Immune-mediated drug-induced liver injury (DILI)

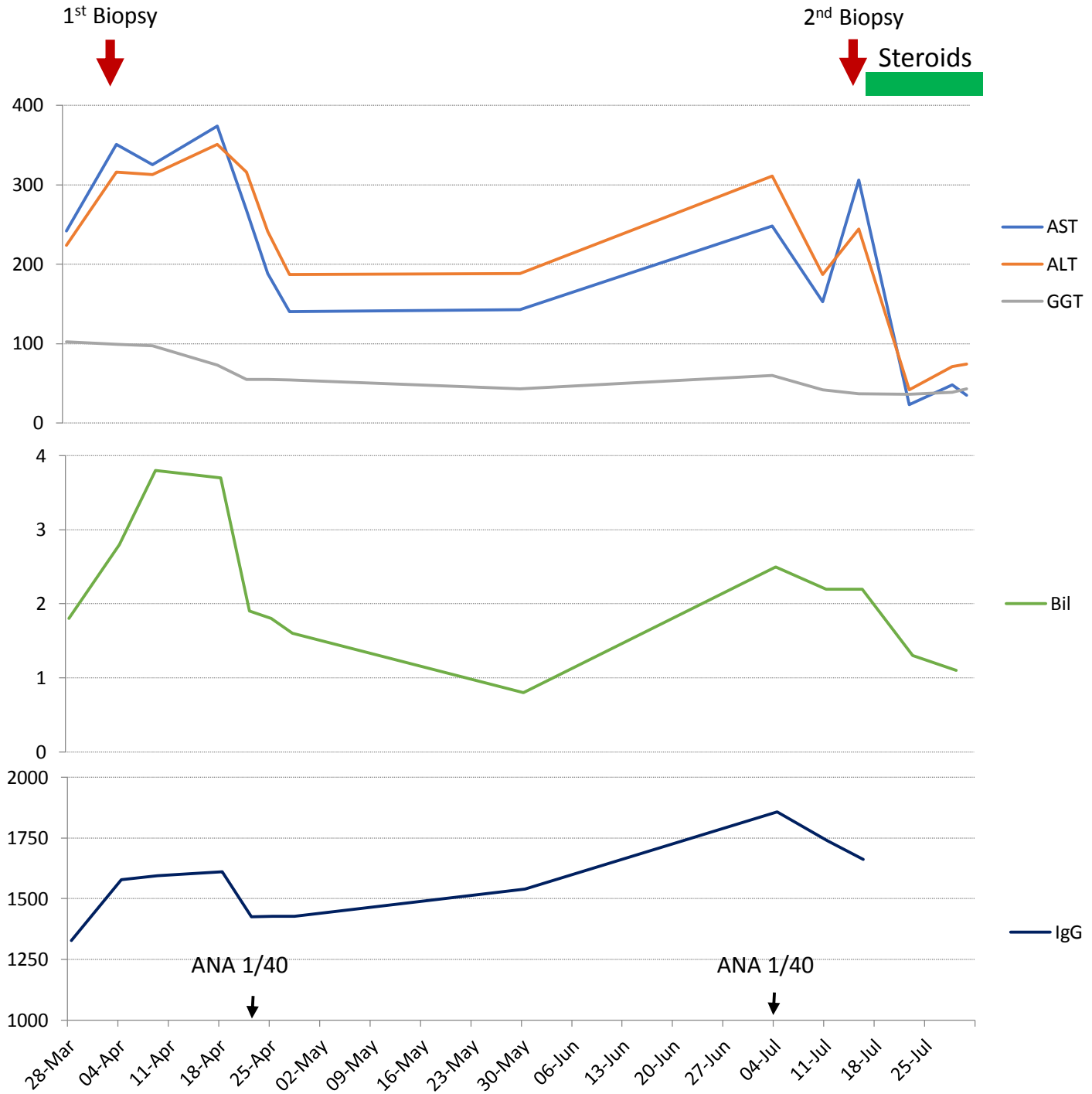
AIH-like DILI and new cancer drugs

DILI *versus* AIH

Drug-induced AIH (DI-AIH)

CASE #1

- A 38-year-old lady referred to us with acute hepatitis following intake of a nutritional supplement containing herbal medicine.
- Fist biopsy - features of acute lobular hepatitis consistent with drug-induced injury, without typical features of AIH.
- The liver injury improved with UDCA, but liver enzymes re-elevated in conjunction with increased IgG.
- Second biopsy - plasma cell-rich chronic active hepatitis with perivenular zonal necrosis, features suggestive of AIH.
- She showed a good response to corticosteroids.


1st Biopsy
2nd Biopsy
Steroids
400
300
200
100
0
AST
ALT
GGT
4
3
2
1
0
Bil
2000
1750
1500
1250
1000
IgG
ANA 1/40
ANA 1/40
28-Mar
04-Apr
11-Apr
18-Apr
25-Apr
02-May
09-May
16-May
23-May
30-May
06-Jun
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20-Jun
27-Jun
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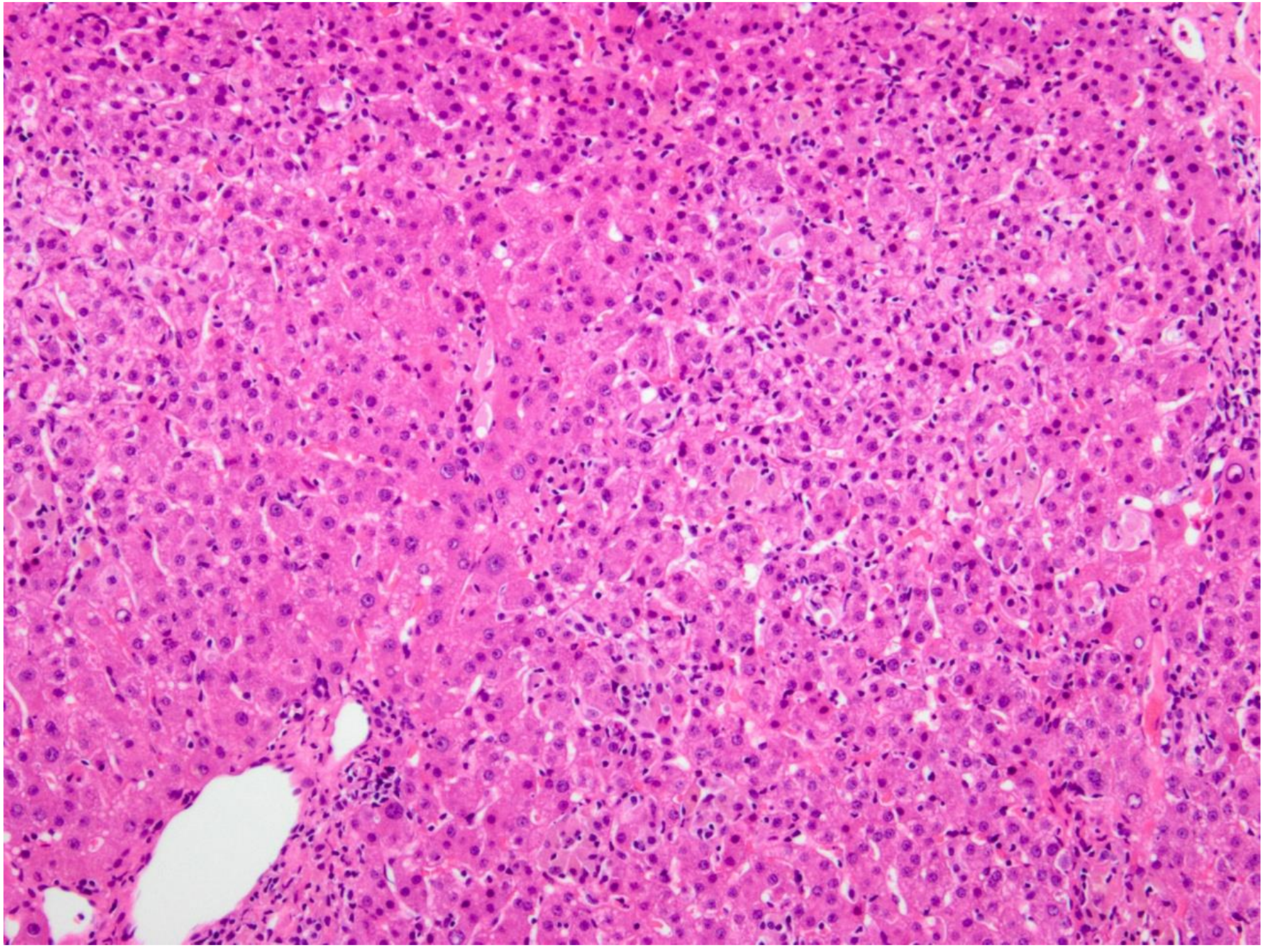
18-Jul
25-Jul

1st biopsy (Predominantly lobular hepatitis in keeping with DILI)



