Liver disease affecting children and teenagers with transition into adult care

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How different is medical liver biopsy in paediatrics?

- Not discussing neonatal biopsies or tumour biopsies
- Not so much!

- Metabolic liver disease
- Autoimmune liver disease

Metabolic liver disease

- Am I missing something?!
- Fewer biopsies are taken now in metabolic liver disease – less chance to see good examples
- Easier when the metabolic disease is known and the purpose of biopsy is staging or in the context of a trial, rarely for conditions associated with neoplasia
- Problem when metabolic disease not suspected clinically or you might be looking at a metabolic disease mimicking something else

Resources

- Ishak paper
- Patterns of histological damage in metabolic disease

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Hepatic Morphology in the Inherited Metabolic Diseases*

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Many of the inherited metabolic diseases (IMD) affect the liver. In some, for example Wilson's disease and primary hemochromatosis, the liver is one of the main "target" organs. On the other hand, involvement of the liver in some IMD, for example [illegible] chondrodystrophy, may be secondary. The histopathologic manifestations of the IMD in the liver are quite variable. Some are characterized by the accumulation of a particular metabolic product in one of the systems of the liver, for example liver cells, canaliculi, or reticuloendothelial cells. Others are manifested by lesions resembling those induced by a variety of other etiologies. Such lesions include cholestasis, acute or chronic necroinflammatory disease, fibrosis, cirrhosis, or benign or malignant tumors. To some extent, these varied manifestations depend on the age of the patient at the time of diagnosis or the stage of the disease. A typical example is alpha$_1$-antitrypsin deficiency that is manifested shortly after birth by "neonatal hepatitis," but later in childhood or adulthood by chronic active hepatitis or cirrhosis.

In this review the IMD are grouped together on the basis of their predominant histopathologic lesions, rather than being discussed in the traditional way (for example, disorders of carbohydrate metabolism or lipid metabolism).

CHOLESTASIS

Acute Cholestasis

"Bland" Cholestasis

Bland cholestasis is typical of benign recurrent cholestasis and recurrent jaundice of pregnancy. The intrahepatic cholestasis of these disorders is generally acute, residual effects are not seen between cholestasis episodes, and long-term sequelae are unknown. Another familial disorder characterized by recurrent cholestasis with lymphedema has been reported.[1,2]

Cholestasis And Giant Cell Transformation

Cholestasis associated with giant cell transformation and with unicellular hepatocytic degeneration is characteristic of neonatal hepatitis; this pattern of injury can result from a variety of insults.[3] Of the IMD manifested initially by neonatal hepatitis, alpha$_1$-antitrypsin is probably the most important. About 10% of homozygous individuals develop neonatal hepatitis after birth.[4] Other less frequent causes include Niemann-Pick disease,[5] the familial cholestasis of North American Indians,[6,7] and arteriohepatic dysplasia.[8–10]

Pseudogland Formation and Fatty Metamorphosis

Acute cholestasis with pseudogland formation and fatty metamorphosis is typical of the early stages of galactosemia and tyrosinemia[11] and to a lesser extent hereditary fructose intolerance. The last condition is mainly manifested by fatty metamorphosis and variable fibrosis.[12,13] All three conditions, but especially galactosemia (if untreated) and tyrosinemia, eventually culminate in cirrhosis.

Chronic Cholestasis

Paucity of Intrahepatic Bile Ducts

Chronic cholestasis with paucity of intrahepatic bile ducts is seen in arteriohepatic dysplasia,[8] coprostanic acidemia,[14,15] and a few other very rare conditions.[11] Despite the remarkable paucity of intrahepatic bile ducts, the cholestasis features in arteriohepatic dysplasia (also known as Alagille's syndrome) are minimal and easily overlooked; they include scattered bile plugs and pseudoxanthomatous foci and mild to moderate copper storage.[8] The loss of bile ducts is progressive from early infancy to childhood, and cholangiodestructive changes have been observed in children between 3 and 6 months of age.[9,10] Distinctive ultrastructural changes have been reported recently by [illegible]

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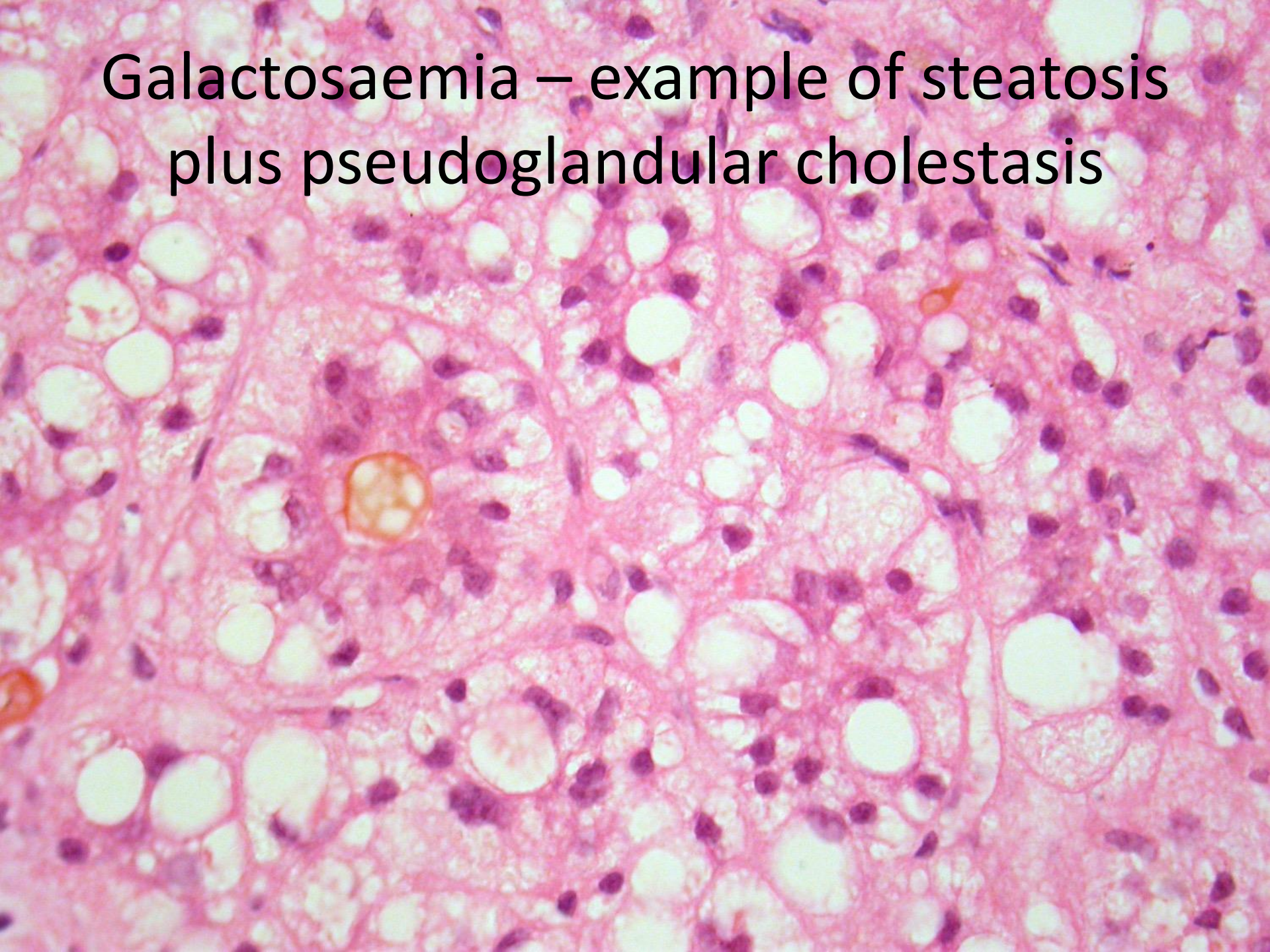
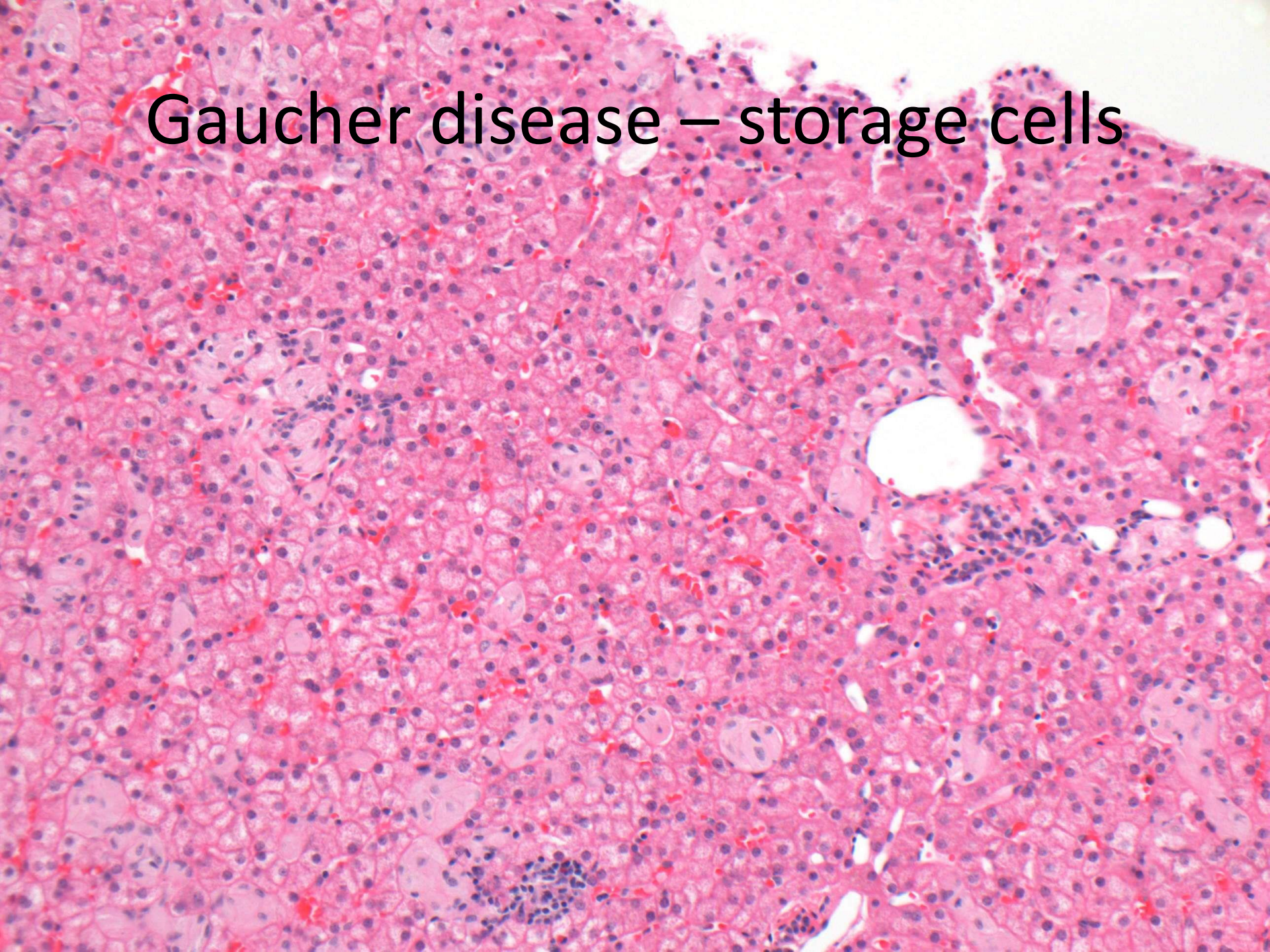
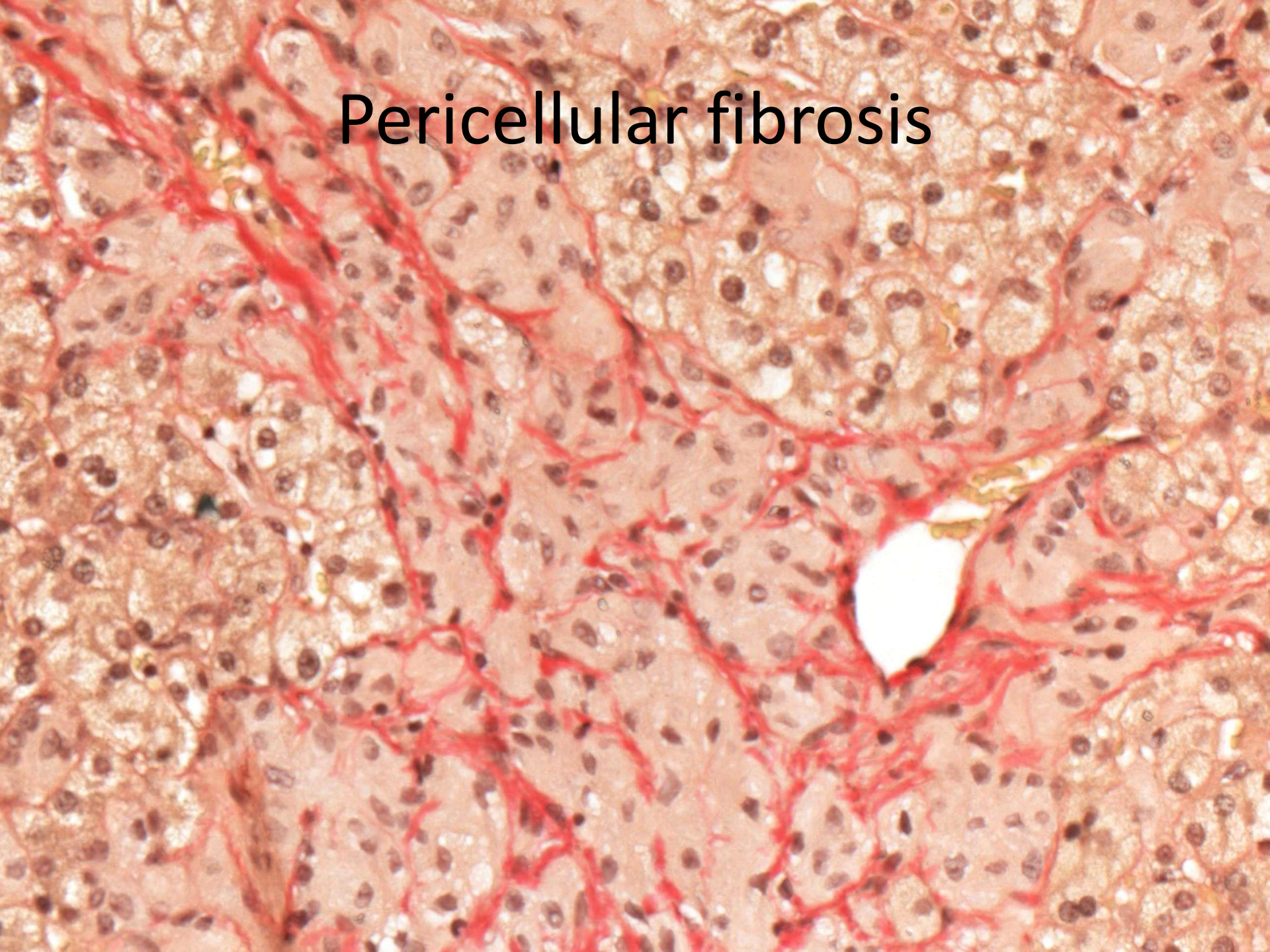
*The opinions and assertions contained herein are the private views of the author and do not necessarily reflect

