Hepatitis: A Pattern-Based Approach

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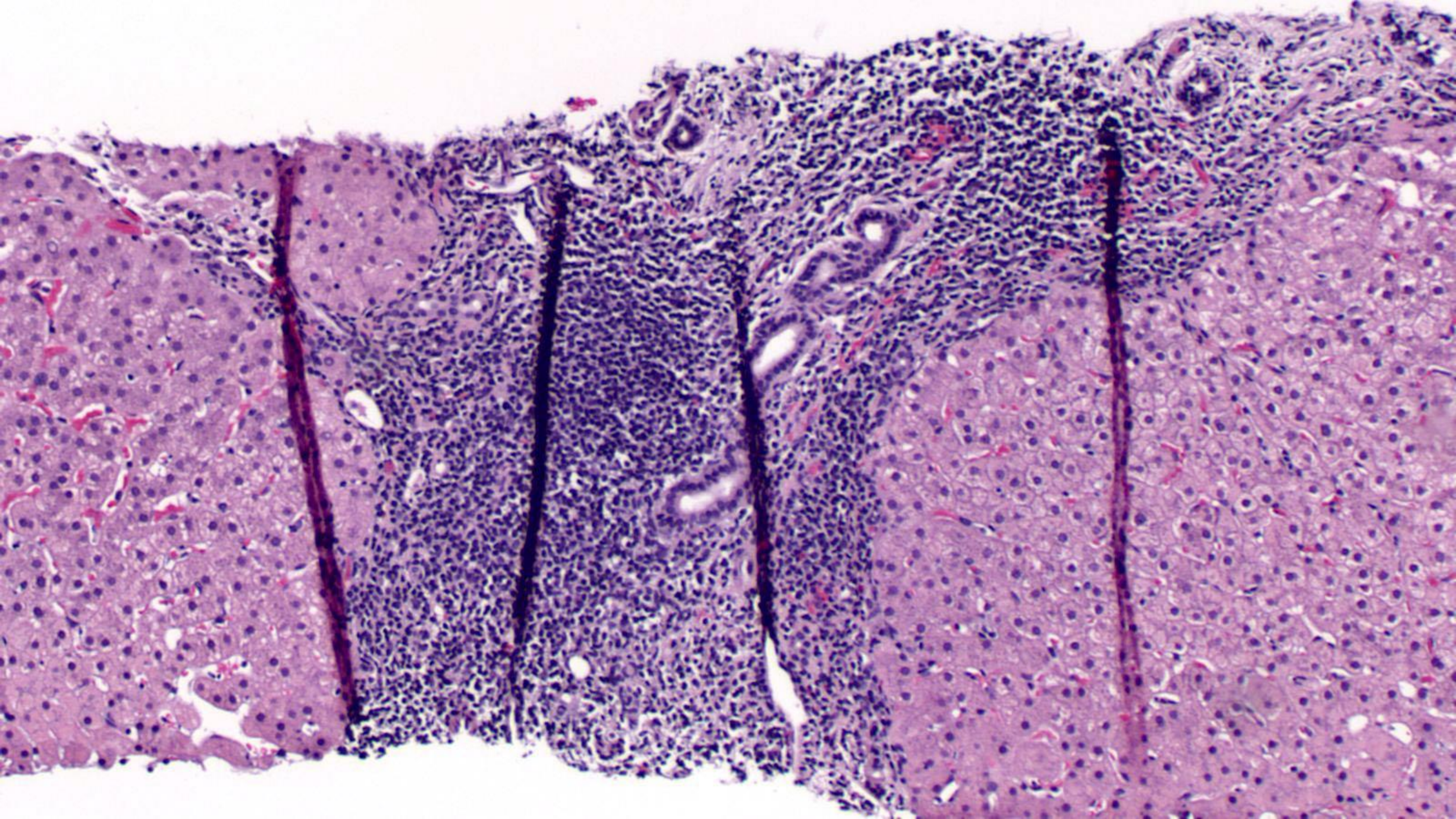
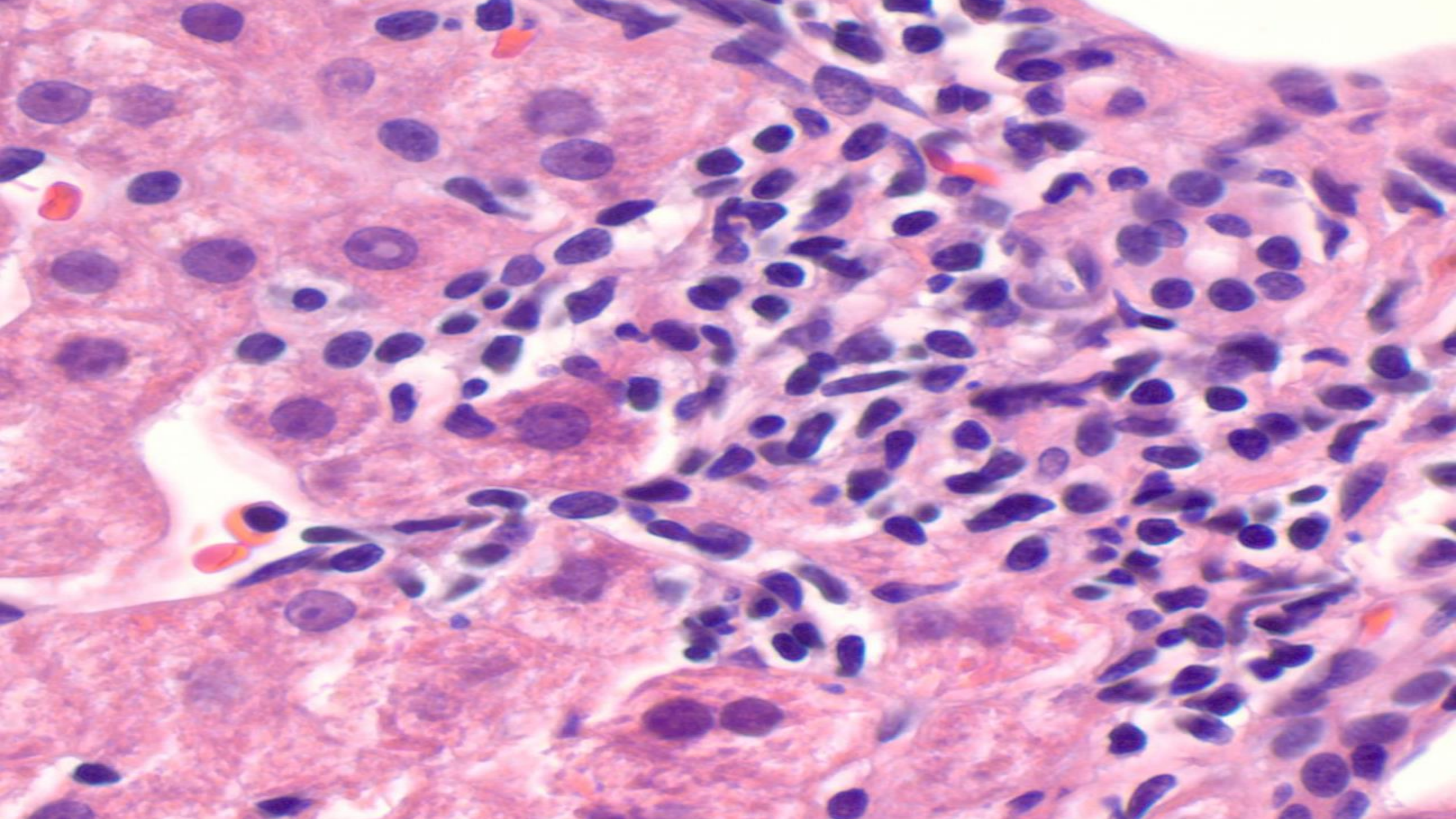
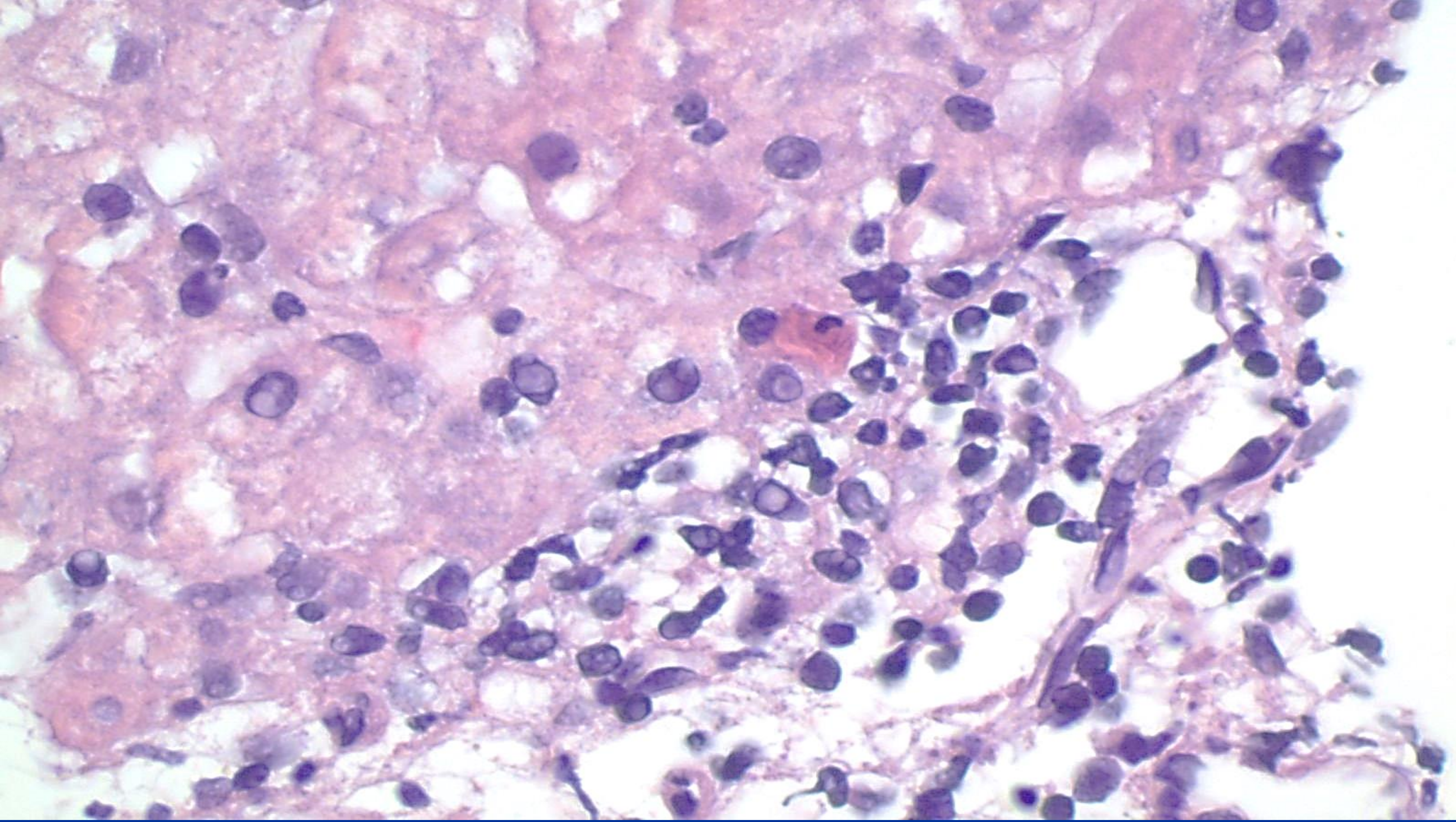
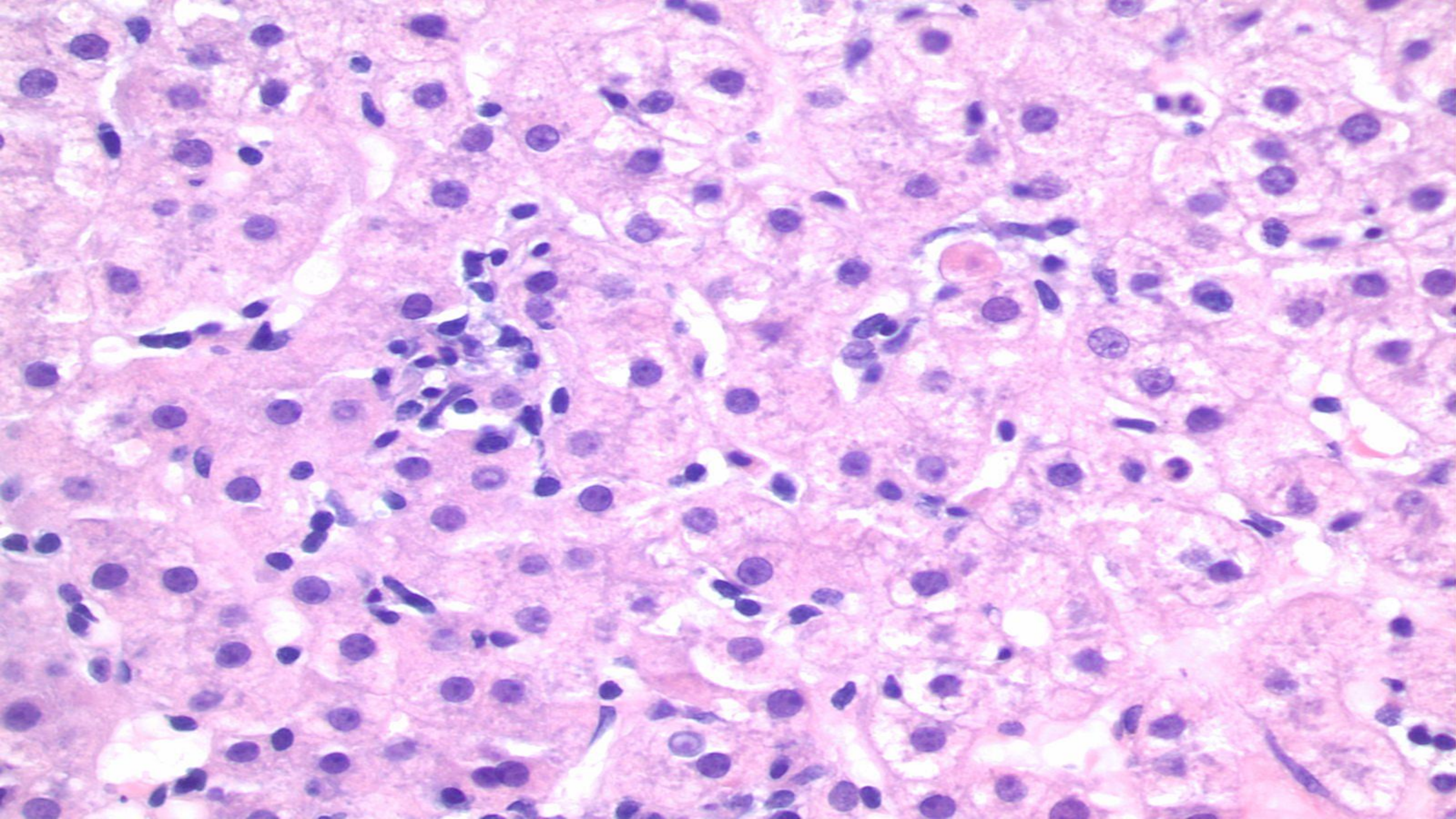
Case

- 55 year old man, elevated LFTs with chronic HCV









Chronic hepatitis

- Chronic hepatitis –
  - Portal based lymphocyte rich infiltrate
  - Activity focused on the interface
  - Varying lobular activity

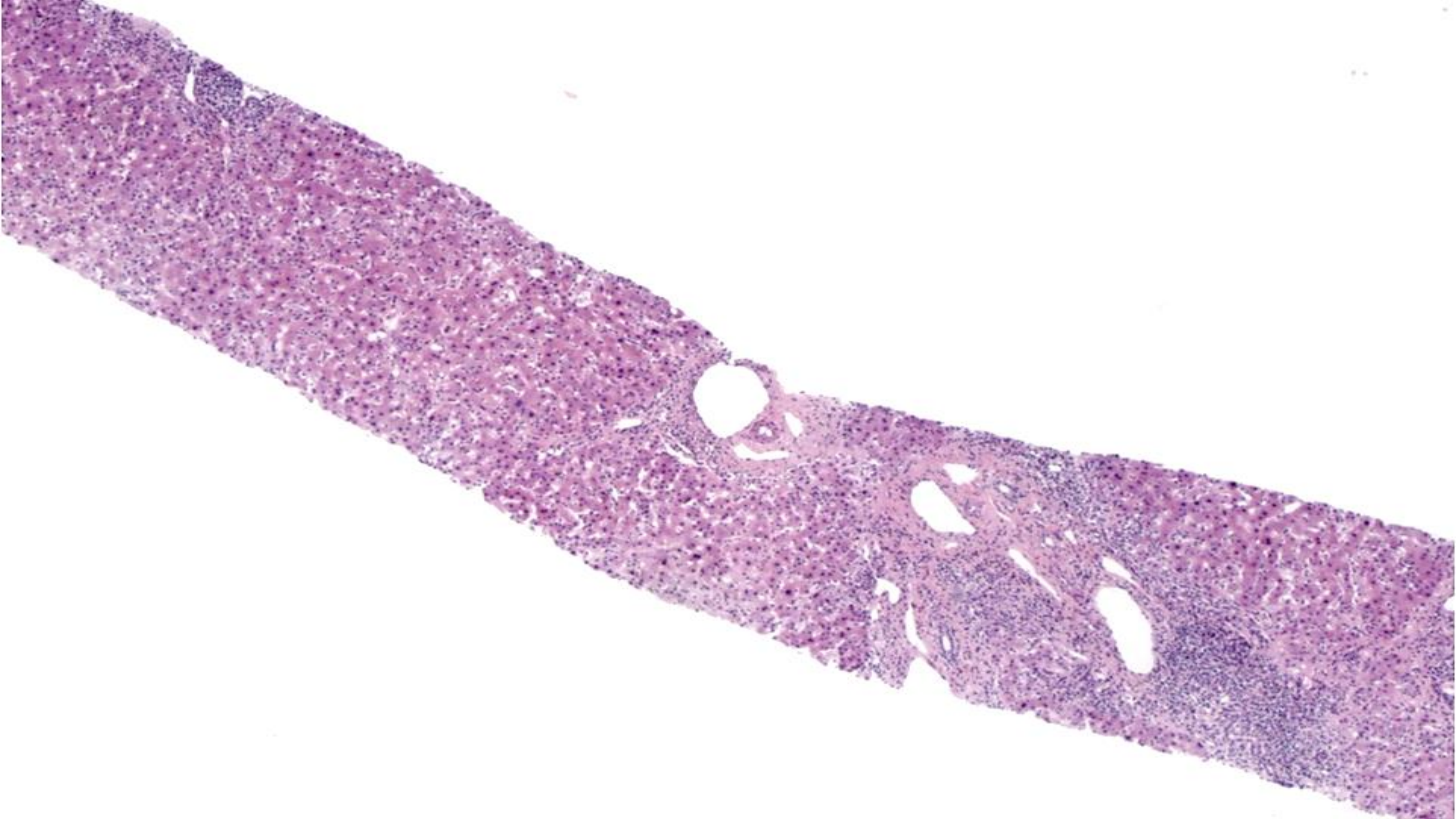
- Differential diagnosis
  - Chronic viral hepatitis
  - Autoimmune hepatitis
  - Metabolic diseases (Wilson's, A1AT deficiency)

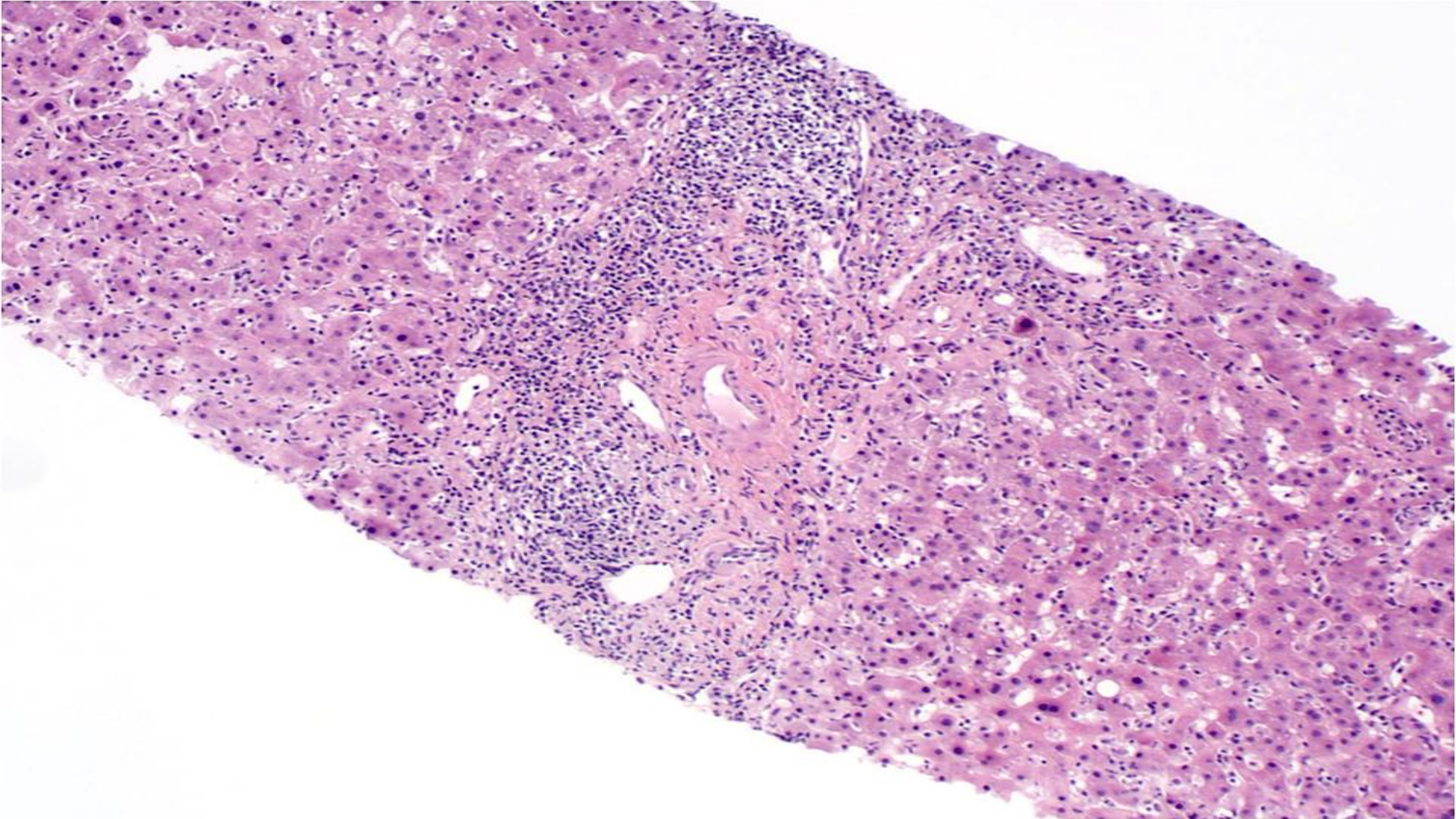
Beyond Chronic Hepatitis
It's all about the lobules!