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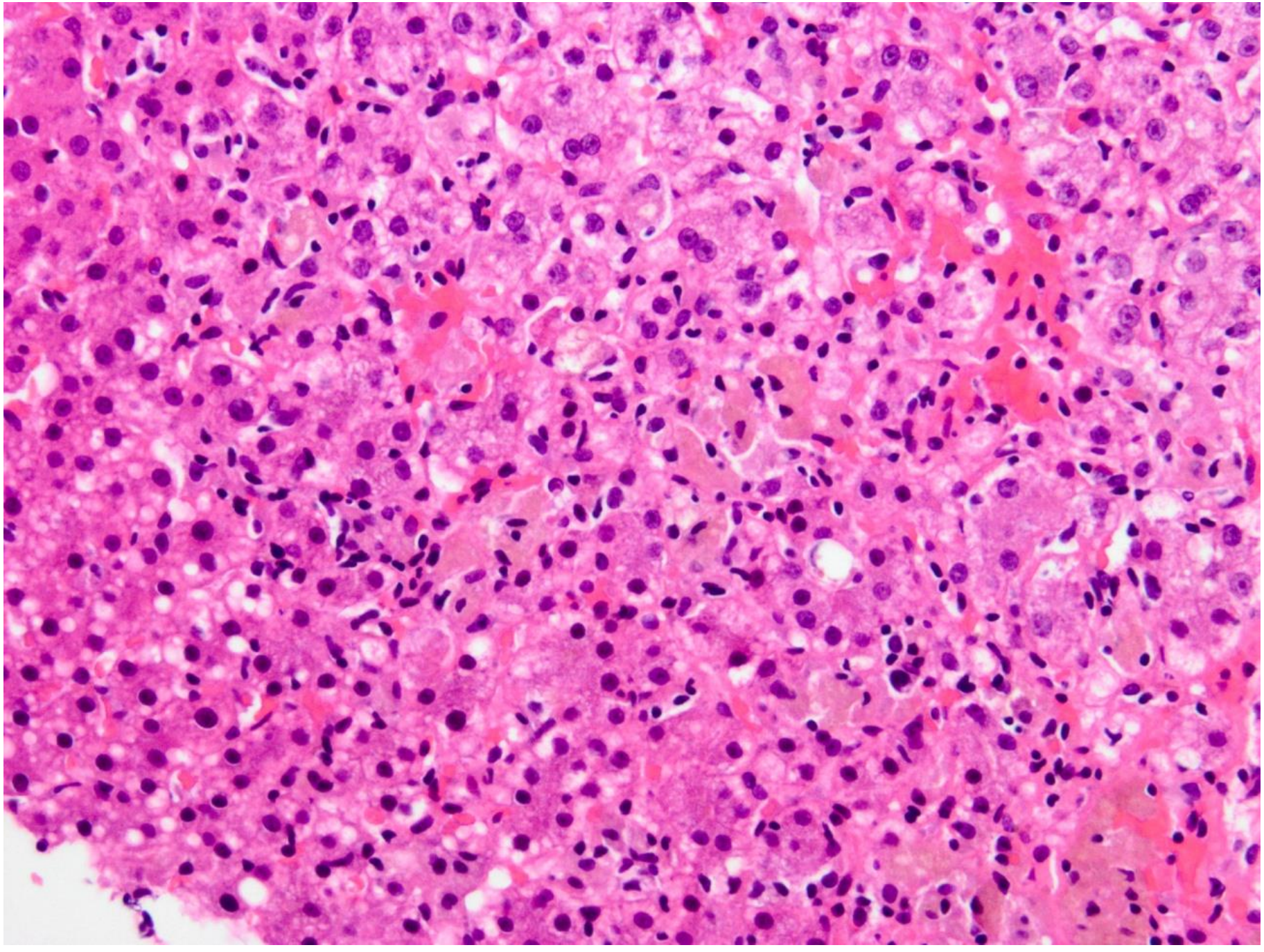
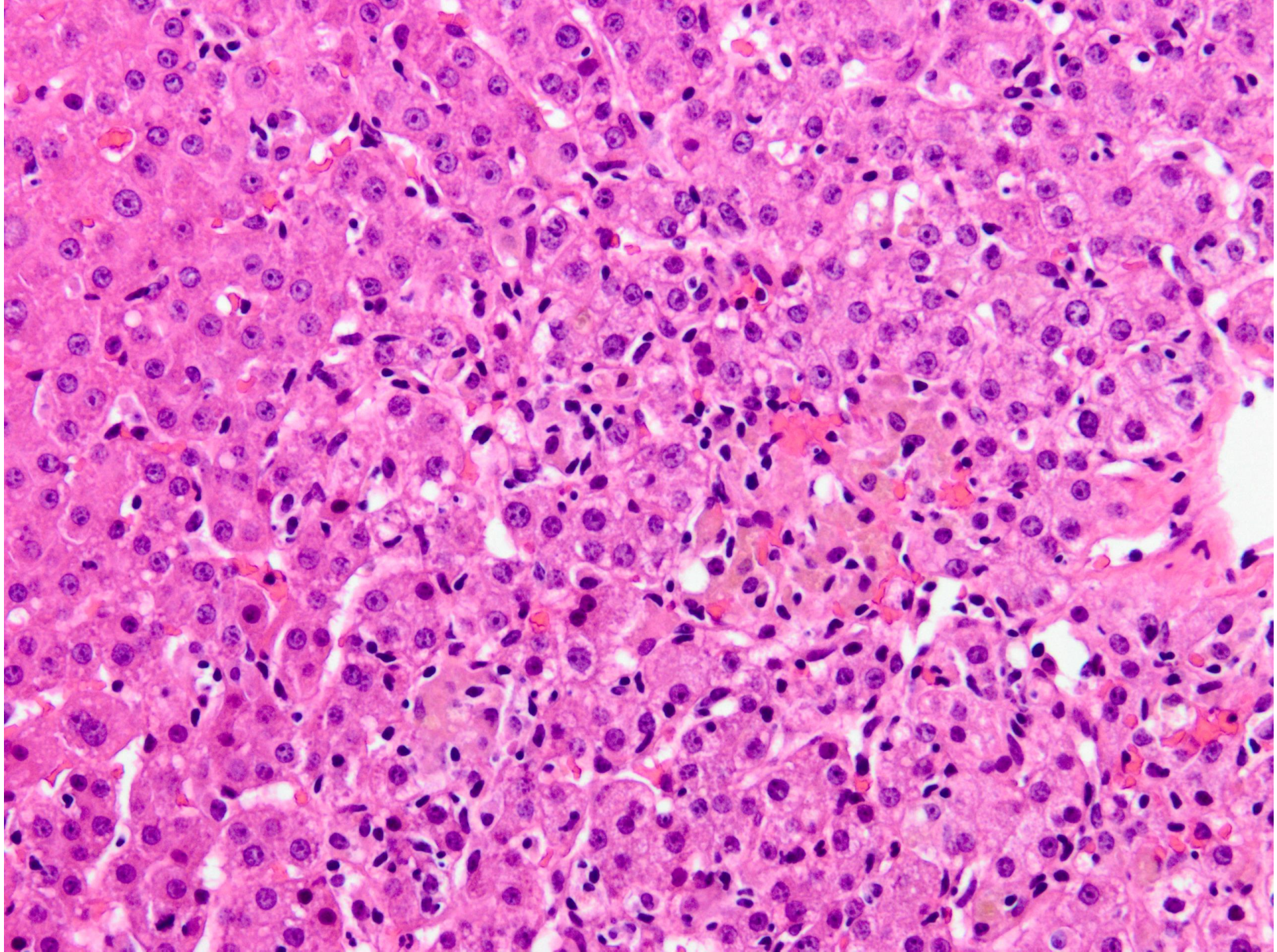
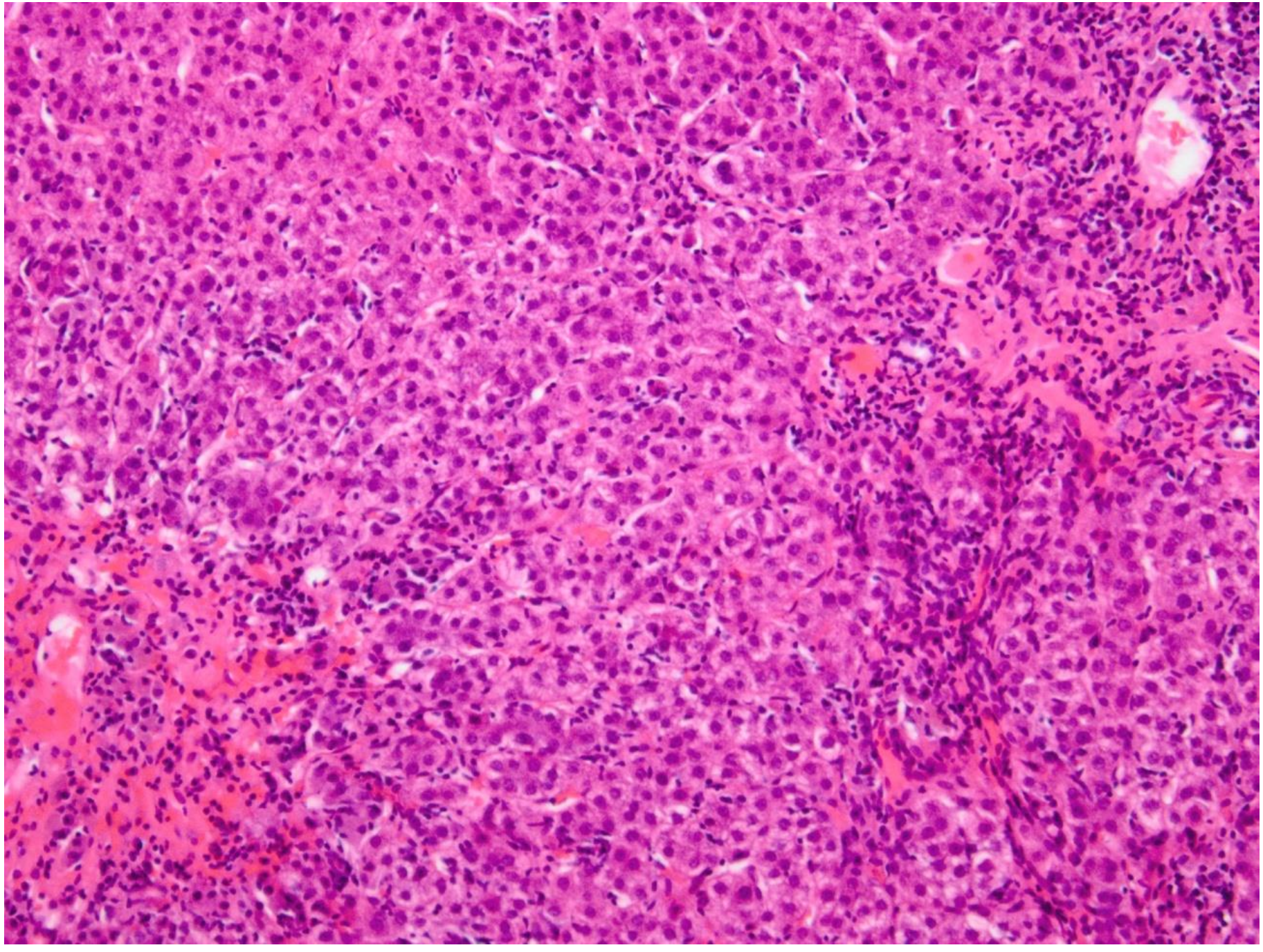