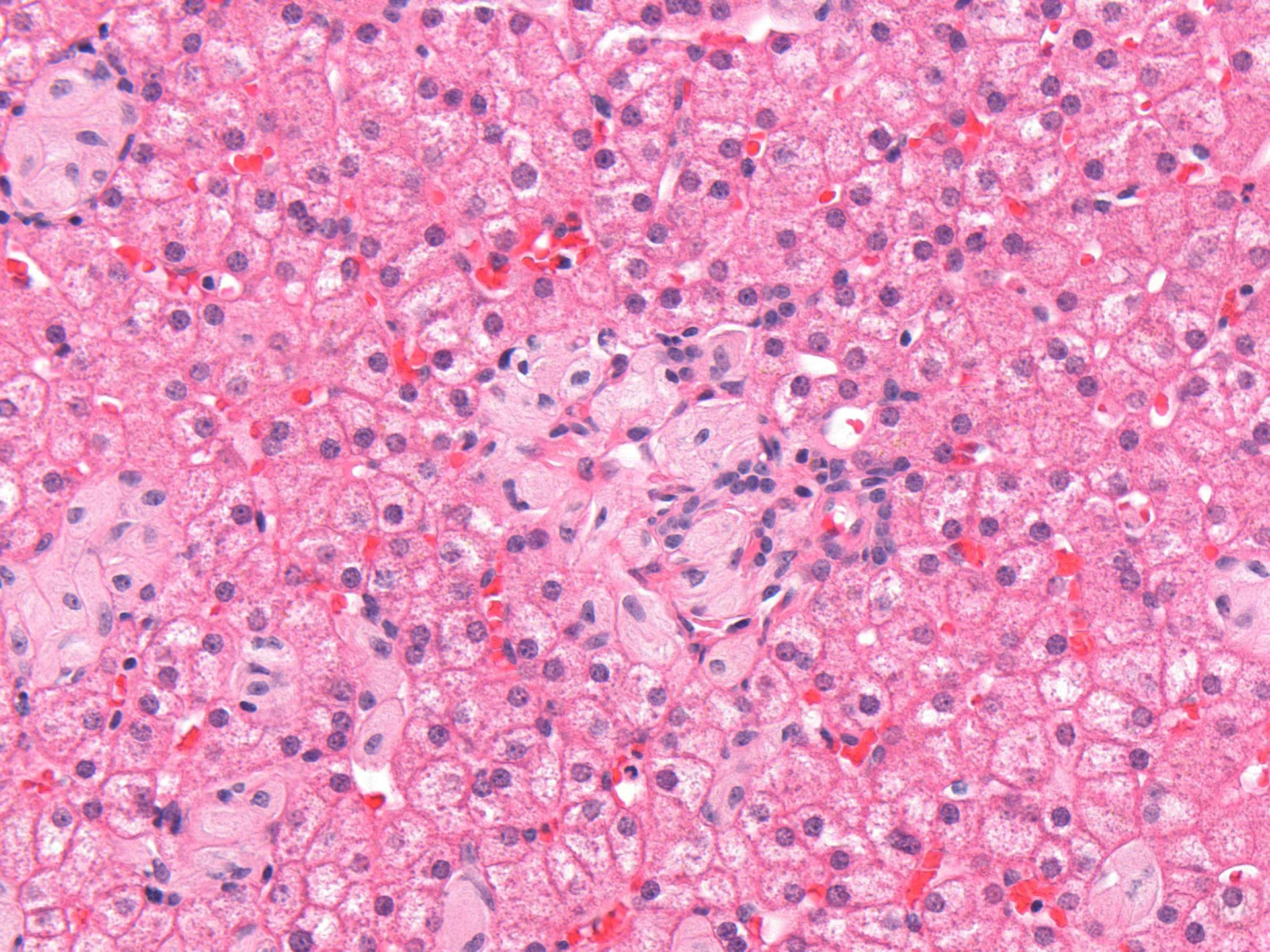
Galactosaemia – example of steatosis plus pseudoglandular cholestasis

