THE EVALUATION OF CHOLESTATIC LIVER DISEASE

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ASSESSING CHOLESTATIC DISORDERS

Assessment of features of bile stasis in the liver

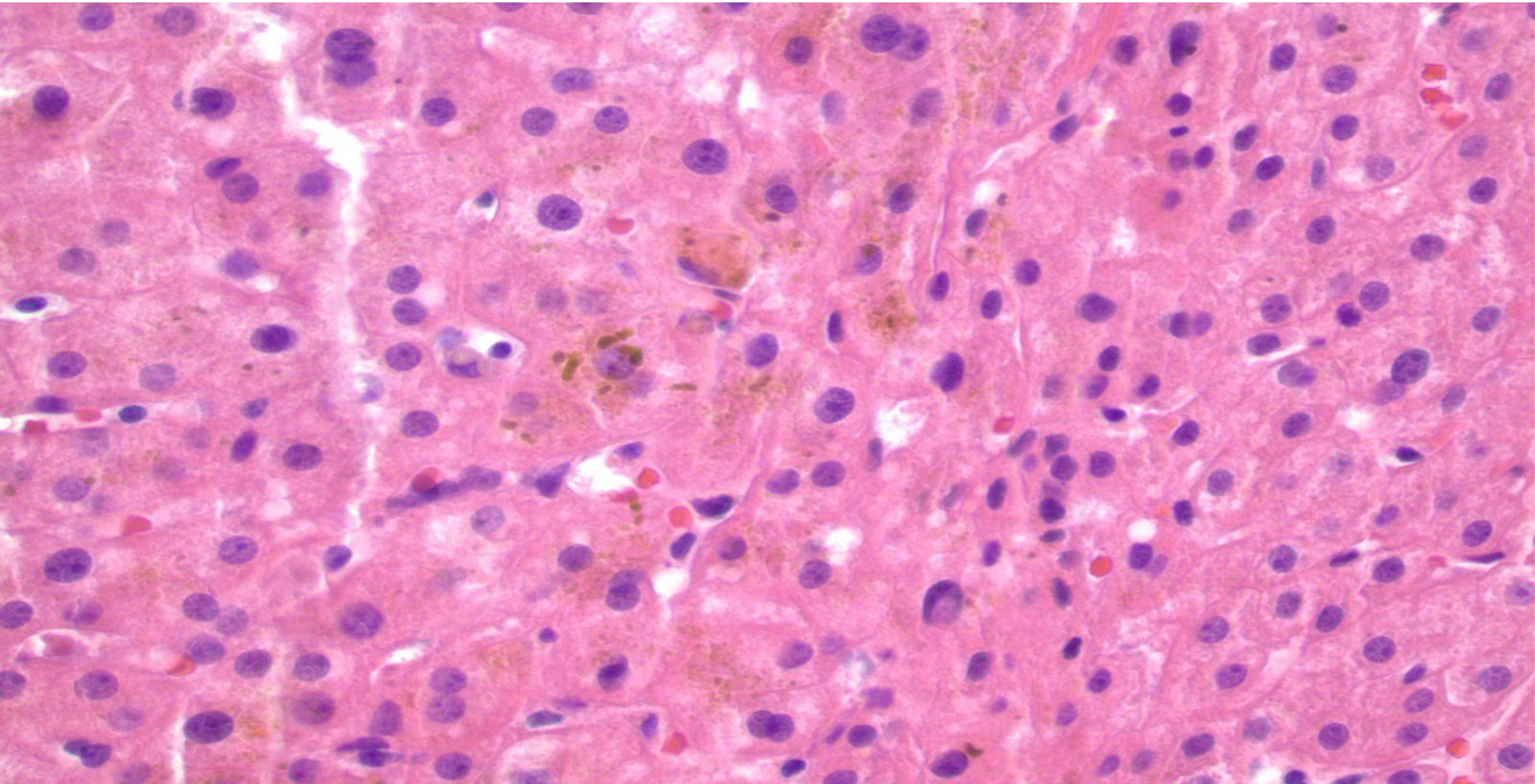
Differential diagnosis for the acutely cholestatic liver biopsy

- The usual differential
- Beyond the usual

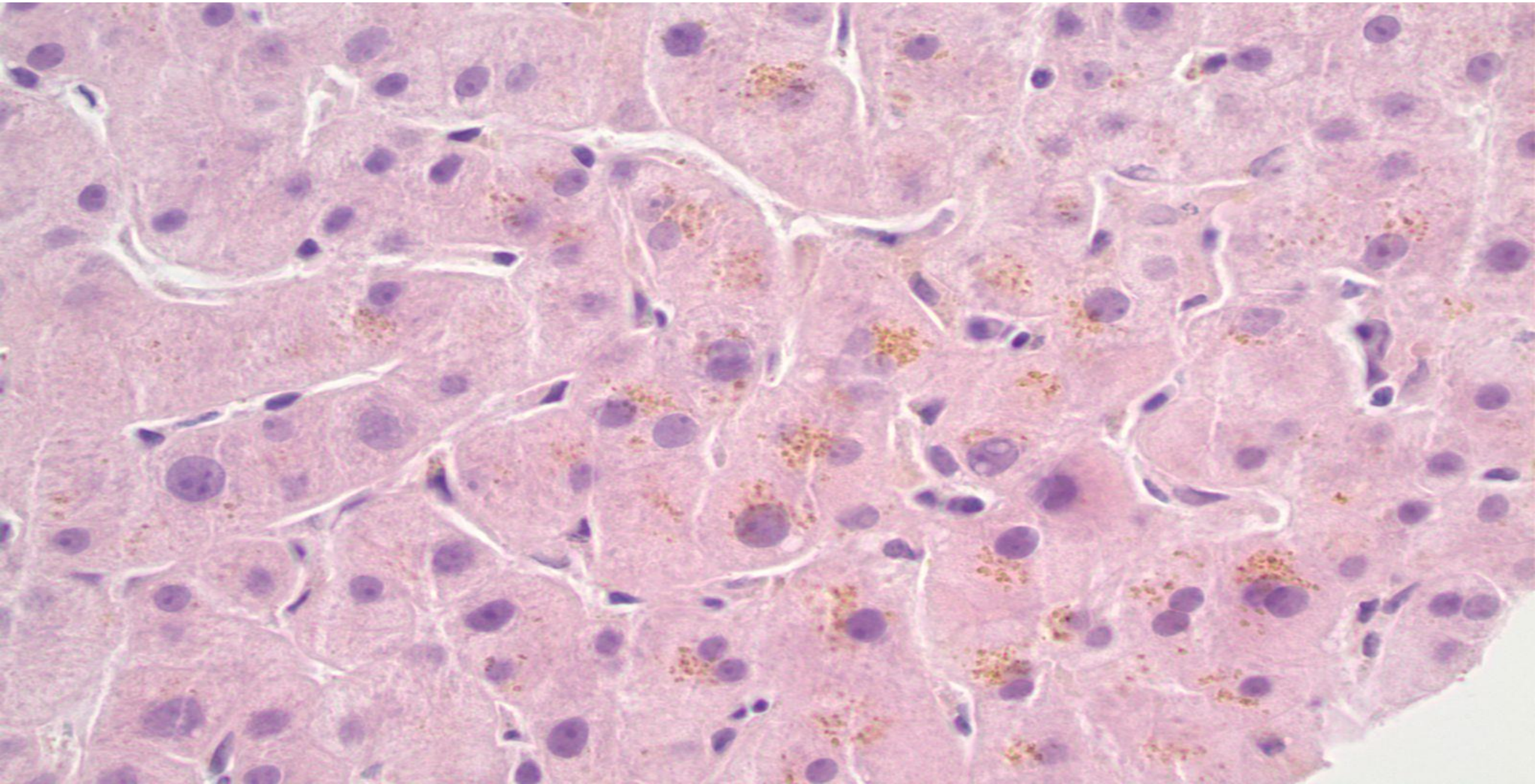
Ductopenia – assessment and differential diagnosis

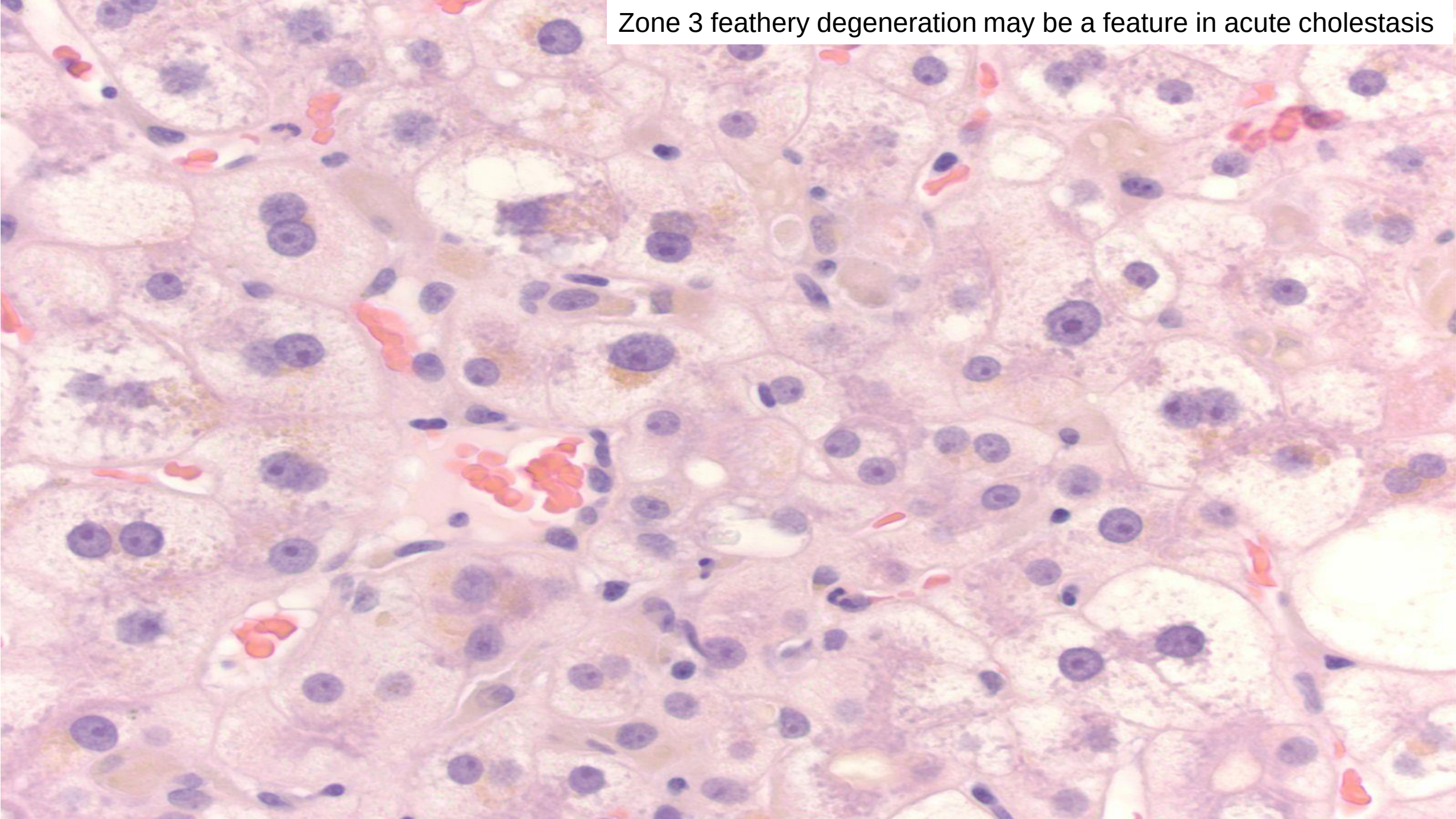
Acute cholestasis in chronic liver disease

Bile in canaliculi is the most reliable way to establish an acute cholestatic process.
Coarse intracellular pigments *might* be bile (but only if there is clinical evidence of cholestasis/jaundice).

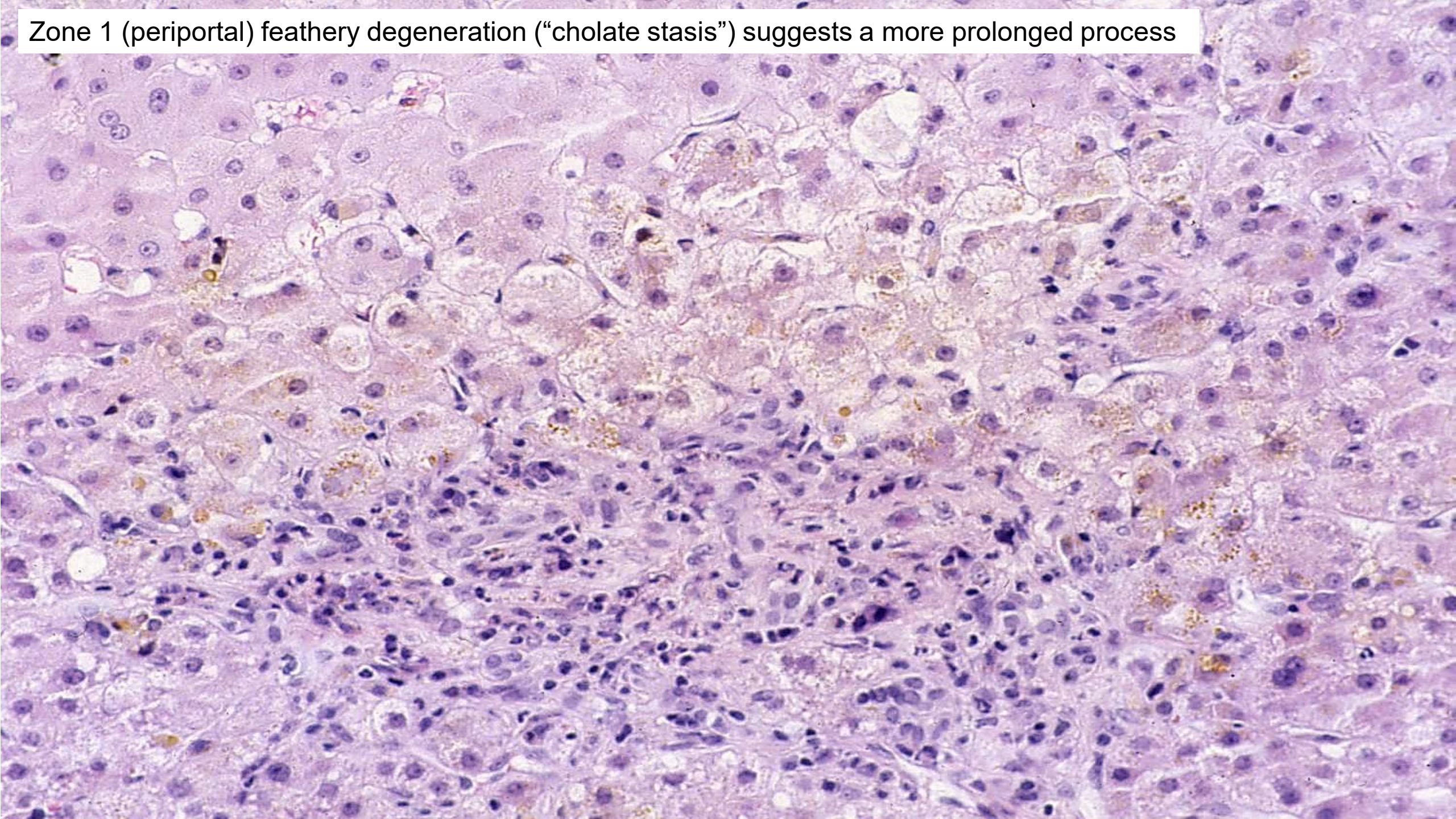


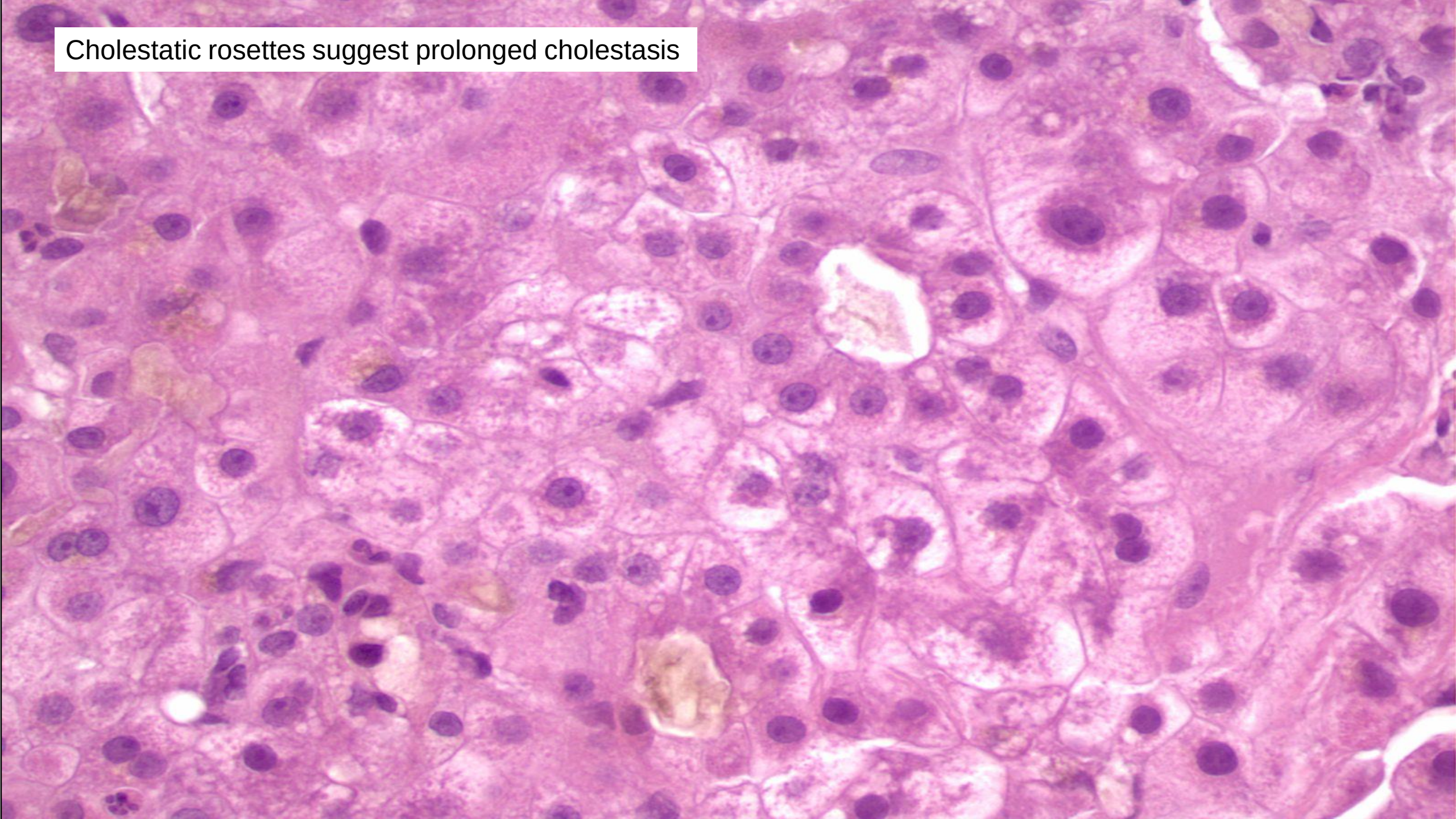
Without intracanalicular bile, use caution interpreting intracellular pigment.
Look for bile plugs, and only conclude the pigment must be intrahepatic bile if the clinical picture is compelling (like jaundice).




Zone 3 feathery degeneration may be a feature in acute cholestasis

Zone 1 (periportal) feathery degeneration (“cholate stasis”) suggests a more prolonged process

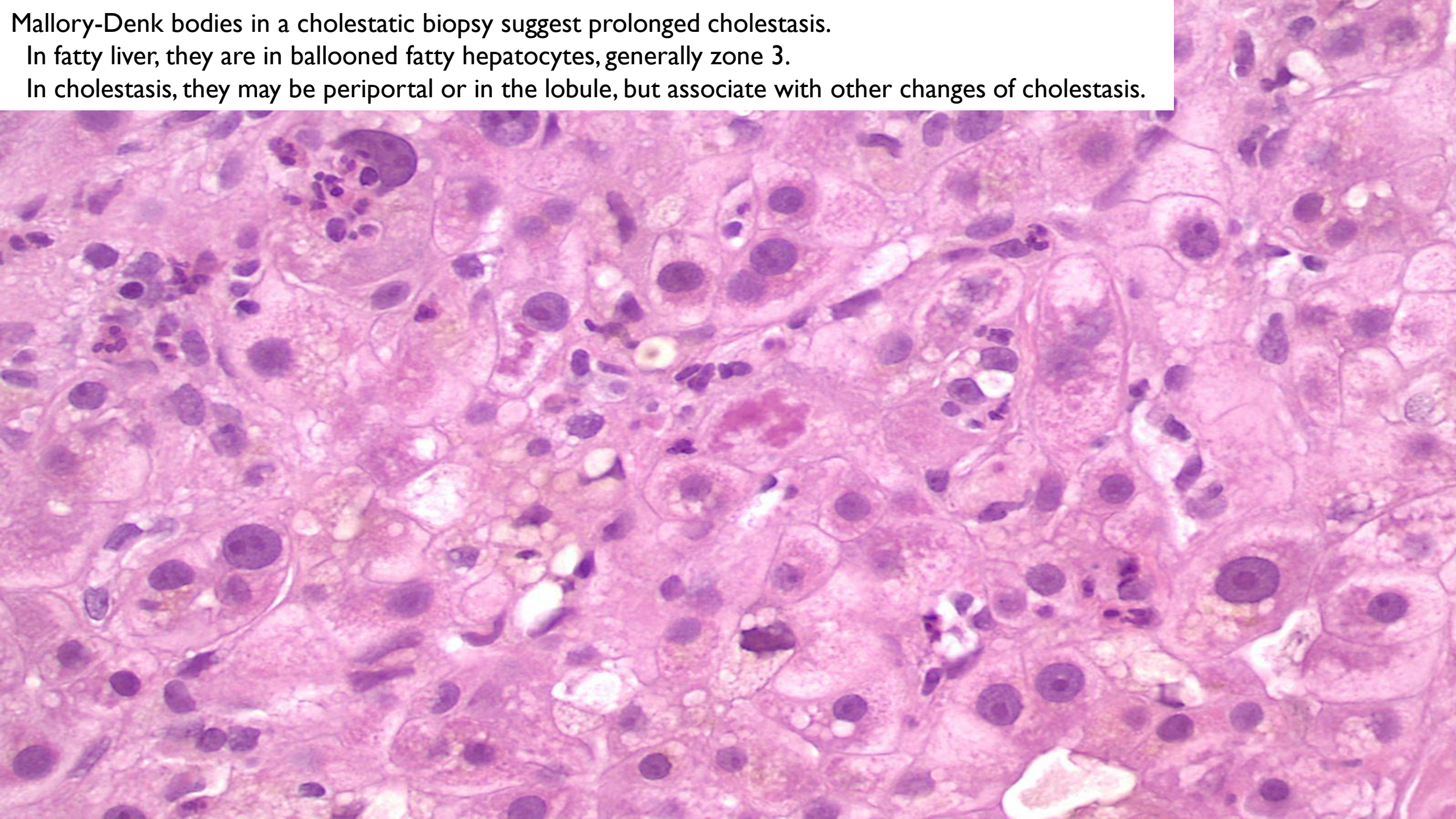



Cholestatic rosettes suggest prolonged cholestasis

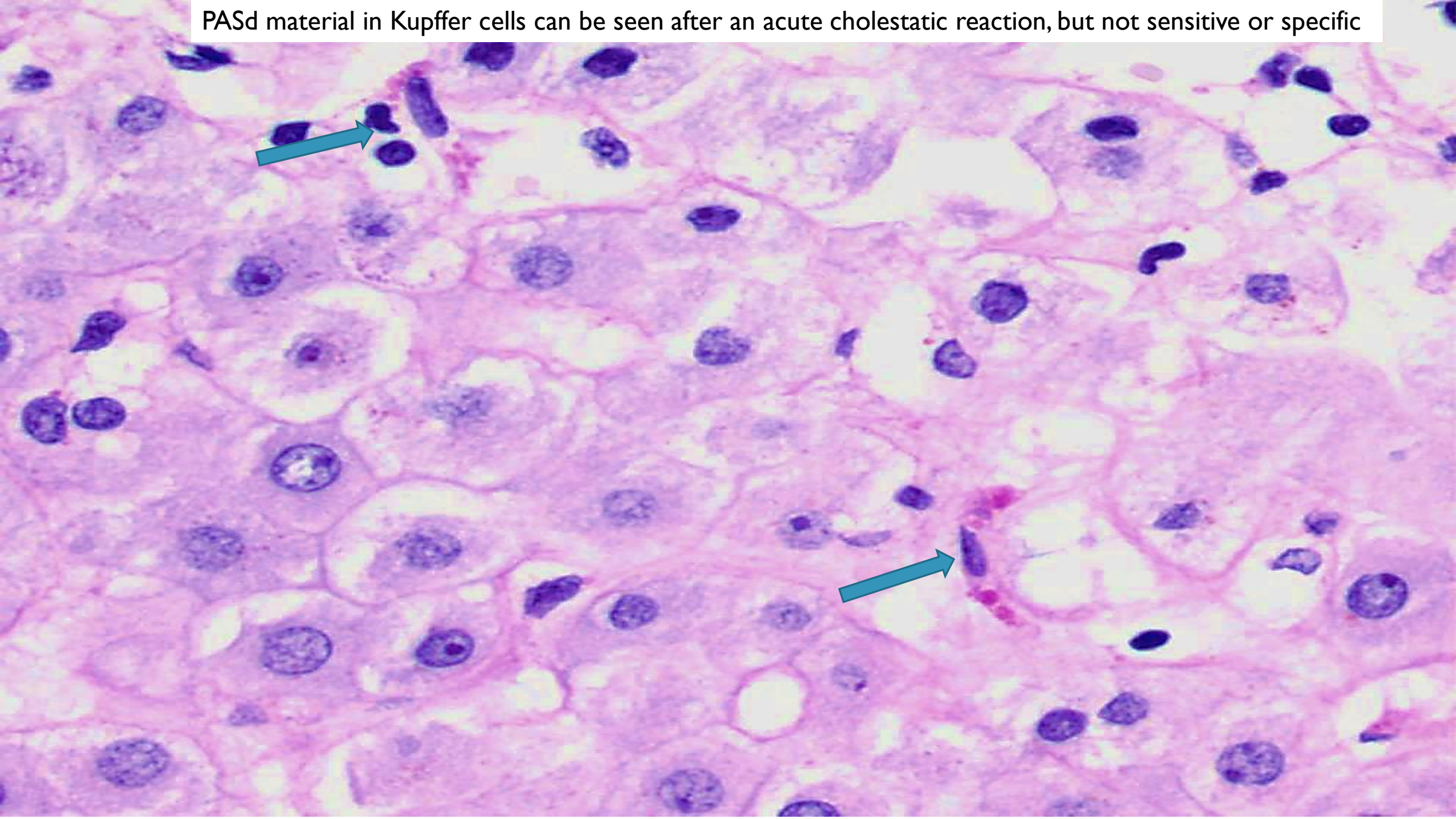
Mallory-Denk bodies in a cholestatic biopsy suggest prolonged cholestasis.