2nd biopsy (Chronic active hepatitis with perivenular zonal necrosis)



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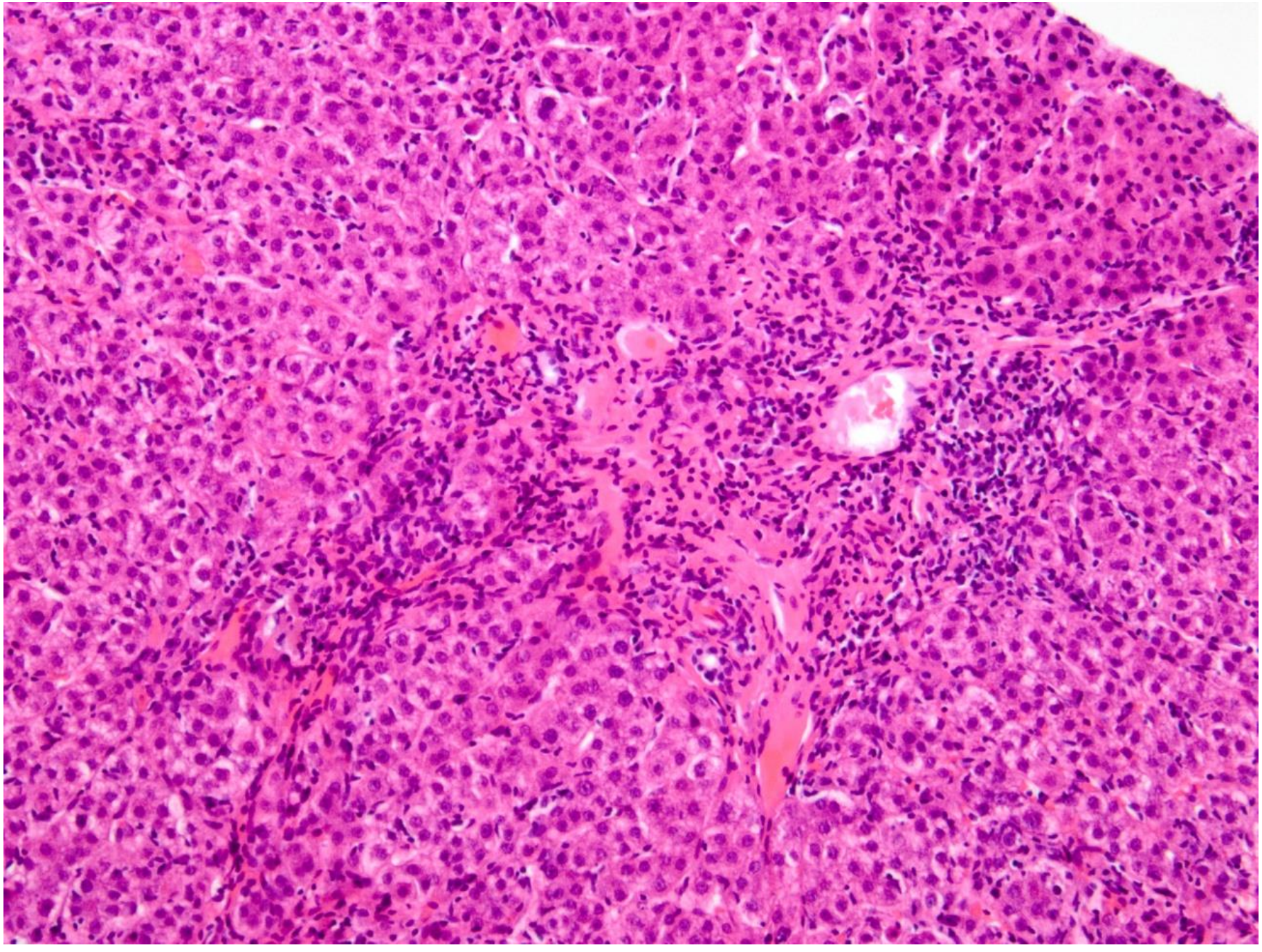

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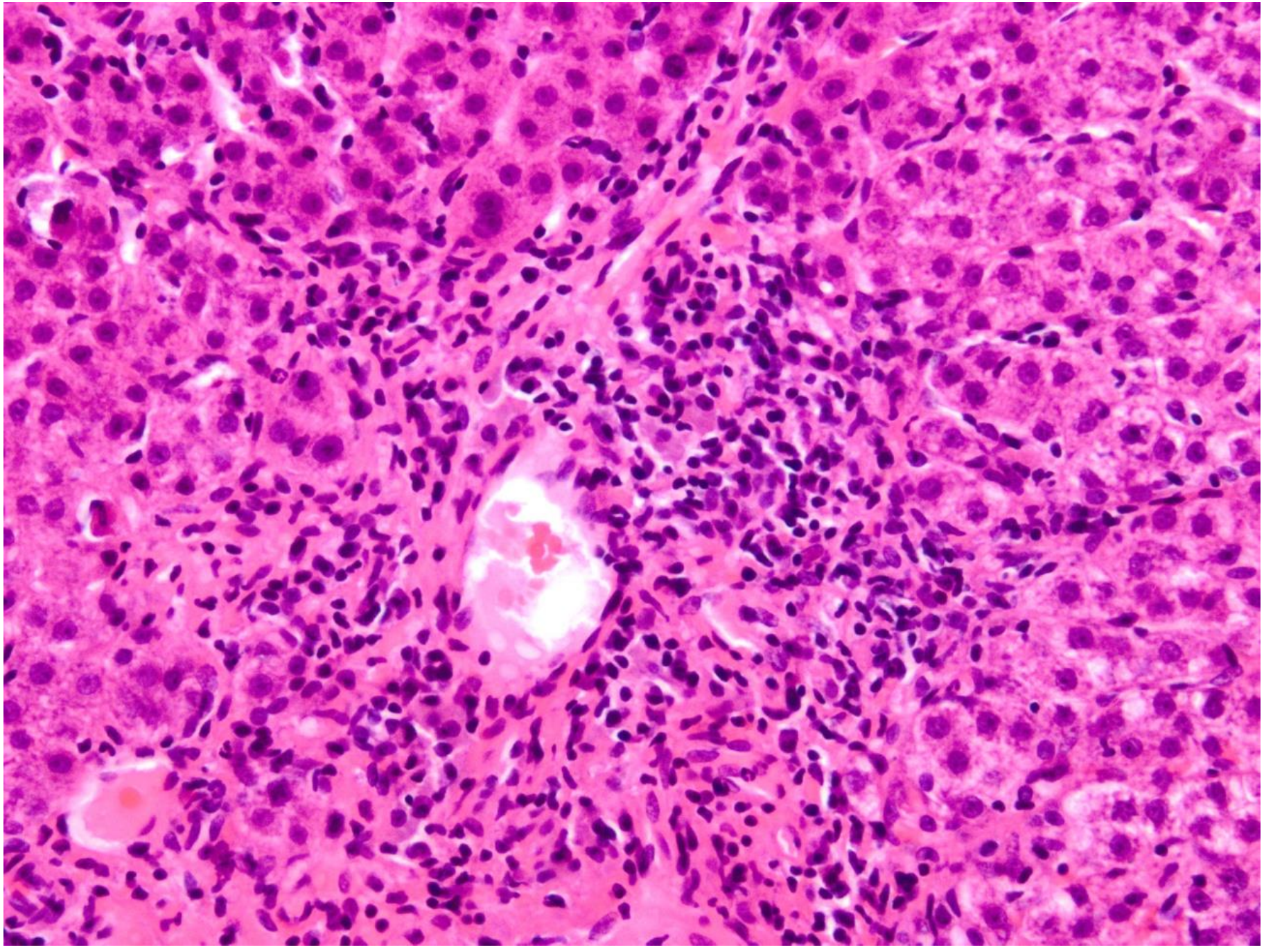

