

Medical Liver Disease Diagnosis by Histologic Pattern



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Liver Biopsy Interpretation

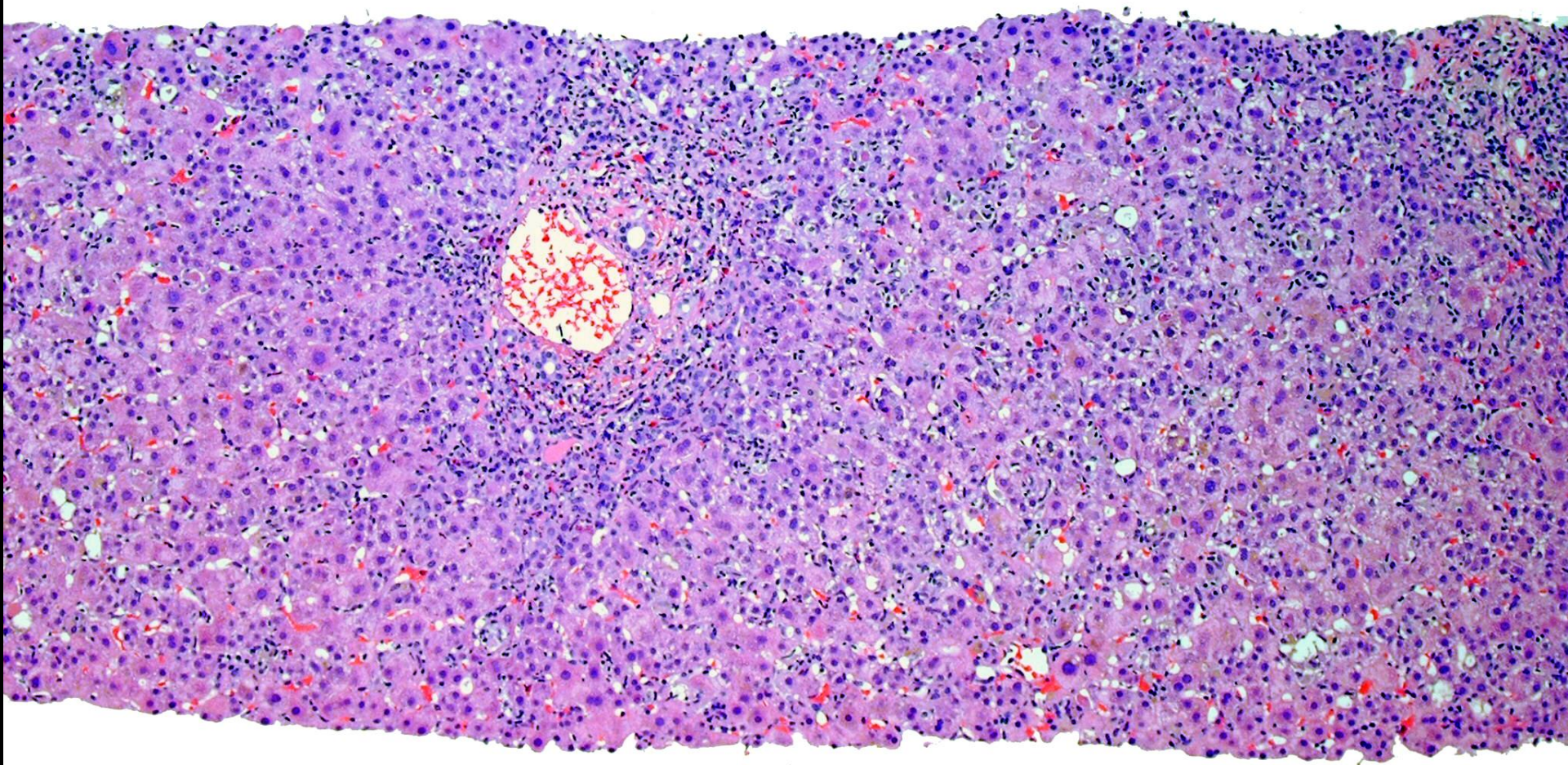
- **Microscopic examination:**
 - Biopsy adequacy
 - Systematic examination
 - Assignment of histologic pattern
 - Search for distinctive features
- **Laboratory results:**
 - Liver chemistry tests (hepatitic versus cholestatic)
 - Liver synthetic function (albumin, PT/PTT, INR)
 - Serologic results
 - Genetic testing
- **Clinical history:**
 - Duration and character of illness
 - Medications, supplements, herbals, and toxic exposures
 - Other systemic diseases
 - Family history, travel history, occupation etc.
 - Physical exam findings

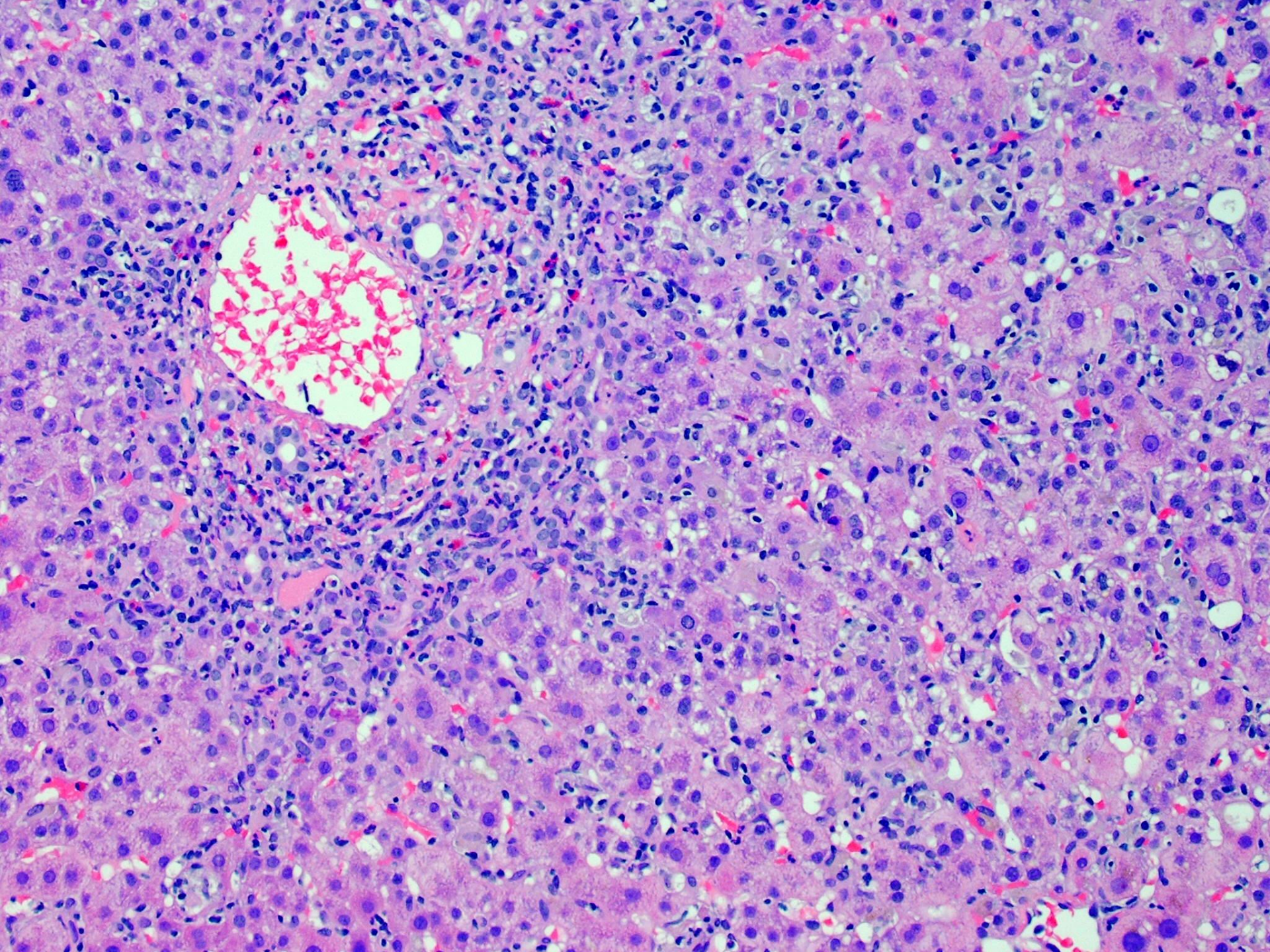
Non-cholestatic Histologic Patterns of Hepatic Injury

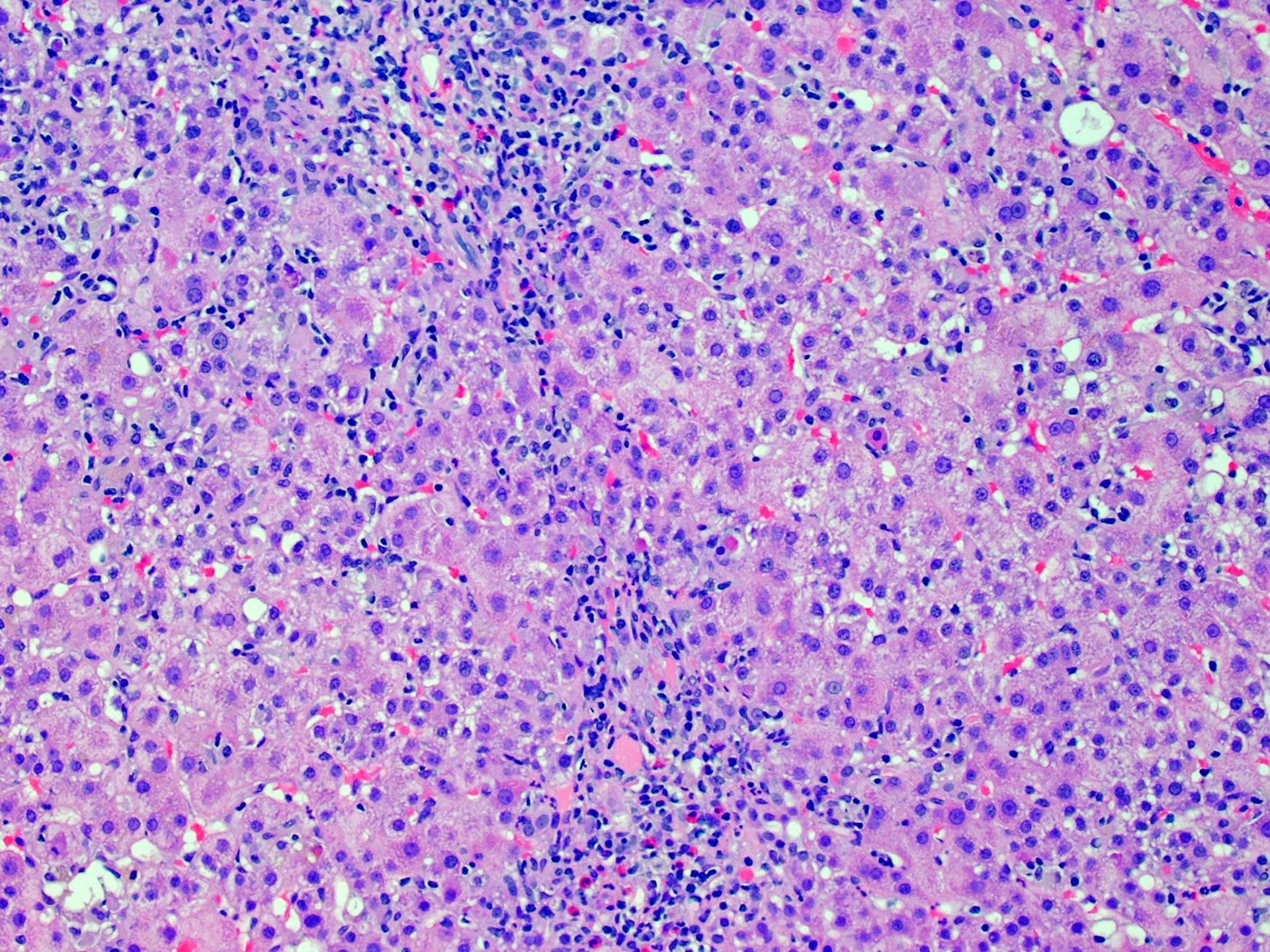
- **Acute hepatitis**
- **Chronic hepatitis**
- **Centrilobular hepatocyte necrosis / dropout**
- **Lobular hepatitis**
- **Random hepatocyte necrosis**
- **Granulomas / granulomatous hepatitis**
- **Microvesicular steatosis**
- **Steatohepatitis**
- **Nearly normal liver**

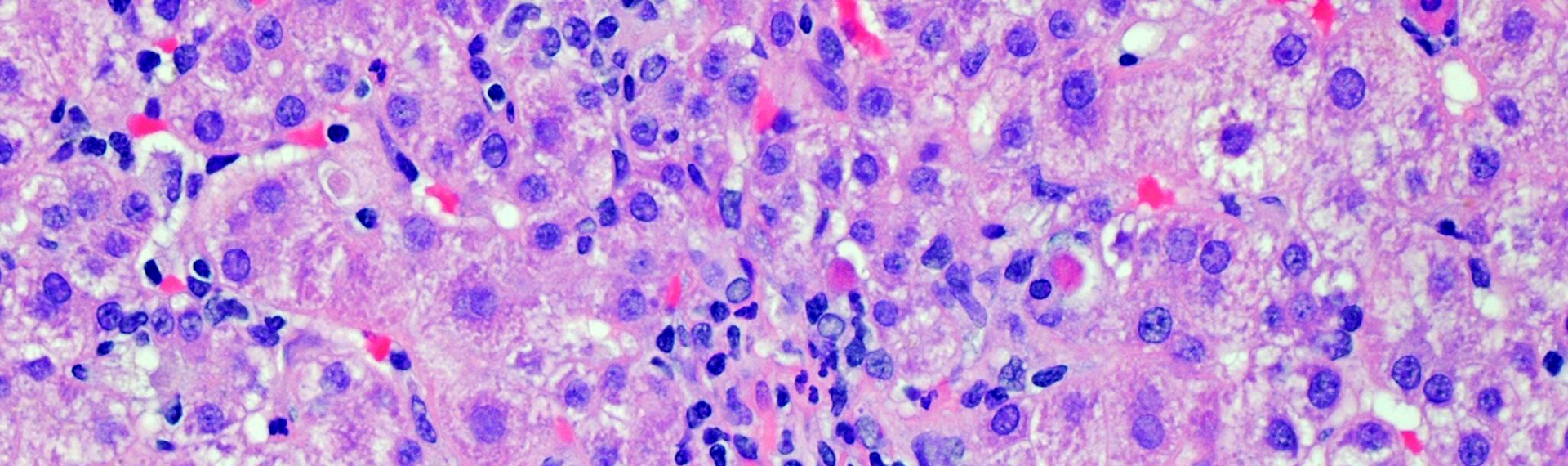
Case 198: Clinical History

- 21 y.o. M presents with fatigue, anorexia & abd pain
- TB = 0.6, AST = 335, ALT = 496, Alk phos = 86
- HAV, HBV, HCV all negative.
- Ceruloplasmin and alpha-1-antitrypsin levels normal
- ANA and anti-SMA titers negative.
- No drugs, alcohol, travel, obesity, or diabetes



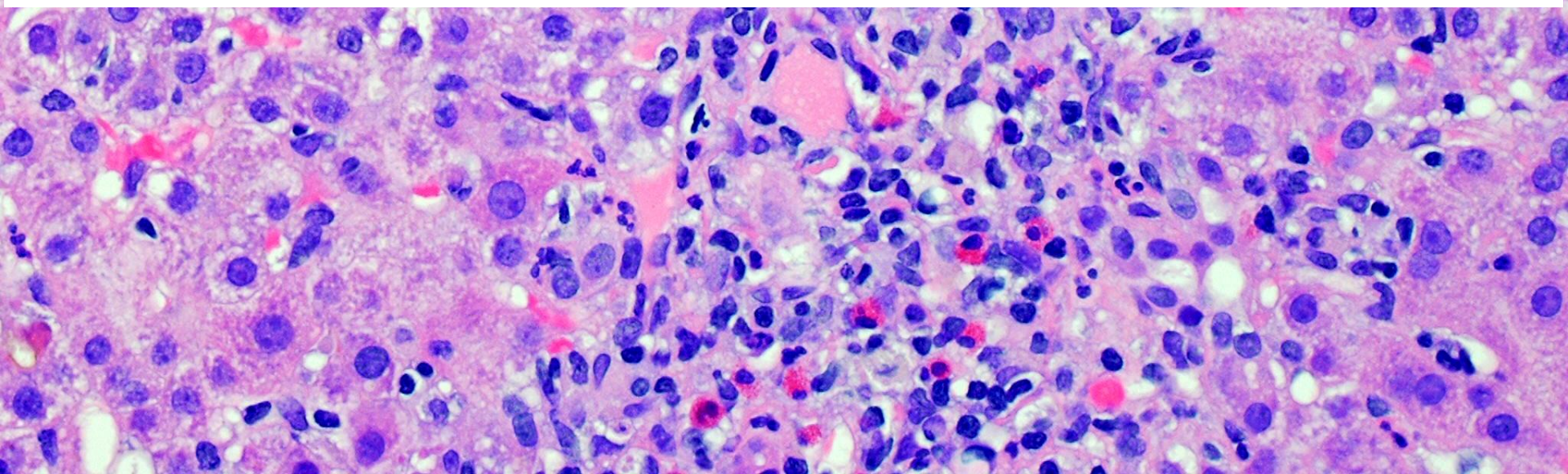






Ecstasy: a common cause of severe acute hepatotoxicity

Victoria Andreu¹, Antoni Mas¹, Miquel Bruguera¹, Joan Manuel Salmerón¹, Vicente Moreno²,
Santiago Nogué³ and Joan Rodés¹



Acute Hepatitis

Generic Histologic Features

- **“Lobular disarray”:**
 - **Ballooned hepatocytes and acidophil bodies**
 - **Individual or confluent hepatocyte dropout**
 - **Zonal, bridging or panlobular necrosis**
 - **Sinusoidal inflammatory cells**
 - **Prominent Kupffer cells (PAS/D stain)**
 - **+/- cholestasis**
- **Mild portal inflammation**
- **No fibrosis**

- **Histologic pattern:**
 - **Acute hepatitis**
- **Diagnosis:**
 - **Drug induced acute hepatitis**
- **Take home points:**
 - **Medications are most common cause of acute hepatitis**
 - **Supplements, toxins & illegal drugs are often overlooked**

Acute Hepatitis

Symptoms: non-specific constitutional symptoms; jaundice

Liver chemistry tests: AST & ALT >>> Alk phos

**Histologic pattern: lobular disarray with minimal portal changes;
no fibrosis**

Drugs and toxins

-
-
-
-
-
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HAV infection

Acute HCV infection

Acute HBV infection

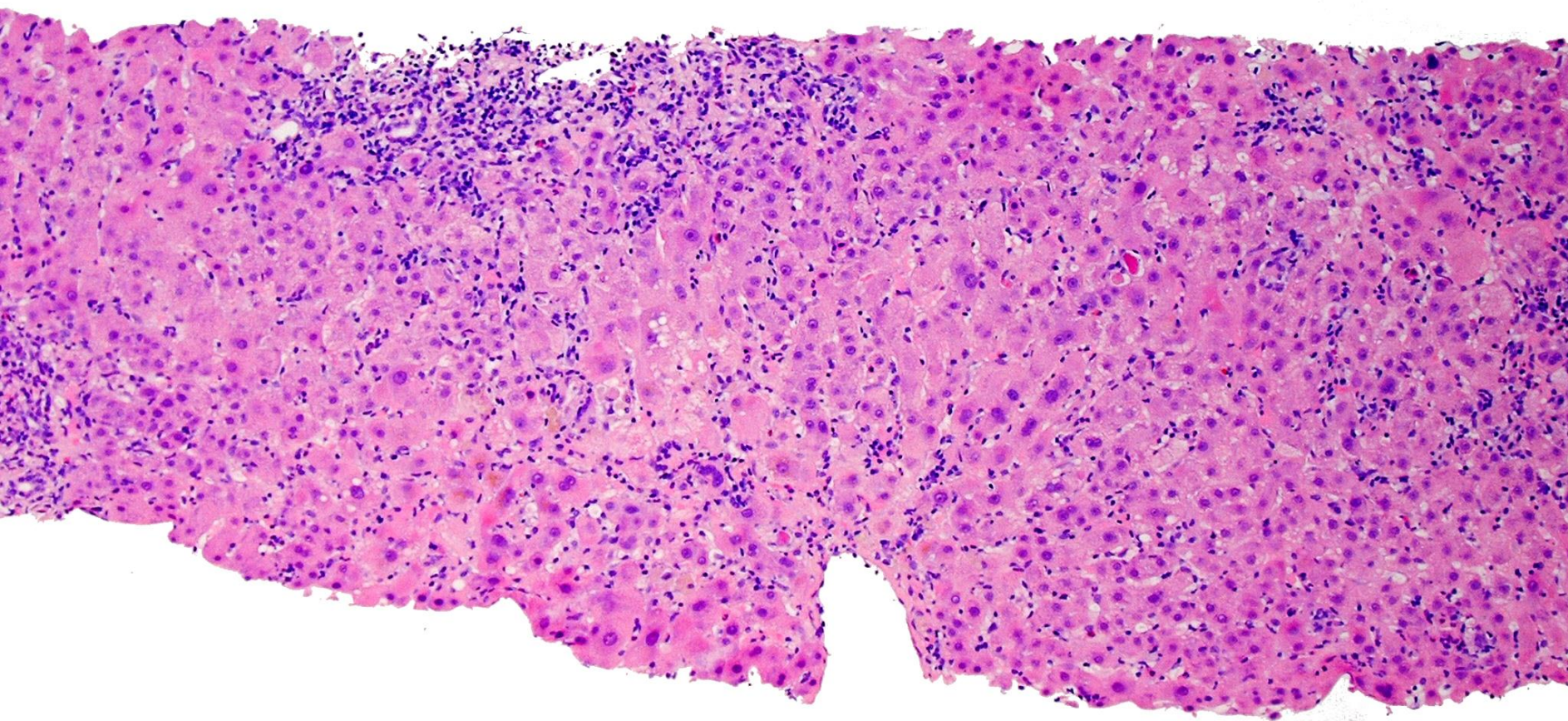
Autoimmune hepatitis

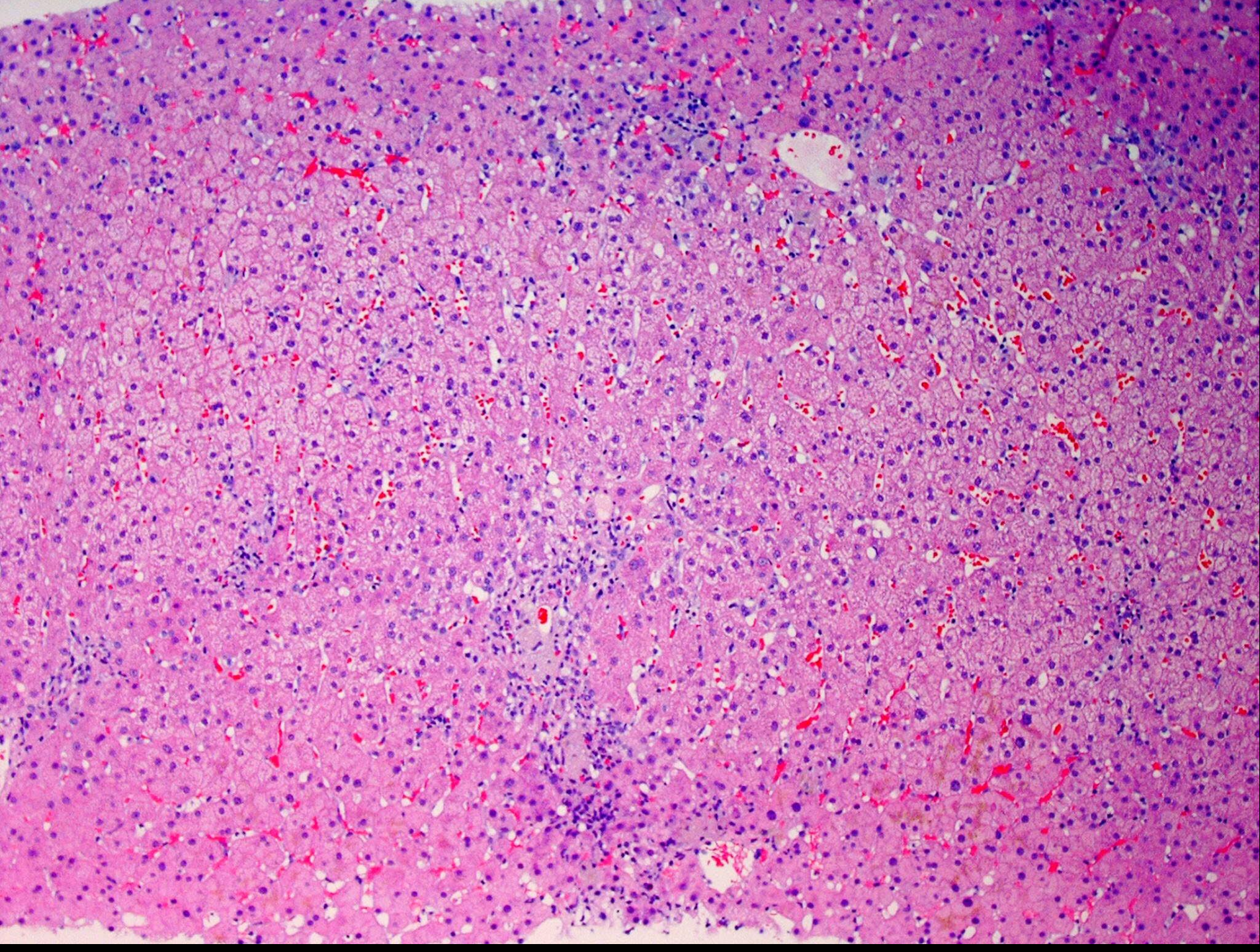
Exotic infections

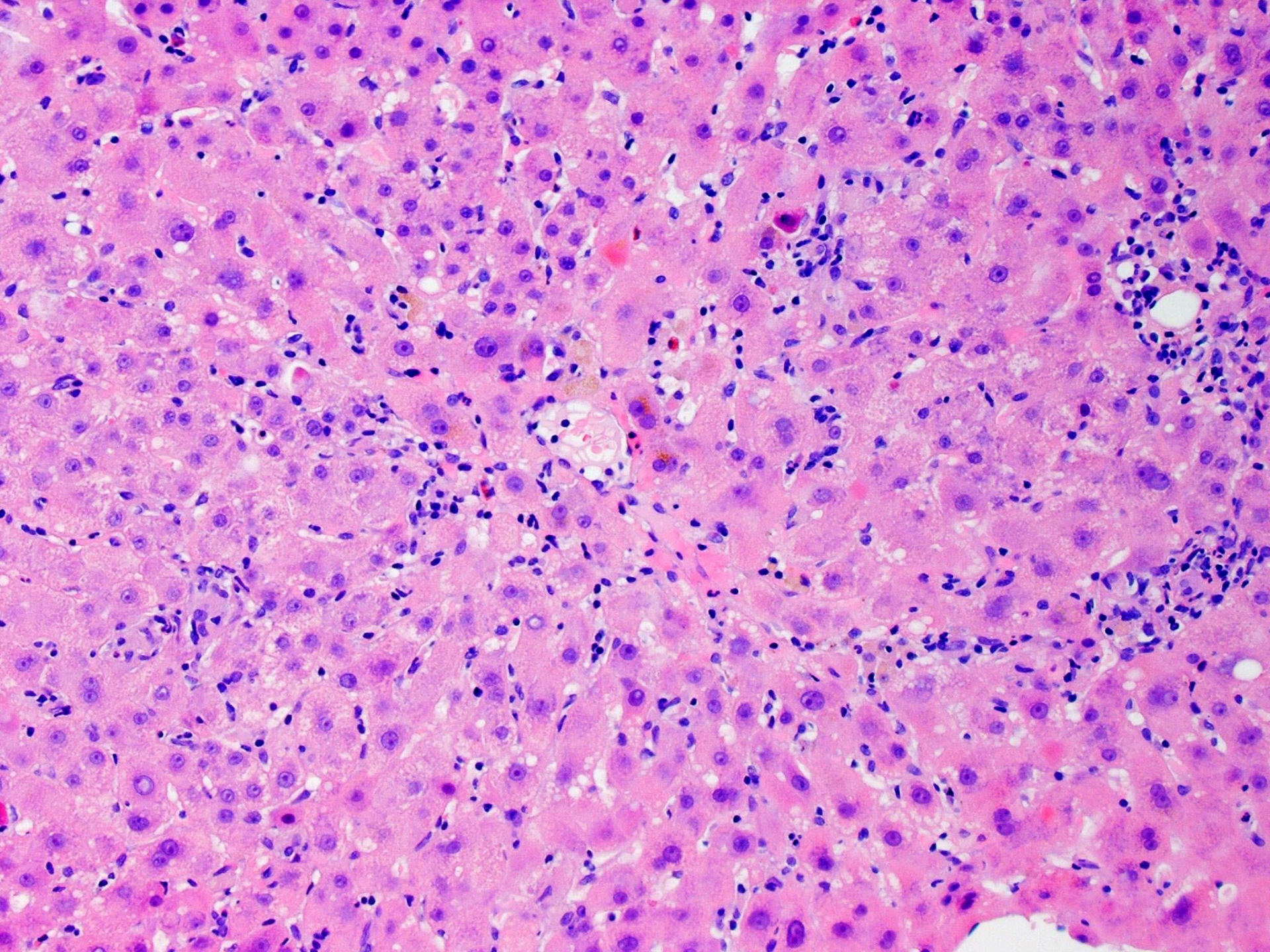
**DIAGNOSIS
BY
SEROLOGIC
TESTING**

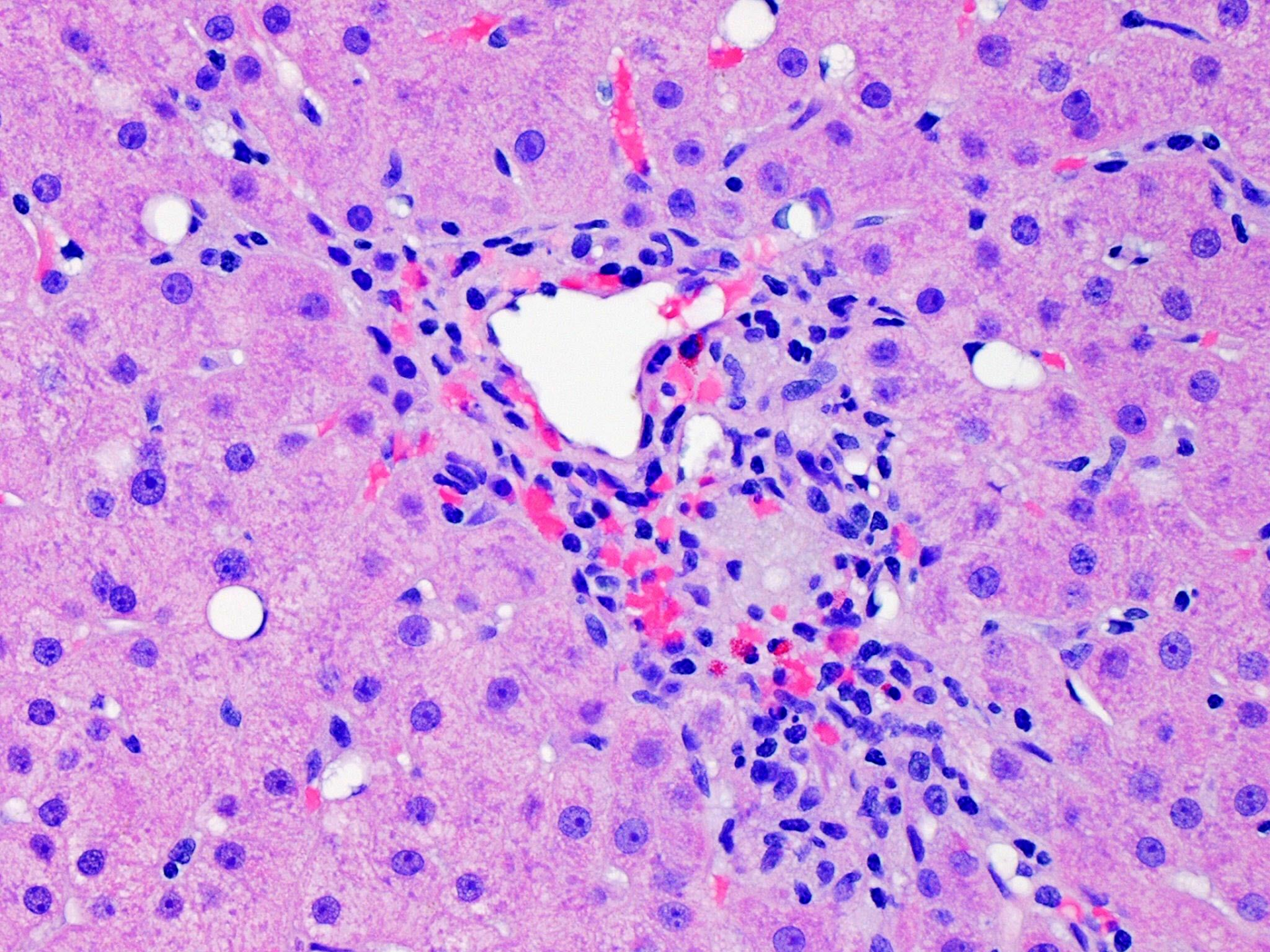
Case 28: Clinical History

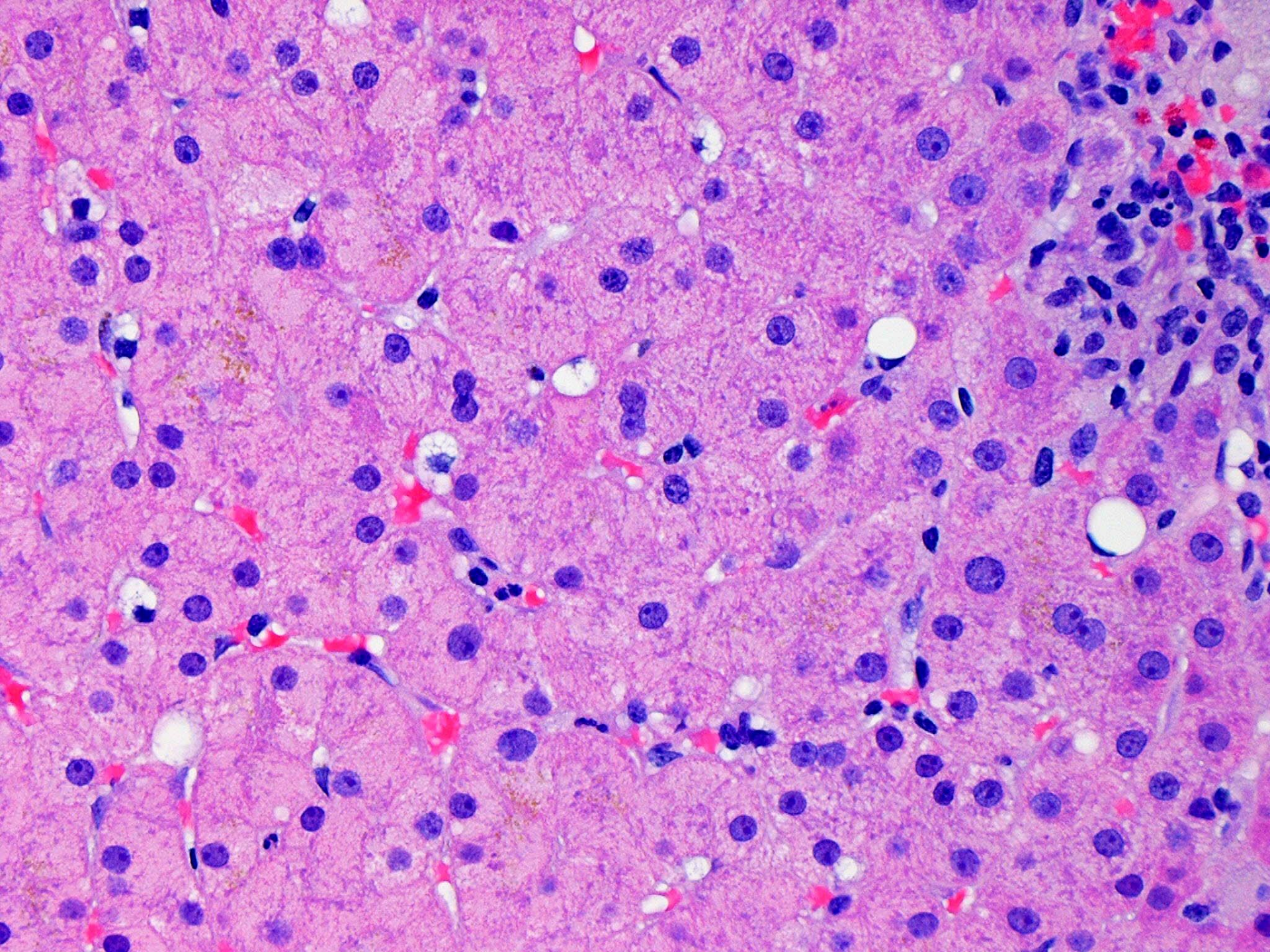
- 52 year old female with persistently elevated LCTs, first noted one year ago
- TB = 0.6, AST = 111, ALT = 167, Alk phos = 86
- Serologic tests for HAV, HBV & HCV all negative
- Ceruloplasmin and alpha-1-antitrypsin levels normal
- ANA and anti-SMA titers negative; AMA = 1:160
- No drugs, alcohol, travel, obesity, diabetes
- Previous episode of increased LCTs with Macroductin 20 years ago









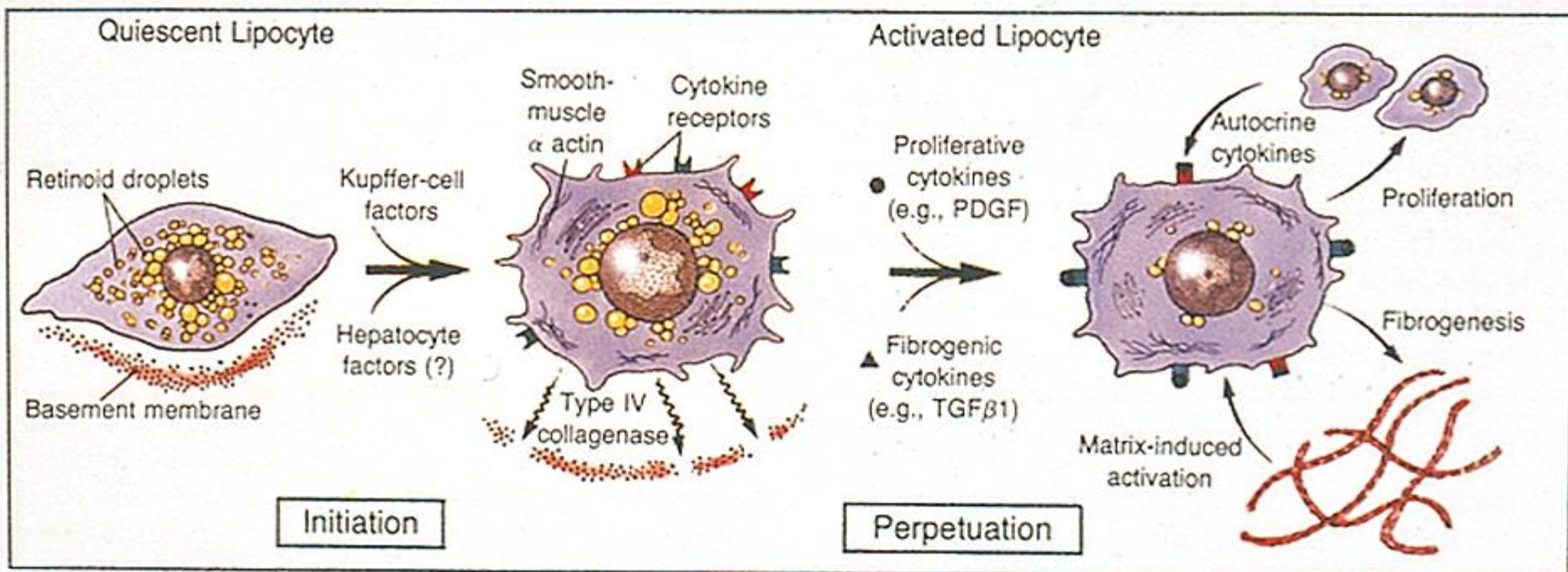


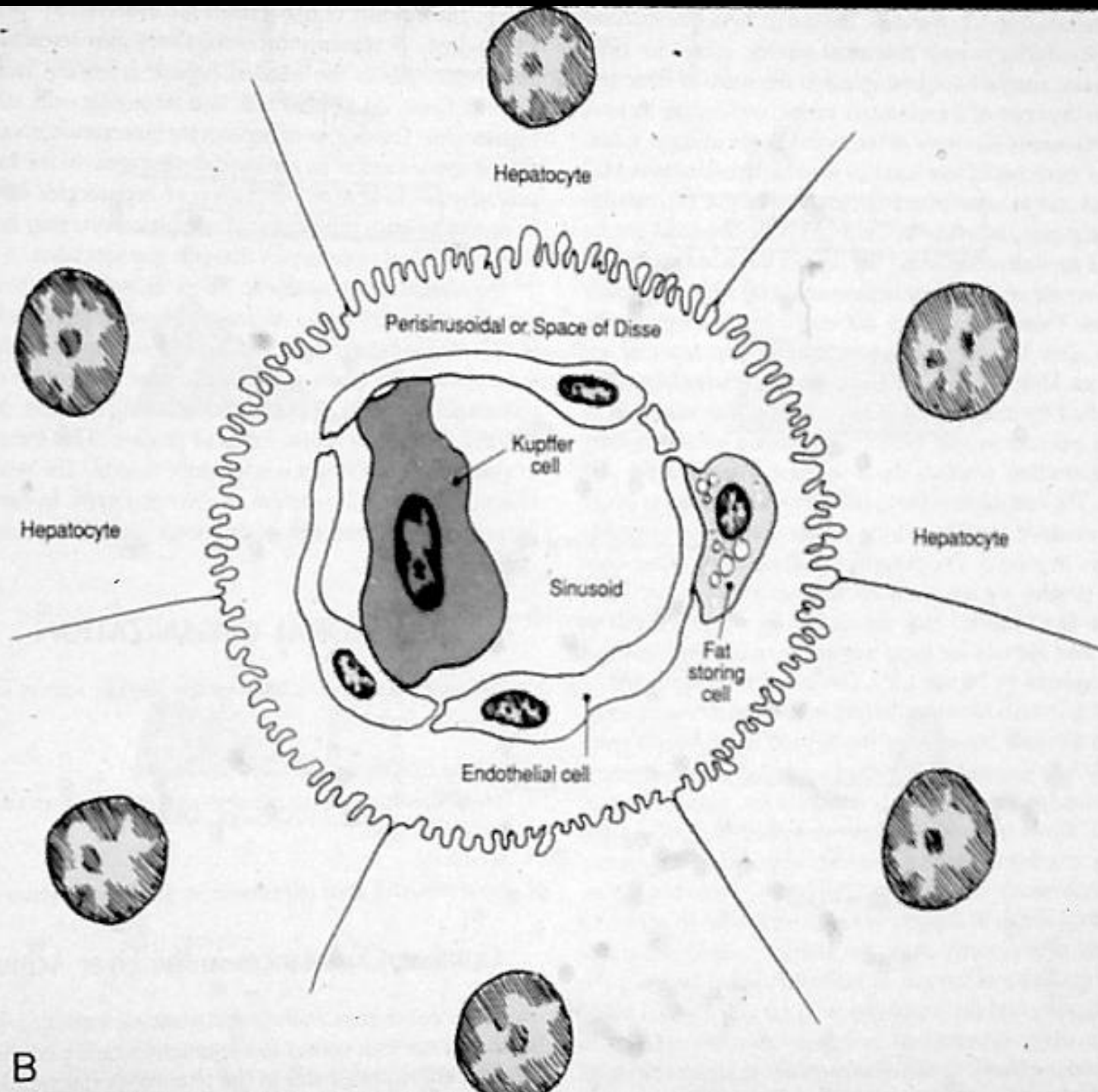
A microscopic image of tissue, likely a histological section, showing numerous cells with dark blue nuclei and pinkish-purple cytoplasm and extracellular matrix. A prominent white, circular structure is visible in the center-right. The text overlay is a white rectangular box with black text.

