Steatotic liver disease

Fatty liver disease

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Non-Neoplastic Liver Pathology
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Working Group of Digestive Pathology
Belgian Society of Pathology

UZ GENT
UNIVERSITEIT GENT
FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

OUTLINE

- NAFLD = *Non-Alcoholic Fatty Liver Disease*
- Steatosis
- Steatohepatitis

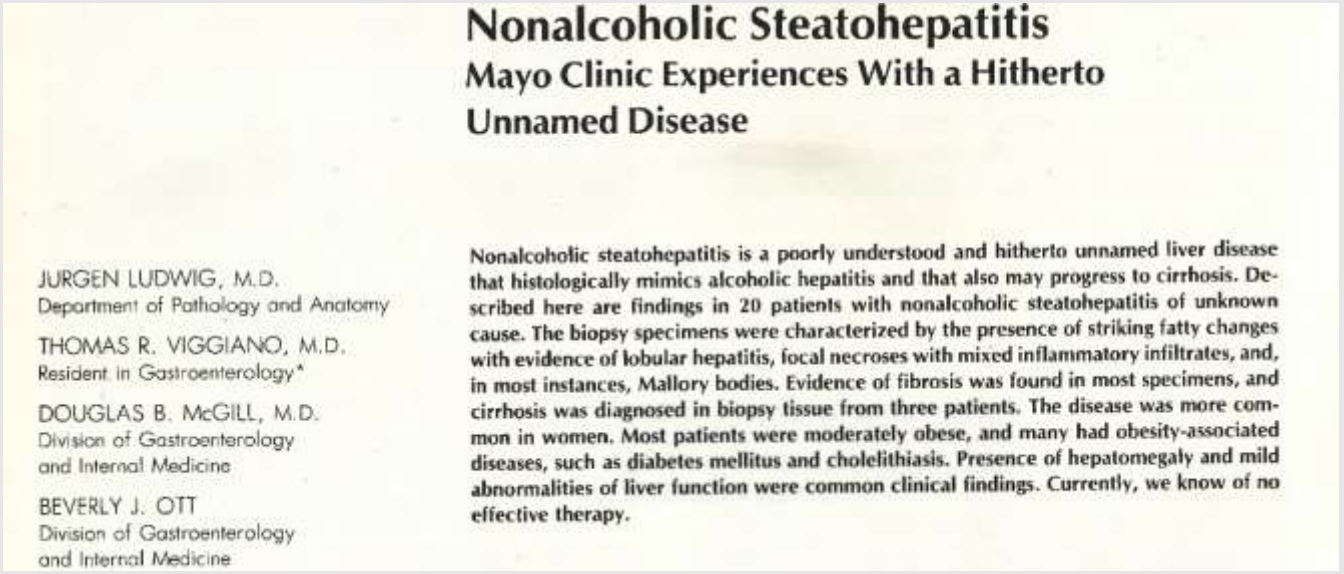
- Fibrosis staging in fatty liver disease
- Cryptogenic cirrhosis
- Diagnostic challenges

Steatosis/Steatohepatitis

Most common etiologies

- NAFLD = *Non-Alcoholic Fatty Liver Disease*

Ludwig J et al, Mayo Clin Proc 1980, 55: 434-438



Nonalcoholic Steatohepatitis

Mayo Clinic Experiences With a Hitherto Unnamed Disease

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Nonalcoholic steatohepatitis is a poorly understood and hitherto unnamed liver disease that histologically mimics alcoholic hepatitis and that also may progress to cirrhosis. Described here are findings in 20 patients with nonalcoholic steatohepatitis of unknown cause. The biopsy specimens were characterized by the presence of striking fatty changes with evidence of lobular hepatitis, focal necroses with mixed inflammatory infiltrates, and, in most instances, Mallory bodies. Evidence of fibrosis was found in most specimens, and cirrhosis was diagnosed in biopsy tissue from three patients. The disease was more common in women. Most patients were moderately obese, and many had obesity-associated diseases, such as diabetes mellitus and cholelithiasis. Presence of hepatomegaly and mild abnormalities of liver function were common clinical findings. Currently, we know of no effective therapy.

- Excess alcohol
- Drugs

NAFLD and Metabolic Syndrome

NAFLD Chronic liver disease, includes steatosis (NAFL) and steatohepatitis

High incidence – Most adults, but also children and teenagers

NAFLD *Non-Alcoholic Fatty Liver Disease*	Related to high incidence of obesity Affects ~25% of adult population worldwide 23,7% for Europe Younossi ZM et al, Hepatology 2016, 64: 73-84
NASH *Non-Alcoholic SteatoHepatitis*	3-16% for Europe Nadalin S. et al, Liver Transp. 2055, 11: 980-986 Minervini MI et al, J Hepatol 2009, 50: 501-510

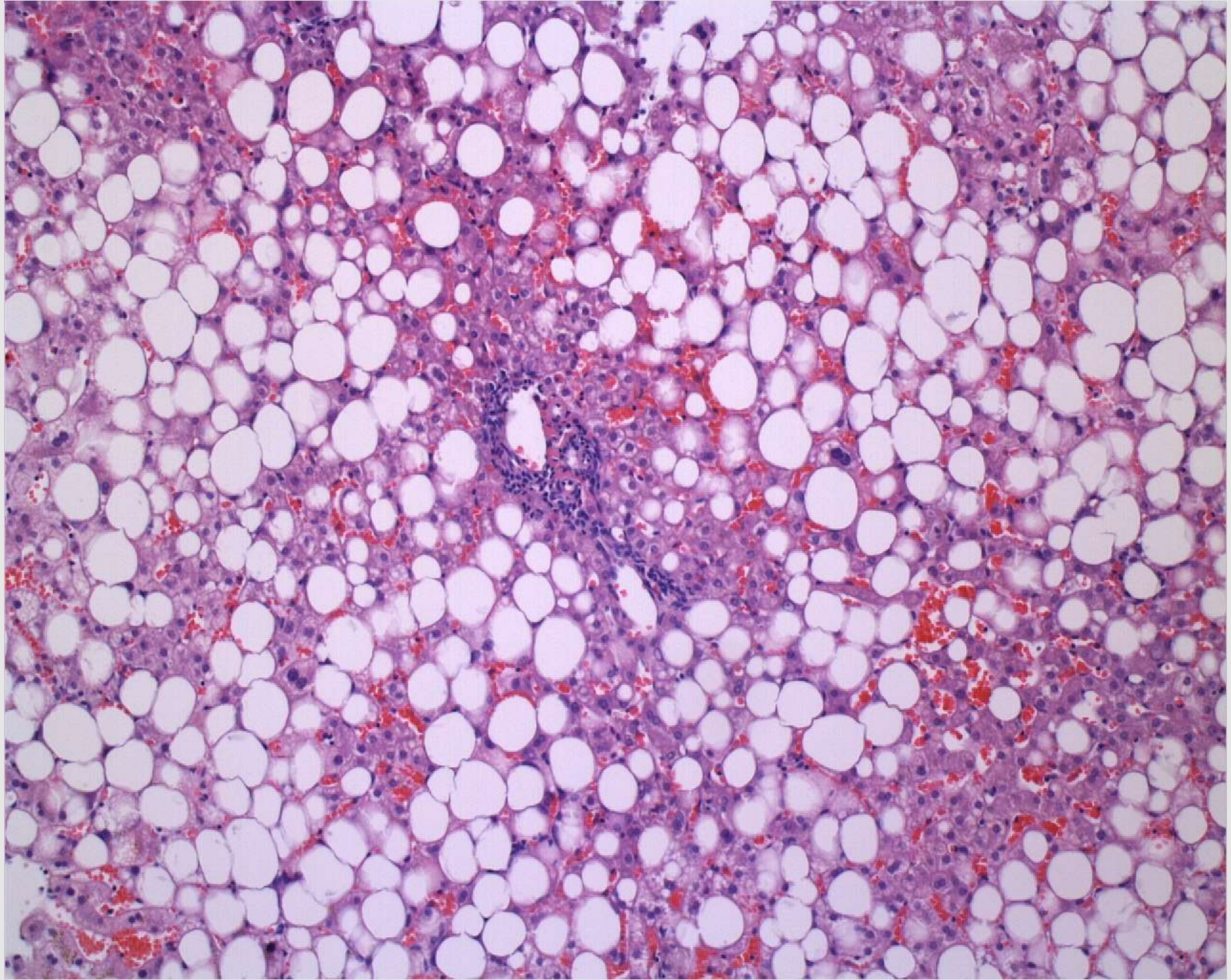
Metabolic syndrome: 3 or more of the following

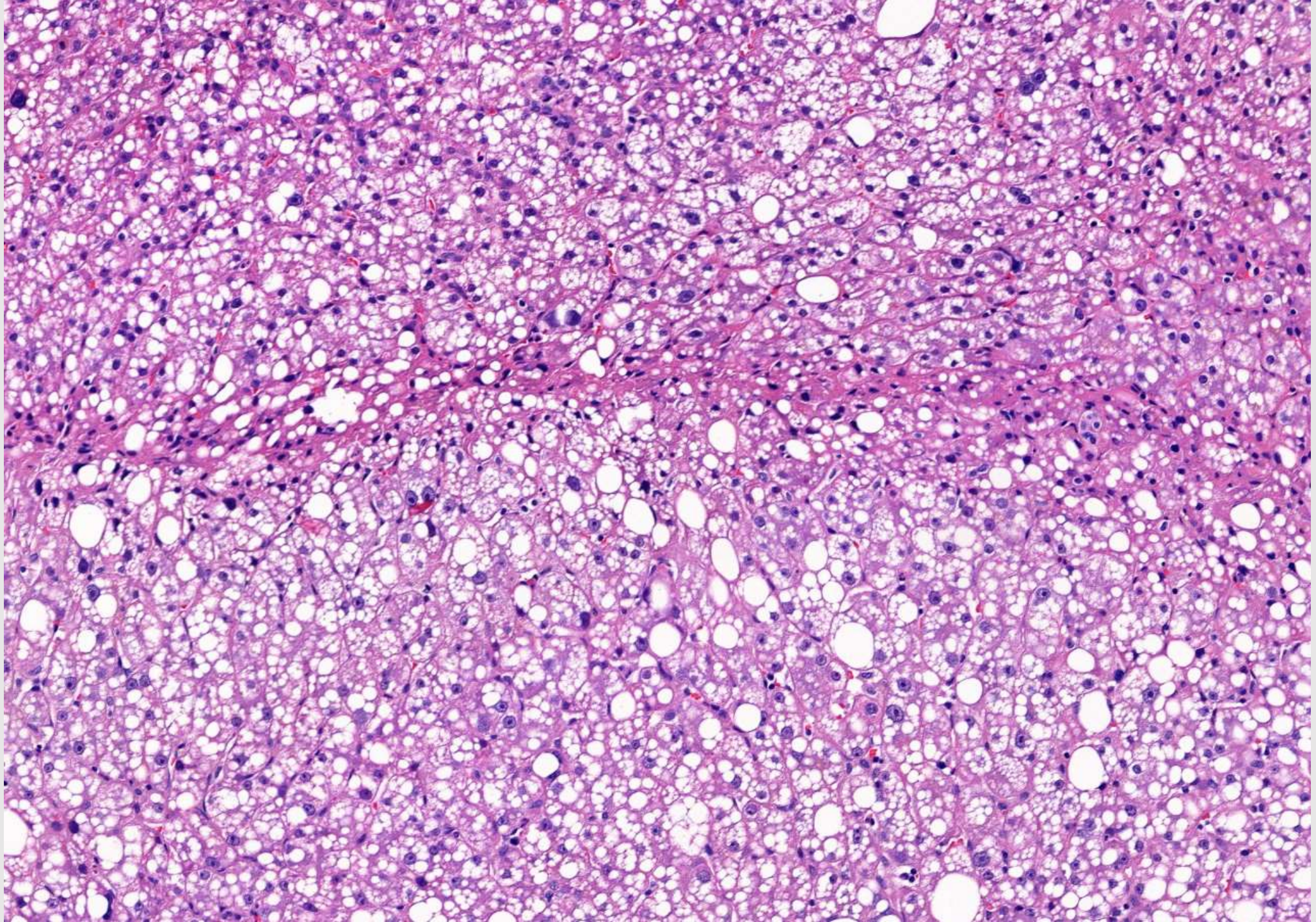
- Central obesity
- Elevated fasting serum glucose and insulin resistance
- High triglycerides
- Low HDL cholesterol
- High blood pressure

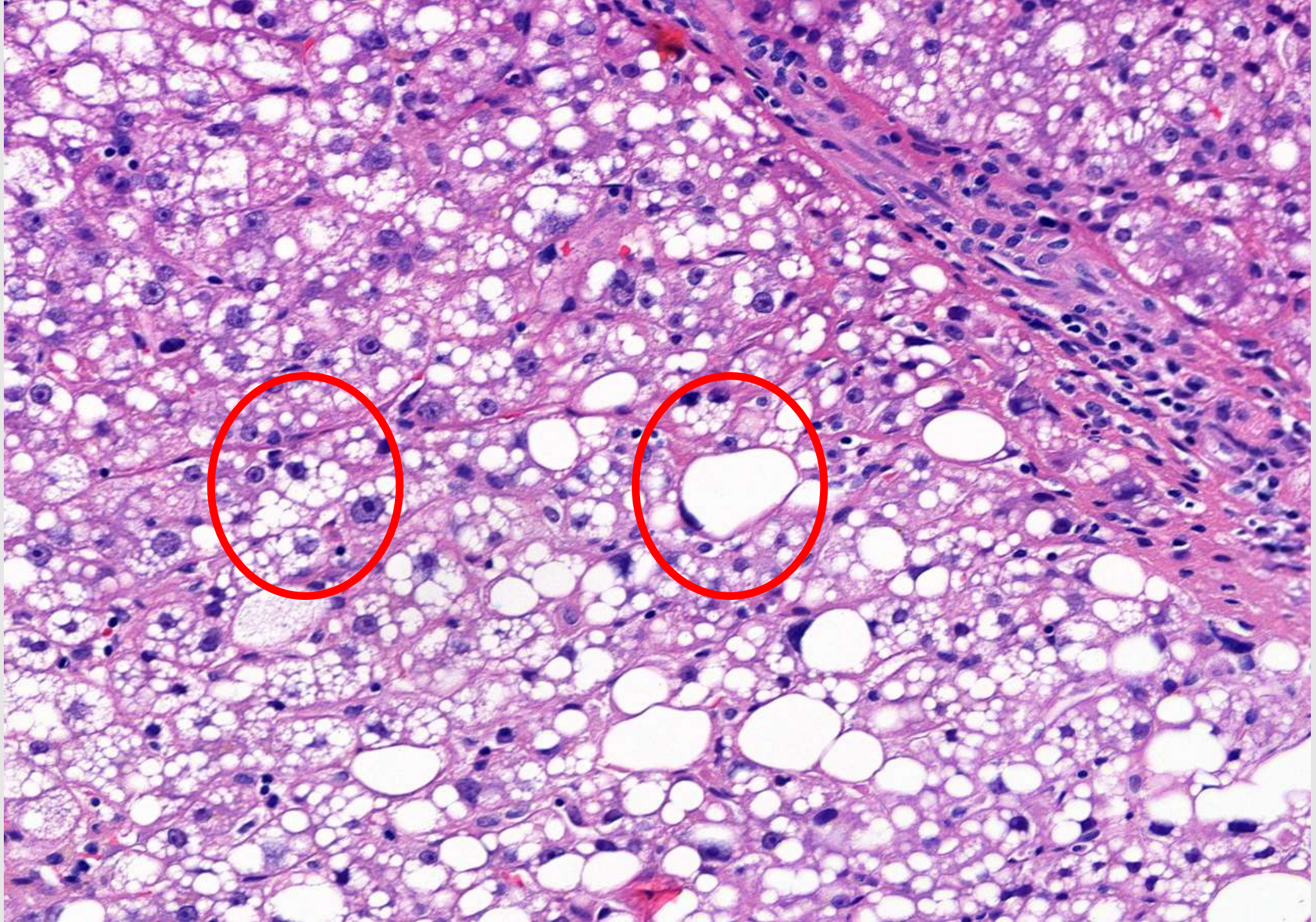
Steatosis

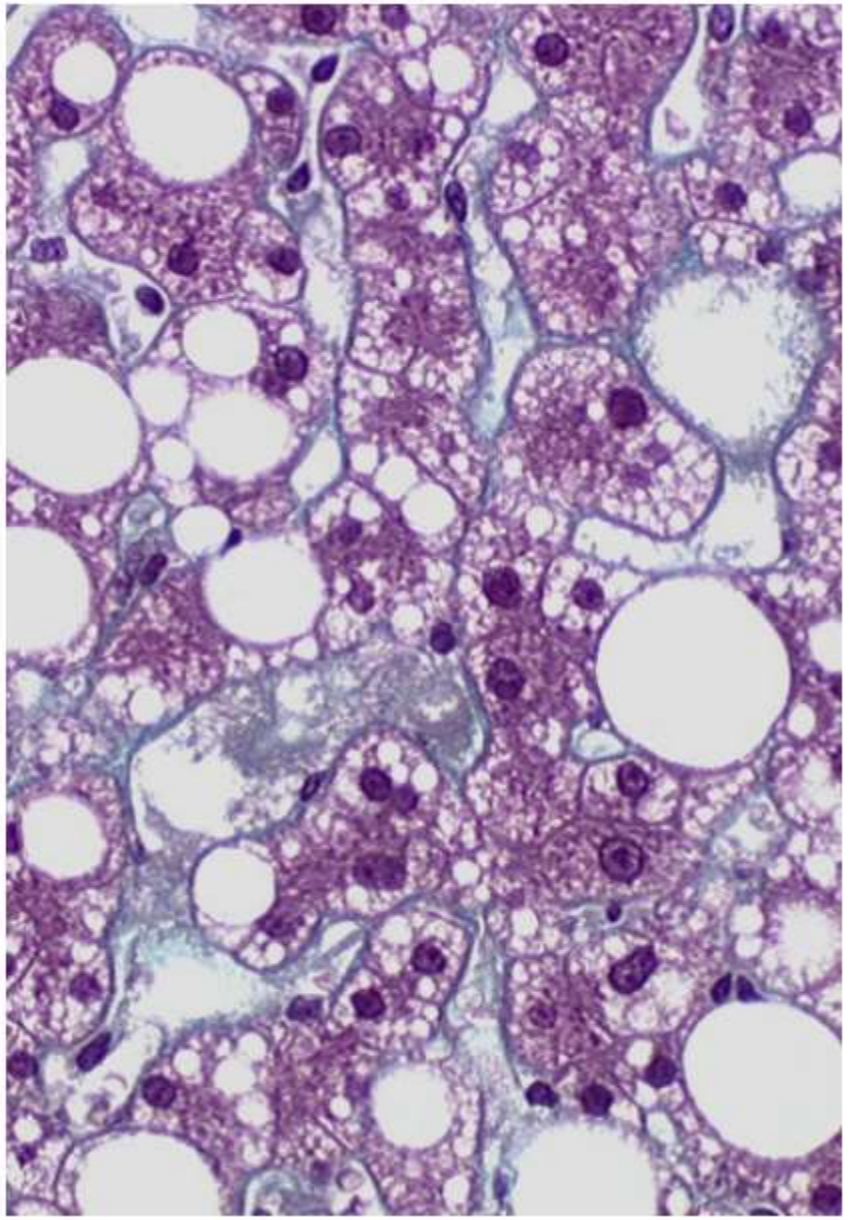
- Macrovesicular steatosis
- Mixed macro-microvesicular steatosis

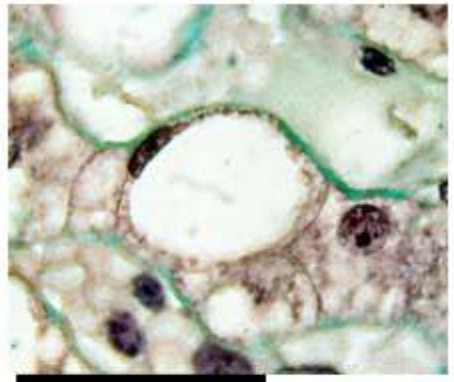
  “macro-mediovesicular steatosis”



