

National Liver Histopathology EQA Scheme

Circulation V.

Glasgow, 6th July 2007

Business Meeting

1. ? Quorate - anticipating 8 members attending.
Steering group members (Chris Bellamy, Joe Mathew, Alastair Burt, Rob Goldin) have sent their views on marking circulation V, to add to this afternoon's.
2. Liver Histopathology Update meeting Thurs 6th December, Lancaster
3. CPA - steering group, questionnaire, SOPs, website arrangements for CPA accreditation of EQA schemes being simplified.

Case 266

48 M. Abnormal LFTs, ?cause.

Diabetic, obese, hypertensive.

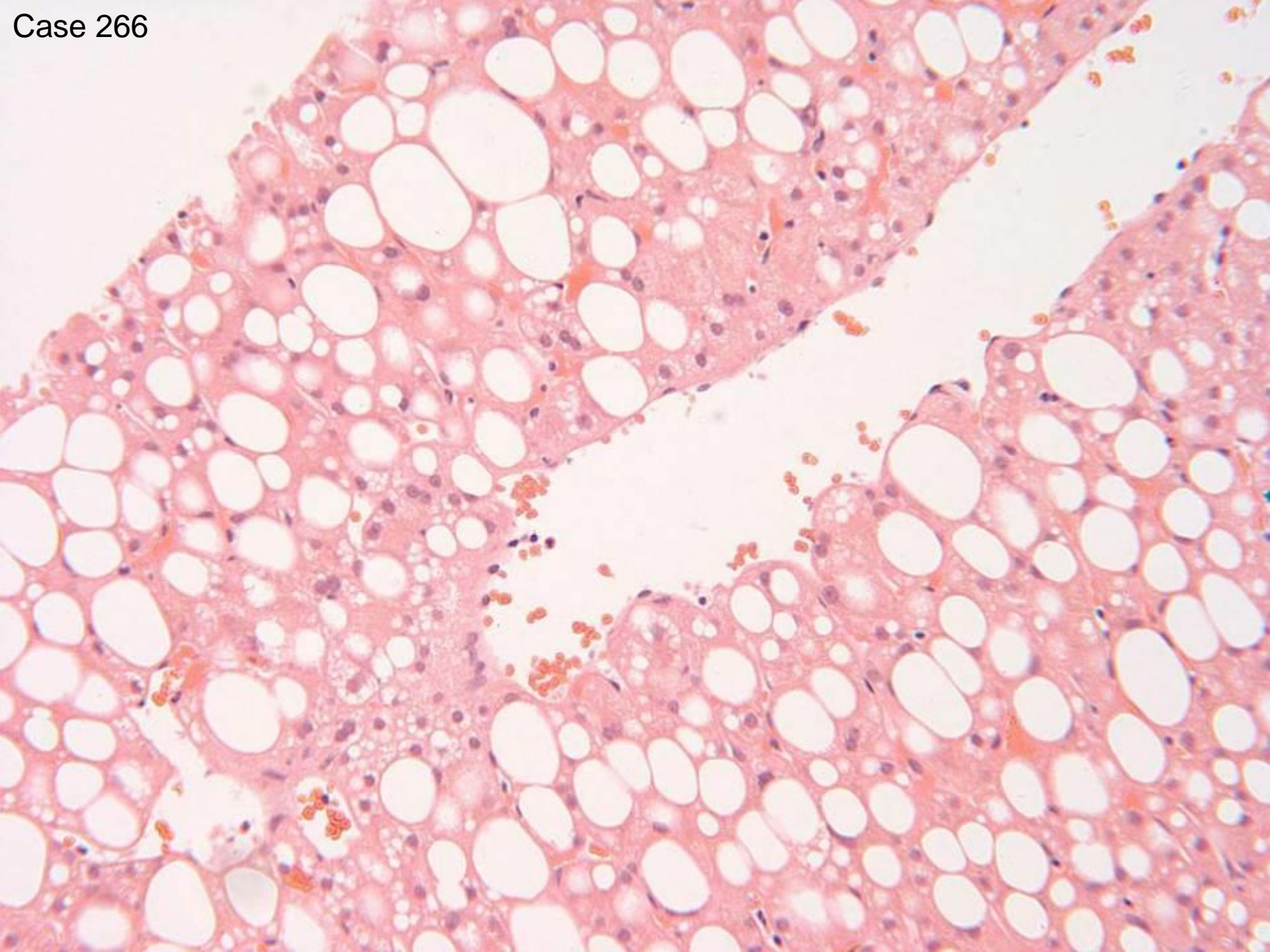
Hepatitis serology negative. Autoimmune profile negative, raised ferritin.



