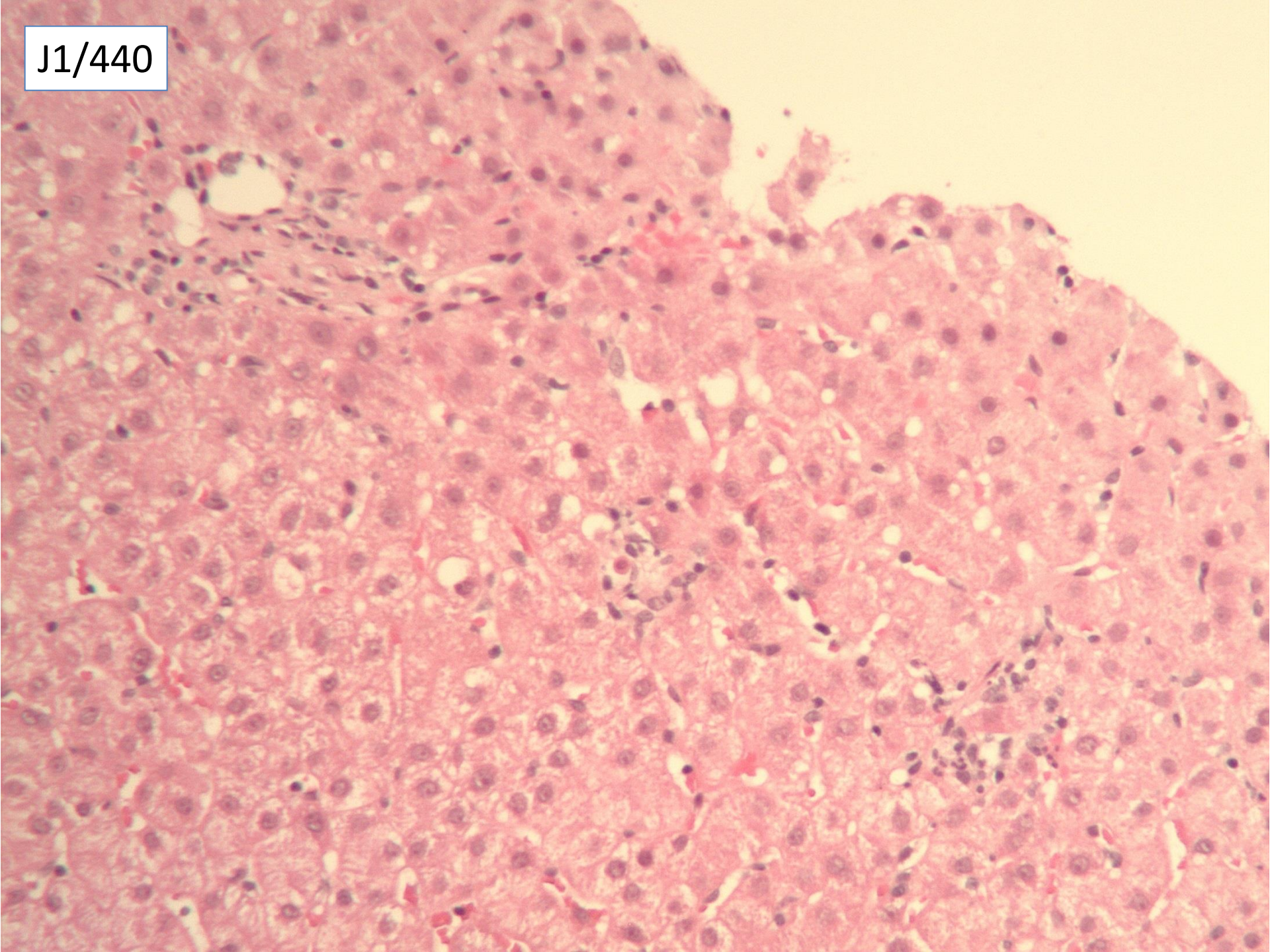
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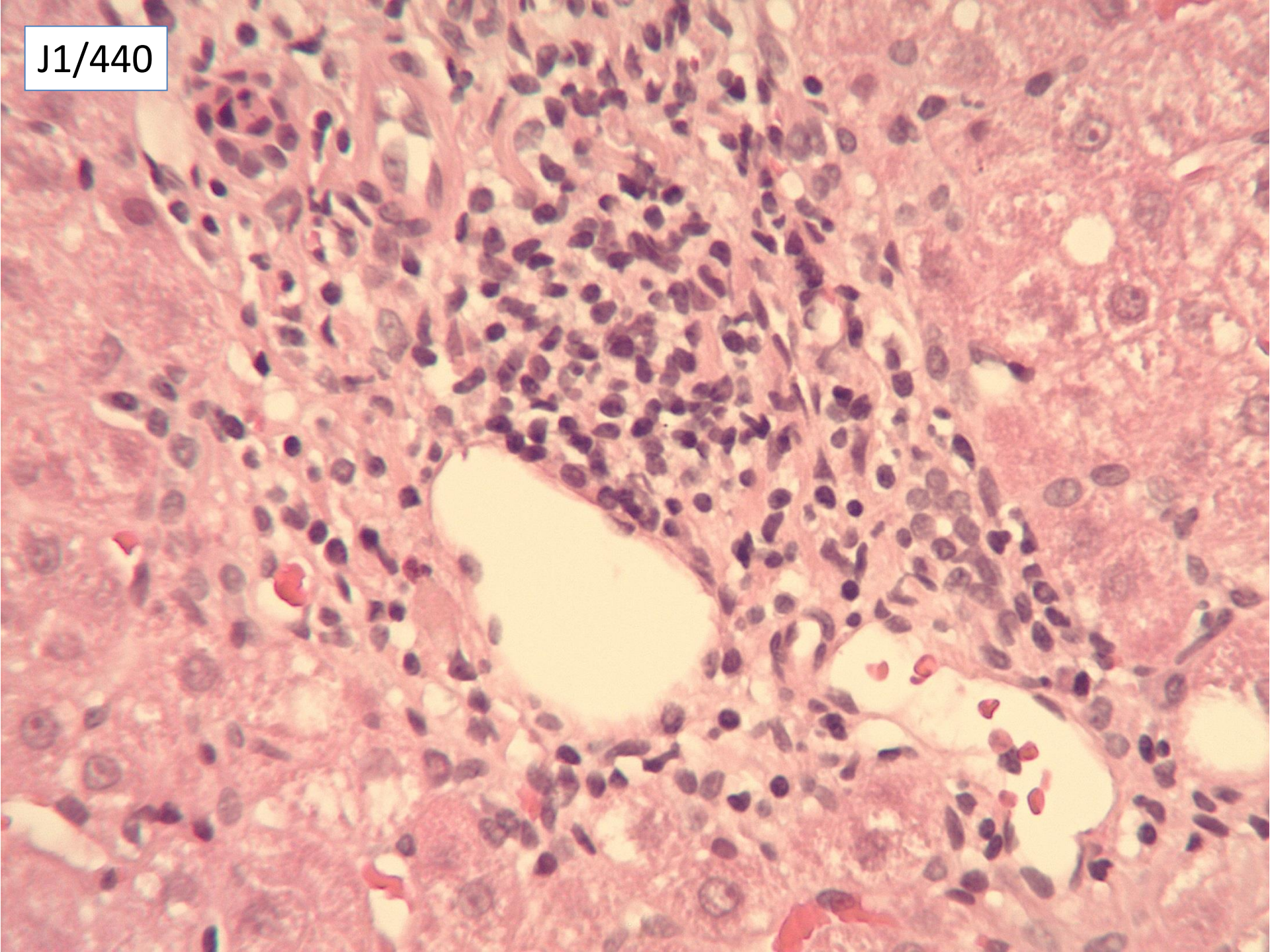
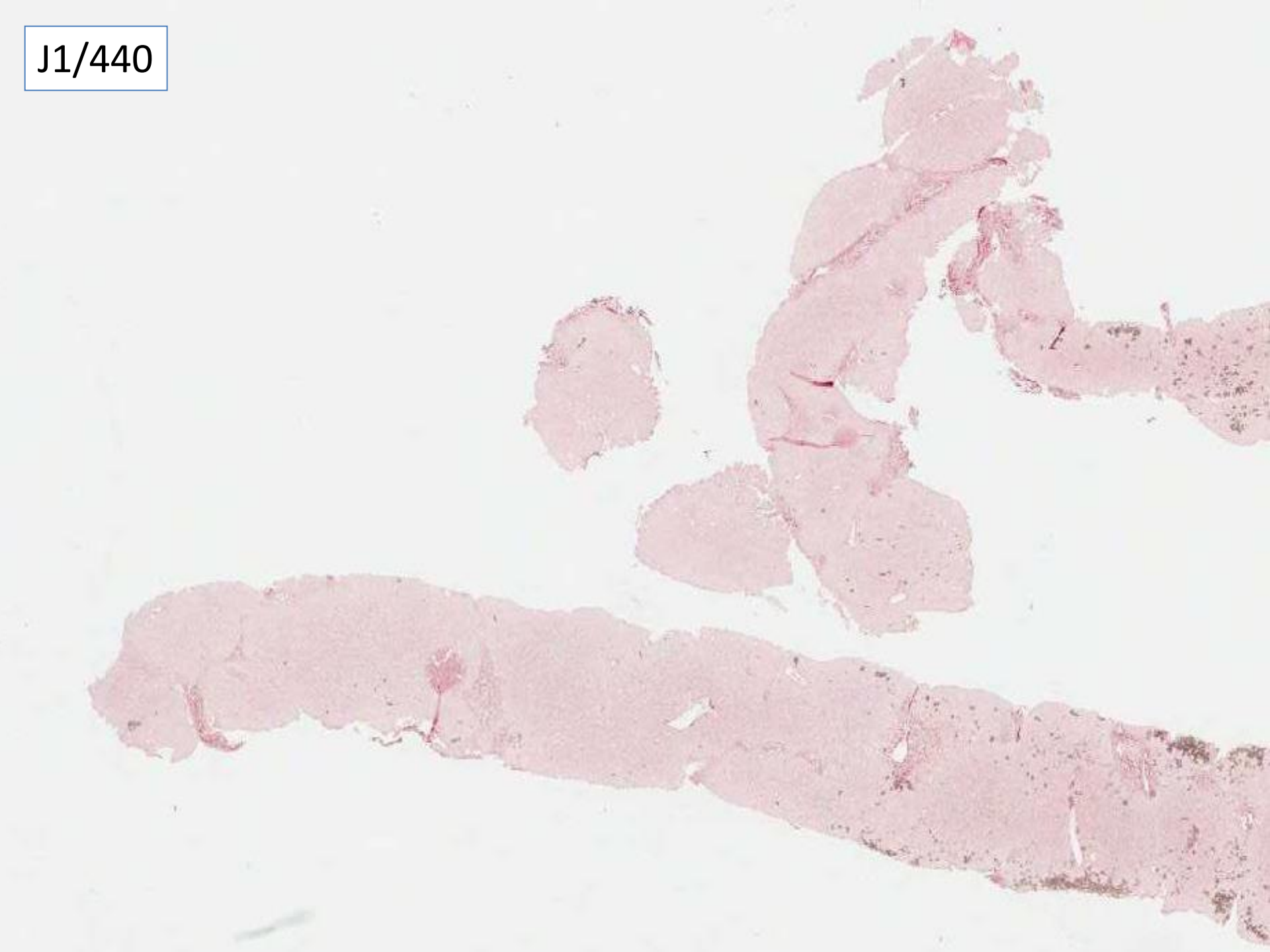
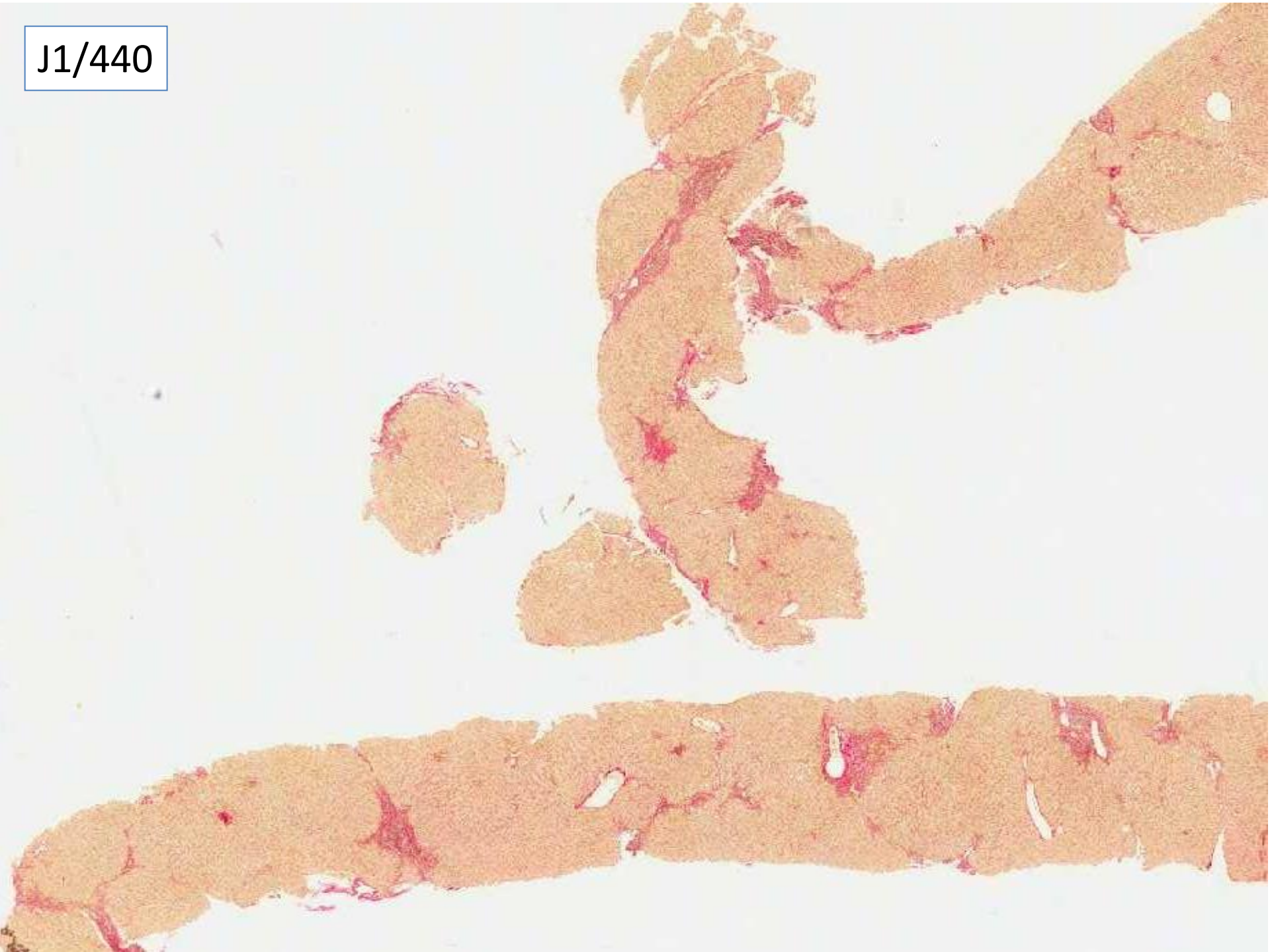
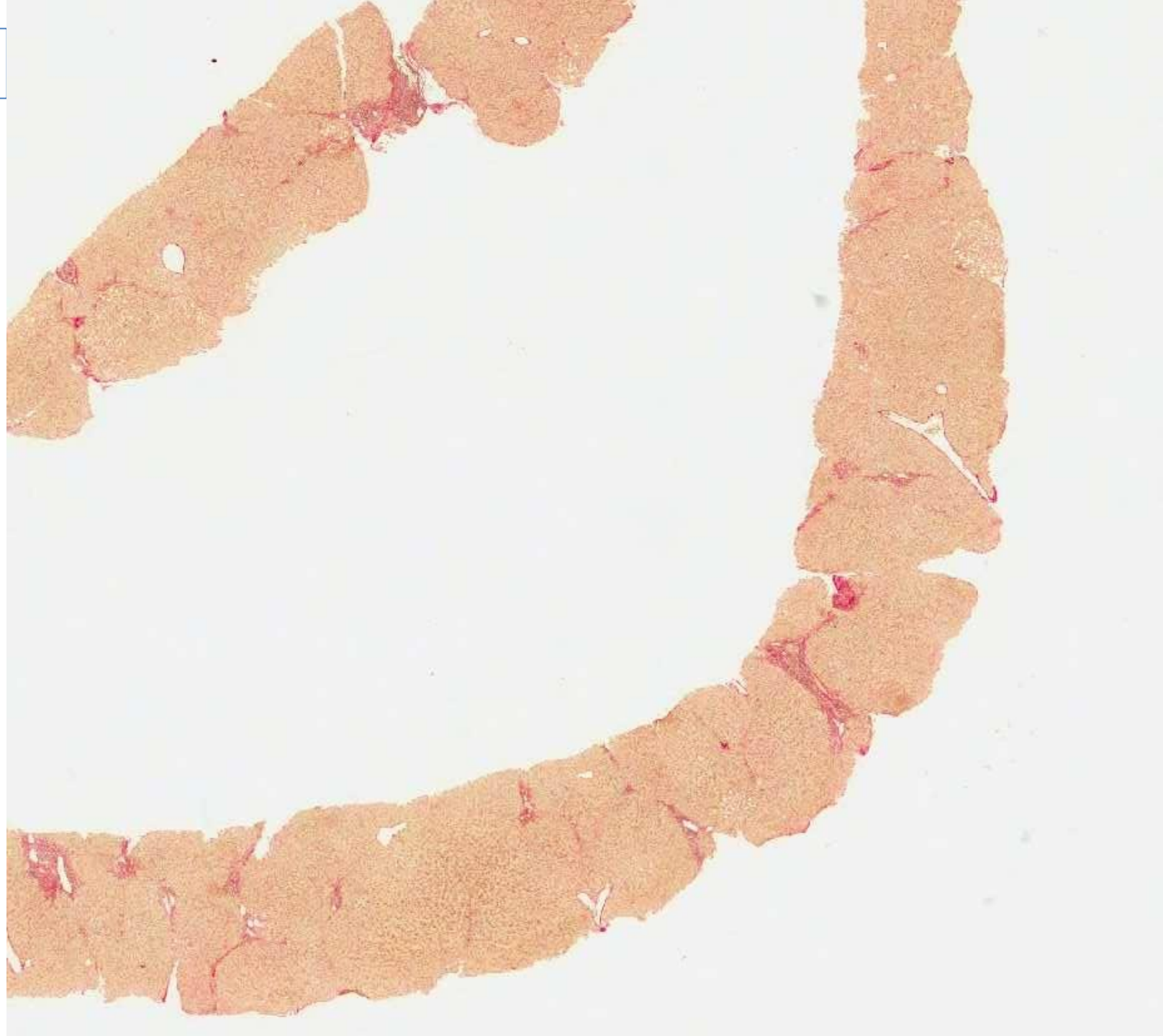

J1/440

J1/440




J1/440

J1/440



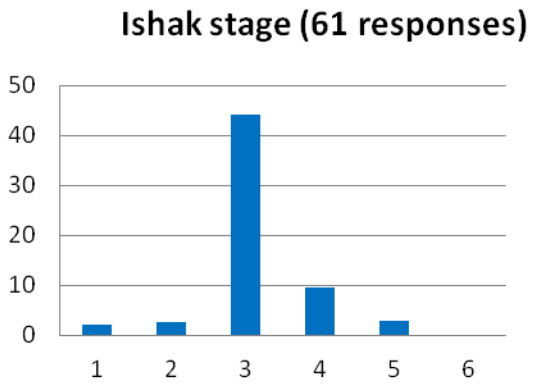
Case J1/440 Age 58, Male

Hepatitis C positive, fibroscan value raised

79 consistent with hepatitis C

2 hepatitis C not mentioned

2 consider co-infection with hepatitis B – due to ? positive Orcein



Metavir (7 responses):
1 F1, 4 F2, F3/F4 2.

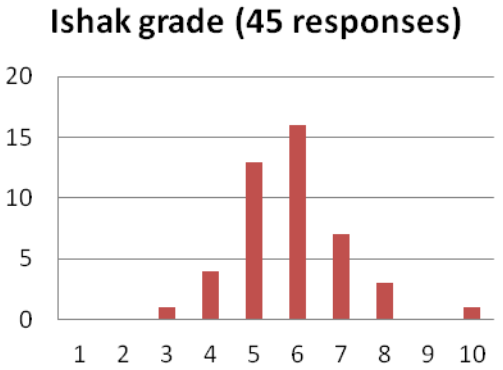
fibrosis: 2 mild,
10 moderate, 4 severe fibrosis

All included stage/assessment of fibrosis.

3 had no mention of severity of inflammation

Steatosis -19 no mention of steatosis

5 steatosis NOS, 1 none, 5 minimal, 39 mild,



Metavir (7 responses) -
3 A1, 2 A2, 2 A3

<u>Suggested scoring:</u> for 10 points, need to state consistent with hepatitis C and include comment on severity.
It is important to include a comment on steatosis, but there is insufficient consistency for 80% agreement so steatosis not scored.

13/13 agree, 0 unsuitable

Case J1/440 Age 58, Male

Hepatitis C positive, fibroscan value raised

Original diagnosis: - hepatitis C, mild portal fibrosis, mild inflammation, mild fatty change.

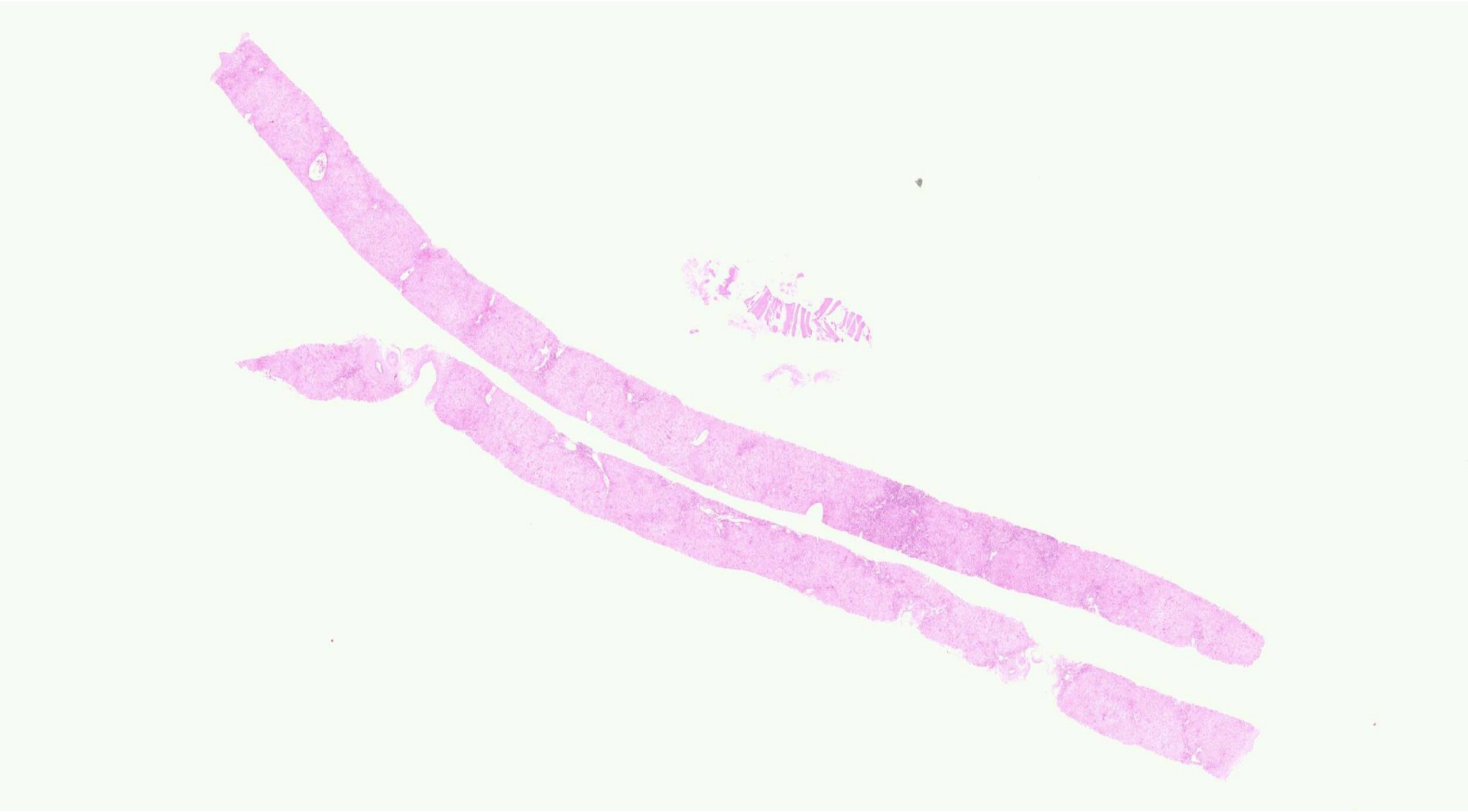
Discussion: need to include comment on grade and stage, although for the EQA this can be by Ishak, Metavir, or free text – whichever is used in routine reporting. The grade/stage is not usually scored, but information included because it enables participants to see how they compare with the group overall.

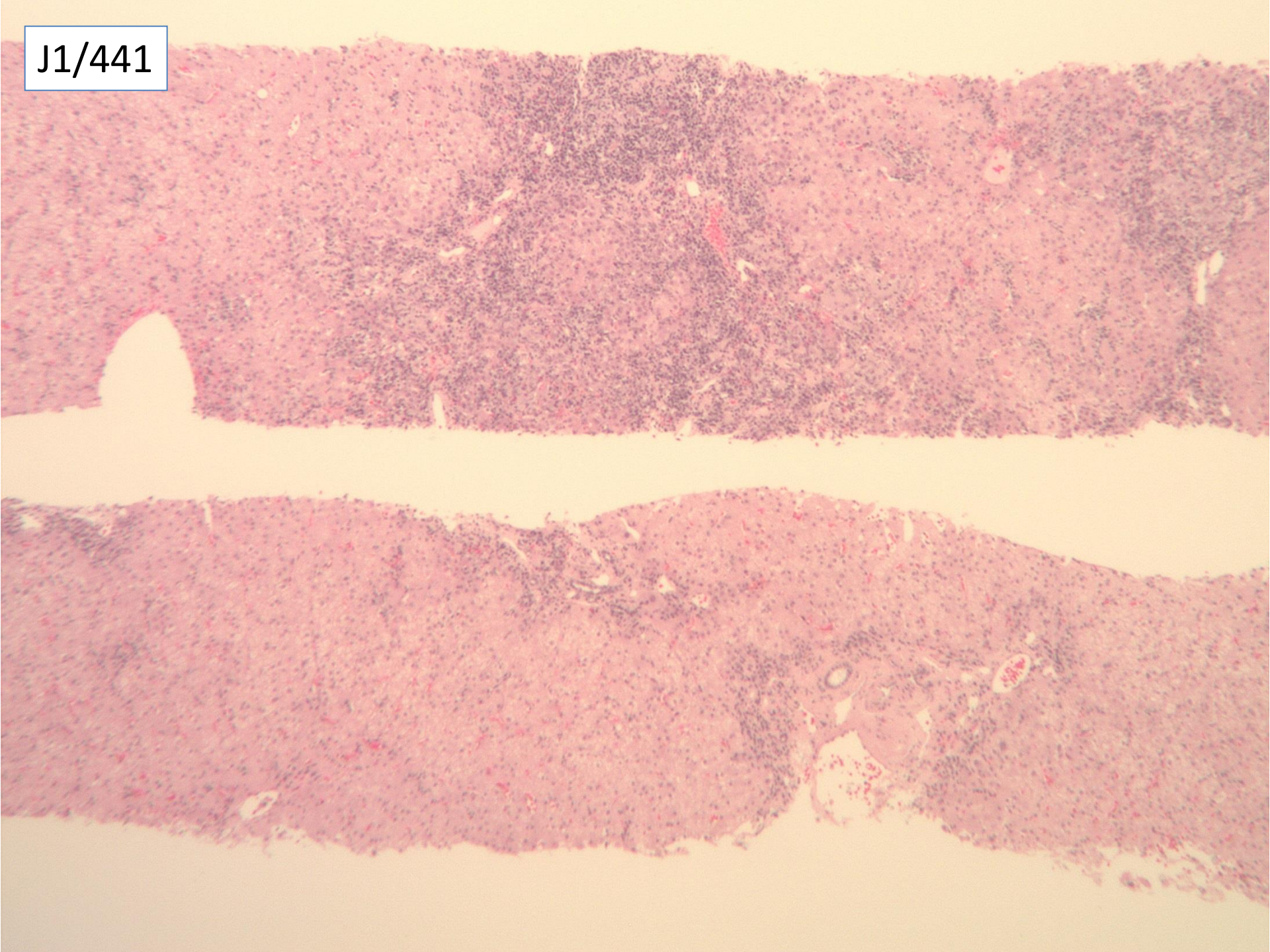
Steatosis is important in hepatitis C and should be scored – see masterclass later.

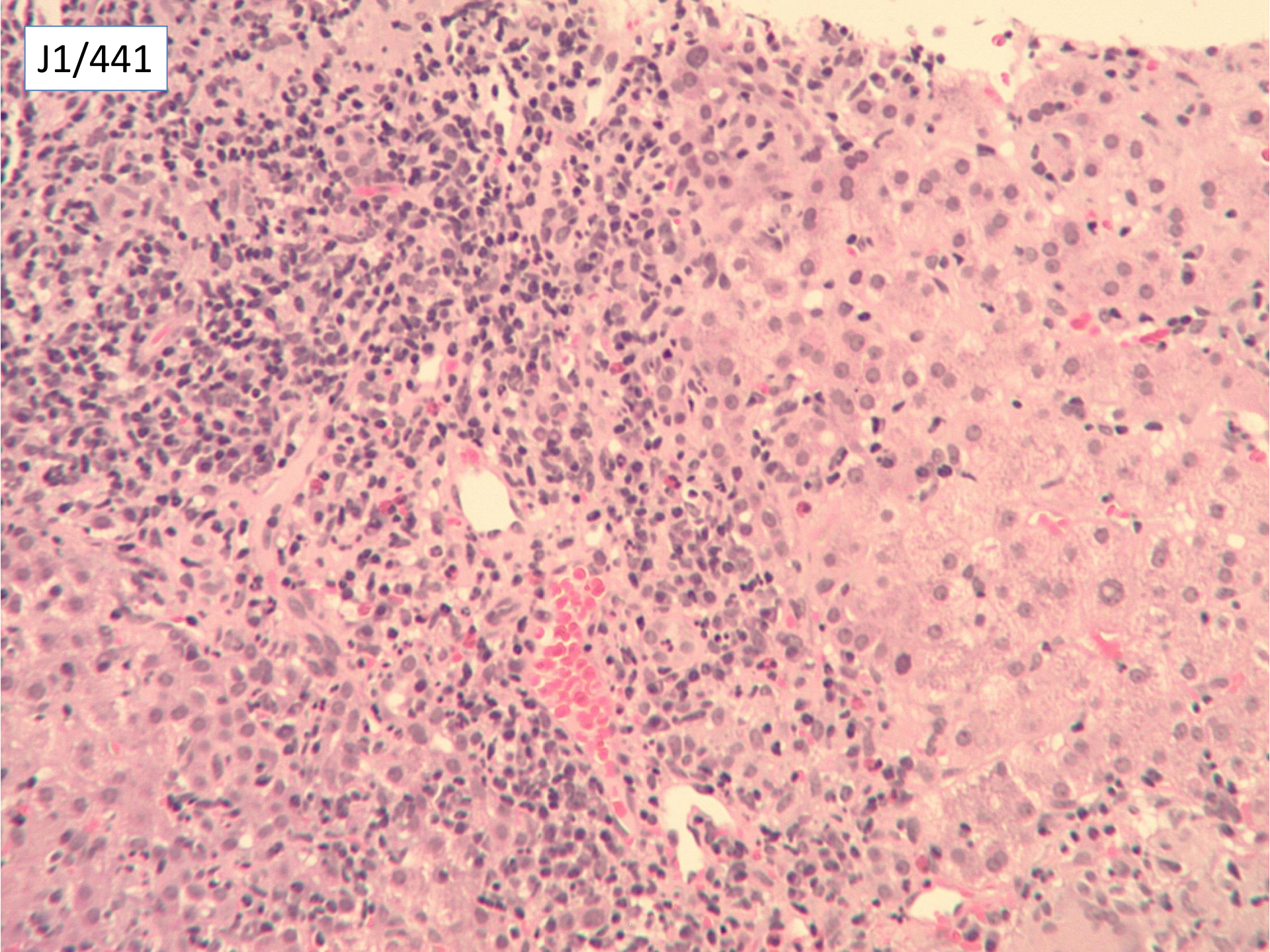
The possibility of hepatitis B may have been raised because Shikata was included – although used here as a connective tissue stain showing long standing fibrosis, rather than for HBsAg.