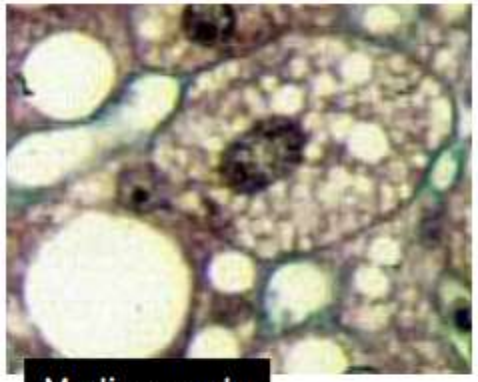




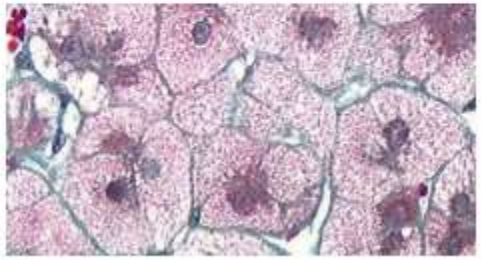




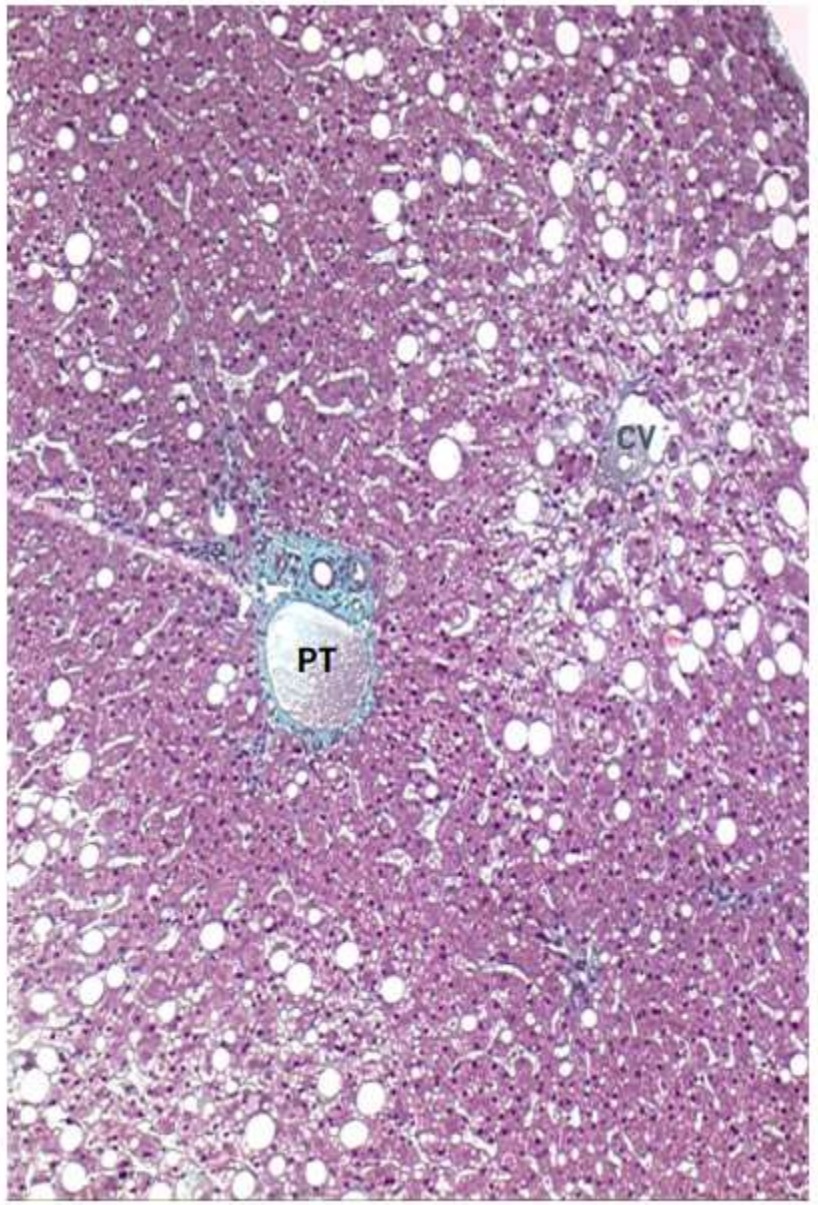
Macrovacuole



Mediovacuole



Microvacuole (rare)

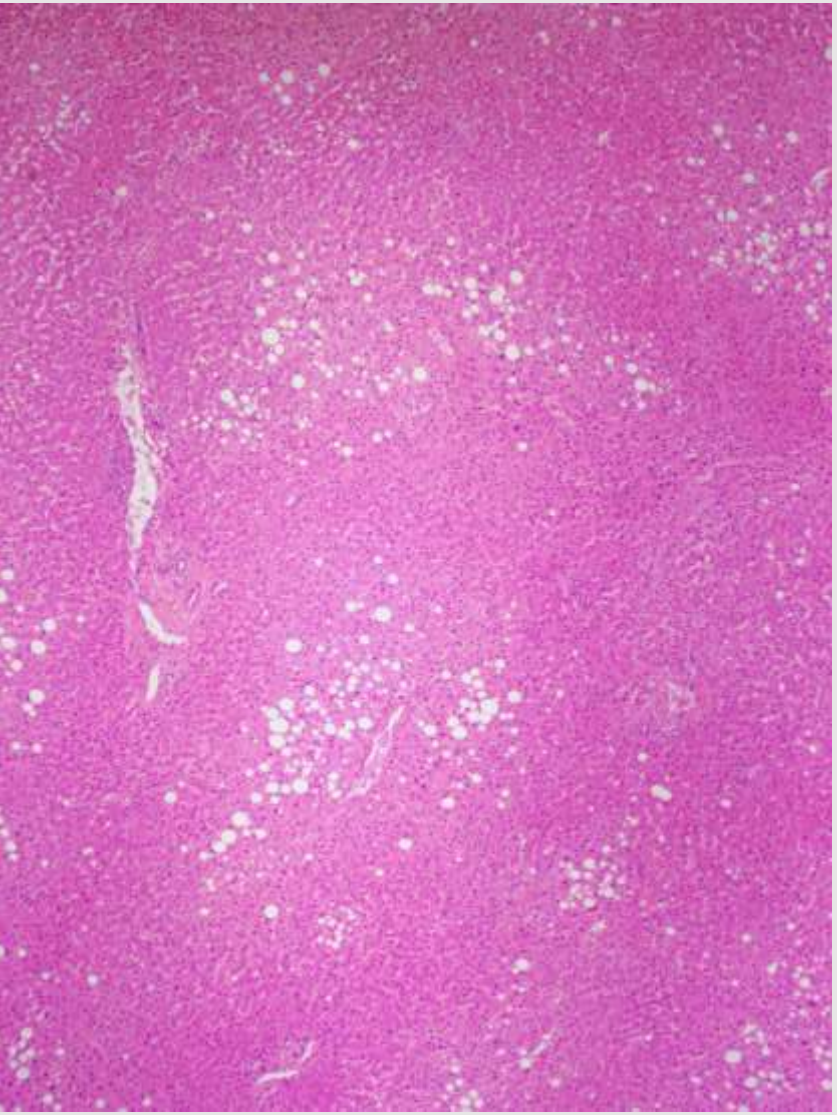


https://www.aphc.info/wp-content/uploads/2014/09/Pierre_BEDOSSA.pdf

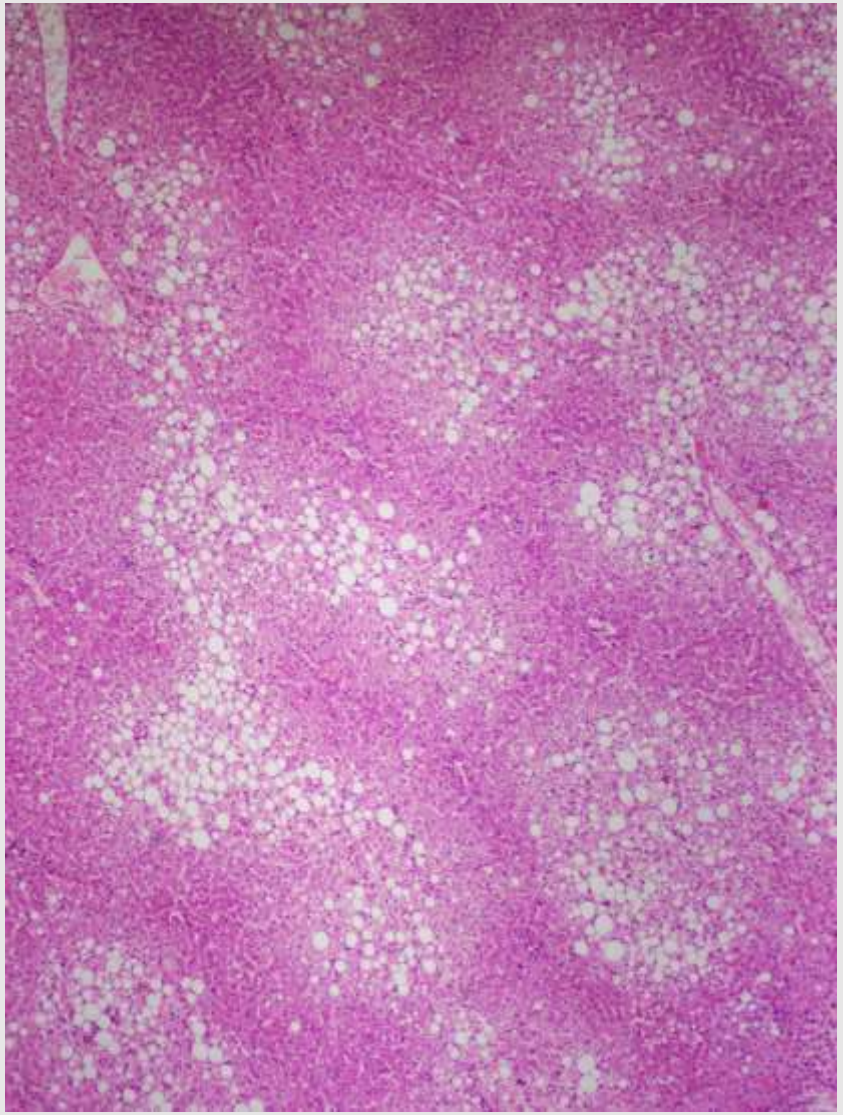
Steatosis

- Involvement
  - **None**
  - **<5% - Minimal**
  - **5-33% - Mild**
  - **34-66% - Moderate**
  - **>66% - Marked**
- Scoring best done on low-power lens (4X or 10X)
- Score by percentage of surface area with macro-mediovesicular fat

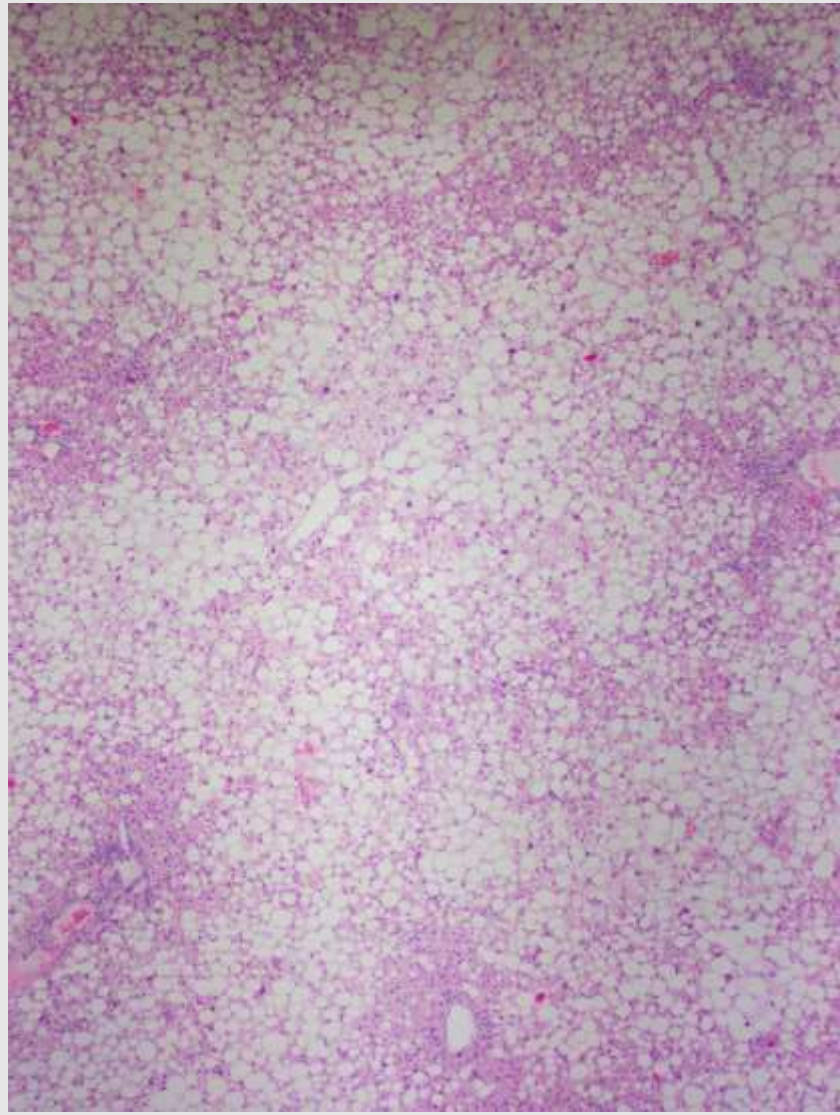
Grade 1, scale 0-3
Mild



Grade 2, scale 0-3
Moderate



Grade 3, scale 0-3
Marked

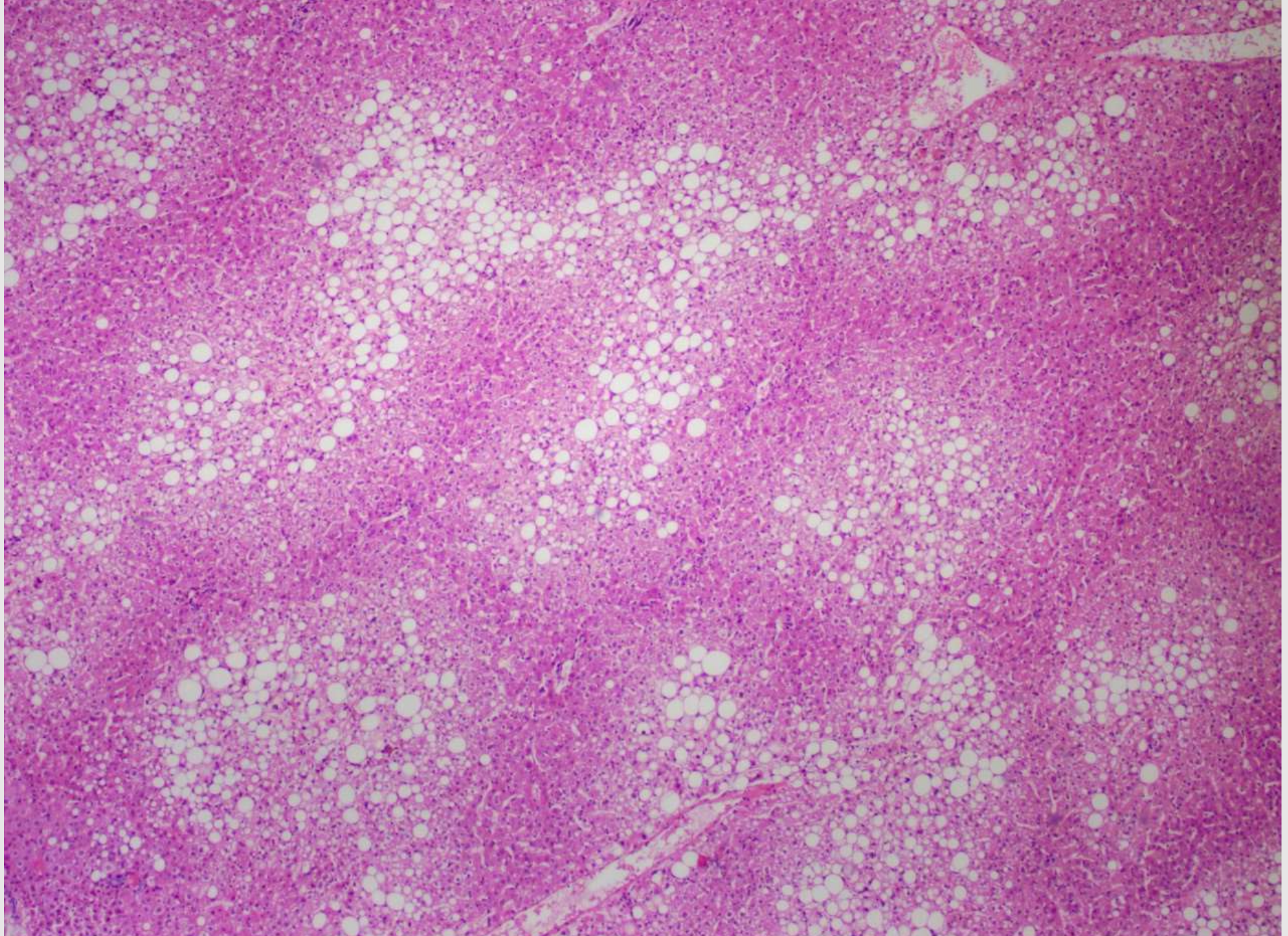


Steatosis

Additional findings

Zonation of fat

- **Zone 3 distribution (centrilobular)**
- Zone 1 distribution (periportal)
- Azonal distribution (randomly scattered) - typically moderate/marked
- Panacinar distribution (diffuse) – typically mild



Steatosis ⇒ Steatohepatitis

Dogma within NAFLD spectrum

Steatosis little risk for fibrosis progression

Steatohepatitis much higher risk for fibrosis progression

New insights into natural history of NAFLD

Distinction between NAFL and NASH of limited prognostic value

Patients with fibrosis progression: NASH features on follow-up biopsy

Suggesting that although NASH may not be present in early phases of the disease, it is a necessary pathogenic driver of fibrosis progression

Singh S et al, Clin Gastroenterol Hepatol 2015, 13: 643-654; McPherson S et al, J Hepatol 2015, 62: 1148-1155

Steatohepatitis

- Steatosis **plus** active injury

- **Active injury**
  - **Ballooned hepatocytes ± Mallory-Denk bodies**
  - **Lobular inflammation**

Steatosis

Without these histologic findings of active injury

Steatohepatitis

- Steatosis **plus** active injury

- **Active injury**
  - **Ballooned hepatocytes ± Mallory-Denk bodies**
  - **Lobular inflammation**

Controversy

Some authors require balloon cells

Some authors require lobular inflammation

Steatohepatitis

- Steatosis **plus** active injury

- **Active injury**
  - **Ballooned hepatocytes ± Mallory-Denk bodies**
  - **Lobular inflammation**

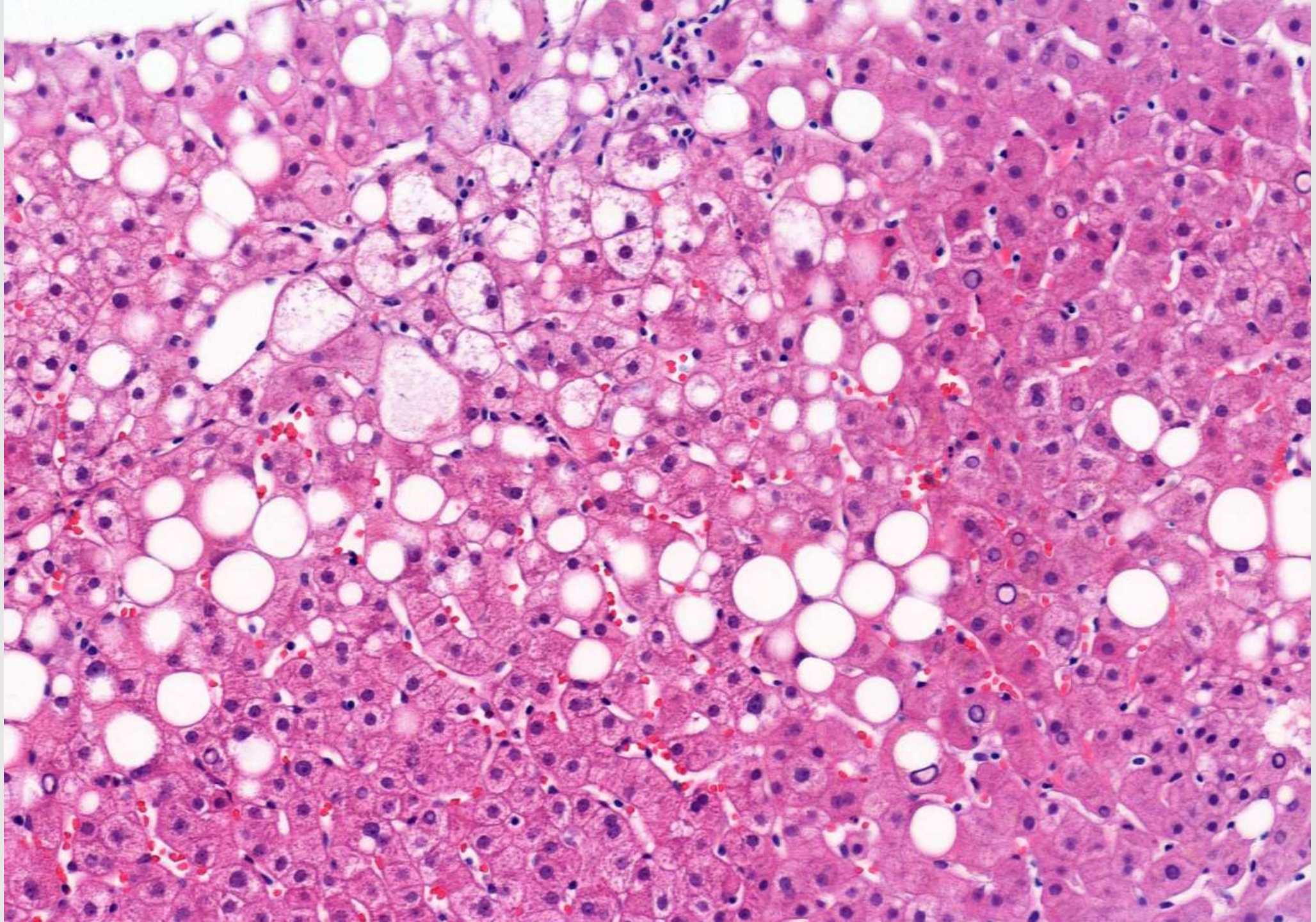
Reasonable approach in daily practice
Convincing balloon cells
and/or
More than trivial lobular inflammation