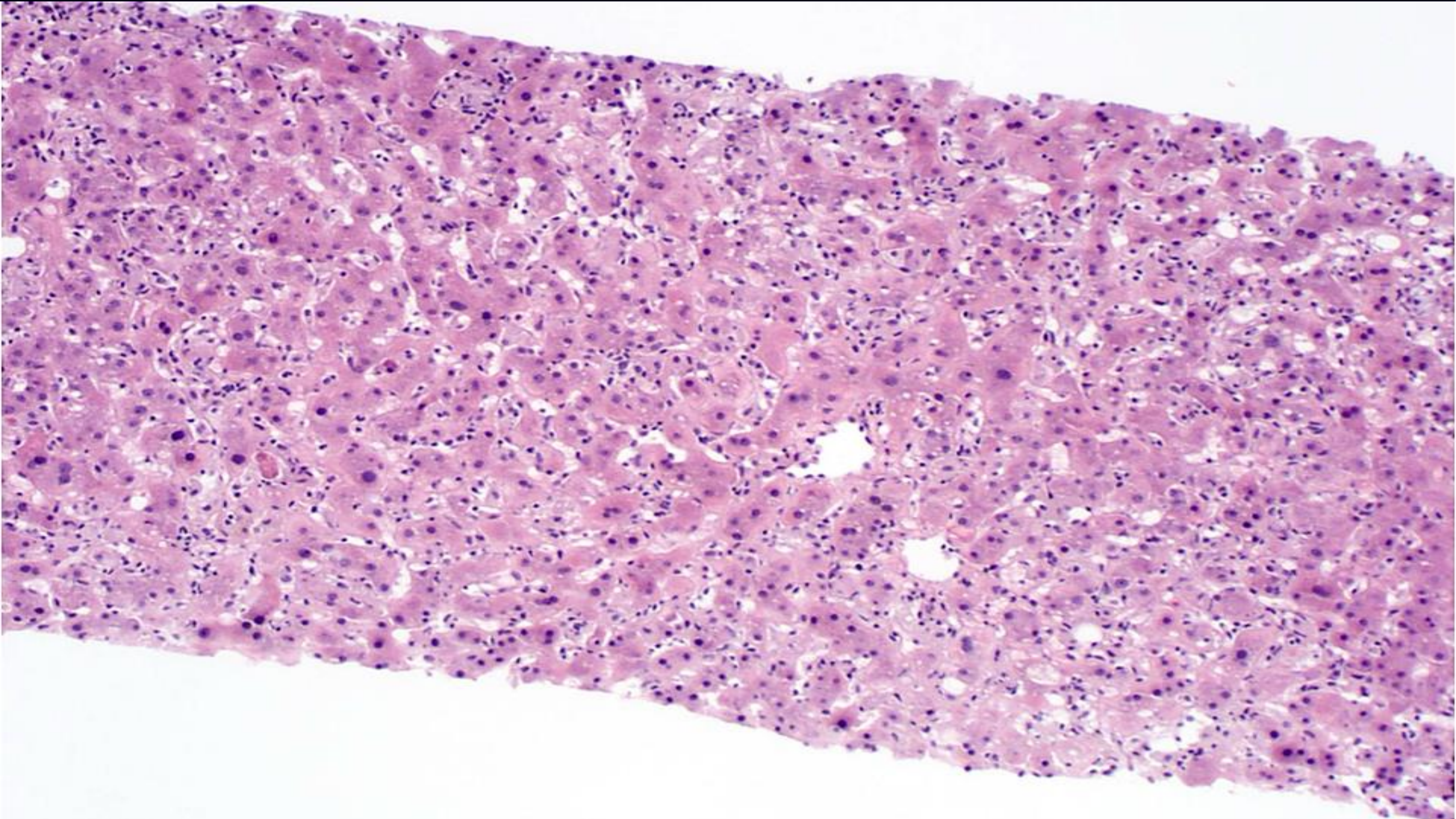
- Panlobular hepatitis
- Lobular hepatitis with sinusoidal infiltrate
- Zone 3 hepatitis

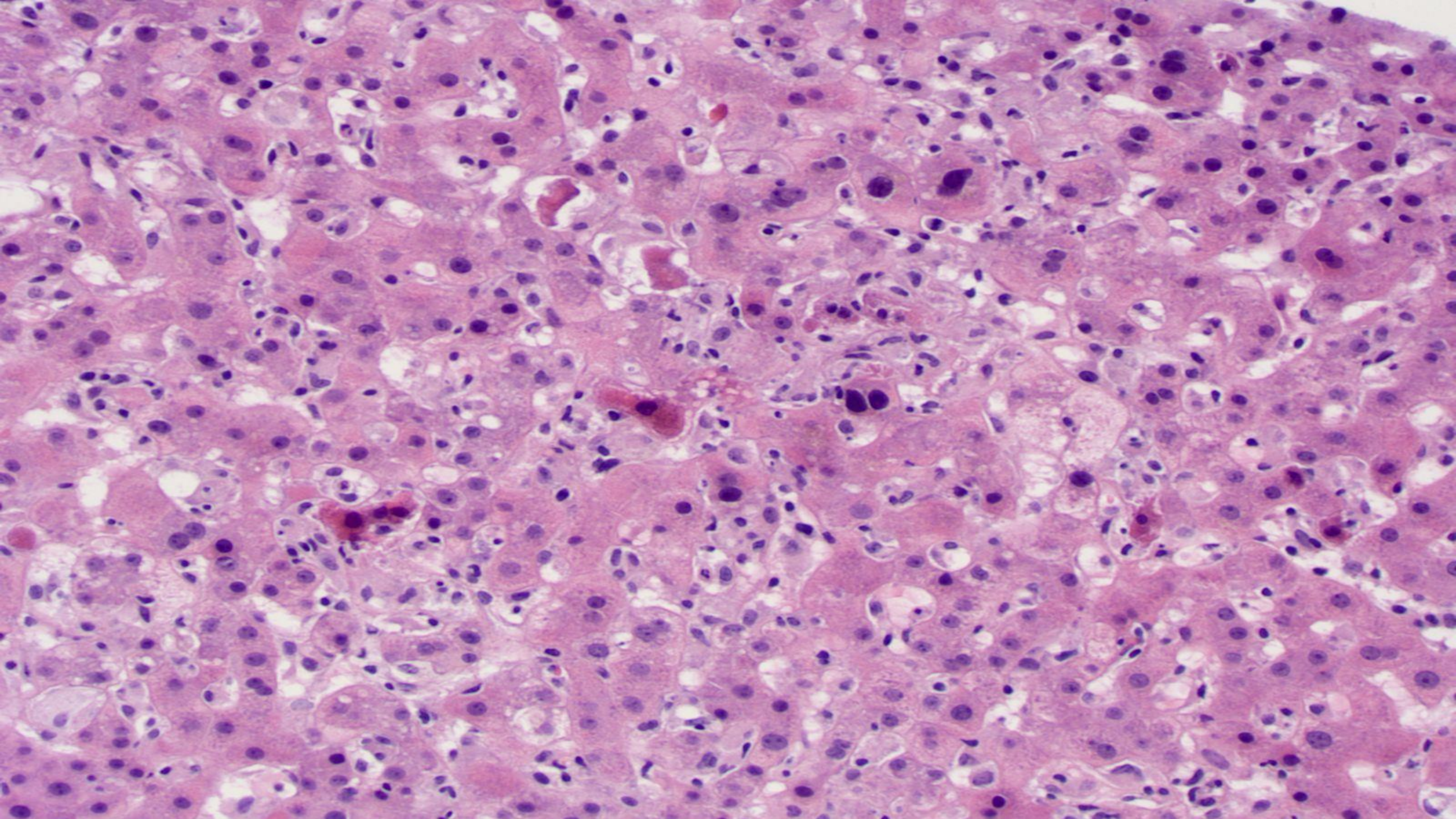
Case

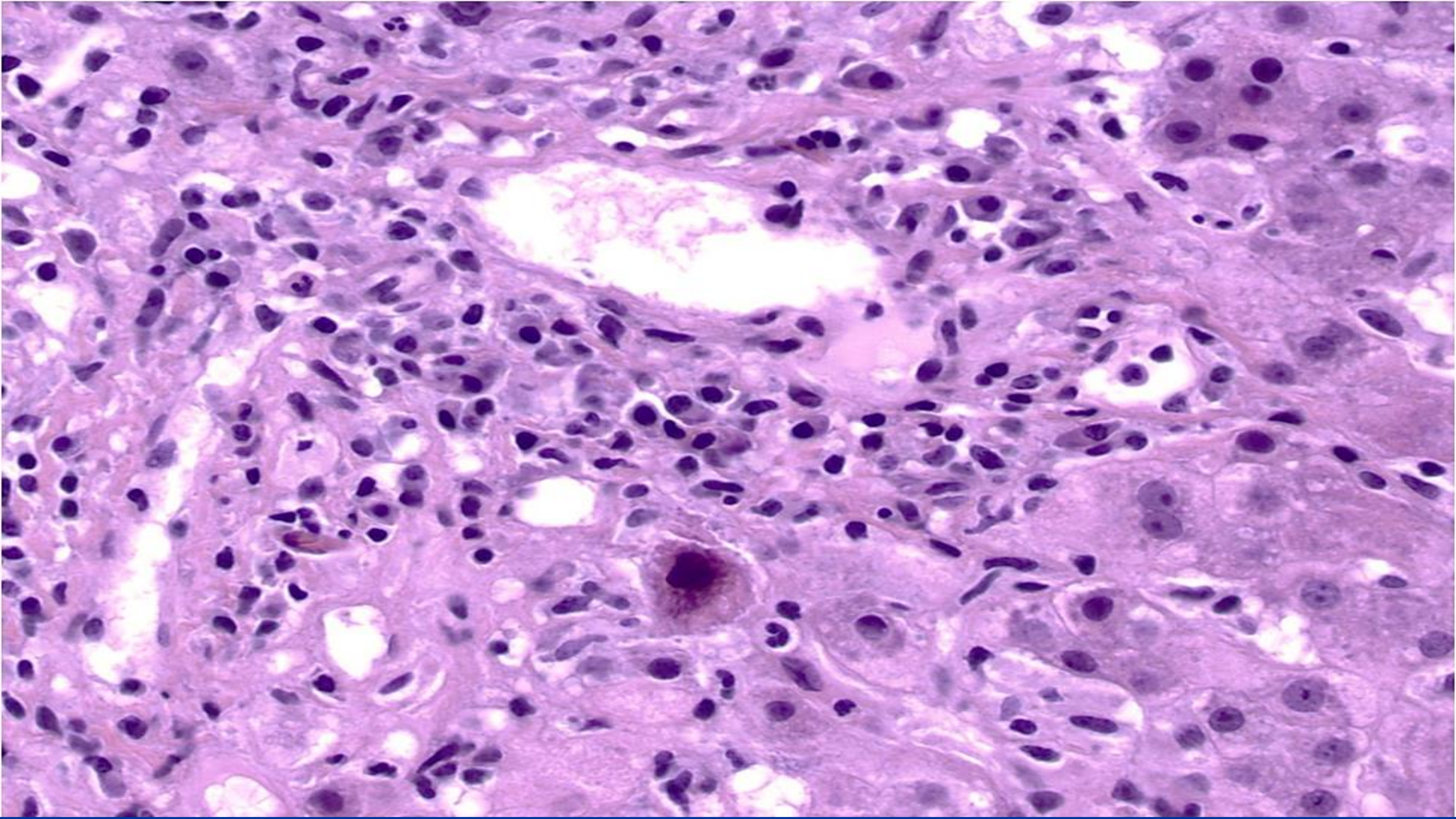
- 56 year old woman; biopsy submitted for “Elevated liver function tests”











Panlobular Hepatitis

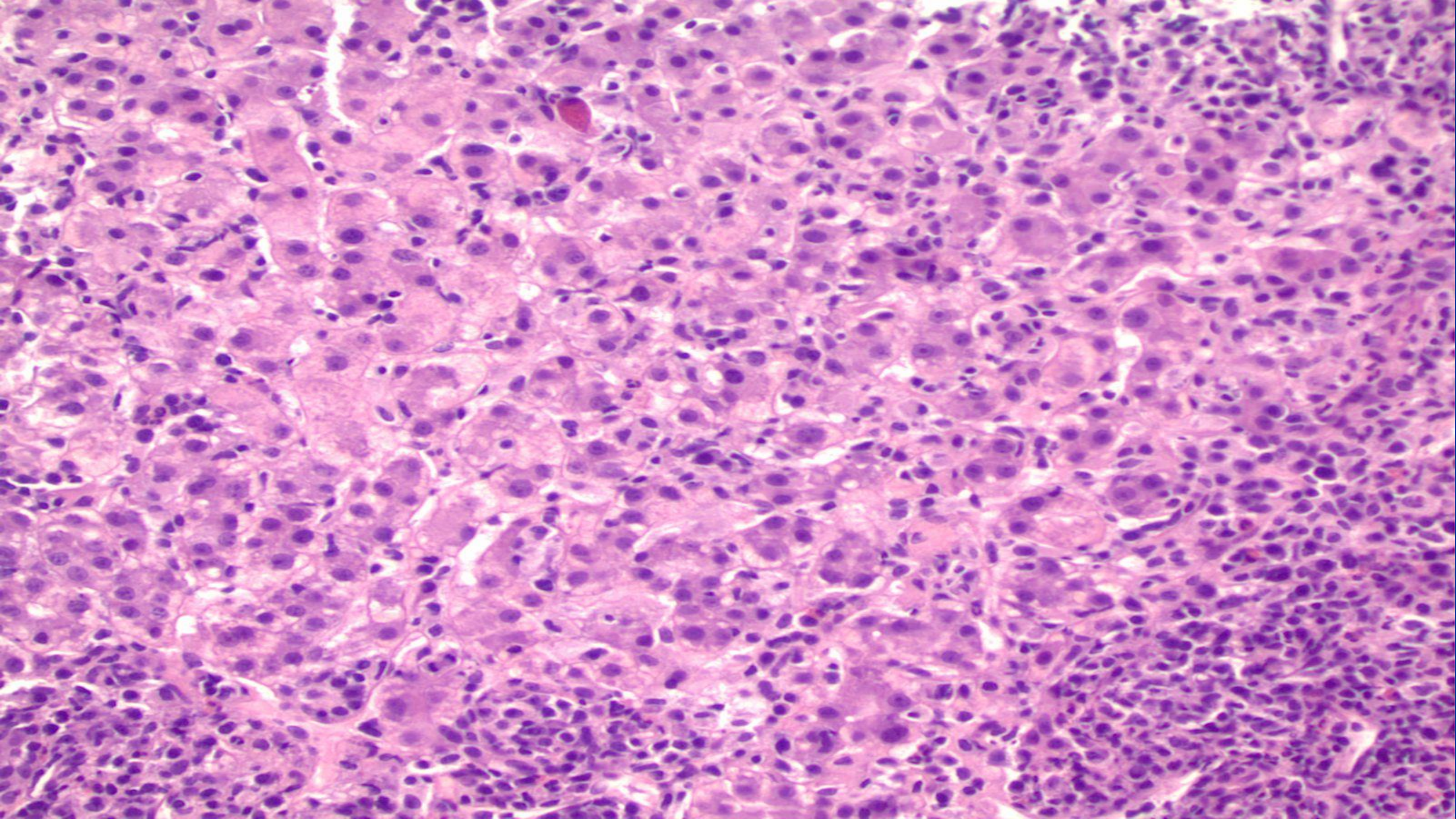
- Mononuclear inflammation and hepatocyte injury of entire lobule (acute hepatitis)
- Portal inflammation and portal expansion is usually seen, and causes confusion with chronic hepatitis.
- **The differential diagnosis for panlobular hepatitis: Acute viral infection, acute autoimmune, drug hepatitis.**
- If there are many plasma cells in clusters, acute autoimmune hepatitis is favored.

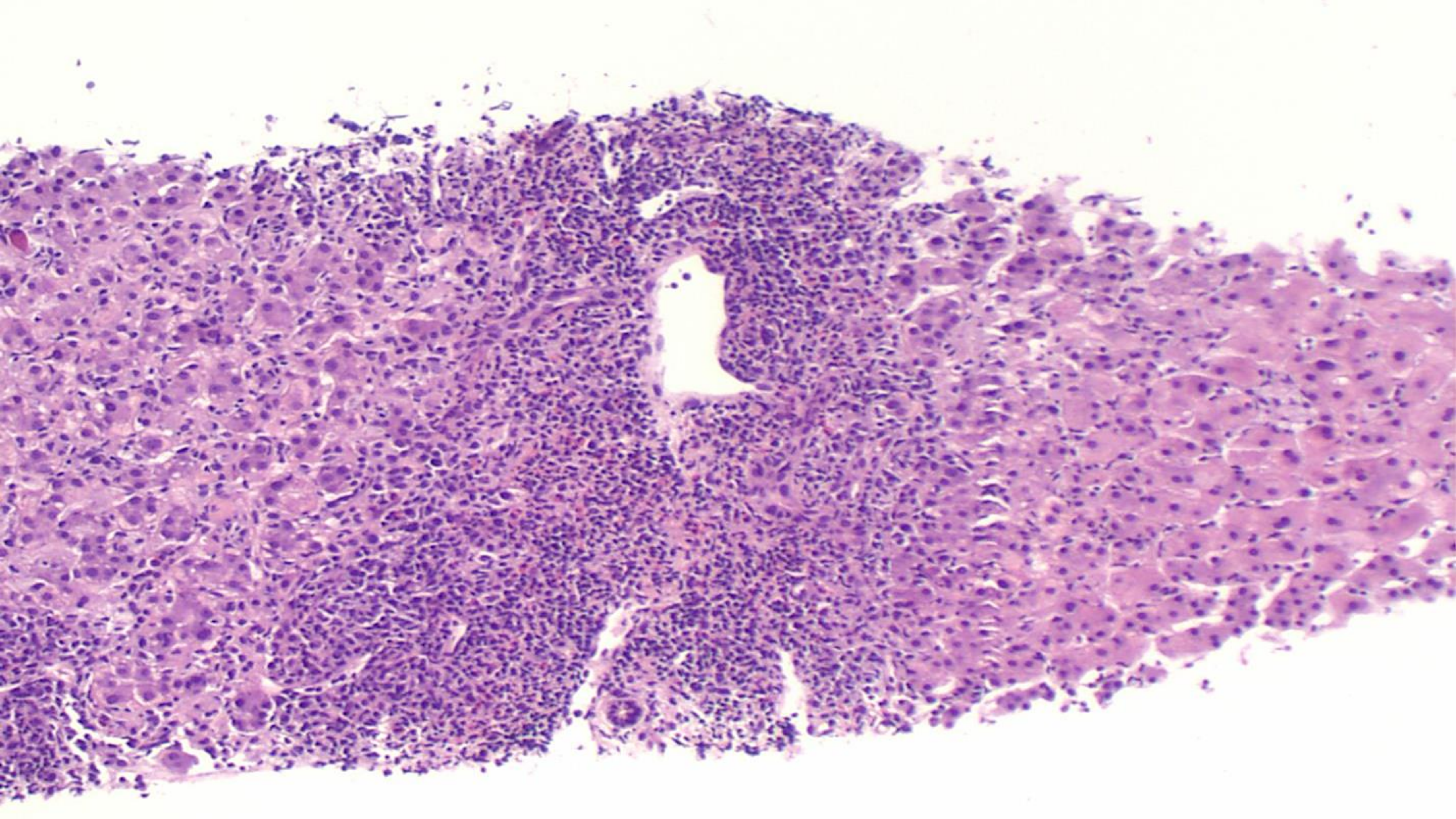
Case continued

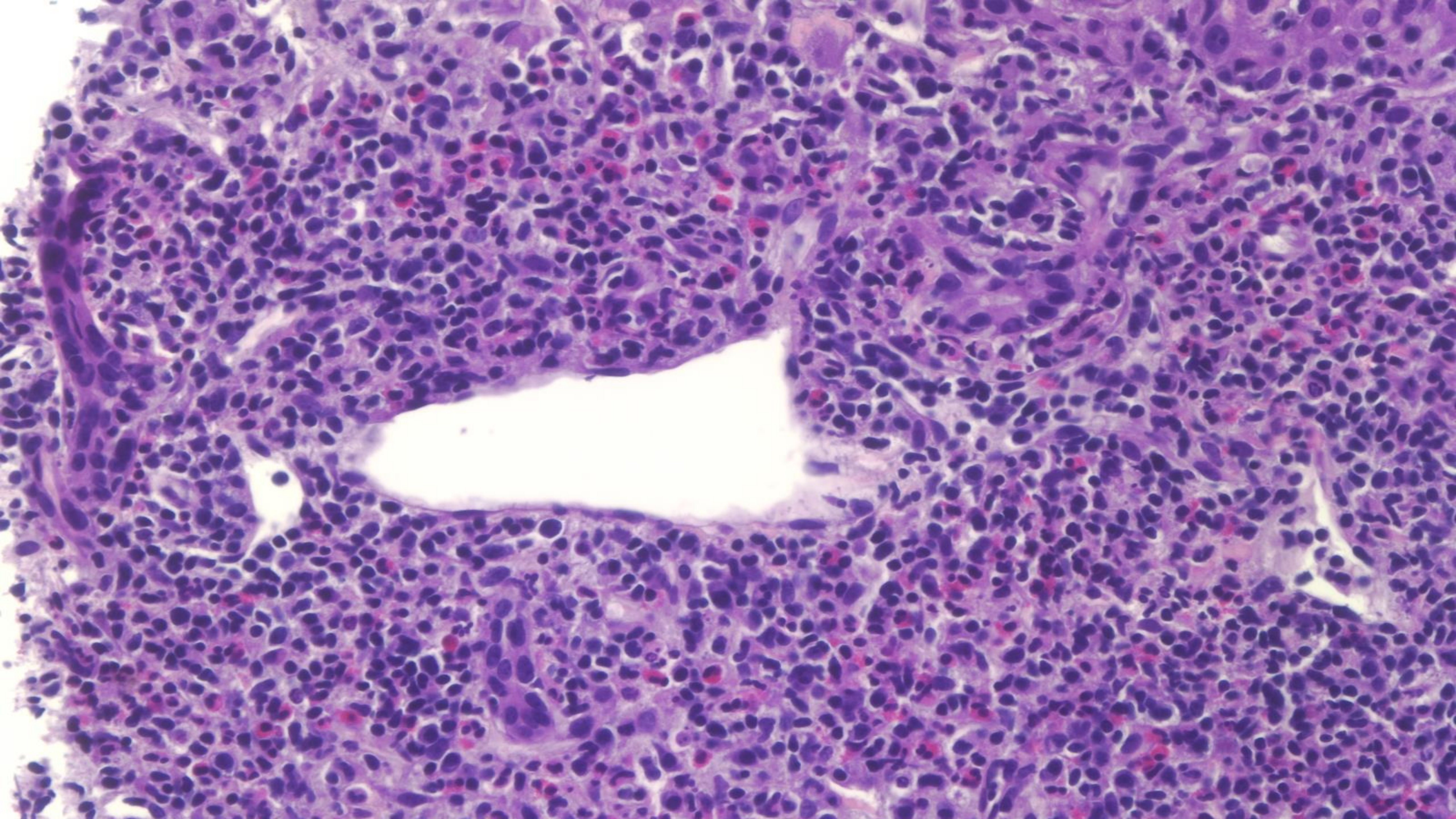
- Diagnosis: Panlobular hepatitis with numerous plasma cells.
  - Differential includes acute presentation of AIH, acute viral infection, and drug hepatitis. The numerous plasma cells would support AIH, but not exclude viral or drug.
- The real facts:
  - Patient presented with jaundice. Transaminases 1000s.
  - ANA positive 1:640. Other studies unrevealing.
  - Started on steroids and LFTs improved rapidly.
- Conclusion: Acute presentation of AIH.

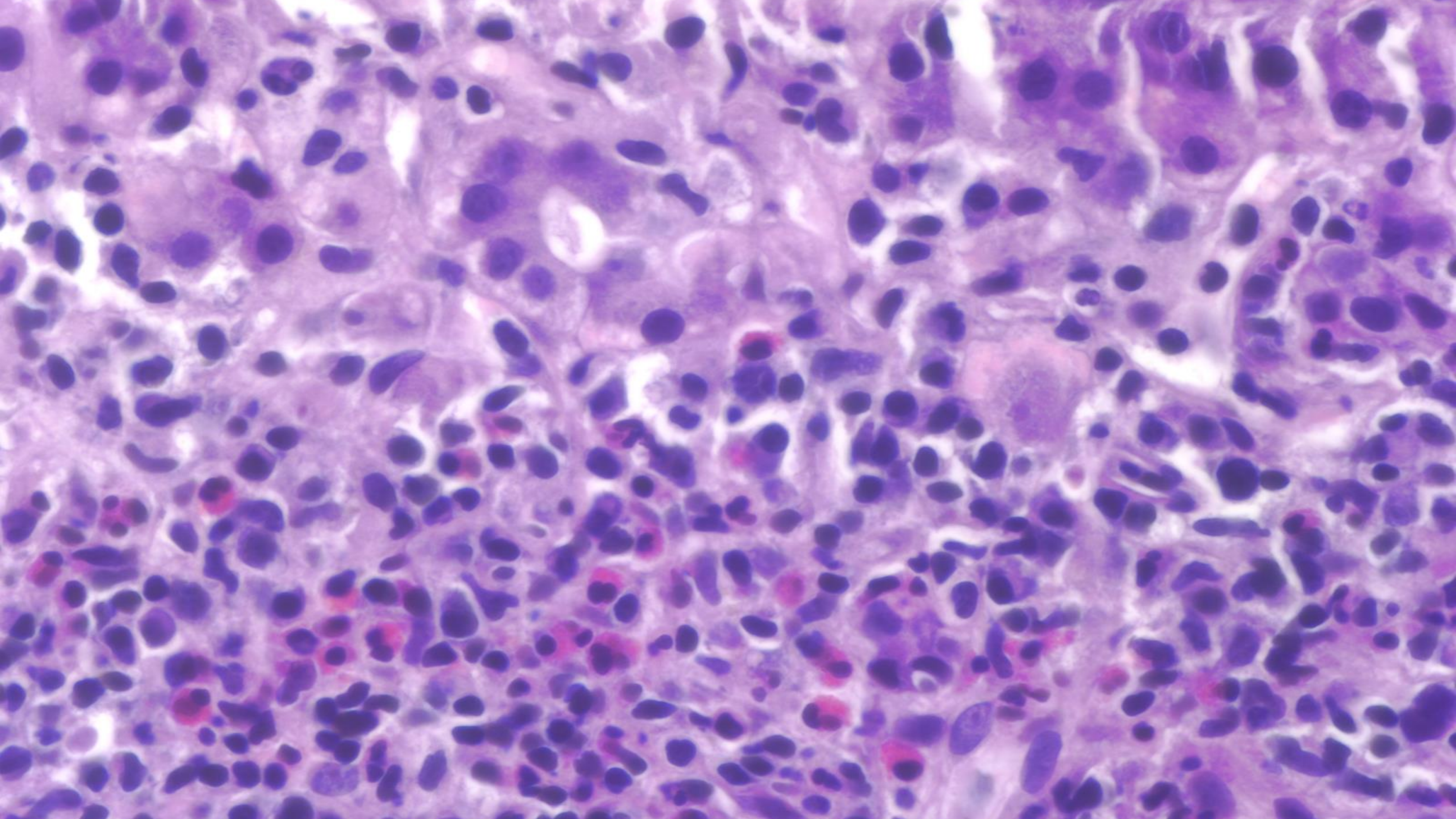
Case

- 13 year old girl who presents with ALT 1090, AST 392, ANA 1:640.