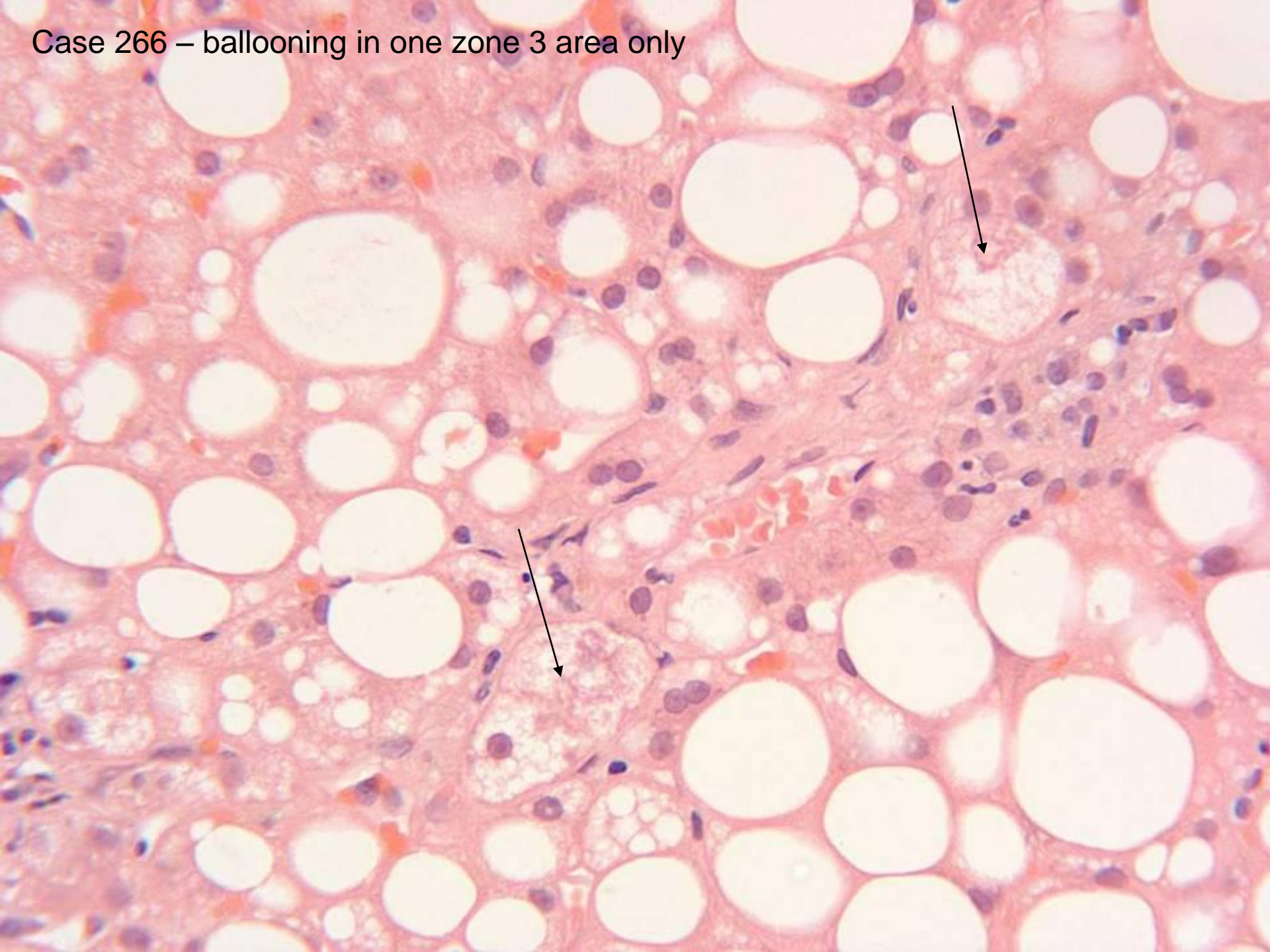
Case 266



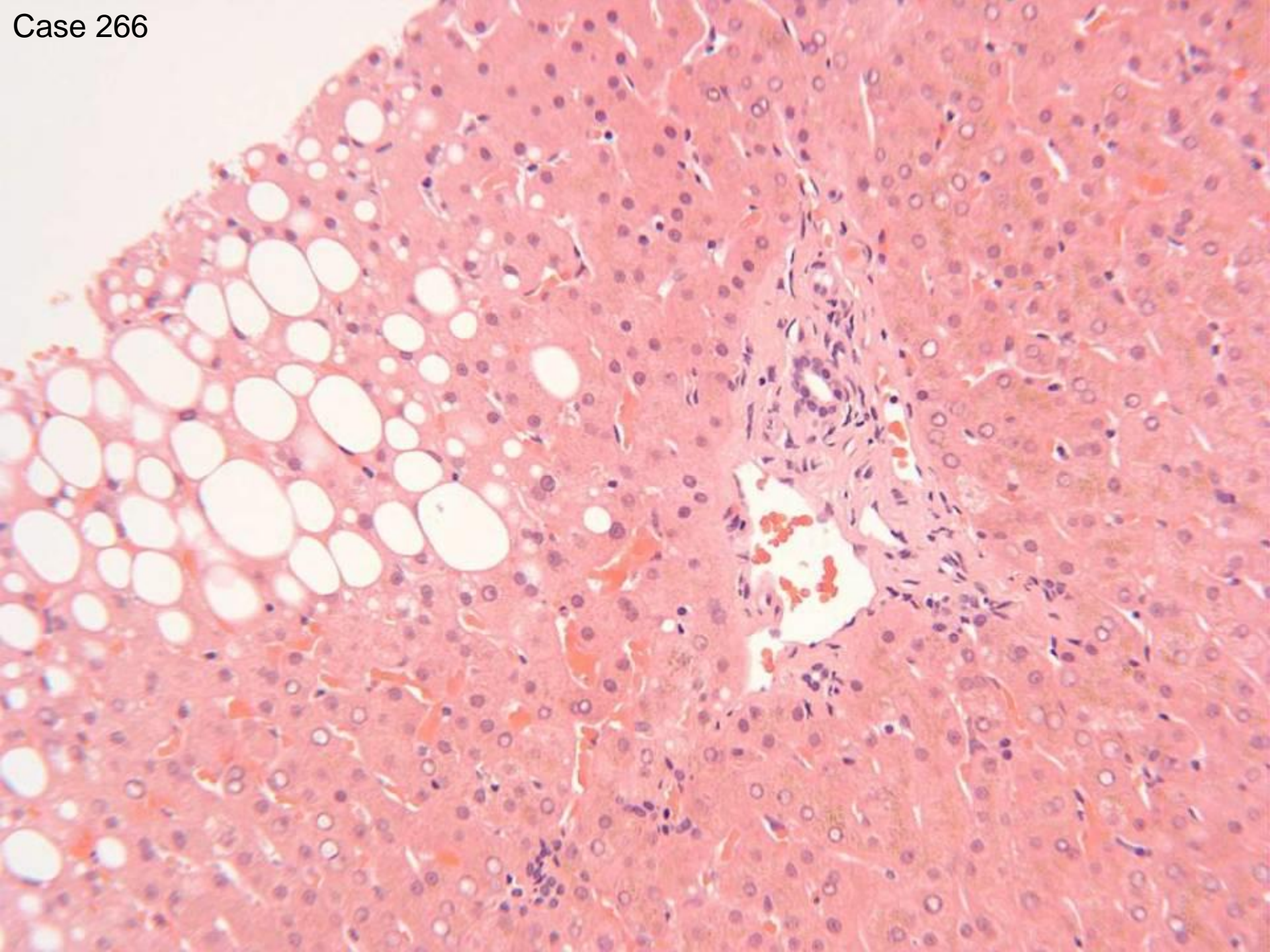
Case 266



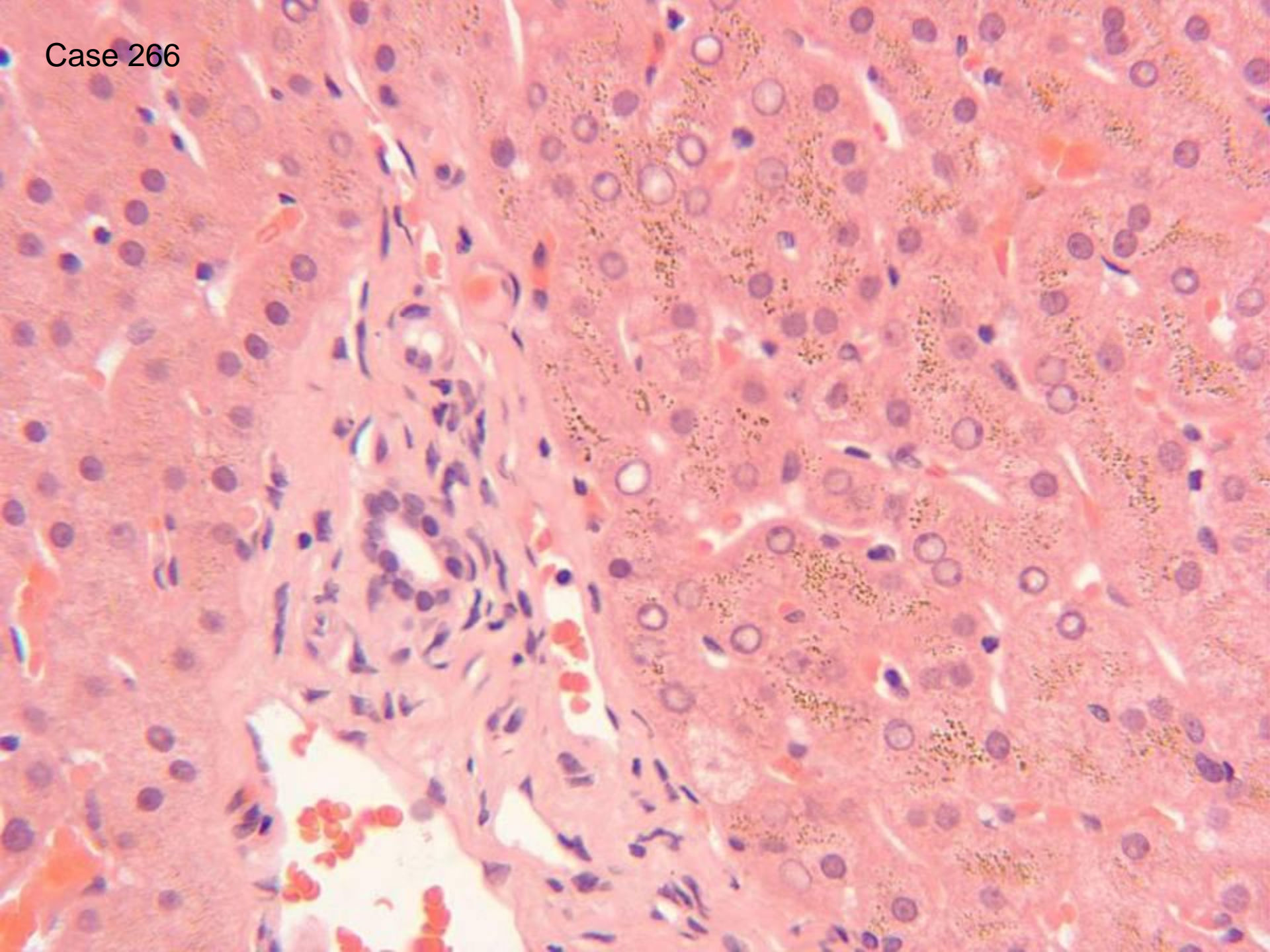
Case 266 – ballooning in one zone 3 area only



Case 266



Case 266



Case 266:

31 Steatosis, c/w NAFLD

23 steatohepatitis, c/w NASH

2 steatosis/minimal steatohepatitis NASH

1 steatohepatitis, no aetiology

2 steatosis, no aetiology

1 hepatitis or NASH

42 comment on siderosis, likely haemochromatosis

16 no mention of iron

1 pigment, probably lipofuscin

15 exclude alcohol

Case 266

Scoring: For full marks, either steatosis or steatohepatitis, with aetiology of non-alcoholic liver disease, and with a comment about increased iron.

Half marks for responses with no comment about iron/need for genetic studies for haemochromatosis, or if no indication that the aetiology of the fatty liver is NAFLD/NASH.