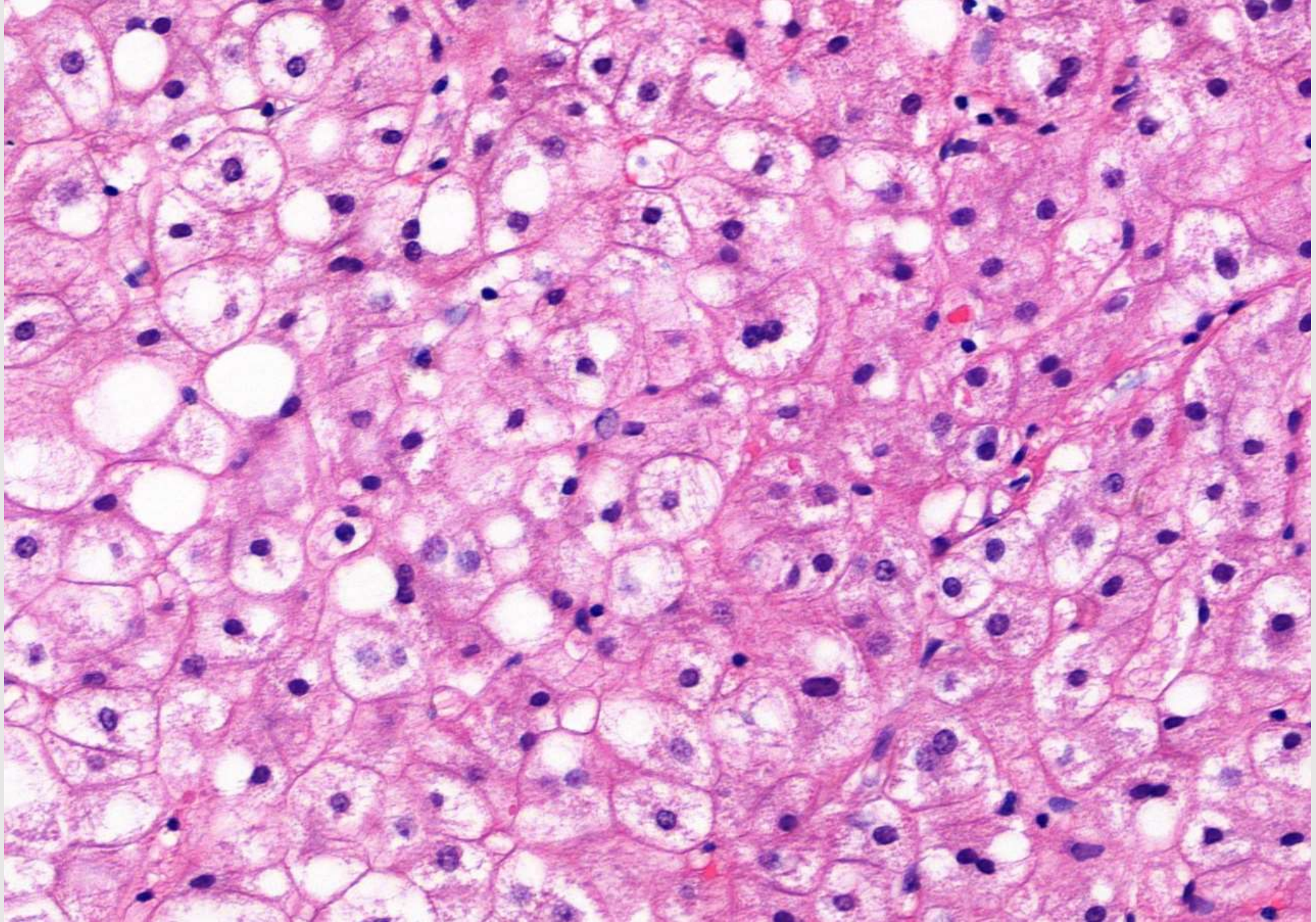
Ballooned hepatocytes
Balloon cells

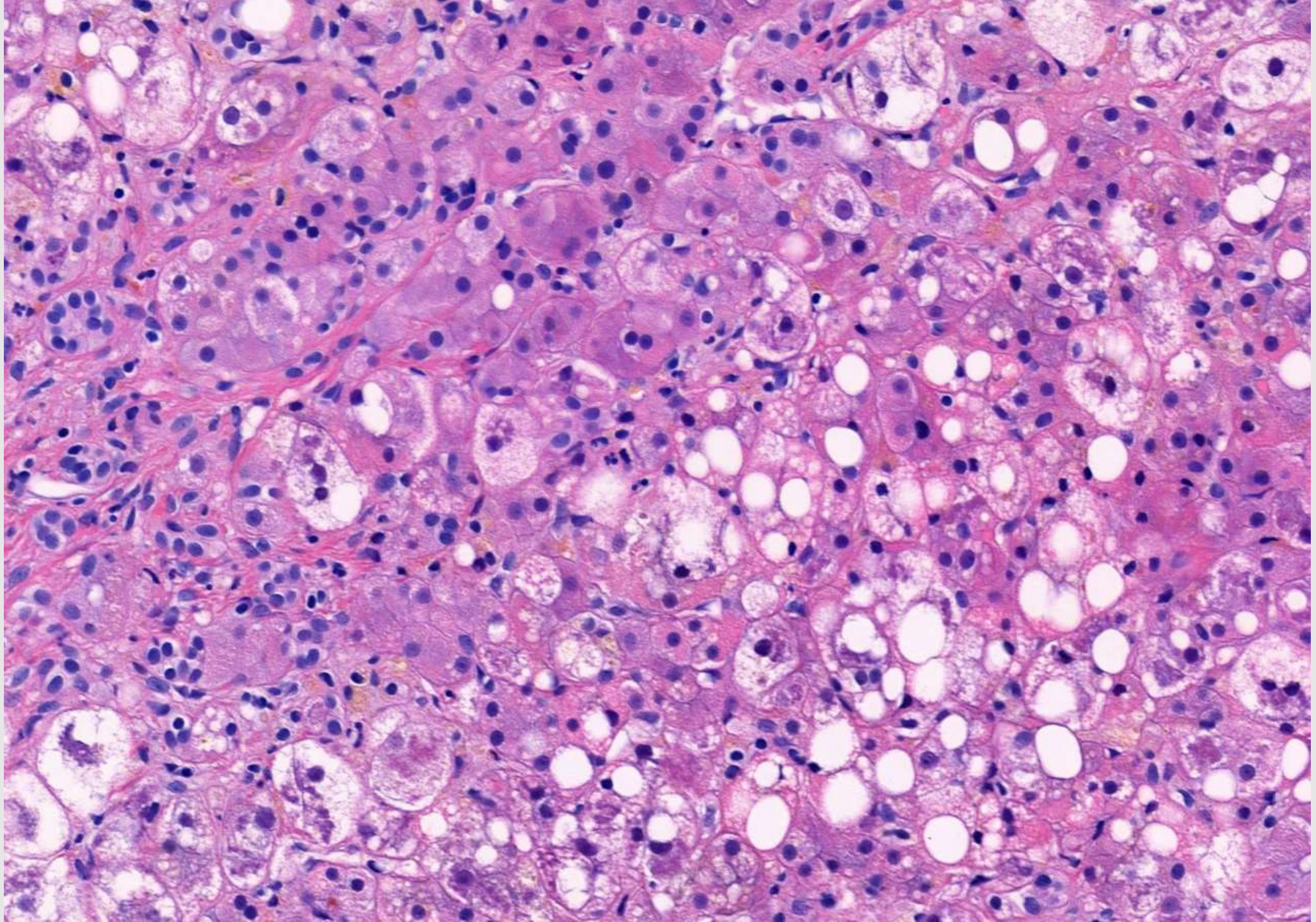
- Hepatocytes that are injured but not yet dead
- Can also be seen in other diseases, e.g. cholestatic liver disease
- In NAFLD most commonly in zone 3
- Often in close proximity to fibrosis

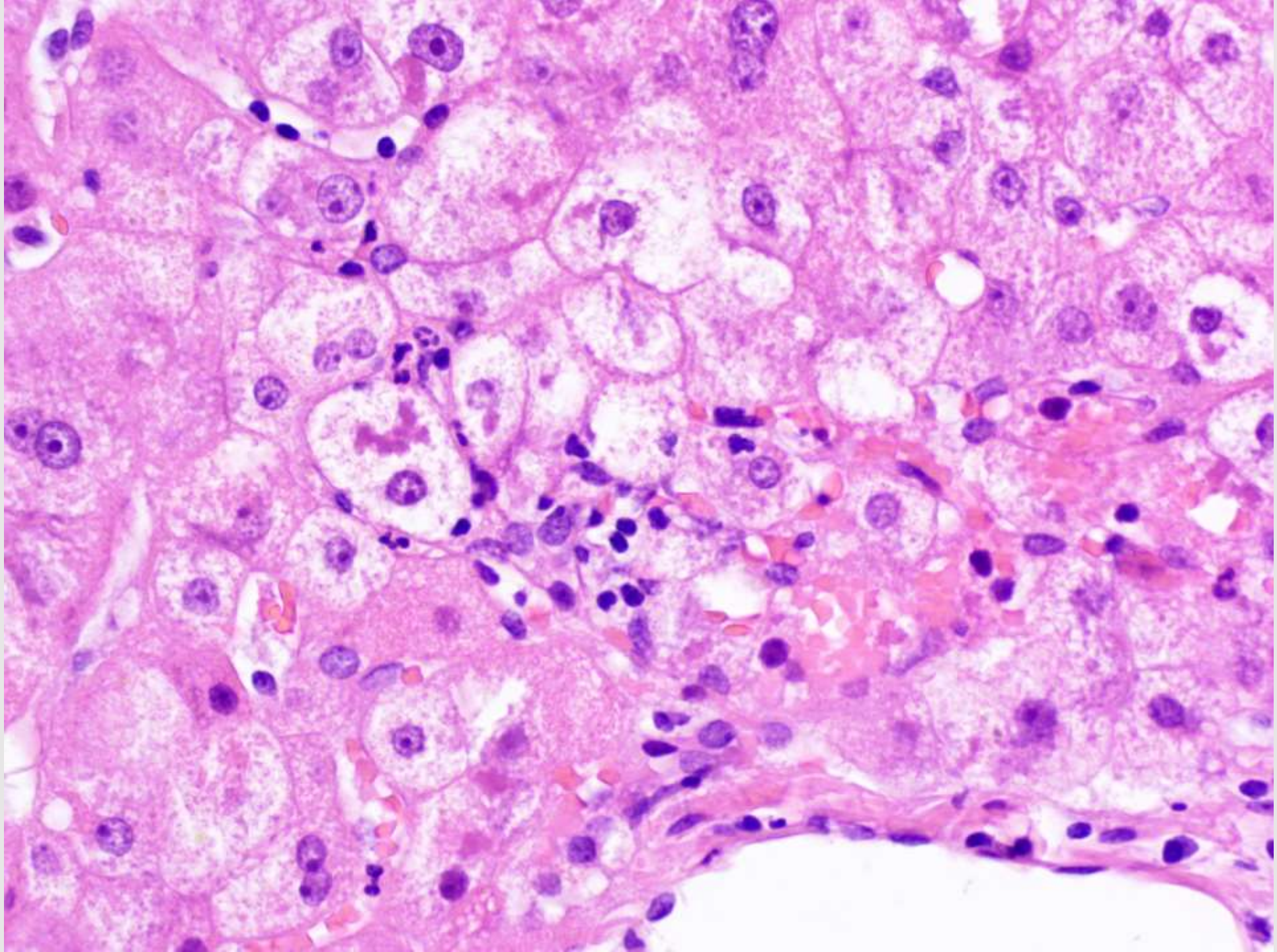
- **Large size**
- **Cytoplasmic clearing**
- **Eosinophilic clumps and sometimes Mallory hyaline**

  Damaged and ubiquitinated cytoskeleton proteins





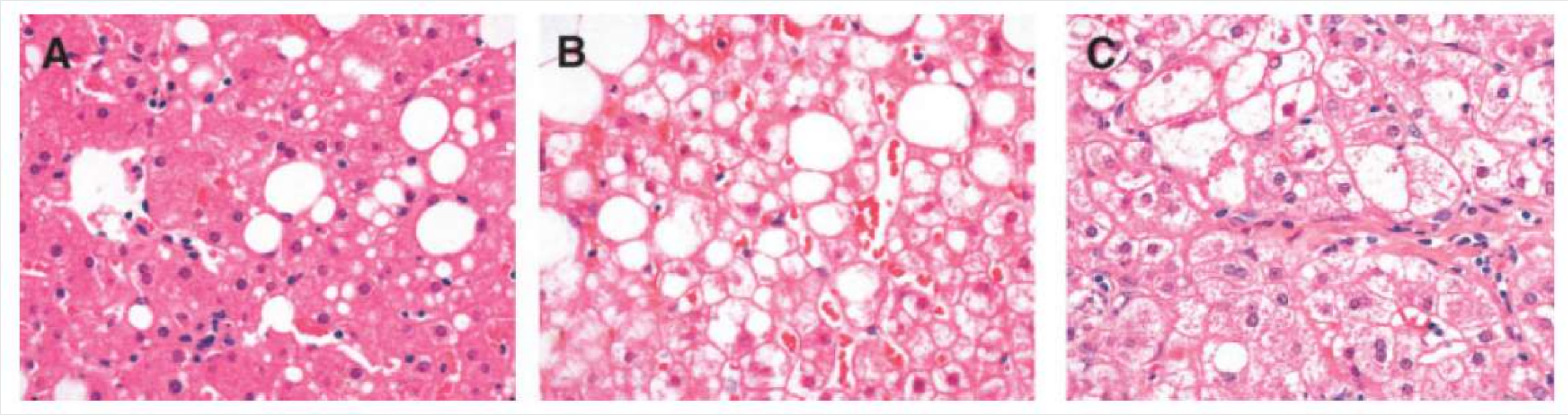




No ballooning

Grade 1 ballooning*

Grade 2 ballooning

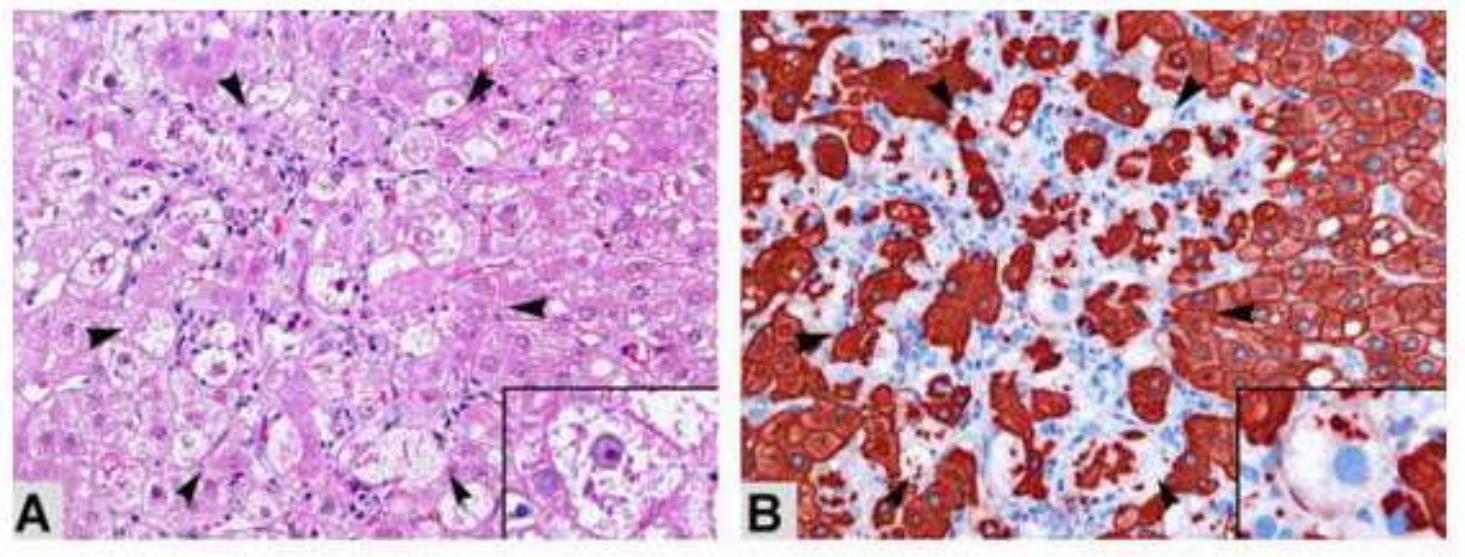


* In no study set case was there absolute concordance among the nine pathologists for a ballooning score of 1. During the second round of reviews, this case was scored as 1 ballooning injury by 8 of the 9 pathologists.

Kleiner DE et al, Hepatology 2005, 41: 1313-1321

What causes hepatocyte ballooning

- Oxidative damage to cytoskeleton
- Intermediate filaments K8/18



- Loss of K8/18 in ballooned cells

Lackner C et al, J Hepatol 2008, 48: 821-828

Inflammation

Lobular inflammation is mostly lymphocytic

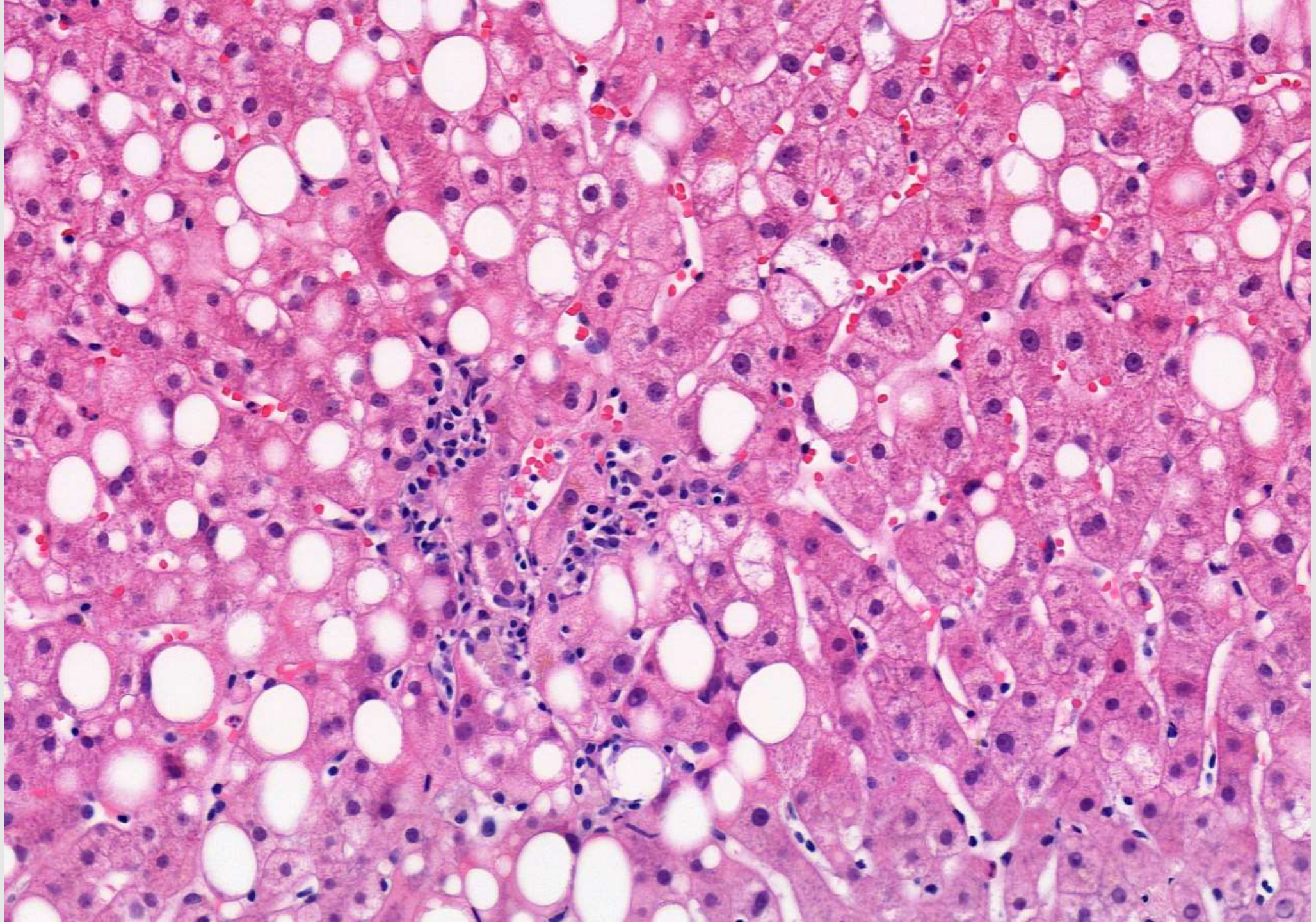
Neutrophils are not necessary, relatively rare in NAFLD

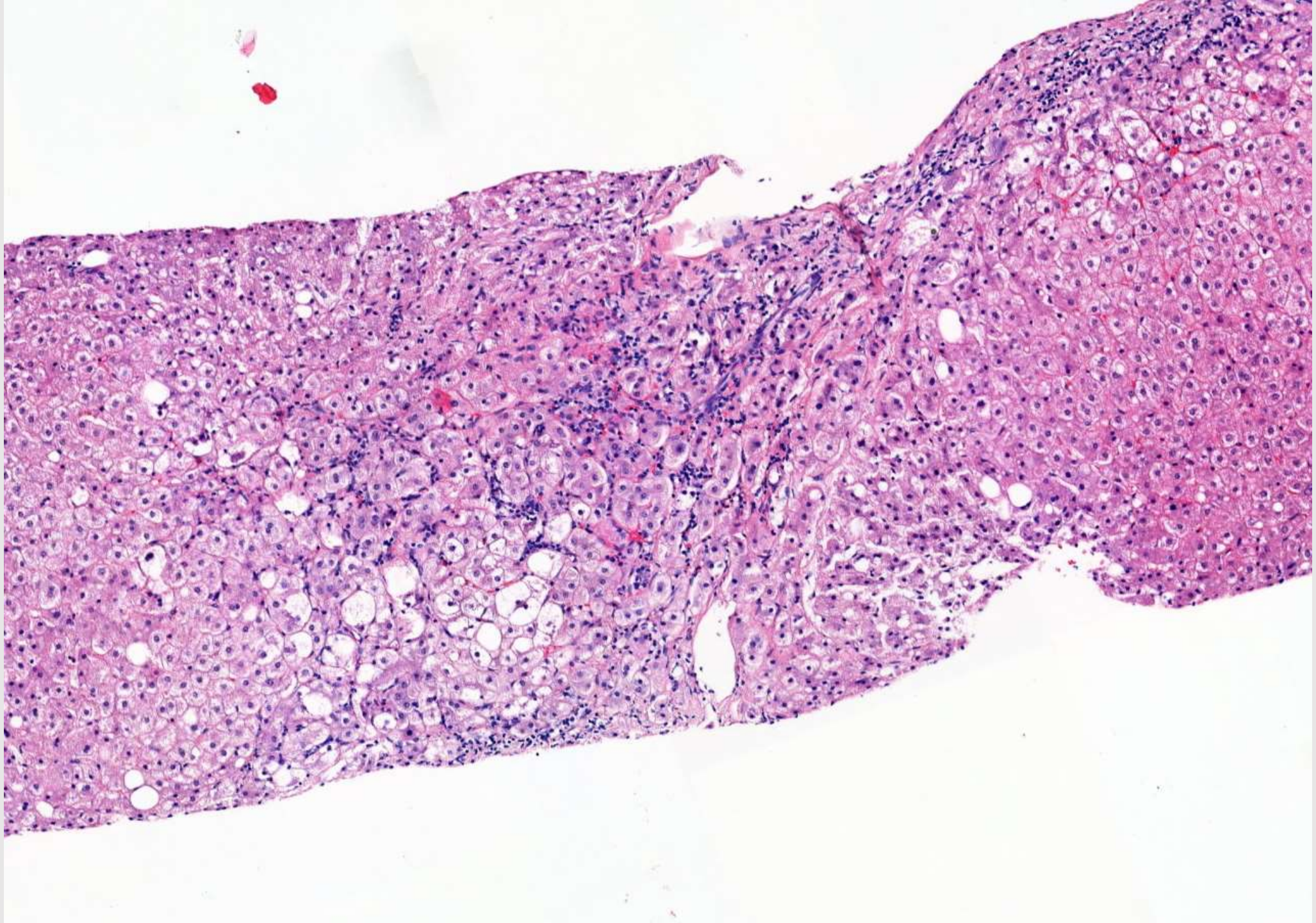
Except when marked active disease with numerous balloon cells and abundant Mallory hyaline