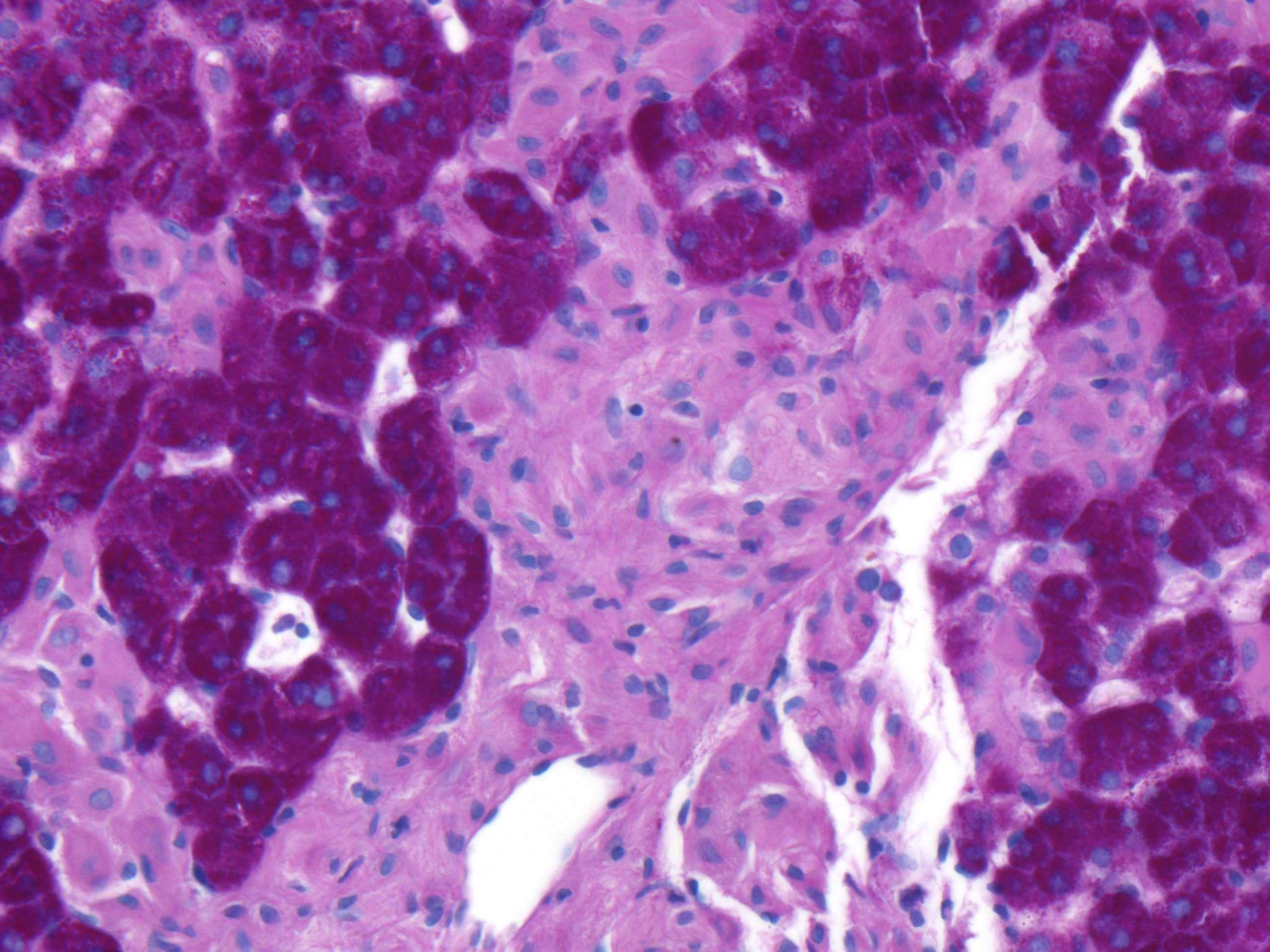


Gaucher disease – storage cells

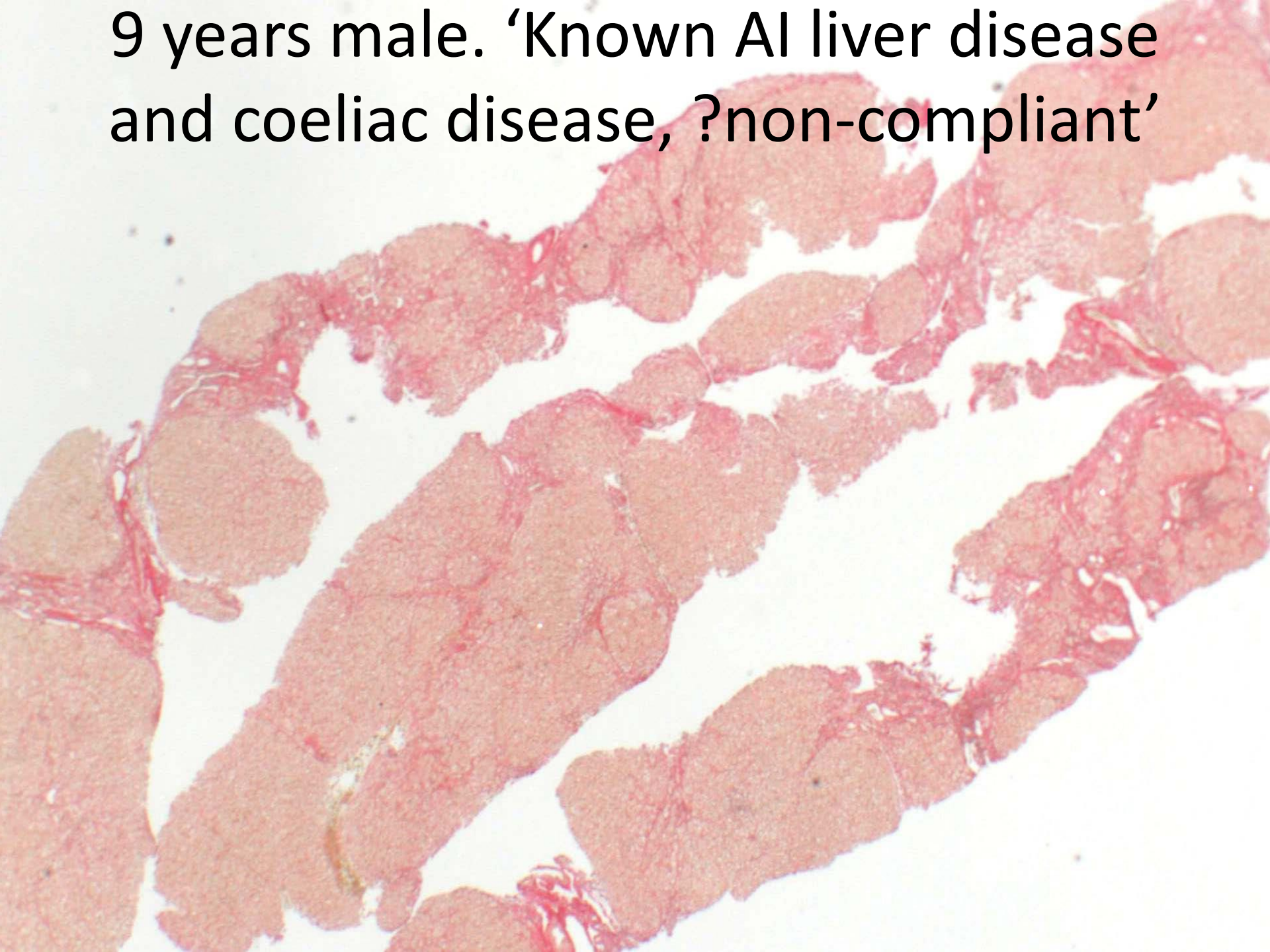


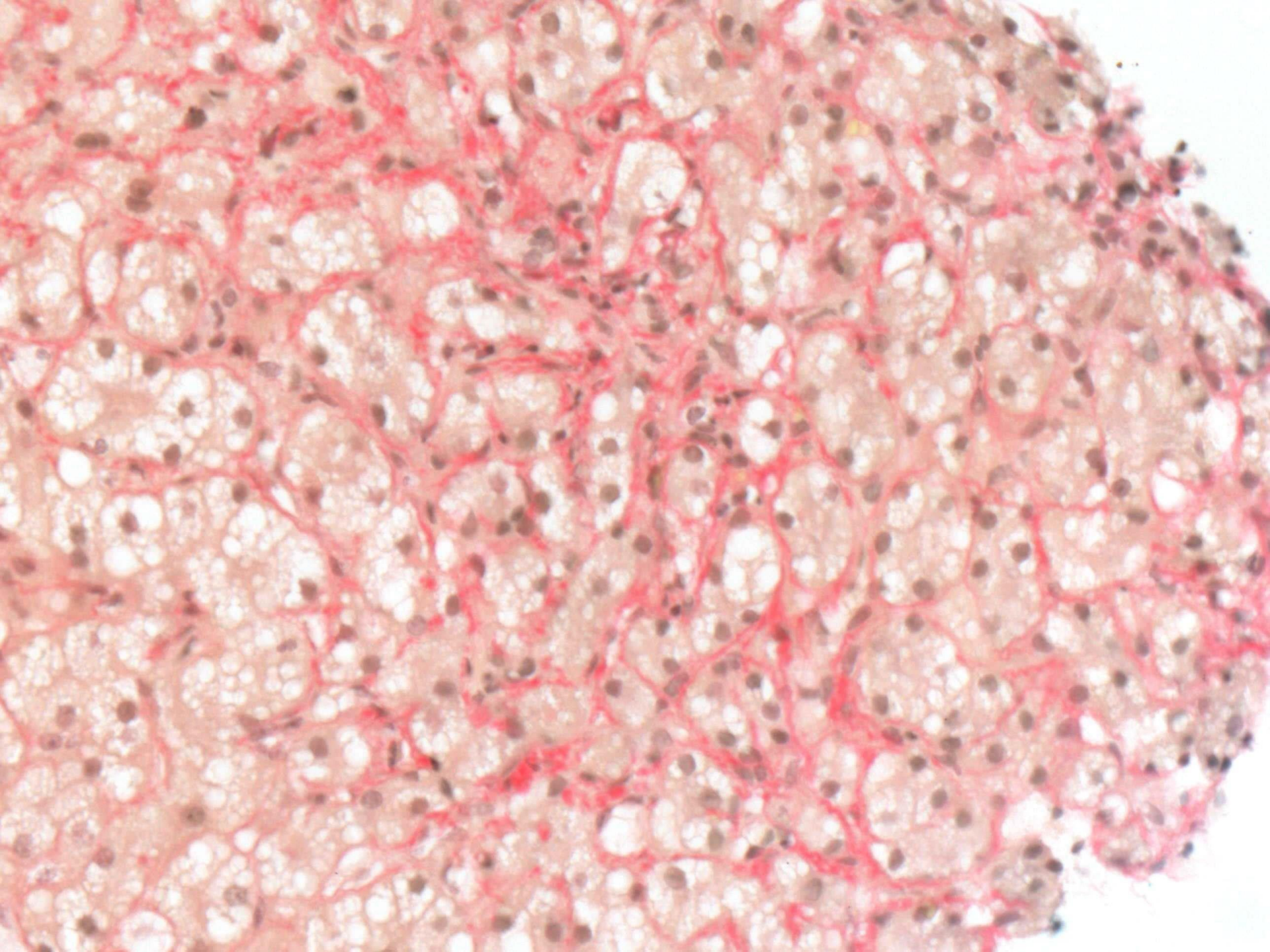

Pericellular fibrosis

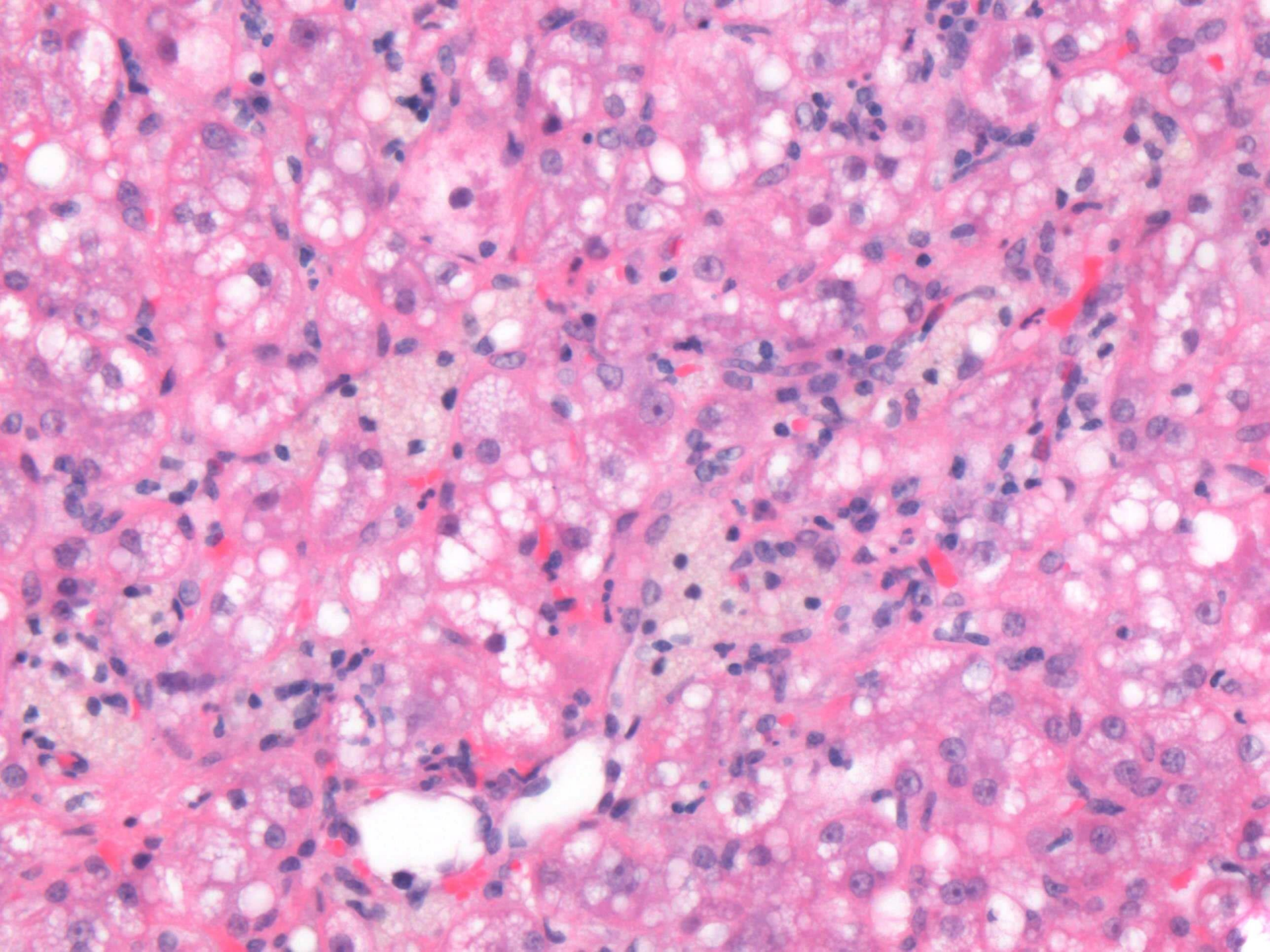




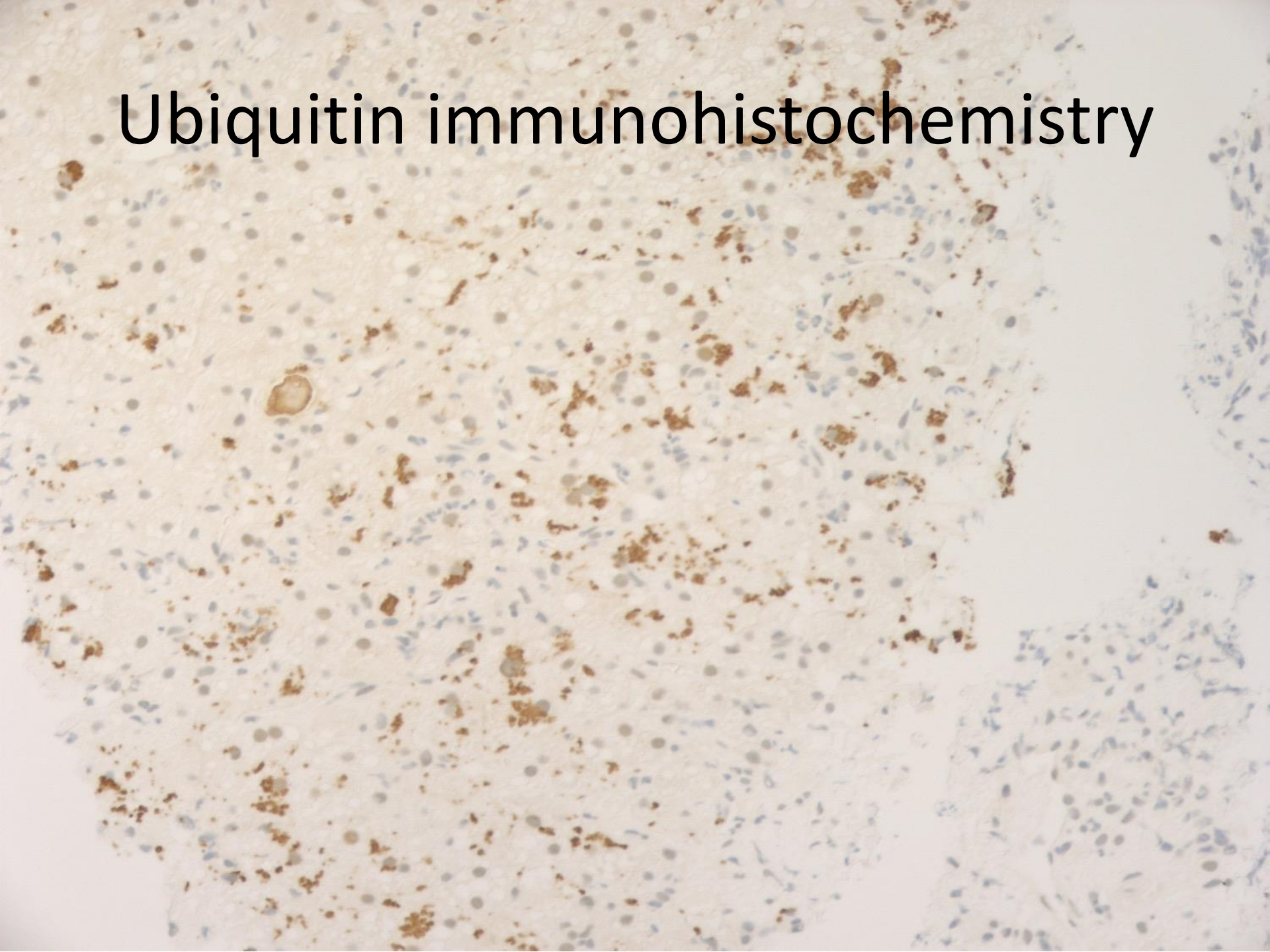
9 years male. ‘Known AI liver disease and coeliac disease, ?non-compliant’







Ubiquitin immunohistochemistry



- MDT ‘not autoimmune hepatitis, looks metabolic’
- Could it be LALD? – lysosomal acid lipase deficiency

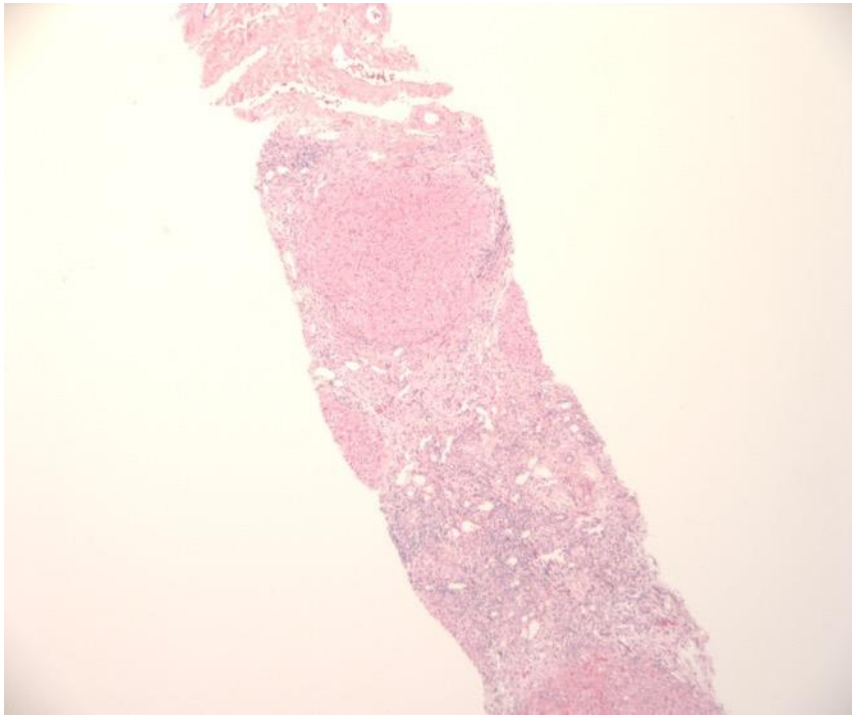
- Nonspecific clinical manifestations, elevated transaminases, high LDL cholesterol, low HDL cholesterol. Hepatomegaly. Early onset cardiovascular disease. Diagnosis can be missed.
- Lysosomal acid lipase is a lipid-metabolizing enzyme that breaks down endocytosed lipid particles and regulates lipid metabolism.
- autosomal recessive, mutations in the *LIPA* gene

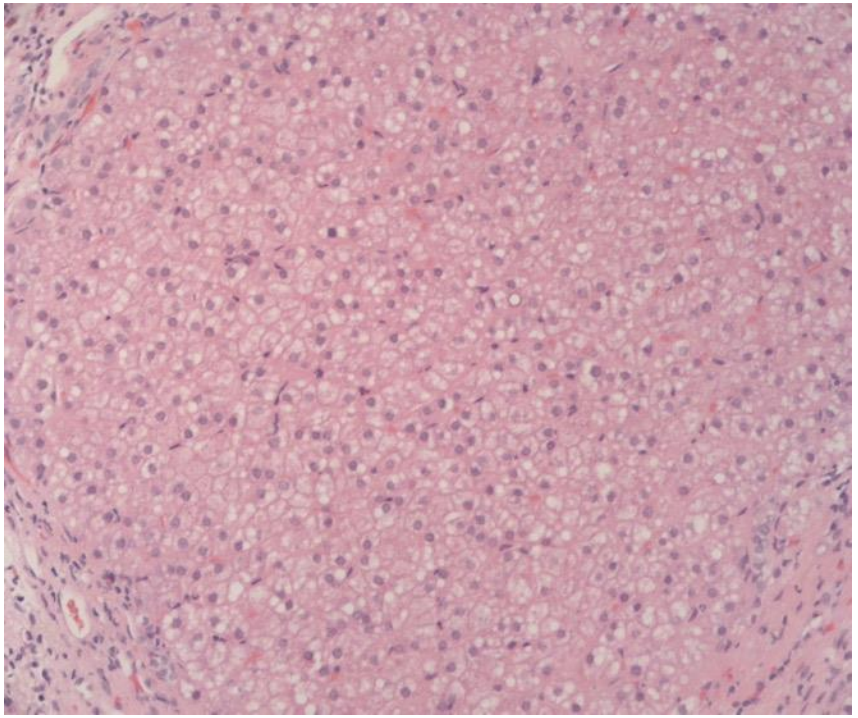
A Phase 3 Trial of Sebelipase Alfa in **Lysosomal Acid Lipase Deficiency**.

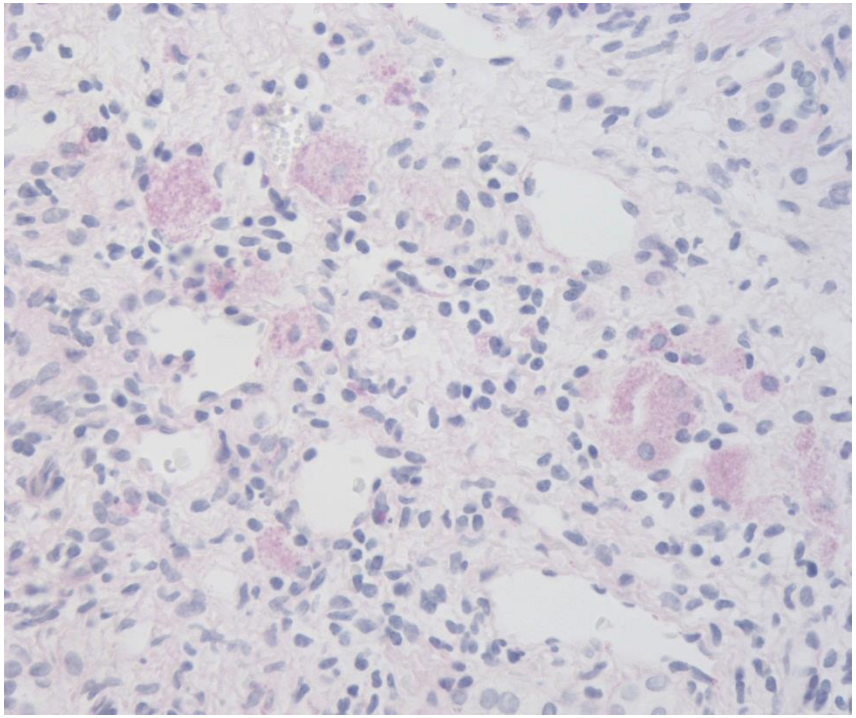
Burton BK, Balwani M, Feillet F, Barić I, Burrow TA, Camarena Grande C, Coker M, Consuelo-Sánchez A, Deegan P, Di Rocco M, Enns GM, Erbe R, Ezgu F, Ficicioglu C, Furuya KN, Kane J, Laukaitis C, Mengel E, Neilan EG, Nightingale S, Peters H, Scarpa M, Schwab KO, Smolka V, Valayannopoulos V, Wood M, Goodman Z, Yang Y, Eckert S, Rojas-Caro S, Quinn AG.