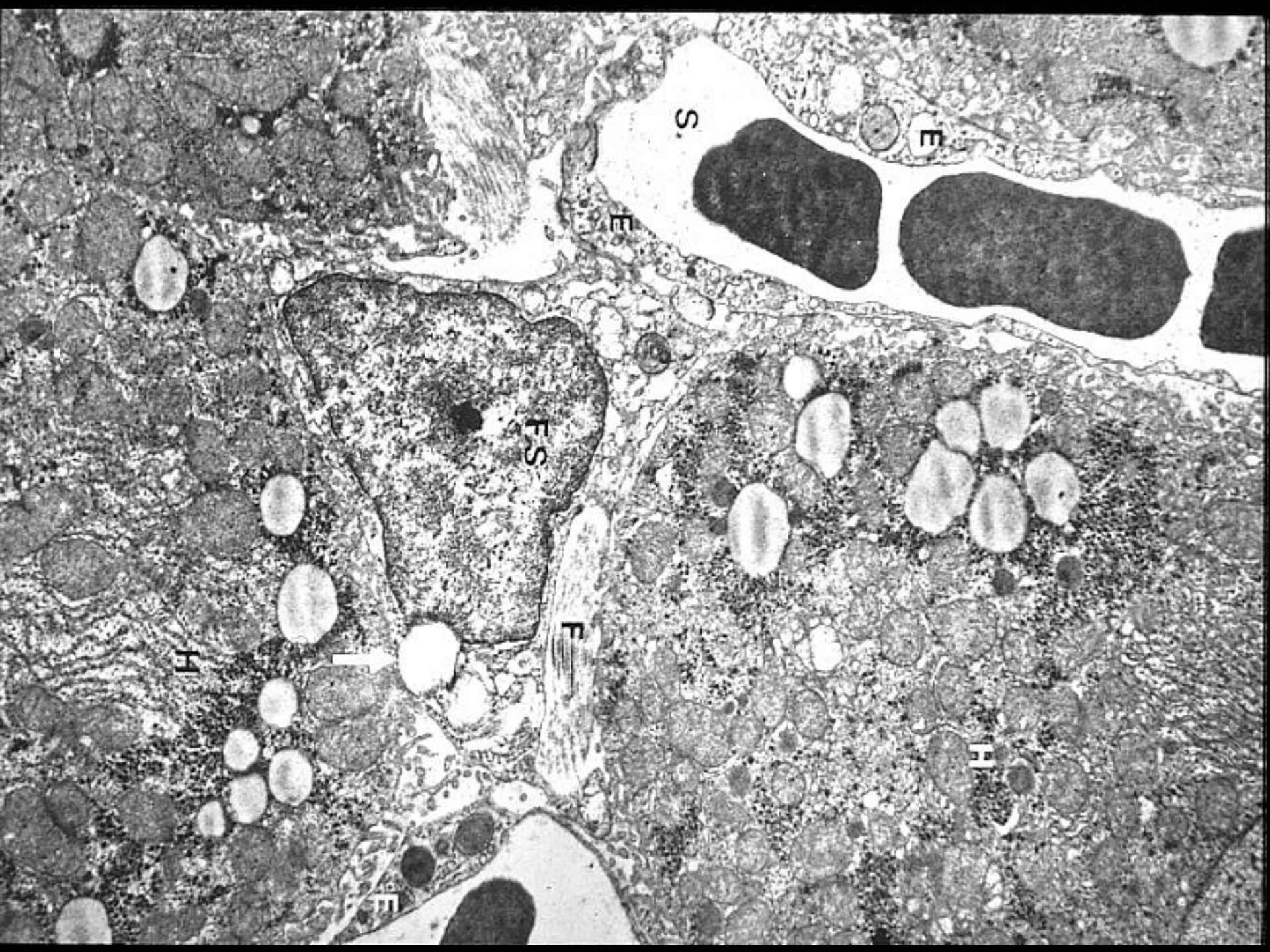
**Regularly takes “woman’s mega-multivitamin”,
vitamin C, vitamin E, acidophilus cream & herbal supplements**

Hepatic Stellate (Ito) Cells

- Not visible by H&E in normal individuals
- Function in health to store vitamin A
- Convert to myofibroblasts in chronic injury states:
 - Important source of collagen
 - Can return to resting stellate cell



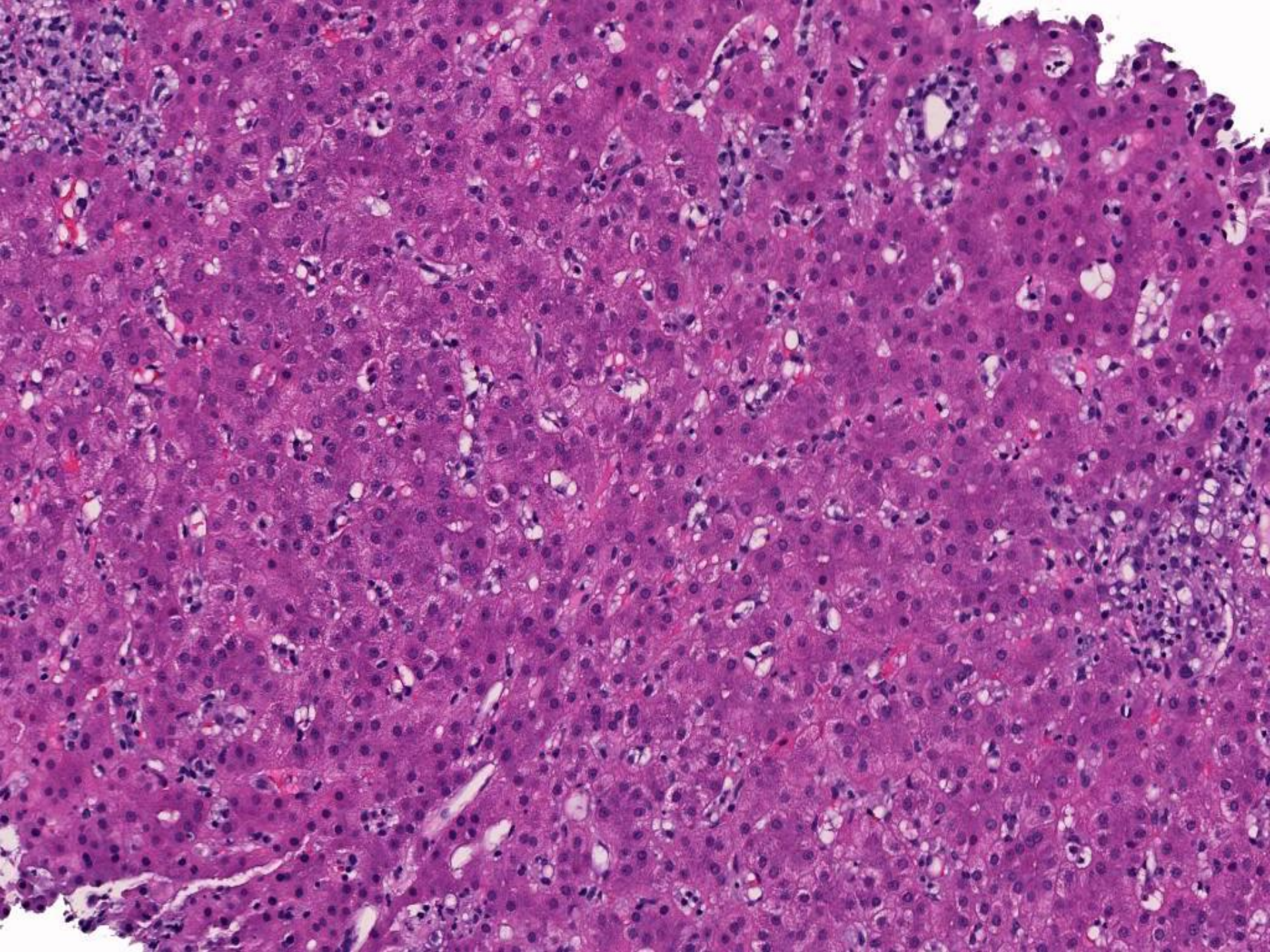


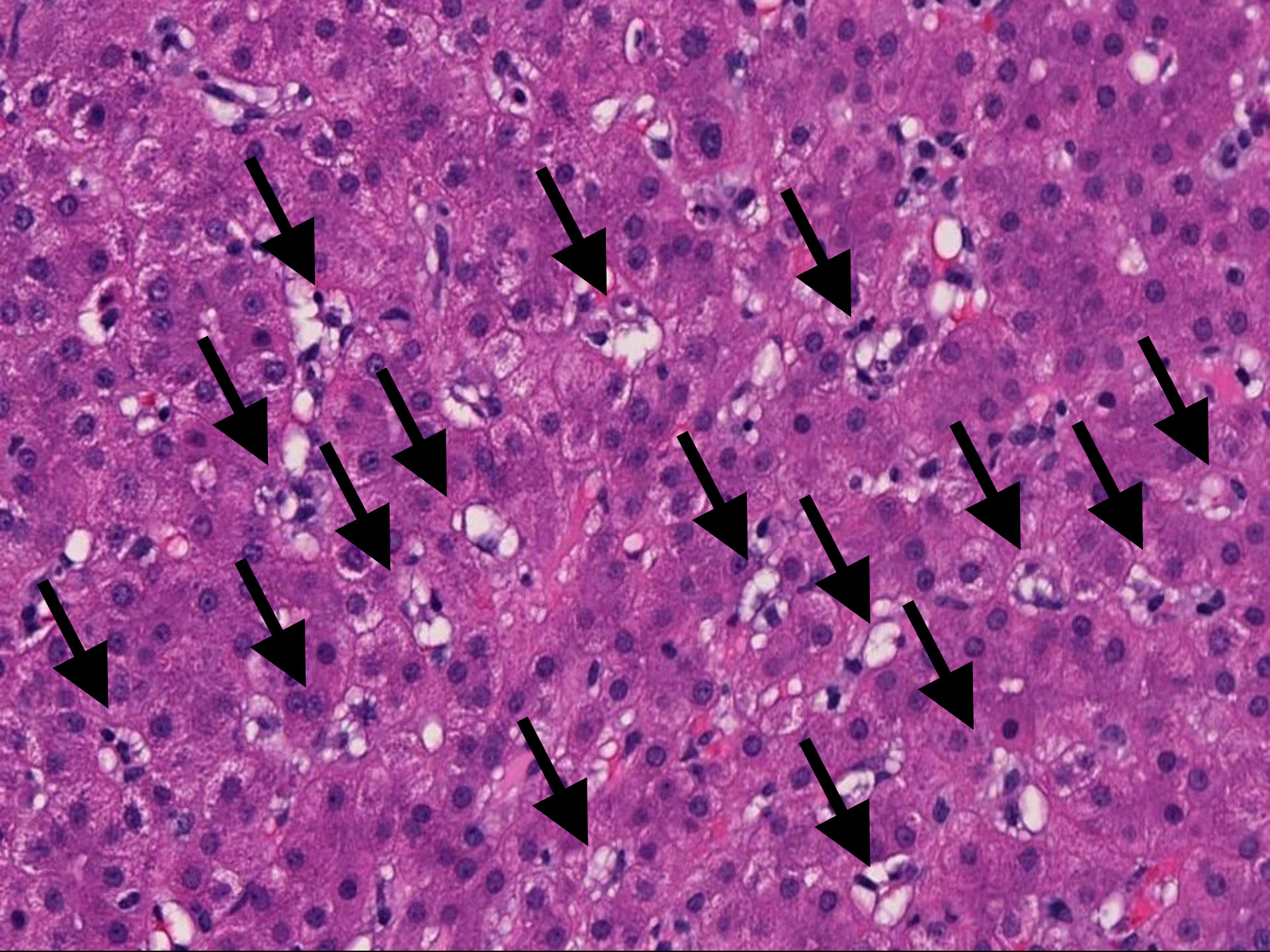


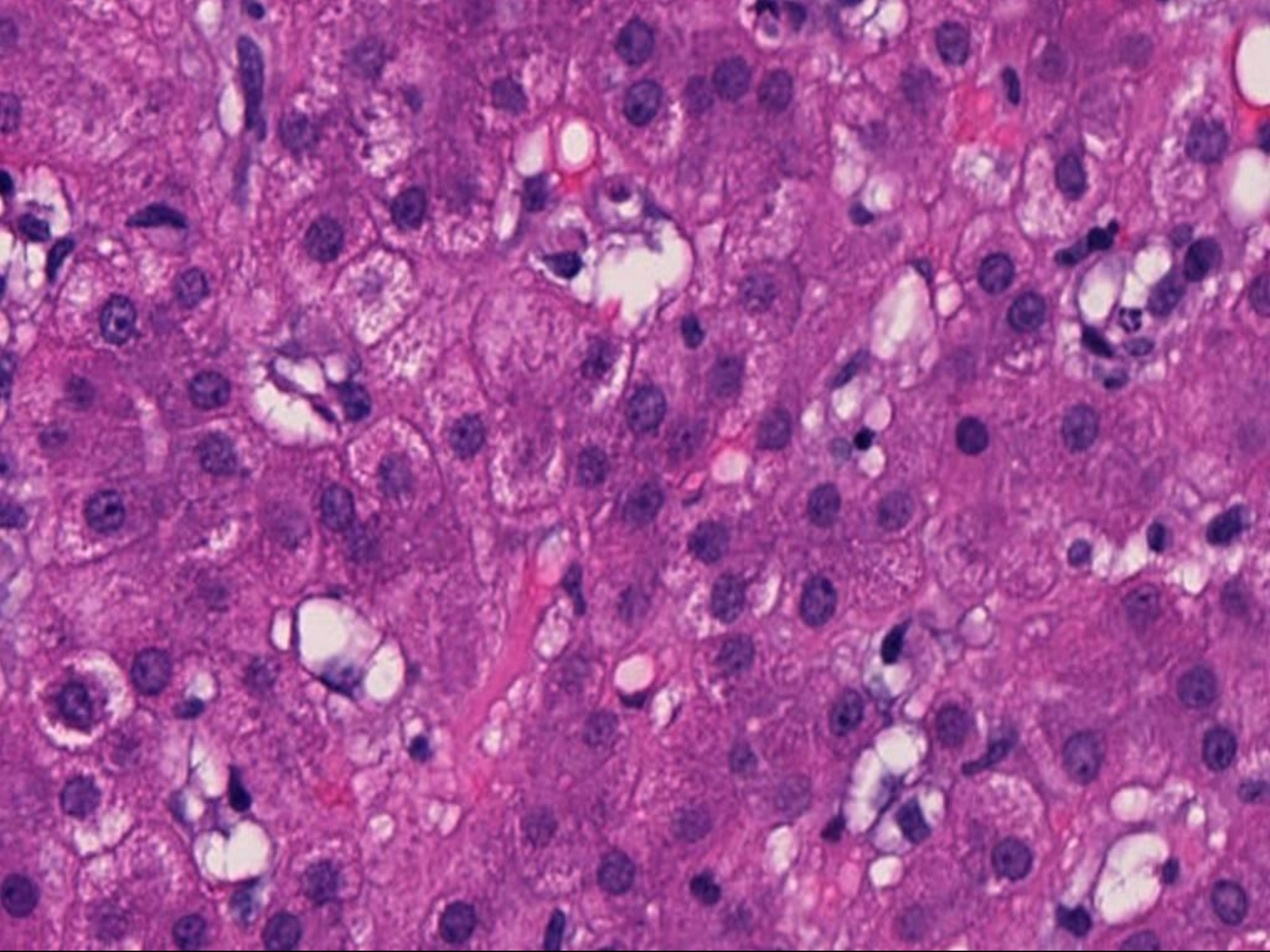
**Case Courtesy of Lizbeth Gallagher, M.D.
Alaska Medical Center, Anchorage**



17 y.o. Inuit Eskimo with esophageal varices and mildly elevated LCTs









The Vitamin A Content and Toxicity of Bear and Seal Liver

By K. RODAHL AND T. MOORE, *From the Dunn Nutritional Laboratory, University of Cambridge,*

It has long been known to travellers that the ingestion of bear and seal liver causes severe poisoning. It is reported that the liver of the polar bear (*Ursus barbata*) is poisonous, although this is less unanimous.

Richardson [1861] reported of an expedition led by Zembla in 1596 ate bear liver. In three cases the illness was fatal. The skin from head to foot was removed. The phenomenon was generally attributed to the poisoning of the liver. On occasions the whole cor



but in other instances according to Koettlitz an English expedition in 1877, ate polar-bear liver without ill effects. Lindhard [1913] reported that among members of an expedition one was shot which, although the liver was healthy, and on the day after it was prepared from the liver, the heart and kidneys were removed without ill effects, the rest of the stew all became sick. This occurred in two victims and most of the others became ill with the symptoms described

1. Specimens of the livers of the polar bear and the seal, *Phoca barbata*, were found to be very rich in vitamin A. Three specimens of bear liver contained 18,000, 18,000 and 13,000 i.u./g. respectively of wet material. A specimen of the seal liver contained 13,000 i.u./g.

2. The ingestion of excessive amounts of bear liver by rats led in one instance to fatal hypervitaminosis A. Other rats which ate slightly smaller amounts of liver showed no obvious sign of injury. The well-known poisonous action of bear liver in man is probably due to its high content of vitamin A.

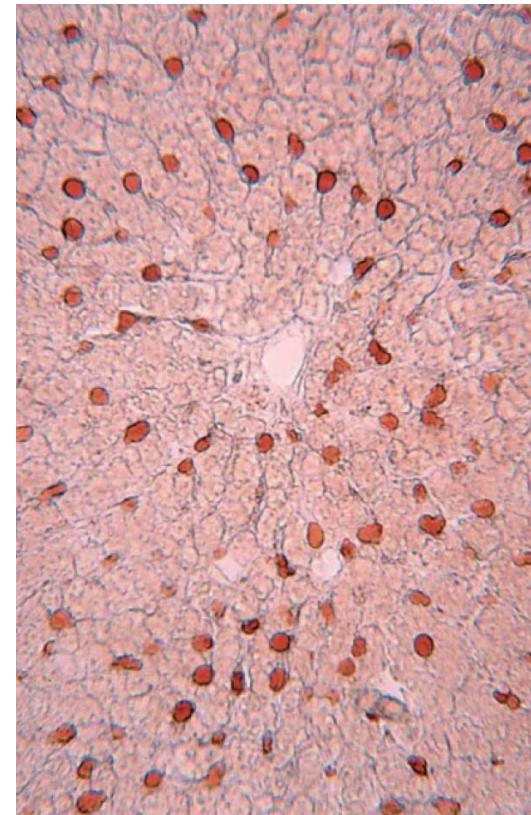
Accumulation of Vitamin A in the Hepatic Stellate Cell of Arctic Top Predators

HARUKI SENOO,^{1*} KATSUYUKI IMAI,¹ YOSHIHIRO MEZAKI,¹ MITSUTAKA MIURA,¹ MAYAKO MORII,¹ MUTSUNORI FUJIWARA,² AND RUNE BLOMHOFF³

TABLE 1. Total retinol contents in livers of arctic animals

Concentration ($\mu\text{mol/g}$ wet weight) Total amount in organ (μmol)

Species	Median (min–max)	Median (min–max)
Arctic animals		
Polar bear ($n = 3$) ^a	18.3 (16.6–23.7)	46,300 (44,500–142,000) ^c
Polar bear ($n = 4$) ^b	33.5 (18.1–48.4)	
Arctic fox ($n = 8$)	18.6 (14.5–24.4)	1,800 (1,230–2,920)
Bearded seal ($n = 14$)	4.7 (0.9–18.8)	16,800 (4,040–84,400)
Ringed seal ($n = 6$)	0.81 (0.17–6.99)	790 (120–6,300)
Glaucous gull ($n = 13$)	6.84 (5.12–10.6)	280 (120–410)
Fulmar ($n = 5$)	2.85 (1.22–3.99)	40 (20–70)
Brünnich's guillemot ($n = 1$)	2.14	40
Puffin ($n = 5$)	1.51 (0.49–2.29)	20 (20–40)
Svalbard reindeer ($n = 7$)	1.10 (0.62–1.28)	900 (300–1,400)
Svalbard ptarmigan ($n = 5$)	0.53 (0.48–0.96)	6 (5–9)
Continental animals		
Brown bear ($n = 13$)	1.05 (0.16–3.88)	
Red fox ($n = 4$)	0.40 (0.01–1.60)	
Grey gull ($n = 8$)	1.25 (0.23–3.64)	

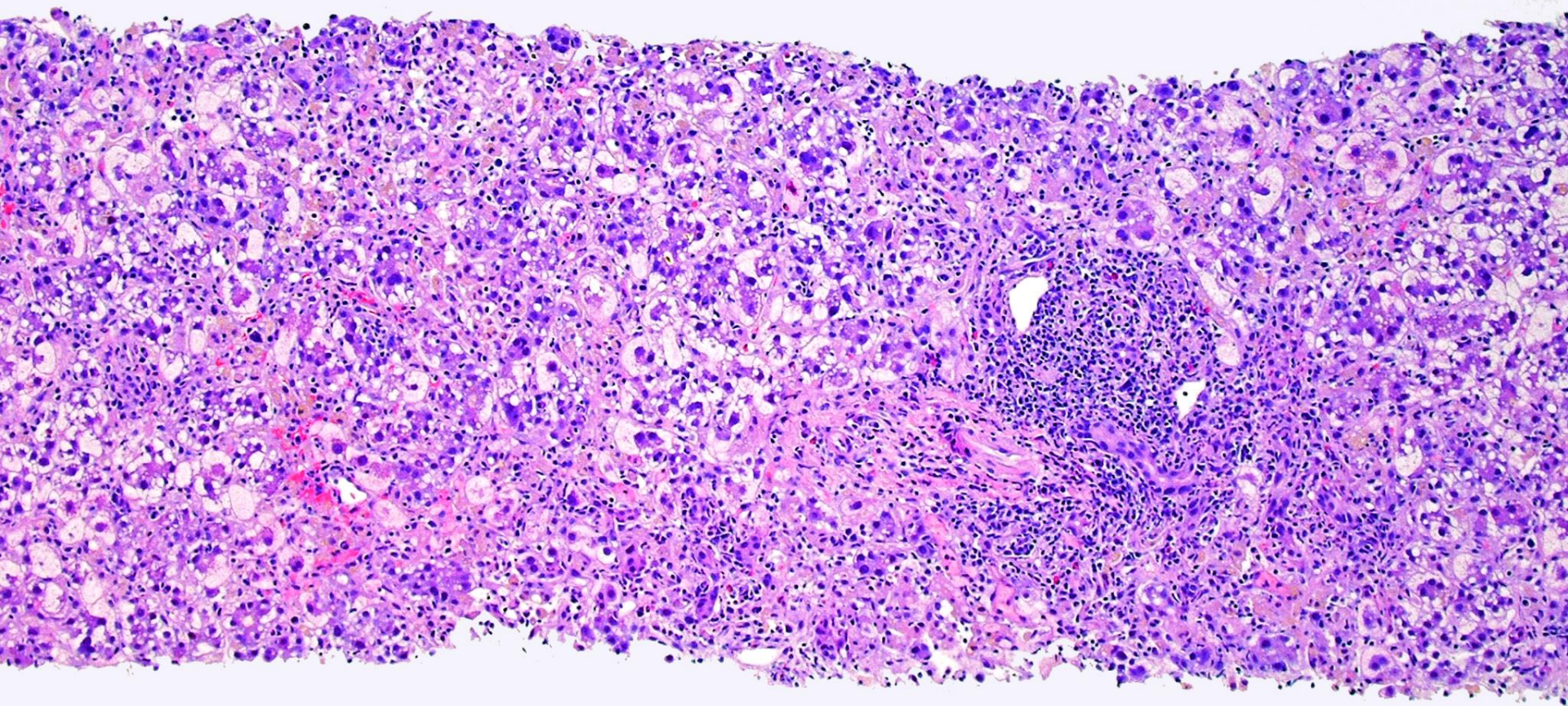


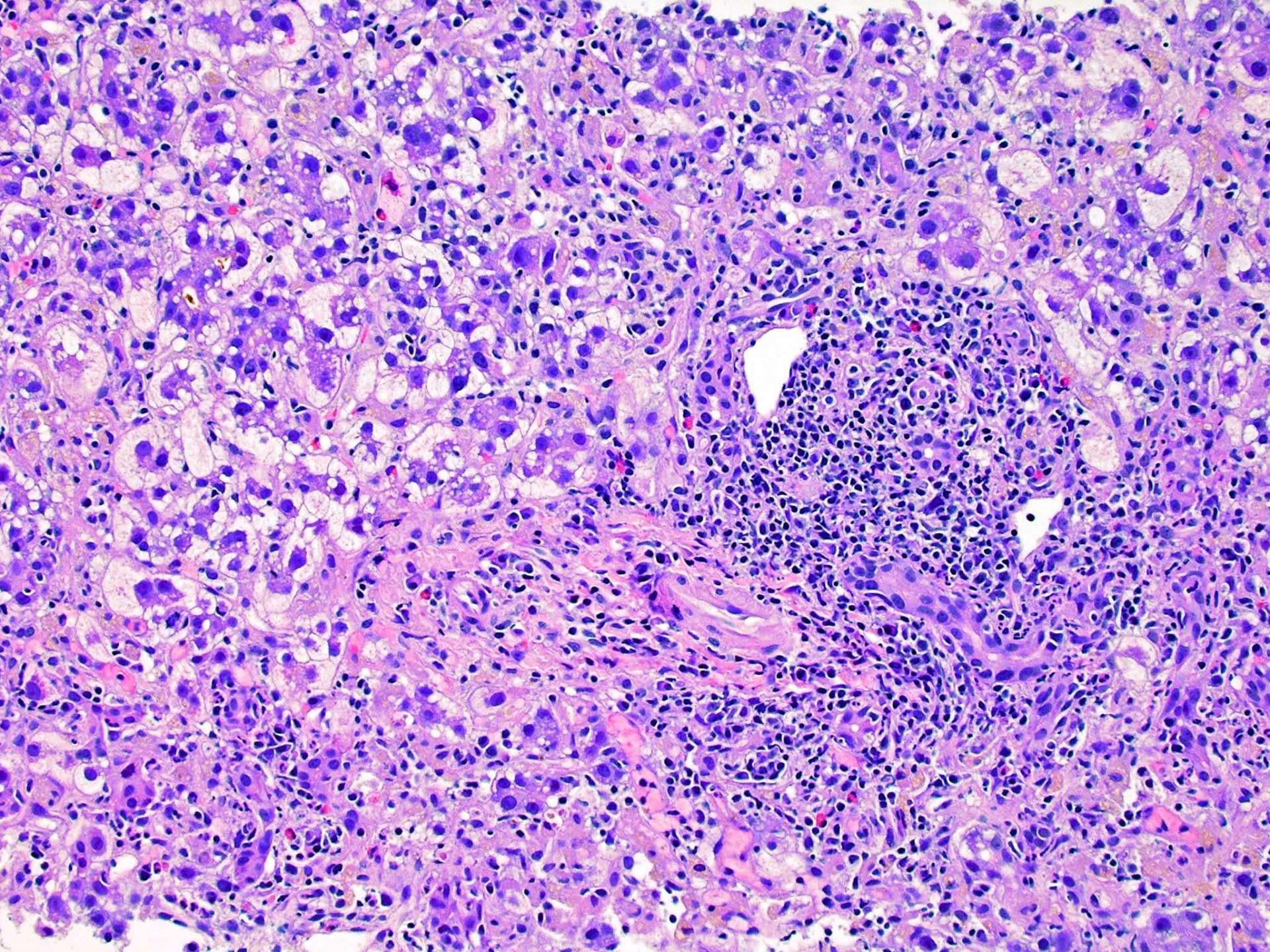
Case 11: Clinical History

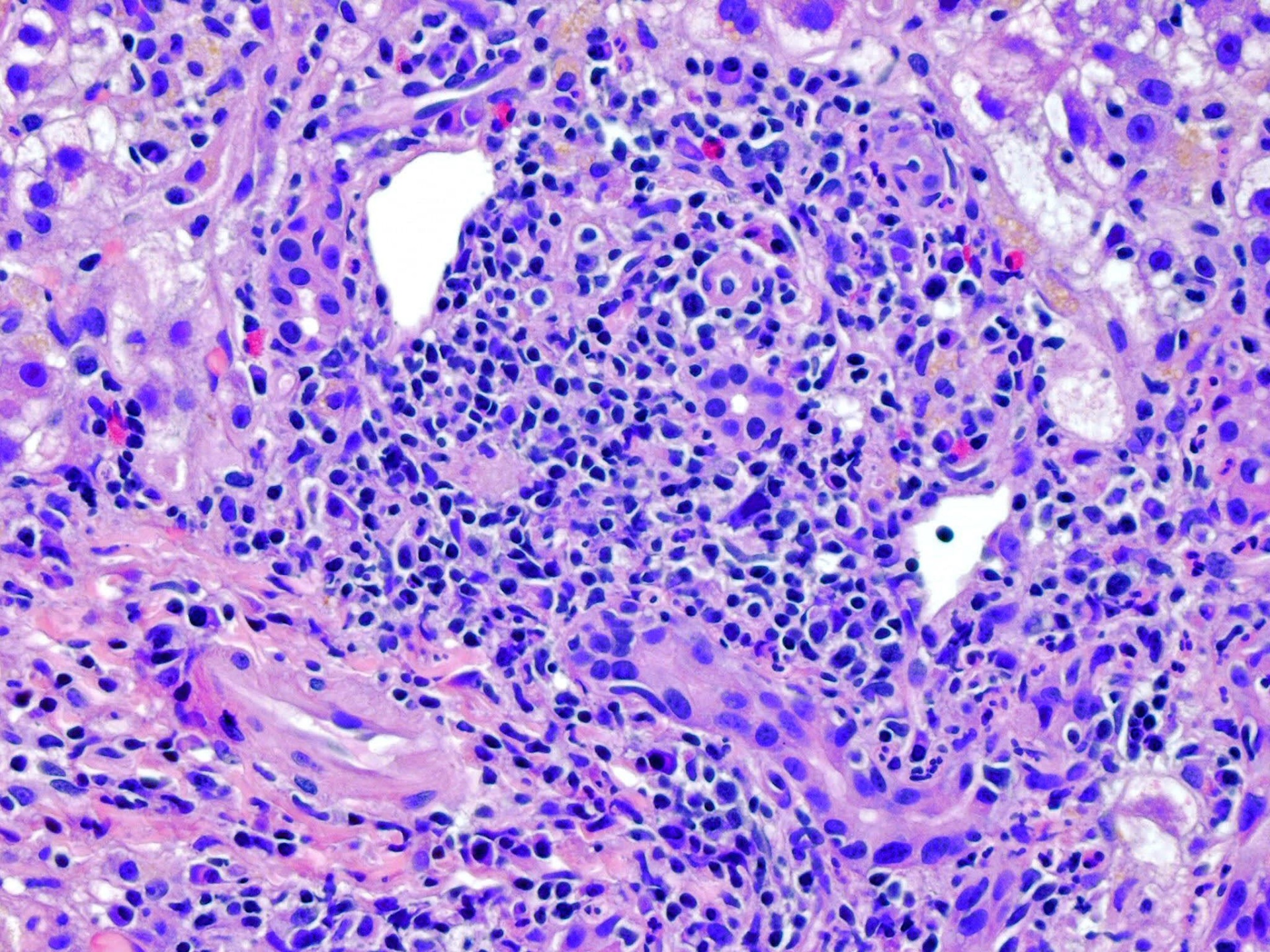
- 34 year old female with abdominal pain, fatigue and nausea and vomiting
- Physical exam – mild scleral icterus
- Travel to India for four weeks (mid January to mid-February)
- No medications except herbal remedy in India

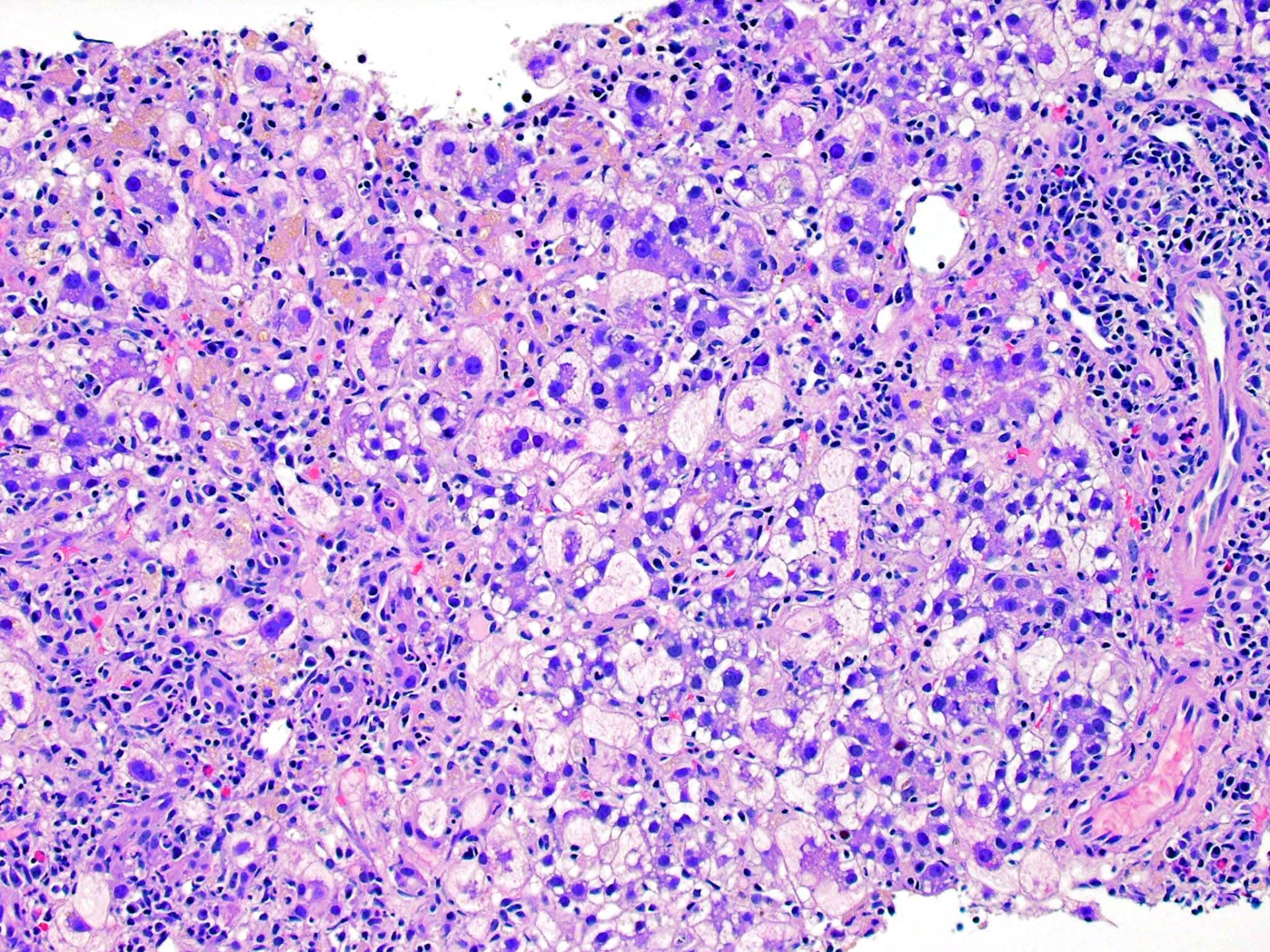
Laboratory Evaluation

- **Serologic tests for HAV, HBV and HCV negative**
- **ANA = 1:160, anti-SMA negative, anti-dsDNA neg.**
- **Ceruloplasmin = 30**
- **Urine toxicology screen negative**
- **EBV, CMV, HSV, HHV-6, Leptospira all negative**
- **TB = 11.0, AST = 4660, ALT = 4756, alk phos = 192**



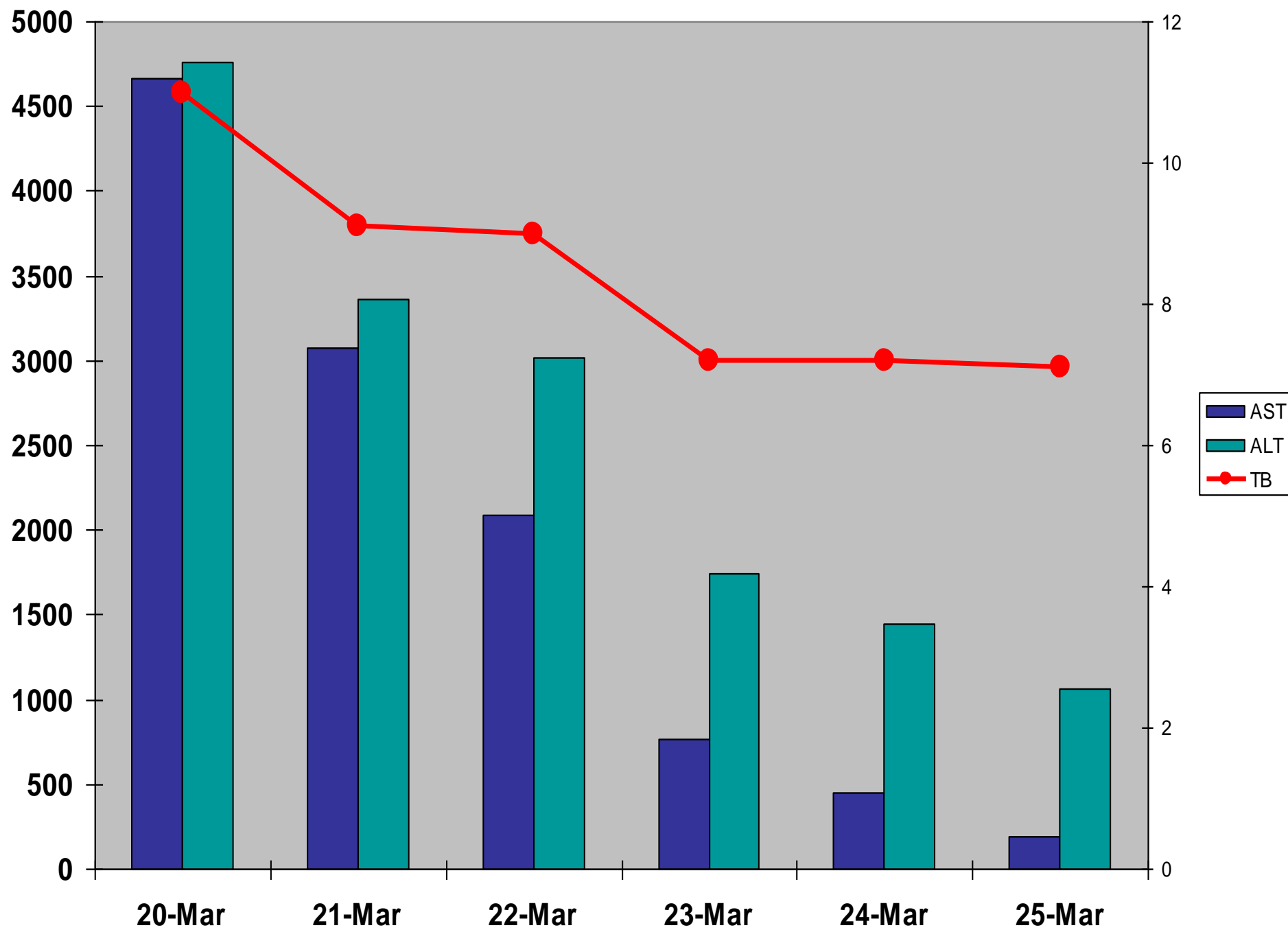


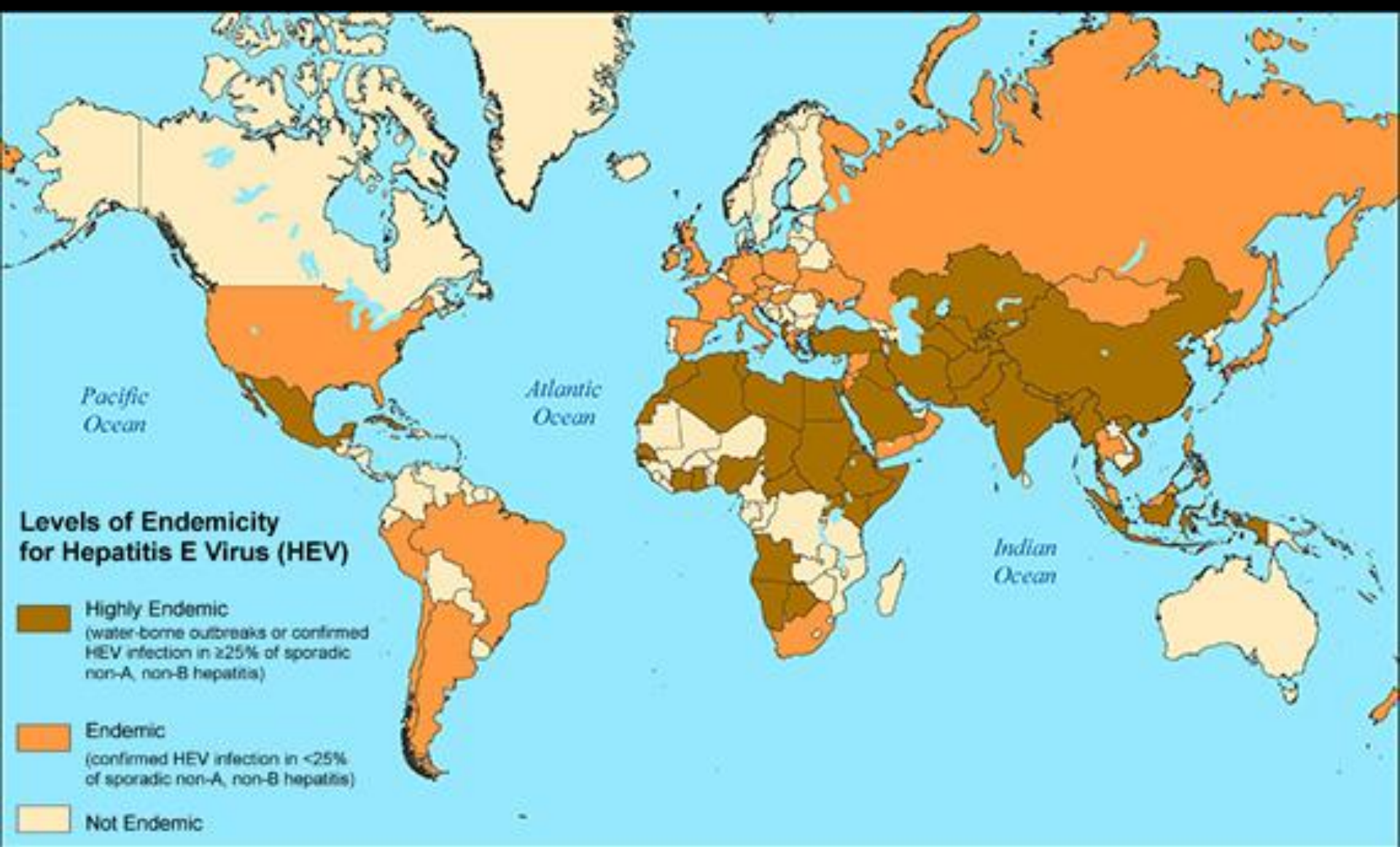




A histological section of liver tissue stained with hematoxylin and eosin (H&E). The image shows a dense population of cells with prominent blue nuclei and pink cytoplasm/extracellular matrix. There are several large, pale, irregular areas that appear to be necrotic or contain large amounts of glycogen. The overall architecture is disrupted, suggesting a pathological process. A white rectangular box is overlaid on the center of the image, containing the text "Serum HEV IgM positive".

Serum HEV IgM positive





Hepatitis E

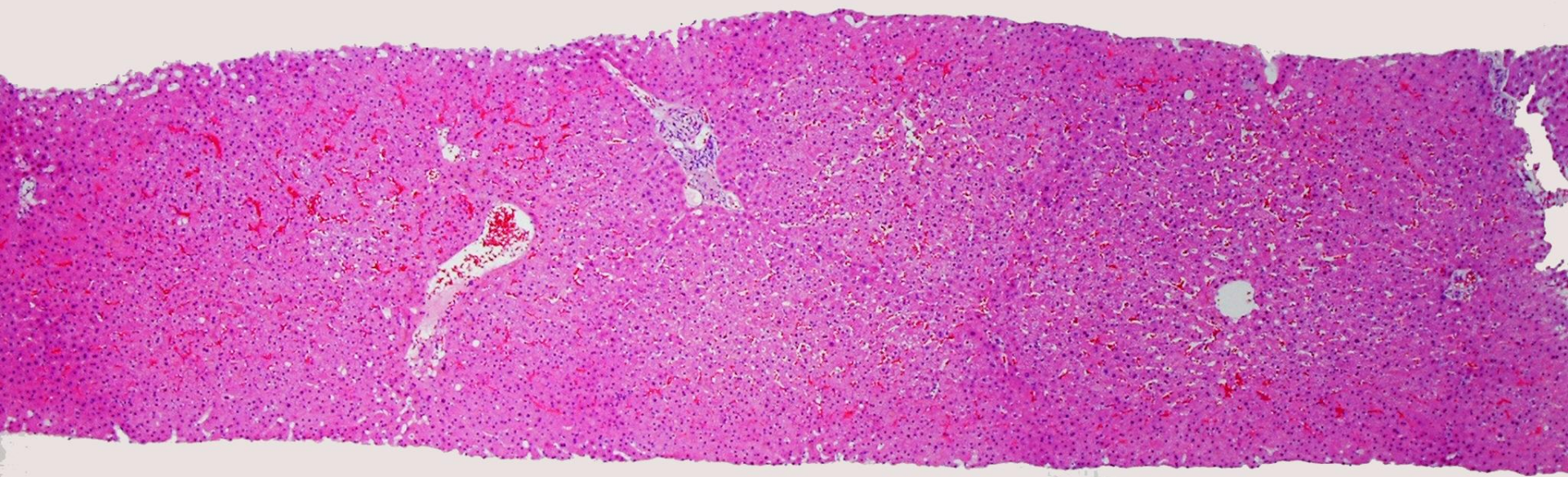
Epidemiologic Features

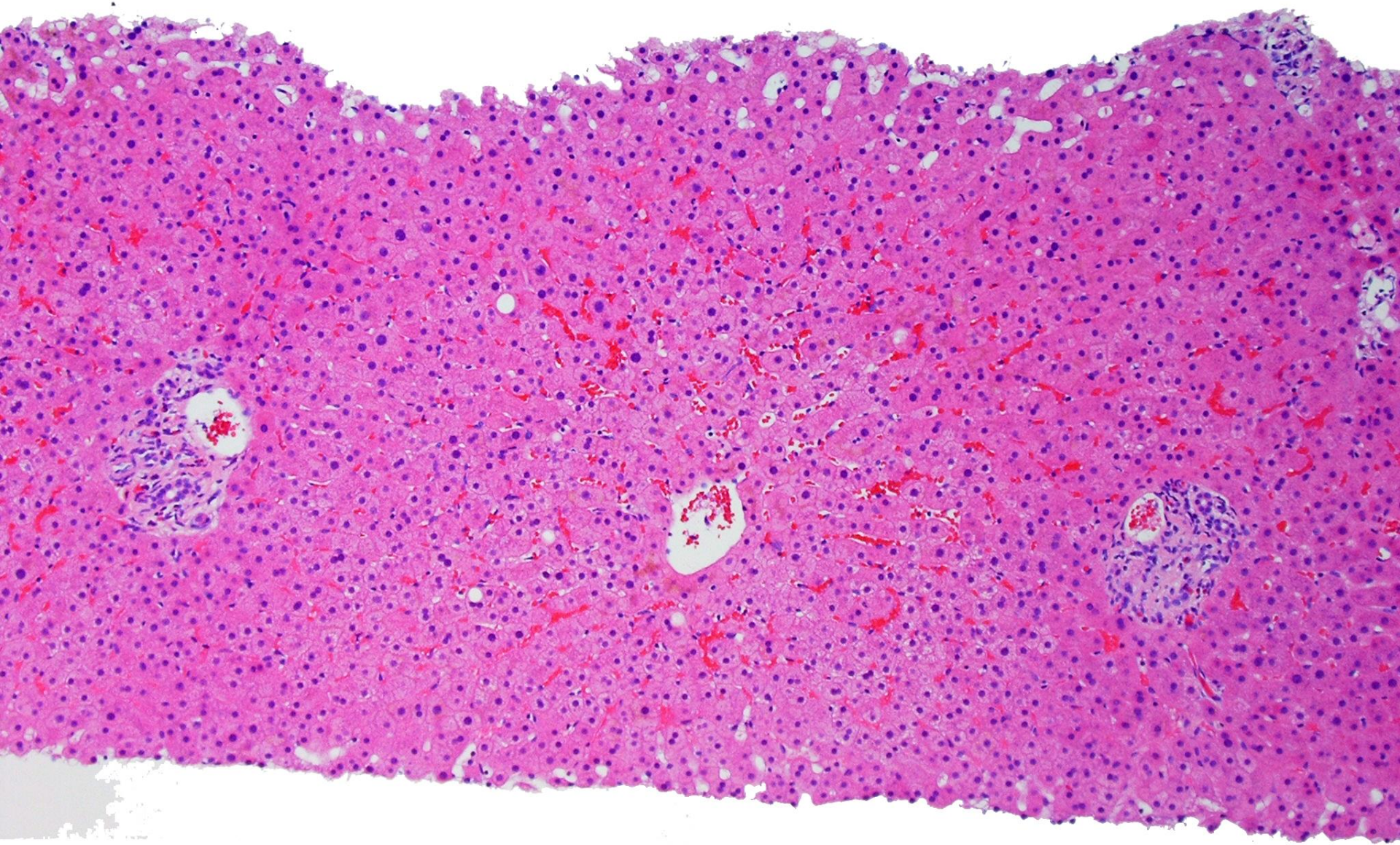
- **Most outbreaks associated with fecally contaminated drinking water**
- **Minimal person-to-person transmission**
- **U.S. cases (6% seroprevalence):**
 - **History of travel to HEV endemic areas**
 - **Occupational contact with farm animals**
 - **Sporadic exposure**

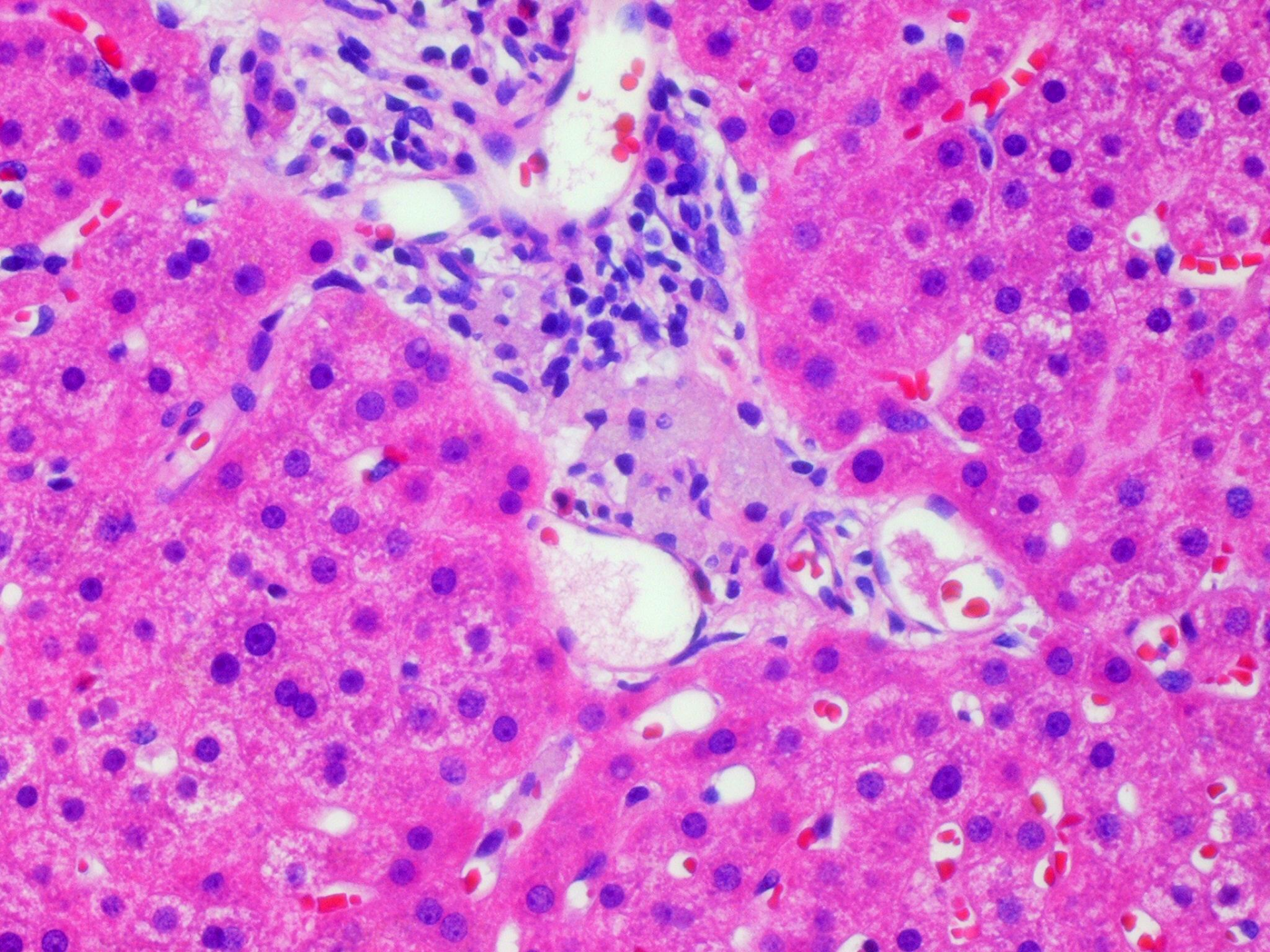
- **Histologic pattern:**
 - **Acute hepatitis**
- **Diagnosis:**
 - **Acute HEV hepatitis**
- **Take home points:**
 - **Drug/toxin is the primary cause of acute hepatitis, but other possibilities should be considered**
 - **Travel history important in selected cases**