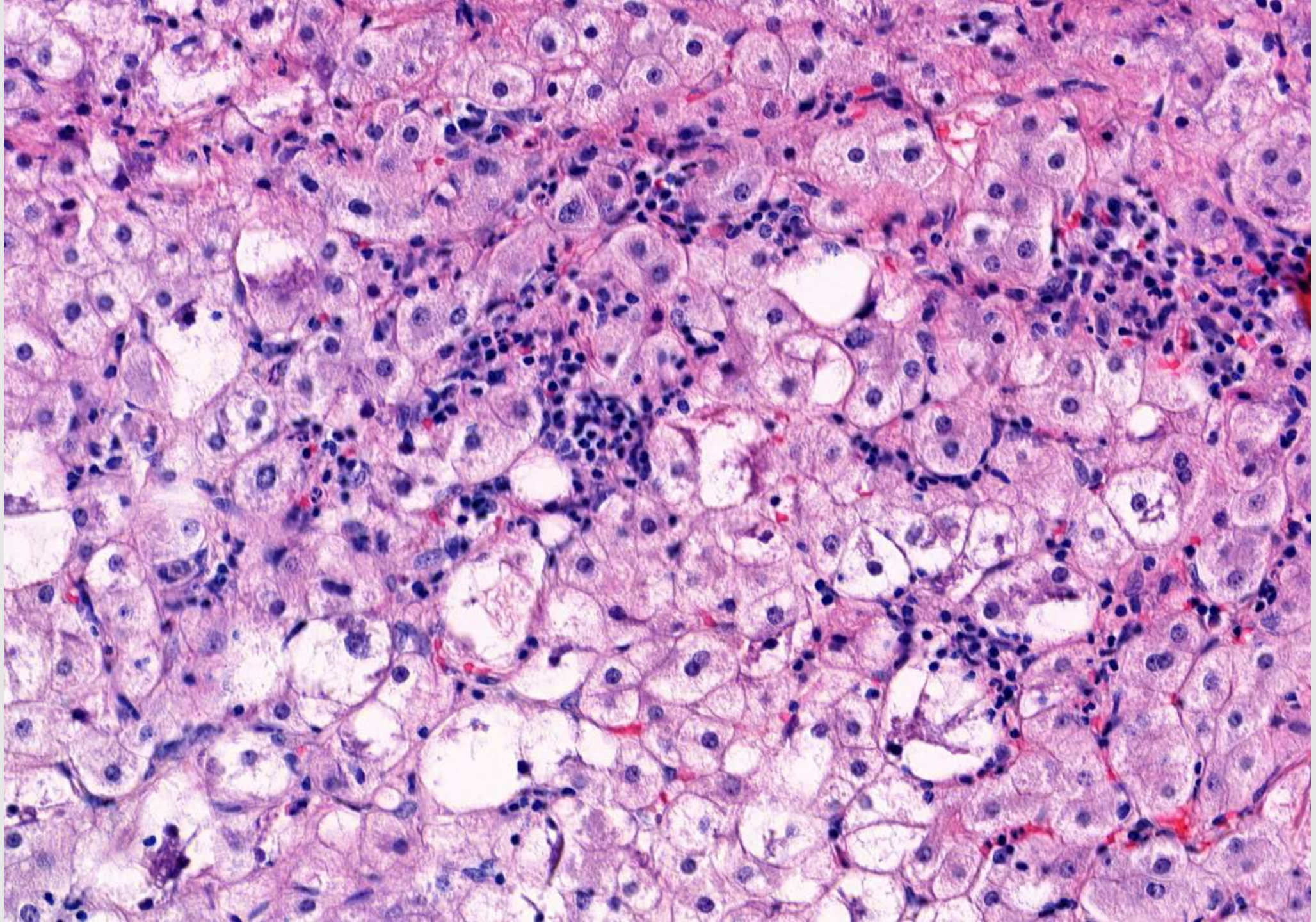
- ~**80%** of NASH has **mild** lobular inflammation
- ~**20%** of NASH has **moderate** lobular inflammation
- ~0% has marked lobular inflammation

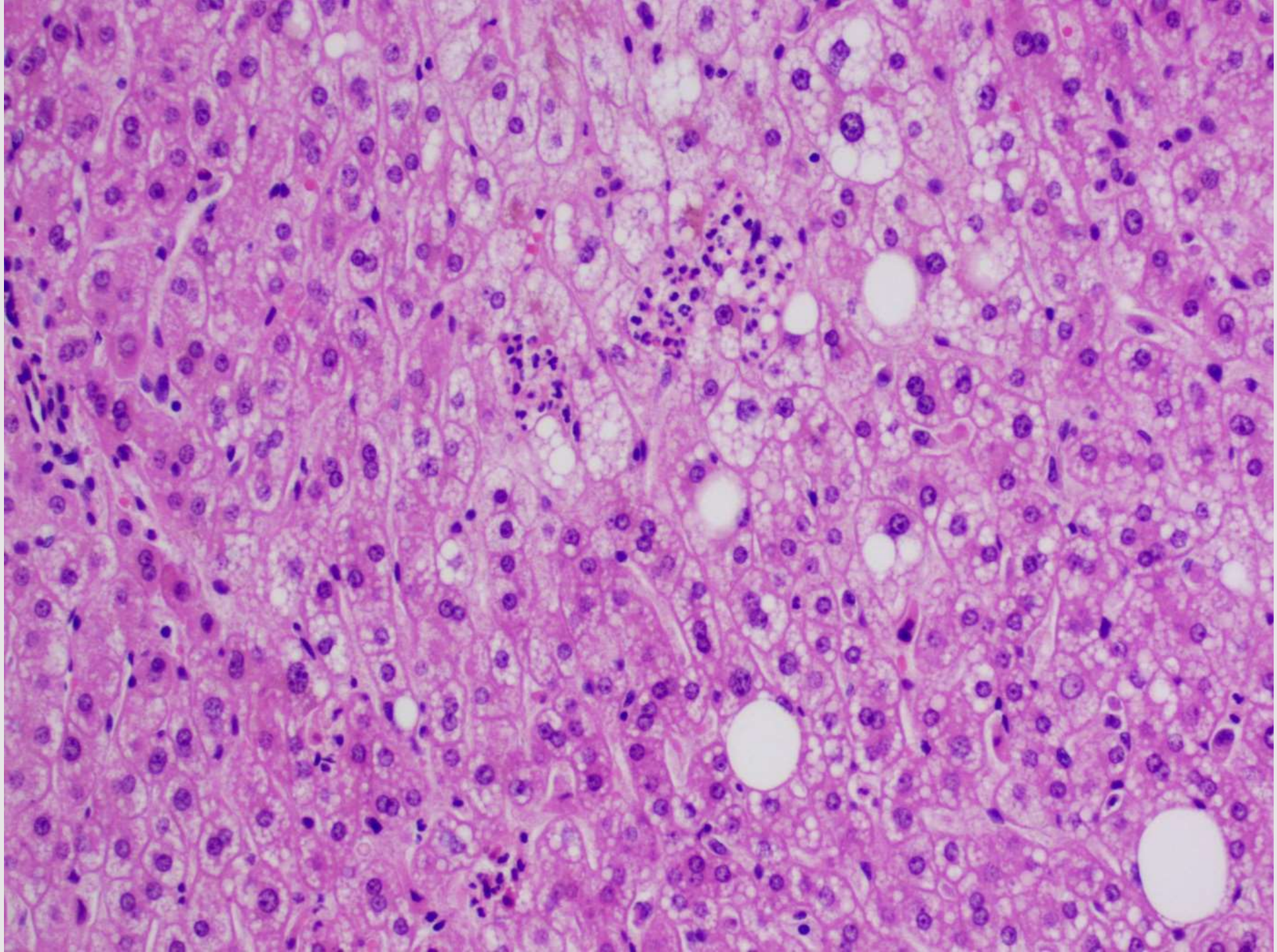
  Should work up for other diseases

Pitfall: surgical hepatitis (wedge biopsies, resections)









Inflammation

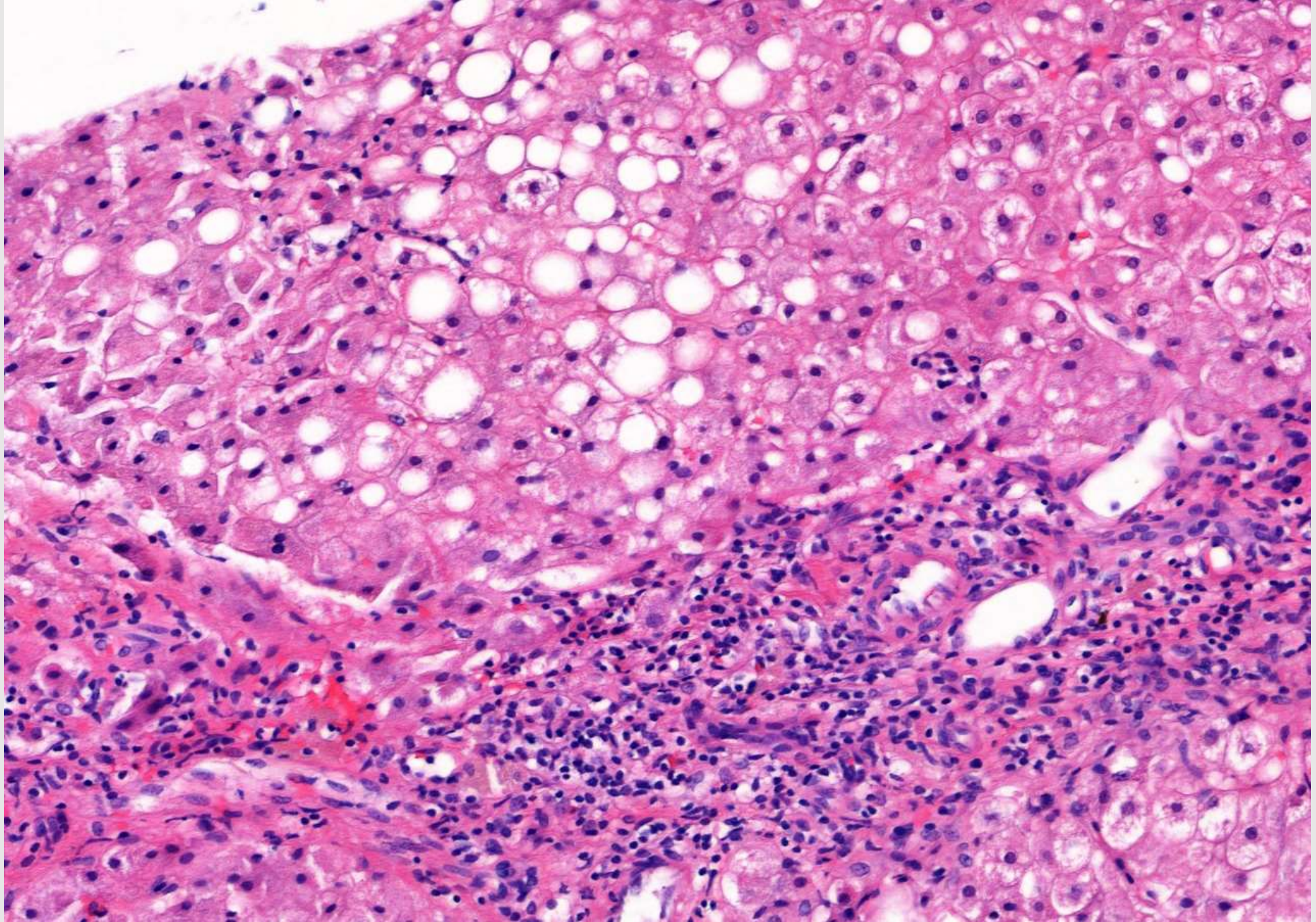
Portal inflammation is mostly lymphocytic

- **Mild**
- **Can be focally moderate**

Portal inflammation: how much is too much

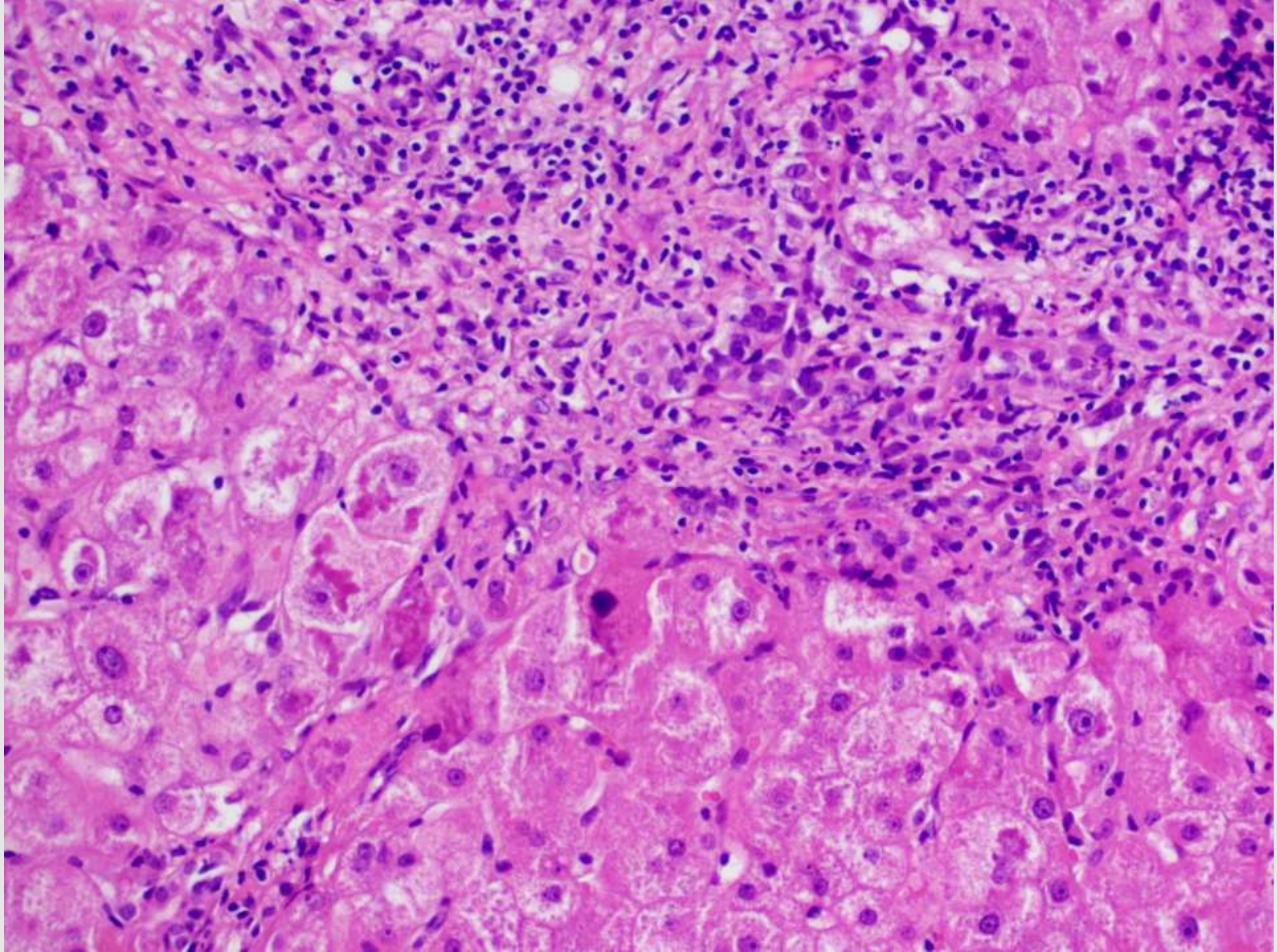
- Moderate but diffuse portal inflammation
- Marked portal inflammation