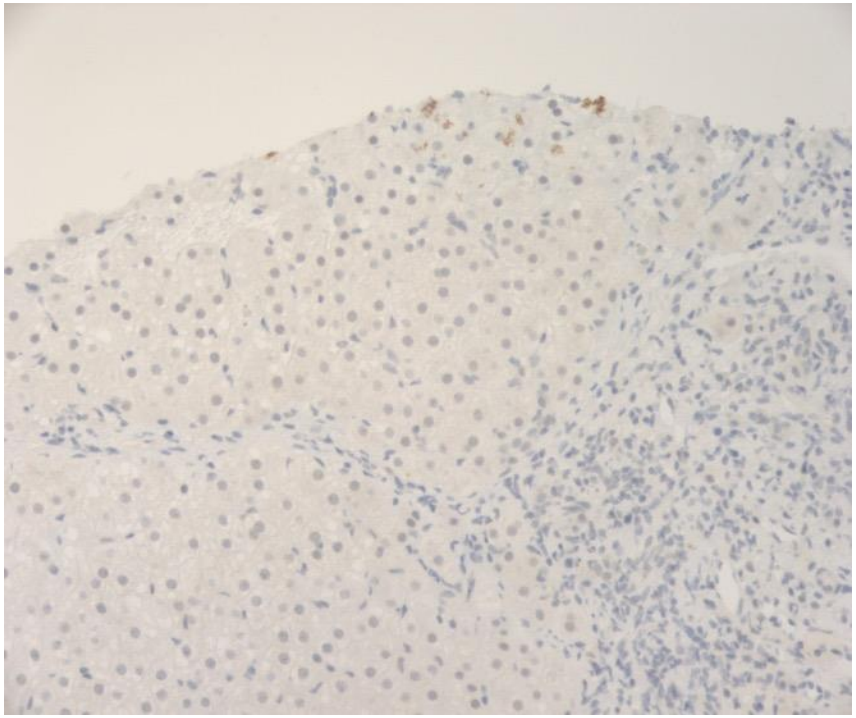
N Engl J Med. 2015 Sep 10

Follow up biopsy 18 months later









Steatosis in paediatric biopsies

- Clue to metabolic disease
- Consider a wider differential diagnosis including lysosomal acid lipase deficiency, Wilsons (both feature Mallory Denk bodies)
- NAFLD (Fatty liver disease as a result of metabolic syndrome) diagnosis of exclusion in childhood

- Any steatosis on Bx 127, 58 (37.4%) NAFLD. 14 (9%) 'metabolic' (GSD 8 urea cycle defect 2 FAOD 2 Mit' DNA depletion sy 1 intermittent ketotic hypoglycaemia 1) younger median 1.7 cf 11 years for all other groups and 14 years for NAFLD. Not included as 'metabolic' Wilsons 3 A1AT 2. 9% 'unclear'.

The **full spectrum** of hepatic steatosis in children.
Hourigan SK, Torbenson M, Tibesar E, Scheimann AO.
Clin Pediatr (Phila). 2015 Jun;54(7):635-42.

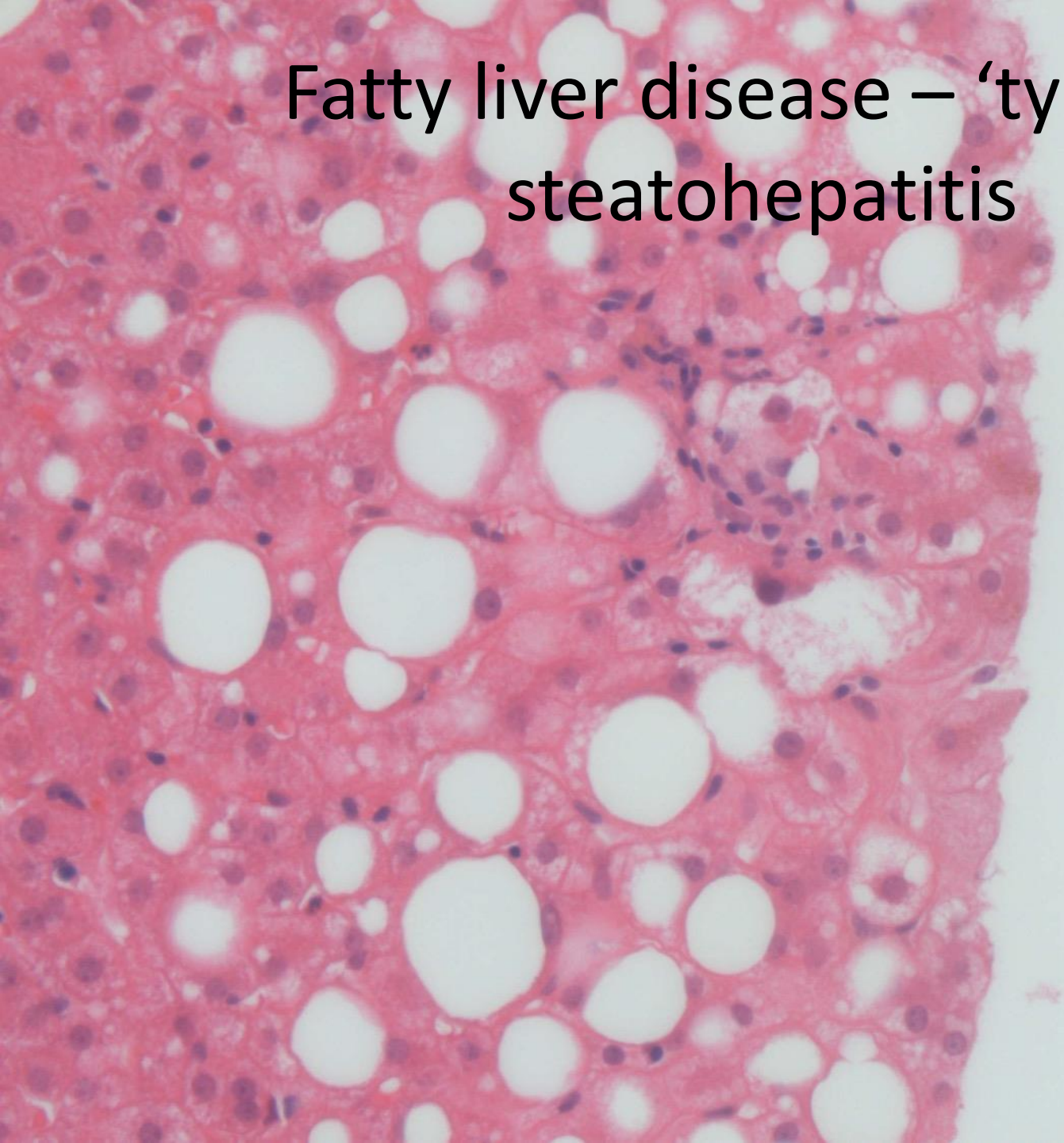
Paediatric NAFLD

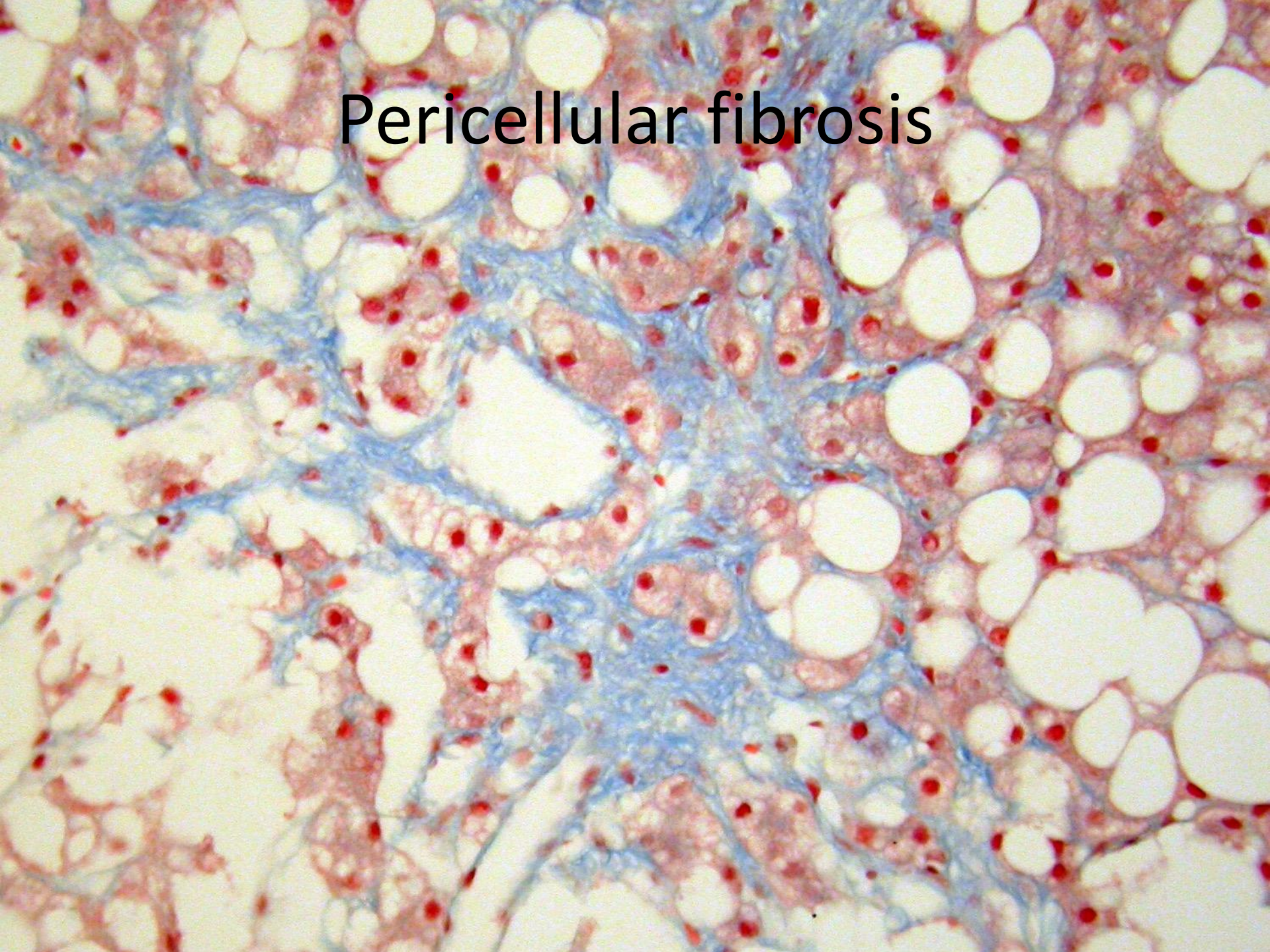
- Can have a different pattern with periportal steatosis and portal fibrosis
- Hourigan study 10% zone 1 overall

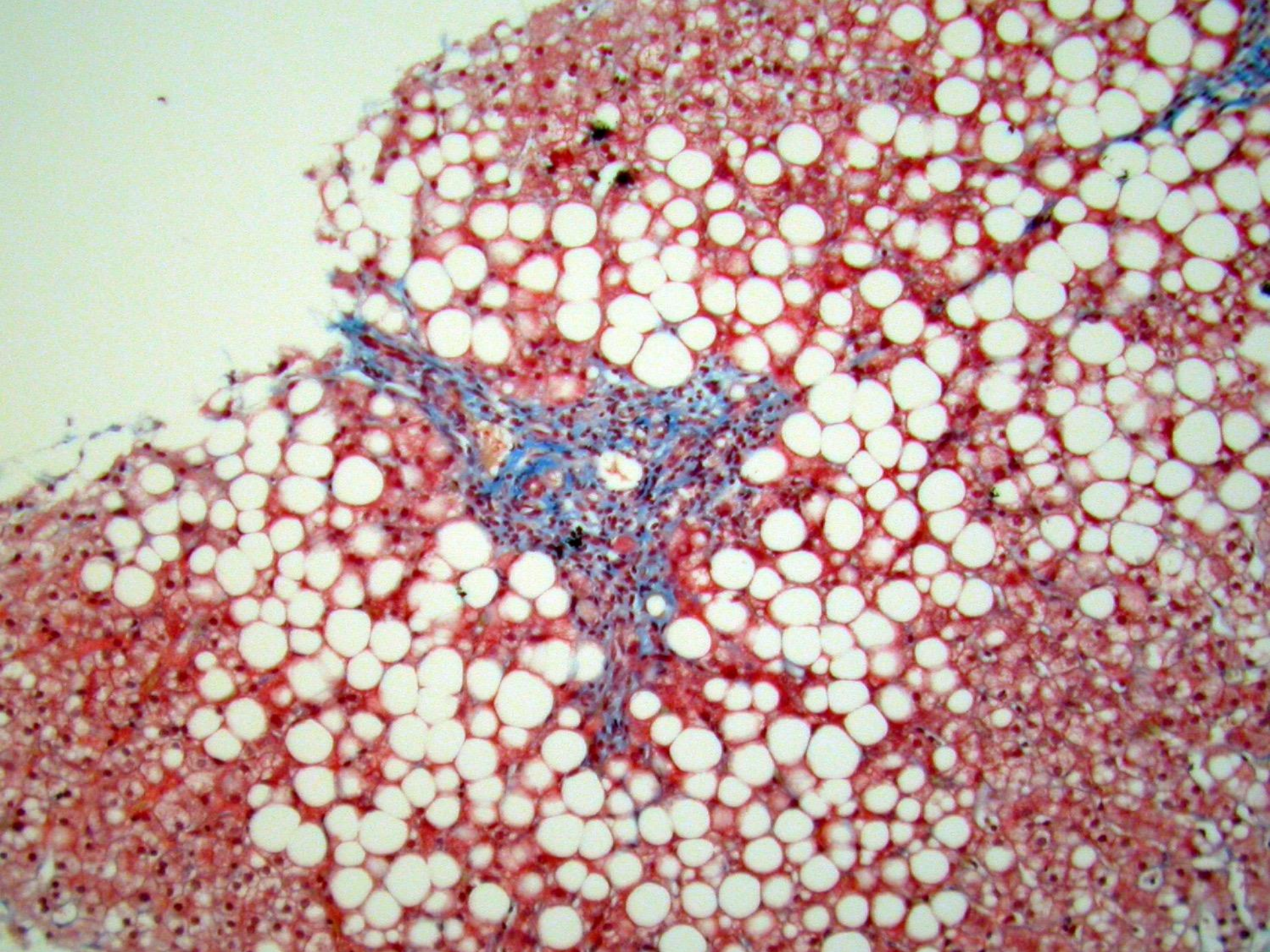
- Liver biopsy – 'no other diagnostic modality has shown sufficient accuracy to be appropriate for clinical use in place of biopsy'
- 'There is a need for consensus as to what constitutes steatohepatitis in children.....'