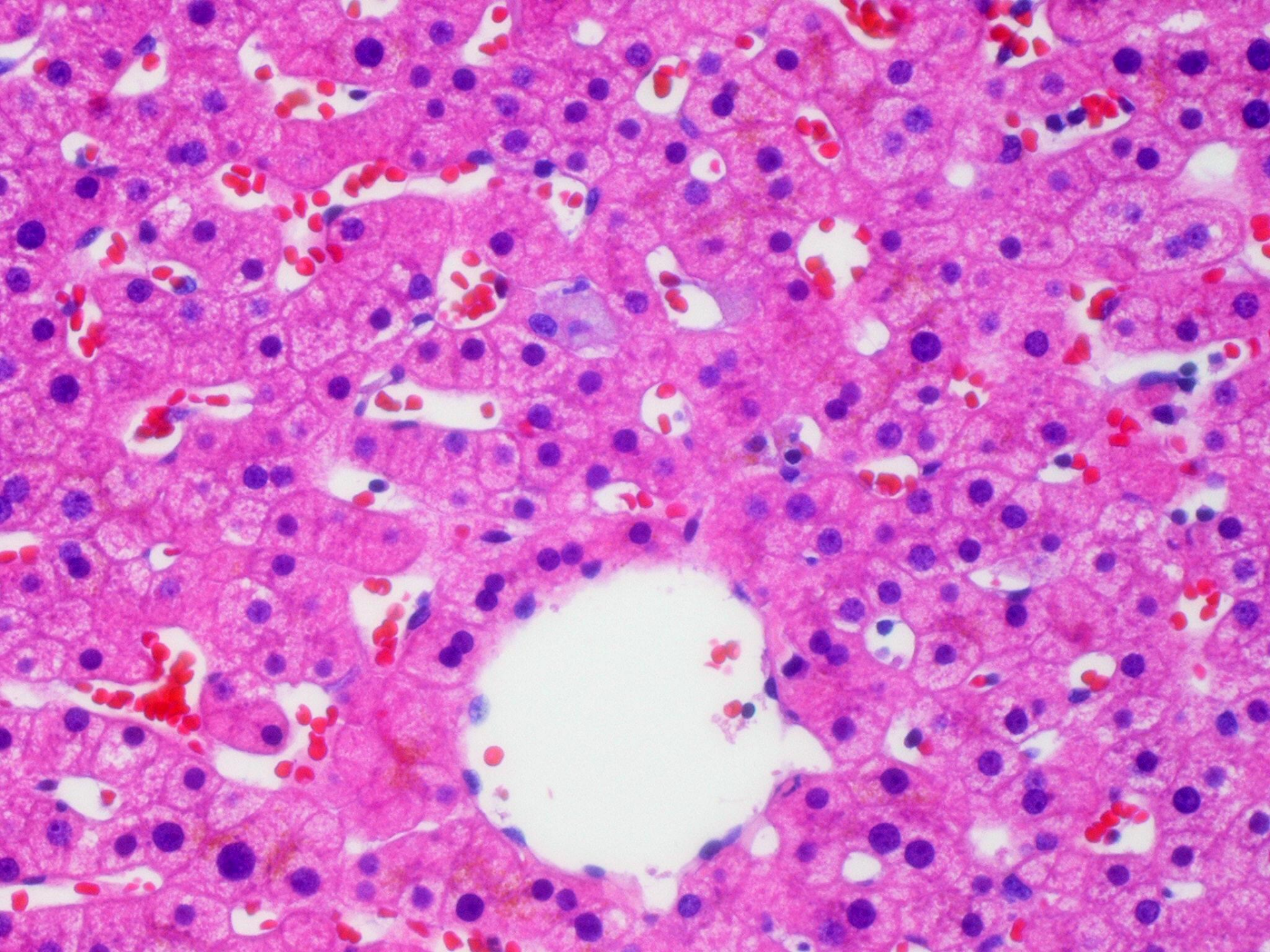
Case 26: Clinical History

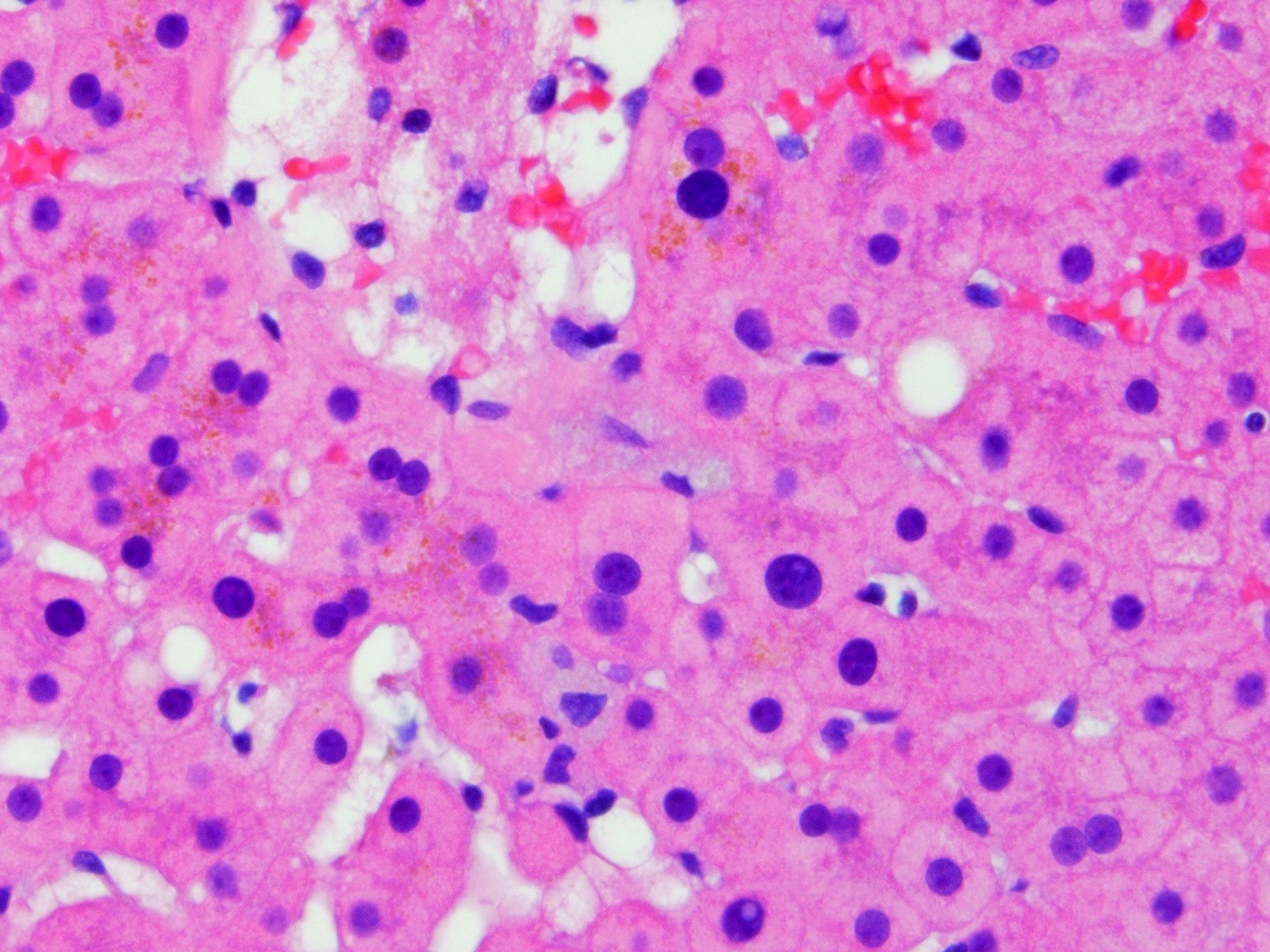
- 55 y.o. F with abdominal pain and headache
- Noted to have mildly elevated LCTs at the time of thyroidectomy for Hashimoto's thyroiditis 1 year ago
- ANA and AMA negative
- Status post cholecystectomy 20 years ago
- TB = 0.7, AST = 986, ALT = 630; alk phos = 107
- HAV, HBV, HCV, HEV, EBV, HHV-6, CMV negative
- ANA = 1:160; anti-SMA & anti-dsDNA negative
- No travel; no high risk behaviors; no ethanol
- Synthroid, Citalopram, Gabapentin, MiraLAX, Citrucel
- Referred to the Univ. of Chicago for liver biopsy

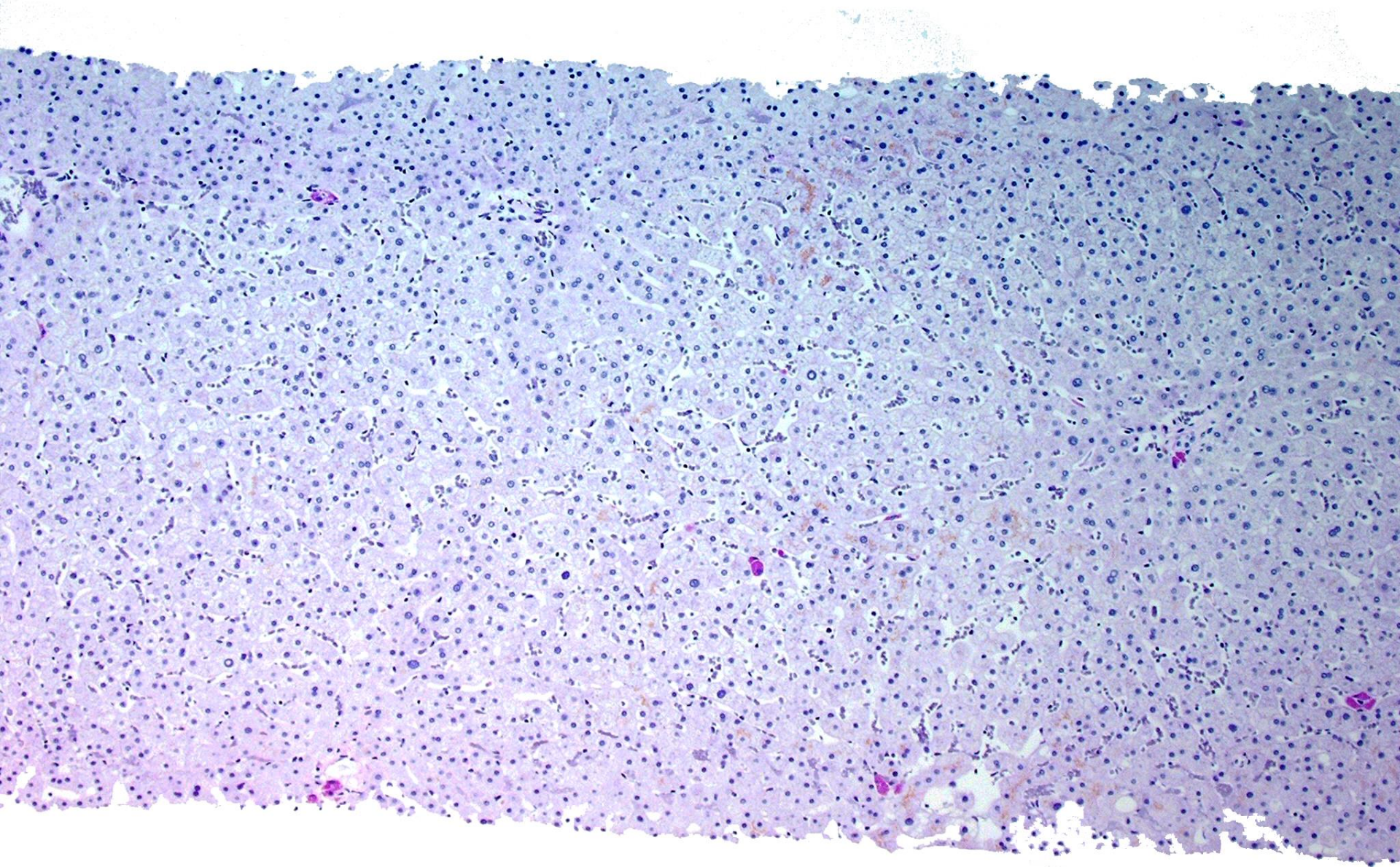


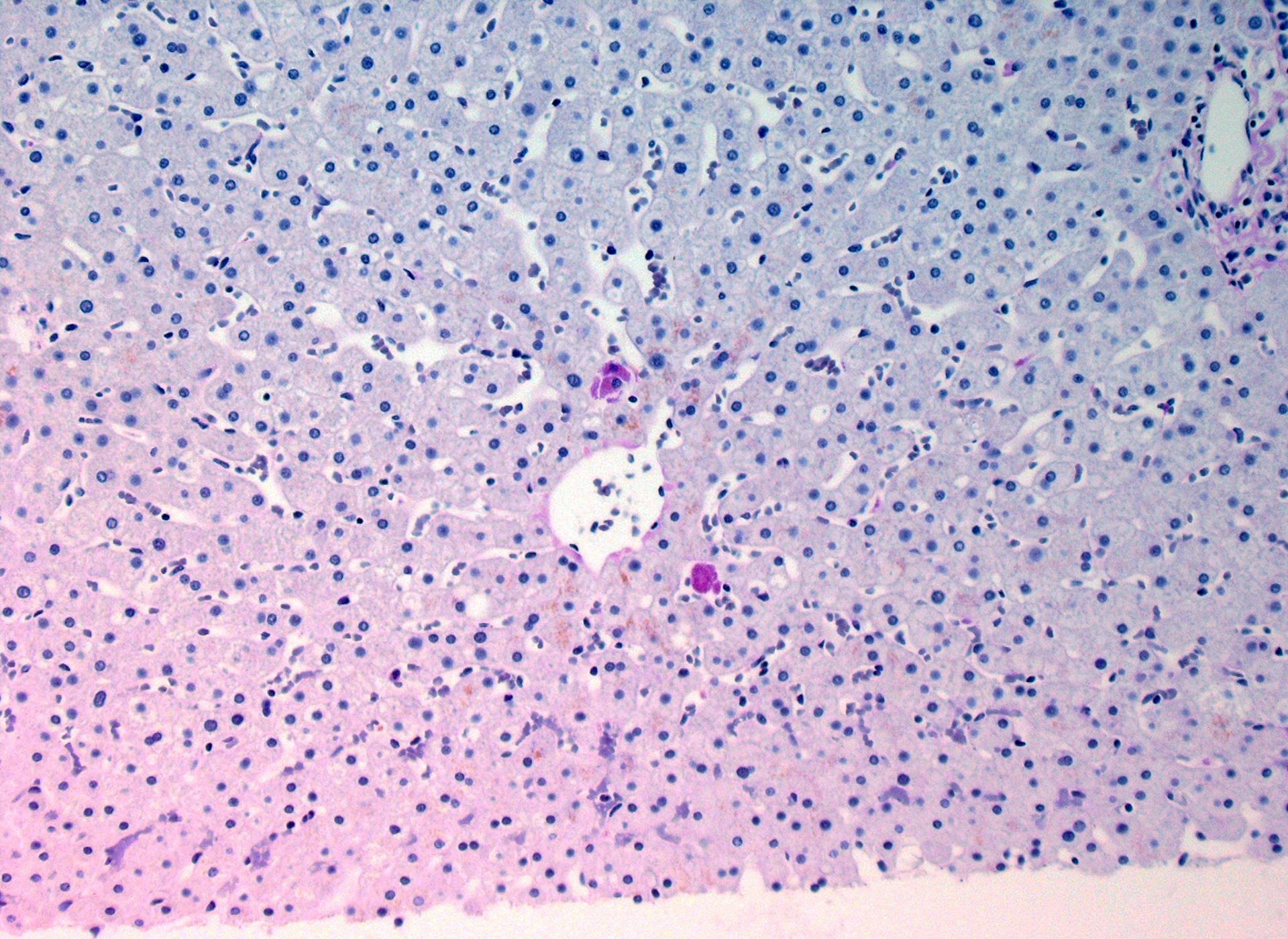


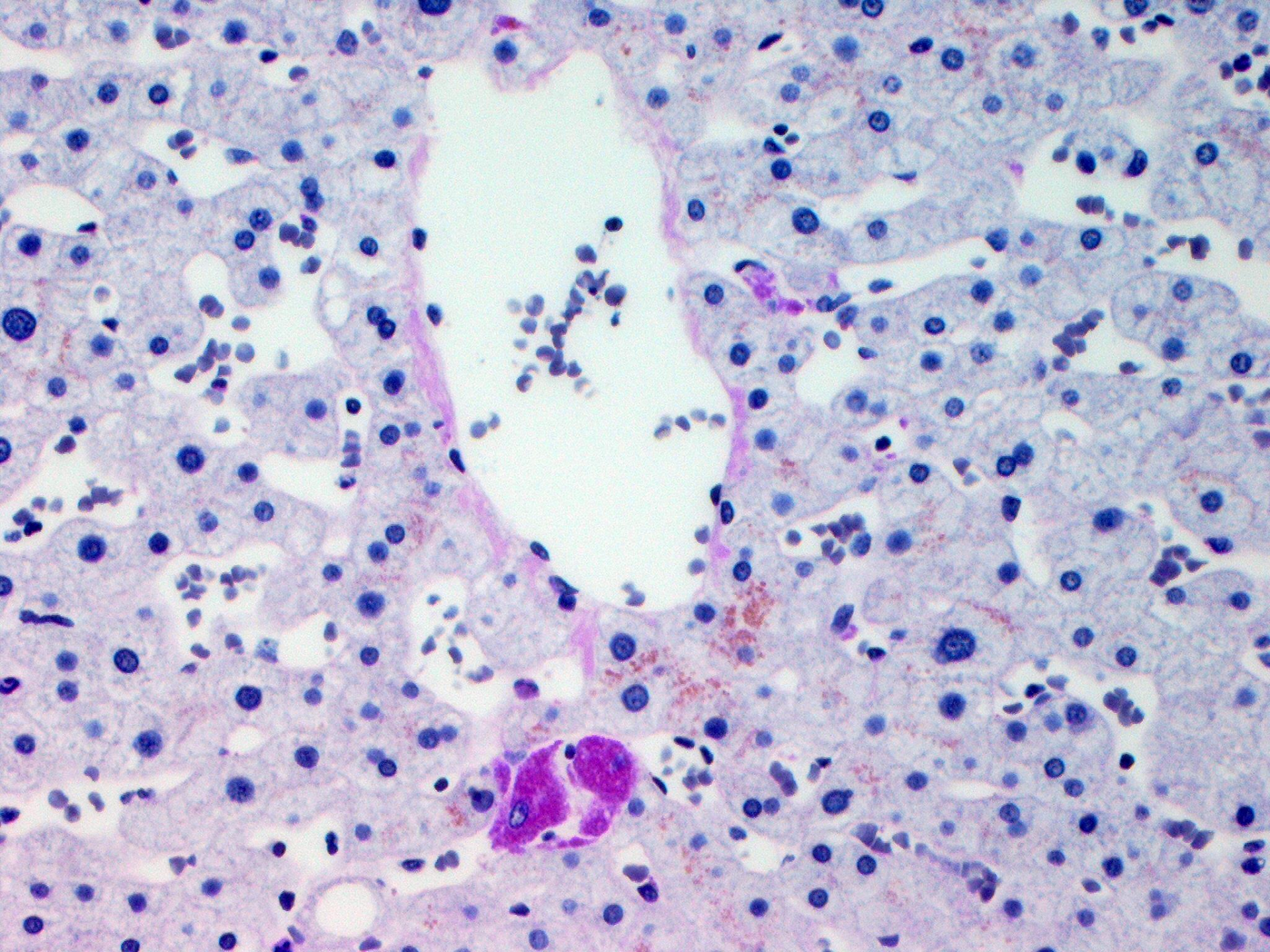












DATE	TB	AST	ALT	AP
10/29/09	0.4	36	24	35
2/11/10	0.3	23	28	44
3/16/10	0.7	986	630	107
3/18/10	0.5	122	413	122
3/31/10	0.3	156	415	147
4/11/10	0.4	66	282	132
5/5/10	0.3	22	22	56

◀ Liver
Biopsy

Gabapentin-Associated Hepatotoxicity

AJG – Vol. 96, No. 12, 2001

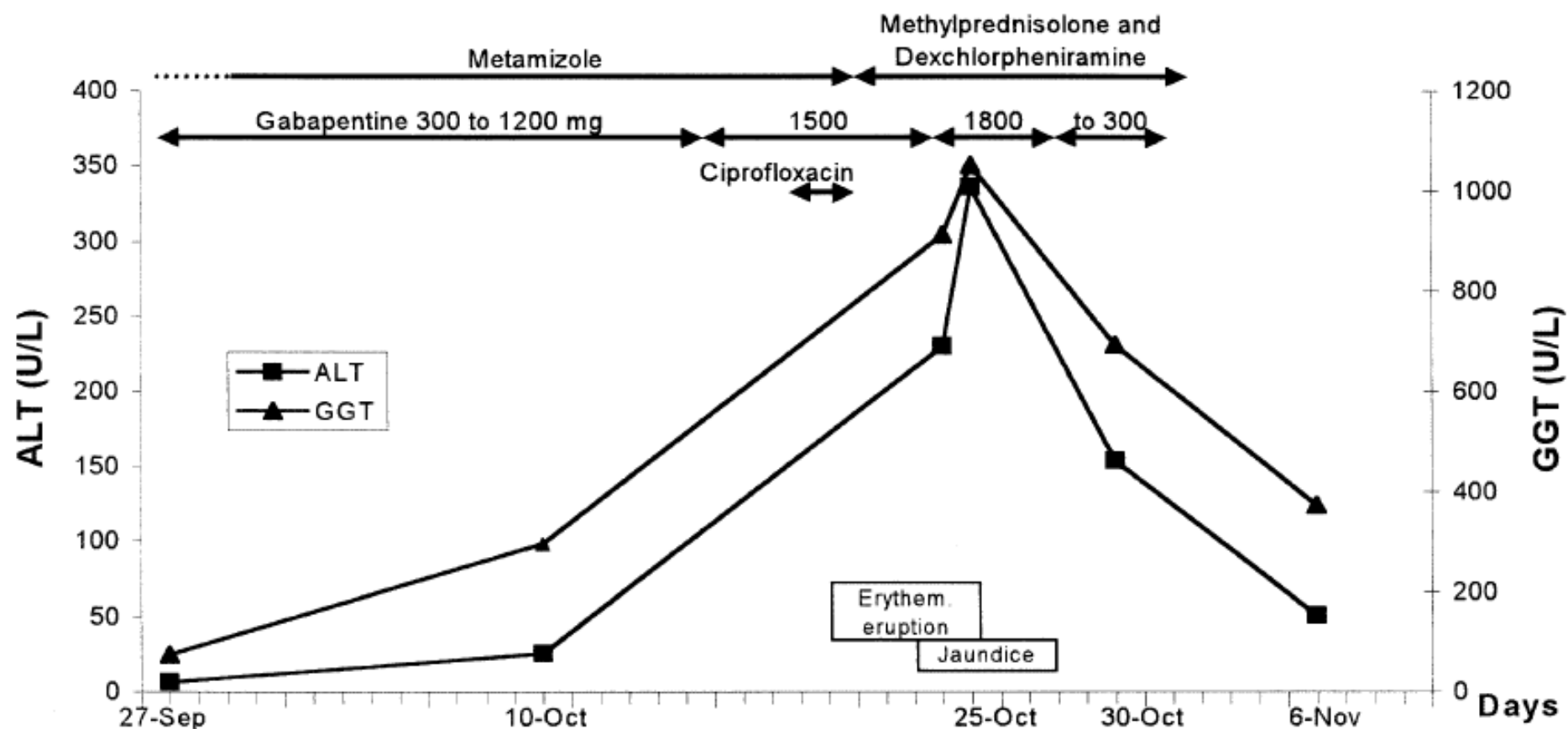


Figure 1. Temporal evolution of ALT and GGT values.

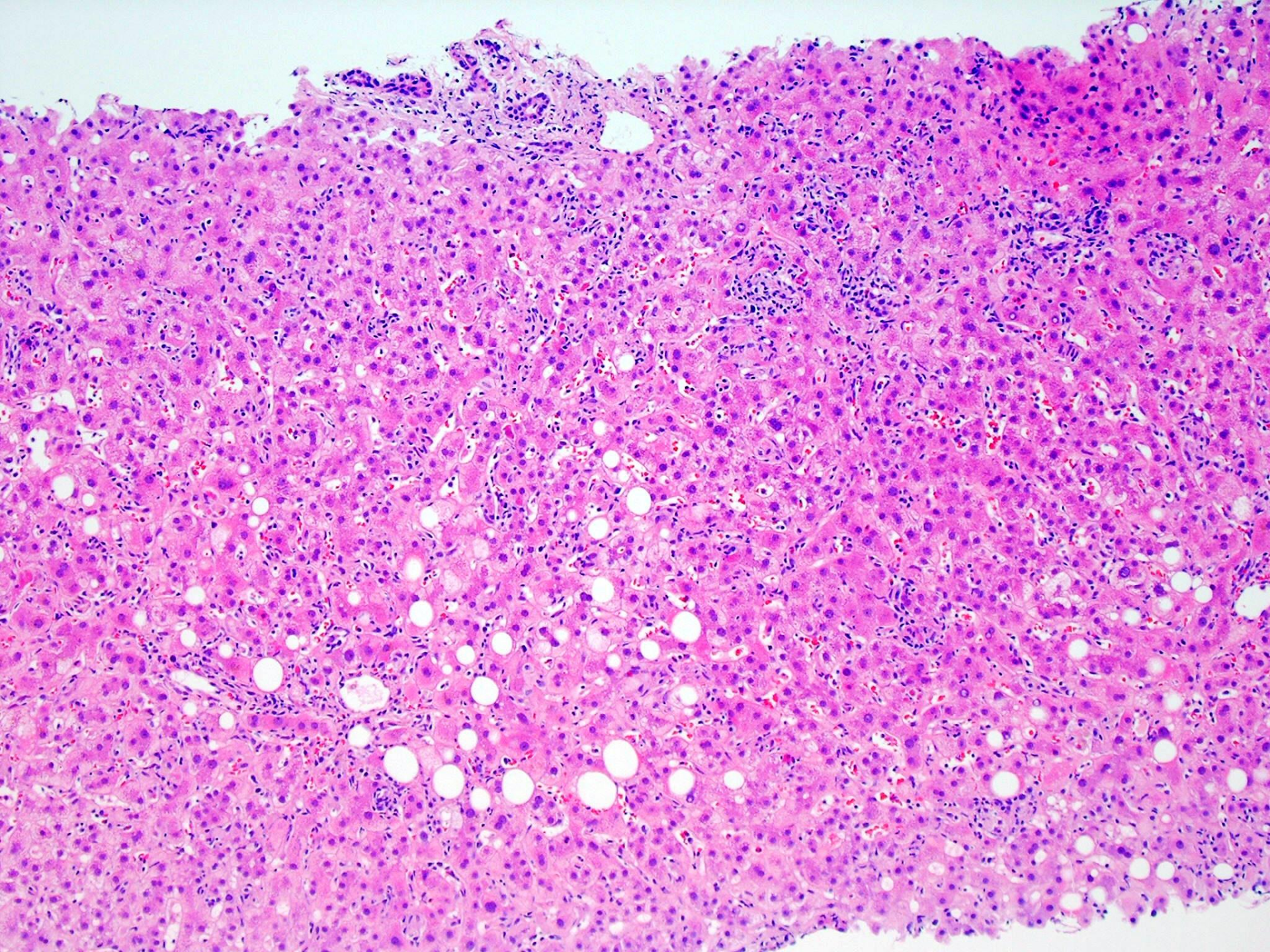
- **Histologic pattern:**
 - **Resolving acute hepatitis**
- **Diagnosis:**
 - **Resolving acute hepatitis, r/o drug induced liver disease**
- **Take home points:**
 - **PAS/D is useful to highlight cellular debris in Kupffer cells**
 - **Provided history can be misleading**

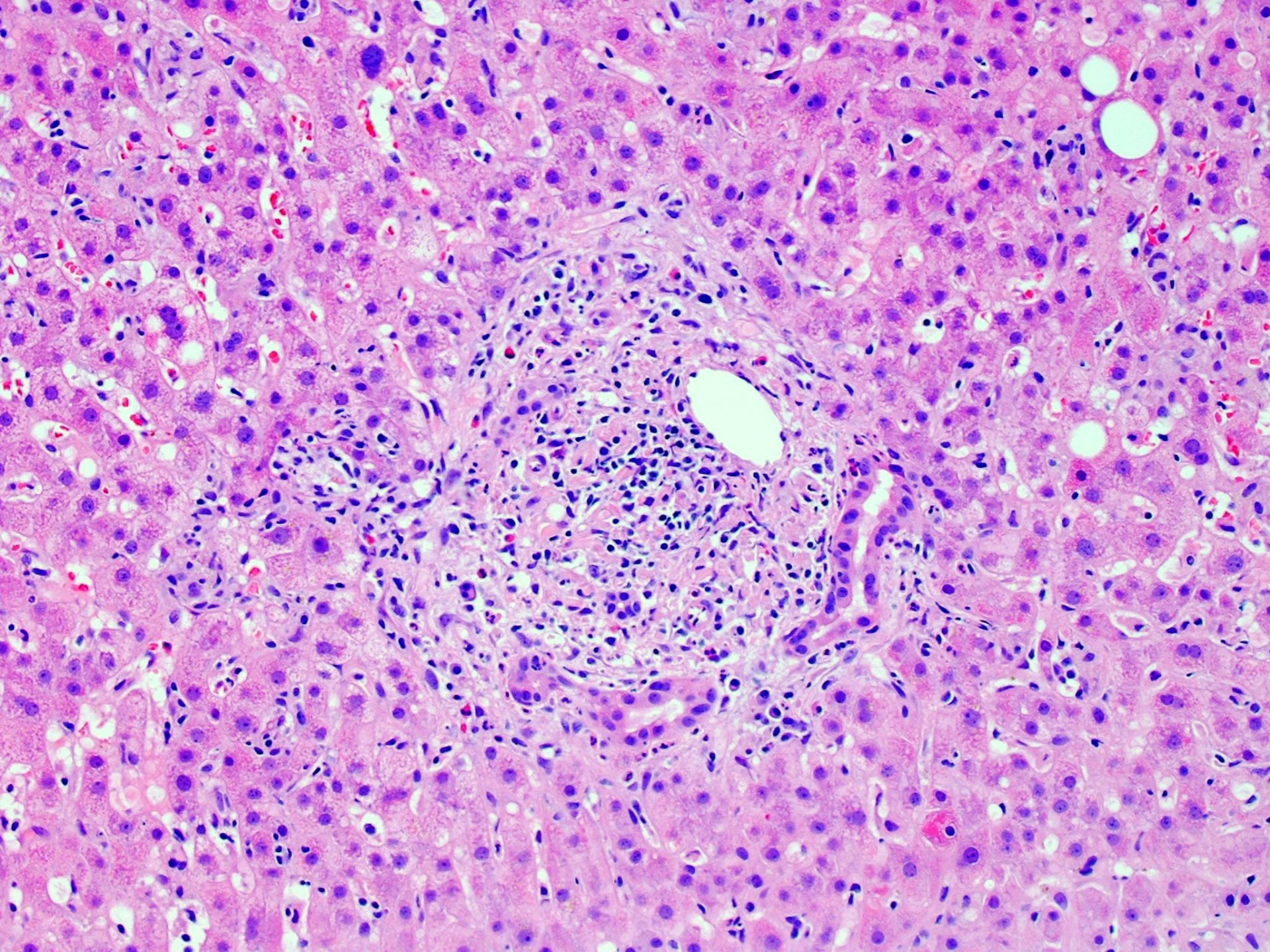
Case 13: Clinical History

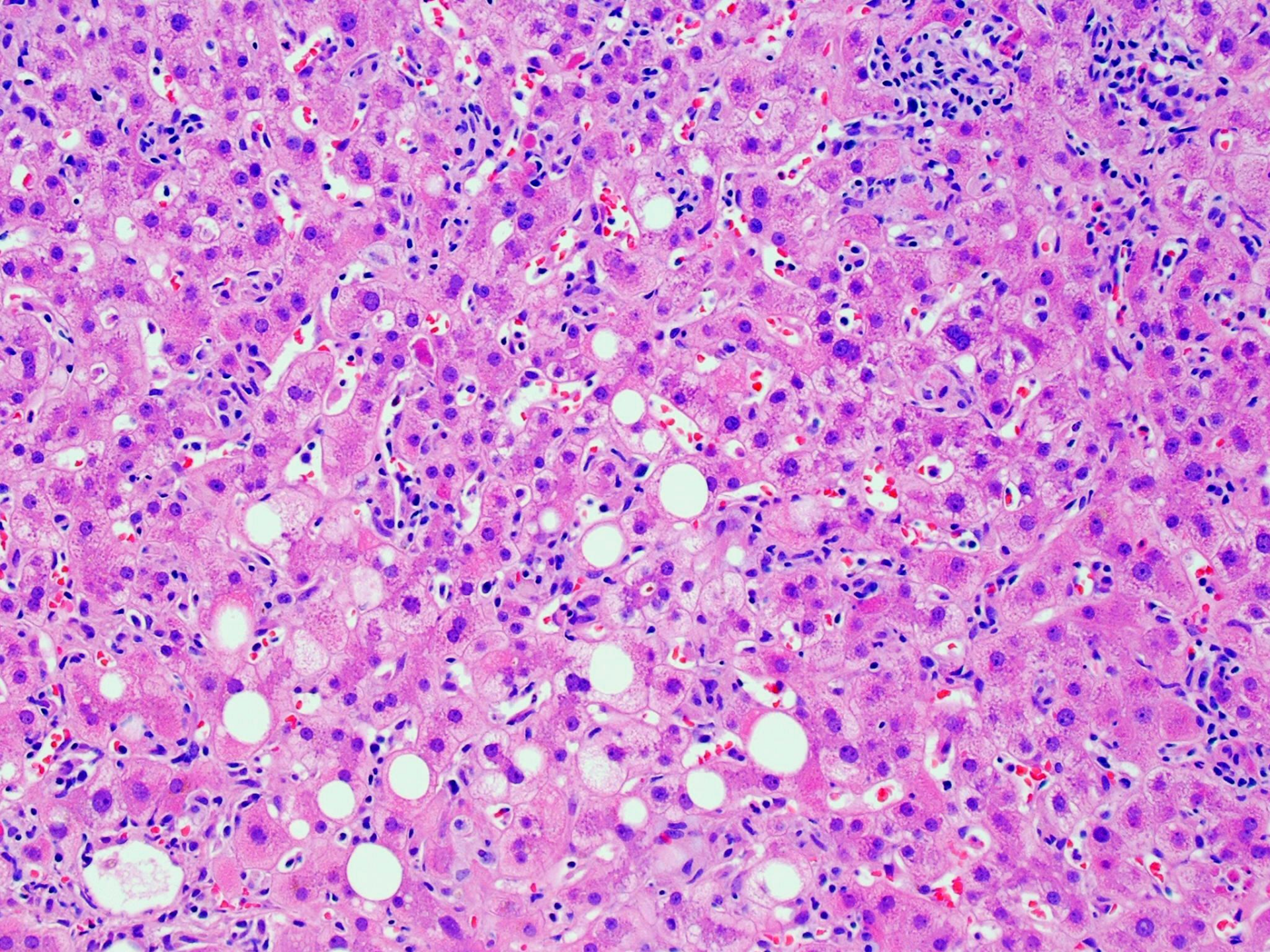
- 45 year old female with 1 week hx of RUQ abdominal pain, malaise, and jaundice
- No history of chronic liver disease
- Not taking any medications and does not drink alcohol
- Physical exam confirmed jaundice and revealed mild epigastric tenderness.

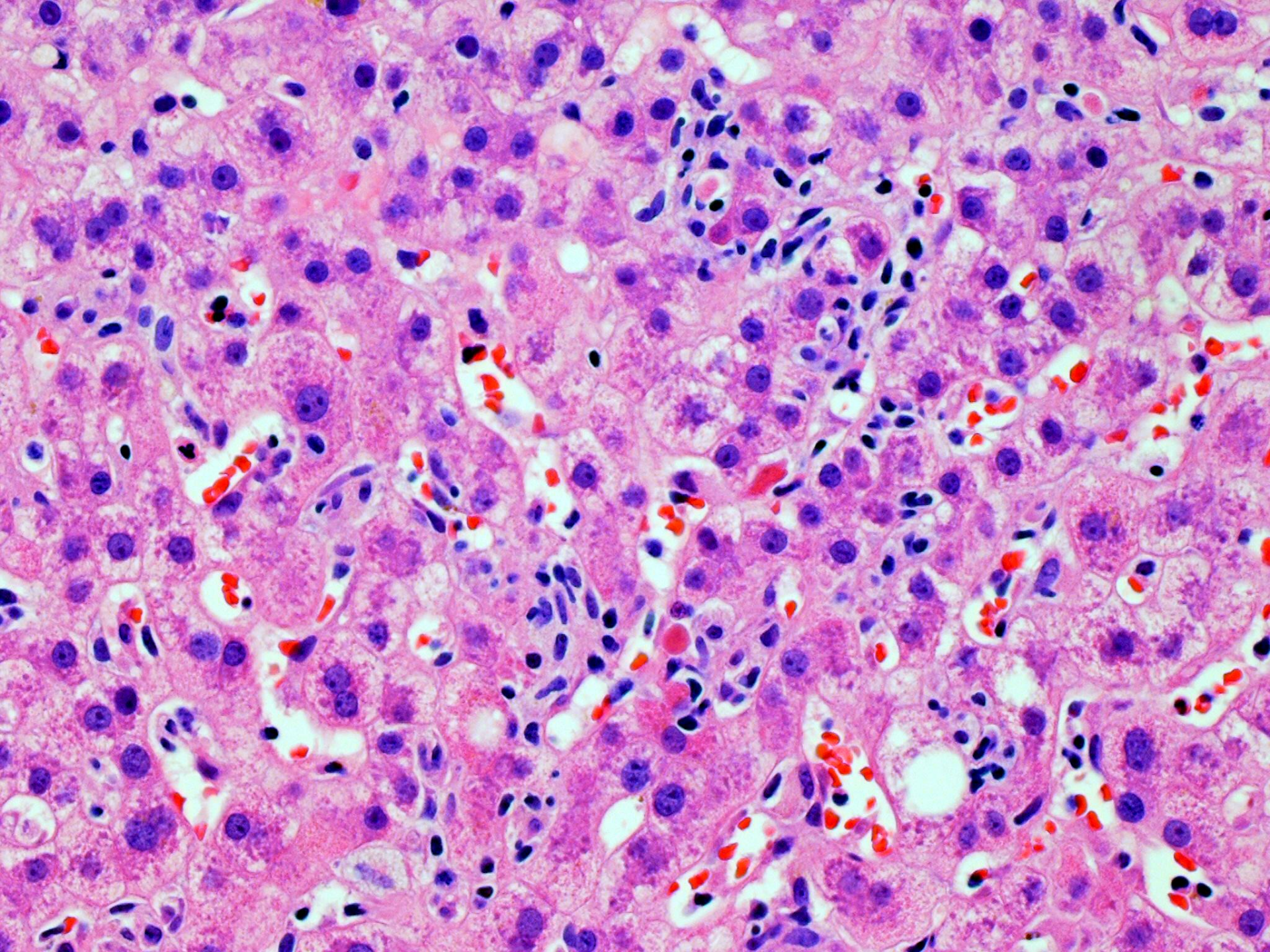
Laboratory Evaluation

- TB = 3.0, AST = 1,144, ALT = 710, Alk phos = 571
- HCV RNA = 11,800,000 IU/ml (genotype 1a)
- HAV, HBV, HEV, EBV, CMV negative
- ANA = 1:320, anti-dsDNA - , anti-SMA – , AMA -
- No hypergammaglobulinemia
- Serum iron, TIBC, ceruloplasmin, 24^h urine Cu – nl
- Pregnancy test negative
- Urine toxicology screen negative
- Doppler U/S & abdominal CT: thickened gallbladder









Follow-up

- **Decreasing HCV viral load:**
 - 672,000 at week 1
 - 498 at 3 week 3
 - Undetectable at week 7

- **Histologic pattern:**
 - **Acute hepatitis**
- **Diagnosis:**
 - **Acute HCV hepatitis**
- **Take home points:**
 - **Serum ANA is often weakly positive (especially in women) and may mean nothing**
 - **Although almost all cases of acute hepatitis in biopsies are drug induced, other causes still must be considered**



Hepatitis C...
Isn't that the one
I have been
vaccinated for?

NO

Histology of Symptomatic Acute Hepatitis C Infection in Immunocompetent Adults

Kathryn Johnson, MD, Ayman Kotiesh, MD,† John K. Boitnott, MD,*
and Michael Torbenson, MD**

(Am J Surg Pathol 2007;31:1754–1758)

TABLE 1. Clinical and Laboratory Findings

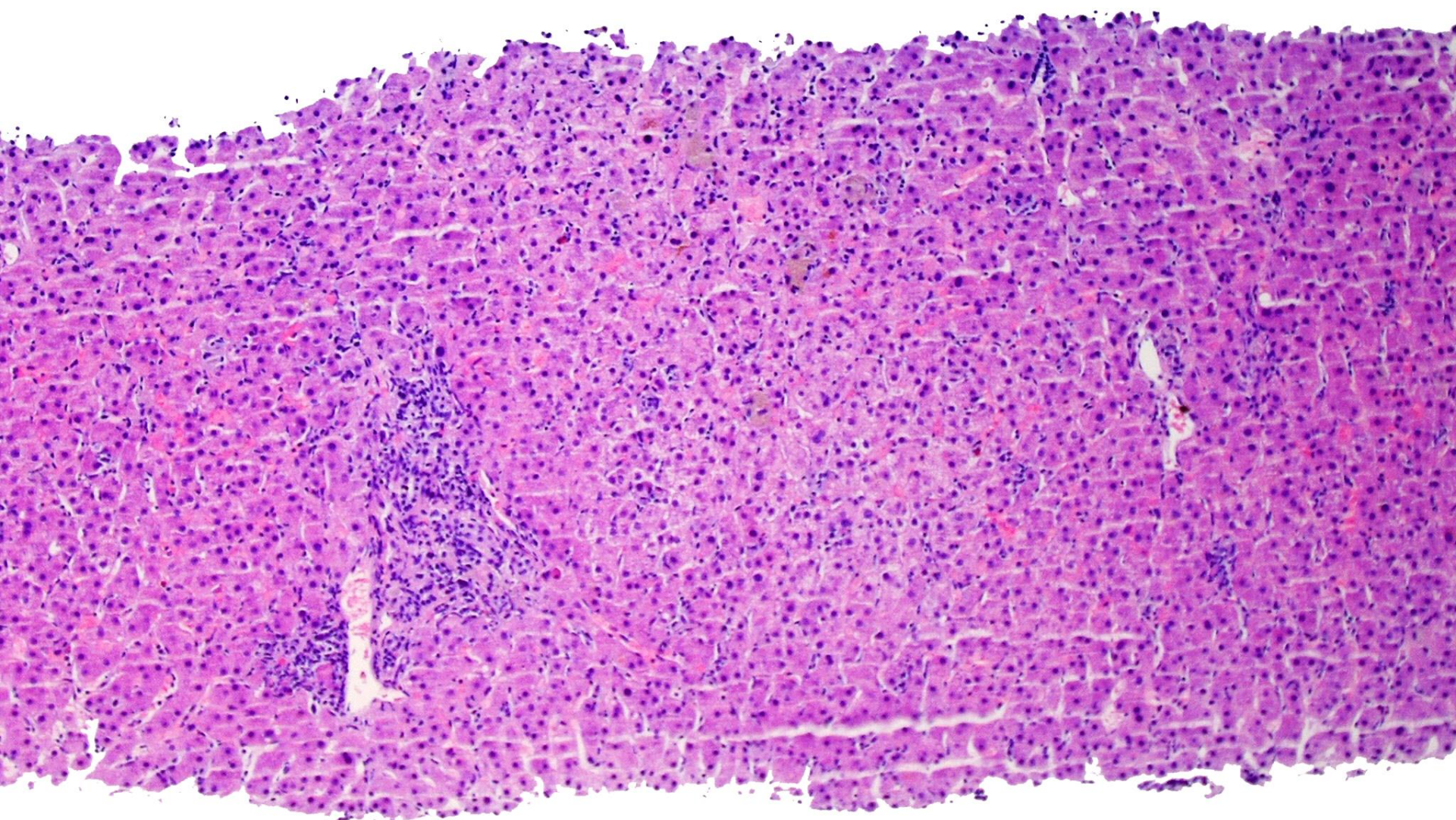
Case	Age/ Sex	HCV Risk Factor	Time Interval From Symptoms* (wk)	HCV Genotype	Maximum ALT/AST (IU/L)	ALT/AST at Biopsy (IU/L)	Alkaline Phosphatase at Biopsy (IU/L)	Bilirubin at Biopsy (mg/dL)
1	67 M	Contaminated radiopharmaceutical	2	1a	> 1000/ > 1000	NA†	NA	> 17
2	50 M	Contaminated radiopharmaceutical	2	1a	1907/2317	108/98	101	14.2
3	45 F	Unknown	8	1a	574/297	128/40	53	0.5
4	63 M	Colonoscopy	8	1b	NA	52/32	83	0.5
5	25 F	Laboratory exposure	18	NA	619/420	236/92	73	0.8

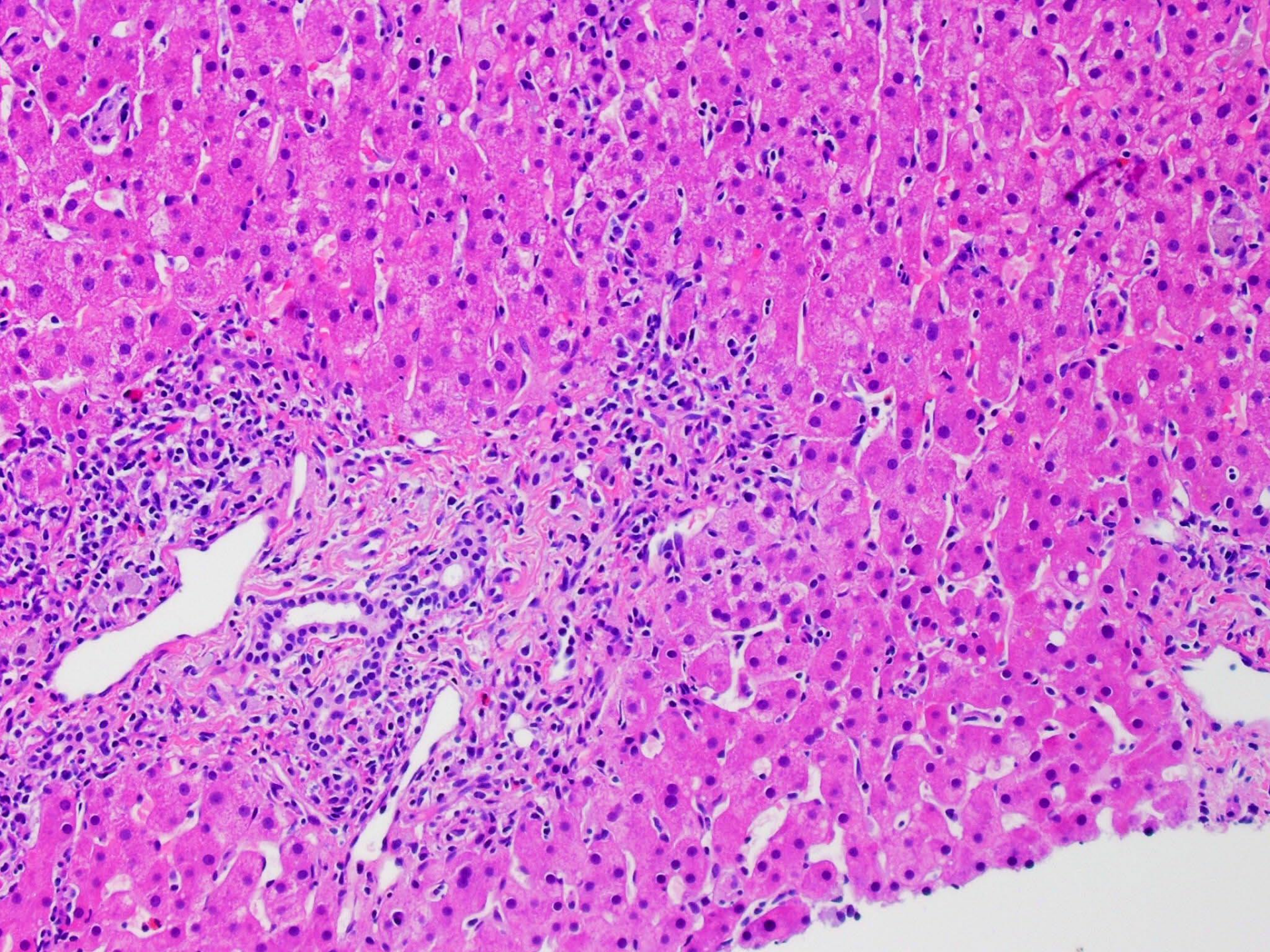
TABLE 2. Histologic Findings

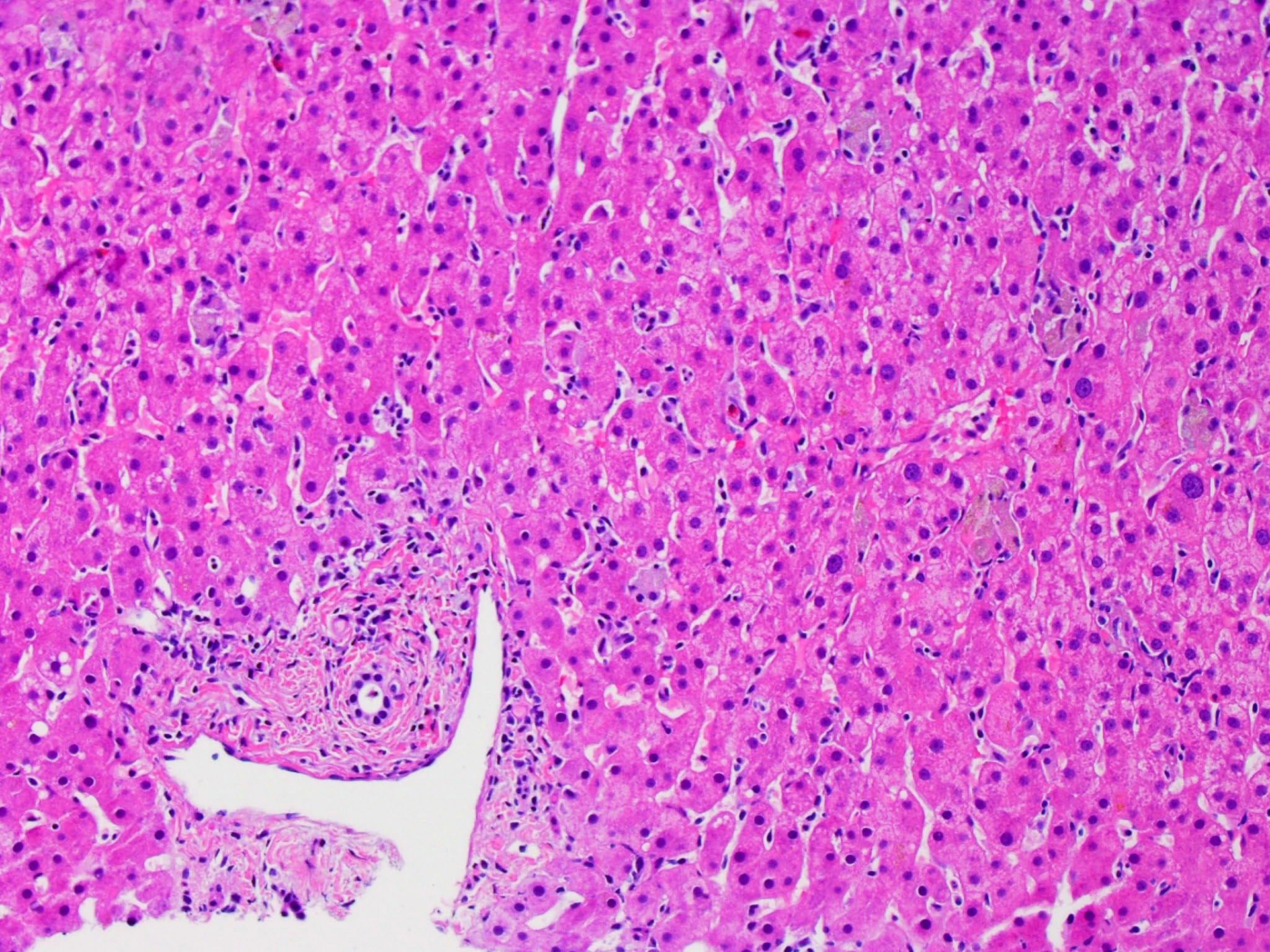
Finding	Case 1	Case 2	Case 3	Case 4	Case 5
Portal lymphocytic inflammation	3	3	1	1	2
Portal neutrophils (scale 1-3)	2	2	0	0	0
Bile ductular proliferation (scale 1-3)	1	1	0	0	0
Interface activity	2	2	0	1	1
Lobular lymphocytic inflammation	3	1	0	3	3
Lobular neutrophilic inflammation (scale 1-3)	2	1	0	0	0
Macrovesicular steatosis (scale 1-3)	0	0	0	2	0
Cholestasis (scale 1-3)	1 H*	3 C†	0	0	0
Lobular pigmented macrophages (scale 1-3)	2	1	2	2	1

