AUTOIMMUNE LIVER DISEASE

Joseph Misdraji, M.D.
jmisdraji@partners.org

Massachusetts General Hospital
Gastrointestinal Pathology Unit

Autoimmune Liver Disease

Autoimmune hepatitis

Primary Biliary Cholangitis

Primary Sclerosing Cholangitis

Overlap syndromes

Autoimmune hepatitis (AIH)

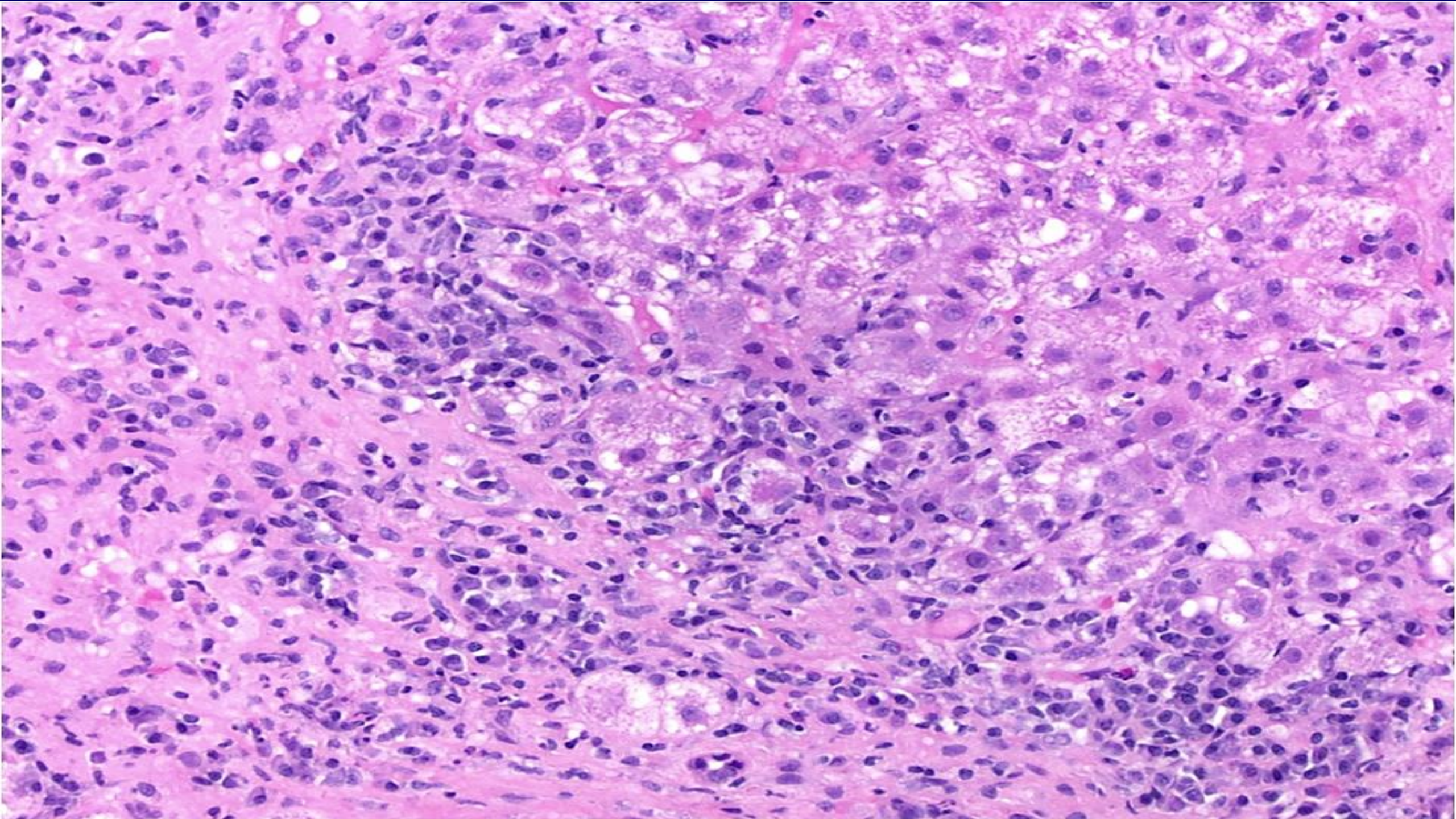
- Females > male (3:2)
- Wide age range
- Fatigue, RUQ pain, jaundice, joint pain
- 10-50% have extrahepatic manifestations (thyroid disease, UC, synovitis, celiac disease)
- > 80% have autoantibodies (ANA/SMA; LKM)
- Hypergammaglobulinemia (IgG) (> 90%)
- Good response to steroid therapy

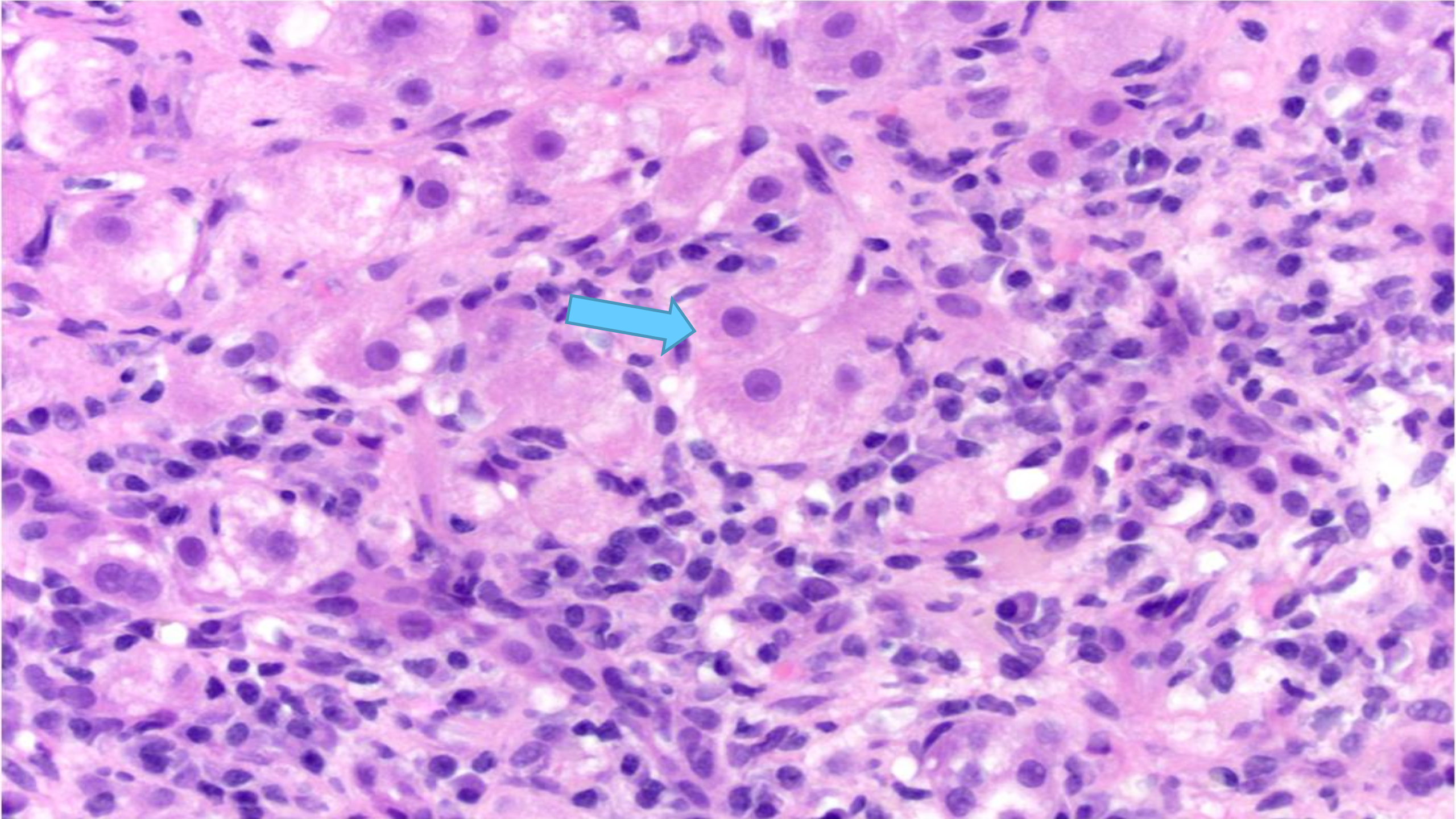
Drug Induced Autoimmune Hepatitis

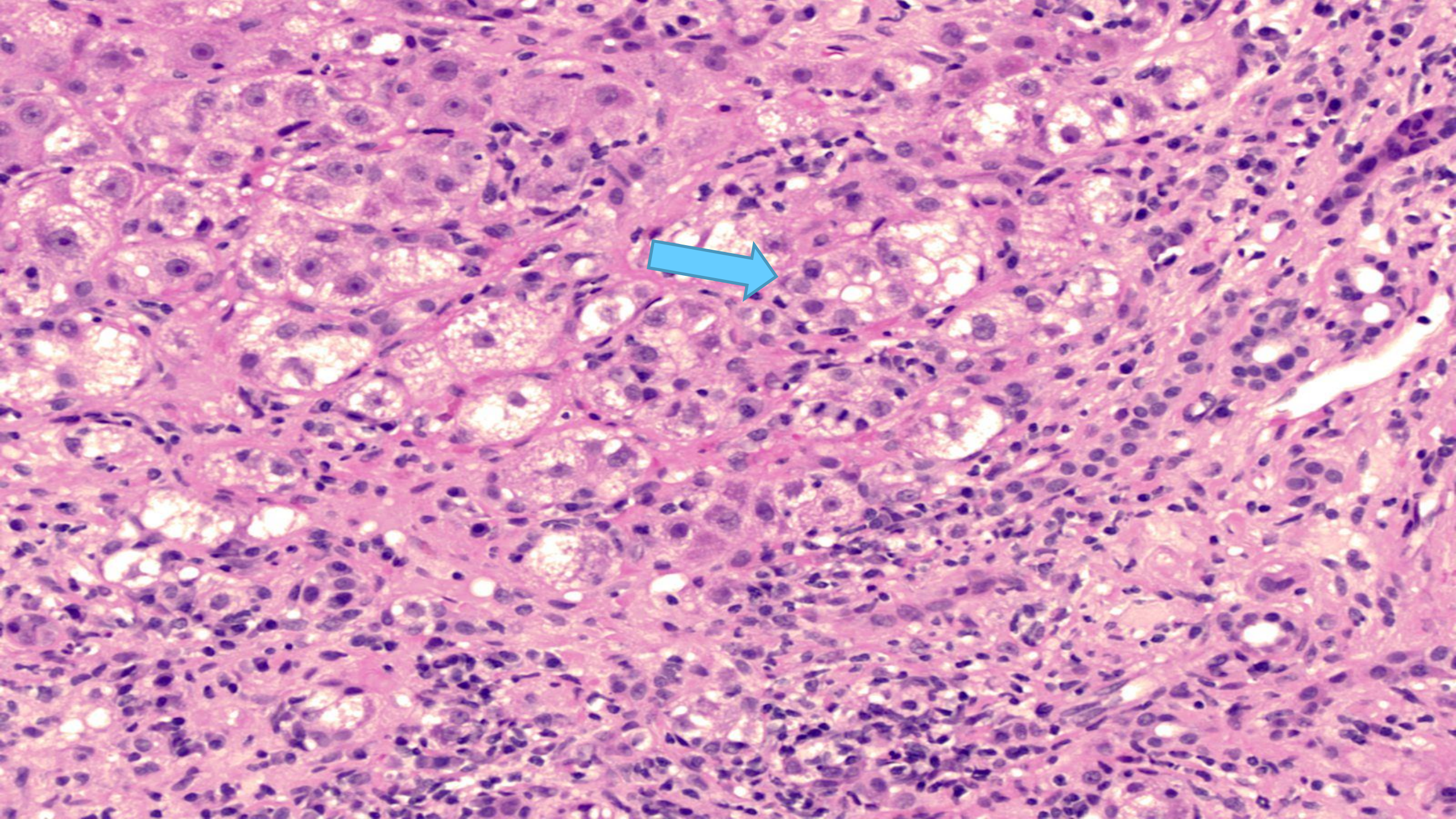
- Histologically indistinguishable from classical AIH (except not cirrhotic at presentation)
- ANA often positive.
- Often resolves with discontinuation of the drug, but may require a limited period of immunosuppression. Does not usually need lifelong immunosuppression like classical AIH.
- Minocycline, nitrofurantoin, infliximab (Remicade), methyldopa, statins, etanercept (Embrel), etc.

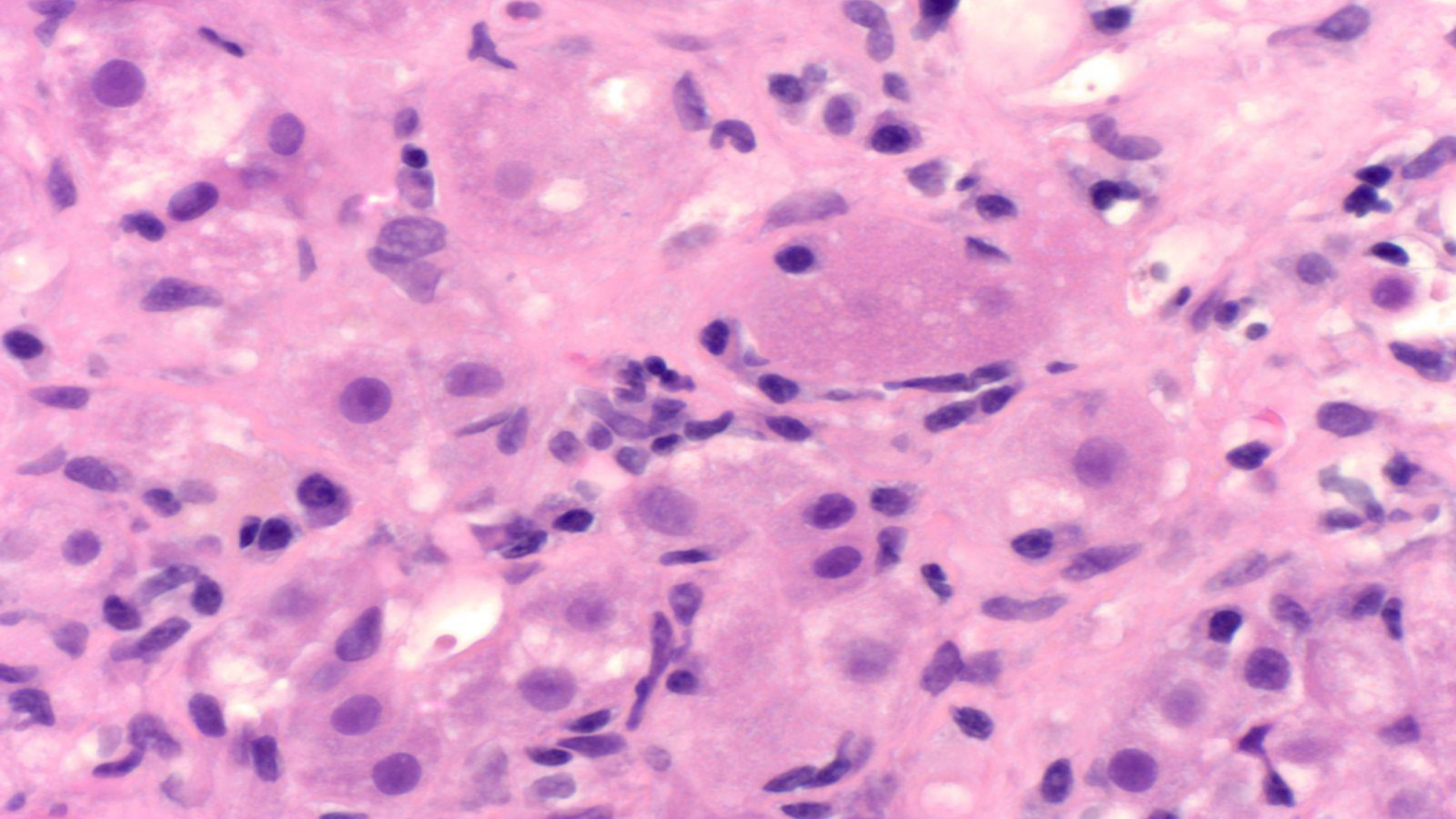
Scoring systems for AIH

- Created in 1999 by the International Autoimmune Hepatitis Group, for research purposes but widely used for clinical purposes
- Simplified in 2008 for more clinical applicability
- Scores various features (serology, histology, clinical factors) and adds up to a probability of having AIH with good sensitivity/specificity
- Includes histologic features considered "typical for AIH" (rosetting and emperipolesis).
  - The sensitivity and specificity of those features has been challenged.









Other morphologic patterns in AIH

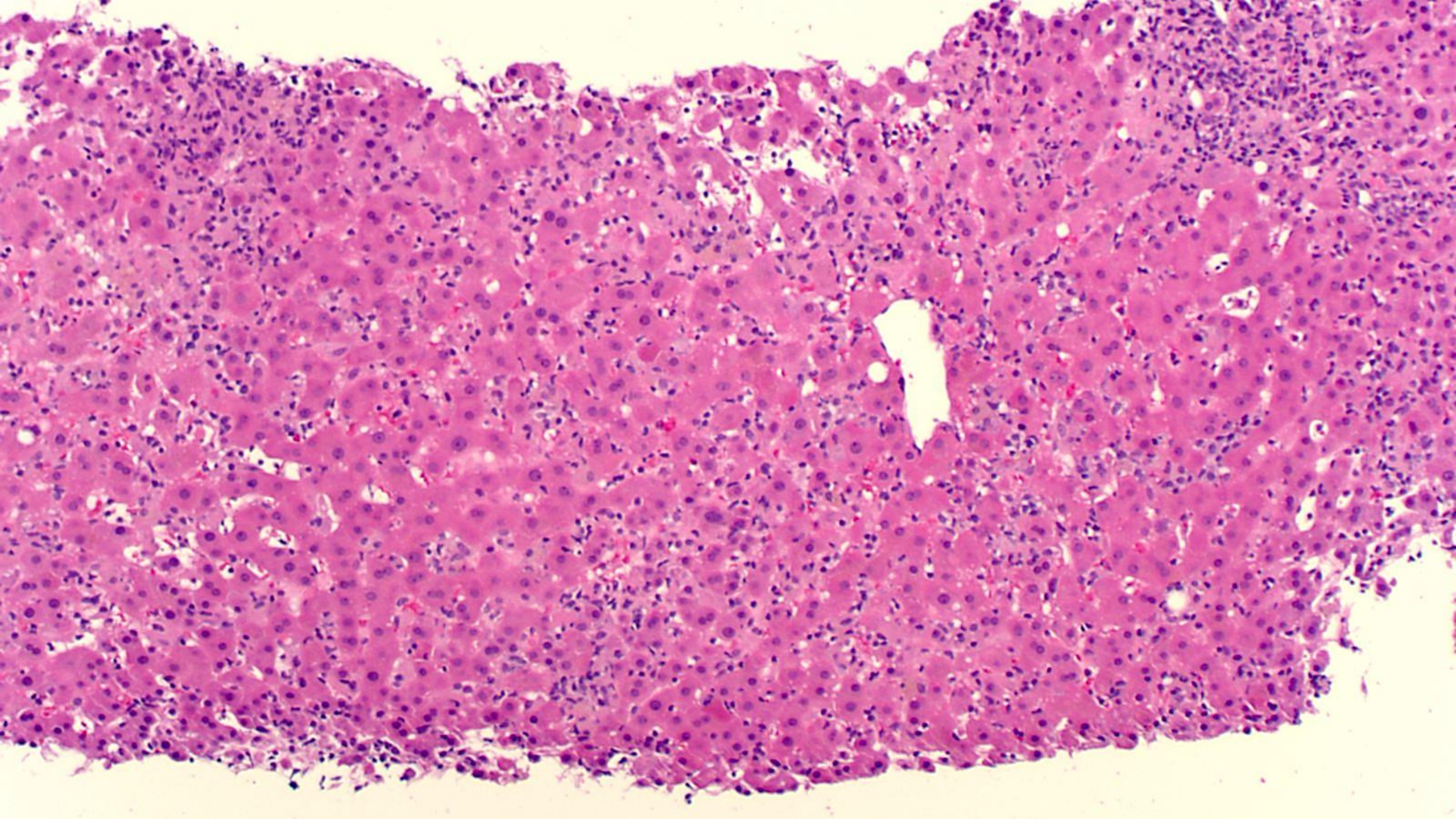
- Panlobular hepatitis
- Centrilobular or zone 3 hepatitis
- Post-infantile giant cell hepatitis

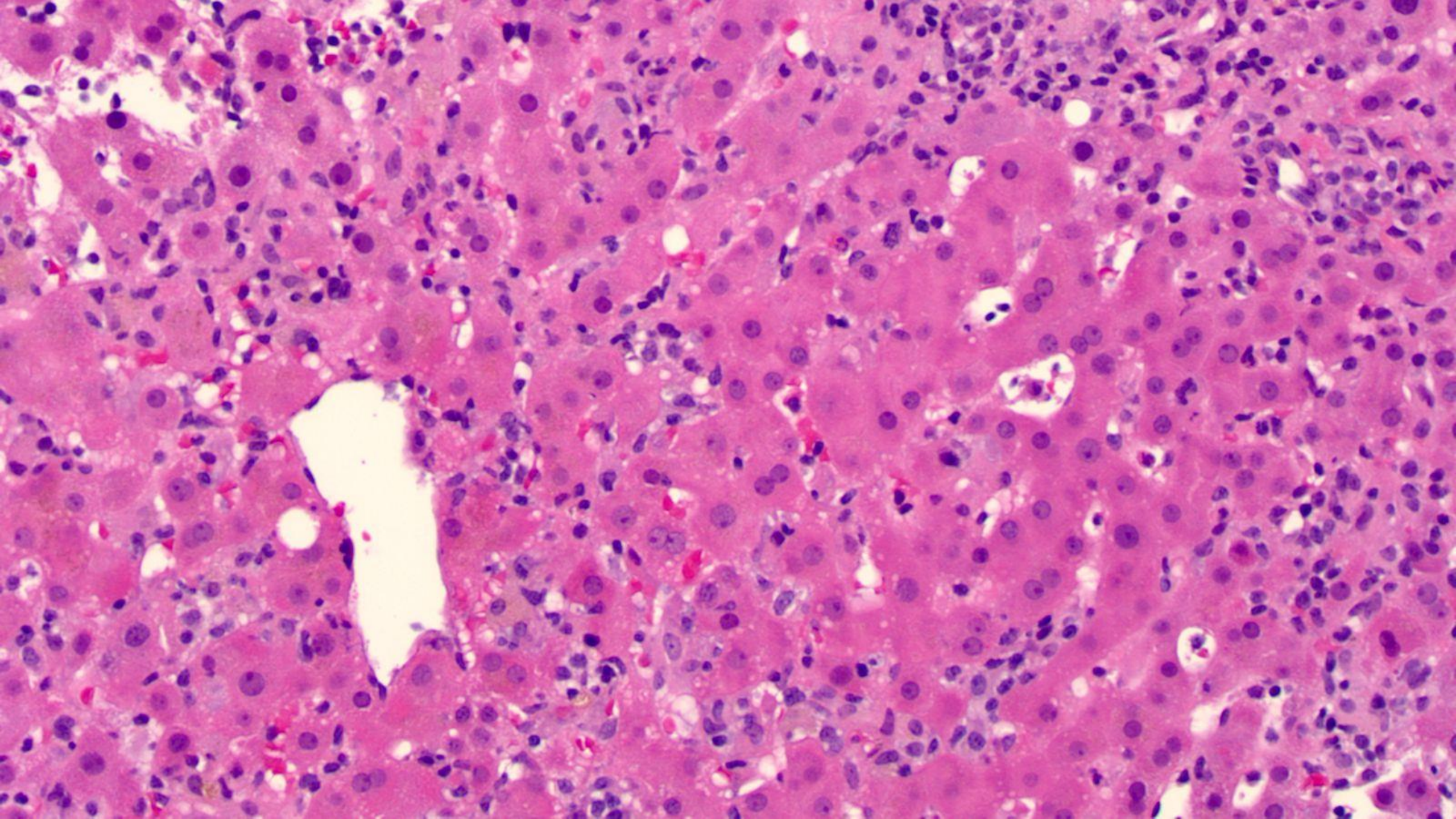
Panlobular: Acute AIH

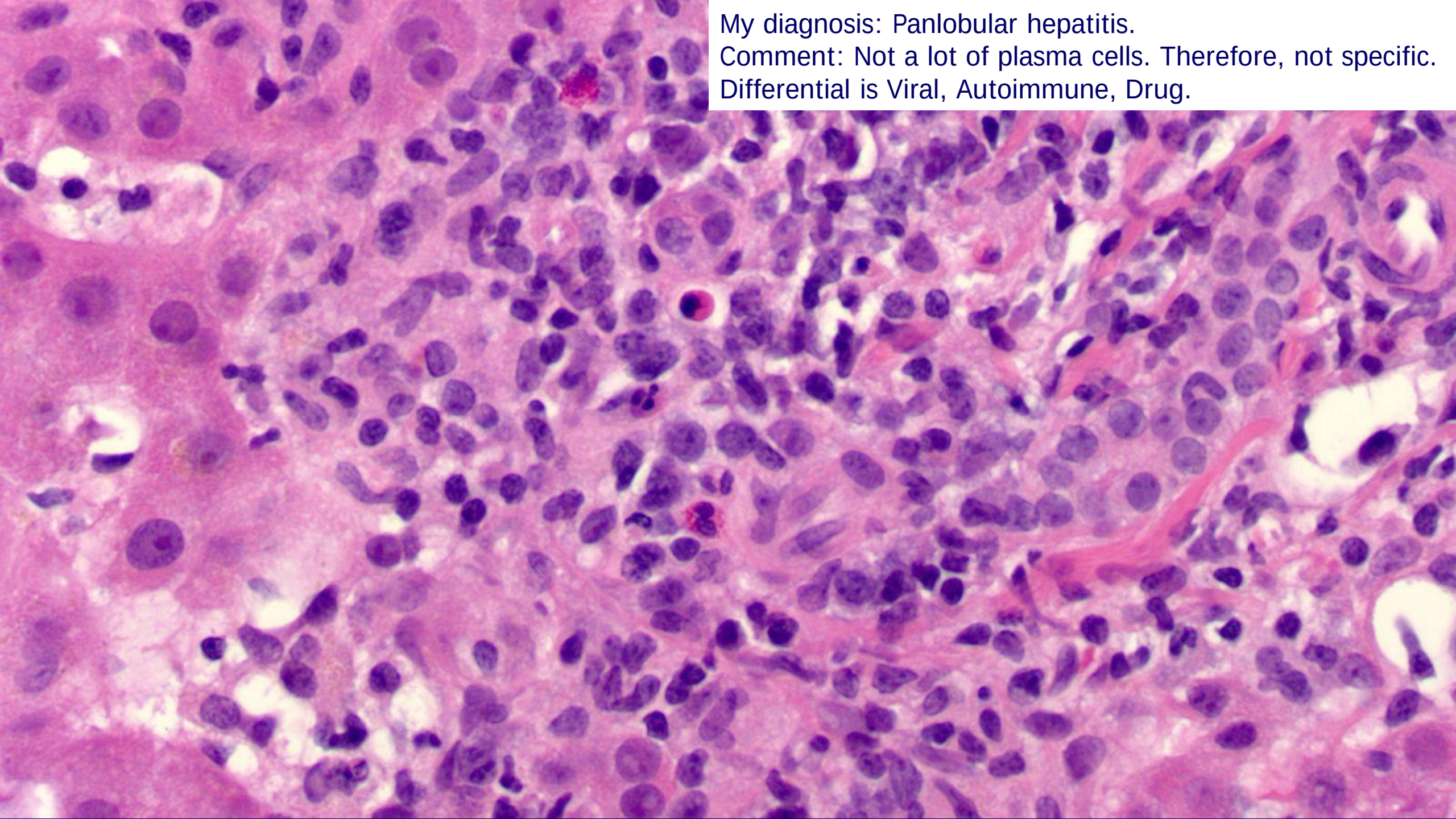
- Up to 40% of cases of AIH present acutely
- Often shows significant lobular activity (often panlobular hepatitis) and periportal necrosis that mimics chronic hepatitis
- One study reported fibrosis/cirrhosis in 60%.

Case

- 33 year old female, admitted for transaminases in the 1000-3000 range
- ANA negative, viral studies negative
- Had taken amoxicillin, 6 months ago, and valacyclovir 2 months ago



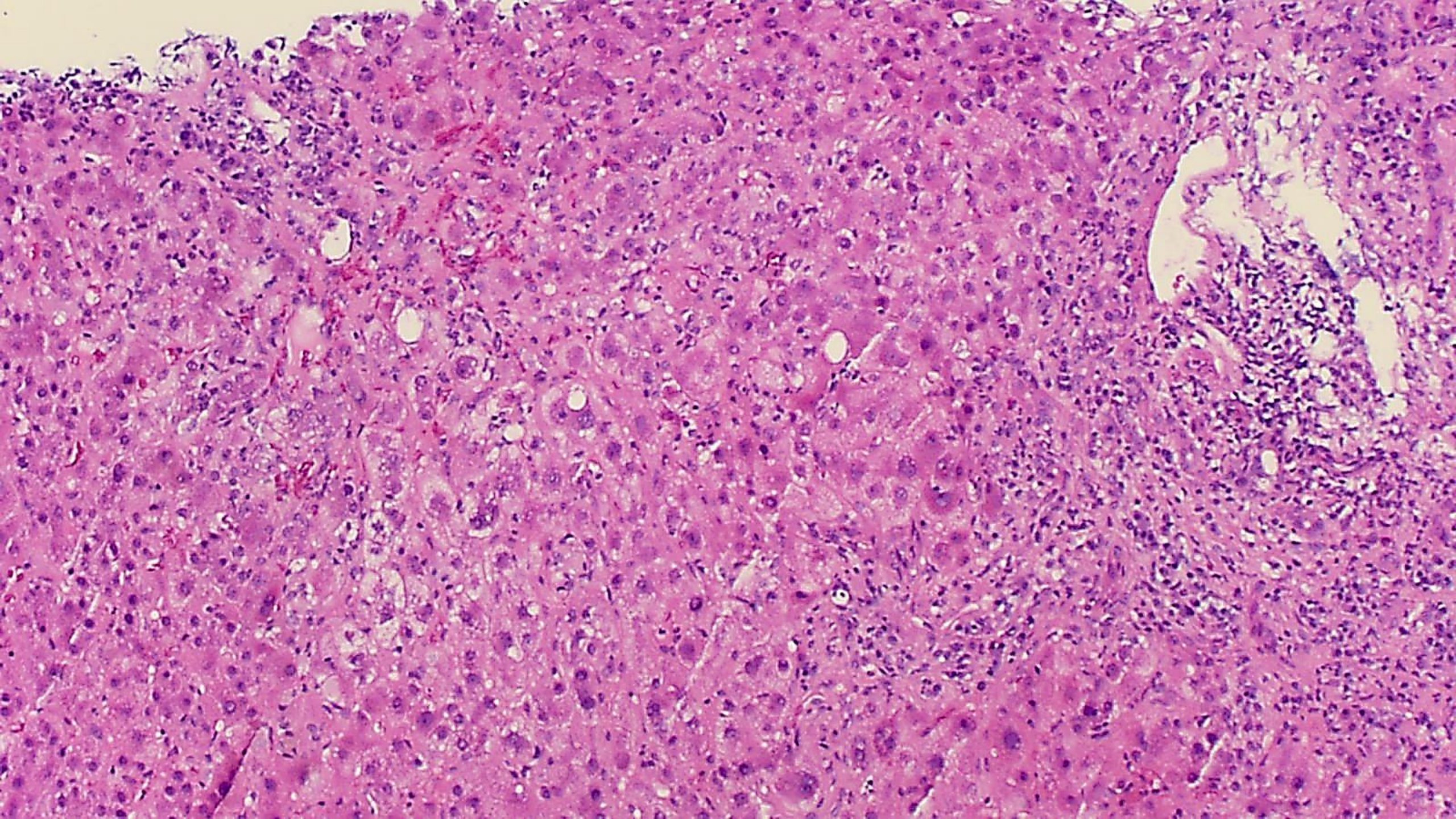


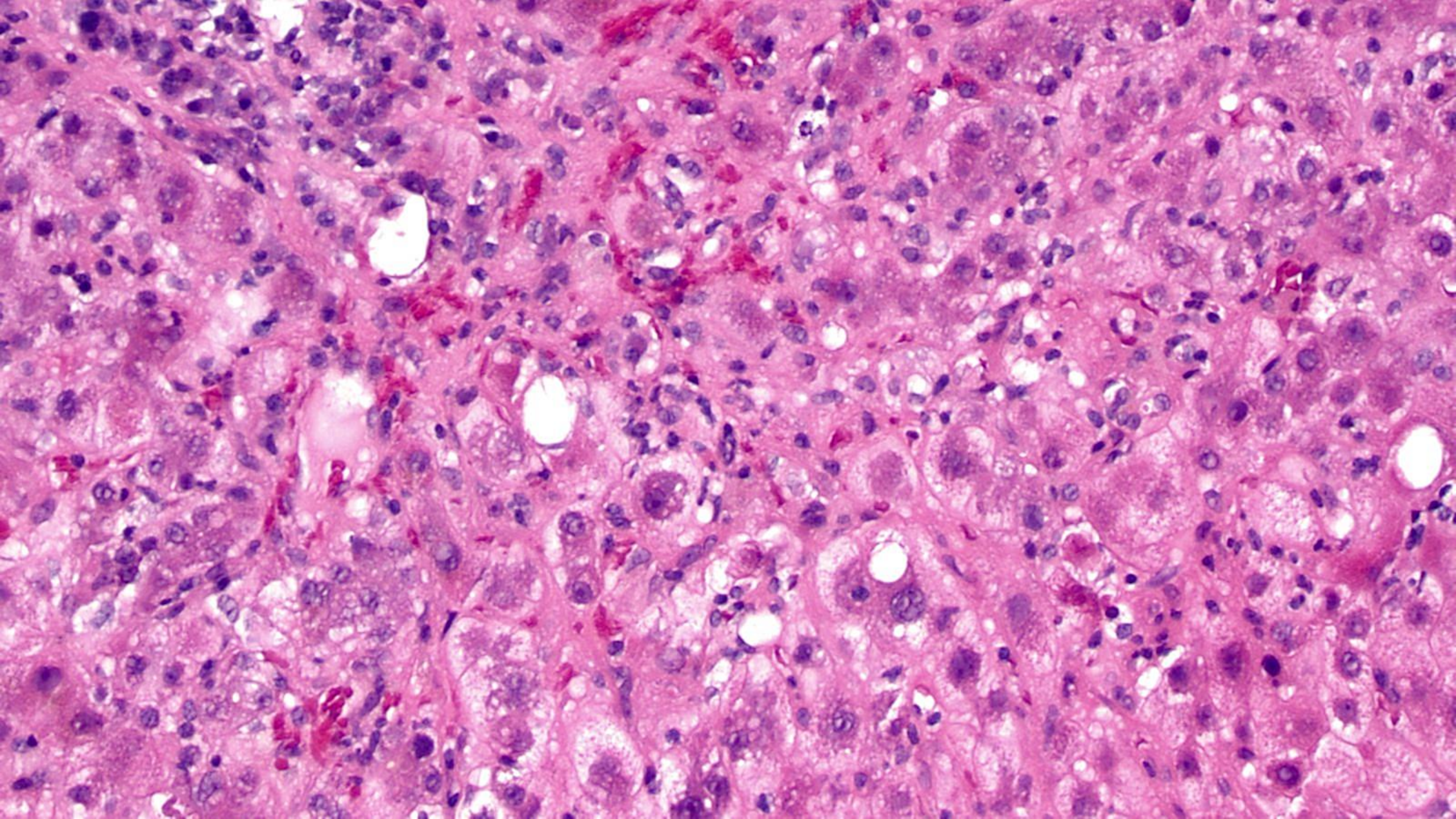


My diagnosis: Panlobular hepatitis.
Comment: Not a lot of plasma cells. Therefore, not specific.
Differential is Viral, Autoimmune, Drug.