In fatty liver, they are in ballooned fatty hepatocytes, generally zone 3.

In cholestasis, they may be periportal or in the lobule, but associate with other changes of cholestasis.



PASd material in Kupffer cells can be seen after an acute cholestatic reaction, but not sensitive or specific



SUMMARY OF ACUTE CHOLESTATIC FEATURES

Bile casts in canaliculi. Use caution if you only see coarse pigment in hepatocytes without casts.

Hepatocytes may show “feathery degeneration” (cytoplasmic pallor)

- In contrast “ballooning” shows more cytoplasmic degeneration with Mallory-Denk bodies but in some cases, the distinction is difficult. Context is key.

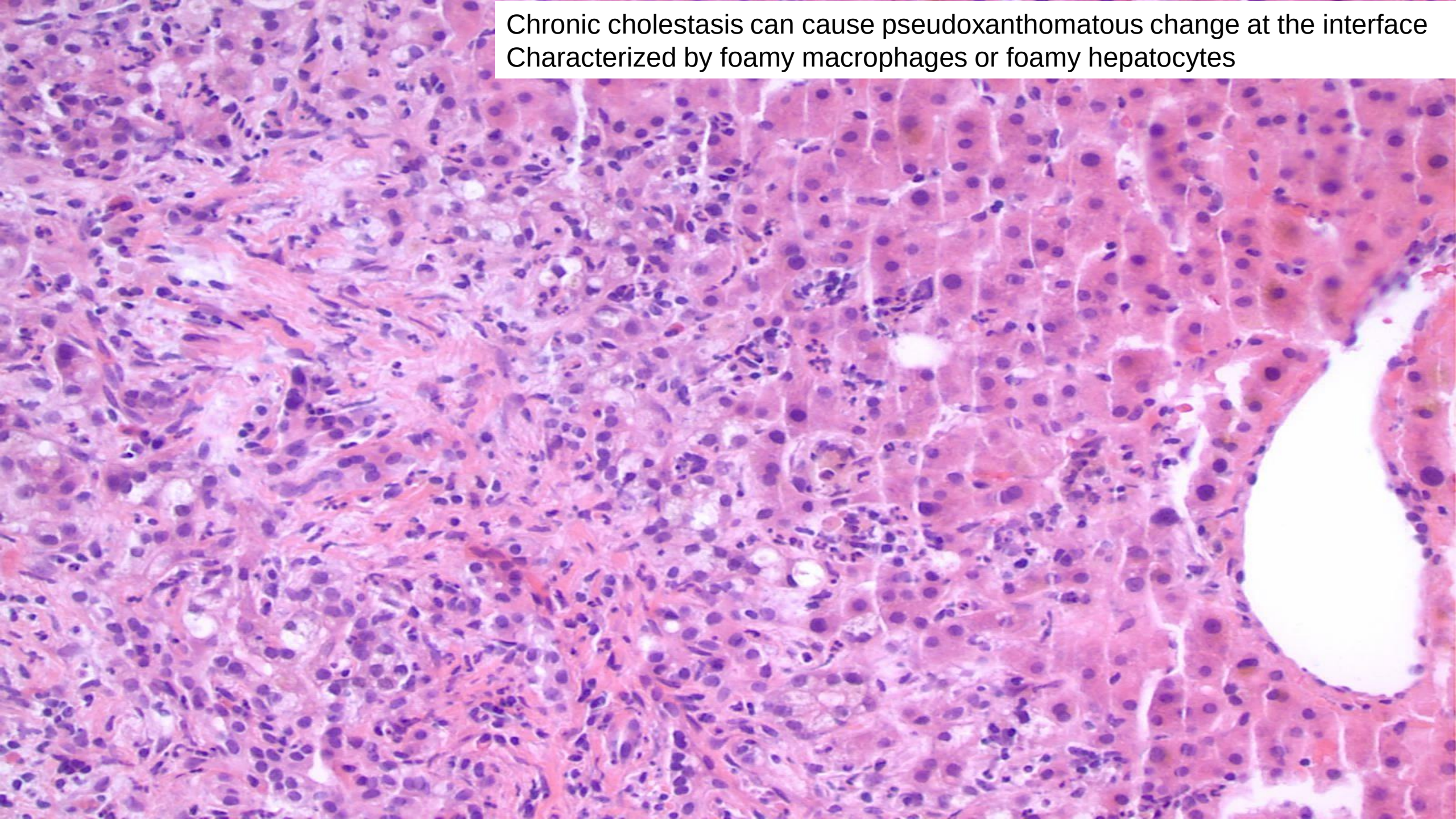
Prolonged cholestasis can show periportal feathery degeneration, cholestatic rosettes, and Mallory-Denk bodies

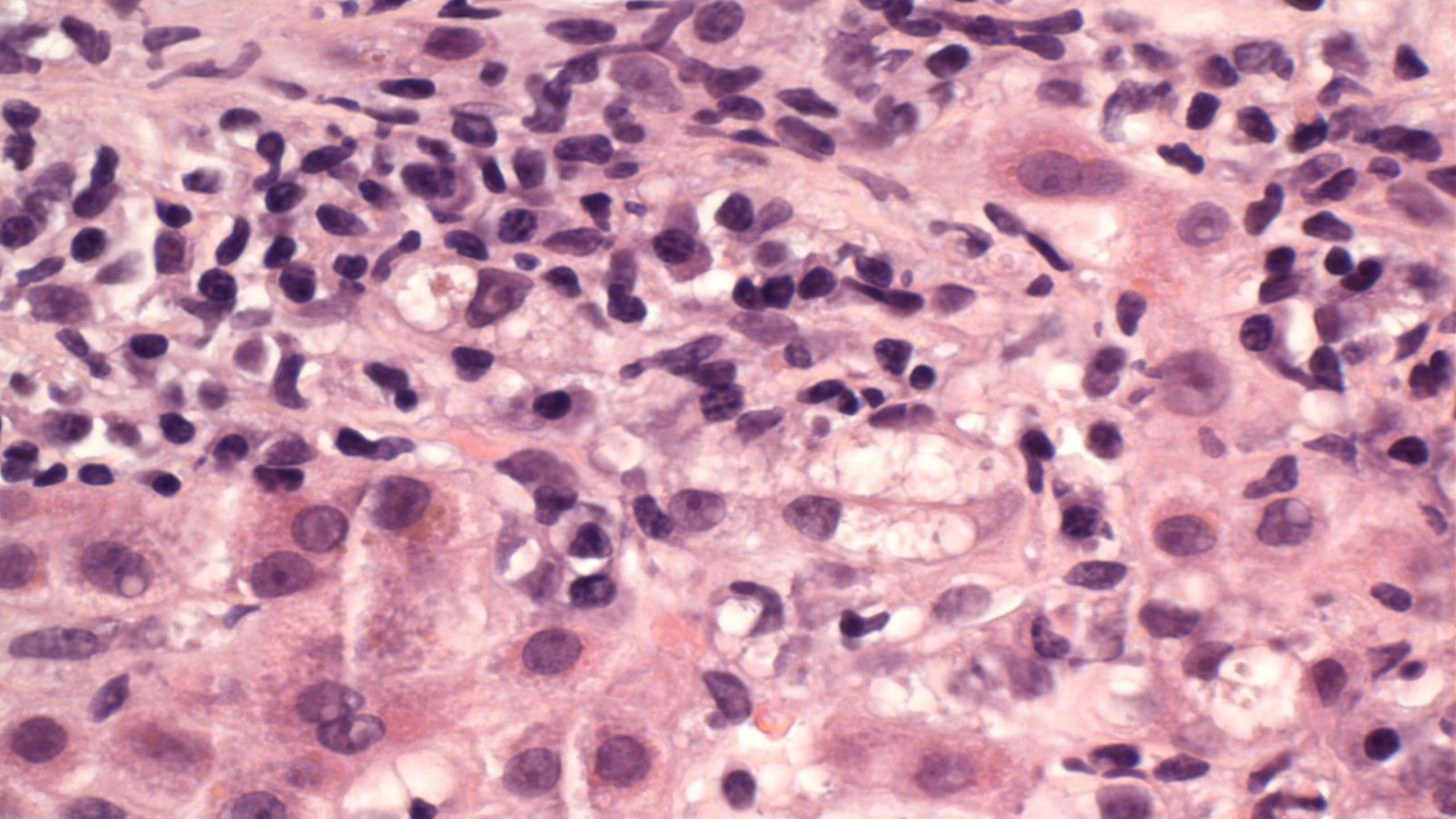
WHAT ABOUT CHRONIC CHOLESTASIS?

Typically, does *not* show bile stasis in the canaliculi, particularly in early stages or at presentation

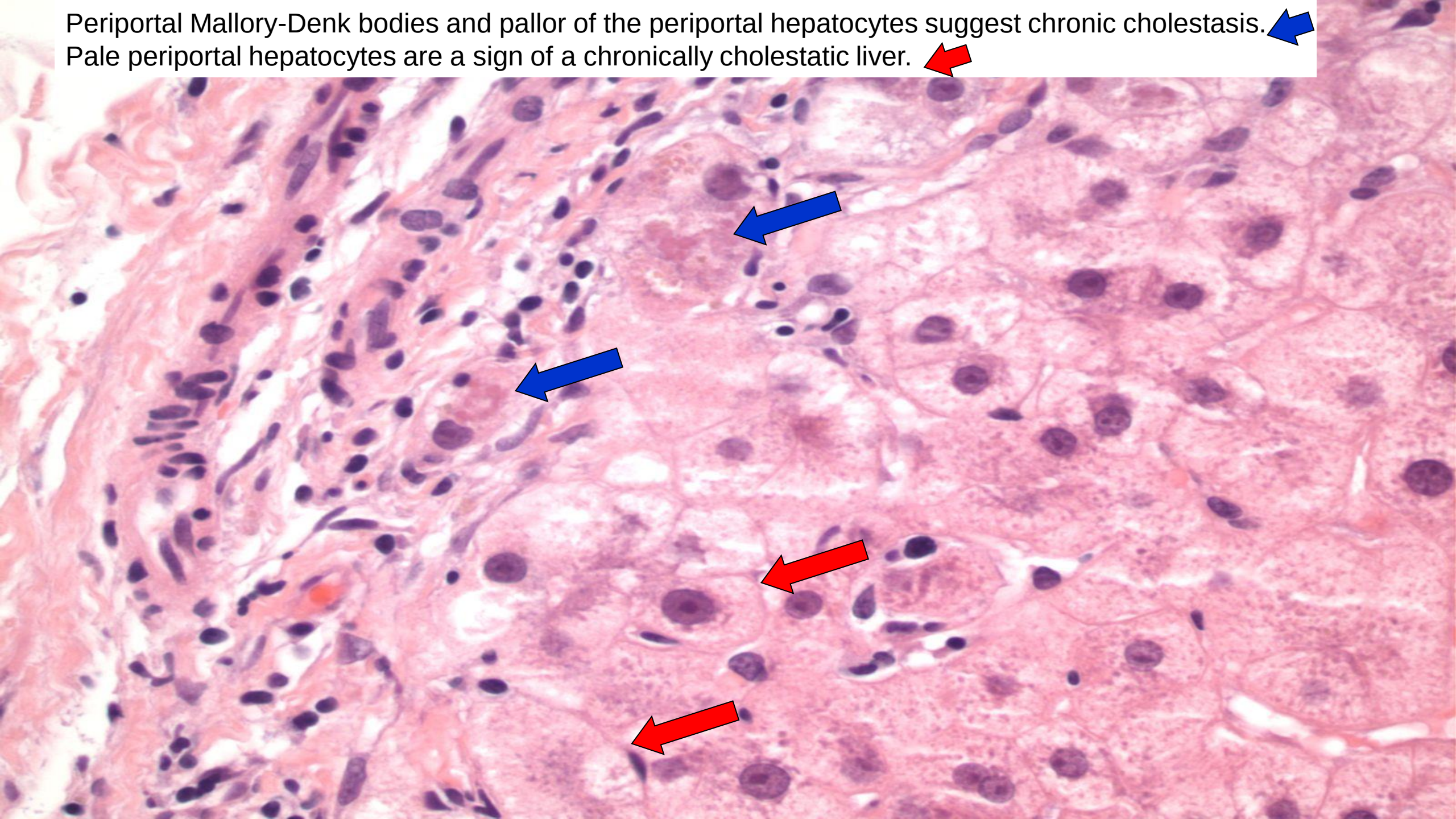
Portal and periportal changes suggest a chronic cholestatic condition

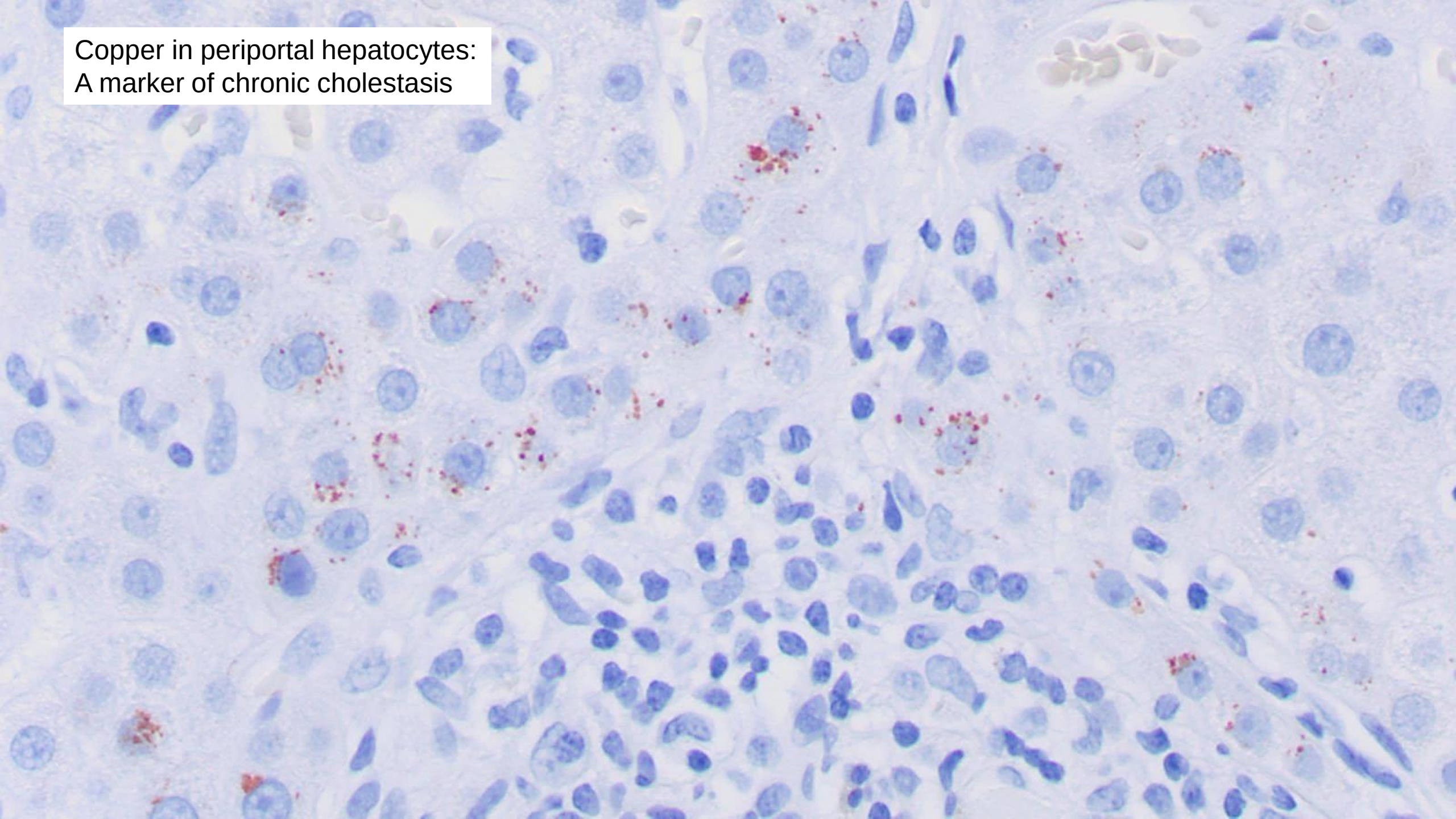
Chronic cholestasis can cause pseudoxanthomatous change at the interface
Characterized by foamy macrophages or foamy hepatocytes



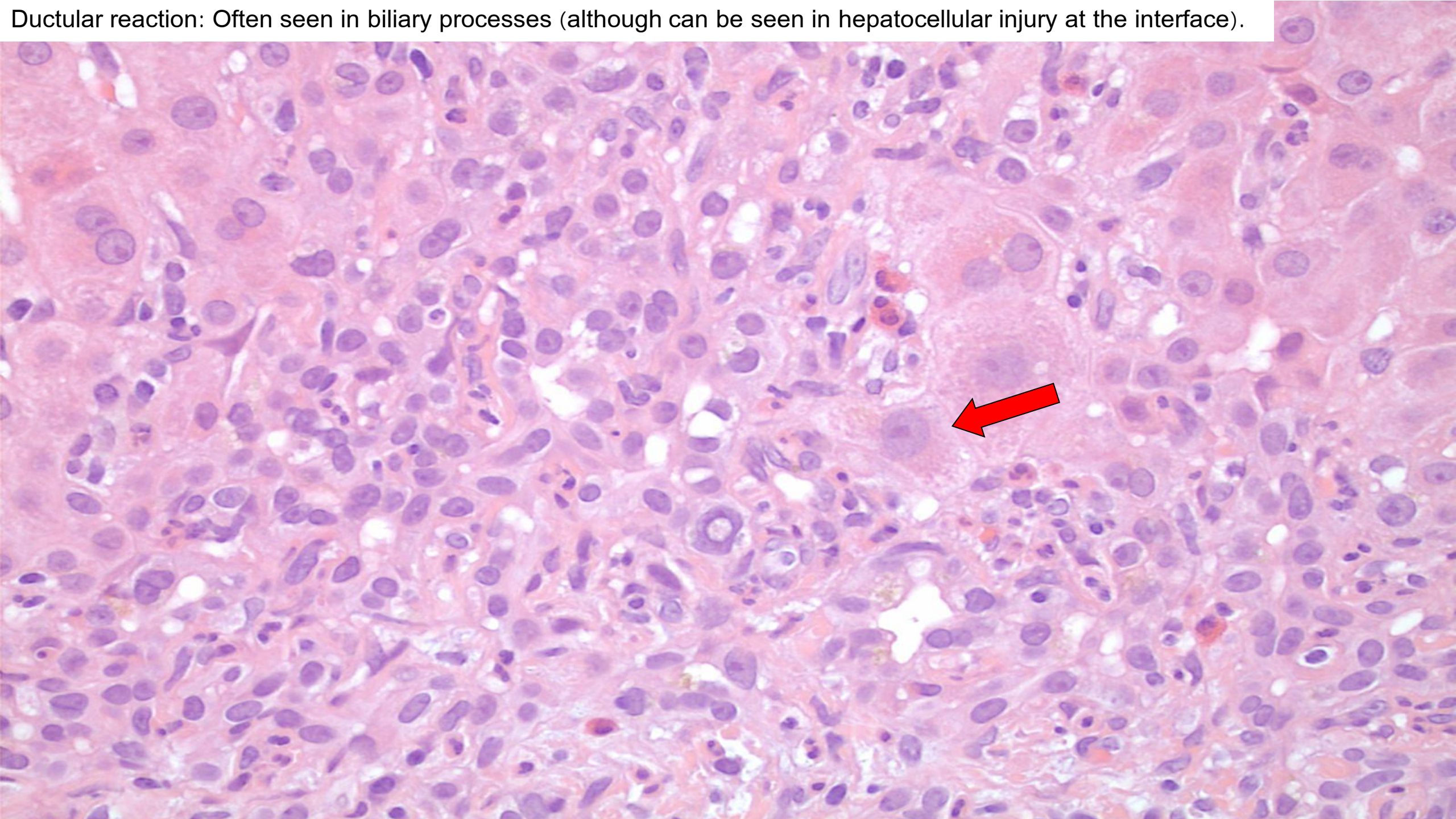


Periportal Mallory-Denk bodies and pallor of the periportal hepatocytes suggest chronic cholestasis.
Pale periportal hepatocytes are a sign of a chronically cholestatic liver.

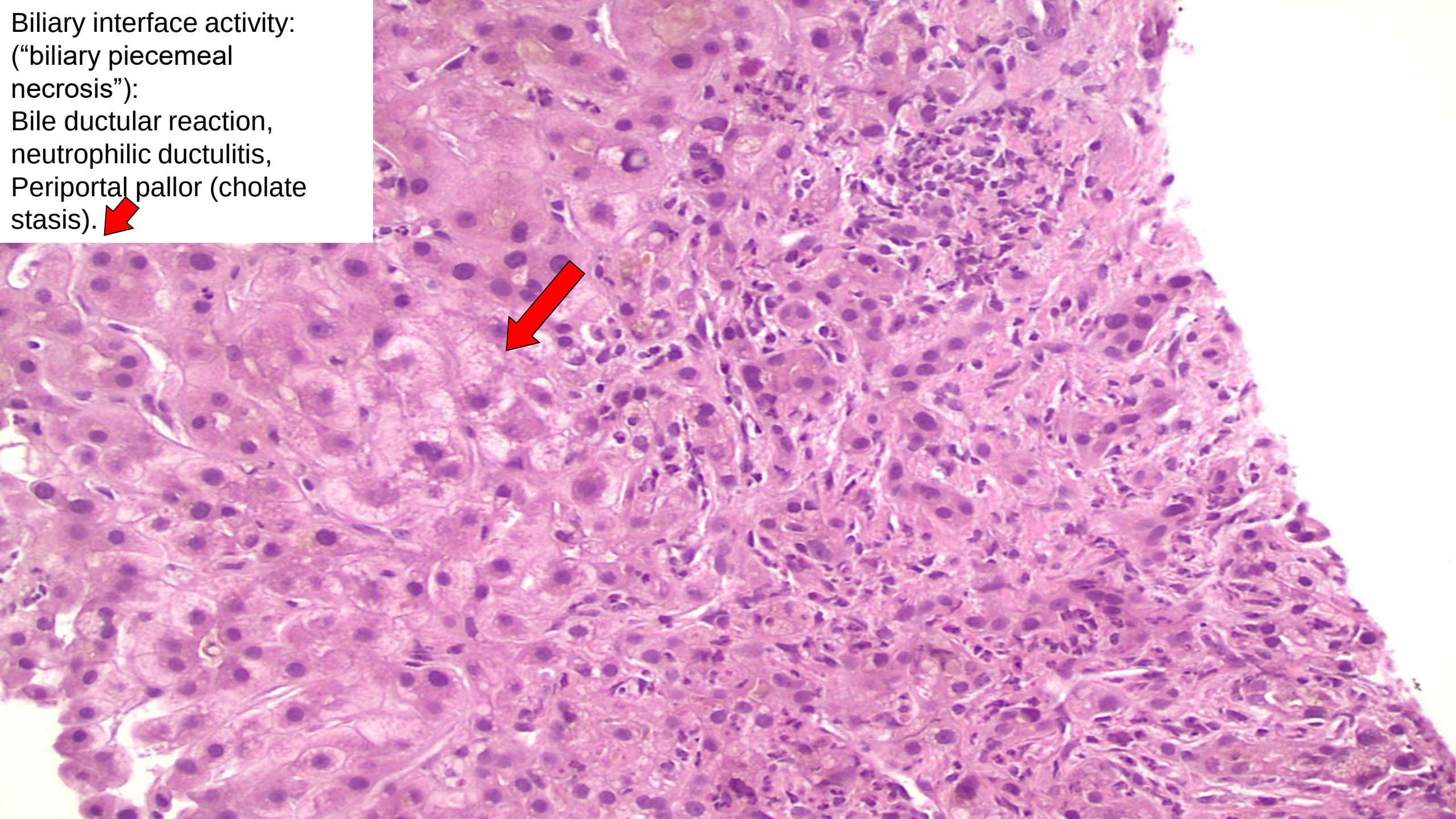



Copper in periportal hepatocytes:
A marker of chronic cholestasis

Ductular reaction: Often seen in biliary processes (although can be seen in hepatocellular injury at the interface).