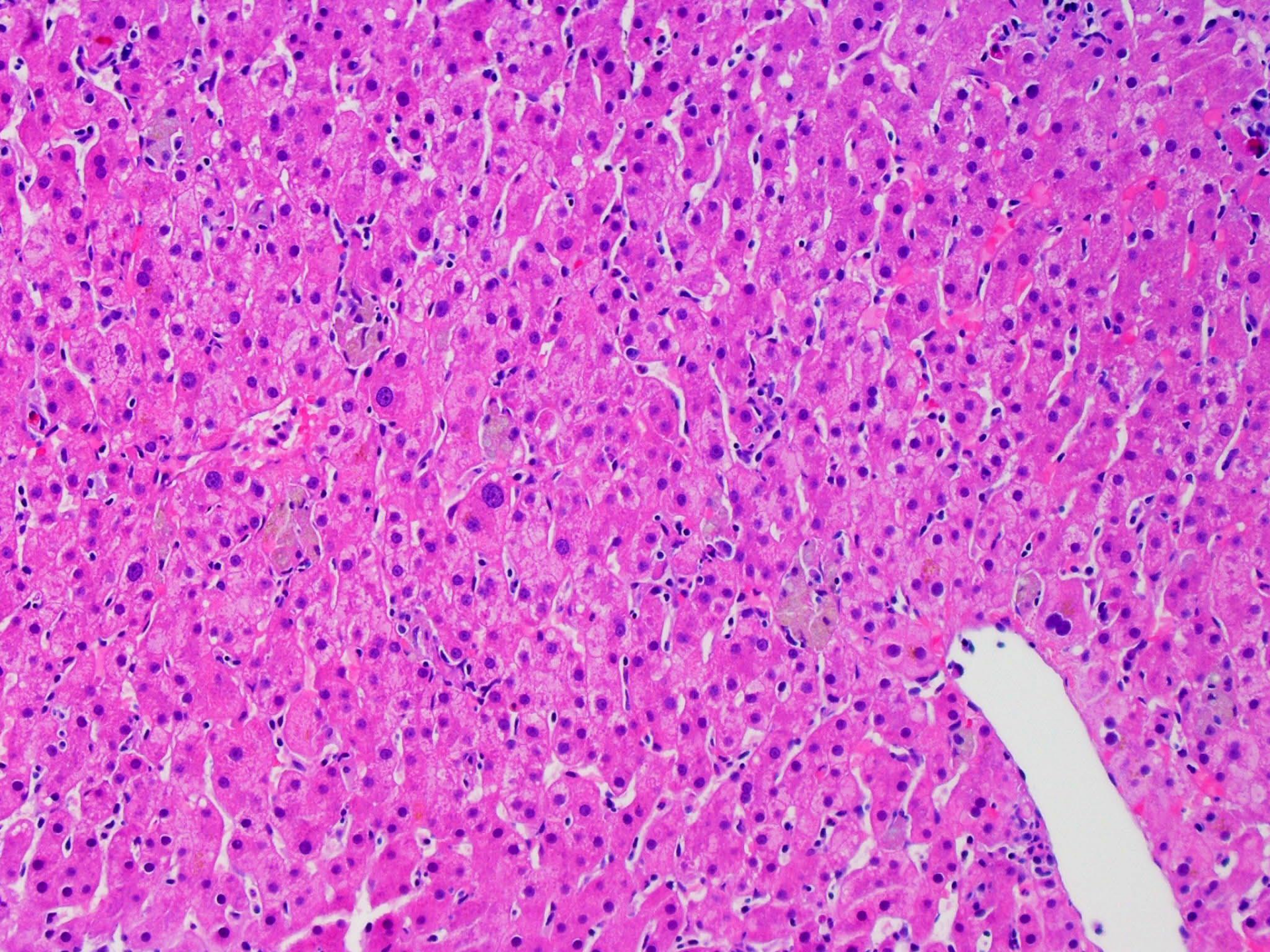
Case 14: Clinical History

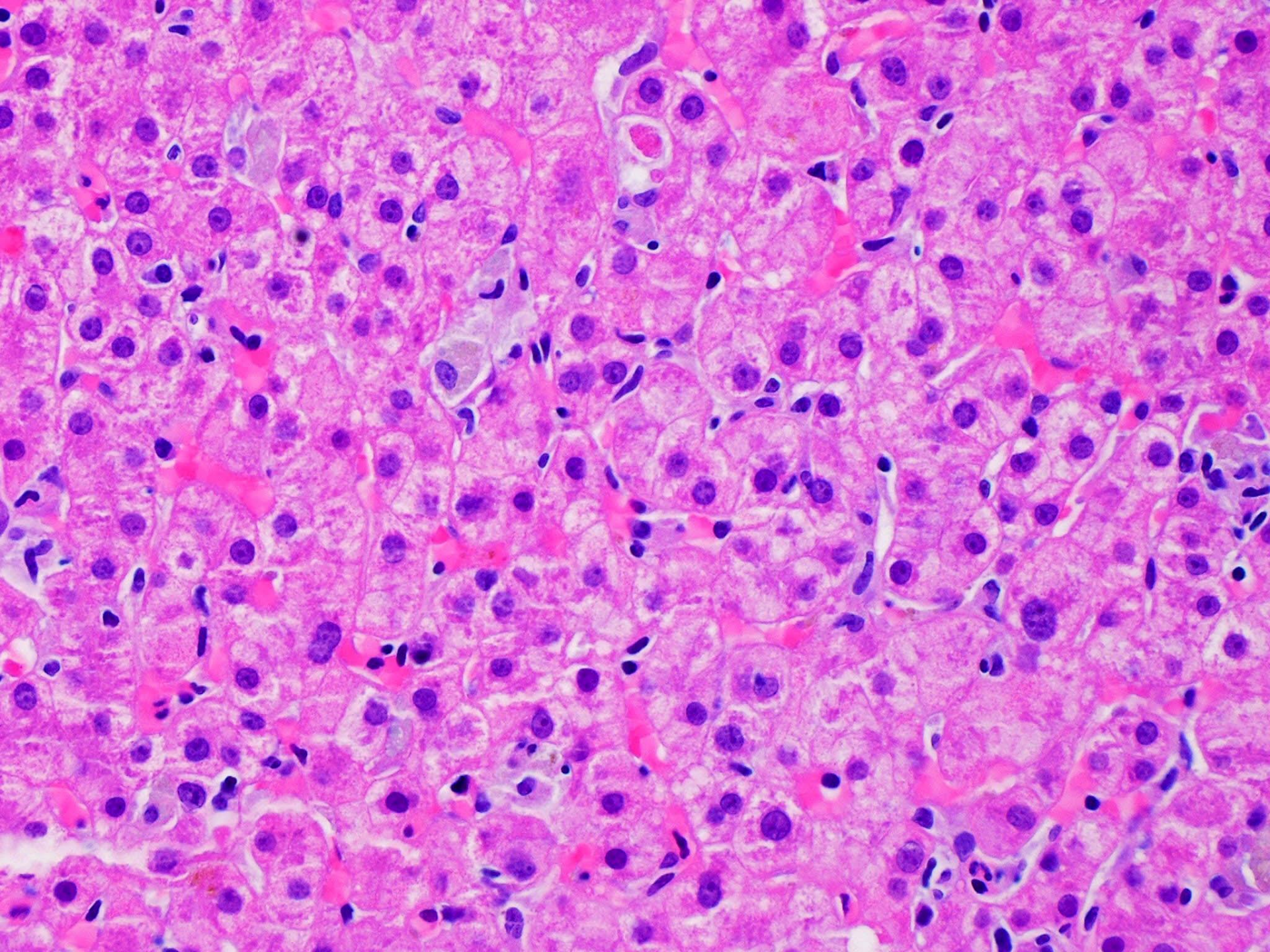
- **57 y.o. M paramedic found to be HCV RNA + at the time of blood donation in 12/07**
- **Needle stick injury on 10/12/07:**
 - Immediate HCV RNA negative; LFTs normal
 - HCV RNA one month later negative again
- **Liver biopsy on 3/24/08 (163 days post-exposure):**
 - TB = 1.0, AST = 300, ALT = 517, Alk phos = 113
 - ANA = 1:80, anti-SMA = 100, anti-dsDNA < 10
 - HCV RNA 526,684 IU/ml; genotype 1B

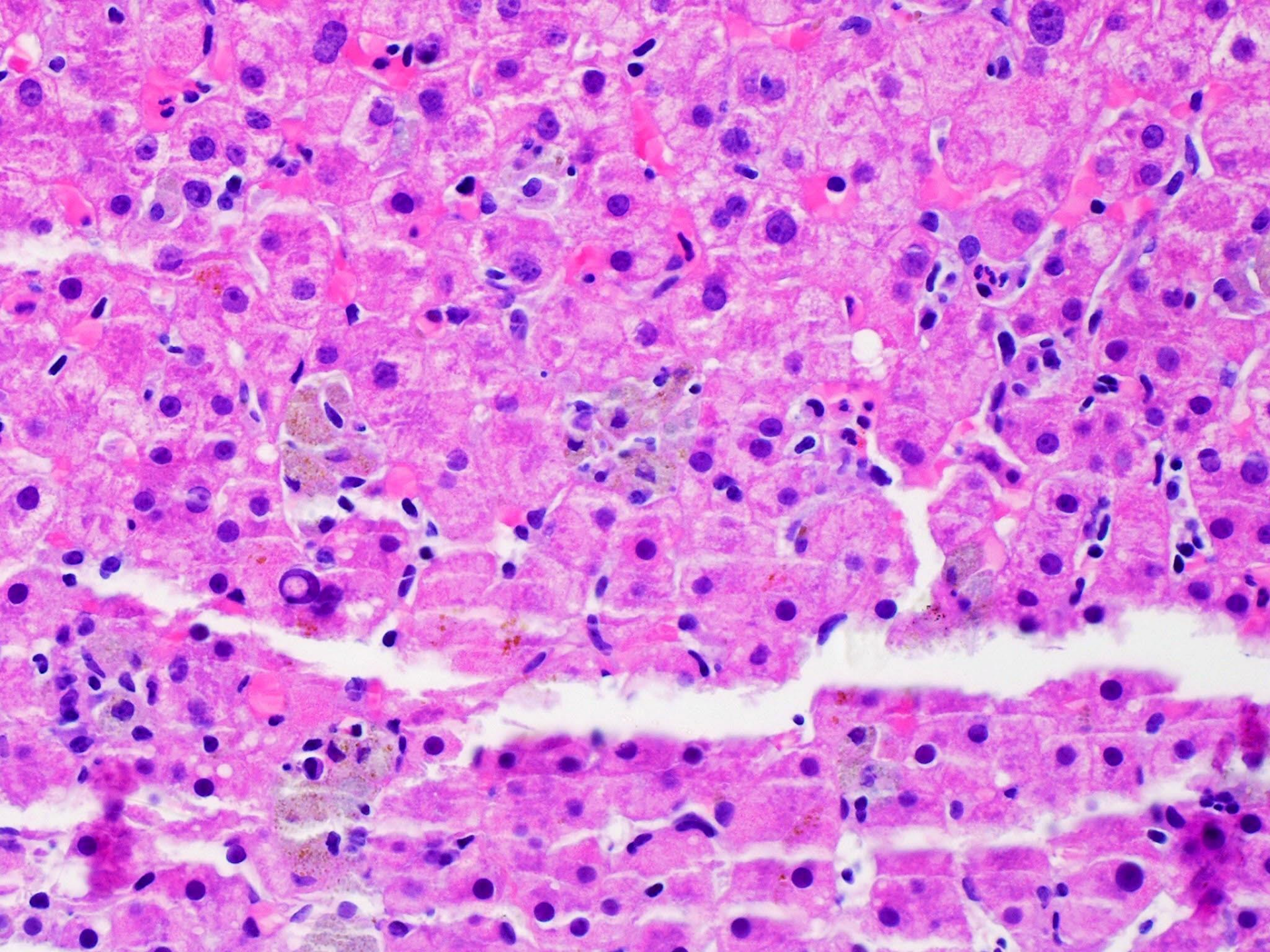


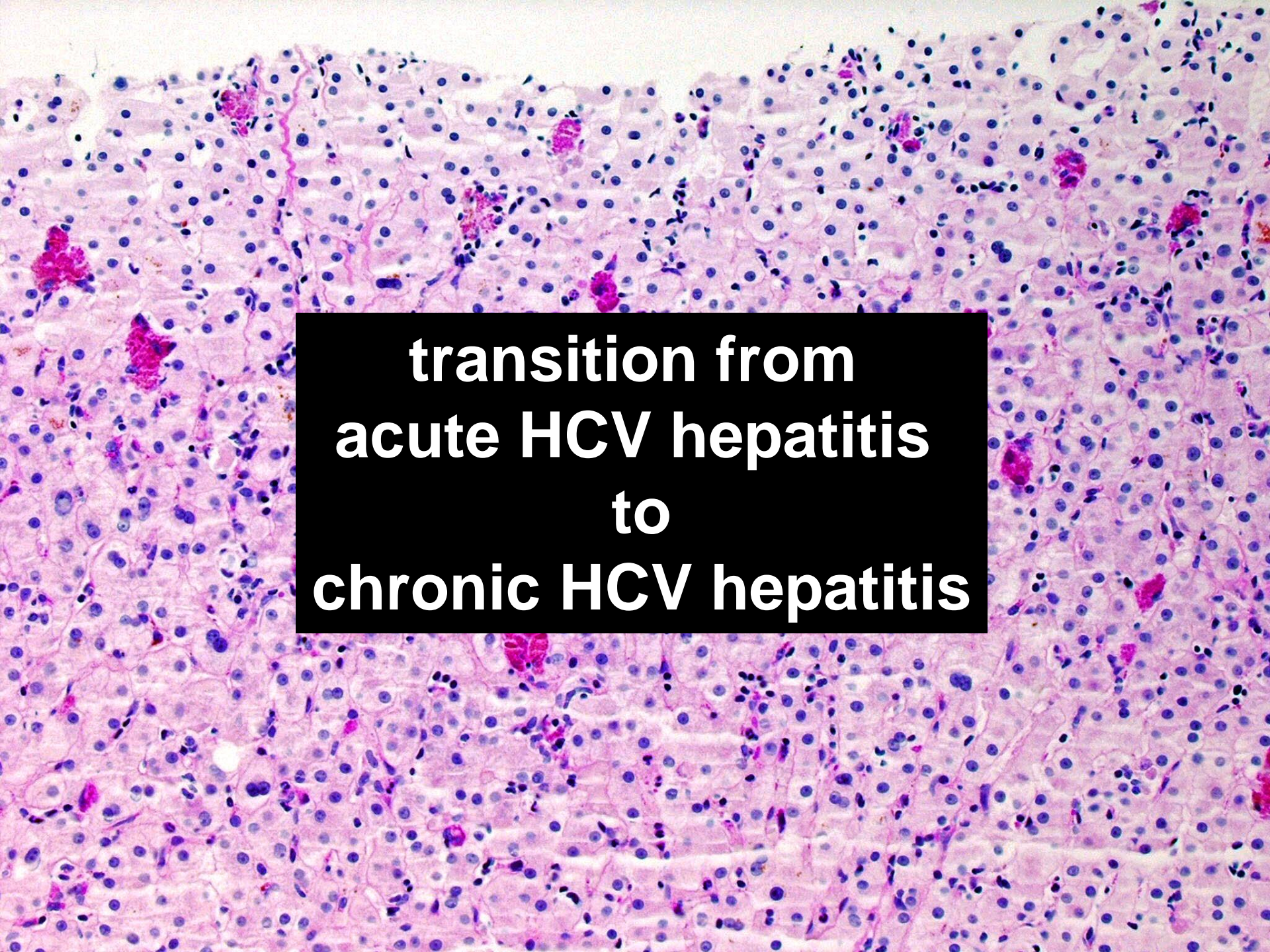












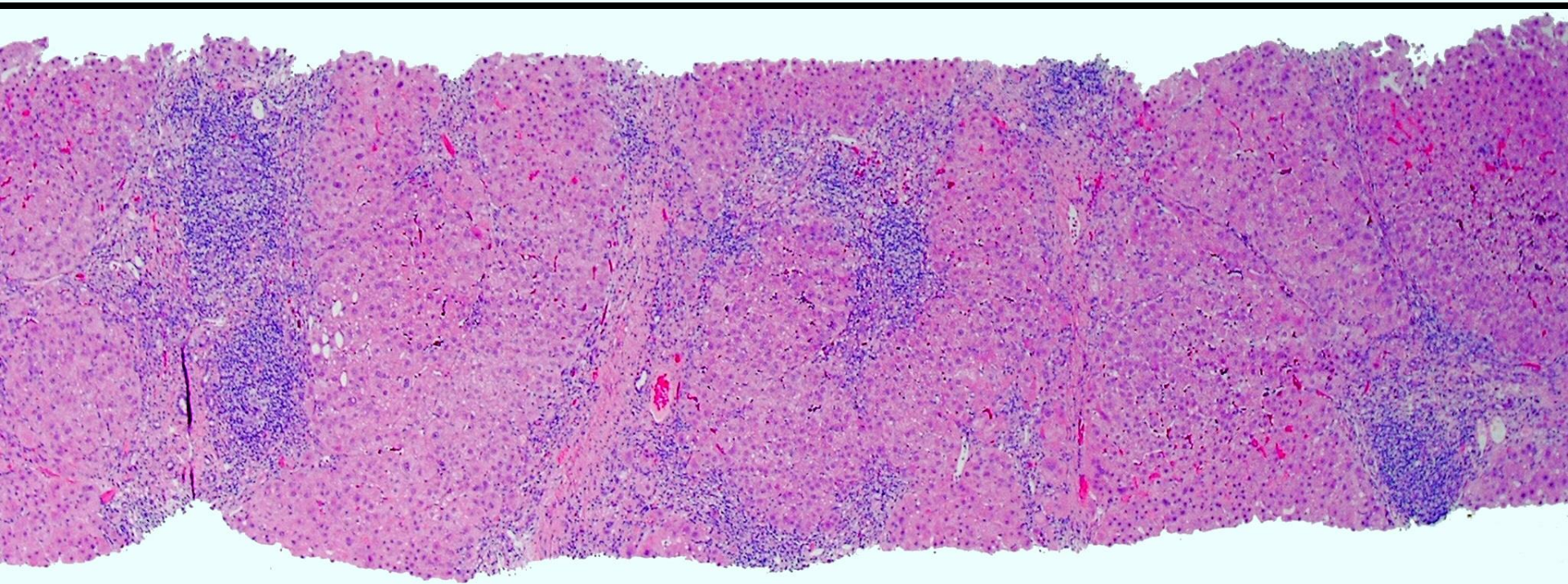
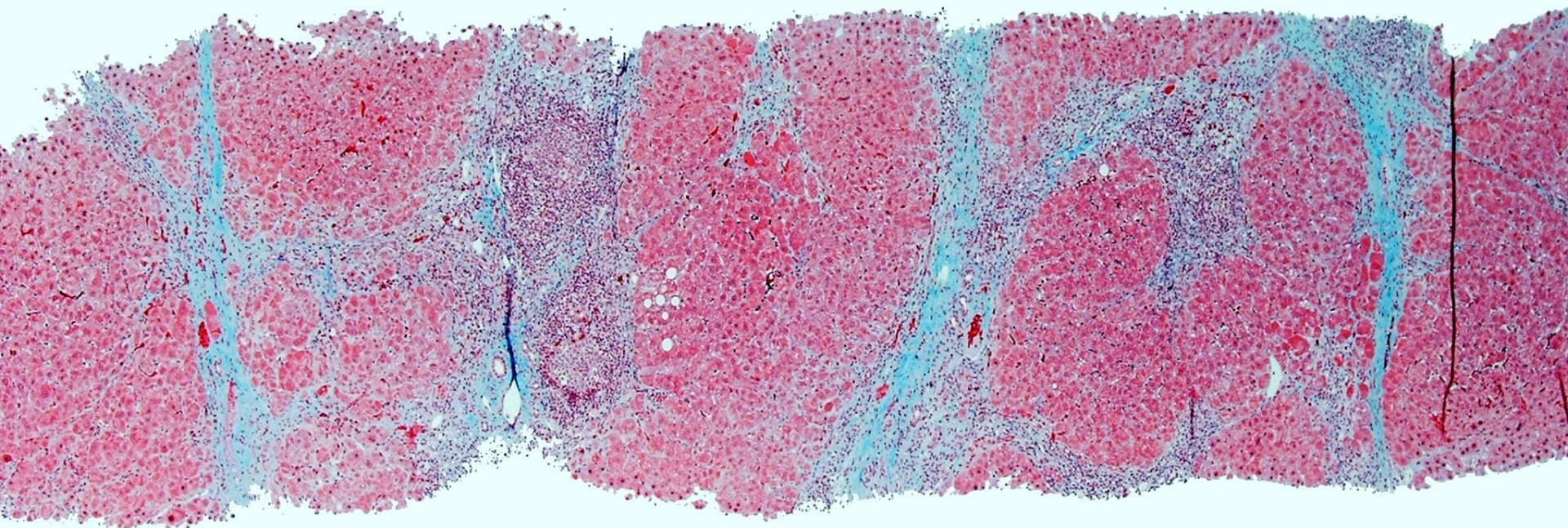
A histological slide of liver tissue stained with hematoxylin and eosin (H&E). The tissue shows a dense population of hepatocytes with prominent nuclei (stained blue) and pink cytoplasm/extracellular matrix. There are several areas of inflammation, indicated by clusters of small, dark-staining cells (likely lymphocytes) and some larger, pink-staining cells (possibly macrophages or plasma cells). The overall architecture suggests a transition from acute to chronic hepatitis.

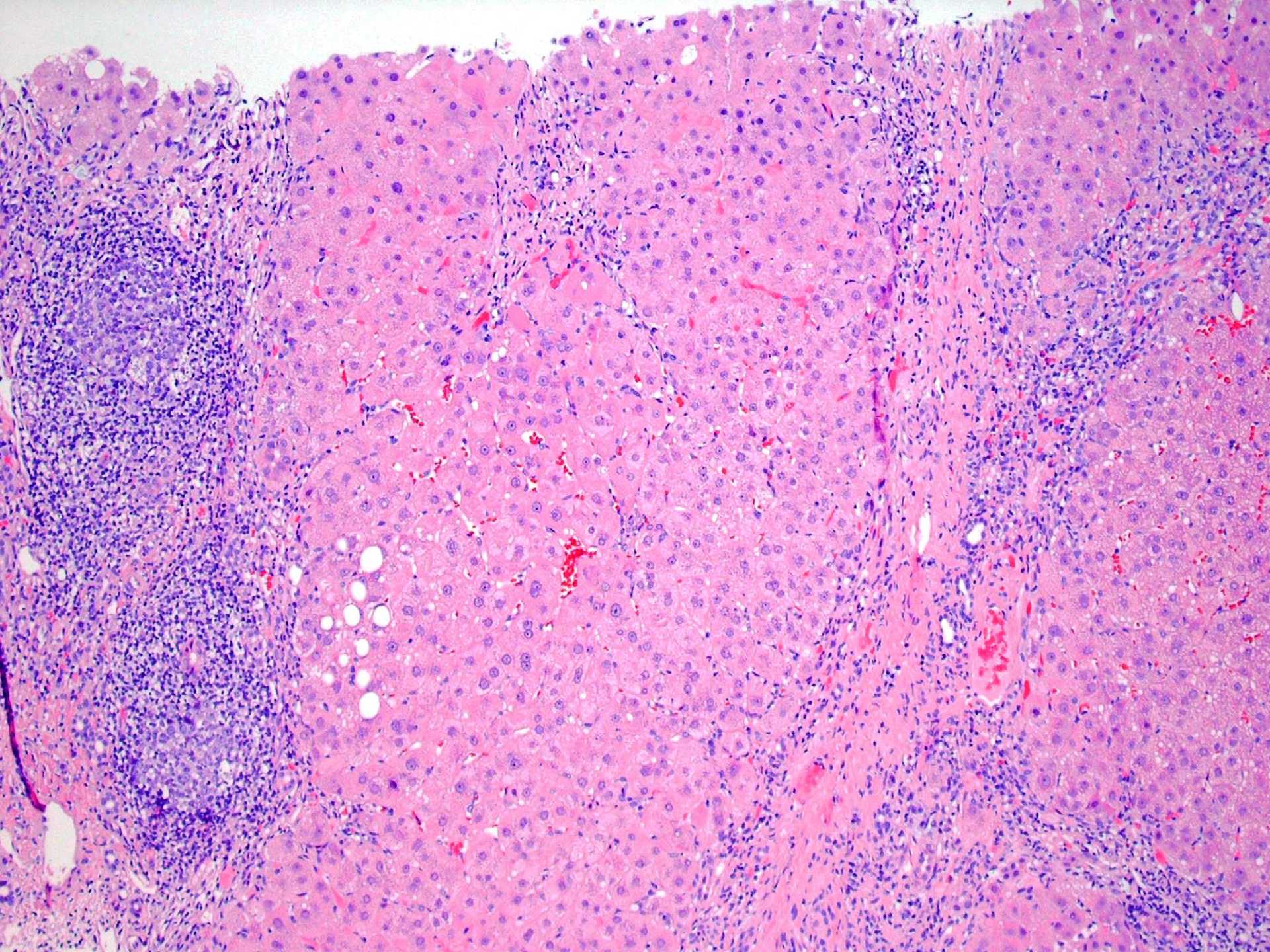
**transition from
acute HCV hepatitis
to
chronic HCV hepatitis**

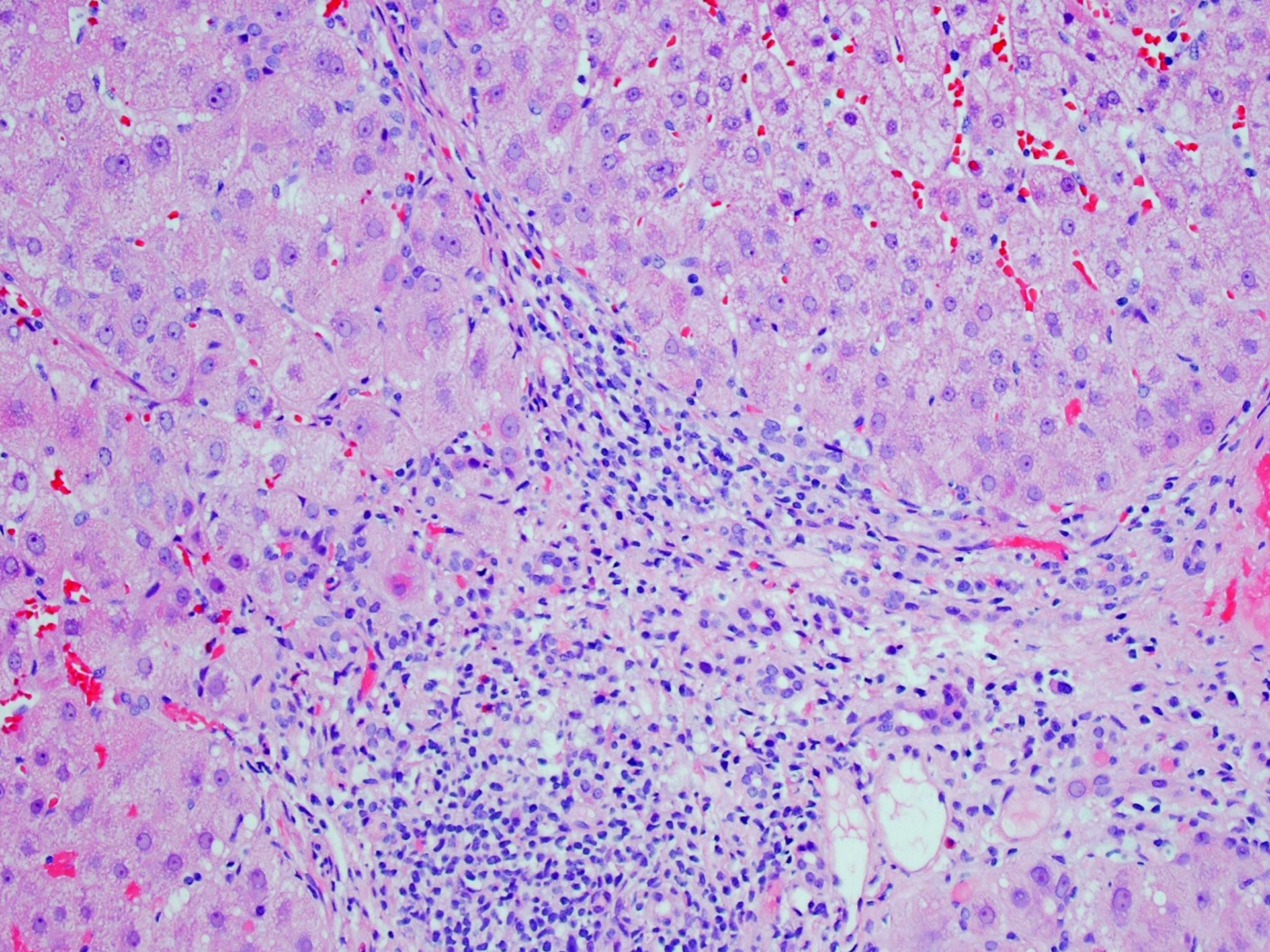


Case 1: Clinical History

- 35 y.o. male with fatigue; teacher of 7th & 8th grade math
- TB = 1.8, AST = 100, ALT = 96, alk phos = 194
- No tattoos, IV drug use, piercing, unprotected sex
- HCV antibody +; genotype 1a; HCV RNA = 347,724 IU
- Platelet count = 66,000; albumin = 3.6
- Spider angiomas on chest; palpable spleen
- Liver biopsy performed for grade and stage

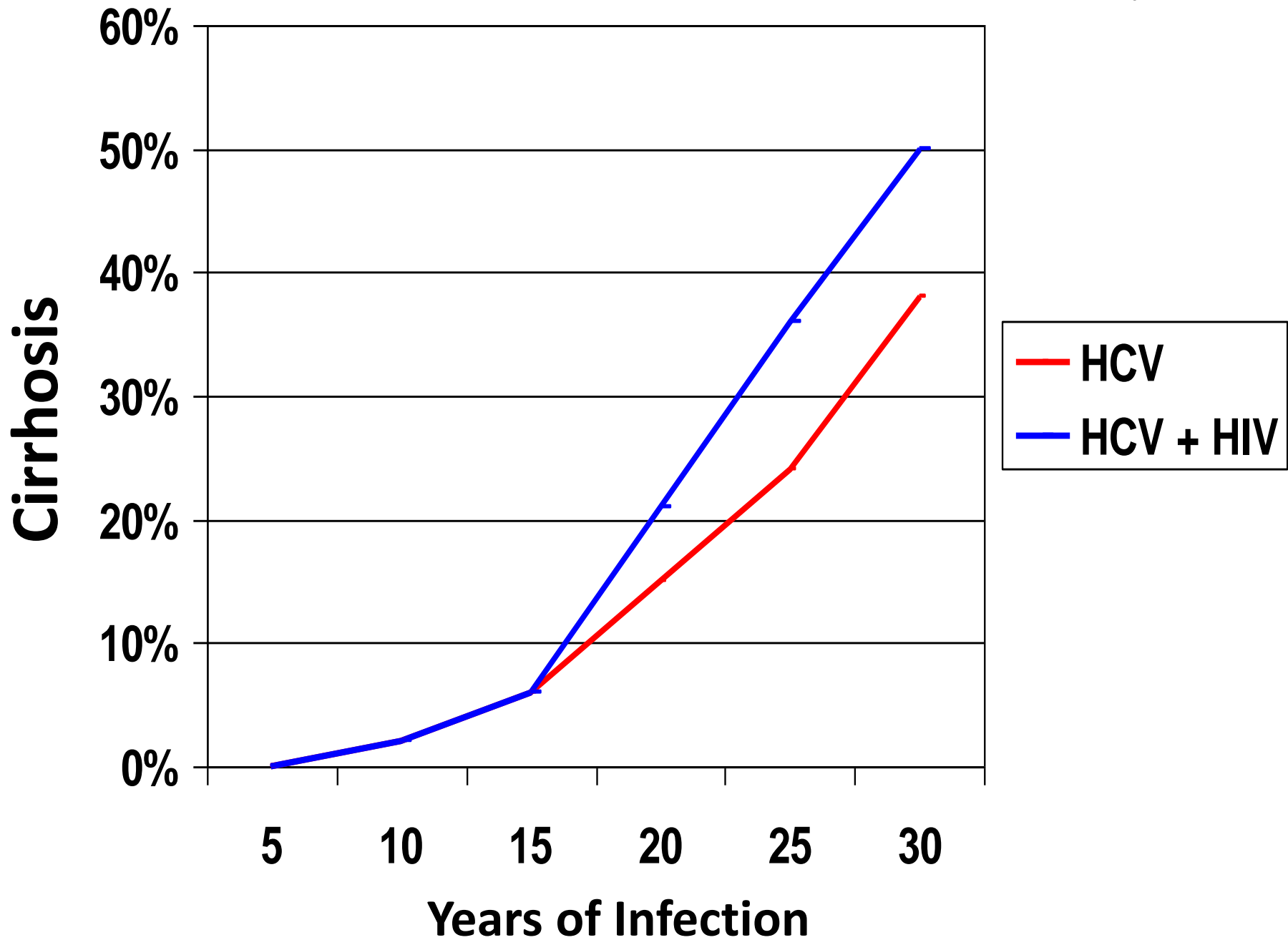


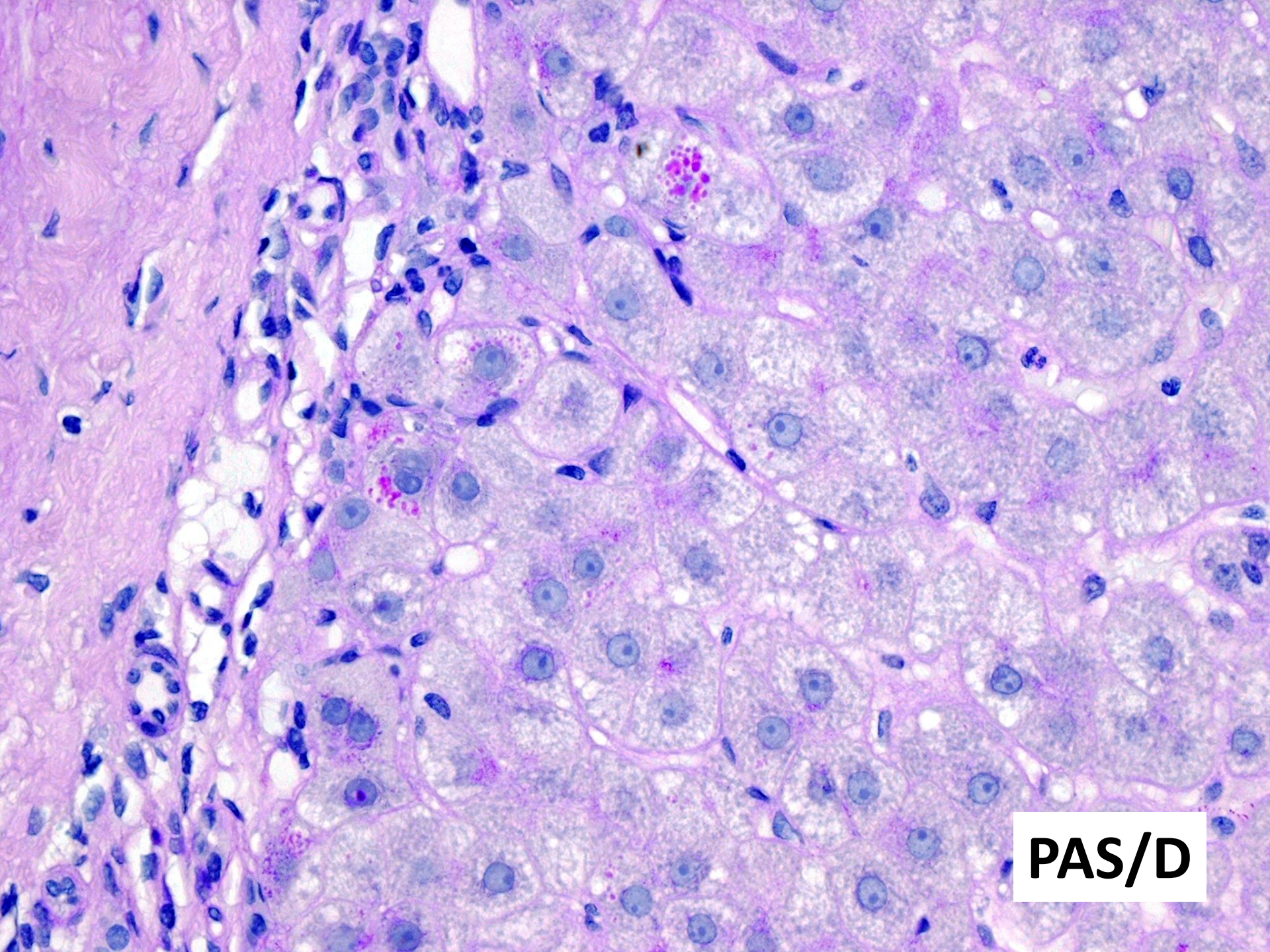




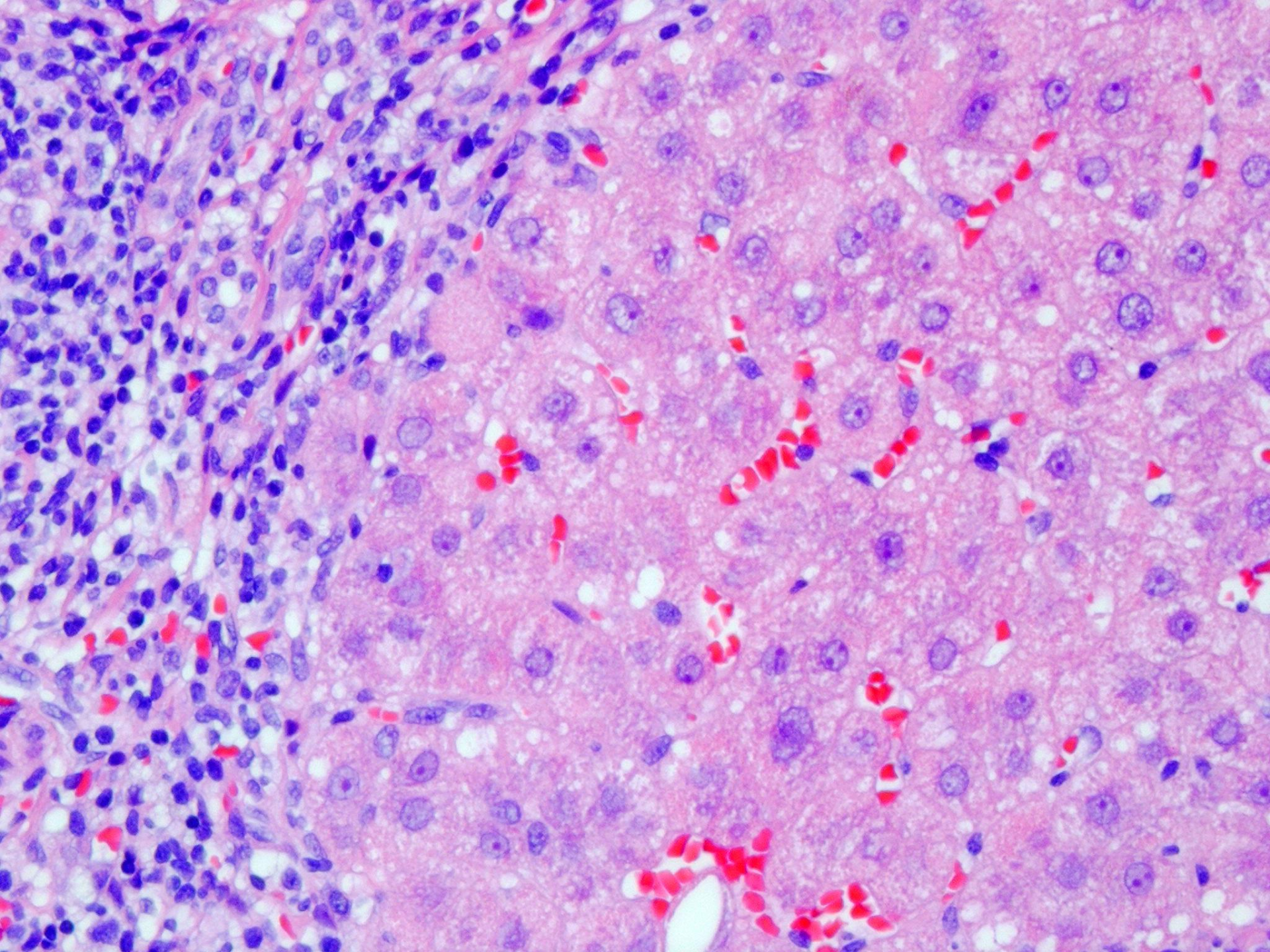
- **Anything strange about this case?**

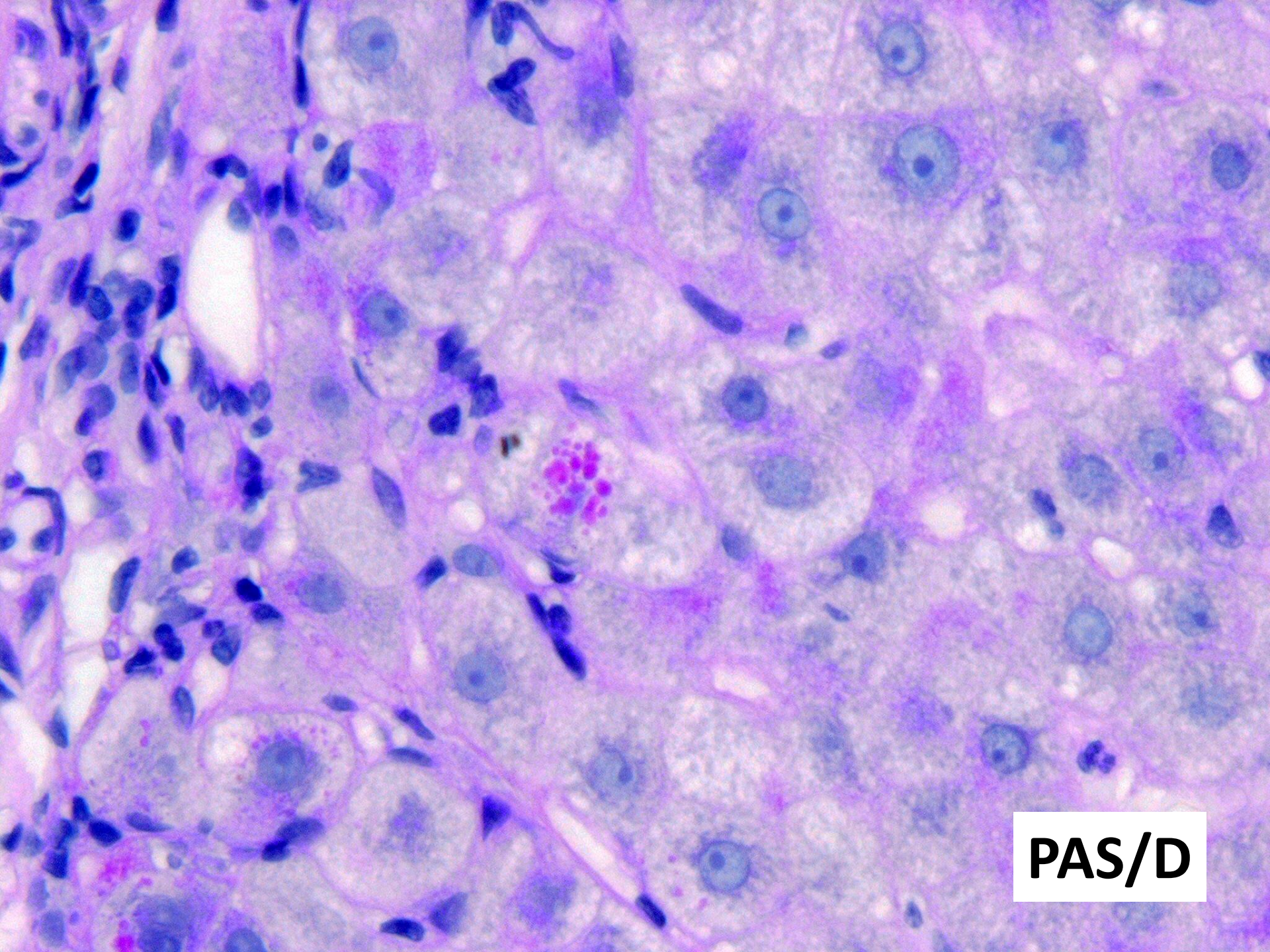
- **No – let's move on**
- **All liver cases are strange – let's move on**
- **I can't read your mind – let's move on**
- **Yes, now that you mention it**





PAS/D





PAS/D

Follow-up

- Alpha-1-antitrypsin level = 85 (92-200 mg/dL)
- Alpha-1-antitrypsin phenotype = MZ



- **Histologic pattern:**
 - **Chronic hepatitis with cirrhosis**
- **Diagnosis:**
 - **Chronic HCV hepatitis (grade 2, stage 4)**
 - **Superimposed alpha-1-antitrypsin deficiency**
- **Take home points:**
 - **Chronic HCV hepatitis is an indolent disease**
 - **HCV related cirrhosis at a young age should make you think of:**
 - **Superimposed steatohepatitis**
 - **Superimposed alpha-1-antitrypsin deficiency**
 - **Superimposed hereditary hemochromatosis**
 - **Superimposed autoimmune hepatitis**

Chronic Hepatitis

Symptoms: non-specific constitutional symptoms; jaundice

Liver chemistry tests: mild inc. AST & ALT >>> Alk phos and TB low

**Histologic pattern: portal changes predominant; +/- fibrosis
minimal lobular changes**

- **Chronic HCV hepatitis**
- **Chronic HBV hepatitis**
- **Autoimmune hepatitis**

Diagnosis by serology
Biopsy for grade and stage

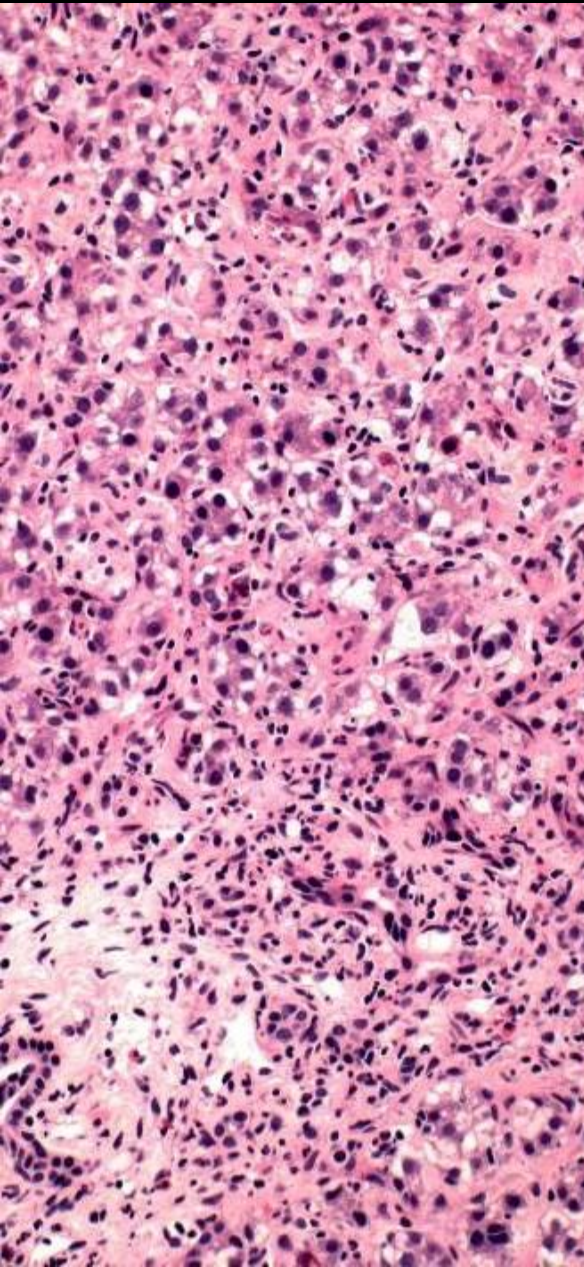
- **Mimics:**

- **Wilson disease**
- **Primary biliary cirrhosis**
- **Non-specific portal inflammation**
- **Biliary obstruction**
- **Celiac disease**