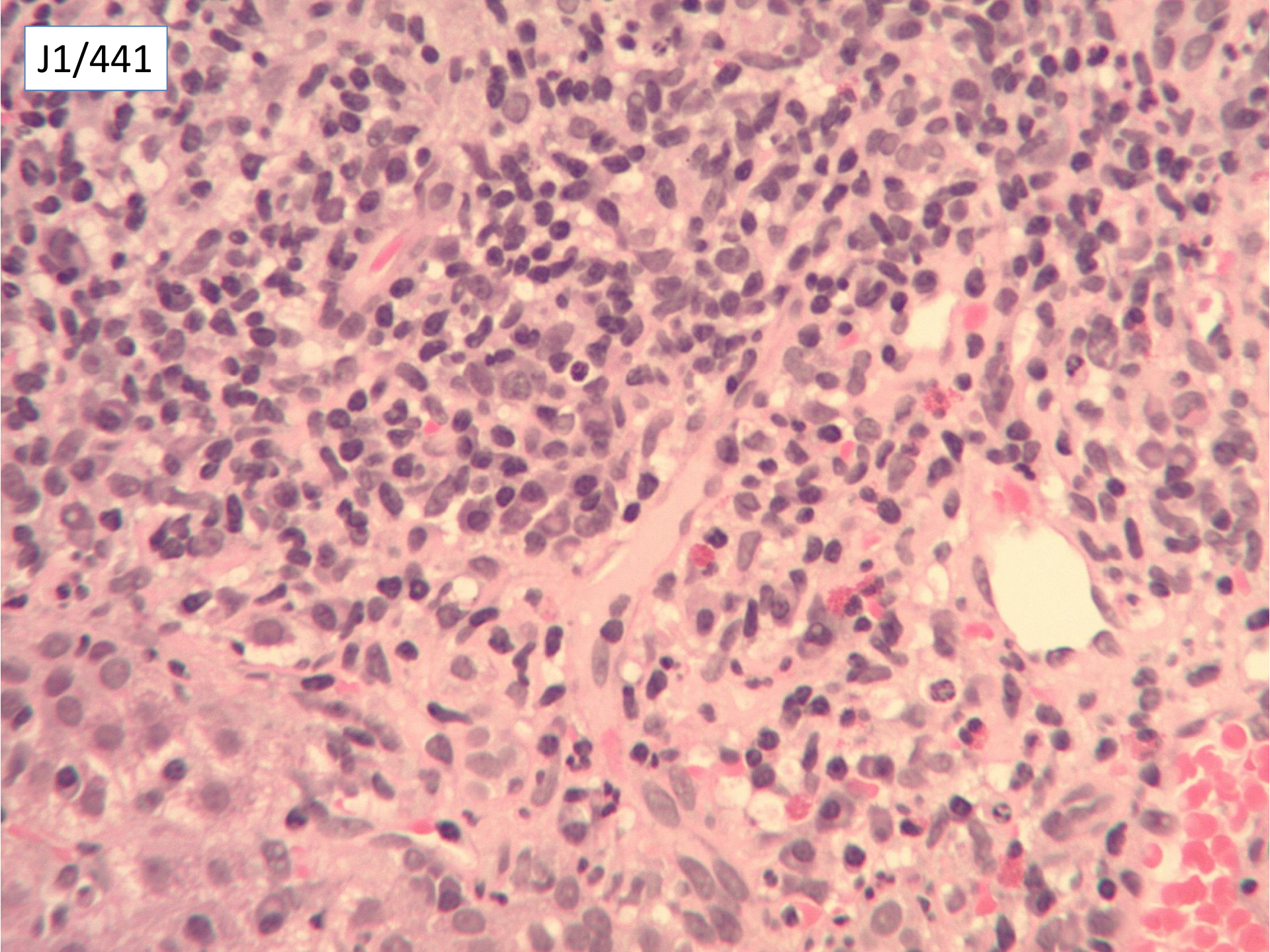
Case J1/441 Age 66, Female

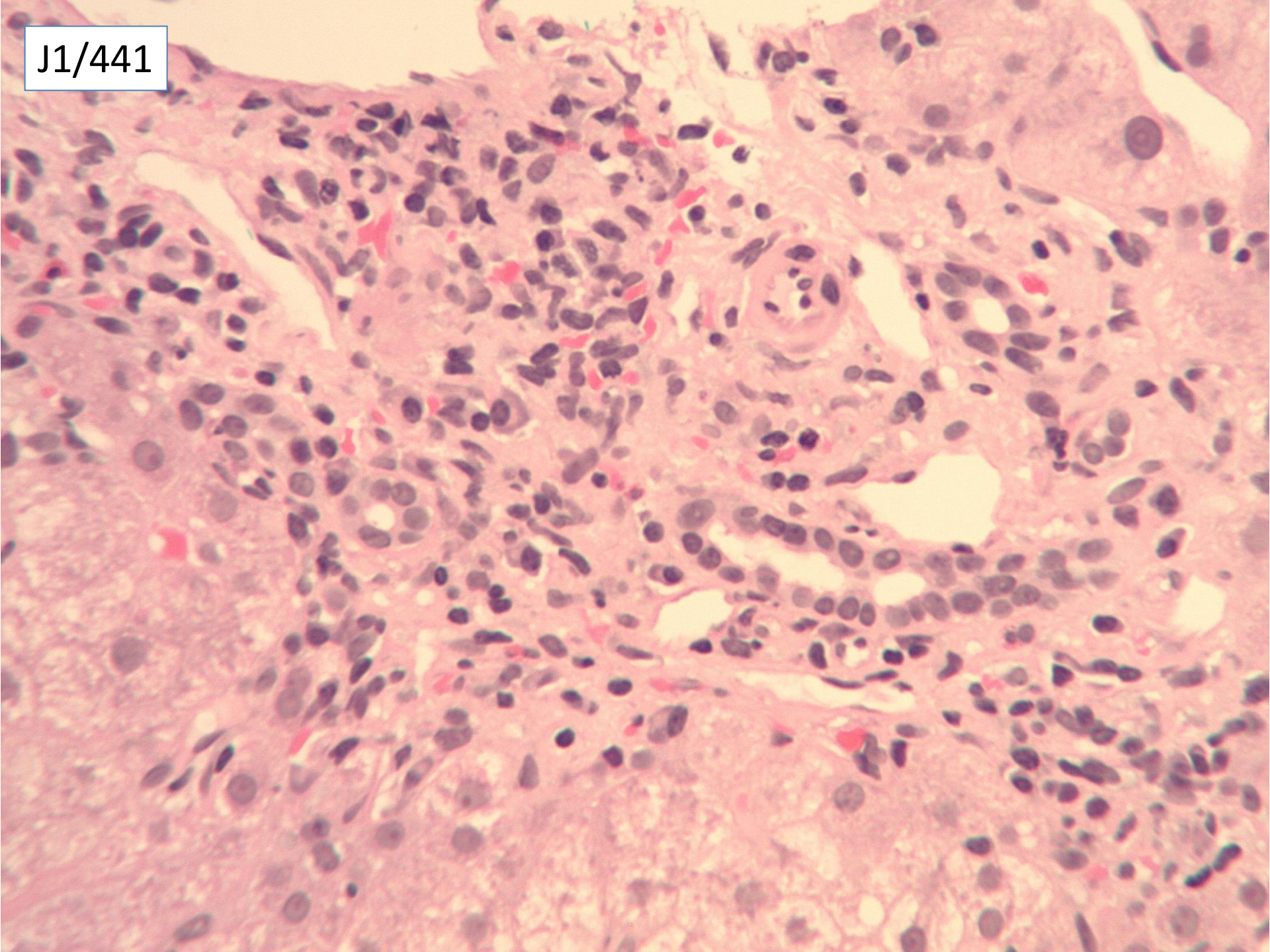
Abnormal LFT's ANA positive, raised lgG * ALT 136, br9, alk p 84,
2 cores 12mm and 15mm



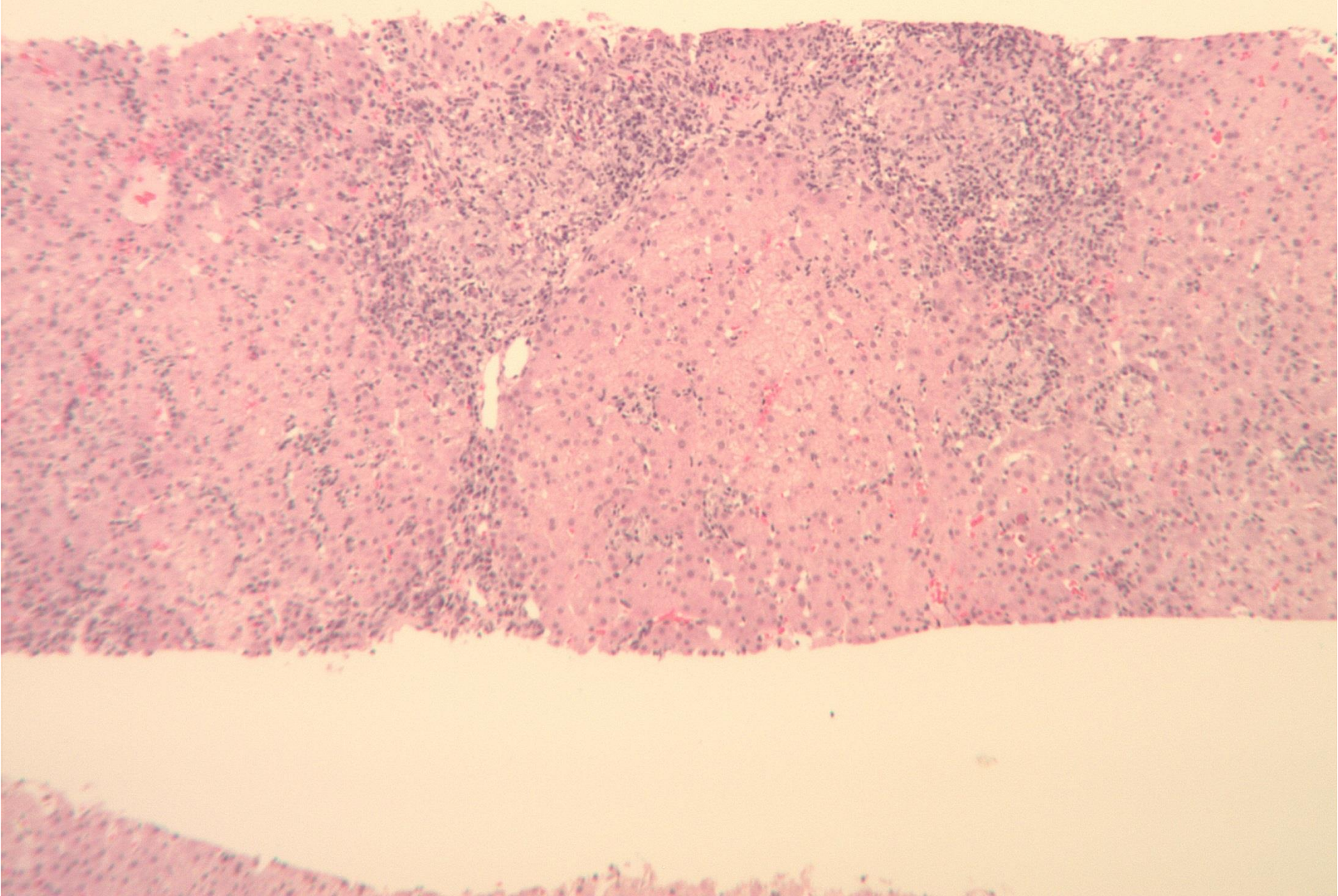

J1/441

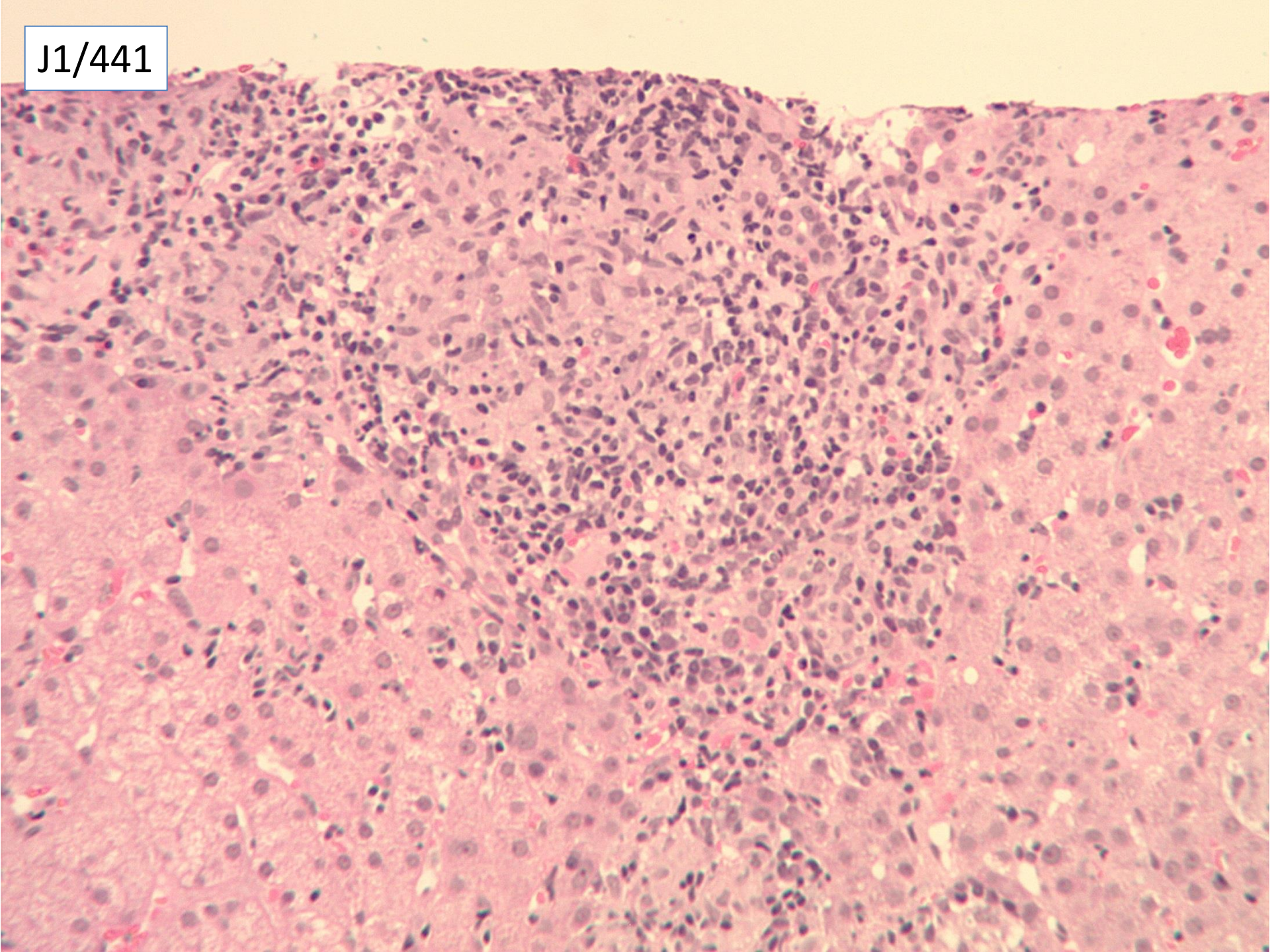

J1/441

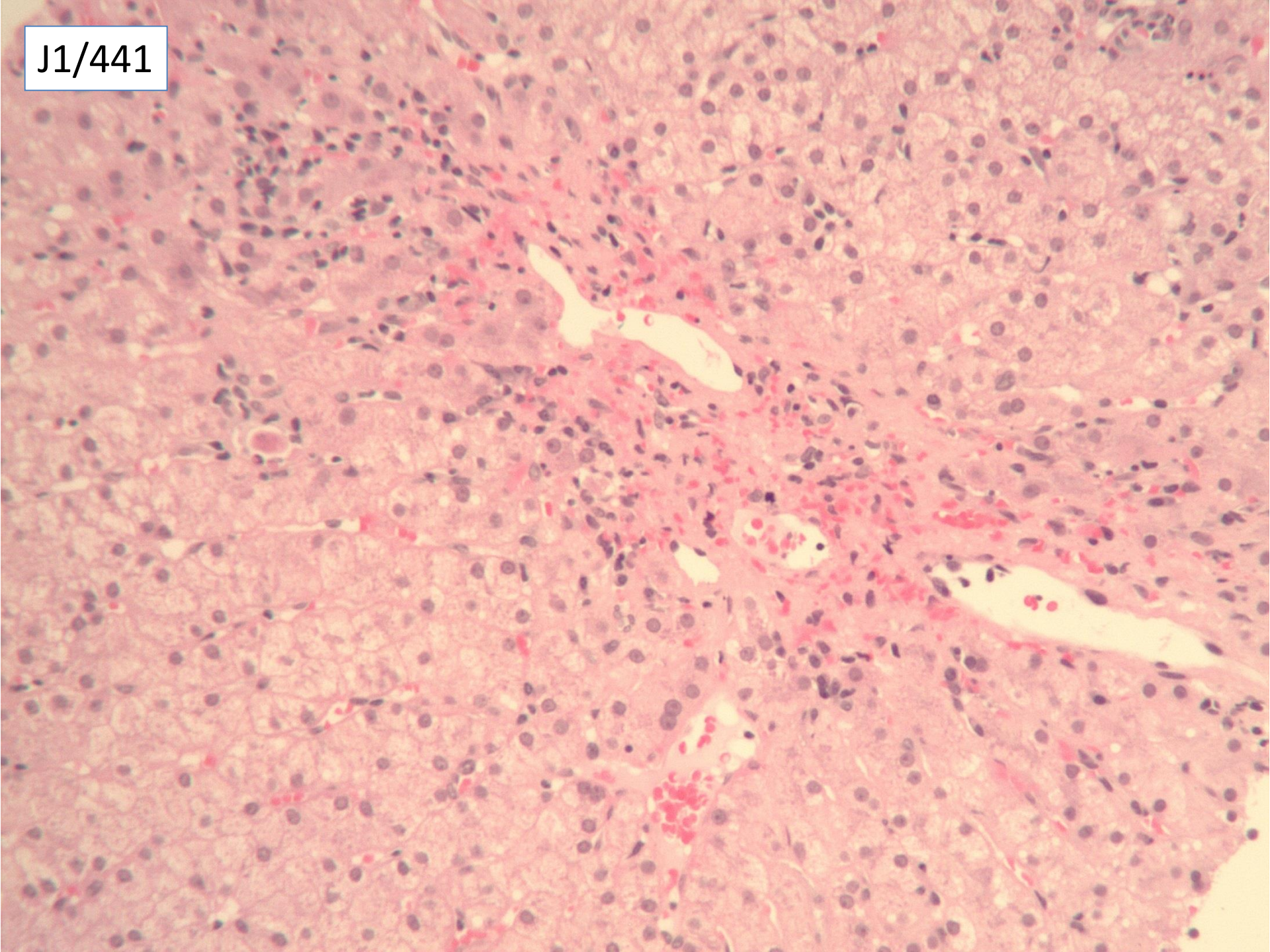

J1/441


J1/441

J1/441




J1/441


J1/441

Case J1/441 Age 66, Female

Abnormal LFT's ANA positive, raised lgG * ALT 136, br9, alk p 84,

60 autoimmune hepatitis
1 acute hepatitis with bridging and confluent necrosis
77 mentioned granulomas
34 PBC
38 AIH/PBC overlap
1 PSC
2 IgG4 disease
1 lymphoma
31 ? drugs as aetiological factor.
16 differential includes TB
30 includes sarcoidosis
1 'other causes of granulomatous liver'

9 needs orcein
6 CK7

Re-collated after meeting discussion:
77 Autoimmune liver disease
AIH/PBC/both, with granulomas
2 Granulomatous disease,
neither AIH nor PBC mentioned
3 Autoimmune hepatitis, neither
granulomas nor biliary mentioned

Comment: suitable for scoring? All diagnoses are very descriptive.
Propose – for 10 points, needs to include chronic inflammatory liver disease, granulomas, and an indication of a differential diagnosis
rather than one clear cut thing??

10/14 agree, 3 unsuitable

Case J1/441 Age 66, Female

Abnormal LFT's ANA positive, raised lgG * ALT 136, br9, alk p 84,

Original diagnosis: c/w AIH, consider PBC overlap

Follow up? Not available

Discussion: cases like this always require clinico-pathological dialogue and so are difficult to evaluate in the context of EQA.

Scoring was agreed as: based on review of text of diagnoses, accept if discussion of the differential and need for additional information.

On review, 77/82 included discussion of differential that included autoimmune disease (either AIH or PBC or both), and mentioned granulomatous inflammation.

Masterclass: Rob Goldin

atypical features in autoimmune hepatitis

Masterclass: Rob Goldin:

“Atypical” AI Hepatitis

Rob Goldin
r.goldin@imperial.ac.uk

WHAT IS TYPICAL AIH?

Original Revised (1999) Criteria for the Diagnosis of AIH

Liver histology	
Interface hepatitis	+3
Predominantly lymphoplasmacytic infiltrate	+2
Rosetting of liver cells	+1
None of the above	−5
Biliary changes	−3
Atypical features	−3

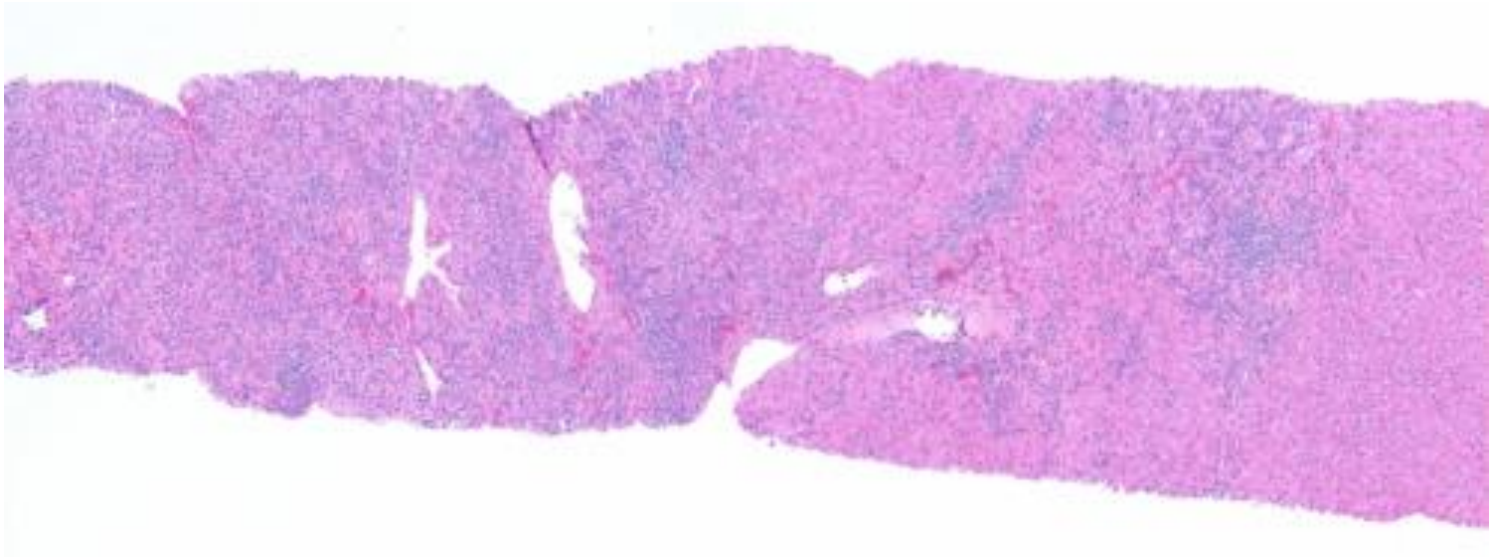
International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis.
J Hepatol 1999;31:929-938.

Simplified Diagnostic Criteria for the Diagnosis of AIH

Liver Histology	Compatible with AIH	+1
	Typical of AIH	+2

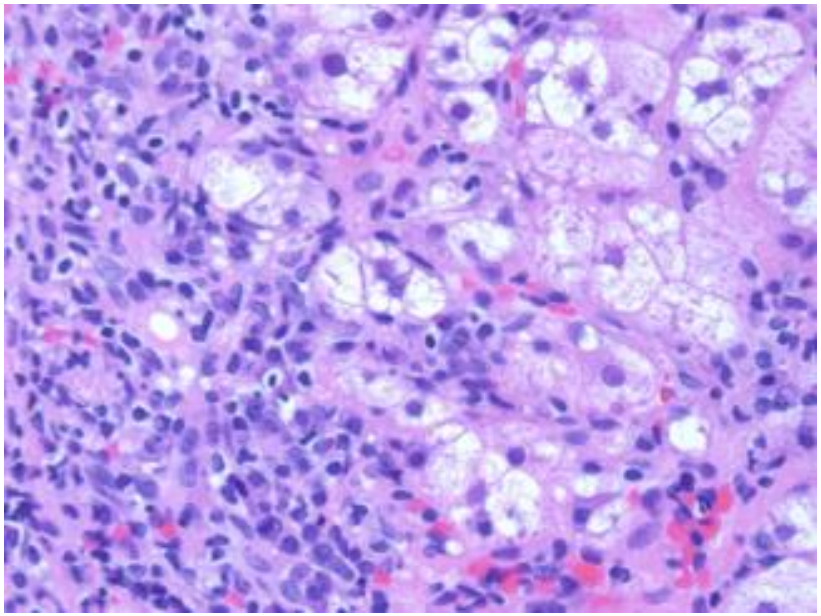
Simplified criteria for the diagnosis of autoimmune hepatitis. HEPATOLOGY 2008;48:169-176.

LKM AIH. this low-magnification image (hematoxylin-eosin, ×20) shows a marked lymphoplasmacytic infiltrate with effacement of the interface.



Clinical Liver Disease
Volume 3, Issue 2, pages 19-23, 5 MAR 2014 DOI: 10.1002/cld.301
http://onlinelibrary.wiley.com/doi/10.1002/cld.301/full#cld301-fig-0007

AIH. This image (hematoxylin-eosin, ×400) shows rosettes.



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http://onlinelibrary.wiley.com/doi/10.1002/cld.301/full#cld301-fig-0004

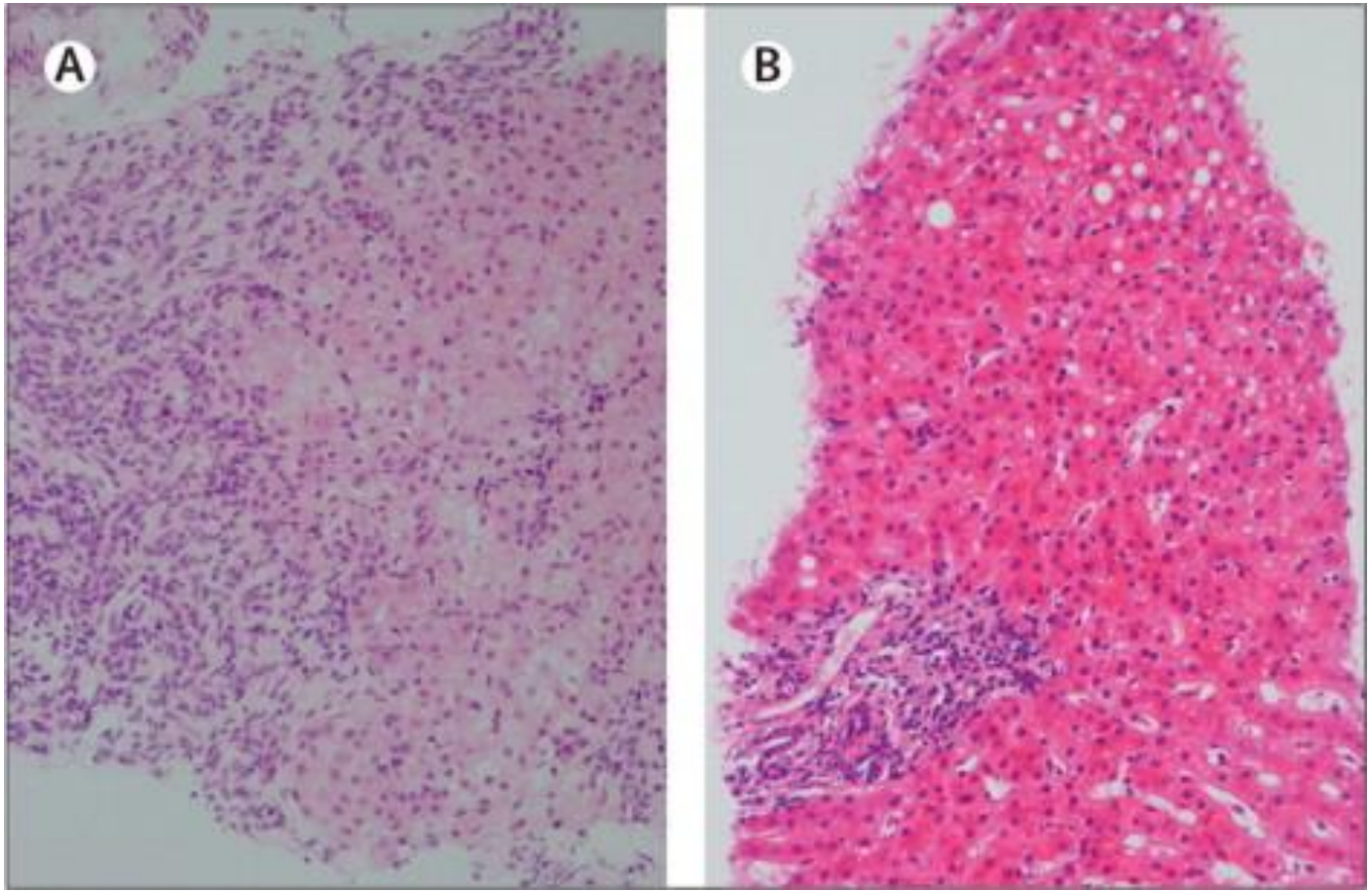


Figure 3 Liver biopsy specimen at presentation (A) and after 2 years of treatment with corticosteroids and azathioprine (B)..

Autoimmune hepatitis

The Lancet, Volume 382, Issue 9902, 2013, 1433 - 1444

http://dx.doi.org/10.1016/S0140-6736(12)62163-1

WHAT IS ATYPICAL AIH?

Review article: the management of autoimmune hepatitis beyond consensus guidelines

Alimentary Pharmacology & Therapeutics
Volume 38, Issue 4, pages 343–364, 2013

Table 2 | Weak or non-existent diagnostic guidelines in autoimmune hepatitis

Diagnostic guidelines	AASLD evidence grade $N = 44$	BSG evidence grade $N = 31$
Performance of liver tissue examination prior to treatment*	I/B	II-3/B1
Diagnostic criteria for acute severe (fulminant) autoimmune hepatitis	None	None
Significance of centrilobular necrosis or concurrent bile duct injury	None	None
Diagnostic criteria in non-White populations	None	None
Diagnosis and treatment of drug-induced autoimmune-like hepatitis	None	None
Diagnostic criteria for overlap syndromes and treatment of component diseases	None	II-3/C1 III/C1

AASLD, American Association for Study of Liver Diseases; BSG, British Society of Gastroenterology.

Evidence categories: AASLD: I/B, High-quality randomised trial/derived from single study. BSG: II-3/B1, case series or uncontrolled observations/moderate-quality evidence/strong recommendation; II-3/C1, case studies or uncontrolled observations/low-quality evidence/strong recommendation; III-3/C1, opinion of respected authorities/low-quality evidence/strong recommendation.

* Contested by Bjornsson E, Talwalkar J, Treeprasertsuk S, Neuhauser M, Lindor K. Patients with typical laboratory features of autoimmune hepatitis rarely need a liver biopsy for diagnosis. Clin Gastroenterol Hepatol 2011;9:57-63.

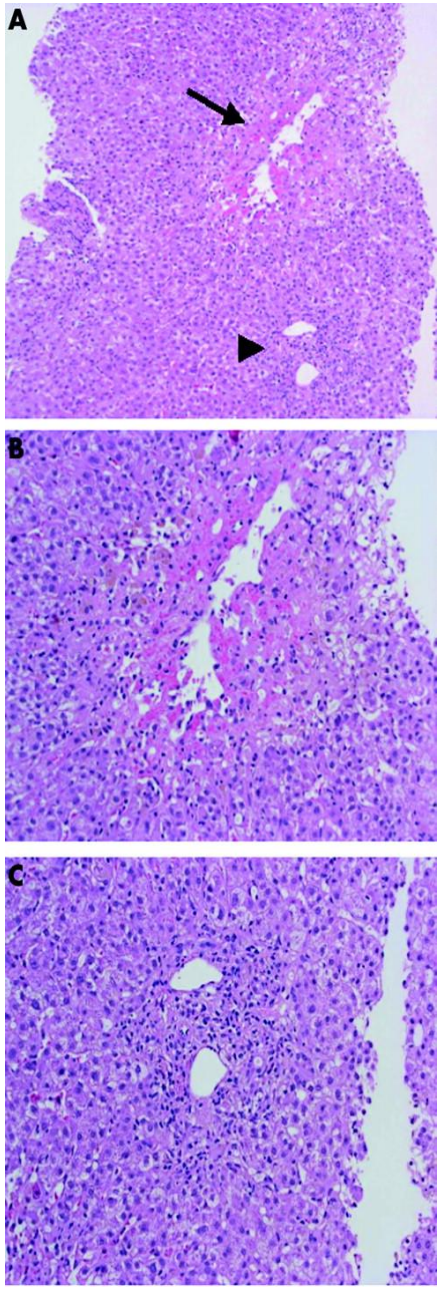
Table 4 | Decision points in the diagnosis of autoimmune hepatitis

Decision point	Prime evidence	Counter evidence	Prevailing judgment
Pre-treatment liver tissue examination	Tissue necessary to distinguish otherwise clinically similar diseases[3, 4]	Tissue not always needed by simplified diagnostic scoring system[10]	Obtain pre-treatment biopsy if possible
Acute severe (fulminant) onset	Diagnosis evident by autoantibodies, plasmacytic infiltration and steroid response[13, 19, 31]	Diagnosis difficult because absent antibodies, normal IgG and nondiagnostic score[21, 22]	Institute short (≤2 weeks) prednisolone trial if uncertain
Centrilobular necrosis	Diagnosis evident by interface hepatitis, plasma cells, hepatocyte rosettes, immune features[12, 13]	Diagnosis difficult because findings associated with hypoxic, ischaemic or drug-induced injury[23]	Treat as AIH if immune features
Isolated bile duct injury	Diagnosis unaffected by coincidental background features and no cholestasis[14, 15, 32]	Diagnosis could be subclinical or evolving cholestatic disease[34]	Treat as classical AIH
Non-White patients	Diagnosis unaffected by atypical phenotype and low scores[8]	Diagnosis of AIH incorrect if criteria unmet[8]	Maintain flexible diagnostic criteria
Drug-induced autoimmune-like hepatitis	Diagnosis evident by clinical and histological features and resolution after drug removal[17, 54]	Diagnosis uncertain because drug exposure coincidental and AIH unresolving[53]	Treat by drug withdrawal and corticosteroids
Overlap syndromes	Serum AP>2-fold ULN, florid duct lesions, abnormal cholangiogram unusual in AIH: findings may affect outcome and justify overlap designation with PBC or PSC[52, 60, 61]	AIH can have atypical features, which affect outcome and do not justify re-designation as overlap with PBC or PSC[5, 34]	Cholestatic component can modify treatment strategy to include UDCA

AIH, autoimmune hepatitis; AP, serum alkaline phosphatase level; IgG, serum immunoglobulin G level; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of the normal range.