Biliary interface activity: (“biliary piecemeal necrosis”):
Bile ductular reaction, neutrophilic ductulitis,
Periportal pallor (cholate stasis).



FEATURES TYPICAL OF CHRONIC CHOLESTASIS

Pseudoxanthomatous transformation at the interface and pallor of periportal hepatocytes.

Copper deposition.

Fibrosis.

Other features are frequent in chronic cholestasis but less informative.

- Mallory-Denk bodies
- Ductular reaction
- Ductopenia

CHOLESTATIC DISORDERS

Usually shows tissue cholestasis

(Differential in acute cholestatic biopsies)

Drug reaction

Large bile duct obstruction

Ascending cholangitis

Gram negative sepsis

Paraneoplastic (particularly Hodgkin's)

Unusual infections

Familial cholestatic syndromes

Pregnancy

Often does not show tissue cholestasis

(Not in the early stages or at presentation.)

Primary Biliary Cirrhosis

Primary Sclerosing Cholangitis

IgG4 cholangitis

Sarcoidosis

Cystic fibrosis

Other small duct cholangiopathies such as ischemic cholangiopathy

USUAL DIFFERENTIAL FOR ACUTE CHOLESTASIS

Features in common among many entities

Bile stasis, portal expansion, duct injury, portal granulocytes

Condition	Pathologic feature
Drug reaction	Eosinophils, granulomas, duct loss
Large bile duct obstruction	Portal edema, neutrophils around small ducts, bile infarcts
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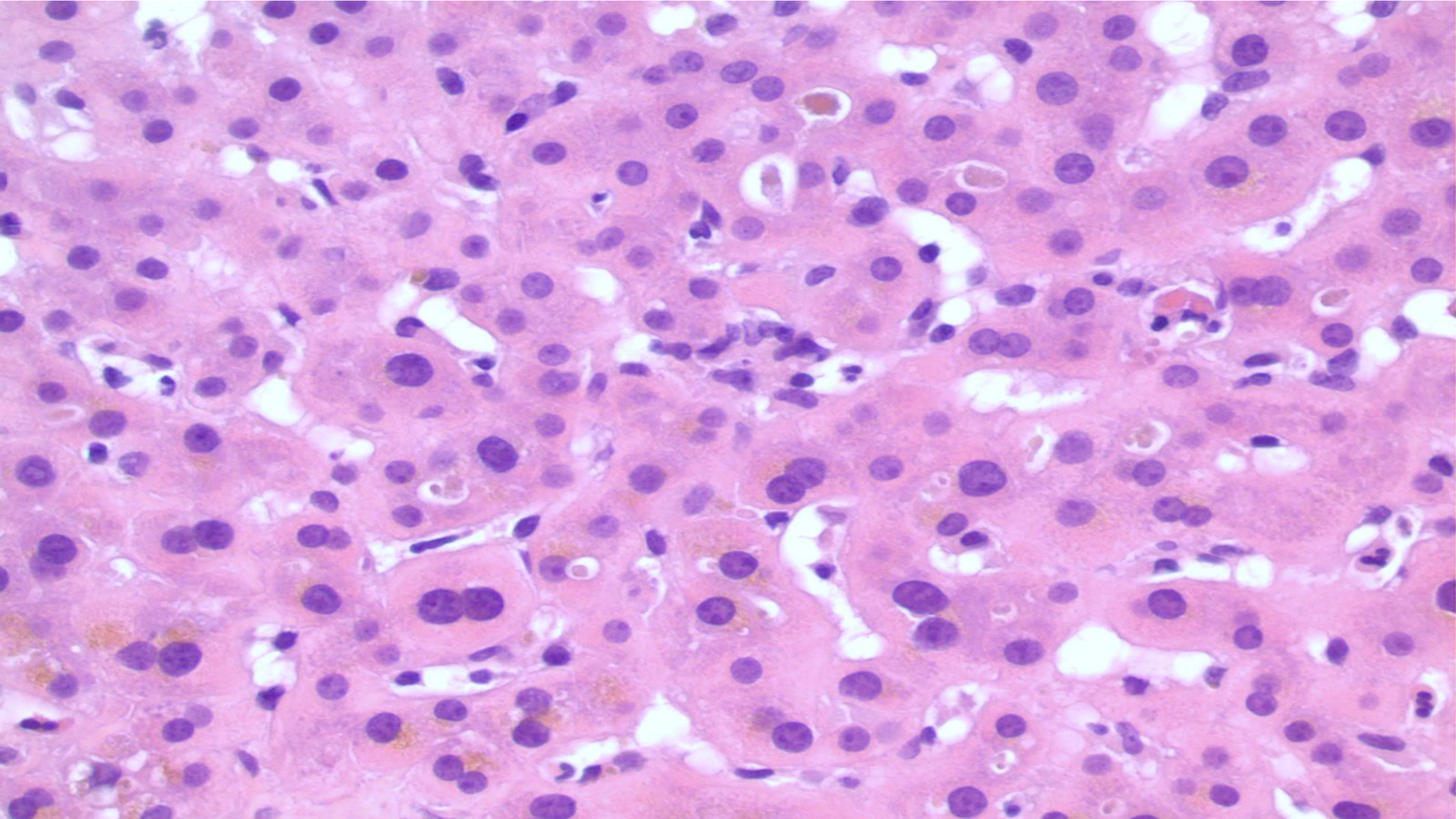
Gram negative infection, sepsis	Cholangiolar cholestasis, many neutrophils in portal areas
Paraneoplastic: Hodgkin's	+/- duct loss, cholestasis, granulomas, sinusoidal dilatation
HAV, HEV	Lobular inflammation and ballooning, plasma cells in HAV
Syphilis or other unusual infx	Pseudotumors, neutrophilic pericholangitis, granulomas, histiocytes

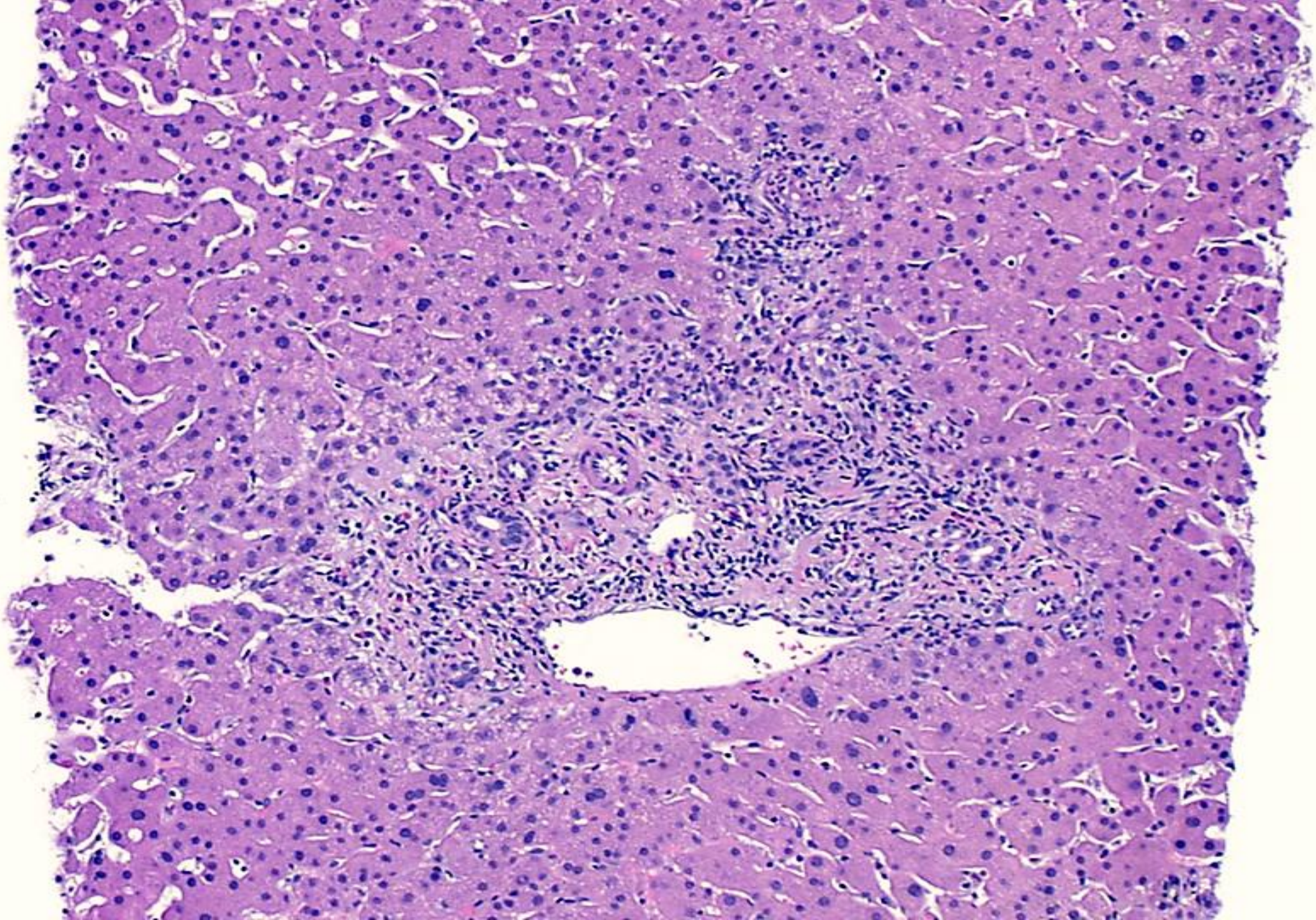
CASE

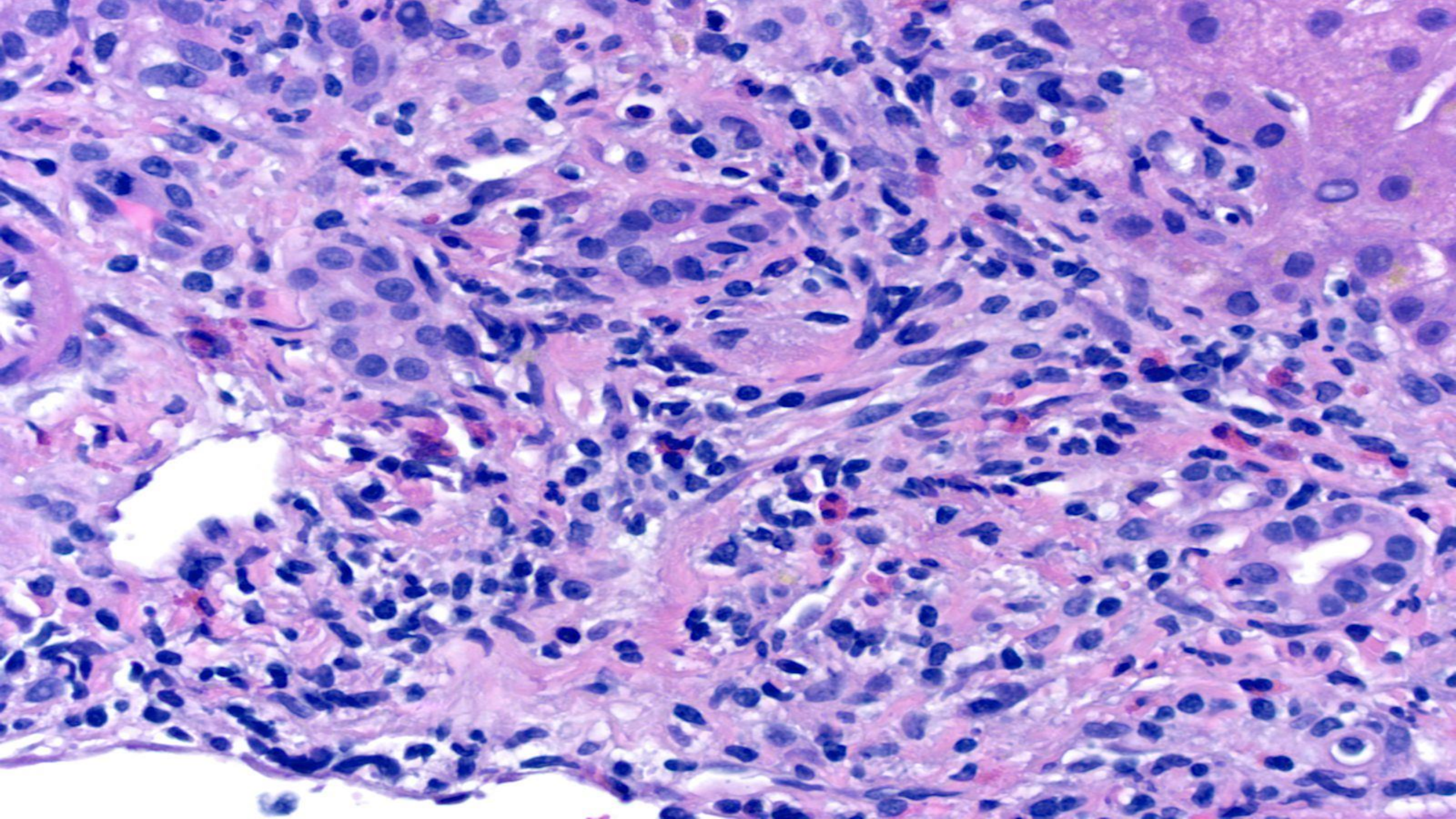
49 year old man presents with jaundice and dark urine, n/v, abdominal distention

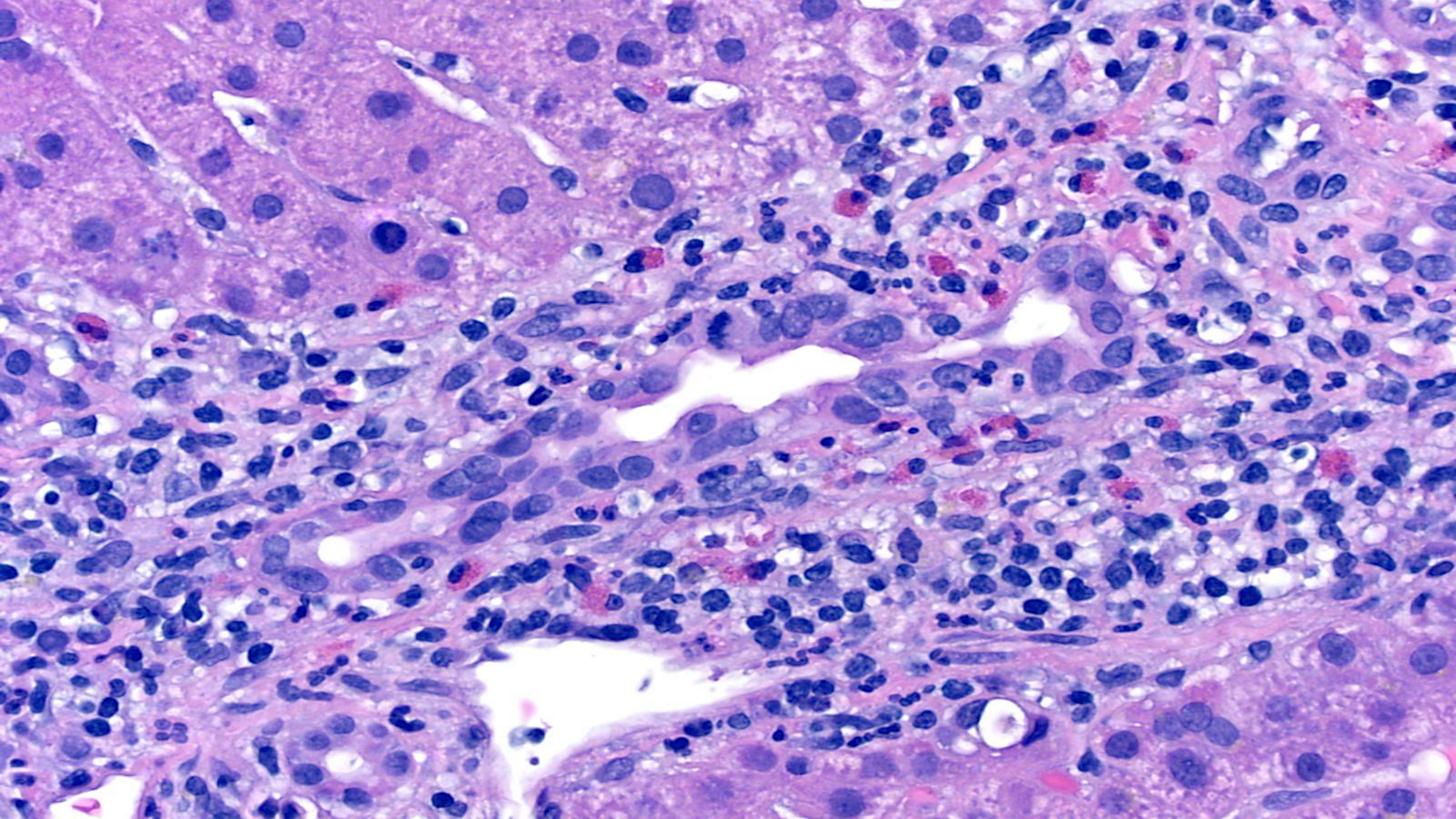
AP 1478, TB 7, MRCP negative, all serology negative

On atorvastatin, triamterene (diuretic), ibuprofen, multiple energy drinks a day, multivitamin – but nothing new and all had been stopped when he was admitted









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CASE CONTINUED

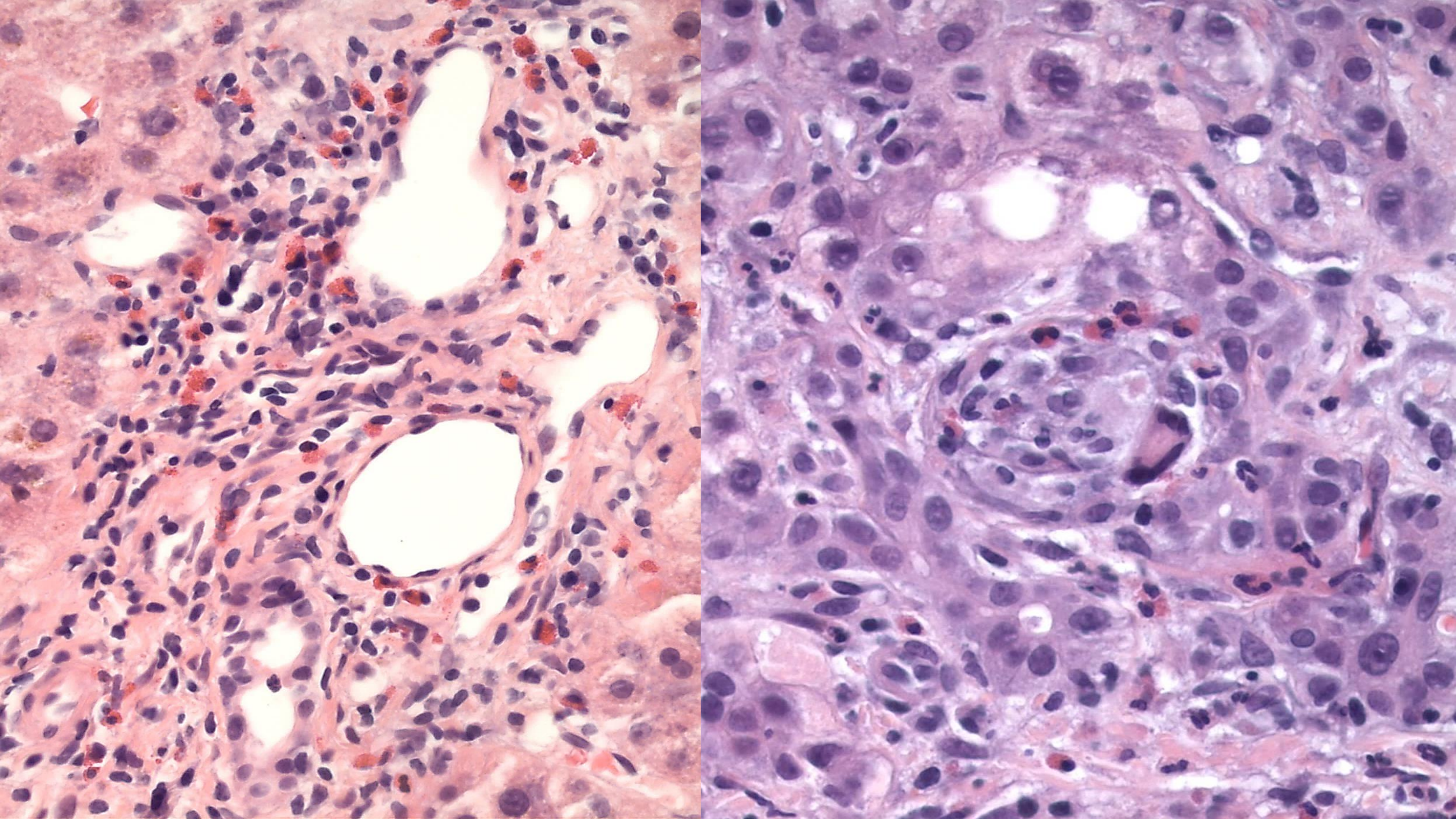
Diagnosis: Cholestasis with portal mixed inflammation and duct injury.

- Because the features are "baseline" non-specific, a broad differential would be appropriate, favoring common things, like drug reaction.
- If the history is more compelling, you can tailor or eliminate the differential diagnosis.

No treatment initiated; slowly improved. Probably a drug toxin that was never identified.

No culprit identified…

- "We see this sometimes", where no culprit drug is identified but still likely a drug reaction
- Cholestatic reactions improve more slowly than hepatitic reactions
- Be prepared with the differential, but be prepared to feel unhelpful too!



CASE

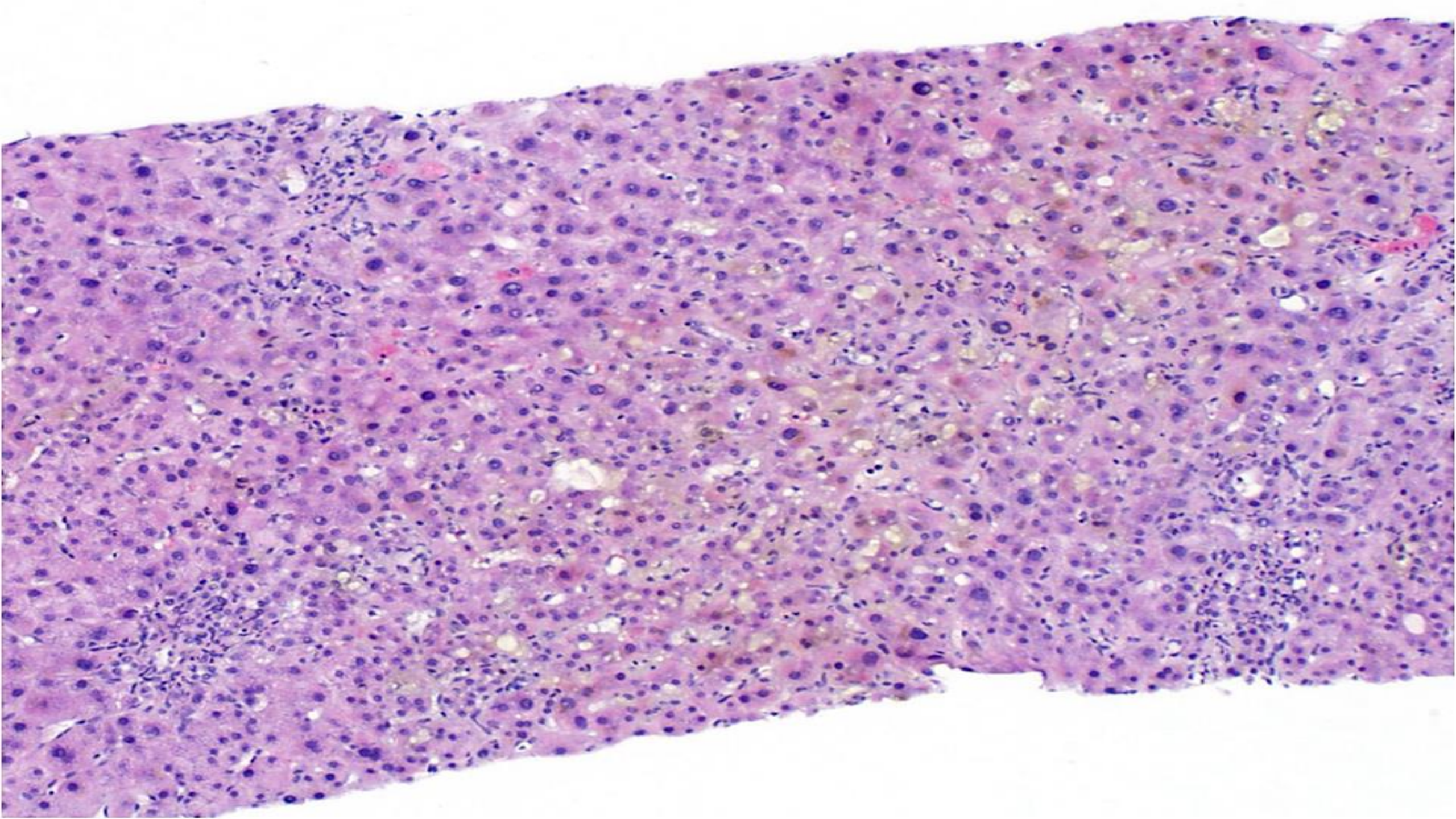
55 year old man, chronic vascular disease.