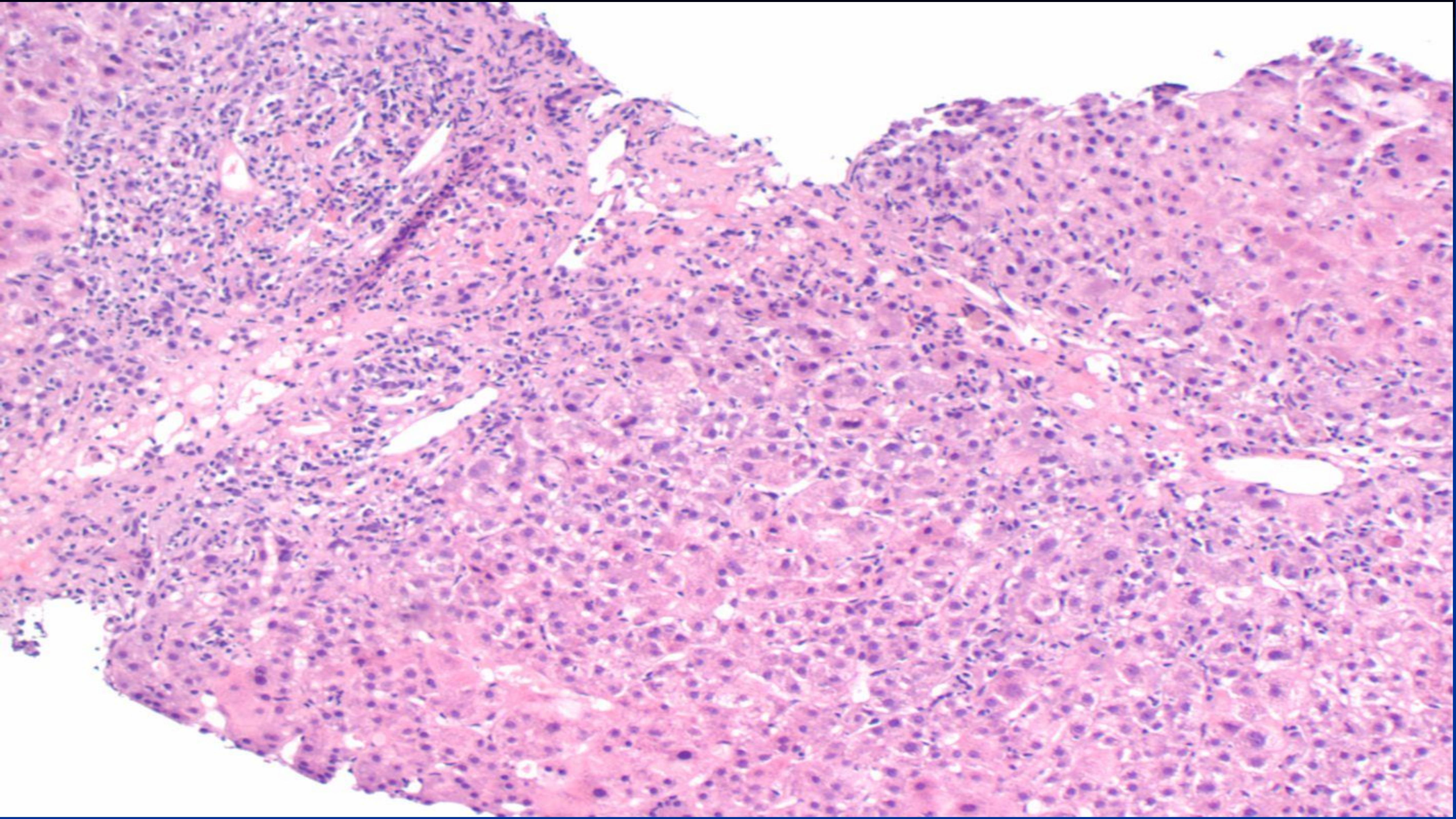


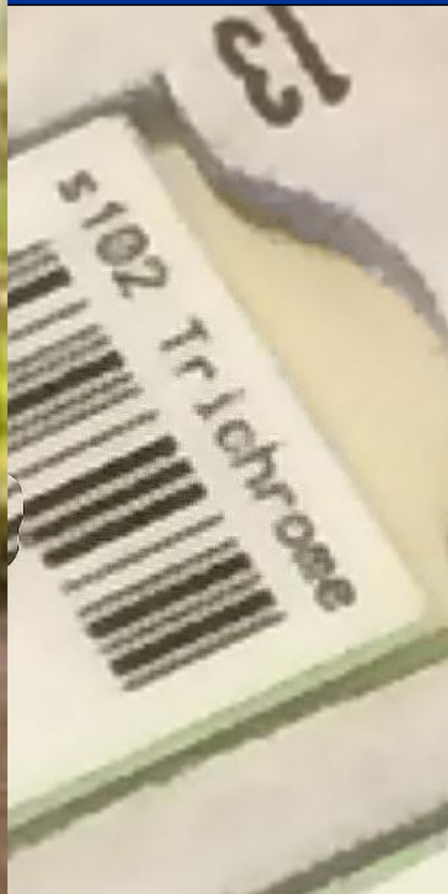


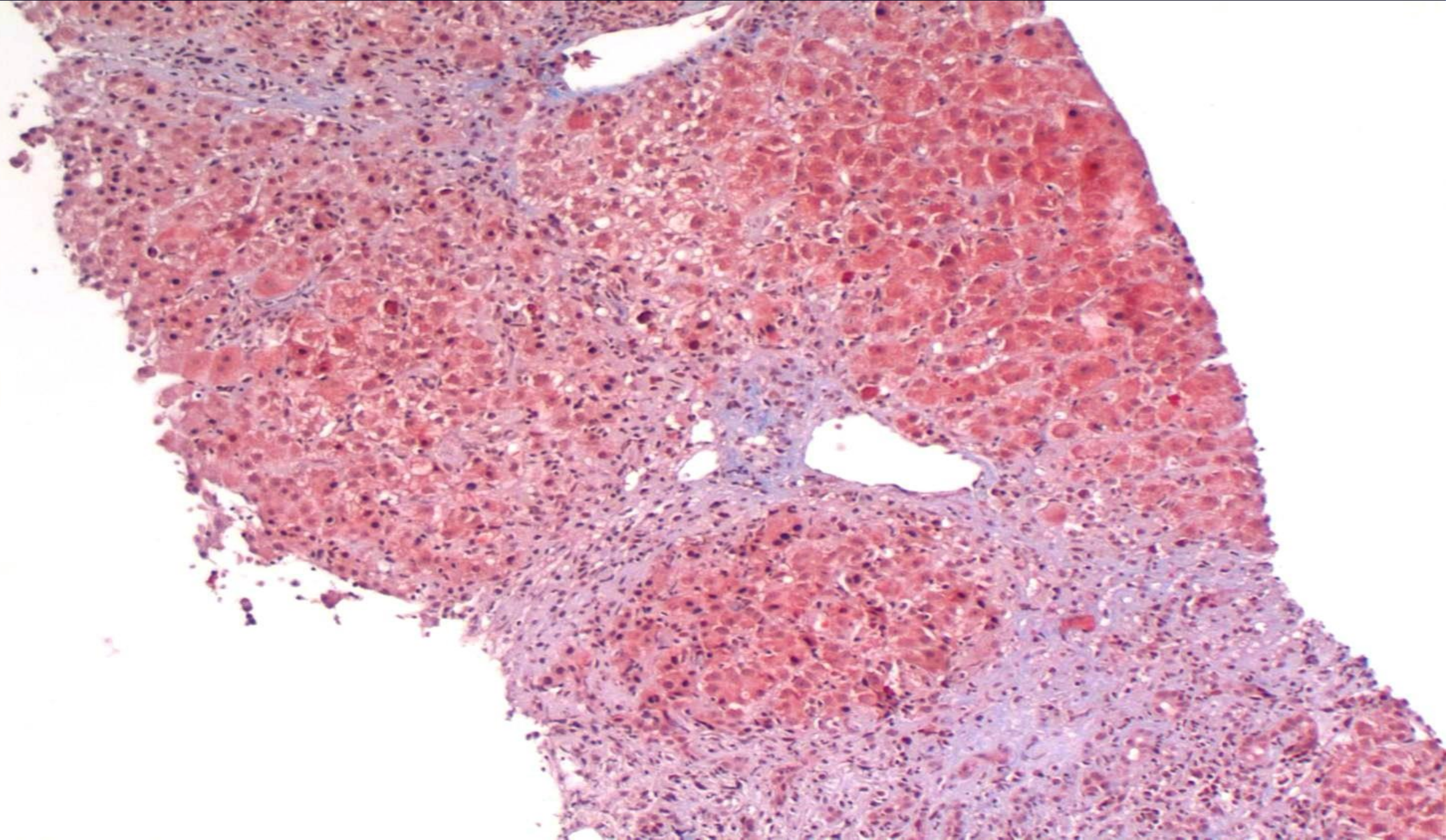


Case continued

- Pathologic diagnosis rendered was marked portal and periportal hepatitis.
  - Pathologist (incorrectly) suggested that the expanded portal tracts suggested chronicity, and that eosinophils suggested drug.
- Final diagnosis: Acute hepatitis A
- Better diagnosis would have been panlobular hepatitis, differential includes Viral, Drug, AIH

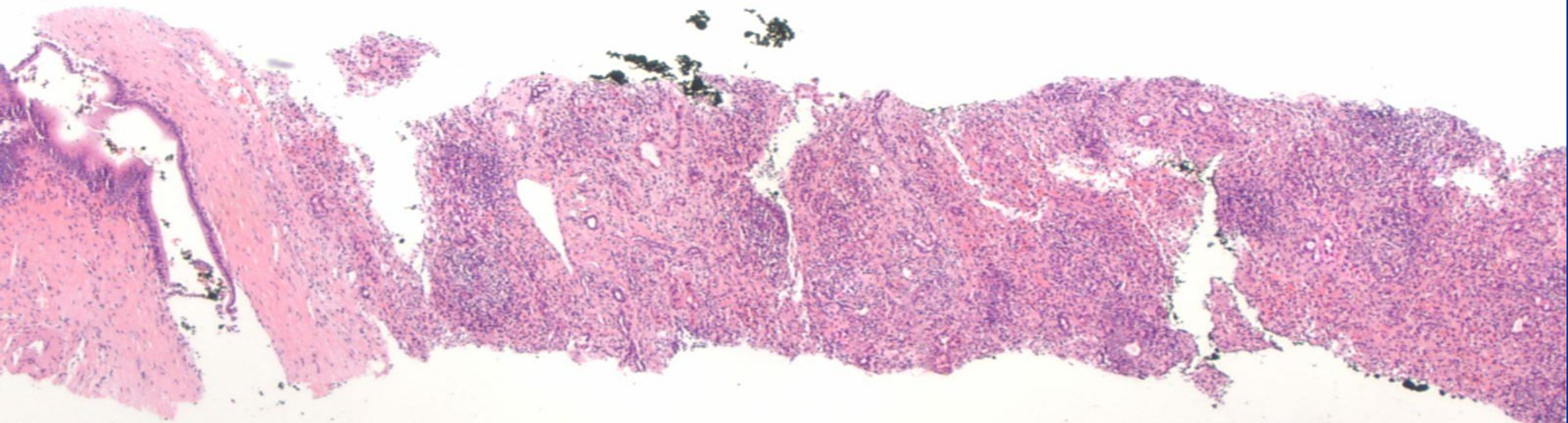


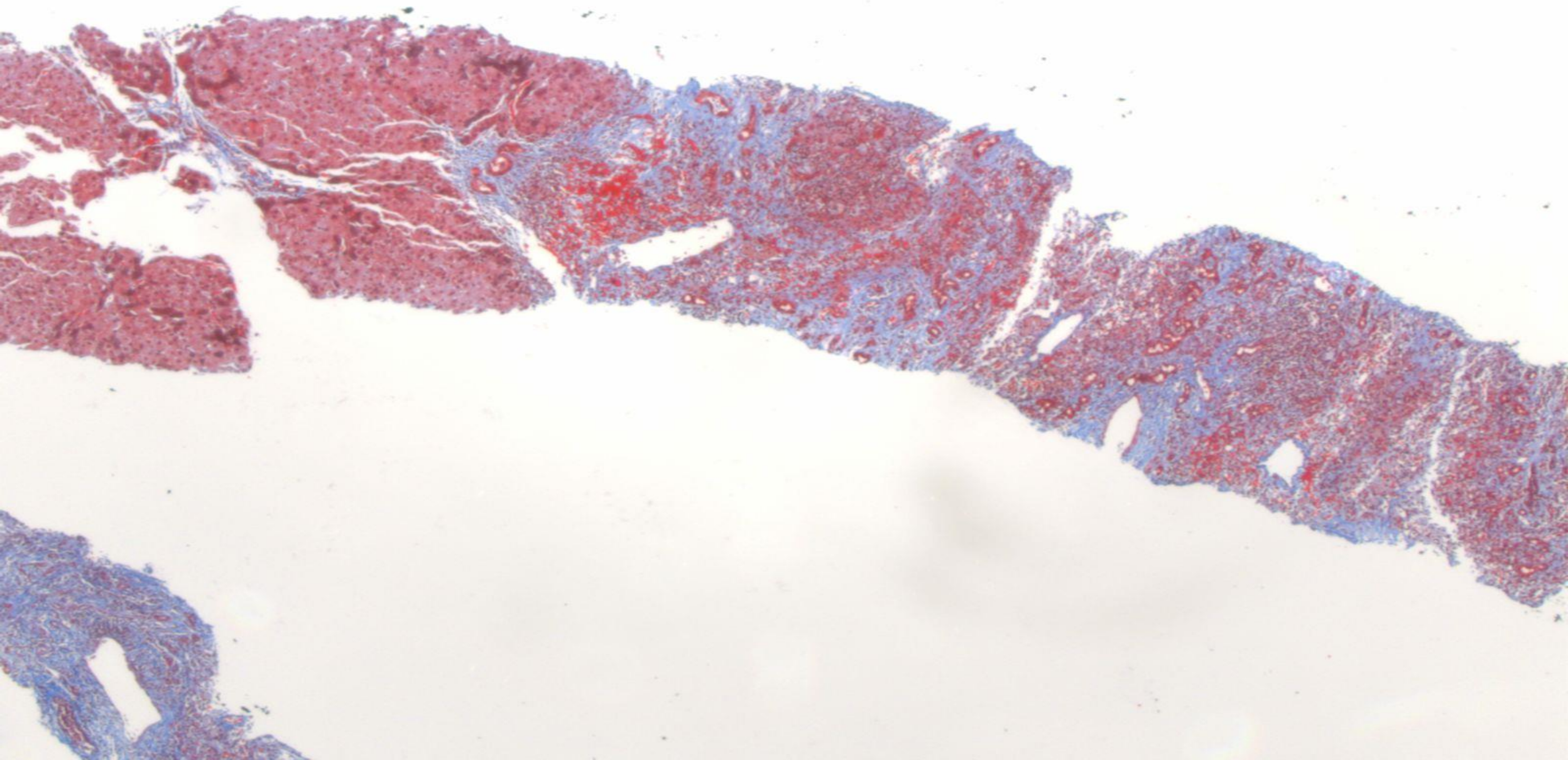

s102 Trichrome

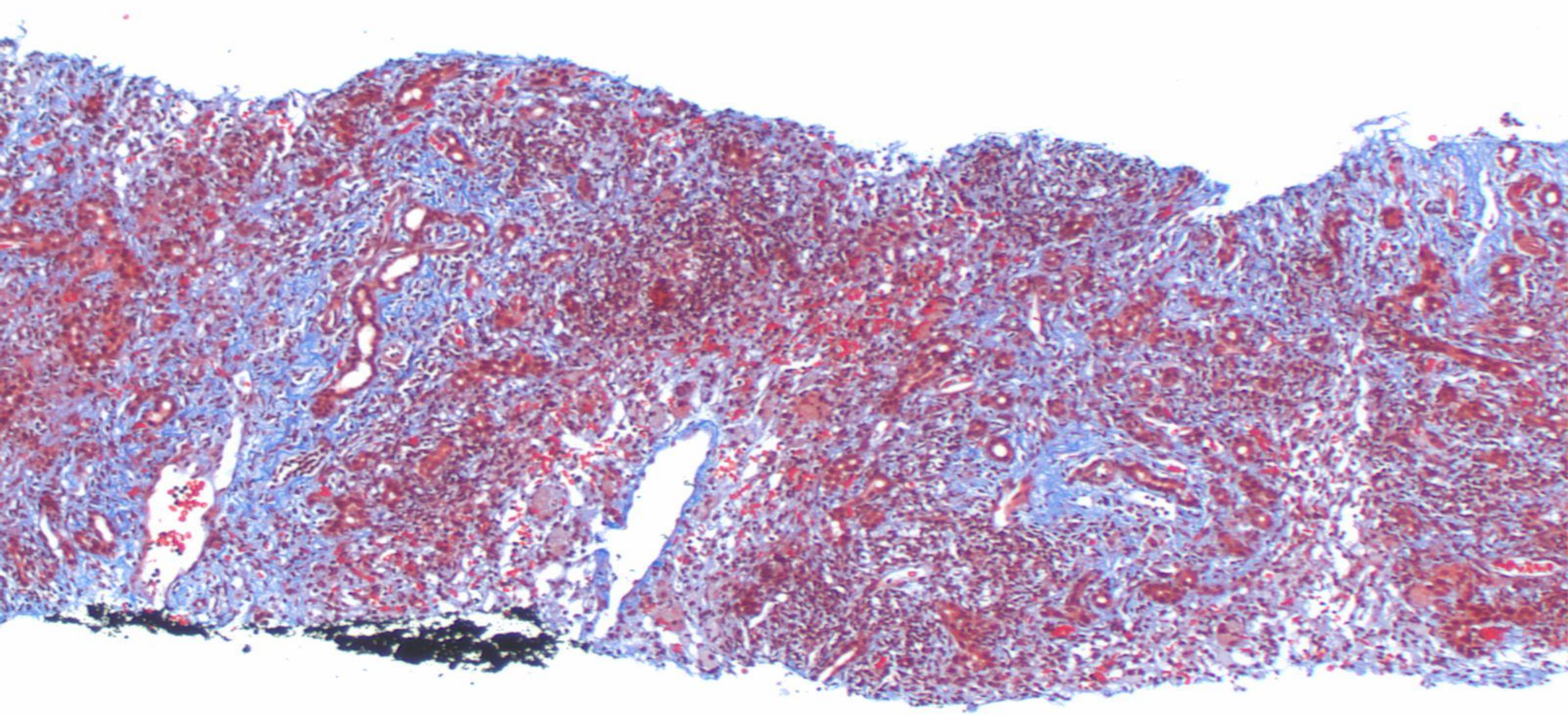


Example

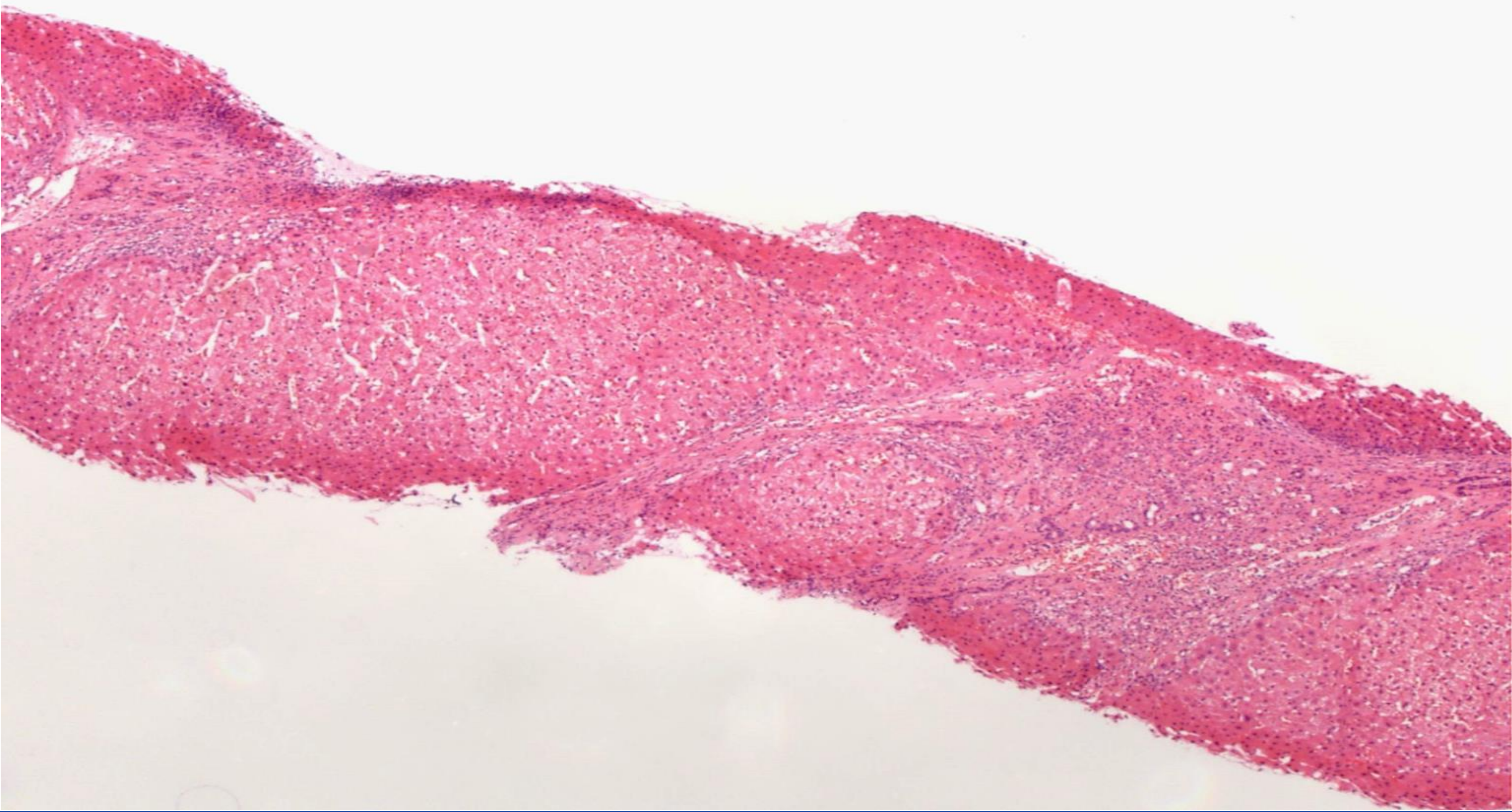
- A 52 year old woman diagnosed with cirrhosis.
- Previously well. Began to feel unwell during a camping trip to Grand Canyon 3 months prior to bx.
- Elevated LFTs (400s initially, 150s seven months later). All studies negative.