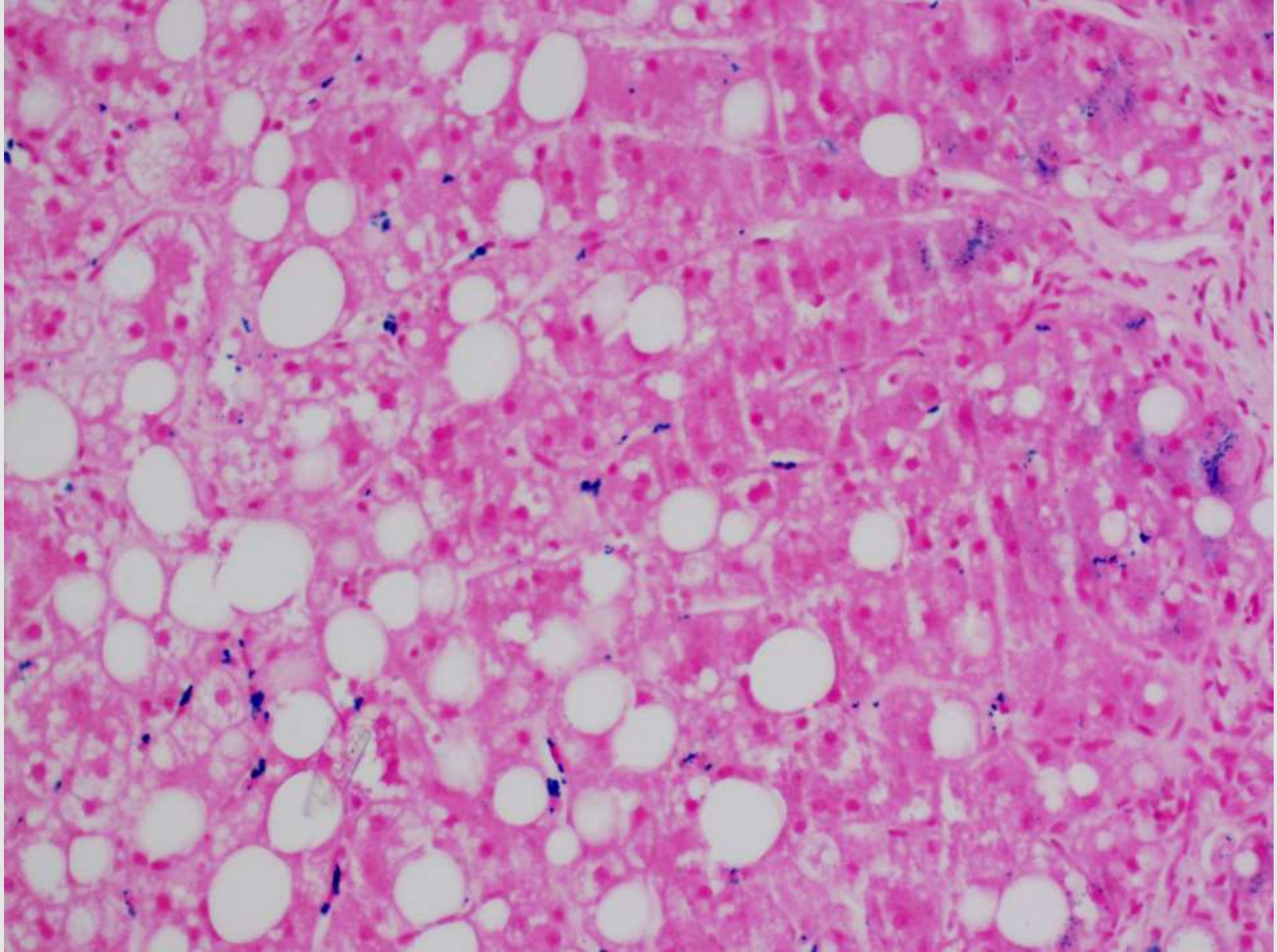
  Should work up for other diseases

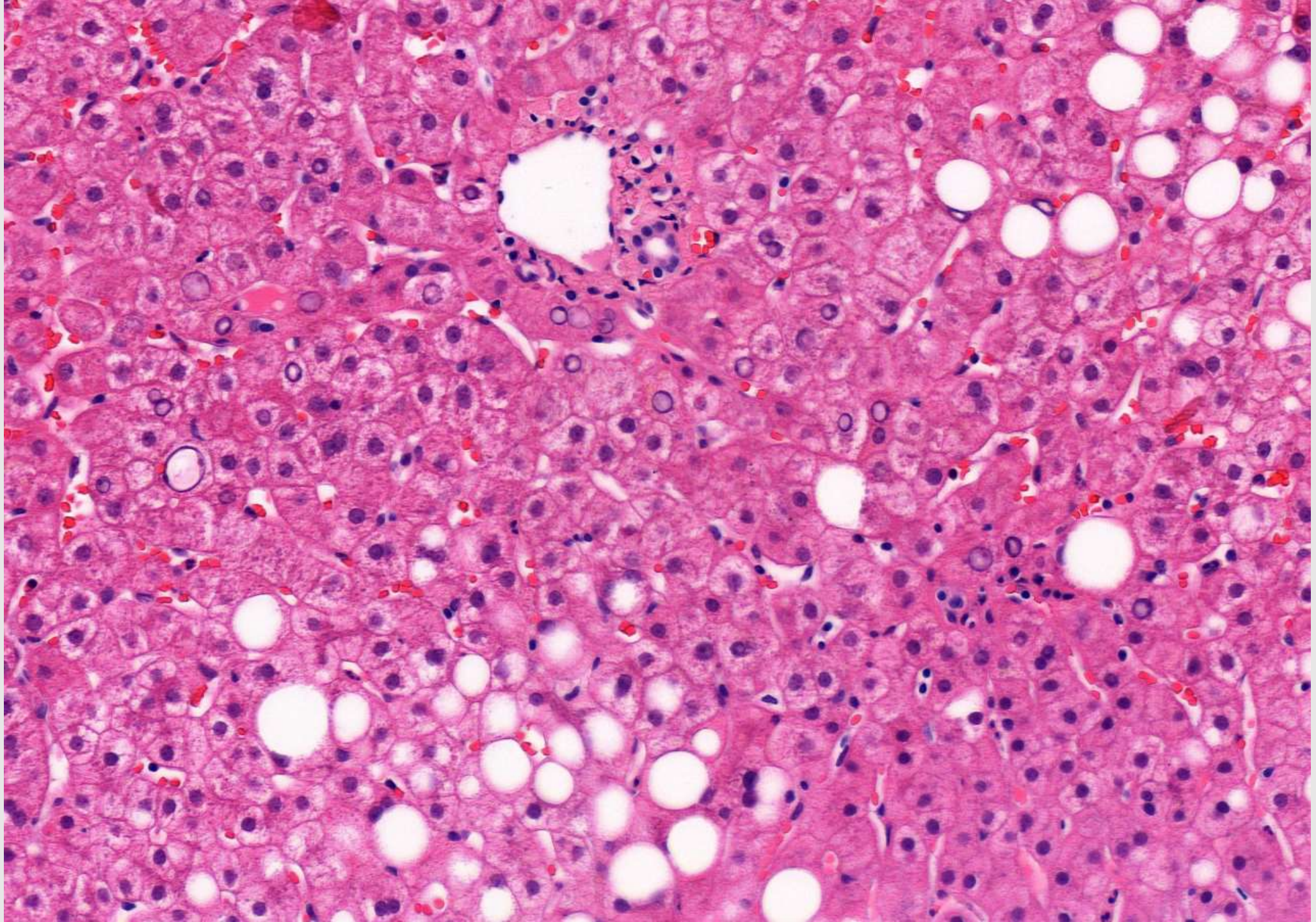


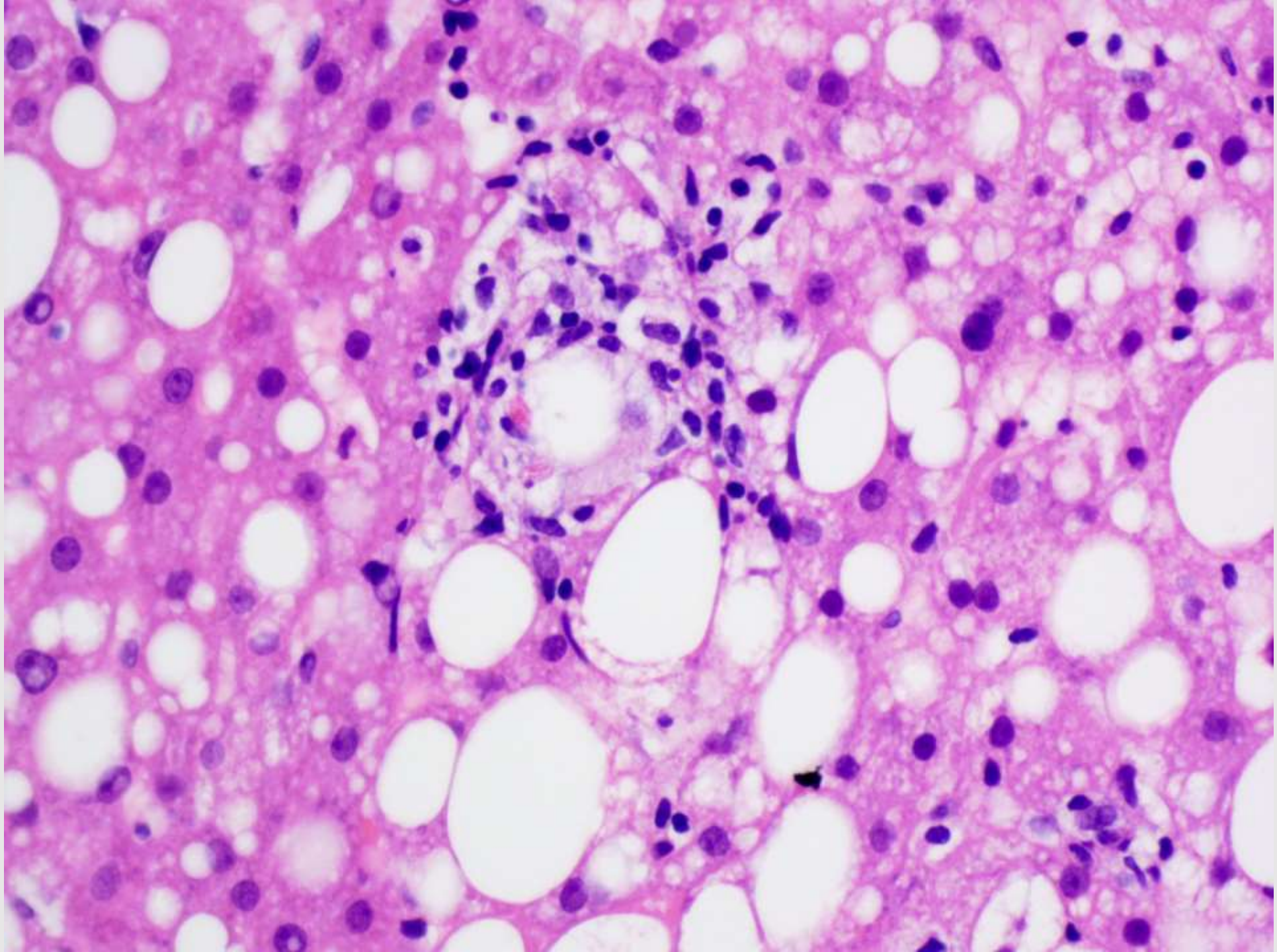
Additional findings
Non-essential features in steatohepatitis

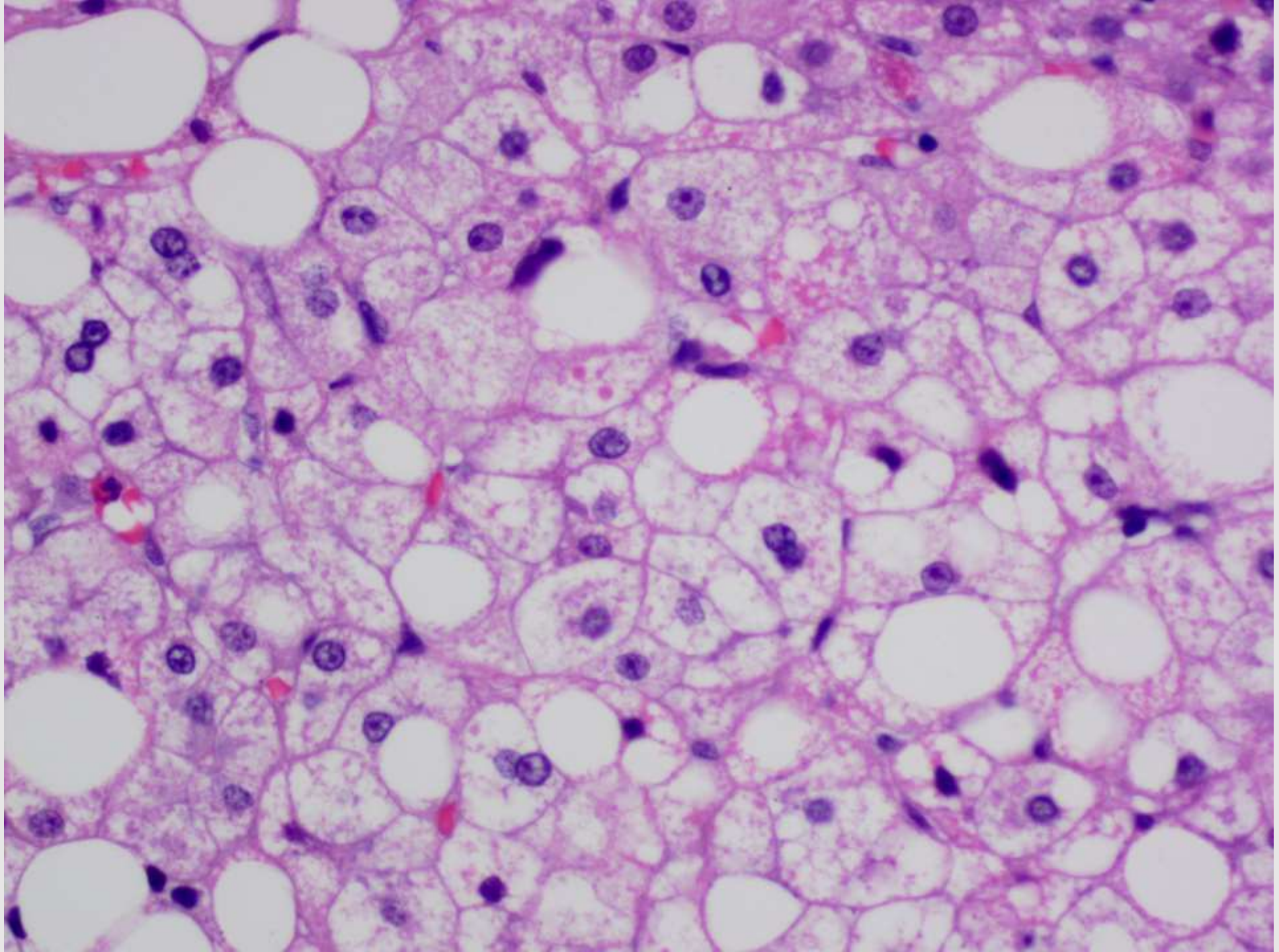
- Mallory hyaline in zone 3
- Mild iron deposits in hepatocytes or sinusoidal cells
- Glycogenated nuclei
- Lipogranulomas
- Megamitochondria
- Acidophil bodies (occasional)
- Microvesicular steatosis foci

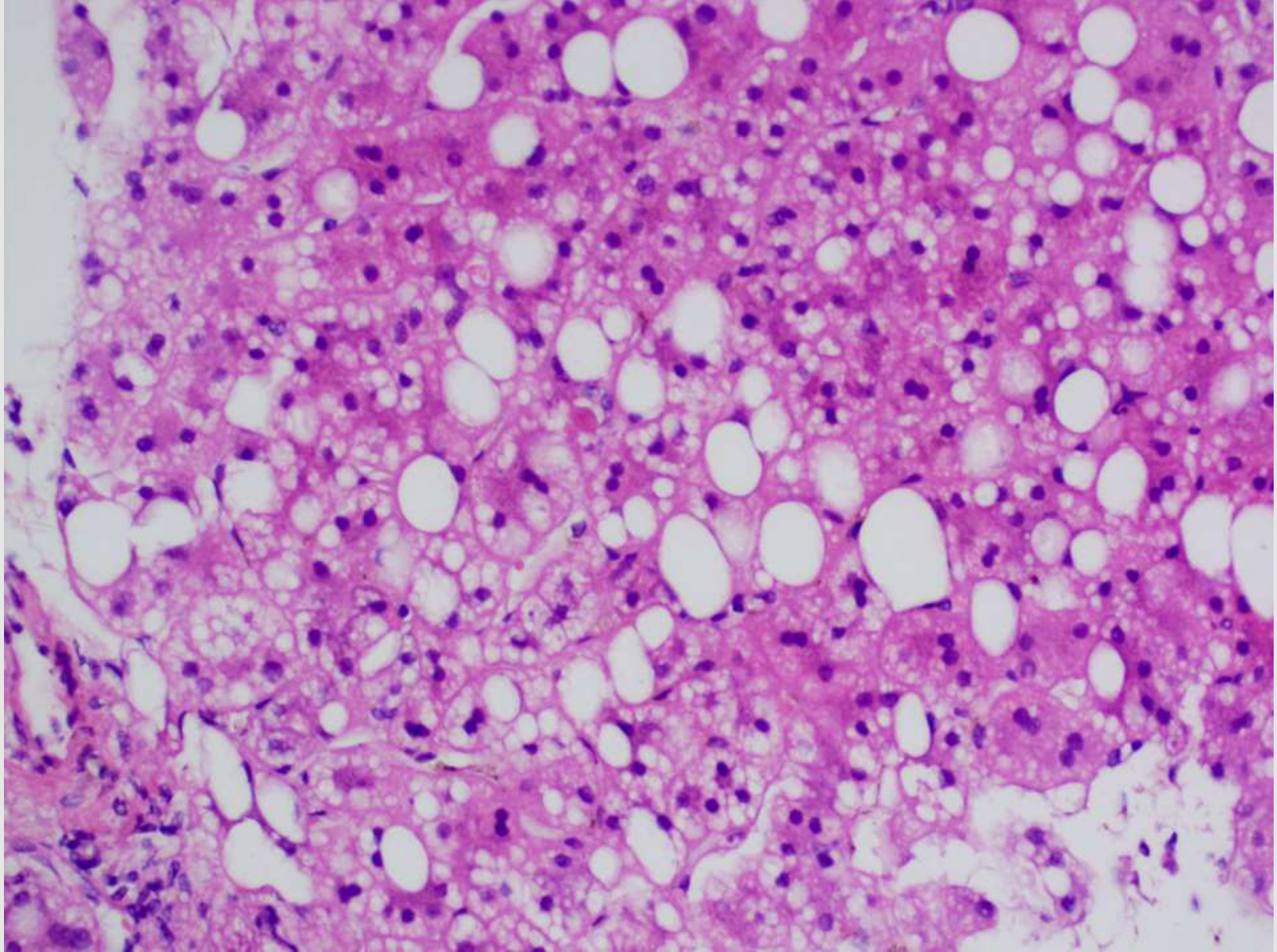












NAFLD Grading ACTIVITEIT

AASLD and NASH CRN (NASH Clinical Research Network) - INTEGRATED APPROACH

NAFLD Activity Score - NAS (Brunt/Kleiner score) - Kleiner DE et al, Hepatology 2005, 41: 1313-1321

Research purposes

- Fat
- Balloon cells
- Inflammation
- Add these to get grade
- Stage fibrosis separately

FLIP CONSORTIUM - ANALYTICAL APPROACH

SAF score - Bedossa P et al, Hepatology 2012, 5: 1751-1759

Morbidly obese patients

- Steatosis
- Activity
- Fibrosis
- Clear separation of fat from the ongoing injury (balloon cells, inflammation)

NAS (NAFLD Activity Score) (Brunt/Kleiner score)

- FAT score
  - 0 = <5% - none
  - 1 = 5-33% - mild
  - 2 = 34-66% - moderate
  - 3 = >66% - severe
- BALLOONED HEPATOCYTE score
  - 0 = None
  - 1 = **Few (rare but definite balloon cells as well as cases that are diagnostically borderline)**
  - 2 = **Many/Prominent**
- LOBULAR INFLAMMATION score **(score as average on 20X)**
  - 0 = None
  - 1 = < 2 foci per lobule
  - 2 = 2-4 foci per lobule
  - 3 = >4 foci per lobule
- Add these to get grade: score is up to 8

  Most cases diagnosed as steatosis have a total score of ≤2

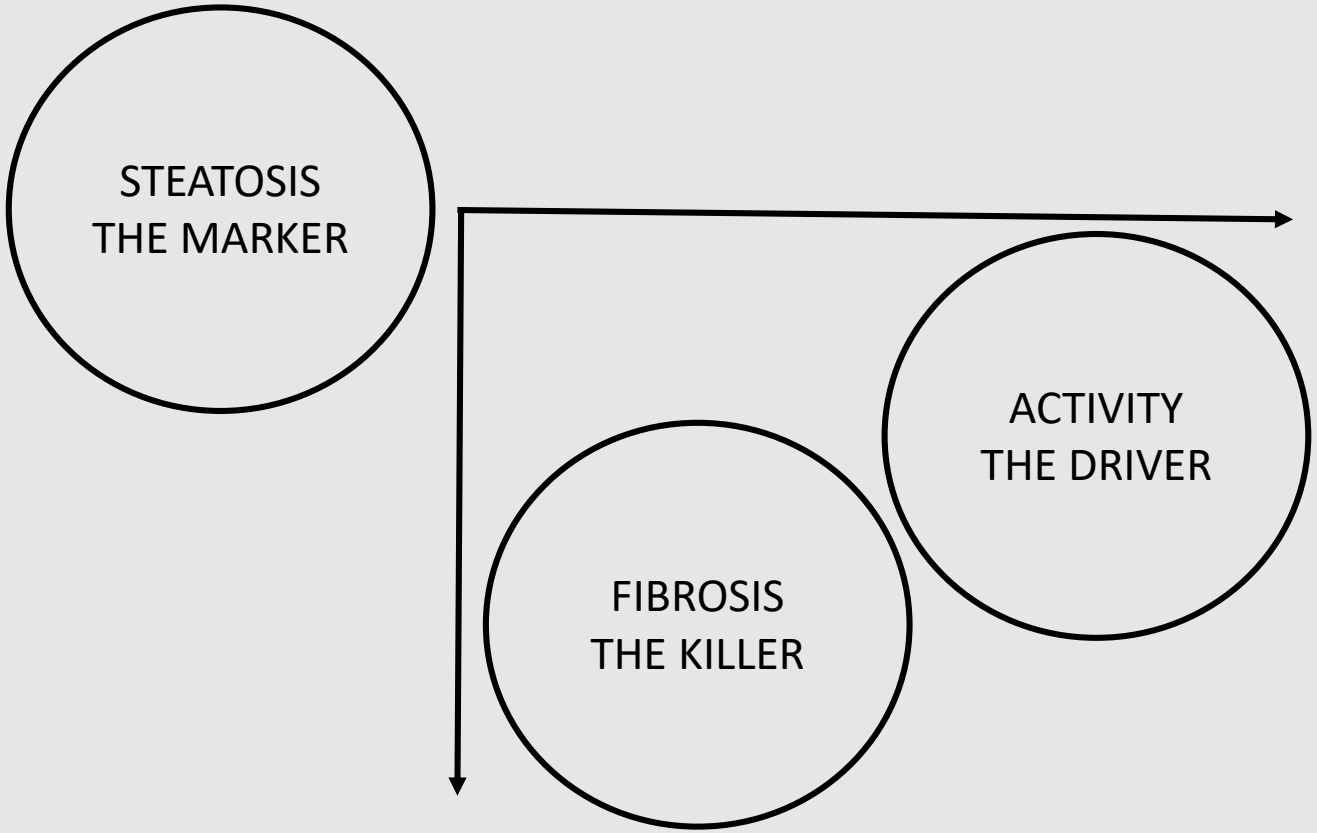
  Most cases diagnosed as steatohepatitis have a total score of ≥5

  Total score 3 or 4 can be either steatosis or steatohepatitis

Remark Bedossa P.

NAS = sum of lesions related to different mechanisms and with different clinical relevance (steatosis vs hepatocellular injury)

→ **SAF score**



Bedossa P et al, Hepatology 2012, 5: 1751-1759; Bedossa P et al, Hepatology 2014, 60: 565-575

SAF score (Steatosis-Activity-Fibrosis)

- **S**teatosis (0-3) as for NAS CRN
- **A**CTIVITY (0-4) = BALLOONING (0-2) + LOBULAR INFLAMMATION (0-2)

0= None	0= None
1= Few, size nl. hepatocyte	1= ≤ 2 foci per 20X field
2= Many, 2X size nl. hepatocyte	2= > 2 foci per 20X field

- **F**ibrosis (0-4) as for NAS CRN

S0-3**A**0-4**F**0-3

The FLIP algorithm

The definition of NASH by an association of 3 features and a clear definition of each of them makes the diagnosis of NASH strongly reproducible