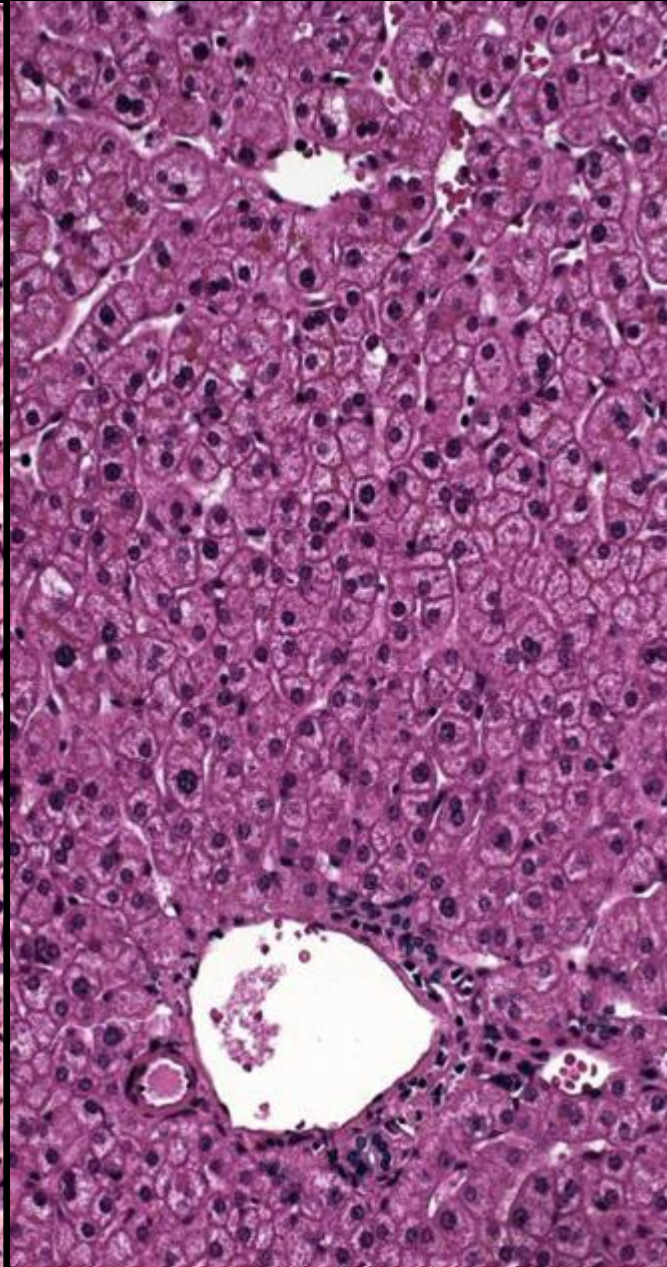
-
-
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-

Drug

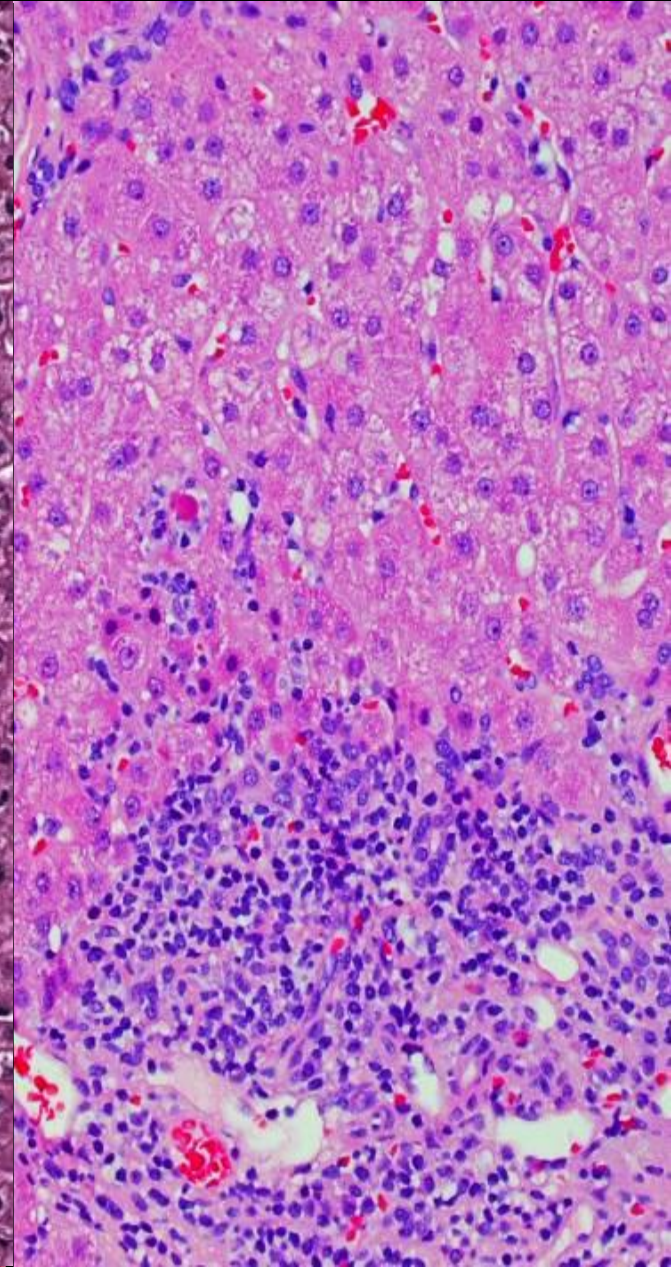
Acute Hepatitis



Normal Liver

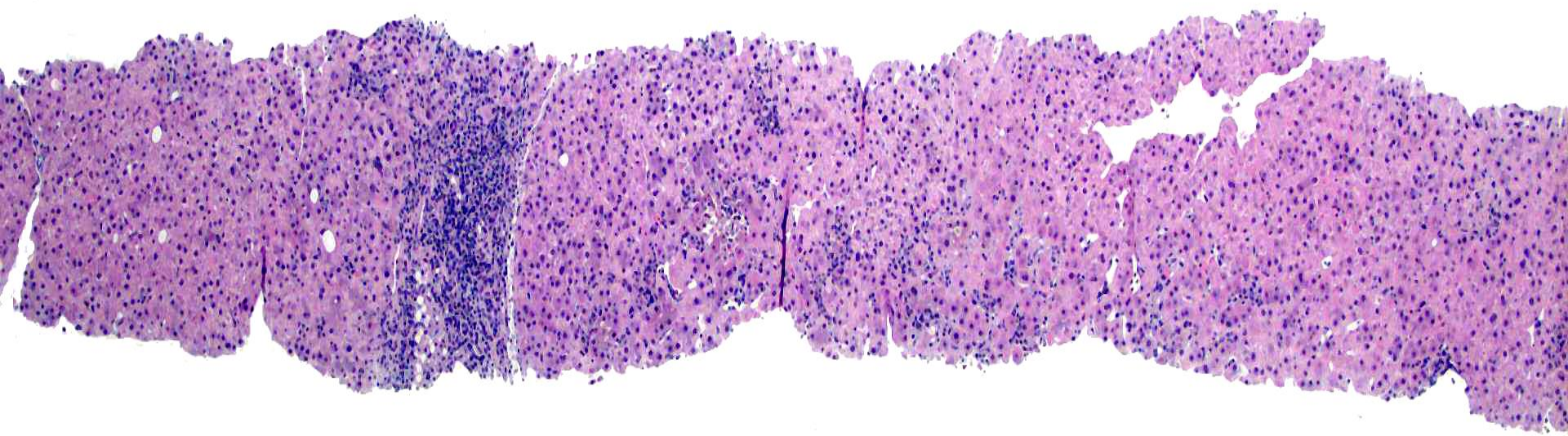


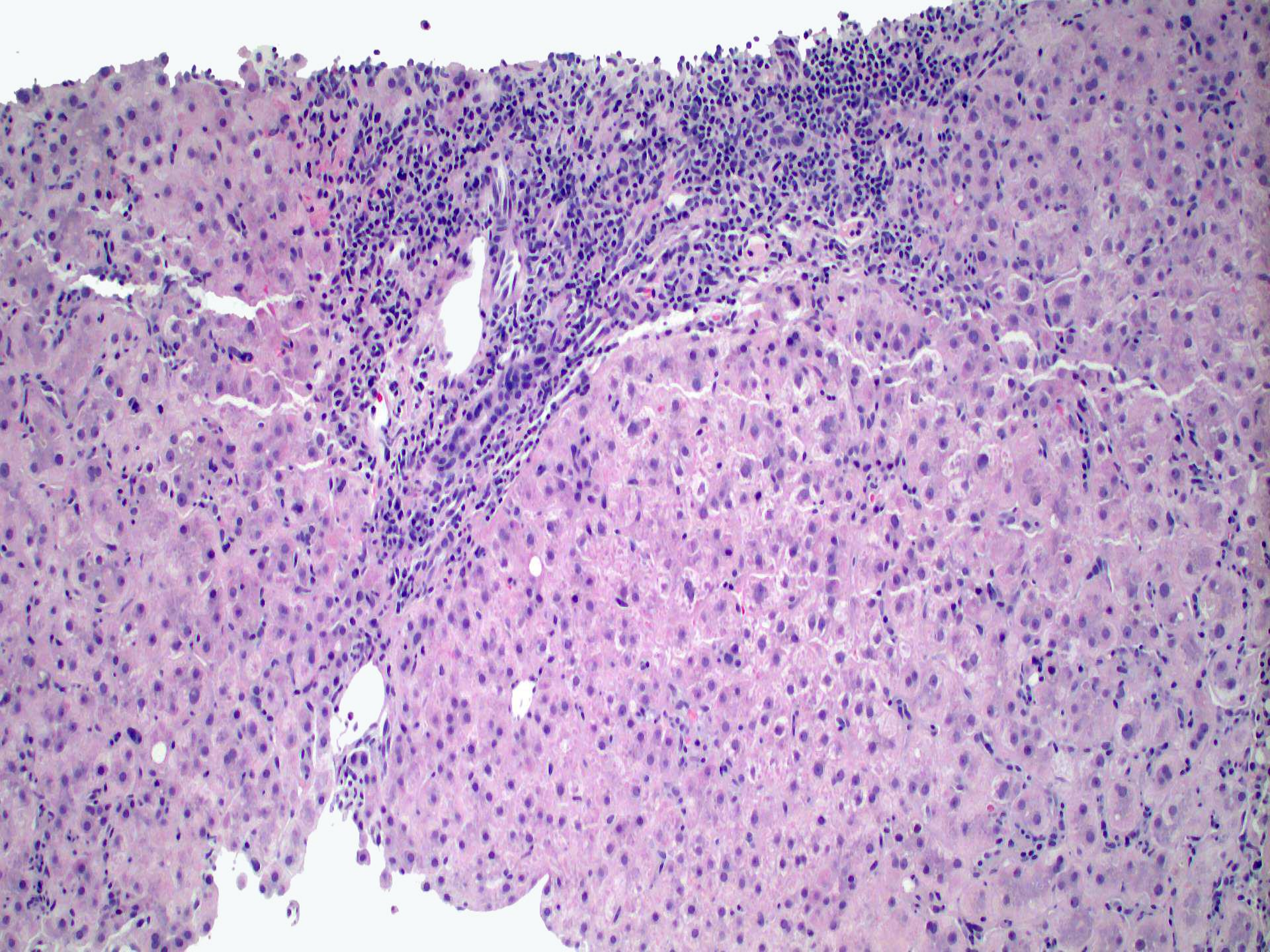
Chronic Hepatitis

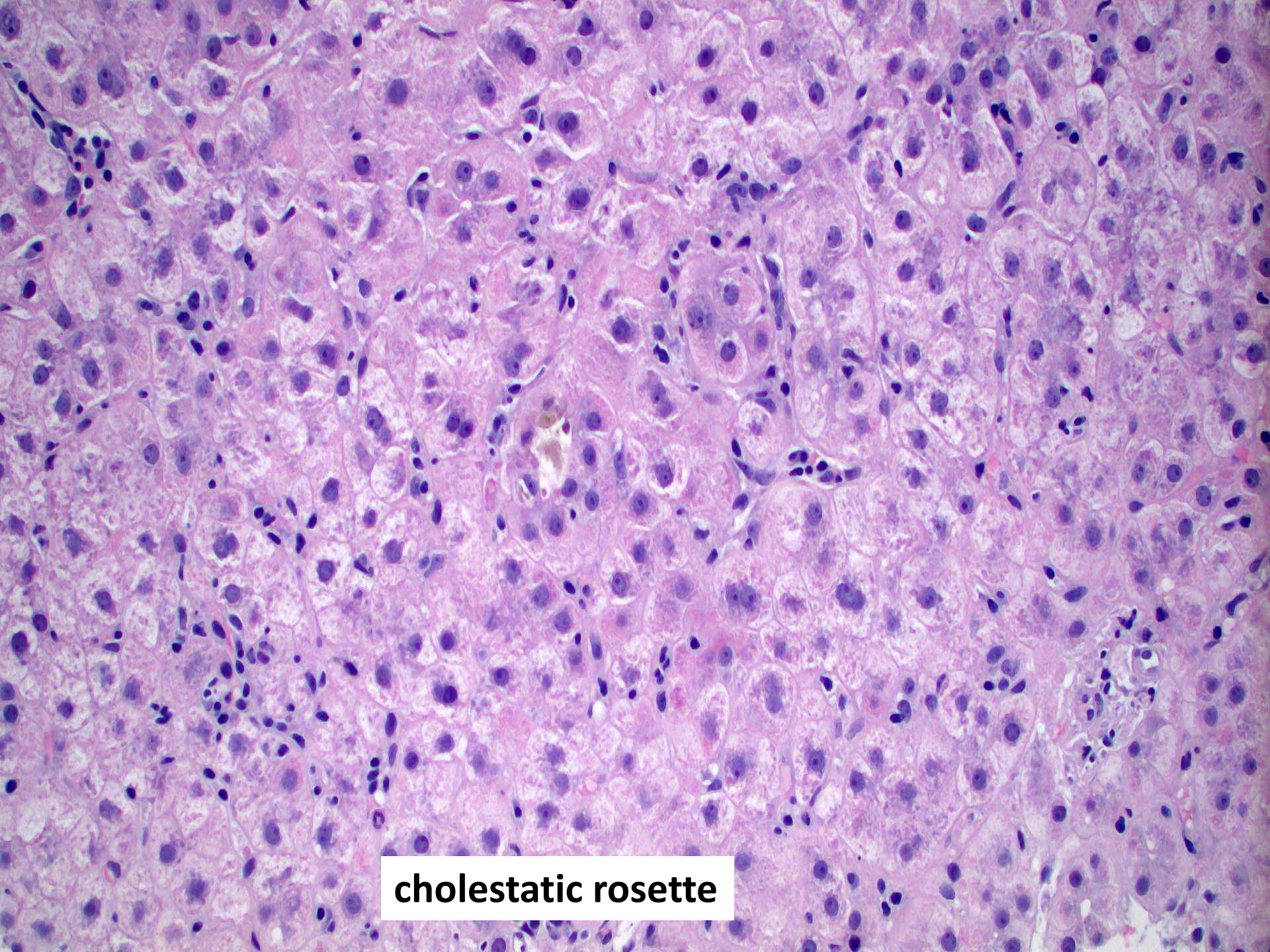


Clinical History

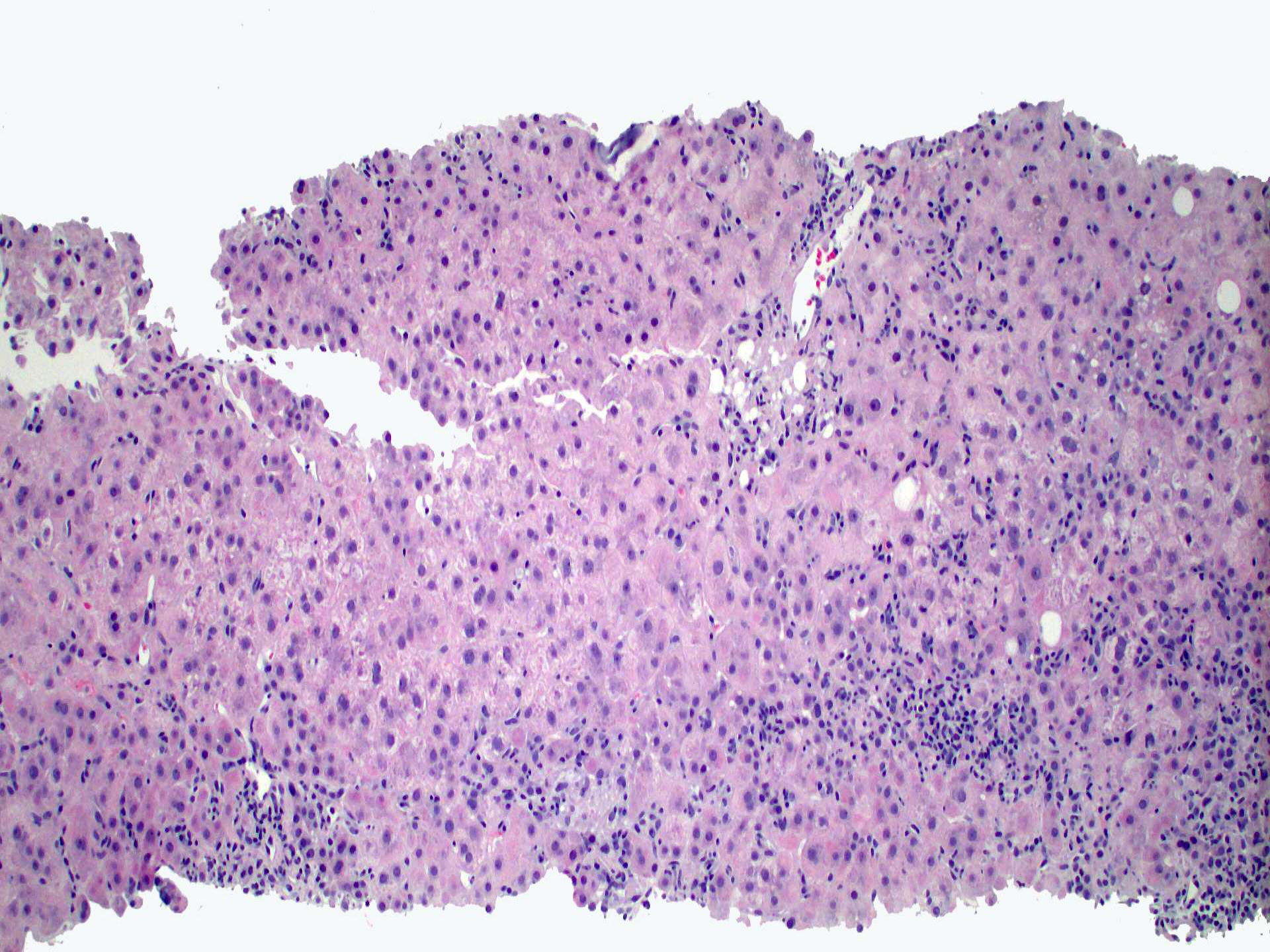
- 70 y.o. M with bipolar disease and polysubstance abuse
- Presents with N&V, RUQ pain & fever – treated with Ibuprofen
- Long Hx HCV hepatitis genotype 1a; viral load = 1719419 IU/mL
- Cholecystectomy 1 year ago
- PE: jaundice; scleral icterus
- TB = 12.5, AST = 293, ALT = 219, alk phos = 327
- HAV, HBV negative; ANA negative; HIV negative
- Meds: Nifedipine; Atenolol; Ondansetron; Sertraline; Tramadol
- U/S and CT scan reveal no biliary obstruction or stones

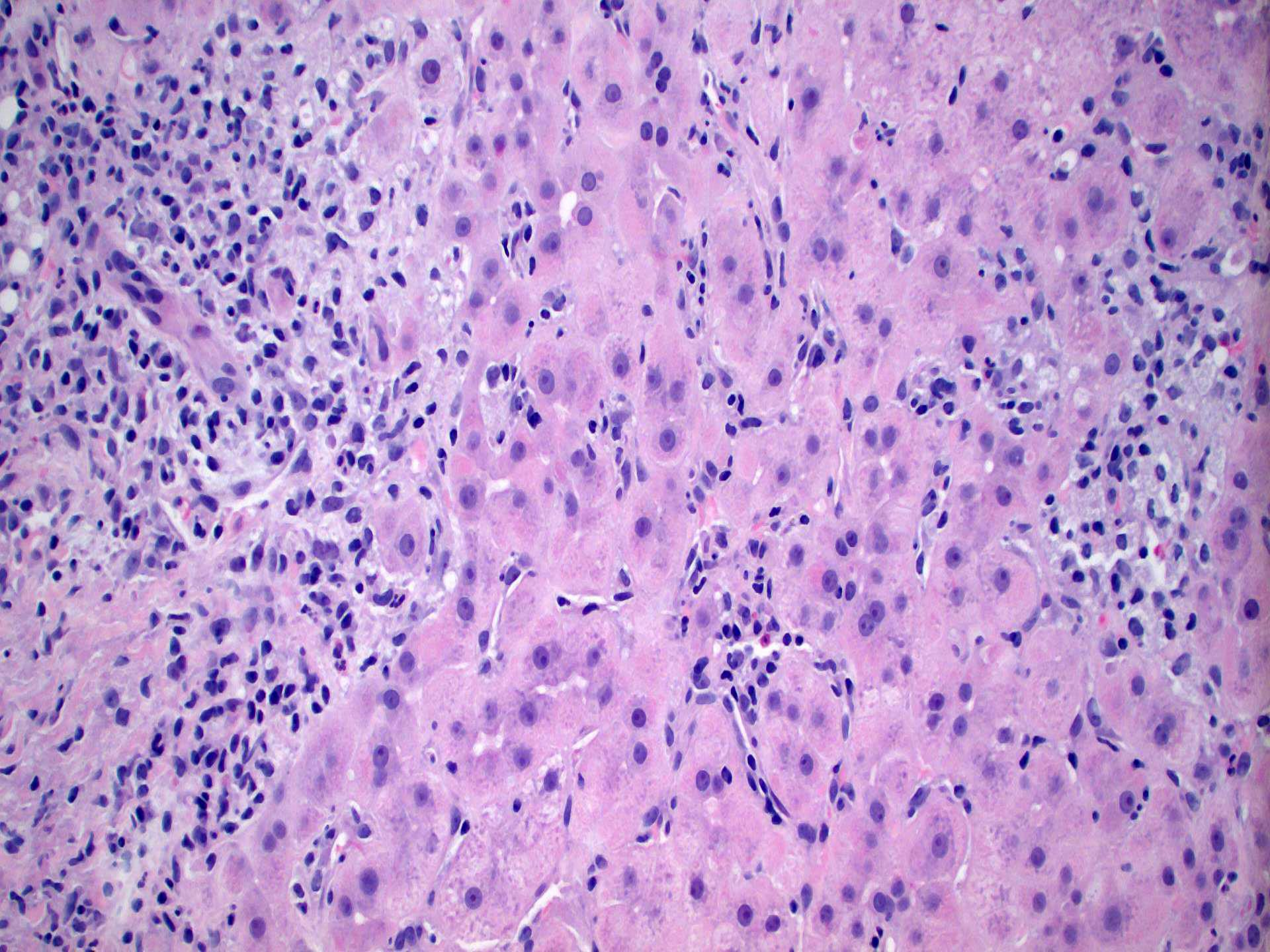


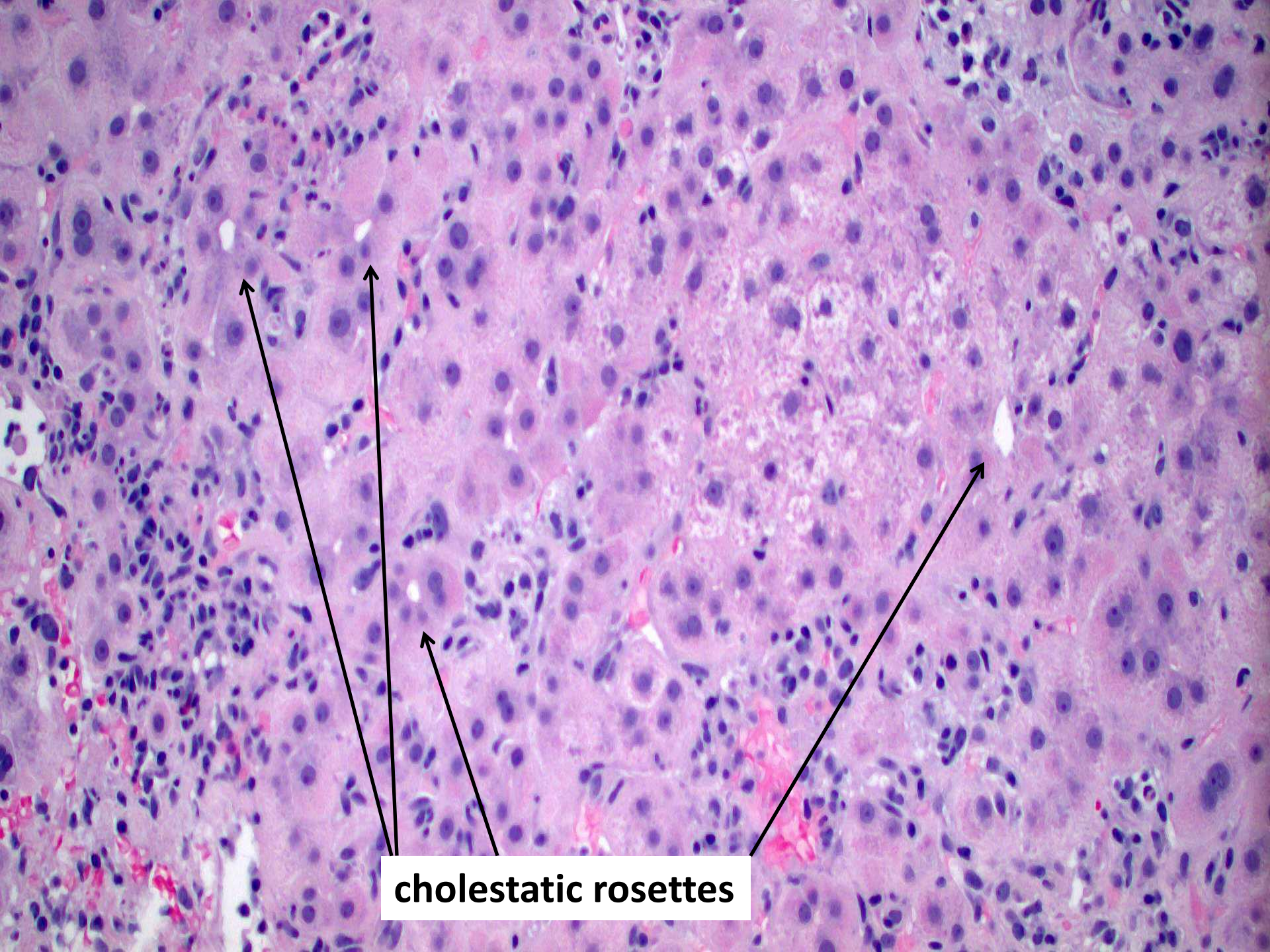




cholestatic rosette







cholestatic rosettes

Needle biopsy; liver:

- Chronic HCV hepatitis (stage 2).
- Superimposed acute cholestatic hepatitis.

See comment.

Comment

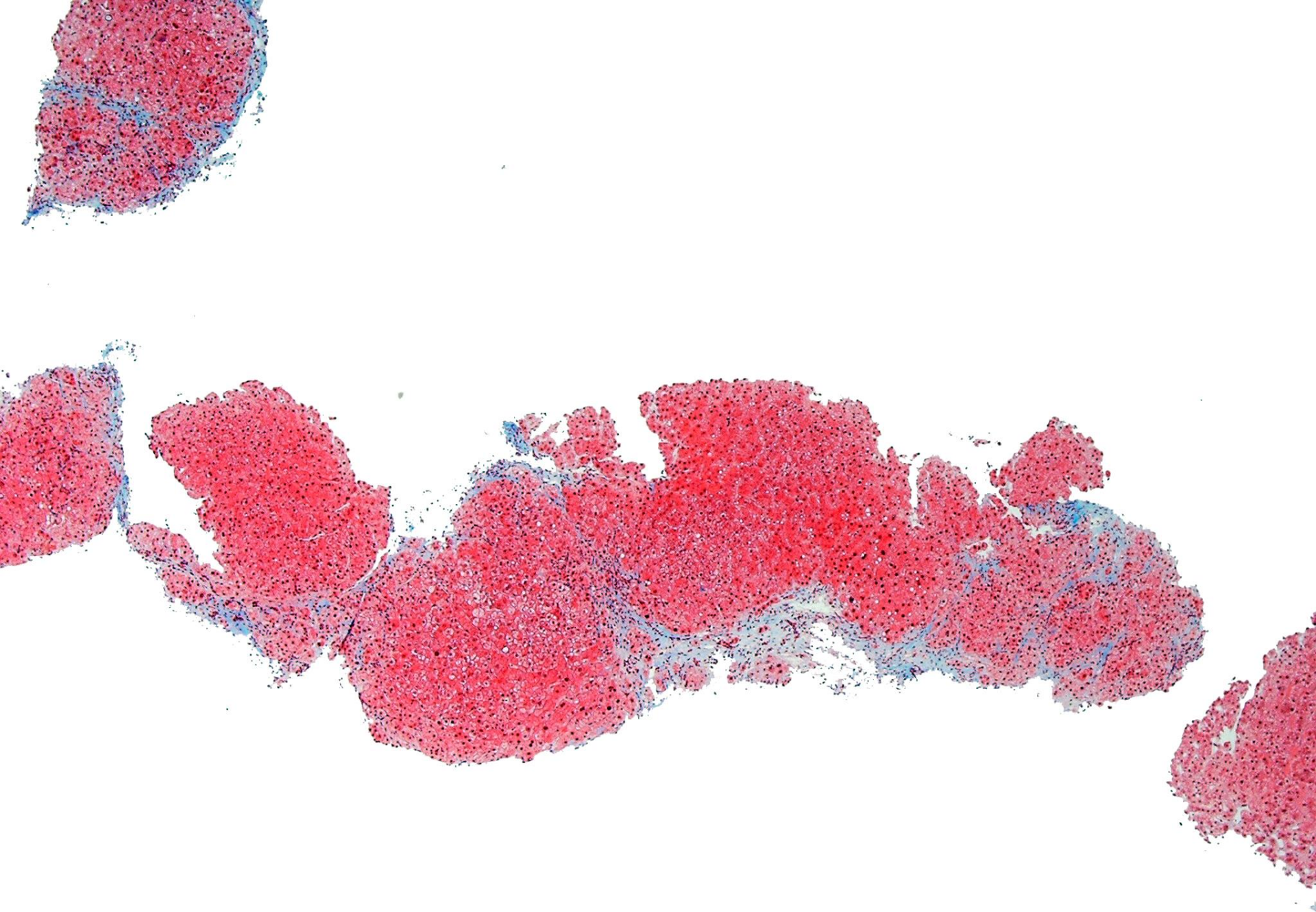
The trichrome and reticulin stains reveal portal and periportal fibrosis. The portal tracts are expanded by dense, predominantly lymphoplasmacytic inflammatory cell infiltrates, with admixed neutrophils and eosinophils. There is extensive interface activity, with associated foci of adjacent parenchymal dropout. Some of the native bile ducts appear injured, and there are areas of prominent bile ductular proliferation. The lobules are notable for moderate hepatocellular and canalicular cholestasis with associated hepatocellular ballooning degeneration. Frequent clusters of inflammatory cells, including neutrophils, and occasional acidophil bodies are also evident. An iron stain reveals mild iron deposition in scattered Kupffer cells and rare hepatocytes.

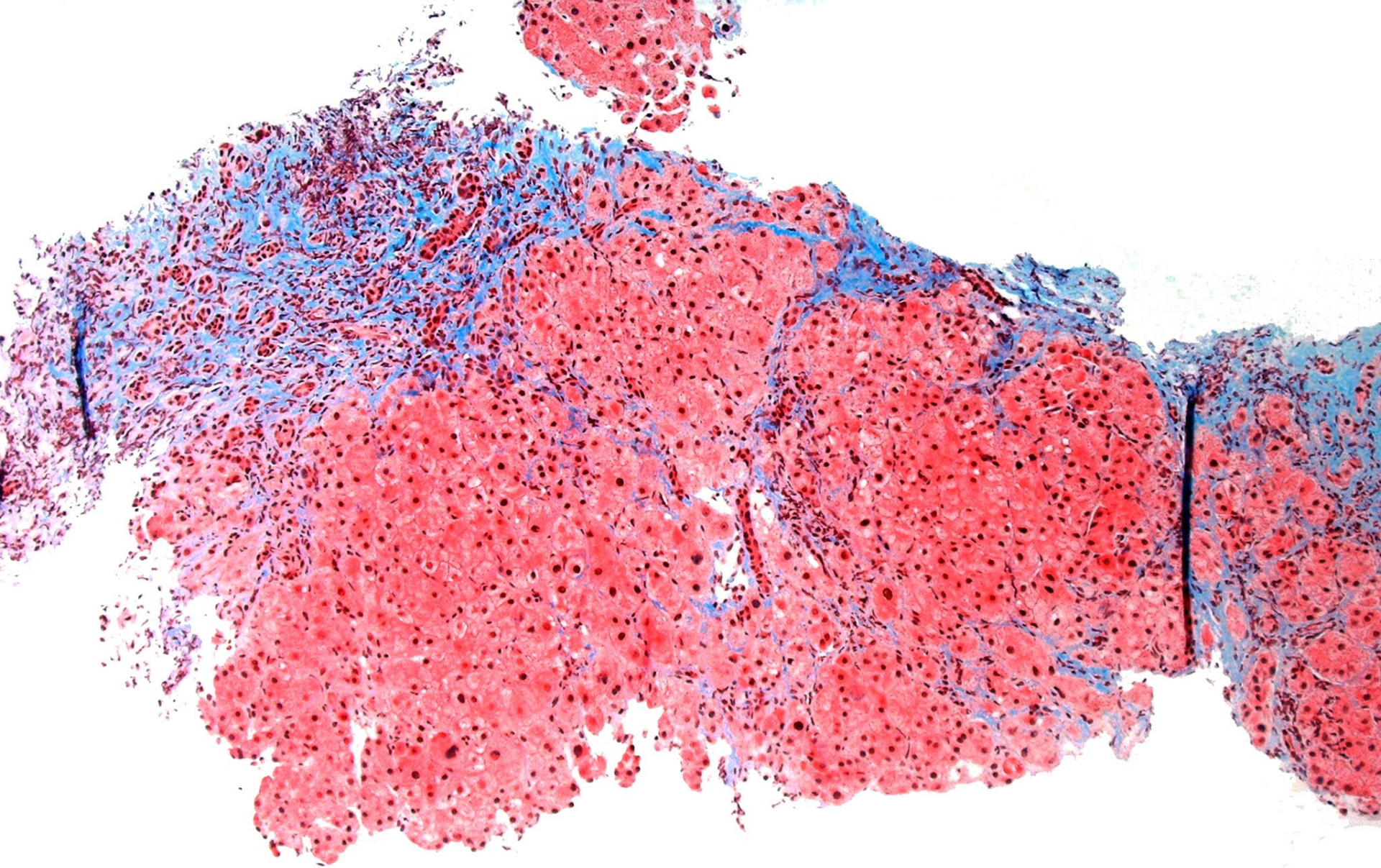
The above findings are consistent with chronic HCV hepatitis with superimposed acute cholestatic hepatitis. Leading etiologic considerations for the patient's acute cholestatic hepatitis include drug-induced injury, viral infections (including hepatitis E virus), or mechanical biliary obstruction. Clinical correlation is necessary. The grade of the patient's chronic HCV hepatitis cannot be accurately assessed due to the presence of superimposed acute cholestatic hepatitis.

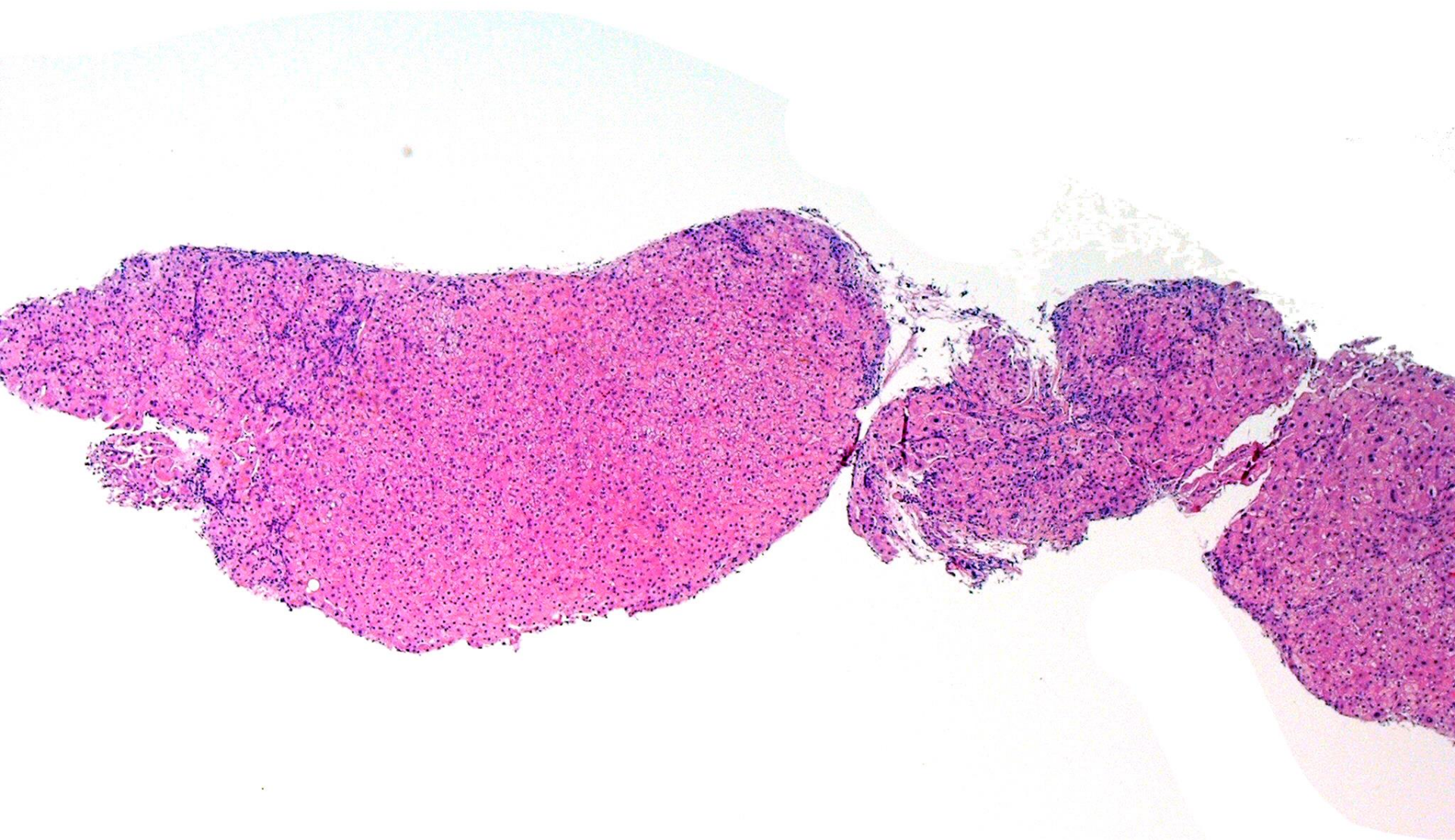
Serum HEV IgM positive (Mayo)

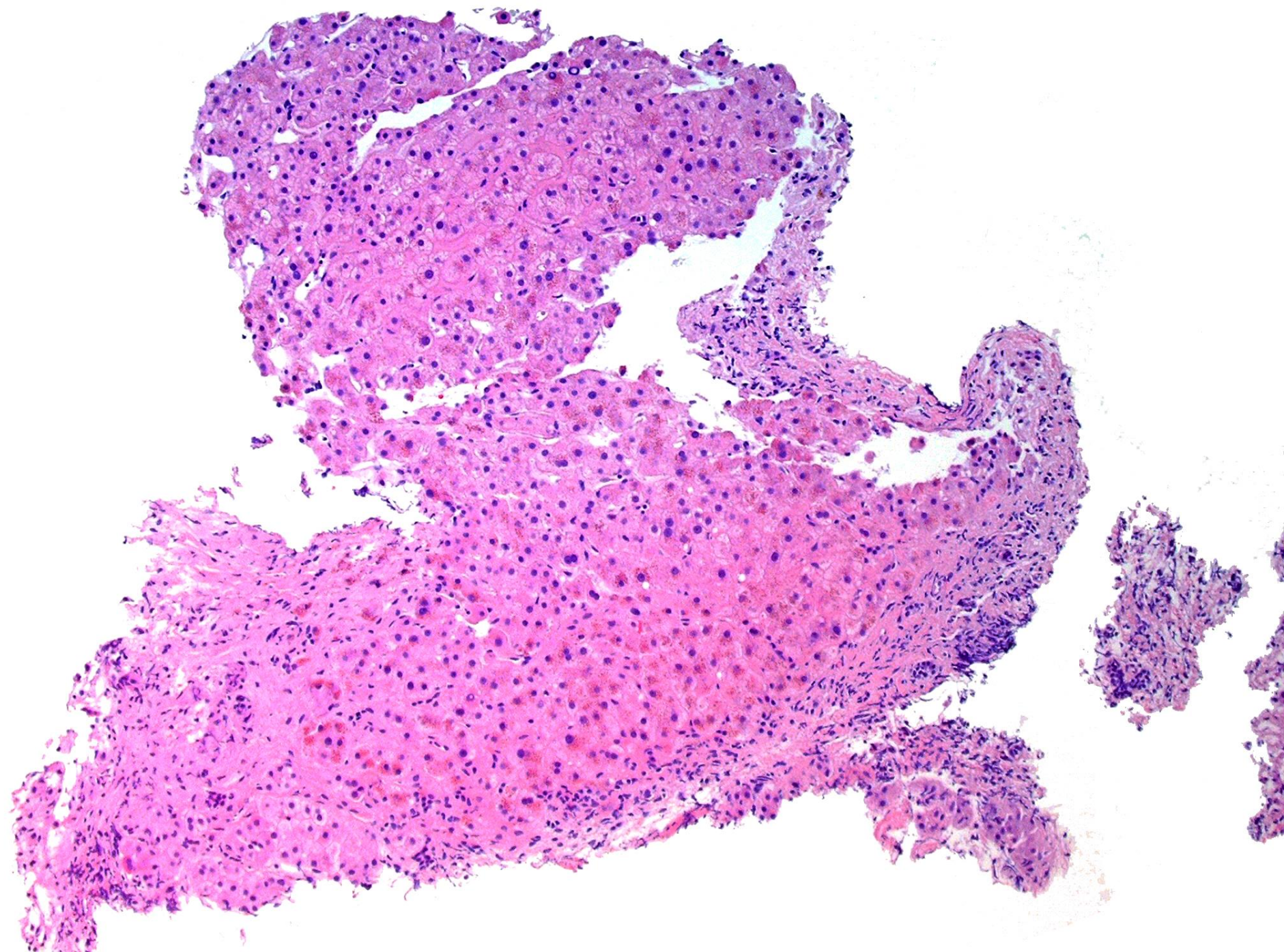
Case 55: Clinical History

- 15 y.o. previously healthy female with attention deficit hyperactivity disorder (ADHD)
- Presents with 3 day Hx of fatigue, malaise, mild abdominal pain
- Also noted headache, dizziness, & blurred vision, and her urine had become progressively darker
- Came to the ER when her mother noticed yellowing of the whites of her eyes
- No medications, alcohol, herbal remedies or drugs
- No travel history, exposure to animals, transfusions
- PE: jaundice, no hepatosplenomegaly, no stigmata of chronic liver disease
- TB = 15.4, CB = 10.0, AST = 91, ALT = 15, alk phos = 33
- Alb = 2.7, PT = 21.9, PTT = 33.0, INR = 2.1
- WBC = 9700, Hg = 5.6, HCT = 16.4









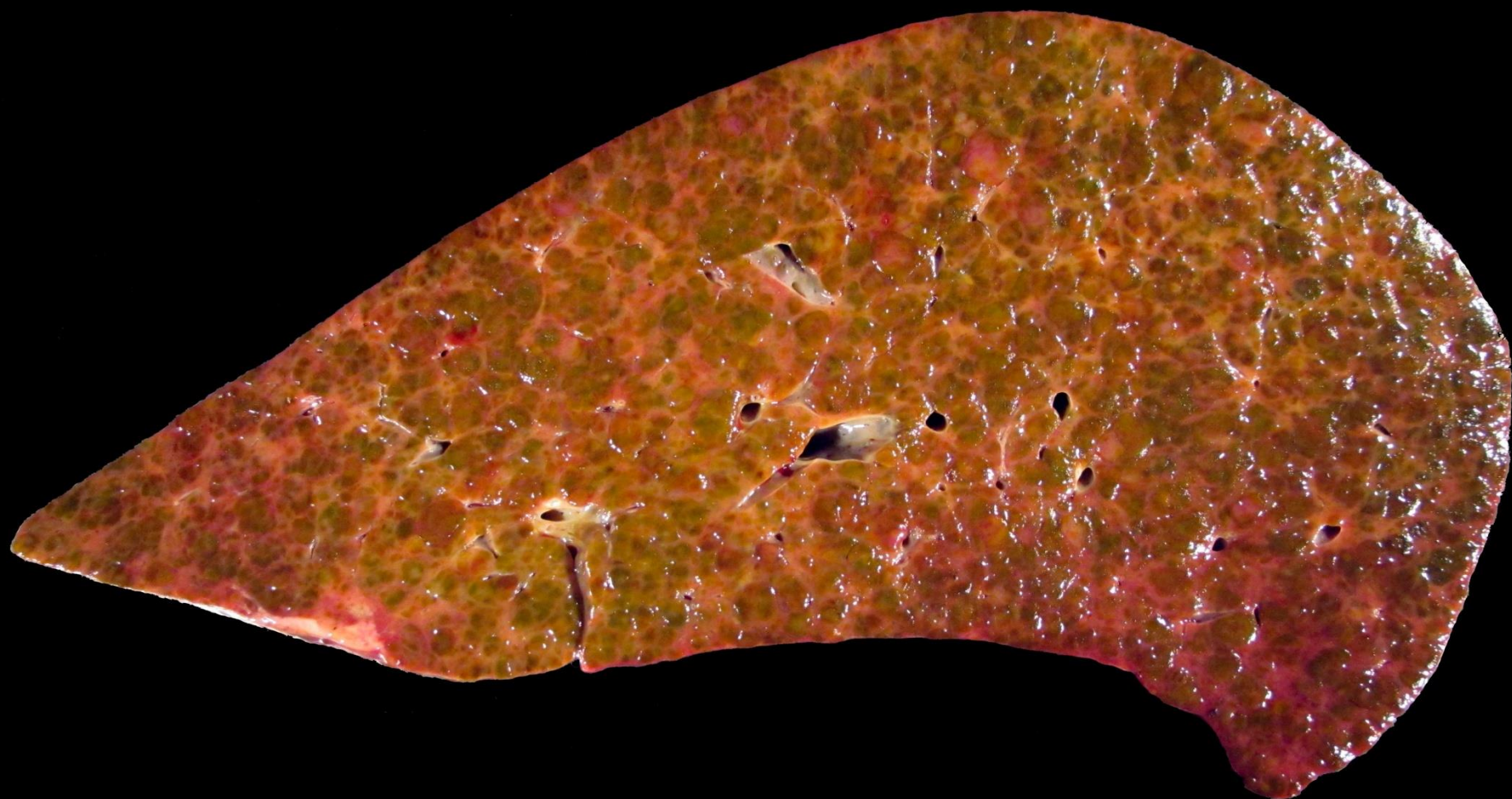


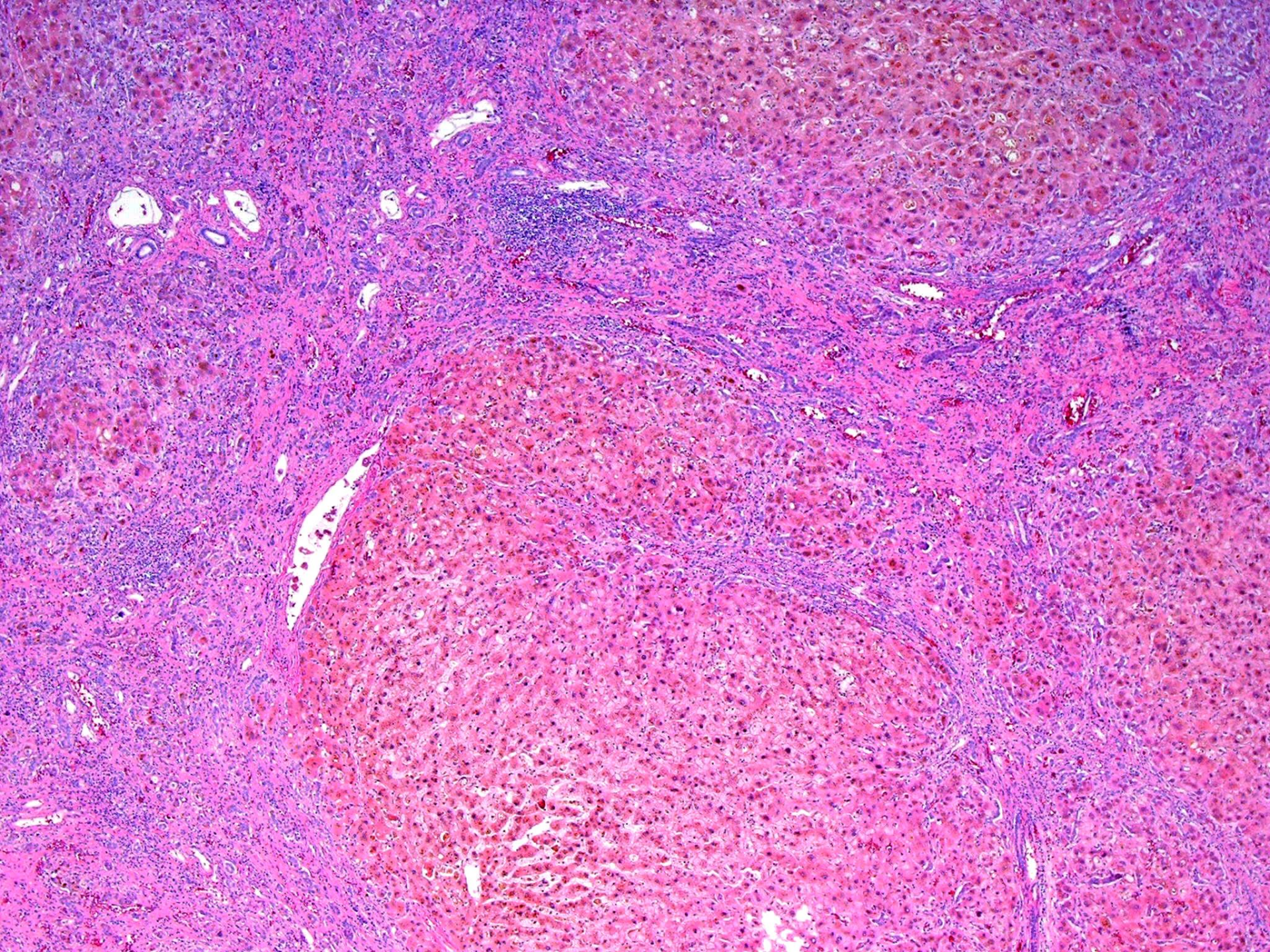
Additional Work-up

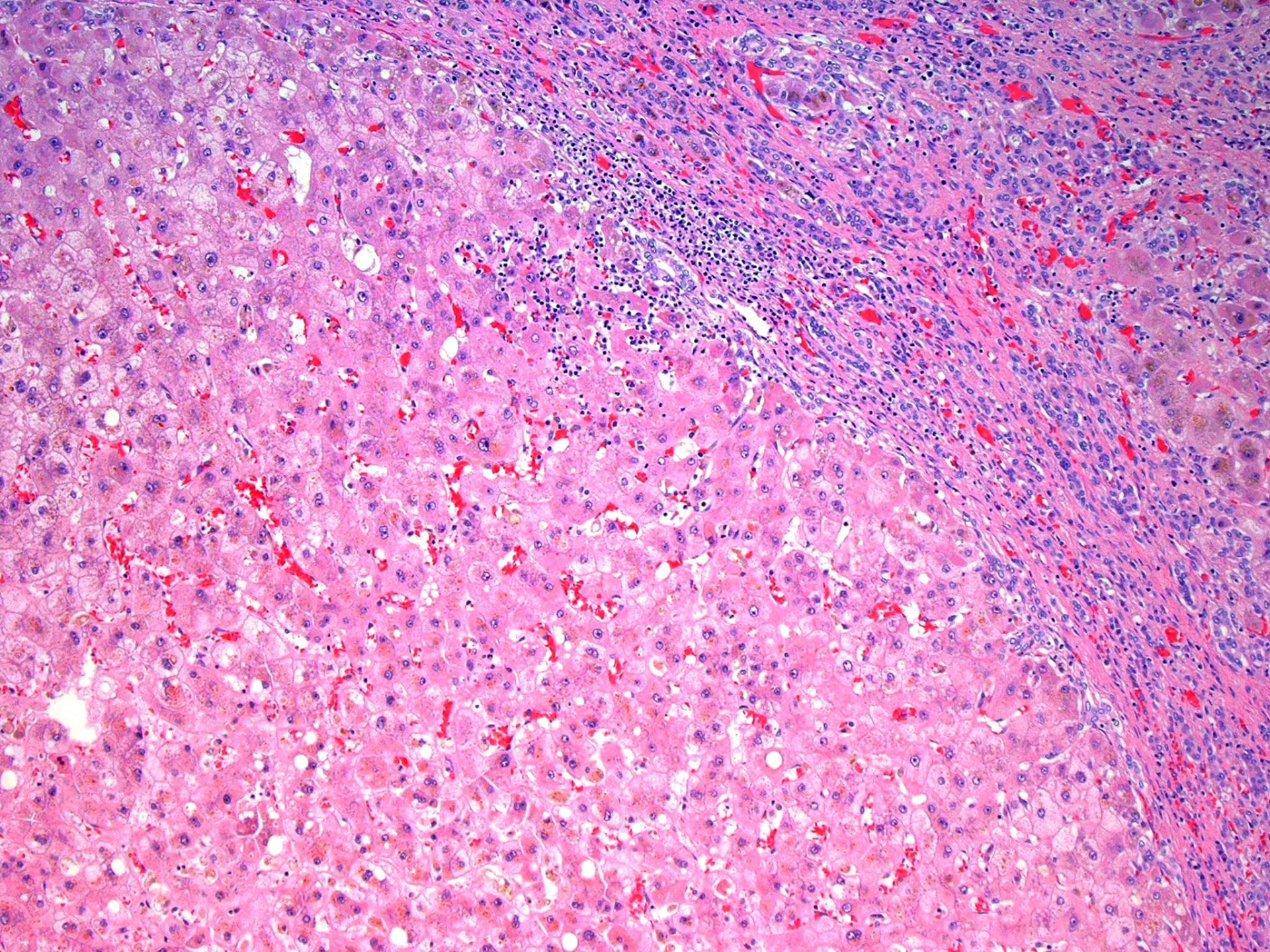
- **ANA = 1:160, anti-SMA = 25**
- **Anti-LKM and anti-dsDNA negative**
- **a-lpha-1-antitrypsin = 185**
- **HAV, HBV, HCV negative**
- **Needle liver biopsy**
-
- **Kieser Fleisher rings identified upon slit lamp examination**
- **Treatment with trientine begun for Wilson's disease**