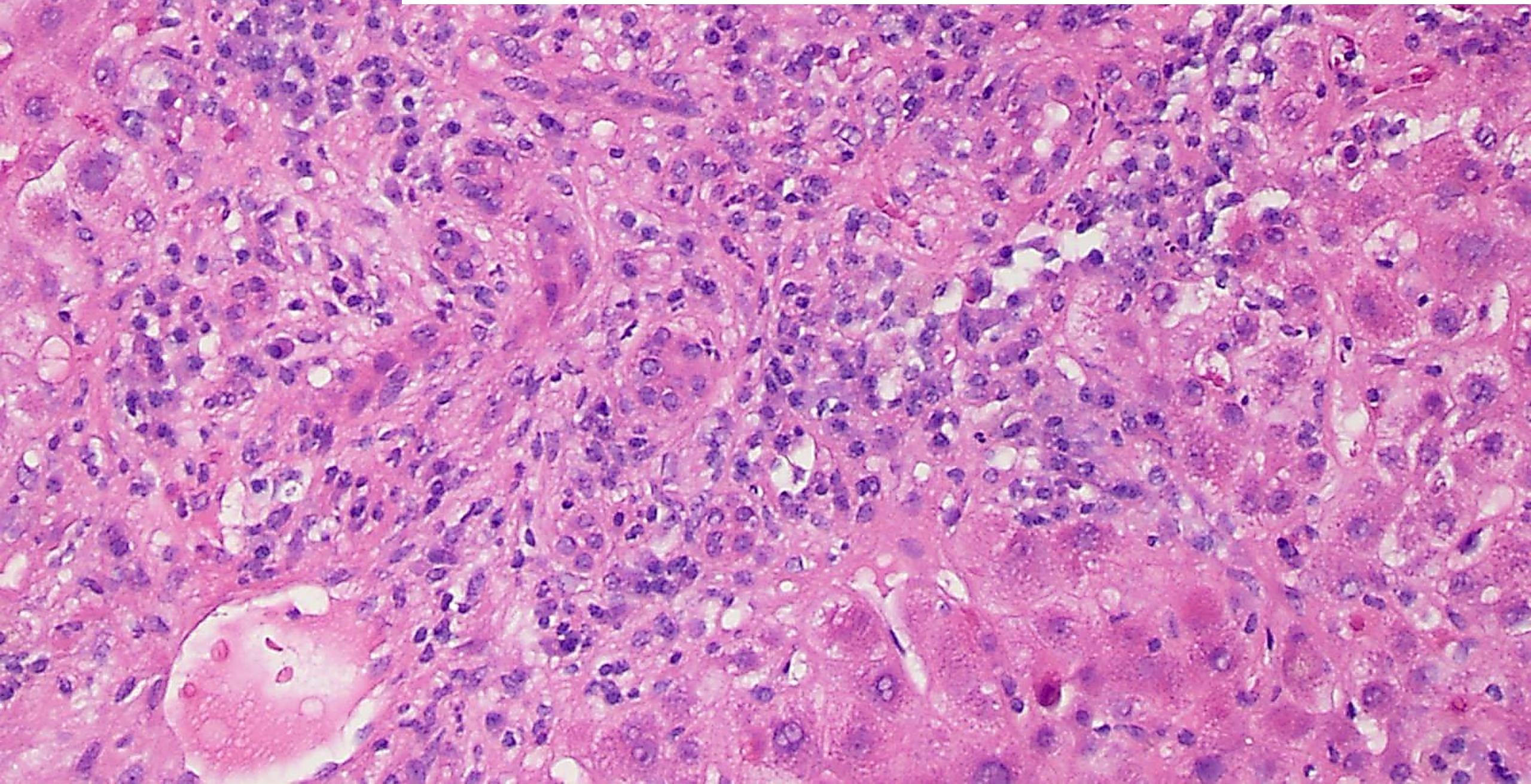
Case

- 80 year old woman who is on nitrofurantoin for UTI
- Notes dark urine and presents with transaminases around 1800
- ANA 1:320
- After nitrofurantoin discontinued, transaminases drop to around 675



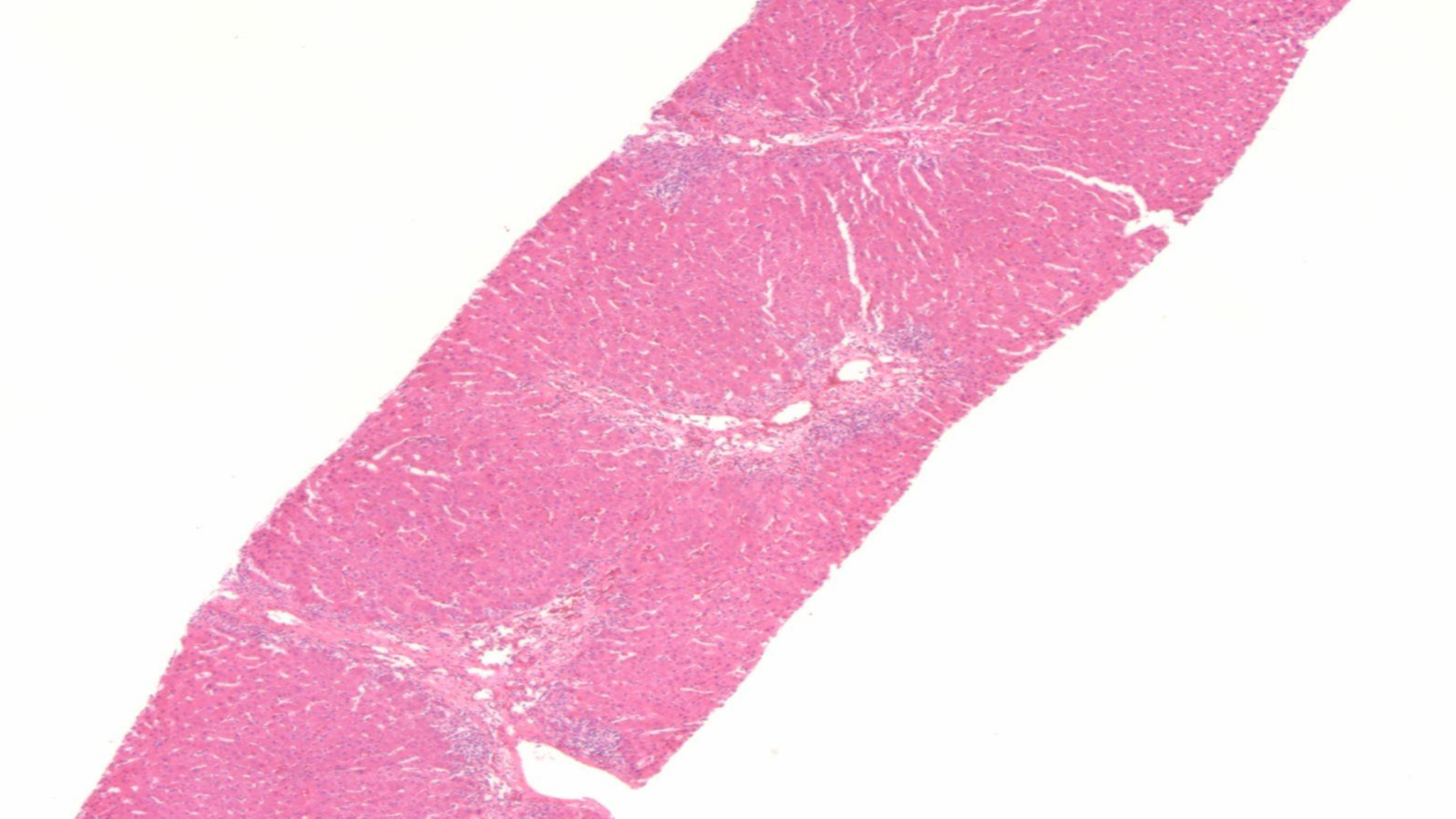


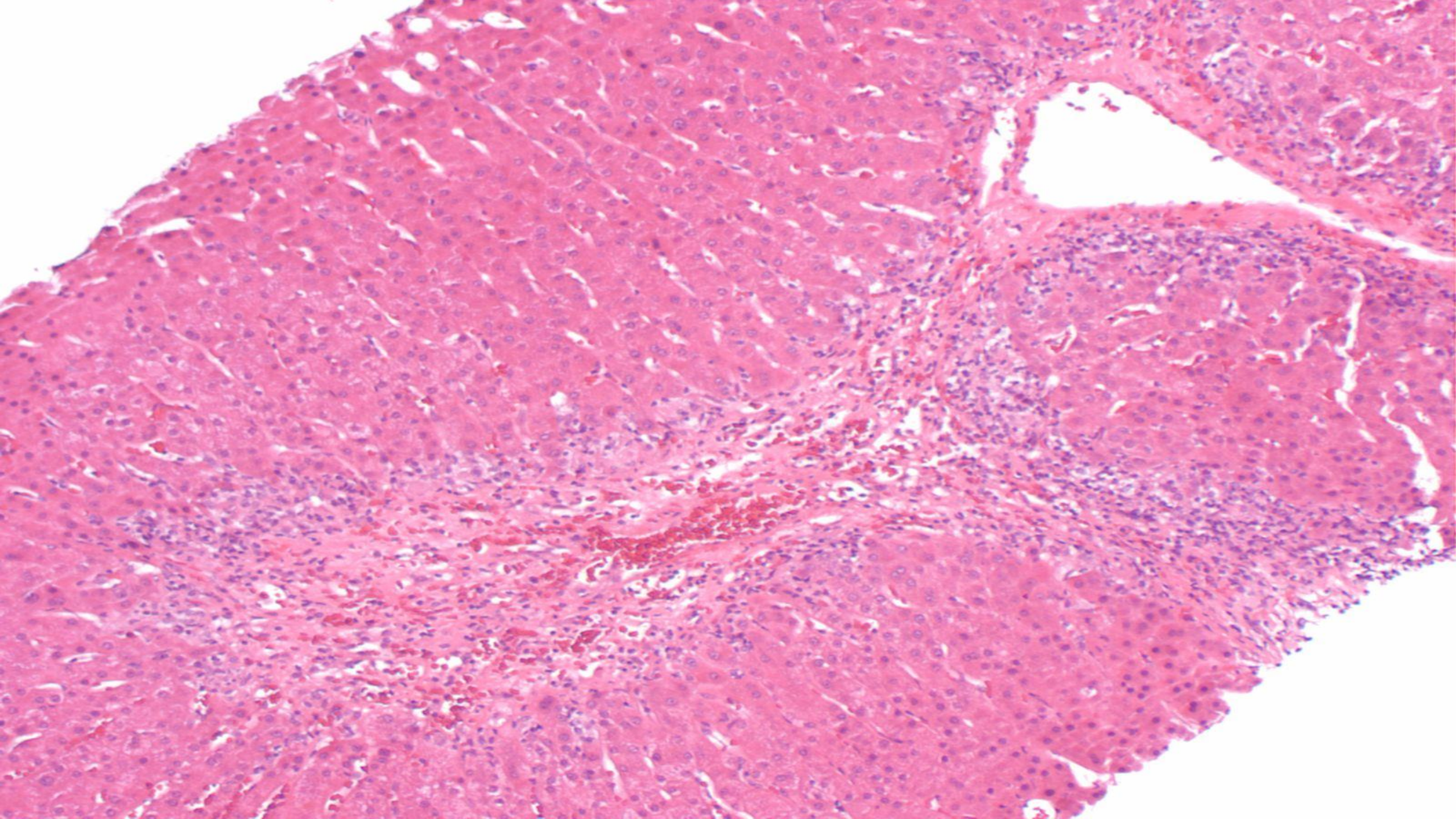
My diagnosis: Panlobular hepatitis with numerous plasma cells, consistent with AIH.
Comment: Given the history, consistent with nitrofurantoin-induced AIH.

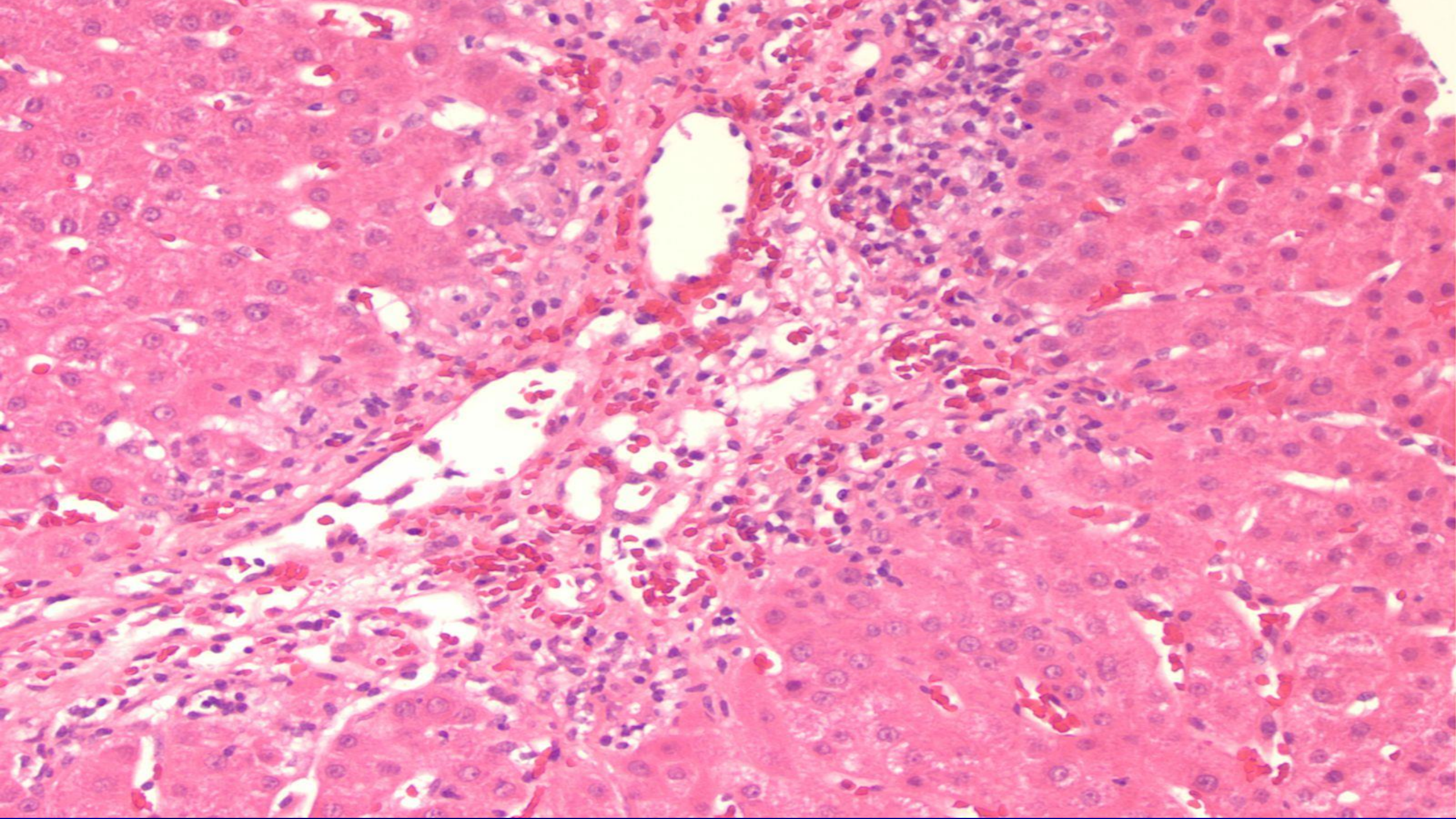


Zone 3 Autoimmune hepatitis

- ANA may or may not be positive
- Plasma cells may or may not 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
- Have seen patients who have this for a long time but do not develop progressive fibrosis
- Differential includes drug reaction

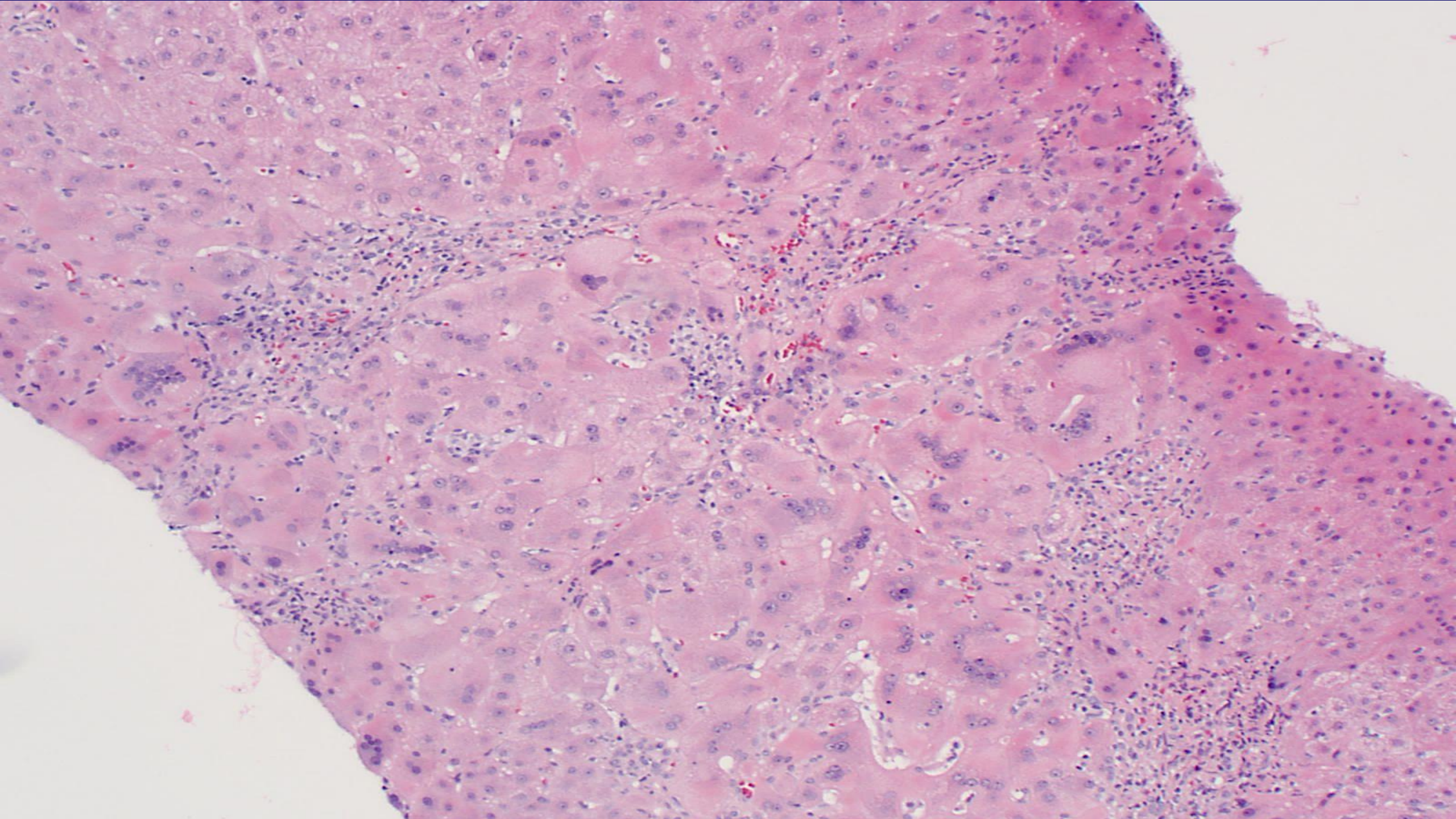


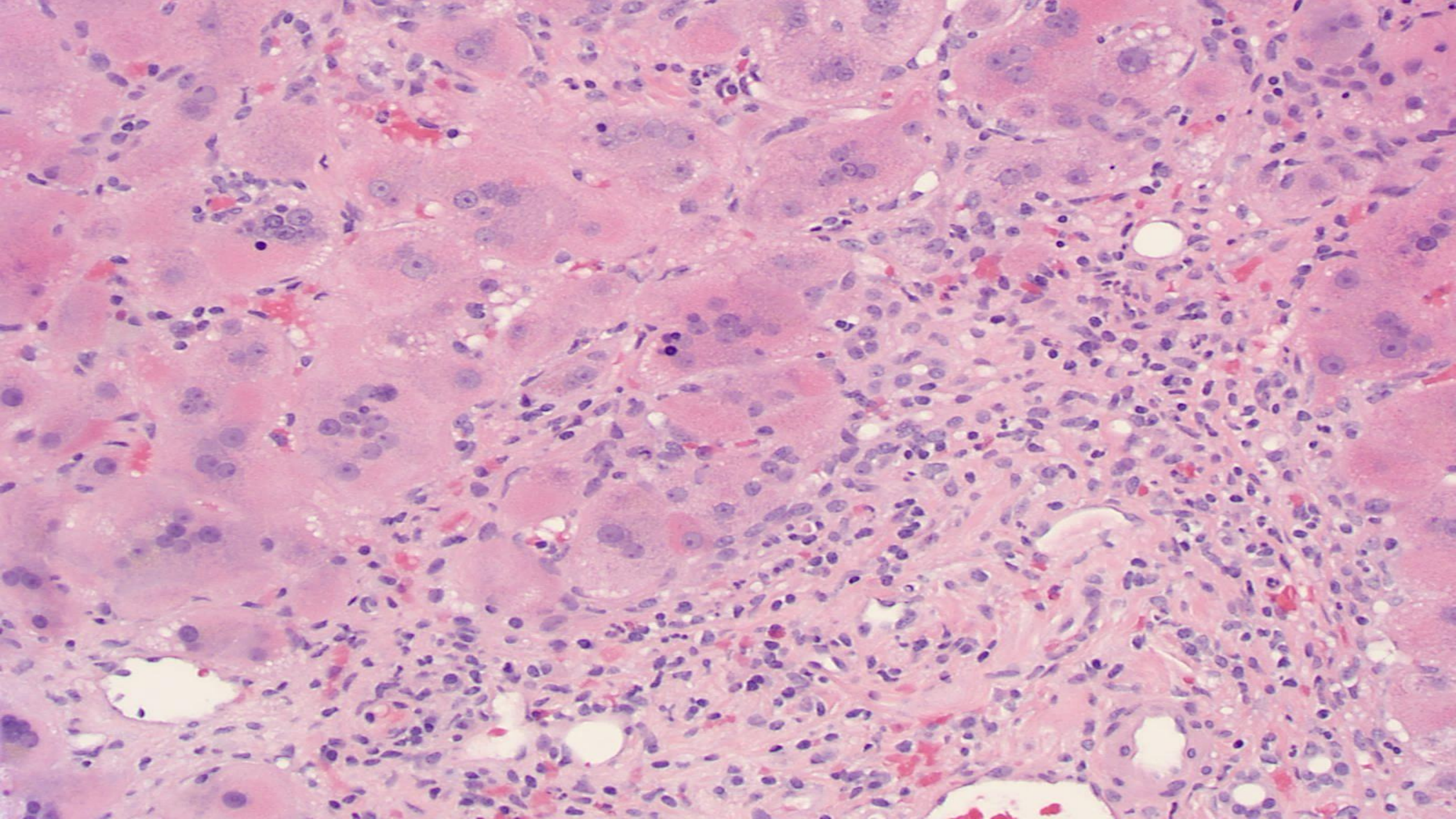




Post Infantile Giant Cell Hepatitis

- Pattern of injury seen in many conditions, including HIV, HCV, drugs, paramyxovirus infection
- Upwards of 40% of cases have autoimmune features or are AIH
- Variable response to therapy; giant cells may persist despite improvement in LFTs



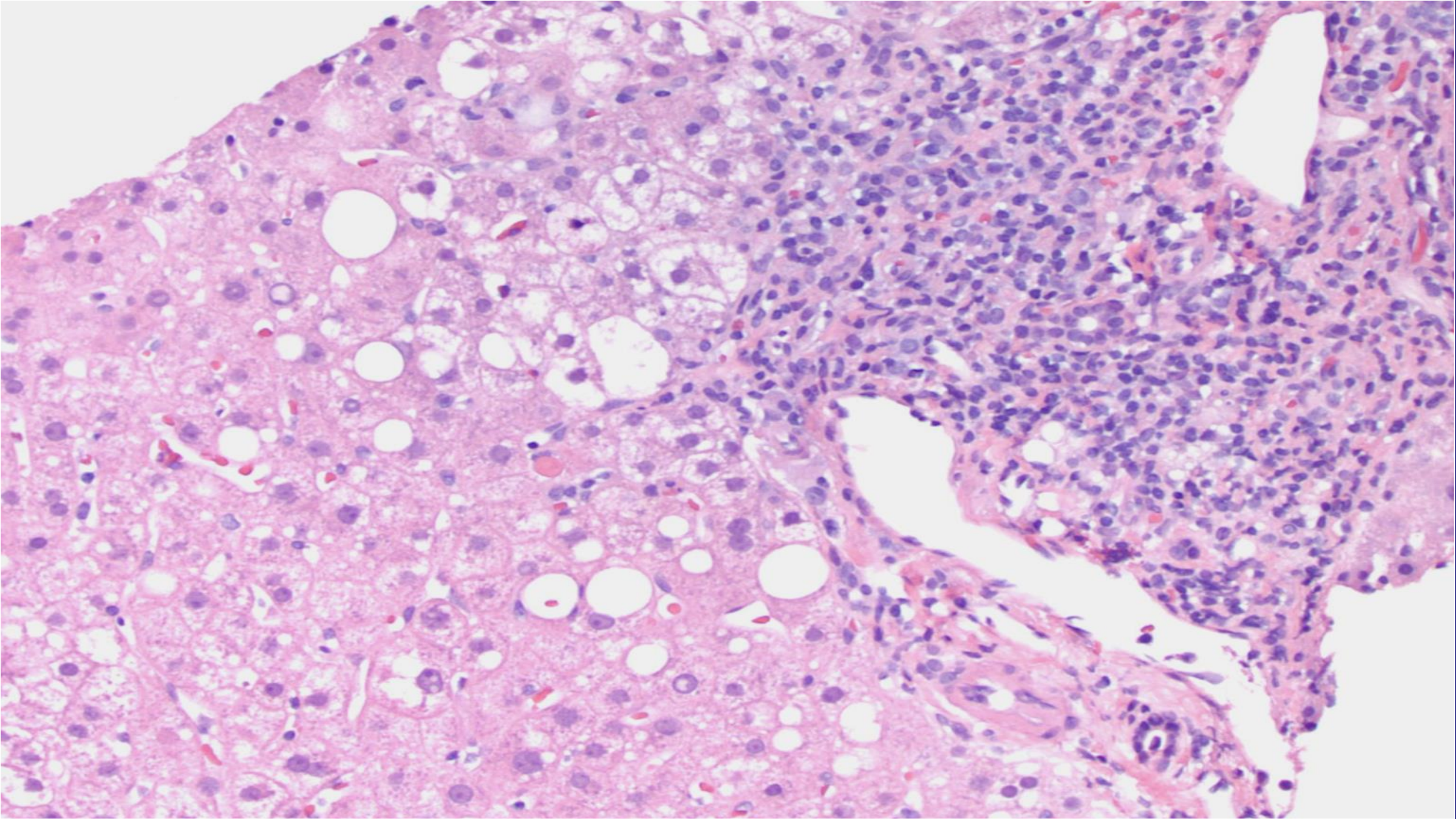


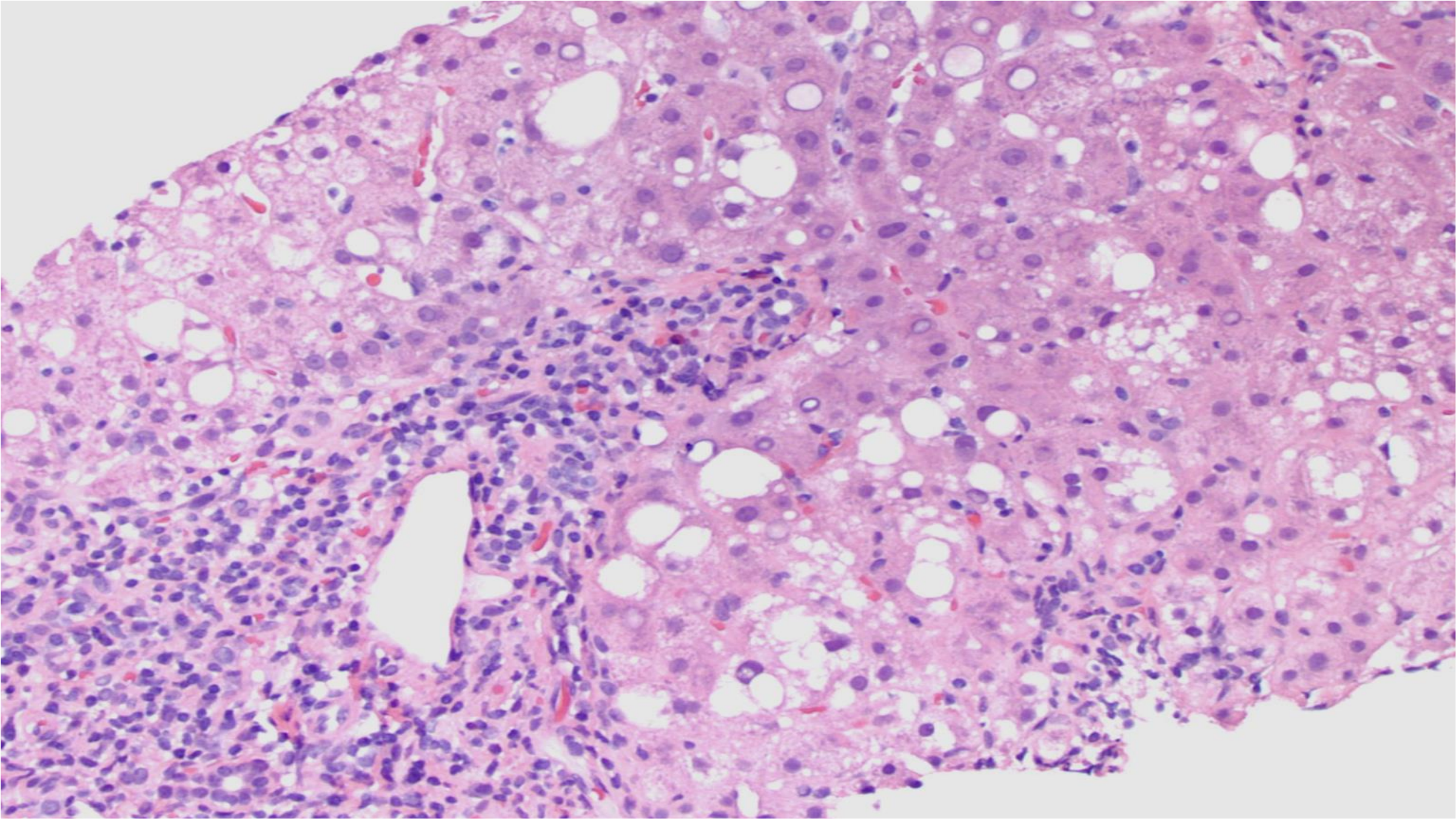
NAFLD vs. AIH

- 10-35% of patients with SH have ANA+
- 5% have SMA
- Women more frequently affected
- Number of plasma cells similar between ANA+ and ANA- patients.
- ANA is a non-specific antibody response in NAFLD