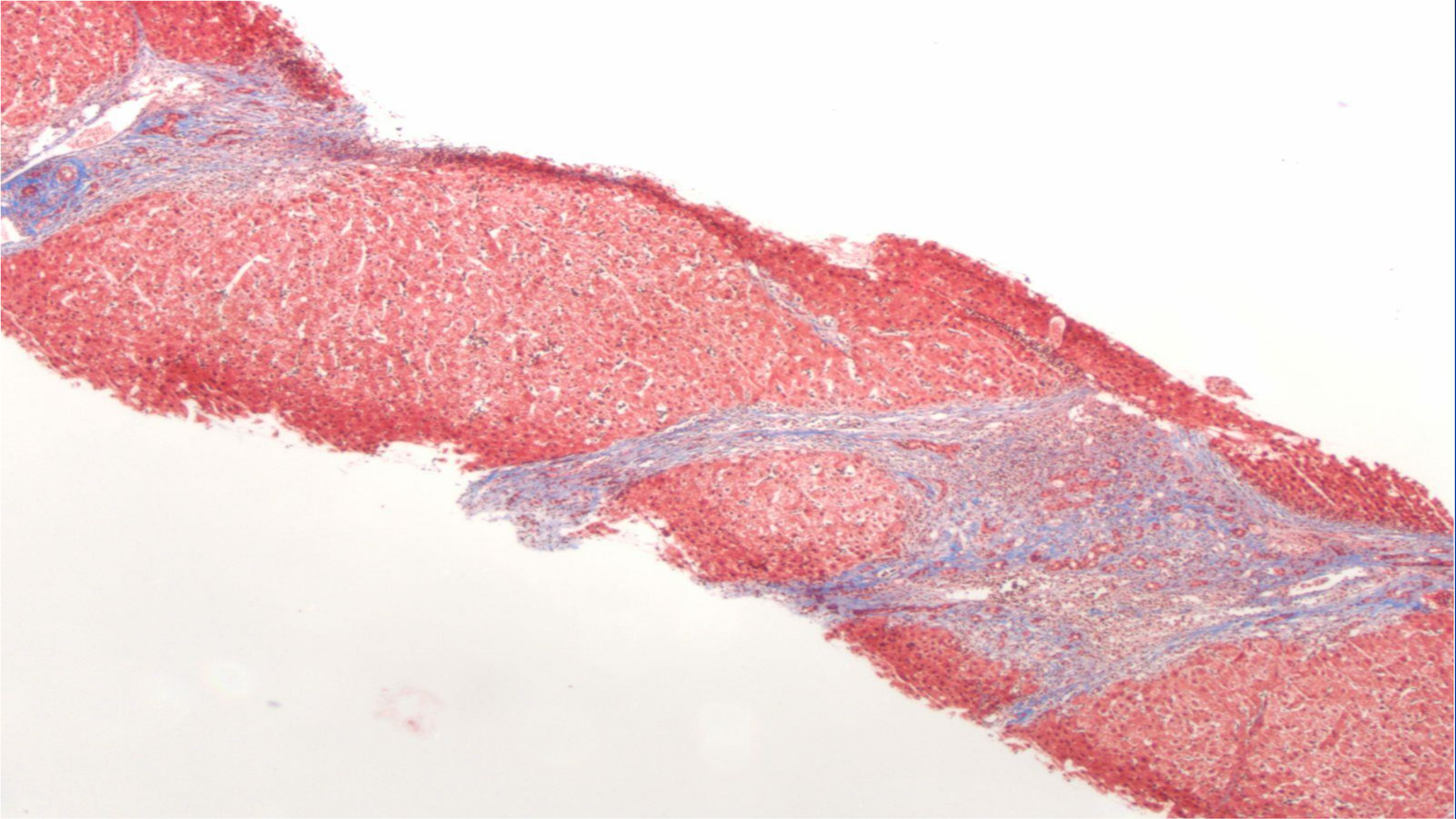


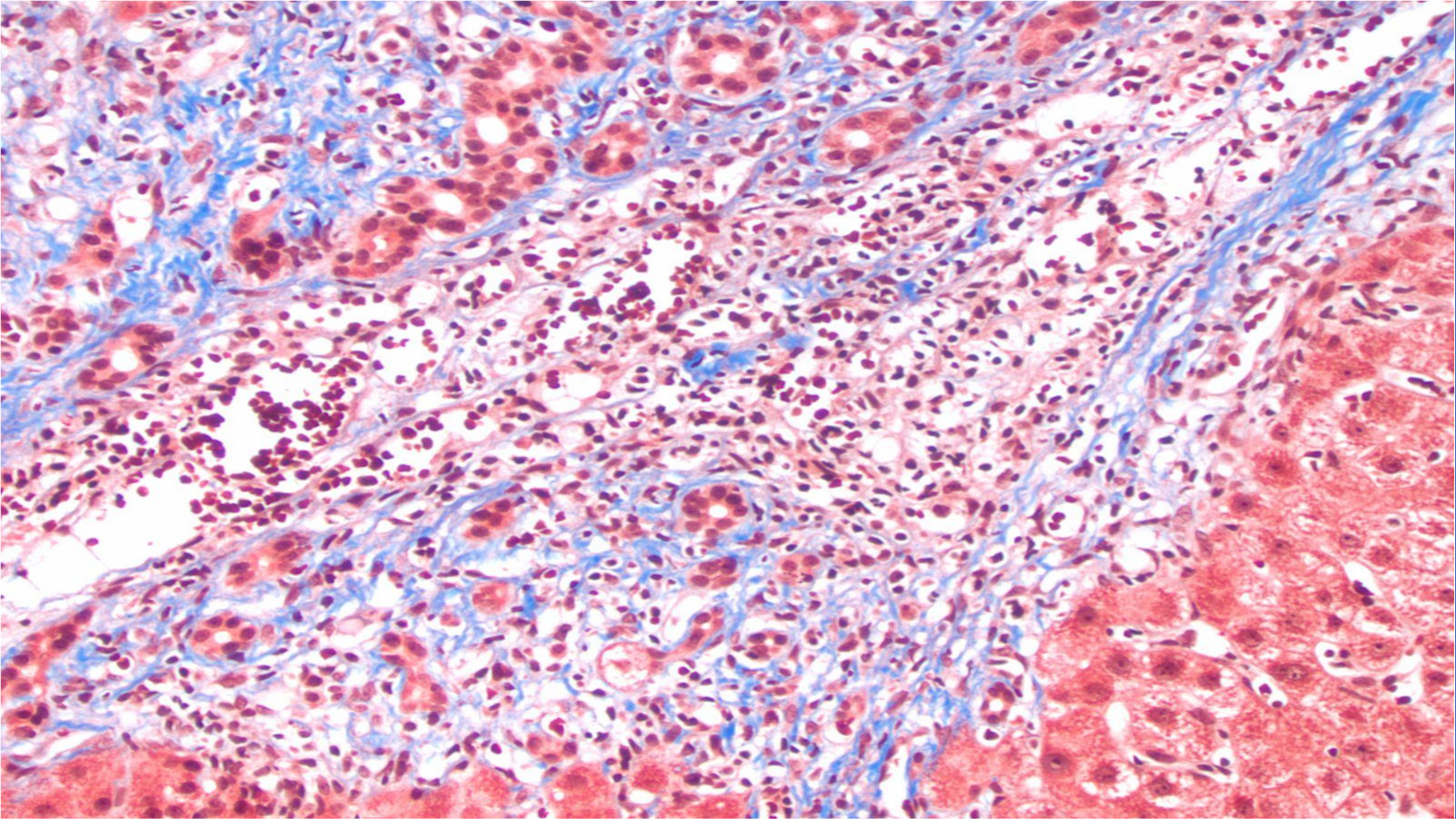




Subsequent biopsy at 8 months





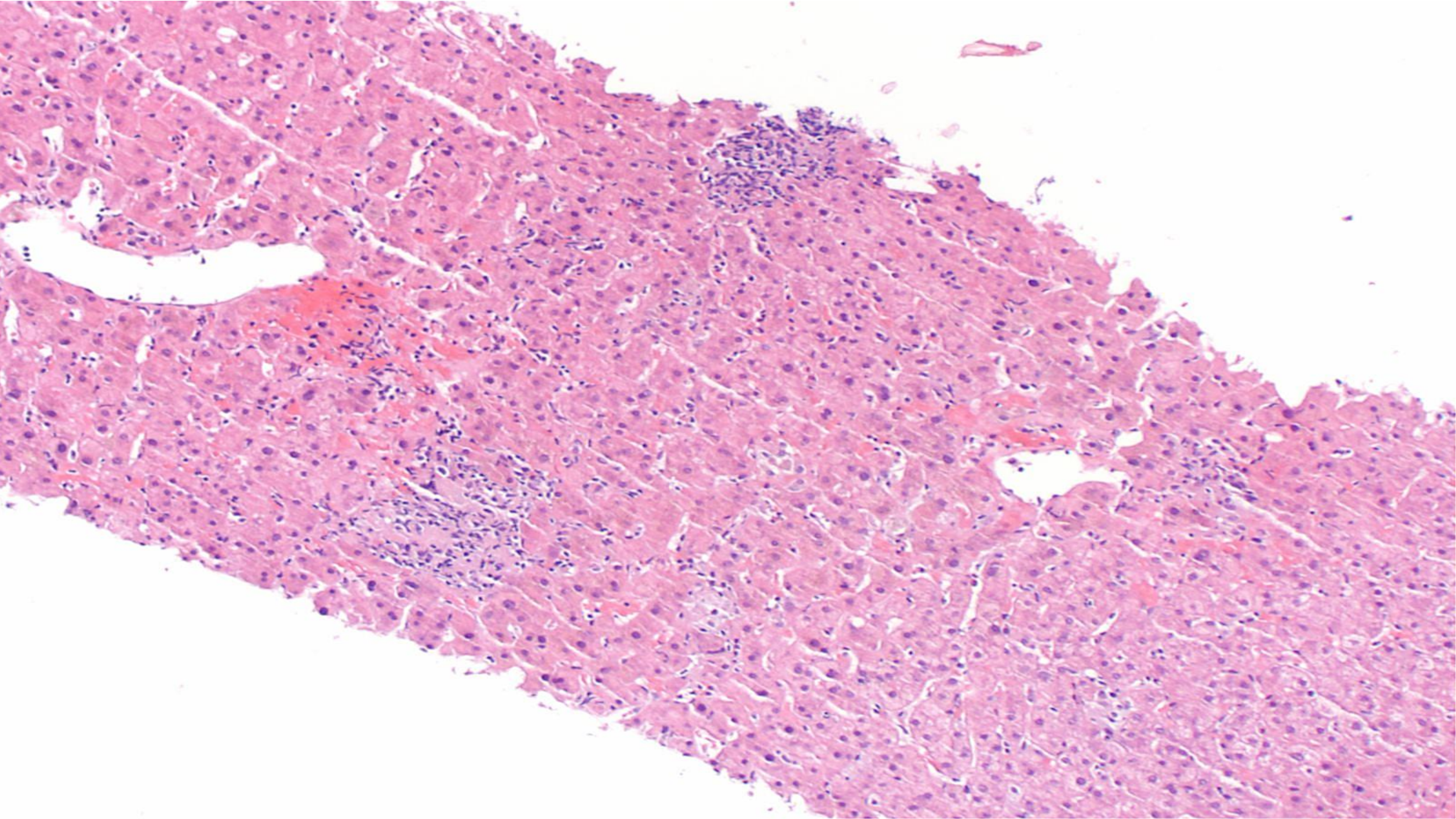


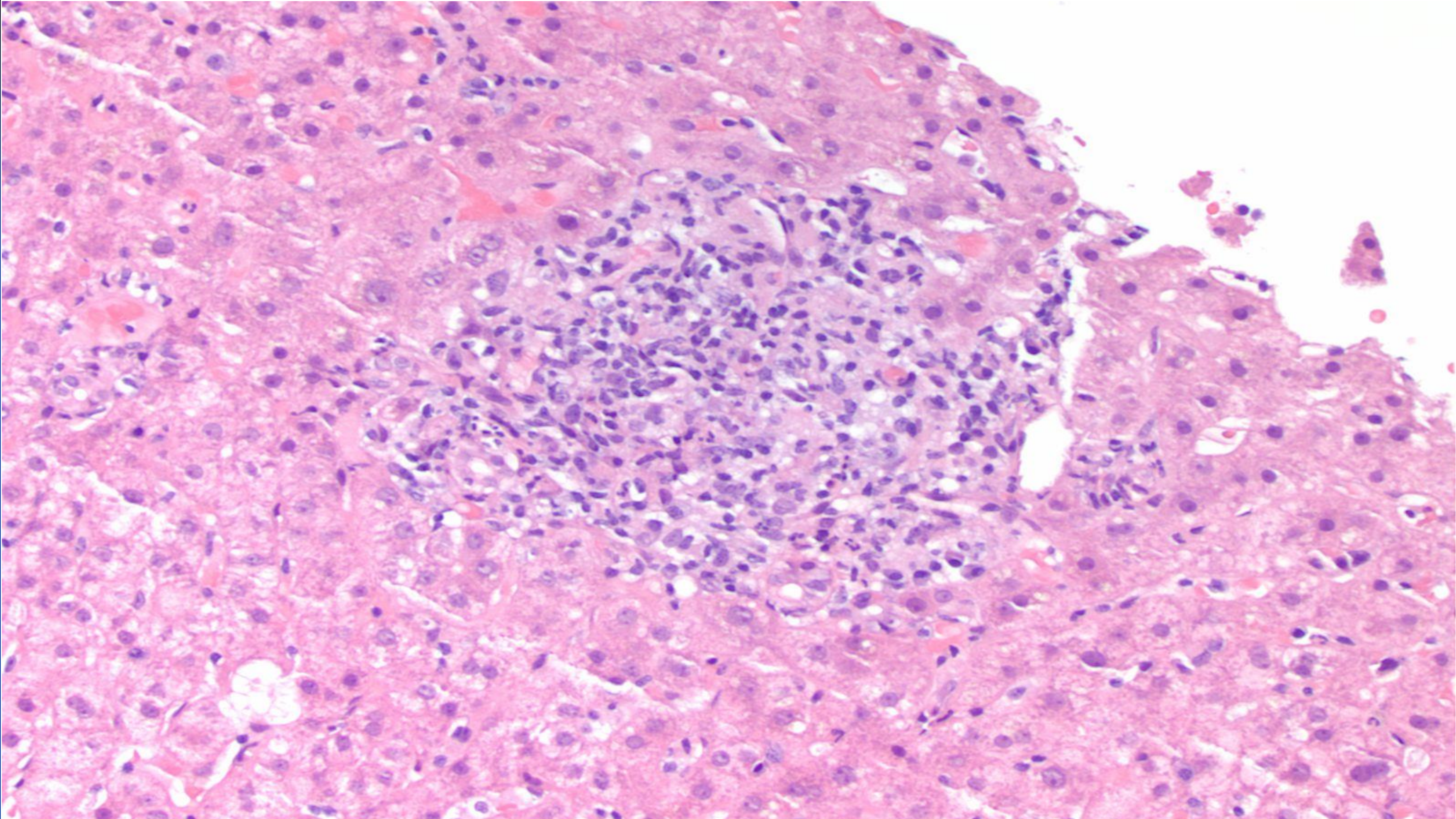
Key Points

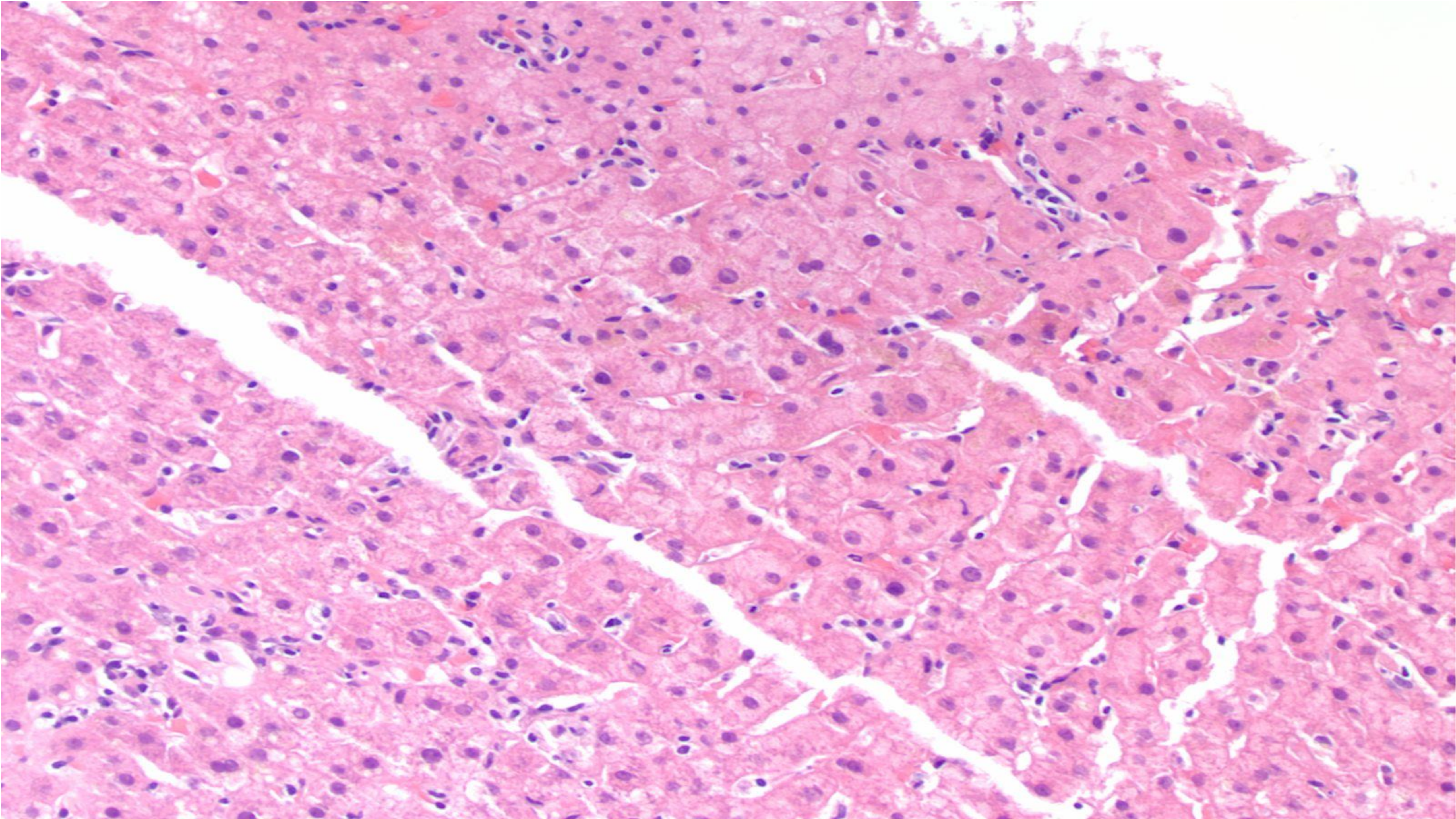
- If the lobules show significant mononuclear inflammation, numerous acidophil bodies, and lobular disarray, consider panlobular hepatitis.
- The differential is Viral, Autoimmune, Drug.
- Expanded portal tracts, collapse, and mixed inflammatory infiltrates are confounding factors.
- Plasma cells, when numerous, suggest acute AIH.
- Exercise caution when interpreting the trichrome stain in a person without known chronic hepatitis, in inflamed biopsies, and consider periportal necrosis or collapse!

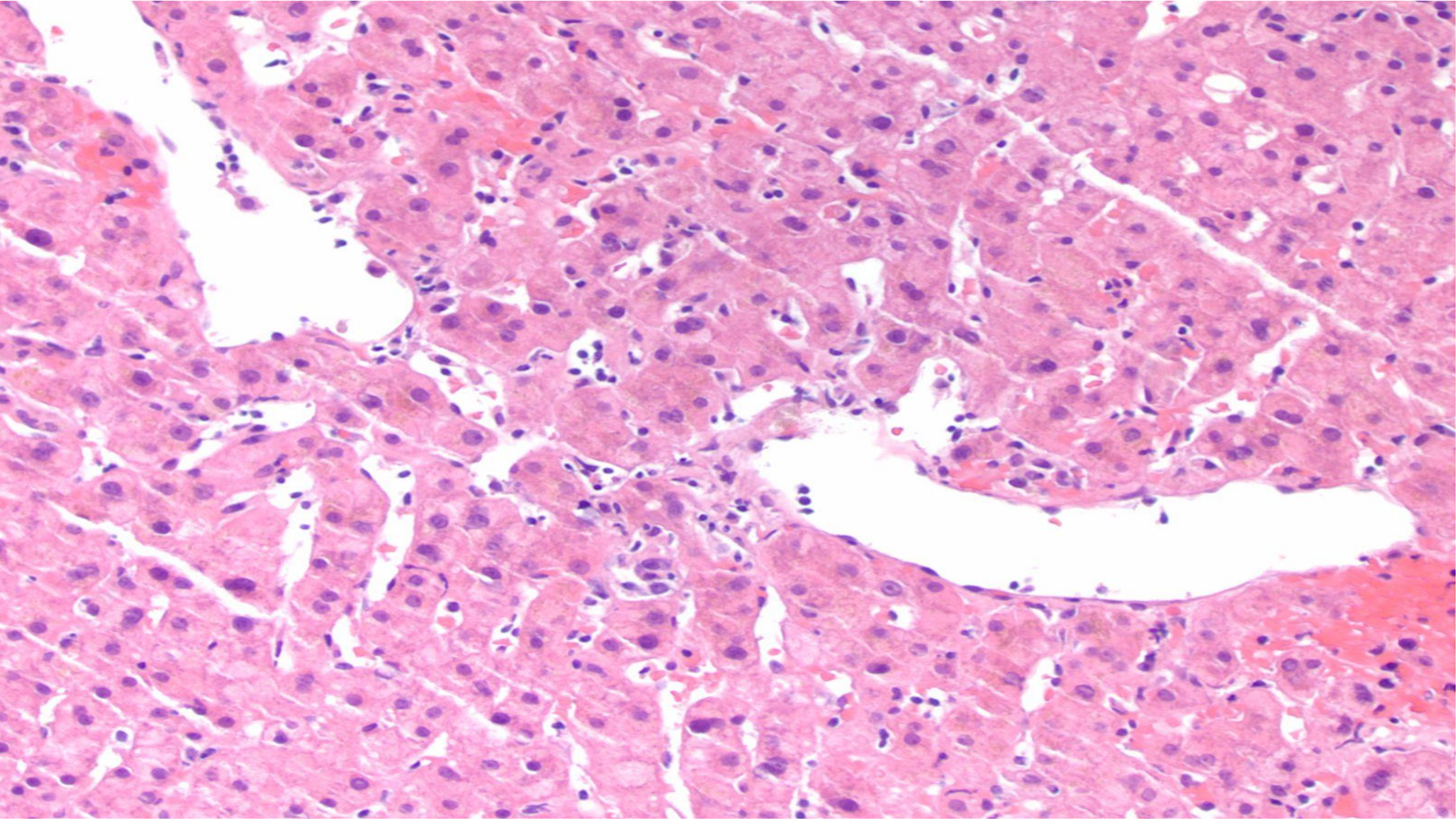
Case

- 66 year old man, previously well, develops a rash, night sweats, jaundice.
- Diagnosed as autoimmune hepatitis (although negative serology), and started on steroids.
- Patient discontinued his medication after 4 weeks.
- Resolved without further therapy.
- Review of slides requested; clinician notes patients with works with hydrocarbons and he wonders if this is related.