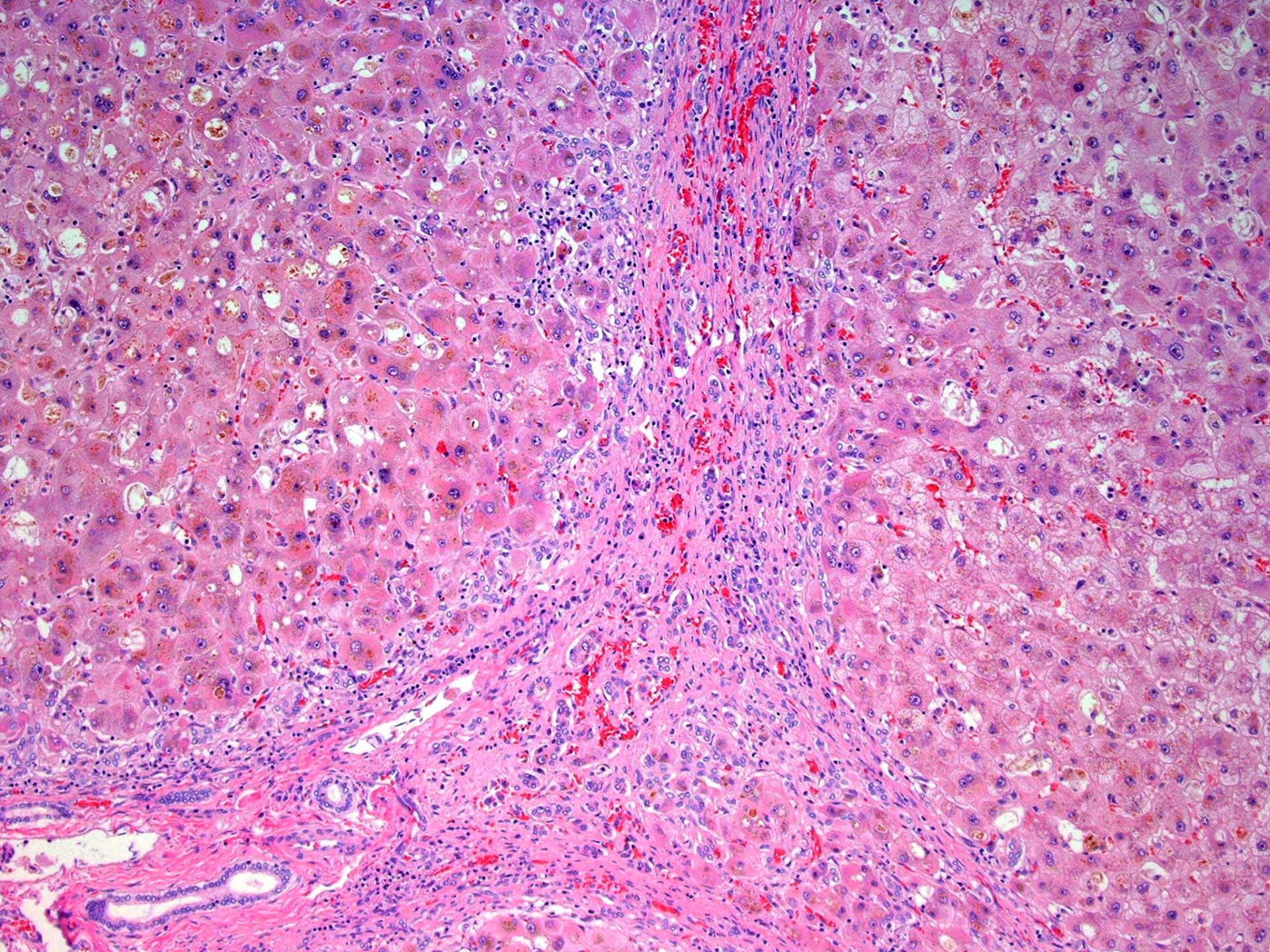


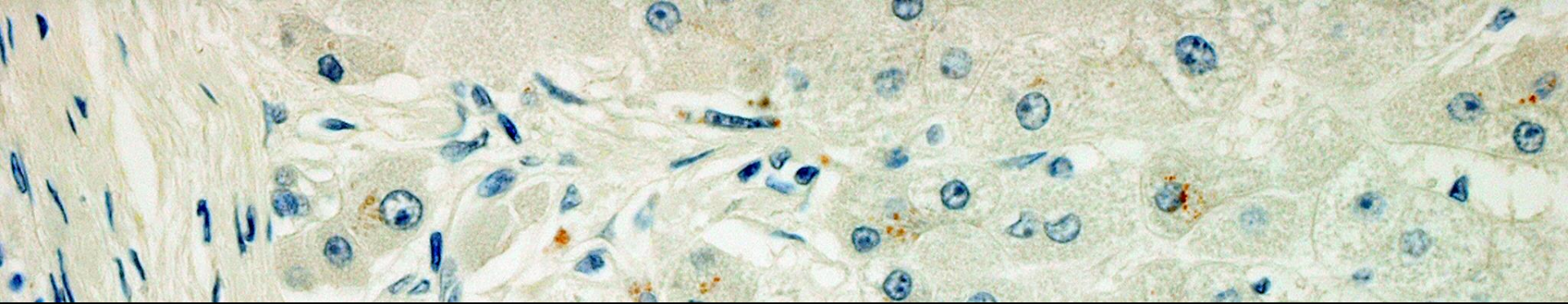
1550 g



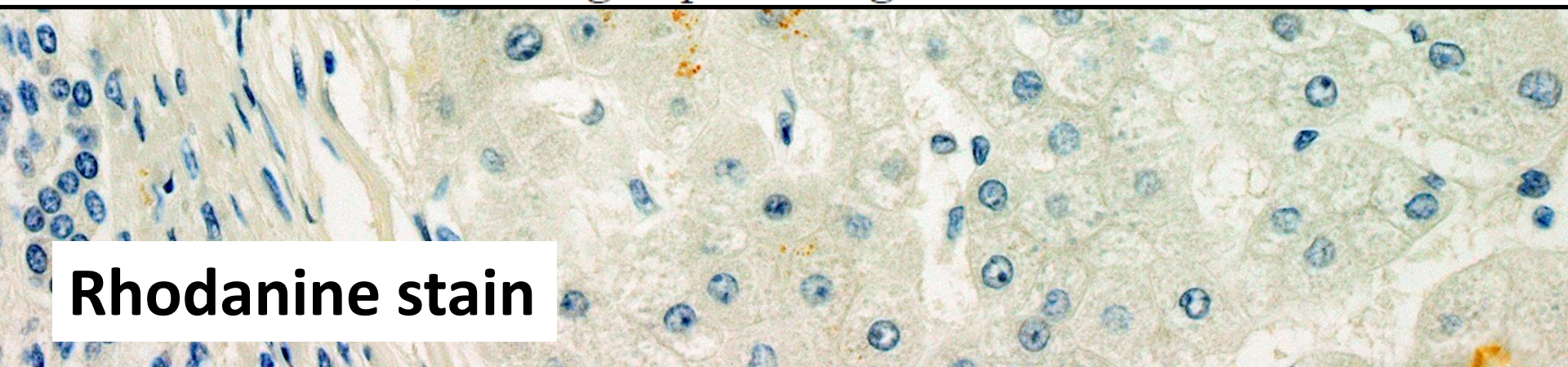








Test	Flat Results	Unit	Reference Value
REPORTED: 11/03/2011			
Copper, liver Ts	H 1506	mcg/g dry wt	10-35
VERY HIGH. This finding is strongly suggestive of Wilson Disease. If this finding is without supporting histology And other biochemical test results, contamination during Collection, handling or processing should be considered.			



Rhodanine stain

- **Histologic pattern:**
 - **Chronic hepatitis with cirrhosis**
- **Diagnosis:**
 - **Wilson disease (stage 4)**
- **Take home points:**
 - **Wilson disease can mimic chronic hepatitis in adults (and steatosis/NASH in children)**
 - **Clues for the diagnosis of Wilson disease:**
 - **Coombs negative hemolytic anemia**
 - **Acute presentation with cirrhosis on biopsy**
 - **Abnormally low serum alkaline phosphatase**
 - **“Seronegative ALH” that doesn’t respond to steroids**
 - **Neuropsychiatric symptoms**



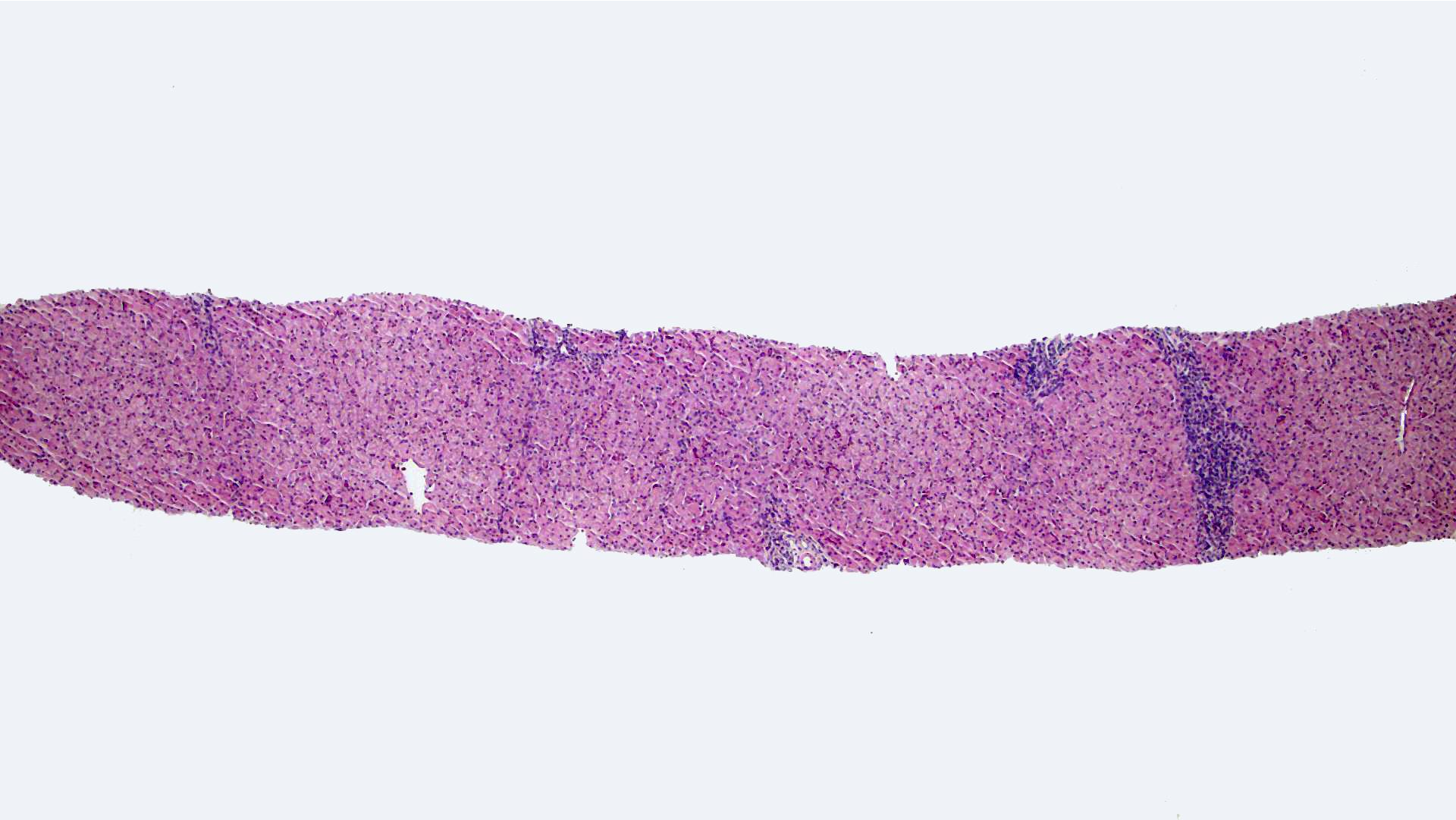
Case 181: Clinical History

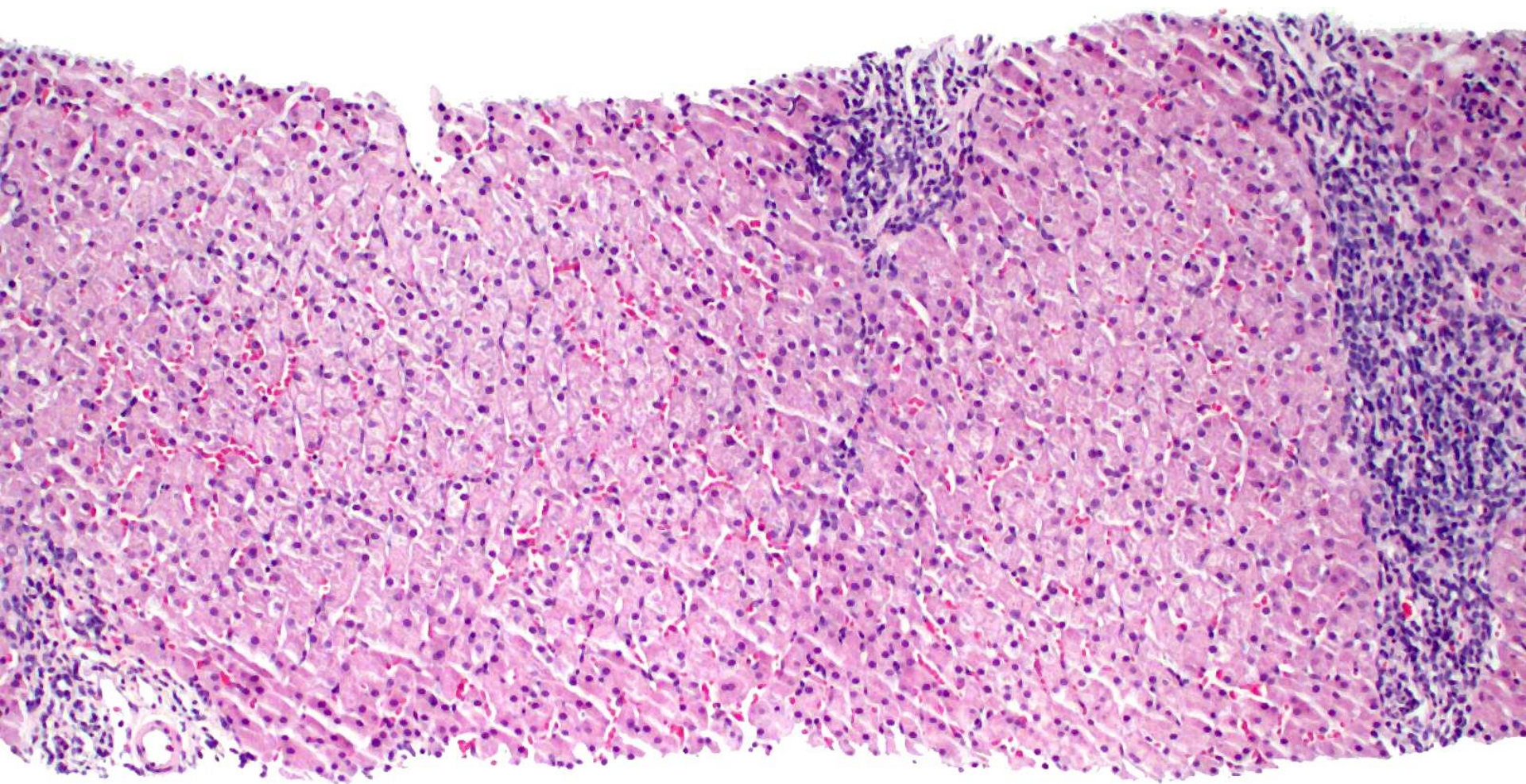
Case courtesy of Dr Y. Li, Advocate Christ Medical Center

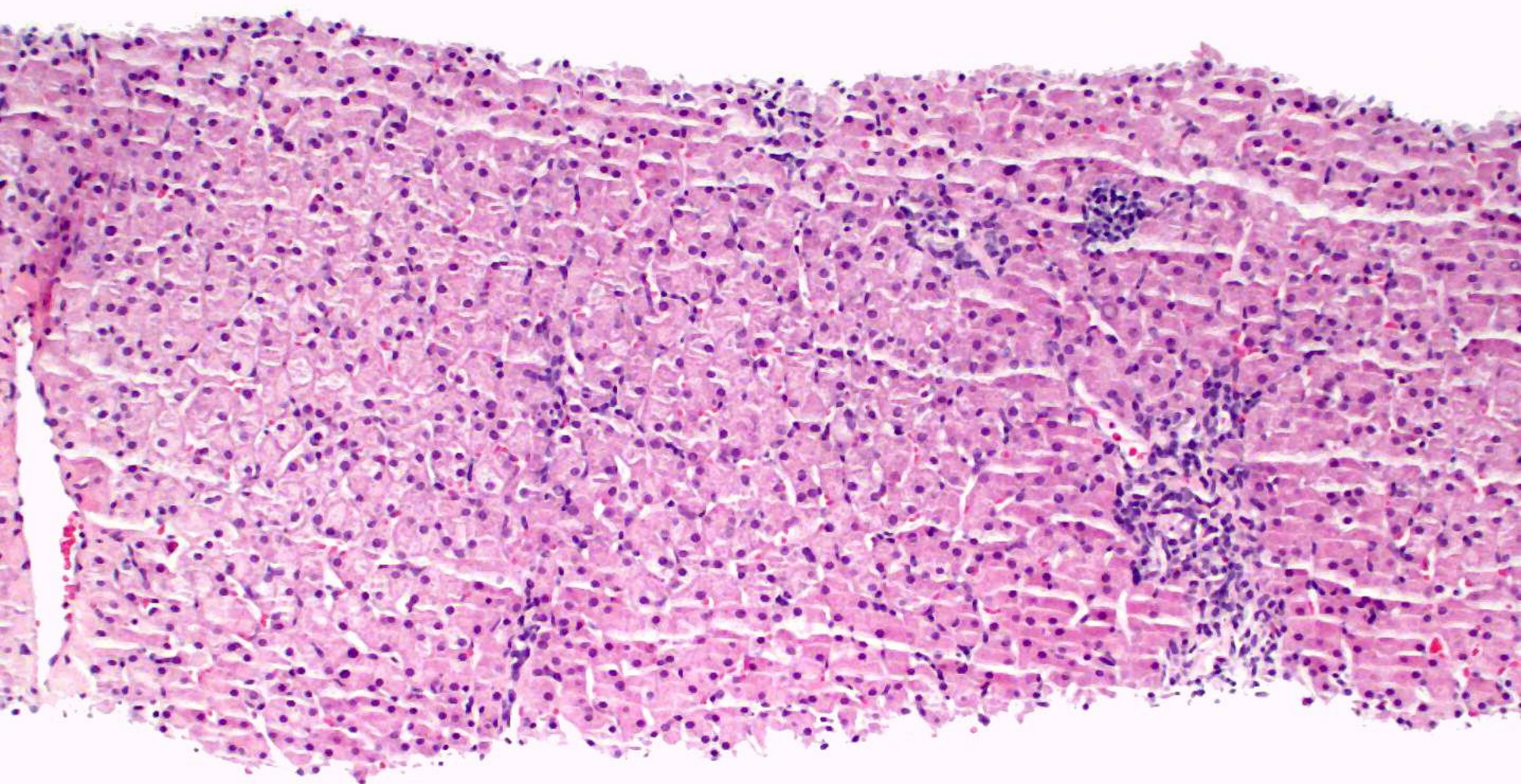
- 7 y.o. F presented with 3 wk Hx of N&V and diarrhea
- Abdominal CT scan was unremarkable
- Monospot test equivocal
- TB = 0.6, AST = 74, ALT = 71, alk phos = 155
- HAV, HBV, HCV, HEV negative
- ANA, anti-SMA, anti-LKM negative
- Ceruloplasmin normal; 24 hour urine copper normal
- Alpha-1-antitrypsin phenotype is PiMM
- No medications, supplements, toxic exposure
- No travel history
- No family history of liver disease

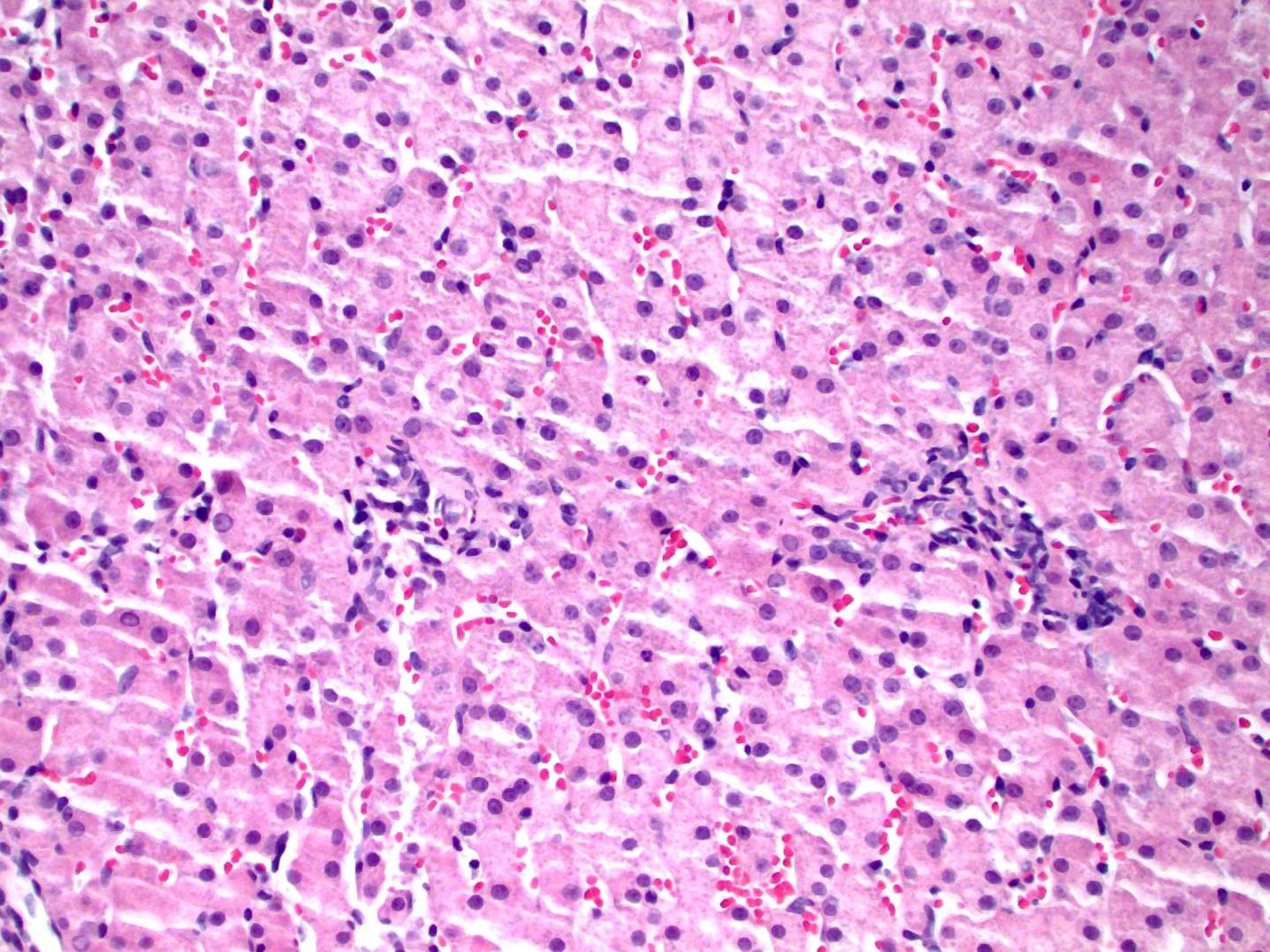
Clinical Follow-up

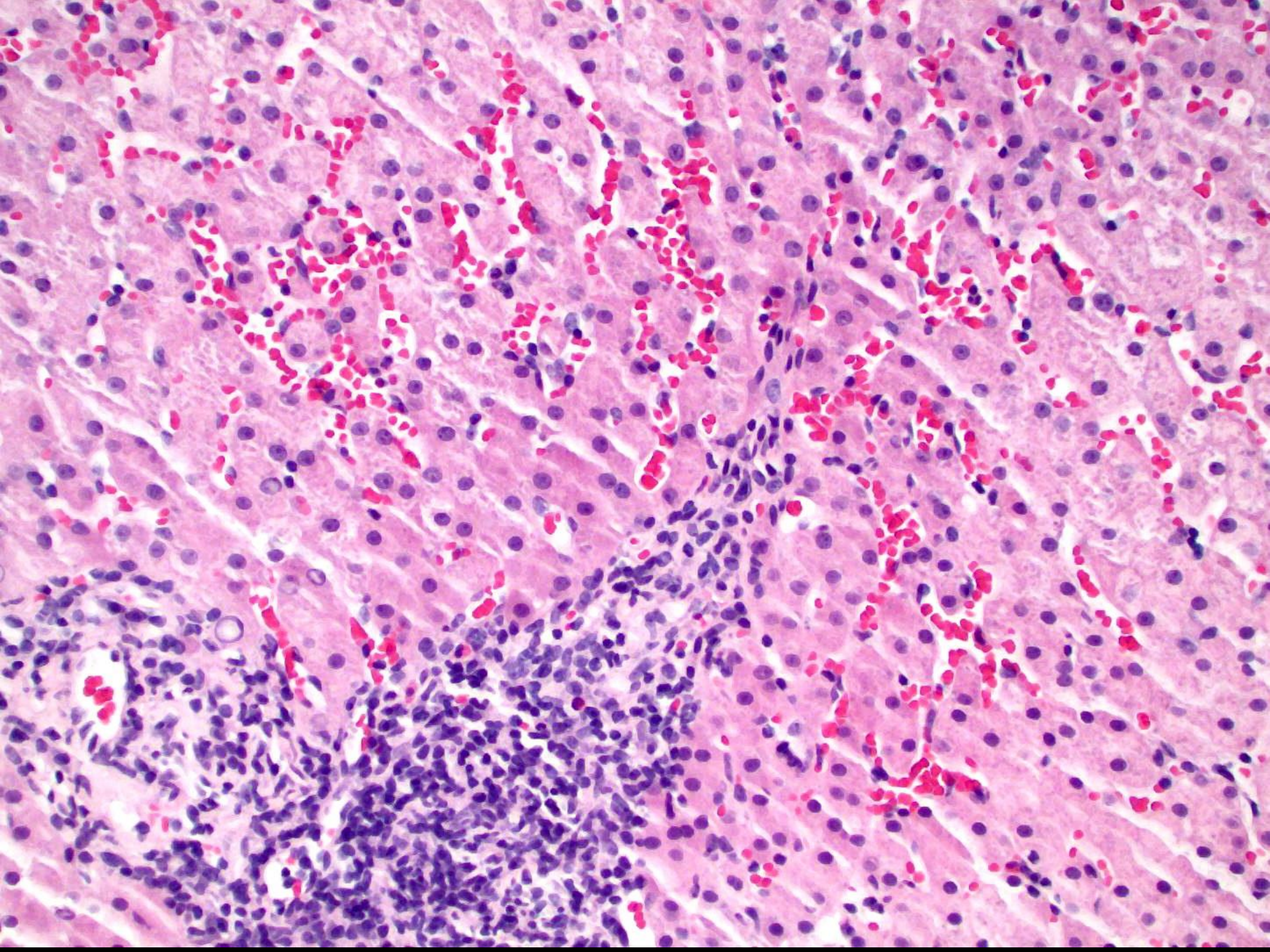
- **EBV serology negative**
- **After 3 mo LCTs remained abnormal**
- **Liver biopsy performed**











How to sign out this case?

- **DX: Mild portal & lobular inflammation**
- **Comment:**
 - There is no evidence of AIH
 - Not typical of EBV hepatitis
 - There is no fibrosis
 - Quantitative copper could be performed to rule out Wilson's disease
 - Could this be celiac disease???

The Liver in Celiac Disease

(HEPATOLOGY 2007;46:1650-1658.)

Alberto Rubio-Tapia and Joseph A. Murray

Table 1. Histological Findings in the Livers of Patients with Celiac Disease

Nonspecific abnormalities (most common)
Periportal inflammation
Increased number of Kupffer cells
Mononuclear infiltration on the portal triad
Steatosis
Microvesicular and macrovesicular
Fibrosis
Cirrhosis

Table 2. Abnormal Liver Chemistry Tests and Effects of a Gluten-Free Diet in Patients with Celiac Disease

Reference	Cases	Abnormal Liver Tests (%)	Responses to a Gluten-Free Diet (%)*
Hagander et al. ⁶	53	39	N/A
Bardella et al. ⁷	158	42	95
Bonamico et al. ⁸	65	57	N/A
Novacek et al. ¹⁶	176	40	96
Jacobsen et al. ²³	171	47	75

False positive TTG can occur in chronic liver disease; anti-endomysial Ab more specific

Chance

**One
Free
Wrong
Diagnosis!**

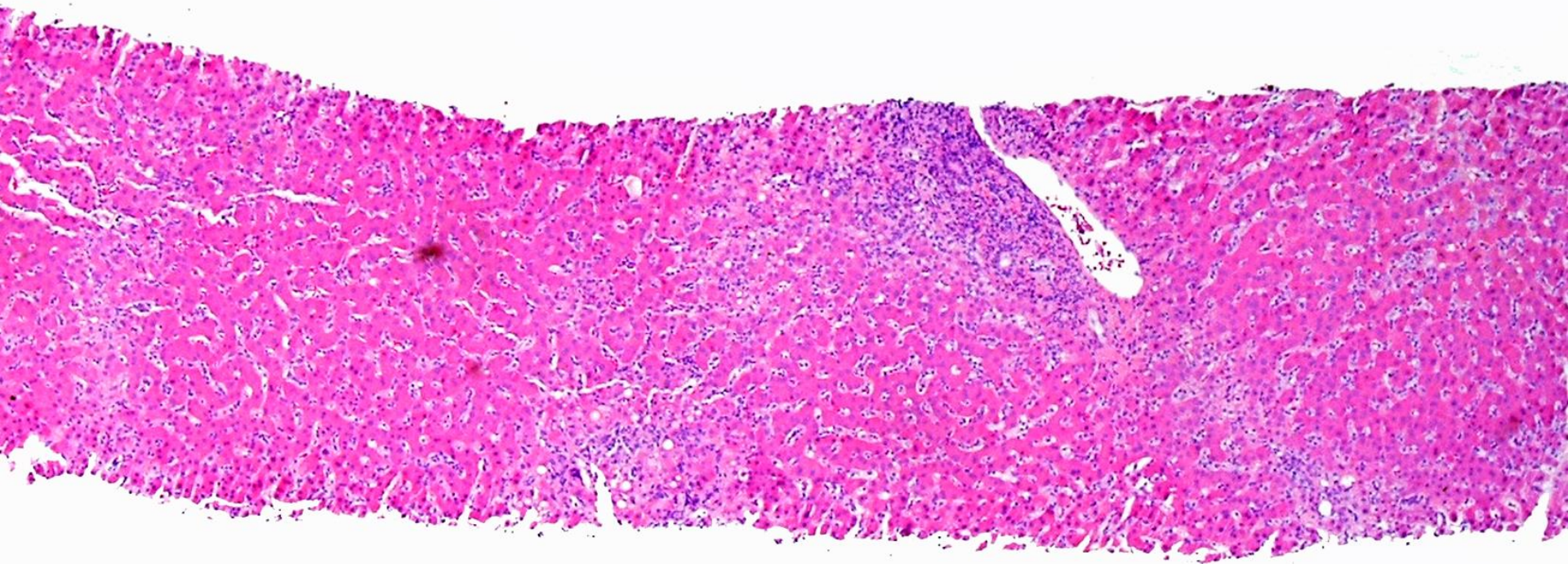


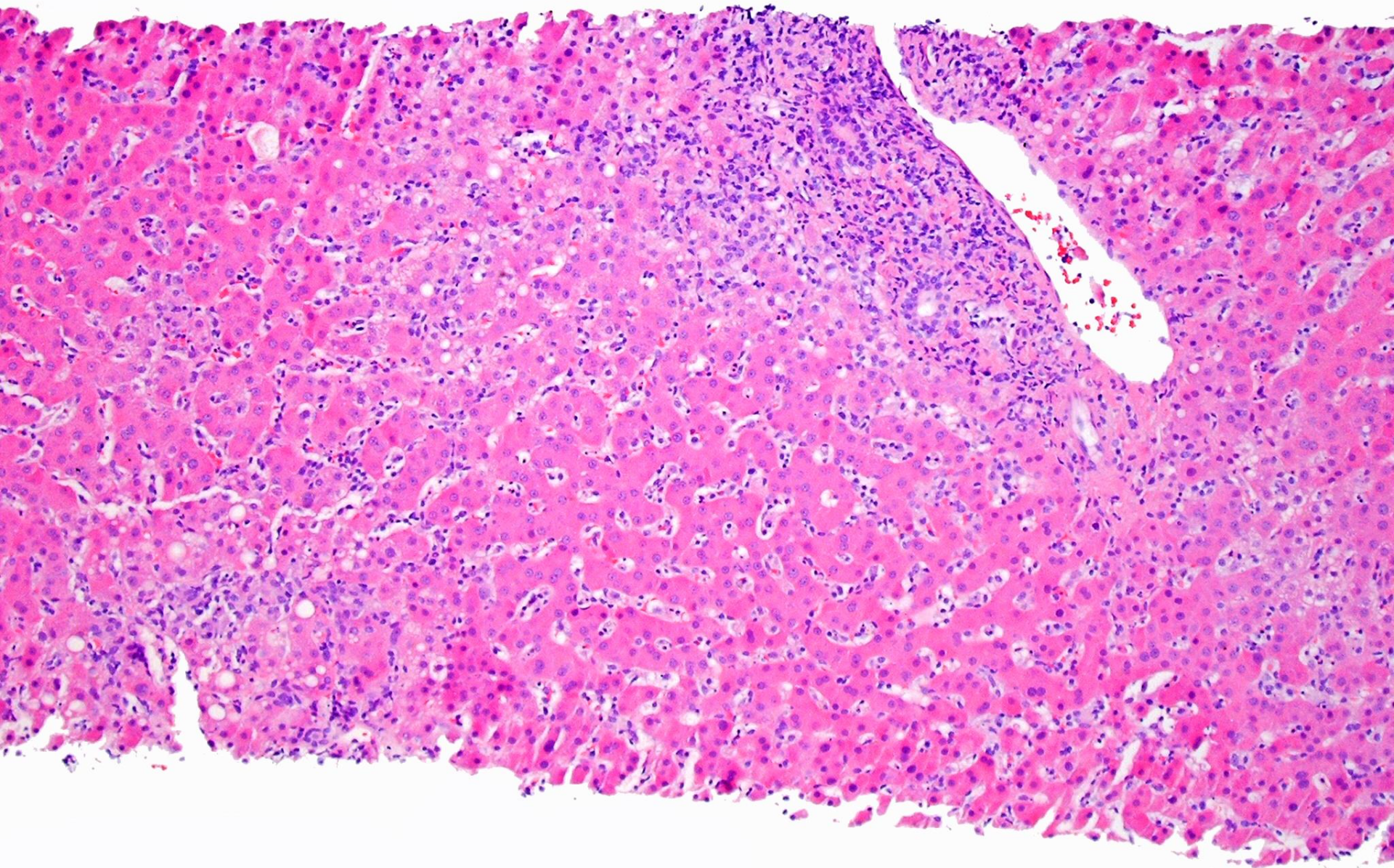
- **Histologic pattern:**
 - **Chronic hepatitis mimic**
- **Diagnosis:**
 - **Mild portal and lobular inflammation**
- **Take home points:**
 - **Don't diagnose chronic hepatitis by reflex**
 - **Don't forget about celiac disease!**

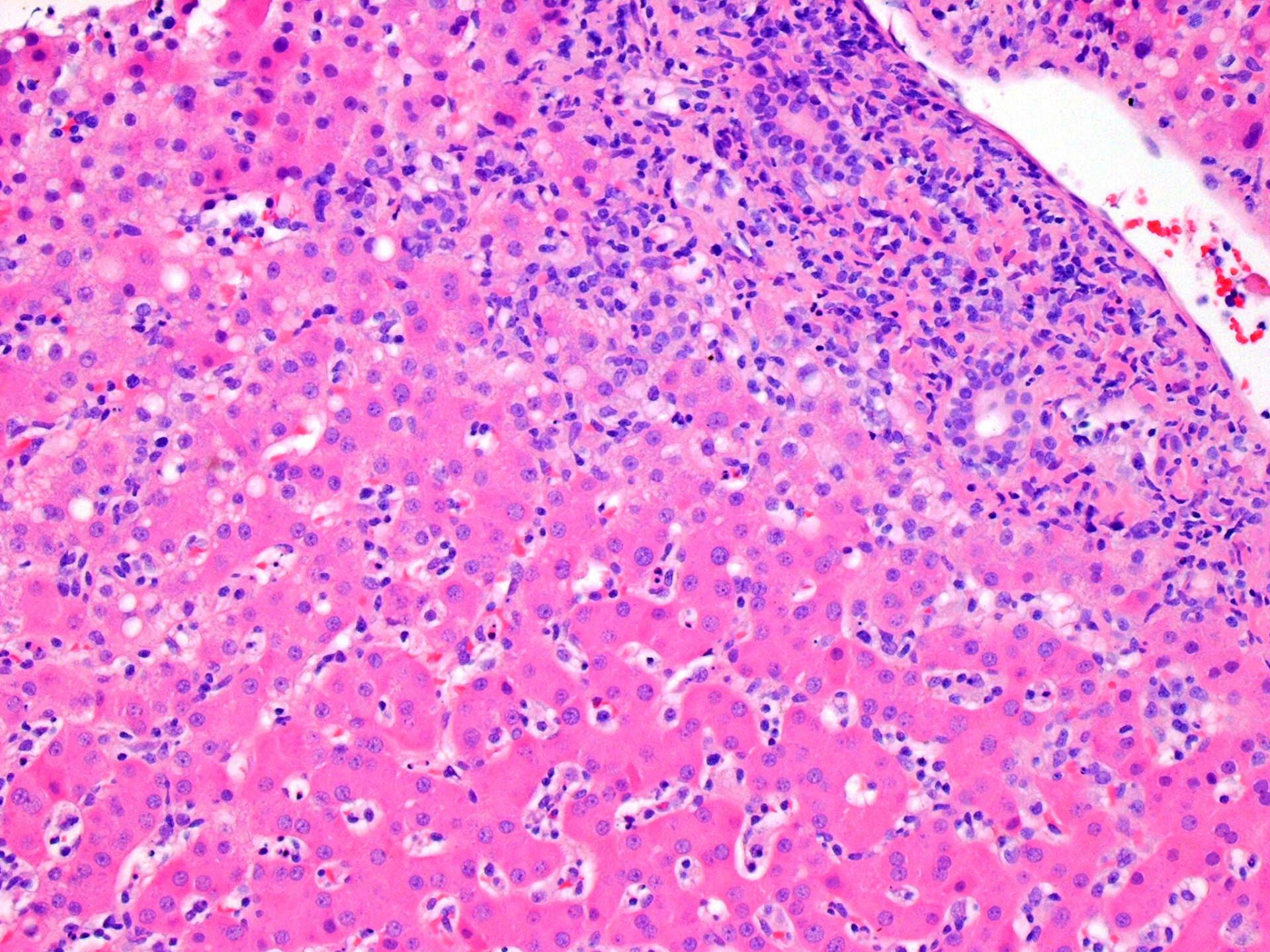
Case 51: Clinical History

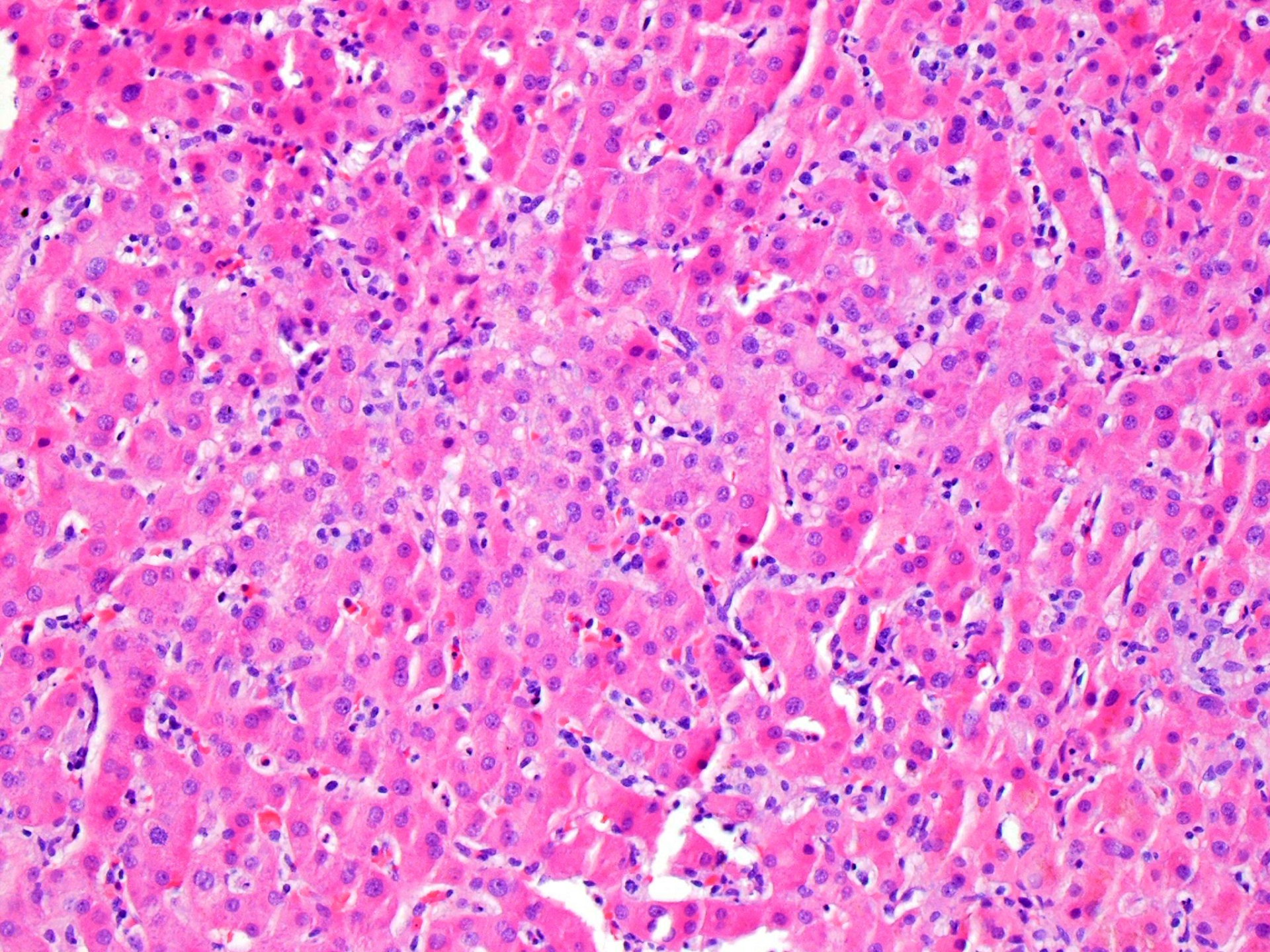
**Case courtesy of Dr. R. Hennaway
Lourdes Medical Center, Camden NJ**

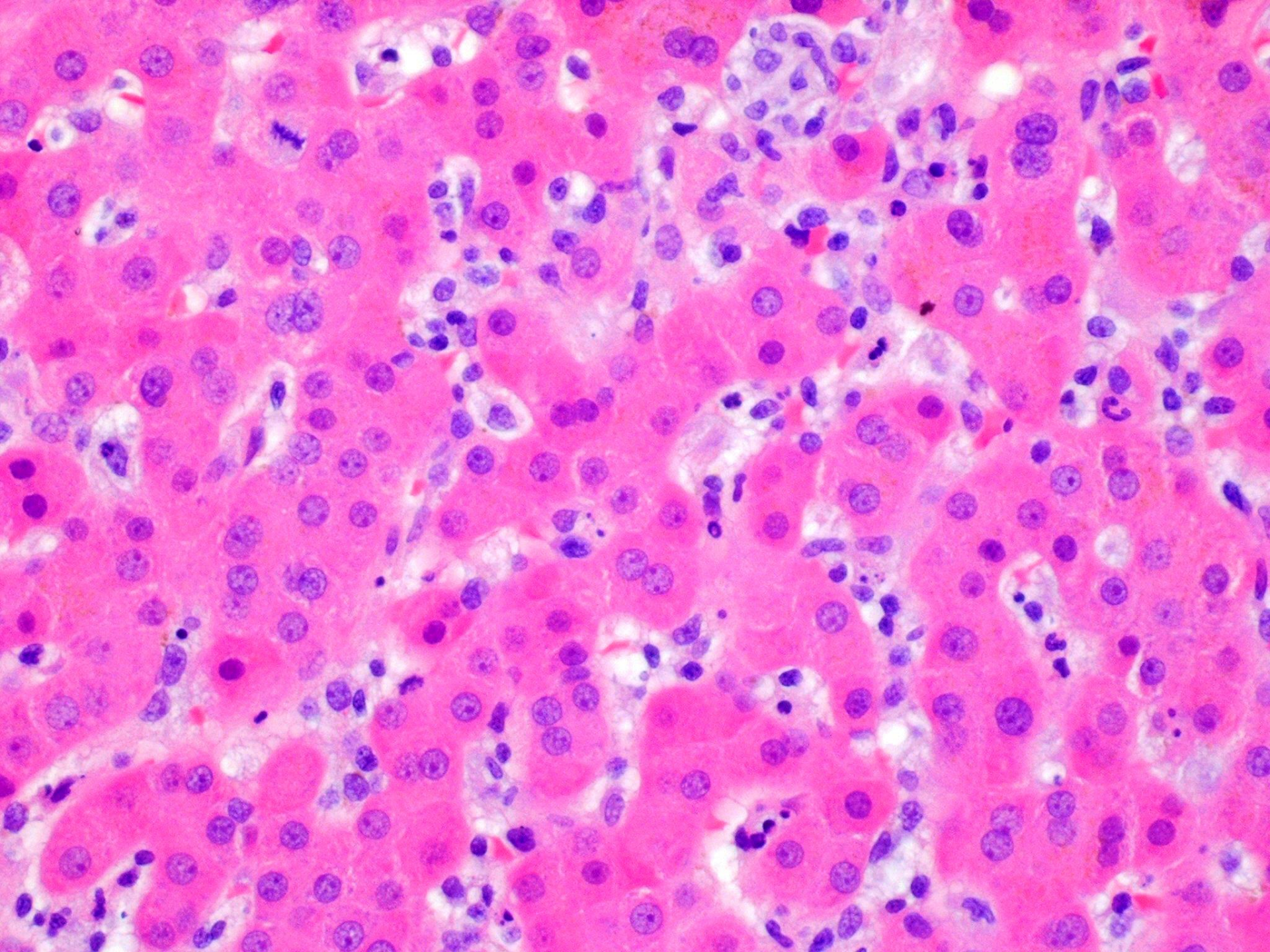
- 19 y.o. M presents with fever, chills, rigor, and N&V
- Admitted when fevers increased and fatigue developed
- TB = 1.2, AST = 95, ALT = 105, alk phos = 225
- HAV, HBV, HCV negative; ANA 1:40
- CT scan reveals:
 - Hepatosplenomegaly
 - Fatty infiltration of the liver
 - Thickening of the gallbladder wall – placed on Zosyn
- TB = 1.5, AST = 122, ALT = 144, alk phos = 212
- Liver biopsy: Drug vs AIH vs Wilson











A histological slide showing a tissue section stained with hematoxylin and eosin (H&E). The tissue is composed of numerous cells, many of which are large and have prominent nuclei. Some cells show dark, dense staining in their nuclei, which is characteristic of EBER-positive cells. A black rectangular box is overlaid on the lower right portion of the slide, containing the text "Serum EBV IgM positive".