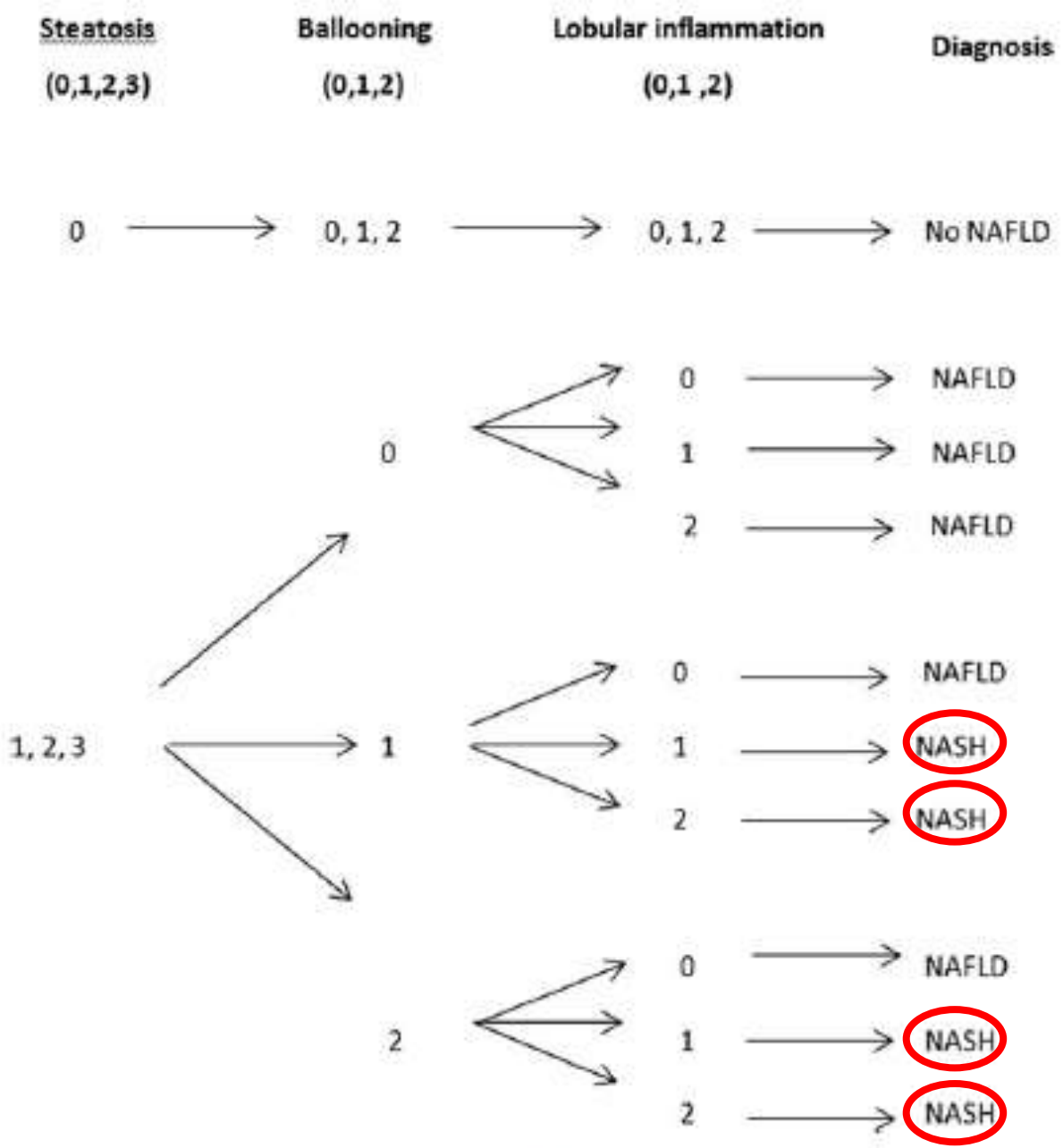
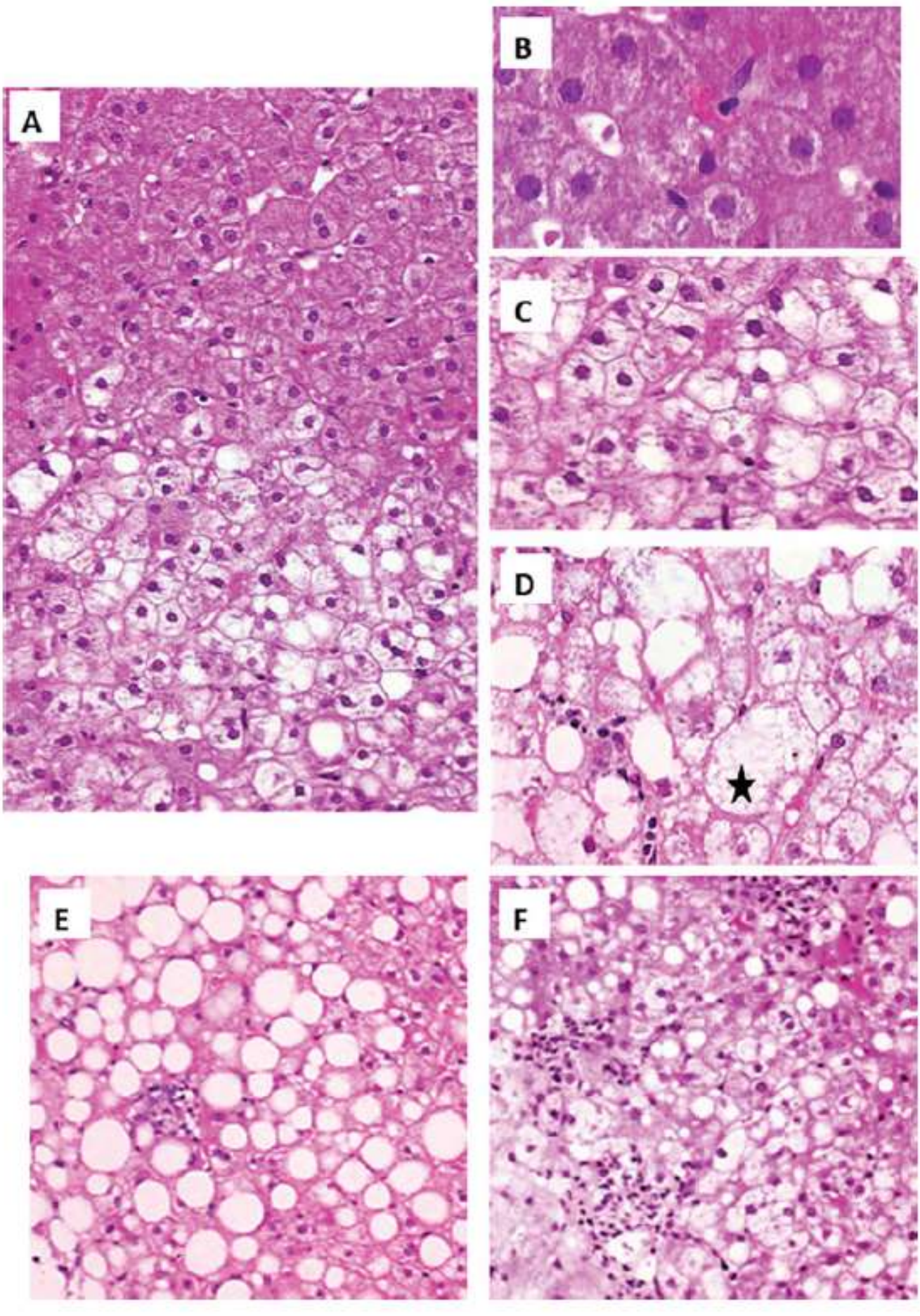


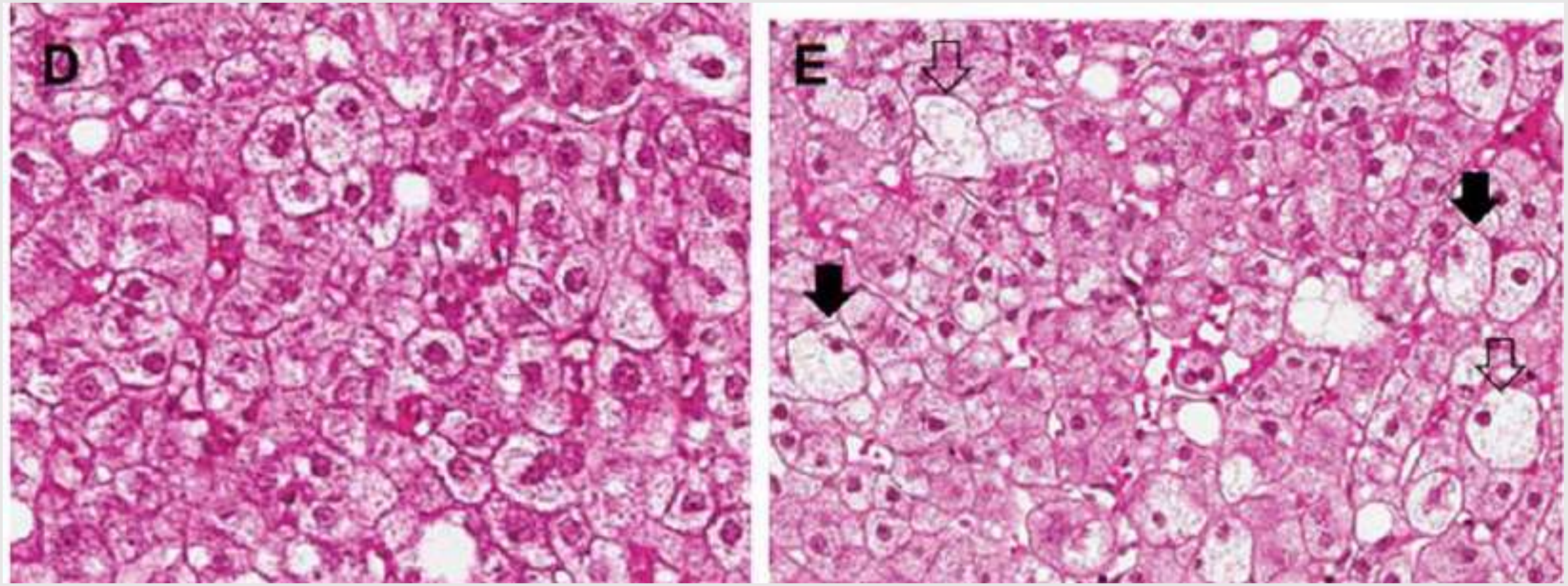
Fig. 2. Diagnostic algorithm for NASH.

Bedossa P et al, Hepatology 2012, 5: 1751-1759



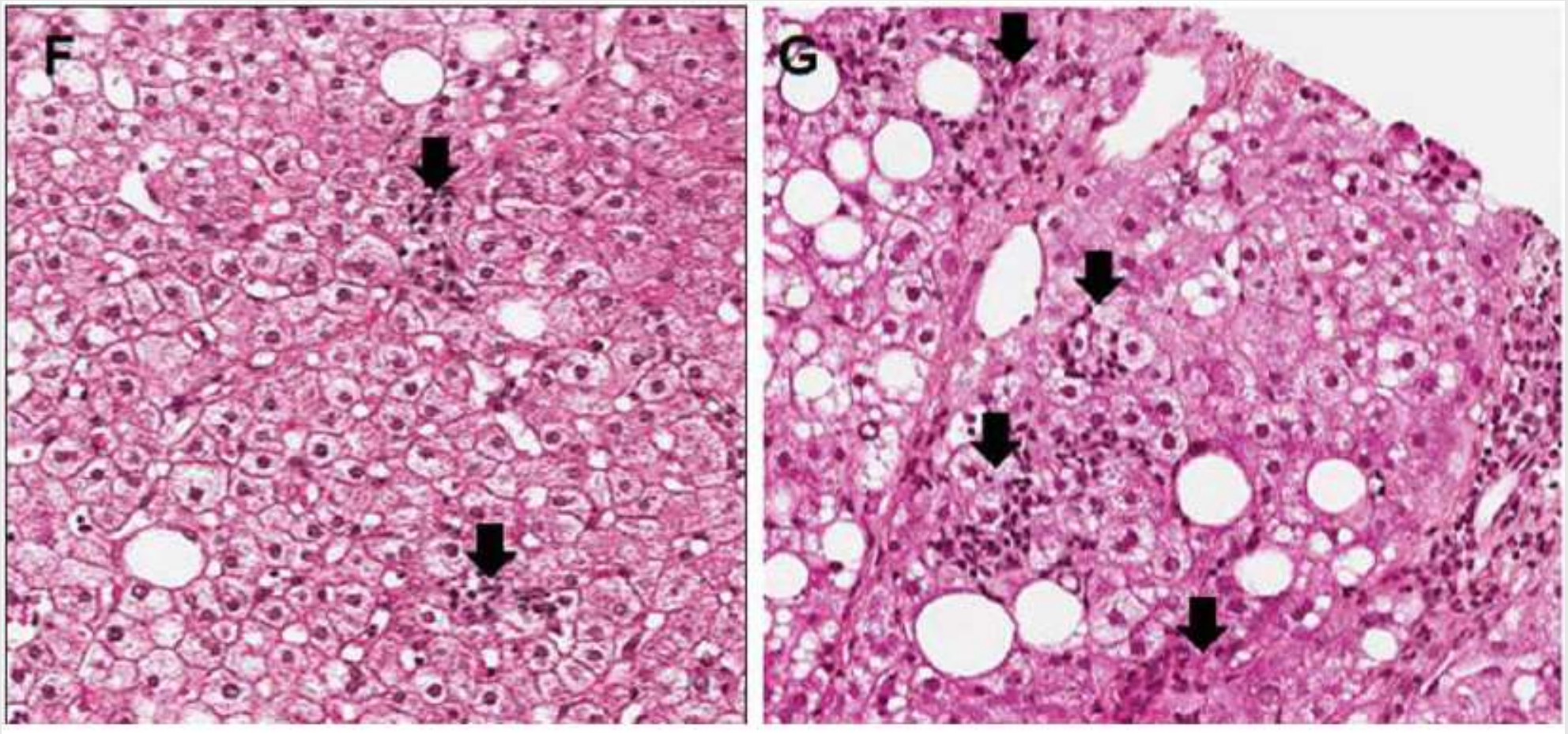
Bedossa P et al, Hepatology 2012, 5: 1751-1759

HEPATOCELLULAR BALLOONING the hallmark of NASH
SHAPE + COLOR + SIZE



Bedossa P et al, Hepatology 2014, 60: 565-575

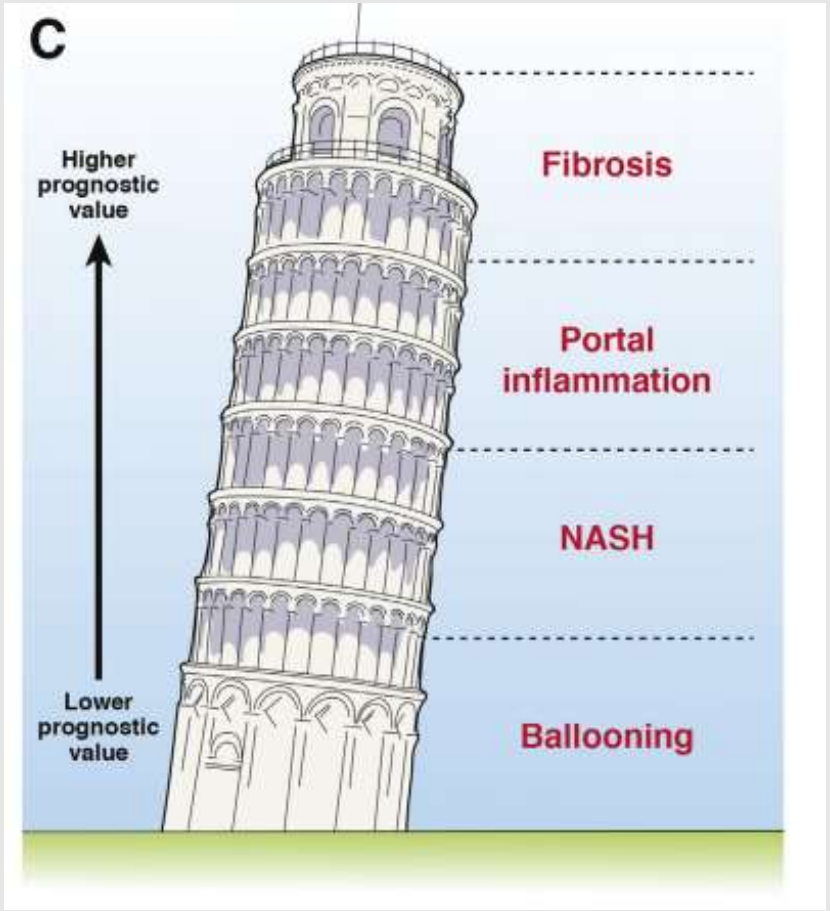
LOBULAR INFLAMMATION



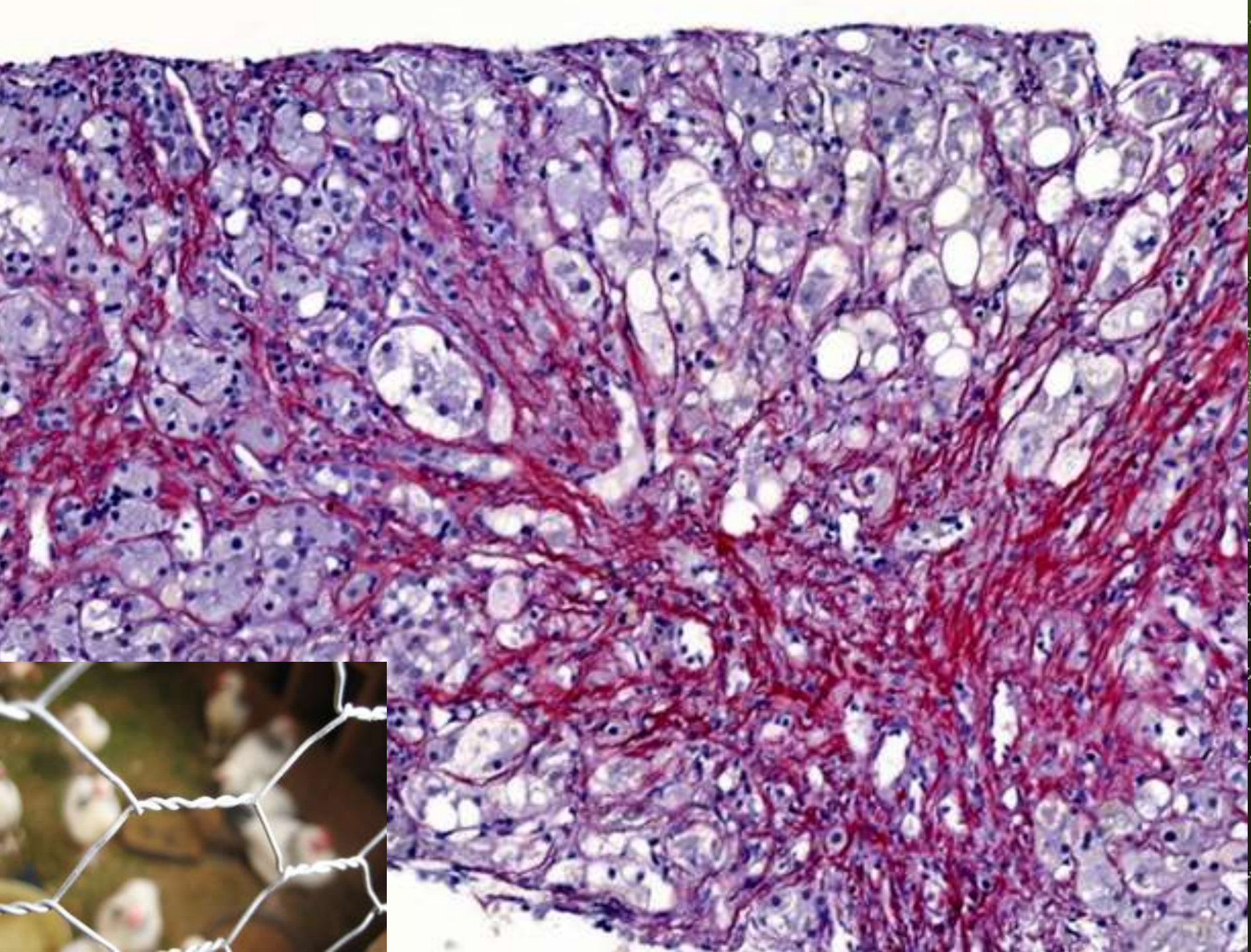
Bedossa P et al, Hepatology 2014, 60: 565-575

Fibrosis staging

- Major prognostic factor



Loomba R et al, , Gastroenterol 2015, 149 : 278-281; Angulo P et al, Gastroenterol 2015, 149: 389-397
Younossi ZM et al, Hepatology 2011, 53: 1874-1882; Ekstedt M et al, Hepatology 2015, 61: 1547-1554



Fibrosis

NAS staging system

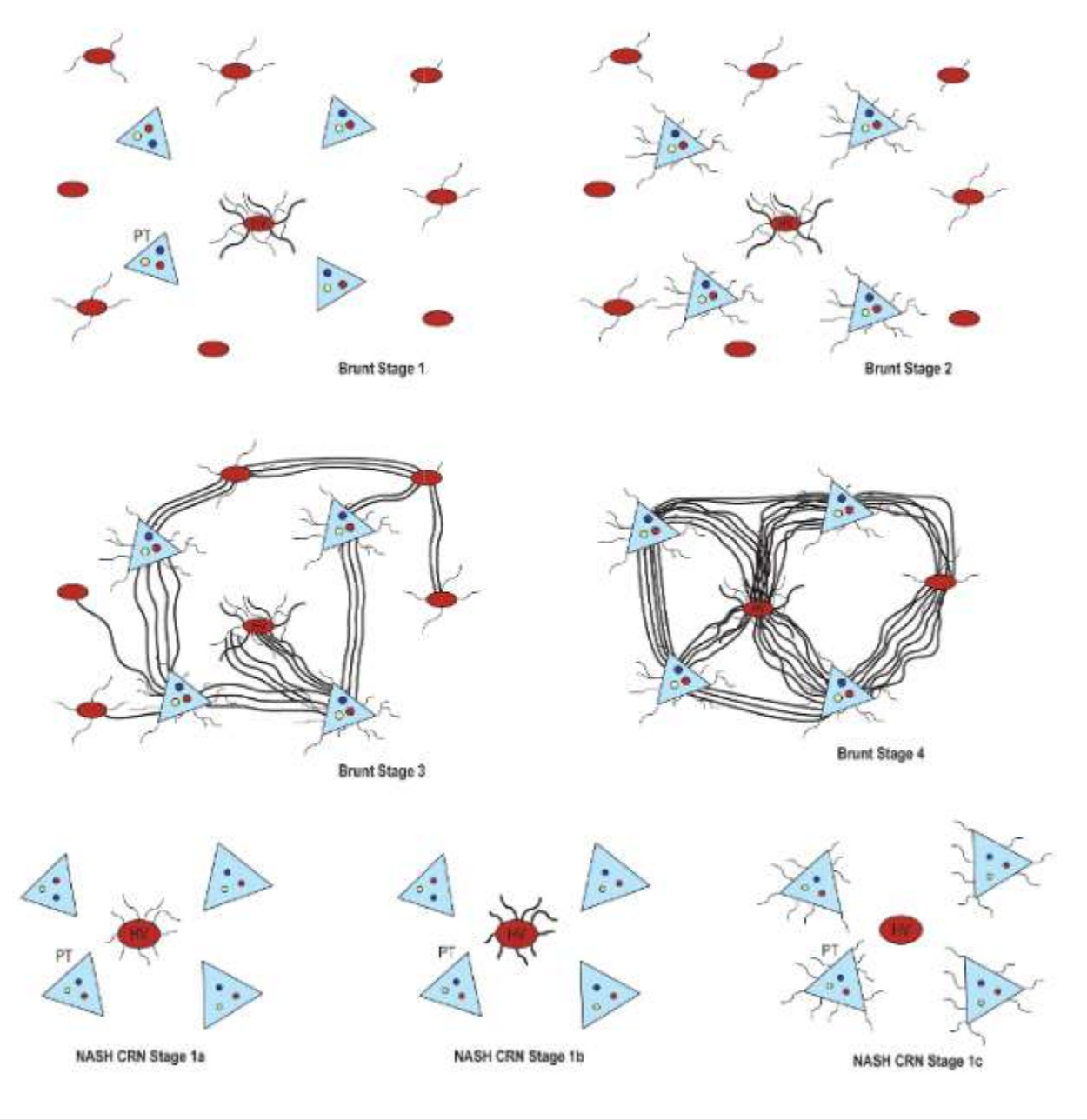
- **F0 = No fibrosis**
- **F1 = Pericellular or portal fibrosis (but not both)**
  - **F1A = Mild pericellular fibrosis (only seen on siriusred/trichrome stain)**
  - **F1B = Moderate pericellular fibrosis (readily seen on HE)**
  - **F1C = Only portal fibrosis with no pericellular fibrosis**
- **F2 = Both pericellular (any) and portal fibrosis (any)**
- **F3 = Bridging fibrosis**
- **F4 = Cirrhosis**