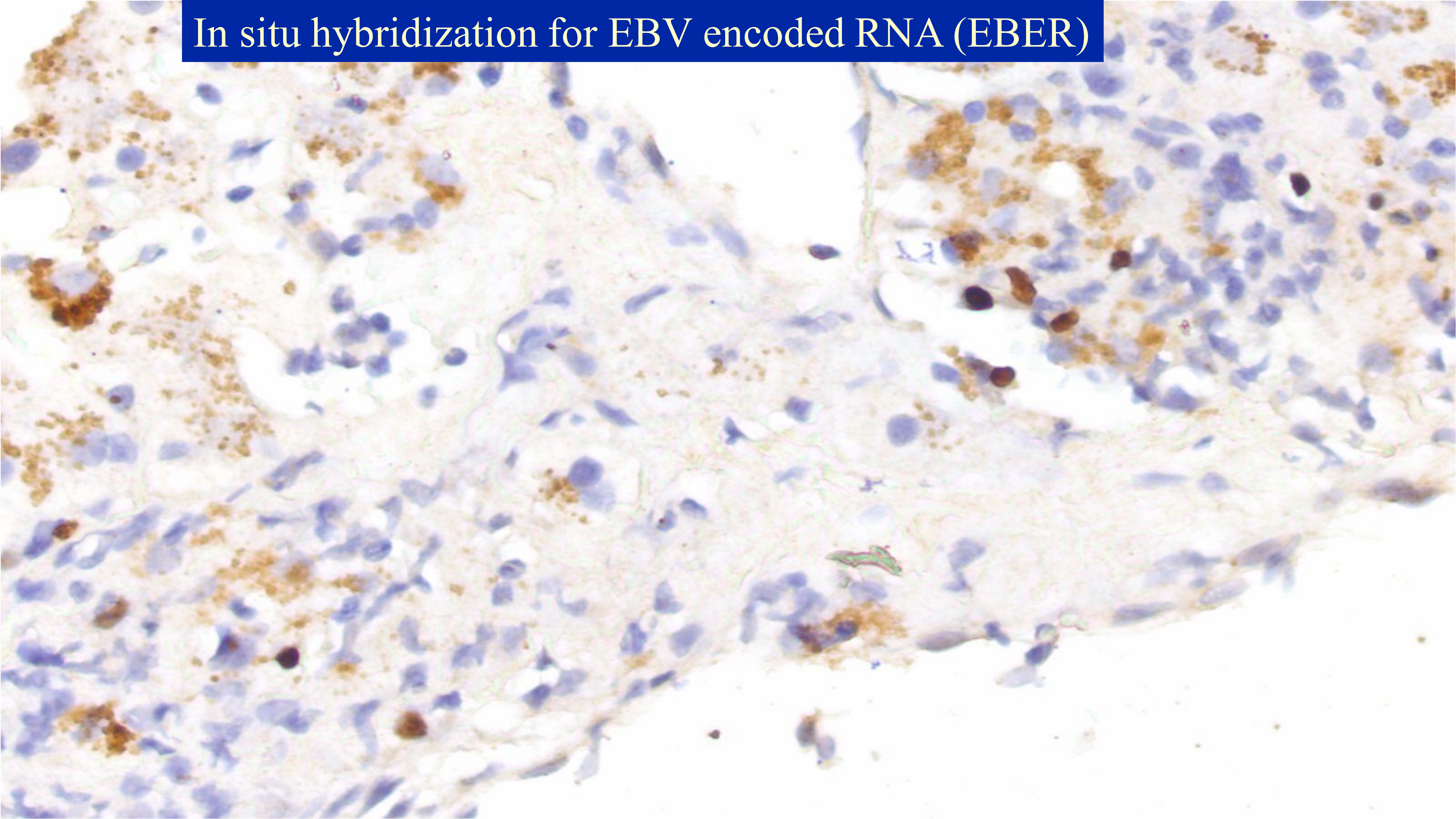


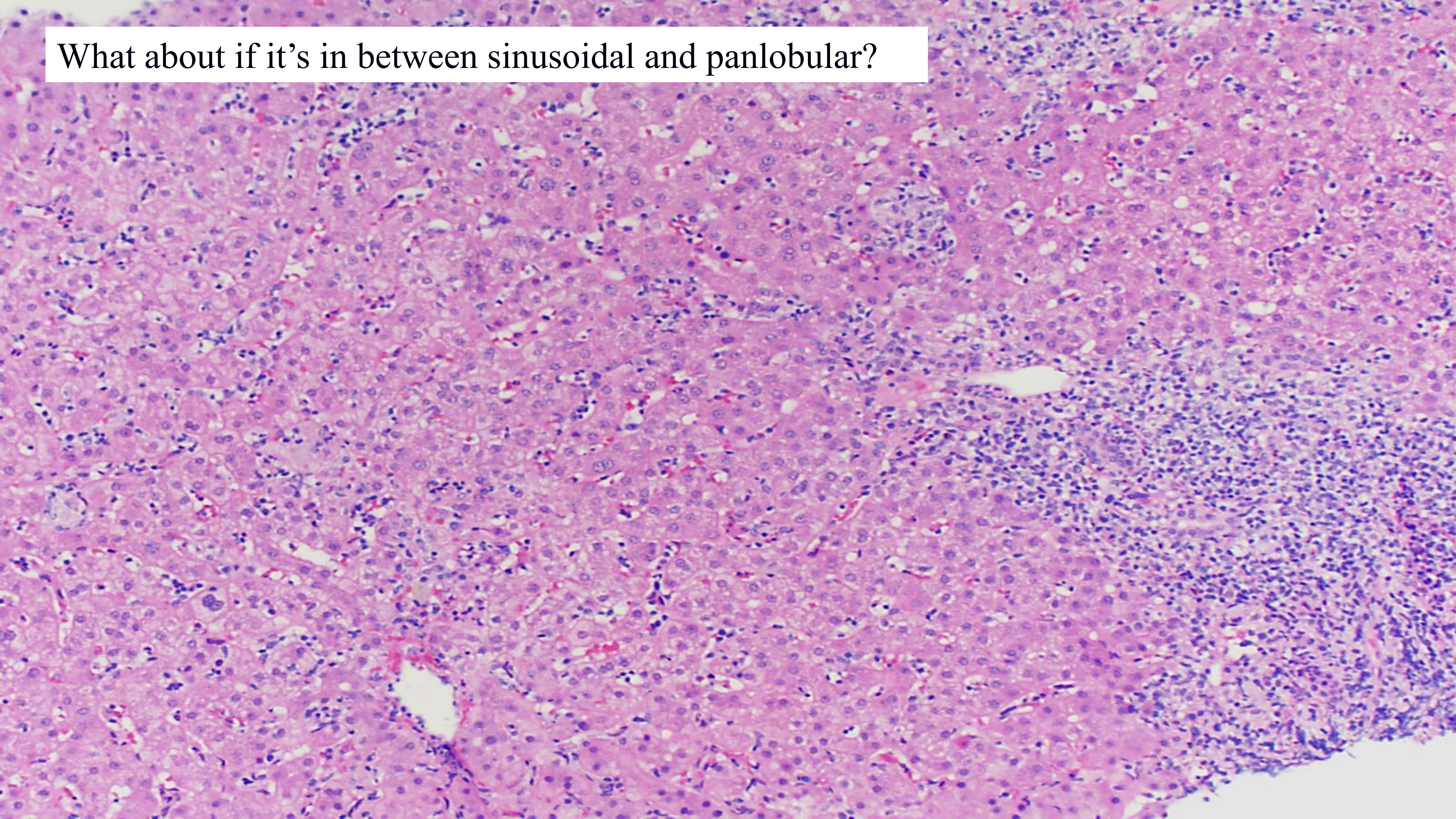


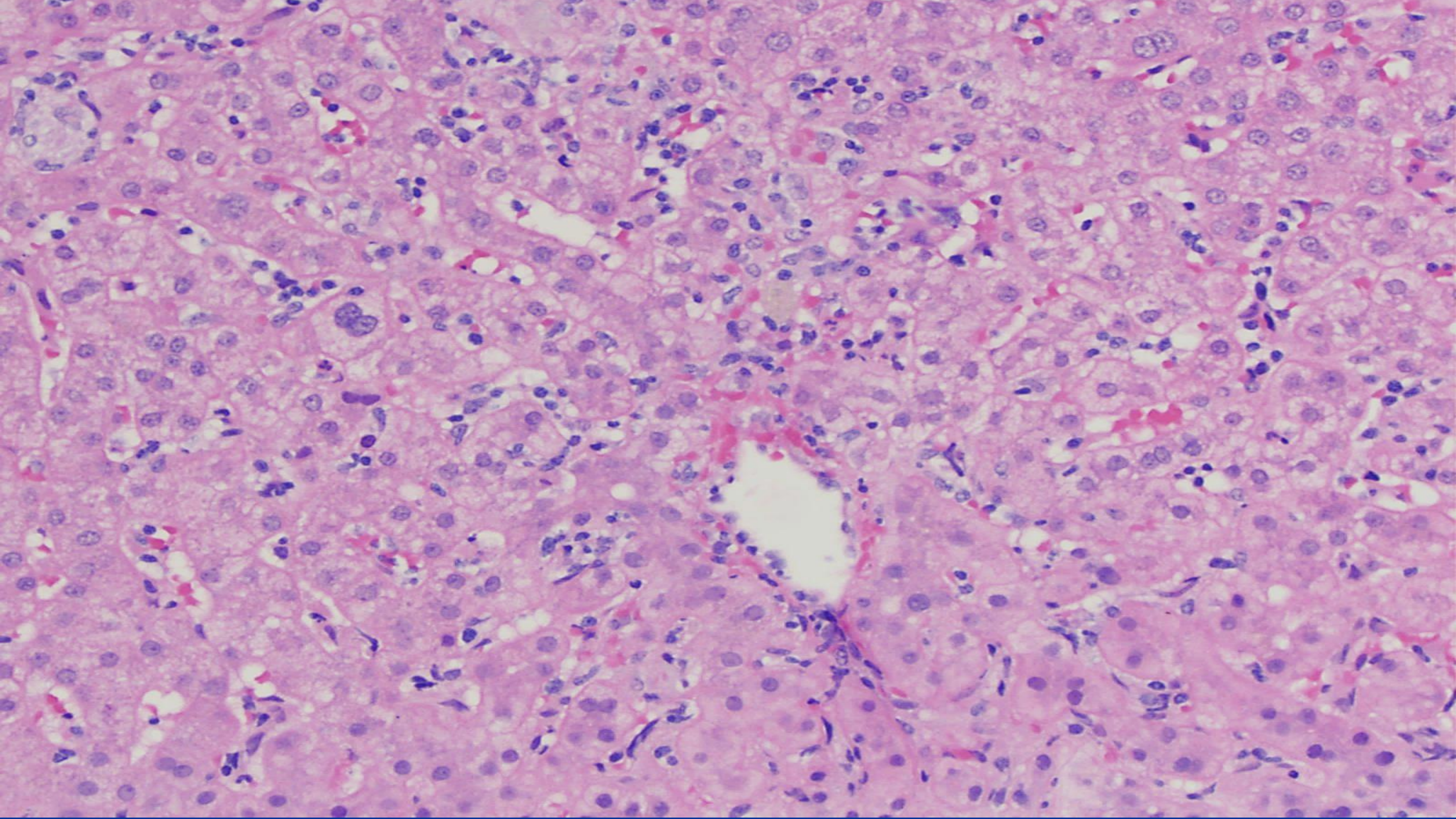


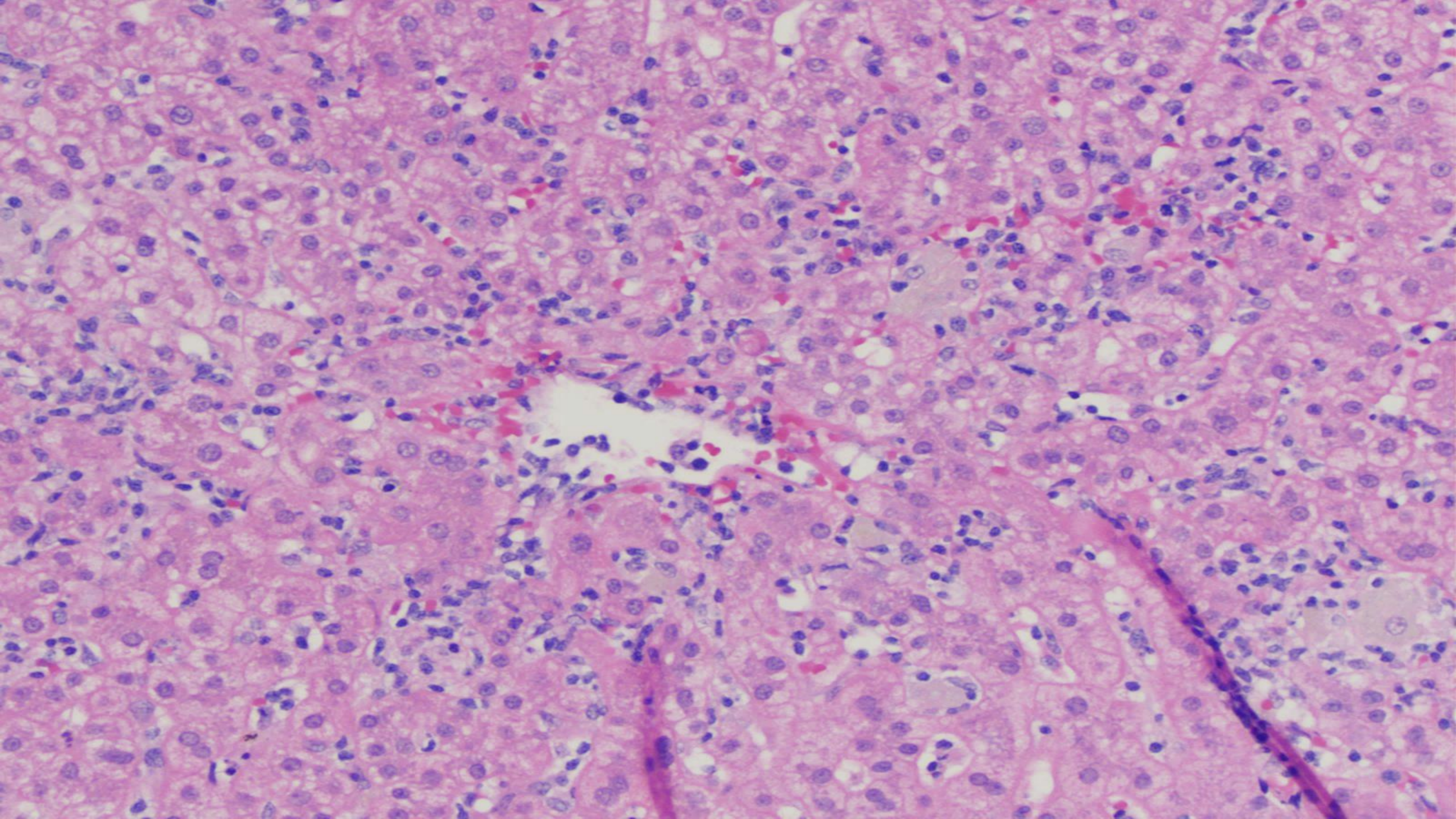
Portal and Lobular Hepatitis with <u>Prominent</u> <u>Sinusoidal</u> <u>Infiltrate</u>

- *EBV
- Other viruses, such as CMV, acute HCV.
- Drug reaction
- Unusual infections – Typhoid fever, Rickettsiae, syphilis
- Other conditions can have sinusoidal infiltration as a background feature - celiac, PBC, sarcoidosis
- AIH is typically more destructive. AIH is not excluded, but unlikely.
- When to consider lymphoma/leukemia
  - Lymphoid cells piled up within sinusoids and atypical
  - EBV in T or NK cells (rather than B cells)


In situ hybridization for EBV encoded RNA (EBER)


What about if it's in between sinusoidal and panlobular?





Differential Diagnosis

Panlobular Hepatitis

Infiltrate throughout lobule with significant hepatocyte injury/death

Viral (HAV, HBV, HEV, unlikely acute HCV)
Drug
Acute onset AIH

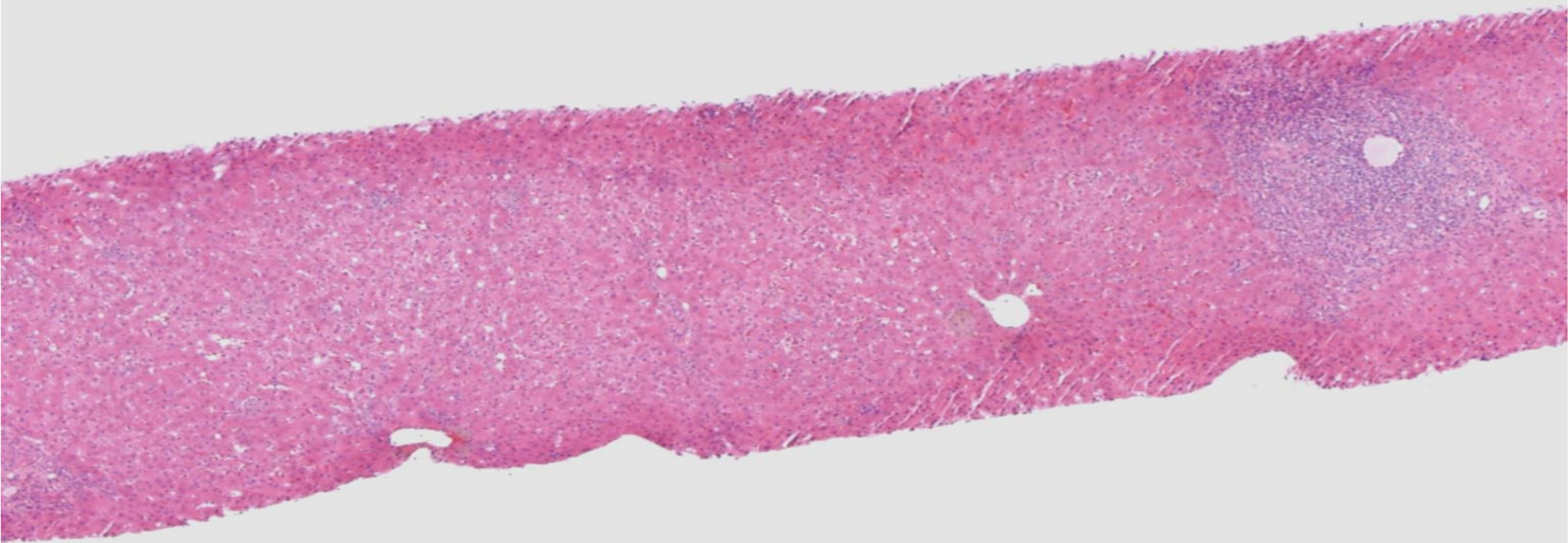
Sinusoidal infiltrate

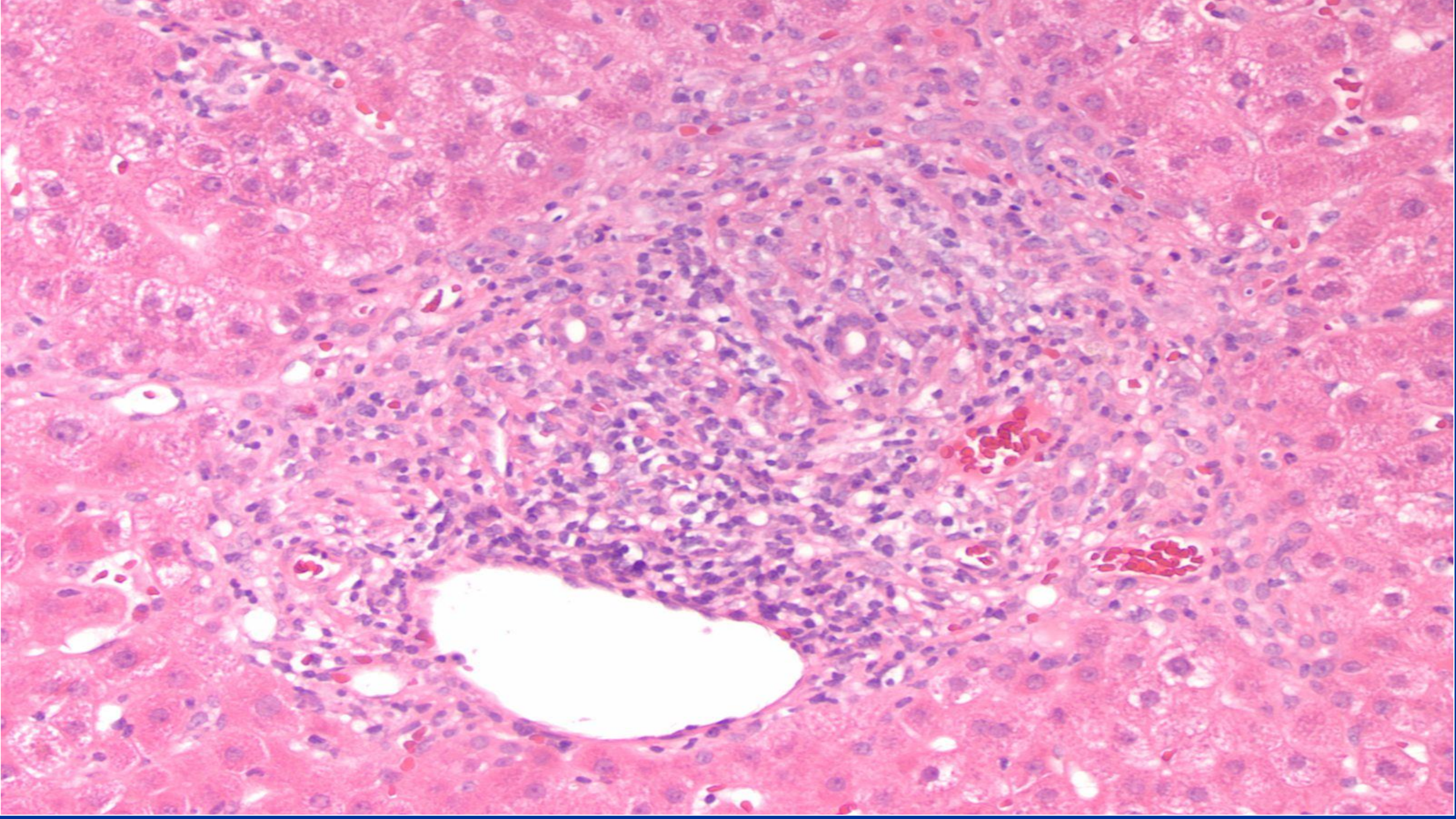
Infiltrate throughout lobule with no/limited hepatocyte injury

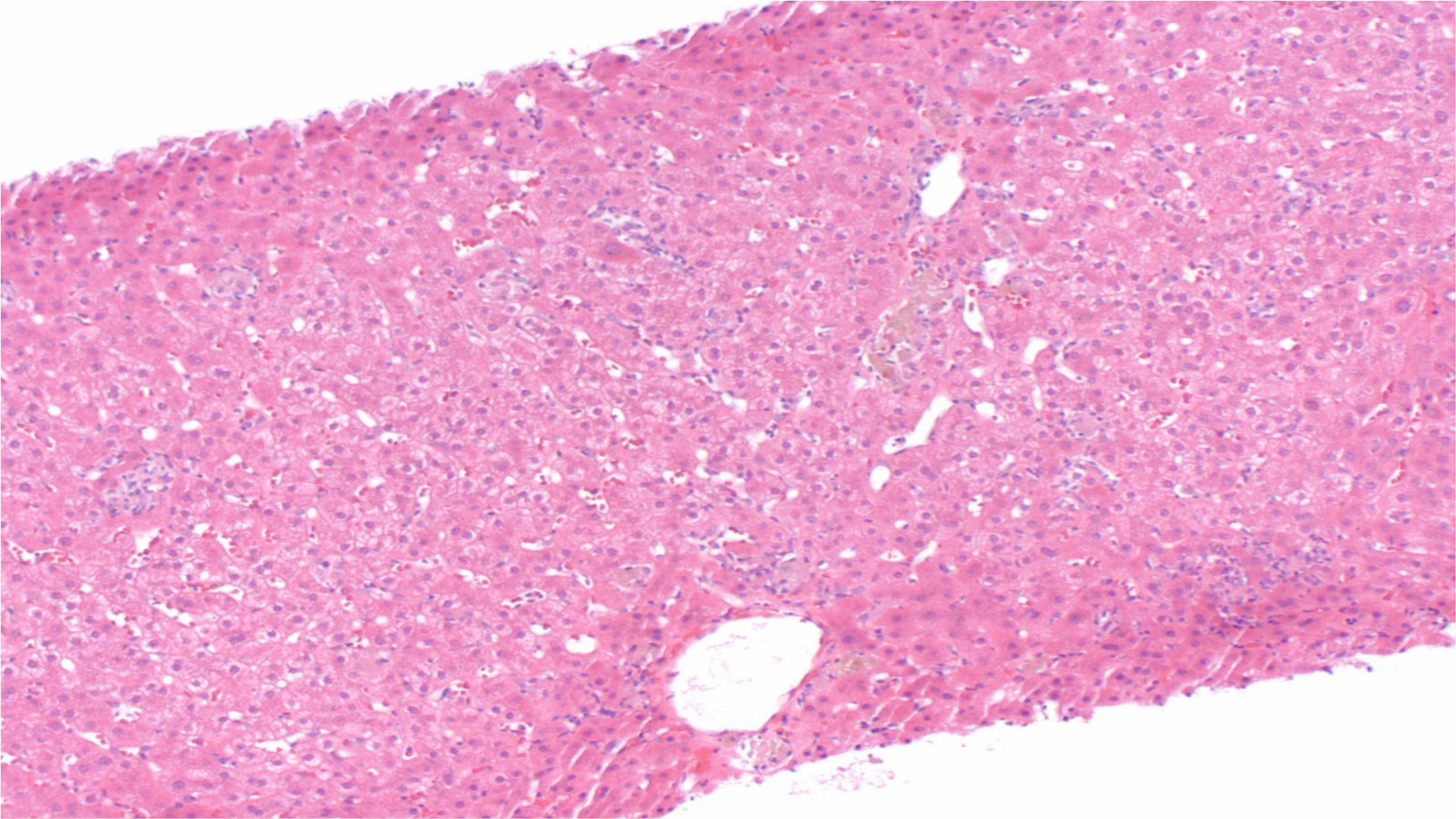
Viral (EBV, CMV, HCV)
Drug
Systemic illness (celiac, sarcoidosis)
Lymphoma/Leukemia
Unlikely AIH