Case

- Biopsy called chronic hepatitis of unknown etiology
- In the comment, the pathologist mentioned “steatosis without ballooning or steatohepatitis”

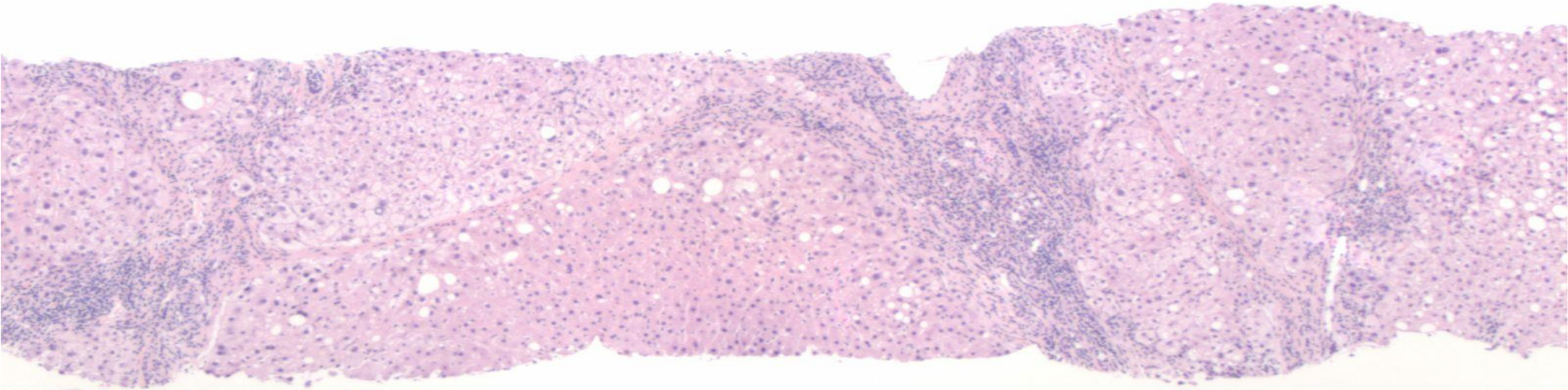


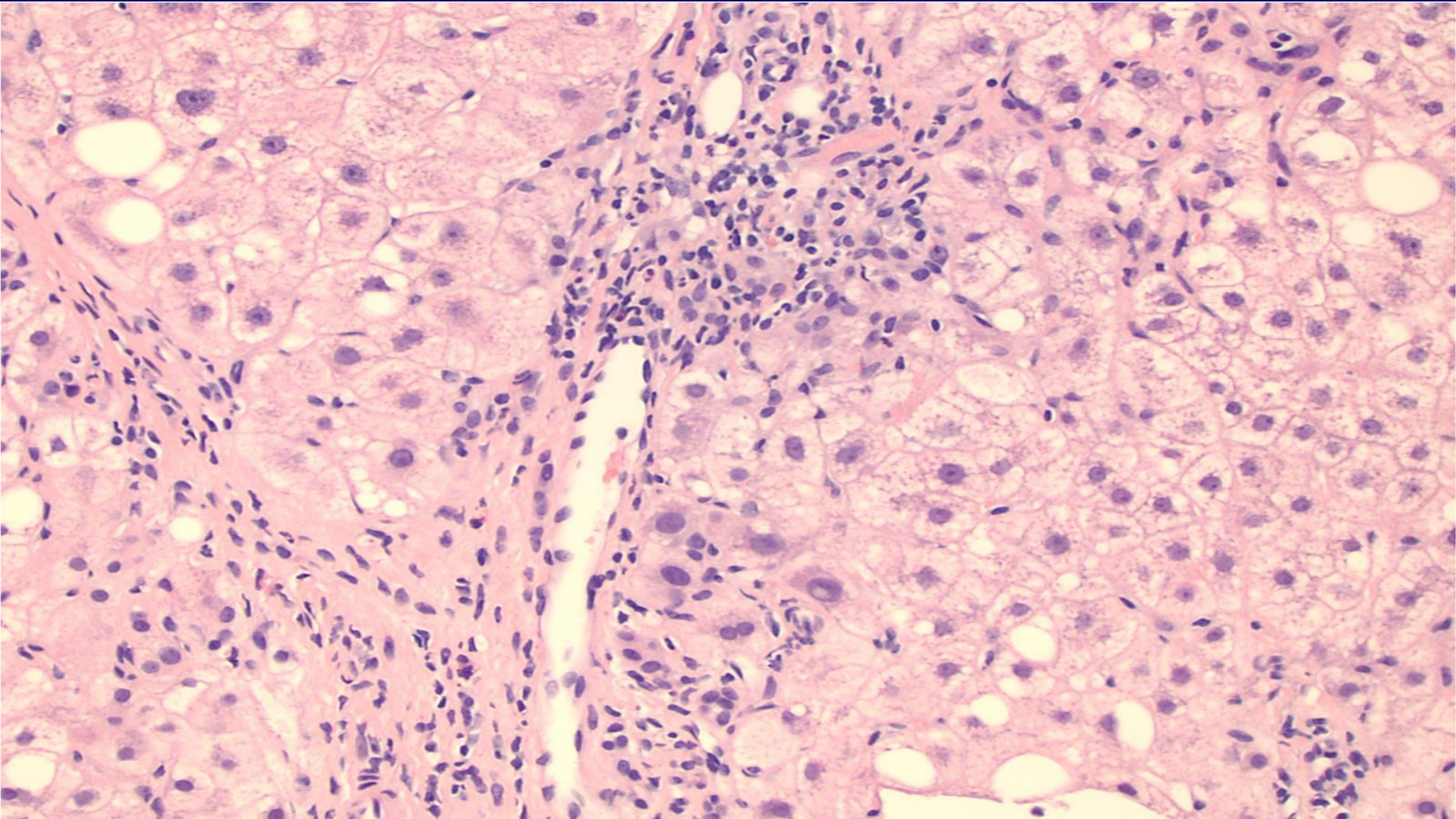


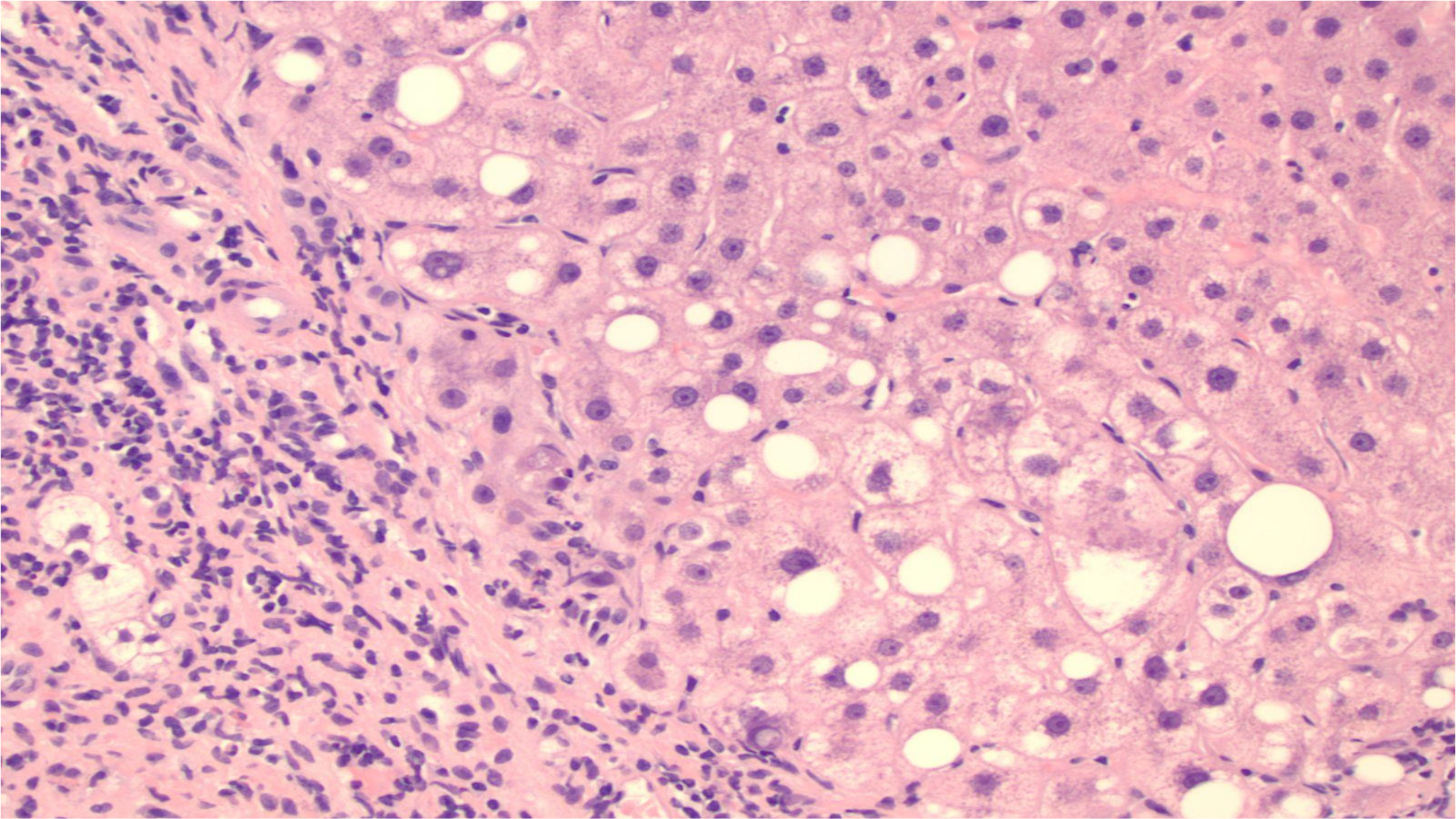
Autoimmune Hepatitis in Cirrhosis

- AIH can “burn out” with non-specific cirrhosis.
- In cirrhosis, the more relevant question becomes: Is it currently active? Does this patient need steroids to prevent decompensation?
- Caveat 1: Don’t overcall non-specific chronic inflammation in fibrotic septae.