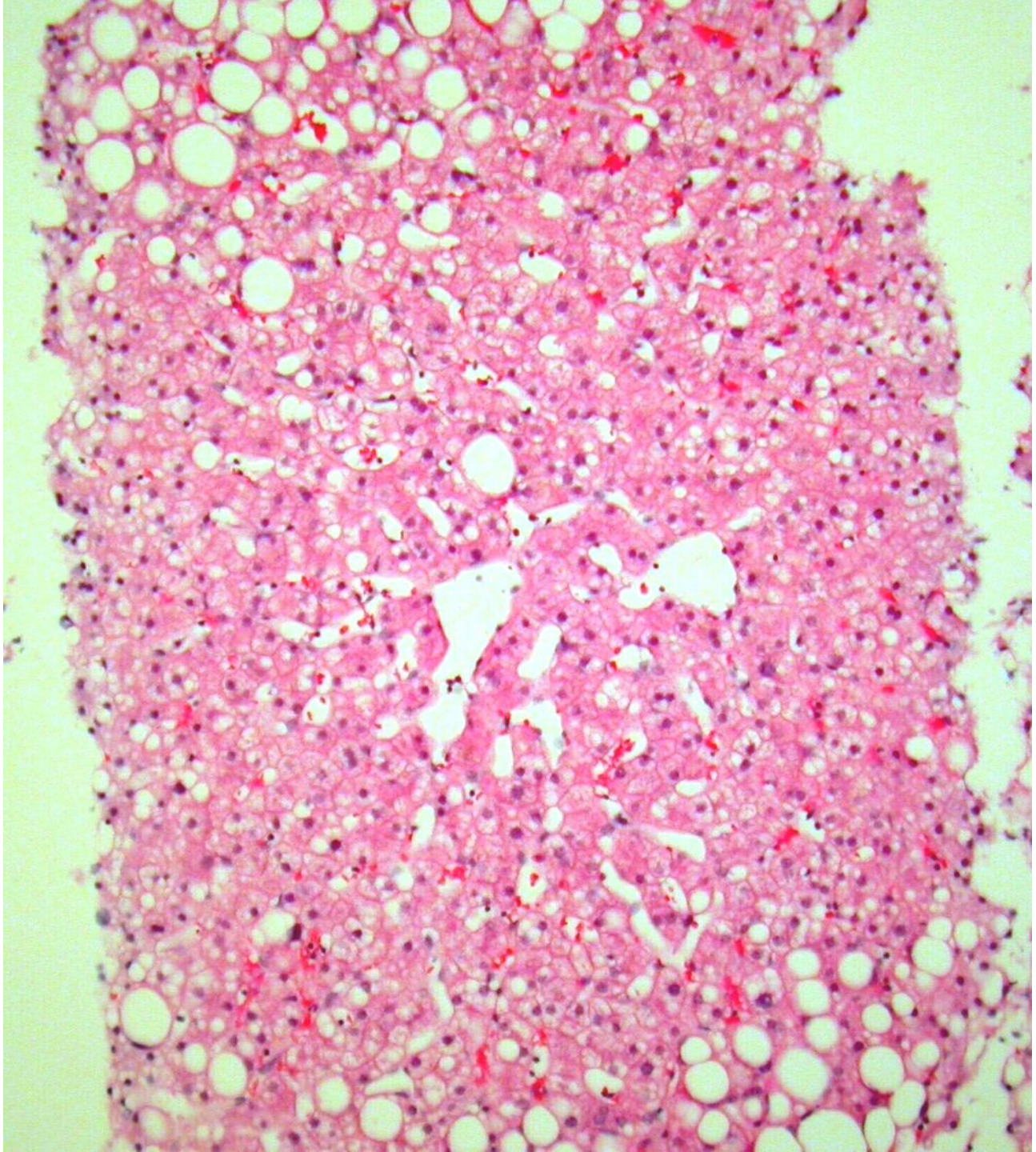
Clinical advances in pediatric nonalcoholic fatty **liver** disease.
Schwimmer JB.
Hepatology. 2016 May;63(5):1718-25.