Centrilobular necrosis in autoimmune hepatitis: a histological feature associated with acute clinical presentation

J Clin Pathol 2006;**59**:246-249, March 1, 2006

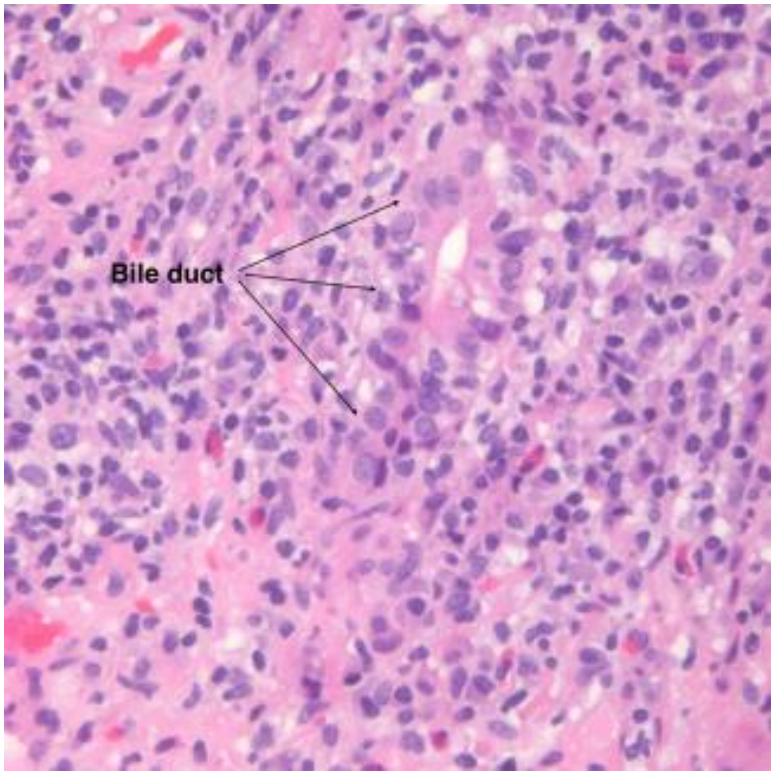


Overlap syndromes: The International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue:
Journal of Hepatology 2011 54 374–385

Feature	AIH	PBC	PSC
Liver biopsy			
Interface hepatitis	Typical finding*	In a proportion of cases**	In a variable number of cases***
Portal inflammation	Portal plasma cell infiltrate	Portal lymphocytic infiltrate	Portal lymphocytic infiltrate
Biliary changes	In a proportion of cases	Typical	Typical
Granulomas	Atypical	Suggestive of PBC, but invariably present	Atypical, but may be observed

*A diagnosis of definite AIH should not be concluded without a liver biopsy.
**A liver biopsy is not required in AMA positive cases. In early disease, characteristic features are uncommon.
***A liver biopsy is not necessary for the diagnosis of large duct PSC, but required for the diagnosis of small duct PSC.

AIH with overlap syndrome. This image (hematoxylin-eosin, ×200) shows nonsuppurative cholangitis consistent with PBC.



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Volume 3, Issue 2, pages 19-23, 5 MAR 2014 DOI: 10.1002/cld.301
http://onlinelibrary.wiley.com/doi/10.1002/cld.301/full#cld301-fig-0006

The Paris Criteria

Chazouilleres O *et al.* Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy *Hepatology* 1998;28:296-301

Patients must meet 2 of 3 criteria for both entities to qualify as overlap

PBC

1. Florid duct lesions
2. AMA
3. Alkaline phosphatase >2x or GGT >5x

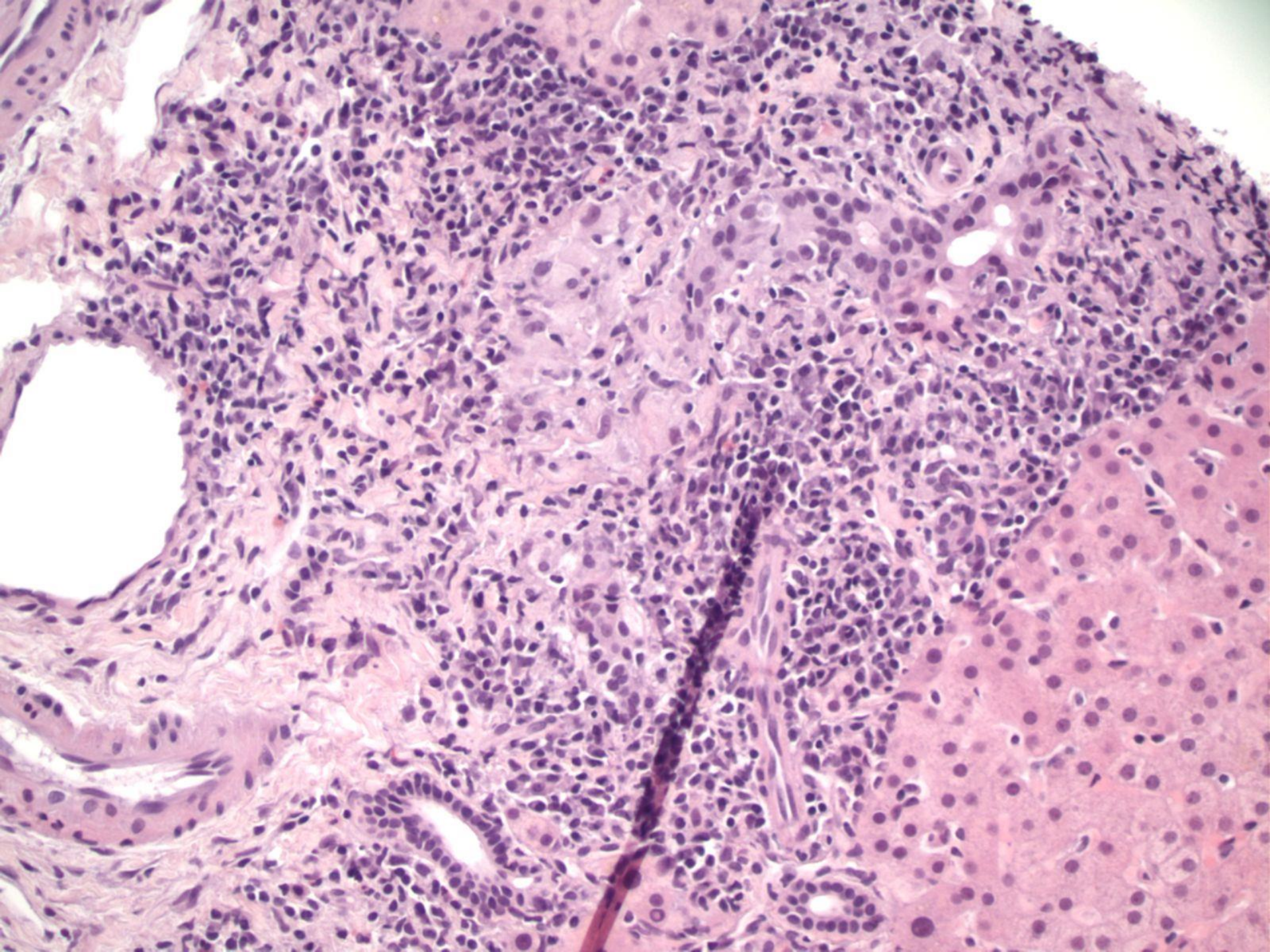
AIH

1. Moderate to severe interface hepatitis
2. IgG >2x or SMA positive
3. ALT >5x

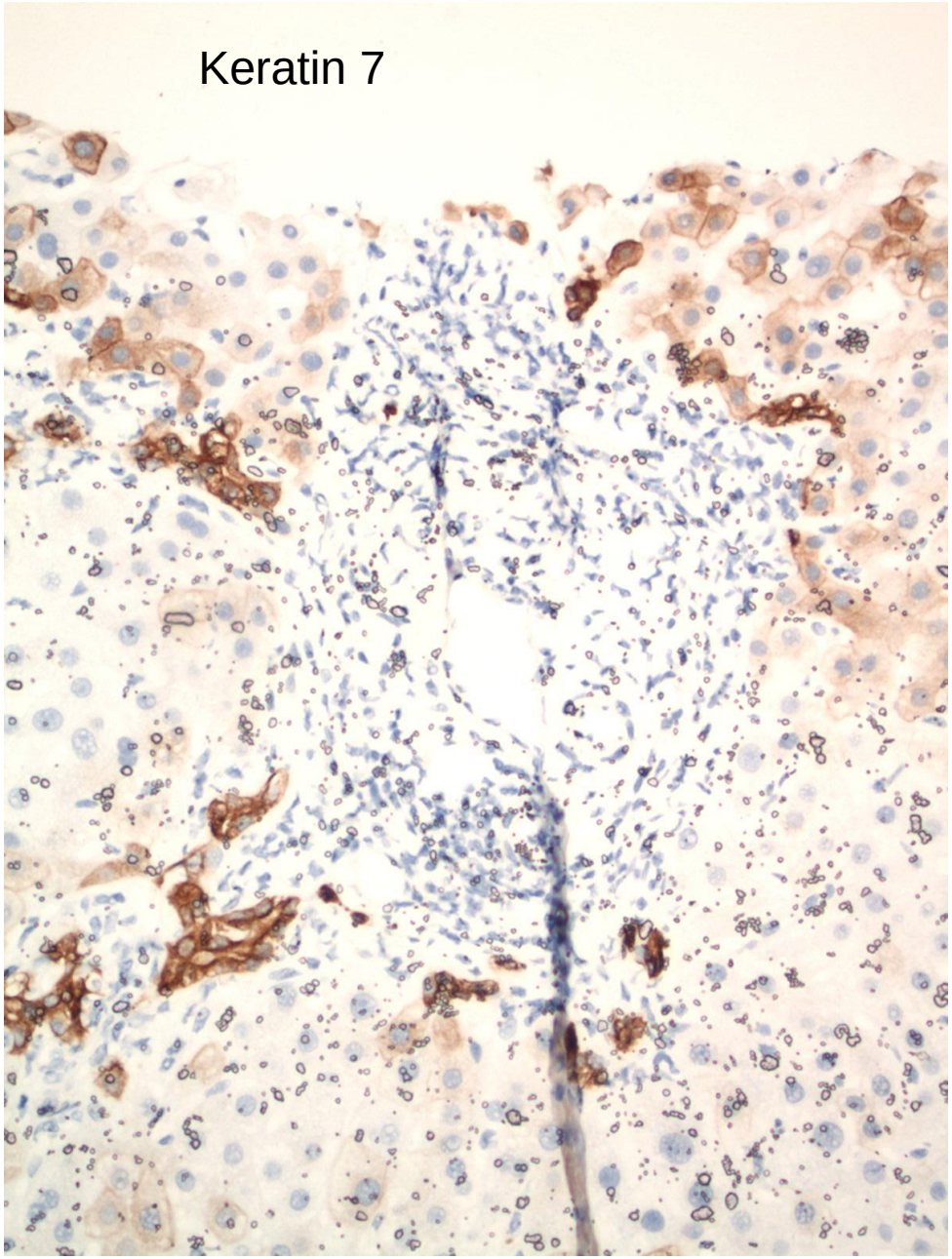
PBC-AIH

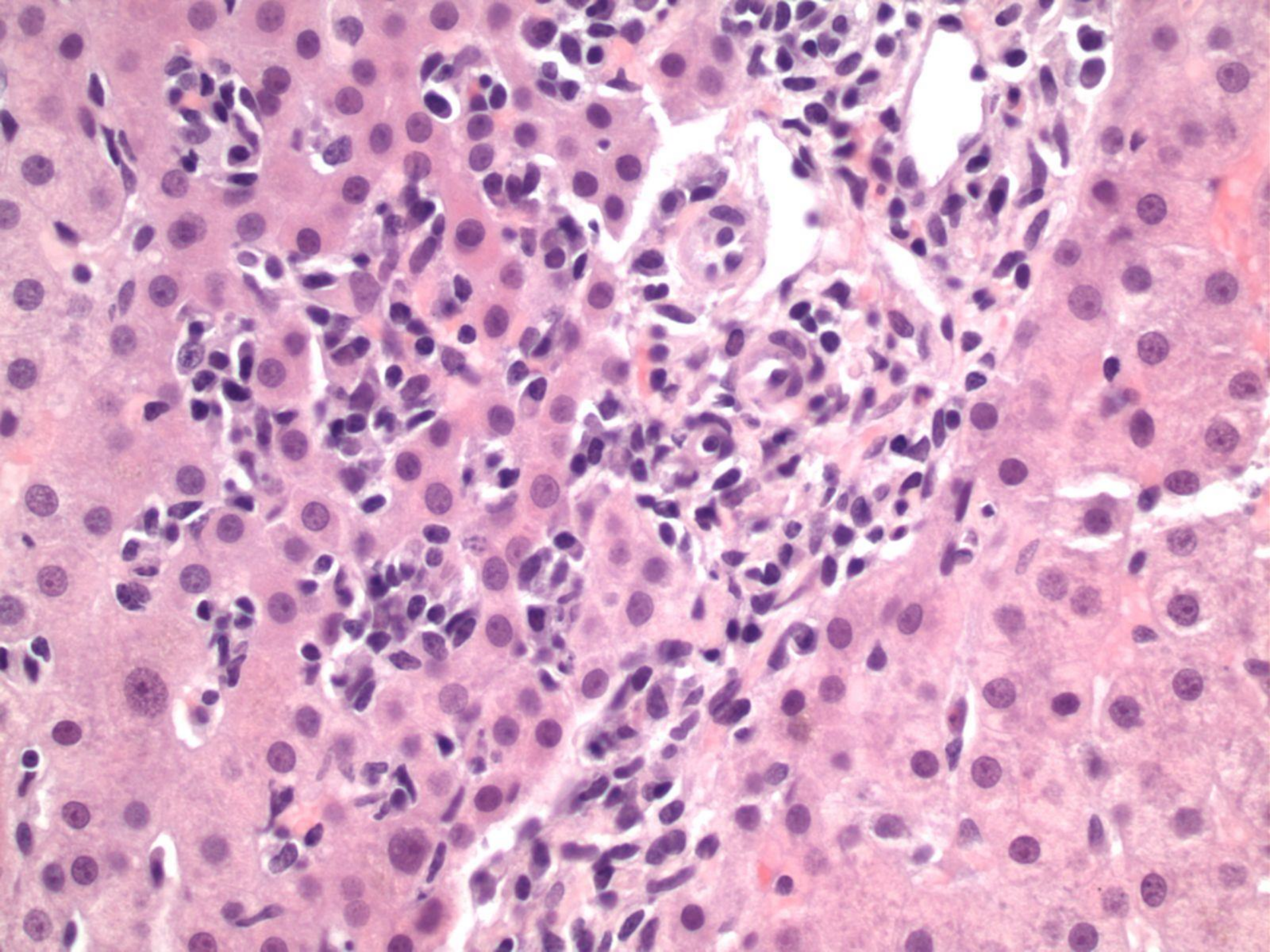
- Paris criteria incorporated into European Association for the Study of the Liver (EASL) guidelines for the management of cholestatic liver disease but with the emphasis on interface hepatitis as a mandatory feature of overlap.

- Recent EASL guidelines recommend combination therapy with UDCA and steroids in patients with overlap. An alternative approach is UDCA monotherapy with the addition of steroids if an adequate biochemical response is not achieved in 3 months.

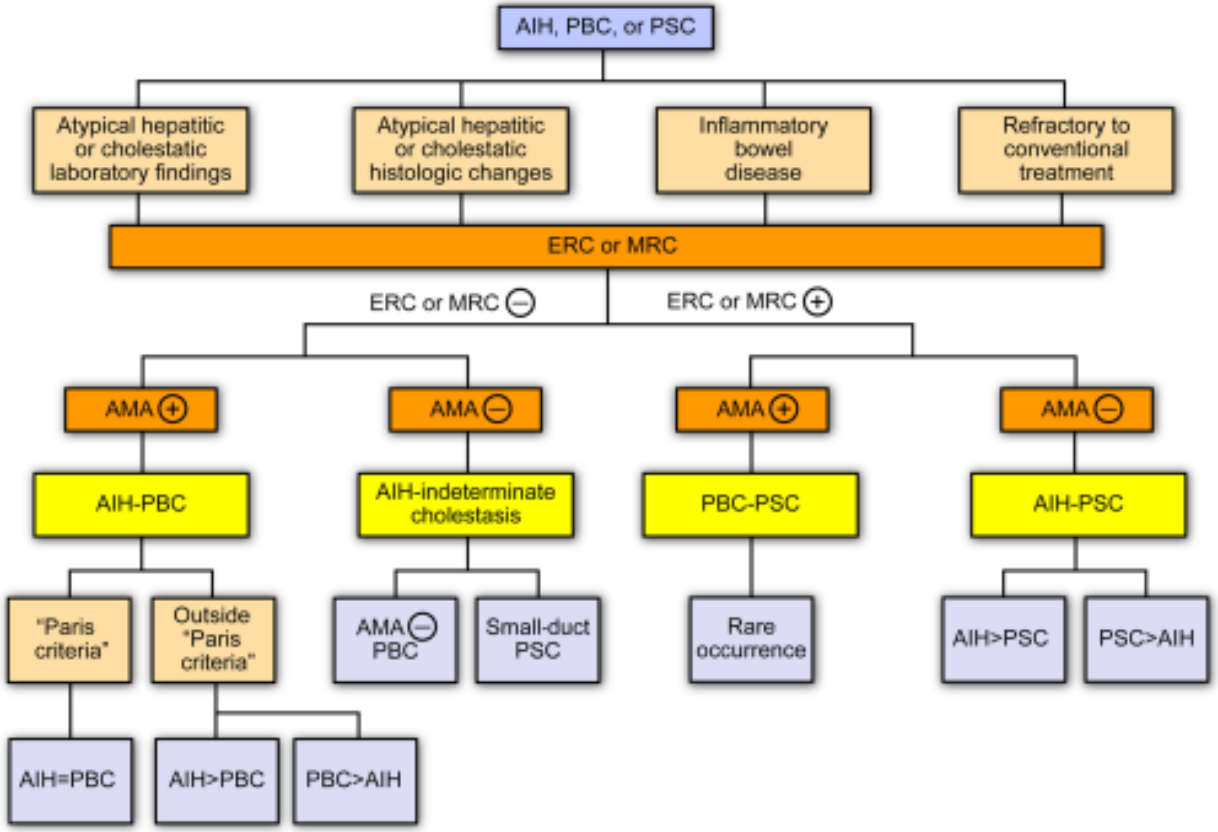


Keratin 7





Overlap syndromes

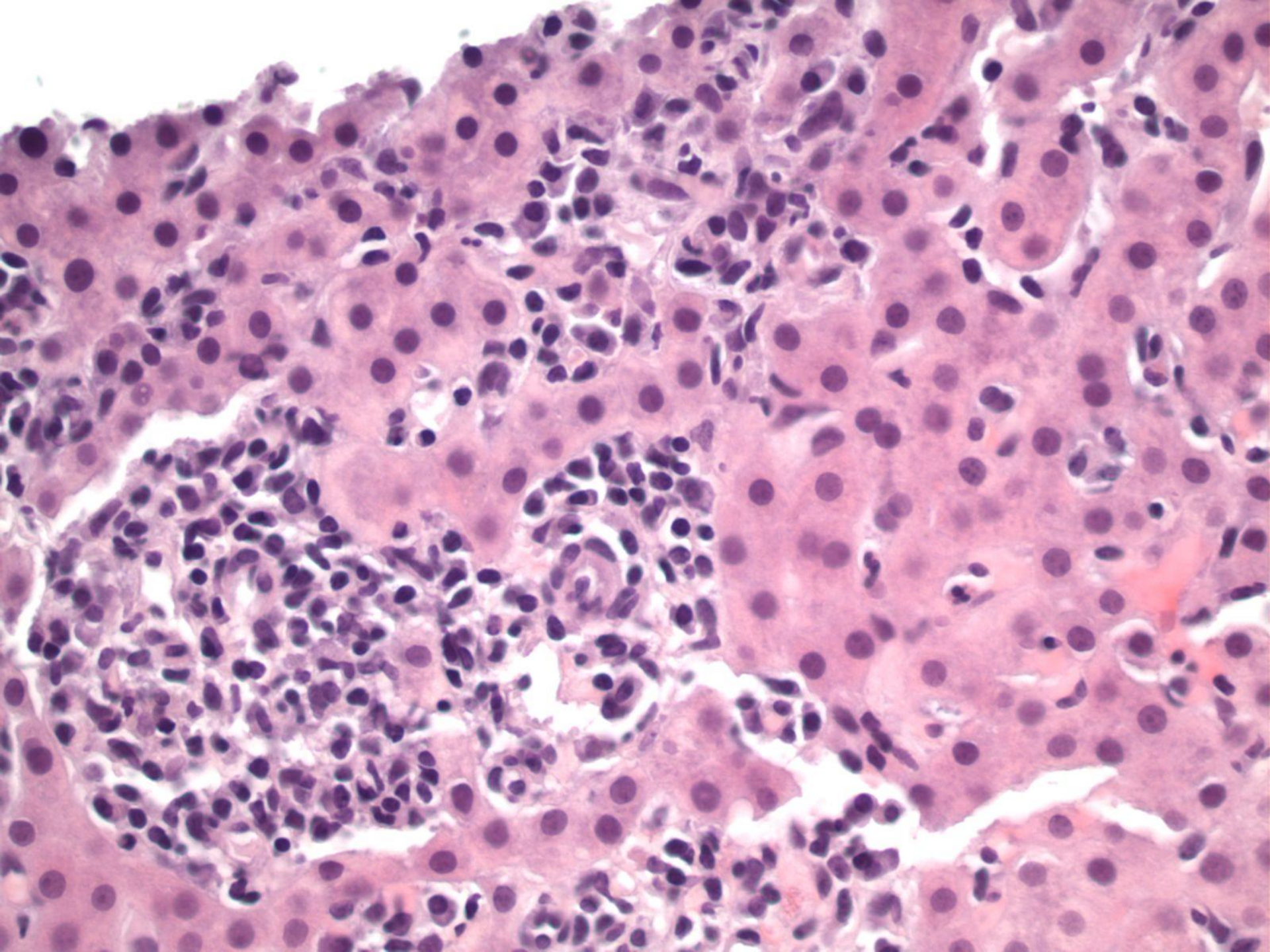


Diagnostic algorithm for the overlap syndromes. Patients with AIH, PBC, or PSC who have atypical hepatitic or cholestatic laboratory or histologic findings have concurrent inflammatory bowel disease, or do not respond to conventional treatments should undergo ERC or MRC.

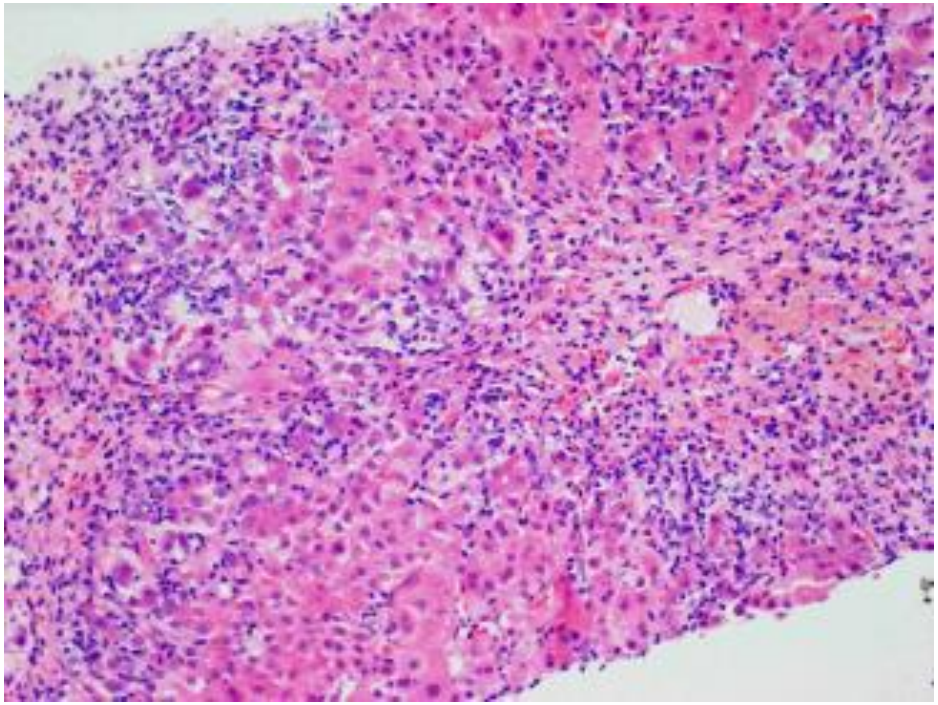
The cholangiographic findings can then be used in conjunction with the presence or absence of AMAs to distinguish between AIH and PBC (AIH-PBC), AIH and an indeterminate cholestatic disease (AIH–indeterminate cholestasis), PBC and PSC (PBC-PSC), and AIH and PSC (AIH-PSC) in patients with the overlap syndromes.

The clinical findings can also be used to distinguish the predominant disease component in each overlap syndrome. The Paris criteria tend to define a syndrome with equivalent AIH and PBC components (AIH = PBC). The other overlap syndromes of AIH and PBC can be either AIH-predominant (AIH > PBC) or PBC-predominant (PBC > AIH). Similarly, patients with the overlap syndrome of AIH and PSC (AIH-PSC) can be either AIH-predominant (AIH > PSC) or PSC-predominant (PSC > AIH).

Clinical Liver Disease
Volume 3, Issue 1, pages 2-5, 10 FEB 2014 DOI: 10.1002/cld.294
http://onlinelibrary.wiley.com/doi/10.1002/cld.294/full#cld294-fig-0002



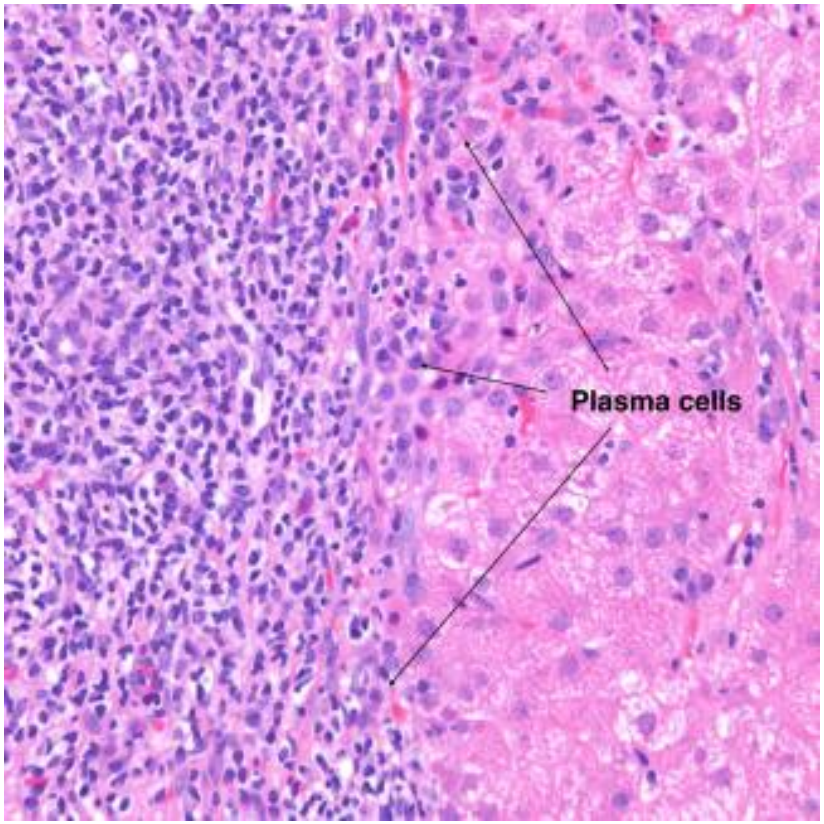
Autoimmune hepatitis: Diagnostic criteria and serological testing



Interface hepatitis is the typical histological feature of AIH and is characterized by a dense portal and periportal lymphocyte and plasma cell infiltrate that disrupts the parenchymal limiting plate (hematoxylin & eosin staining; original magnification ×40).

Clinical Liver Disease
Volume 3, Issue 2, pages 38-41, 5 MAR 2014 DOI: 10.1002/cld.321
http://onlinelibrary.wiley.com/doi/10.1002/cld.321/full#cld321-fig-0002

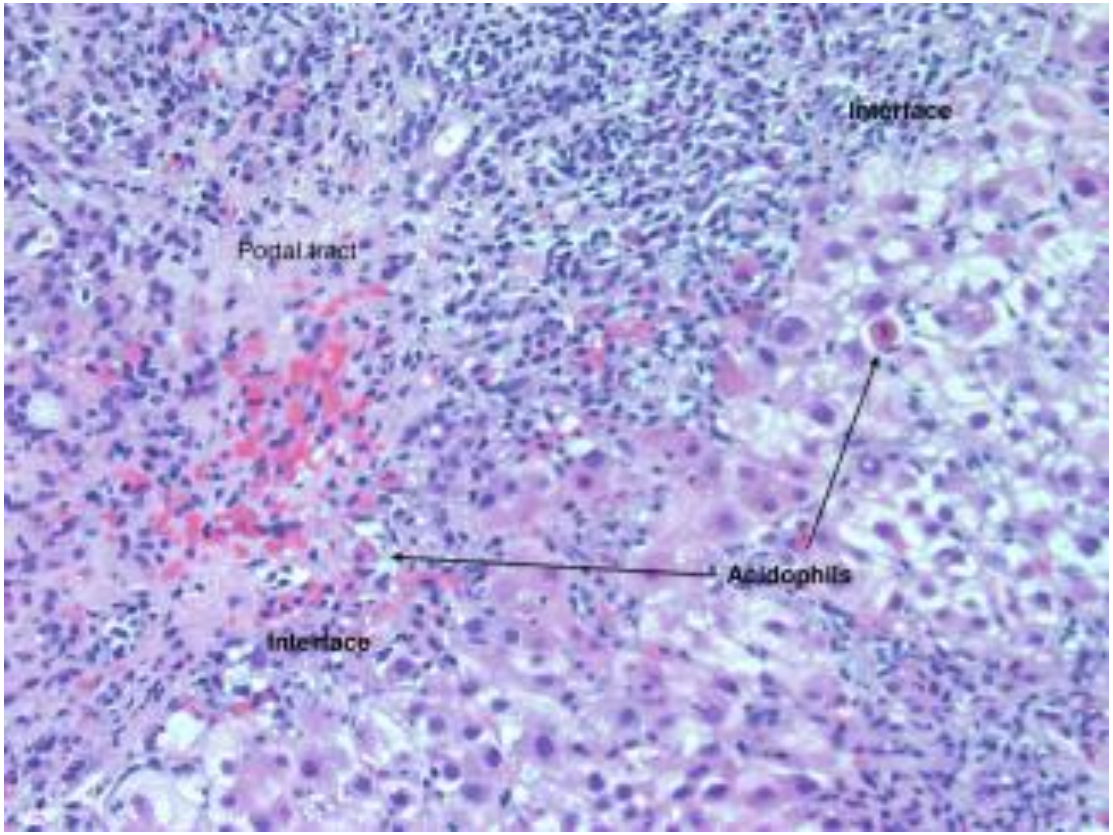
Autoimmune hepatitis: Histopathology



AIH. This high-magnification image (hematoxylin-eosin, ×400) shows a predominantly lymphocytic portal infiltrate with clusters of plasma cells at the interface.