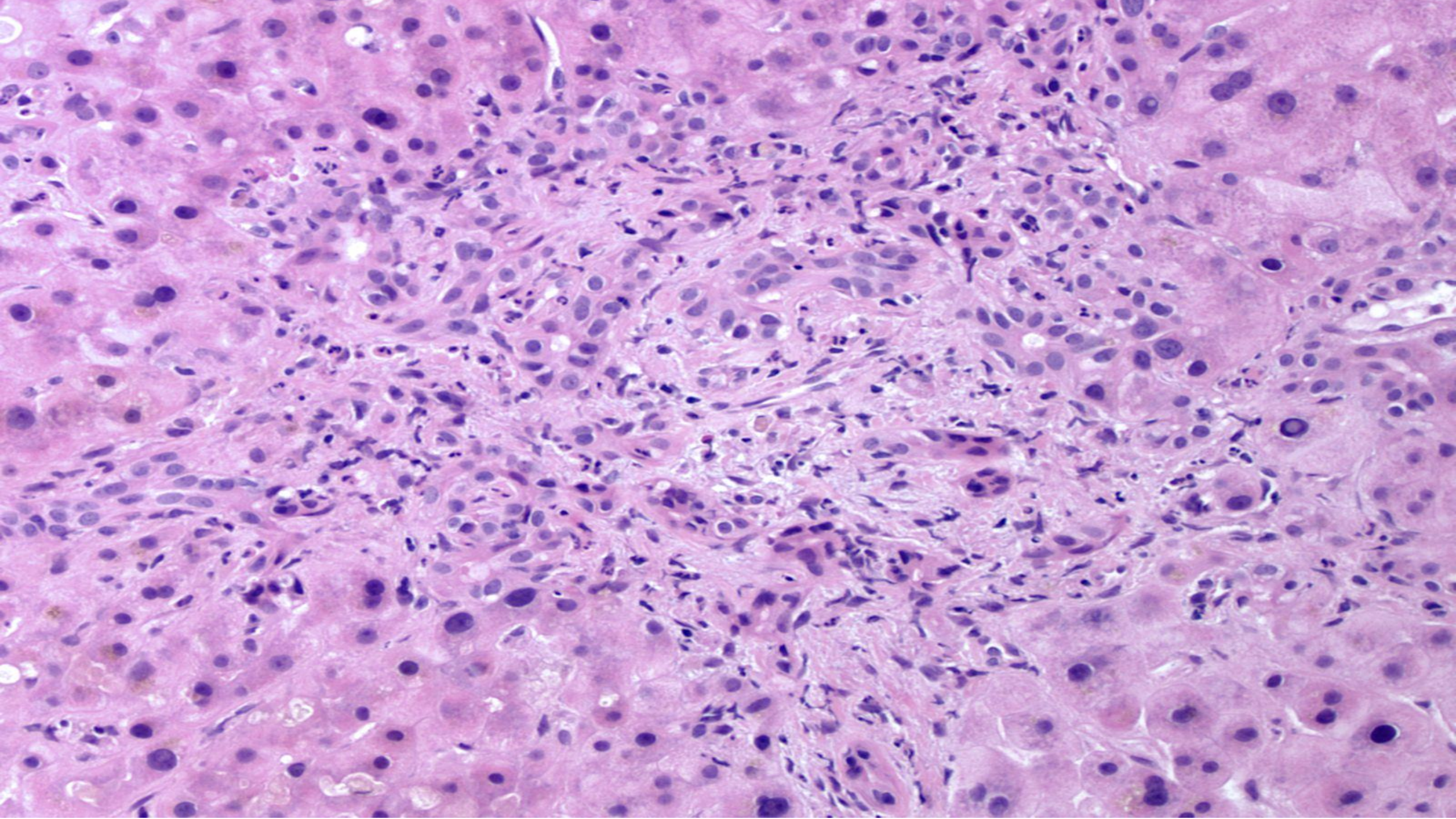
Undergoing iliac artery stenting, artery ruptures, requiring tamponade.

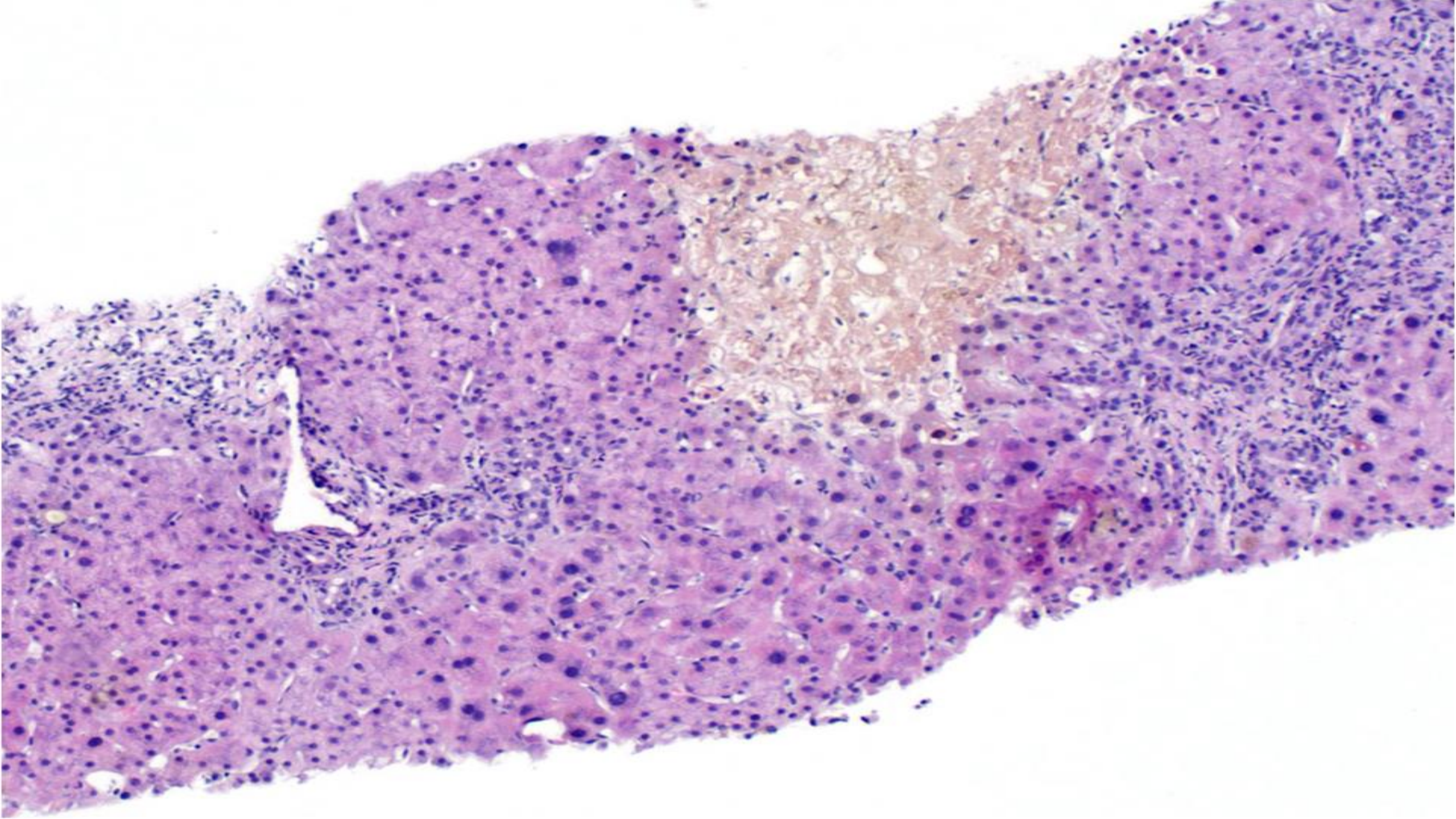
Shortly after discharge, a neighbor tells him he looks yellow.

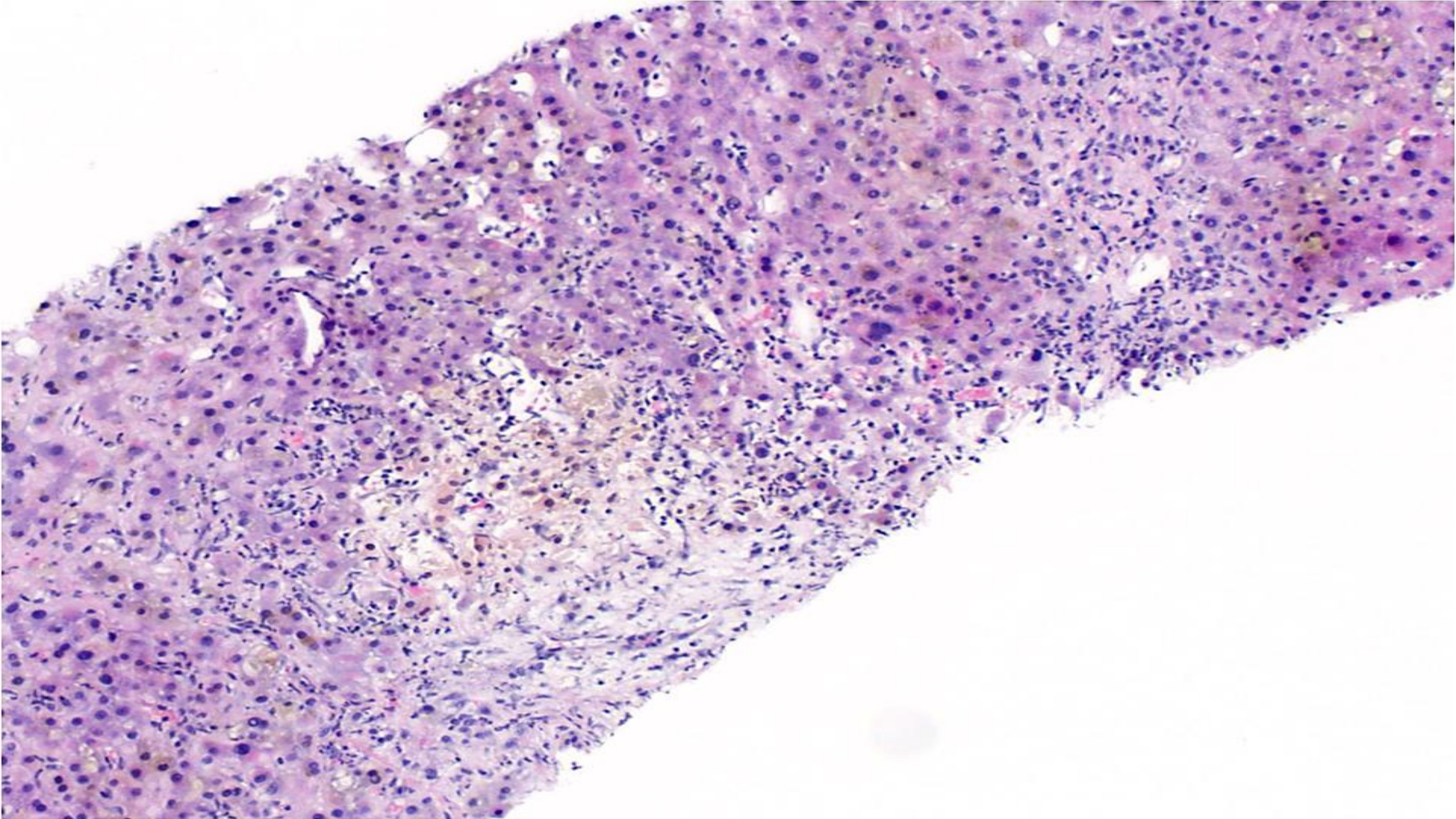
ERCP showed short stricture of CBD, stented, but failed to resolve jaundice.

Continues to do poorly, with superimposed renal failure, and dies.









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LARGE DUCT OBSTRUCTION

Usually a mechanical obstruction due to tumors, stones, or strictures of the bile duct.

Abdominal pain, fever, rigors, prior biliary surgery, and older age suggest obstruction.

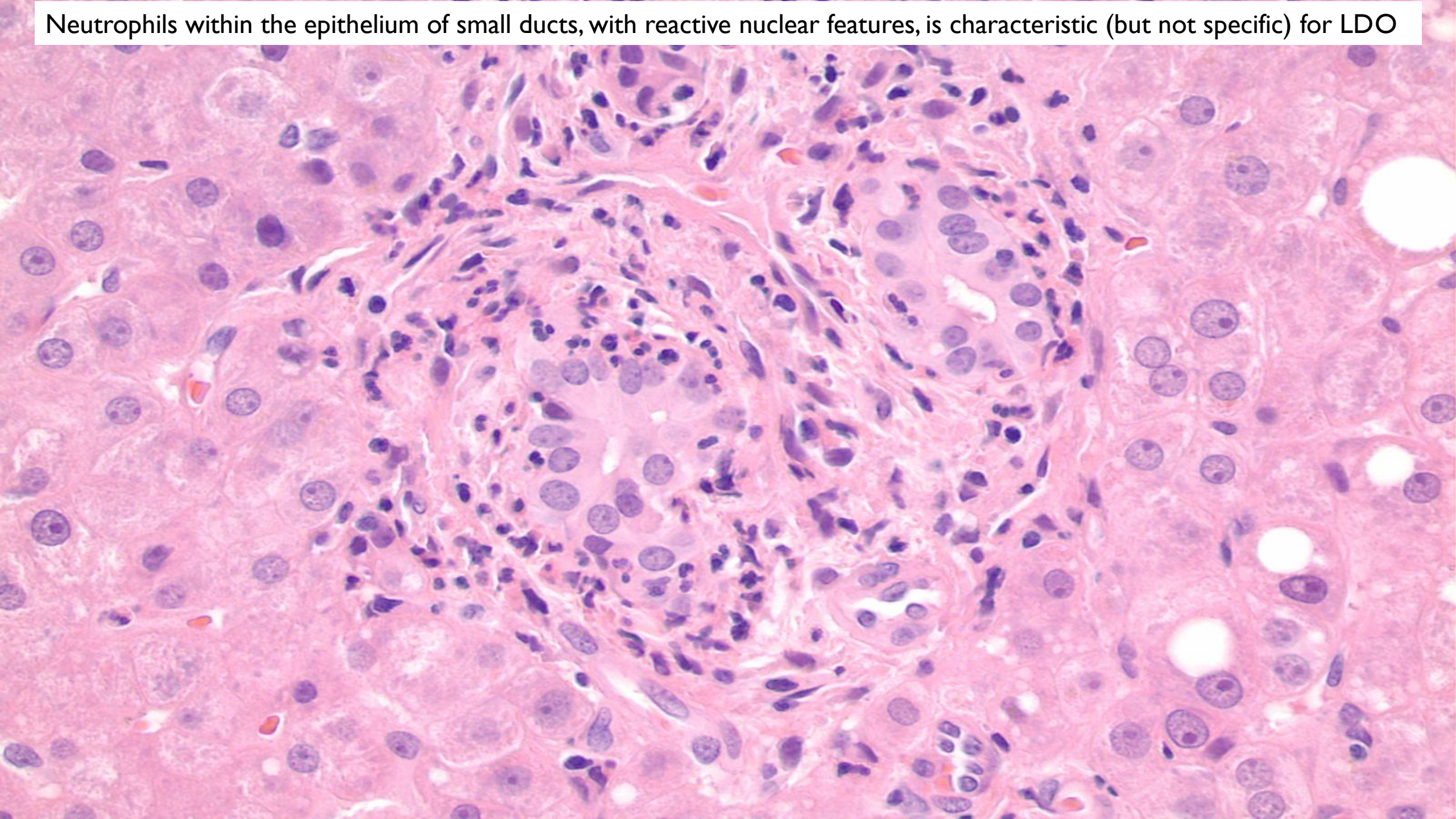
Ultrasound detects dilated ducts in about a quarter of patients.

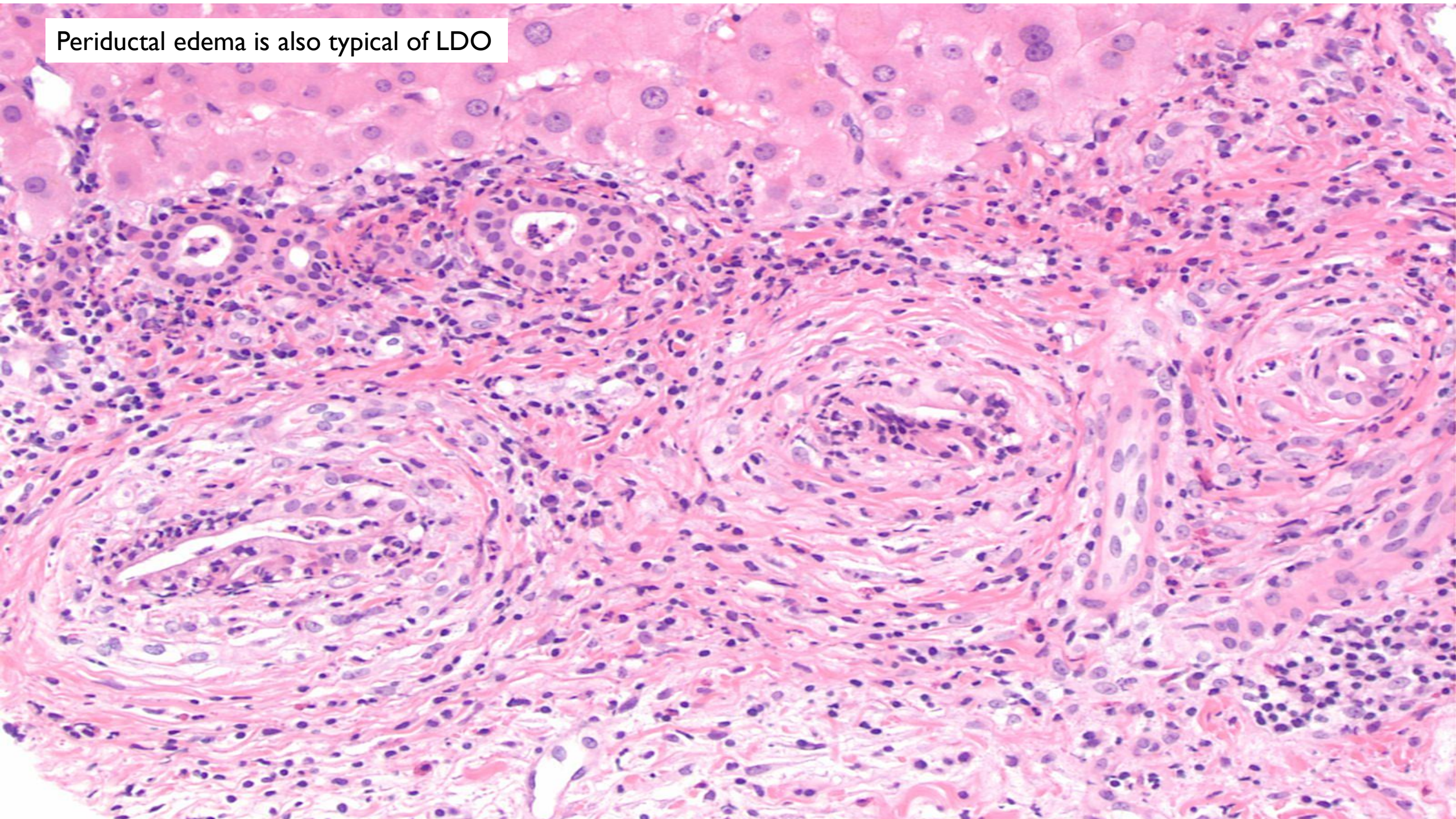
Intermittent obstruction – consider if bile stasis is minimal and portal changes are mild (passing stones, sphincter of Oddi syndrome).

Primary sclerosing cholangitis rarely presents with a tight stricture and histologically looks indistinguishable from large duct obstruction

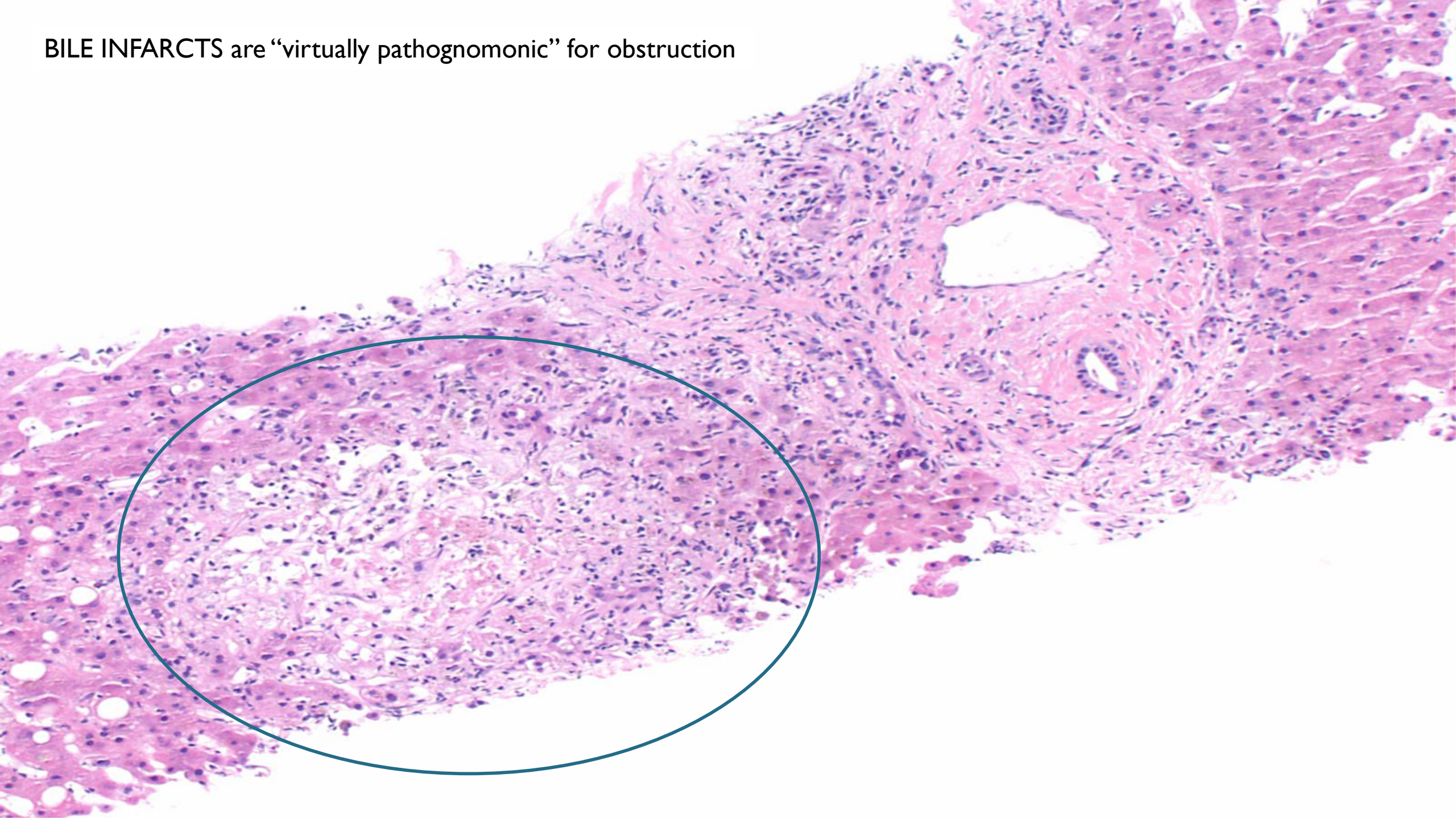
Ischemia can cause duct dysfunction, histologically resembling LDO or PSC