Case 266

Discussion: Is a comment about exclusion of alcohol as an aetiology necessary of appropriate? - felt not to be in this case with a clear history of obesity and diabetes, and glycogenated nuclei. The question of alcohol would have been more relevant had there been more ballooning/Mallory's.

There was some discussion about the usefulness of a category of borderline or minimal steatohepatitis for biopsies like this. This exists in the Keiner NAFLD activity score (NAS) for biopsies with a score of 3-4 (Kleiner DE et al. Hepatology 2005;41;1313-1321).

Ballooning degeneration is the most important (but least reproducible) feature of steatohepatitis, since it indicates hepatocyte injury rather than passive accumulation of lipid. The importance of recognising steatohepatitis is that hepatocytes are being damaged by the excess of fat/oxidative stress, with the resulting activation of fibrogenic mechanisms and potential for progressive disease.

Case 266

Original diagnosis: siderosis, consistent with hereditary haemochromatosis. Also mild steatohepatitis, consistent with NASH.

Follow up information: homozygous for C282Y.
Ferritin 1000. Hypertensive and NIDDM.

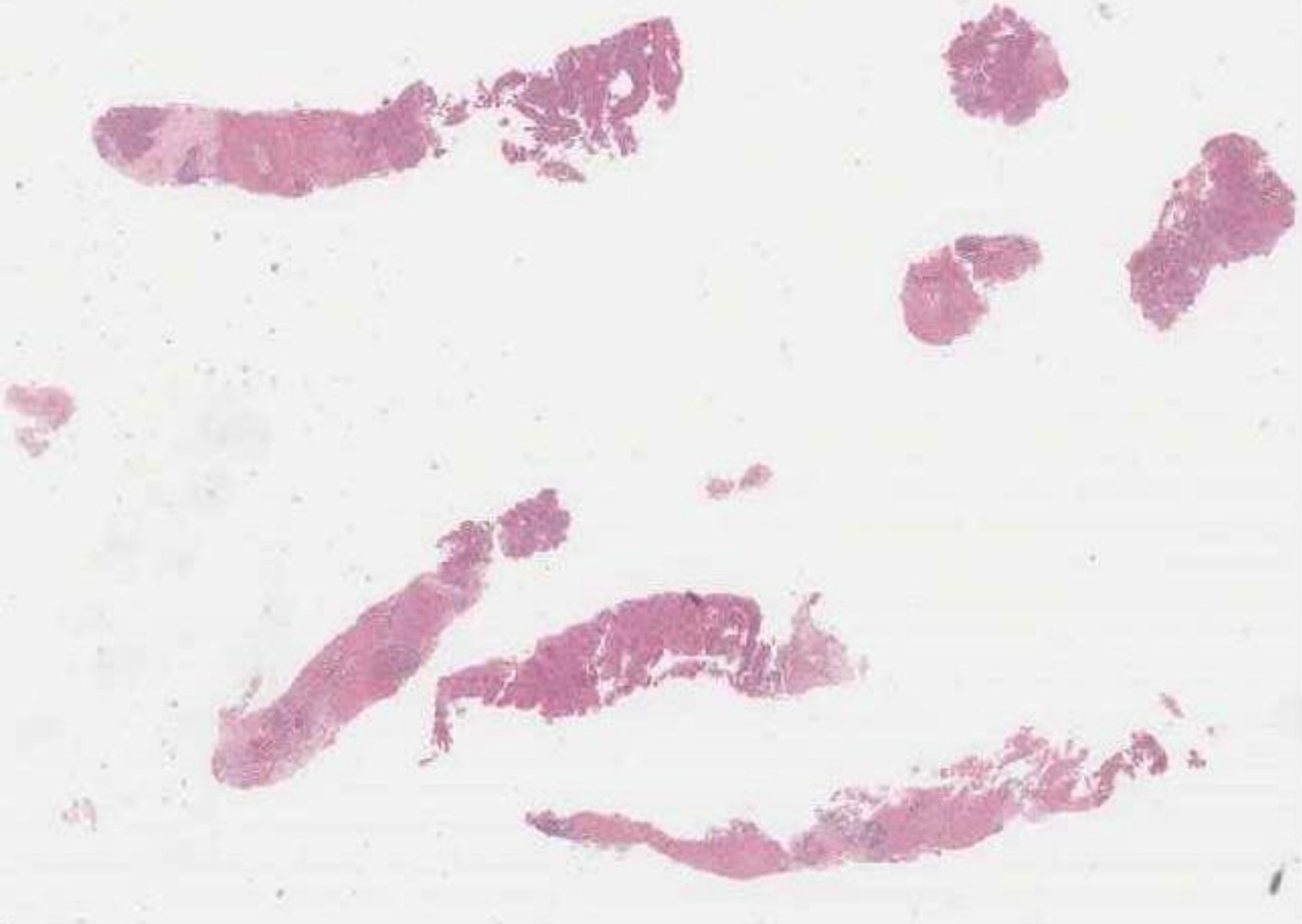
Case 267

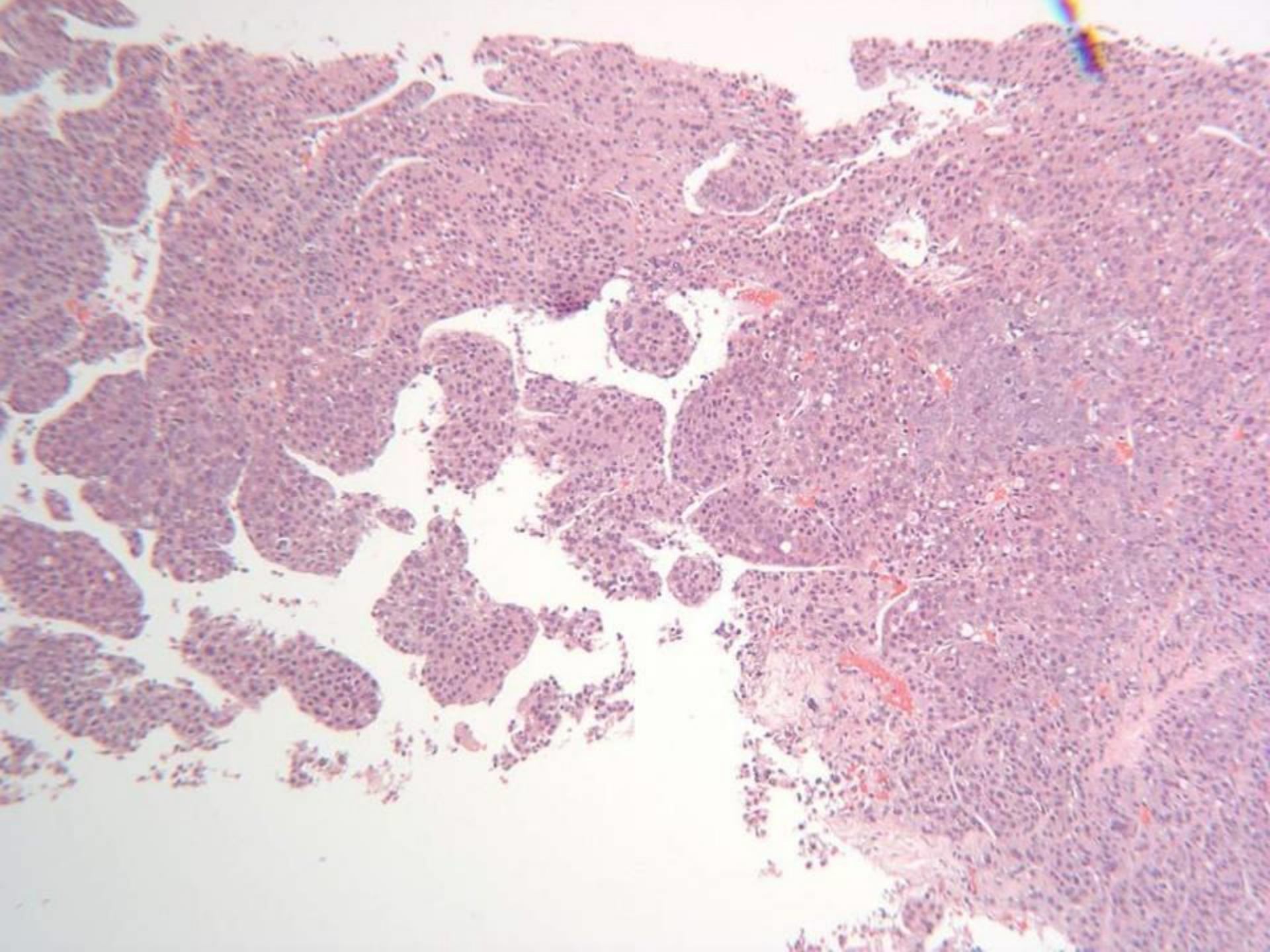
72M.