Clinical Liver Disease
Volume 3, Issue 2, pages 19-23, 5 MAR 2014 DOI: 10.1002/cld.301
http://onlinelibrary.wiley.com/doi/10.1002/cld.301/full#cld301-fig-0003

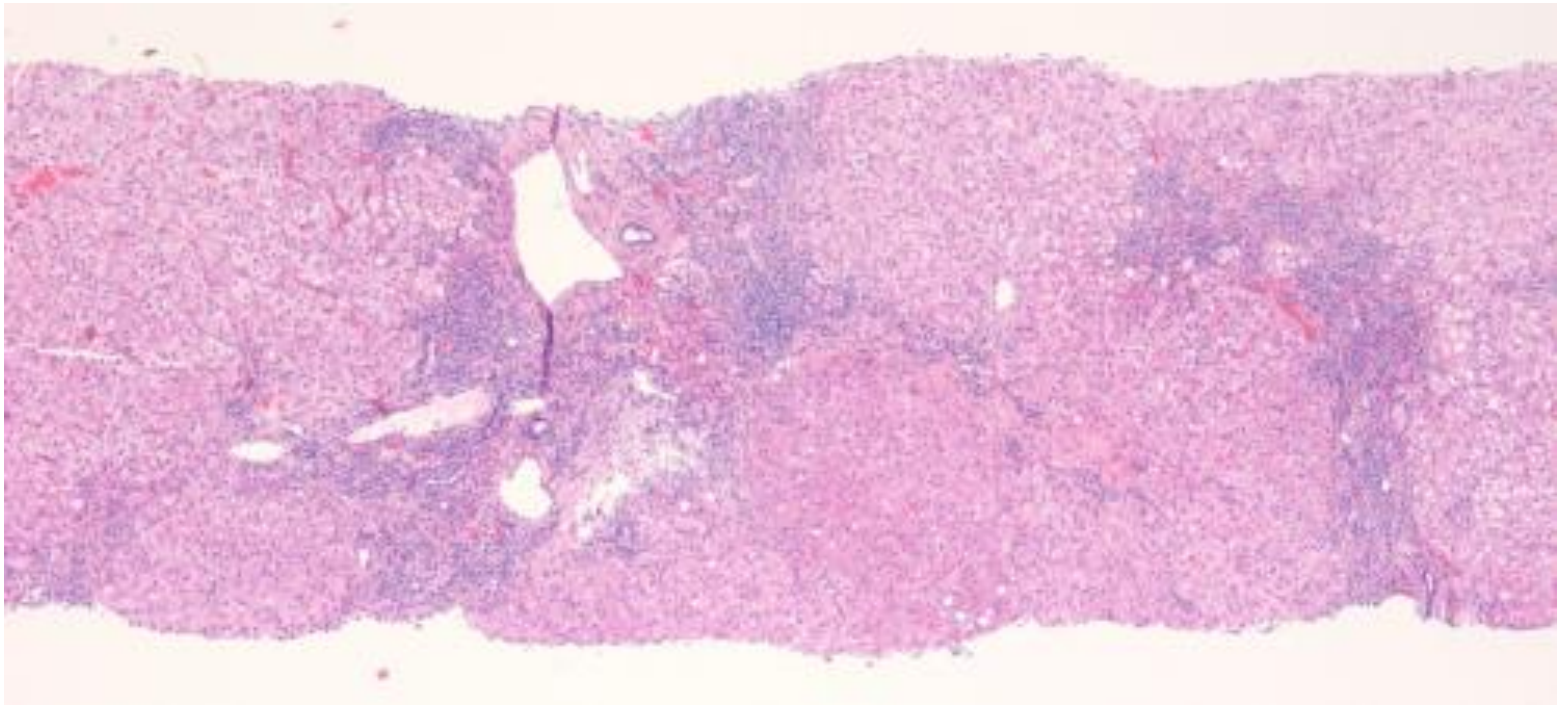
Autoimmune hepatitis: Histopathology



AIH. This medium-magnification image (hematoxylin-eosin, ×200) shows a portal tract with an intense lymphoplasmacytic infiltrate effacing the interface with rosette formation and hepatocyte necrosis (acidophilic bodies).

Clinical Liver Disease
Volume 3, Issue 2, pages 19-23, 5 MAR 2014 DOI: 10.1002/cld.301
http://onlinelibrary.wiley.com/doi/10.1002/cld.301/full#cld301-fig-0002

Autoimmune hepatitis: Histopathology

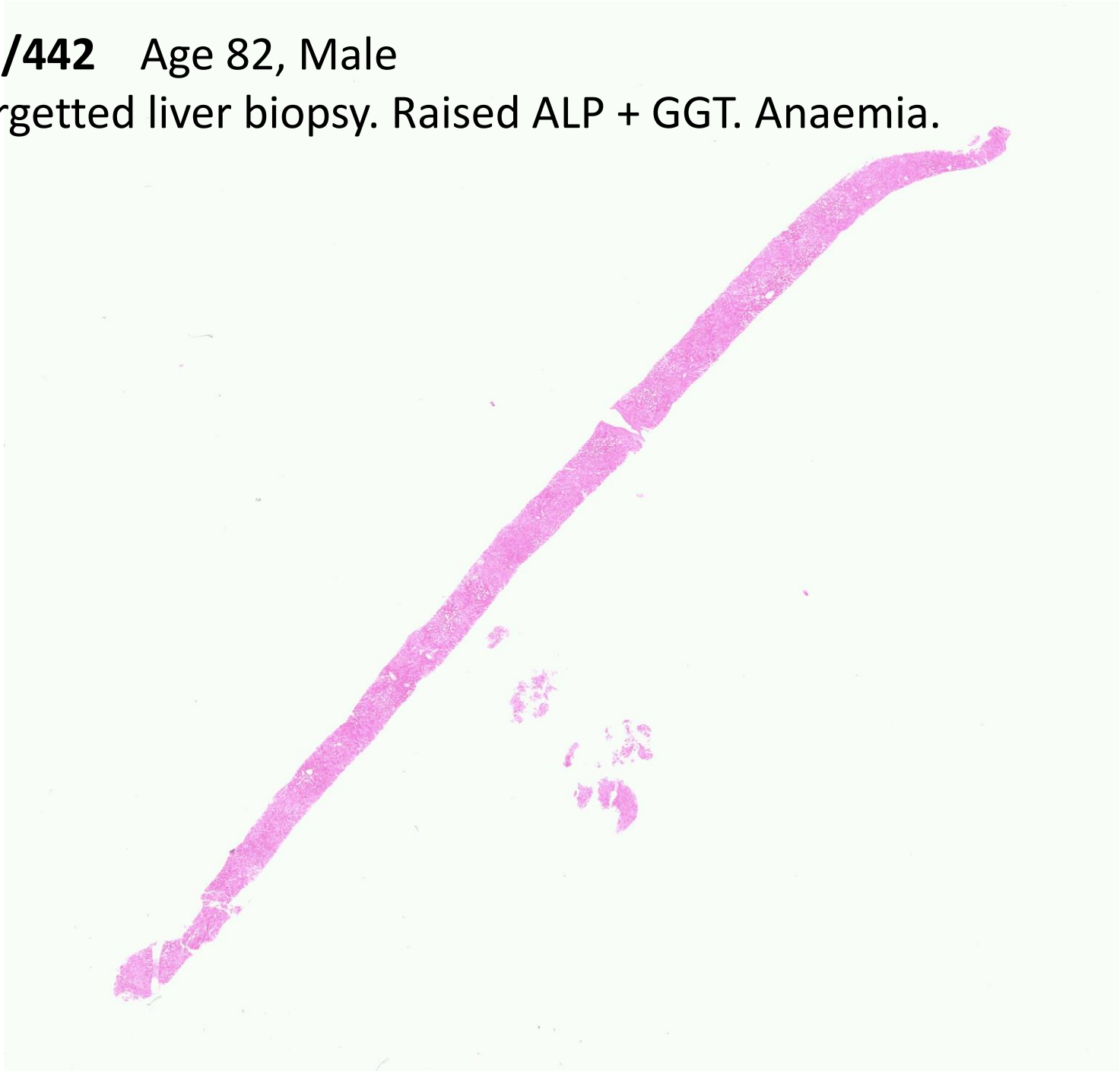


AIH. This low-magnification image (hematoxylin-eosin, ×40) shows expanded portal tracts with effacement of the interface by a lymphoplasmacytic infiltrate including many plasma cells. The connective tissue stain shows early fibrosis and regenerative activity with 2-cell-thick liver plates and early nodule formation.

Clinical Liver Disease
Volume 3, Issue 2, pages 19-23, 5 MAR 2014 DOI: 10.1002/cld.301
http://onlinelibrary.wiley.com/doi/10.1002/cld.301/full#cld301-fig-0001

Case J1/442 Age 82, Male

Non-targetted liver biopsy. Raised ALP + GGT. Anaemia.



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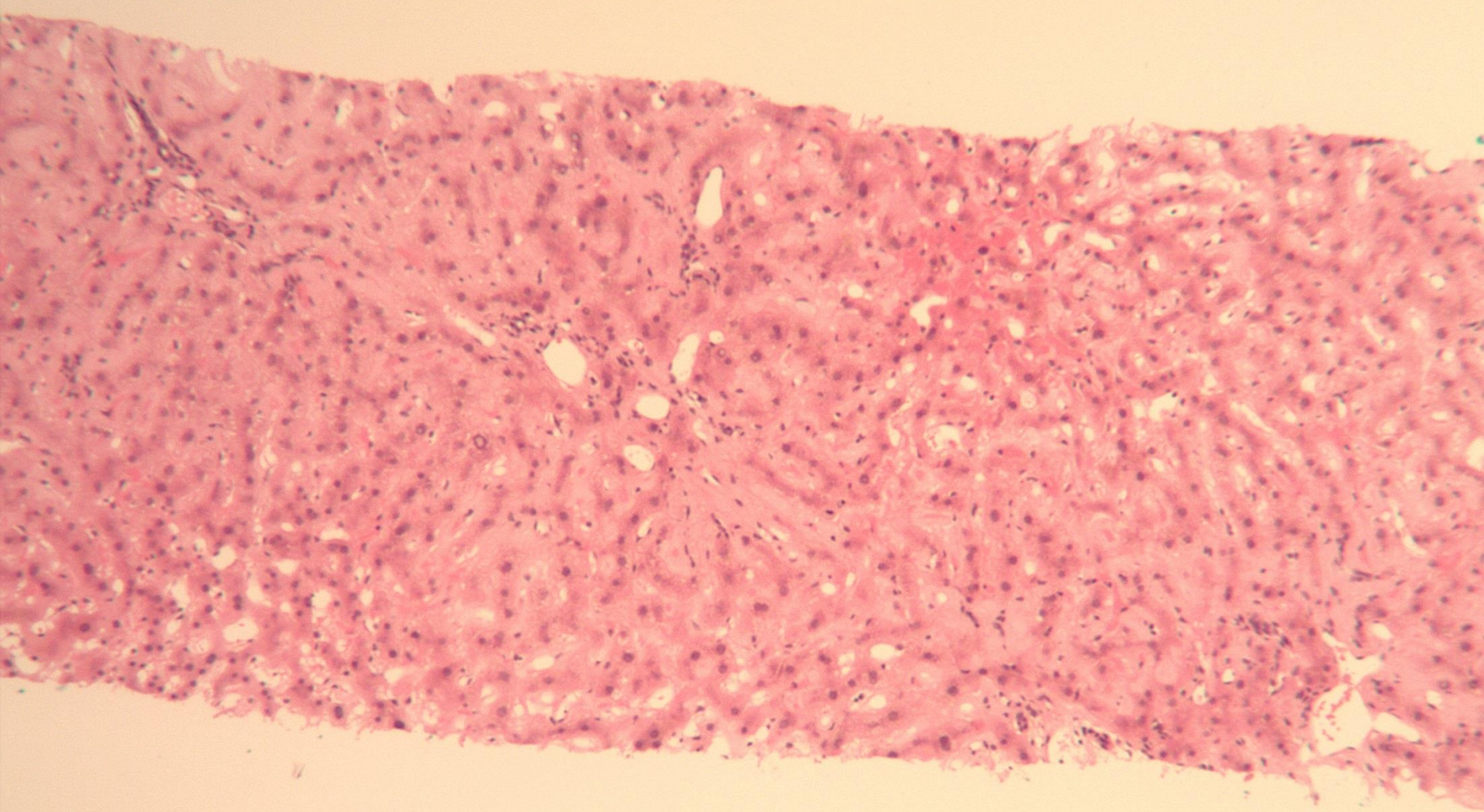

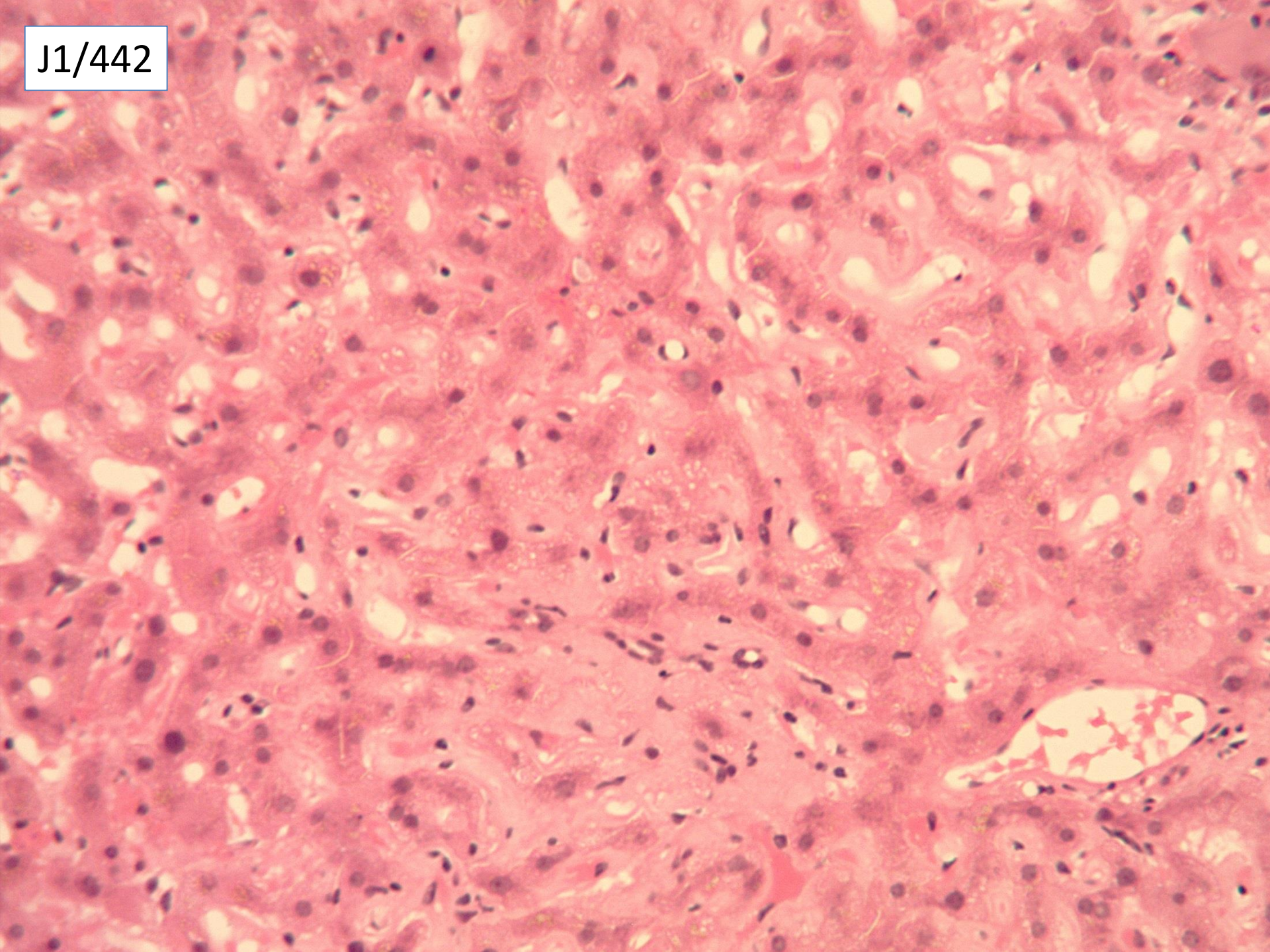
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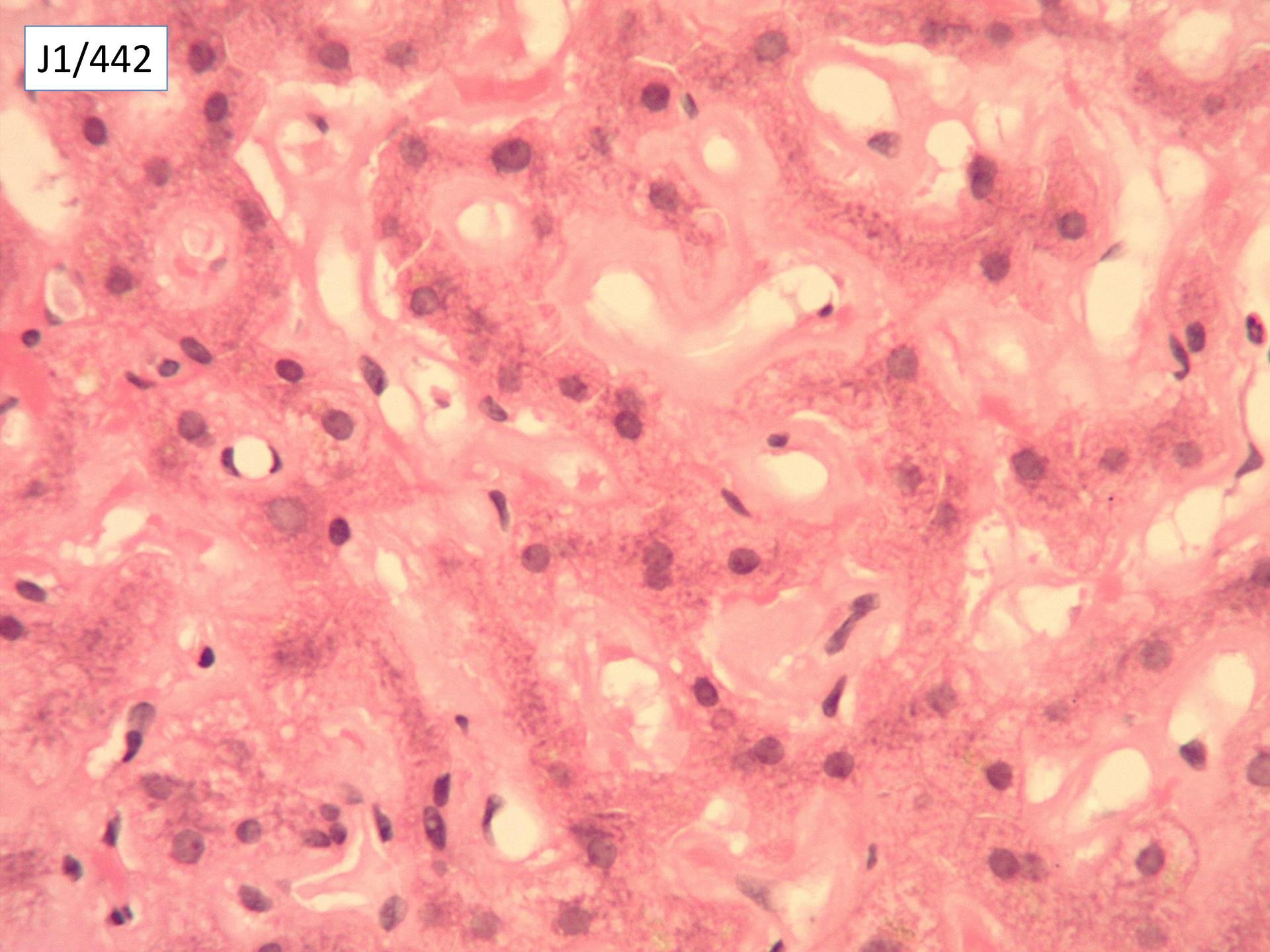
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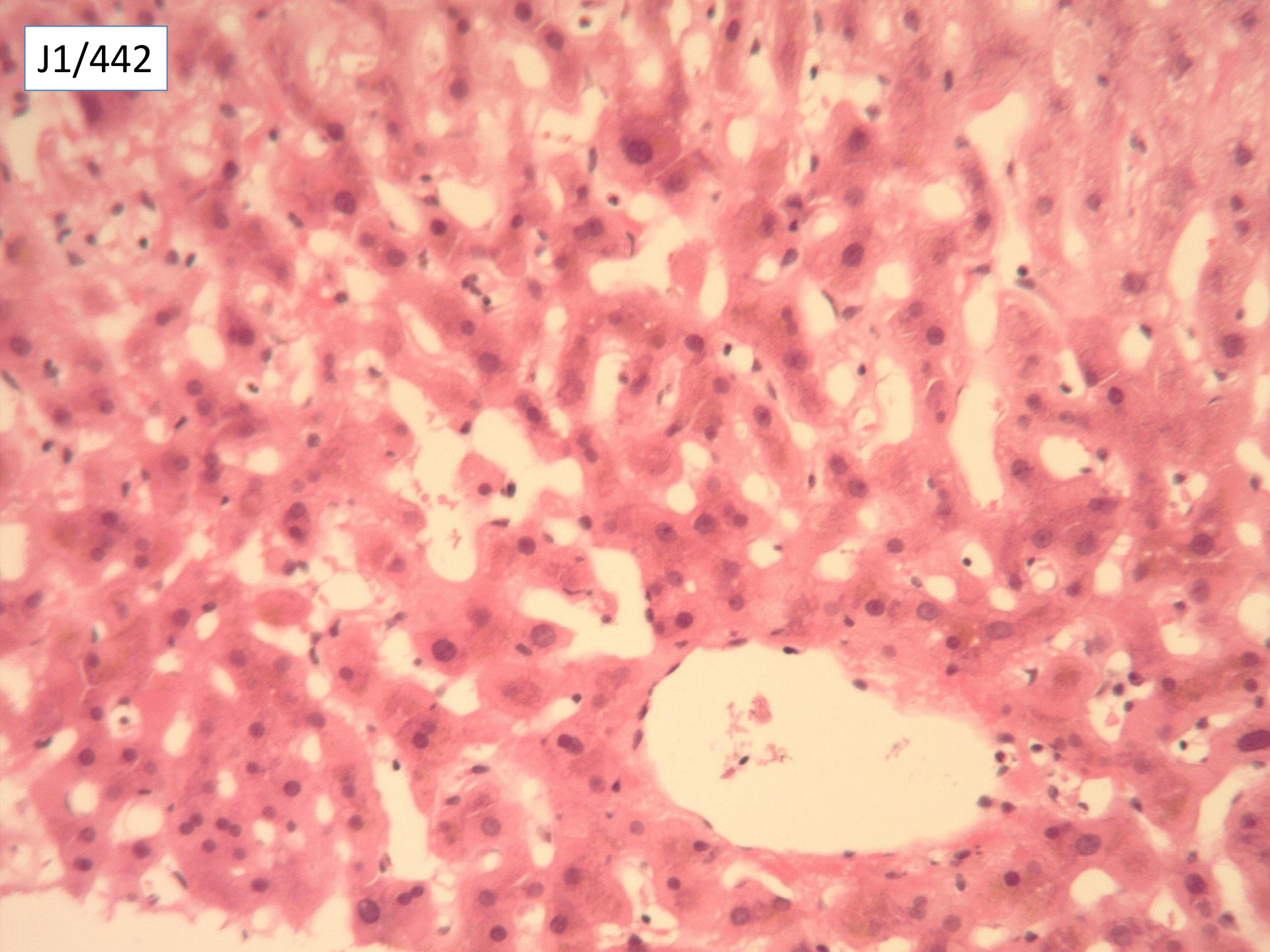
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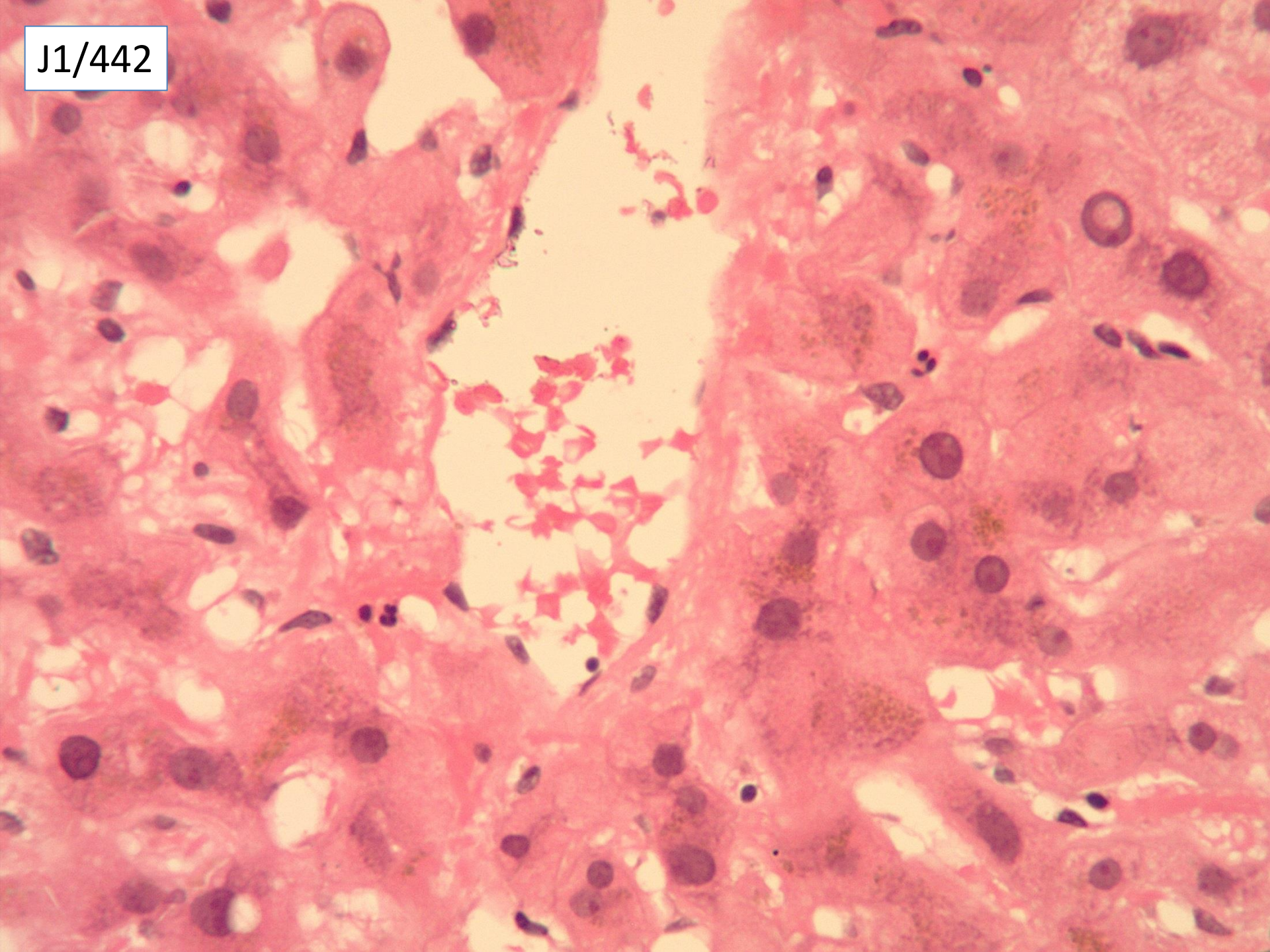

J1/442

Case J1/442 Age 82, Male

Non-targetted liver biopsy. Raised ALP + GGT. Anaemia.

77 Amyloid

1 heart failure ? BCS ?? amyloid – needs stains

2 sinusoidal dilatation, congestion, no mention of amyloid

1 cholestatic histology and biochemistry, Large bile duct obstruction

1 cholestasis and bile duct damage ? PSC

Suggested scoring: at last an easy one to score.
For 10 points – amyloid as only or main diagnosis
Amyloid in differential but not first score 5 points.
No mention of amyloid, score 0 points.

14/14 agree, 0 unsuitable

Case J1/442 Age 82, Male

Non-targetted liver biopsy. Raised ALP + GGT. Anaemia.

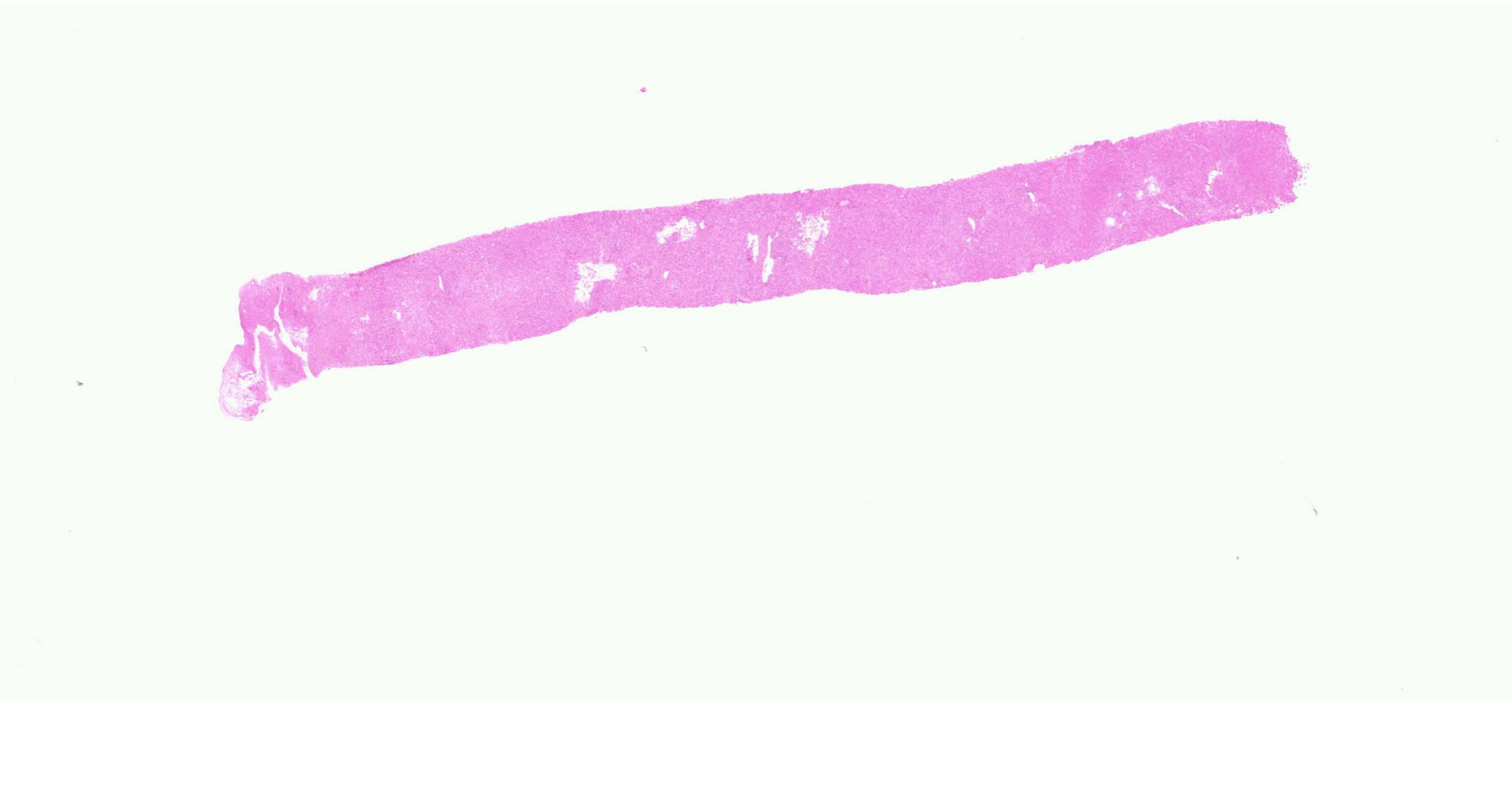
Original diagnosis: hepatic light chain deposition disease.