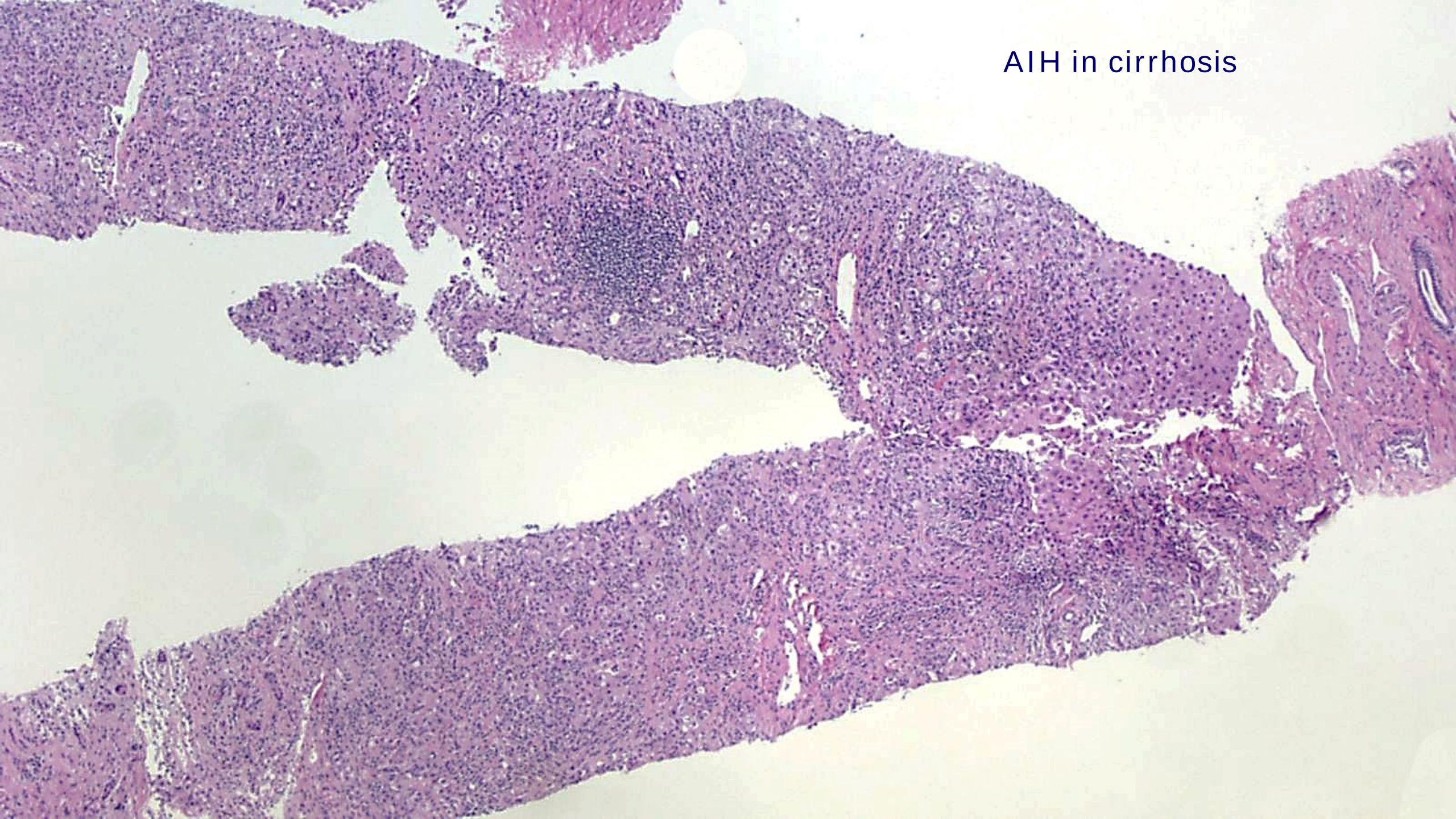
End stage NAFLD

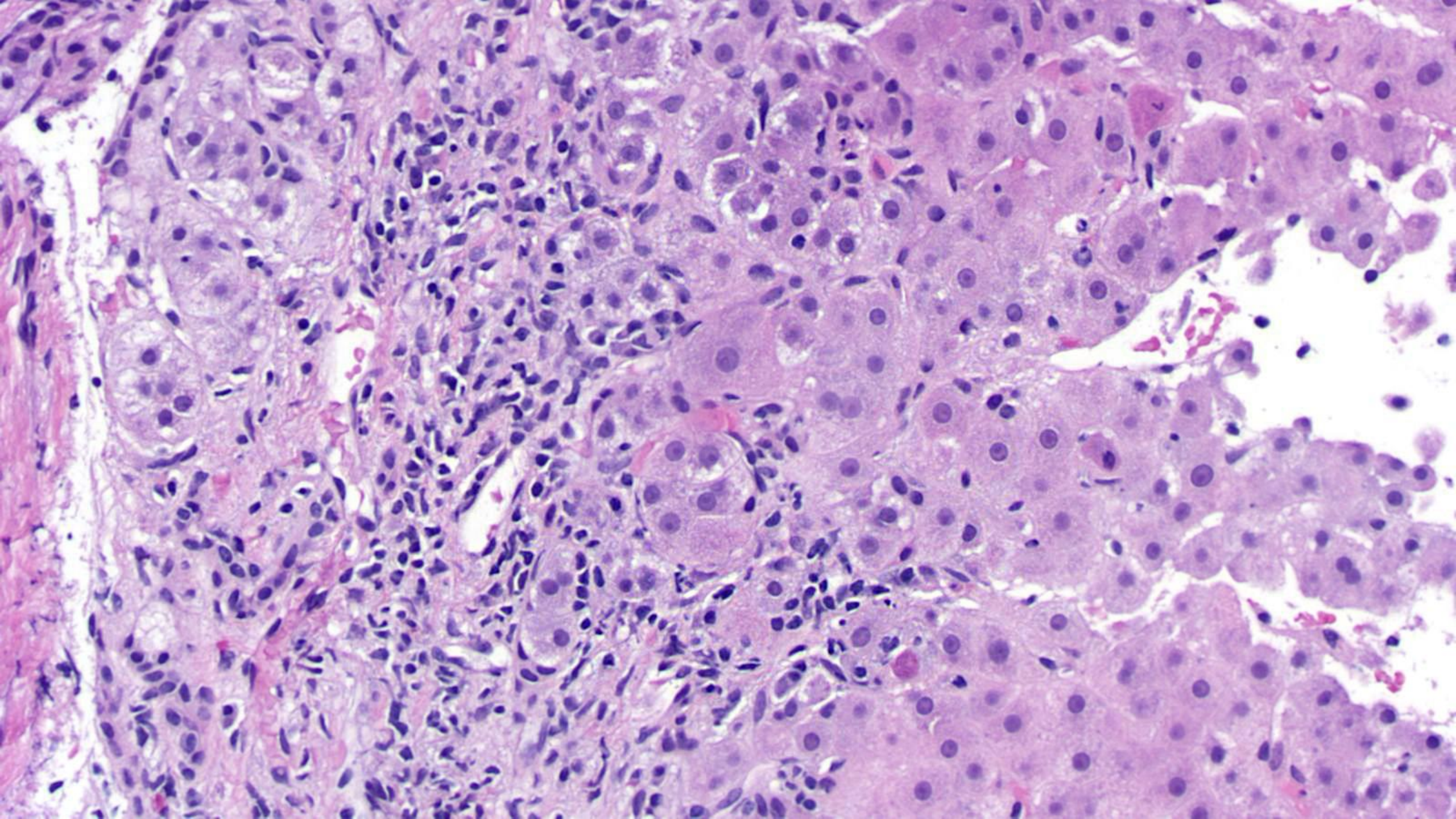


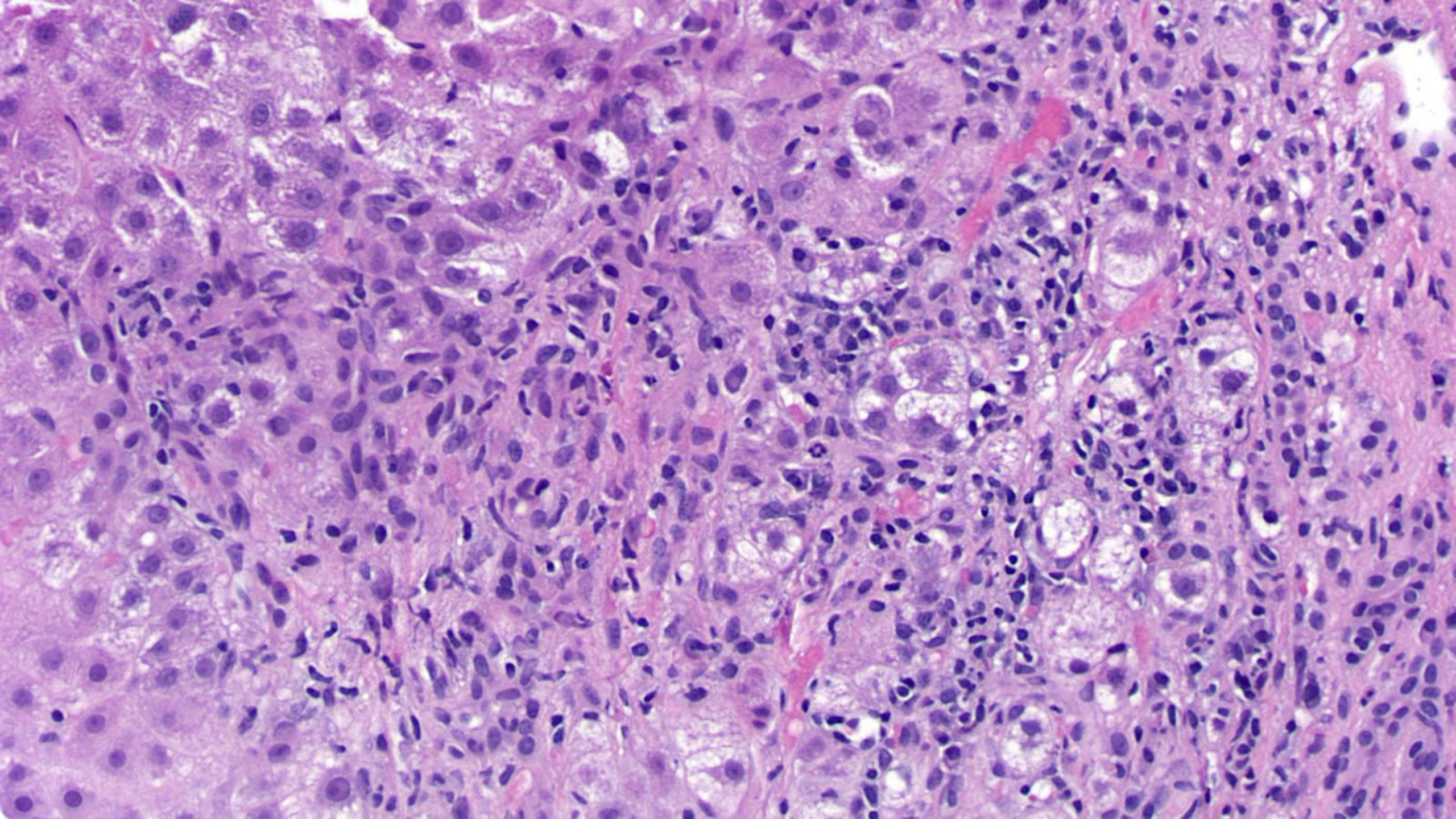


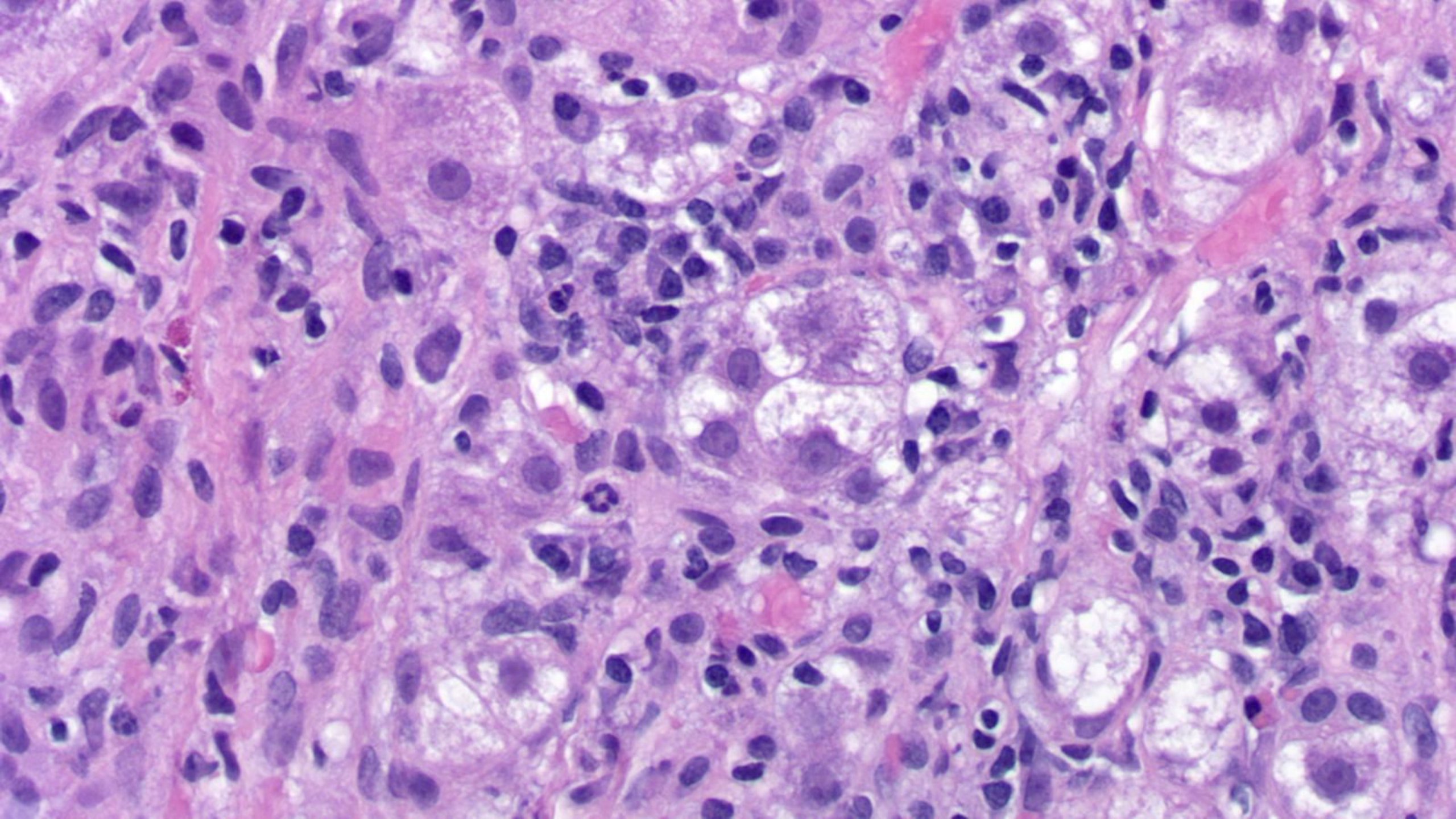


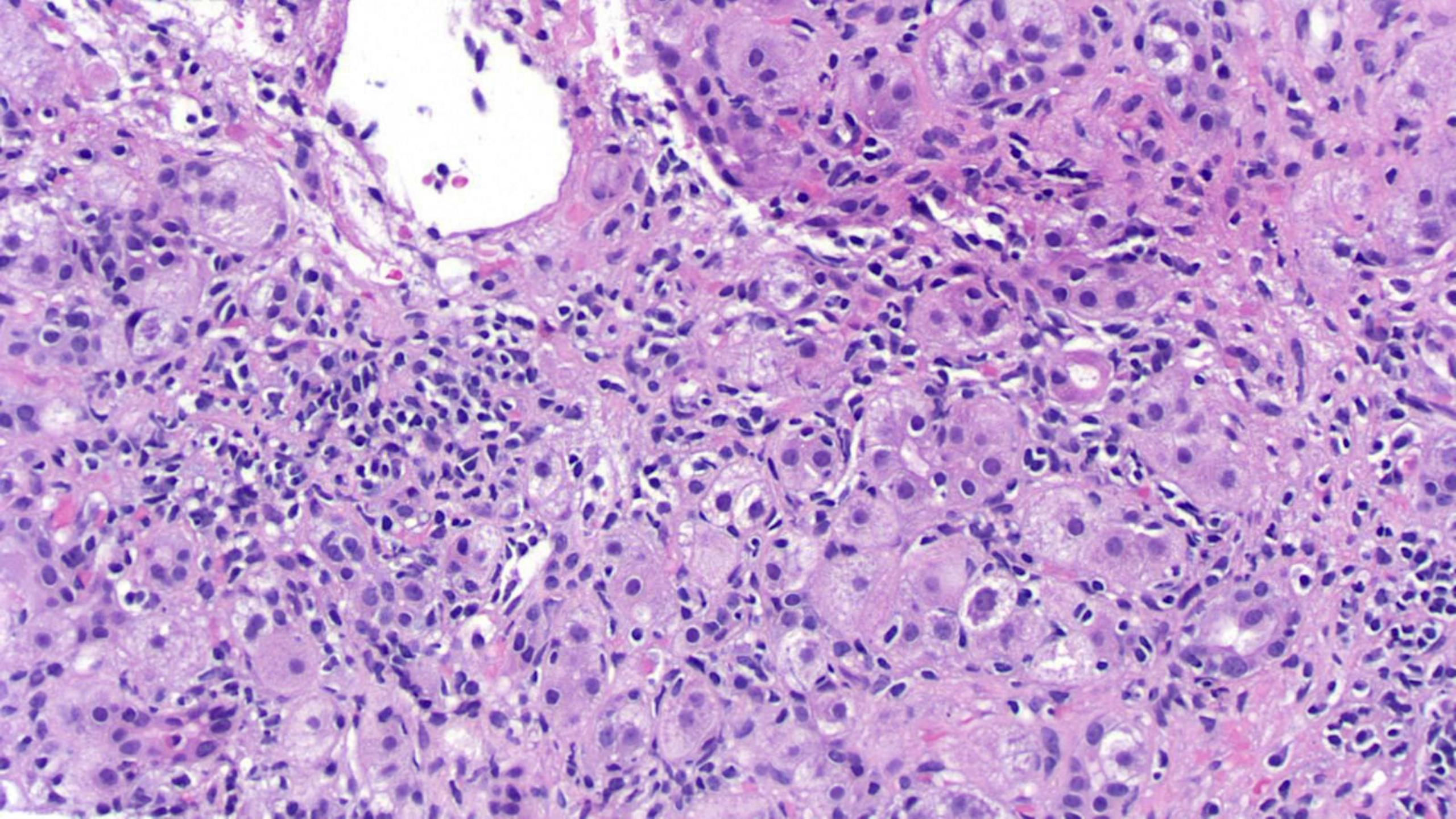
AIH in cirrhosis









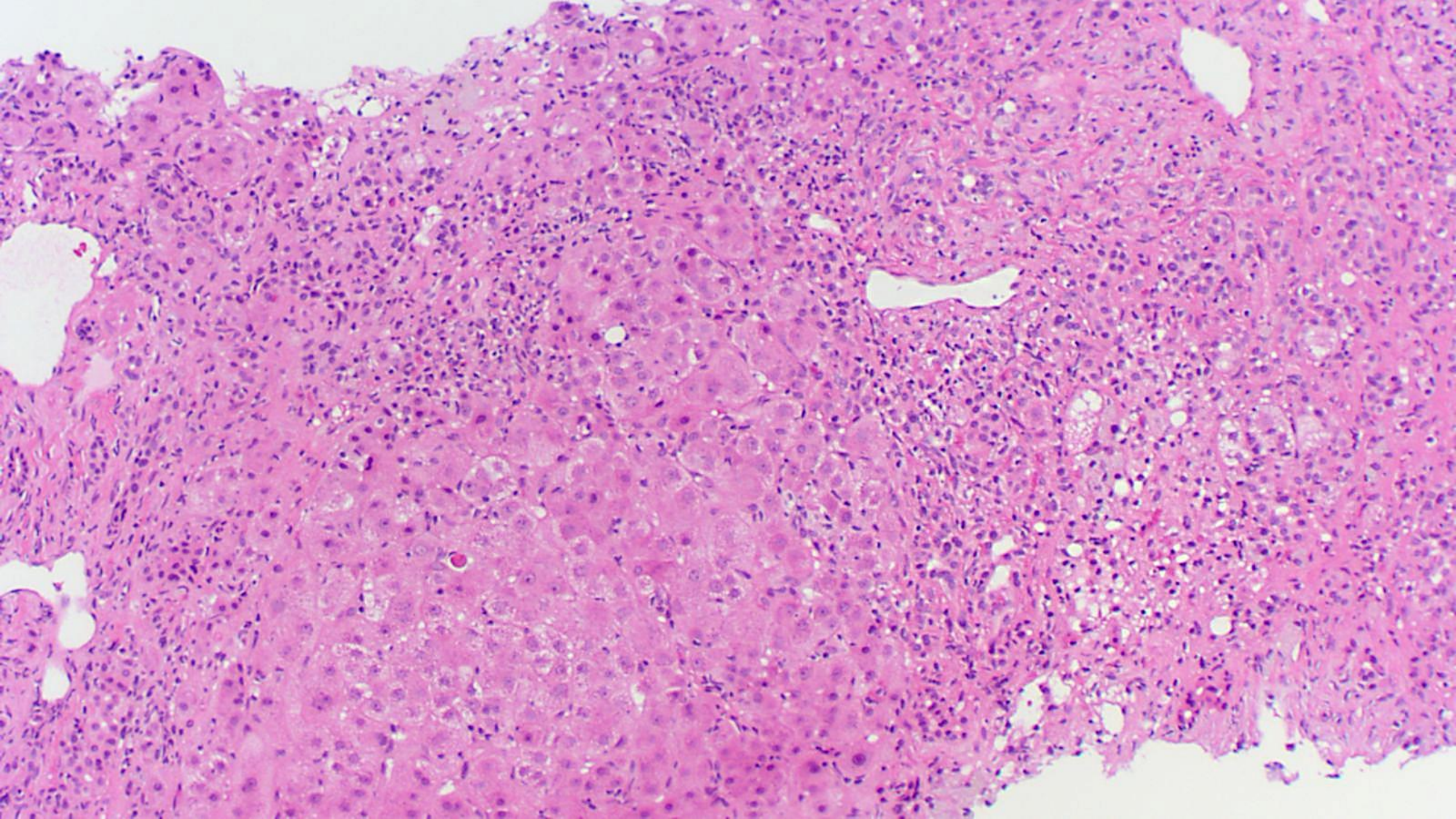


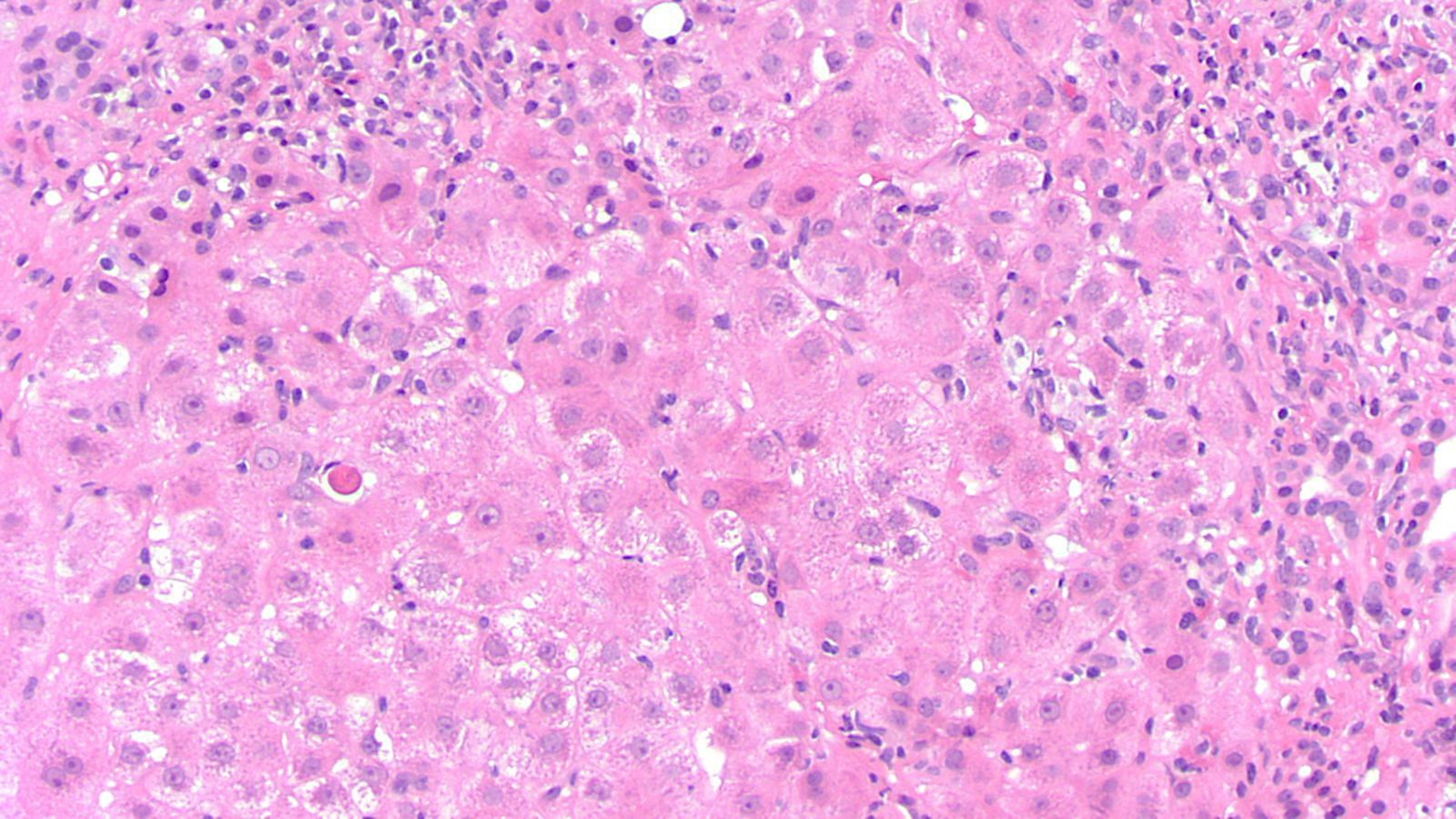
Autoimmune Hepatitis in Cirrhosis

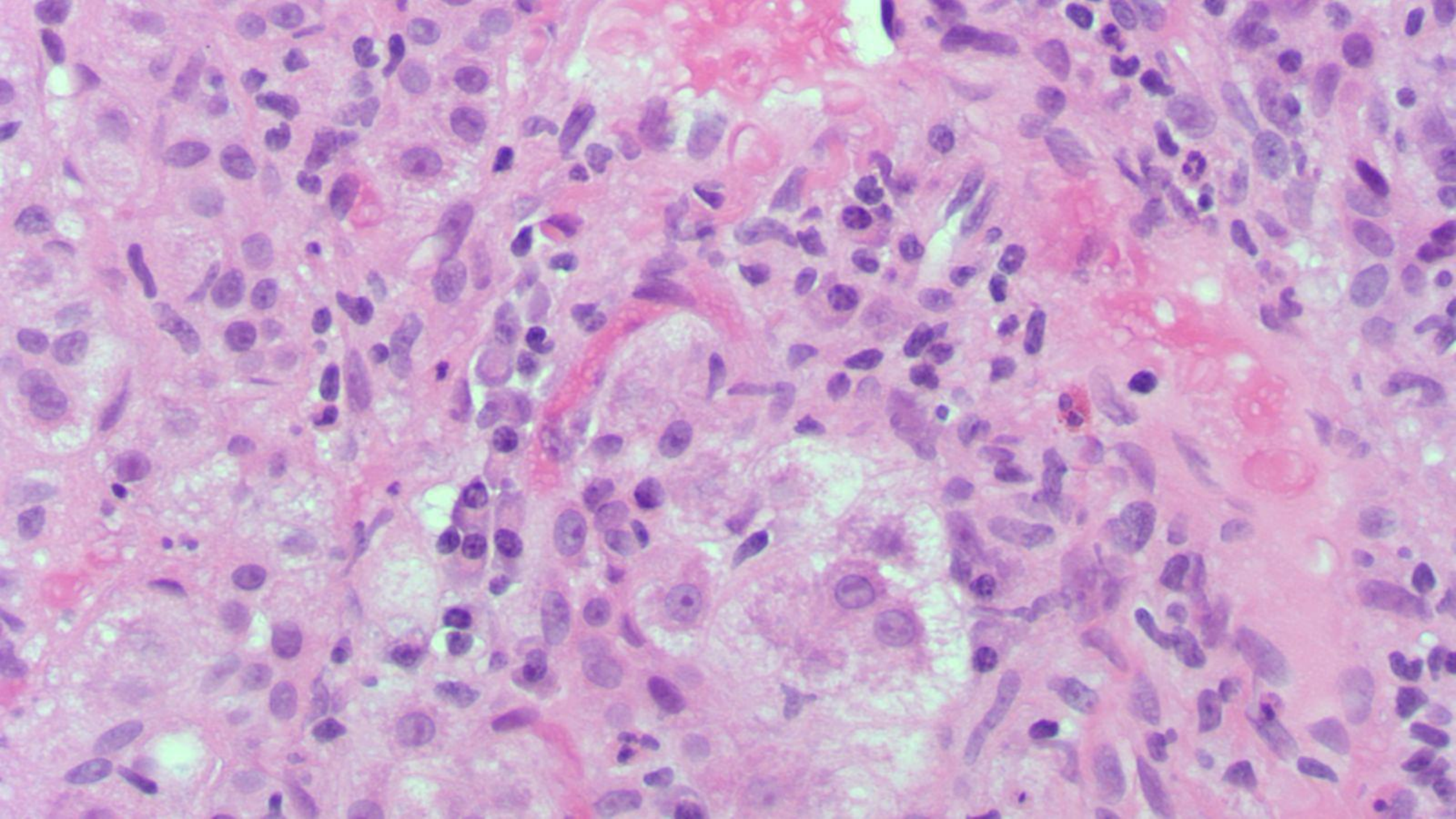
- AIH can "burn out" to non-specific cirrhosis.
- Is it currently active?
- Caveat 1: Don't overcall non-specific chronic inflammation in fibrotic septae.
- Caveat 2: If it is inflamed enough that you are convinced it's an active inflammatory process, are you sure it is really cirrhotic?

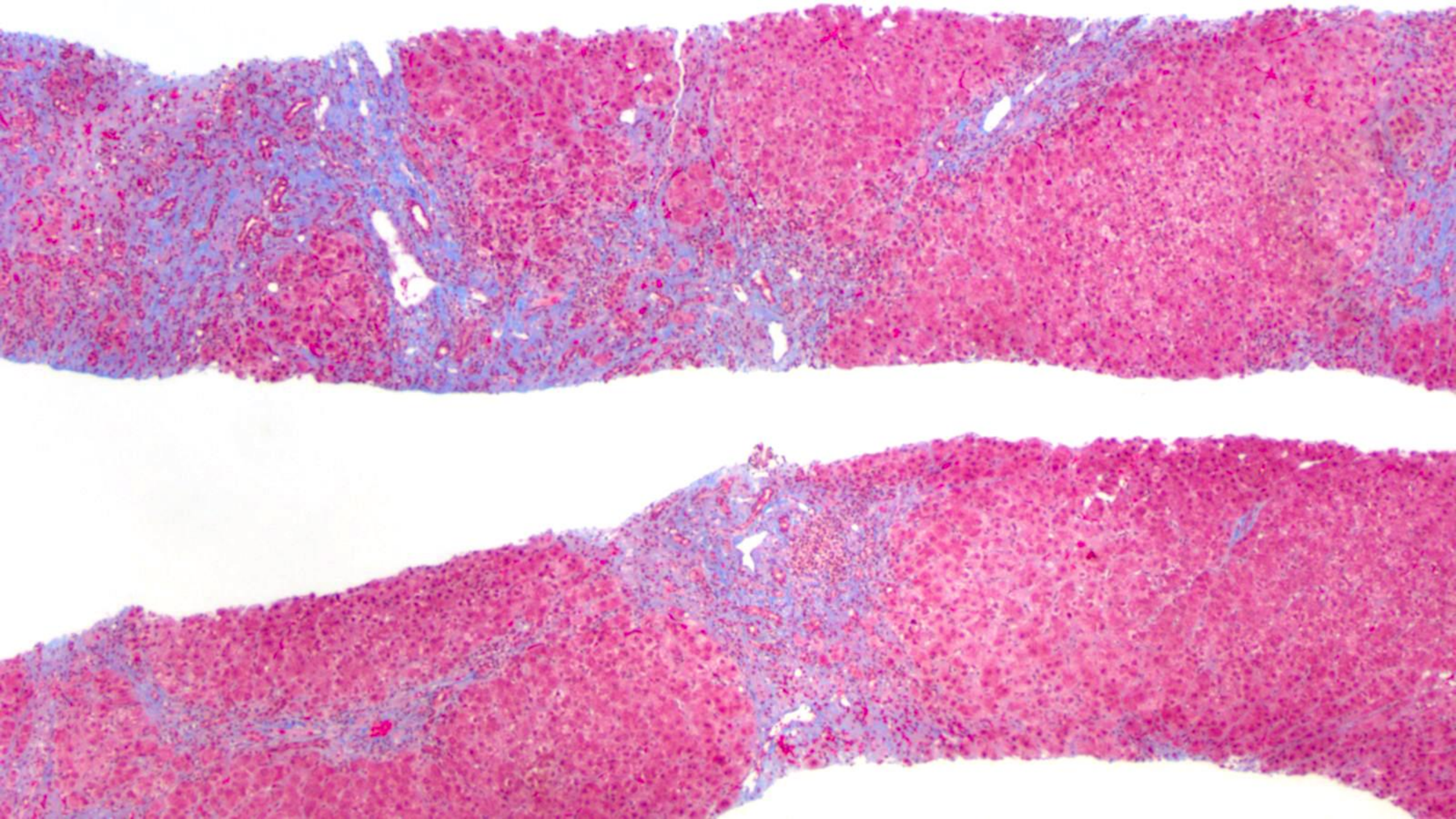
Case

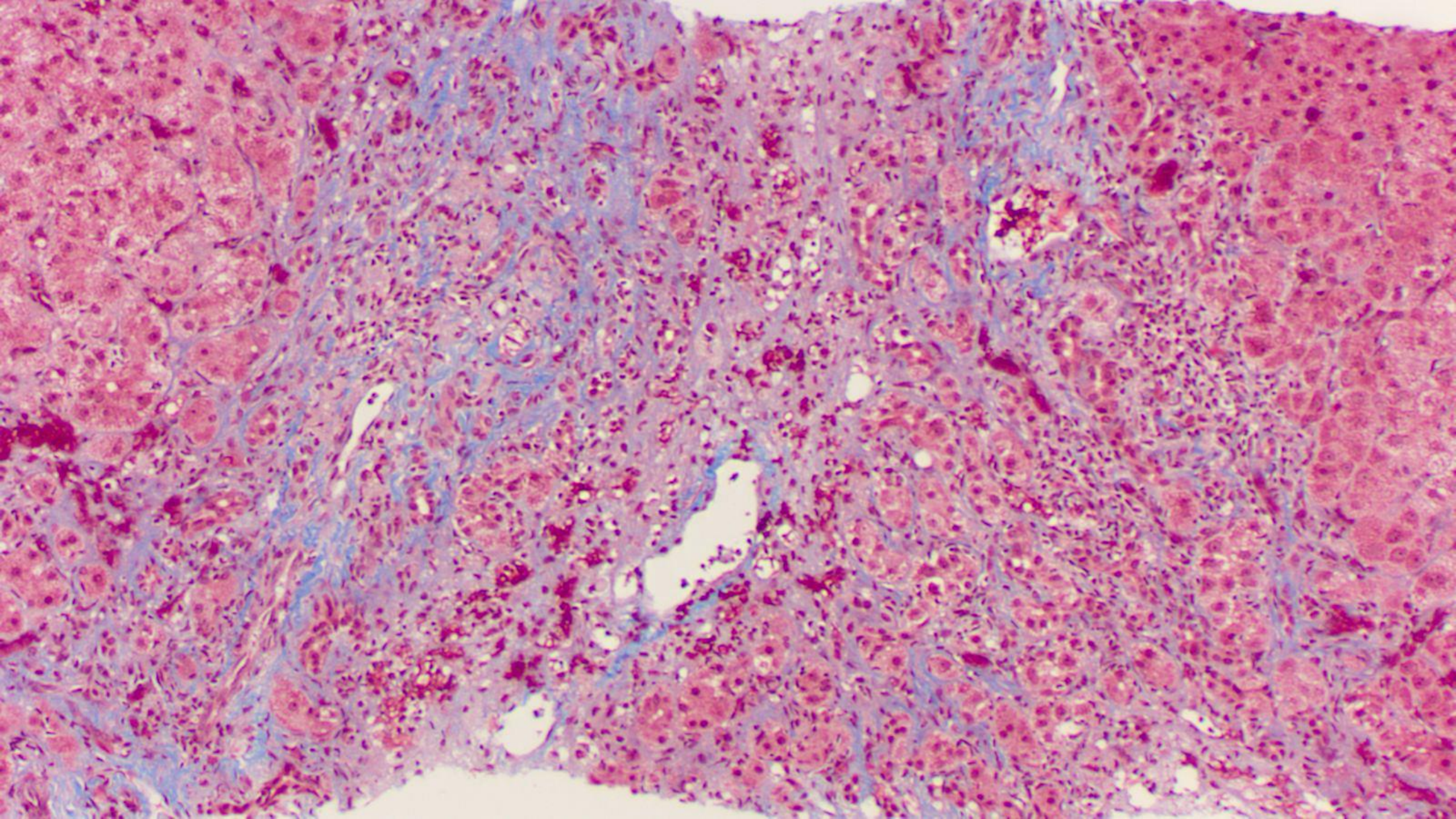
- 80 year old female, clinical history provided “Hep C cirrhosis”
- After it was signed out as HCV cirrhosis, the clinician informs the pathologist that the patient cleared HCV long ago. The real story: She fell ill recently on a cruise, with edema. IV steroids didn’t seem to help. Blood work showed elevated IgG, SMA+, AST 735, ALT 427

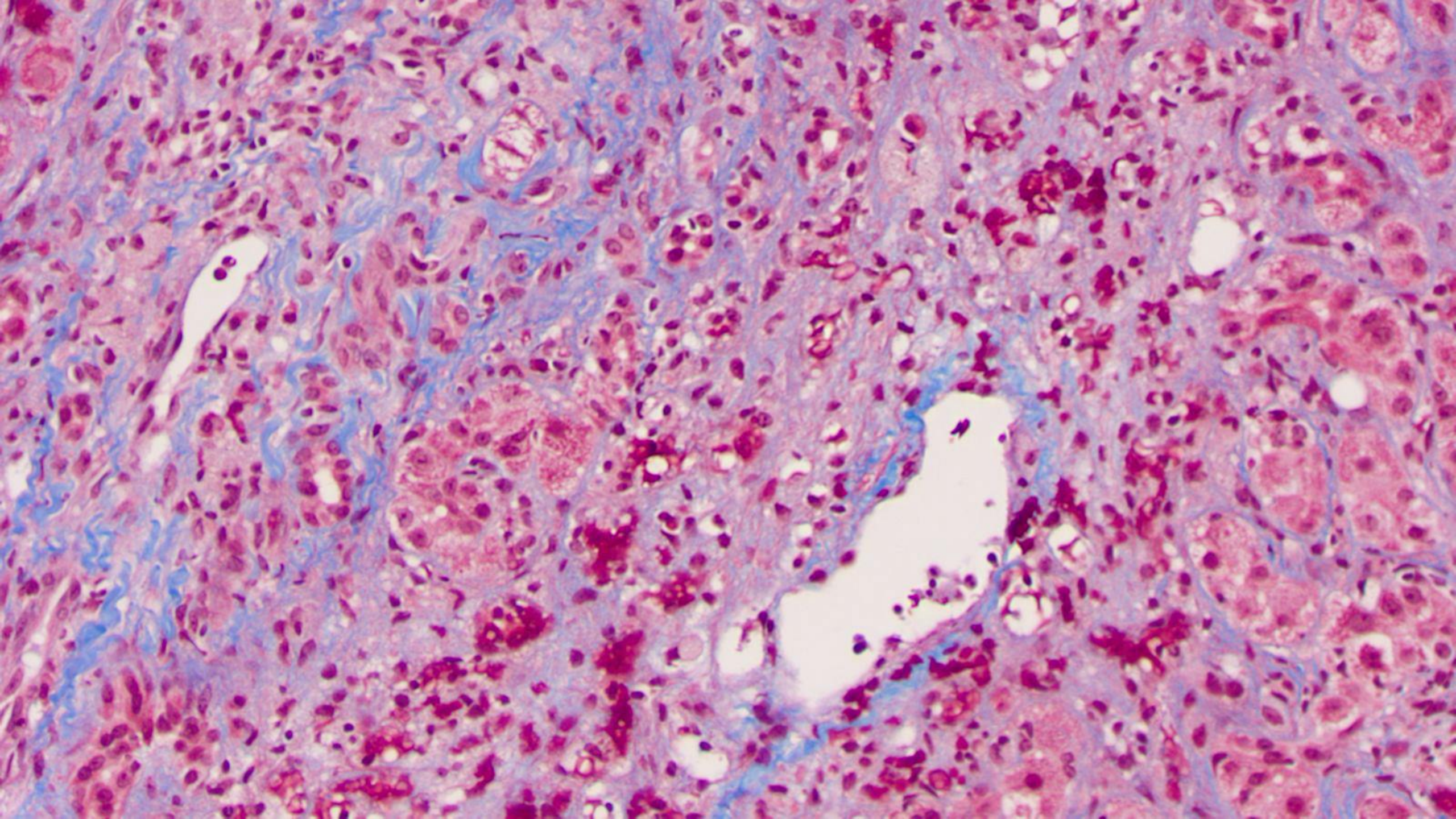












Primary Biliary Cholangitis

Non-suppurative destructive cholangiopathy of small and intermediate sized ducts (≤ 100 μ)

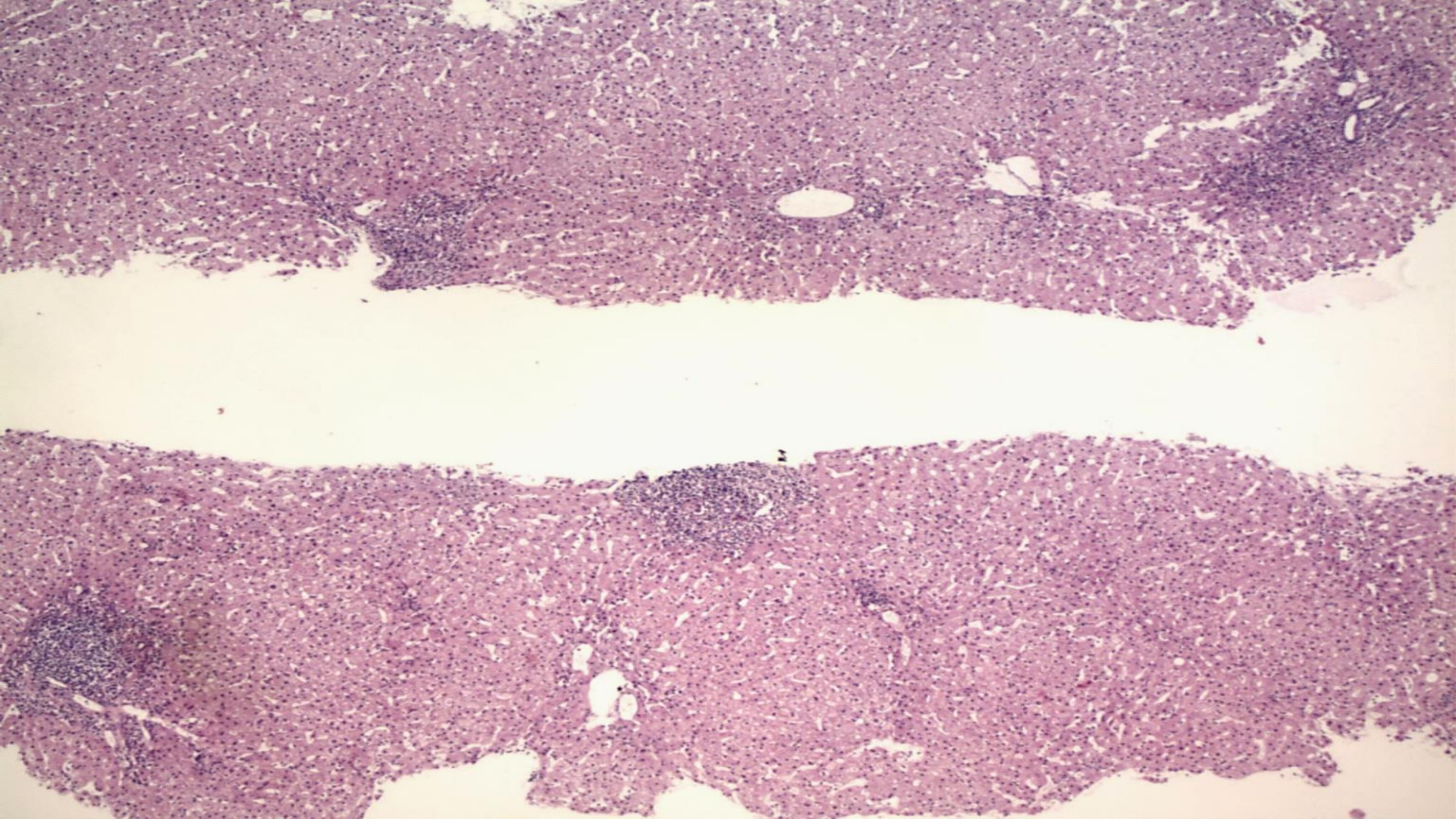
- Female:male = 9:1
- Median: 50 yrs. Not reported in children.
- Present with elevated Alk Phos, pruritus.
- Elevated IgM, cholesterol
- Associated with other autoimmune disorders (particularly autoimmune thyroid disease, sicca syndrome, CVID)

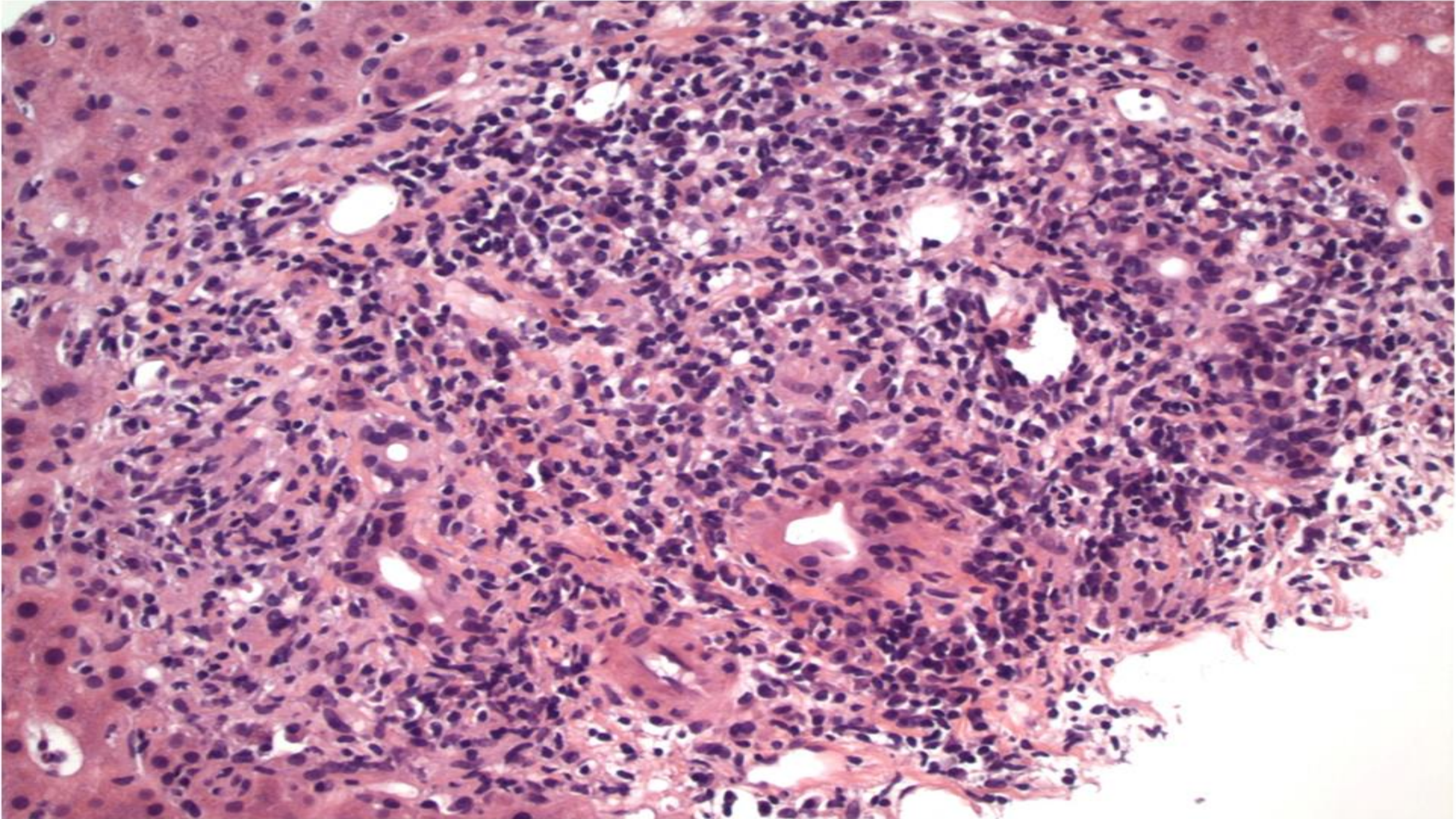
Autoantibodies in PBC

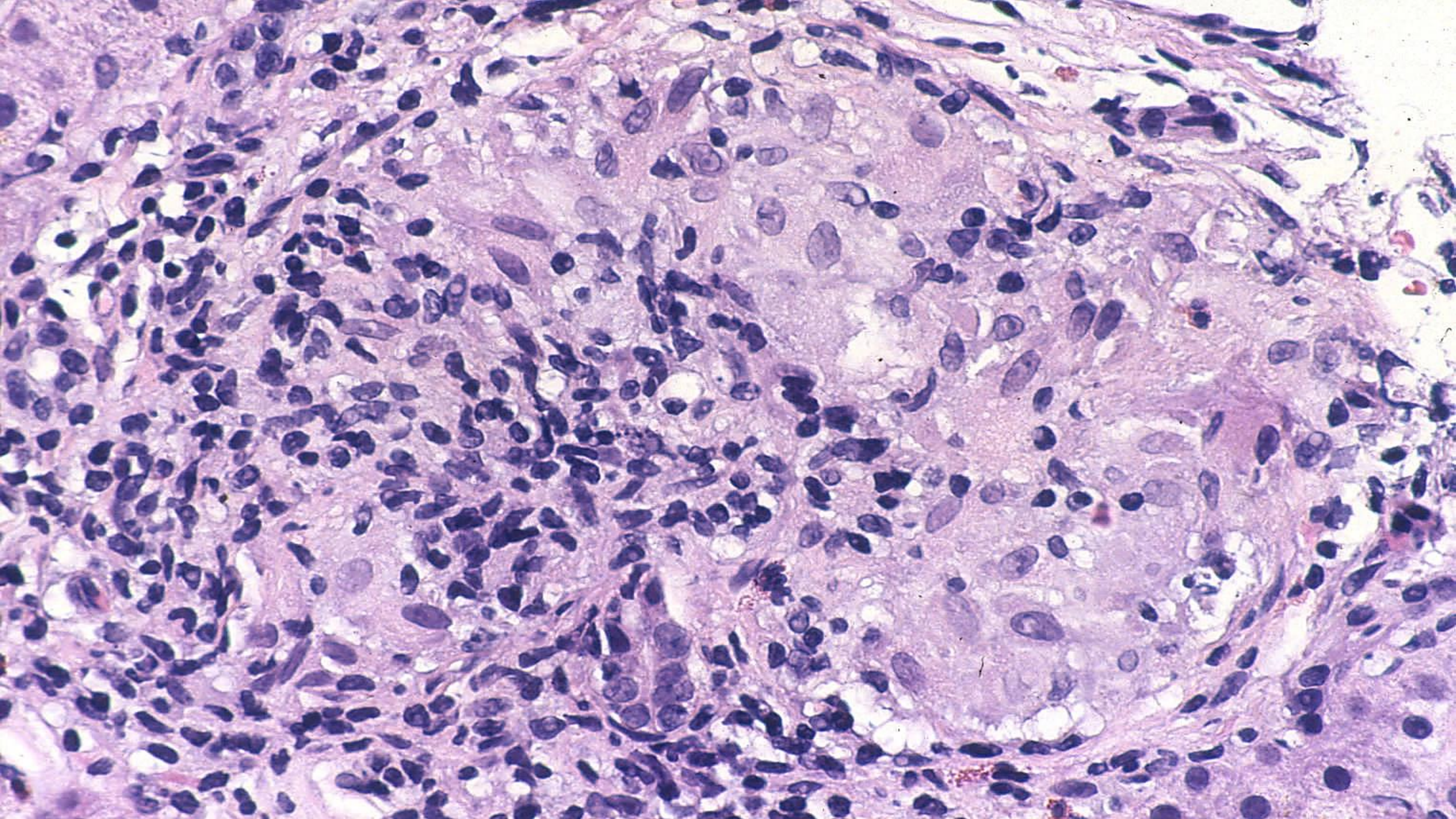
- AMA in over 90% of patients.
- AMA is not diagnostic of PBC.
  - PBC requires histologic confirmation and/or clinical evidence of cholestasis.
- ANA 30%. Helpful when AMA negative
  - "Autoimmune cholangitis" or "AMA negative PBC"
  - Can be submitted with "r/o AIH"