Weight loss, abnormal liver function tests,
CT - large tumour in liver,
alpha feto protein ?20,000,
?hepatocellular carcinoma.

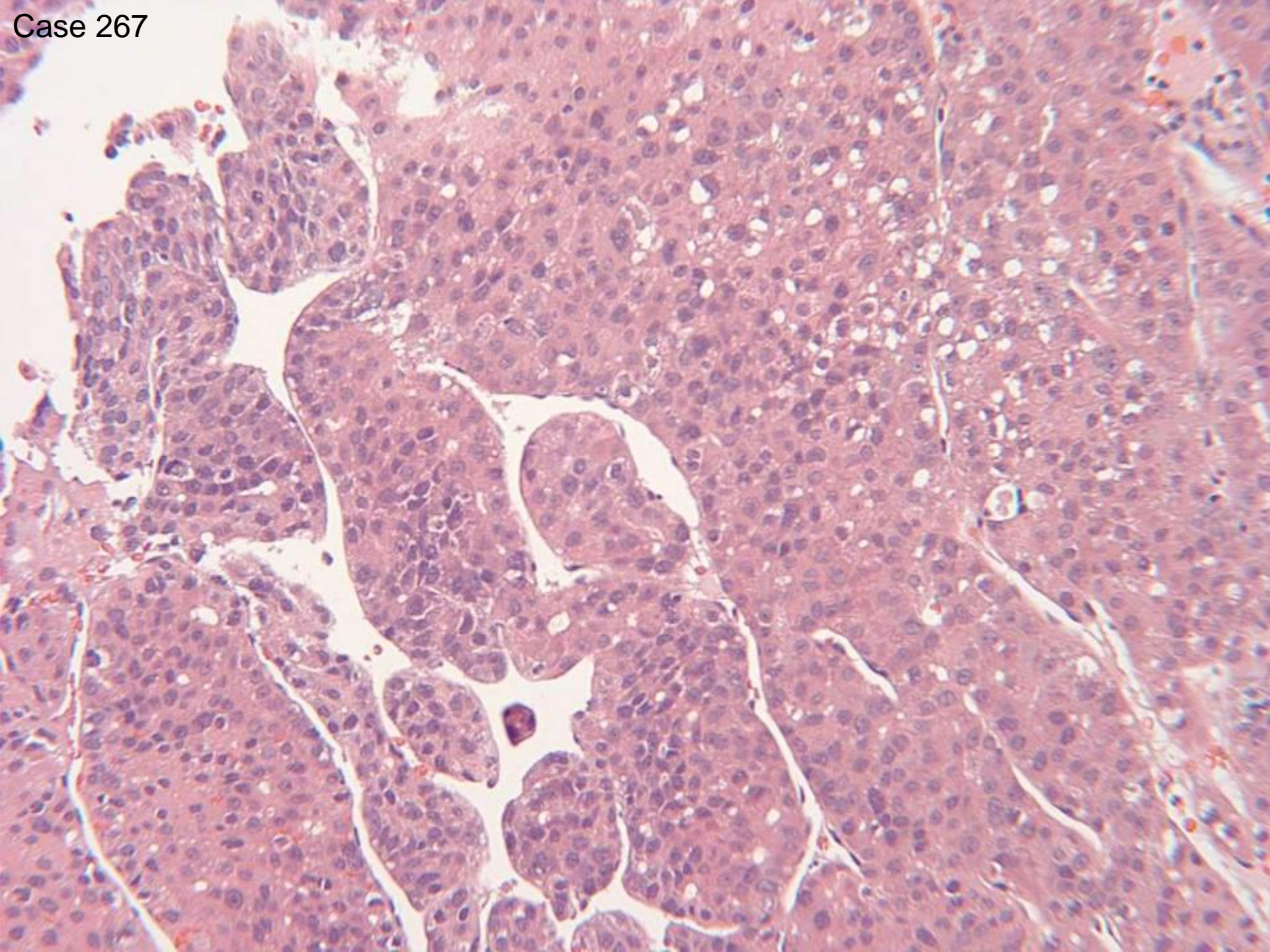
ICC carried out - negative CK7 and CK20, CD10
& CD 13 showed ?small occasional canaliculi
among tumour cells, alphafeto protein
equivocal.