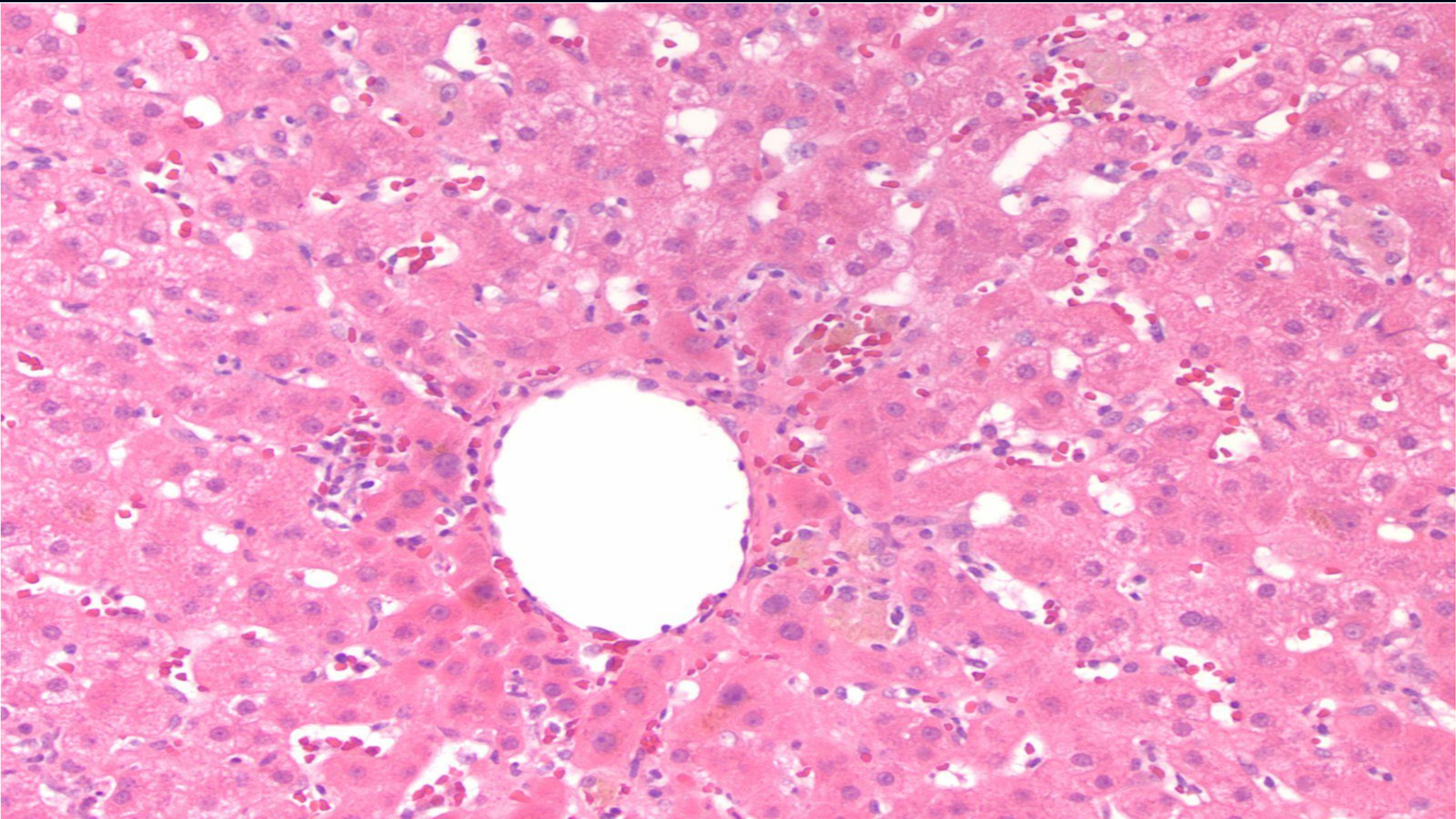
Case

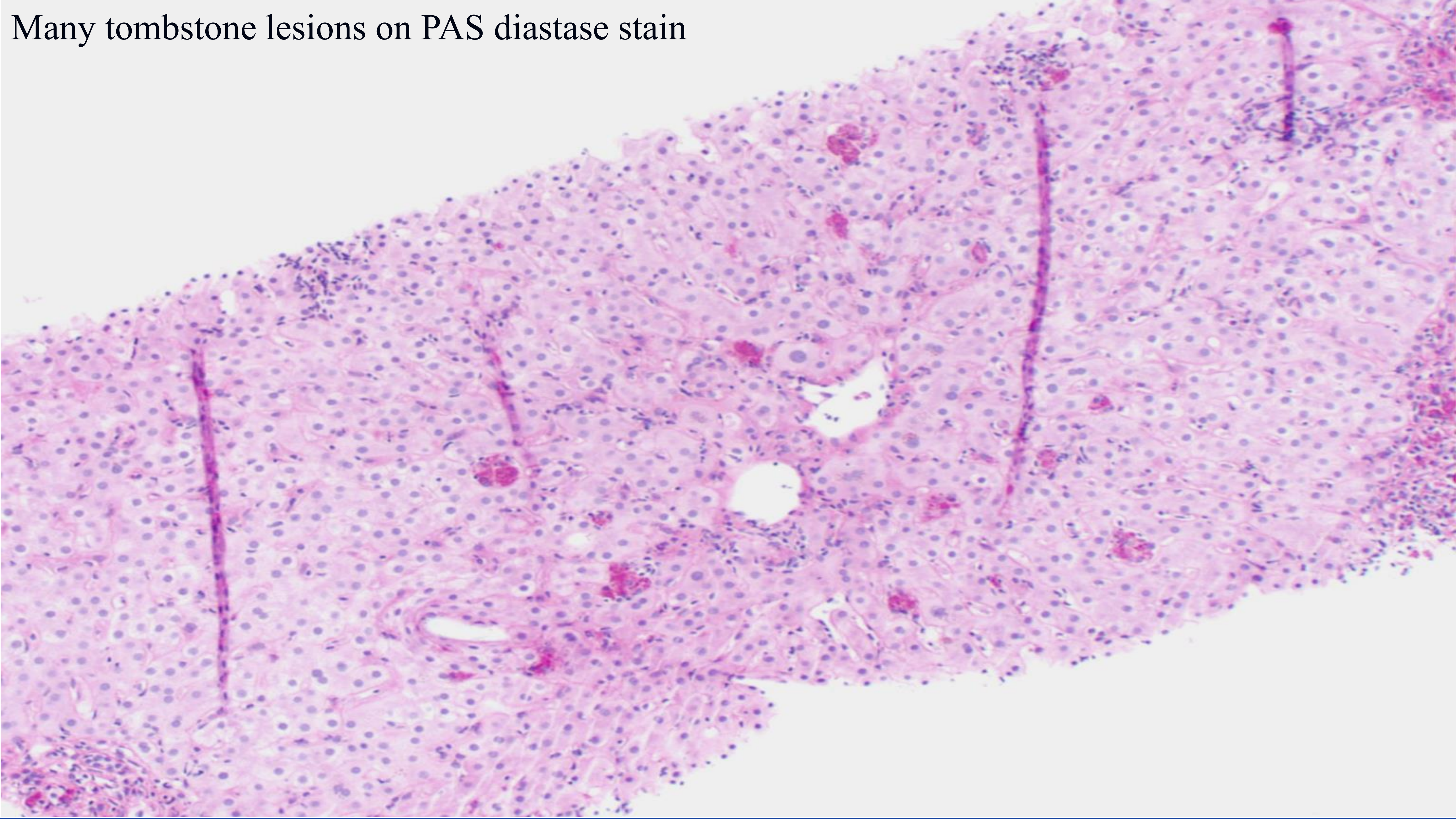
- 55 year old woman.
- Liver biopsy for "hepatitis C"
- Biopsy diagnosed as "Moderately active chronic hepatitis" with stage 2 of 6 Ishak (portal fibrous expansion of most portal tracts, without bridging).
- Clinician calls to ask for confirmation of "chronic" HCV because she wasn't sure if it was acute or chronic.

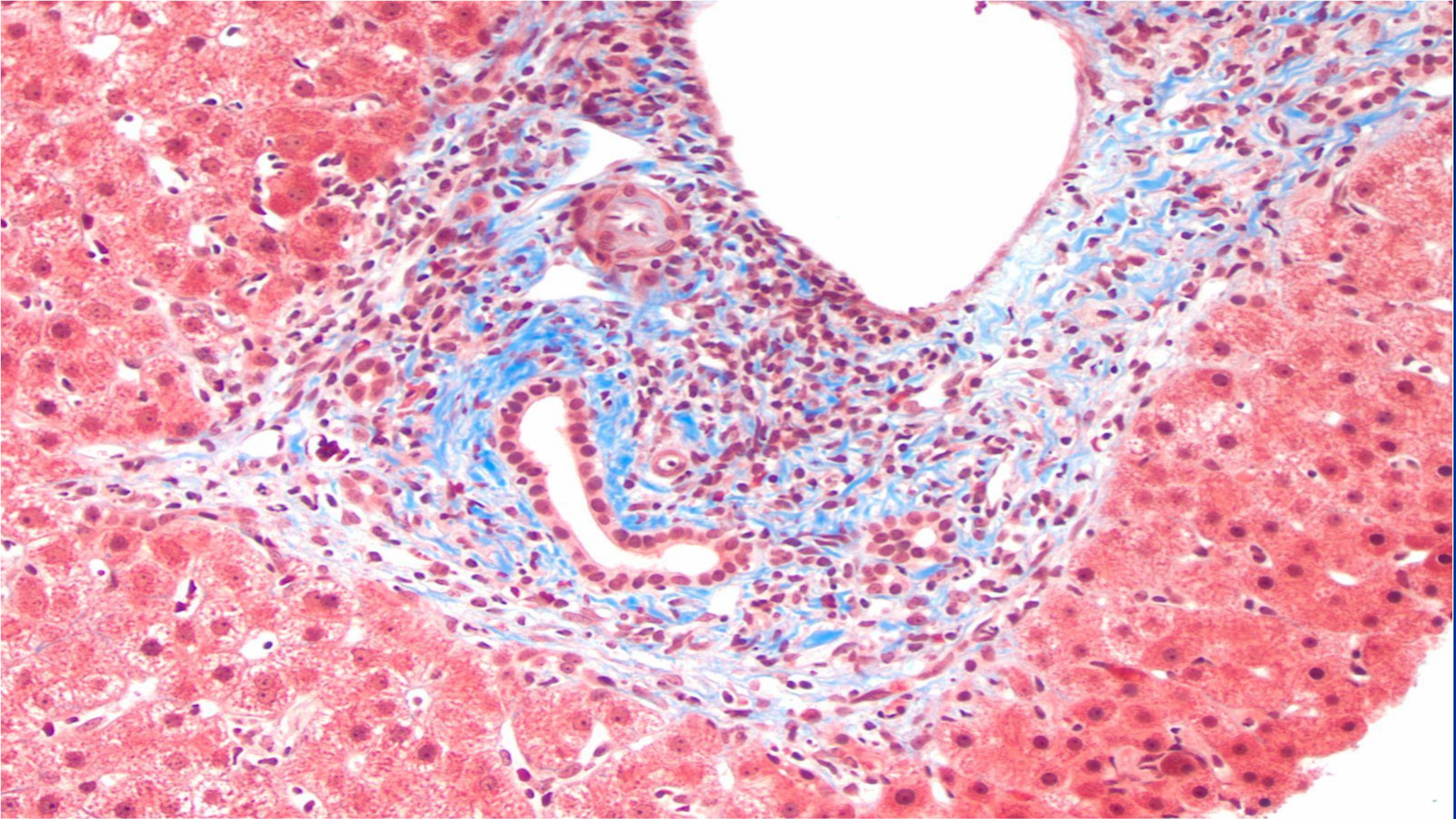









Many tombstone lesions on PAS diastase stain



Acute HCV

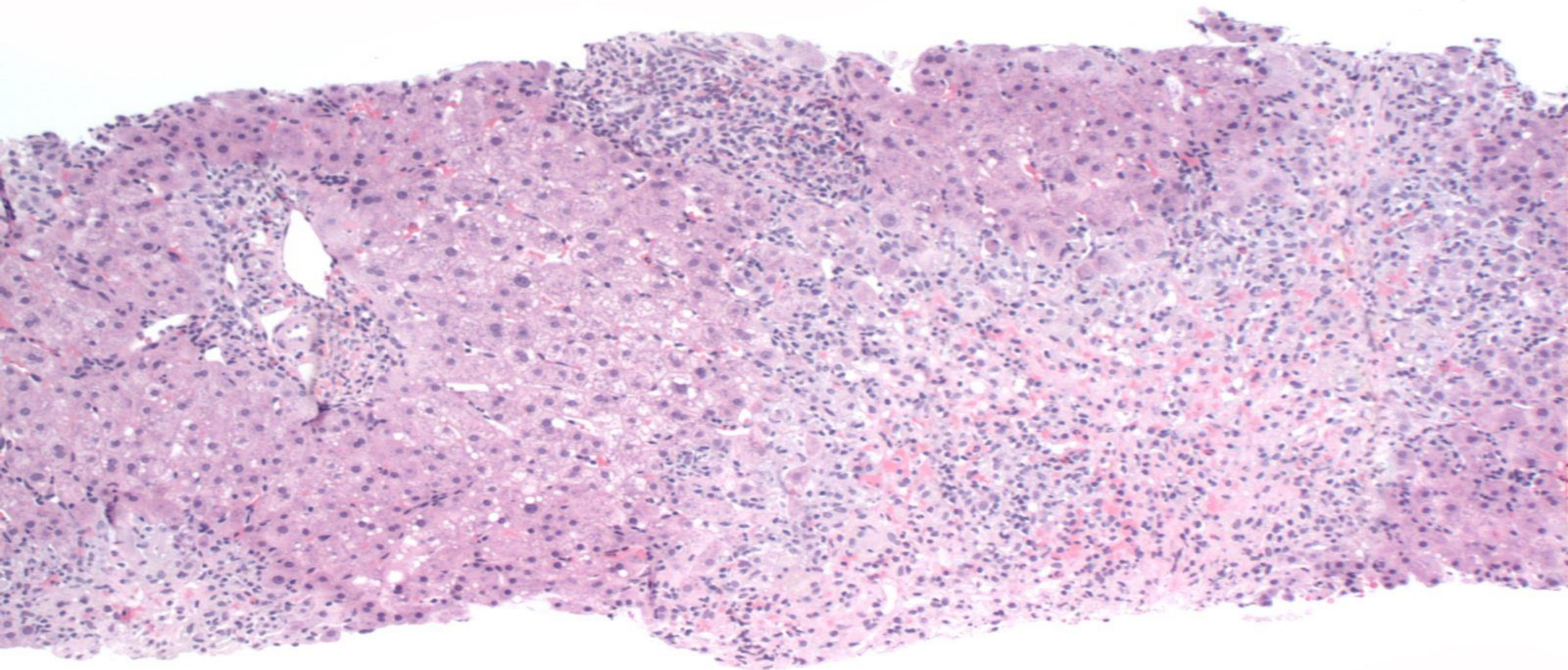
- Accounts for 15% of acute hepatitis
- Usually asymptomatic or present with only slight fatigue, so unusual to see acute HCV
  - Rarely presents with jaundice
- Often shows similar features to chronic HCV but with more lobular inflammation, more numerous acidophil bodies and many ceroid laden macrophages
- Portal expansion may mimic fibrosis

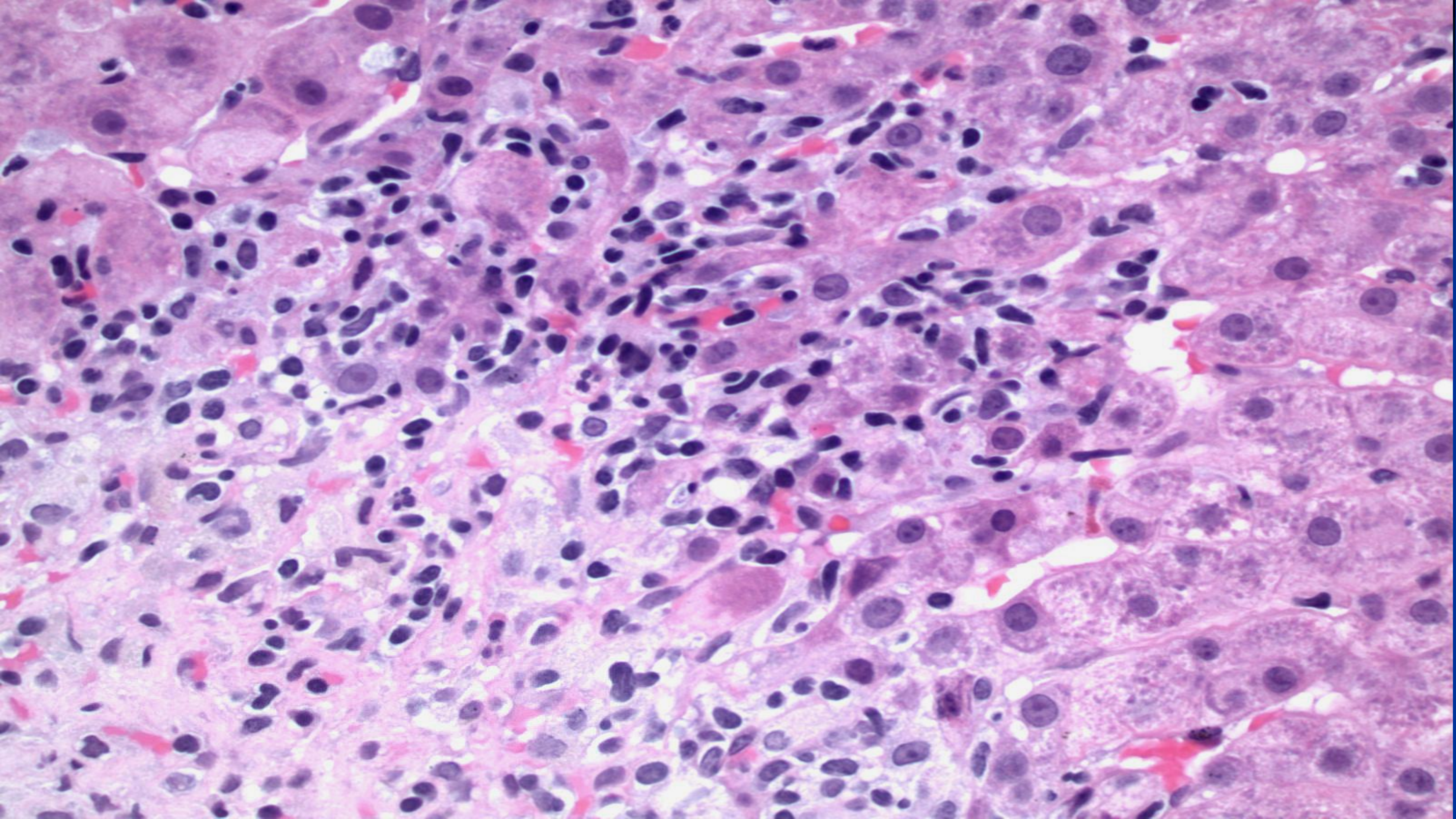
Key Points

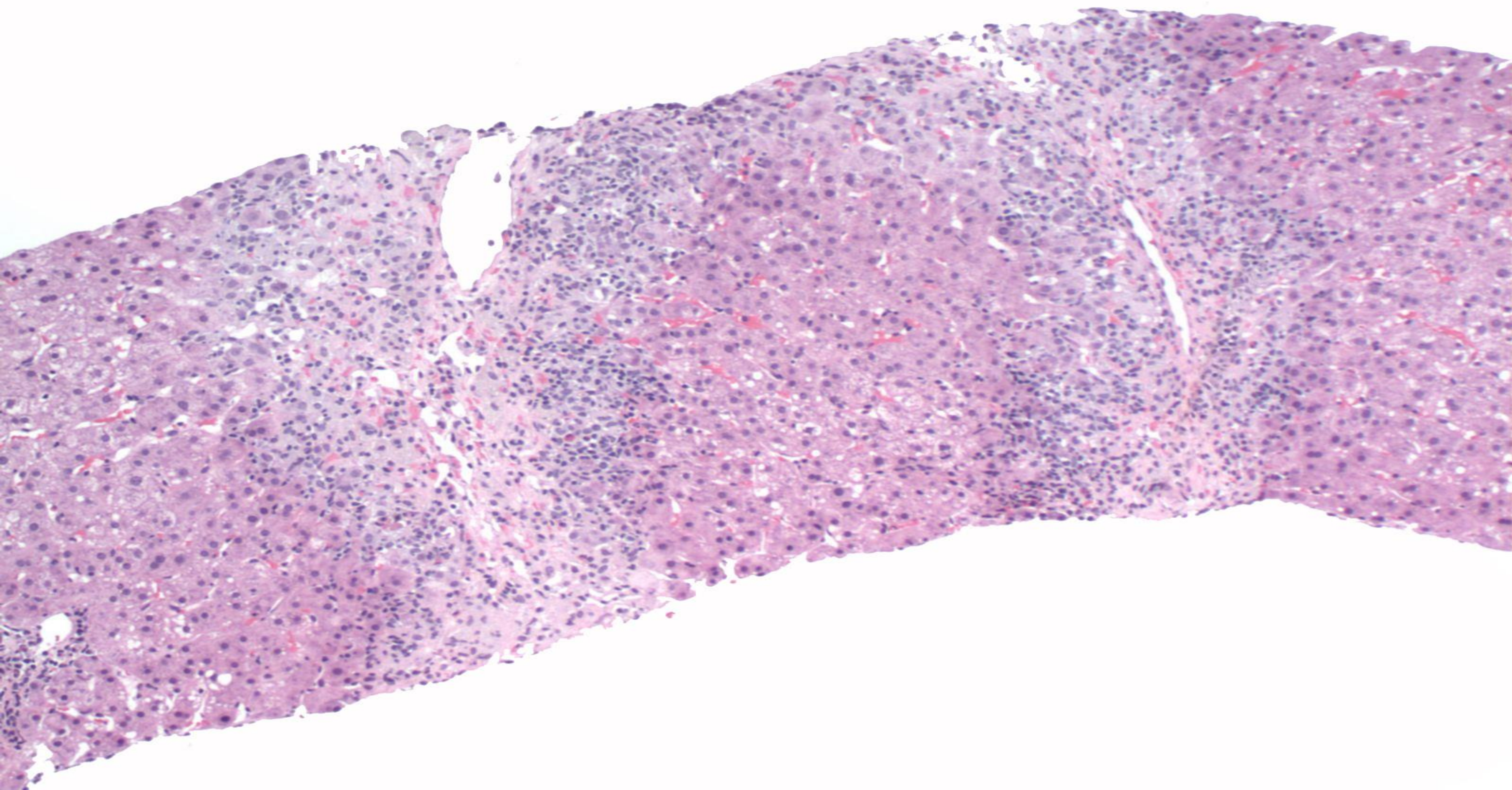
- Lobular hepatitis with a predominant sinusoidal pattern of infiltration has a distinct differential diagnosis, with EBV being a leading consideration.
- This pattern is not highly suggestive of AIH.
- Some cases may have features intermediate between "panlobular hepatitis" and "lobular hepatitis with sinusoidal infiltrate" and these cases have the broadest differential.

Case

- 45 year old female with recent LFT elevations (ALT 1280).
- Biopsy interpreted as severe chronic active hepatitis with marked bridging fibrosis and early nodule formation.
- Clinician and patient alarmed at the potential for cirrhosis despite acute presentation.
- Low titer SMA, otherwise negative autoimmune markers.







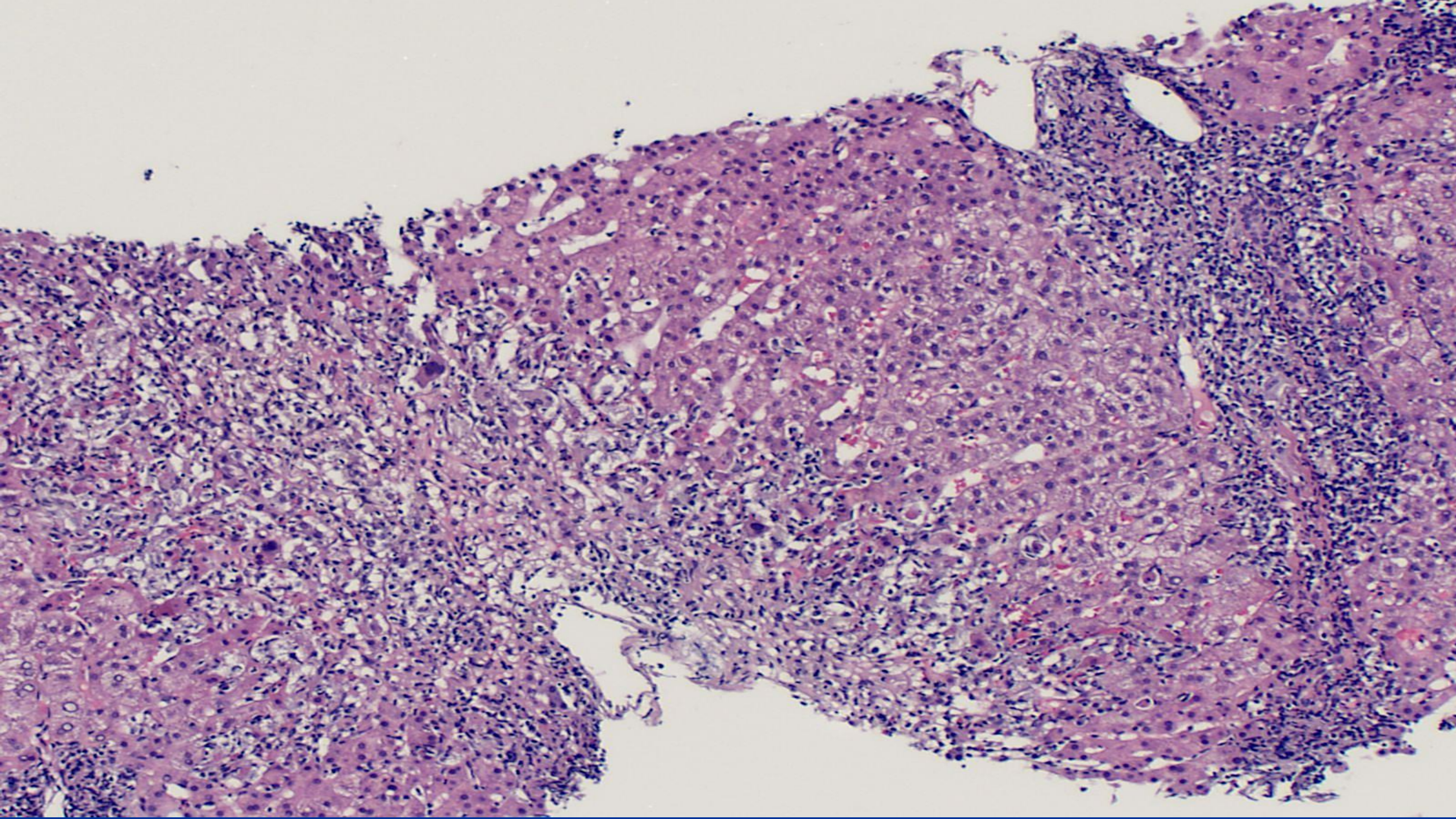
Follow up

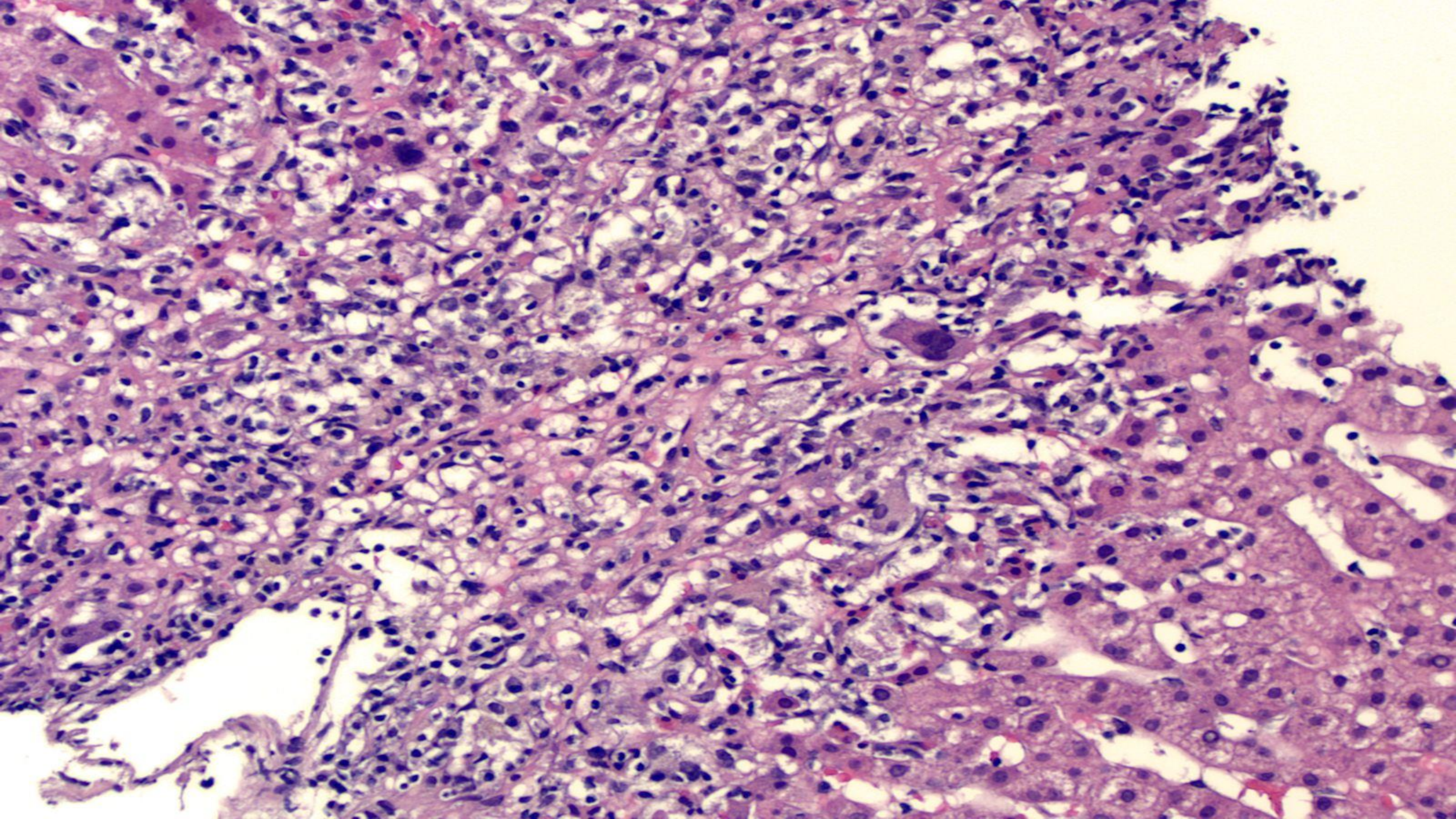
- Better pathologic diagnosis "Zone 3 hepatitis with centrilobular necrosis", differential includes AIH and drug.
- LFTs resolved without therapy – presumably a toxic reaction.
- Clinician attributed the event to weight loss program with nutritional shakes.