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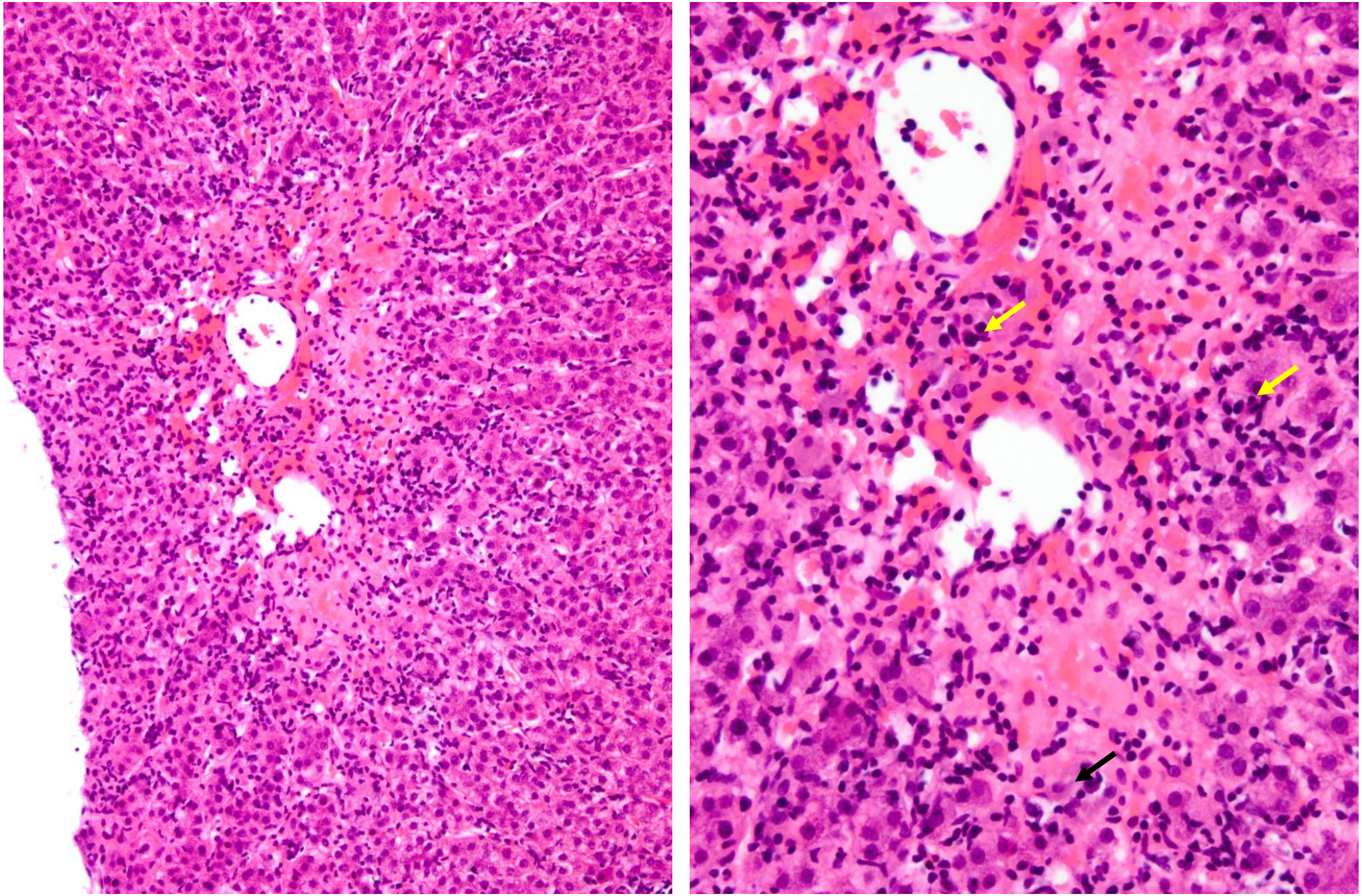