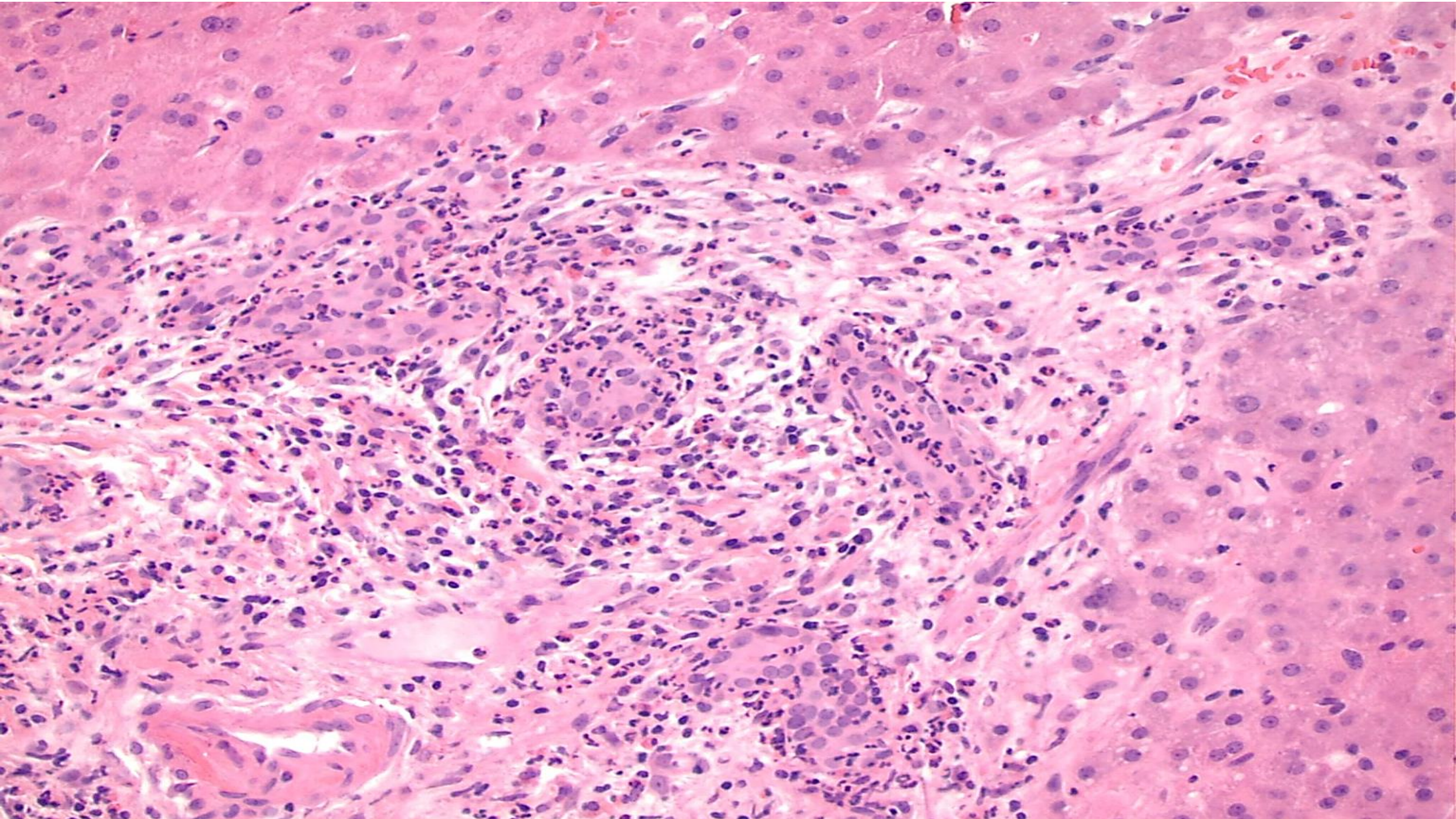
Neutrophils within the epithelium of small ducts, with reactive nuclear features, is characteristic (but not specific) for LDO




Periductal edema is also typical of LDO

BILE INFARCTS are "virtually pathognomonic" for obstruction





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NOT SO USUAL DIFFERENTIAL FOR ACUTE CHOLESTASIS

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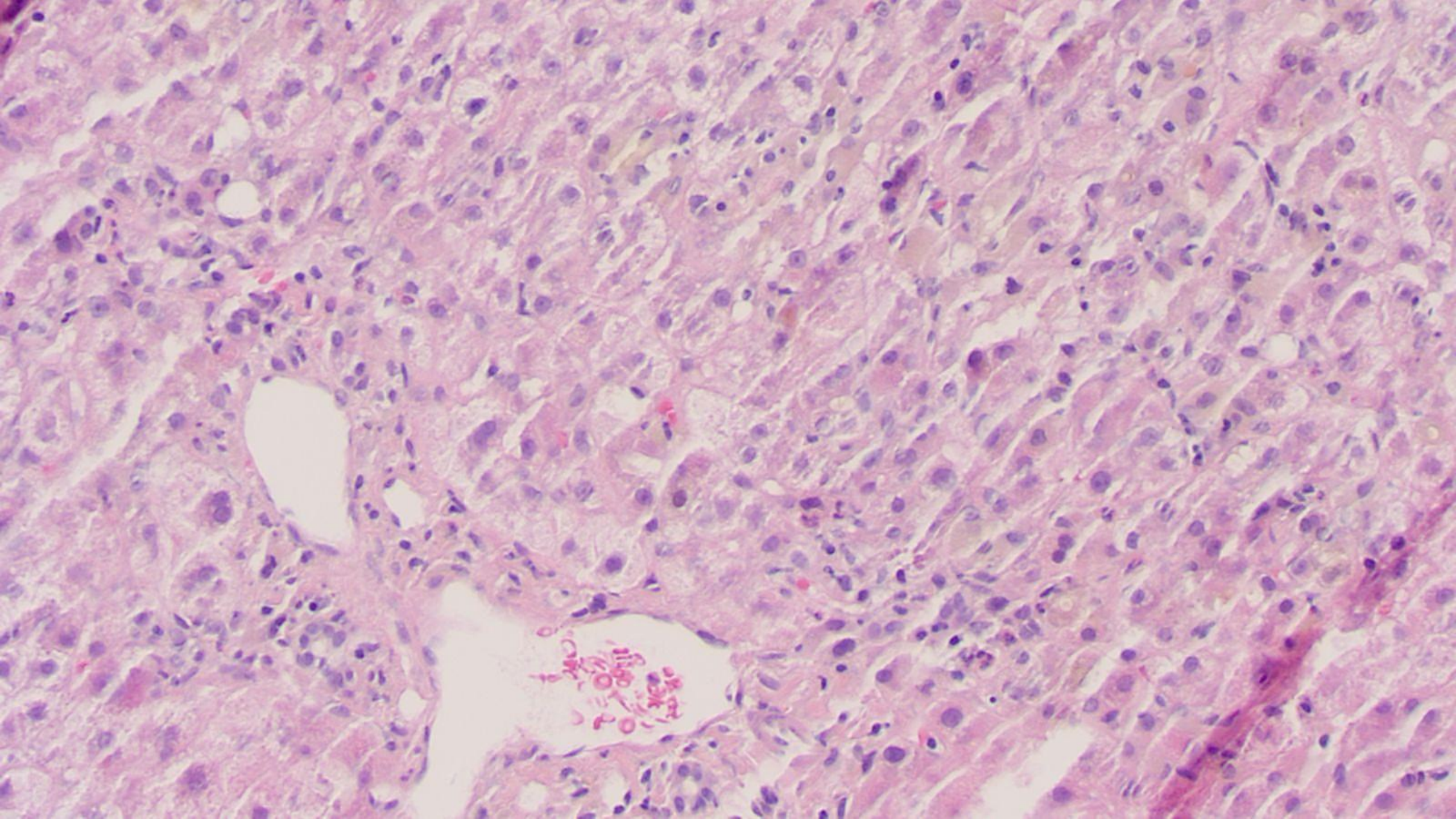
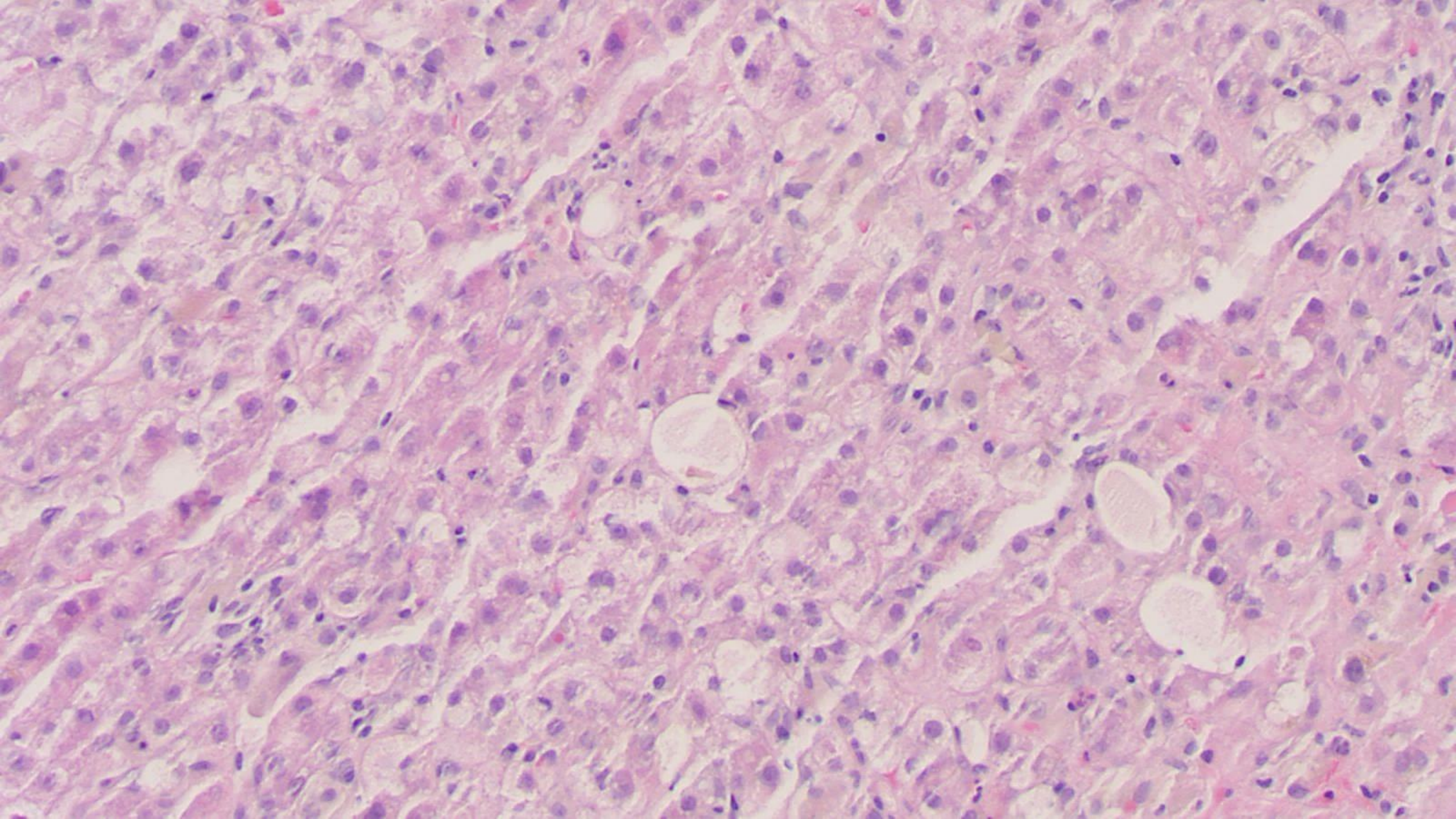
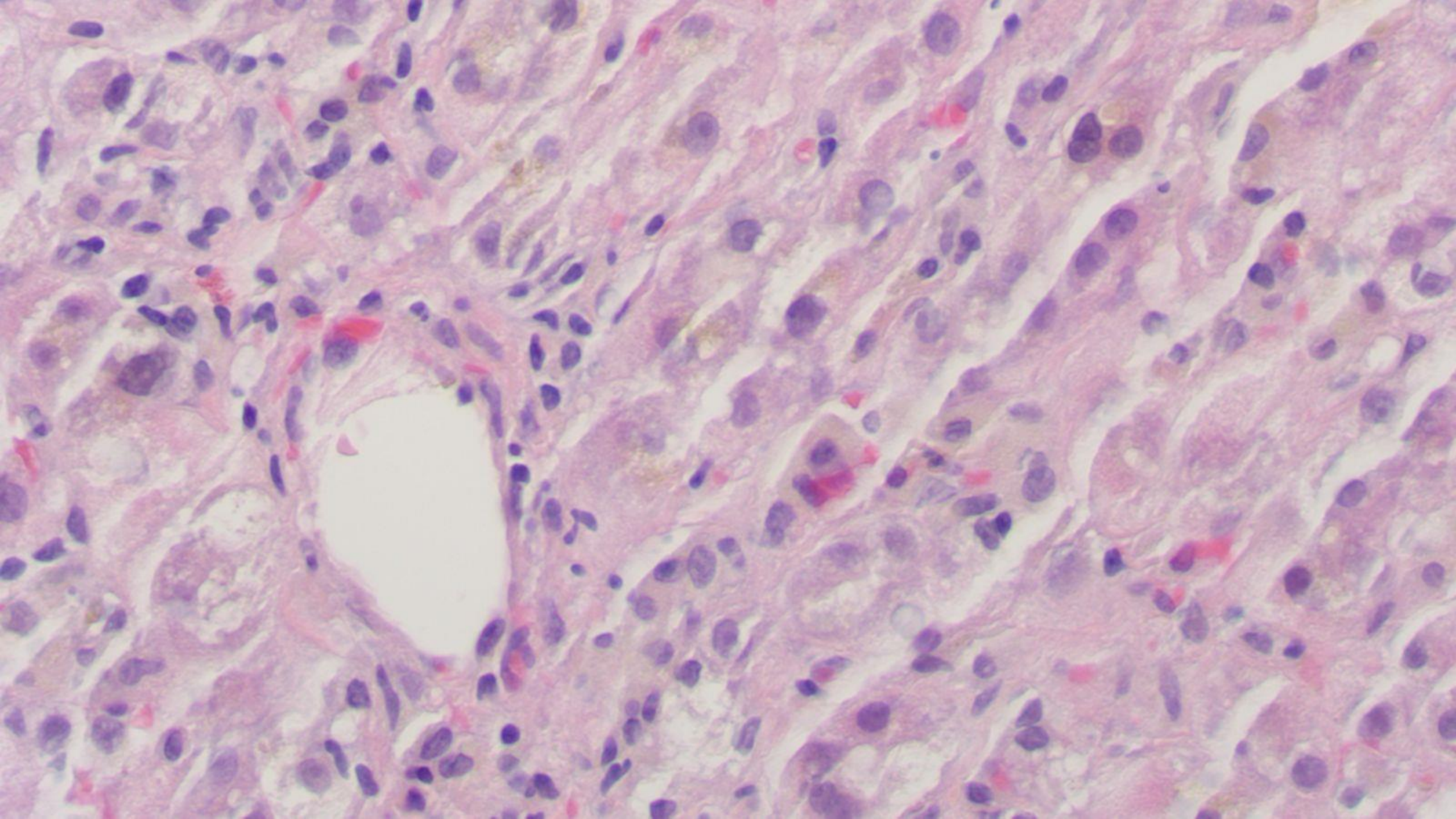
CASE

Nepalese man who develops cholestatic hepatitis







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CASE

54 year old gay man on PrEP (Pre-exposure prophylaxis to prevent HIV transmission).

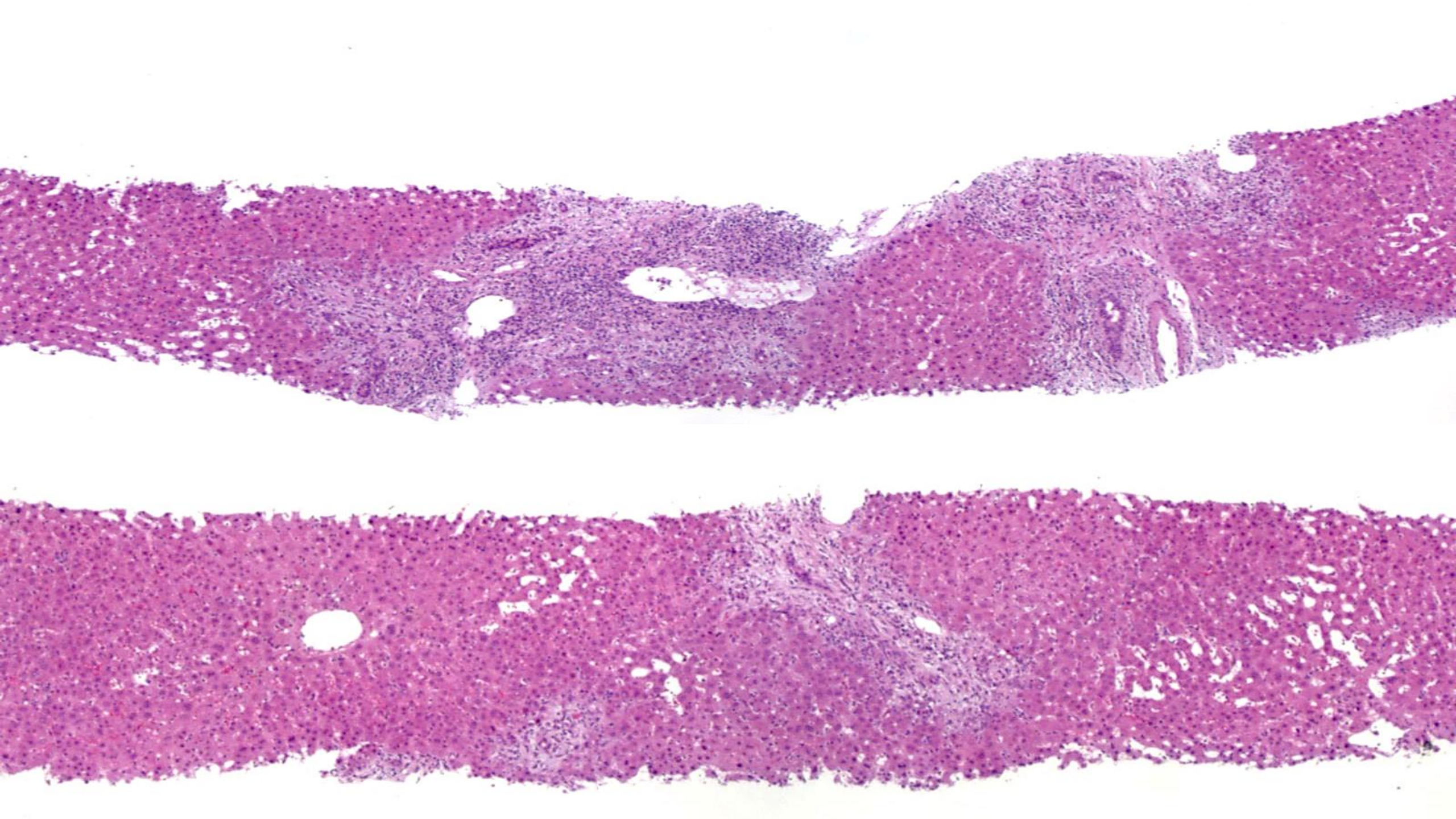
He recently had Entomoeba diarrhea and was on metronidazole.

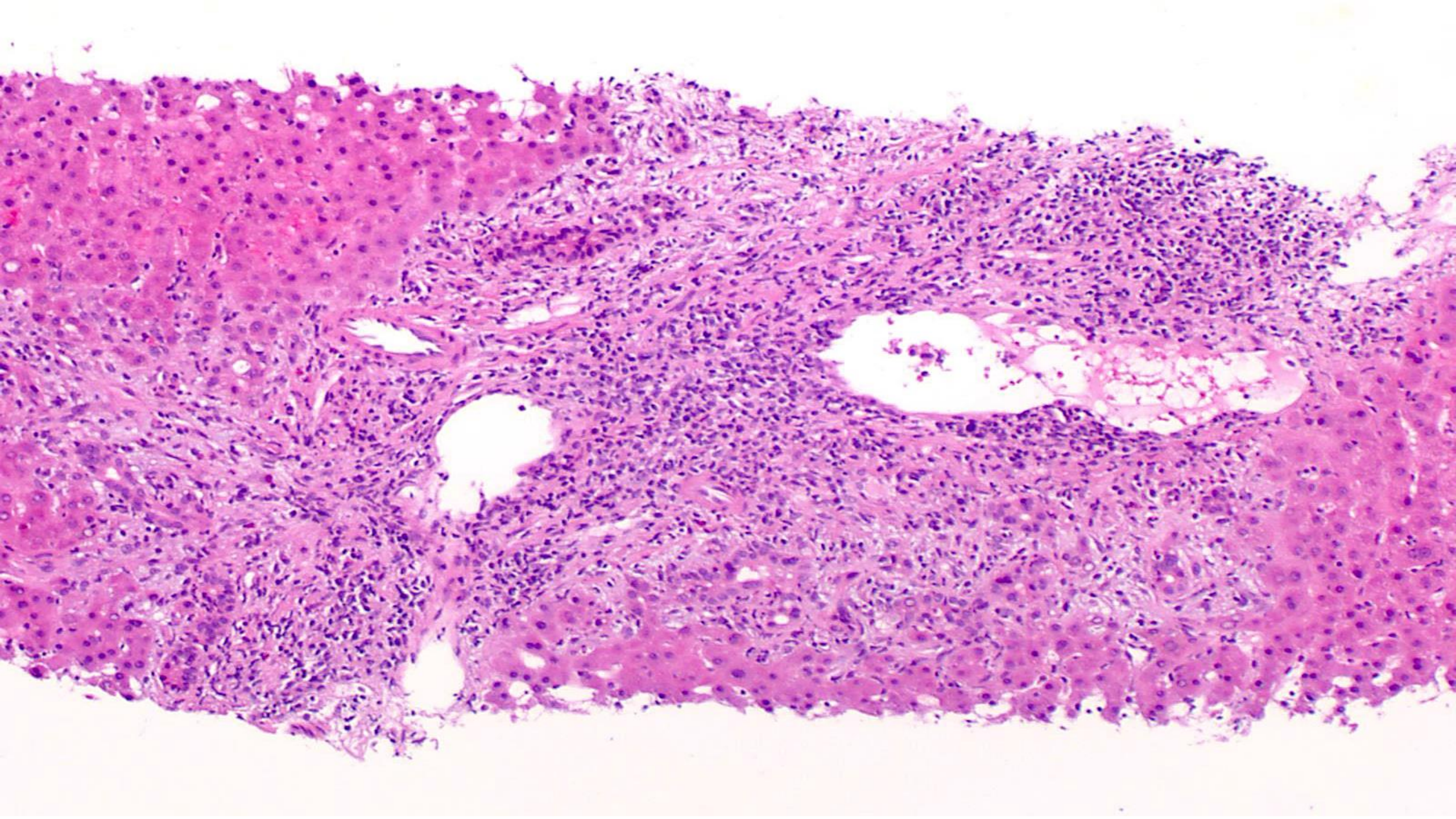
3 days after starting metronidazole, develops rash.

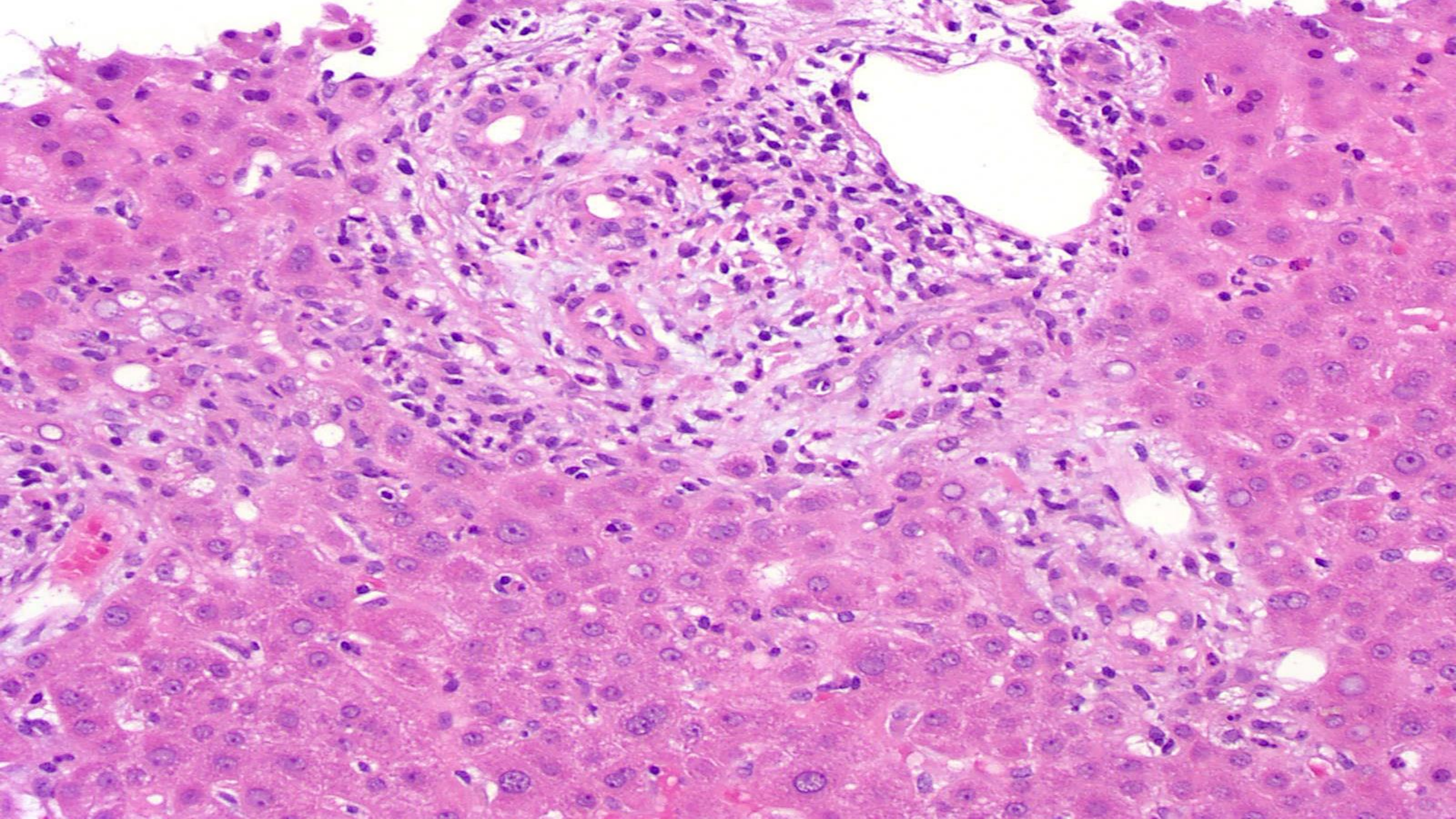
Mild pleuritic chest pain, headache, sore lymph nodes, and sore throat.