Fibrosis

NAS staging system

- **F0 = No fibrosis**
- **F1 = Pericellular or portal fibrosis (but not both)**
  - **F1A = Mild pericellular fibrosis (only seen on siriusred/trichrome stain)**
  - **F2A = Moderate pericellular fibrosis (readily seen on HE)**
  - **F1C = Only portal fibrosis with no pericellular fibrosis**
- **F2 = Both pericellular (any) and portal fibrosis (any)**
- **F3 = Bridging fibrosis**
- **F4 = Cirrhosis**

Portal fibrosis does not mean there is another disease



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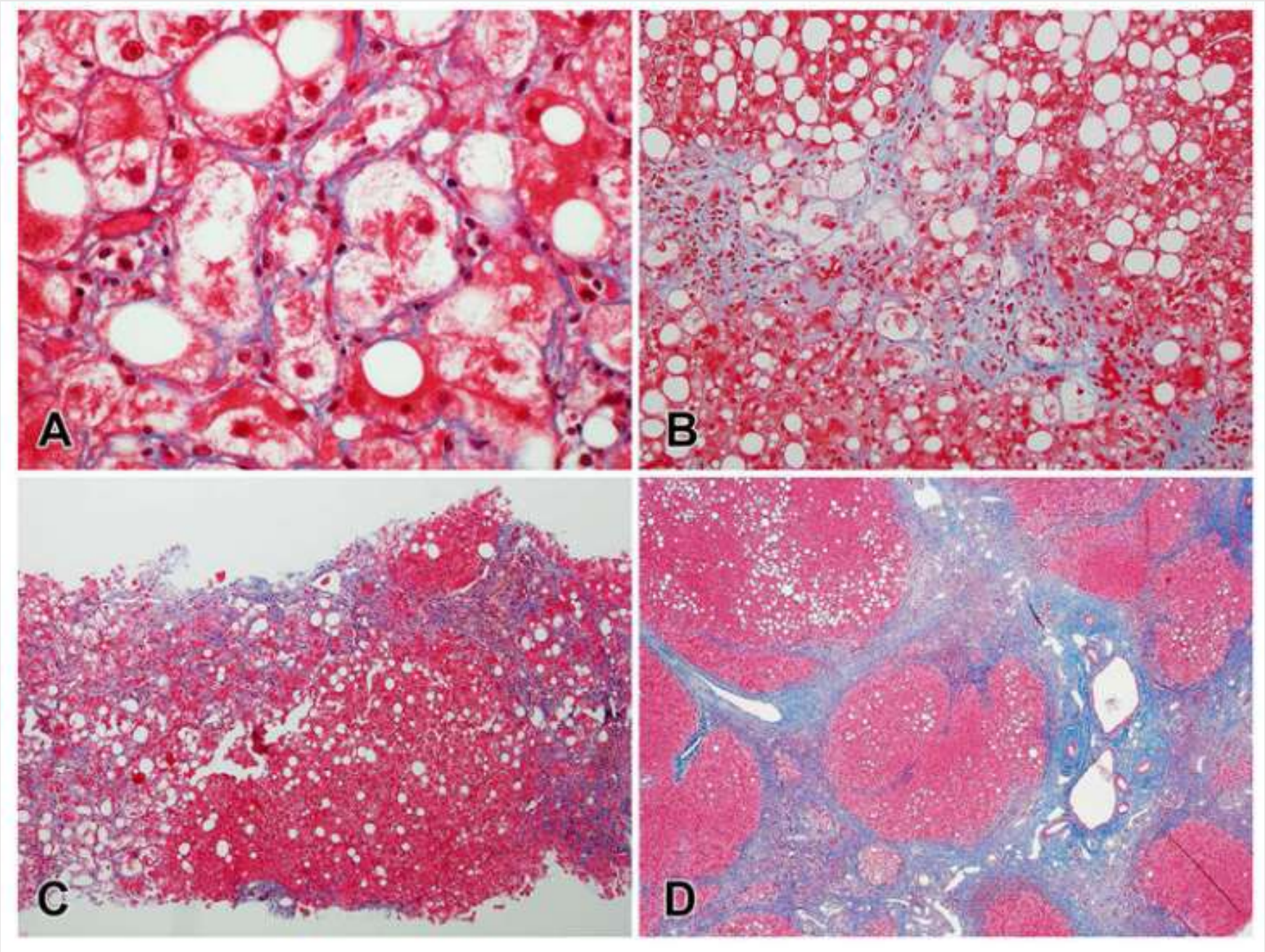
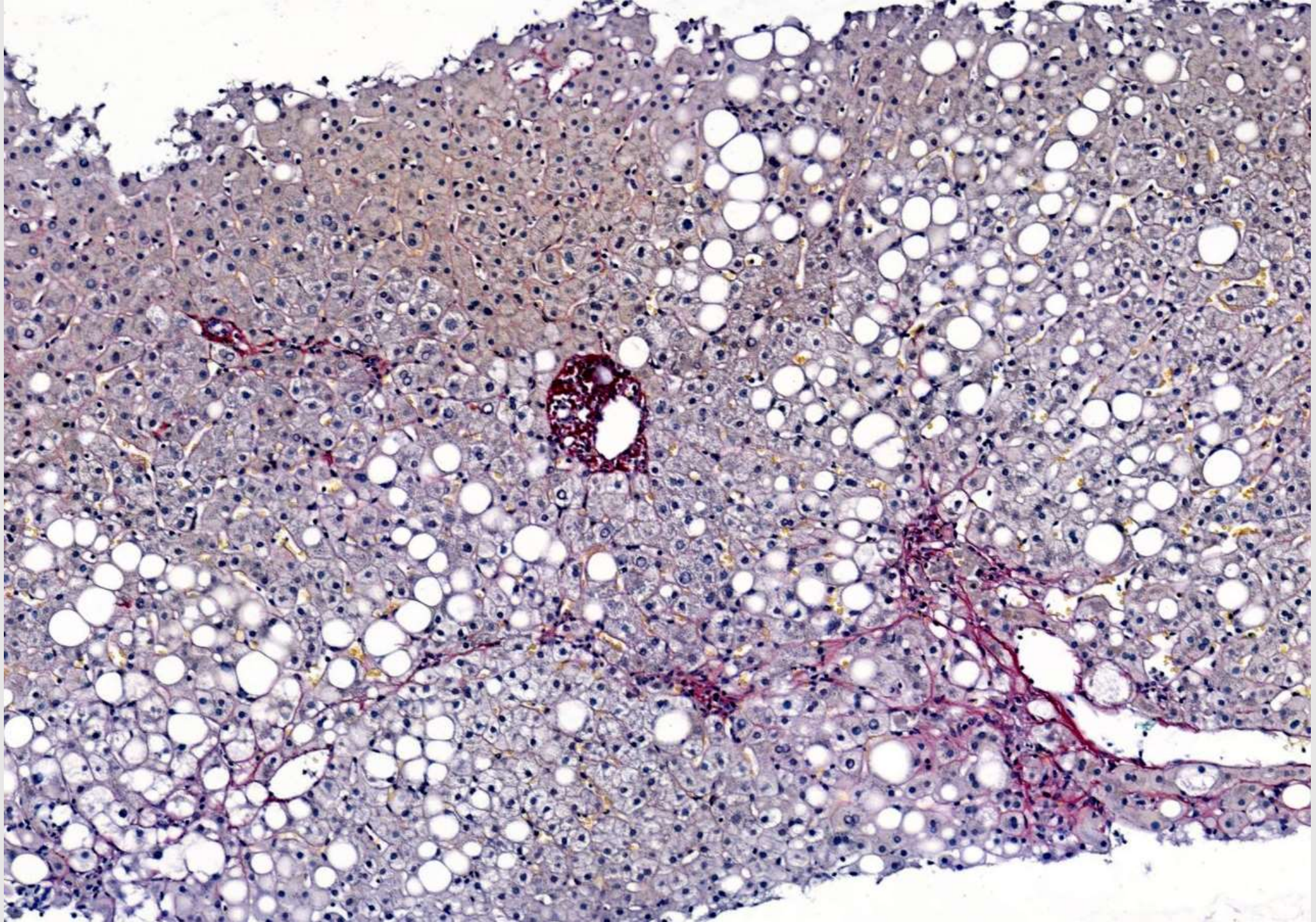
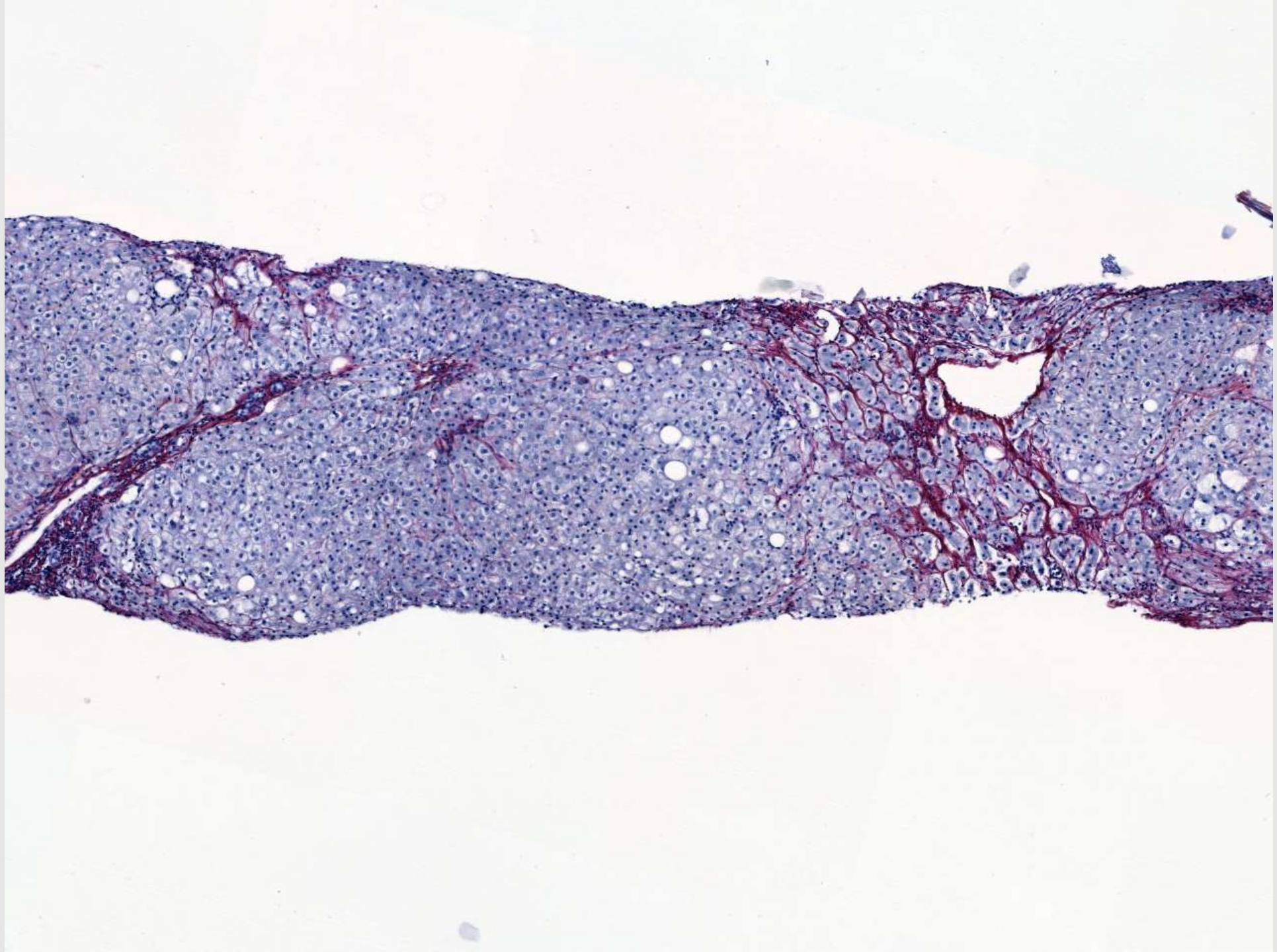
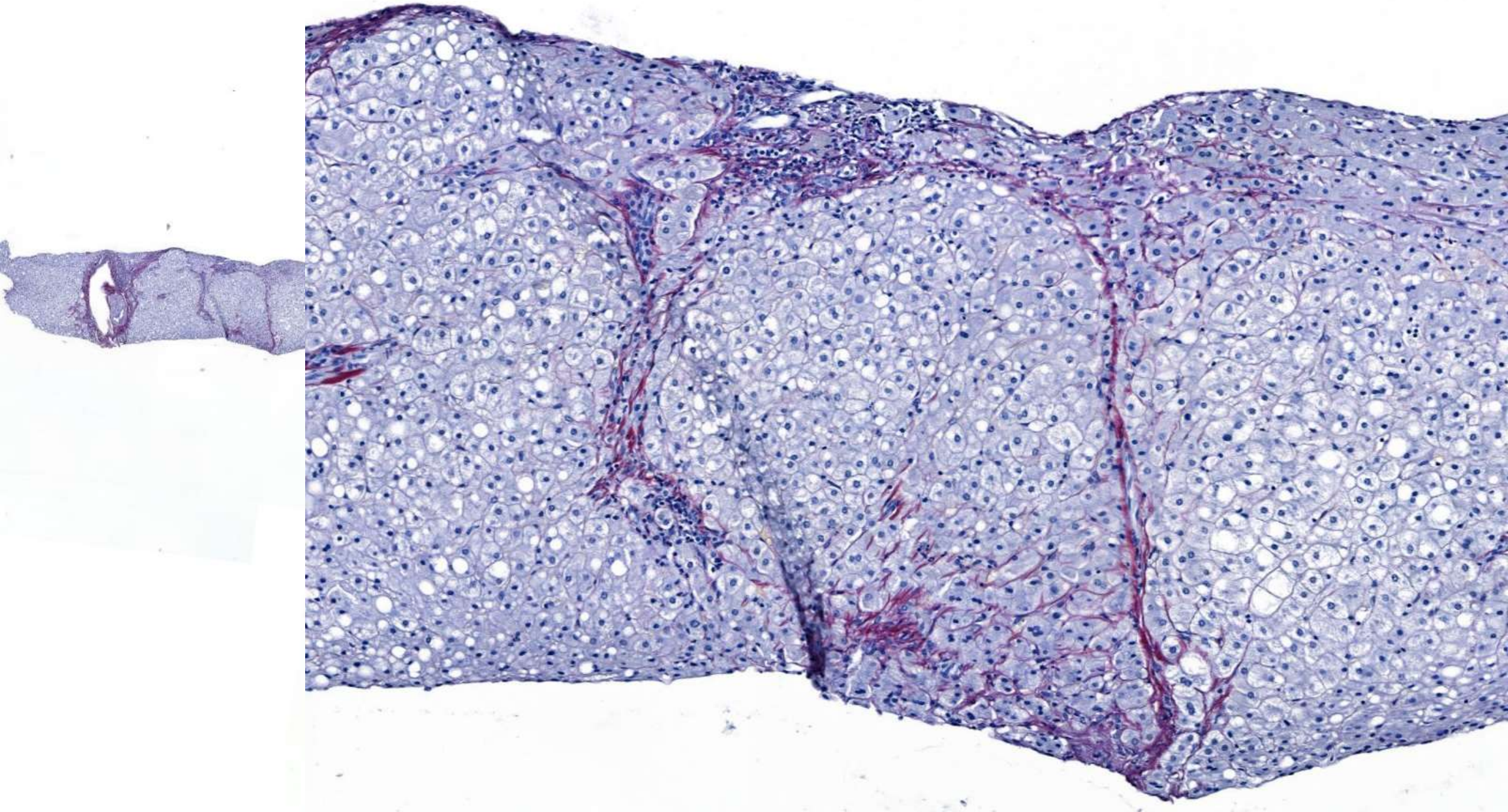


Kleiner DE et al, Clin Liver Dis , 2016, 20: 293-312







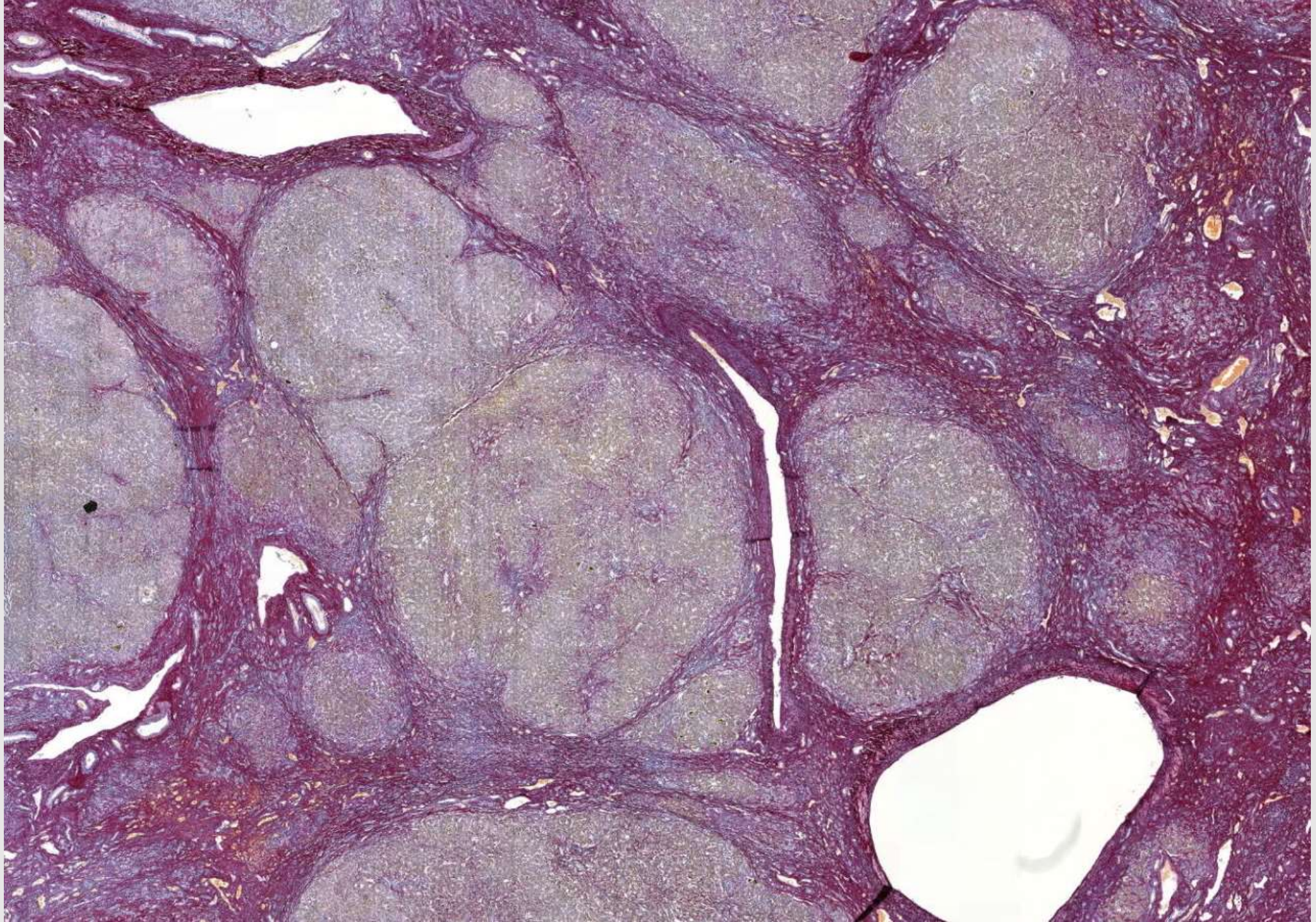
Cryptogenic cirrhosis

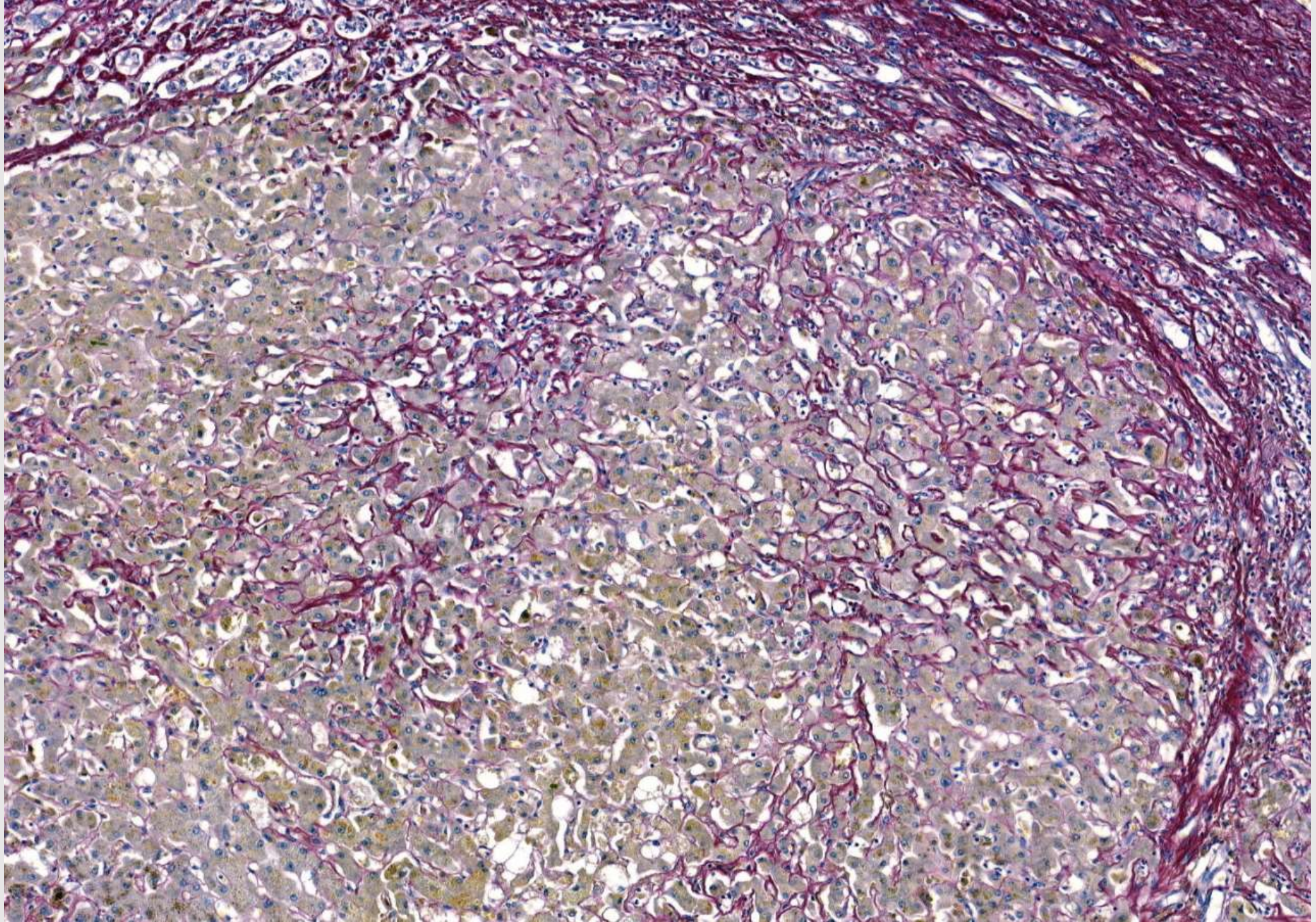
Cirrhosis with steatosis and/or ballooned hepatocytes