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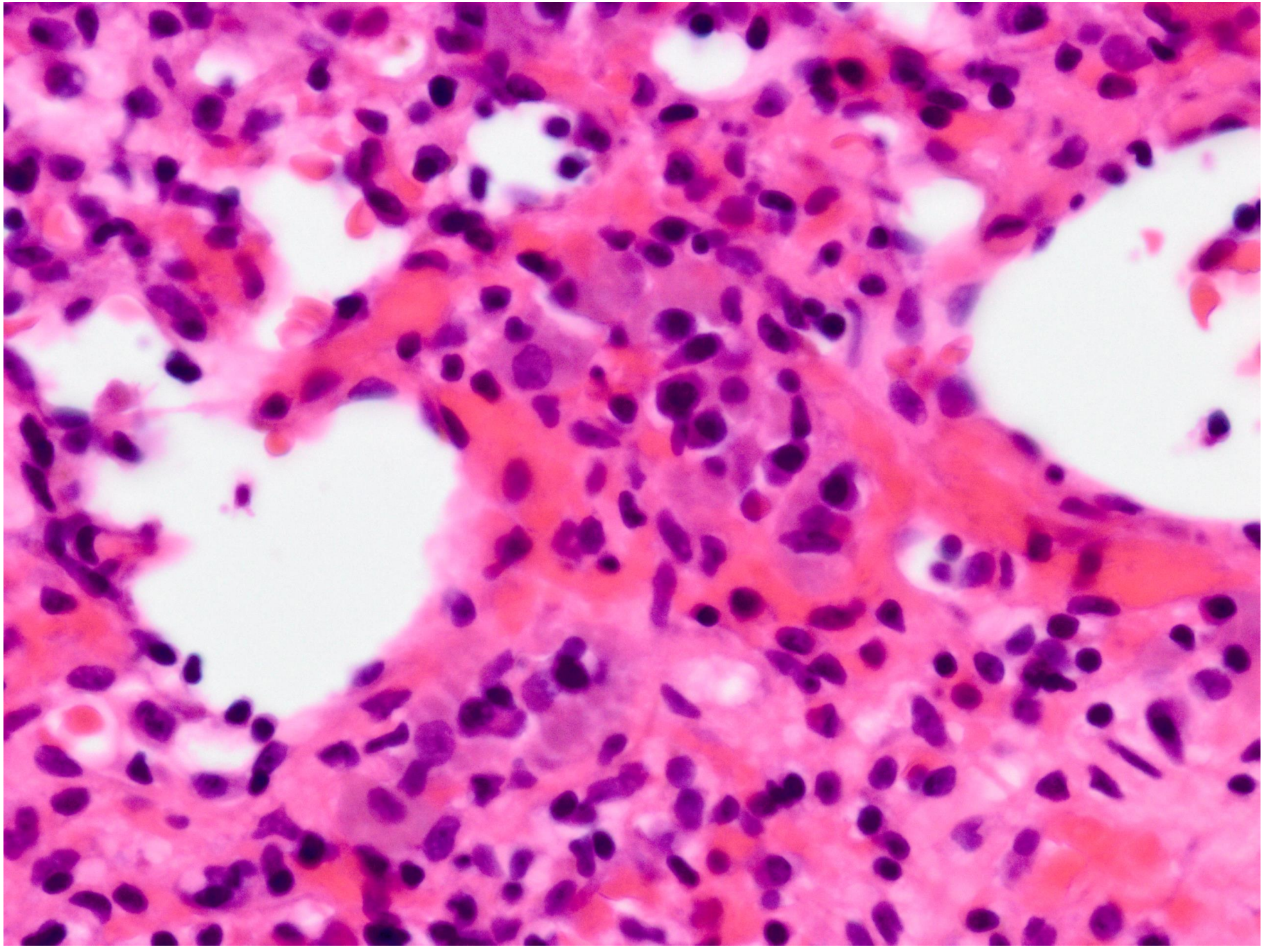
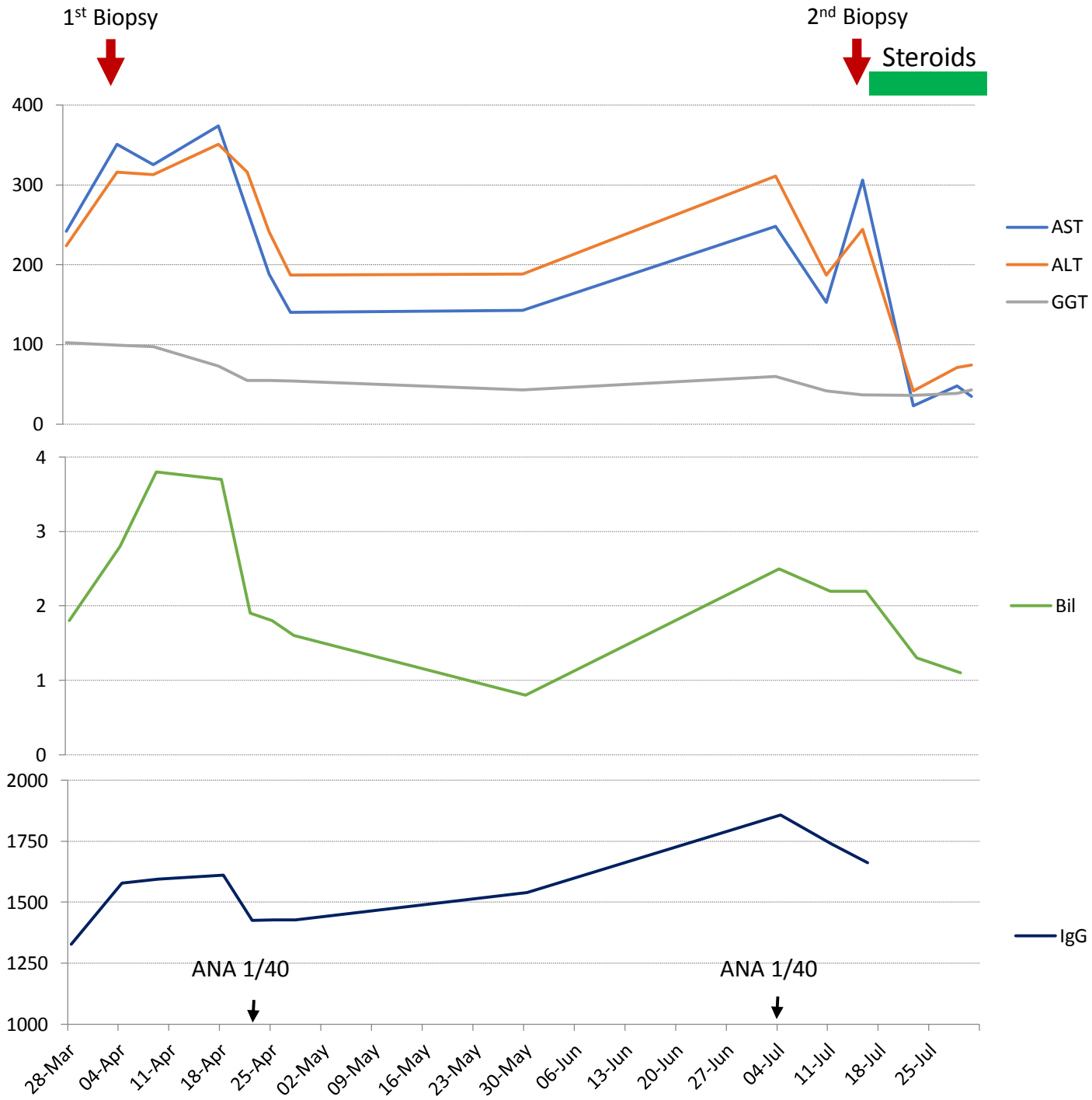
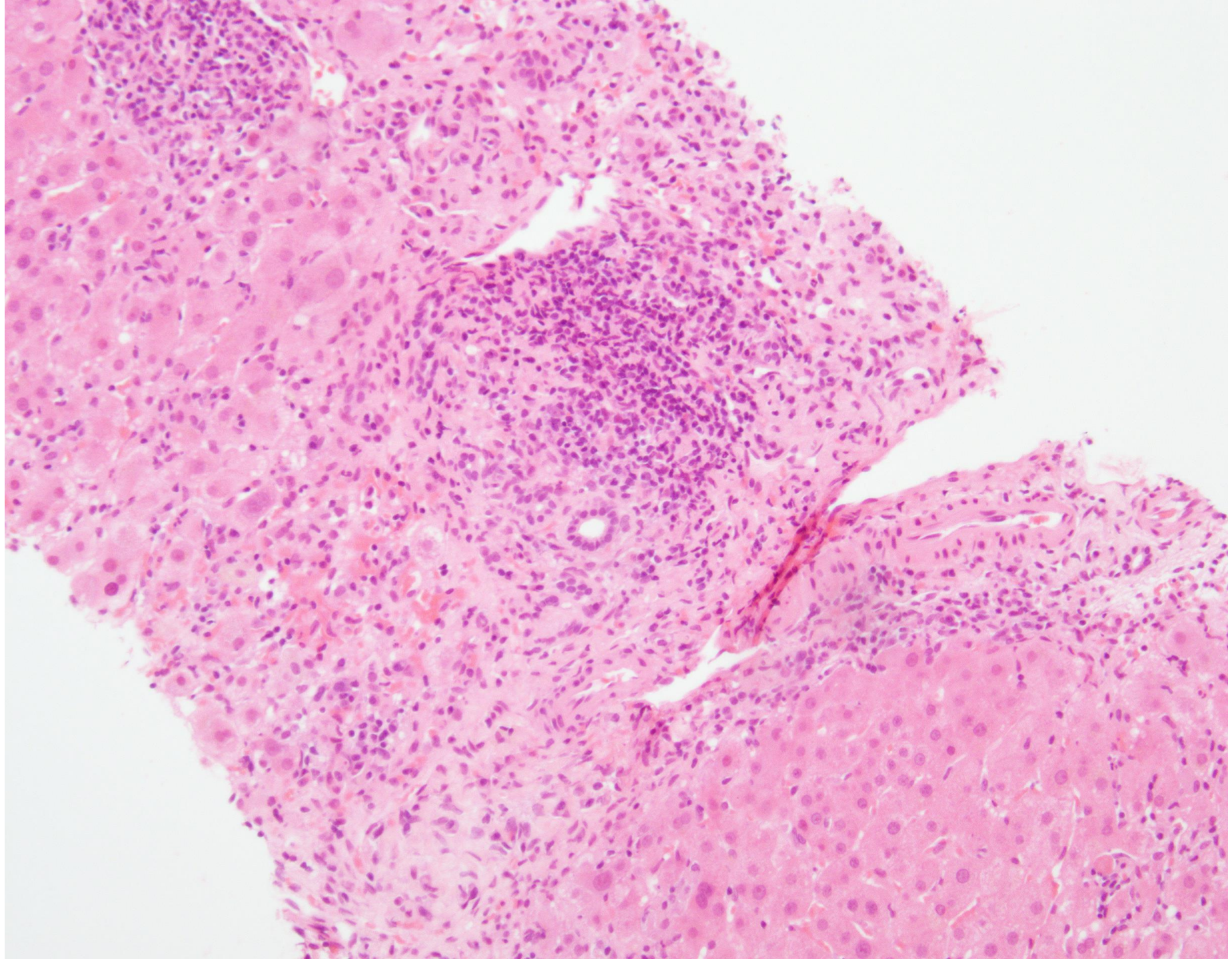