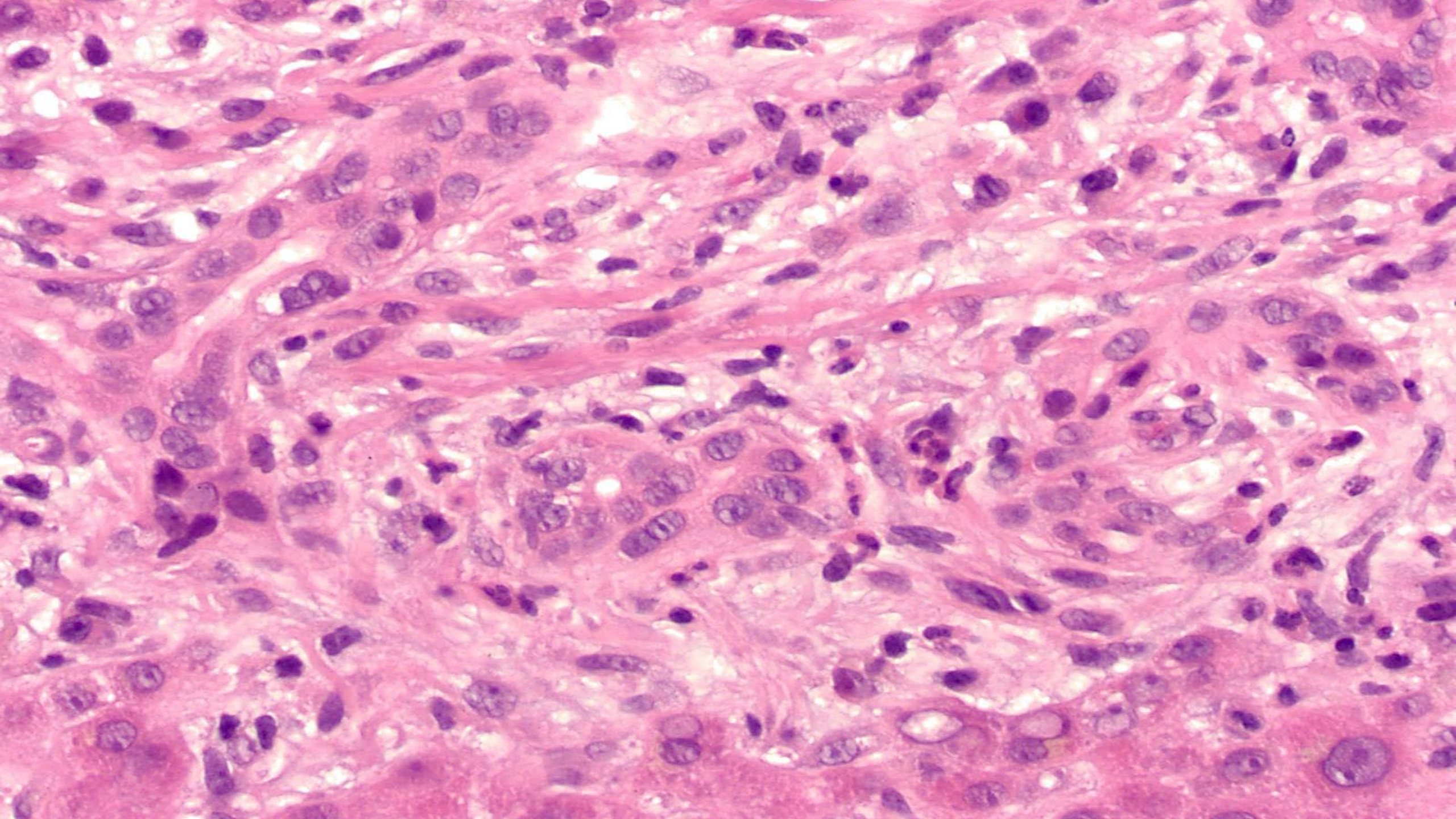
Lab value peaks: AST 274, ALT 202, AP 526, TB 6.9

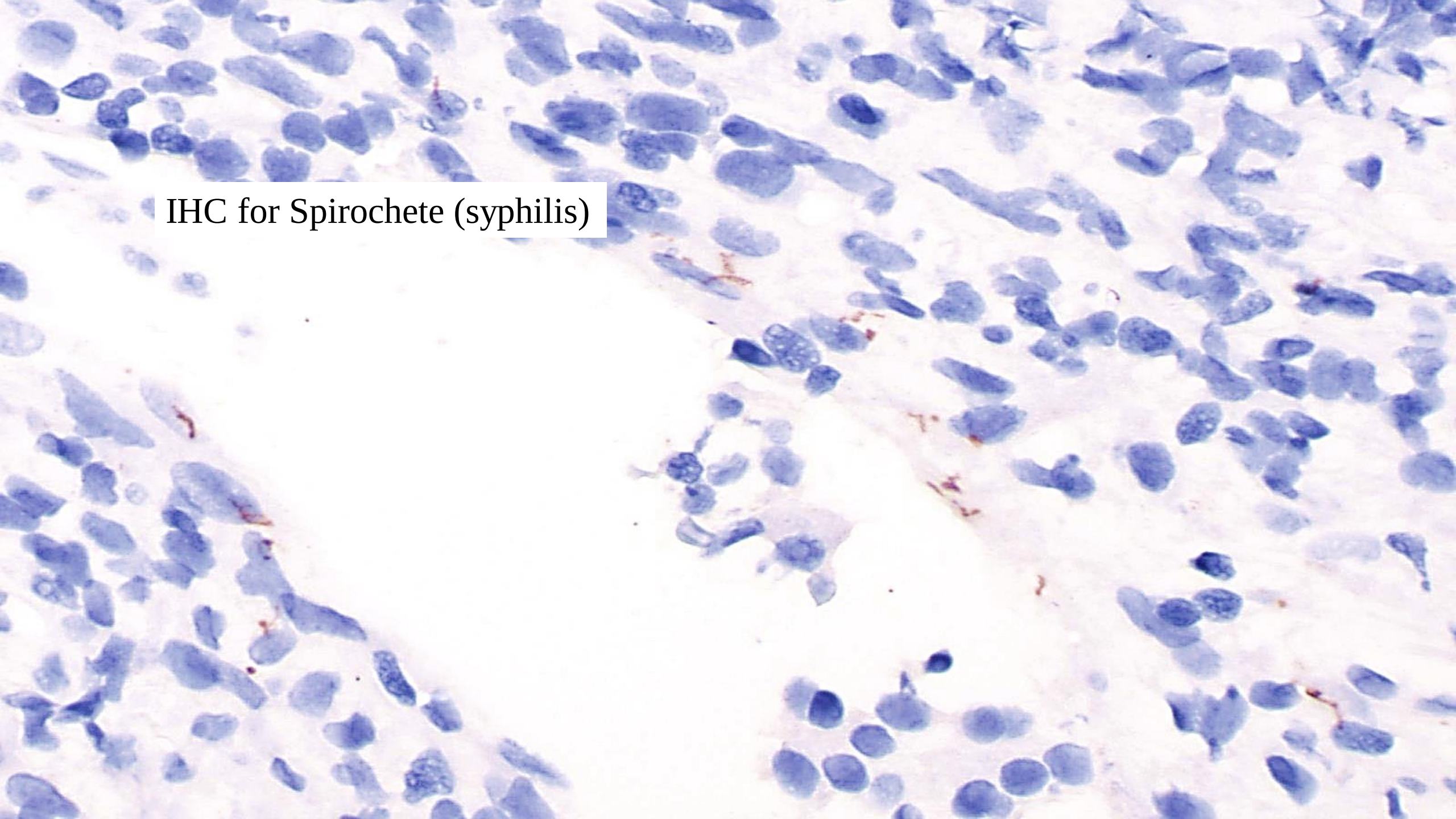
Rush biopsy is ordered, rule out drug, autoimmune, infection.










IHC for Spirochete (syphilis)

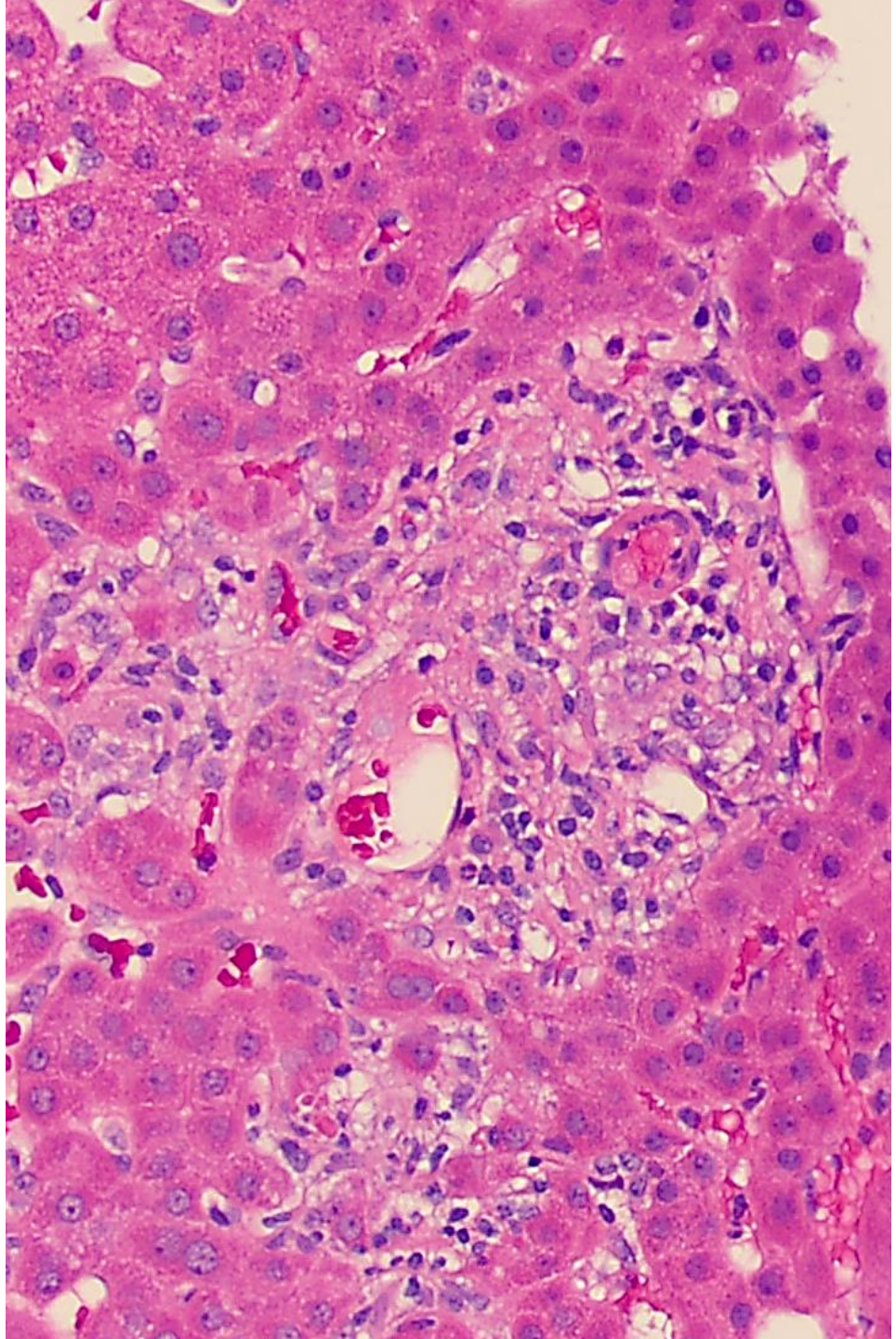
DUCTOPENIA

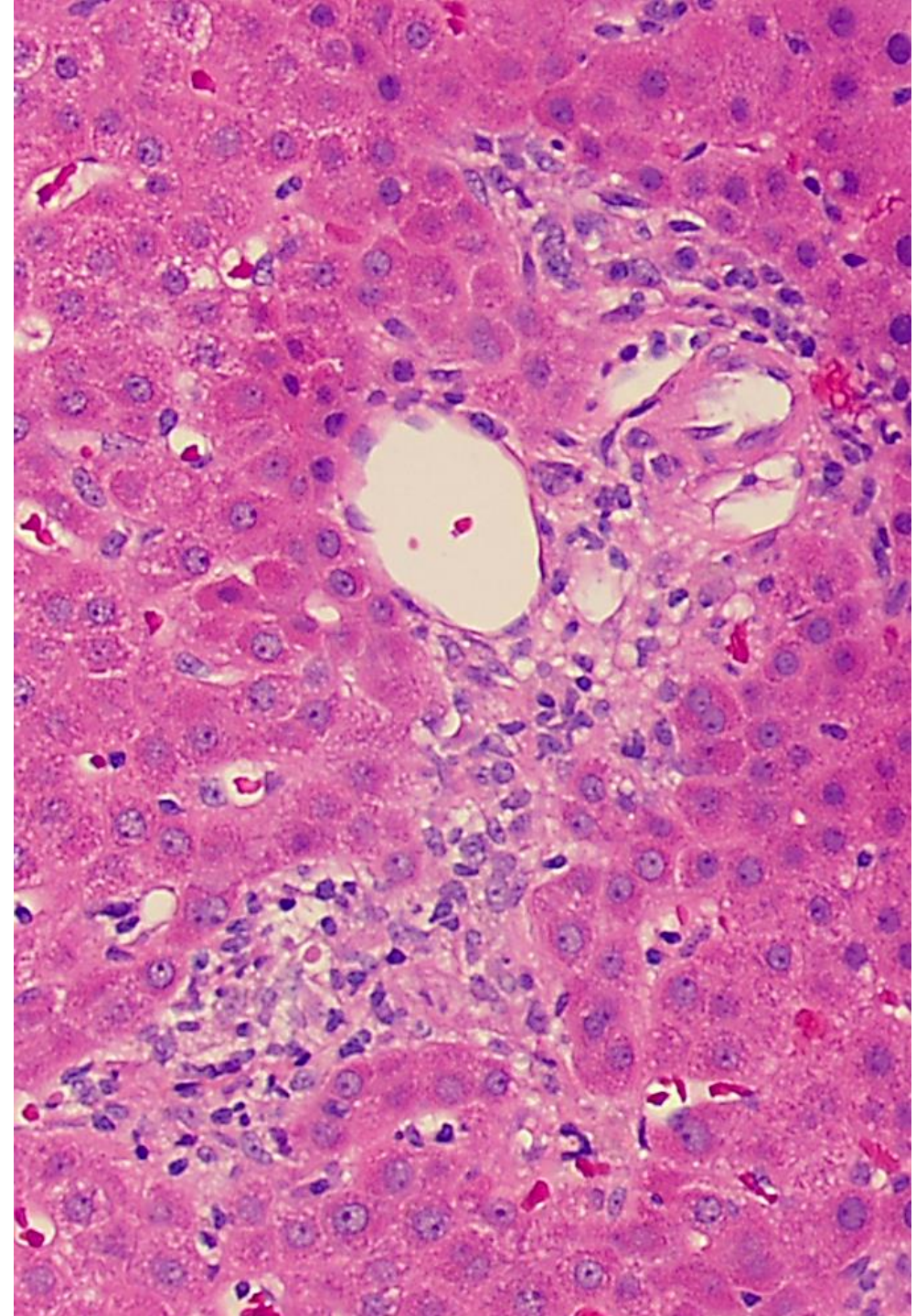
Absence of interlobular bile ducts in 50% of portal tracts (10 or more portal tracts considered adequate)

May or may not be associated with ductular reaction, depending on etiology and patient.

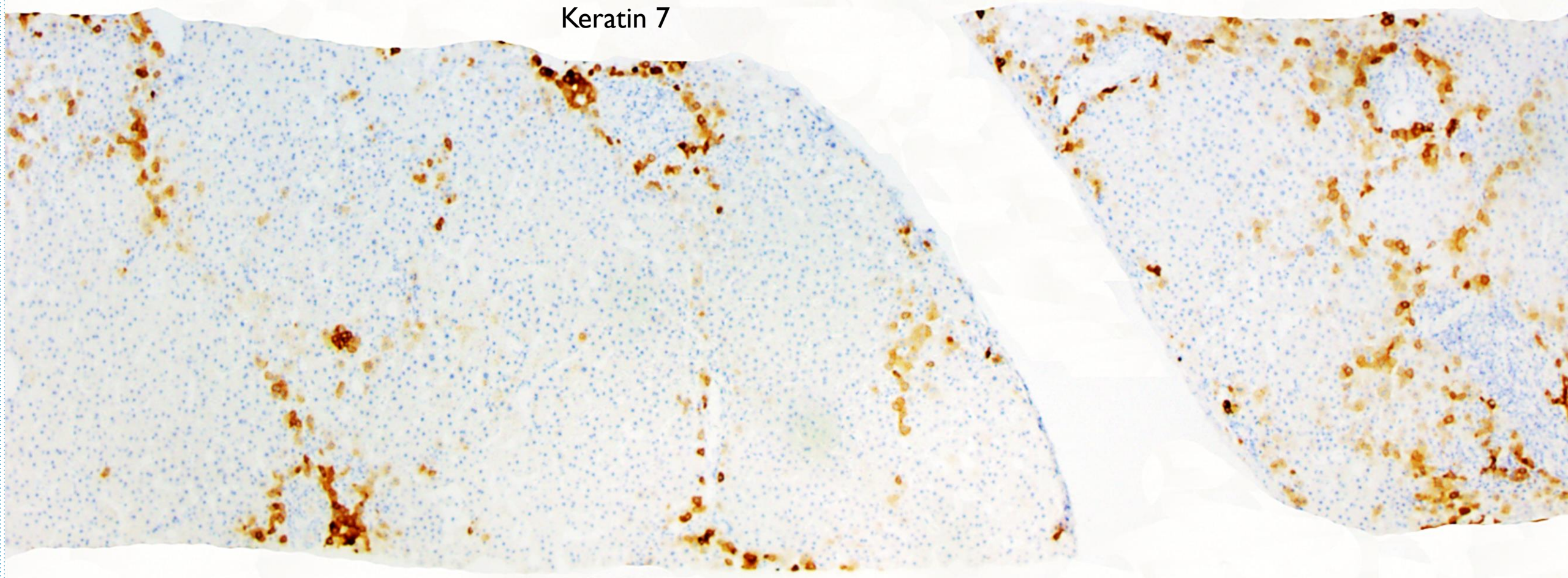
Evaluate with keratin 7 (or keratin 19)

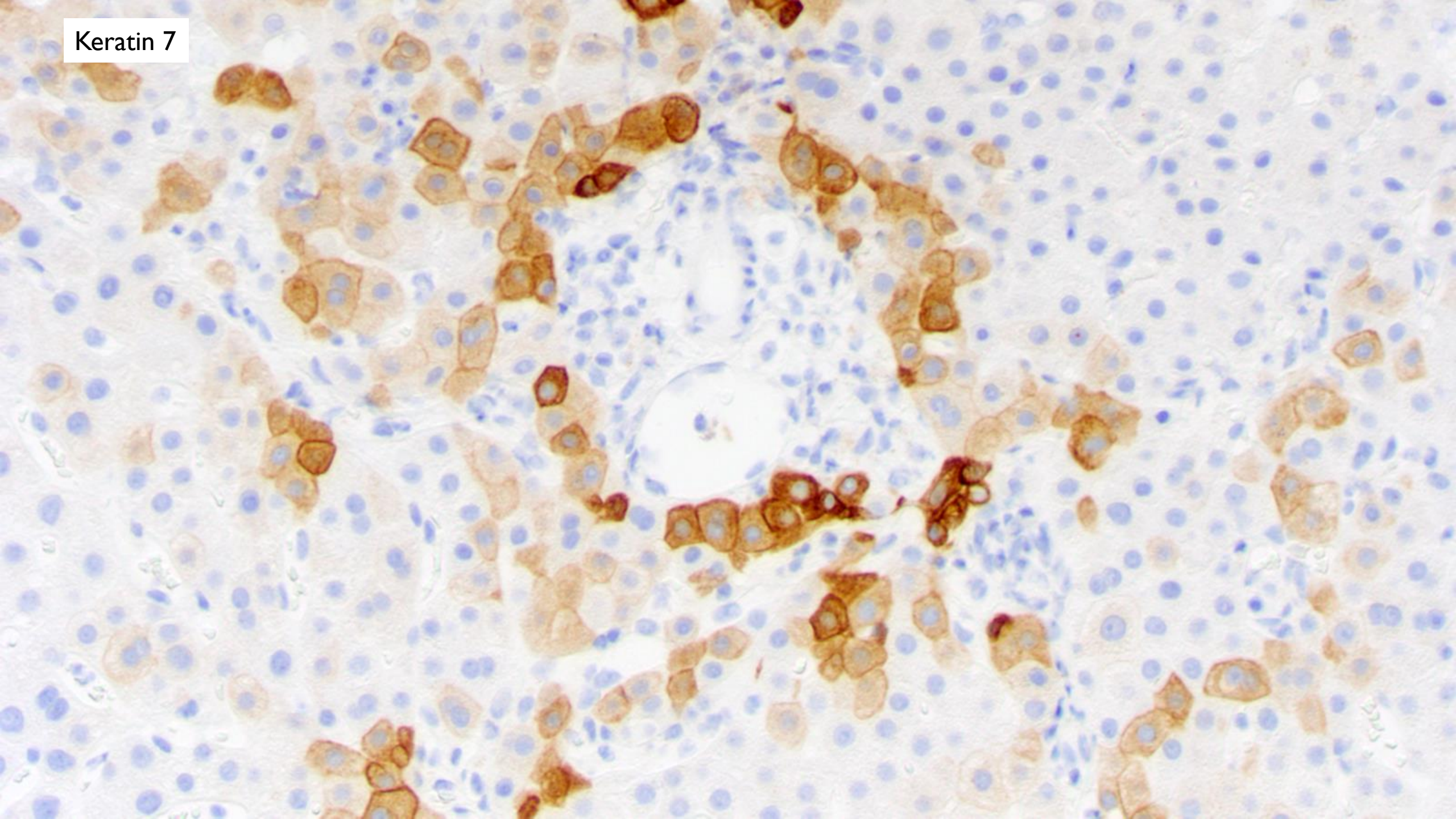
- In chronic cholestasis, periportal hepatocytes express keratin 7 (biliary metaplasia) and this is somewhat informative in itself, and helps identify portal tracts.