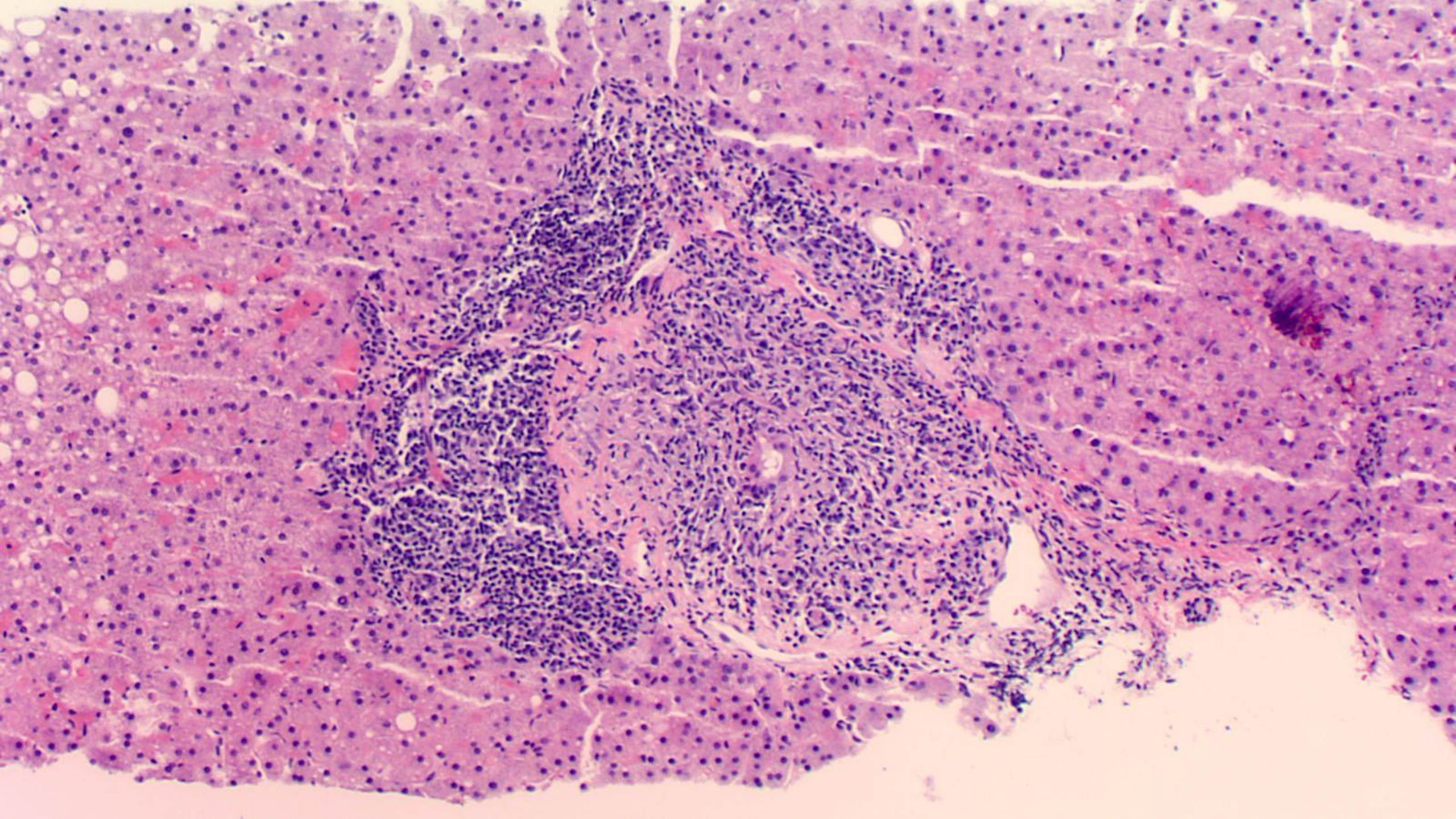
Staging PBC

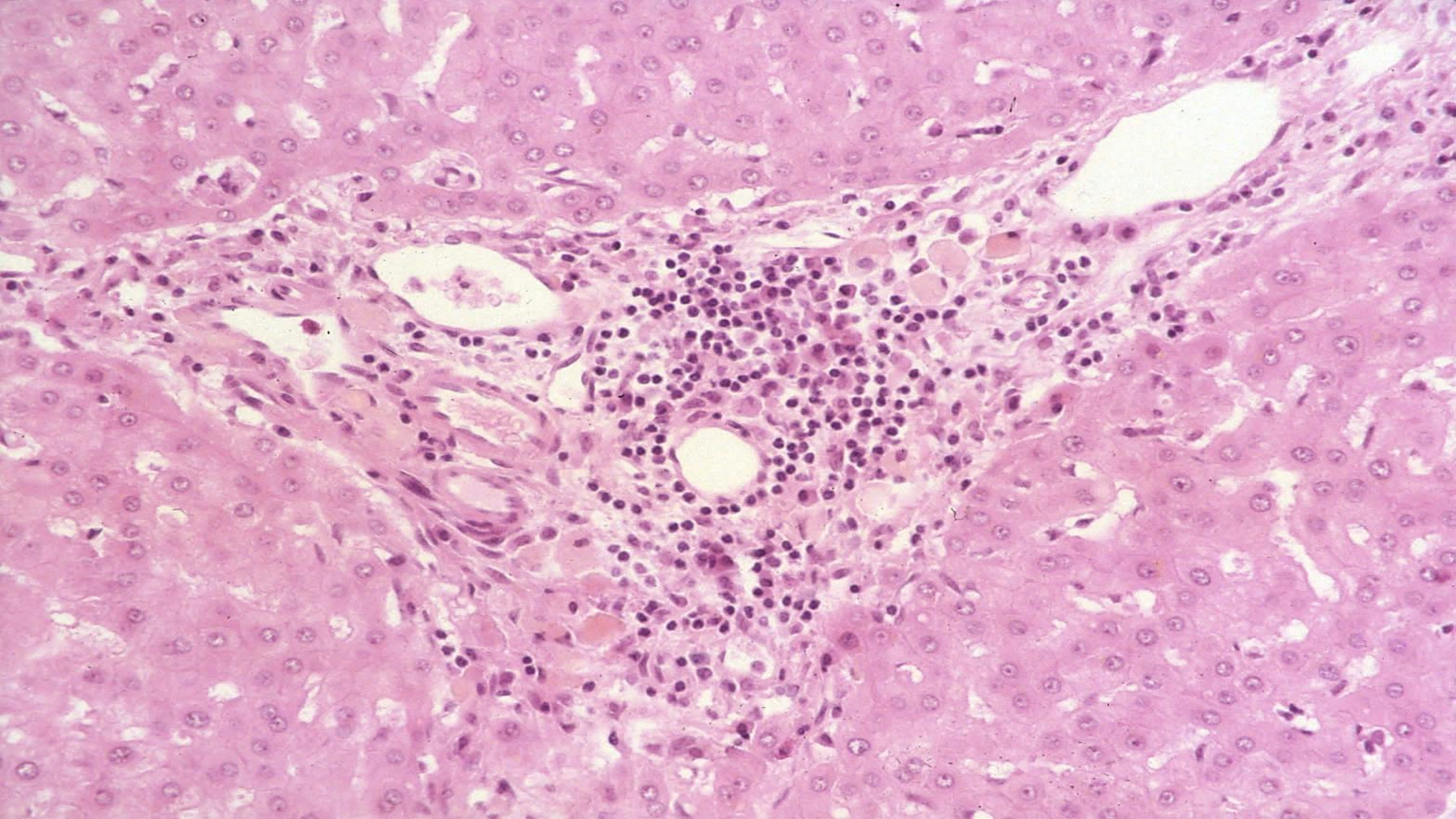
Stage	Clinical	Scheuer	Ludwig	Prominent features
1	Early	Florid duct lesion	Portal	Florid periductal inflammation and ductal necrosis
2	Progressive	Ductular proliferation	Periportal	Piecemeal necrosis and ductular proliferation
3		Scarring and fibrosis	Scarring and fibrosis	Fibrosis without regenerative nodules
4		Cirrhosis	Cirrhosis	Cirrhosis

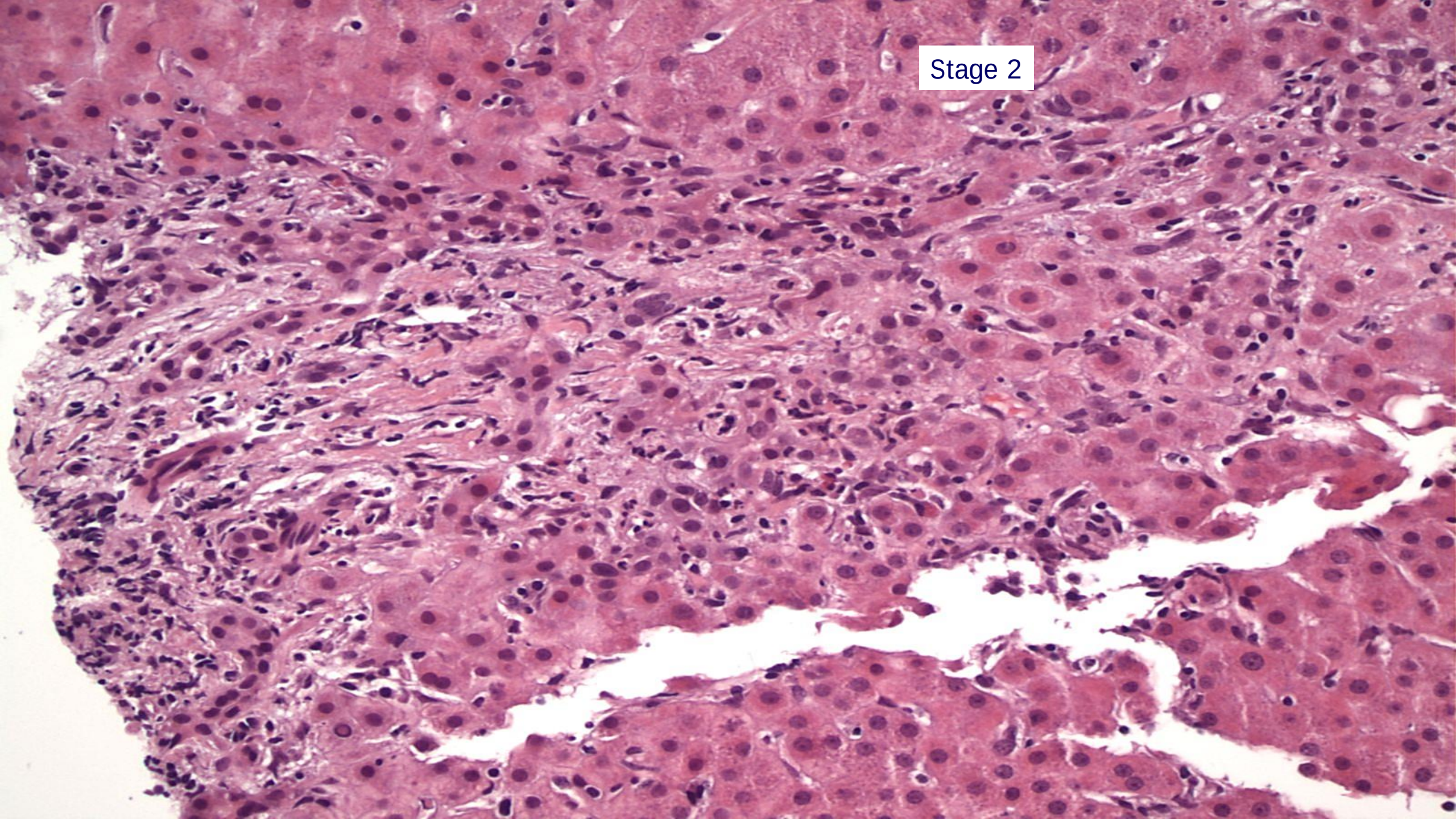


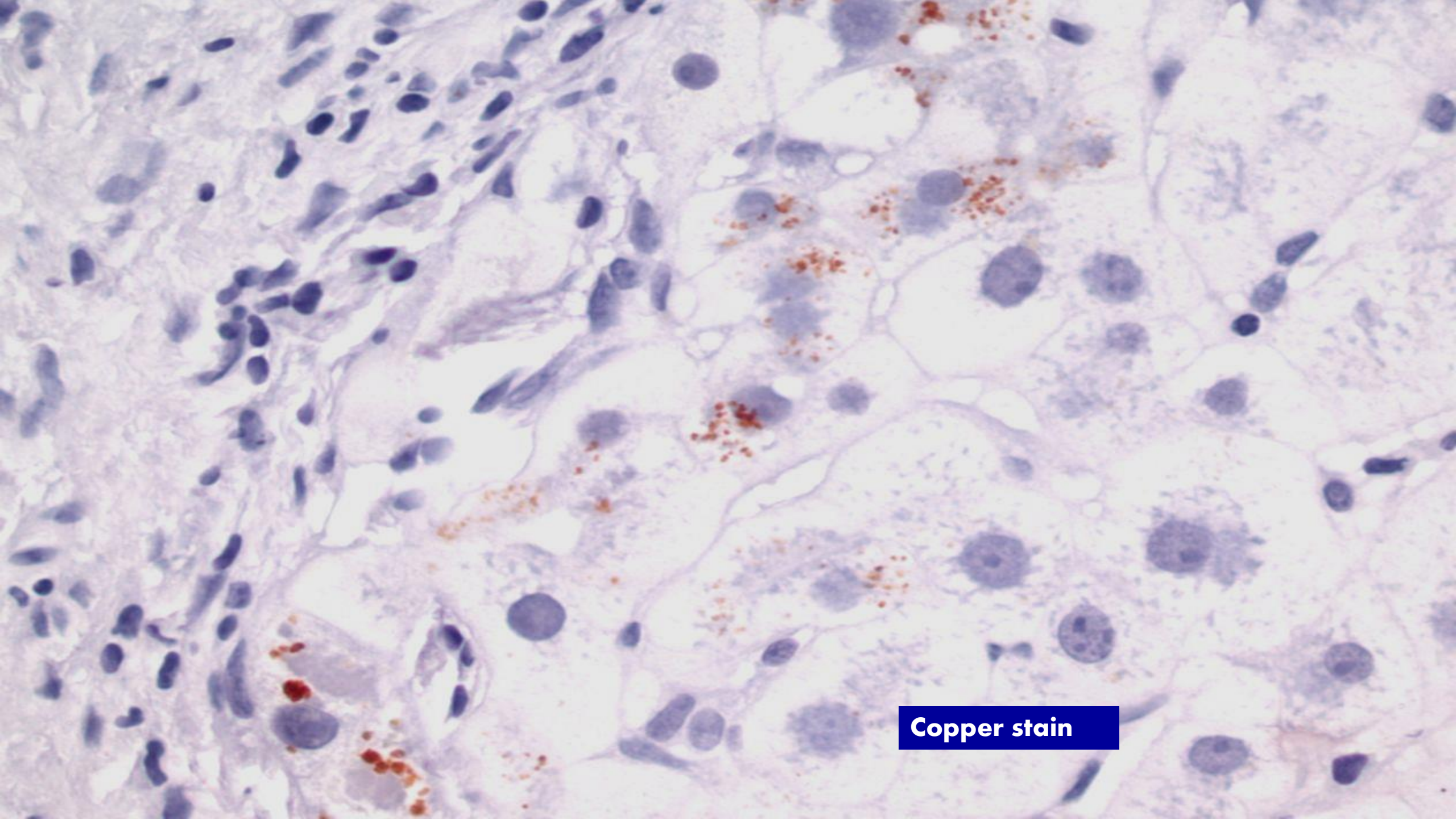


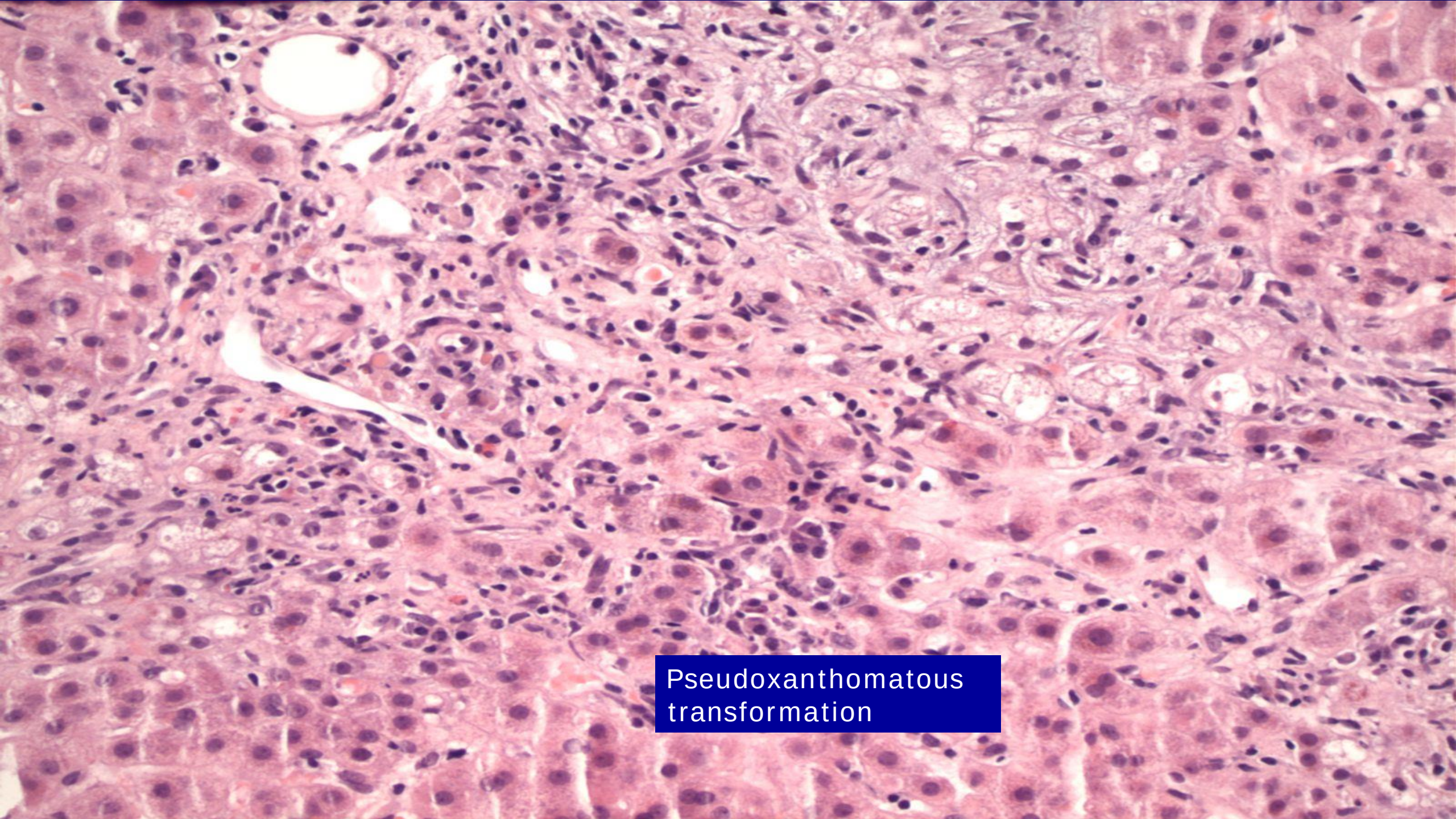




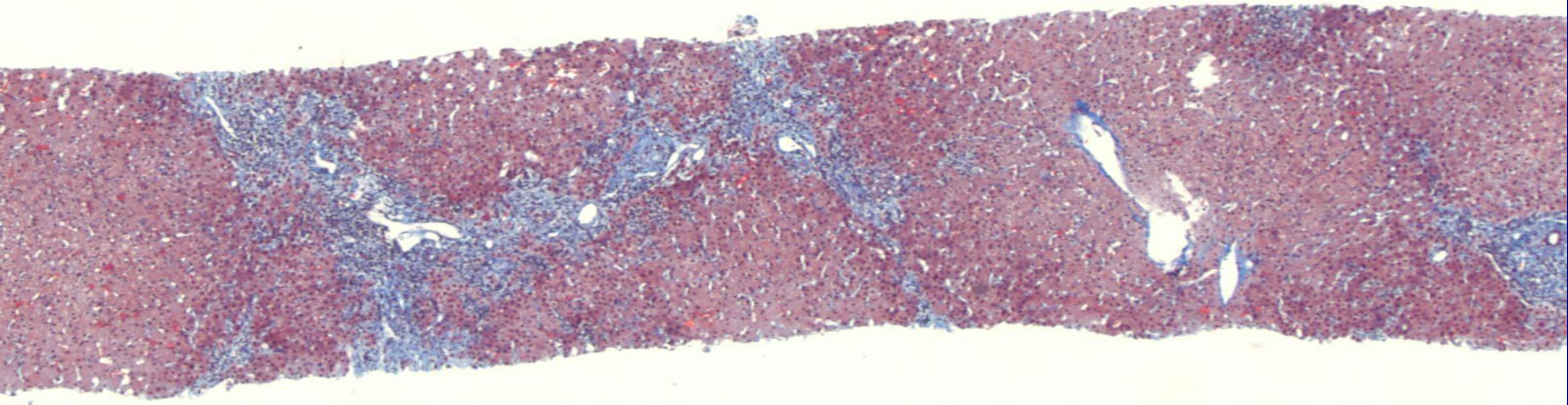



Stage 2

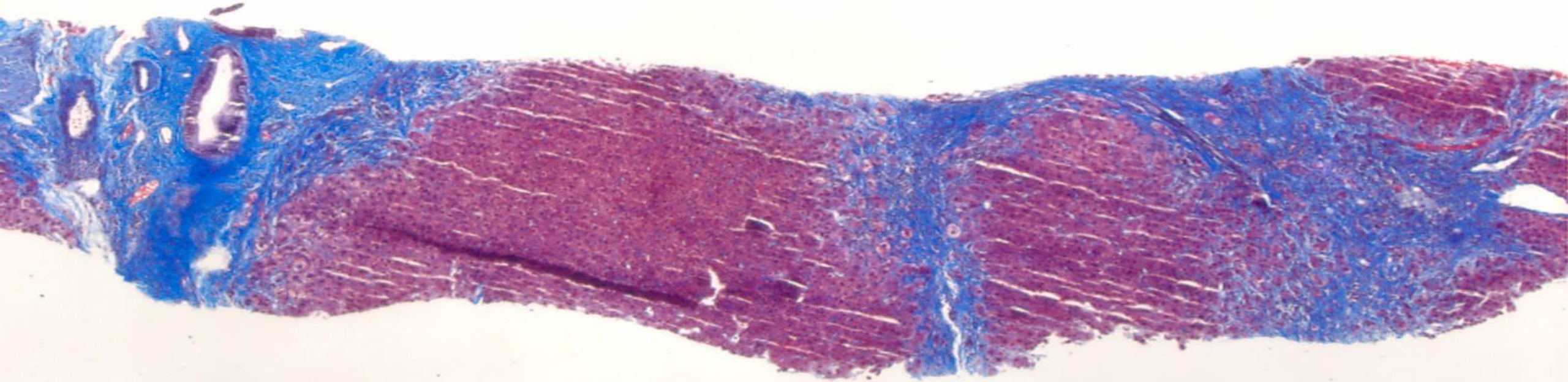

Copper stain


Pseudoxanthomatous transformation

Stage 3



Stage 4



Primary Biliary Cholangitis: Treatment

- Ursodeoxycholic Acid
- Unclear benefit from the addition of anti-inflammatory agents in patients who fail to respond to urso alone: methotrexate, colchicine.
- Novel therapies include budesonide, fibrates, and obeticholic acid (farnesoid X receptor agonist)

Biopsies not diagnostic for PBC

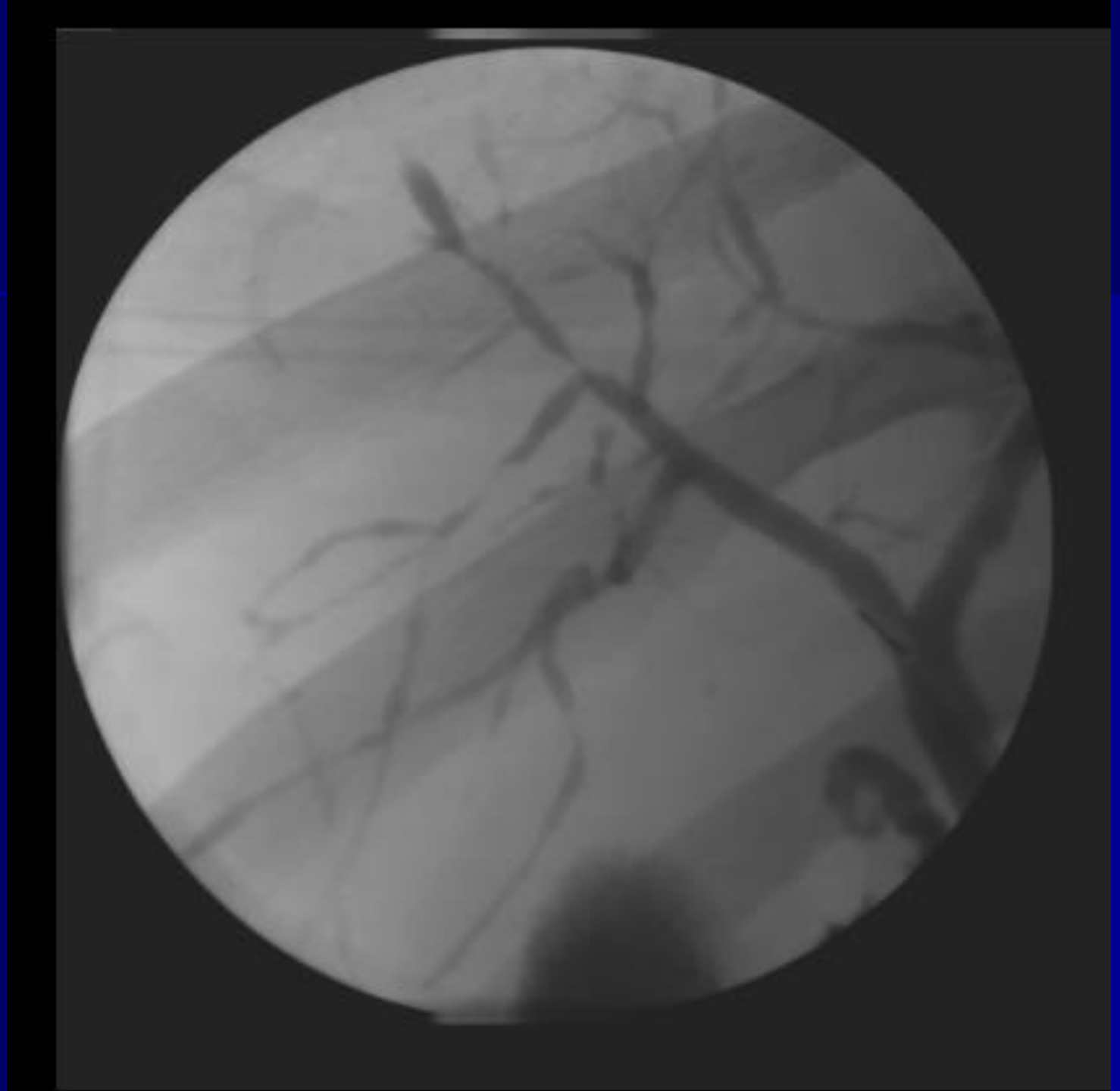
- When the clinical concern is PBC and the biopsy is not diagnostic, it may reflect patchy disease
- Copper stain to evaluate for chronic cholestasis
- Keratin 7 stain to evaluate for duct loss, biliary metaplasia of periportal hepatocytes, and ductular reaction
- *4-5 additional deeper H&Es. Look for florid duct lesions or granulomas.

Primary Sclerosing Cholangitis (PSC)

- Occurs more often in men (60%).
- Most patients under 40 at diagnosis; can begin in childhood or even neonatal period.
- Most patients with PSC (70%) have or will develop IBD. 5% of patients with IBD develop PSC.
- Cholangiocarcinoma develops in 10-15%.

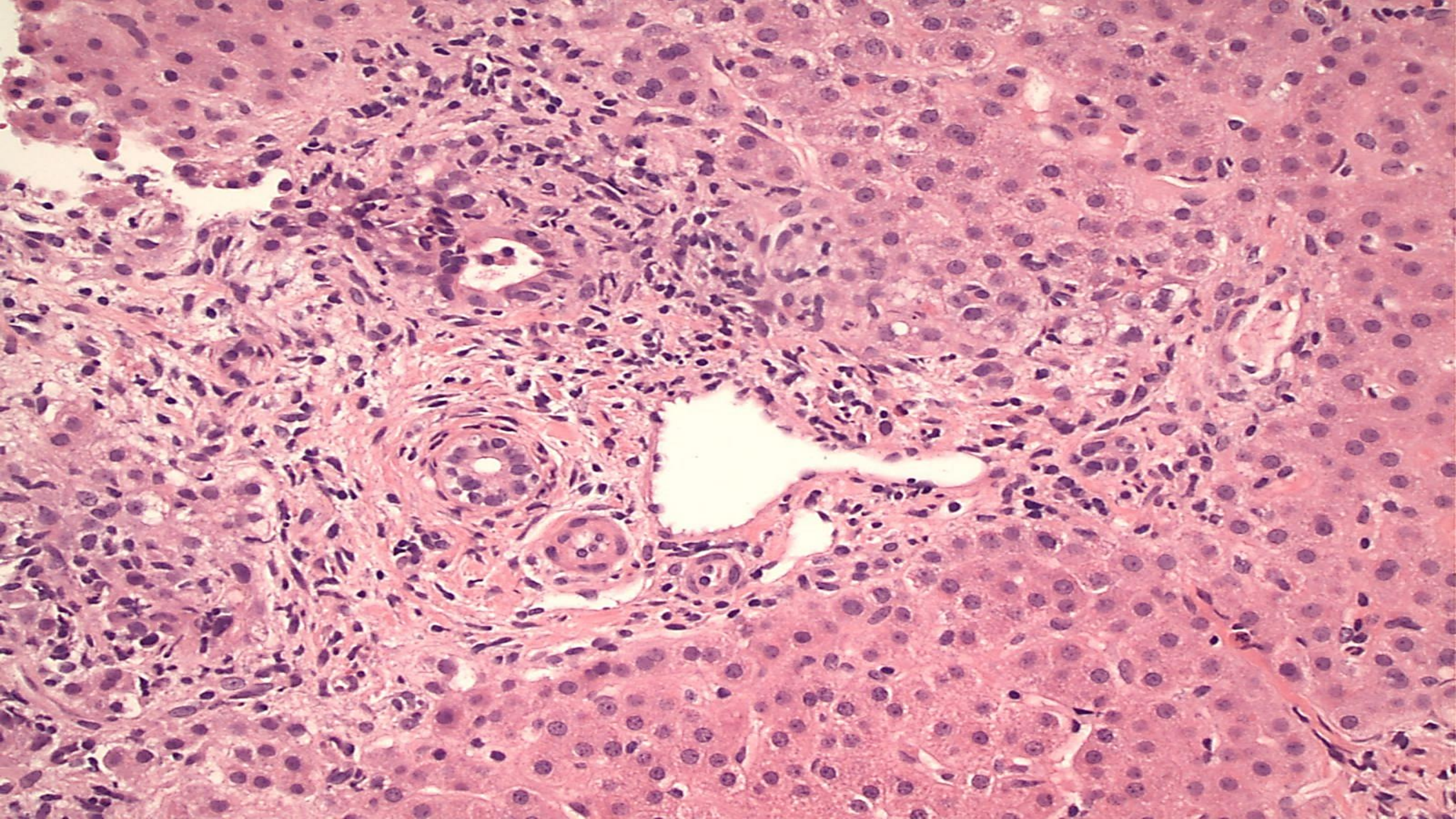
Laboratory parameters in PSC

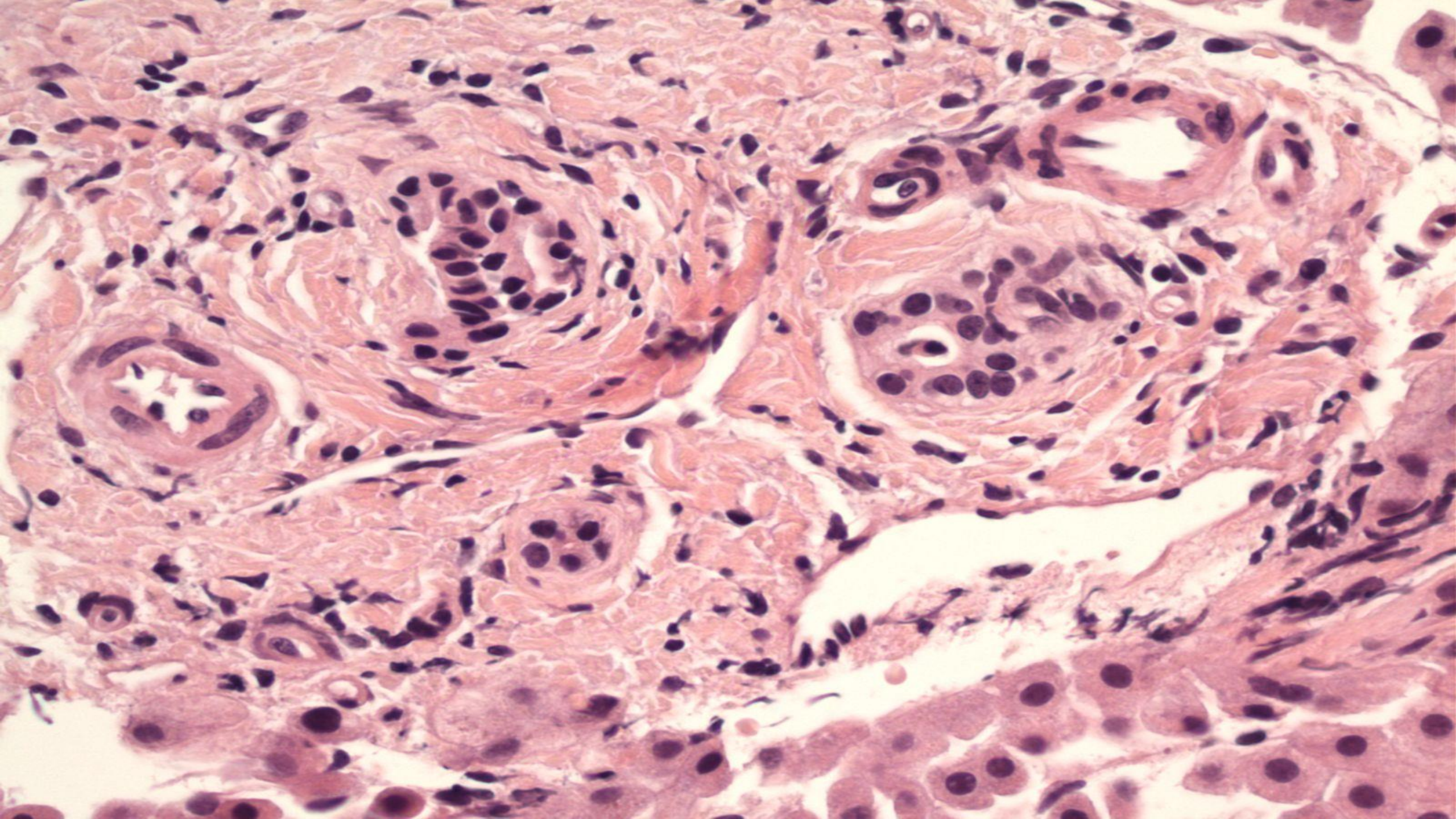
- Liver function tests are of a “cholestatic” pattern (elevated alkaline phosphatase).
- IgM is not usually elevated.
- AMA negative.
- ANA and ANCA may be present.