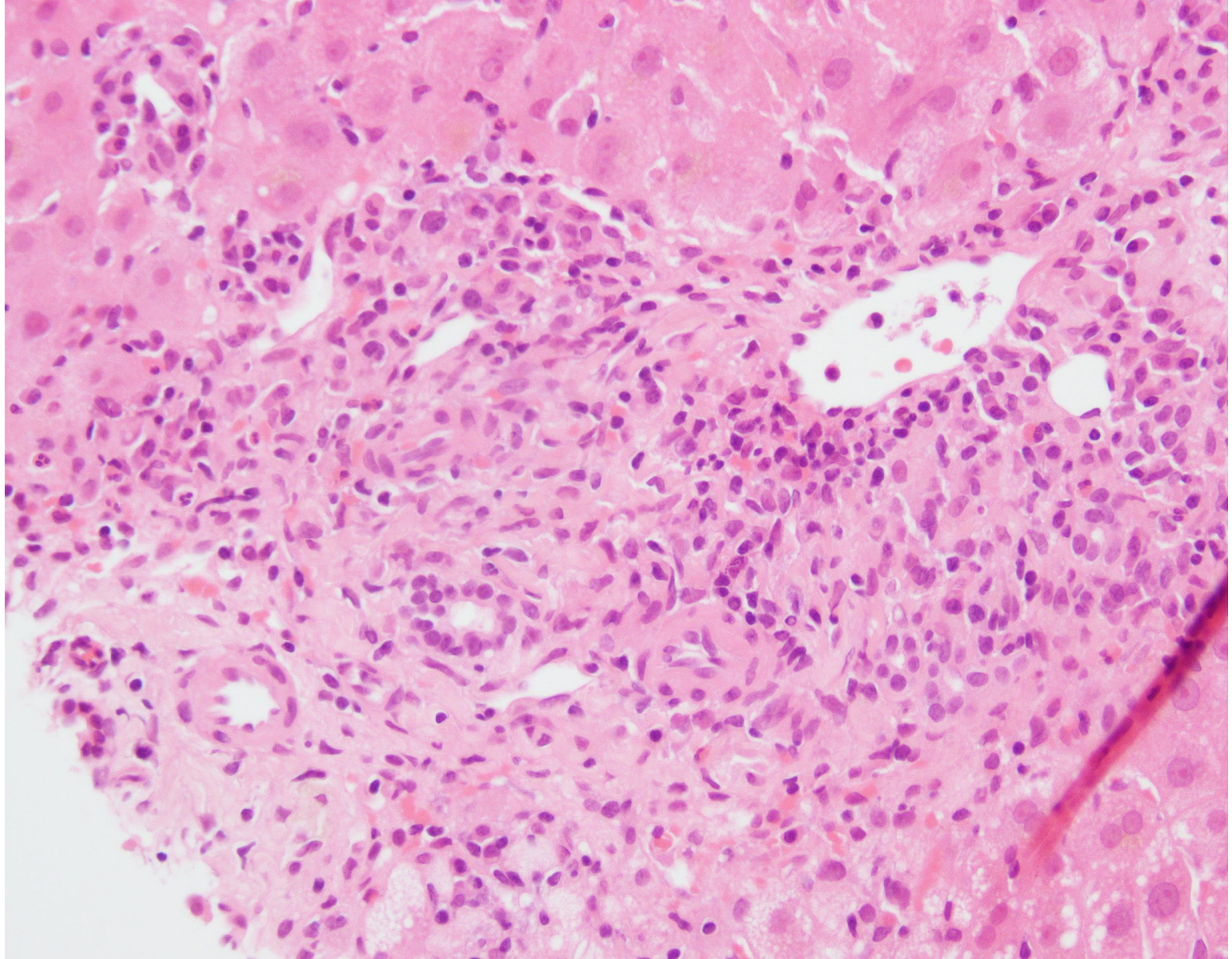


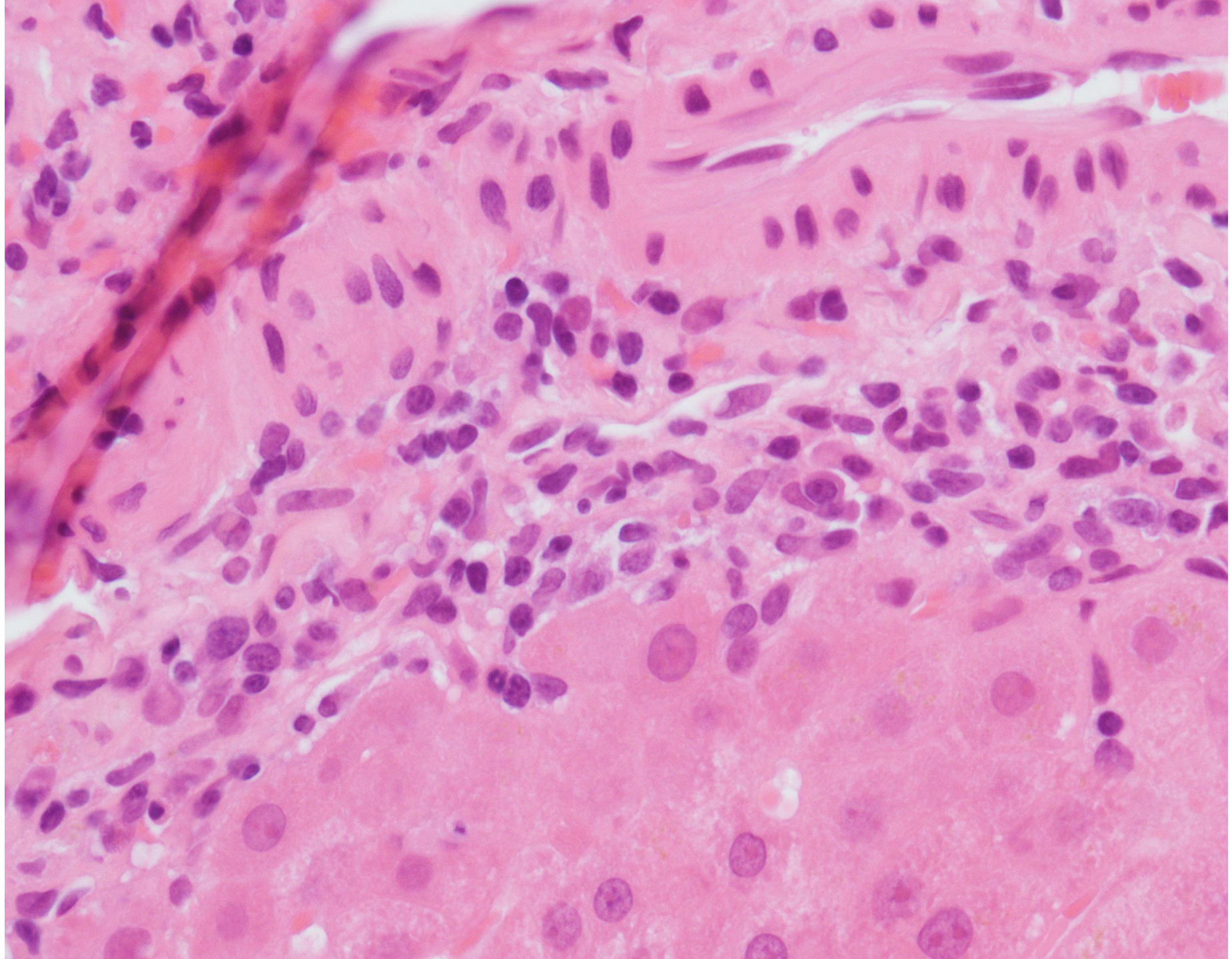
She is still on steroids with three episodes of relapse during tapering off.