Case 267

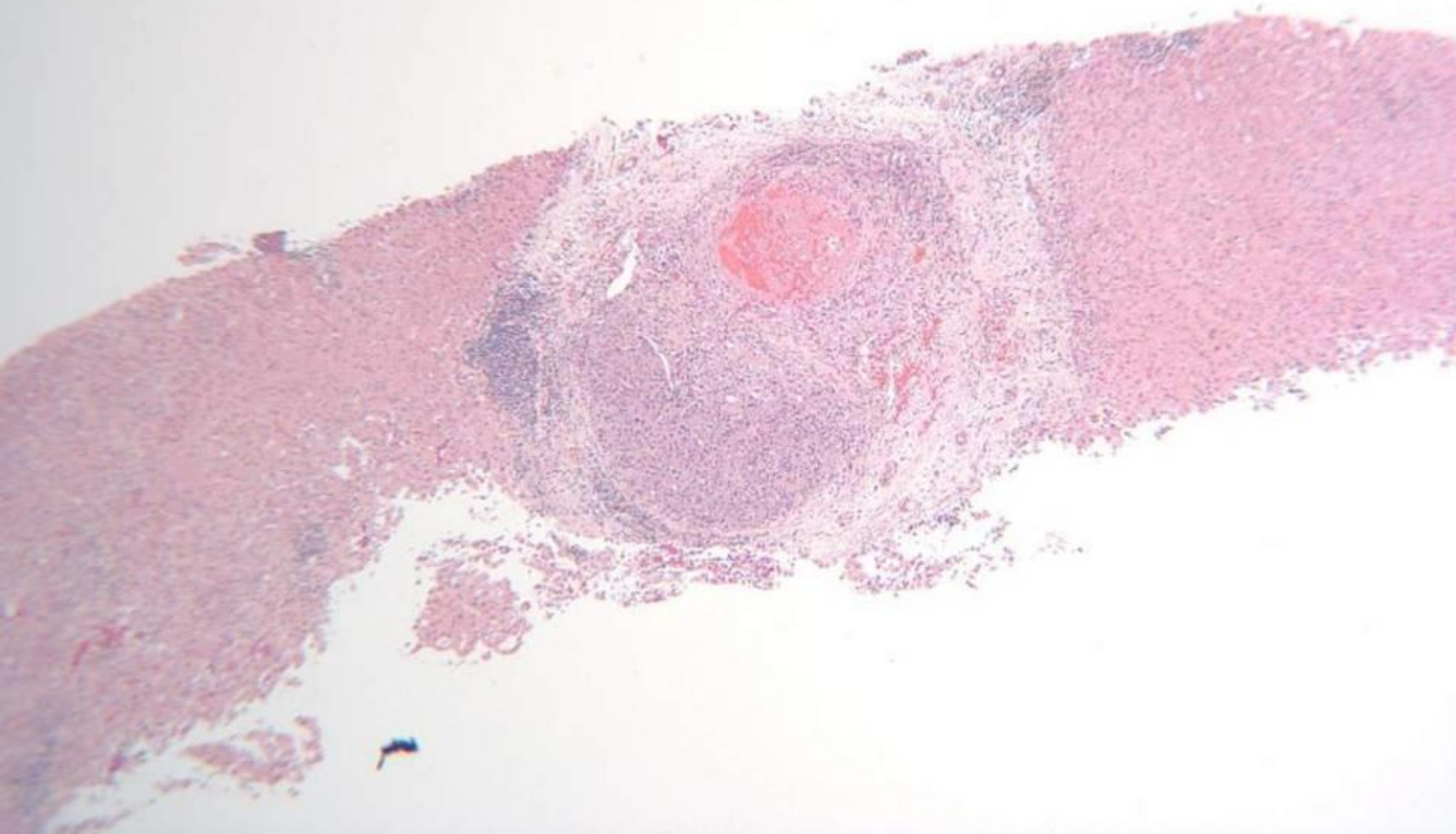




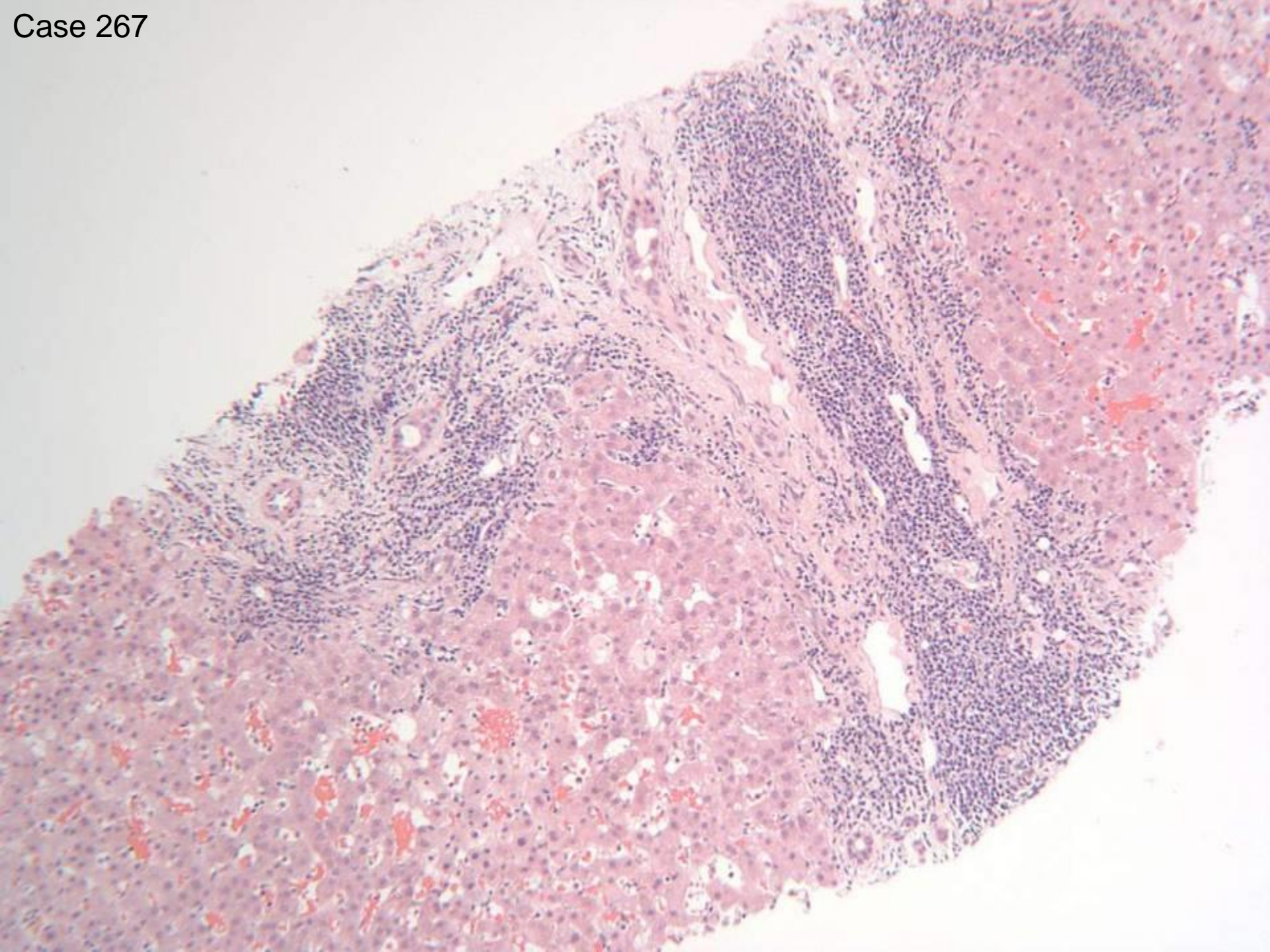
Case 267



Case 267



Case 267



Case 267

58 hepatocellular carcinoma, of which

34 NOS

1 well differentiated

17 moderately differentiated/grade 2-3

3 poorly differentiated

1 carcinoma, probably hepatocellular

2 liver cell cancer

comments:

10 background cirrhosis/probable cirrhosis

2 background due to adjacent mass lesion

8 vascular invasion

Any immunohistochemistry suggested?

34 no

25 yes

Case 267

Scoring: full marks for hepatocellular carcinoma, half marks for 'liver cell cancer' (imprecise terminology). There was sufficient evidence in this case (morphology, high AFP) without additional immunohistochemistry being necessary for diagnosis.

Case 267

Discussion: related to grading, vascular invasion and background liver.

Grading - concensus for moderate/grade 2-3, but not essential in biopsies. Resected HCCs are often heterogeneous, and grading on biopsy has little effect management.

Vascular invasion is clearly present in this case, is of more prognostic relevance than grading, and should be included in biopsy reports.

There is fibrosis and inflammation in the biopsy, but in the vicinity of the tumour so may not be representative of the rest of the liver. A biopsy remote from the tumour would be required to assess for cirrhosis, and is important if surgical management is considered. Conversely, a biopsy of the tumour itself is contraindicated if surgery is an option.

Case 267

Original diagnosis: hepatocellular carcinoma

Case 268

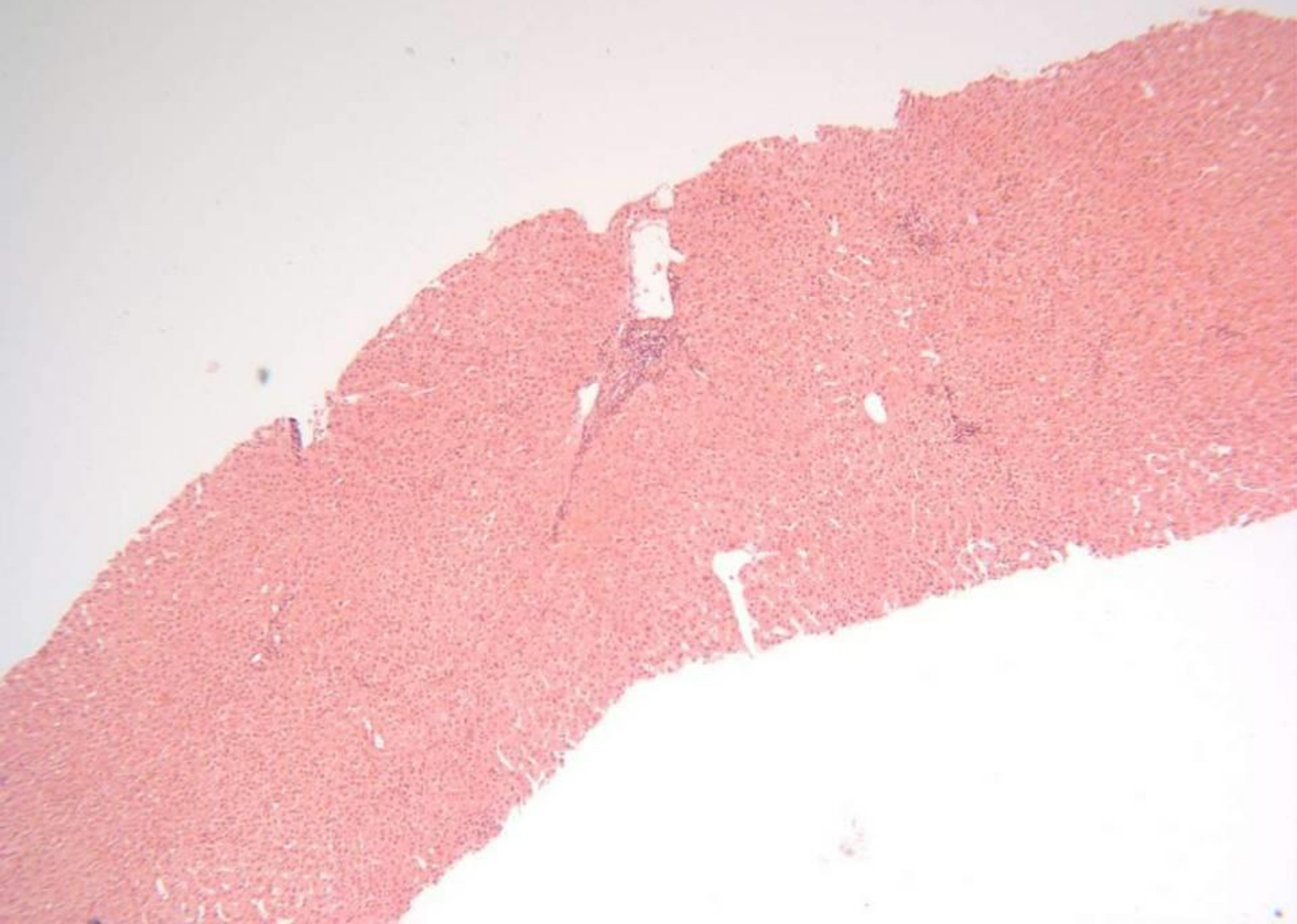
54F.