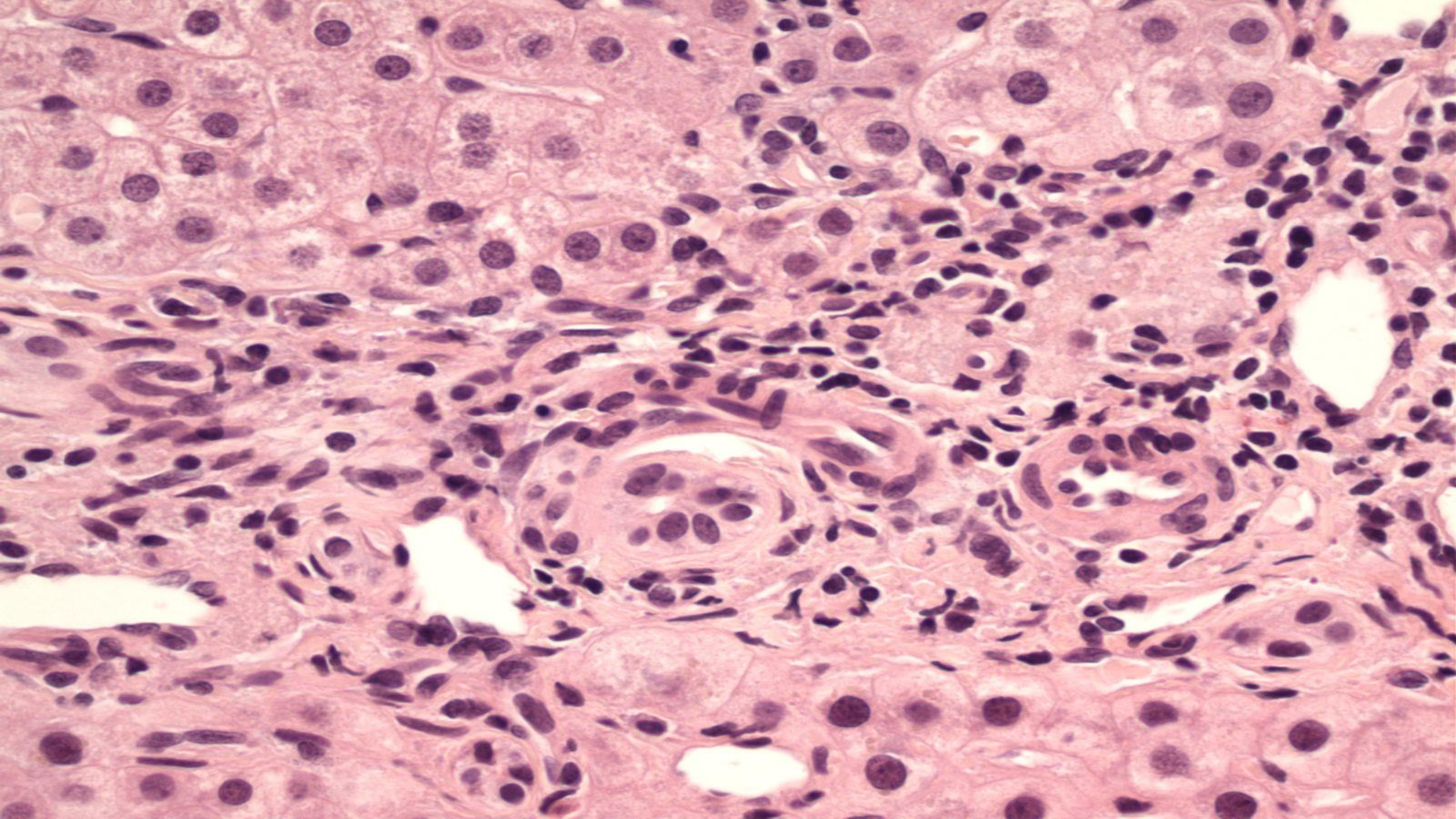


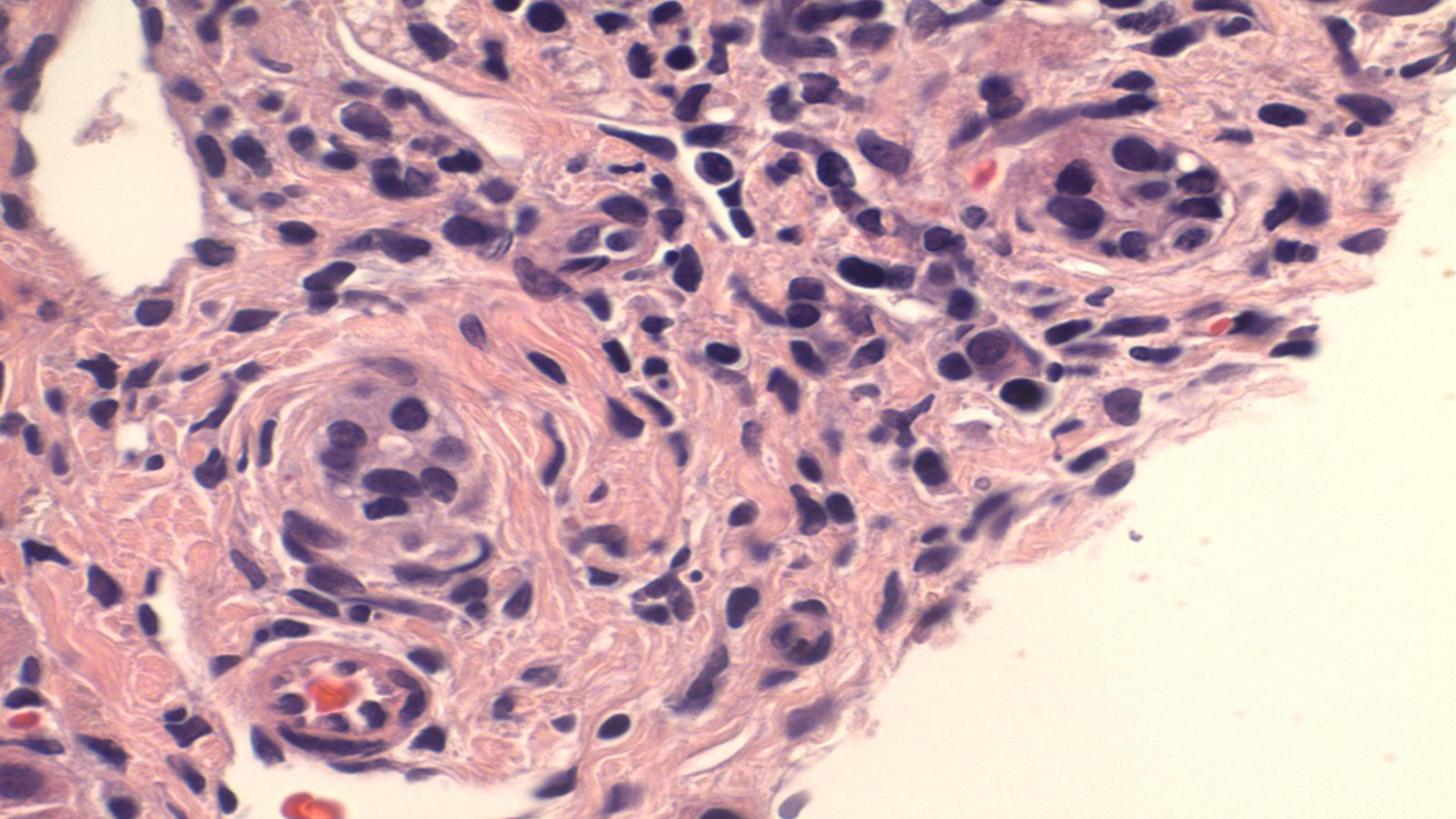
Small Duct PSC

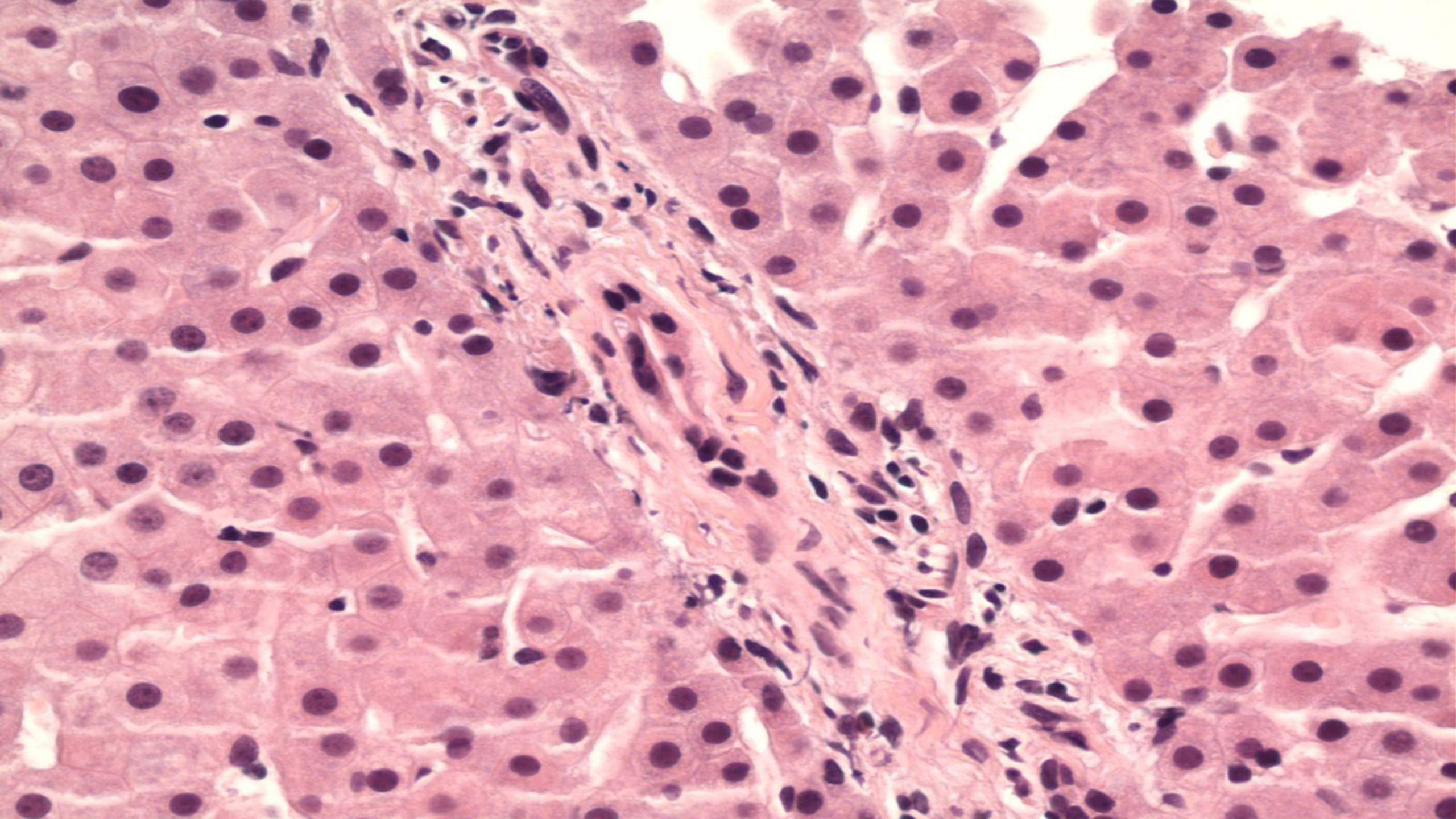
- Histologic features of PSC in liver biopsy without cholangiographic evidence of large duct PSC.
- Easier to make a case in a patient with IBD, but a history of IBD is not required.
- 20% progress to large duct PSC.
- Cholangiocarcinoma develops only in those who progress to large duct disease.

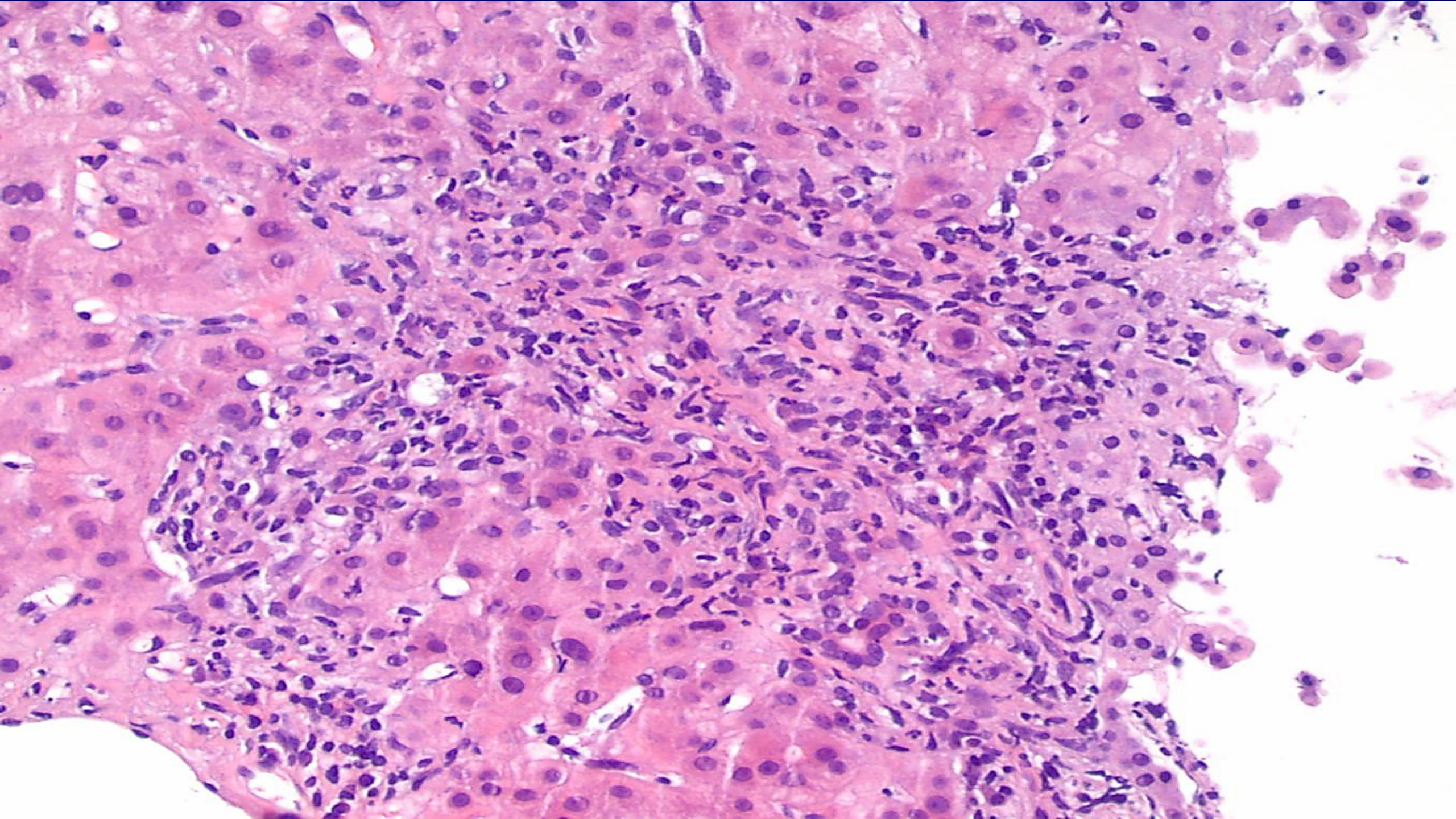


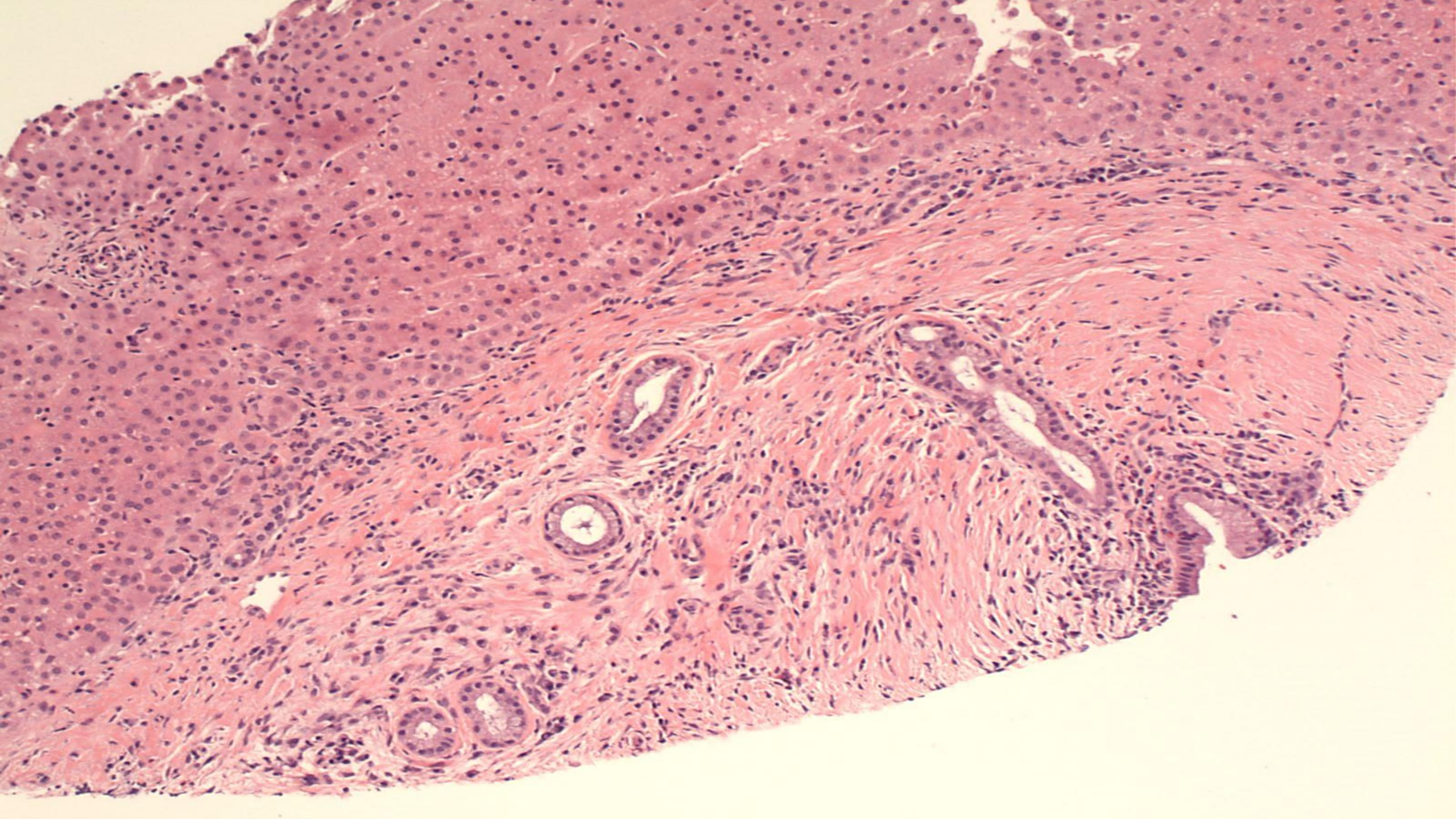












Management of PSC

- Dilatation of strictures when symptomatic.
- Ursodeoxycholic acid improves biochemical parameters.
- Although steroids are believed to be of little benefit, a subset does benefit.
  - Some might have IgG4 cholangiopathy.
  - Children with “autoimmune sclerosing cholangitis”.
- Transplantation.

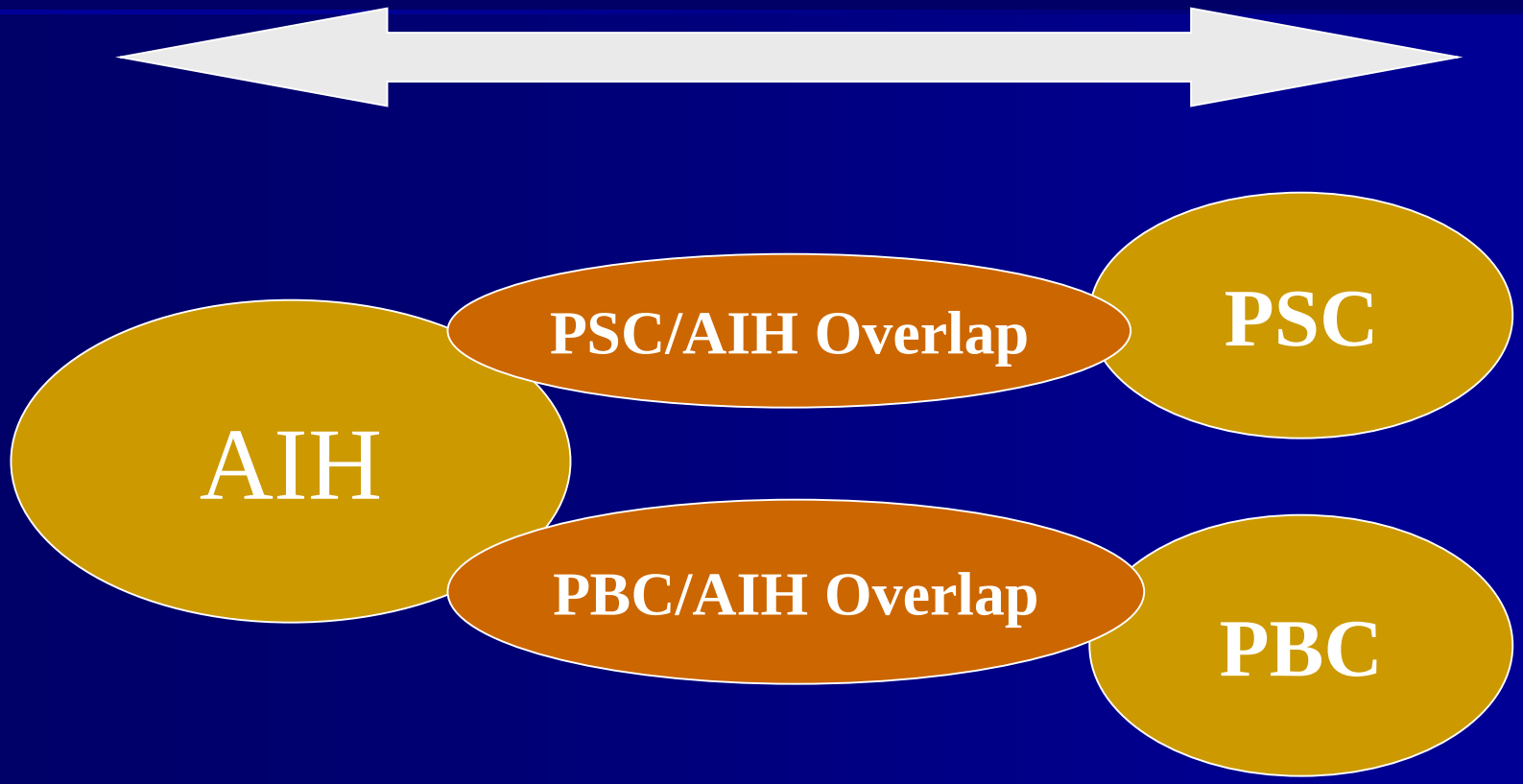
Hepatocellular Injury **Bile Duct Injury**

AIH

PSC

PBC

Hepatocellular Injury **Bile Duct Injury**



EITHER CONCURRENTLY OR CONSECUTIVELY

AIH/PBC Overlap: Paris criteria

Chazouilleres *et al.* Primary Biliary Cirrhosis-Autoimmune Hepatitis Overlap Syndrome *Hepatology* 1998.

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

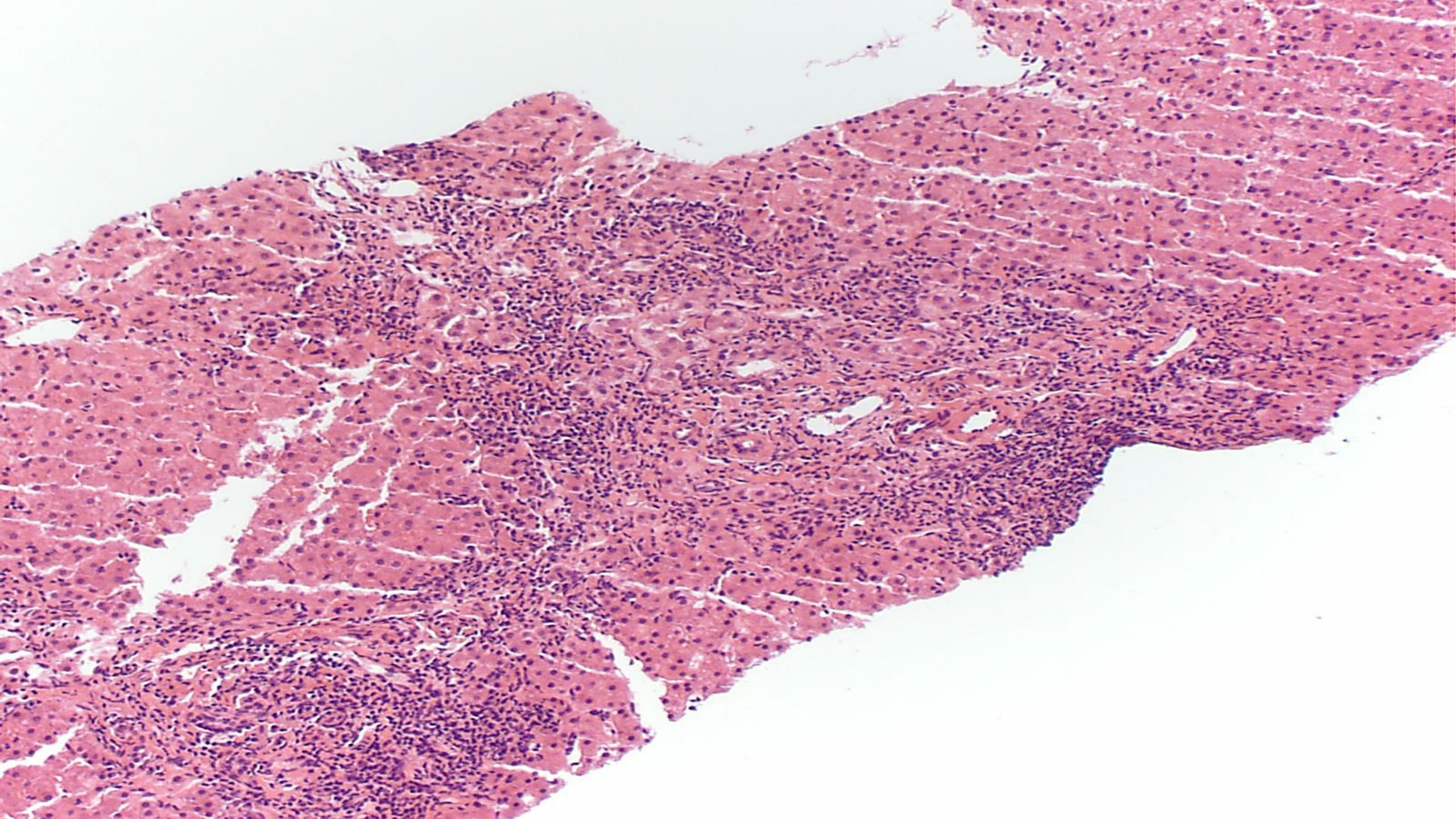
1. Moderate to severe interface hepatitis
2. IgG >2x or SMA positive
3. ALT >5x

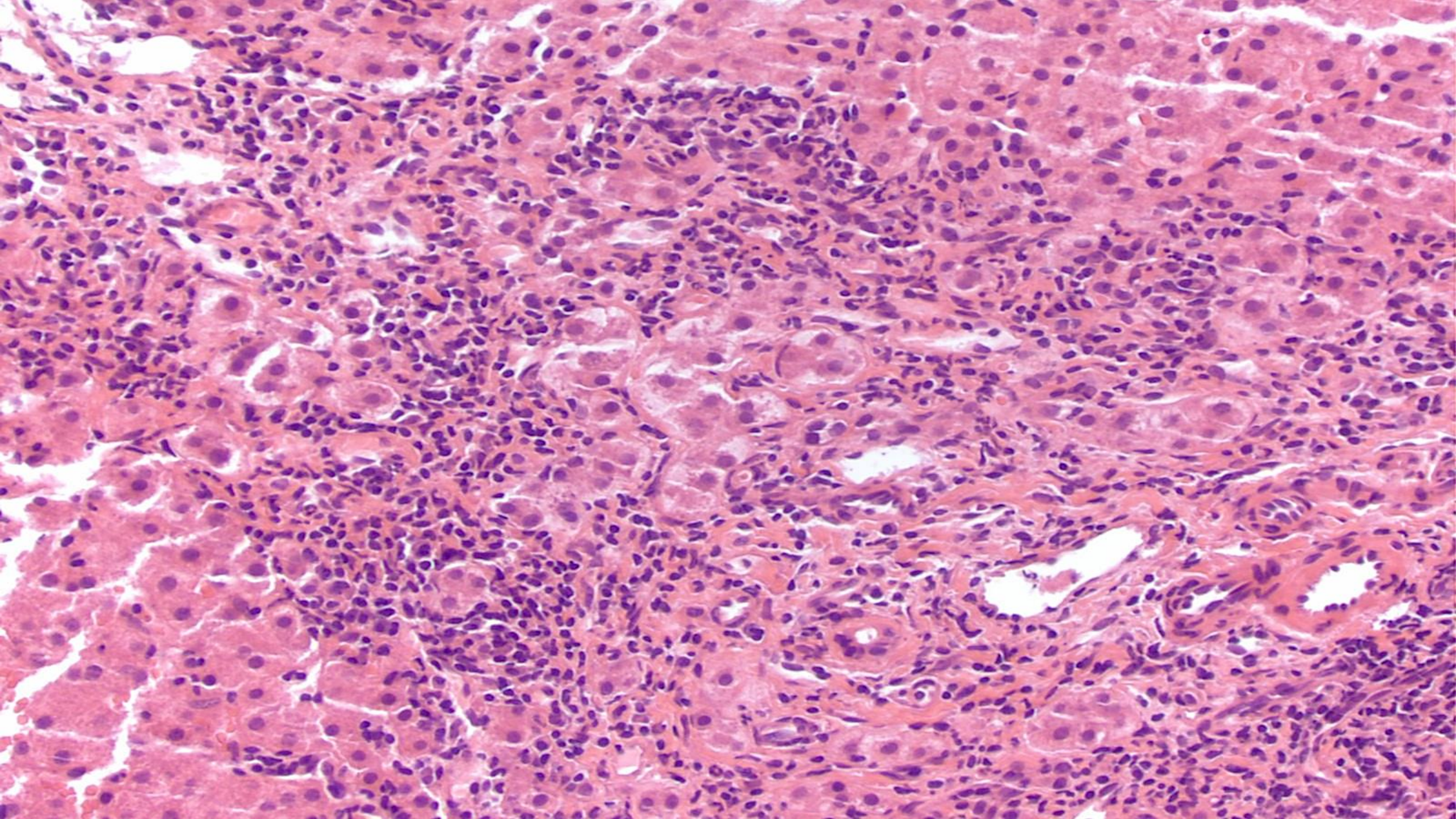
PBC-AIH

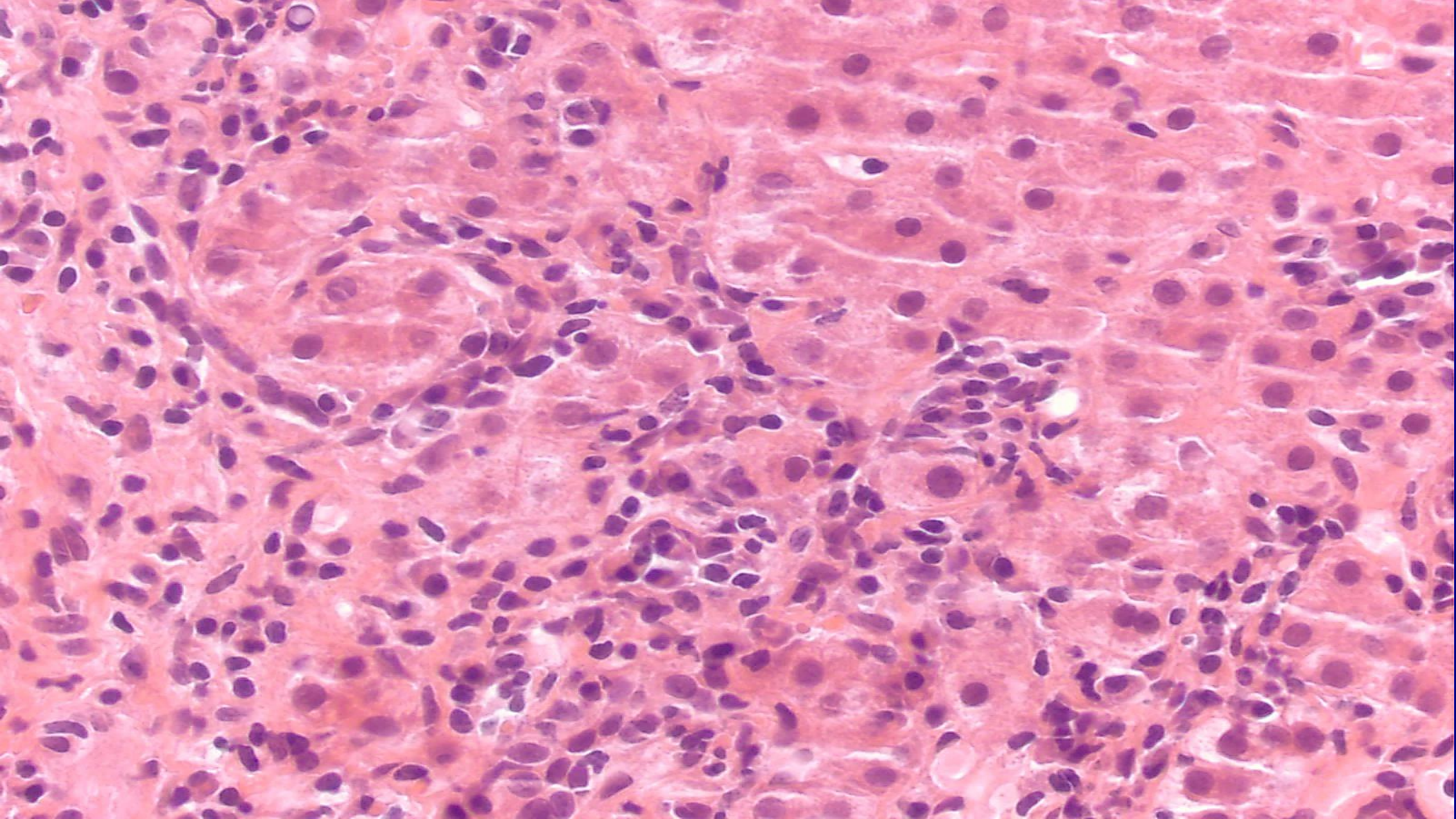
- Not recommended to use AIH score system on patients with PBC to label them overlap.
- Paris criteria incorporated into European Association for the Study of the Liver (EASL) guidelines for the management of cholestatic liver disease but with the emphasis on interface hepatitis as a mandatory feature of overlap.