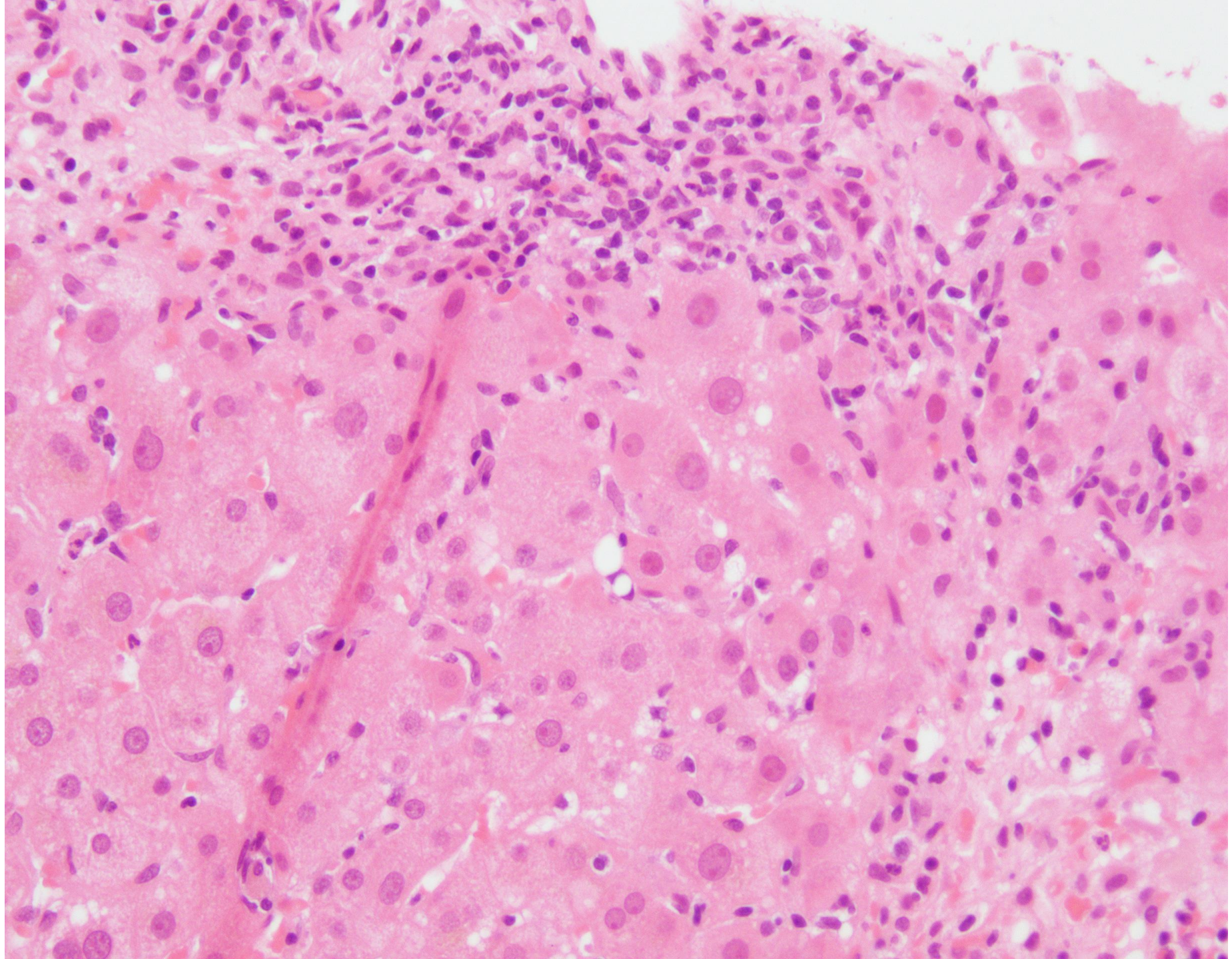
CASE #2

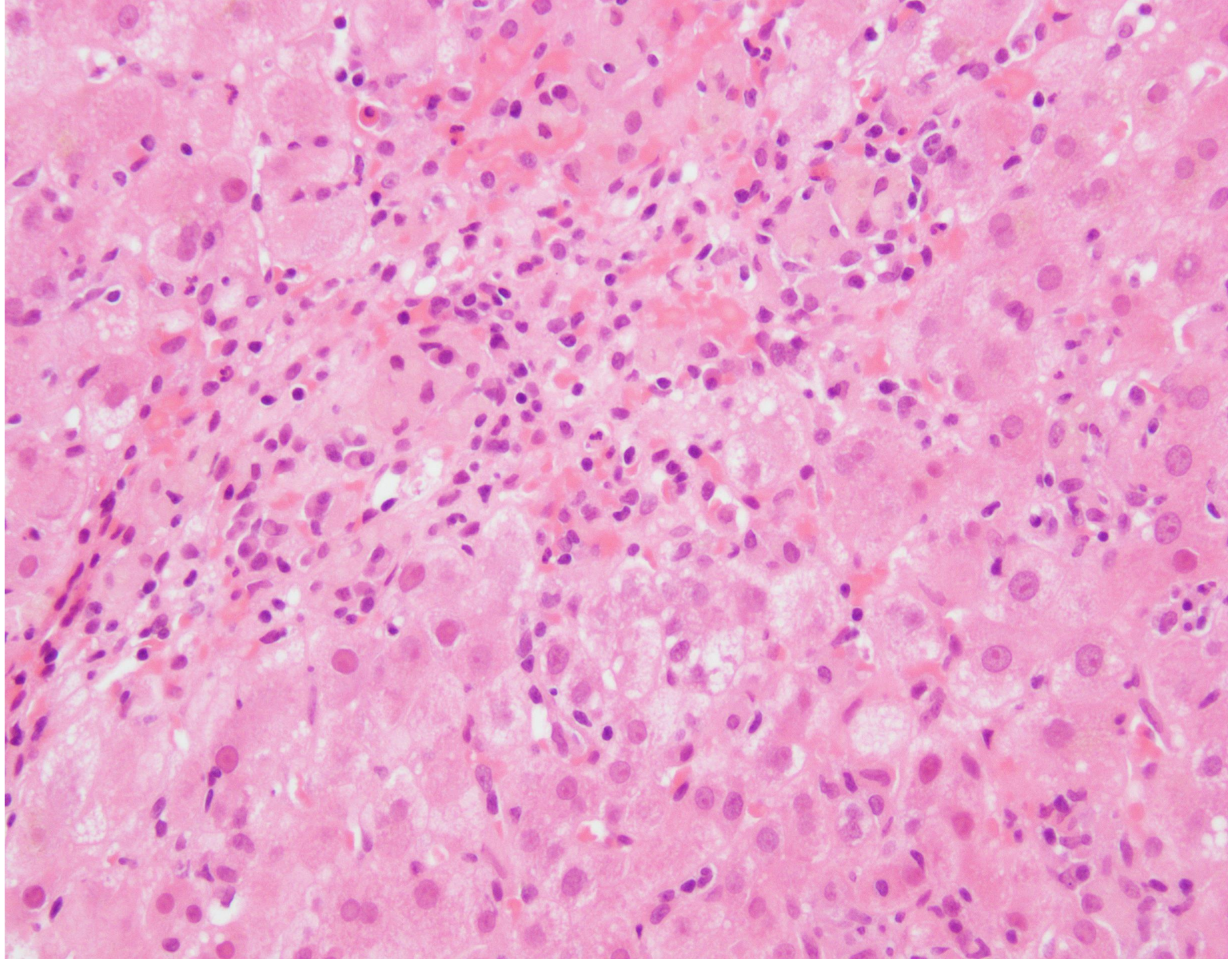
- 46-year-old lady, who was diagnosed with ulcerative colitis a few years ago
- Her colitis flared, and she entered the infliximab program. Baseline pre-treatment liver function tests were unremarkable.
- Towards the end of the third infliximab infusion, she felt significant pruritus and fatigue.
- Bilirubin 27 umol/L (normal <22); ALP 174 U/L (30-130); ALT 321 U/L (<50); GGT 53 U/L 9-36); ANA negative; SMA 1/320; IgG normal
- Liver biopsy

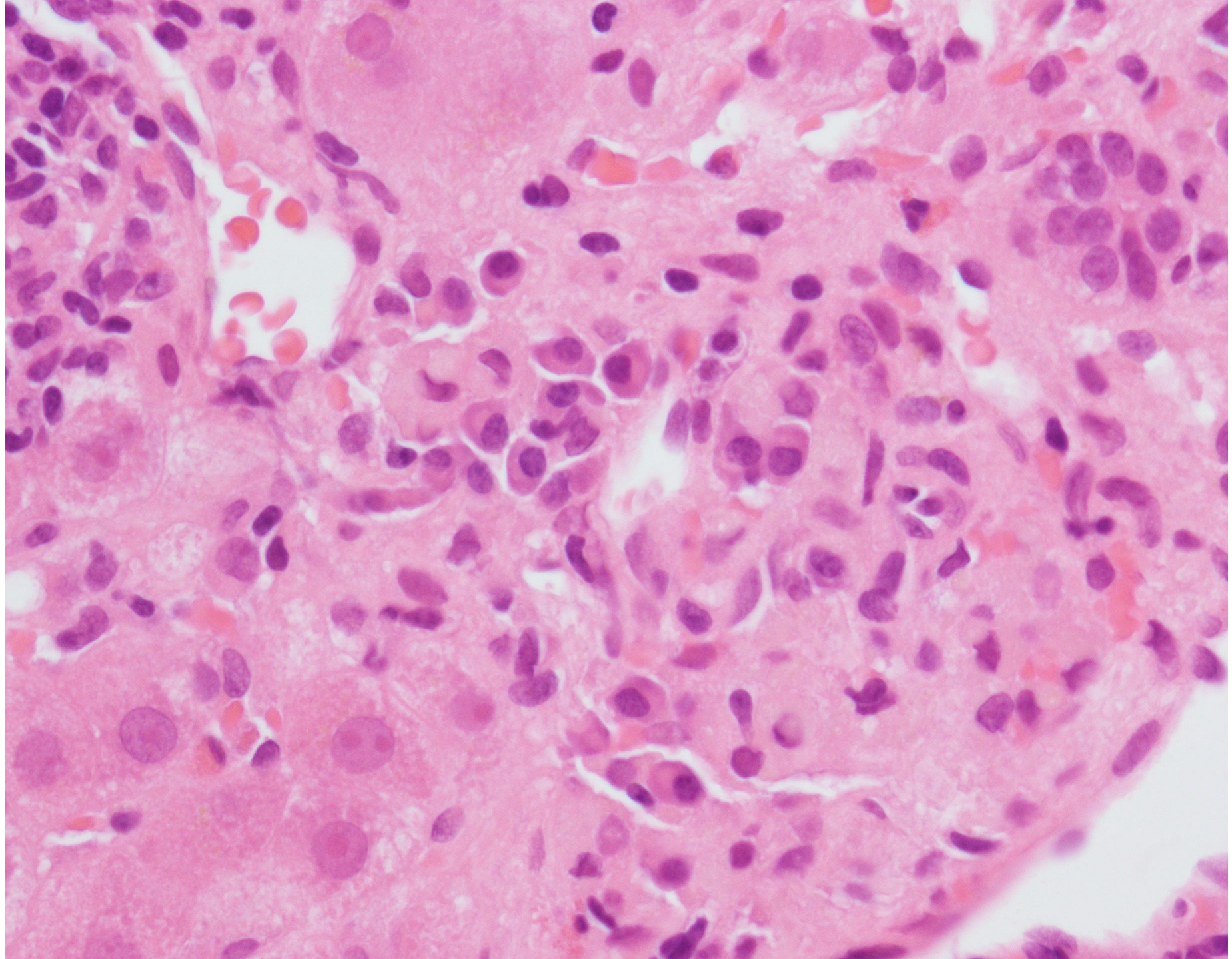












CASE #2

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- Towards the end of the third infliximab infusion, she felt significant pruritus and fatigue.
- Bilirubin 27 umol/L (normal <22); ALP 174 U/L (30-130); ALT 321 U/L (<50); GGT 53 U/L 9-36); ANA negative; SMA 1/320; IgG normal
- Liver biopsy
- Responded well to predonisolone (30 mg a day) with liver enzymes normalized in a few months.
- Currently on low-dose steroids (5 mg a day). No relapse until know (2 years)

How do we diagnose those cases?