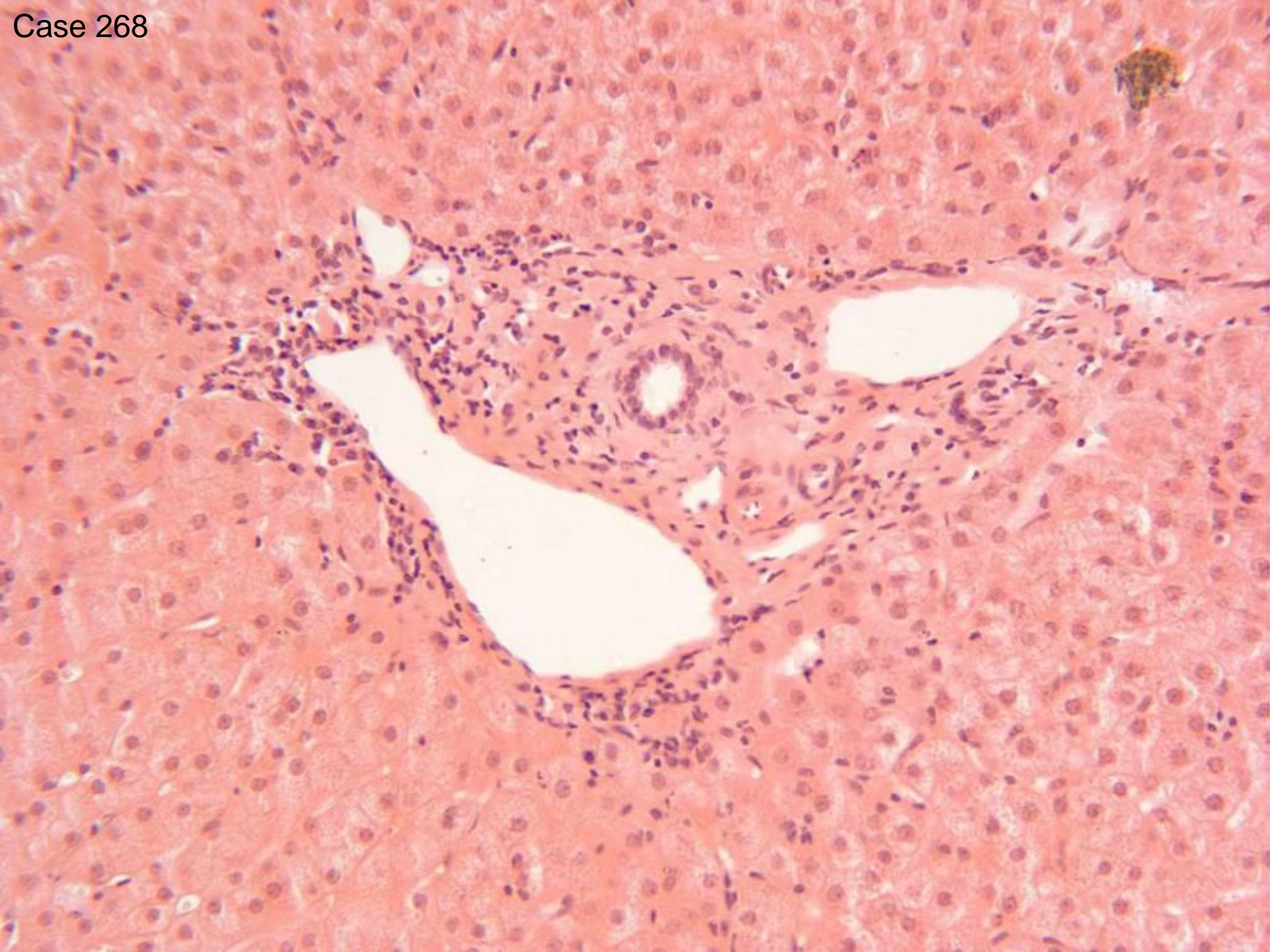
HCV antibody positive. Normal LFT,
heterogenous liver

Case 268

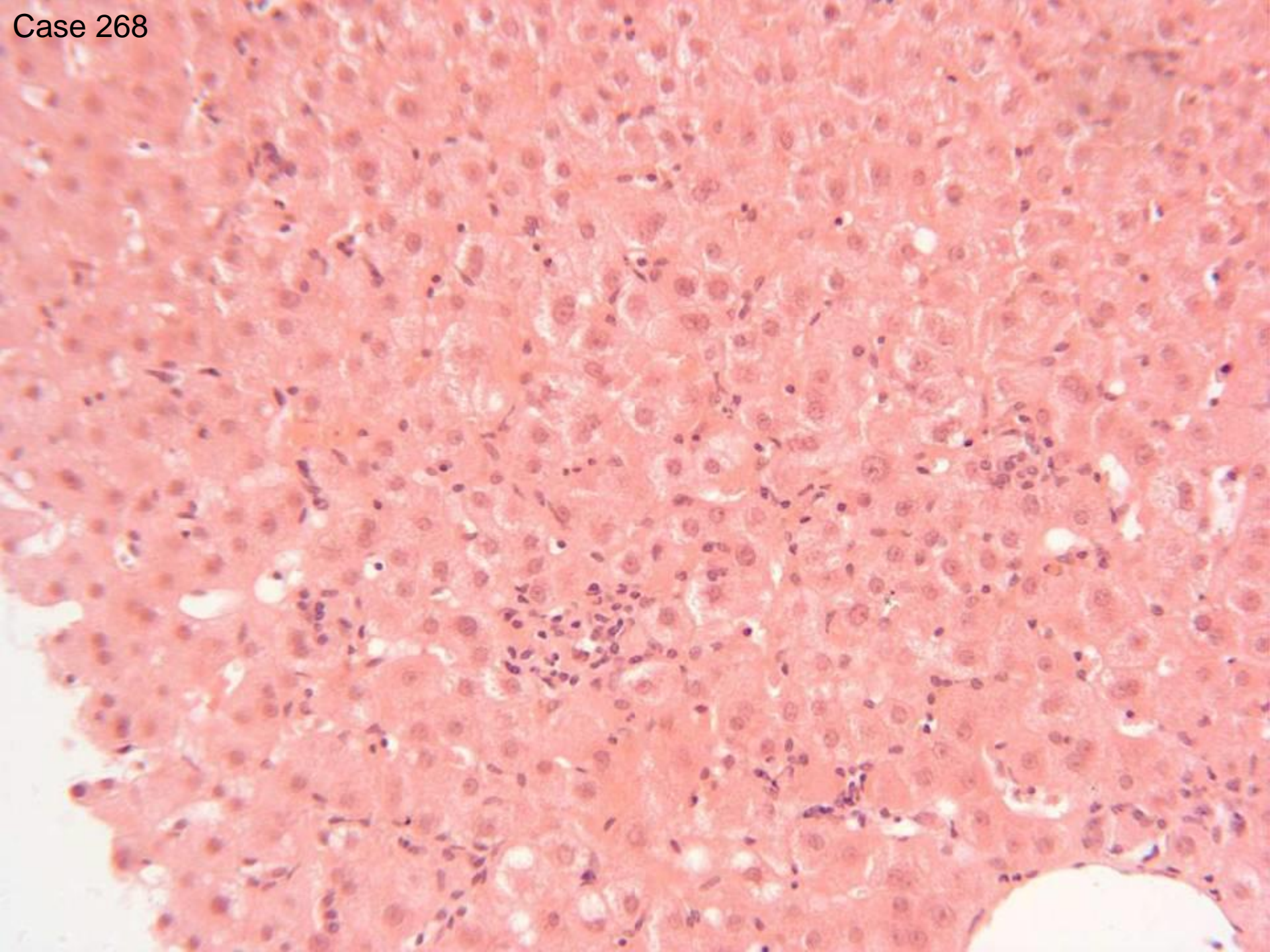


Case 268





Case 268



Case 268

58 hepatitis C, of which

4 no indication of severity.

48 gave text comment about severity, of which:

35 mild

6 mild-moderate

6 moderate

33 gave Ishak grade, of which:

3 grade 4

19 grade 4

6 grade 5

4 grade 6

2 grade 7

2 gave Metavir score

several comments about relative prominent lobular activity.