Keratin 7

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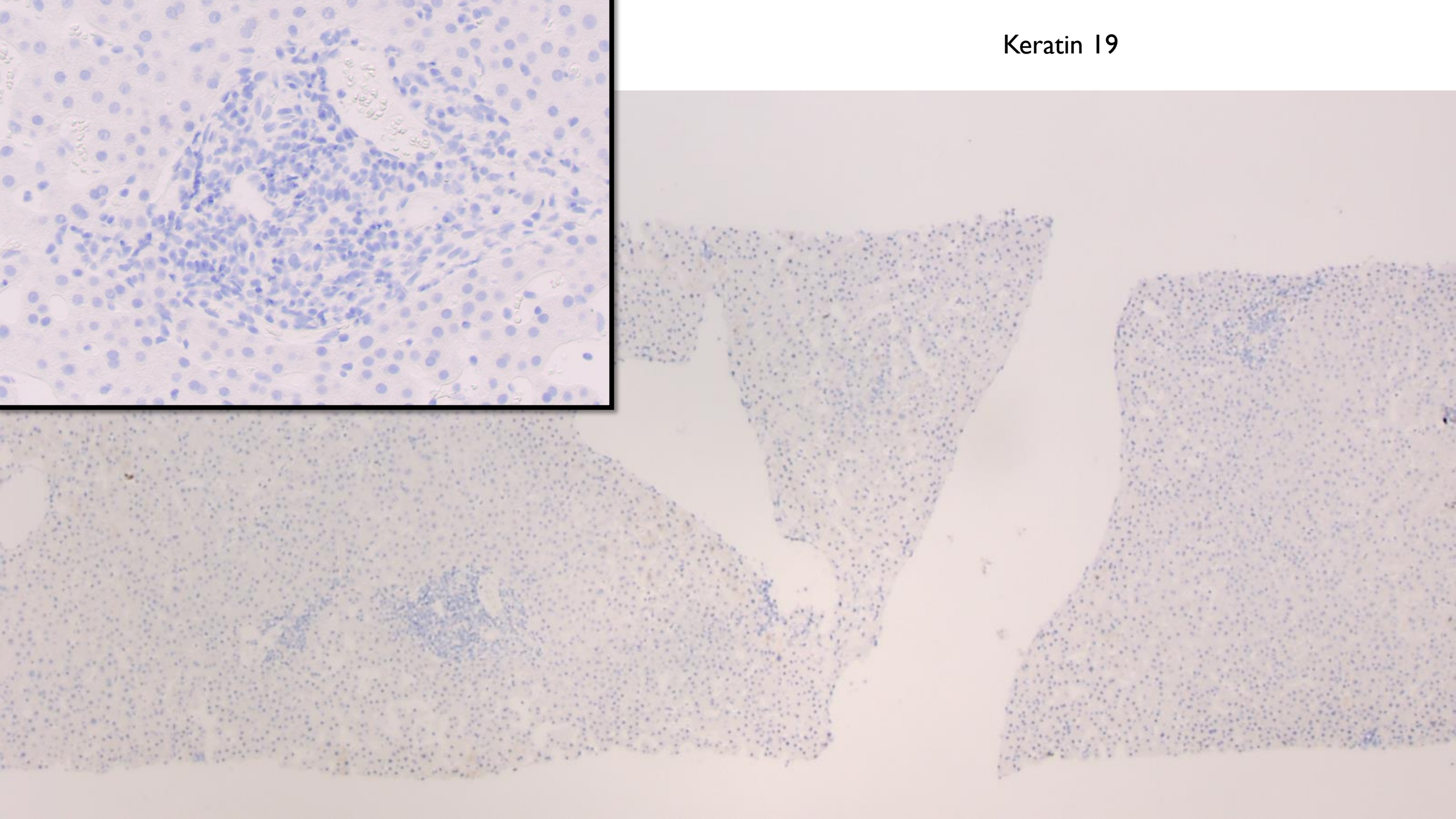
Keratin 19



DUCTOPENIA

PBC or PSC

Sarcoidosis

Ischemic cholangiopathy

Drugs (vanishing bile duct syndrome)

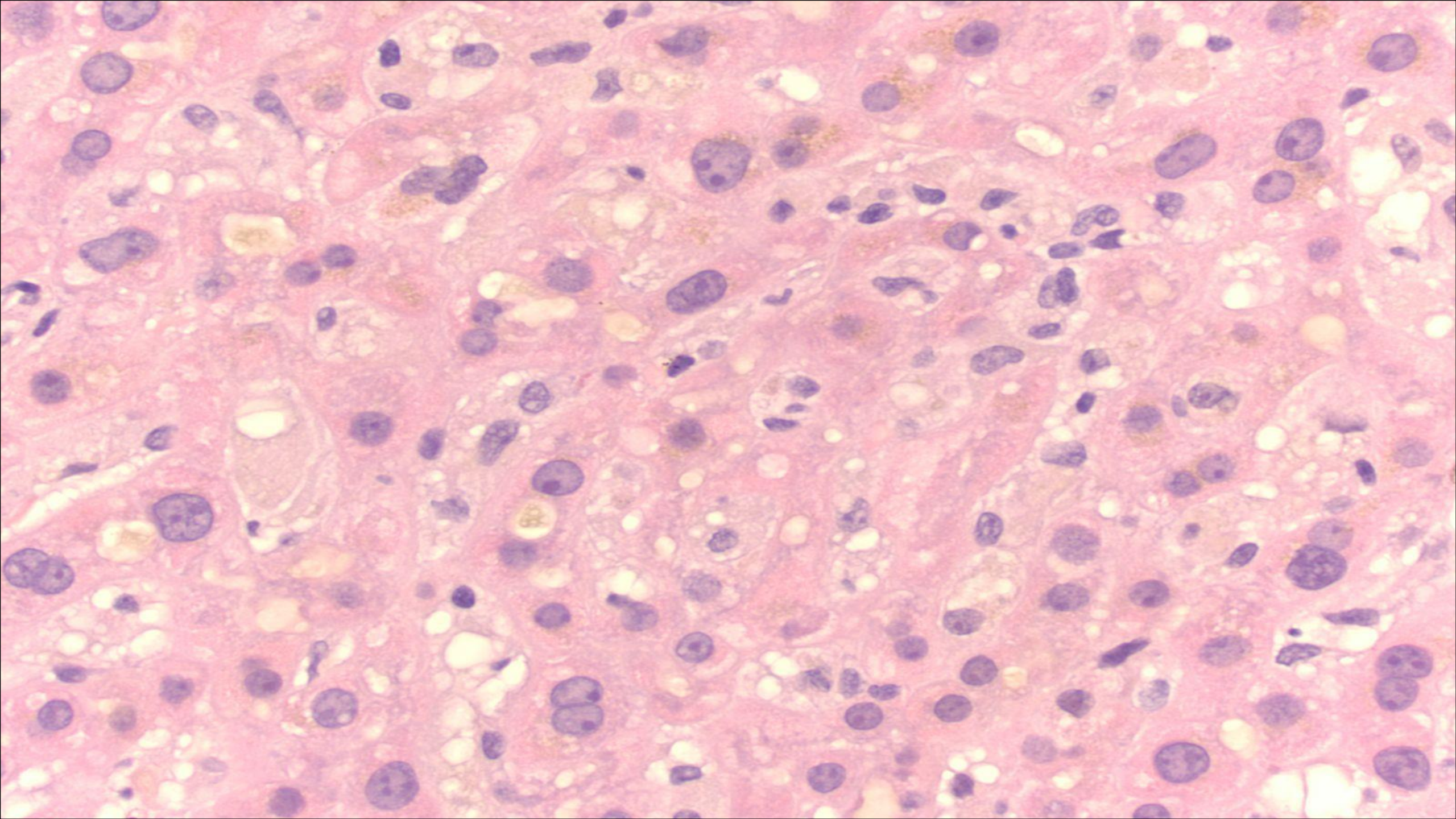
Hodgkin's disease

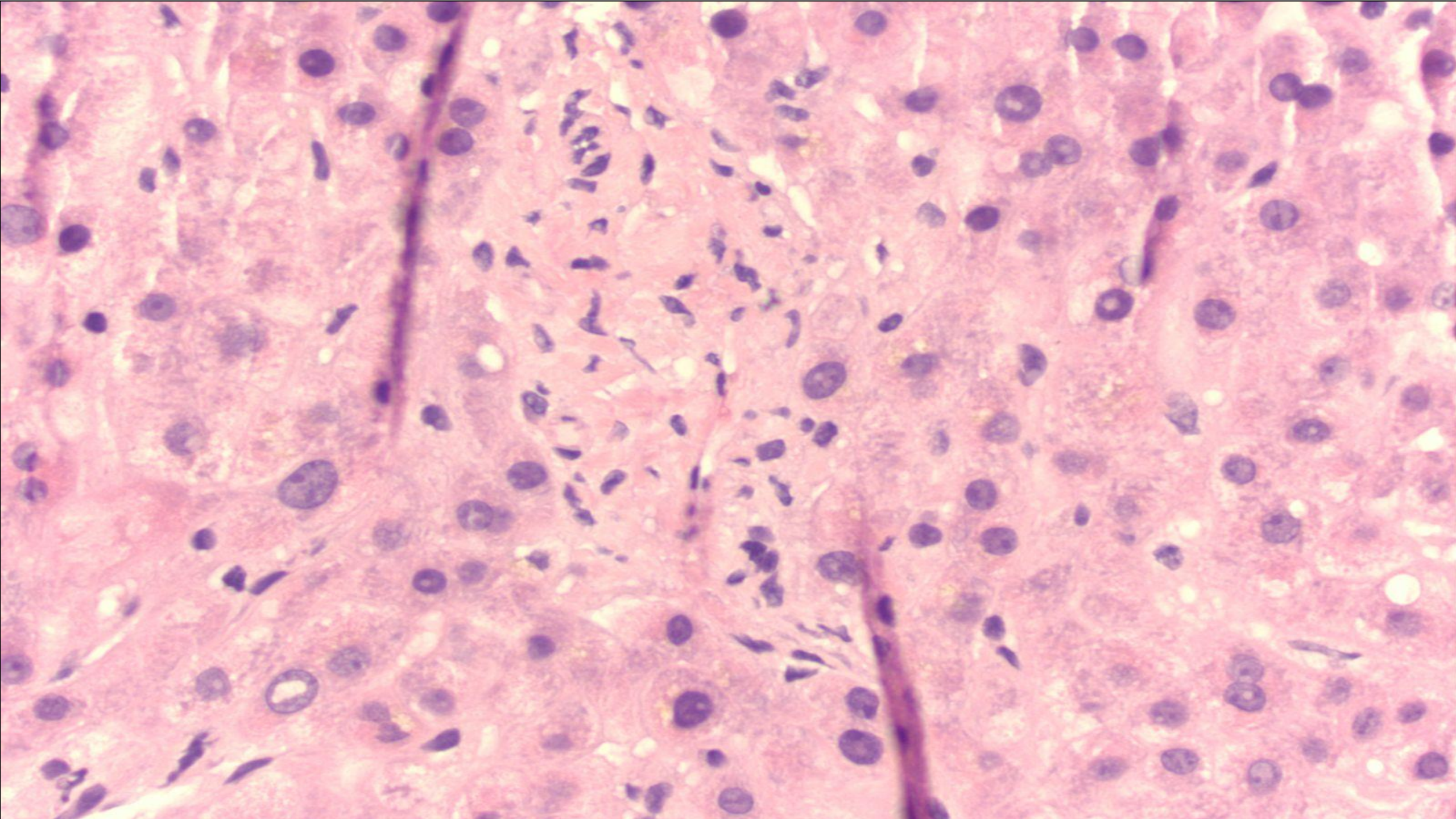
Allograft chronic rejection and GVHD

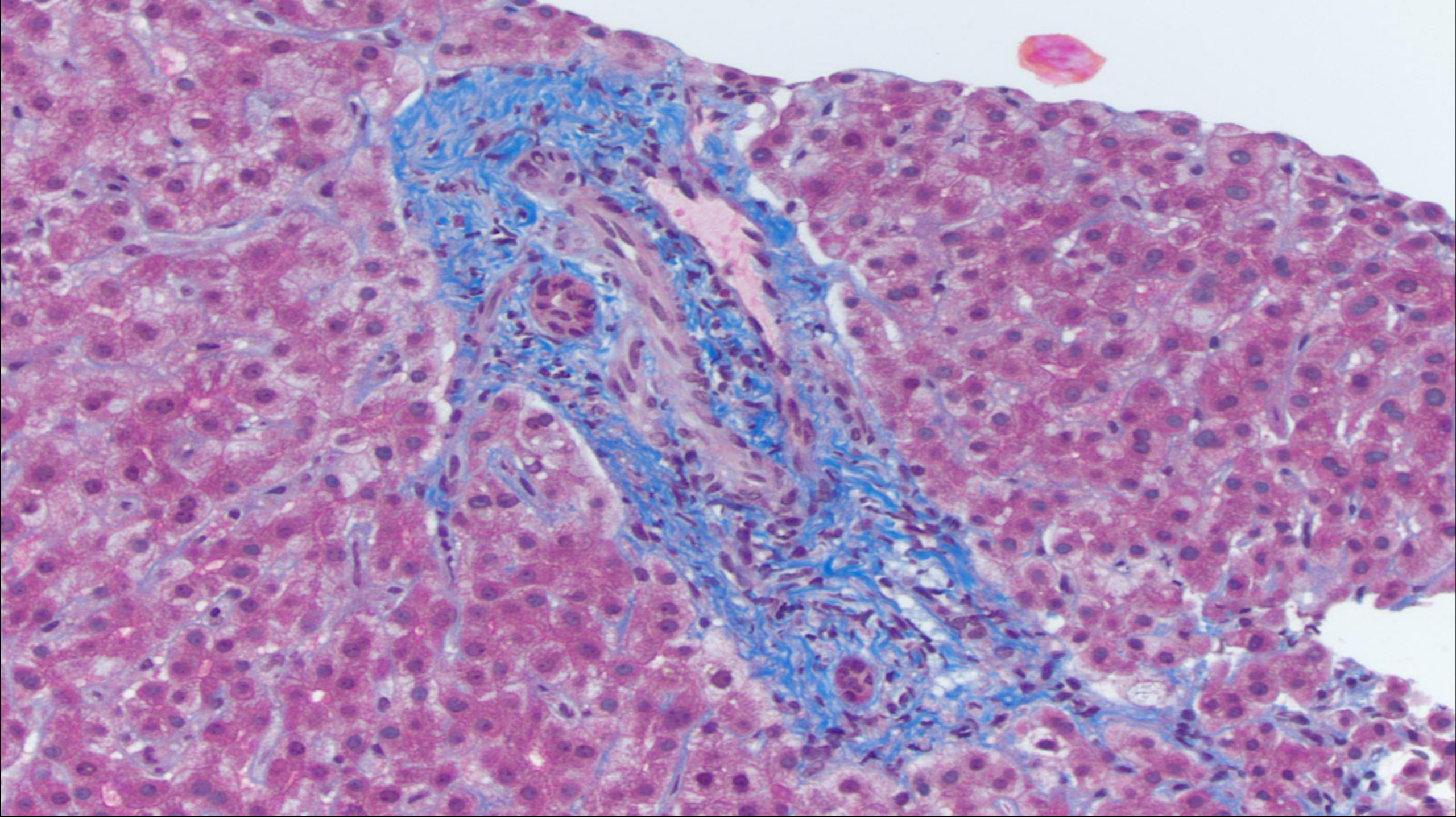
Idiopathic

CASE

Middle aged woman with recent onset of cholestatic pattern of LFT abnormality







CASE FOLLOW UP

Diagnosed as cholestasis with ductopenia.

- Challenging to reconcile acute cholestasis with duct loss.
- A broad differential and discussion, including PBC/PSC, drugs, idiopathic…but forgot one possibility.

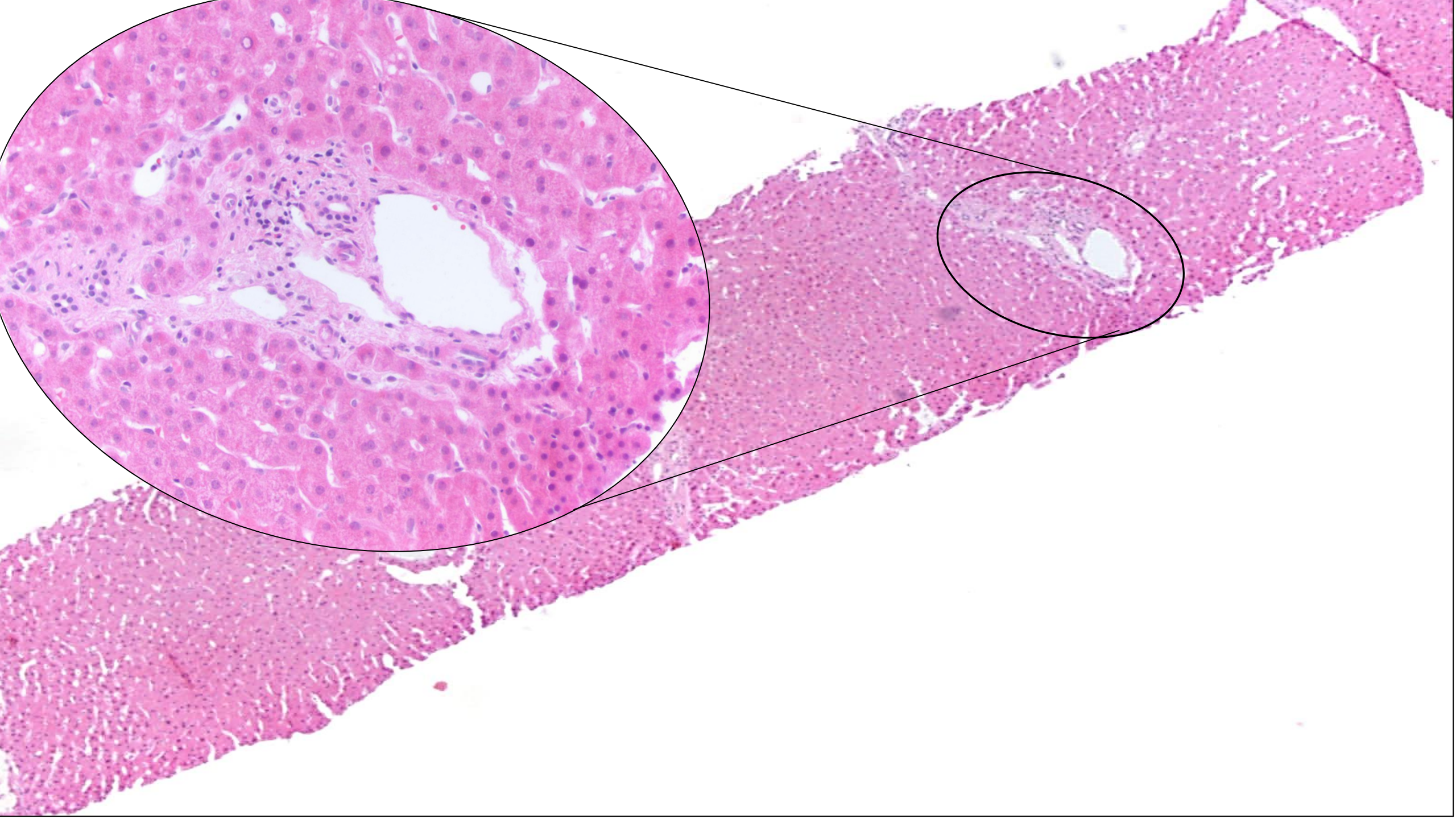
Ultimately diagnosed with mediastinal Hodgkin's lymphoma.

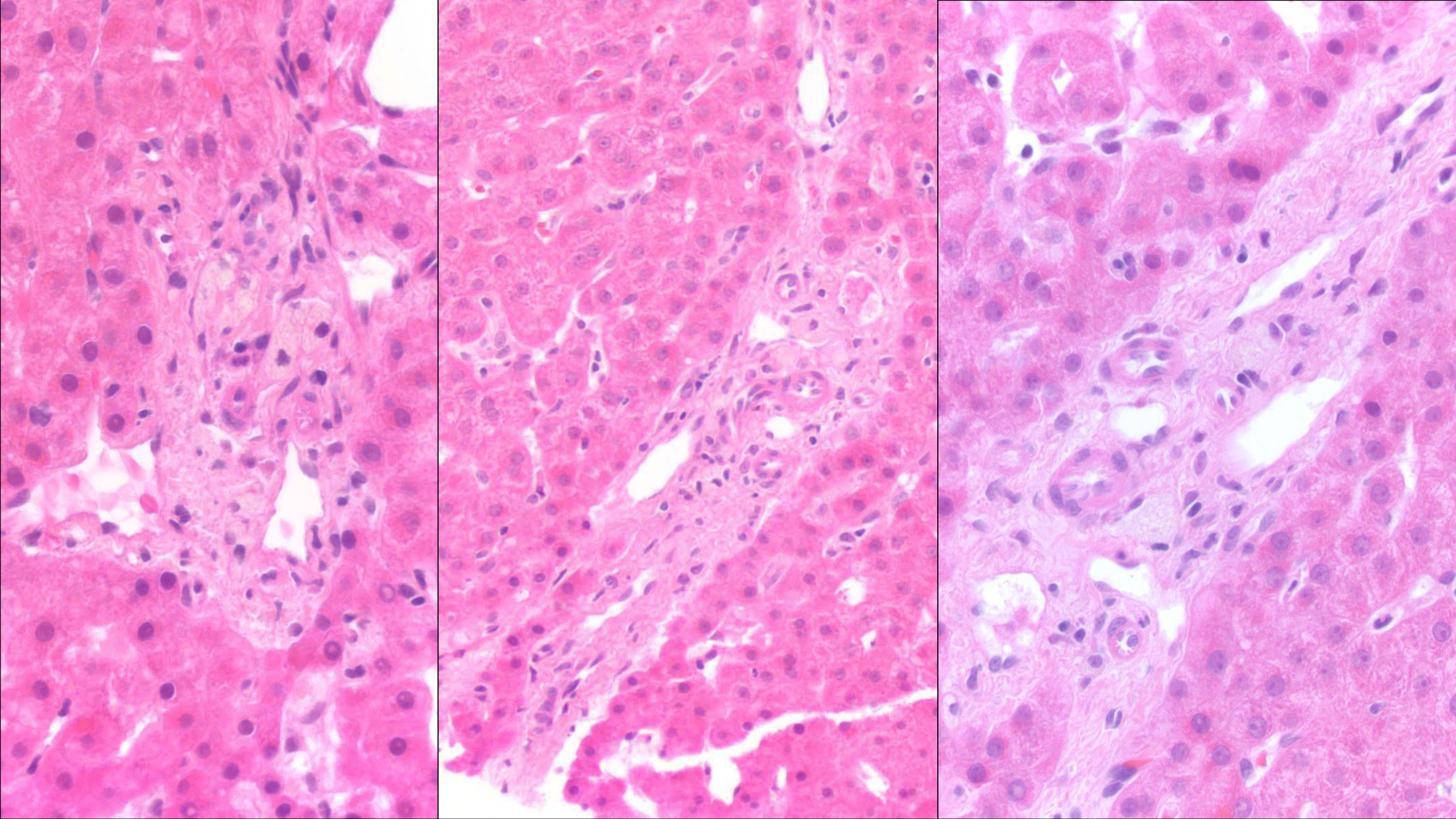
The clinicians were not impressed…

CASE

28 year old woman with "elevated LFTs". The biopsy was interpreted as unremarkable at a local hospital.

Backstory: She was well until she became pregnant, when she developed cholestasis of pregnancy. Afterwards, her alkaline phosphatase remained in the 400 range. She was pruritic. A workup was negative.





IDIOPATHIC ADULTHOOD DUCTOPENIA

Proteins on the canalicular membrane transport bile components (e.g. Bile salt export protein [BSEP], Multidrug resistance protein 3 [MDR3]).

Homozygous mutations cause progressive familial intrahepatic cholestasis (PFIC 2 and PFIC 3), neonatal cholestatic disorders.

Heterozygosity reported in cholestasis of pregnancy, ductopenia, cholestatic drug reactions, cryptogenic cirrhosis, with familial clustering.

Look for ducts – in every portal tract – in patients with chronic alk phos elevations but a relatively “normal” biopsy!

CHOLESTASIS IN THE SETTING OF CHRONIC LIVER BIOPSY

In frankly cirrhotic liver:

- May indicate decompensation secondary to infection (spontaneous bacterial peritonitis), variceal bleed, or liver failure.
- Frequently seen with steatohepatitis in alcoholic cirrhosis.

Acute cholestasis with background of chronic cholestasis:

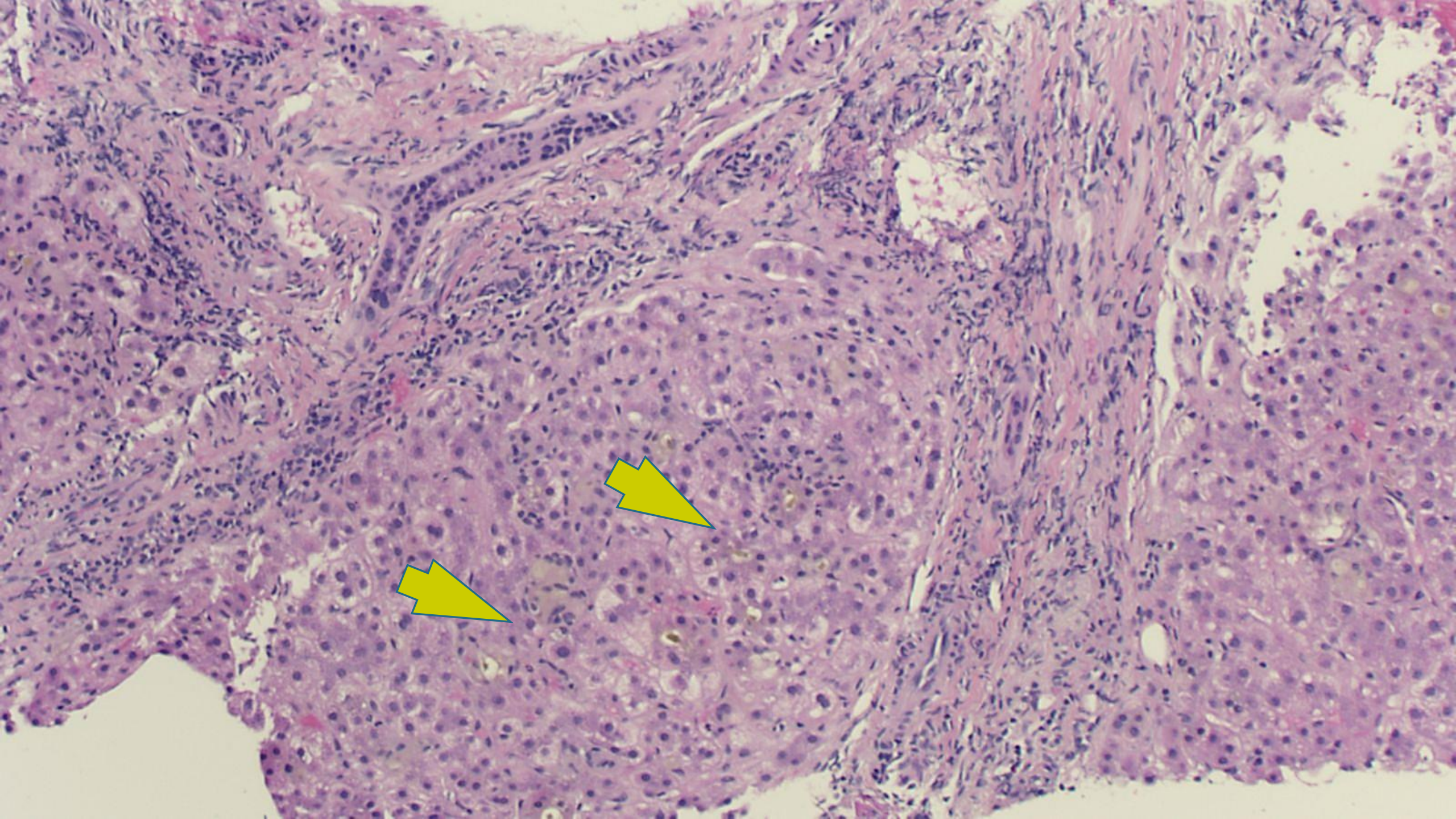
- Primary sclerosing cholangitis with a tight stricture.
- Patients with chronic biliary disease who discontinue medications abruptly.