Serum EBV IgM positive

EBER

Lobular Hepatitis

Symptoms: non-specific constitutional symptoms; jaundice

Liver chemistry tests: mild inc. AST & ALT >>> Alk phos and TB low

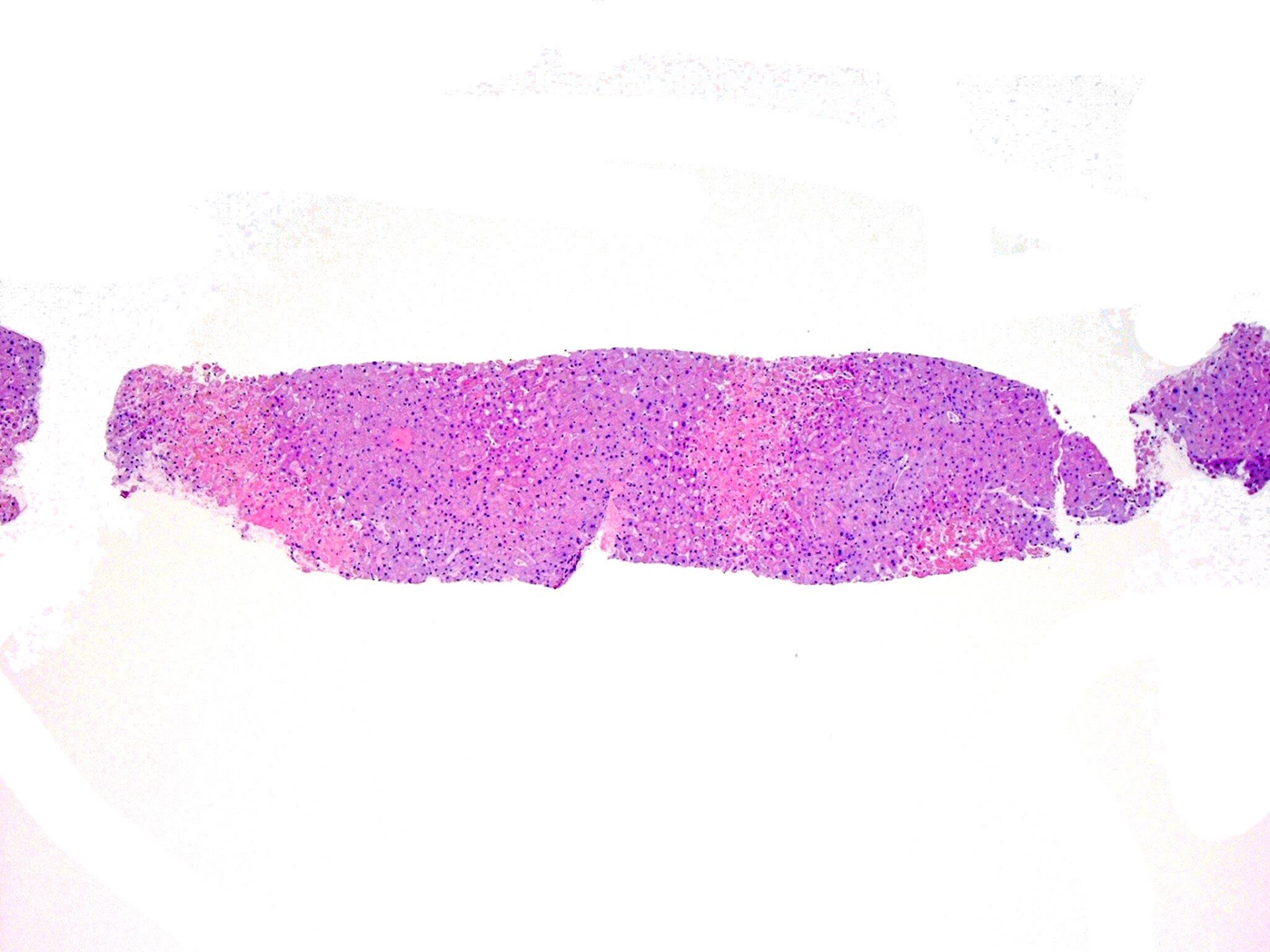
**Histologic pattern: sinusoidal mononuclear cell infiltrates;
no lobular disarray; minimal portal inflammation**

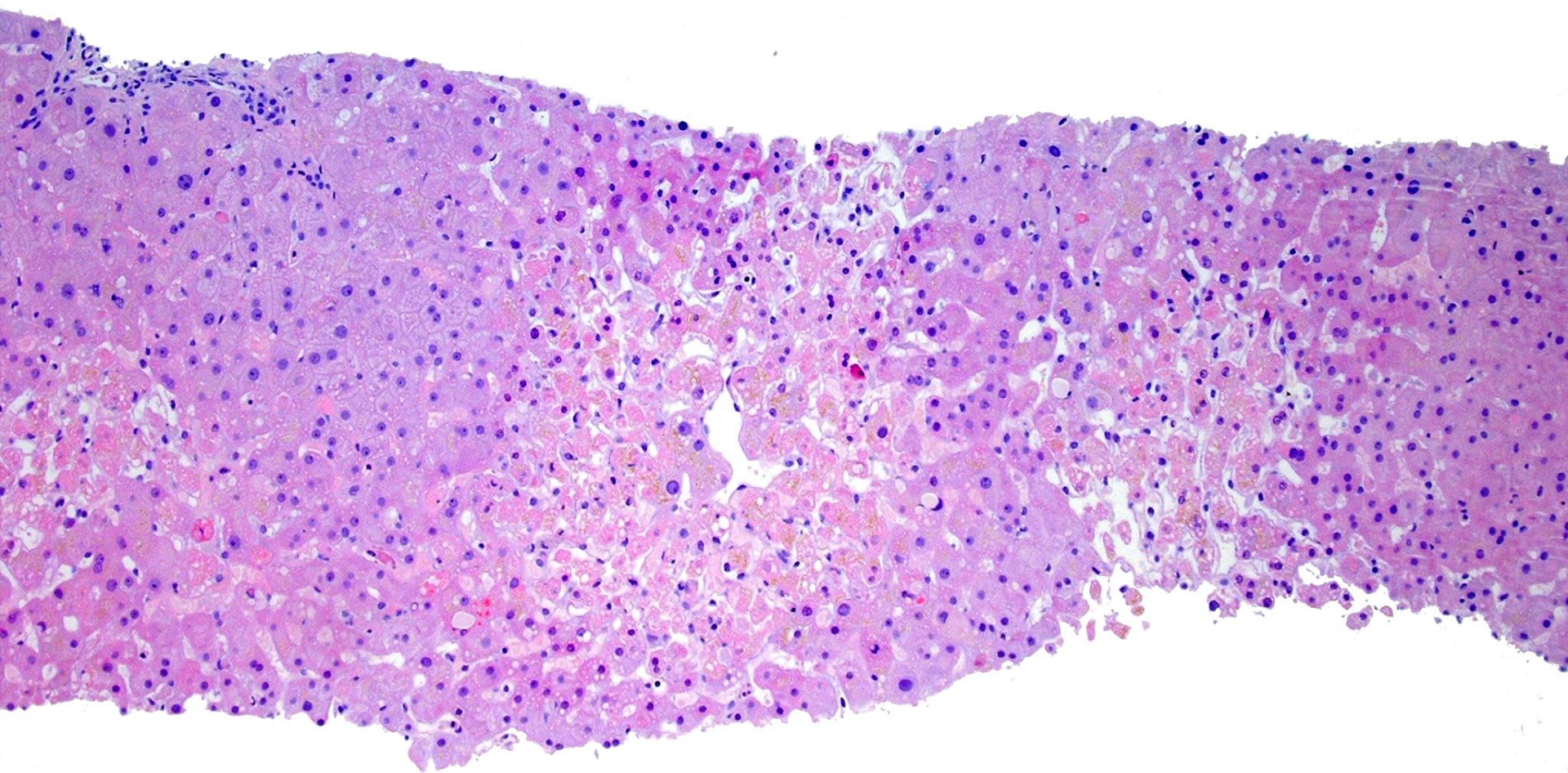
- **Drugs**
 - **Diphenylhydantoin**
 - **Para-aminosalicylic acid**
 - **Sulfonamides**
 - **Dapsone**
- **EBV hepatitis**
- **CMV hepatitis**
- **(Rubella and toxoplasmosis)**

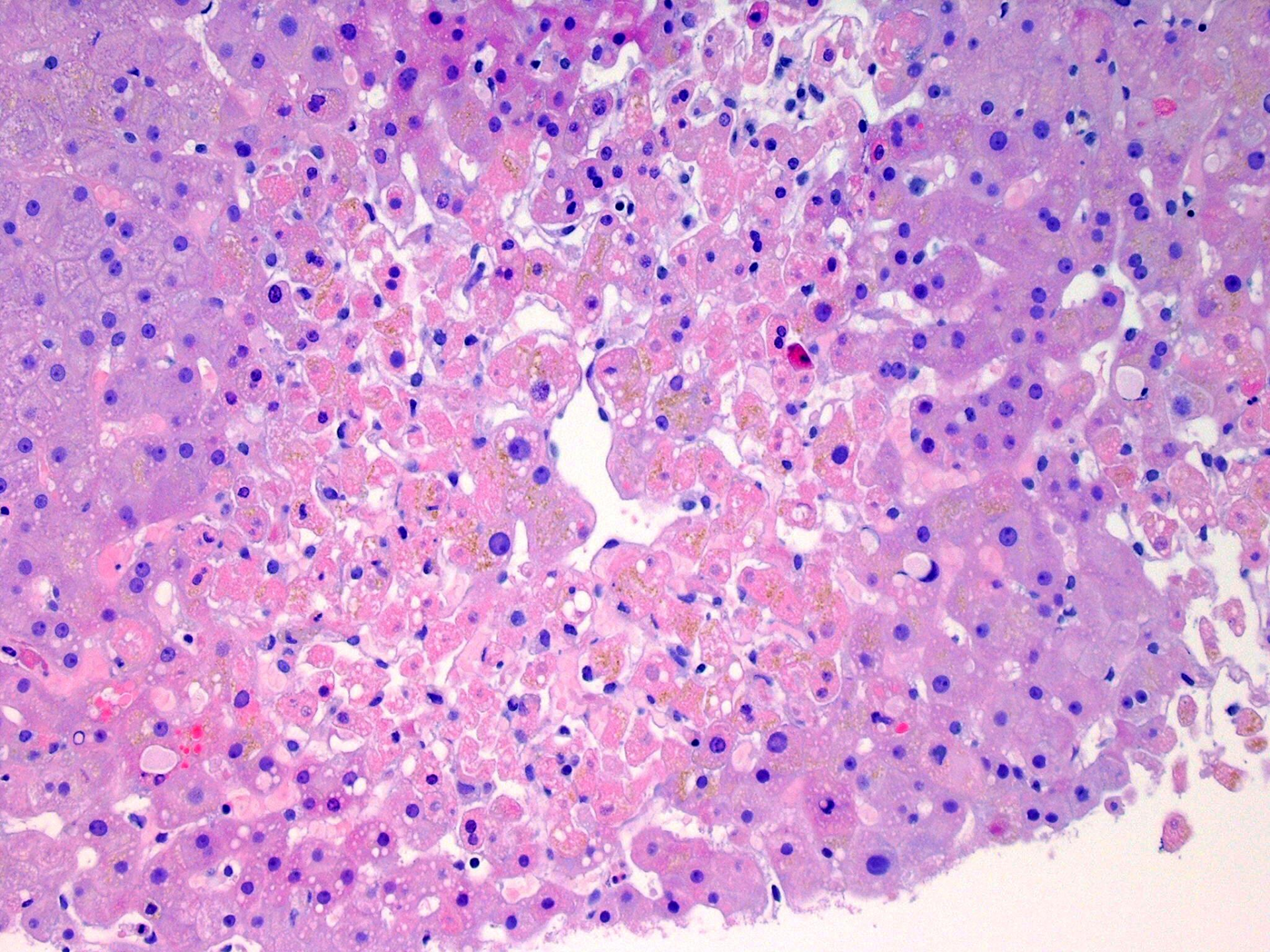
- **Histologic pattern:**
 - **Lobular hepatitis**
- **Diagnosis:**
 - **EBV hepatitis**
- **Take home points:**
 - **EBER highlights rare lymphocytes**
 - **Could be Dilantin too**

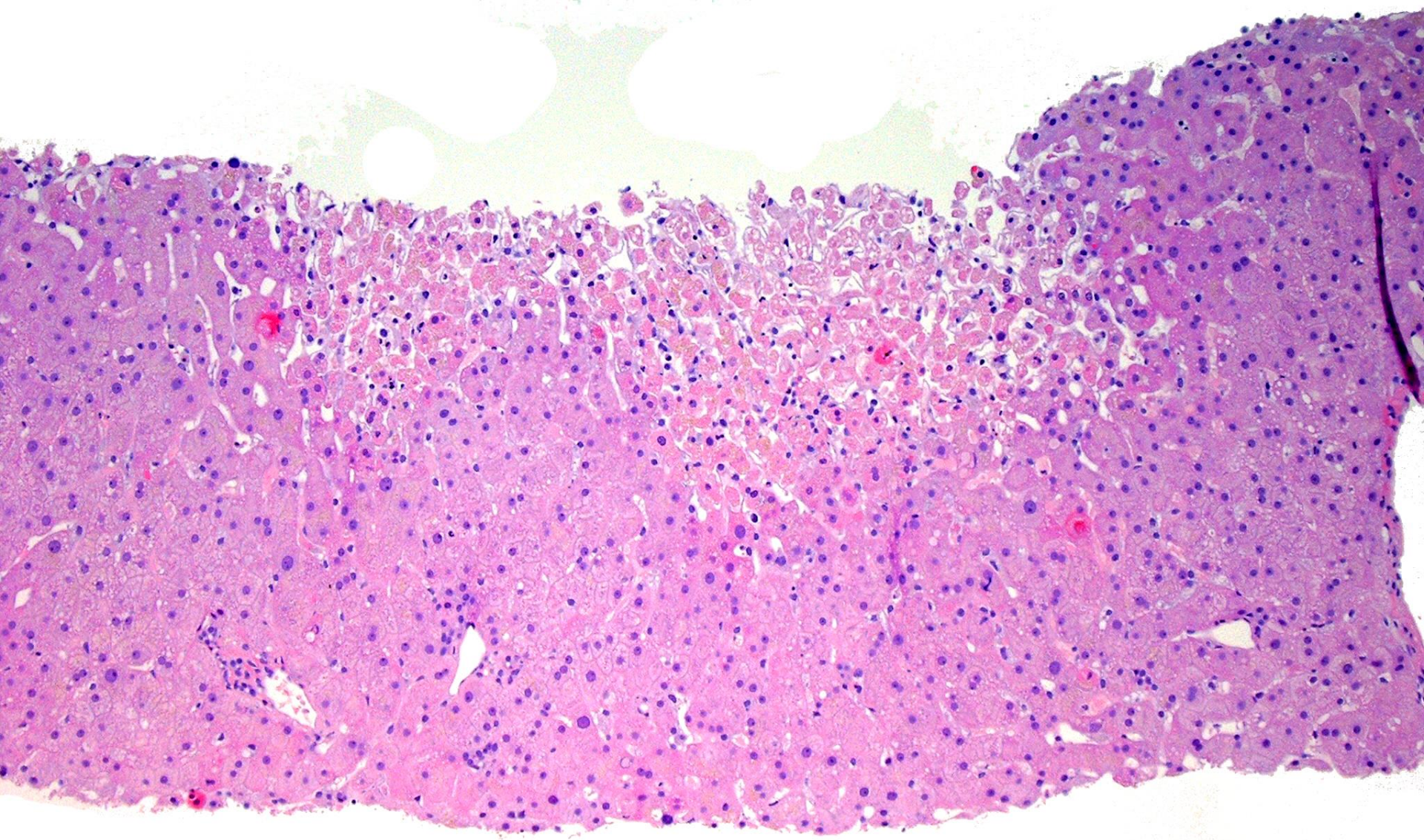
Case 96: Clinical History

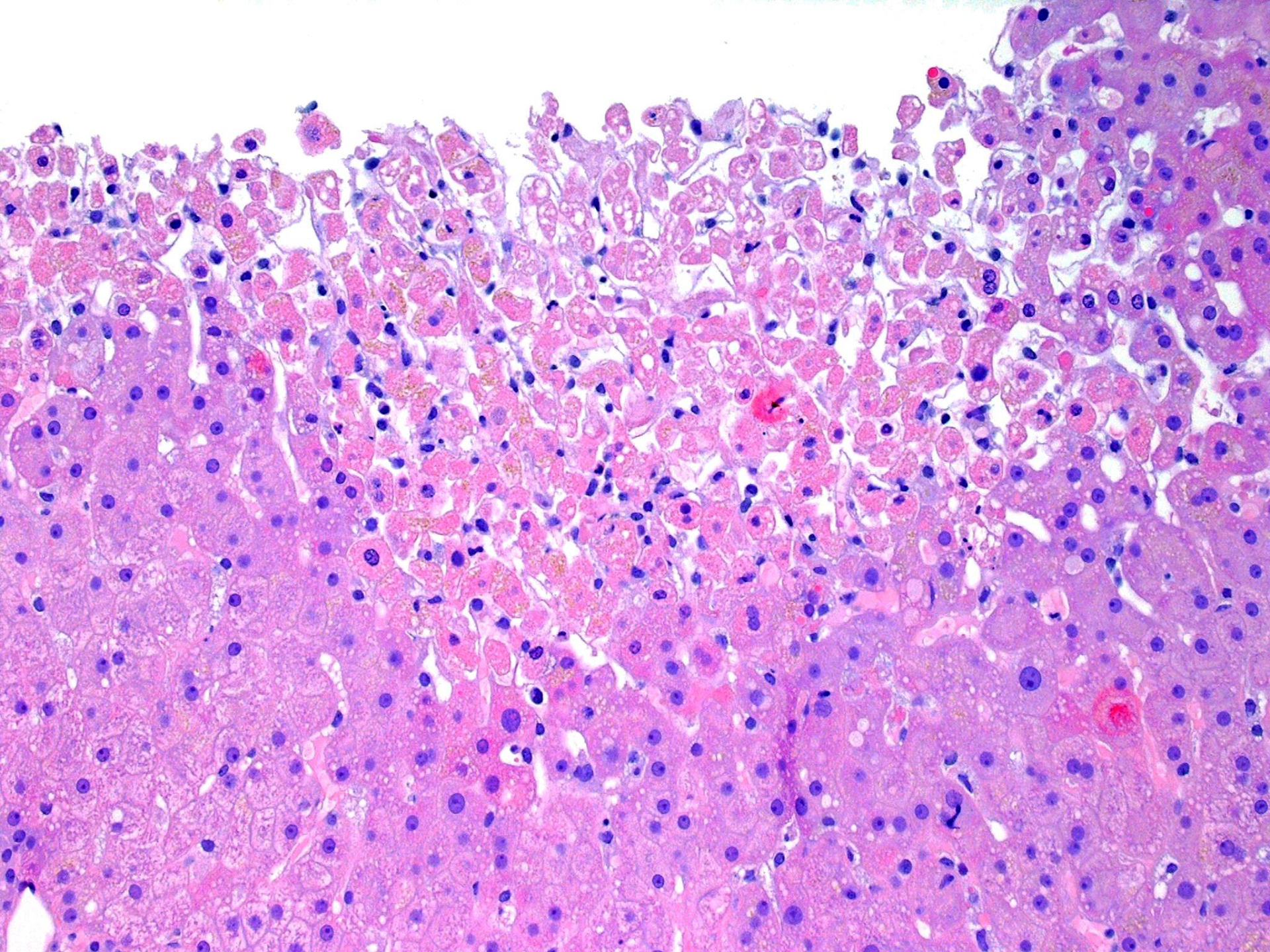
- 65 y.o. F presented in 12/10 with polyarthrititis
- Rheumatology work-up negative, but prednisone started
- Seen in ED 3/11 with SOB and a CT scan revealed multiple bilateral pulmonary nodules
- Biopsy revealed active histoplasmosis
- Started on Itraconazole 200 mg bid in August, 2011
- Seen again in the ED 2/12 with cough, SOB, fatigue and muscle weakness
- CT reveals indeterminate opacities worrisome for infection
- Multiplex respiratory virus PCR positive for RSV A
- TB = 1.9, AST = 1207, ALT = 683, alk phos = 69

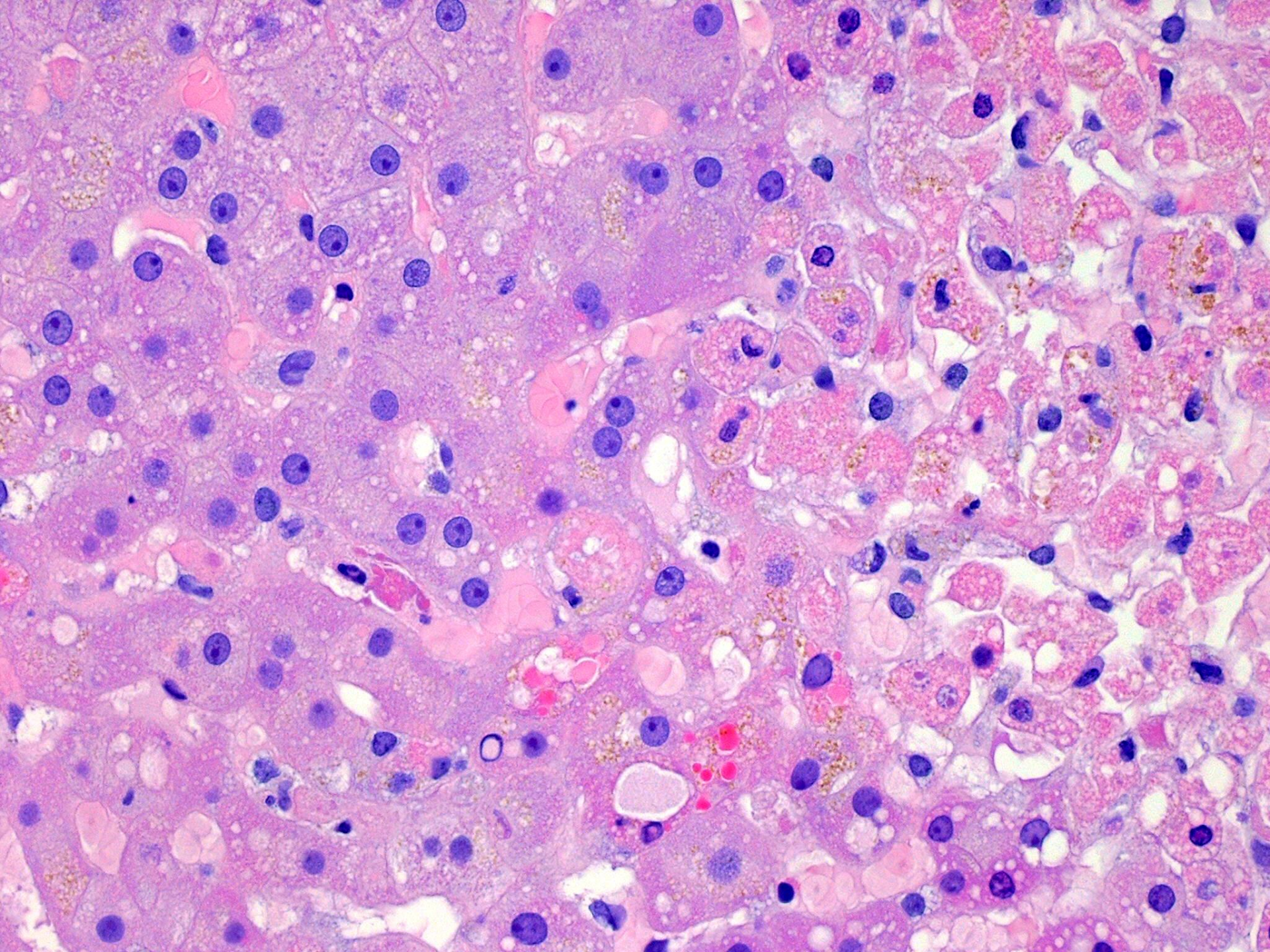




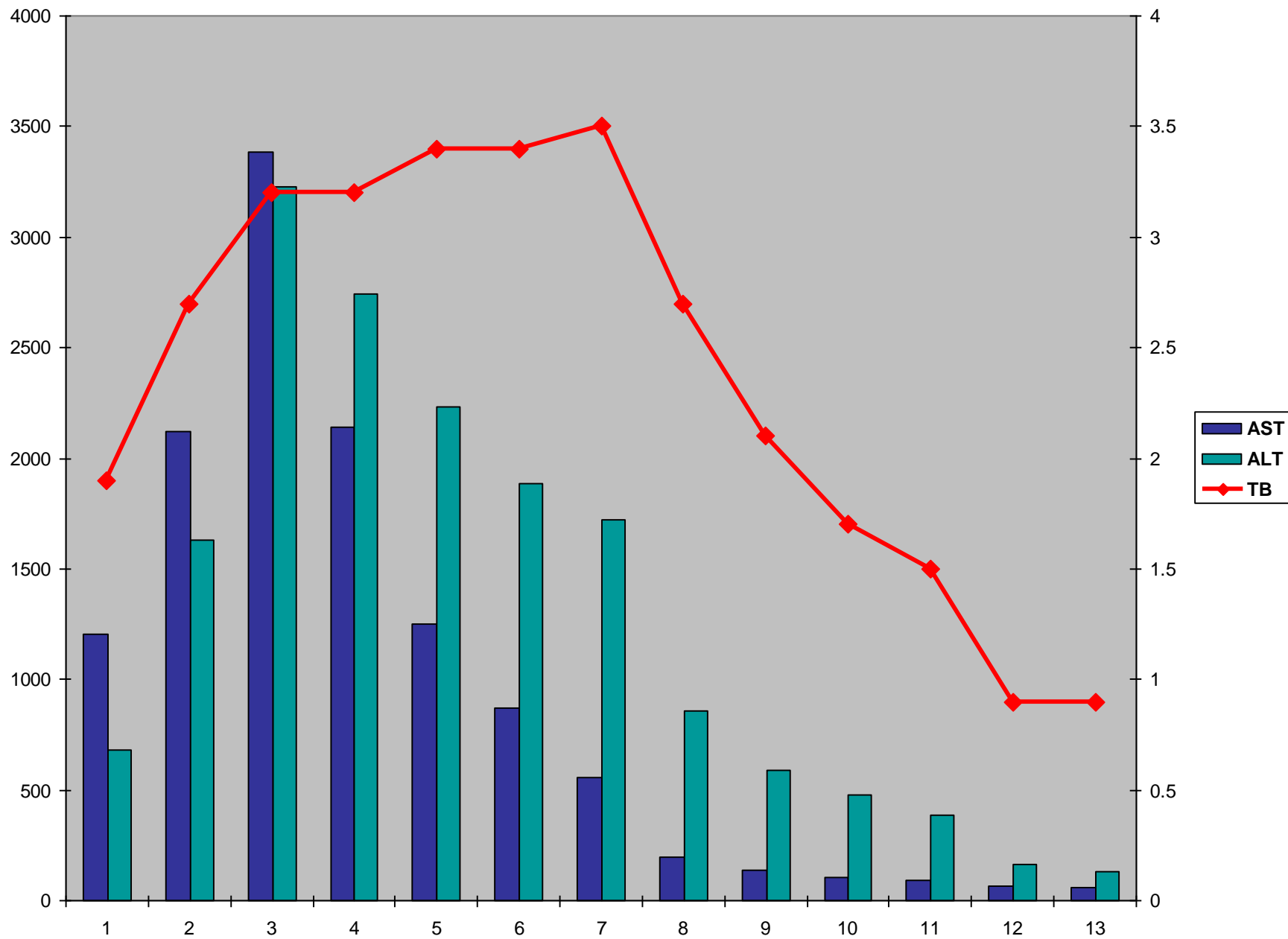








Stopped Itraconazole



Centrilobular zonal necrosis/dropout

Symptoms: non-specific constitutional symptoms; ascites

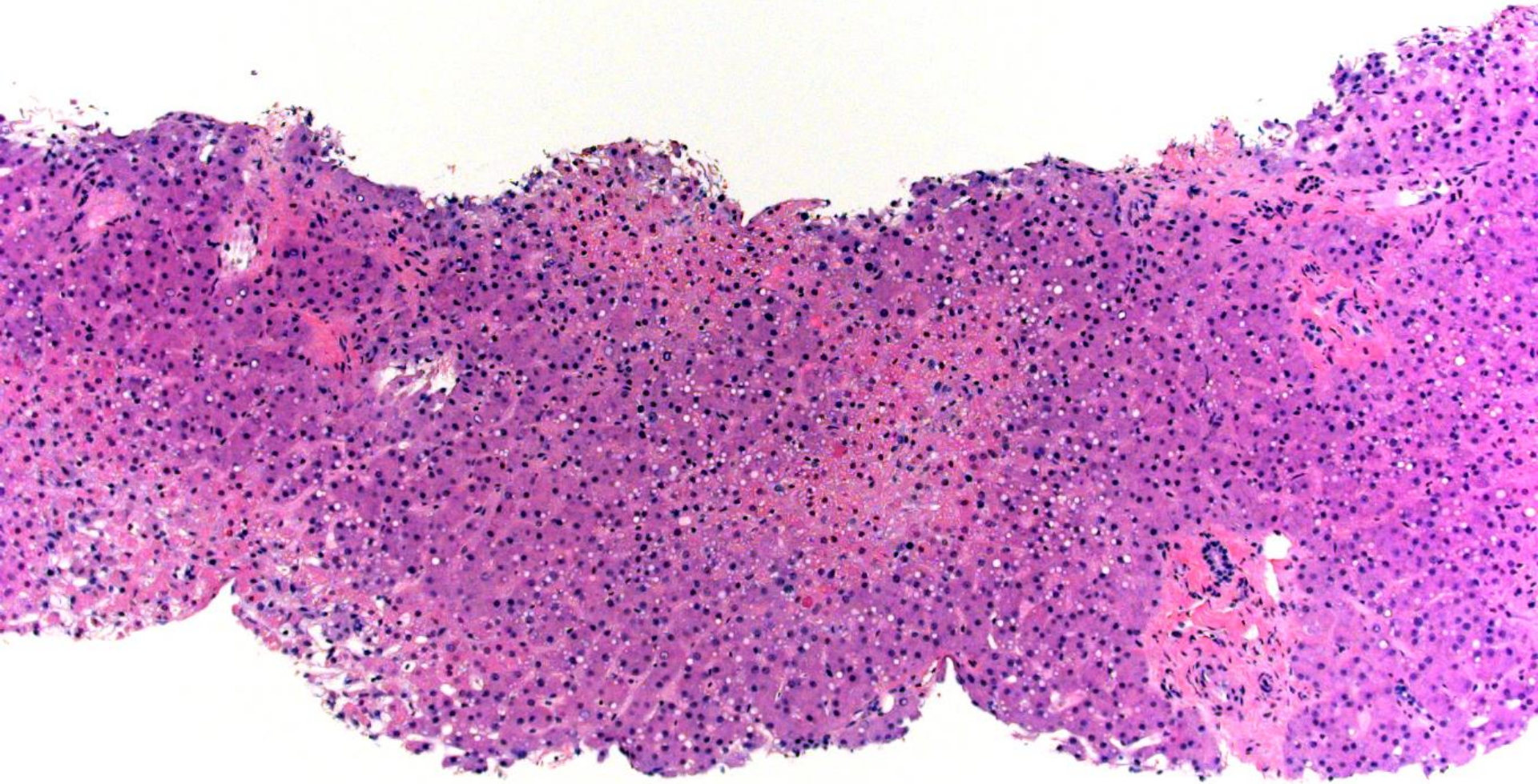
Liver chemistry tests: depends on etiology

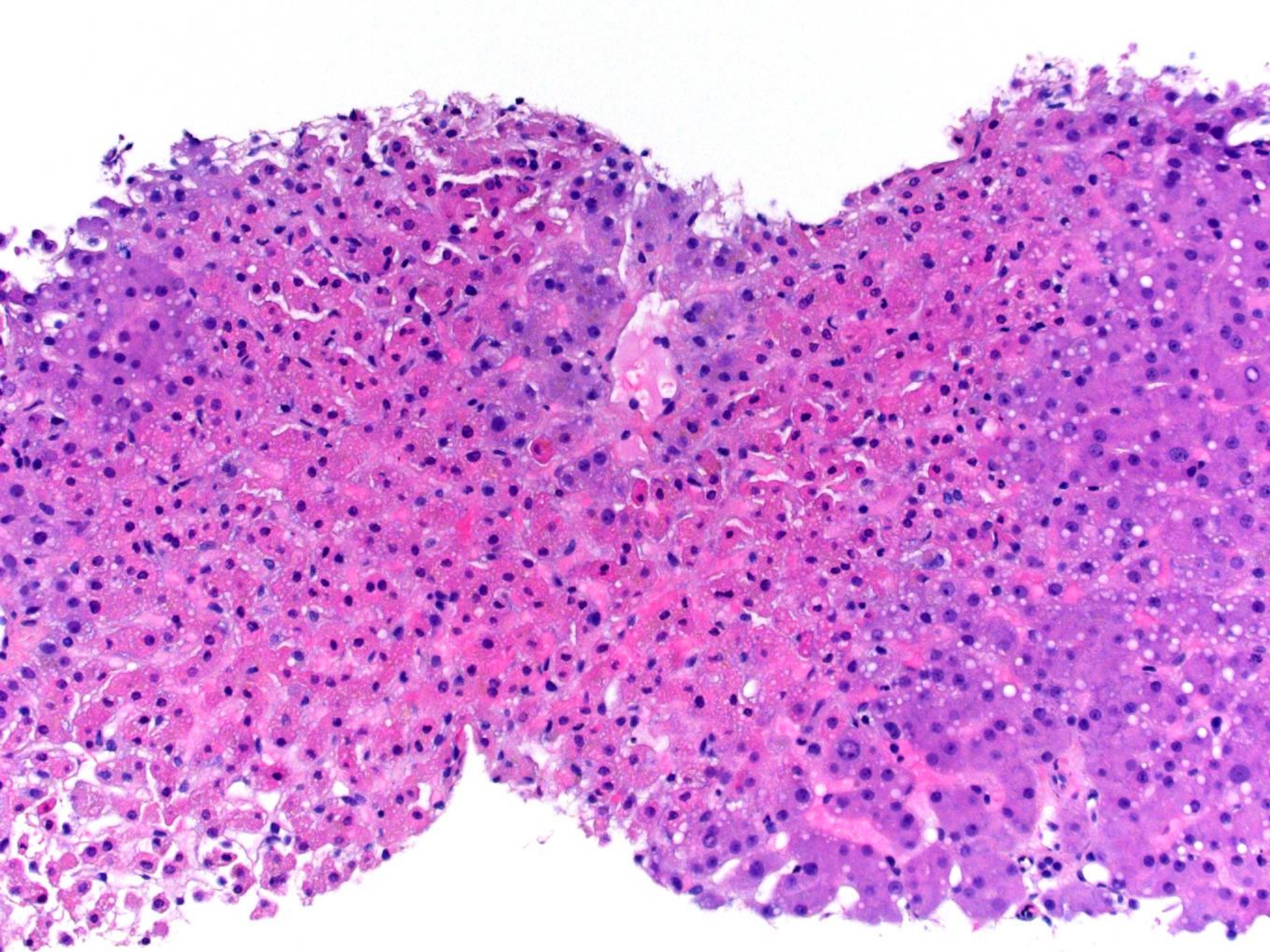
Histologic pattern: centrilobular hepatocellular injury

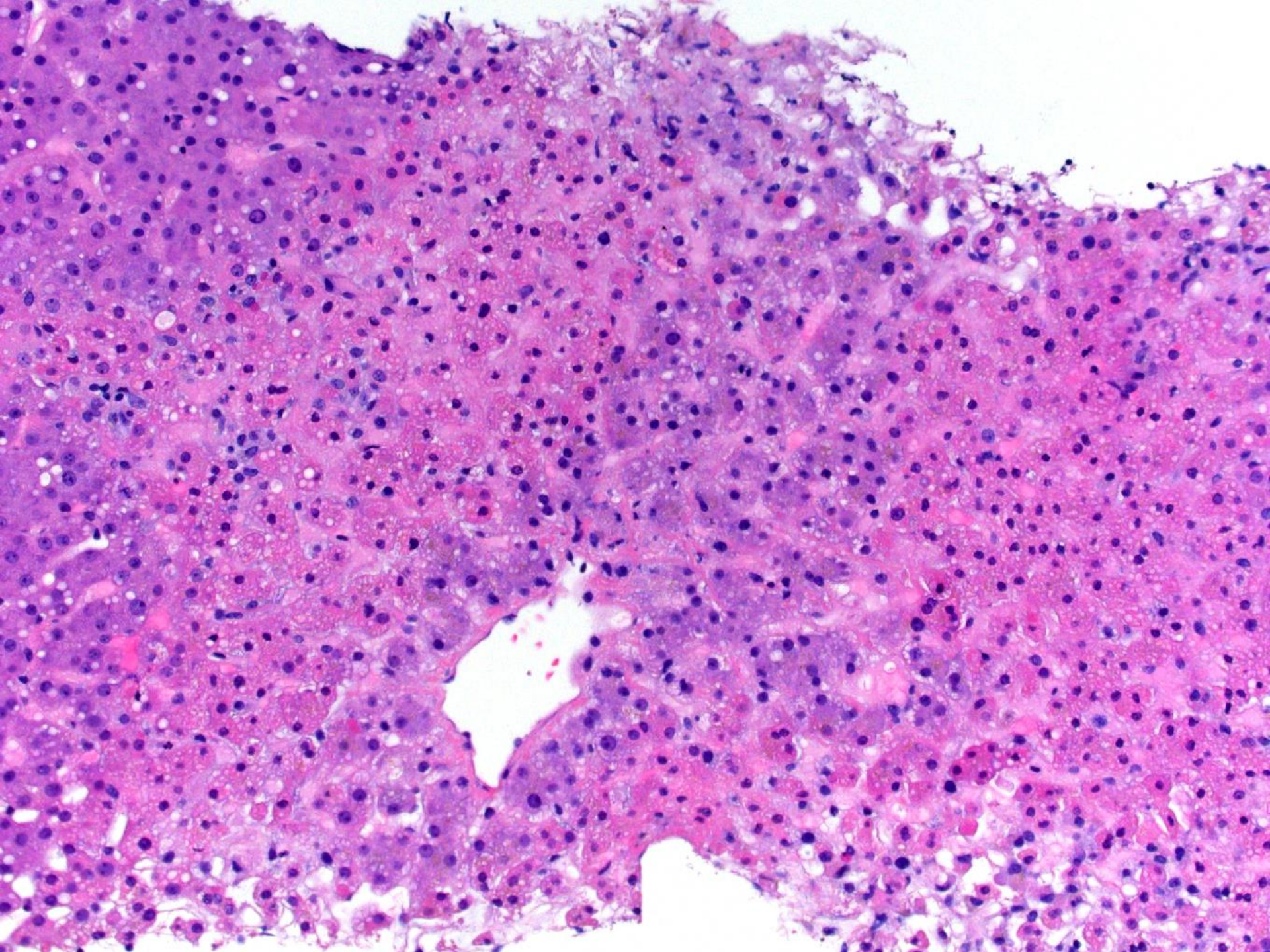
- **Drug toxicity:**
 - Acetaminophen
 - Many other drugs (too numerous to list)
- **Ischemic hepatopathy**
- **Hepatic venous outflow obstruction:**
 - Budd Chiari syndrome
 - Right sided heart failure
 - Obstruction by tumor
- **Veno-occlusive disease**
- **Autoimmune hepatitis**

- **Histologic pattern:**
 - **Centrilobular necrosis (dropout)**
- **Diagnosis:**
 - **Centrilobular necrosis, r/o drug toxicity**
- **Take home points:**
 - **Find the drug**

8 y.o. F with myocarditis causing cardiogenic shock





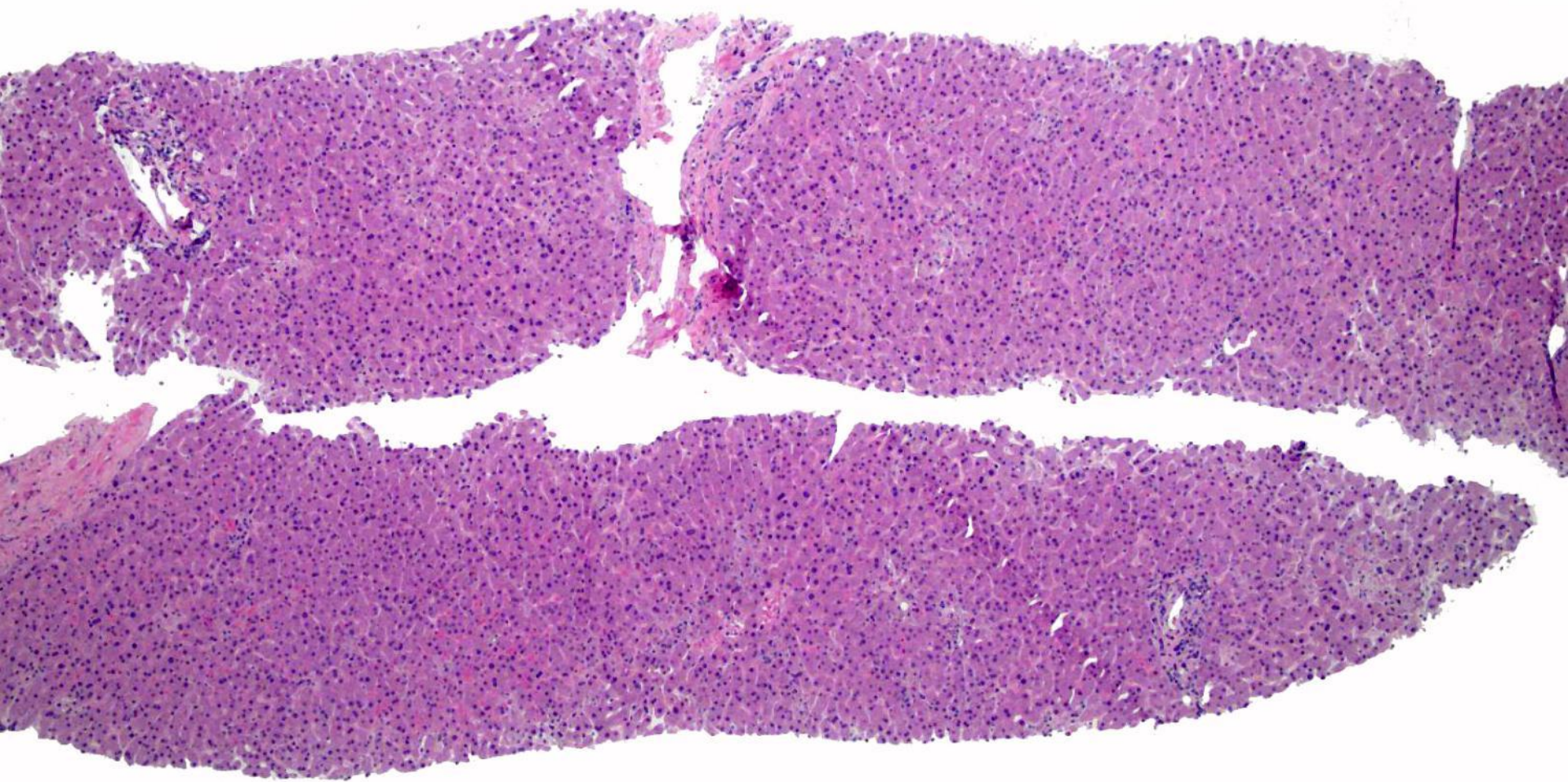


Clinical History

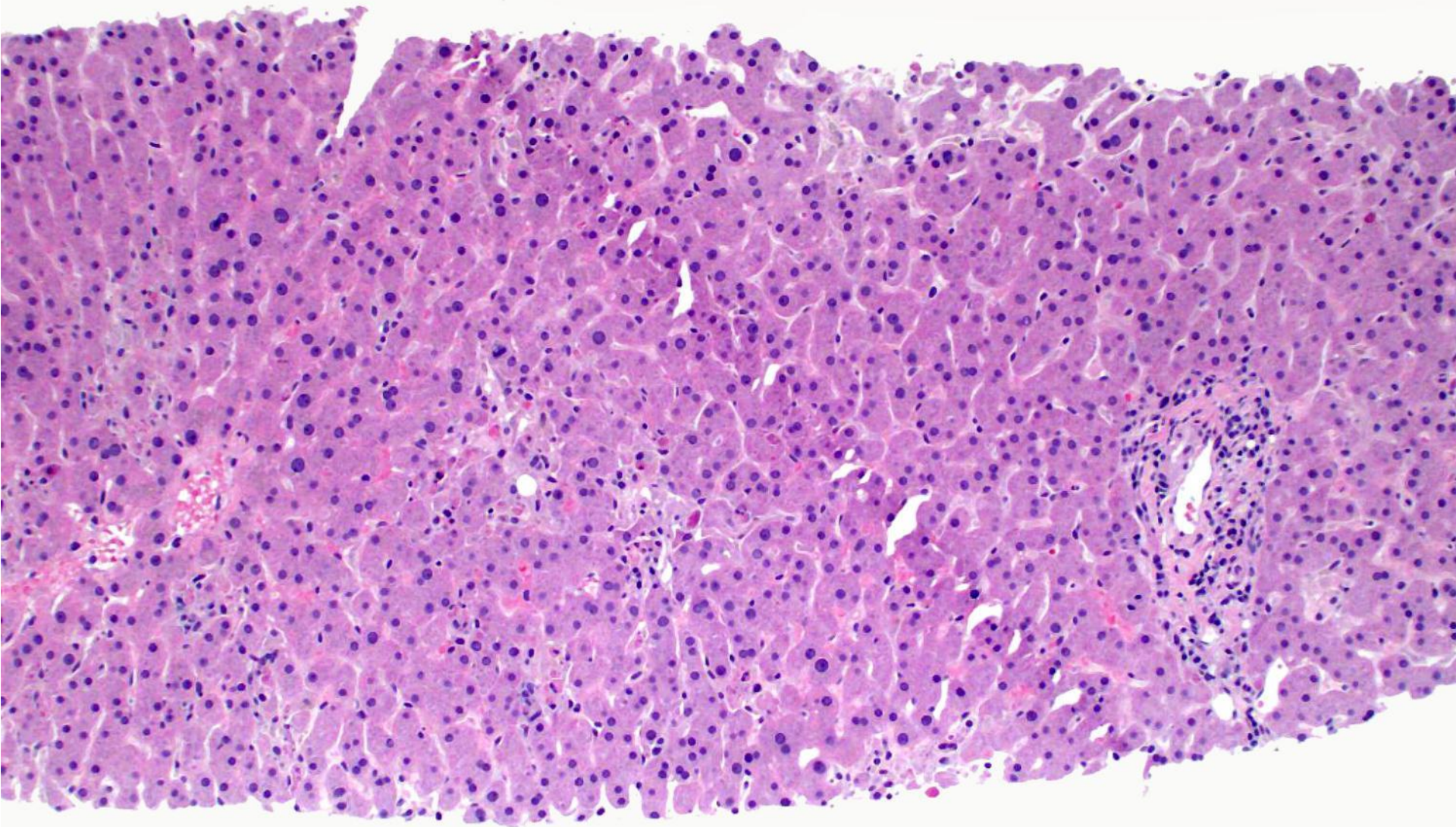
- 39 y.o. HIV positive M presents with one month Hx of dry cough, N&V and hiccups, resulting in 20 lb weight loss
- Diagnosis of HIV 5 years ago; never treated
- HIV viral load > 70,000; CD4 count = 12
- Bilateral upper lobe opacities concerning for pneumocystis
- QuantiFERON-TB Gold indeterminant; sputum AFB negative
- Histoplasma urine antigen negative
- BAL:
 - Pneumocystis positive
 - Respiratory virus panel negative
 - Started on Bactrim and prednisone
- Steadily rising LCTs
- HAV, HBV, HCV, HEV negative; ANA negative