Original diagnosis: chronic hepatitis, HCV, minimal fibrosis, mild activity.

Case 268

Scoring: Both the aetiology (hepatitis C) and some indication of the severity of the chronic hepatitis were required. Chronic hepatitis C with no other comment scored 0.

The range of grades is included for interest - it is helpful to know how one's score compares with the rest of the participants.

Discussion: the lobular activity was more evident than portal inflammation in this case - perhaps this is a recent infection with hepatitis C, (although perhaps unlikely in this case in a 54 year old female).

Case 269

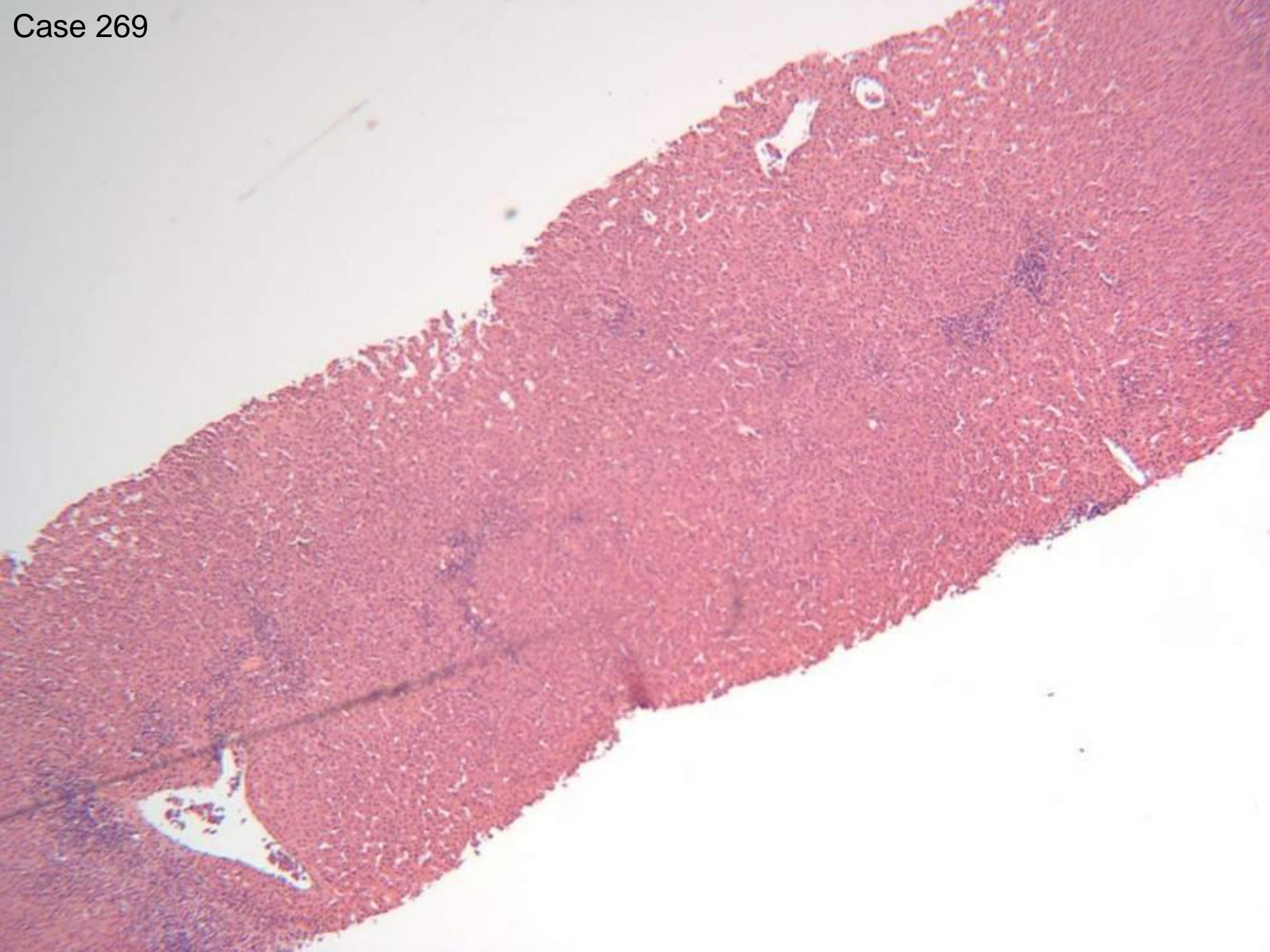
50F.

Cholestatic liver function tests.

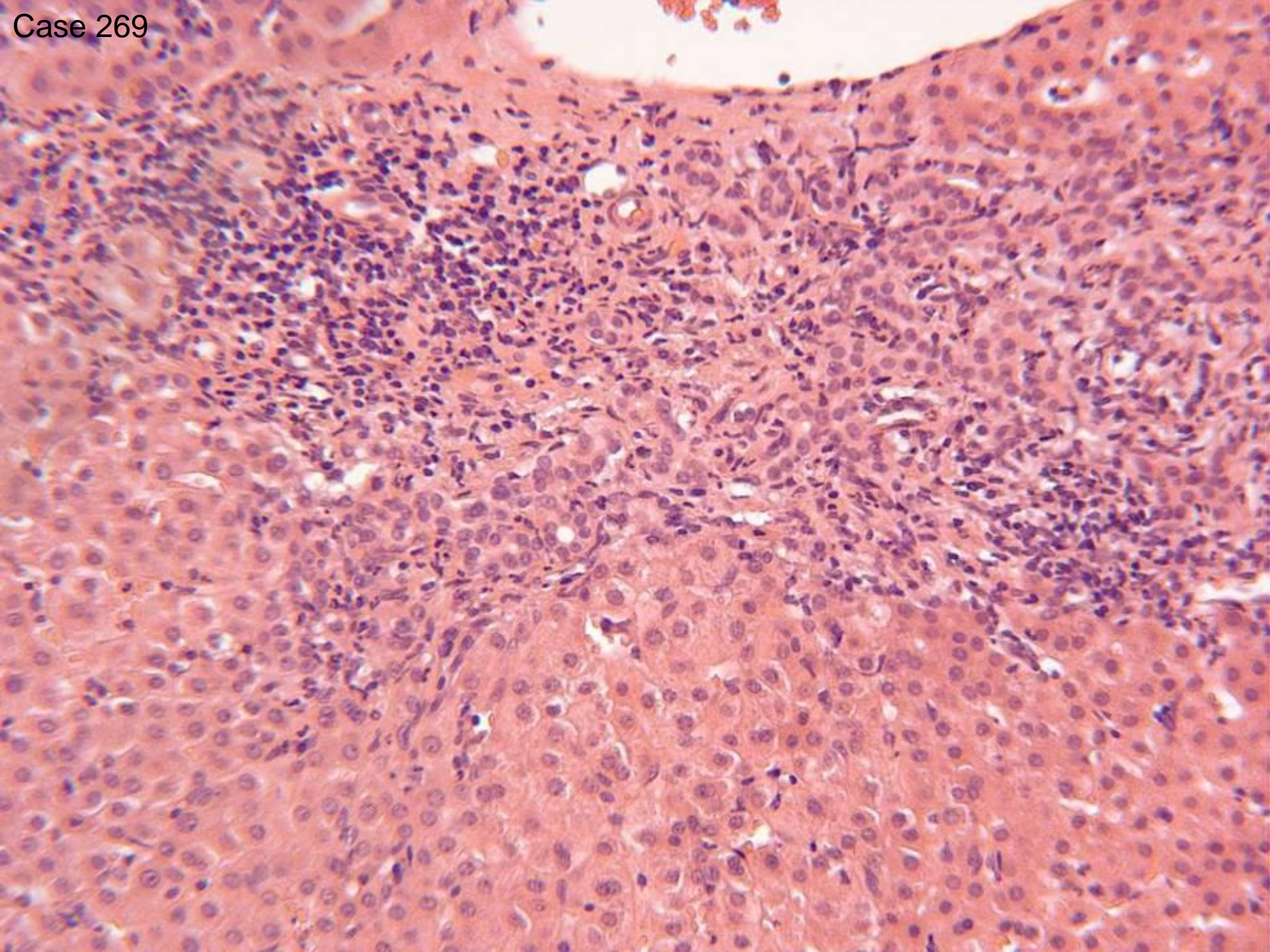
Abundant copper associated protein
deposition on Orcein stain.