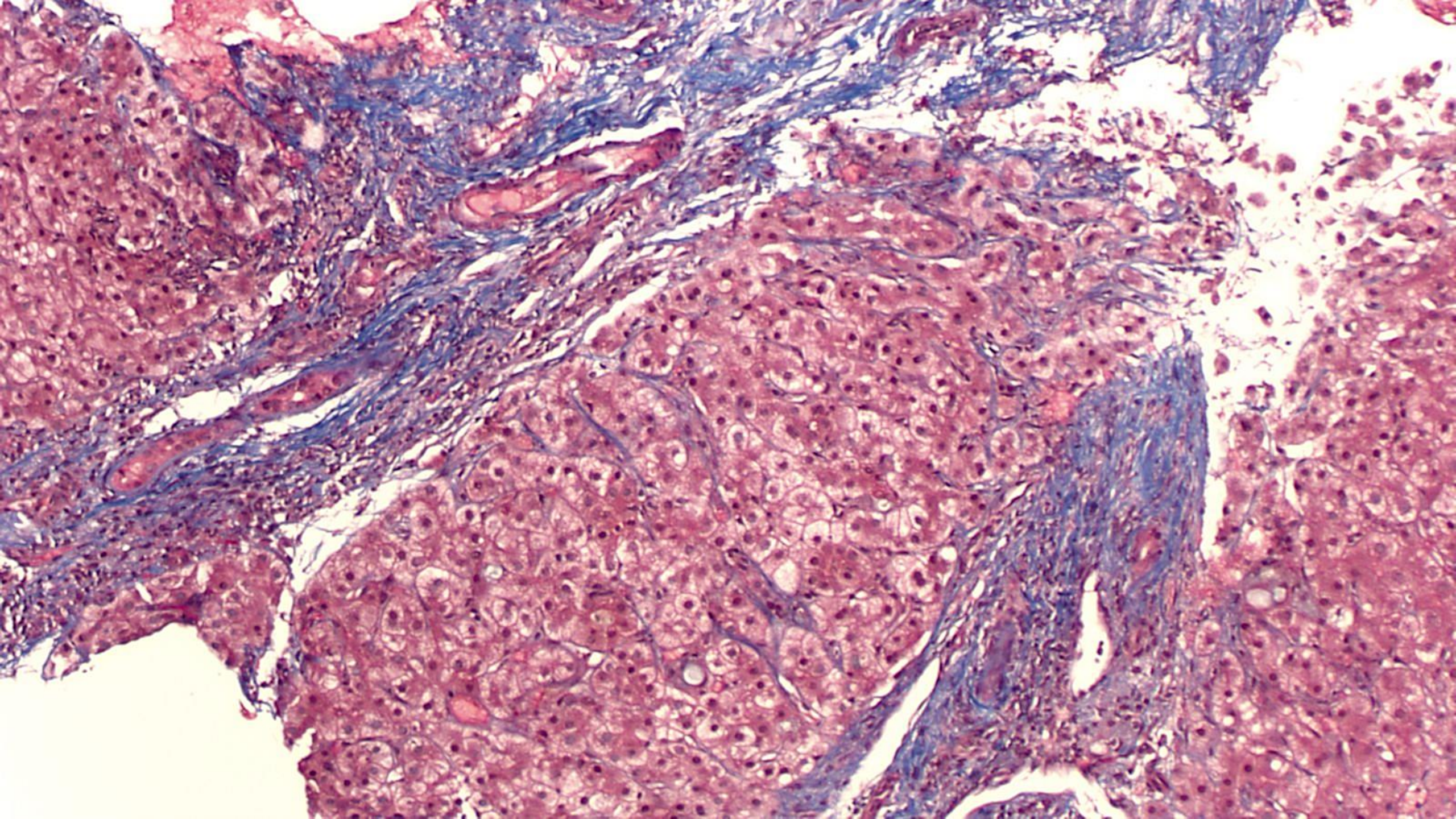
CASE

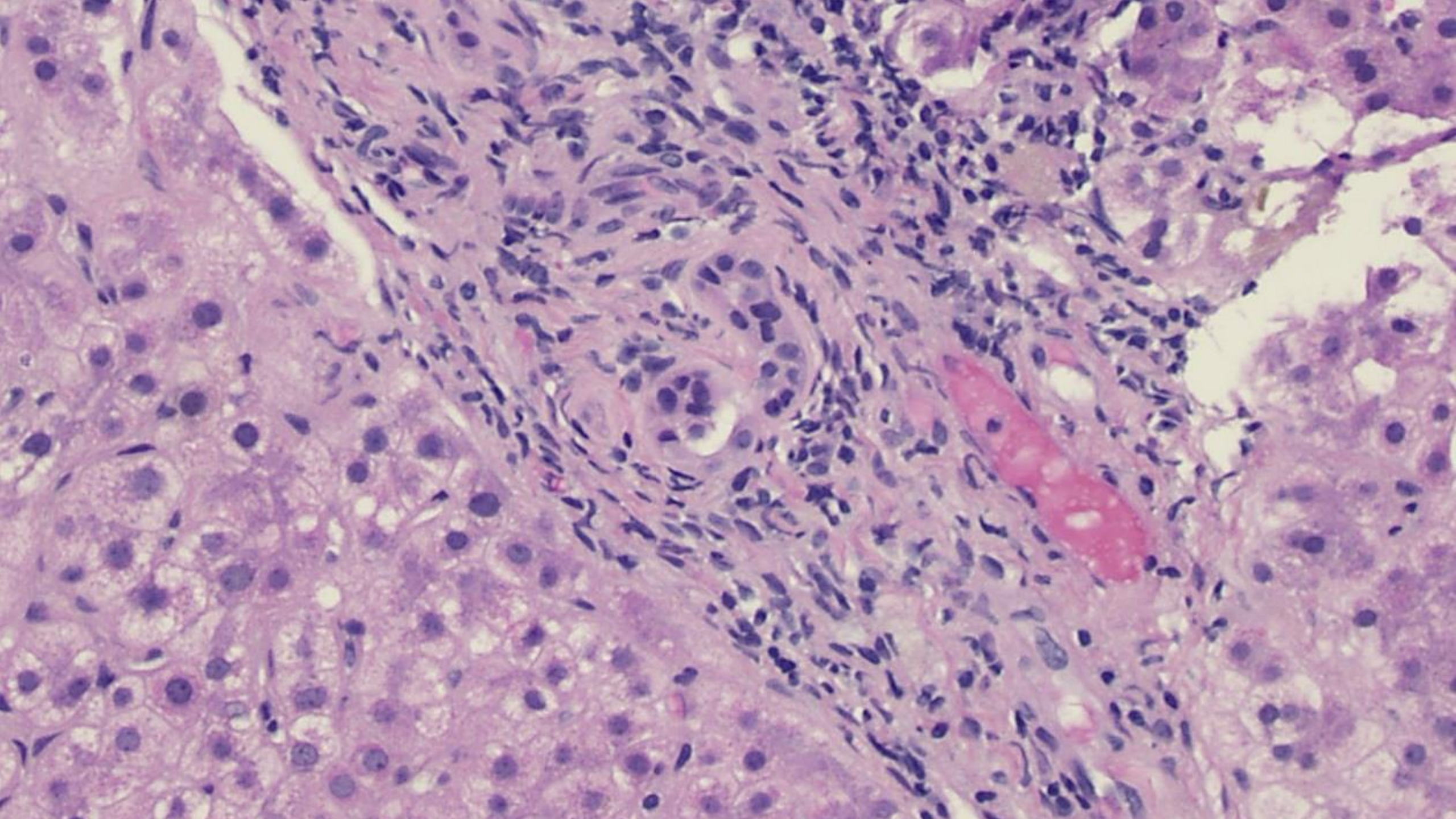
45 year old woman presented in 2017 with pruritus. LFTs were found to be elevated with a cholestatic pattern.

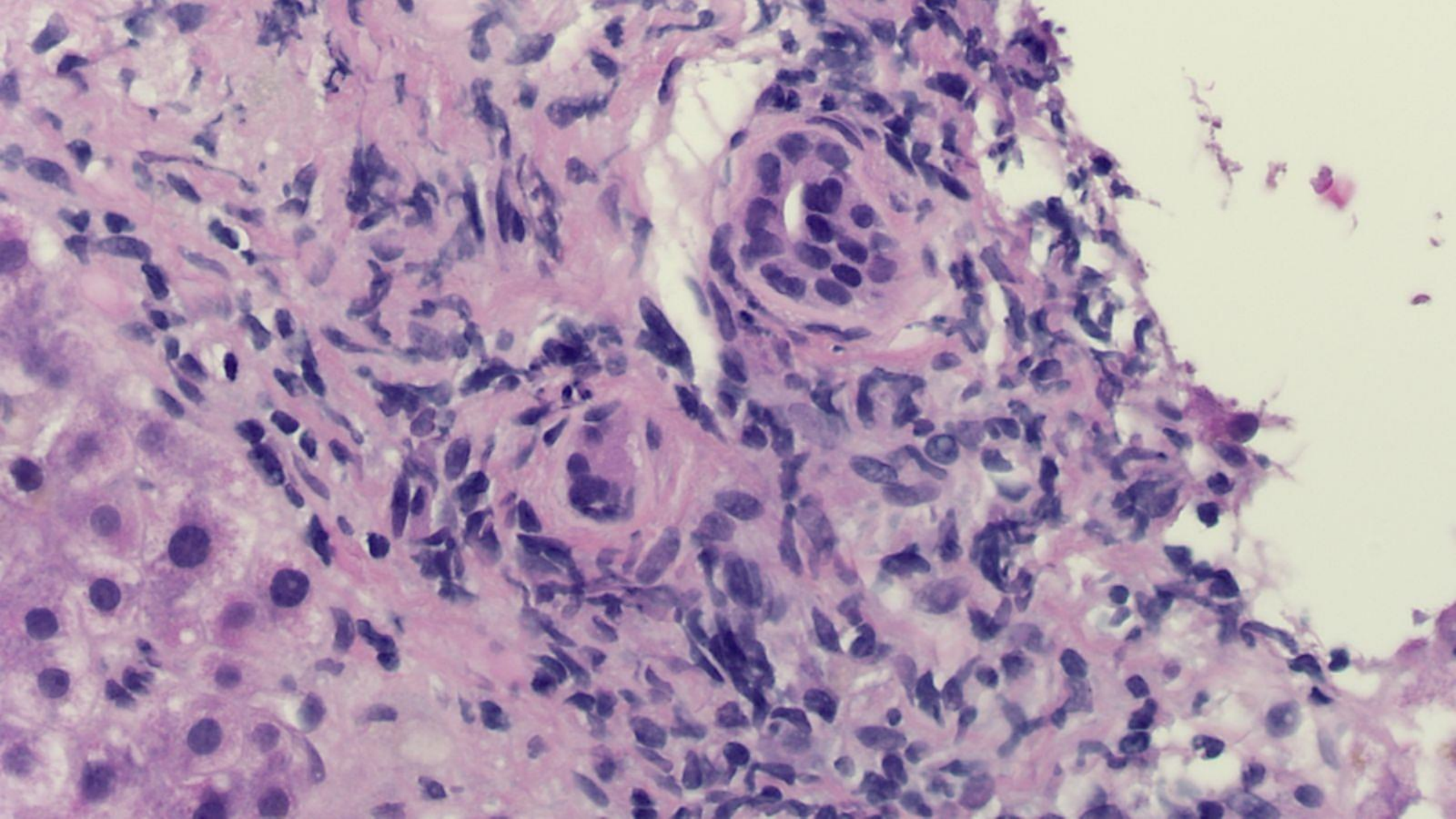
She was admitted later that year with worsening jaundice. She underwent an MRCP, which was described at an outside hospital as negative. She then had a liver biopsy. The biopsy was interpreted as drug reaction.

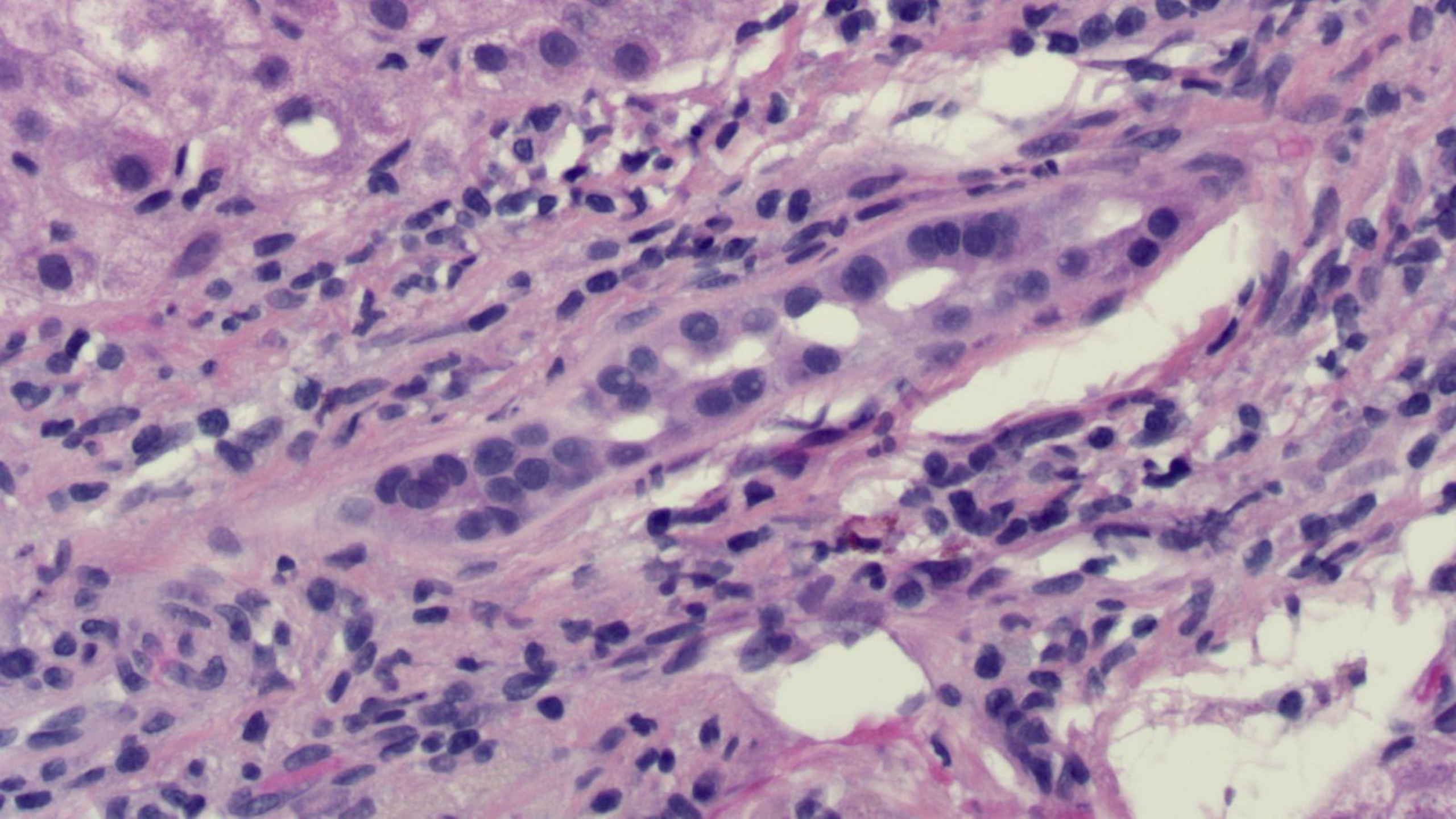
She has a mildly elevated ANA. AMA is negative.

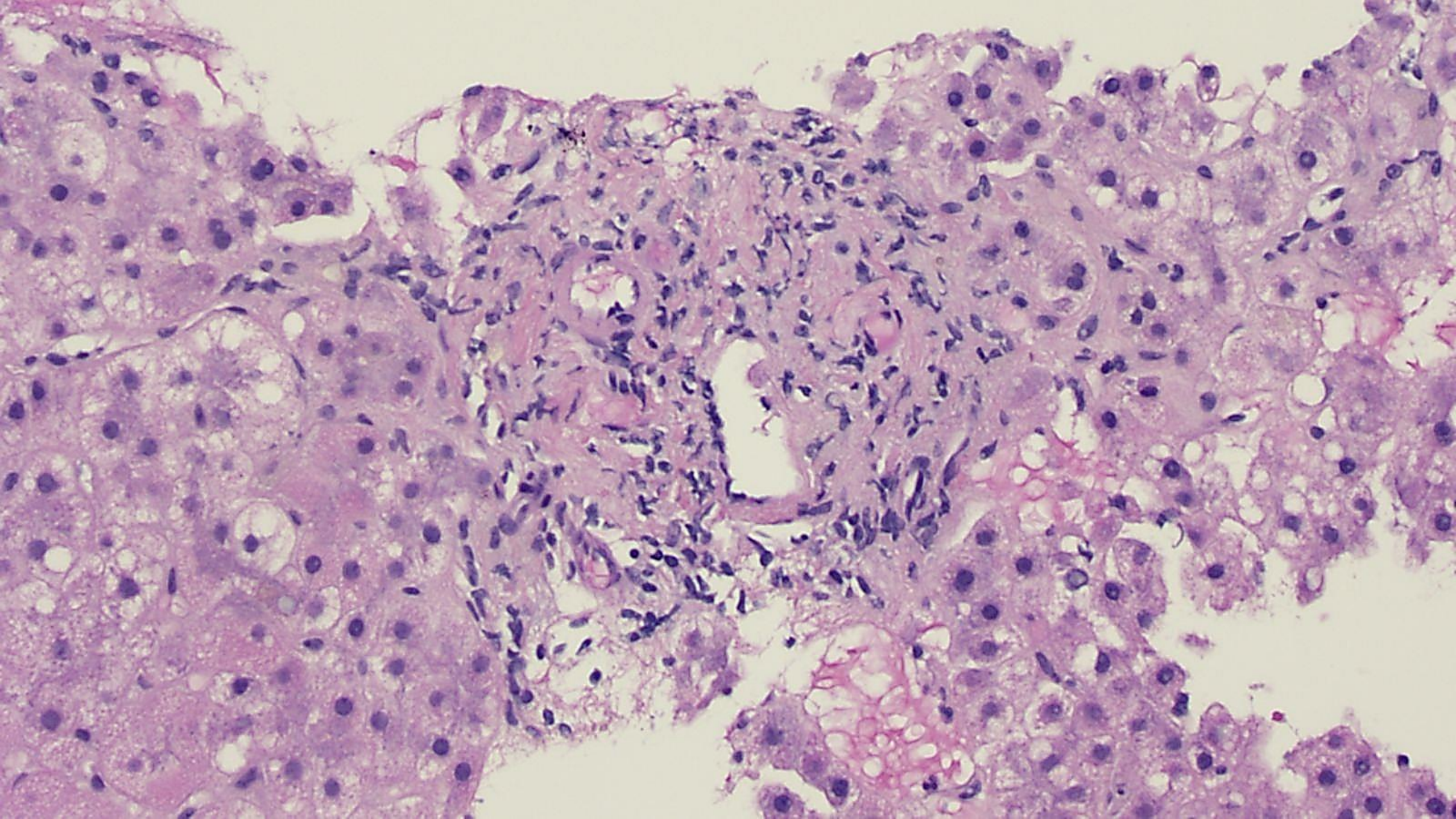


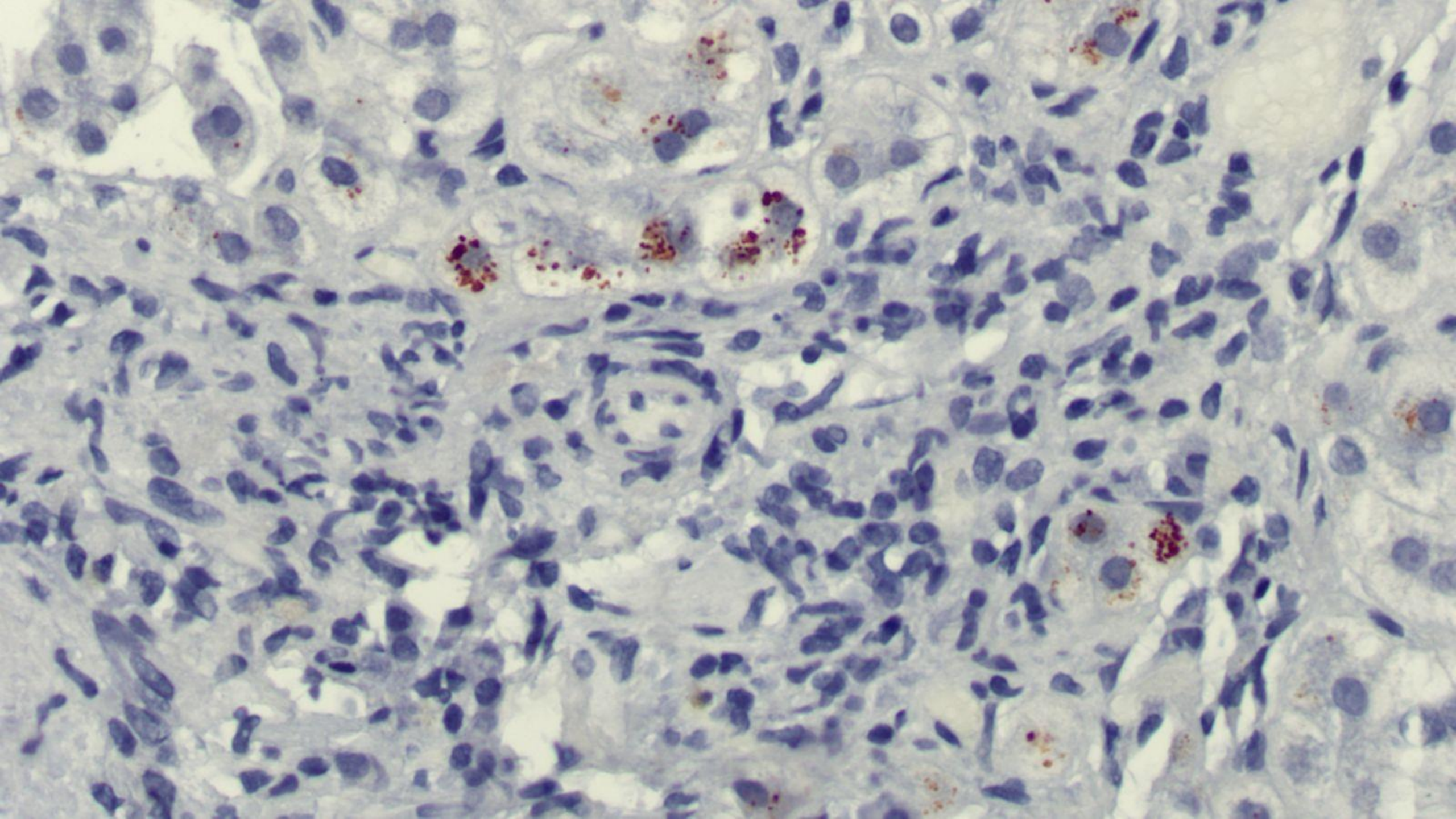












PATHOLOGIC DIAGNOSIS: CHOLESTATIC LIVER WITH BRIDGING FIBROSIS, DUCT INJURY, AND DUCT LOSS.

Some of the features are consistent with chronic cholangiopathy.

The bile stasis indicates a superimposed acute cholestatic process.

Possibilities include PSC with a tight stricture or late stage presentation of PBC.

Vanishing duct syndromes due to drugs and paraneoplastic cholestasis to Hodgkin's disease can also cause cholestasis and duct loss, but neither of these is favored due to the chronic changes.

ERCP RESULTS

Contrast opacification demonstrates prominent ductal dilatation with multifocal areas of narrowing in a beaded morphology in the intrahepatic ducts and a high-grade stricture of the common bile duct.

The appearance is consistent with sclerosing cholangitis with a dominant extrahepatic stricture.

SUMMARY

Bile stasis is usually seen in acute cholestatic processes.

Common to many of these disorders is portal expansion, duct injury, and granulocytes in portal areas.

In cases that clinically are not obvious drug reaction or LDO, the full differential diagnosis of acute cholestasis needs to be considered. Portal changes may narrow the differential (e.g., bile infarcts, many neutrophils, granulomas).

Ductopenia is usually seen in chronic cholangiopathy but can be seen in acute conditions, such as paraneoplastic cholestasis or drug reaction.

When there is bile stasis together with evidence of chronic cholestasis (fibrosis, copper), consider an acute process superimposed on chronic disease or decompensated chronic liver disease.