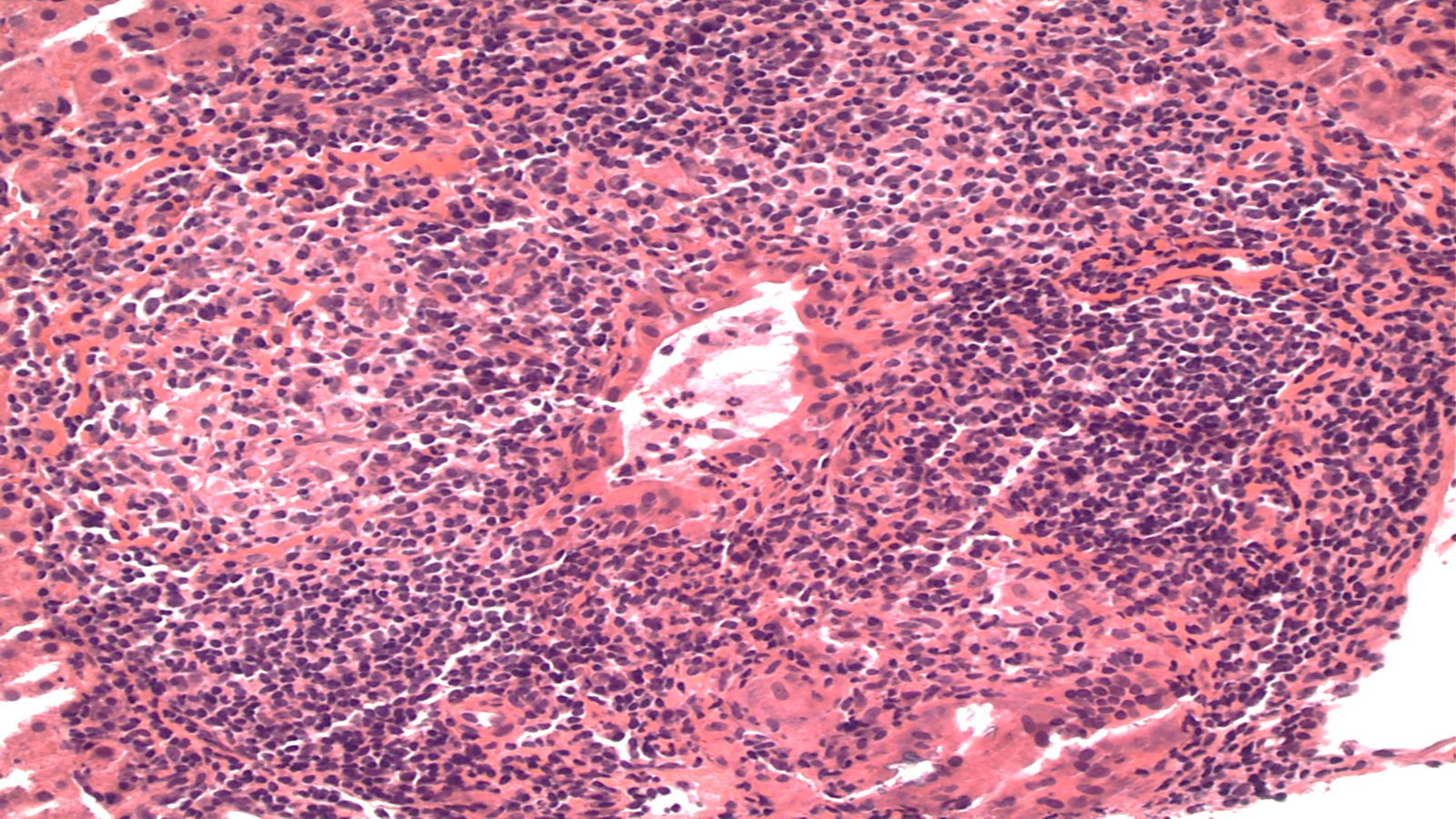
Treatment of Overlap

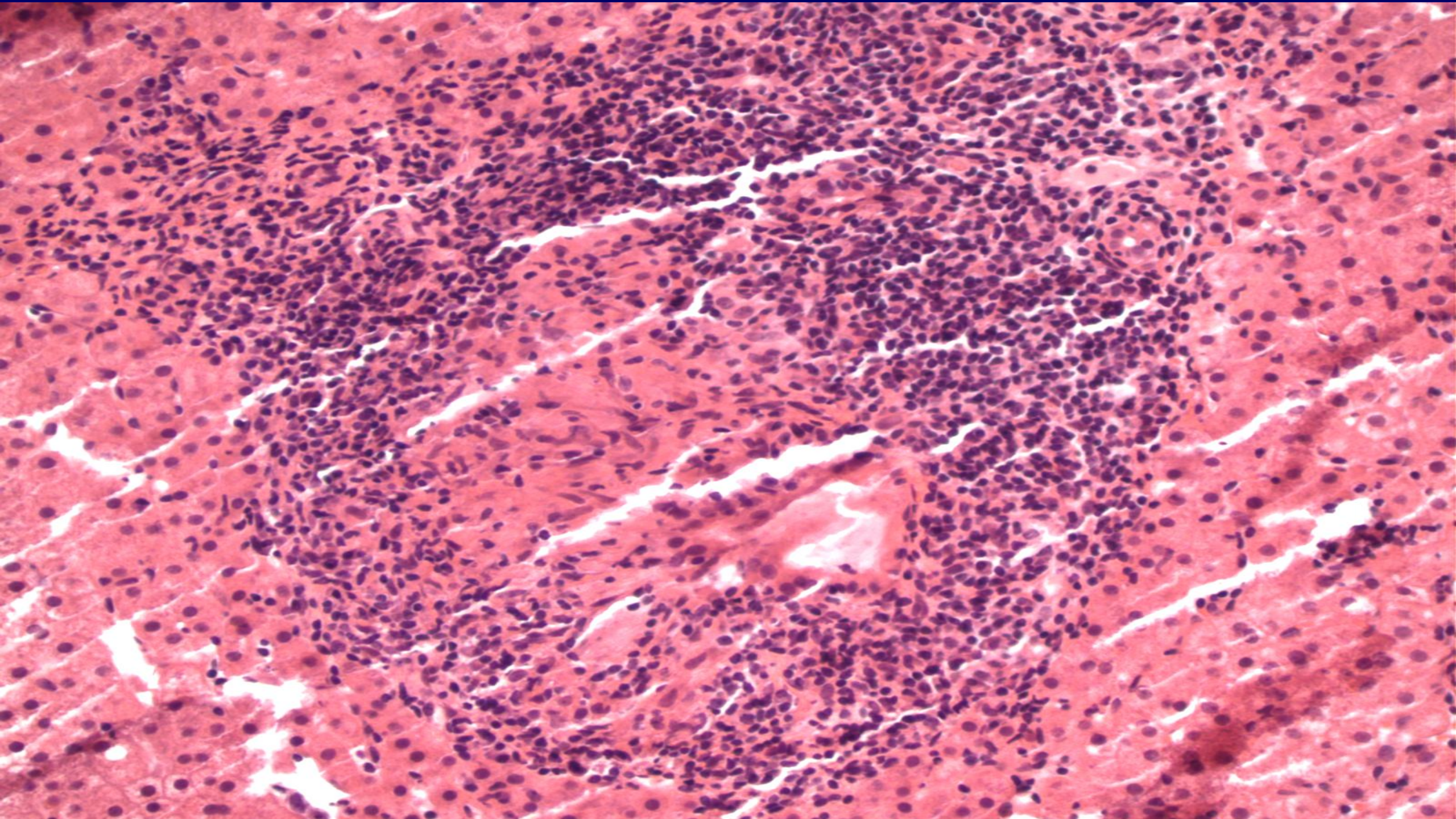
- Recent EASL guidelines recommend combination therapy with UDCA and steroids in overlap. An alternative approach is UDCA monotherapy, adding steroids if an adequate biochemical response is not achieved in 3 months.
- Some authorities consider that overlap should be initially treated according to the predominant disease, and time given to allow for a full treatment response before additional therapies are considered. Treatment can be tailored as the disease evolves over time.





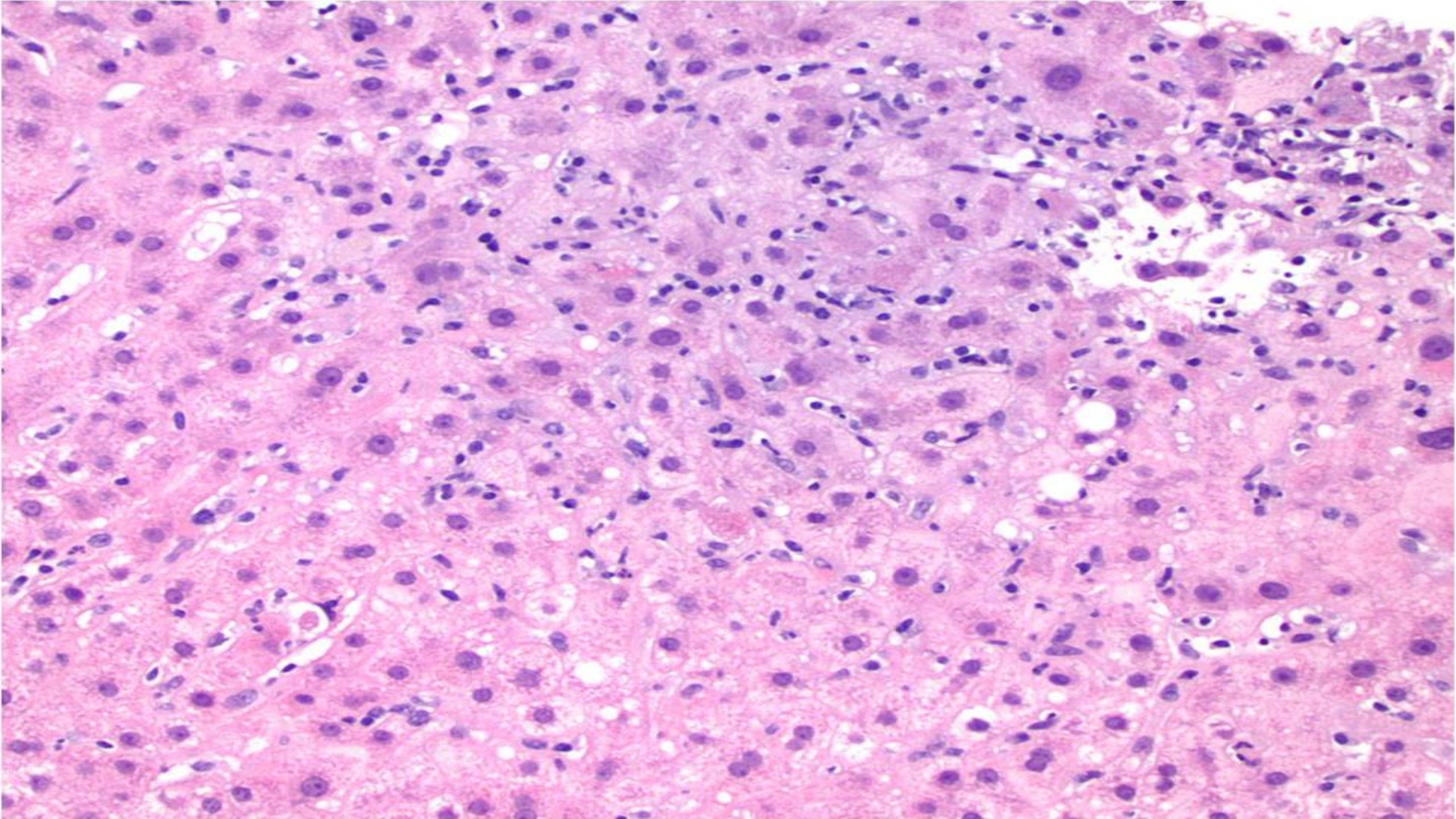


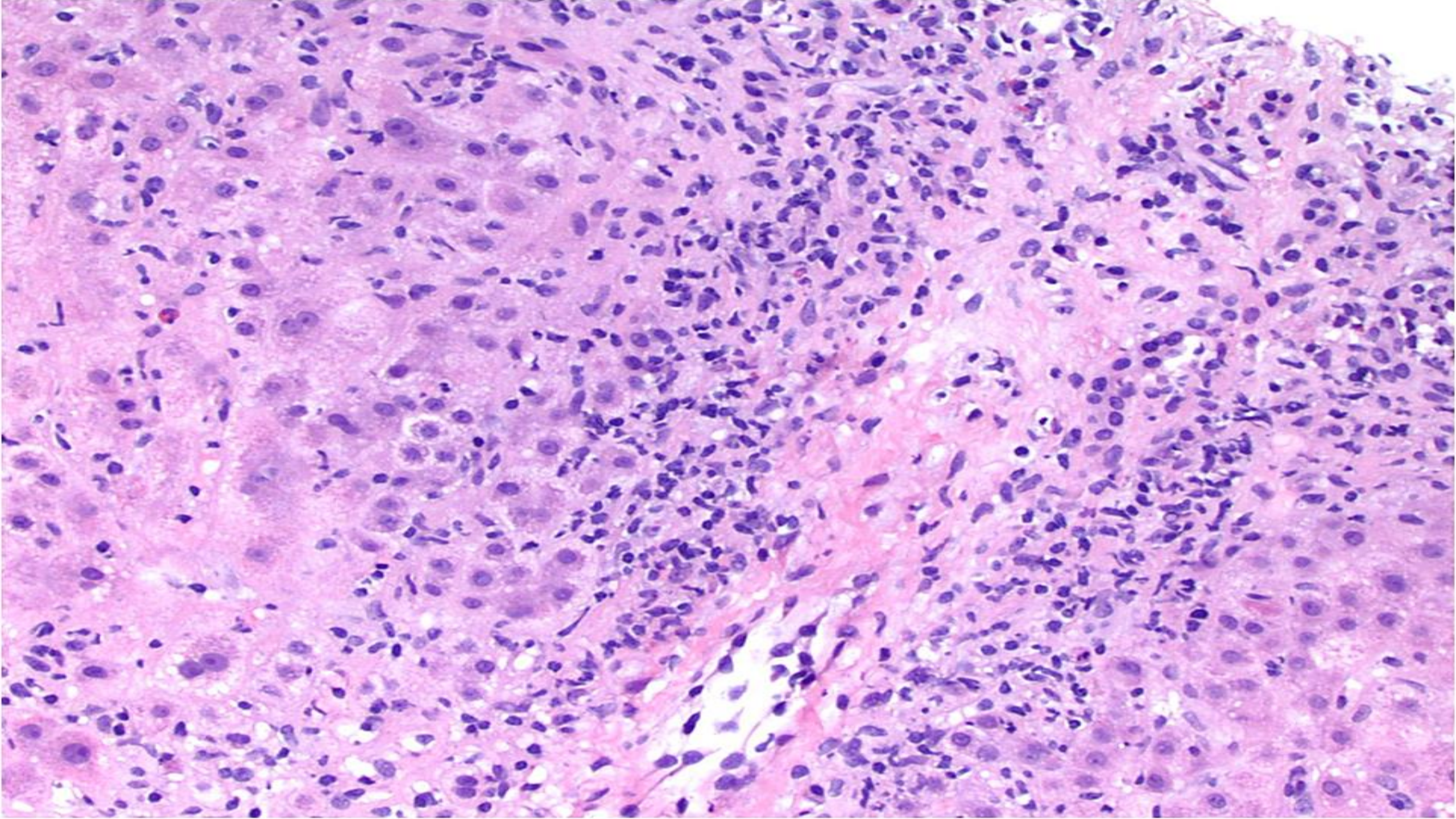


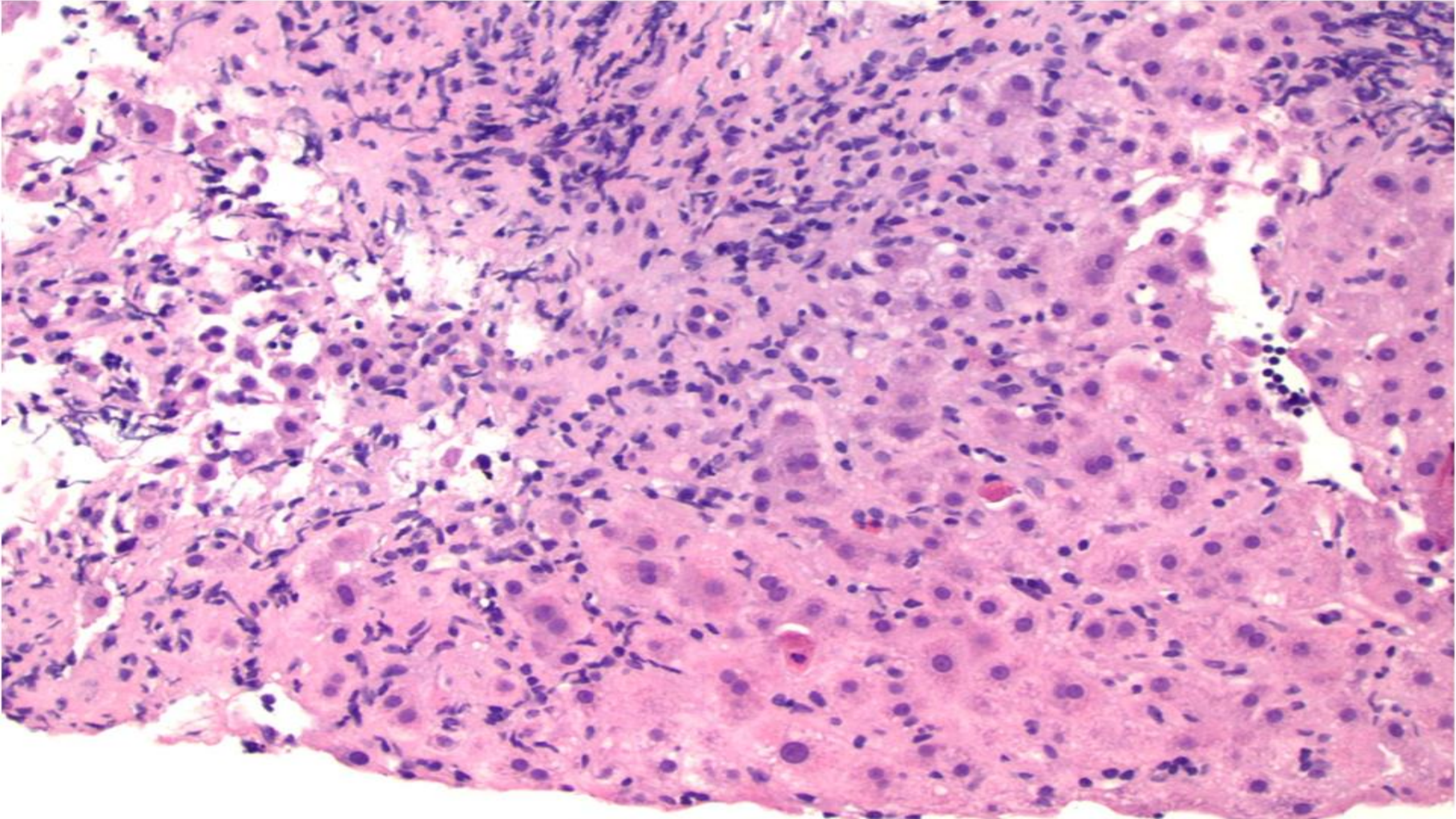


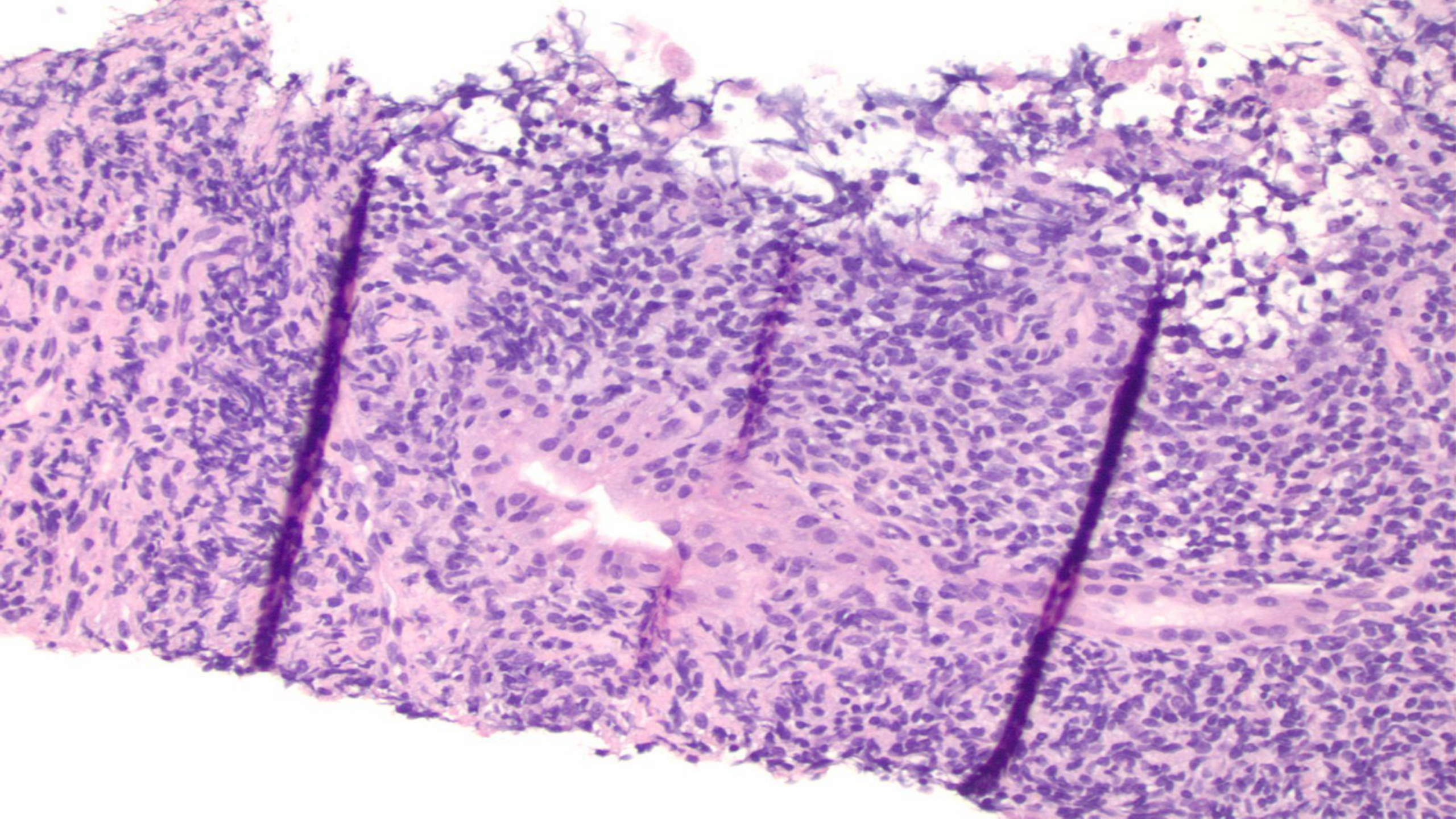
Case

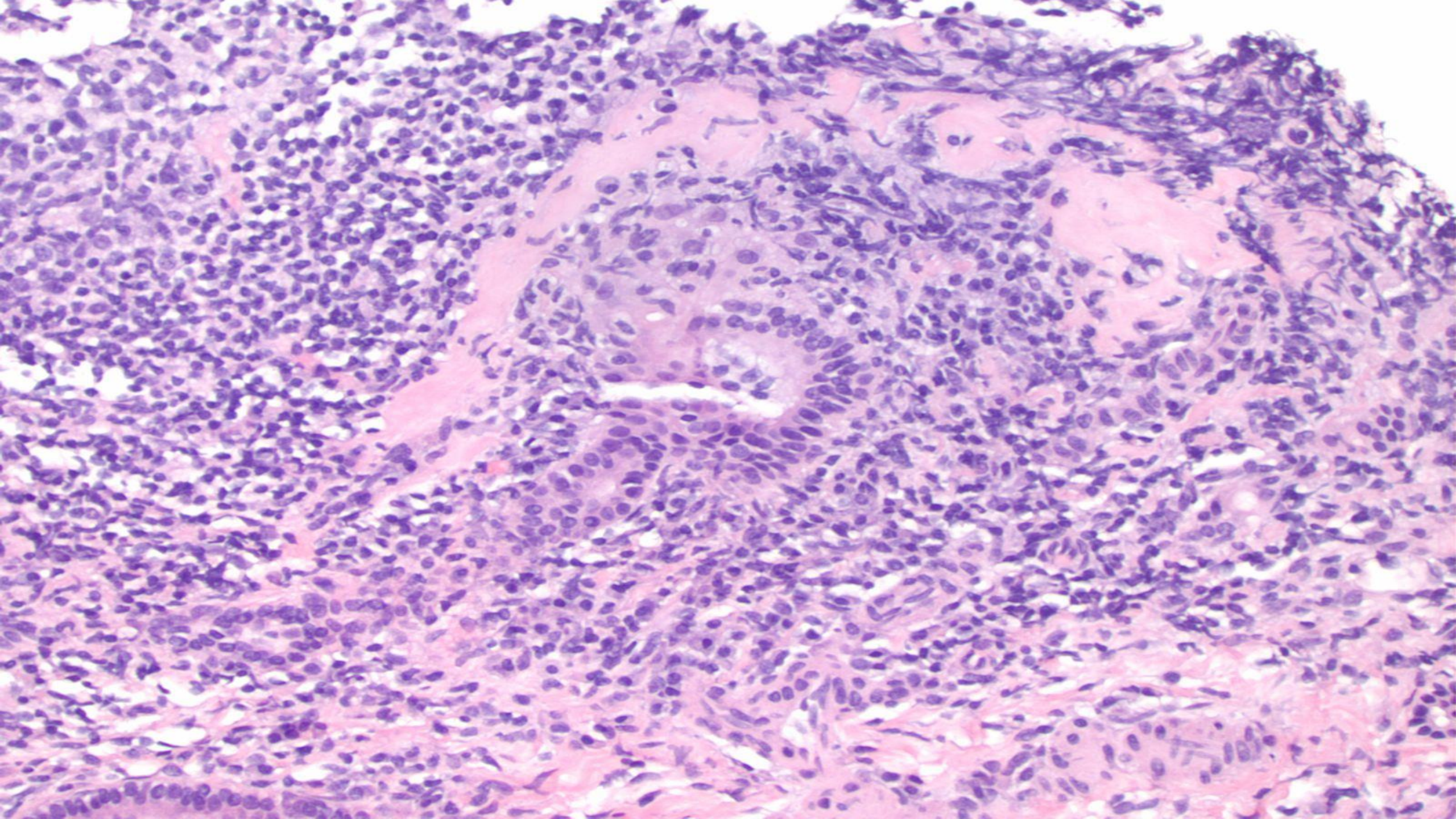
- 51 year old woman
- alk phos 147, AST 414, ALT 771
- ANA 1:160, SMA 1:40
- AMA 1:320