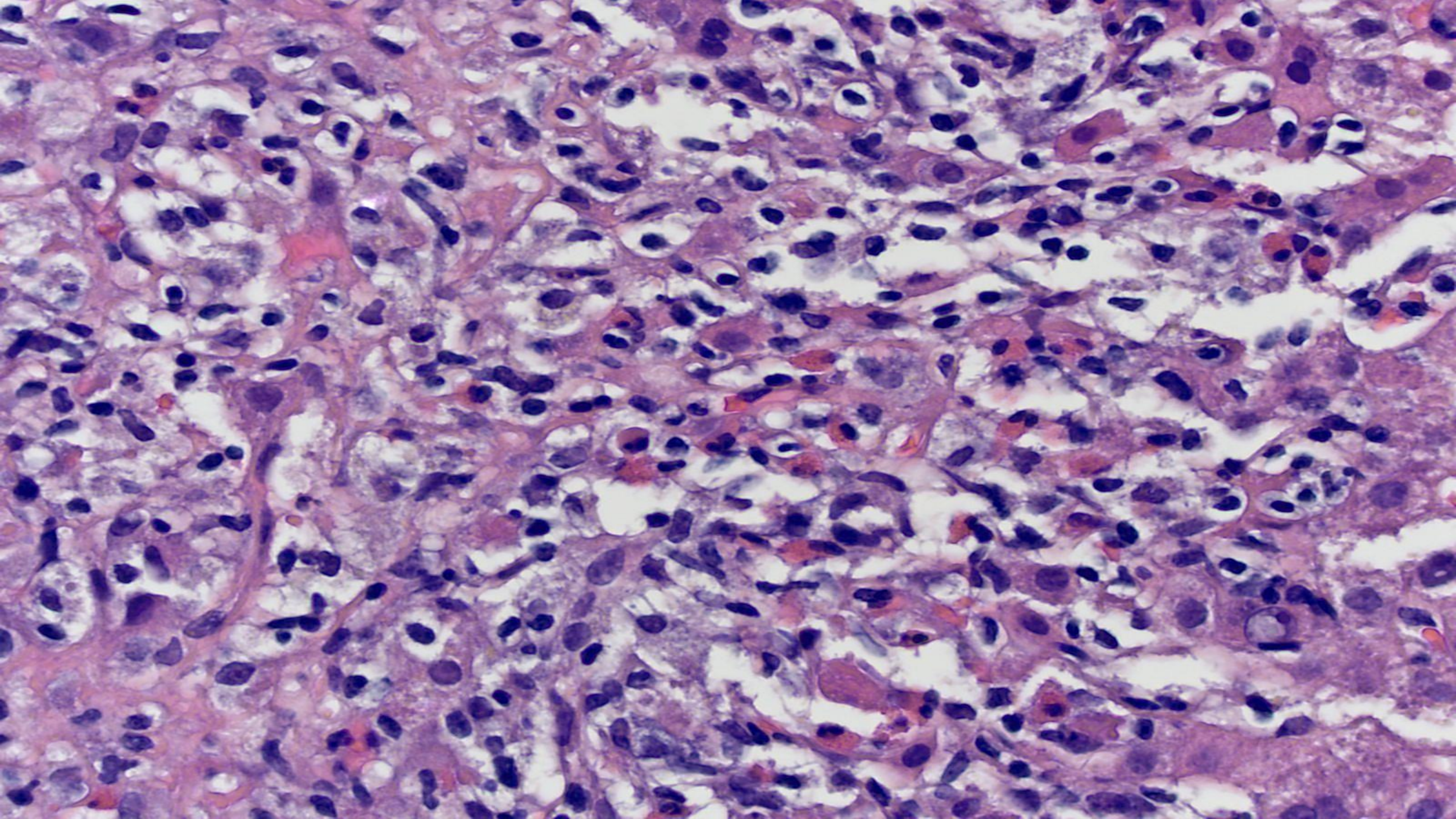
Zone 3 Hepatitis

Inflammation and hepatocyte loss predominantly in the centrilobular region with relatively less portal inflammation

- *AIH, variant pattern. Tends to be more lymphocytic, +/- plasma cells
- Drug reaction – May have more histiocytes and eosinophils.
- Acute viral hepatitis – Not usually restricted to zone 3 but can be accentuated in zone 3. Zone 3 viruses would include dengue.
- Ischemia, outflow obstruction – Hemorrhagic or coagulative necrosis
- Specific situations – hepatitic GVHD, rejection, checkpoint hepatitis

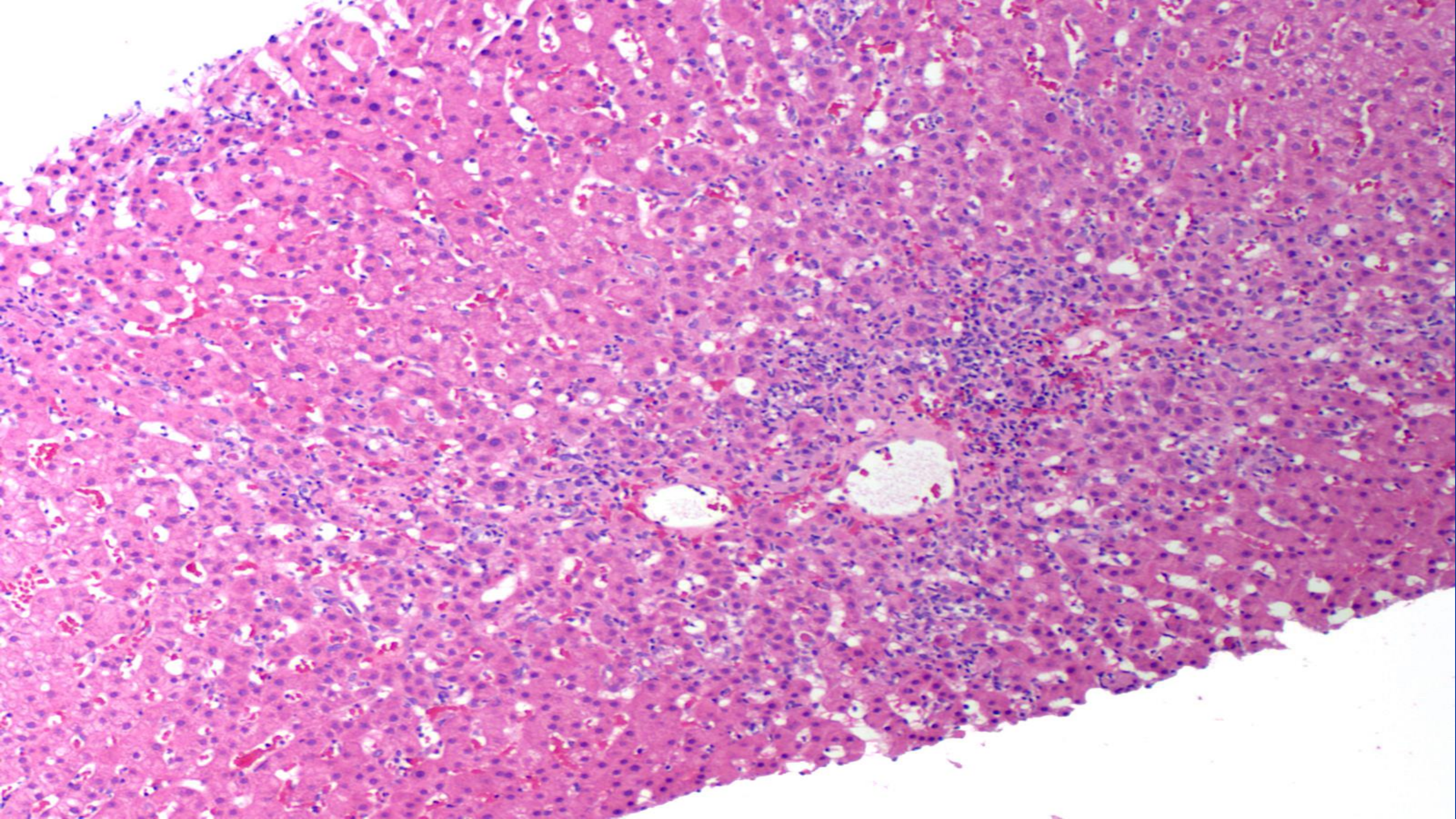


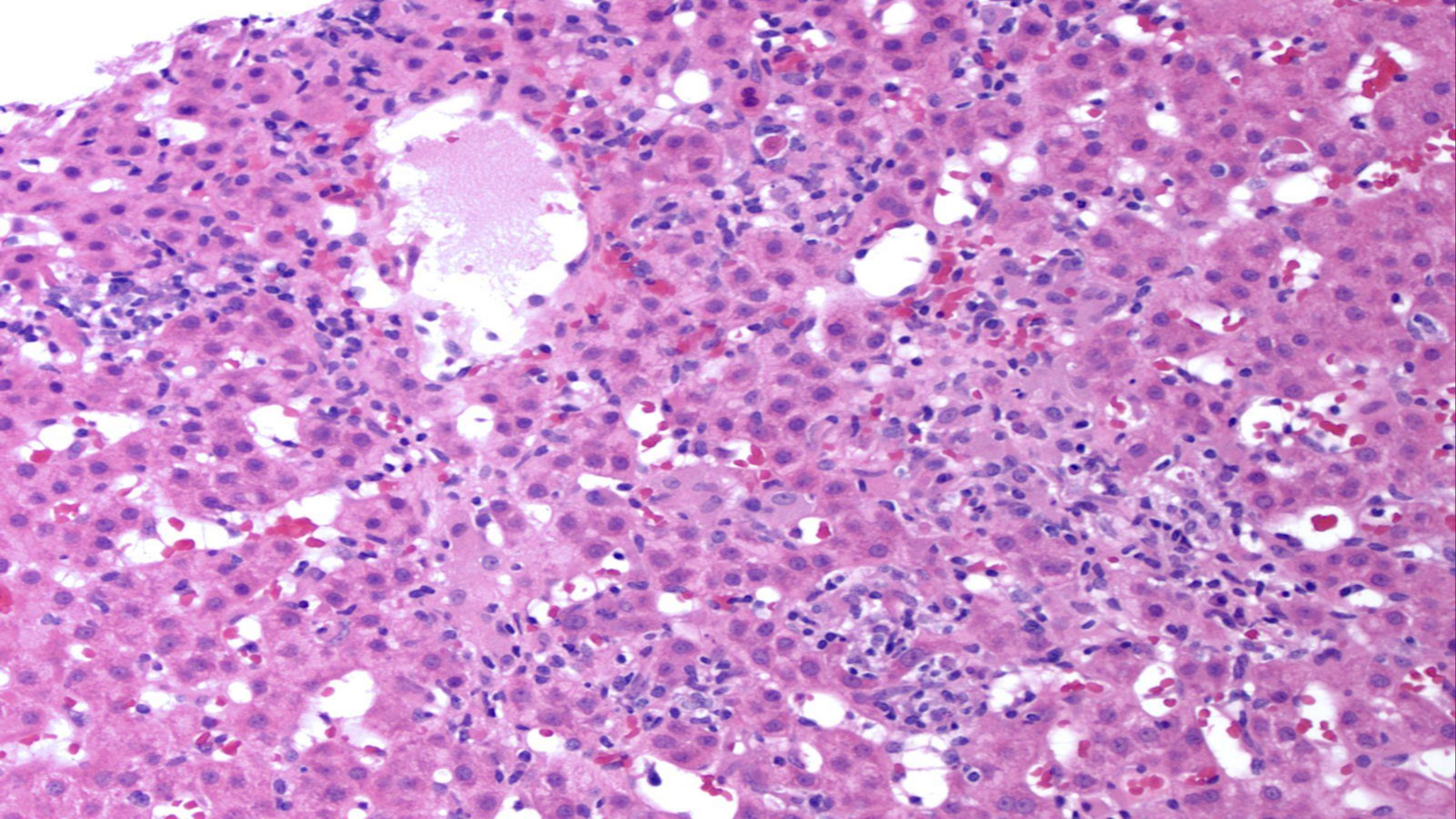


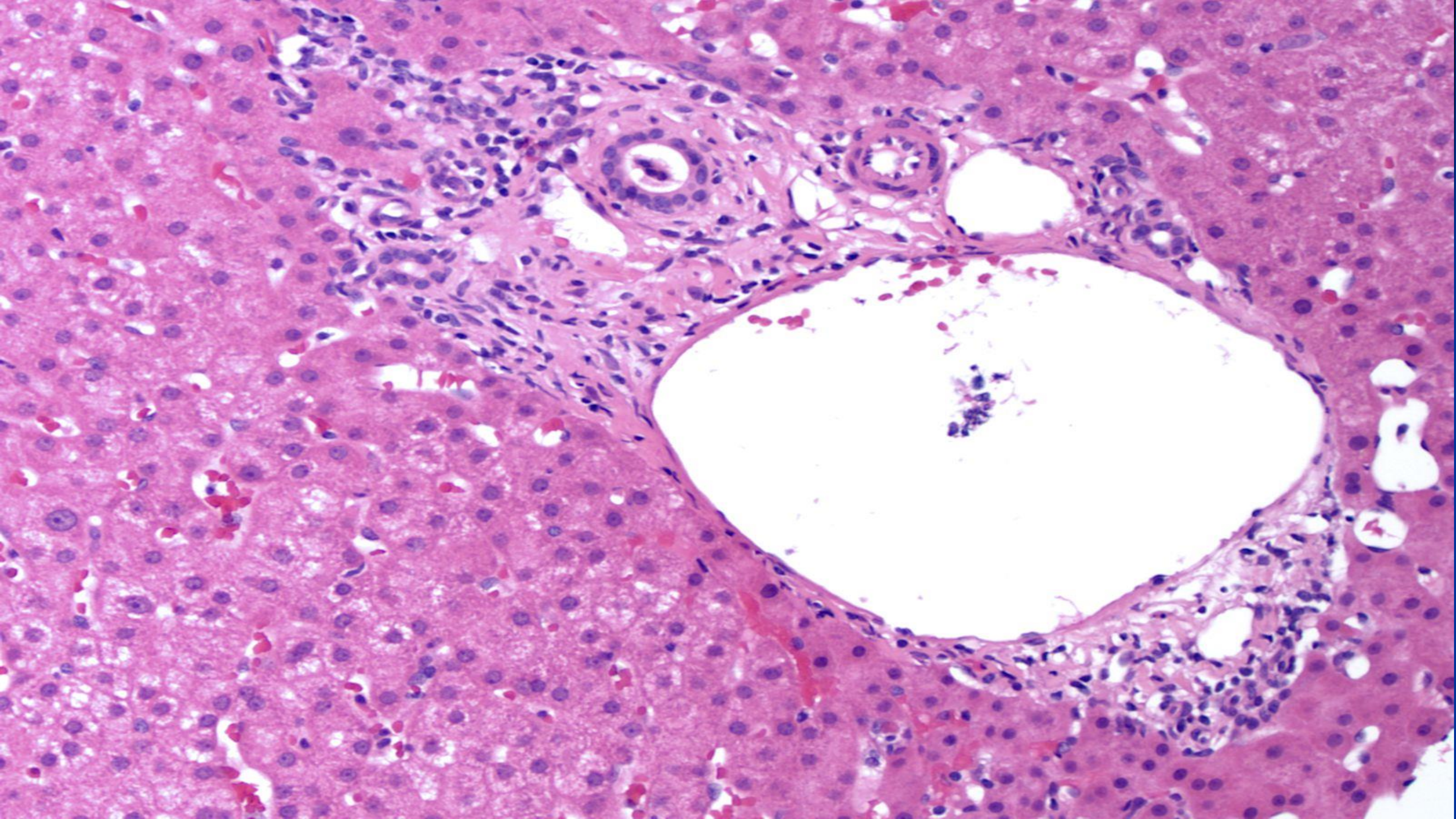


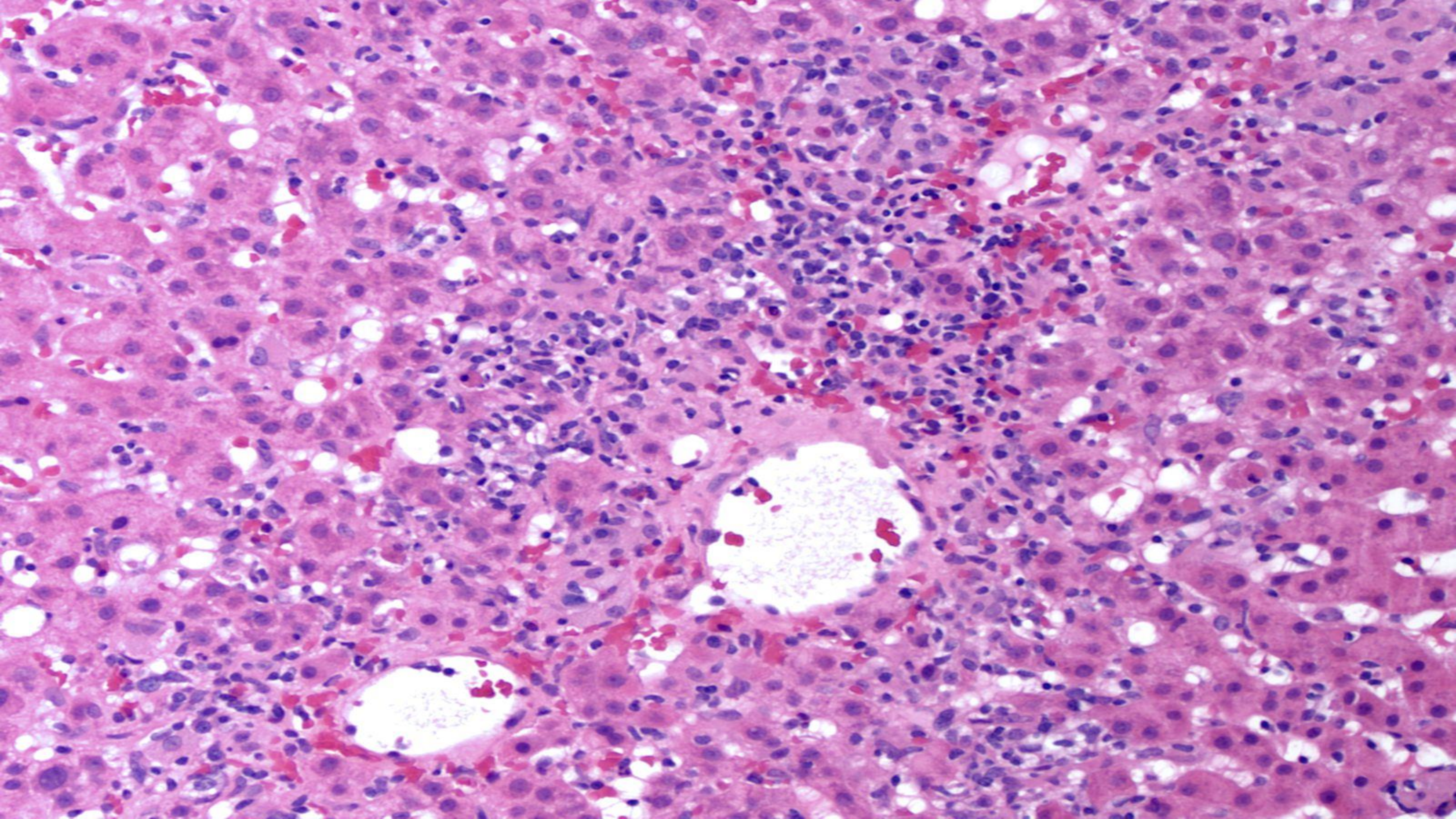
Case

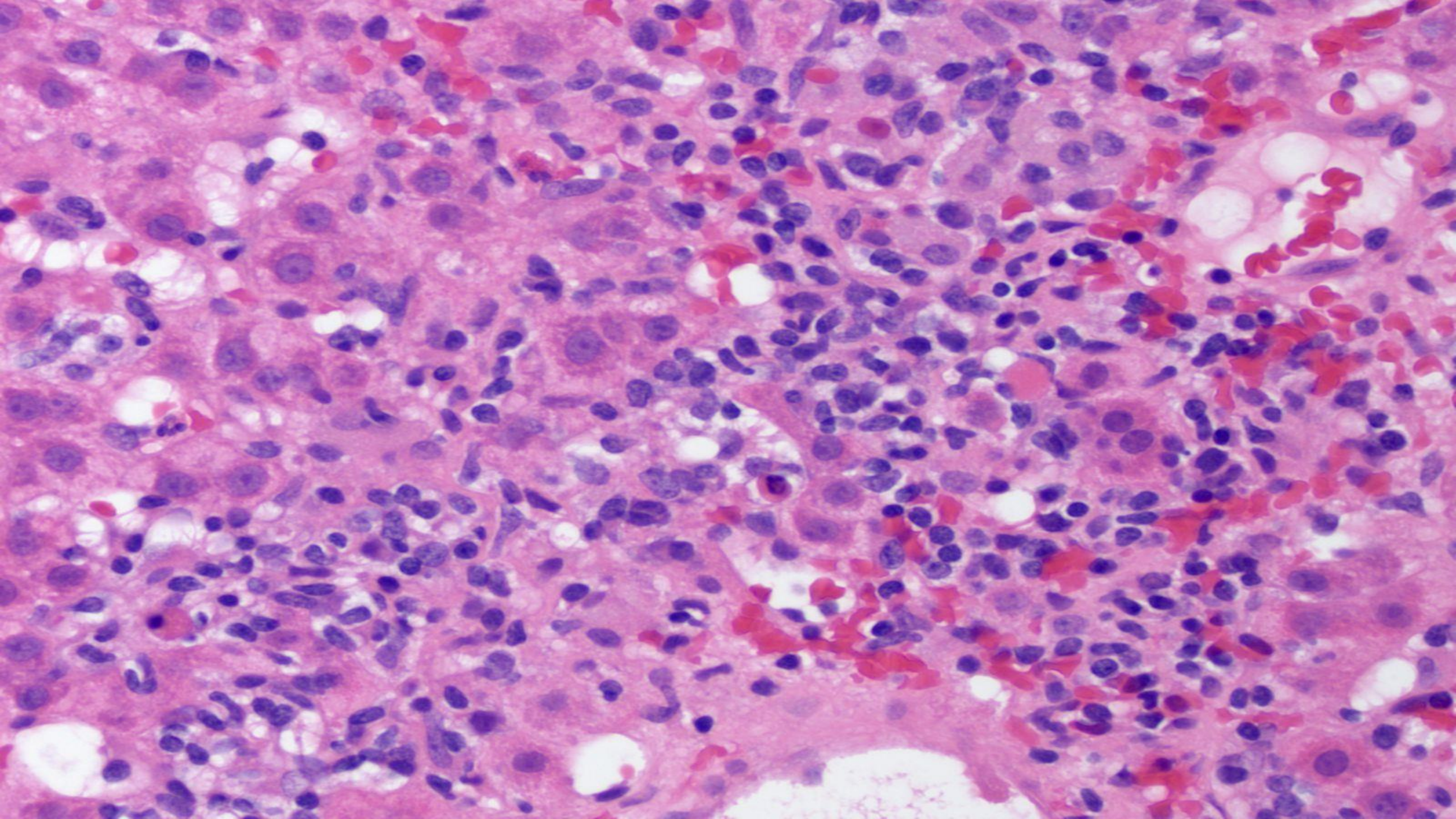
- 31 year old woman, recently on Terbinafine for onychomycosis (but not currently). Presents with elevated LFTs for 4 months (ALT 129-144)
- ANA negative; SMA 1:160
- One month later, ALT 98, and biopsy performed
- Diagnosis initially rendered: Moderately active chronic hepatitis