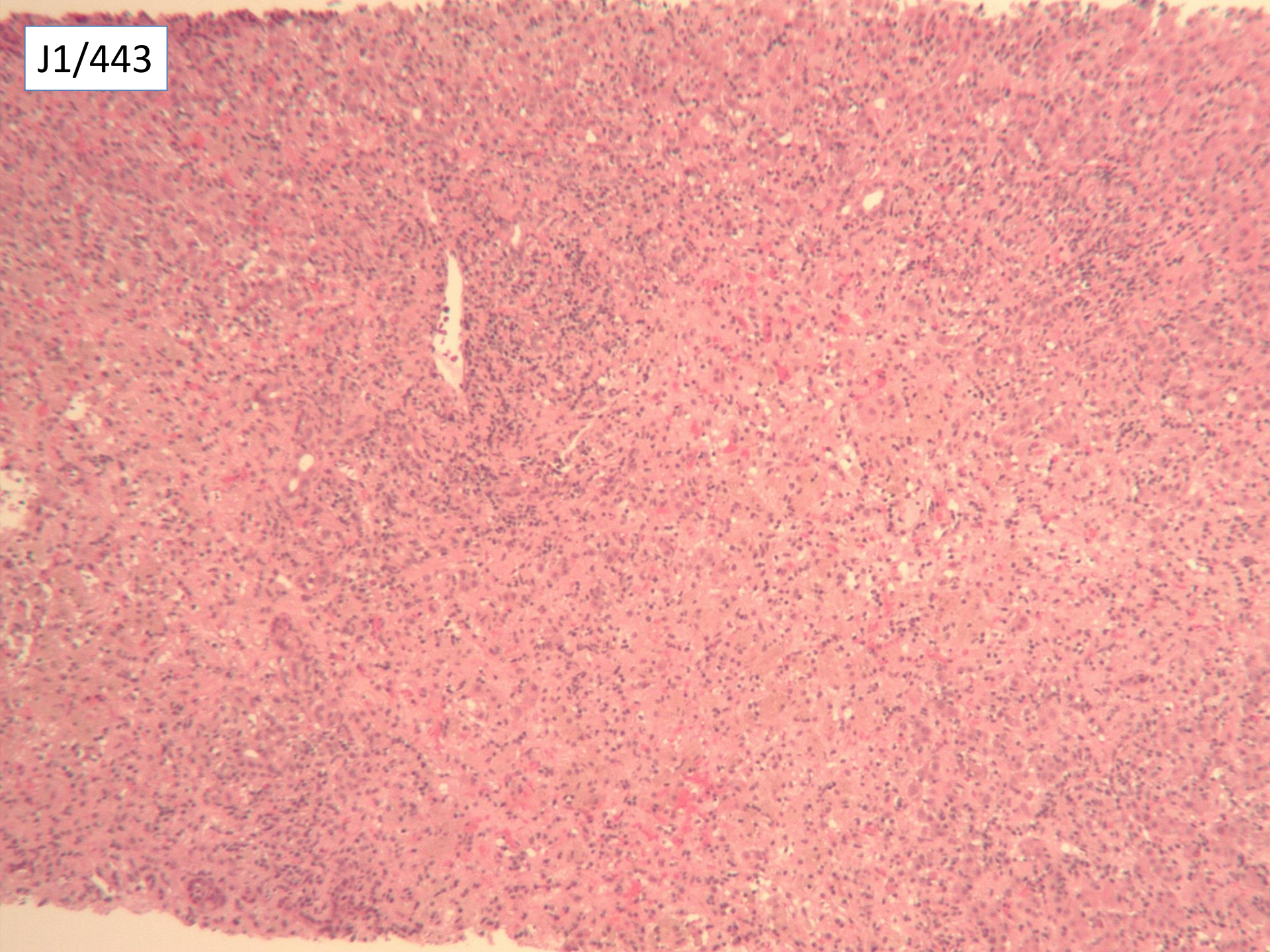
Immunohistochemistry for light chains is non contributory.

Comment: light chain deposition disease and amyloid look the same on H&E sections – need Congo red (amyloid) and PASD (light chain deposition disease) for diagnosis.

Case J1/443 Age 53, Female

Deranged LFT's presented with lethargy and itch, recent course of antibiotics

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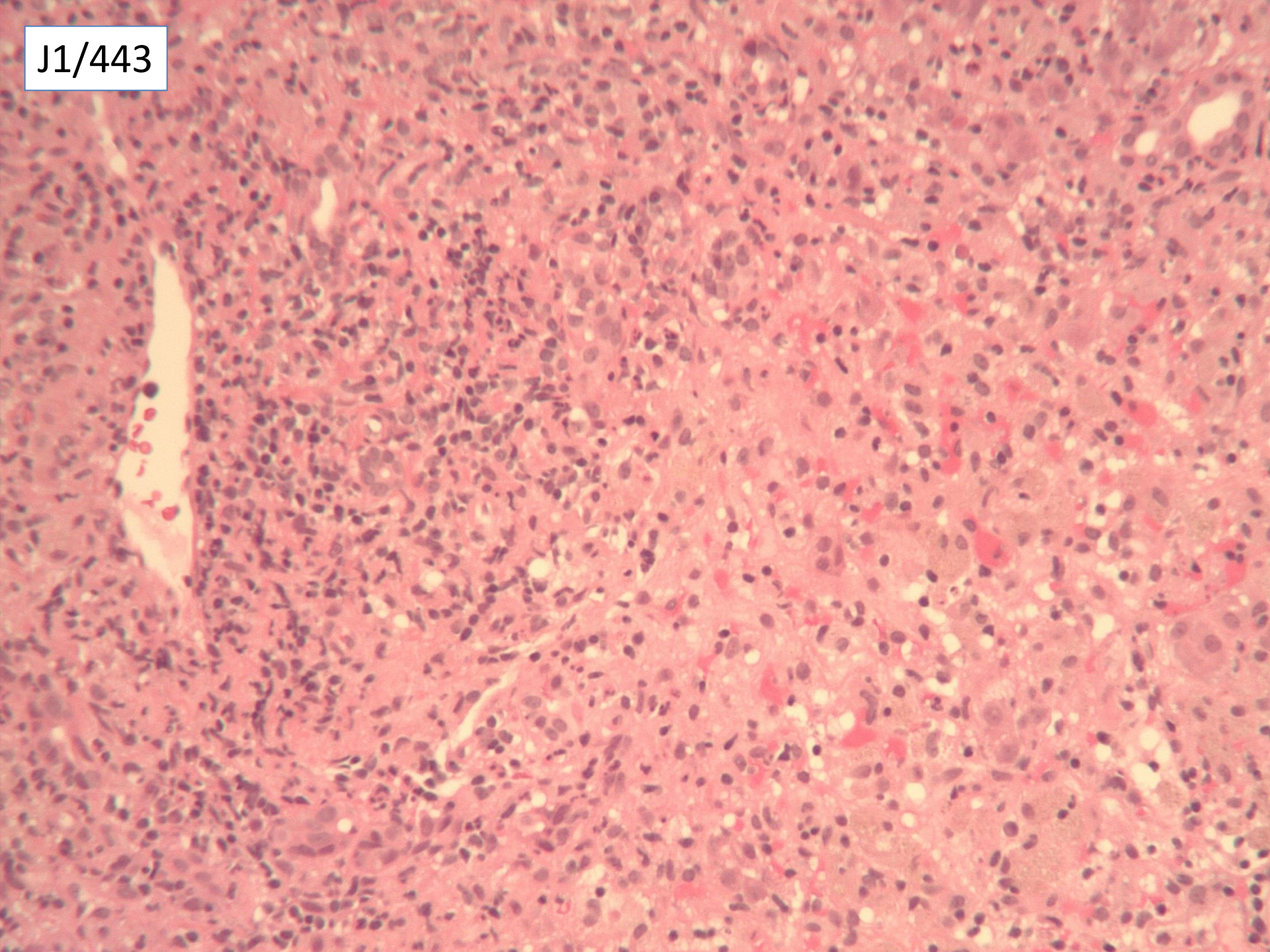
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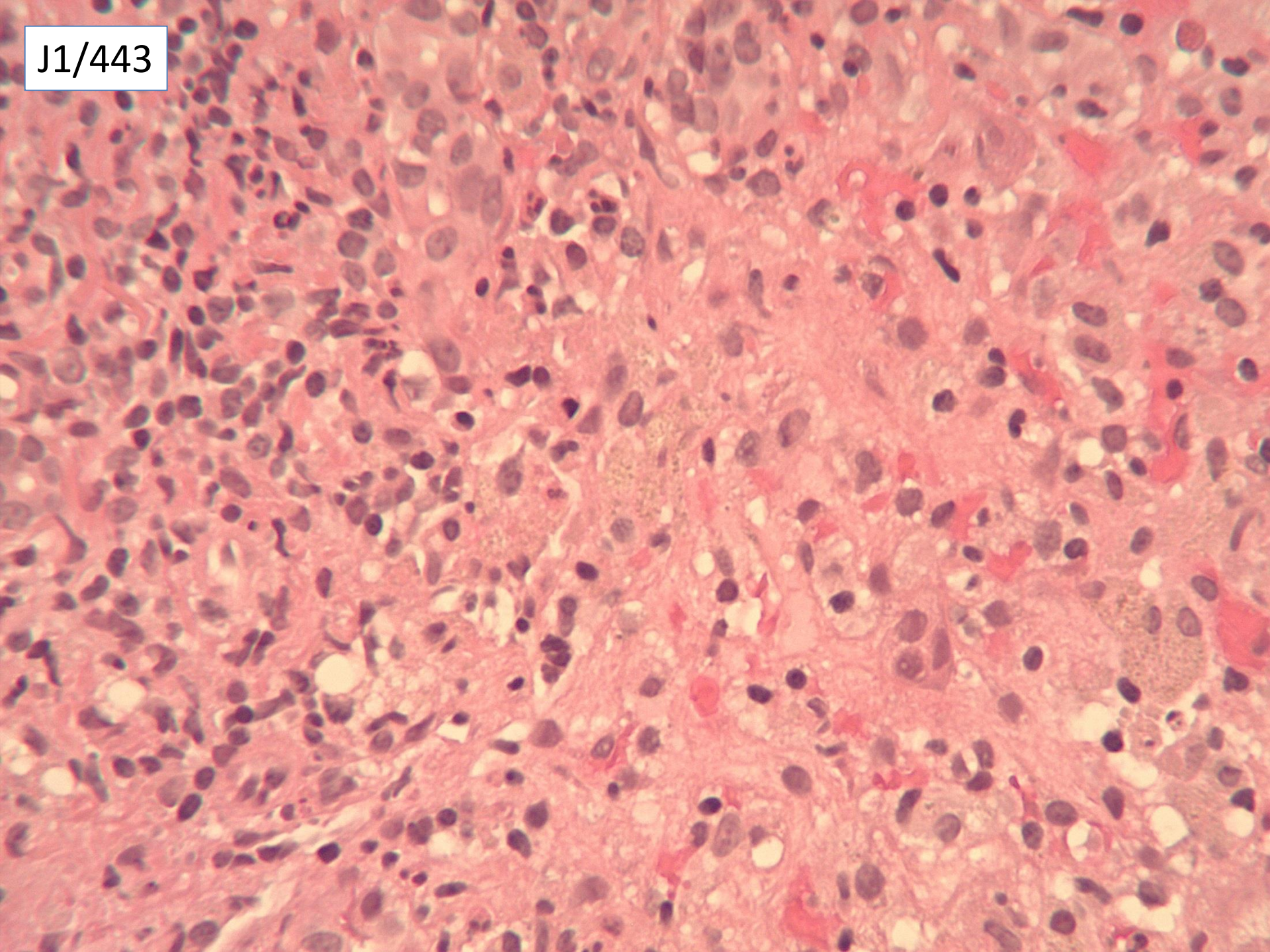
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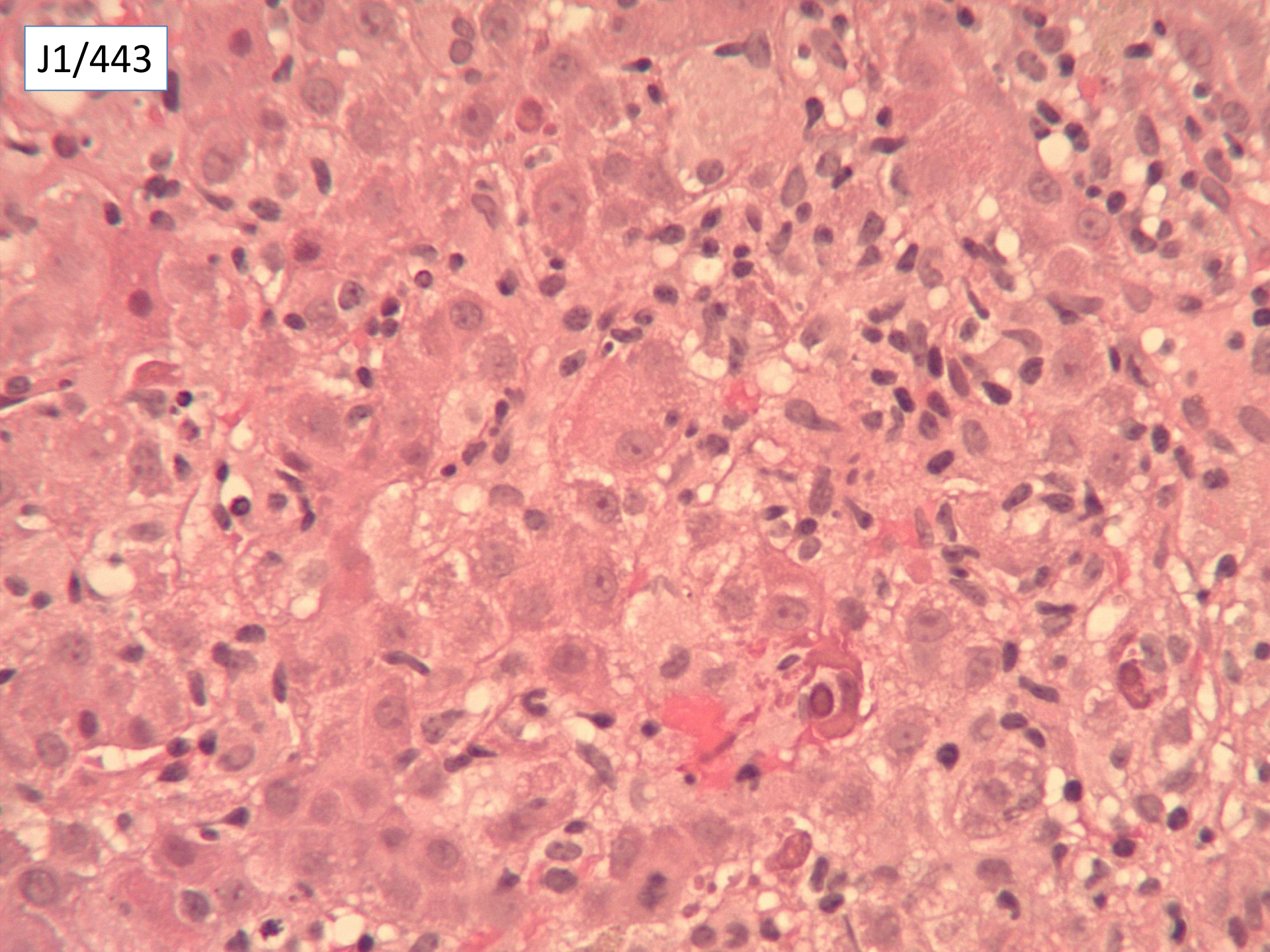
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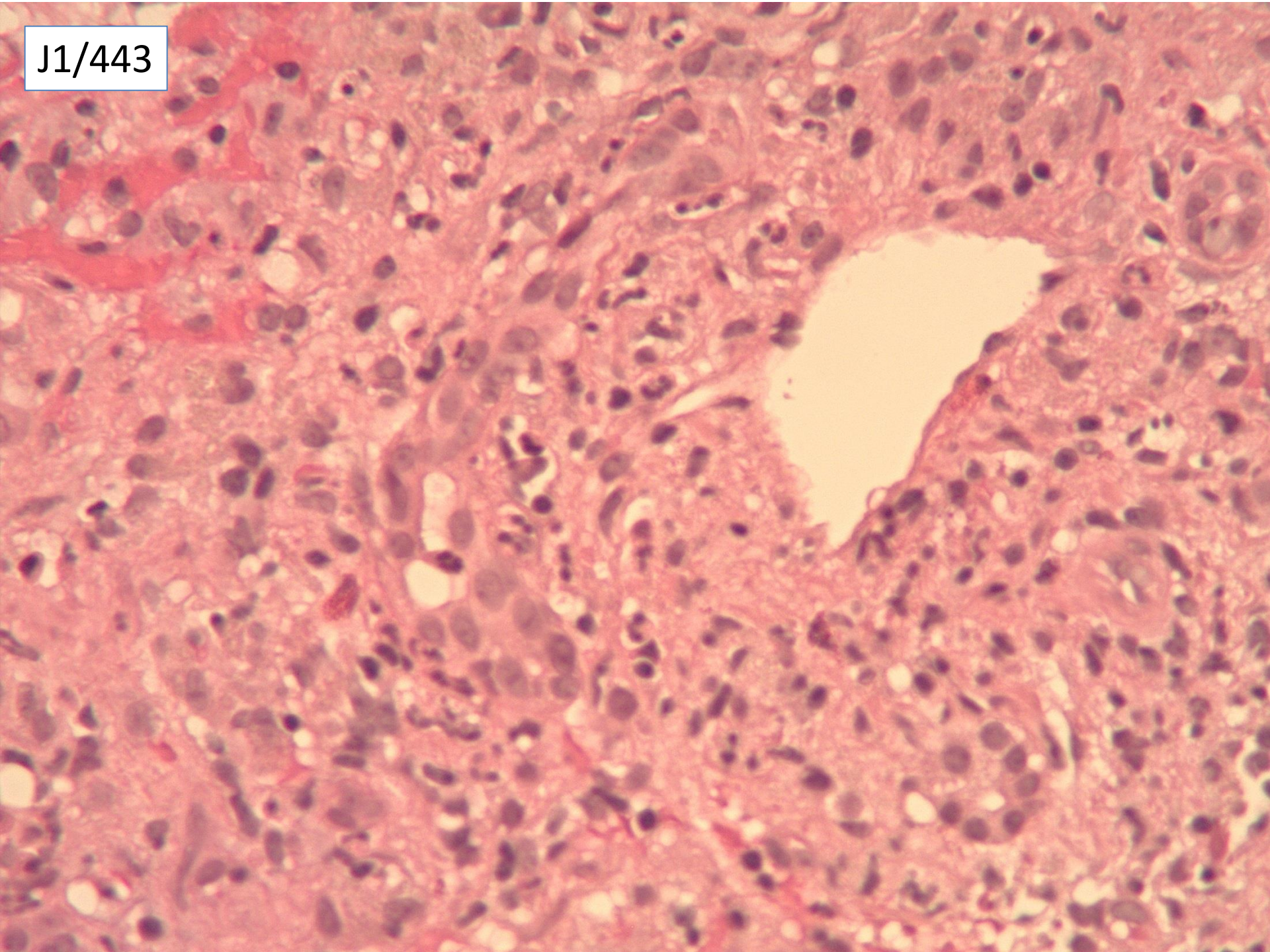
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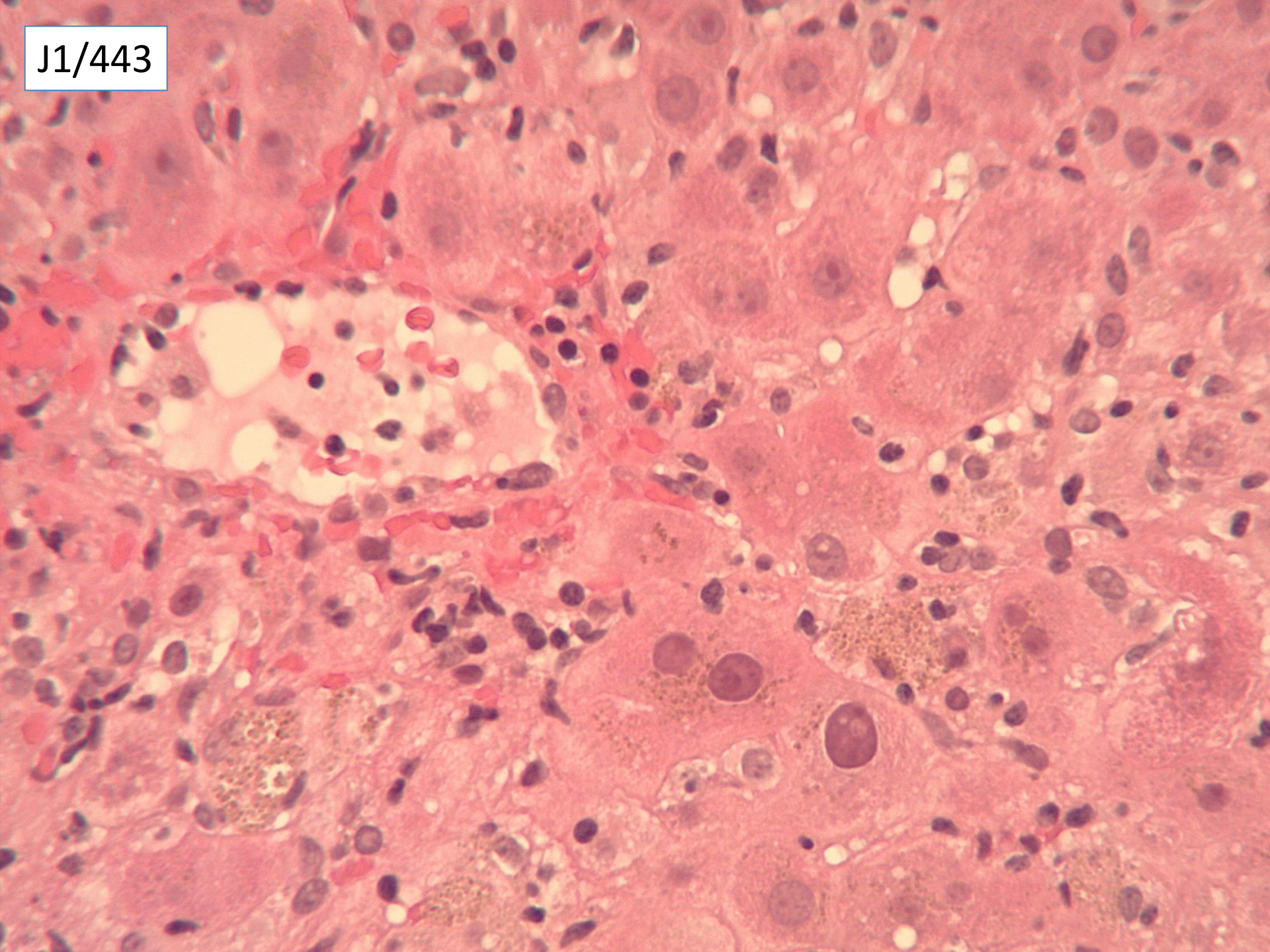

J1/443

Case J1/443 Age 53, Female

Deranged LFT's presented with lethargy and itch, recent course of antibiotics

54 acute hepatitis with confluent or bridging necrosis

26 acute hepatitis

1 cholestatic hepatitis with bile infarcts

35 cholestasis or bilirubinostasis

2 ballooning and Mallory bodies

38 consistent with drugs (only aetiology)

28 consistent with drugs, exclude others – viral, AIH

11 consistent with drugs, exclude viral

3 consistent with drugs, exclude AIH

1 drugs not mentioned – severe acute cholestatic hepatitis with haemorrhage, veno-occlusive disease

1 "bile infarcts associated with cholestasis, exclude infection and other drugs"

Suggested scoring: for 10 points – acute hepatitis and include drugs as aetiology.

Responses with bile infarcts or ballooning/Mallory bodies are misleading – 5 points.

14/14 agree, 1 unsuitable

Case J1/443 Age 53, Female

Deranged LFT's presented with lethargy and itch,
recent course of antibiotics

Original diagnosis: drug induced hepatitis

Follow up: The patient had received nitrofurantoin shortly before the presentation with acute liver injury. She developed liver failure and required transplantation.

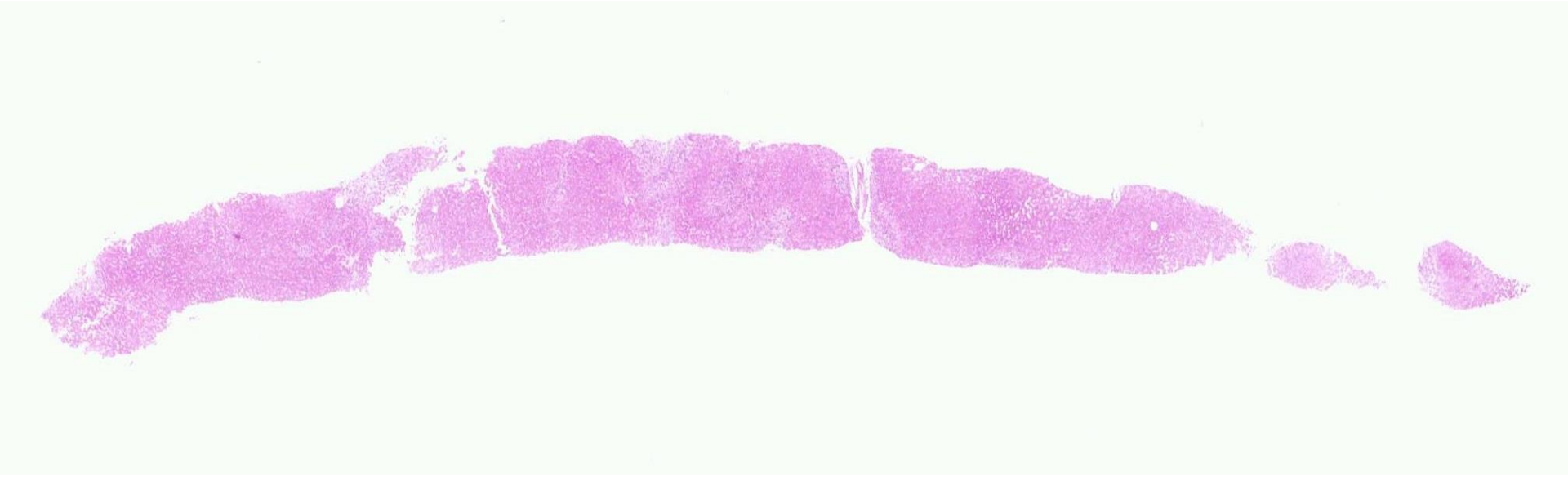
Commented that severity of acute hepatitis with confluent necrosis (as here) is an important histopathological marker of higher risk of liver failure.

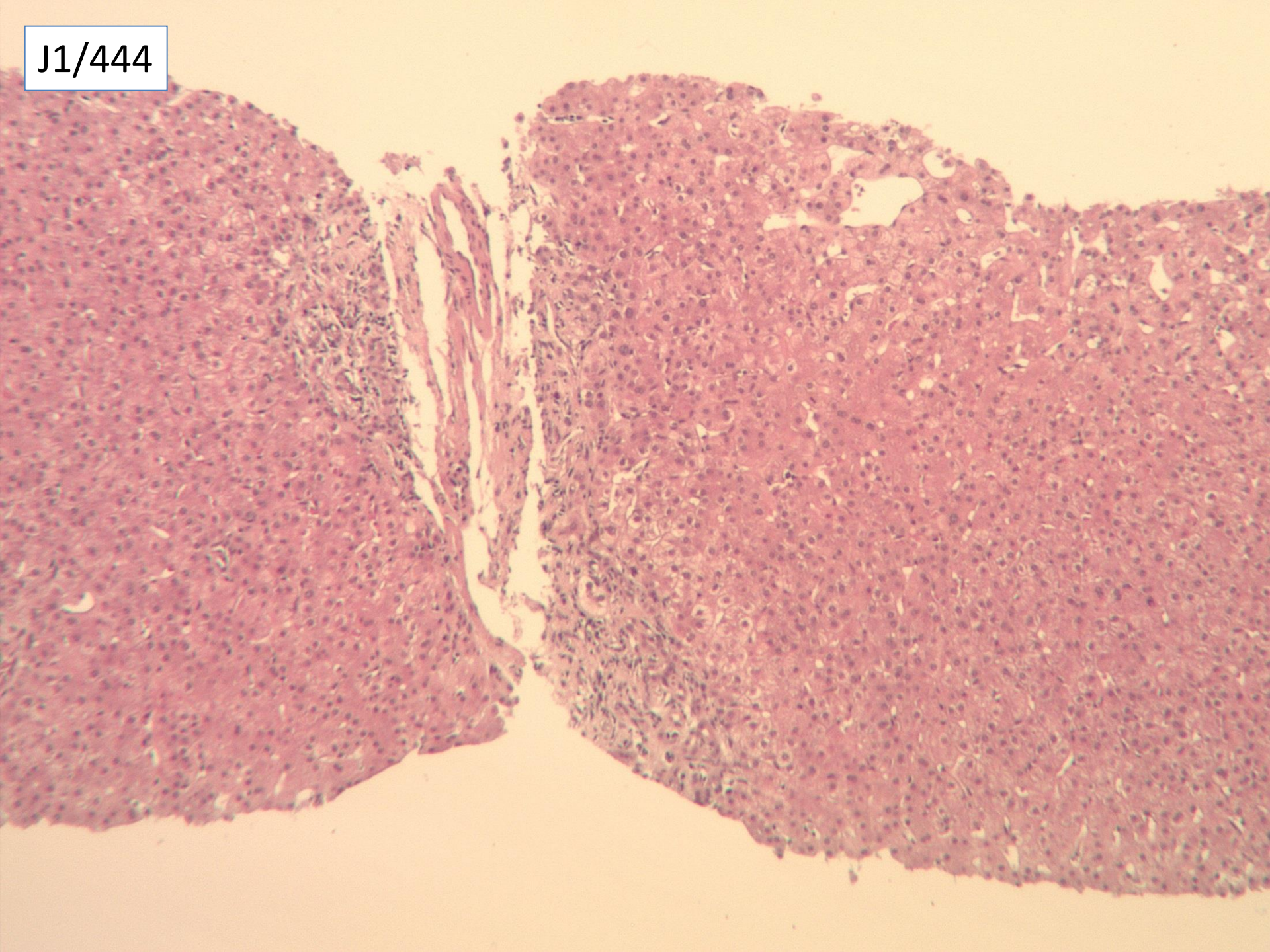
Case J1/444 Age 64, Female

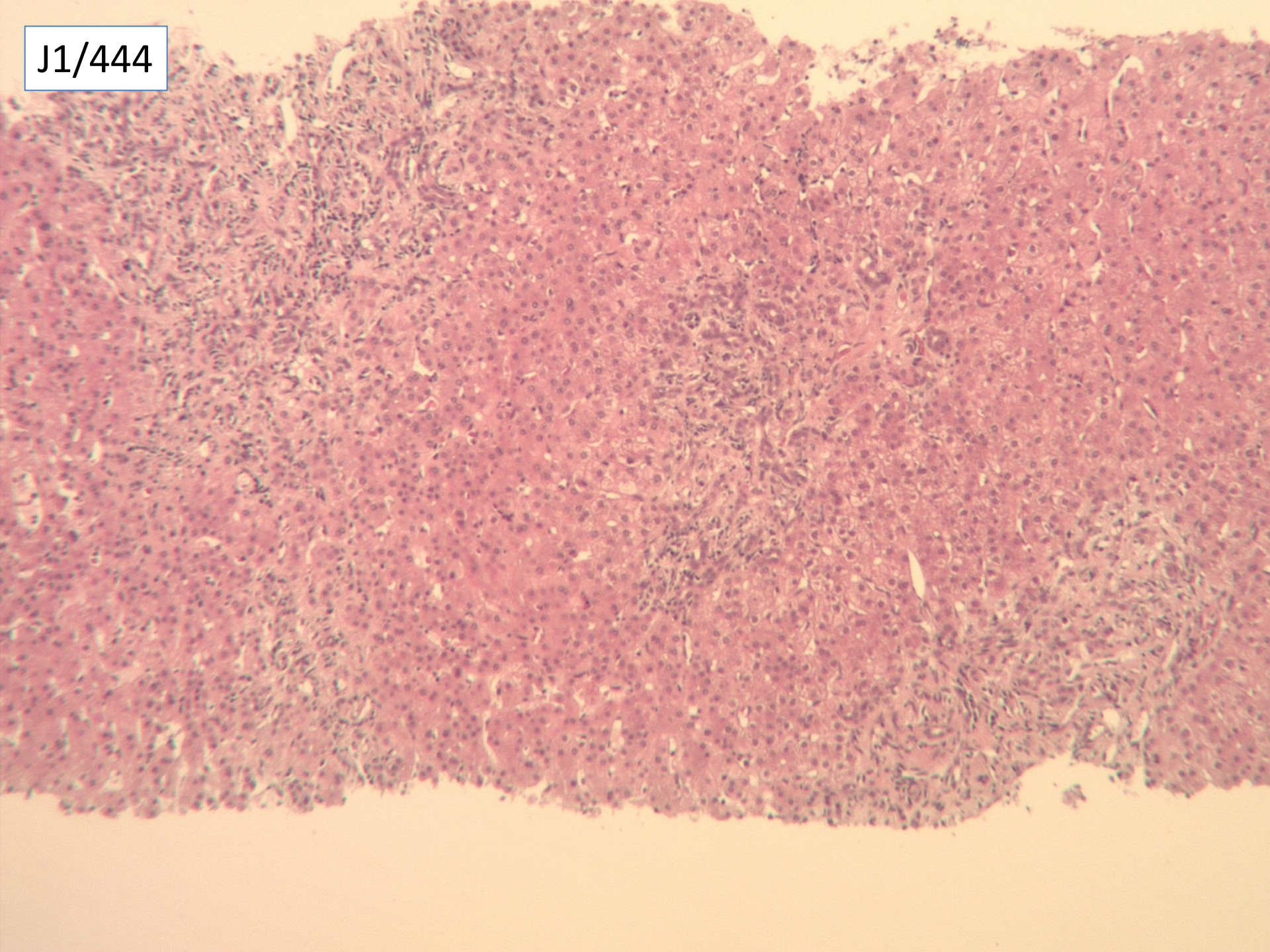
Liver transplant for PBC in 1995 (18 years ago). Deranged LFTs.

Anastomotic stricture in 2007 stented, follow up ERCP = no stricture.