Fatty liver disease – ‘typical’ steatohepatitis

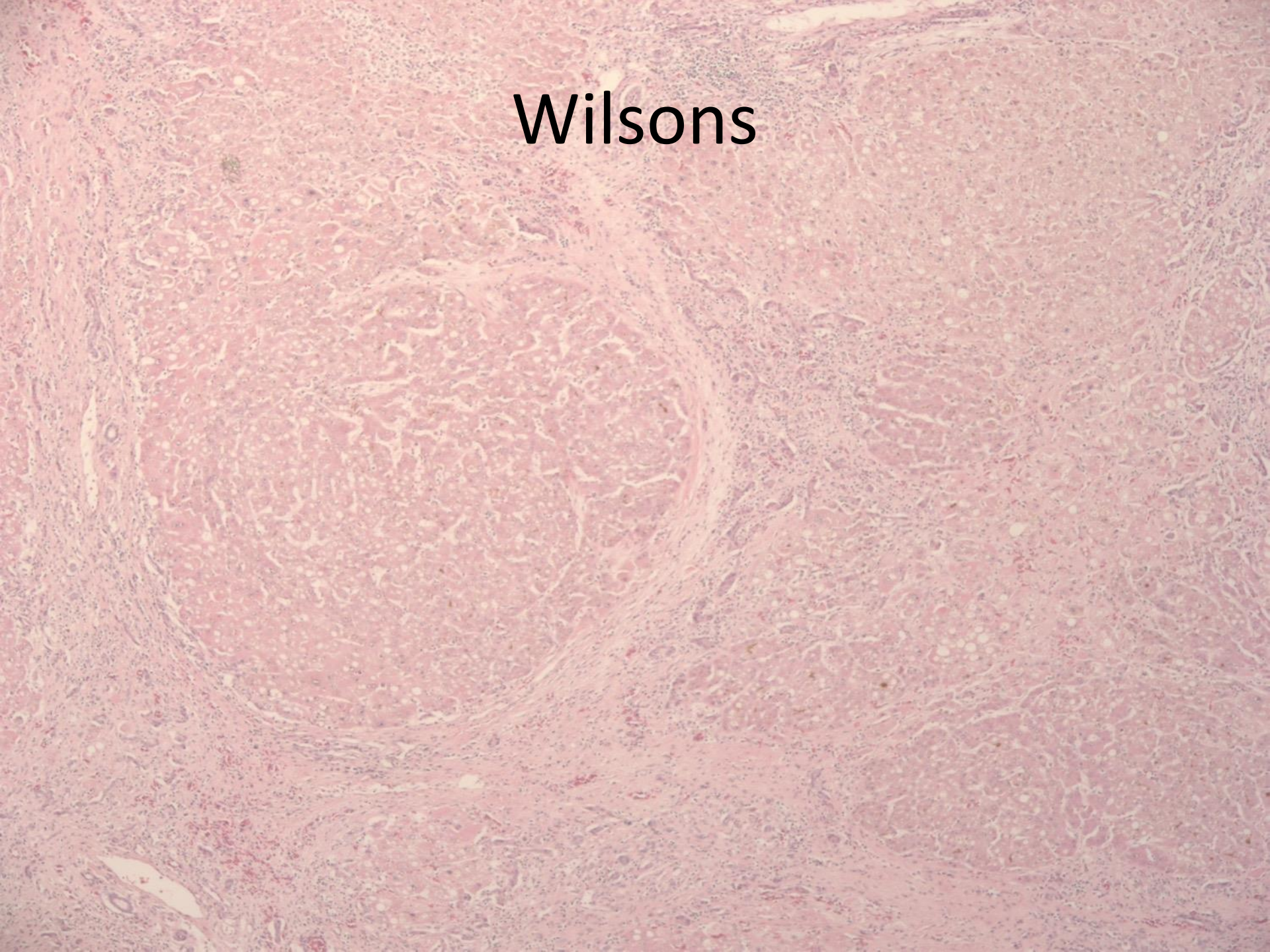


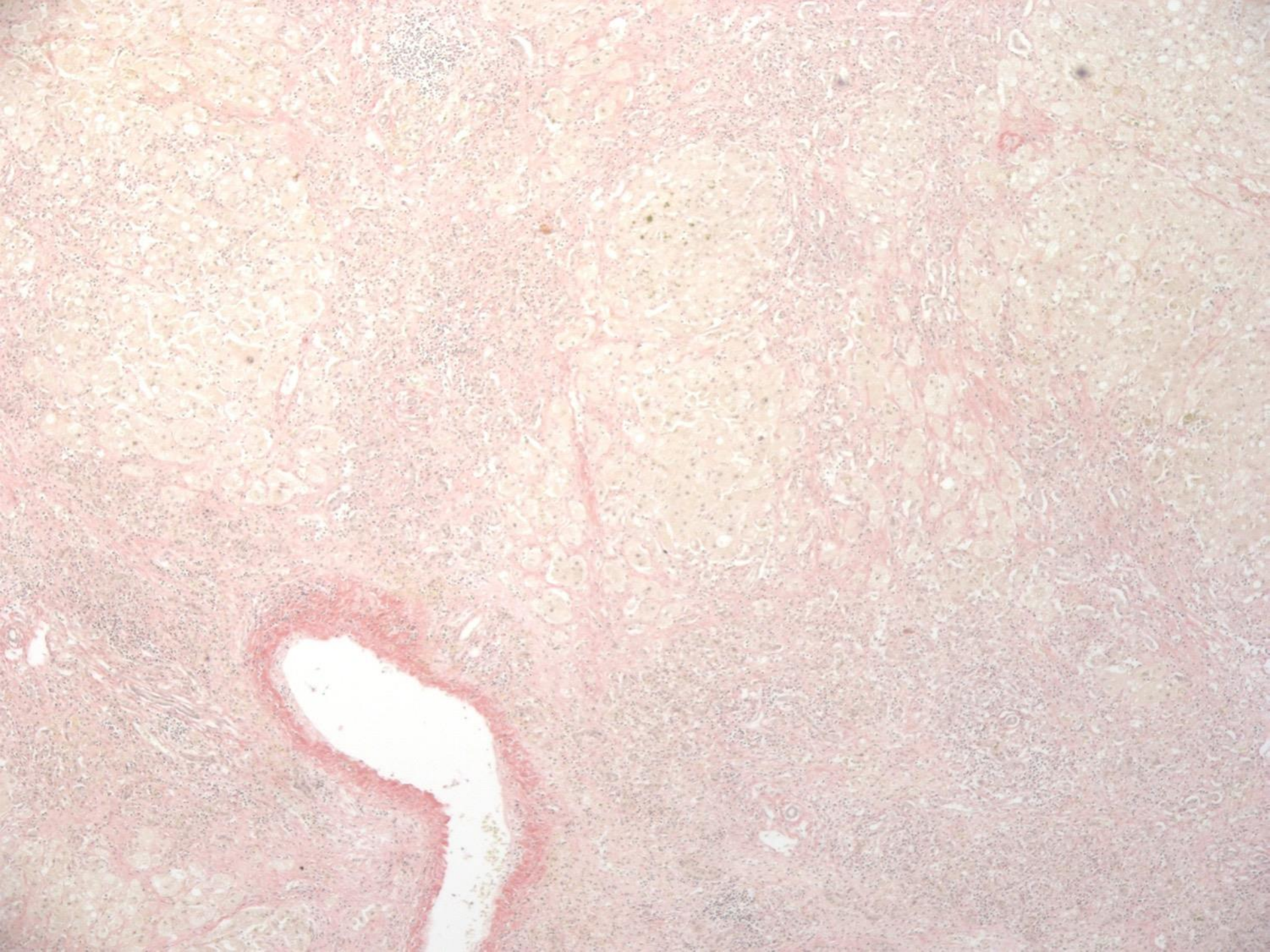

Pericellular fibrosis

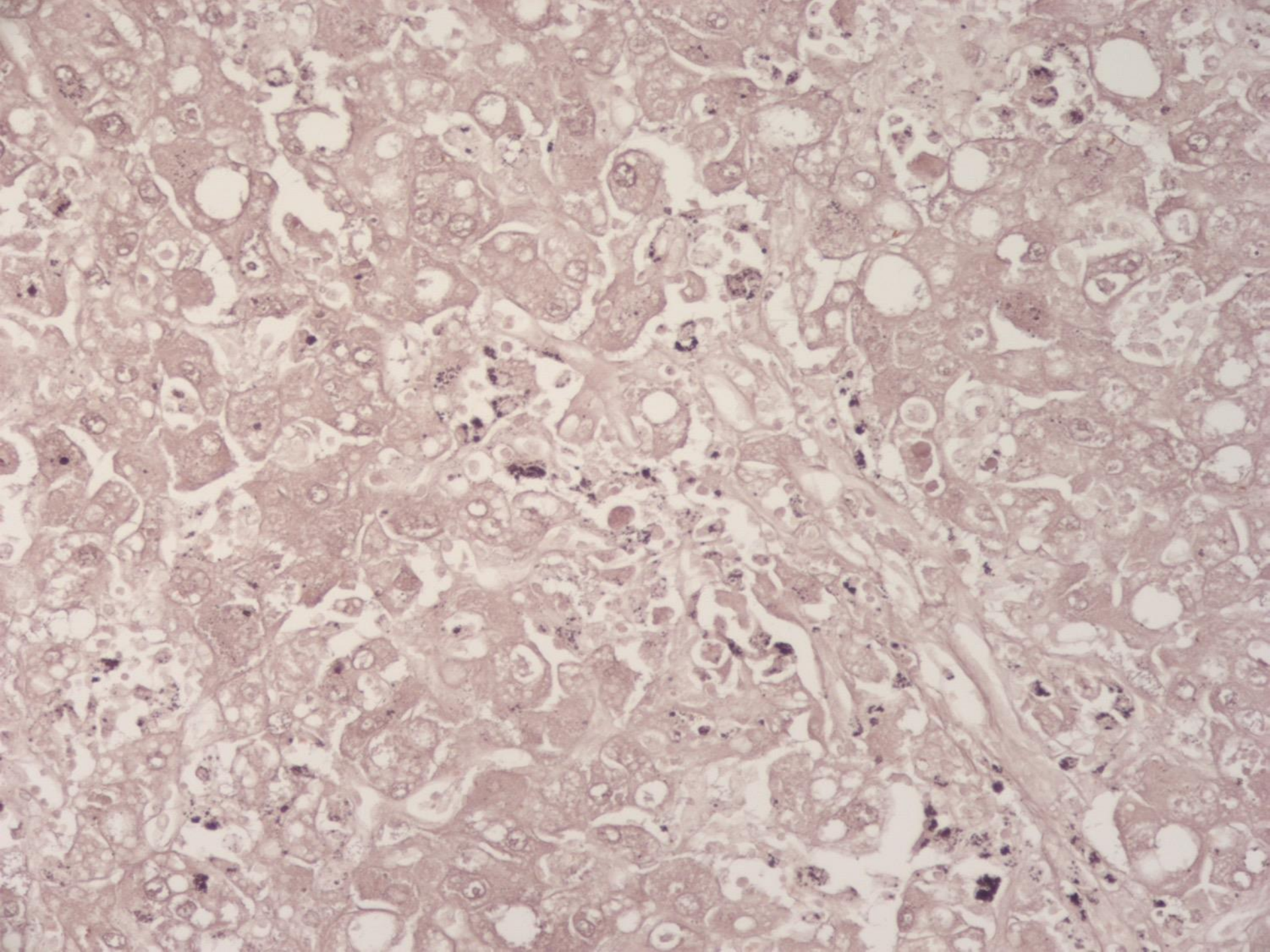




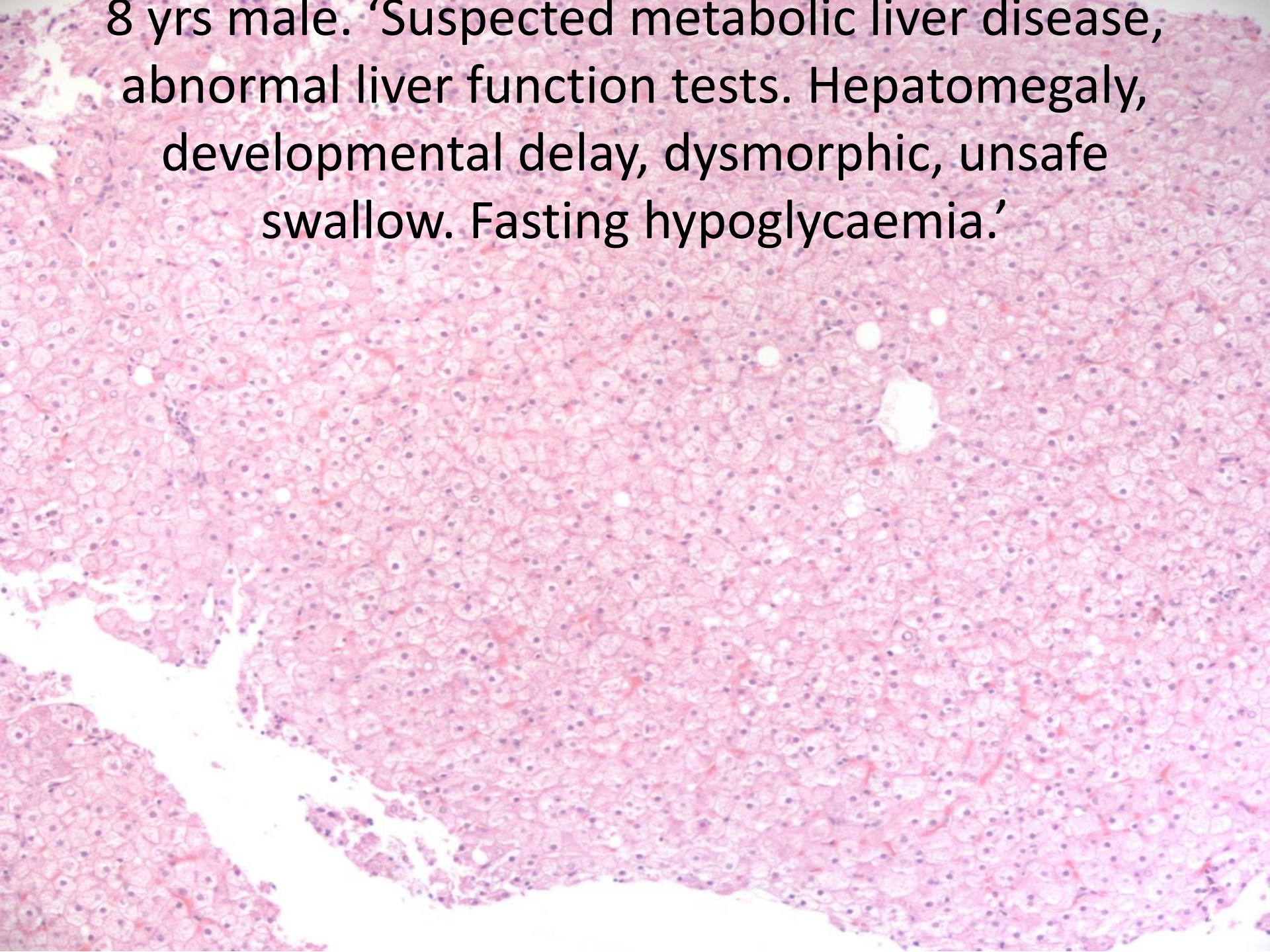
Wilsons



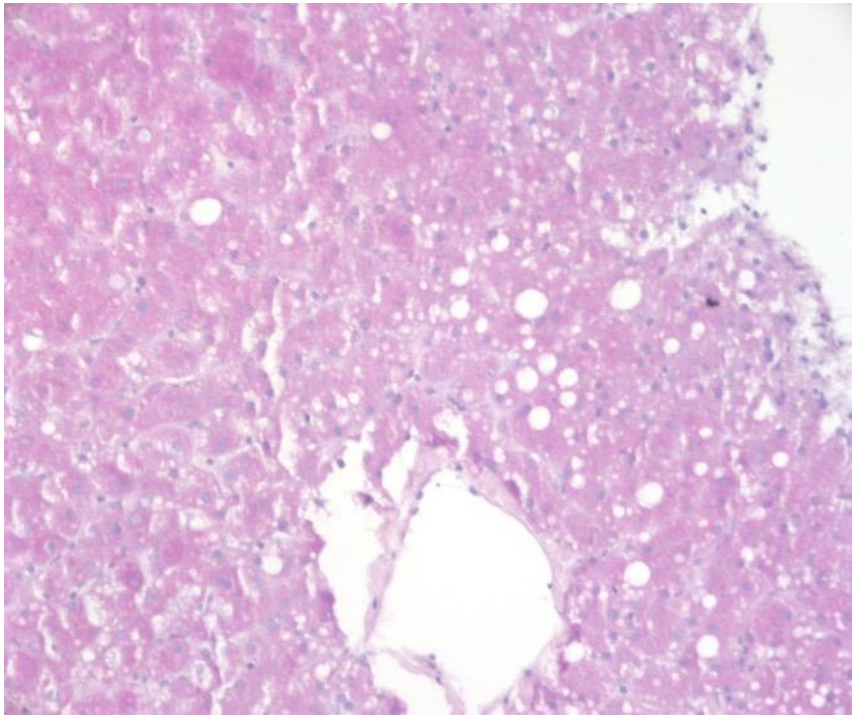


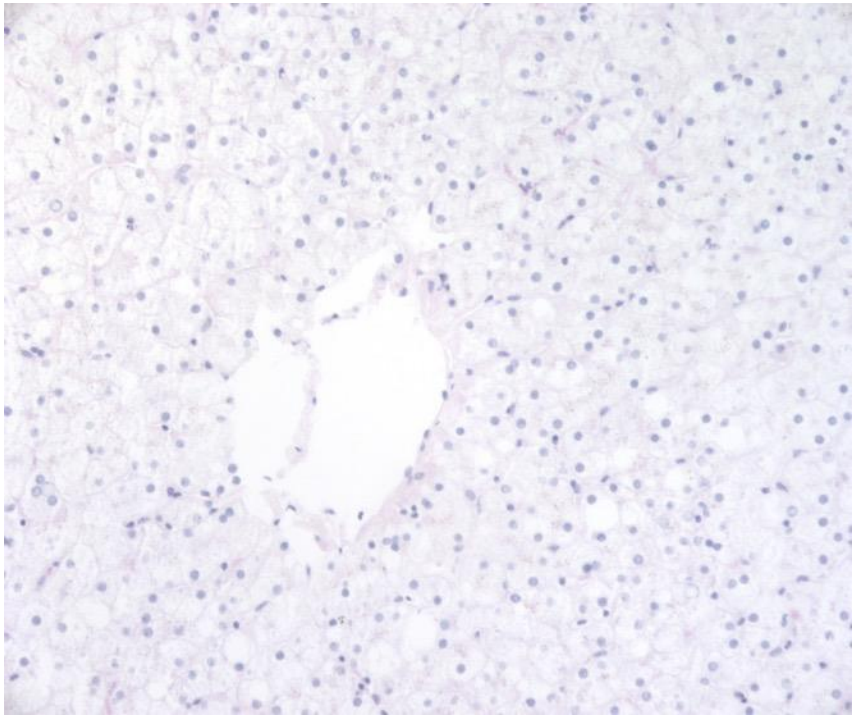


8 yrs male. ‘Suspected metabolic liver disease, abnormal liver function tests. Hepatomegaly, developmental delay, dysmorphic, unsafe swallow. Fasting hypoglycaemia.’

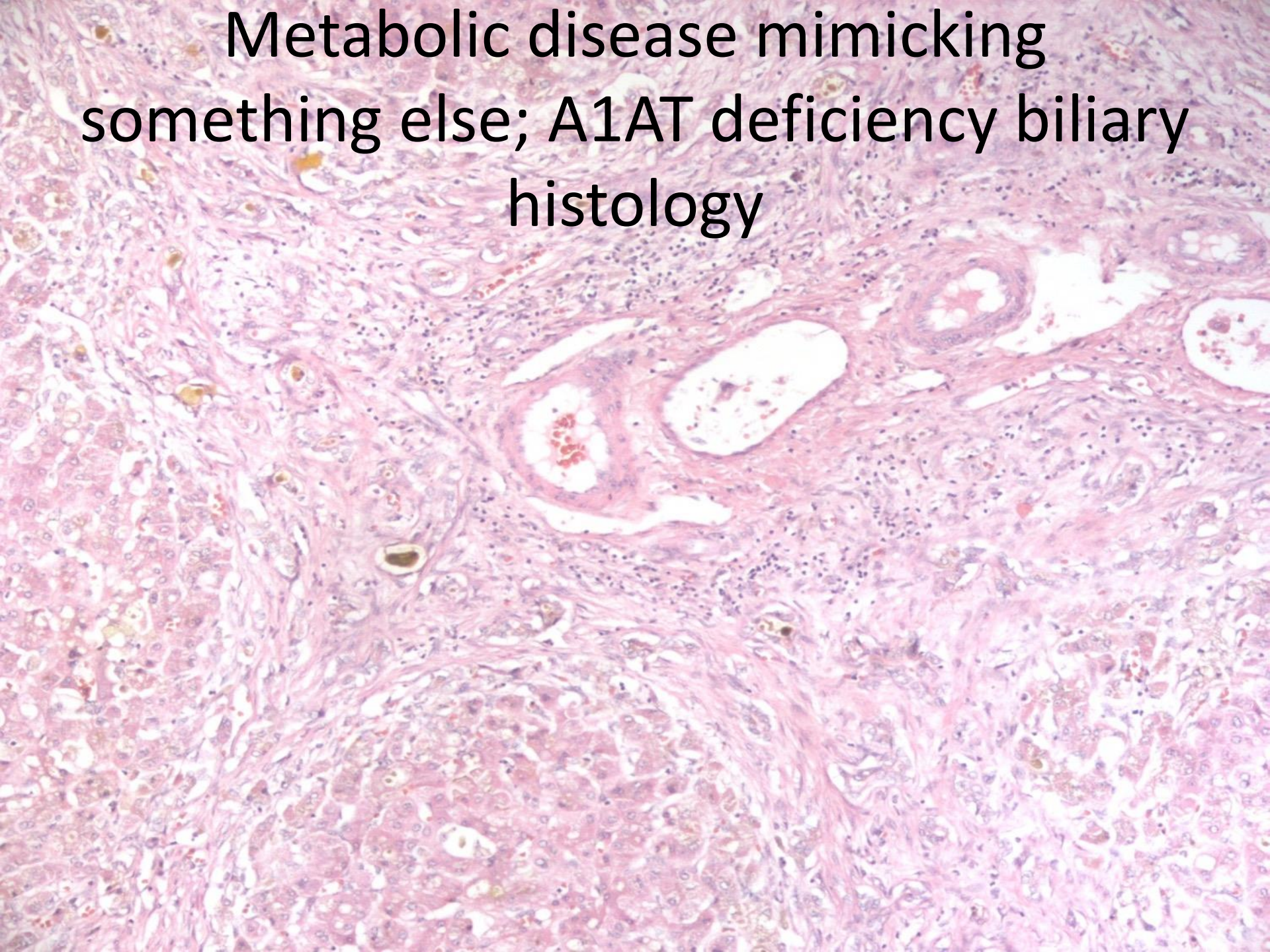


Confirmed GSD1a homozygous on genetic testing (unusual UK mutation, close consanguinity)





Metabolic disease mimicking something else; A1AT deficiency biliary histology



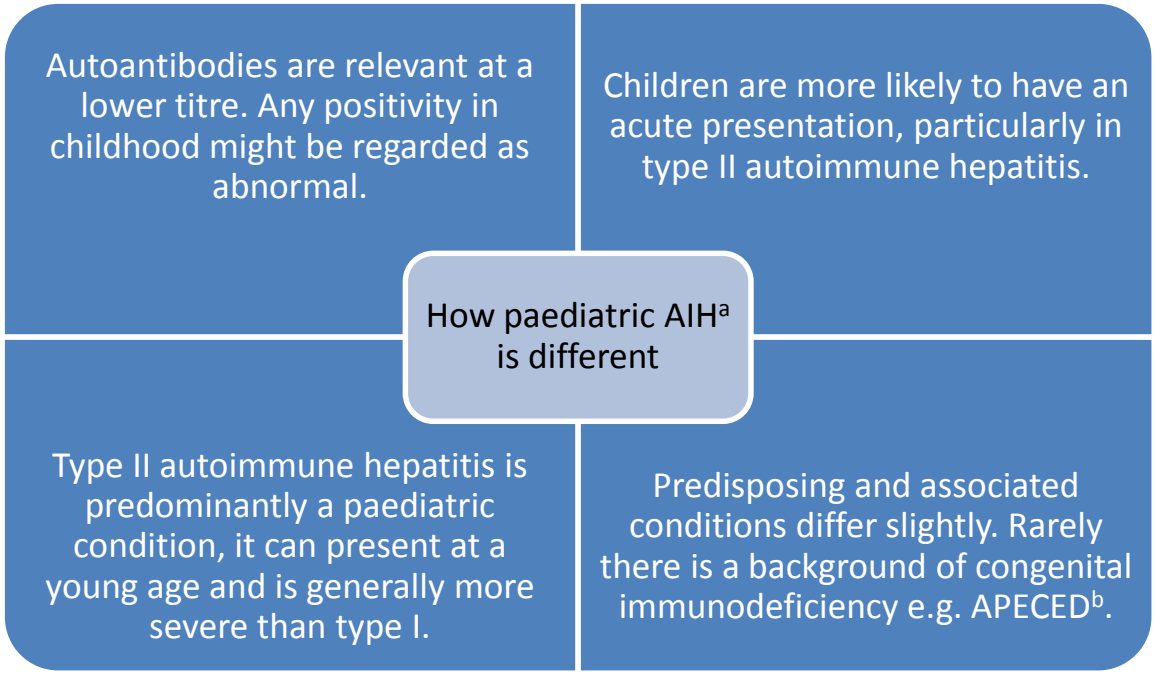
Pathologists role in metabolic disease

- Changes can be subtle
- Its only the atypical ones that are biopsied
- Helpful to raise the possibility of metabolic liver disease by recognising certain patterns, not expecting to come up with a specific diagnosis
- NAFLD as a diagnosis of exclusion and can feature periportal changes
- Excluding other diseases