Labs during Admission

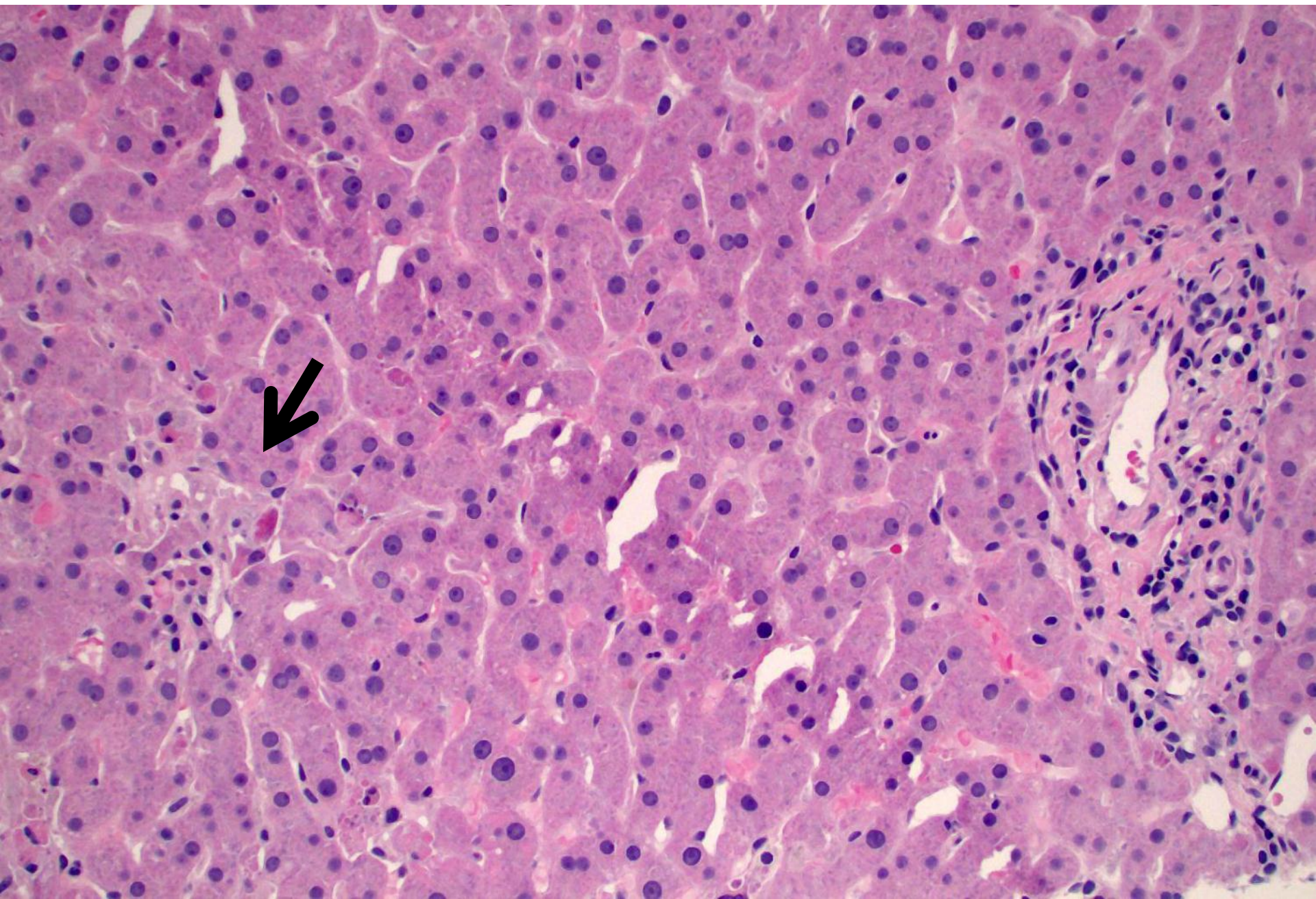
- 9/27: TB = 0.3, AST = 69, ALT = 34, Alk phos = 96
- 9/28: TB = 0.2, AST = 121, ALT = 59, Alk phos = 95
- 9/29: TB = 0.2, AST = 207, ALT = 112, Alk phos = 96
- 9/30: TB = 0.2, AST = 802, ALT = 397, Alk phos = 175
- 10/1: TB = 0.5, AST = 677, ALT = 346, Alk phos = 148
- 10/2: TB = 0.4, AST = 1506, ALT = 734, Alk phos = 156

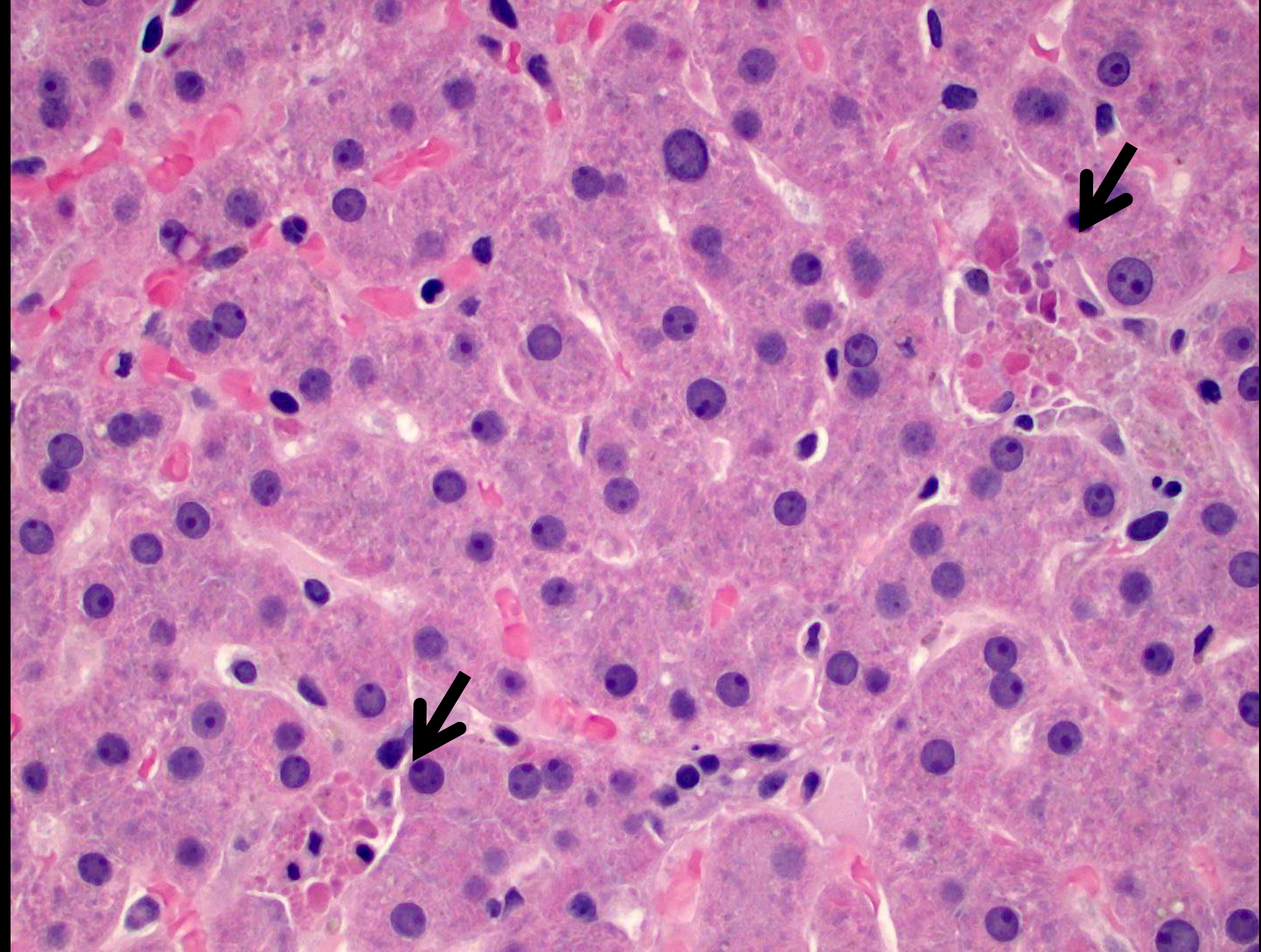


Minimal portal and lobule inflammation

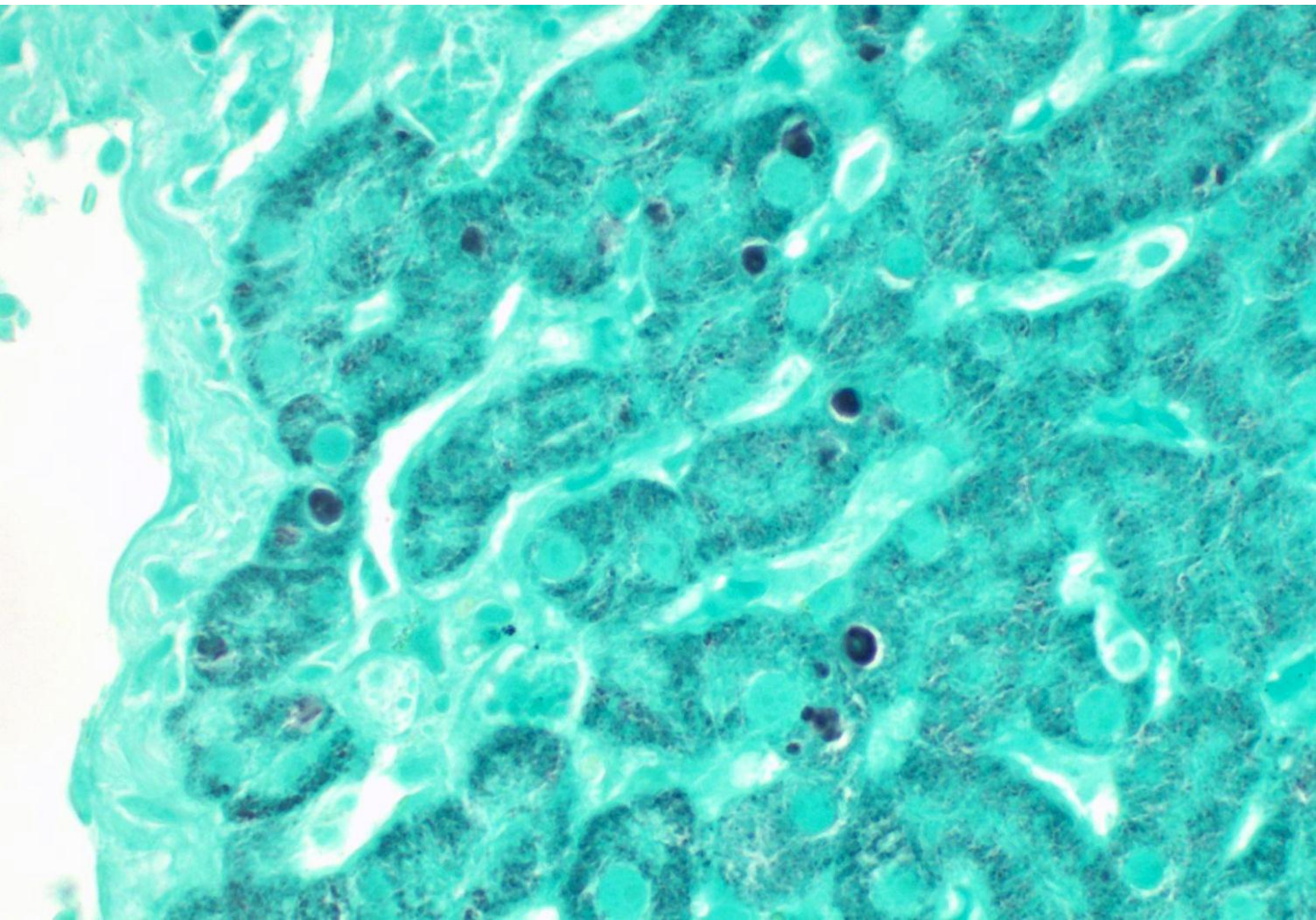


Random focus of patchy hepatocyte necrosis (arrow)





GMS stain: *Pneumocystis jiroveci*



Clinical Follow-up

- **Switch to intravenous Pentamidine**
- **10/3 TB = 0.5, AST = 1473, ALT = 859, Alk phos = 186**
- **10/4 TB = 0.4, AST = 682, ALT = 628, Alk phos = 219**
- **10/5: TB = 0.3, AST = 396, ALT = 506, Alk phos = 221**
- **10/6: TB = 0.7, AST = 412, ALT = 568, Alk phos = 254**
- **10/7: TB = 0.6, AST = 251, ALT = 523, Alk phos = 260**

-

Random necrosis

Symptoms: constitutional symptoms → quick progression to liver failure

Liver chem tests: rapidly increasing AST & ALT >>> Alk phos and TB low

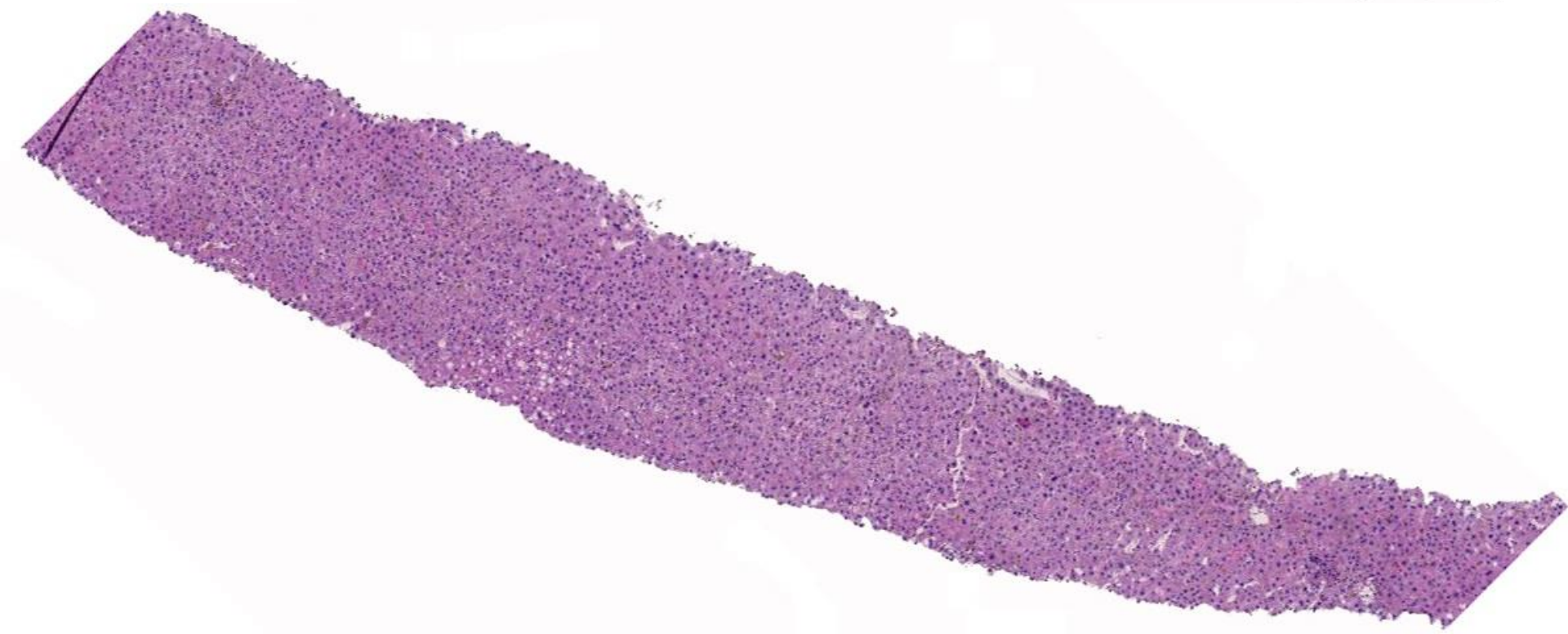
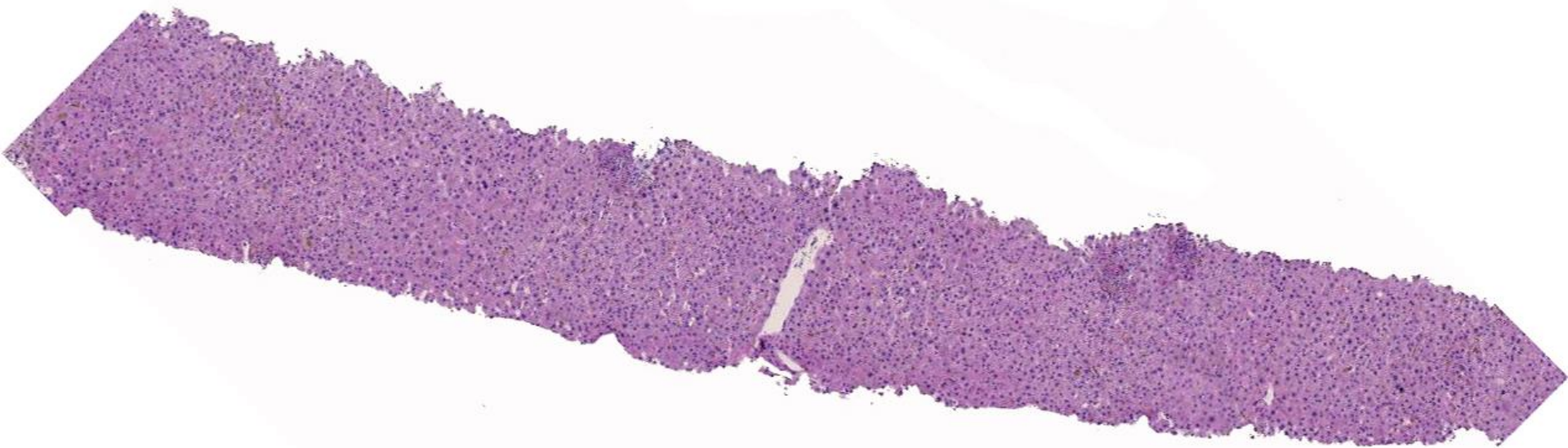
**Histologic pattern: random foci of hepatic necrosis; little inflammation,
massive necrosis**

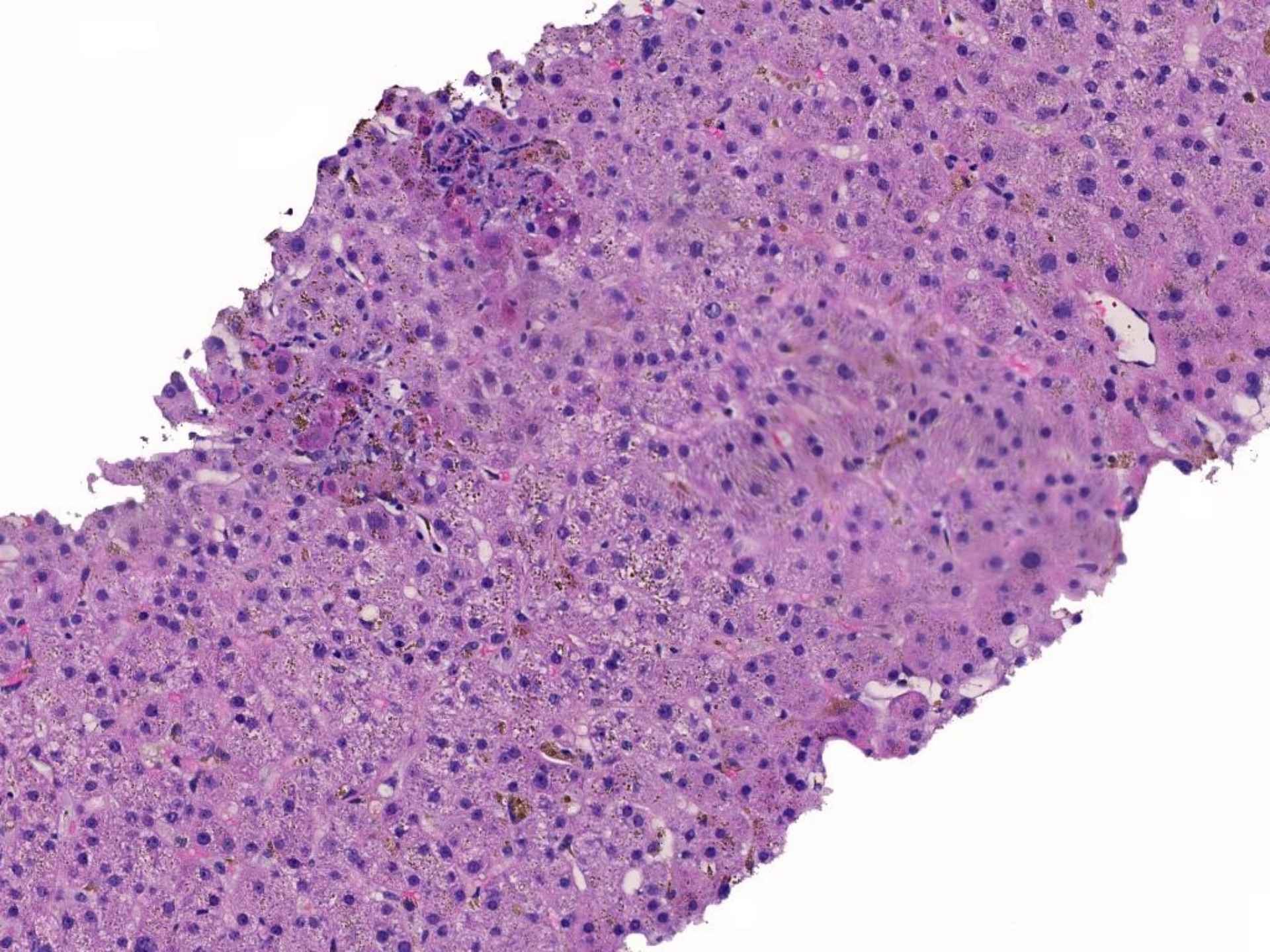
- **Adenovirus**
- **Herpes simplex virus**
- **Histoplasma**
- **Pneumocystis**
-
-
- **Drug**

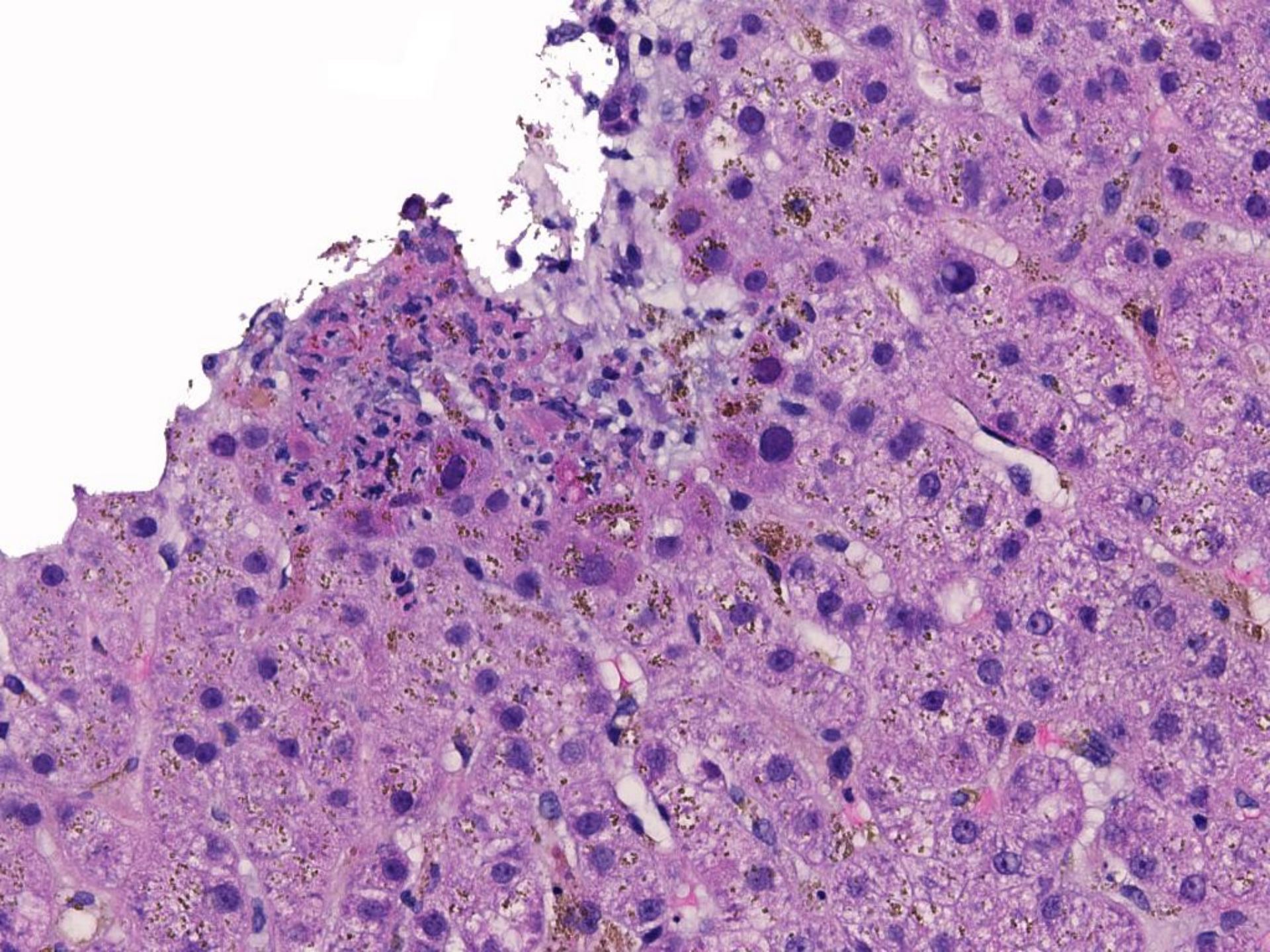
- **Histologic pattern:**
 - Random hepatocyte necrosis
- **Diagnosis:**
 - Pneumocystis hepatitis
- **Take home points:**
 - Look carefully in immunocompromised patients

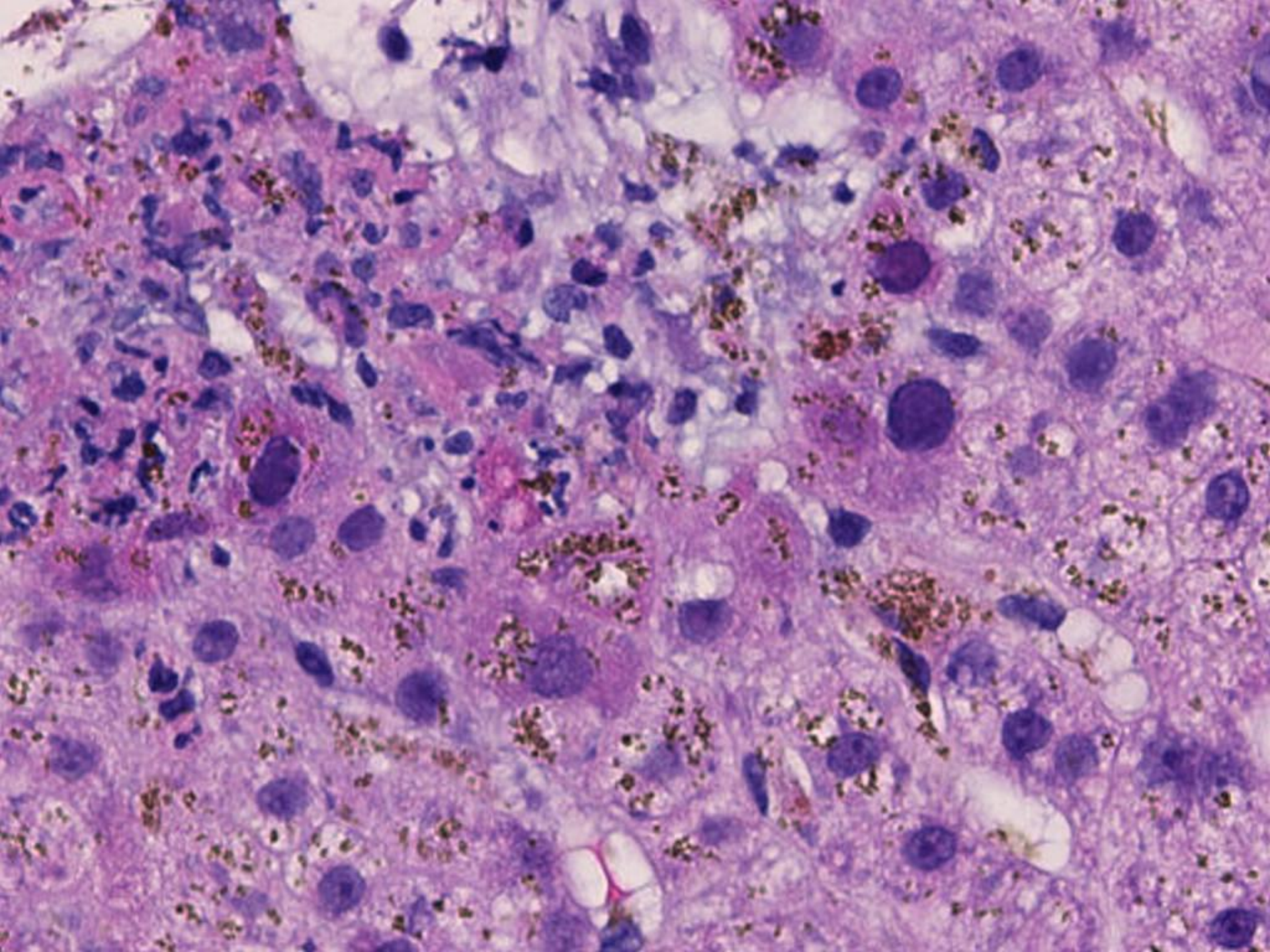
Case 43: Clinical History

- 40 y.o male diagnosed with ALL in 10/01, treated successfully with chemotherapy
- Relapse in 11/03 and underwent unrelated stem cell transplantation in 4/04
- Admitted 06/04 for persistent neutropenic fevers
- TB = 0.7, AST = 620, ALT = 540, Alk phos = 88
-
- Liver biopsy performed



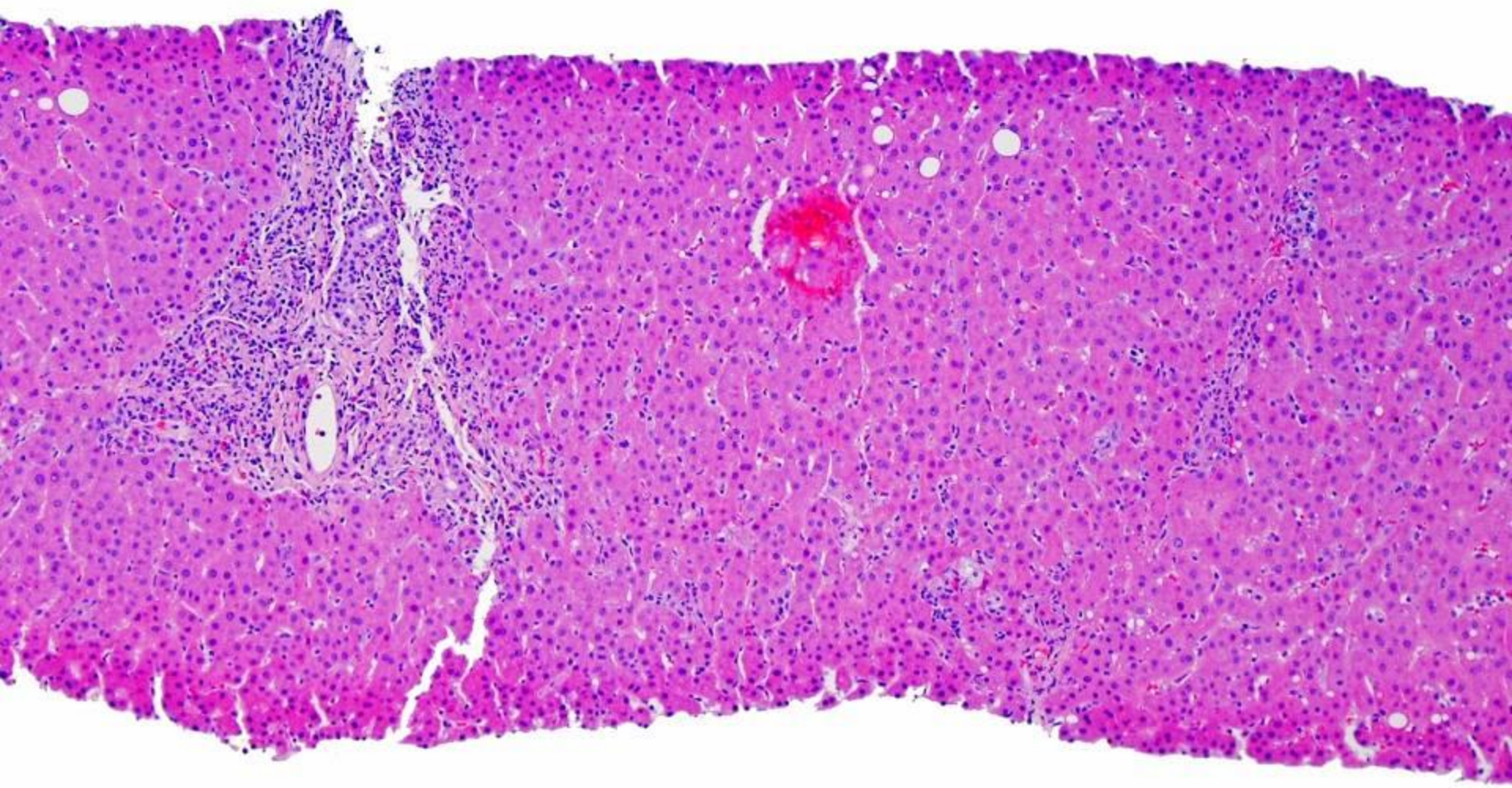


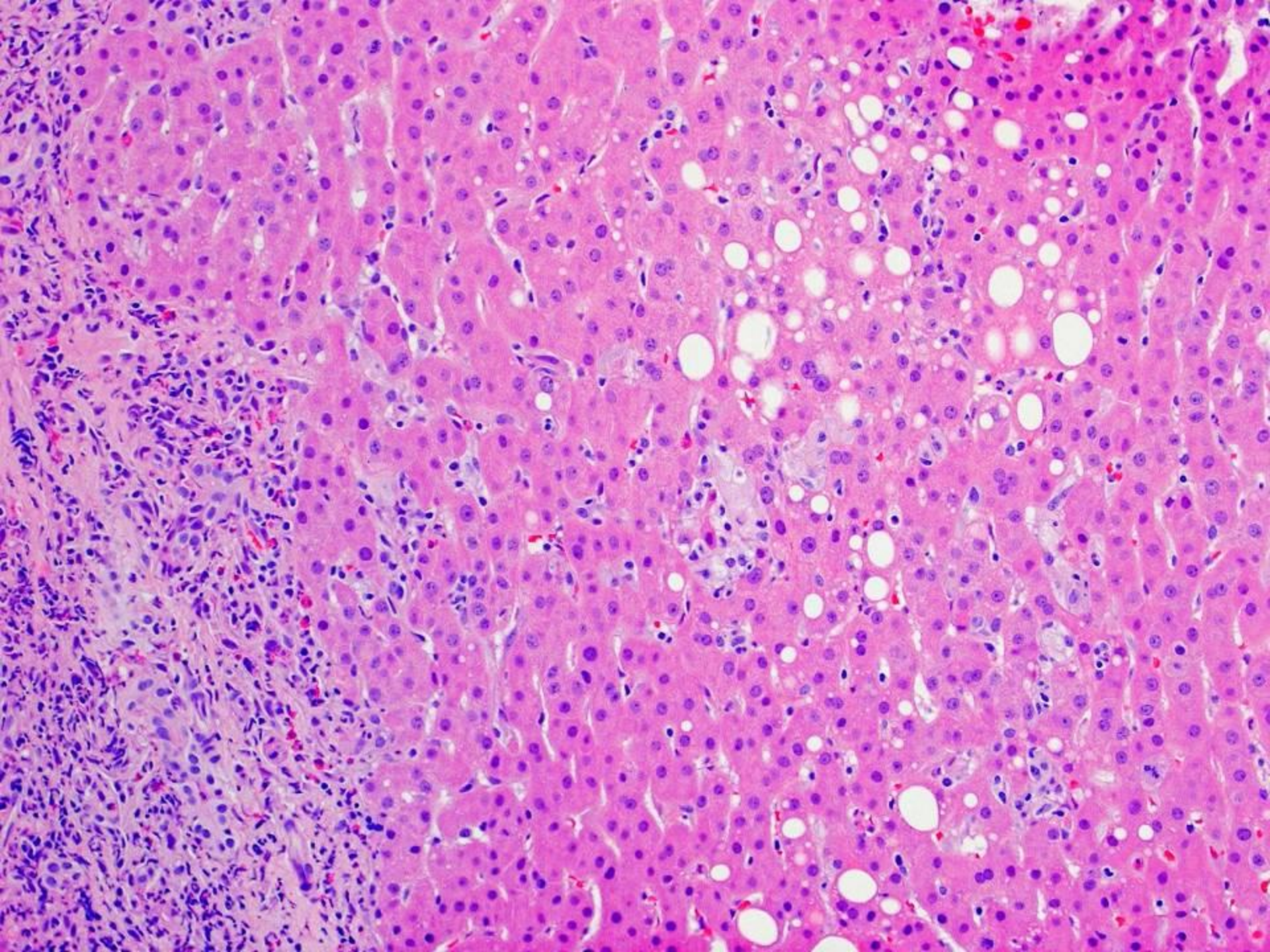


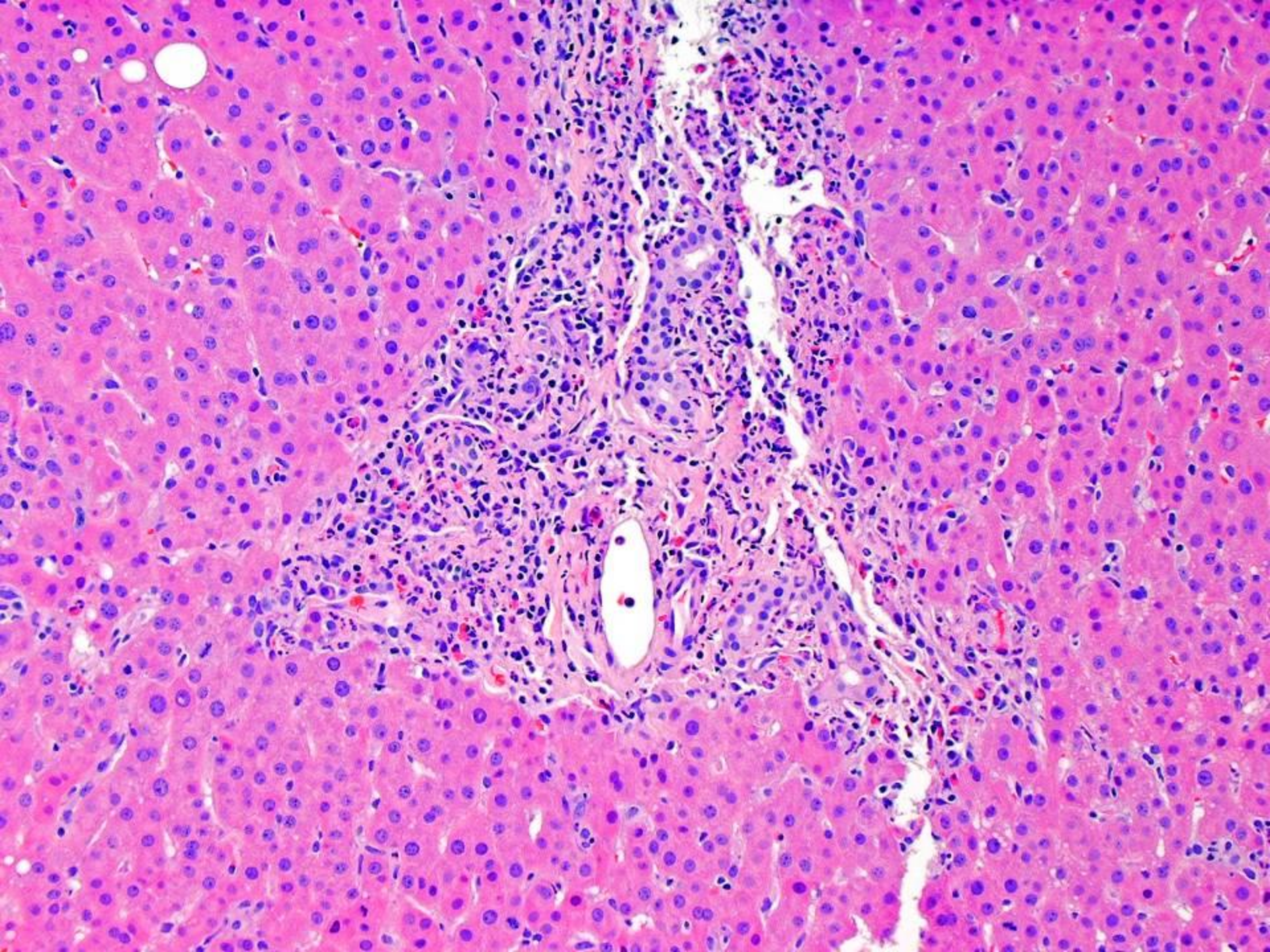


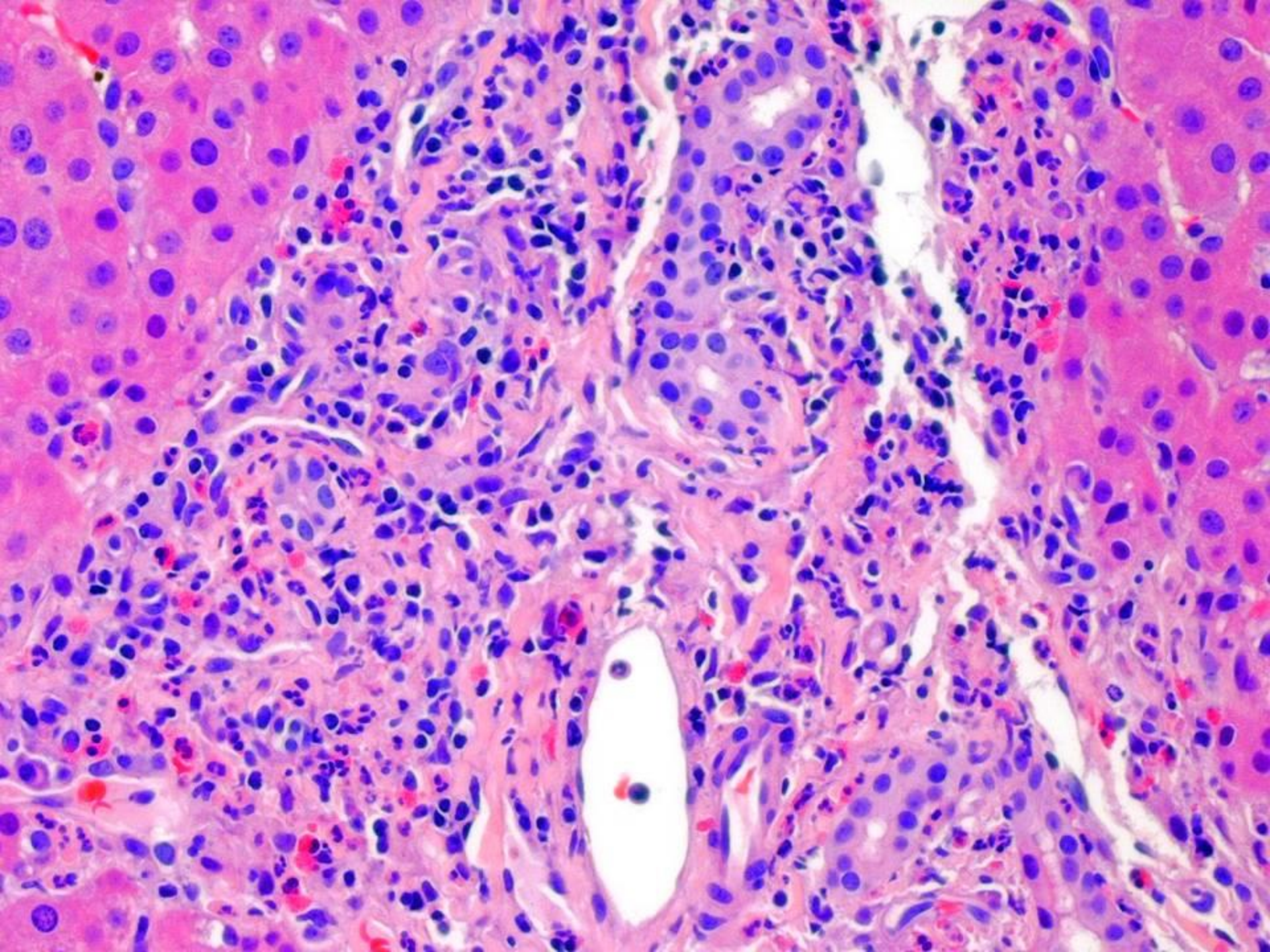
Clinical History

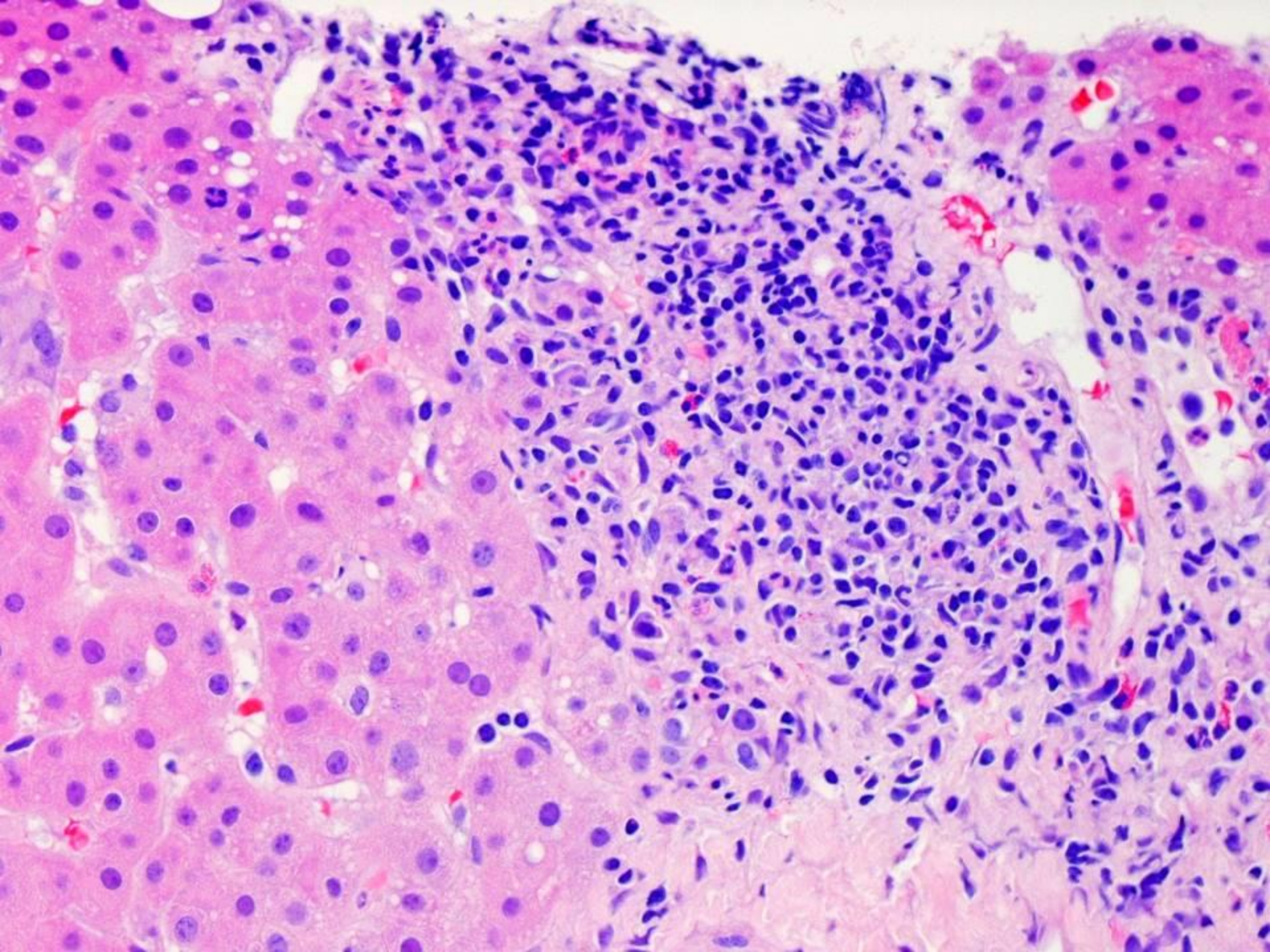
- 30 y.o. F with a 1 month history of fever (101-103 F)
- She also developed a diffuse macular rash and significant arthralgias
- Her only medication is an inhaler for seasonal asthma.
- There is no family history of liver disease or recent travel
- Laboratory evaluation:
 - TB = 0.3, AST = 111, ALT = 141, Alk phos = 71 (hepatitis)
 - ANA negative; anti-SMA = 1:40; no hypergammaglobulinemia
 - Serologic tests for HAV, HBV, HCV negative
 - Serum ceruloplasmin and alpha-1-antitrypsin levels are normal











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★ Performing your original search, *fever rash arthralgia hepatitis*, in PubMed will retrieve [24 records](#).

[J Clin Rheumatol](#). 1996 Apr;2(2):85-8.

Parvovirus b19 infection associated with acute hepatitis, arthralgias, and rash.

[Weinberg JM](#), [Wolfe JT](#), [Fratton AL](#), [Werth VP](#), [Naides SJ](#), [Spiers EM](#).

Department of Dermatology (J.M.W., J.T.W., V.P.W., E.M.S.) and Department of Pathology (A.L.F.), University of Pennsylvania; Department of Internal Medicine, Division of Rheumatology, University of Iowa and the Iowa City Veterans Affairs Medical Center (S.J.N.).

Abstract

Human parvovirus B19 is responsible for a wide variety of clinical syndromes, including erythema infectiosum, or fifth disease, polyarthritis, aplastic crisis in patients with hemolytic anemia, and chronic anemia in immunocompromised persons. Liver enzyme abnormalities are an infrequently reported association of parvovirus B19 infection in adults. We present a case of an acute transient hepatitis in the setting of parvovirus B19 infection, associated with arthralgias and an erythematous, edematous rash on the hands and leg.

PMID: 19078035 [PubMed]

[+](#) **LinkOut - more resources**

Elevated Parvo b19 IgM titer (8.78)
Elevated Parvo b19 IgG titer (6.06)



- **Histologic pattern:**
 - Not clear
- **Diagnosis:**
 - Hepatitis (weak)
- **Take home points:**
 - As a last resort, Pubmed it

Histologic Patterns

- **Acute hepatitis**
- **Chronic hepatitis**
- **Lobular hepatitis**
- **Centrilobular necrosis/dropout**
- **Random necrosis**
- **Granulomas and granulomatous hepatitis**
- **Nearly normal**
- **Cholestatic / biliary**
- **Microvesicular steatosis**
- **Macrovesicular steatosis and steatohepatitis**