Rising ALP? Recurrent PBC? Chronic rejection




J1/444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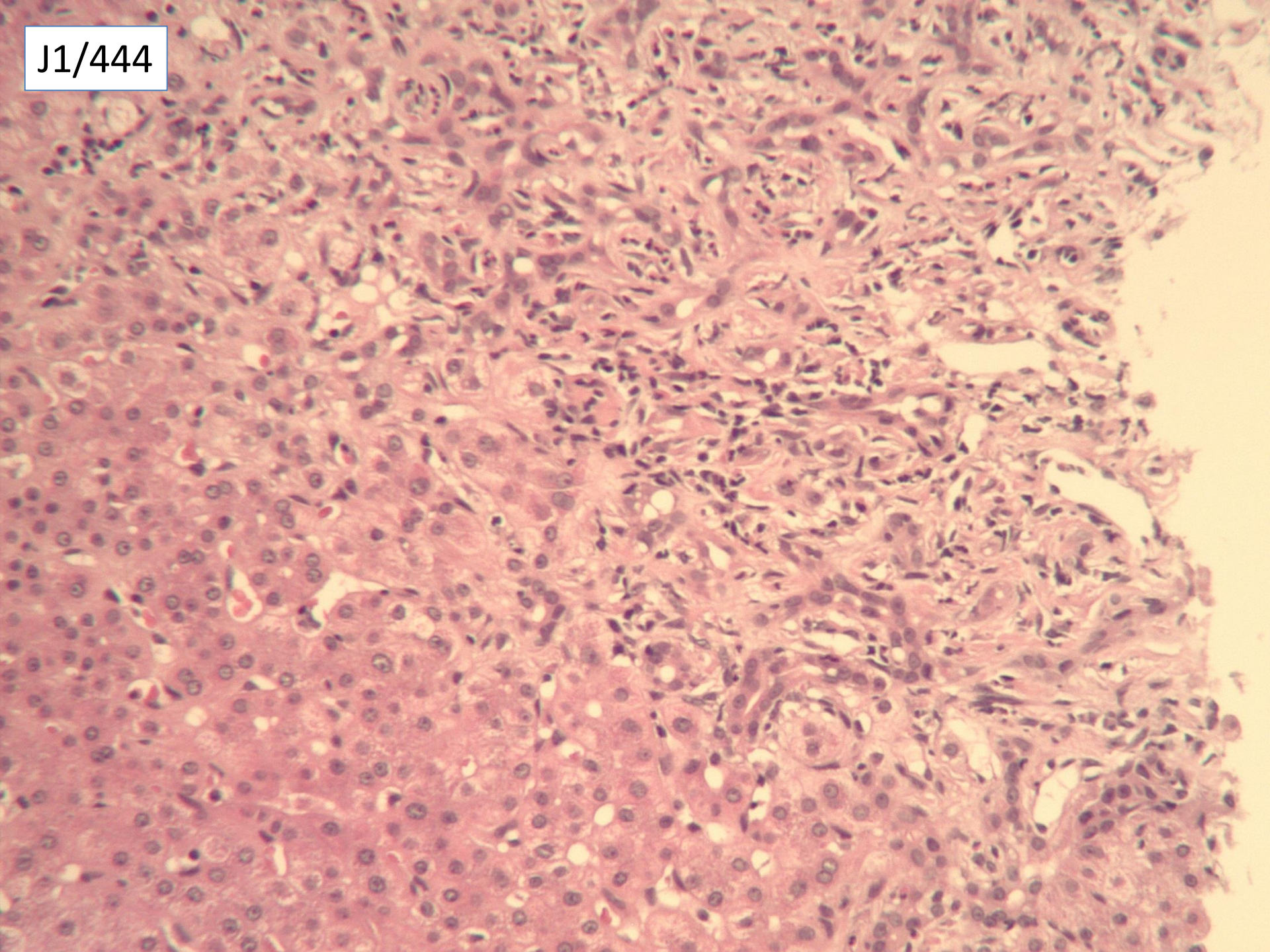
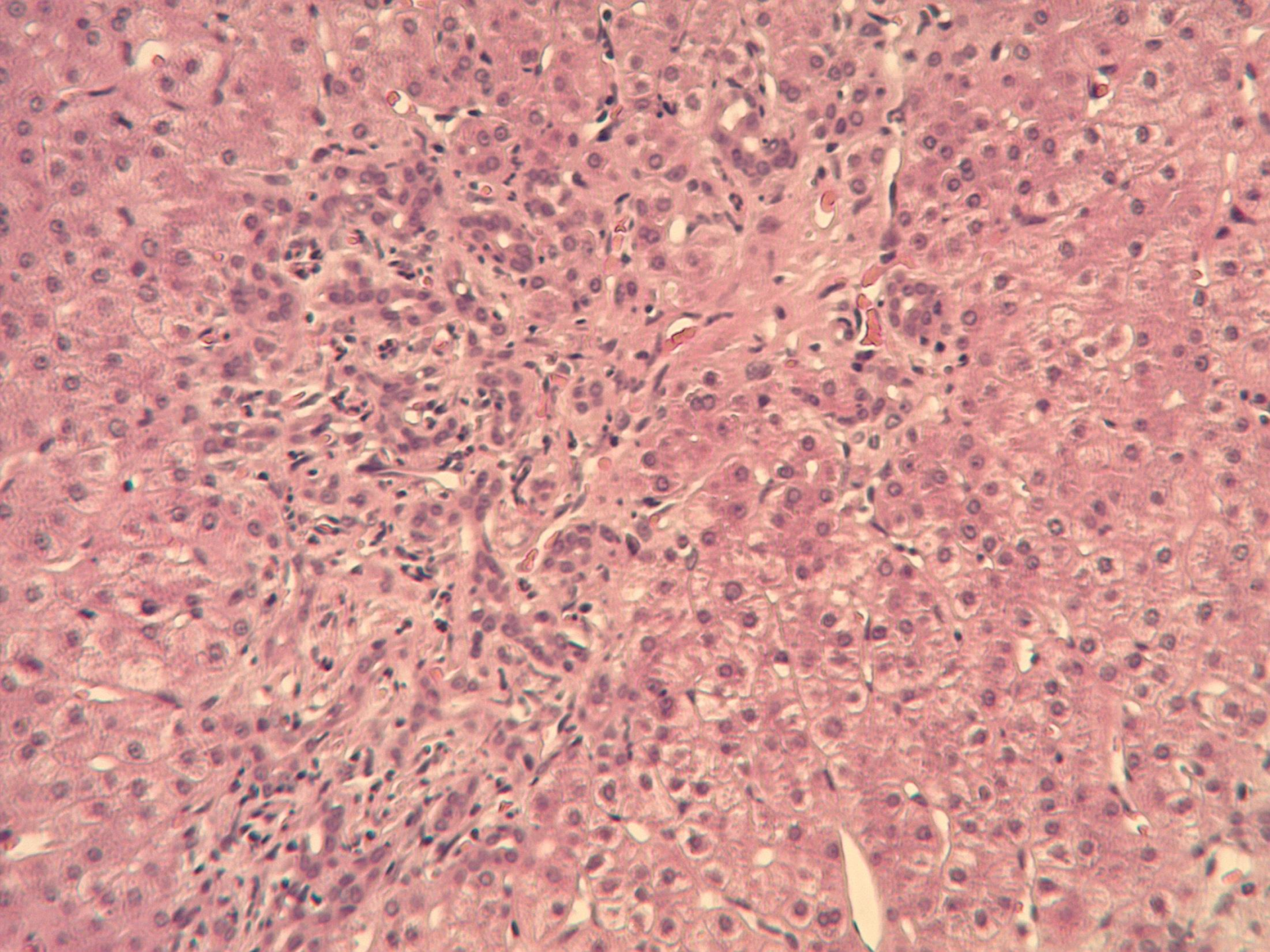
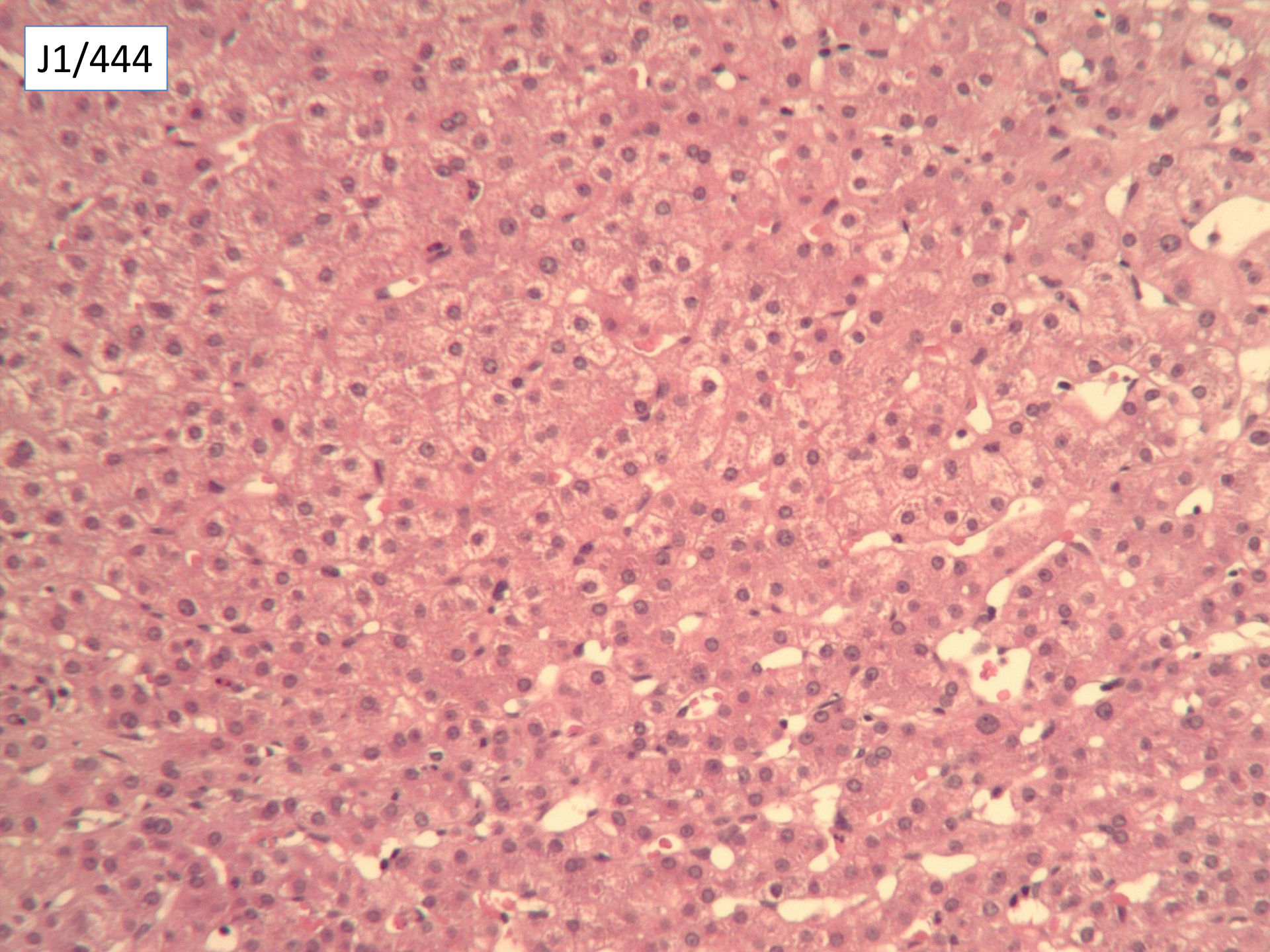

J1/444

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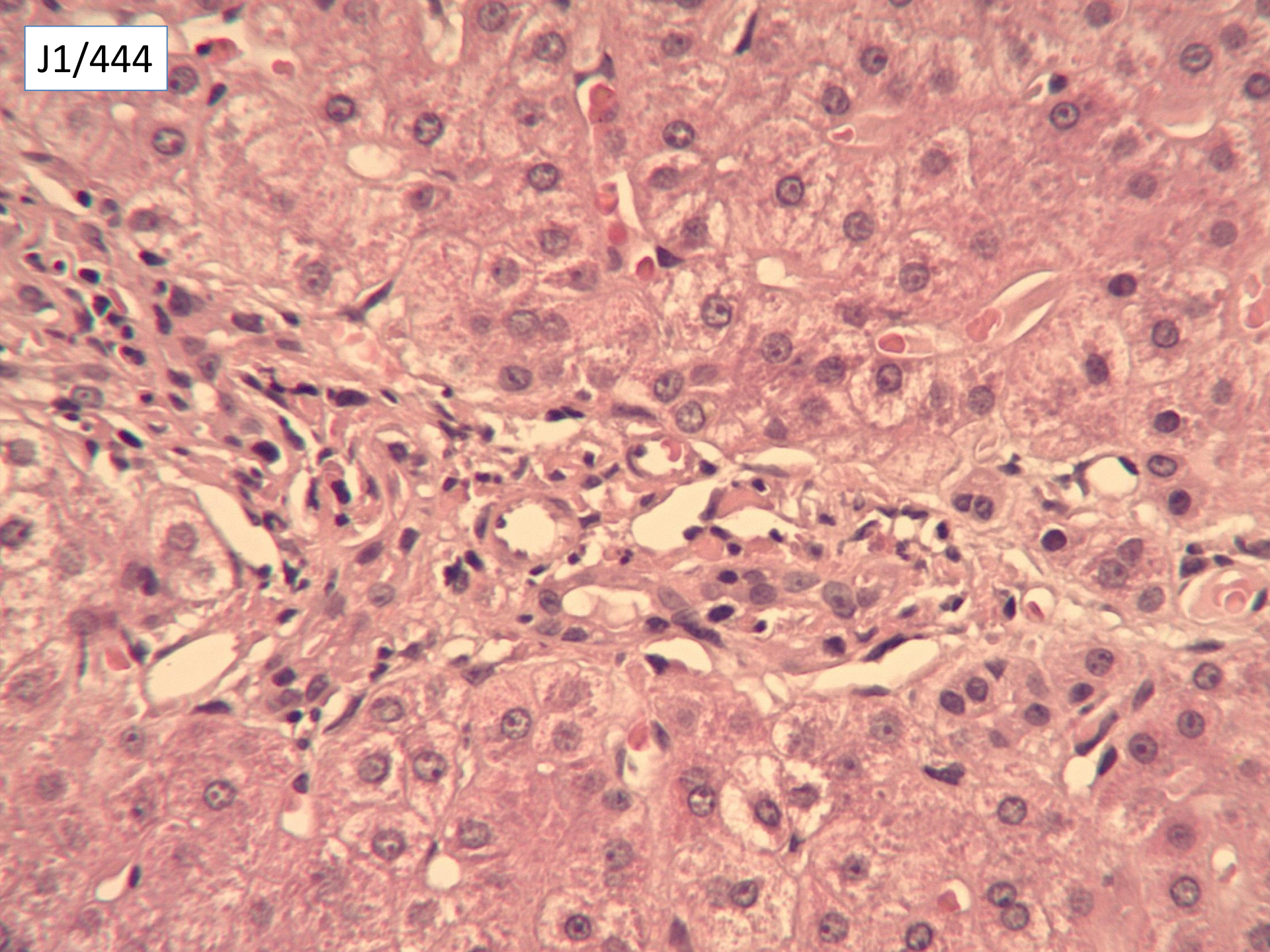
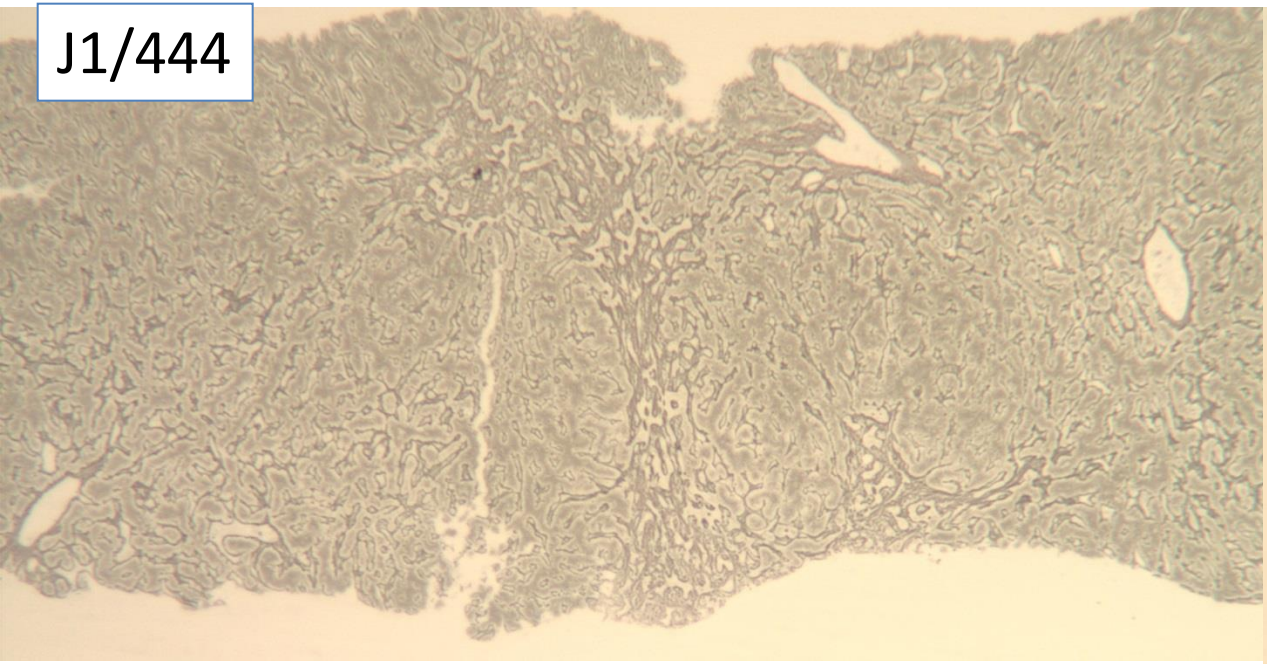
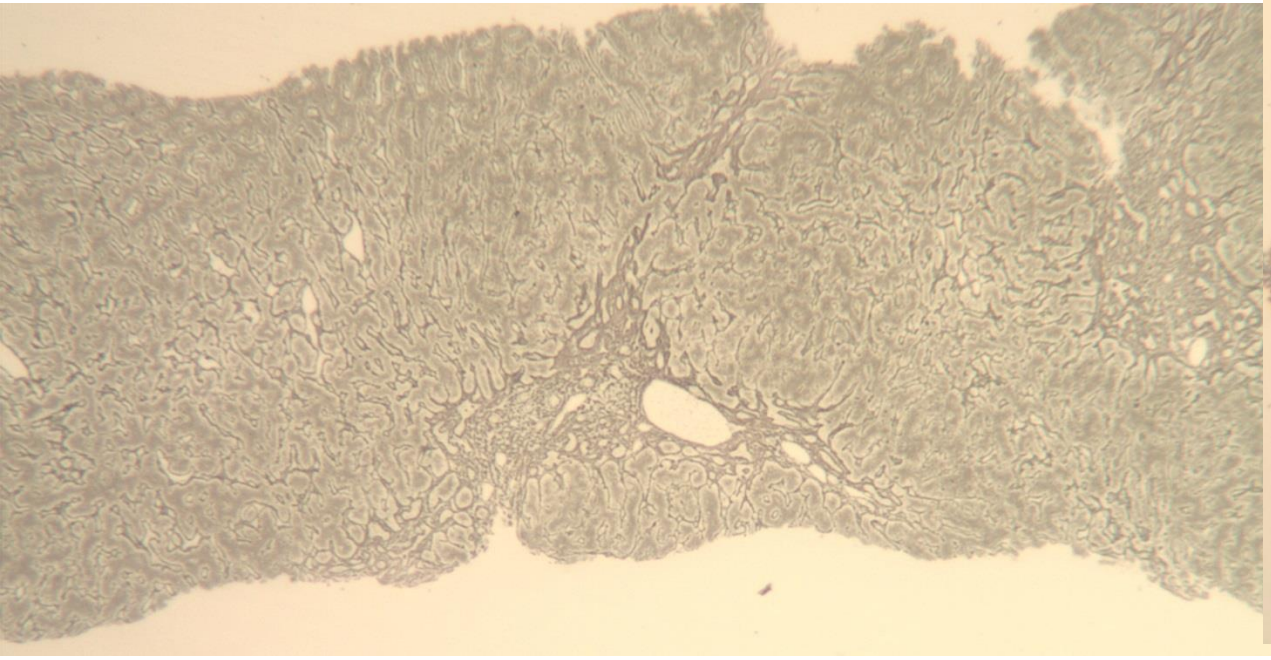
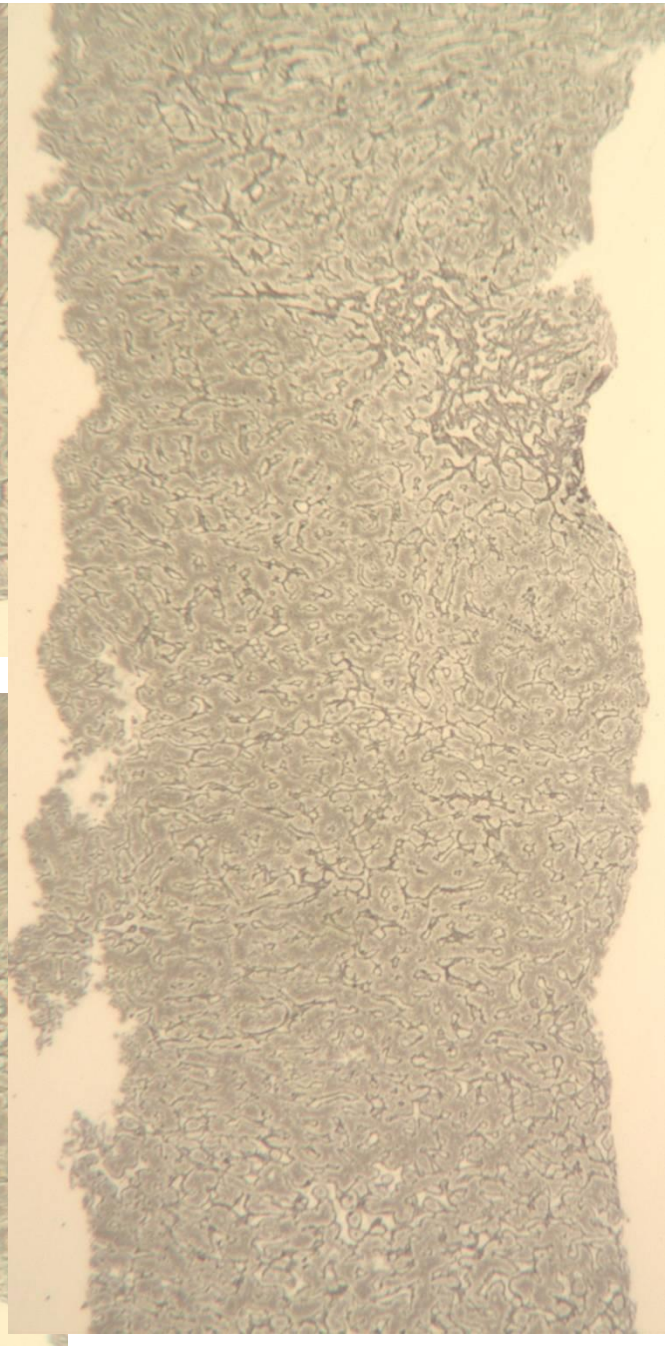

J1/444

J1/444







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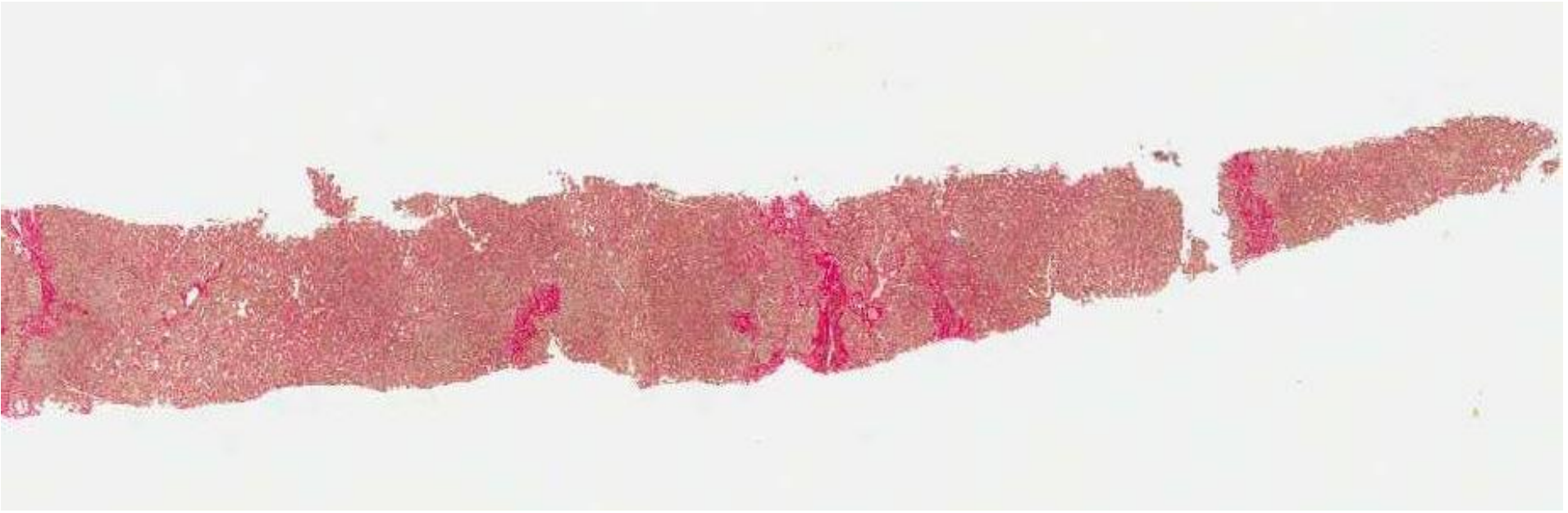


Case J1/444 Age 64, Female

Liver transplant for PBC in 1995 (18 years ago). Deranged LFTs. Anastomotic stricture in 2007 stented, follow up ERCP = no stricture. Rising ALP? Recurrent PBC? Chronic rejection

82 pattern of chronic biliary disease
45 duct loss
3 no duct loss
67 ductular reaction

41 copper associated protein
6 ?? copper associated protein
4 no copper associated protein

65 - includes PBC in differential, whether or not most likely
13 PBC not mentioned at all
1 not PBC

31 recurrent PBC most likely, with differential
4 PBC or stricture, drug, rejection, none favoured
2 PBC or stricture
10 recurrent PBC as only diagnosis
14 PBC not mentioned
12 Large bile duct obstruction favoured over PBC
4 ductopenic chronic rejection favoured overPBC
1 PBC or chronic rejection

/ contd:

Suggested scoring: probably unsuitable for scoring. All recognised this is a biliary pattern of disease. All but 13 mentioned PBC among the differential diagnosis.
So alternatively, for 10 points include biliary pattern of disease and include PBC.
5 points if PBC not mentioned.

8/13 agree, 3 unsuitable

Case J1/444 Age 64, Female

Liver transplant for PBC in 1995 (18 years ago). Deranged LFTs.

Anastomotic stricture in 2007 stented, follow up ERCP = no stricture.

Rising ALP? Recurrent PBC? Chronic rejection

82 pattern of chronic biliary disease

45 duct loss

3 no duct loss

67 ductular reaction

41 copper associated protein

6 ?? copper associated protein

4 no copper associated protein

1 chronic hepatitis, consistent with biliary stricture, not rejection or PBC

3 large duct obstruction or chronic rejection

4 biliary obstruction

5 chronic rejection as only diagnosis

1 GVHD favoured over PBC

1 ascending cholangitis, no differential

1 cholangitis +/- chronic rejection

1 chronic obstruction, not PBC or chronic rejection

2 should not be scored "don't put in except for fun"

Plus many 'I do not do transplant biopsies'

Should late transplant biopsies be included in EQA?
Should all transplant biopsies be referred to the transplant centre?
Should members be able to opt out of transplant biopsies?

Case J1/444 Age 64, Female

Liver transplant for PBC in 1995 (18 years ago). Deranged LFTs.
Anastomotic stricture in 2007 stented, follow up ERCP = no stricture.
Rising ALP? Recurrent PBC? Chronic rejection

Original diagnosis: chronic biliary disease with bridging fibrosis. Differential diagnosis includes recurrent PBC and late effects of biliary stricture. Chronic rejection less likely.

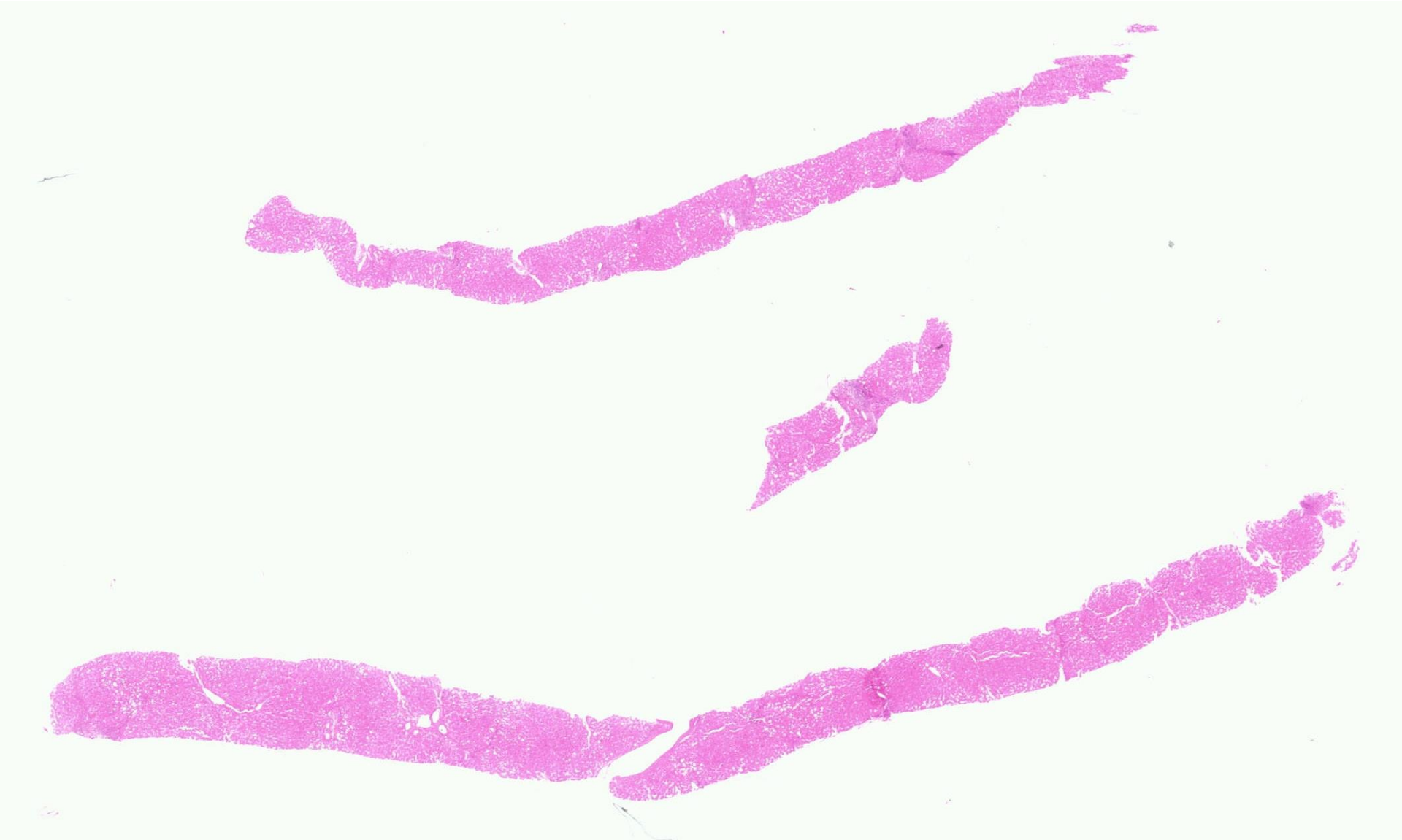
Follow up: plan for MRCP, but the patient was unable to tolerate this. She developed severe pruritis. Later, worsening renal failure and died from sepsis 8 months after this biopsy.