Cirrhosis with histologic features of NAFLD best considered NASH cirrhosis. Some cases may show residual pericellular fibrosis

"Burnt out NASH cirrhosis"

- Typical steatohepatitis features, including fat, regress with progression of fibrosis and may be lost with cirrhosis
- Many cases labelled as cryptogenic cirrhosis; since this population has a high incidence of type 2 DM, NASH is considered to be the most likely etiology
- Rule out other etiologies and correlate with NASH risk factors



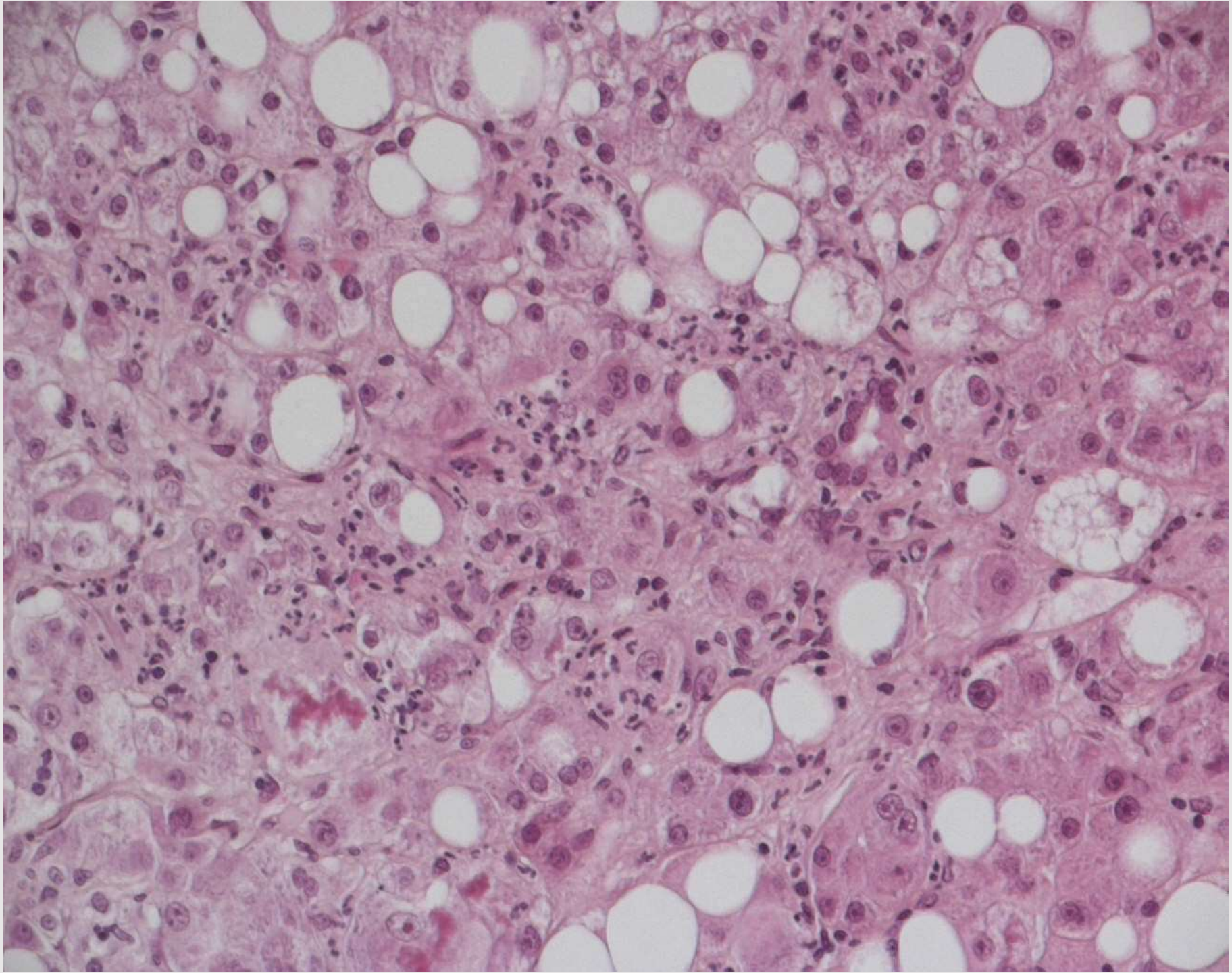


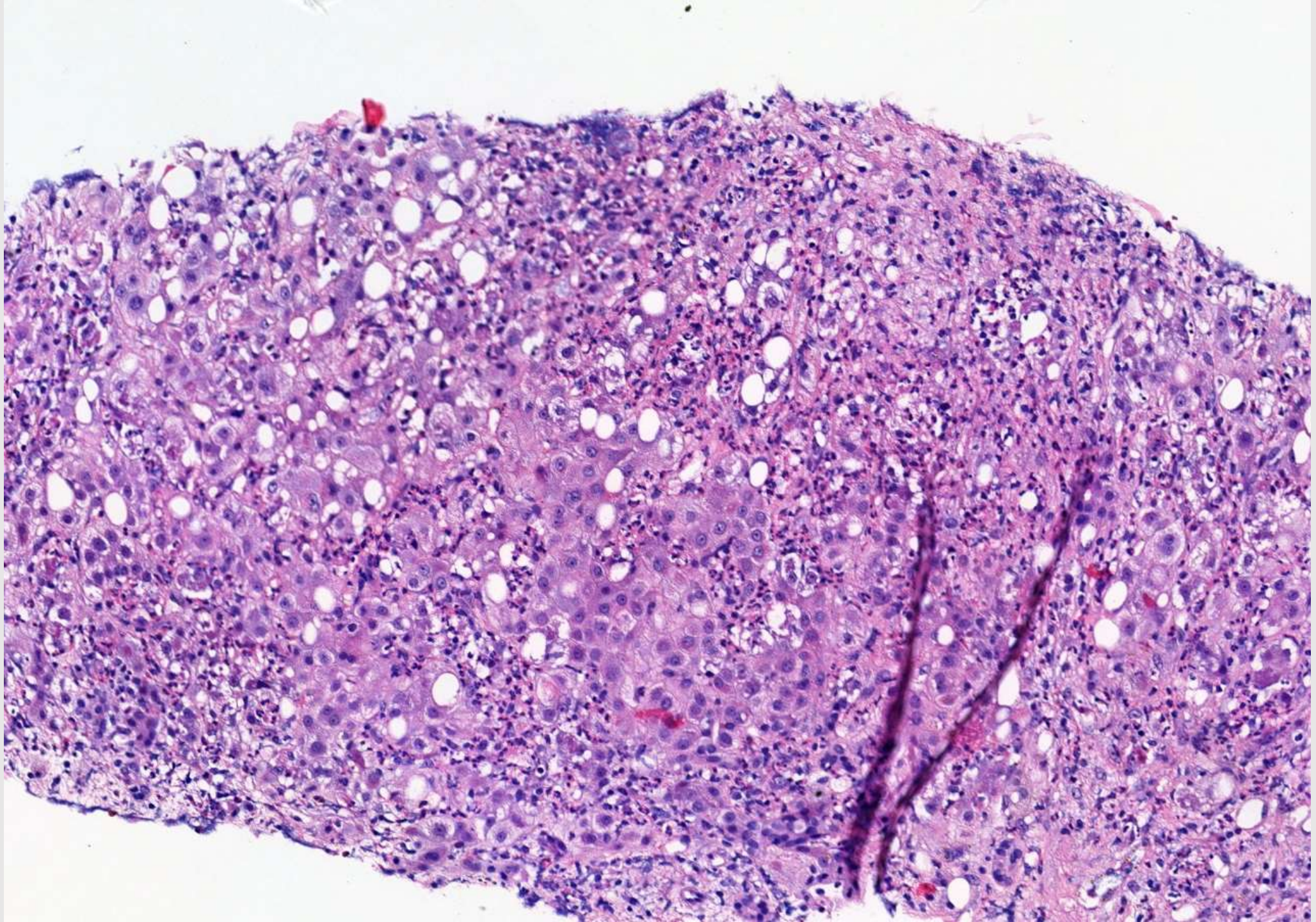
Diagnostic challenges

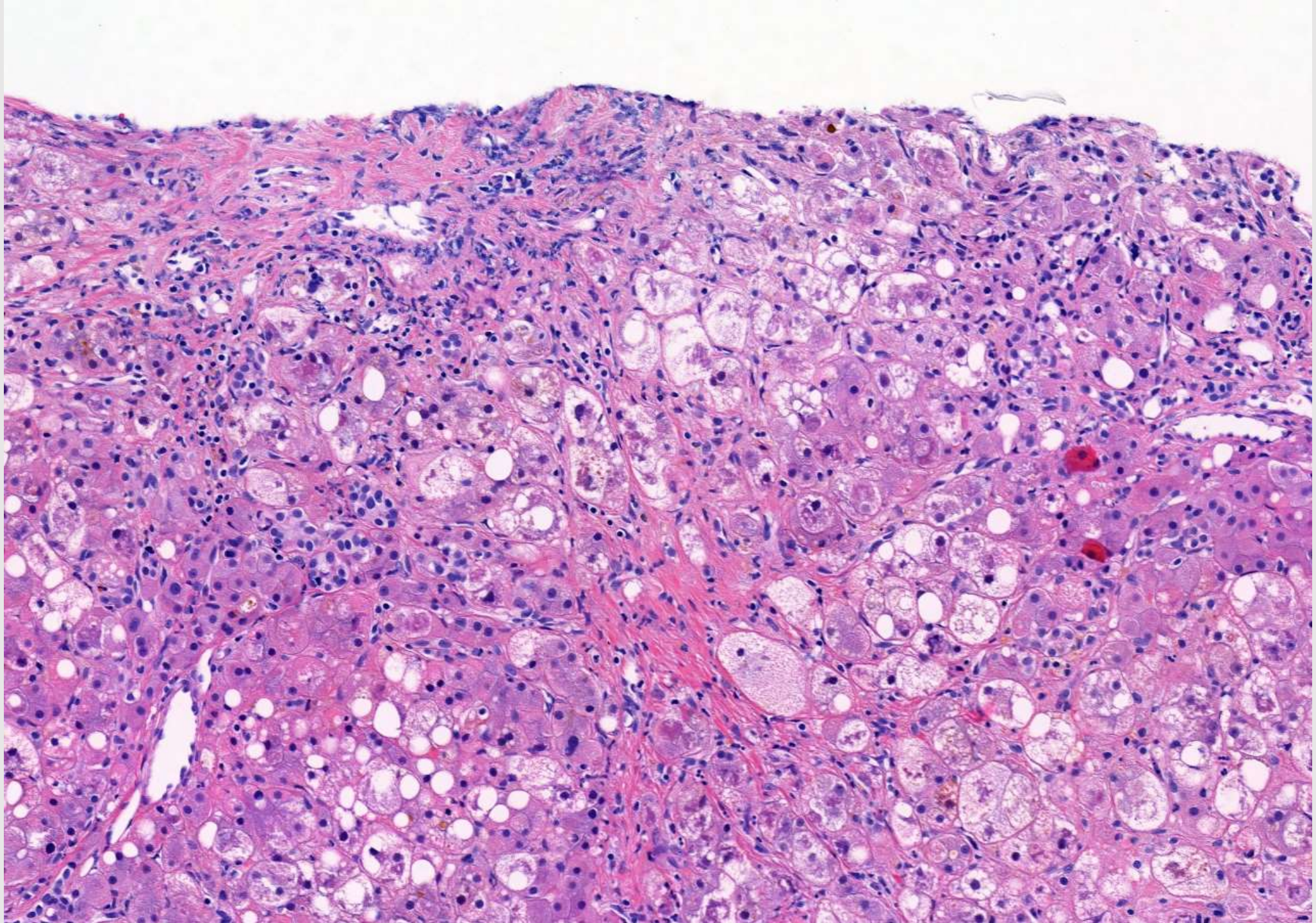
Alcoholic steatohepatitis

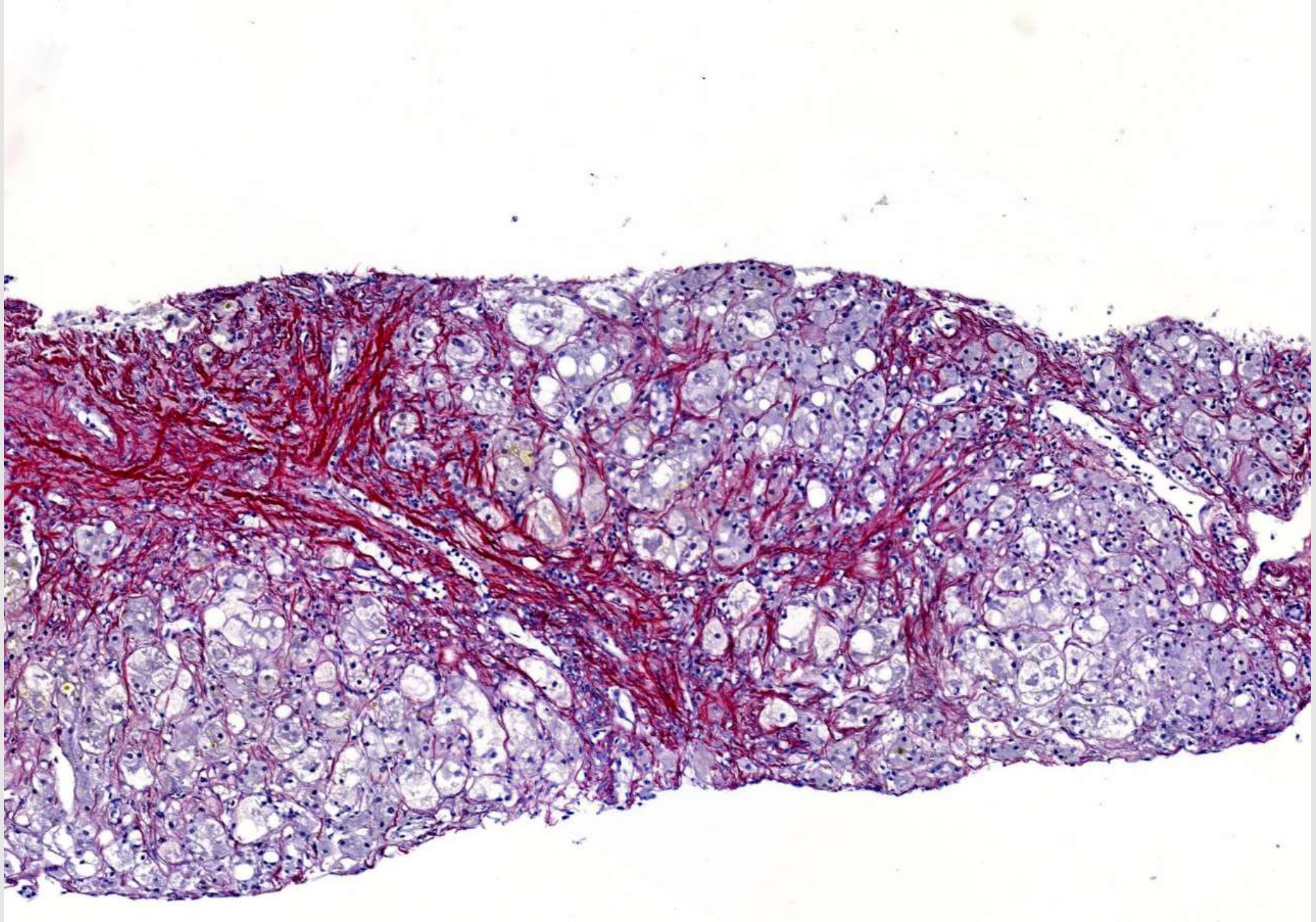
Can not be definitively distinguished from NASH by histology

	NASH	ASH
Steatosis	++	+
Ballooned hepatocytes	+	++
Lobular inflammation	+	++
Mallory hyaline	+	++
Neutrophil infiltrate	+	++
Cholestasis	+/-	+
Obliterated CV	+/-	+









Drug induced steatohepatitis

Histological changes identical to NASH have been identified in patients without NASH risk factors exposed to certain drugs

- Amiodarone
- Irinotecan
- Methotrexate
- Perhexiline Maleate
- Tamoxifen
- Steroids
- Estrogen

Metabolic disorders

Wilson disease

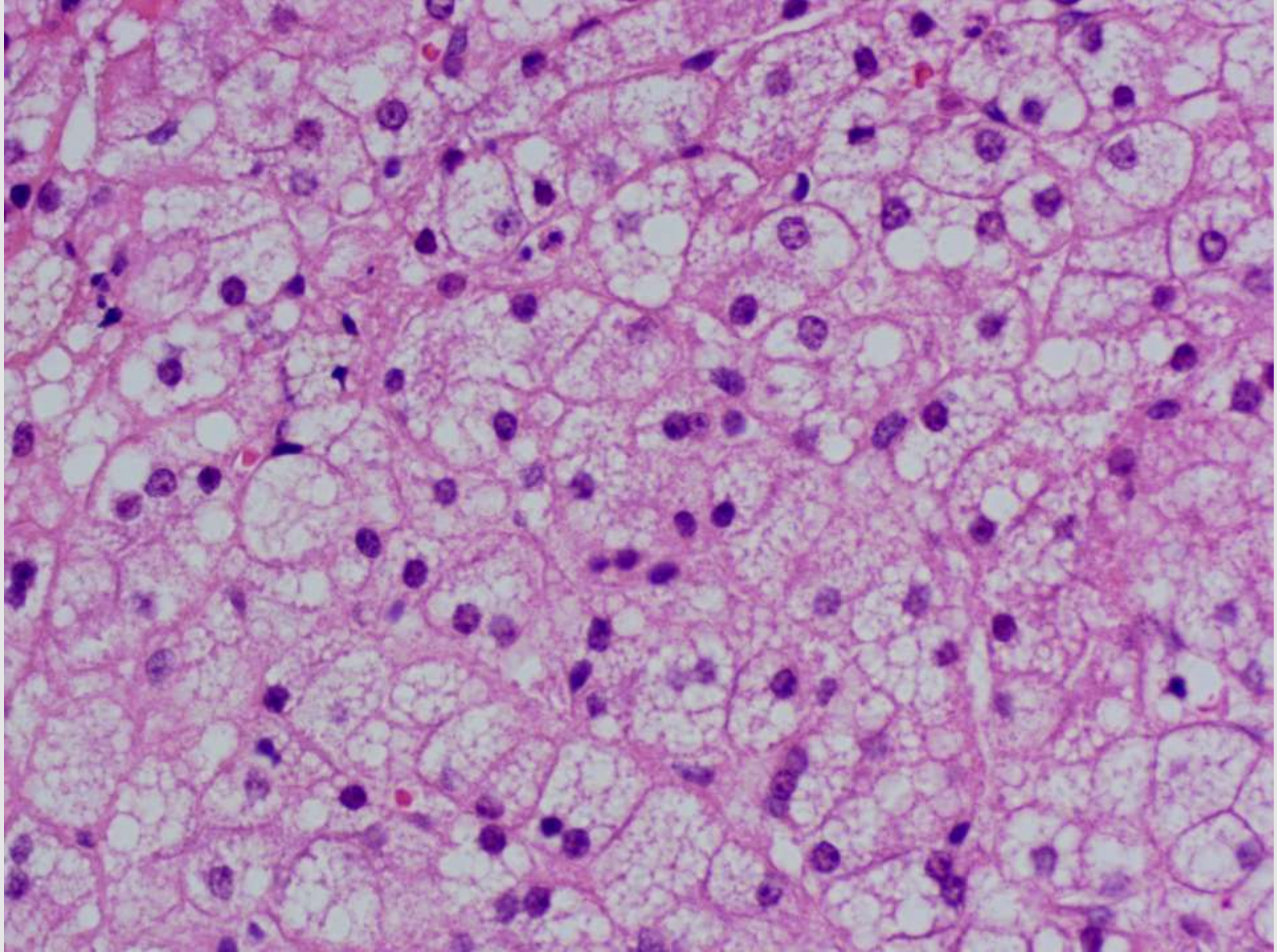
Steatosis (non-zonal), glycogenated nuclei, Mallory hyaline in periportal hepatocytes, swollen hepatocytes, portal inflammation, and fibrosis

Microvesicular steatosis

- **Pure** microvesicular steatosis **does not occur in NASH** and indicates severe mitochondrial injury

  - Reye syndrome - salicylates
  - Acute fatty liver of pregnancy
  - Drug (cocaine, tetracycline, antiretrovirals, valproate)
  - Rare genetic disorders
  - Alcoholic foamy degeneration

- Many NAFLD cases will have minor component of microvesicular fat



SUMMARY

STEATOHEPATITIS

- **Most are NASH or alcohol-related**
- **Steatosis = Fat (no other injury)**
- **Steatohepatitis = Fat + Liver injury**

  Balloon cells/Lobular inflammation
- **Distinctive pattern of fibrosis with pericellular fibrosis**

Thank you for your attention