AIH, DILI or drug-induced AIH?

	Case #1	Case #2
Sudden onset soon after new medication	Yes	Yes
Autoantibodies (ANA or SMA)	Yes (ANA1/40)	Yes (SMA 1/320)
IgG elevation	Yes	No
AIH-like histology	Yes	Yes
Good response to steroids	Yes	Yes
Relapse during tapering off steroids	**Yes**	**No**

Drug-Induced Autoimmune Hepatitis: Clinical Characteristics and Prognosis

Einar Björnsson,[1,2] Jayant Talwalkar,[2] Sombat Treeprasertsuk,[2] Patrick S. Kamath,[2] Naoki Takahashi,[3] Schuyler Sanderson,[4] Matthias Neuhauser,[2] and Keith Lindor[2]

Drug-induced autoimmune hepatitis (DIAIH) has been reported to be caused by several drugs. There is a lack of data comparing these patients with other patients with autoimmune hepatitis (AIH). A search was performed using the Mayo Clinic diagnostic medical index for AIH patients and DIAIH patients identified over 10 years. Individuals with overlap syndromes and decompensated liver disease were excluded. Overall, 261 patients (204 females, median age 52) were identified, and 24 (9.2%) were DIAIH cases with a median age of 53 (interquartile range, 24-61). Two drugs, nitrofurantoin (n = 11) and minocycline (n = 11), were the main causes. A similar proportion of DIAIH patients had positive antinuclear antibodies (83% versus 70%) and smooth muscle antibodies (50% versus 45%) as compared with AIH patients. Histological grade and stage were similar in patients with DIAIH versus AIH; however, none of the DIAIH patients had cirrhosis at baseline; this was present in 20% of matched AIH cases. Liver imaging was normal in all minocycline cases. Eight of 11 (73%) nitrofurantoin patients had abnormalities on hepatic imaging (mainly liver atrophy), a finding seen in only 8 of 33 (24%) of a random sample of the rest of the AIH group ($P = 0.0089$). Corticosteroid responsiveness was similar in DIAIH and the AIH patients. Discontinuation of immunosuppression was tried and successful in 14 DIAIH cases, with no relapses (0%), whereas 65% of the AIH patients had a relapse after discontinuation of immunosuppression ($P < 0.0001$). *Conclusion:* A significant proportion of patients with AIH have drug-induced AIH, mainly because of nitrofurantoin and minocycline. These two groups have similar clinical and histological patterns. However, DIAIH patients do not seem to require long-term immunosuppressive therapy.

(Hepatology 2010;51:2040-2048)

261 cases of AIH
24 (9%) = drug-induced
22 (8%) = nitrofurantoin or minocycline

Table 3. Comparison Between DILI/AIH and AIH Alone

	DIAIH	AIH	P Value
Grade (Batts and Ludwig)	3 (2-3)	3 (2-3)	NS
Portal inflammation	2 (2-3)	2 (2-3)	NS
Lymphoplasmacytic (absent/present)	19/23 (83%)	22/23 (96%)	NS
Interface hepatitis	2.5 (1.5-3.0)	2.0 (1.0-3.0)	NS
Lobular hepatitis	2.0 (1.0-3.0)	2.0 (1.0-3.0)	NS
Zone 3 necrosis	15/23 (65%)	12/22 (55%)	NS
Confluent necrosis	7/23 (30.4%)	2/22 (9%)	NS
Rosette formation	7/22 (31.8%)	5/22 (22.7%)	NS
Stage	0 (0-2)	1 (0-3)	0.06
Compatible	8/24 (33%)	8/24 (33%)	NS
Typical	16/24 (66%)	15/24 (63%)	
Atypical	0	1/24 (4%)	

No significant difference in histology between DI-AIH and classical AIH

Table 1. Comparison of the Demographics, Seropositivity, AIH Score, Histology, Treatment, and Liver Tests at Presentation in Patients with Autoimmune Hepatitis (AIH) and Those with Drug-Induced Liver Injury (DIAIH)

	AIH Patients (n = 237)	DIAIH (n = 24)	P Value
Age	52 (37-62)	53 (24-61)	NS
Sex, females (%)	184 (78%)	20 (92%)	NS
ANA positive (%)	165/237 (70%)	20 (83%)	NS
SMA positive (%)	106/237 (45%)	12/24 (50%)	NS
Both ANA and SMA (%)	69/237 (29%)	9/24 (38%)	NS
Seronegative (%)	29/237 (12%)	1/24 (4%)	NS
Simplified AIH score:			
Probable or definite (%)	181/237 (76%)	19/21 (90.5%)	NS
Immunosuppressive therapy (%)	222/237 (94%)	21/24 (88%)	NS
Steroids and azathioprine (%)	191/222 (86%)	12/21 (57%)	0.0024
Steroids alone (%)	31/222 (14%)	9 (43%)	0.0024
Trial of discontinuation successful (%)	18/52 (35%)	14/14 (100%)	<0.0001
AST (<48 U/L)	392 (154-1031)	679 (291-956)	NS
ALT (<55 U/L)	480 (185-1141)	728 (255-1141)	NS
ALP (115 U/L)	241 (138-350)	376 (229-514)	0.0166
TB (<1.0 mg/dL)	2.0 (1.0-8.0)	4.0 (1.0-12.0)	NS
Albumin (>3.5 g/dL)	3.4 (2.95-3.7)	3.1 (2.6-3.6)	NS
INR (<1.2)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	NS
IgG (<1500 g/dL)	2020 (1618-2702)	1905 (1600-2455)	NS
Gamma globulins (<1.7 g/dL)	2.5 (2.0-3.2)	2.55 (2.2-3.1)	NS
Jaundice at presentation	110/237 (46%)	12/24 (50%)	NS

No relapse in DI-AIH cases!

Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL
OF HEPATOLOGY

Infliximab-induced liver injury: Clinical phenotypes, autoimmunity and the role of corticosteroid treatment

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- A total of 36 patients with infliximab-induced DILI were identified.
- Type of liver injury was predominantly hepatocellular (64%). Median peak liver enzymes: ALT 393 U/L, AST 283 U/L, ALP 116 U/L, and bilirubin 13 µmol/L.
- A total of 25 (69%) were positive for anti-nuclear antibody and/or had elevated IgG.
- Corticosteroids were initiated in 17 (47%).
- Corticosteroids were tapered in all patients, with no cases of relapse during the follow-up period of 1,245 (820-2,698) days.

J Hepatol 2021 (in press)

Drug-induced autoimmune hepatitis (DIAIH)

- Cases with drug-induced clinical onset and AIH-like histology/serology have been called as DIAIH.
- According to AIH scoring systems, ‘DI-AIH’ cases are categorized as probable / definite AIH.
- ‘DIAIH’ is indistinguishable from classical AIH by serology, histology and response to steroids.
- However, underlying biology seems to differ between the two conditions, with discontinuation of steroids being successful in most cases of DI-AIH without relapse.

Editorial

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Drug induced liver injury and its relationship to autoimmune hepatitis

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Table 1
DILI and AIH: suggested diagnoses and clinical characteristics.

	Characteristics
AIH with DILI	Patients with known AIH; probably chance association; often advanced fibrosis on histology
Drug-induced AIH True AIH	Patients with unrecognized AIH or predisposition to AIH, in whom AIH is unmasked or induced by DILI; good response to steroids; relapse after withdrawal of immunosuppression with the need for continued immunosuppressive treatment; chance association of drug intake in a patient with first presentation of AIH cannot be ruled out — Case 1
Immune-mediated DILI AIH-like hepatitis	Clinical, biochemical, and histological signs similar to AIH; eosinophilia and rash may be present; usually no advanced fibrosis; good response to steroids; remission is maintained after successful withdrawal of steroids — Minocycline, nitrofurantoine, TNF-a inhibitors — Case 2

Drug-induced AIH

J Hepatol. 2011 Oct;55(4):747-9

What pathologists need to describe in the histology report

1. Microscopic changes are **AIH-like**, which justifies corticosteroids use.
2. There are two possibilities: **drug-induced AIH (true AIH)** and **immune-mediated AIH-like DILI**
3. Follow-up data (e.g., **relapse during tapering steroids**) will be informative.
4. **Steroid discontinuation is possible** in most cases of immune mediated DILI.

- In cases, which had a TNF-a inhibitor for IBD, the presence or absence of PSC needs to be described. **Pitfall!**

Can we discriminate classical AIH from immune-mediated, AIH-like DILI by histology ?

- Limited data is available.
- It is impossible in most cases.
- The presence of scarring fibrosis favours classical AIH. Caveat: Long-term use of minocycline and nitrofurantoin can have fibrosis.
- Extensive eosinophilic infiltration favours immune-mediated DILI.


Thank you for your attention