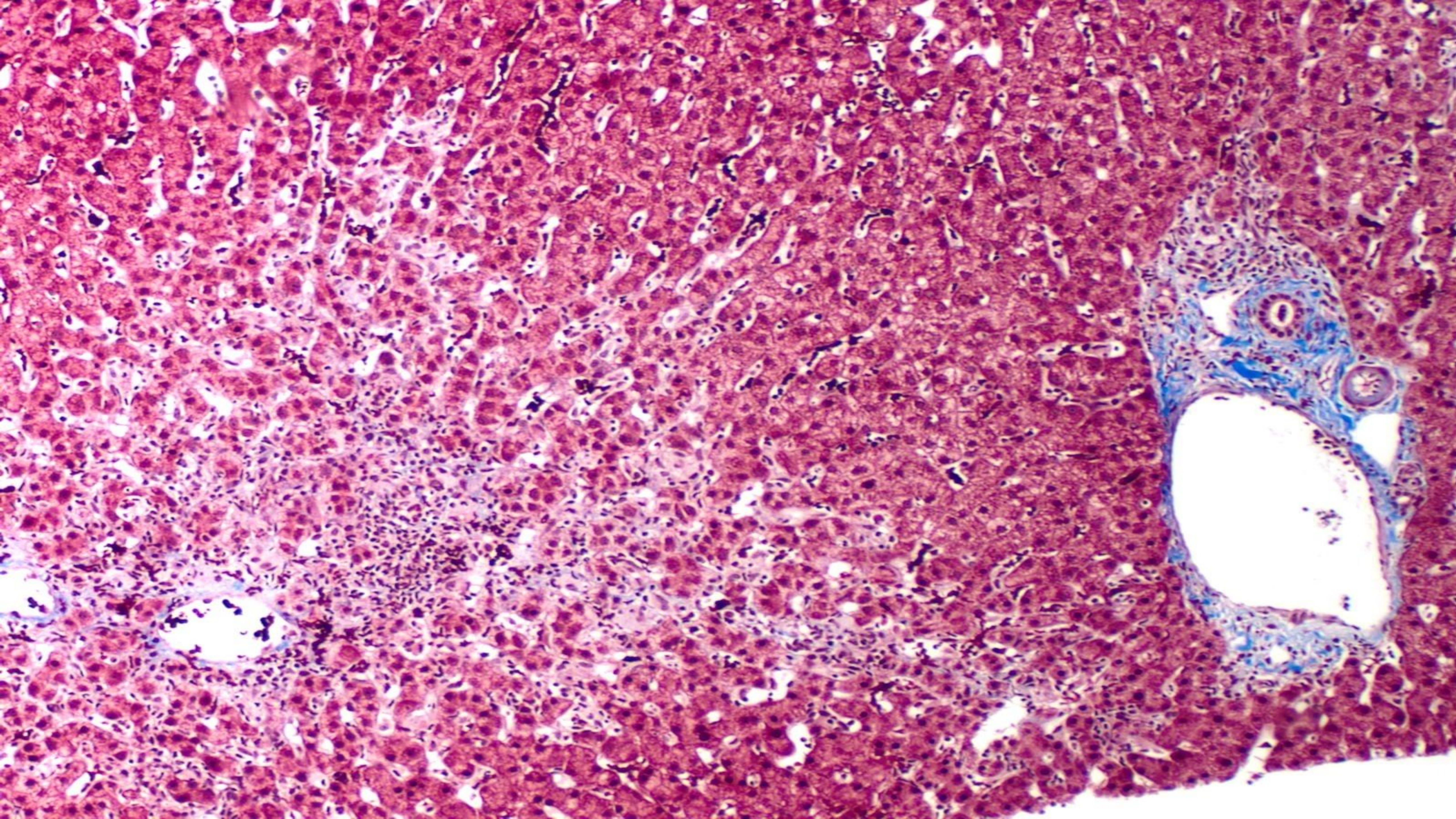






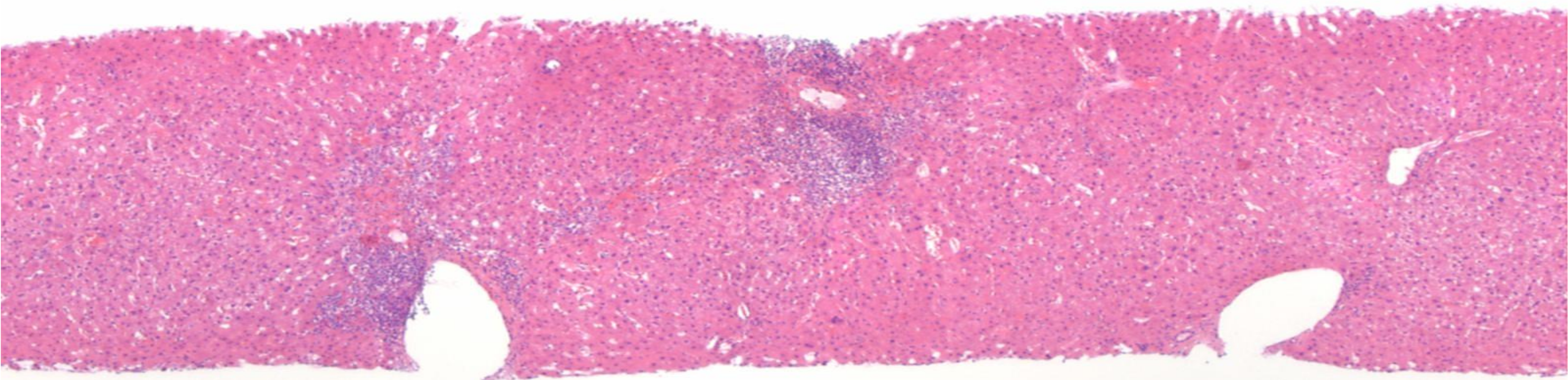


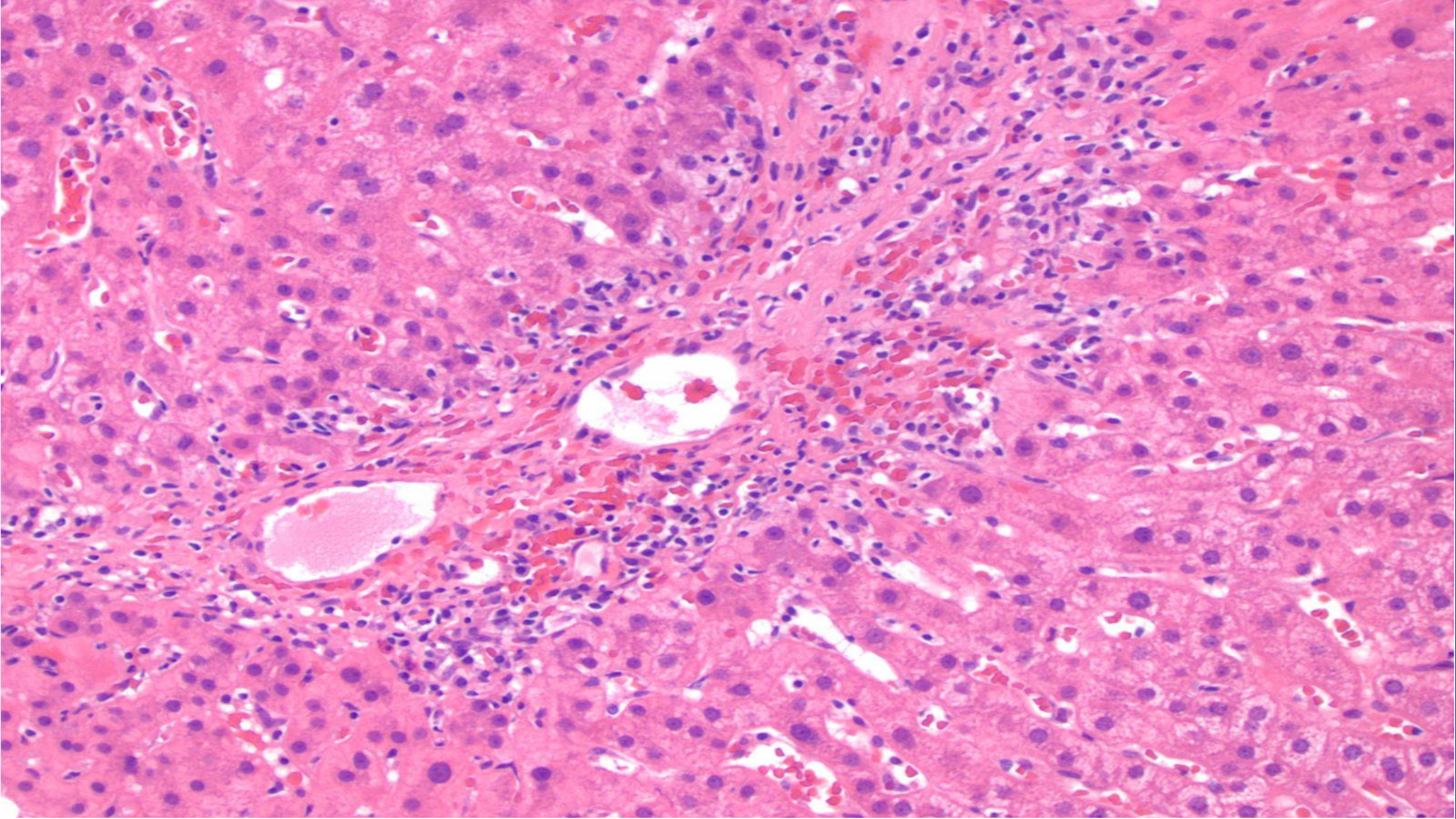


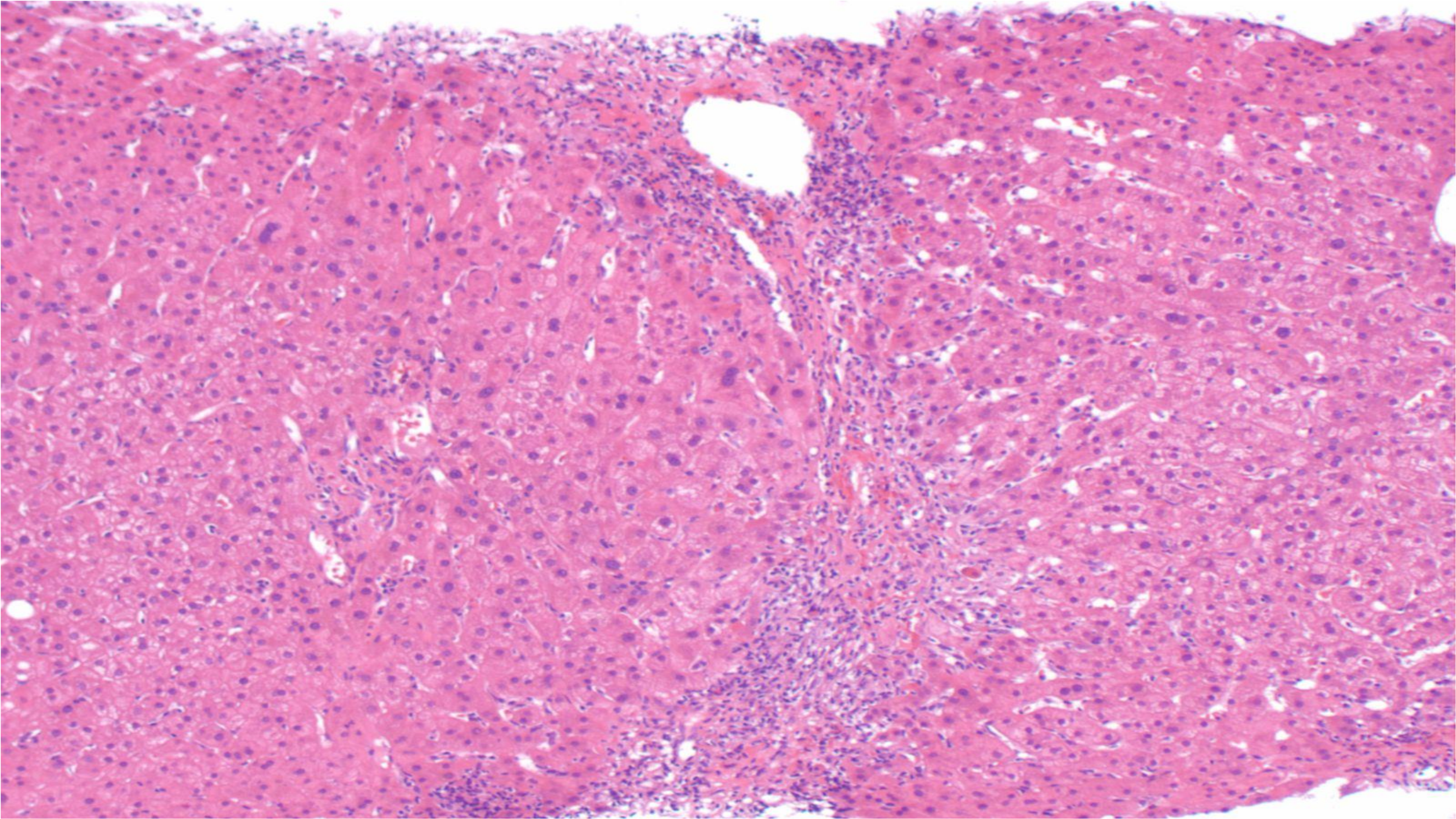


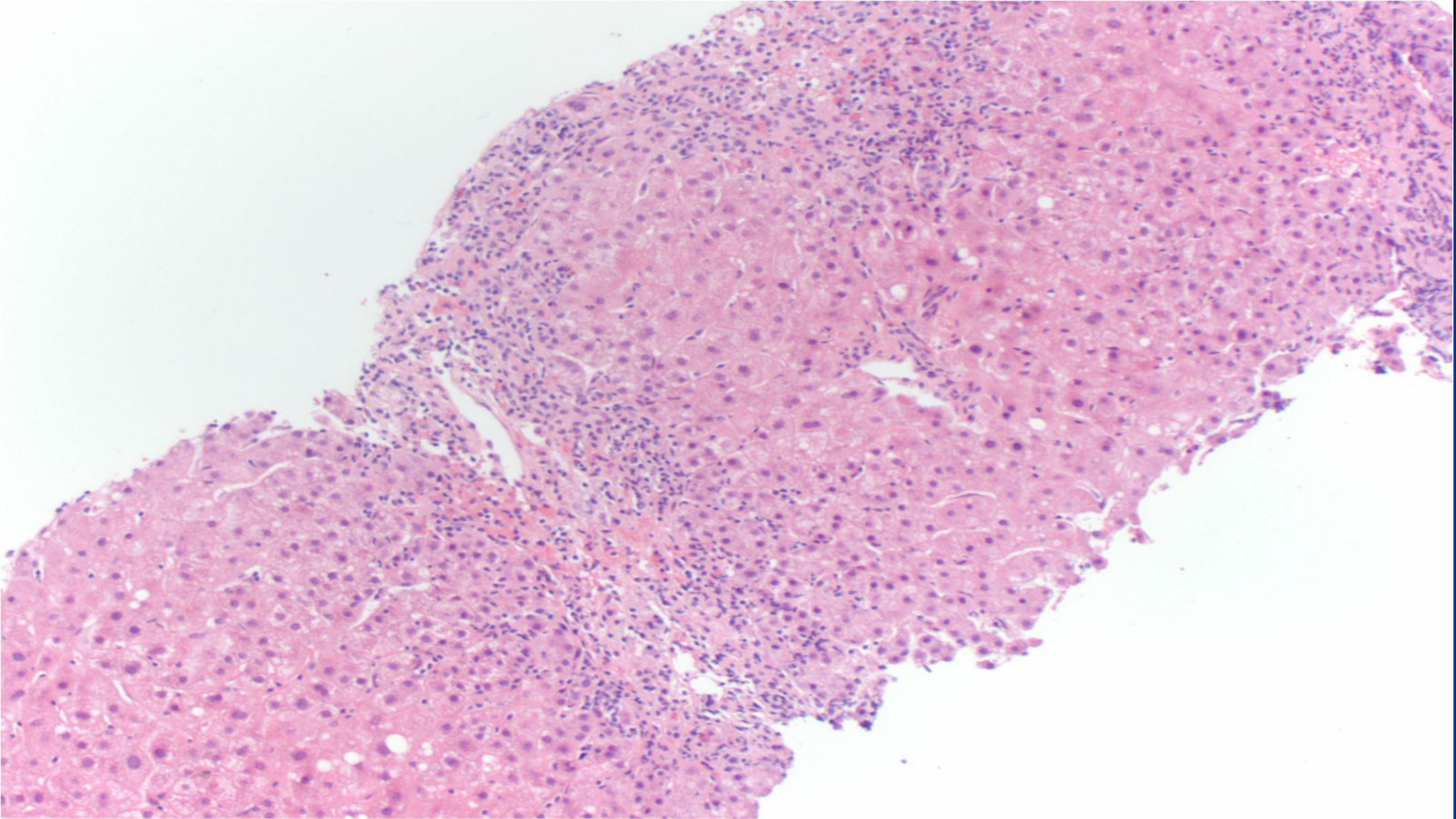
Zone 3 Autoimmune hepatitis

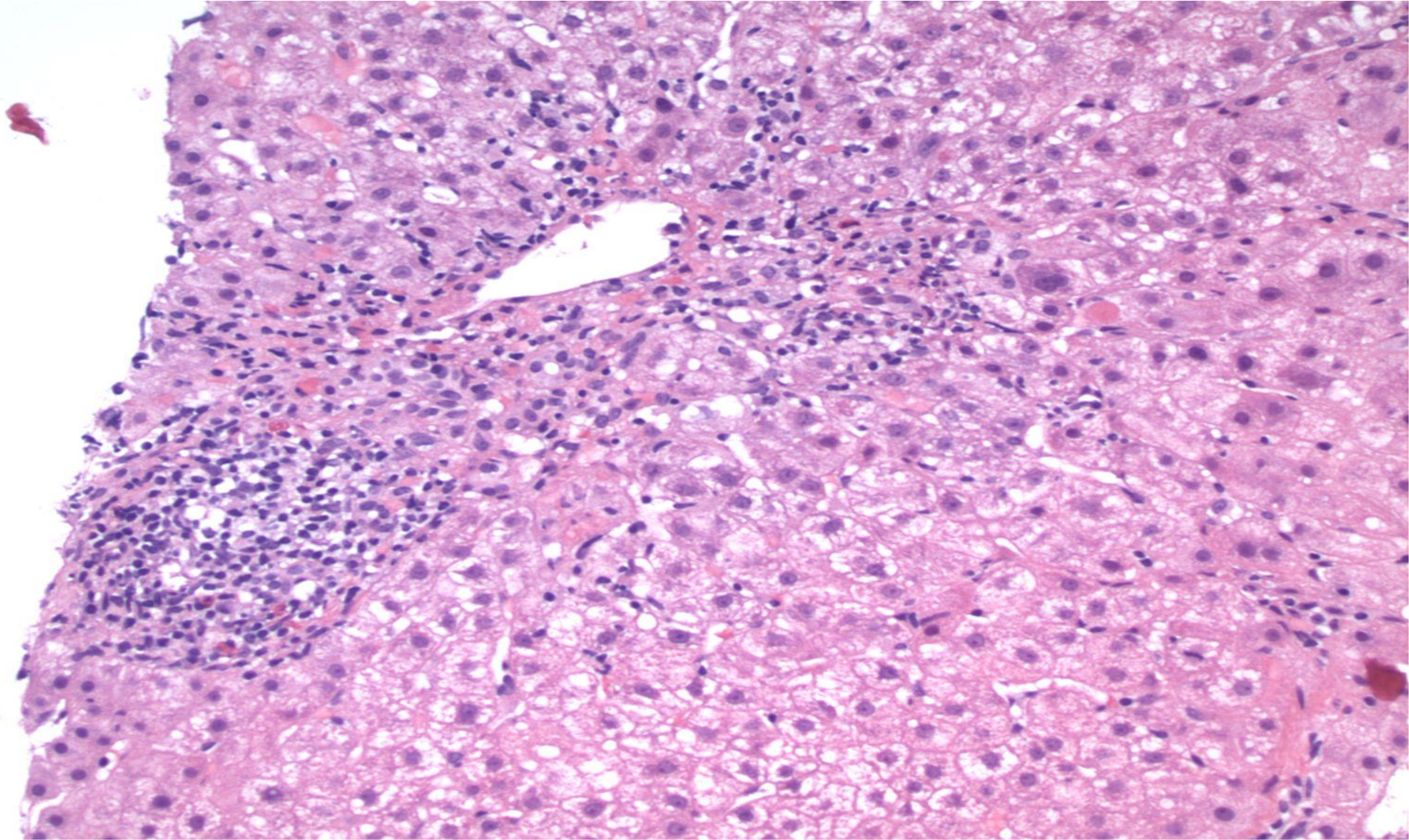
- ANA may or <u>may not</u> be positive
- Plasma cells may or <u>may not</u> be present but at least many lymphocytes and acidophil bodies
- Responds well to steroids
- May remain zone 3 or become portal in the future biopsies
- Some patients seem to have this for a long time but do not develop fibrosis

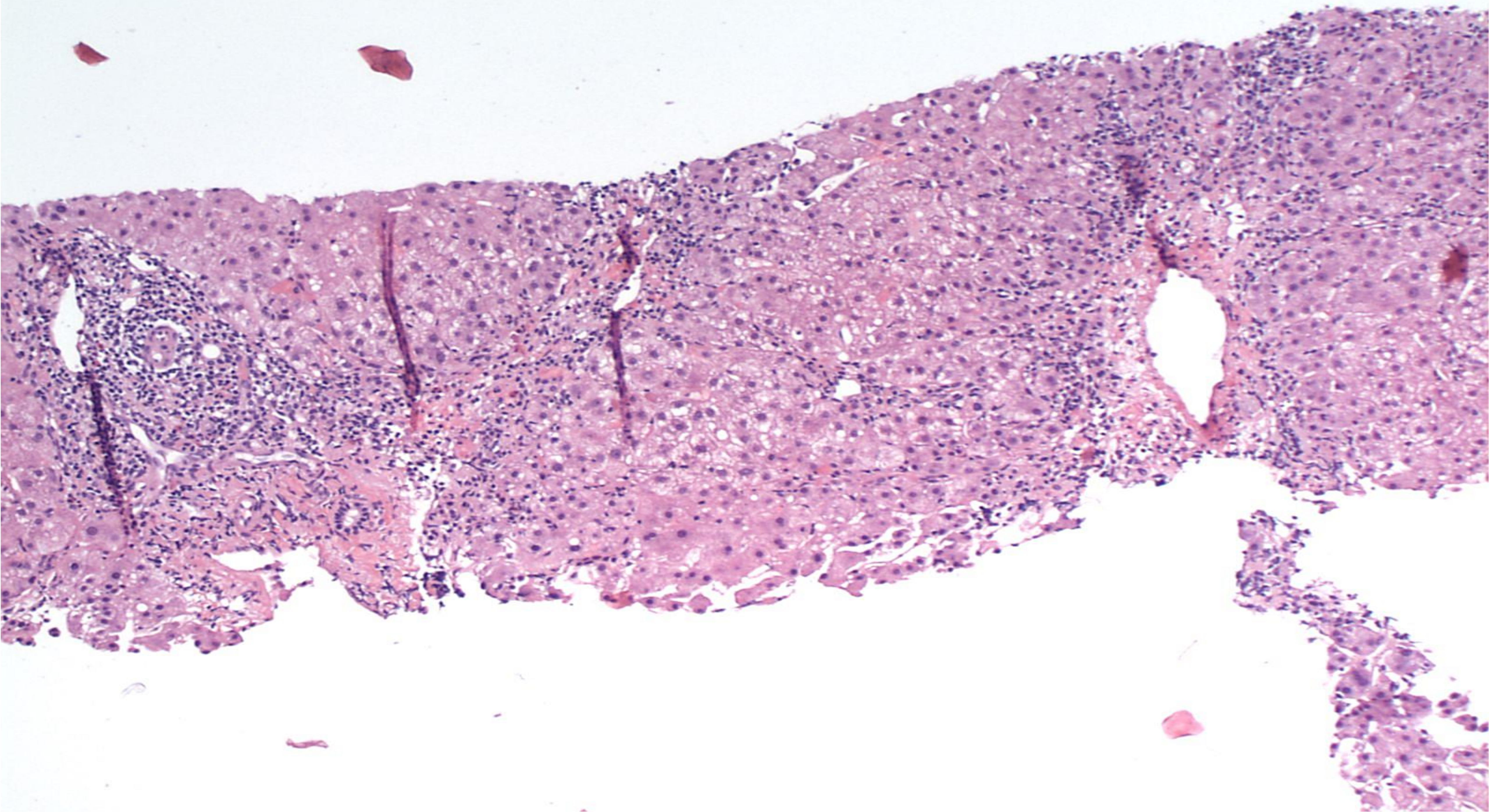












Key Points

- Zone 3 hepatitis or necrosis is often mistaken for portal based hepatitis.
- The most likely explanations are autoimmune hepatitis and a drug reaction.
- Zone 3 autoimmune hepatitis does not always have high ANA or plasma cells.
- Some cases of AIH will be lymphocyte rich and some drug reactions will be histiocyte/eosinophil rich, but beware!

Summary

- Chronic hepatitis is biopsied less today, but there is a tendency to diagnose liver biopsies with mononuclear infiltrates as "chronic hepatitis." Inflamed and expanded portal tracts add to the confusion.
- In a biopsy with significant lobular inflammation and damage, consider panlobular hepatitis. Differential V-A-D. Look for plasma cells to emphasize AIH.
- If the lobular infiltrate is strikingly sinusoidal, consider EBV and other specific entities.
- If the inflammation is zone 3, the differential is autoimmune hepatitis and toxic drug reaction.