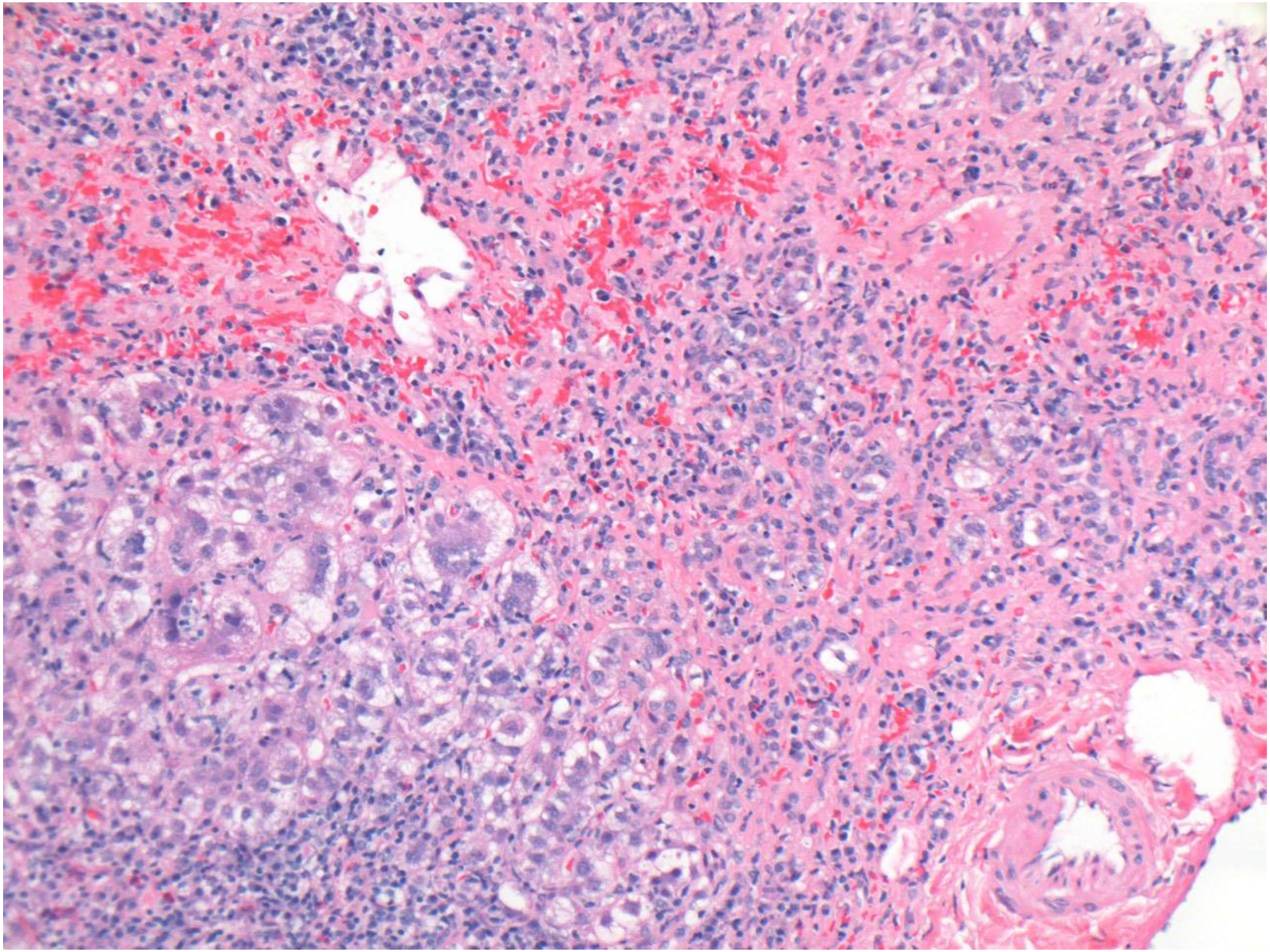
Autoimmune liver disease

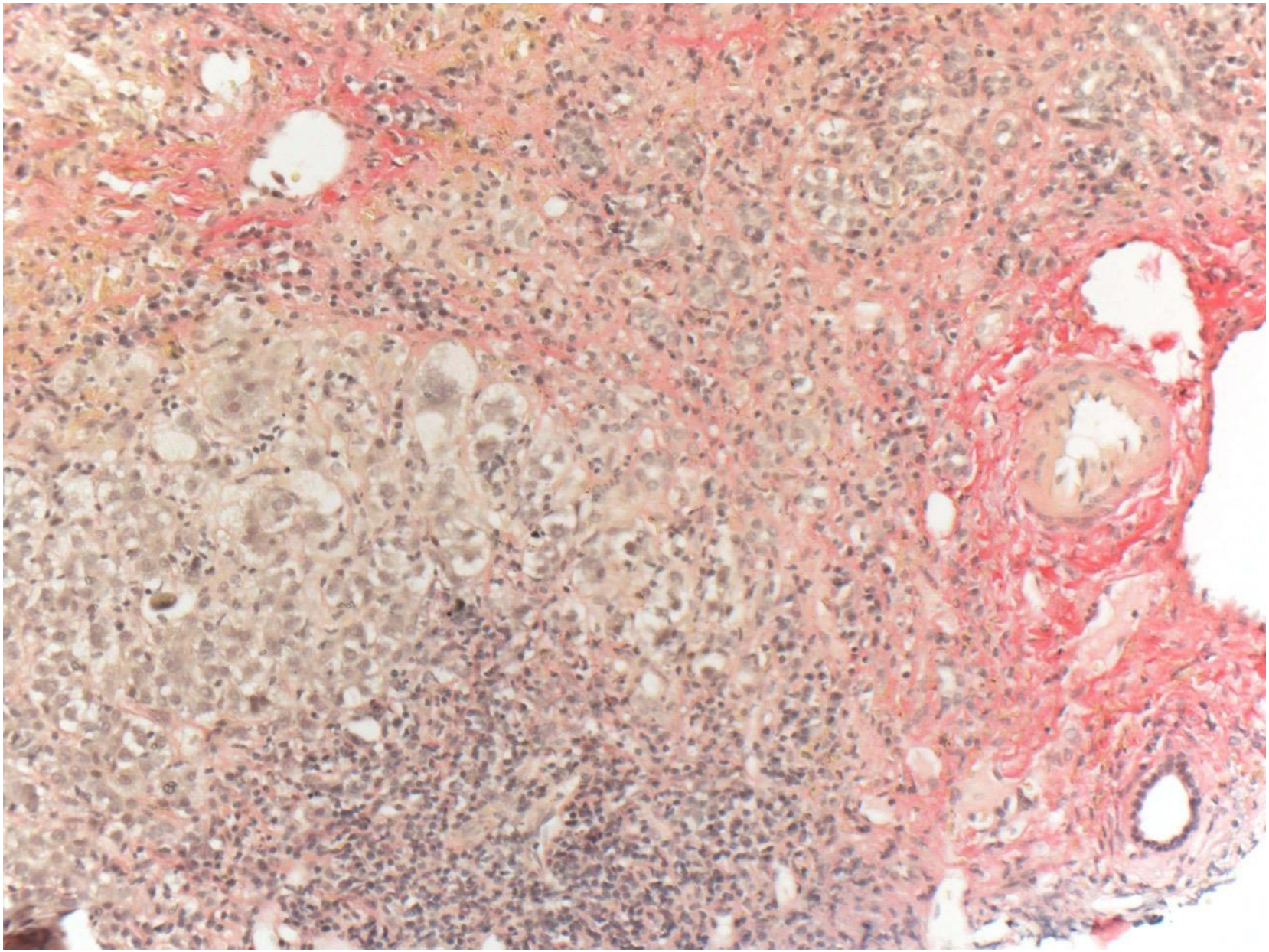
- AIH and PSC, don’t see PBC in childhood