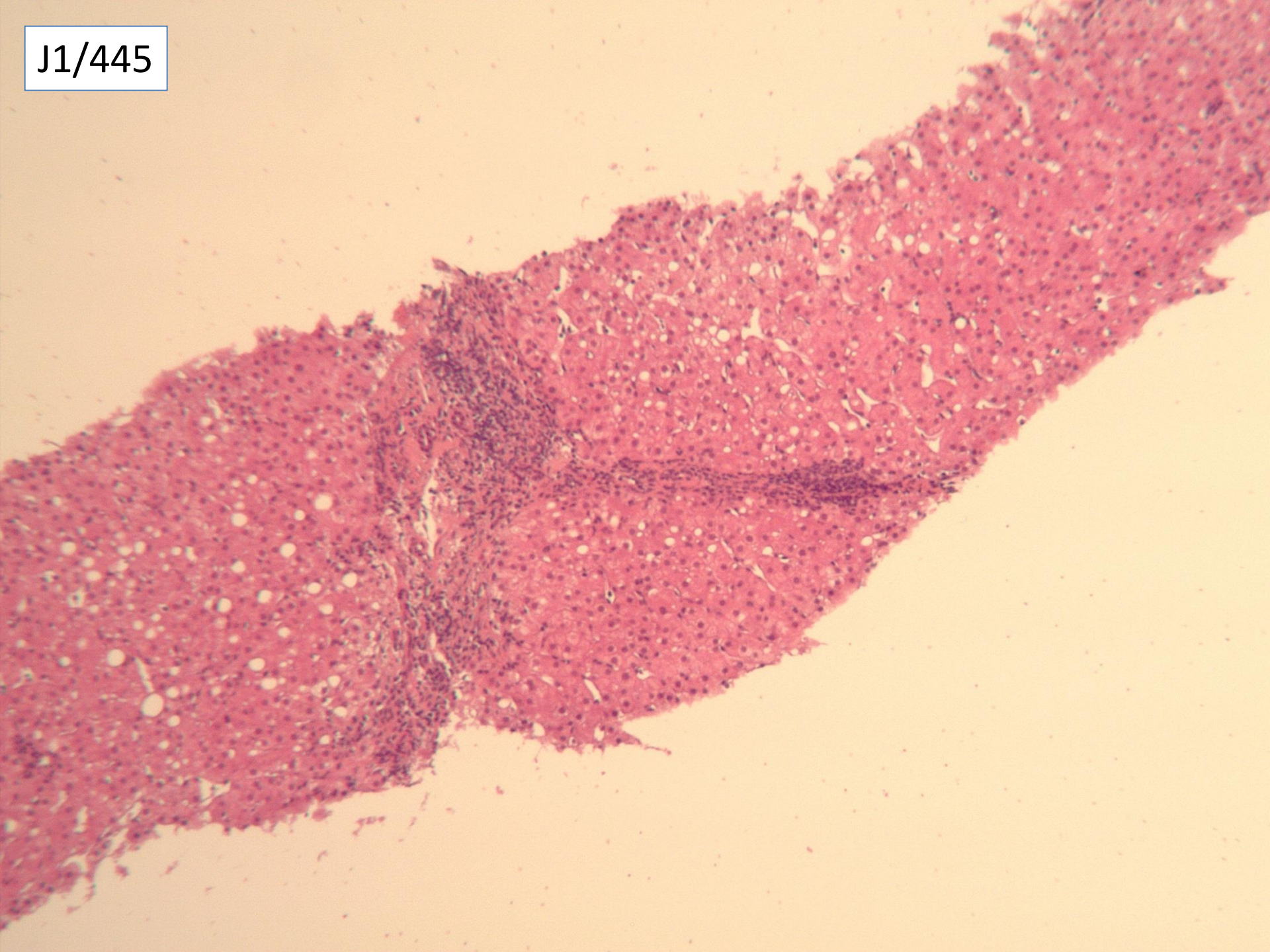
Discussion: Should late post transplant biopsies be included in the EQA scheme? – agreed that they should not be excluded, since increasingly received outside the transplant centre. Patterns of disease are similar, so initial assessment is possible.

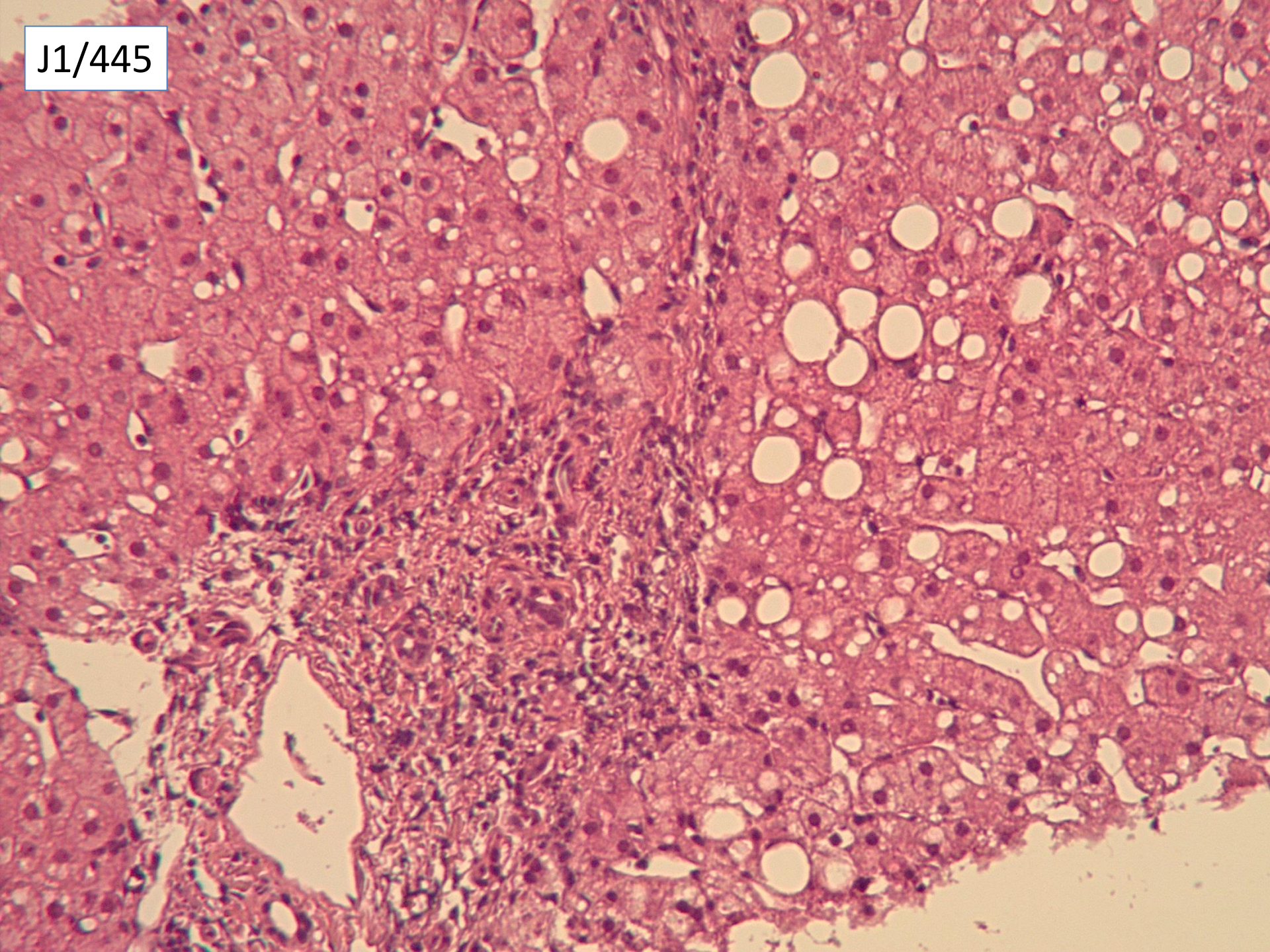
It is good practice to also refer the biopsies to the original transplant centre, so that they can be reviewed in context of previous histology and clinical history.

Case J1/445 Age 34, Male

Hepatitis C ? Fibrosis




J1/445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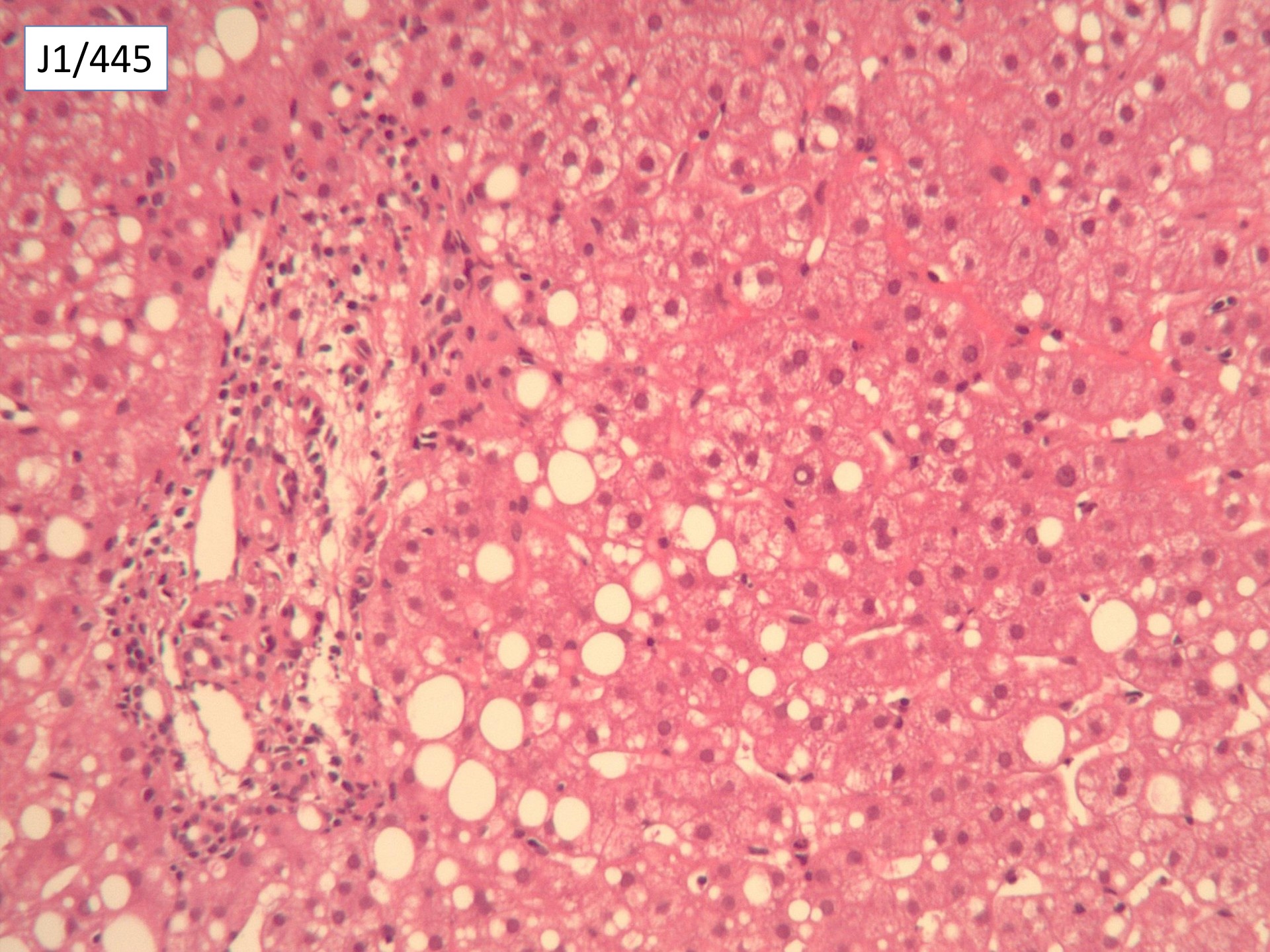
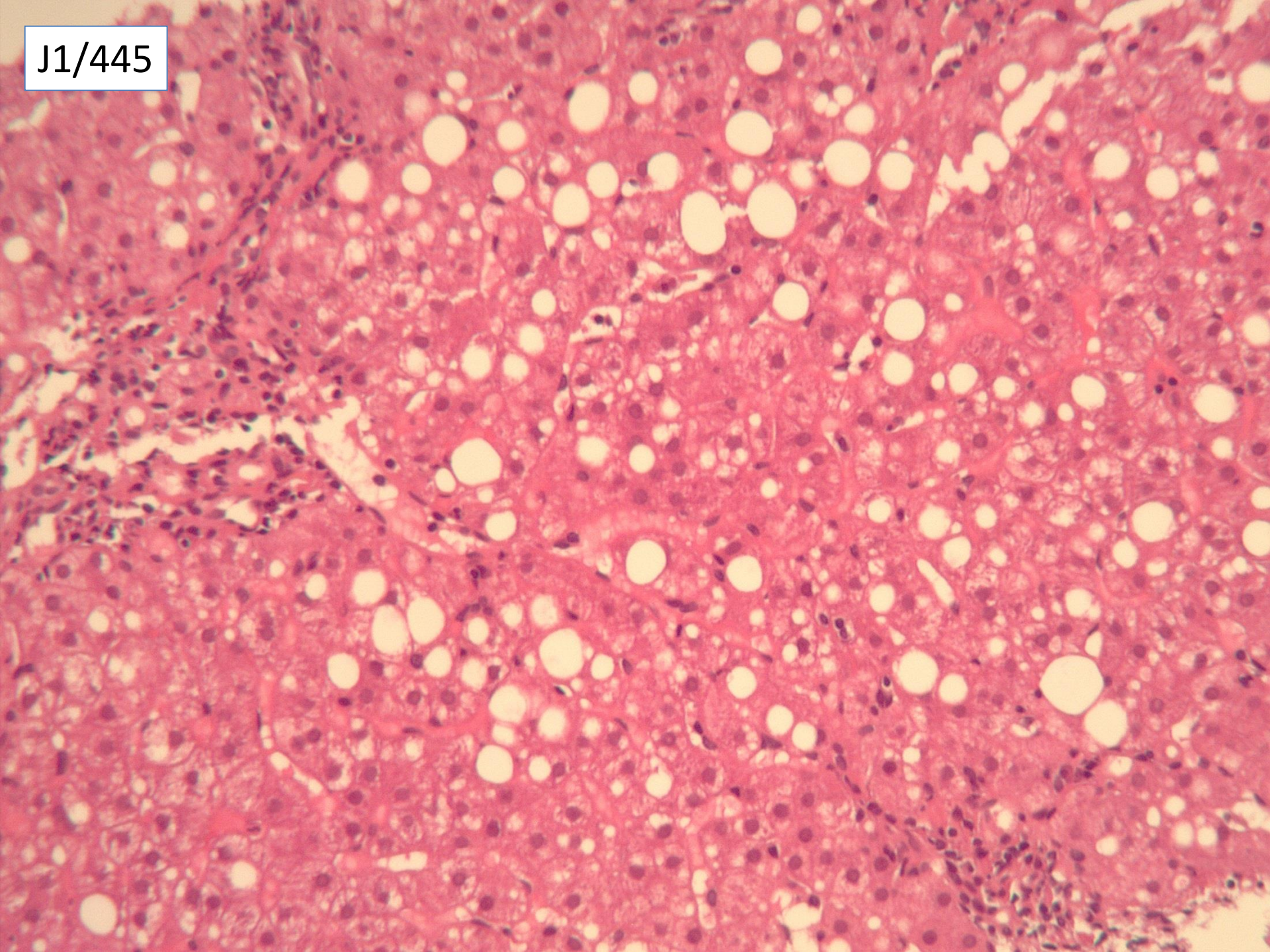
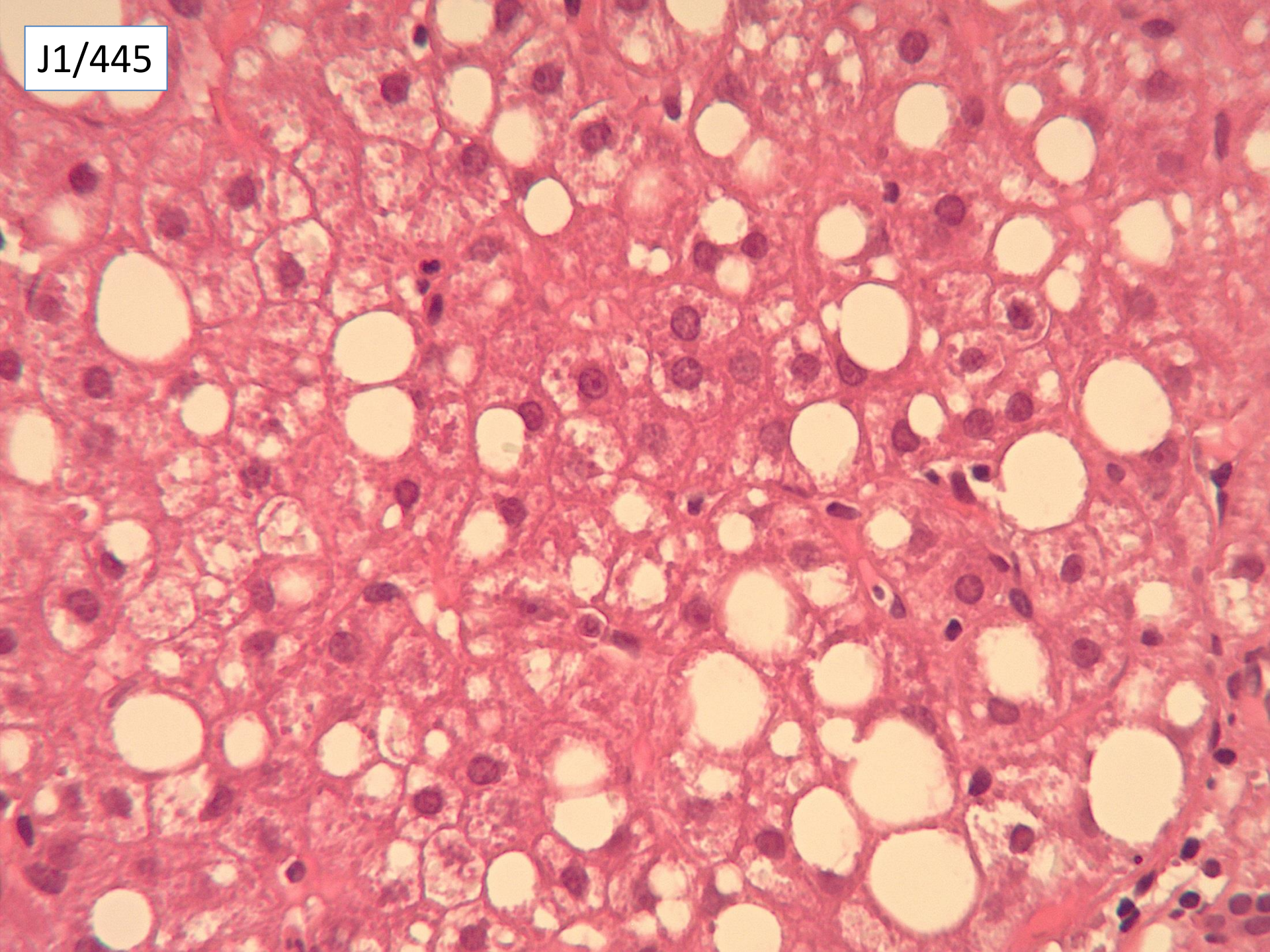

J1/445


J1/445


J1/445

Case J1/445 Age 34, Male
Hepatitis C ? Fibrosis

78 hepatitis C

4 hepatitis C not mentioned

63 steatosis

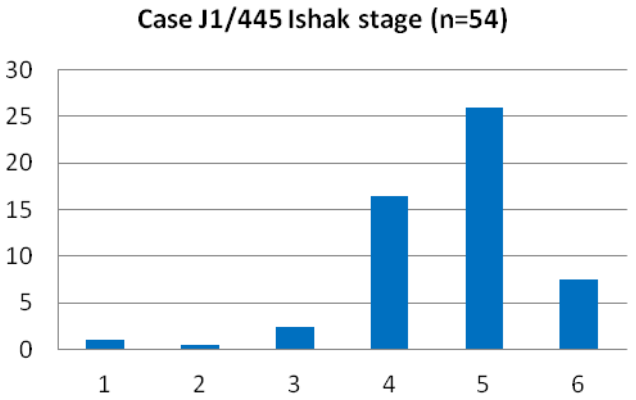
6 steatohepatitis

1 'no particular features of hepatitis C, could all be steatohepatitis'

17 ? risk factors for fatty liver disease

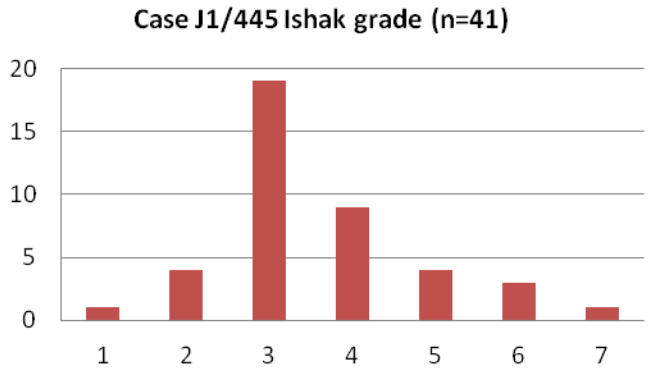
4 ? genotype type 3 to account for steatosis

8 fat not mentioned



Stage – fibrosis: 2 moderate or no bridging,
3 mod-severe or bridging,
9 developing cirrhosis or late stage
6 cirrhosis

Metavir: 2.5 F3, 4.5 F4.



Grade: 5 no severity indicated.
24 minimum or mild inflammation
5 moderate inflammation

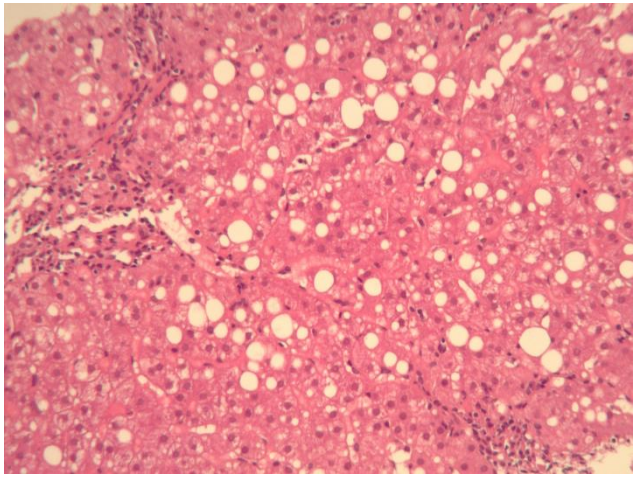
Metavir: 6 A1, 1 A2

<u>Suggested scoring:</u> For 10 points, indicate consistent with hepatitis C, and include an assessment of the fibrosis stage and degree of activity. Lose 5 if no steatosis (see next slide)
Lose 5 points if no grade/activity assessment.

14/14 agree, 0 unsuitable

Case J1/445 Age 34, Male

Hepatitis C ? Fibrosis



Should we indicate severity of steatosis?

8 steatosis not mentioned

6 steatosis not further qualified
25 mild
6 mild-moderate
19 moderate
1 moderate-severe
4 severe

% steatosis: 10%, 20%, 20%, 30%, 30%, 50%, 50% 80%, 80%,

3 steatohepatitis
6 possible steatohepatitis
10 stated not steatohepatitis

Other ways of expressing severity:

Fatty change ++
Grade 2 steatosis
Grade 3 (marked) steatosis
Diffuse
Prominent
Little
trivial

Case J1/445 Age 34, Male

Hepatitis C ? Fibrosis

Original diagnosis: moderate necroinflammatory change with portal inflammation and interface hepatitis (Ishak - necroinflammatory score 6) moderate architectural change with at least bridging fibrosis and some concern about an incomplete nodule (Ishak stage score 5) Chronic HCV.

Masterclass: Dina Tiniakos

Fatty liver disease in HCV

Chronic Hepatitis C

Liver biopsy in selected patients – WHY?

- **increased success rate of new therapeutic schemes**
  - **triple therapy for HCV genotype 1**

    peg-interferon α/ribavirin + protease inhibitor (telaprevir or boceprevir)
  - **double therapy for all other HCV genotypes**

    peg-interferon α/ribavirin

- **noninvasive methods for evaluation of fibrosis**
  - combination algorithms of biomarkers of inflammation and fibrosis
  - liver stiffness measurement (transient elastography-Fibroscan®)

EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

Journal of Hepatology **2014** vol. 60 | 392–420

Chronic Hepatitis C

Liver biopsy in selected patients – WHEN?

- contradictory results of noninvasive tests for fibrosis assessment – **"grey zone"**

- known or suspected mixed aetiology for CLD
  HBV, **metabolic syndrome, alcoholism**, autoimmunity

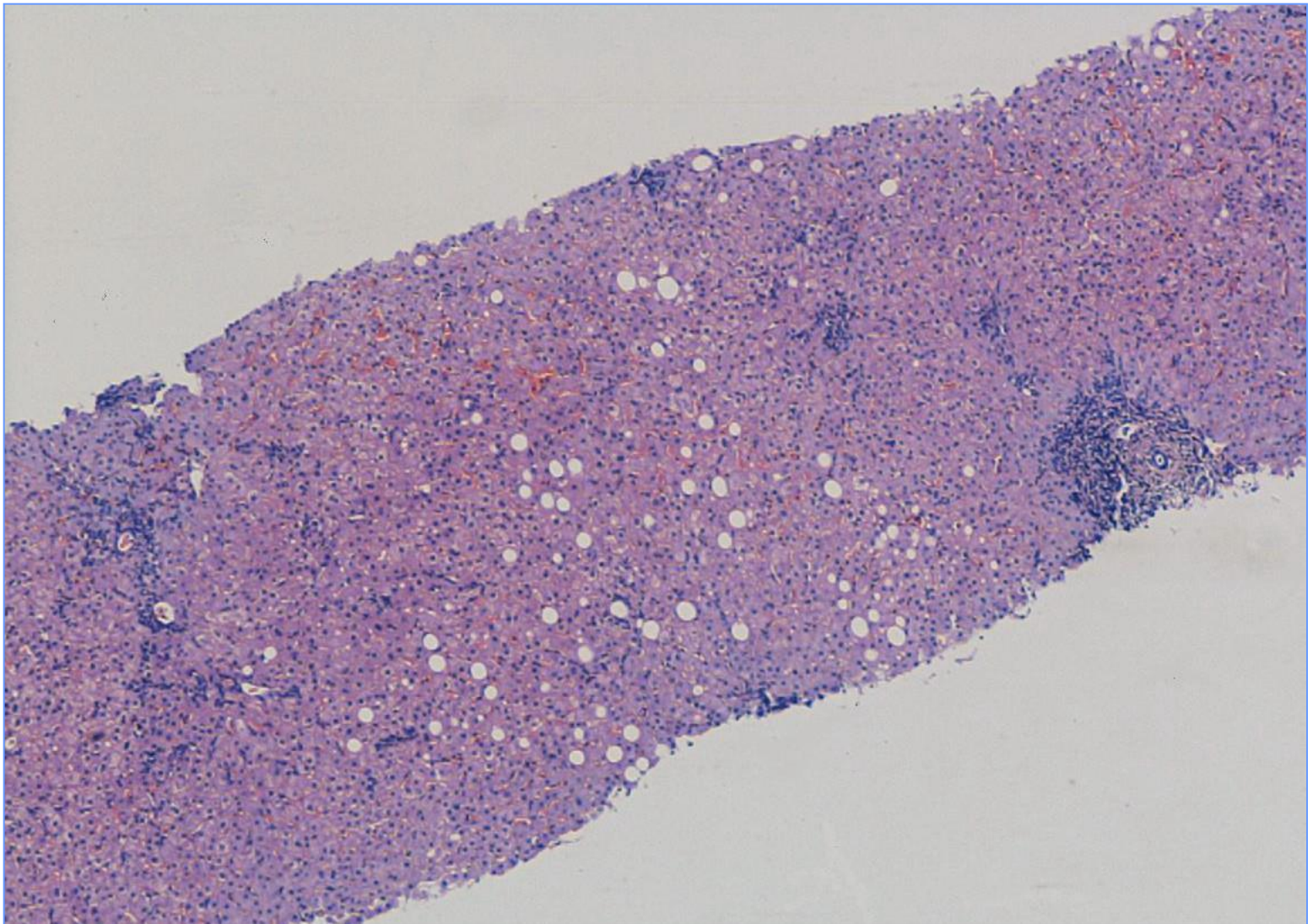
- differentiation between F3 & F4
  - when cirrhosis is not clinically obvious
  - to start screening for HCC

EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

Journal of Hepatology **2014** vol. 60 | 392–420

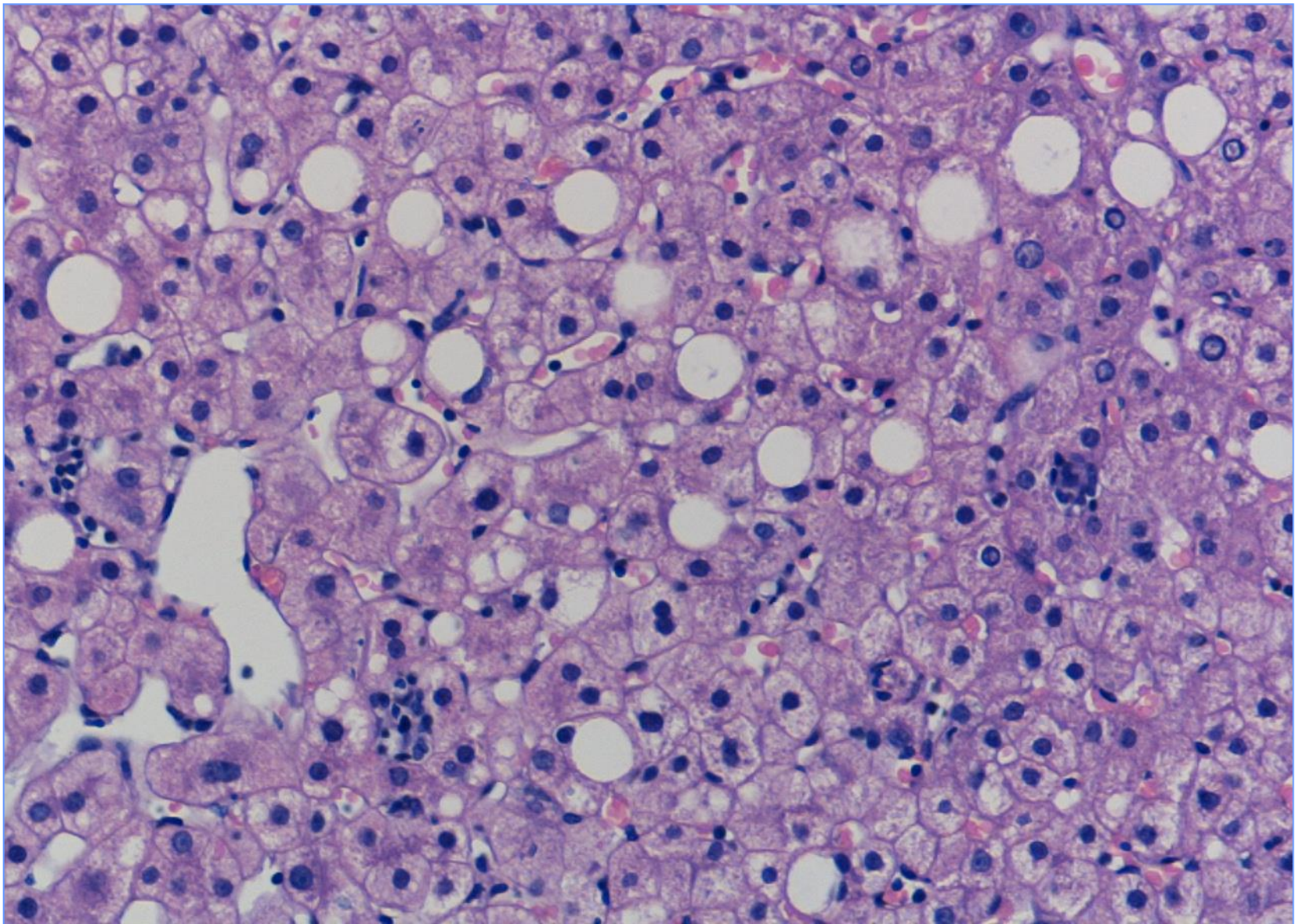
Steatosis in CHC

- Common finding, 40%-86% CHC biopsies
- Usually mild

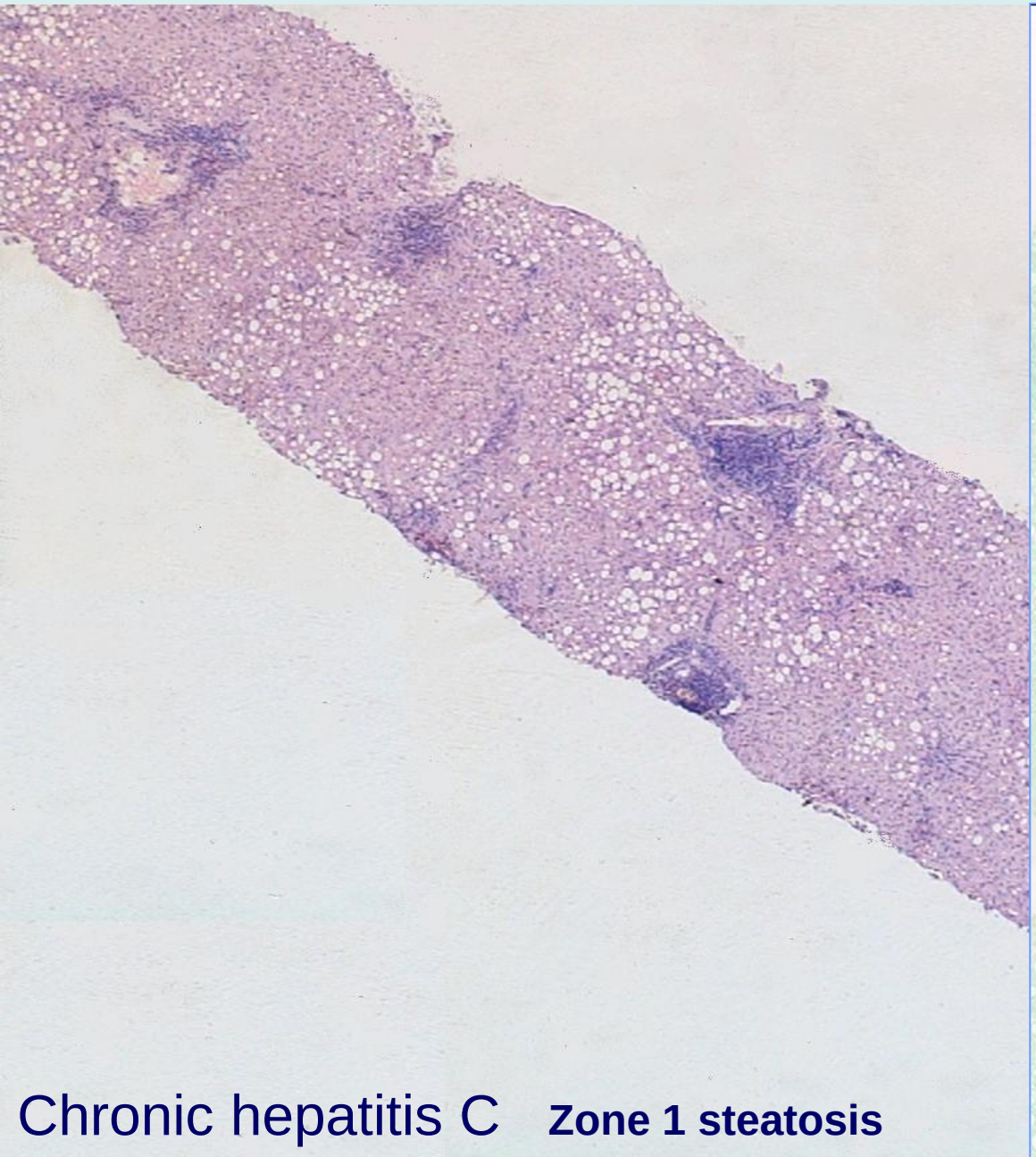


Steatosis in CHC

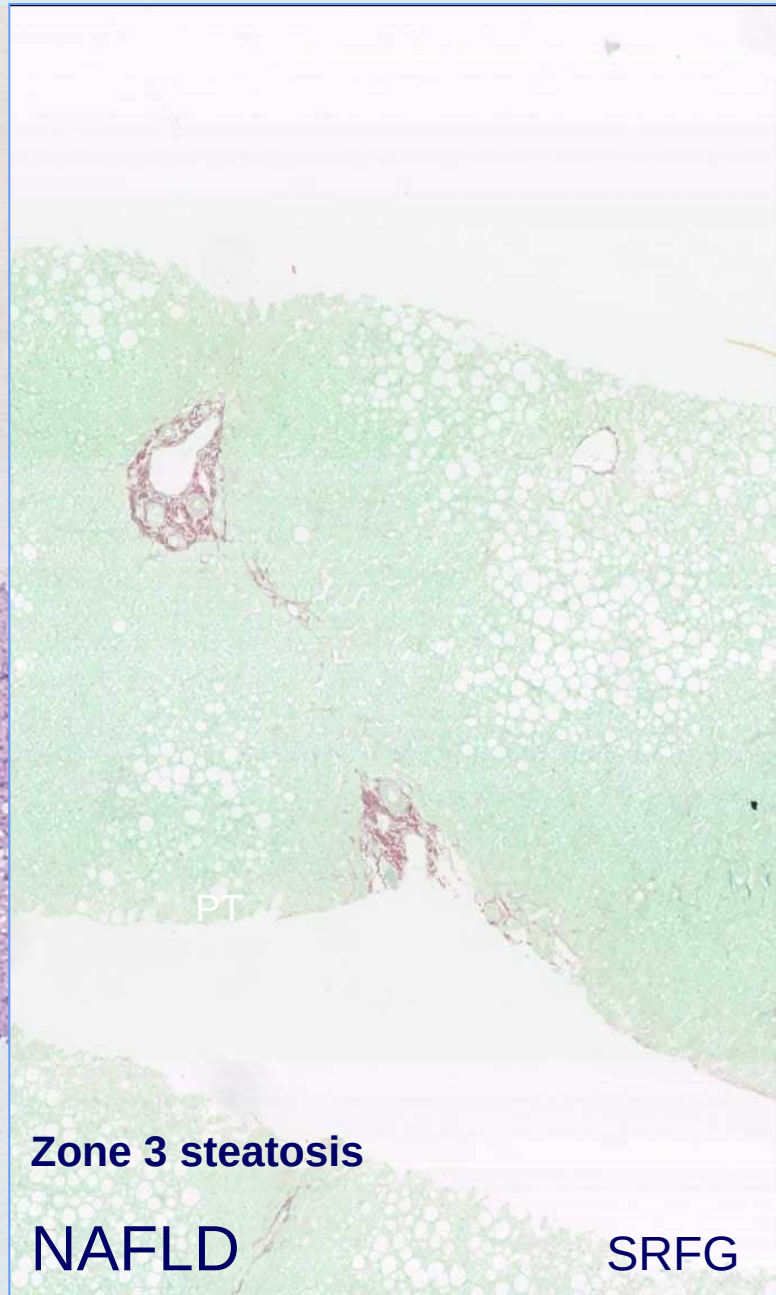
- Frequently macrovesicular



Chronic hepatitis C



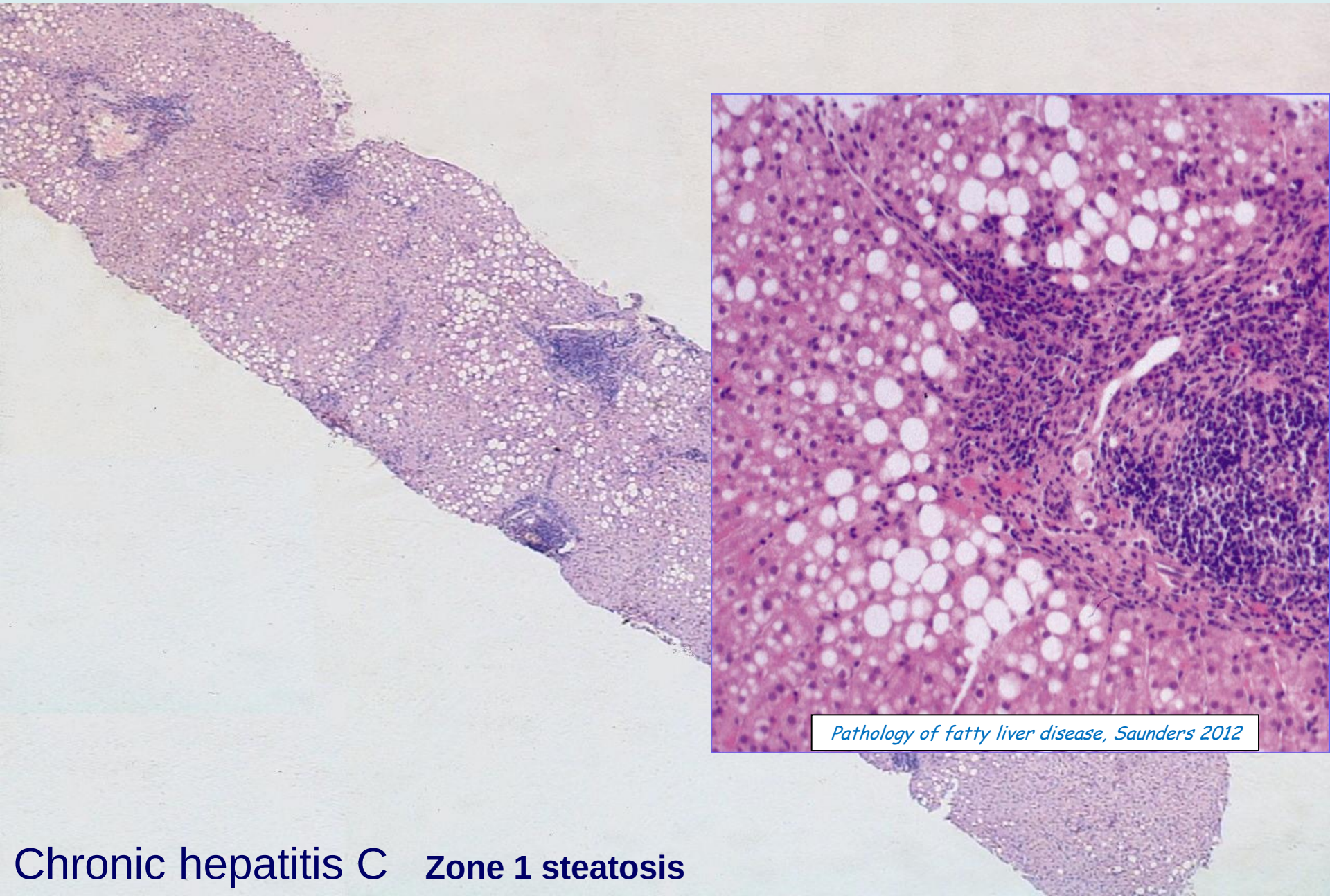
Chronic hepatitis C **Zone 1 steatosis**



Zone 3 steatosis

NAFLD SRFG

Chronic hepatitis C



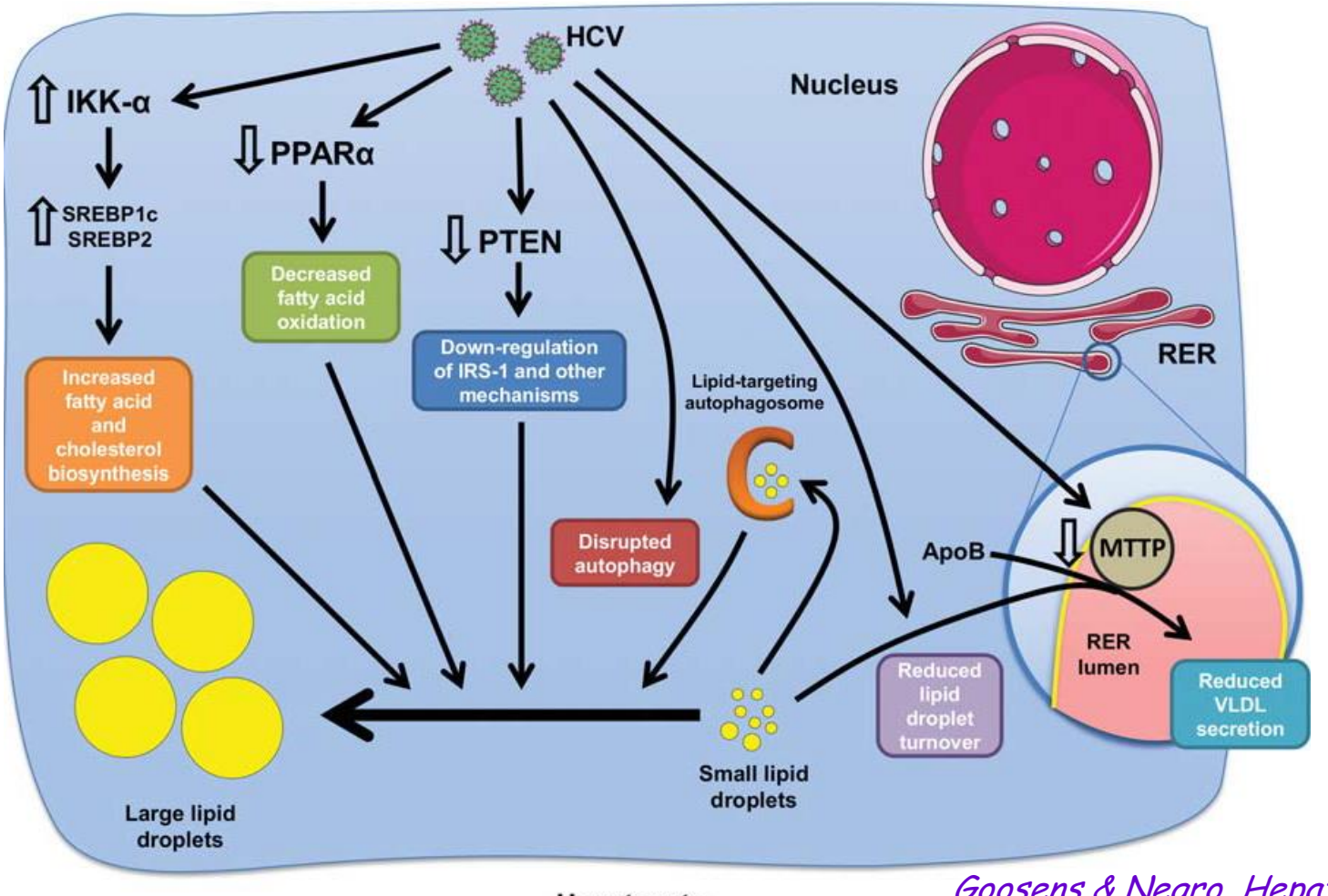
Pathology of fatty liver disease, Saunders 2012

Chronic hepatitis C **Zone 1 steatosis**

Steatosis in CHC

Pathogenesis differs according to virus genotype

Genotype 3: **direct cytopathic effect**



Goosens & Negro, Hepatology 2014

Steatosis in CHC

Pathogenesis differs according to virus genotype

Genotype 3: **direct cytopathic effect**

Genotype 1 and other genotypes: **host metabolic factors**

- features of the metabolic syndrome
  (↑ BMI, ↑ fasting plasma glucose, dyslipidemia, hypertension)
- insulin resistance

Schaefer & Chung, Semin Liv Dis 2013
Goosens & Negro, Hepatology 2014

Steatosis in CHC

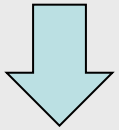
Pathogenesis differs according to virus genotype

Genotype 3: **direct cytopathic effect**

Genotype 1 and other genotypes: **host metabolic factors**

- features of the metabolic syndrome
  (↑ BMI, ↑ fasting plasma glucose, dyslipidemia, hypertension)
- insulin resistance

Global spread of the metabolic syndrome



The pathogenesis of steatosis and insulin resistance in CHC may often be **dual: viral and metabolic**

Schaefer & Chung, Semin Liv Dis 2013
Goosens & Negro, Hepatology 2014

Steatosis in CHC

Pathogenesis differs according to virus genotype

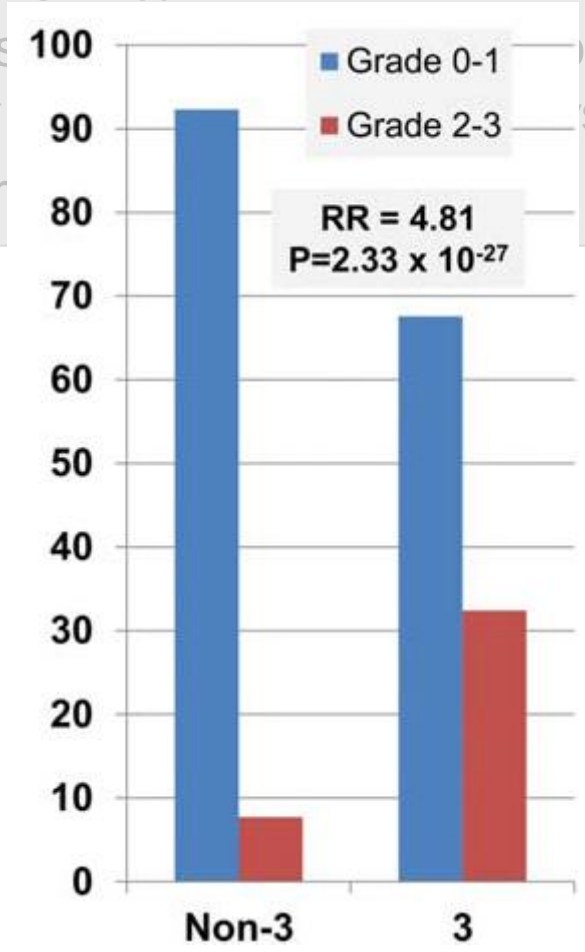
Genotype 3: **direct cytopathic effect**

Genotype 1 and other genotypes: **host metabolic factors**

- features
- (↑ BMI, ↑
- insulin r

me

slipidemia, hypertension)



Goosens & Negro, Hepatology 2014

Steatosis in CHC

Pathogenesis differs according to virus genotype

gen3 steatosis

- severity is related to HCV replication
- disappears after successful antiviral treatment
- **does not predict accelerated fibrosis progression**
- **may not impact on response to treatment (?)**

Cheng, J Viral Hepat 2014

Non-gen3 steatosis

- unaffected by antiviral treatment
- **associated with fibrosis progression**
- **may reduce response to treatment**

Goosens & Negro, Hepatology 2014
Sato, Hepatol Res 2014

Steatosis in CHC

- may affect the performance of liver stiffness measurement (gen1)

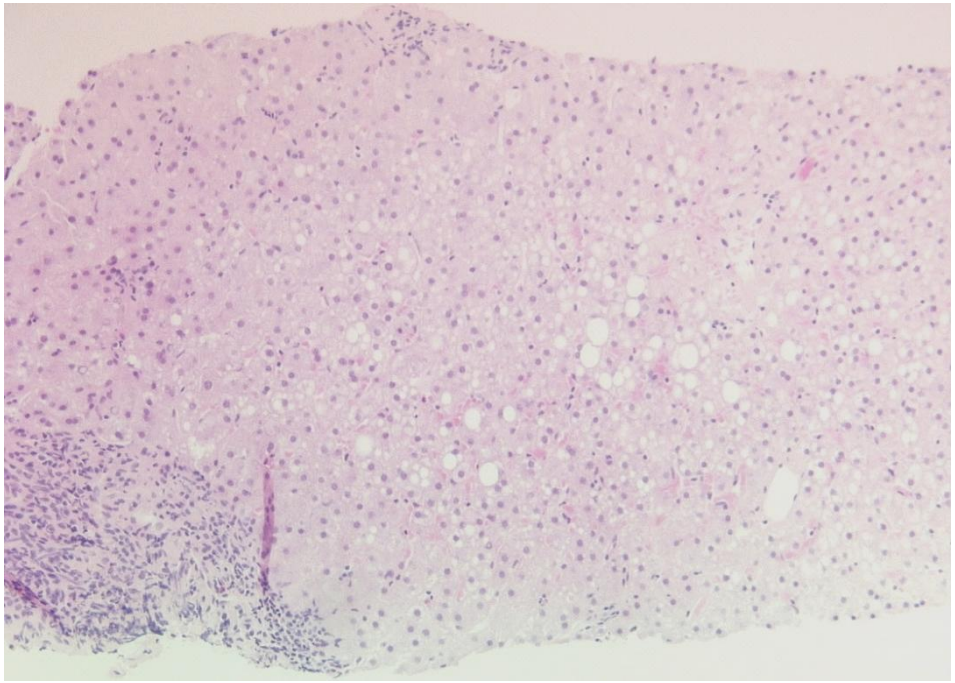
Macaluso, J Hepatol 2014

- is associated with carotid atherosclerosis

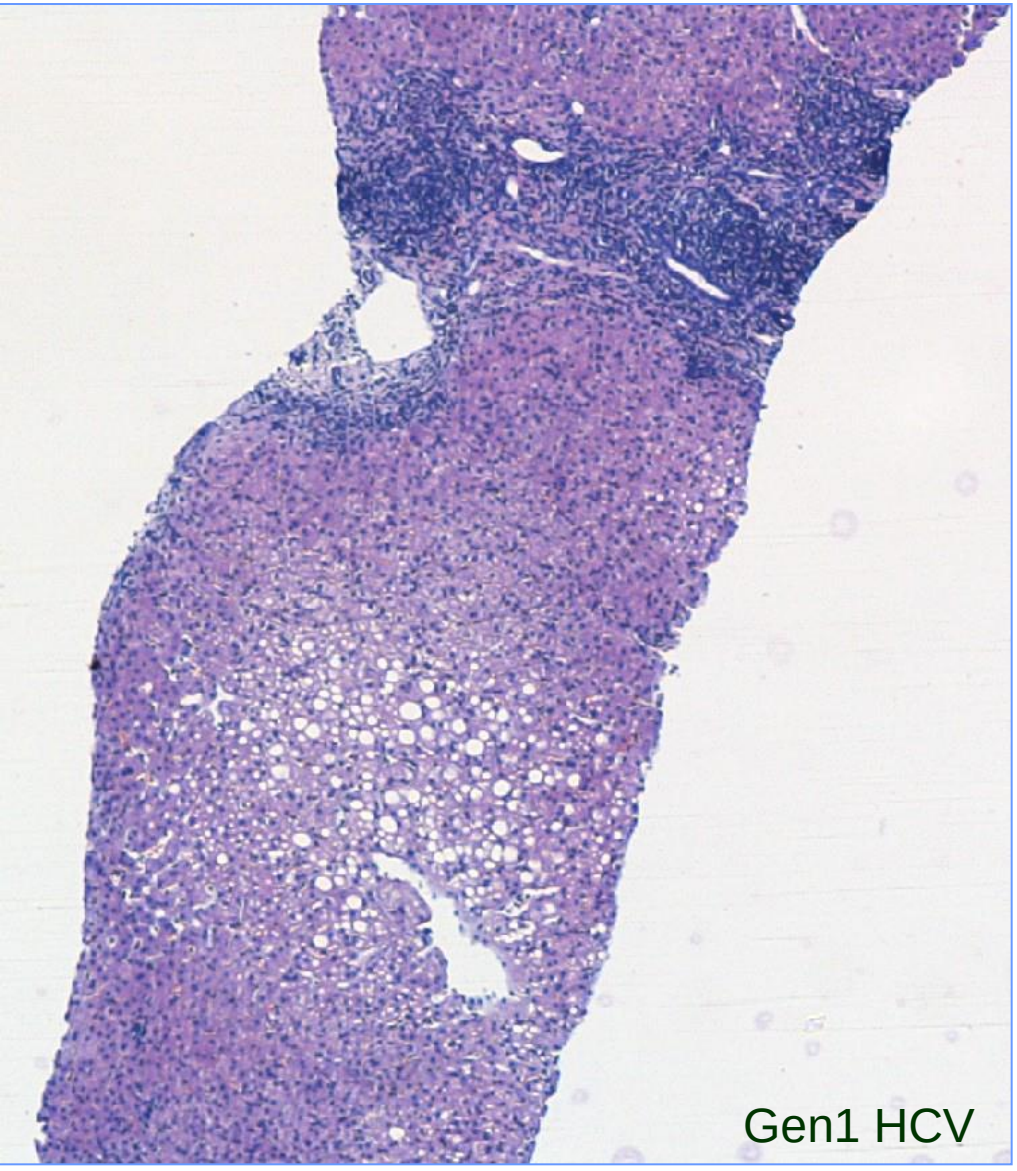
Adinolfi, Atherosclerosis 2012

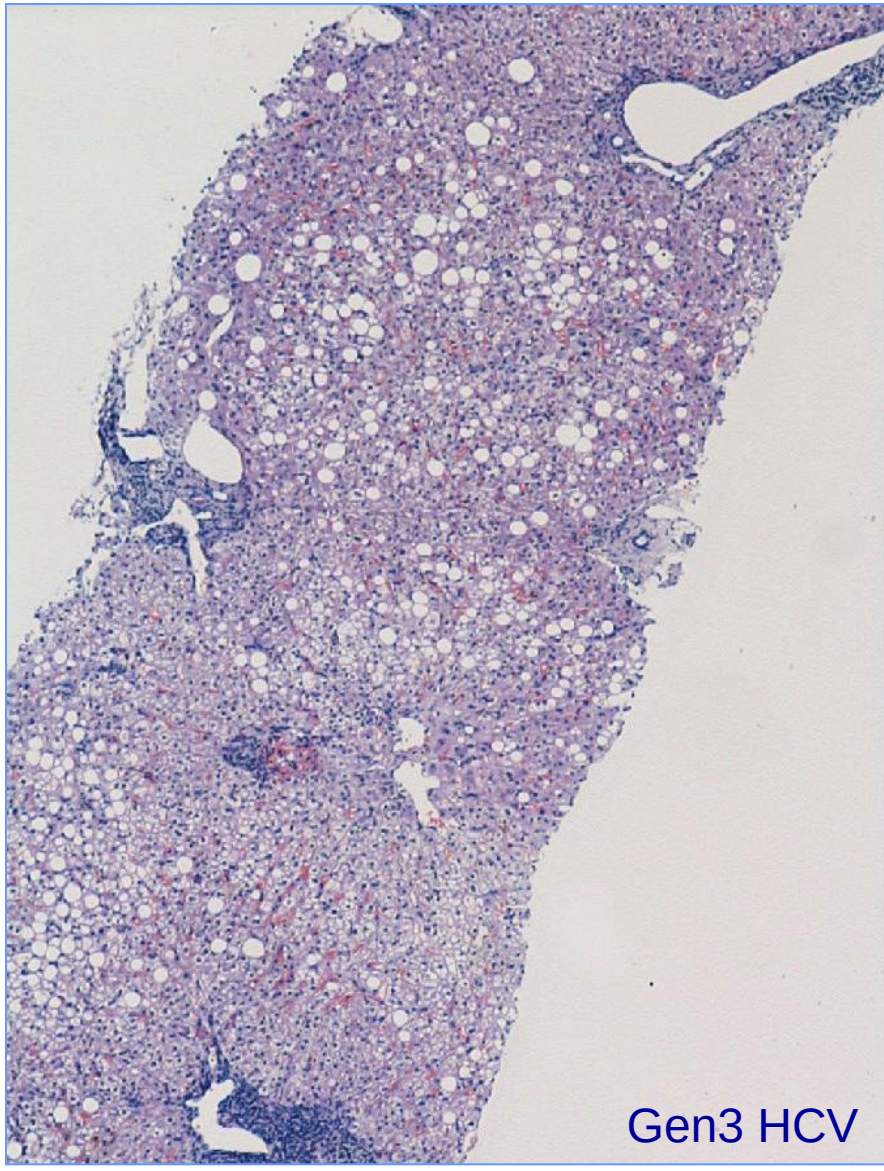
- related to increased frequency of HCC development

Goosens & Negro, Hepatology 2014



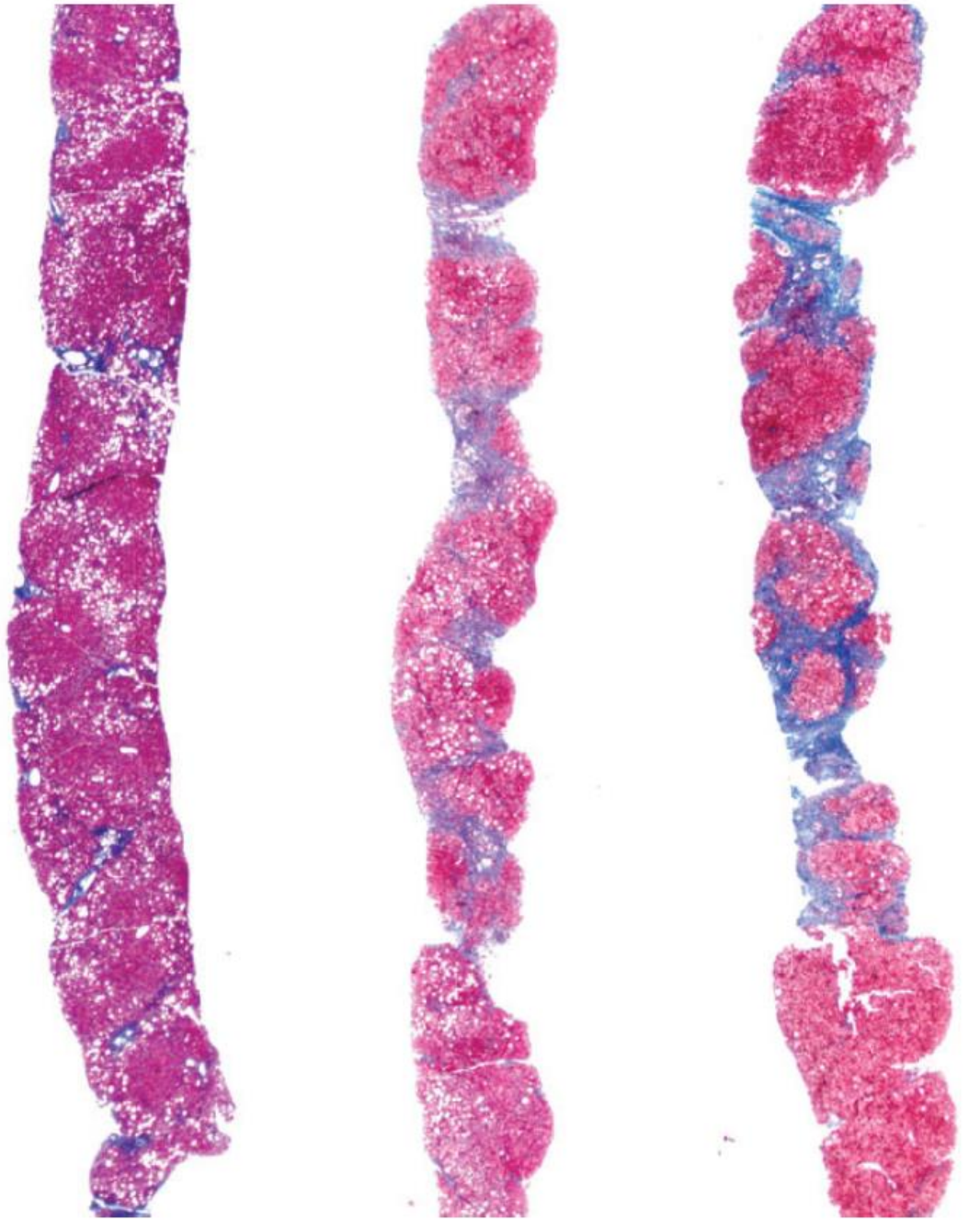
Steatosis in CHC





HALT-C trial

Lok Hepatology 2009



Baseline Year 1.5 Year 3.5

Concurrence of CHC and Steatohepatitis

- CHC is the most common chronic liver disease diagnosed with concurrent SH: **5-9% of CHC**
- more common with HCV genotype 3
- not associated with metabolic disturbances
- correlates with advanced fibrosis stage

Brunt, Mod Pathol 2003
Bedossa, Hepatology 2007

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Brunt, Mod Pathol 2003
Bedossa, Hepatology 2007

- may **accelerate disease progression**

Rakoski, Clin Gastroenterol Hepatol 2011

- **may decrease response to antiviral treatment**

Negro, J Viral Hepat 2012

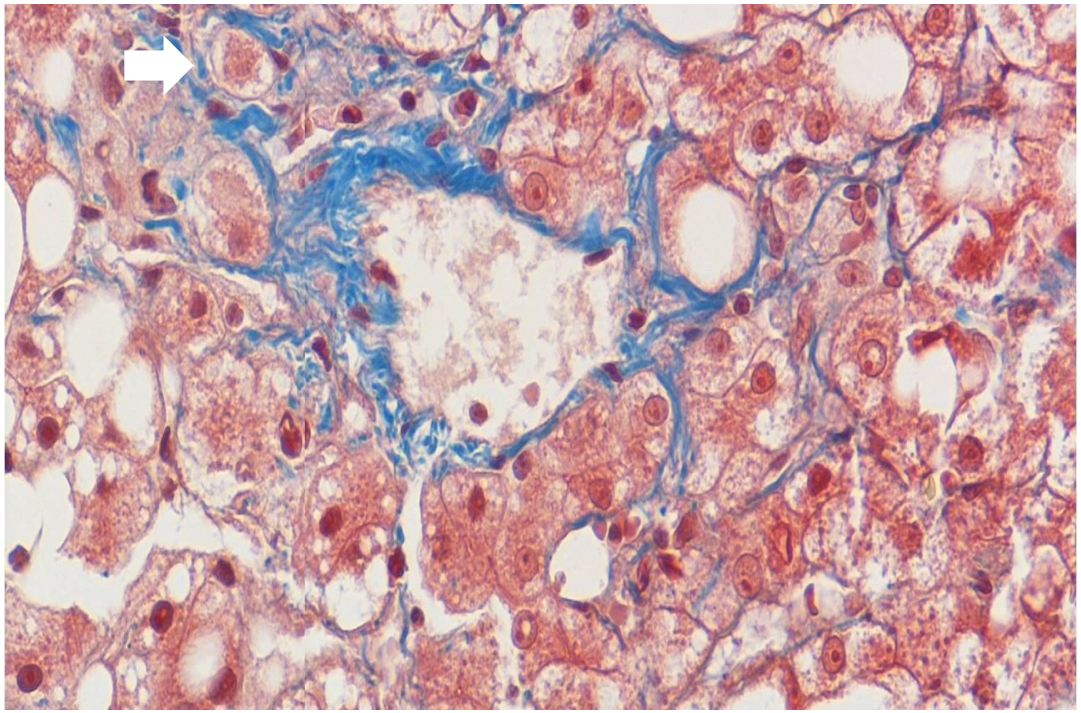
Concurrence of CHC and Steatohepatitis

Diagnosis of concurrent CHC and SH is a challenging task!

There are no established set of criteria

In addition to steatosis and lobular inflammation:

- characteristic zone 3 perisinusoidal fibrosis
- hepatocellular ballooning in zone 3



Brunt, Mod Pathol 2003
Bedossa, Hepatology 2007
Ye & Brunt, Gastroenterology 2014

Steatosis/steatohepatitis in CHC

In a CHC biopsy:

- comment on steatosis (type, extent, topography)

  i.e. macrovesicular type

  moderate severity (or grade 2)

  zone 3 predilection

- assess for concurrent steatohepatitis

- **prognostic information for fibrosis progression**
- **predictive information for response to therapy**
- clarification of possible discordance between liver stiffness measurements and histological staging

The end

circulation J1

Spring 2014