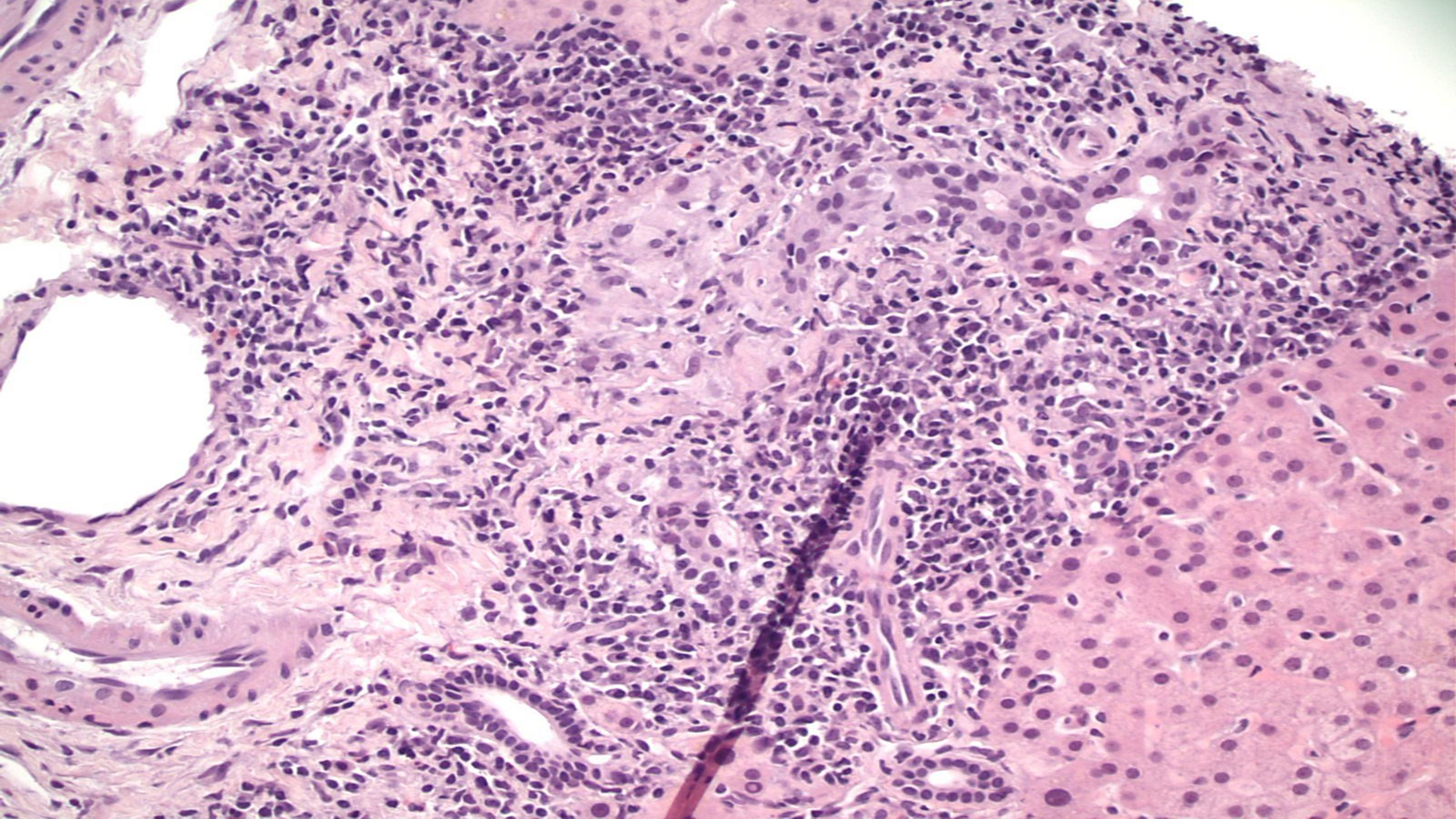


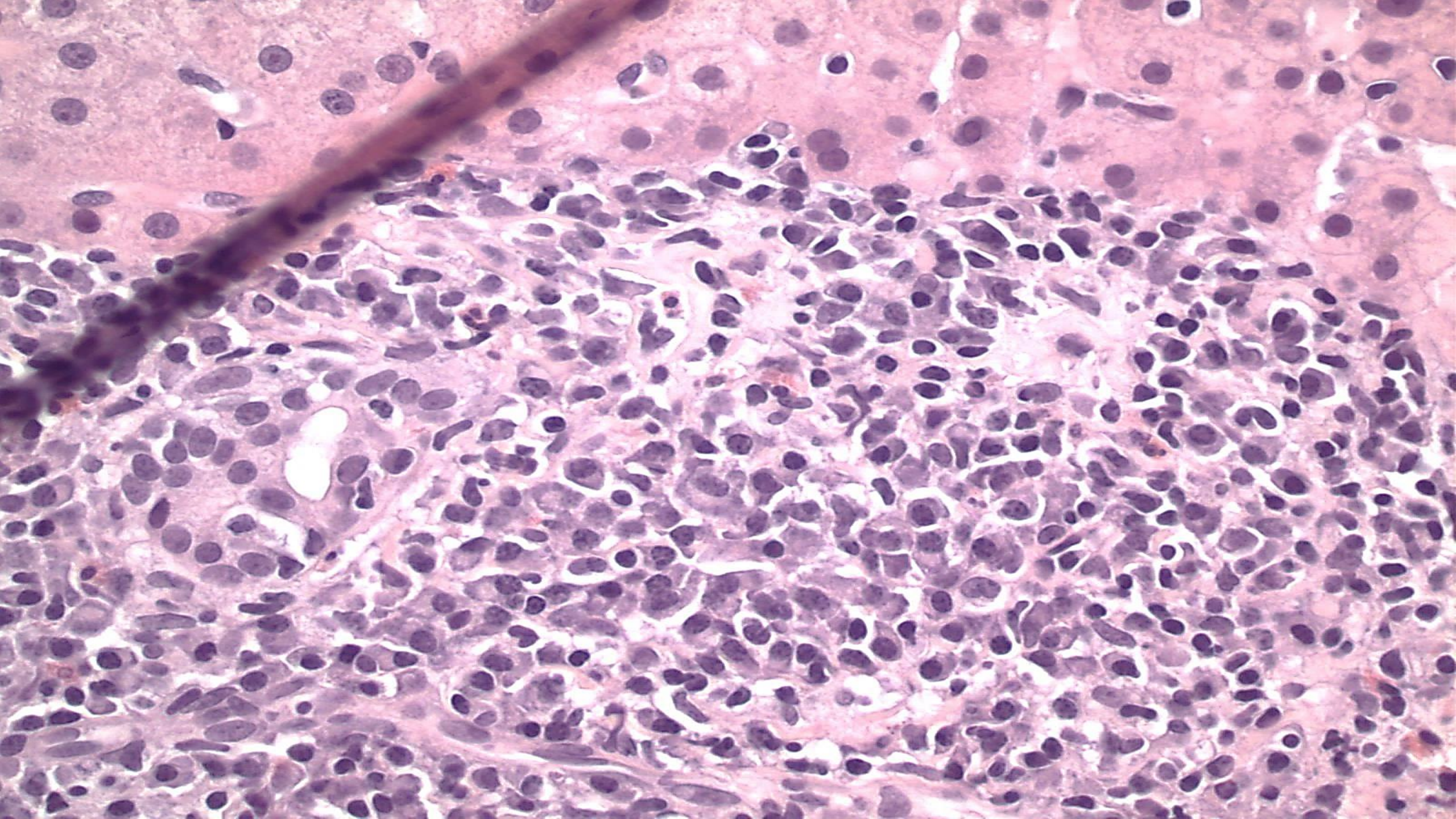


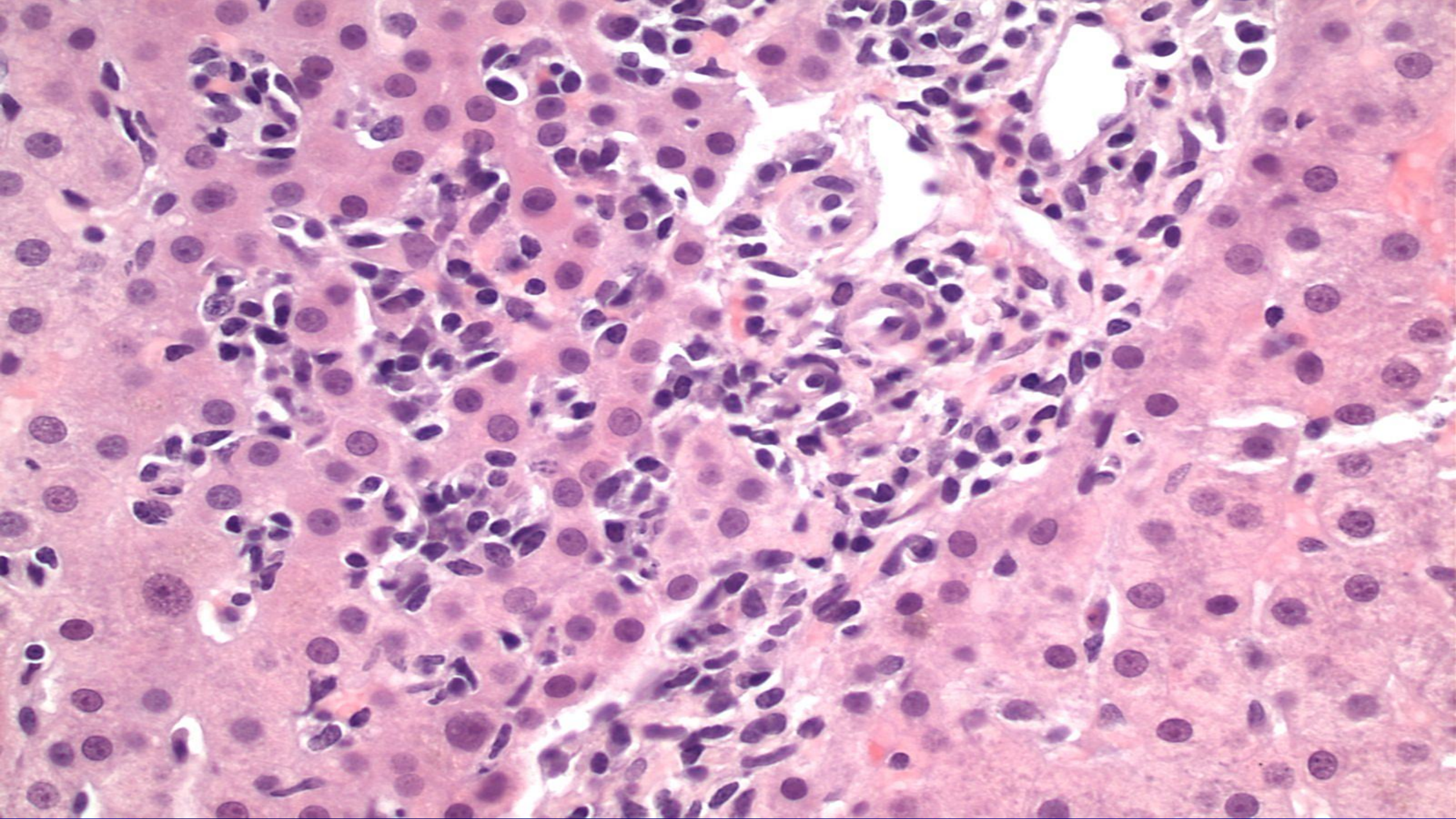


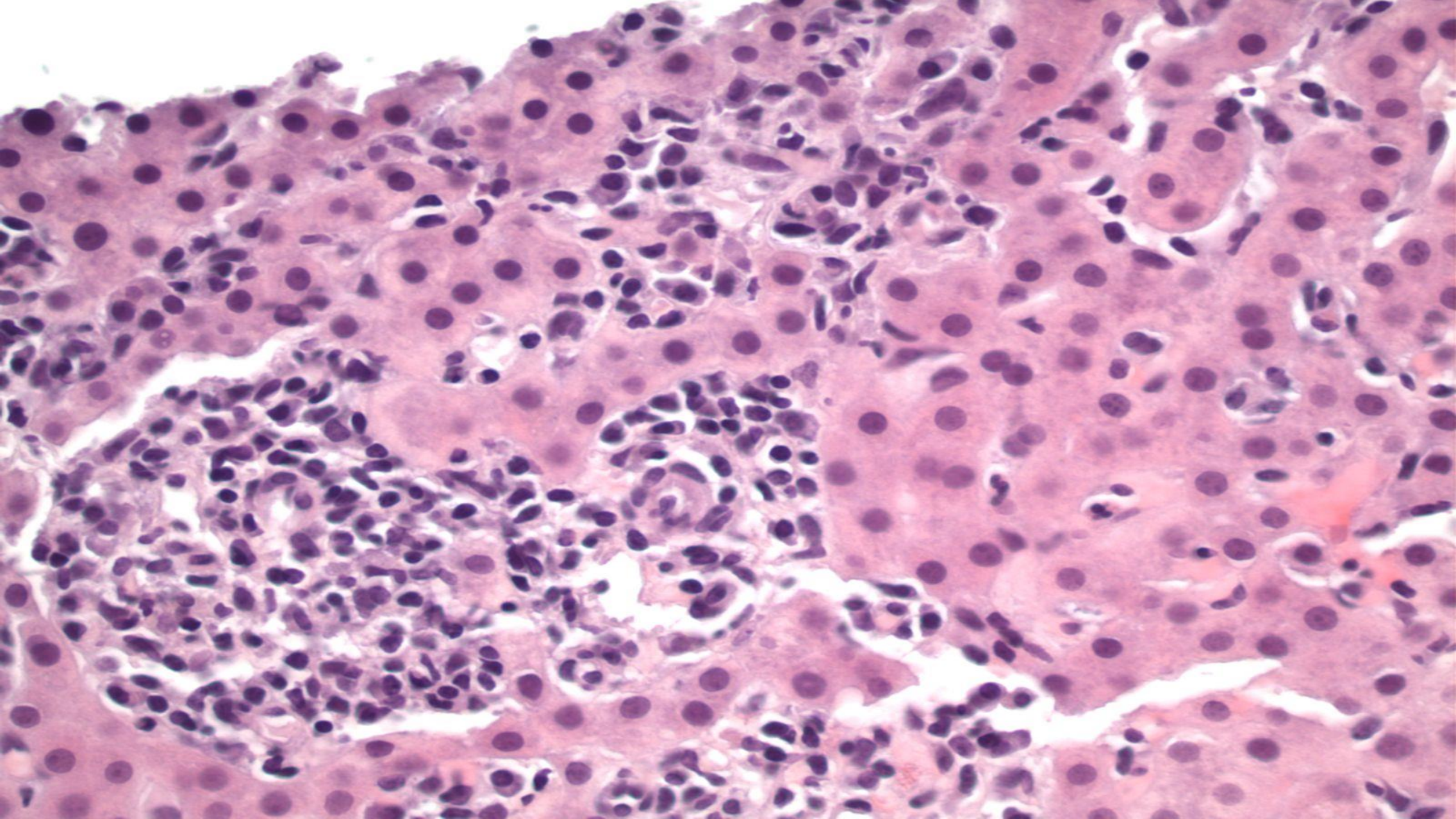
What is not overlap…

- Biopsies of PBC with
  - Numerous plasma cells in portal tracts
  - Periportal lymphocytic infiltration without hepatic destruction
- Biopsies of AIH with focal lymphocytic cholangitis without AMA or biochemical cholestasis



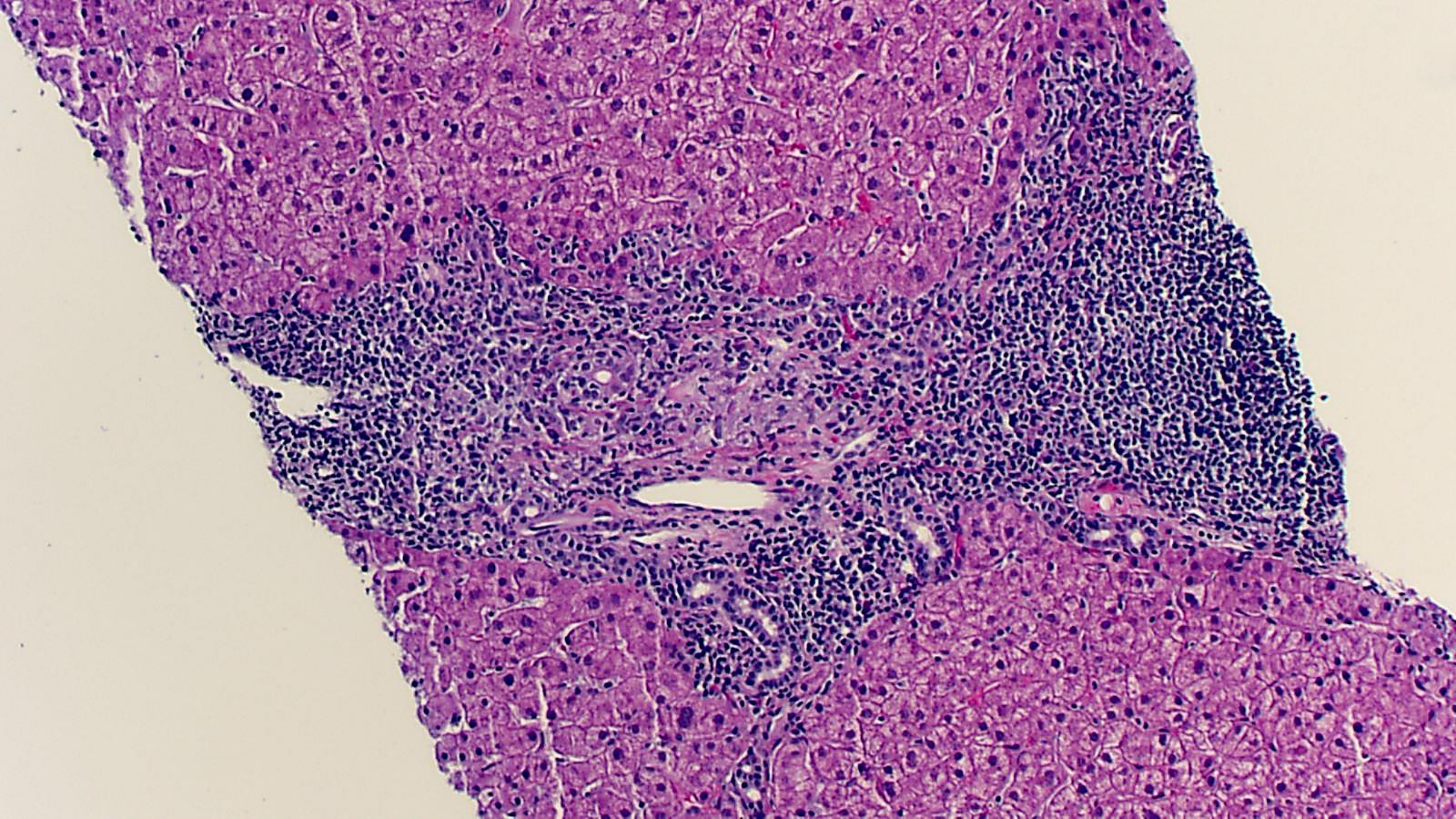


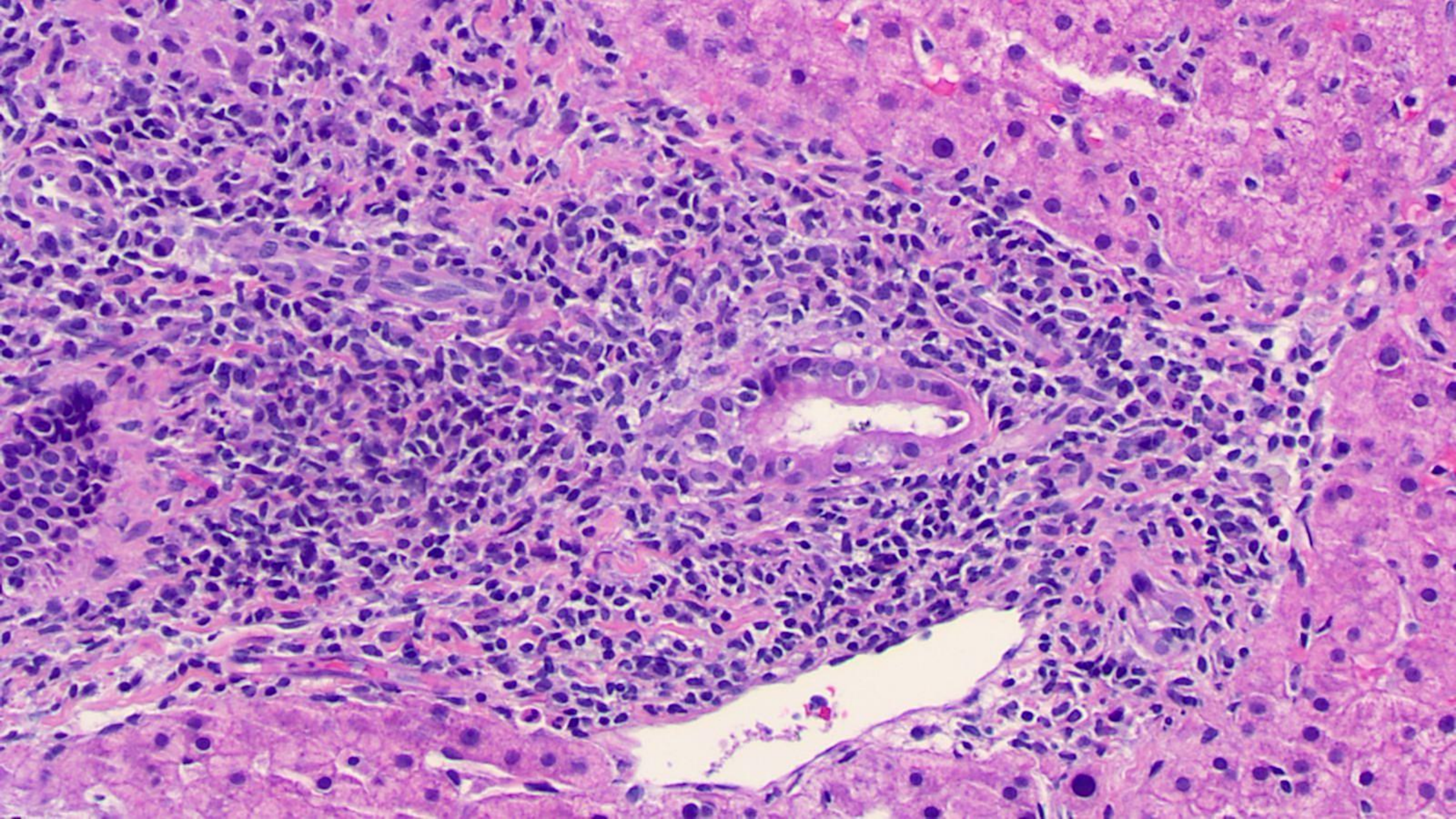


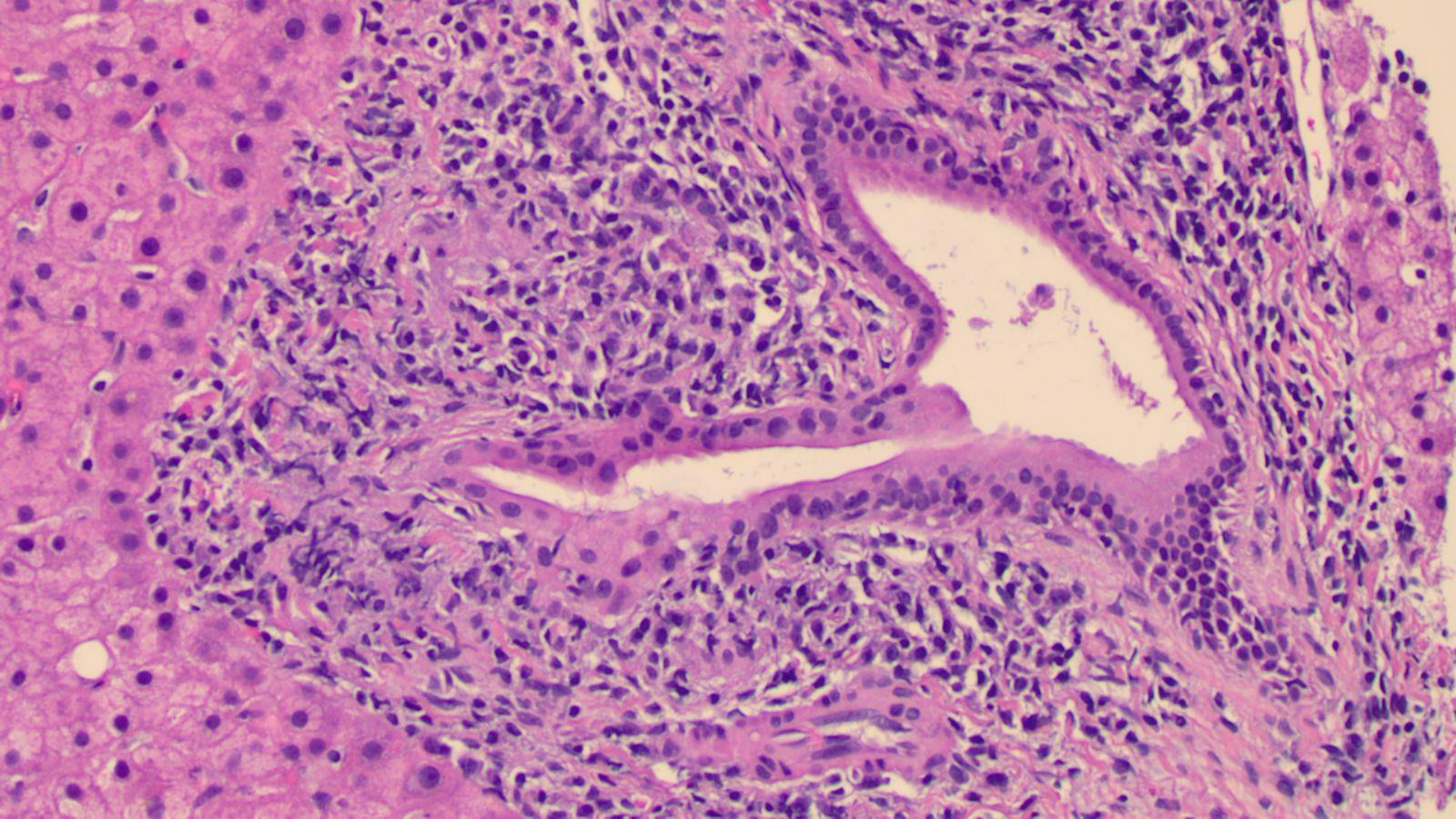


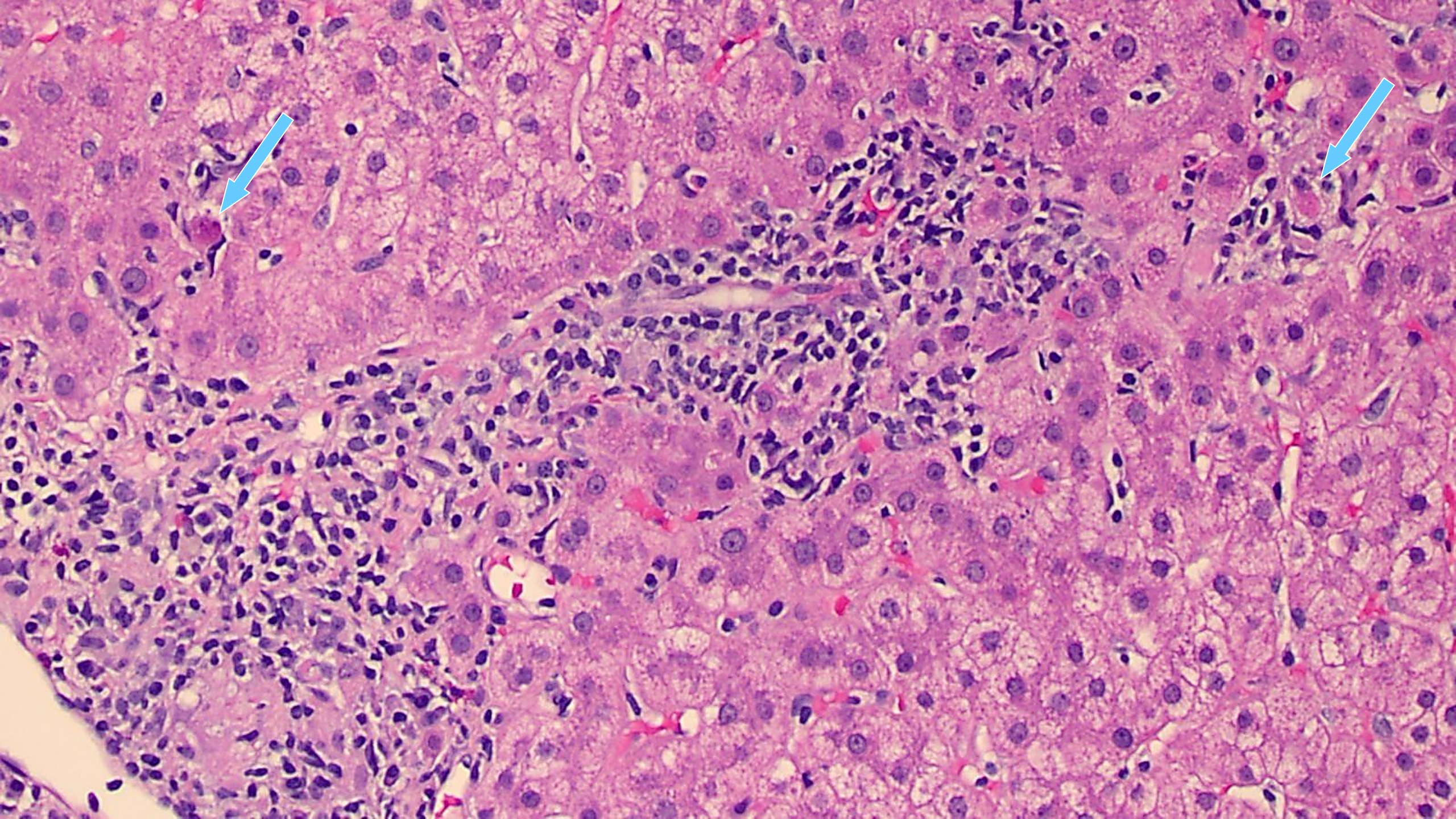
Challenging Case

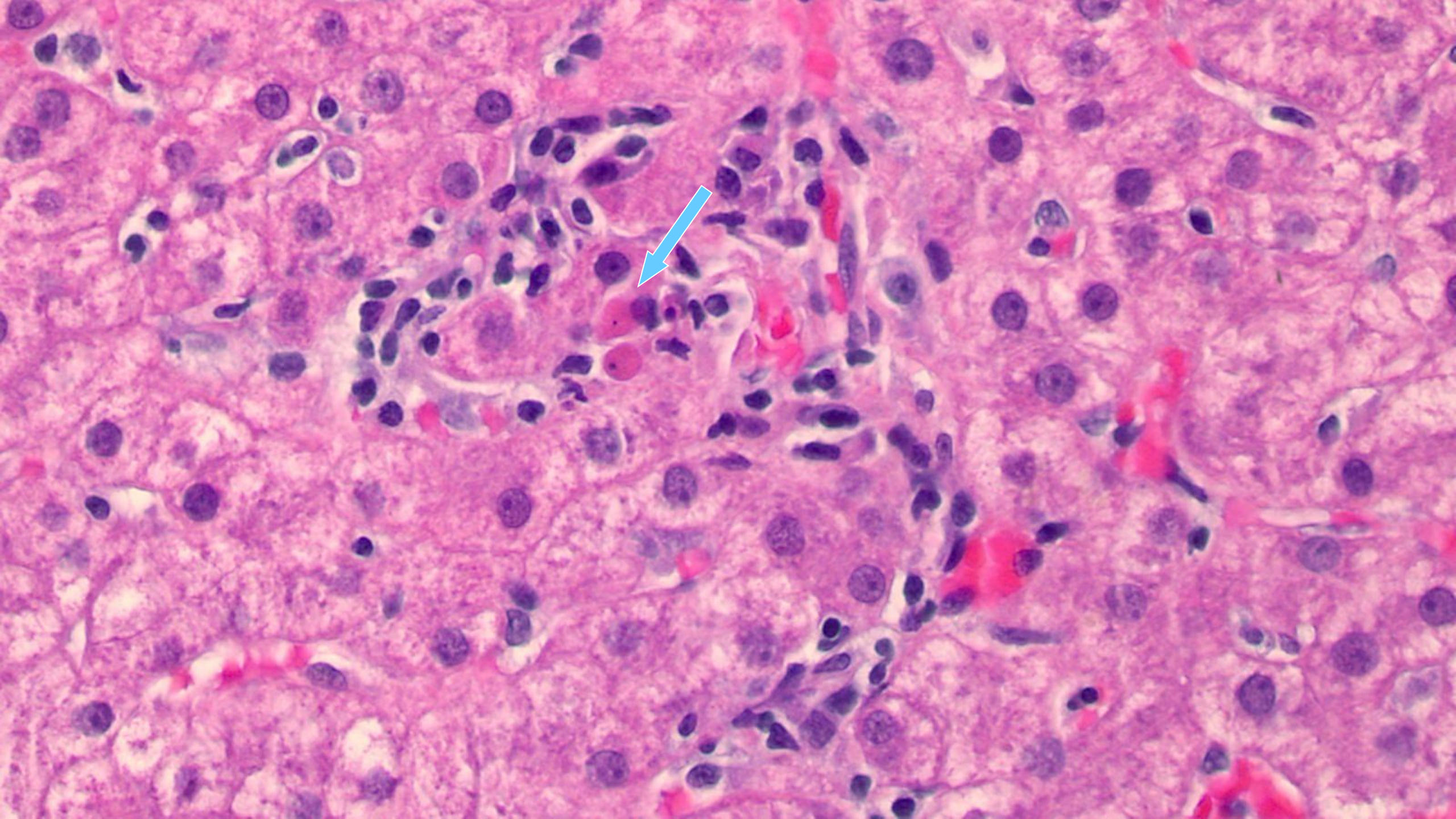
- 37 year old male bartender
- Two months prior to biopsy, ALT 424 and AST 185. Down to 269/118 month before biopsy
- ANA 1:2560, AMA positive, SMA negative
- Biopsy interpreted at OSH as consistent with overlap PBC/AIH











My diagnosis

- Destructive non-suppurative cholangitis with duct loss, consistent with PBC.
- Comment: The mild hepatitic component and elevated LFTs raise the question of overlap, but technically Paris criteria not met since there is not “moderate to severe” hepatitis. Might be inflammatory PBC.

Follow up

- Given risks of long-term IS, they wean azathioprine, and monitor LFTs.
- ALT 53 -> 72 so AZA and Budesonide restarted. Initially drop to 60, then climb to 86.
- He is making smoothies with “green stuff". He went to Aruba and drank up to 5 drinks/day.
- 2 weeks after stopping the “green stuff” ALT 68
- 3 months later, ALT 72. Increase dose of AZA.

I wish I could trade my heart in for another liver. Then I could drink more and care less.