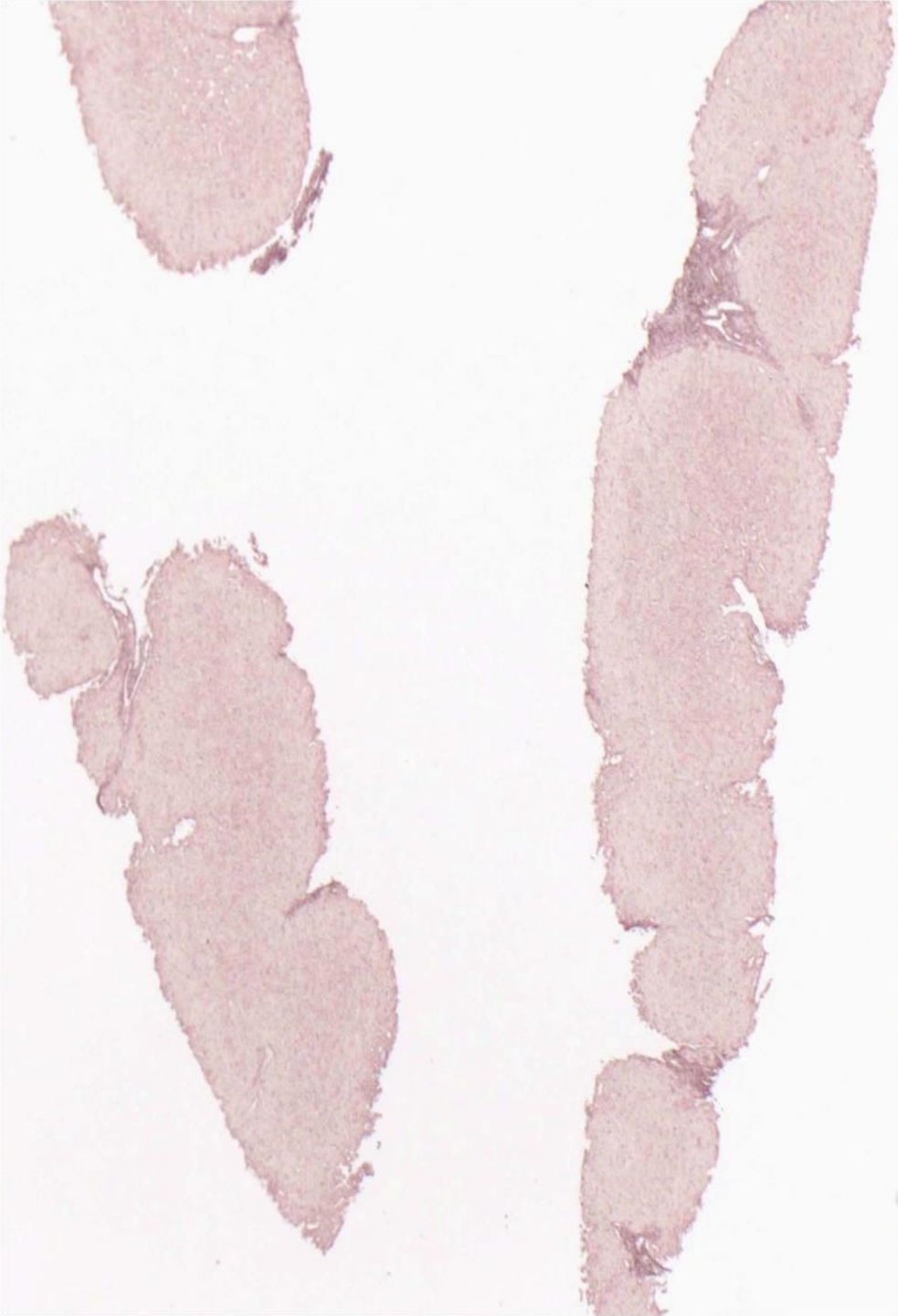
Autoimmune hepatitis

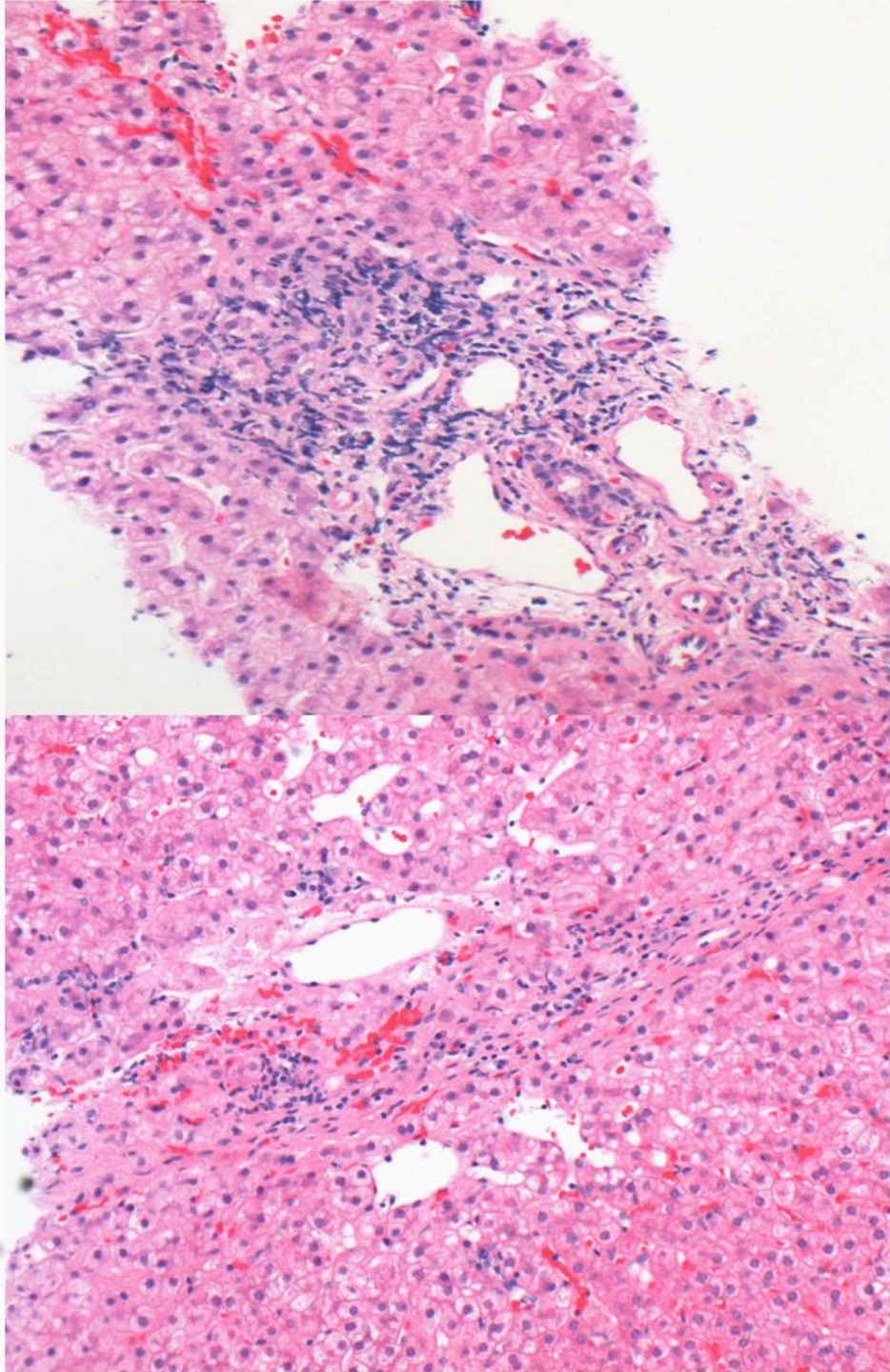


a Autoimmune hepatitis b Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy

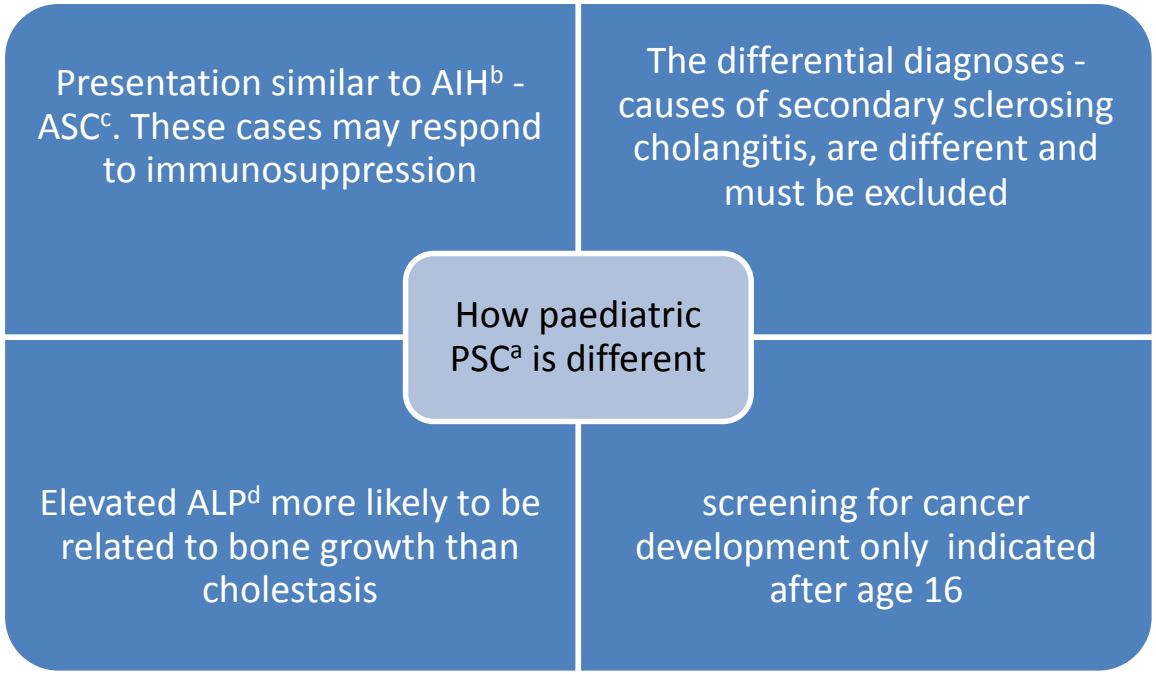






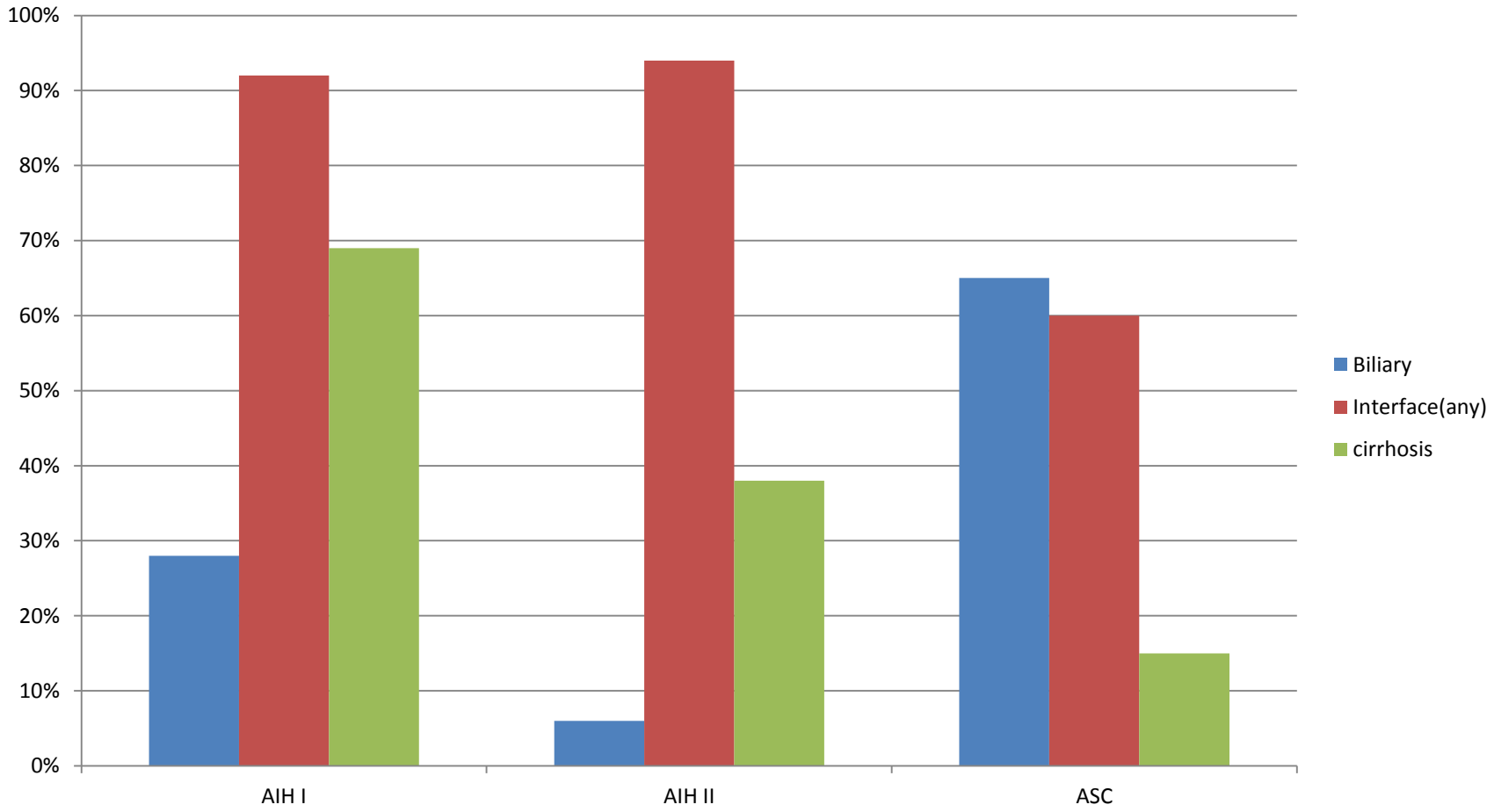


Primary sclerosing cholangitis



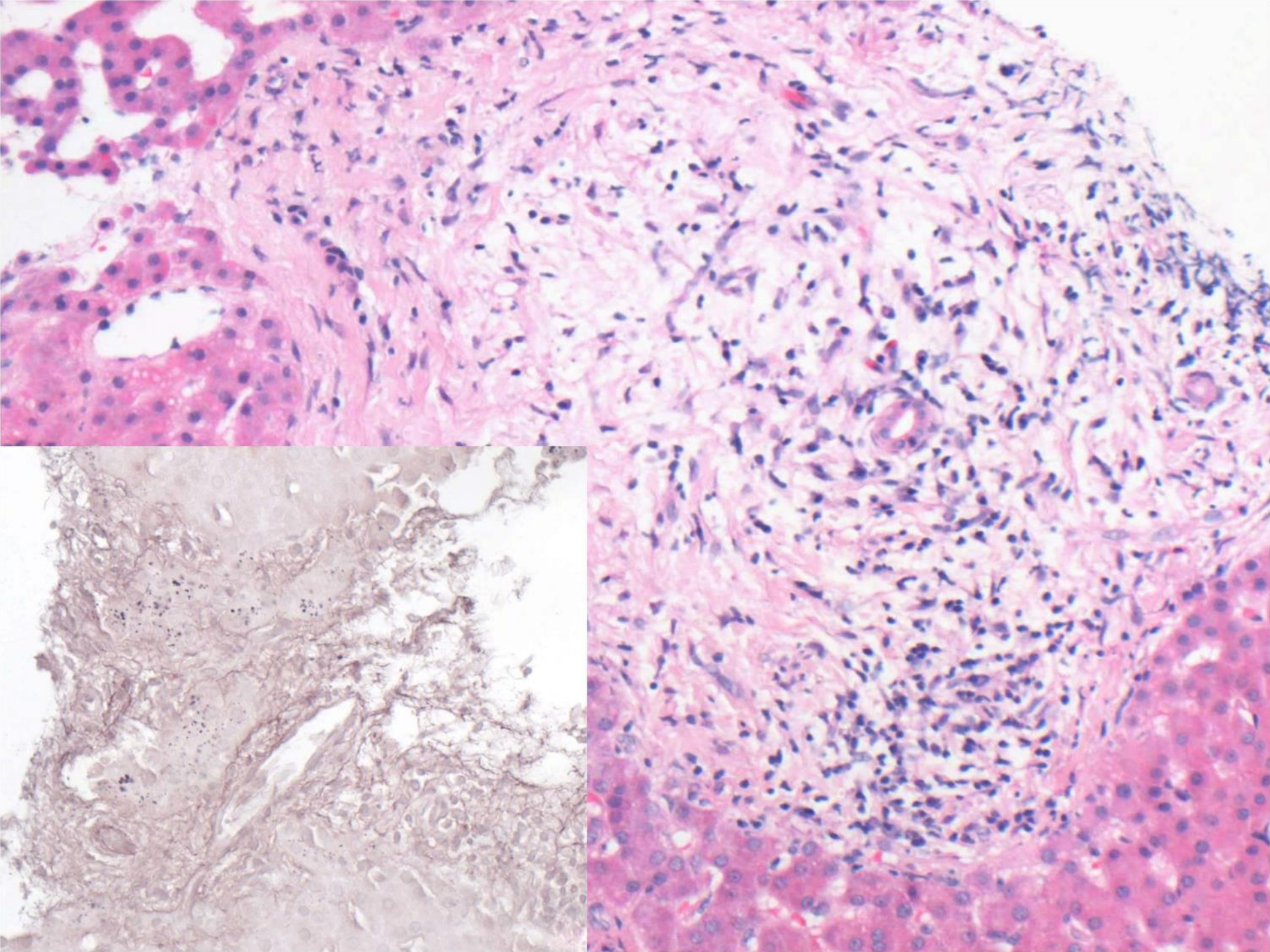
a Primary Sclerosing Cholangitis b Autoimmune Hepatitis c Autoimmune Sclerosing Cholangitis d Alkaline Phosphatase

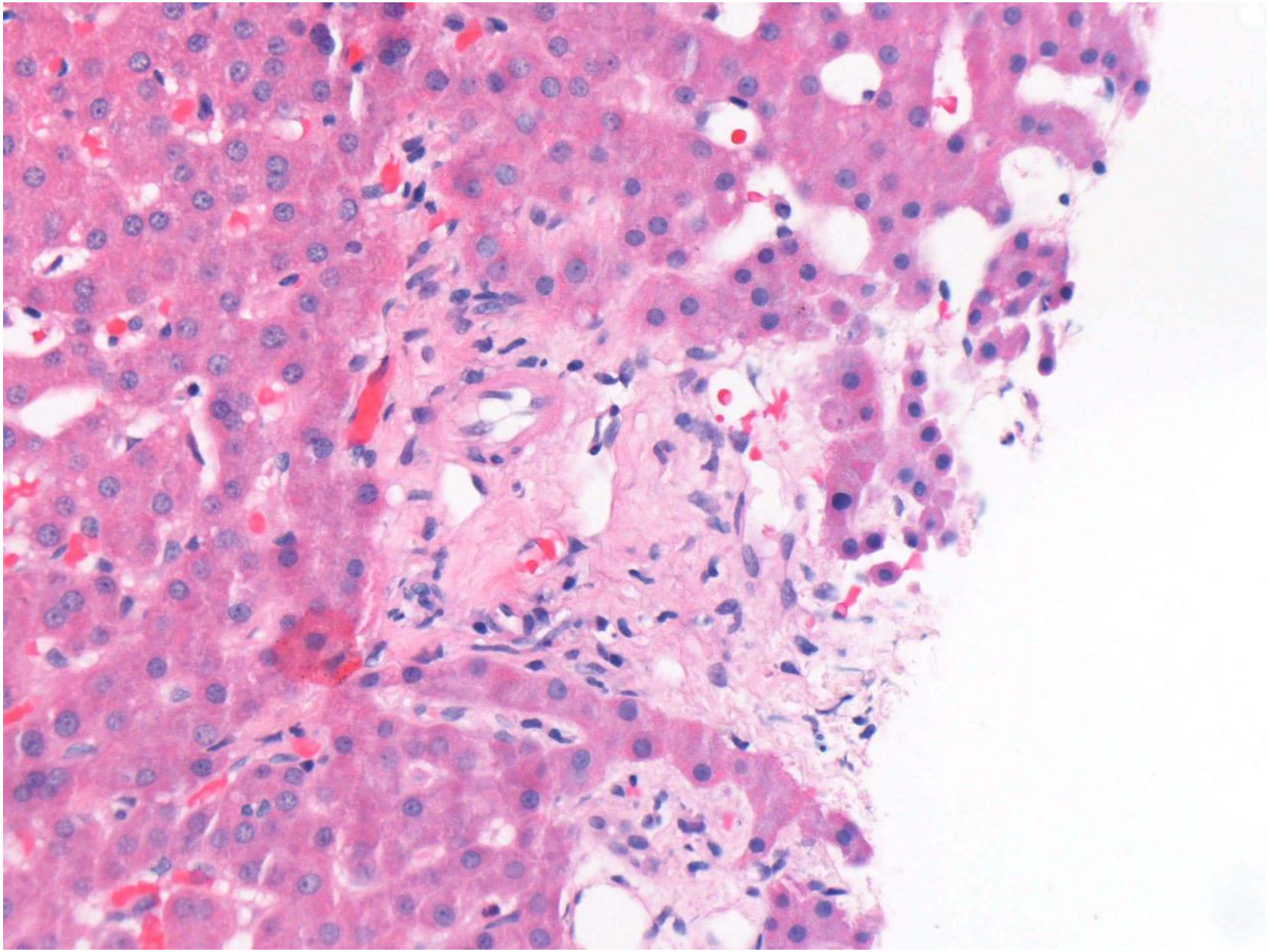
Gregorio GV, Portmann B, Karani J, et al. Autoimmune hepatitis/-sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology 2001 Mar; 33: 544e53.



Biopsy interpretation in autoimmune liver disease

- Describe the patterns present in a biopsy, inflammatory and/or biliary, the relative dominance of one pattern over another and assessments of severity.
- Helps to guide management and with coming to an overall diagnosis once all modalities; biochemical, serological and radiological are bought together at MDT.





Pediatric liver pathology in the UKLPG

- Survey responses, approximately 1/3 of EQA members report paediatric biopsies.
- UKLPG rep as central point of contact for paediatric interest group.