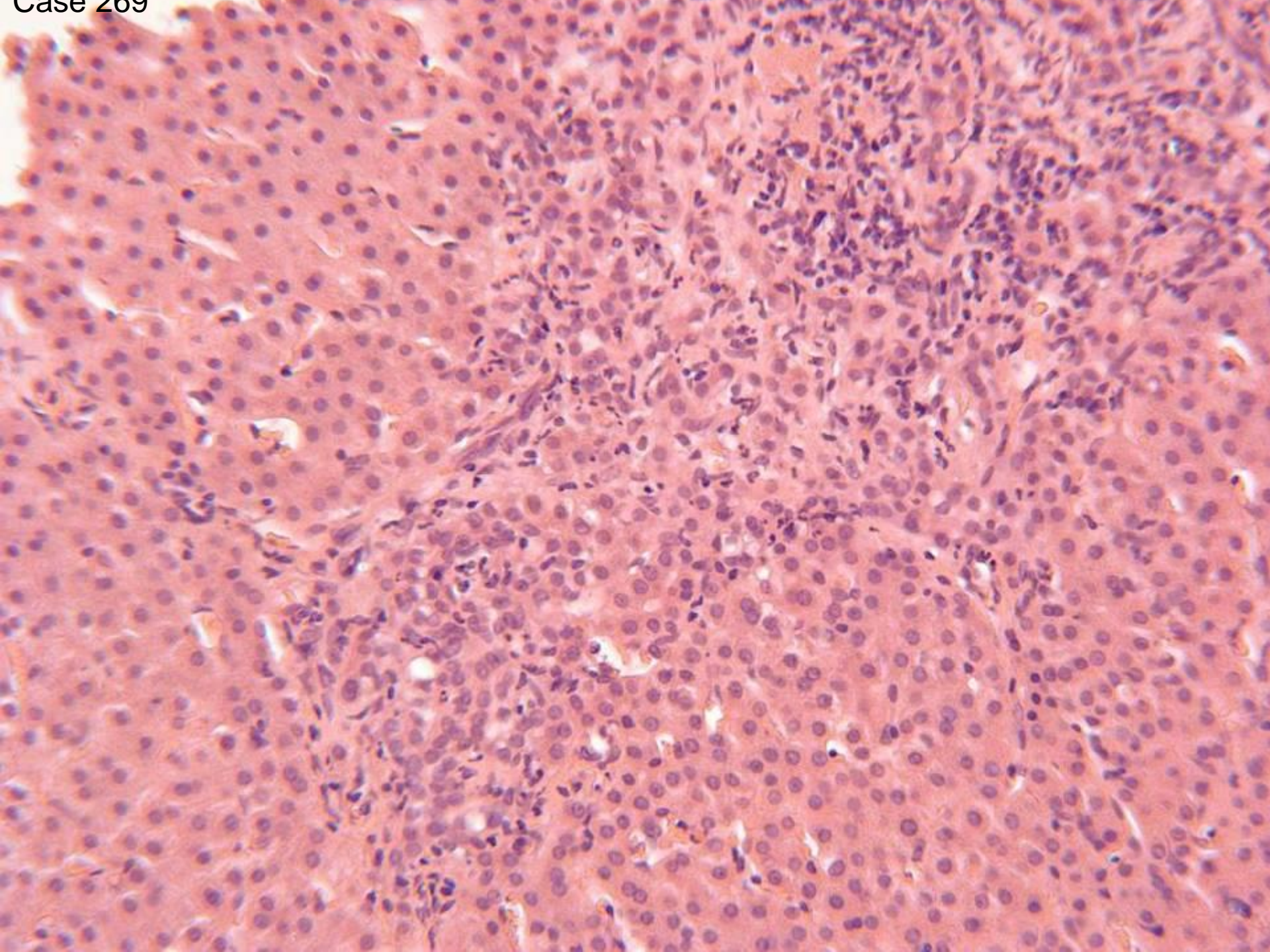


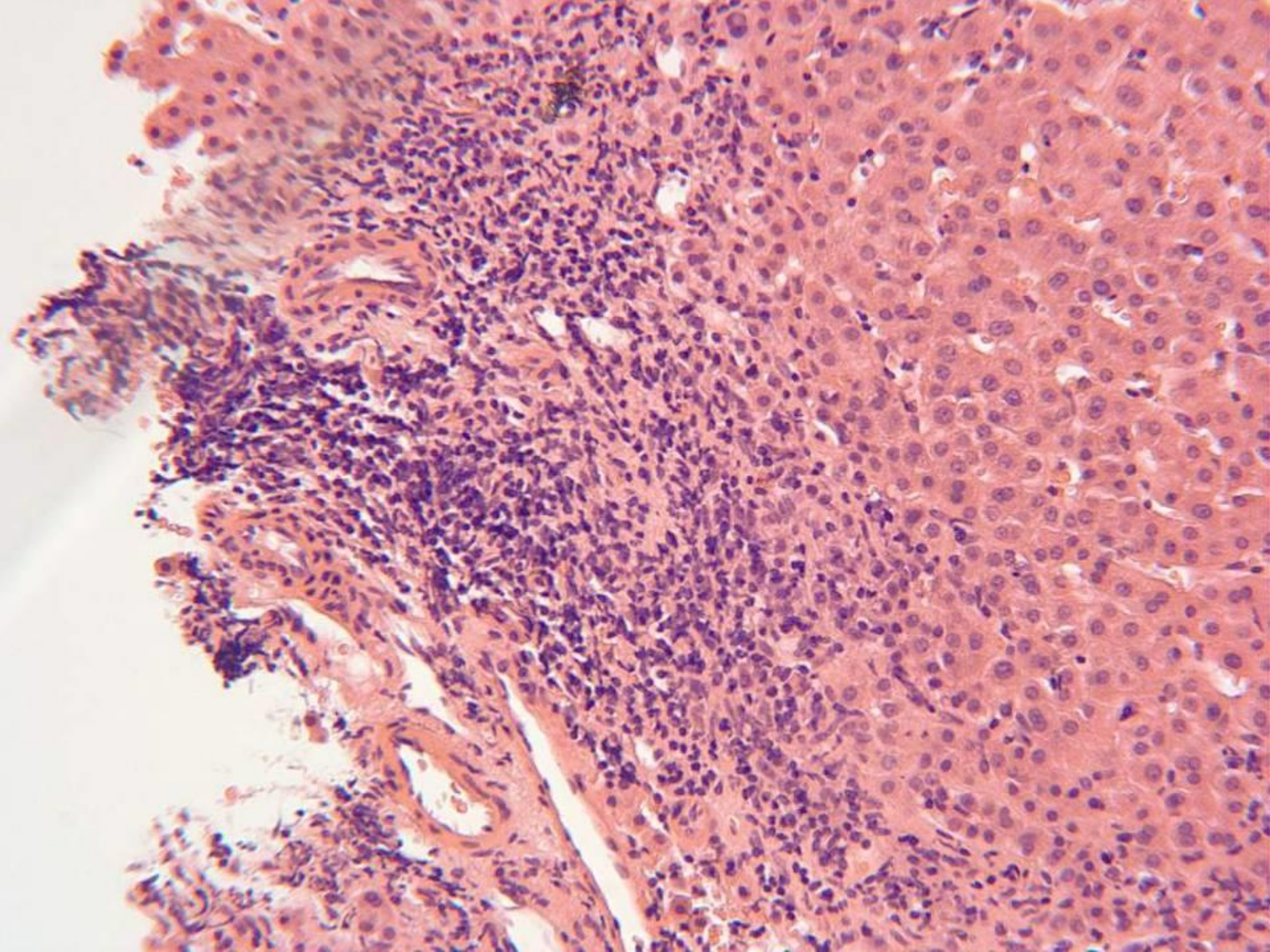
Case 269



Case 269







Case 269

44 PBC as main diagnosis

11 chronic biliary disease - exclude PBC/PSC

1 chronic hepatitis ? cause

1 chronic hepatitis ? autoimmune

1 subacute cholestatic reaction

1 bile duct obstruction, any cause (includes PBC but features do not fit with PBC)

1 bile duct obstruction ?stone/tumour. ?sclerosis.

comment:

50 need AMA/serology

8 AMA not mentioned

Original diagnosis: primary biliary cirrhosis

Case 269

Scoring: The histology with the history of cholestatic LFTs and abundant copper associated protein was sufficient for a diagnosis of chronic biliary disease.

Score 0 for responses other than chronic biliary disease.

Granulomas were present in 50% slides circulated, influencing the likelihood of PBC as the specific diagnosis. The recognition of copper associated protein as a marker of chronic biliary disease in non-cirrhotic liver with portal inflammation/ ductular reaction is important.

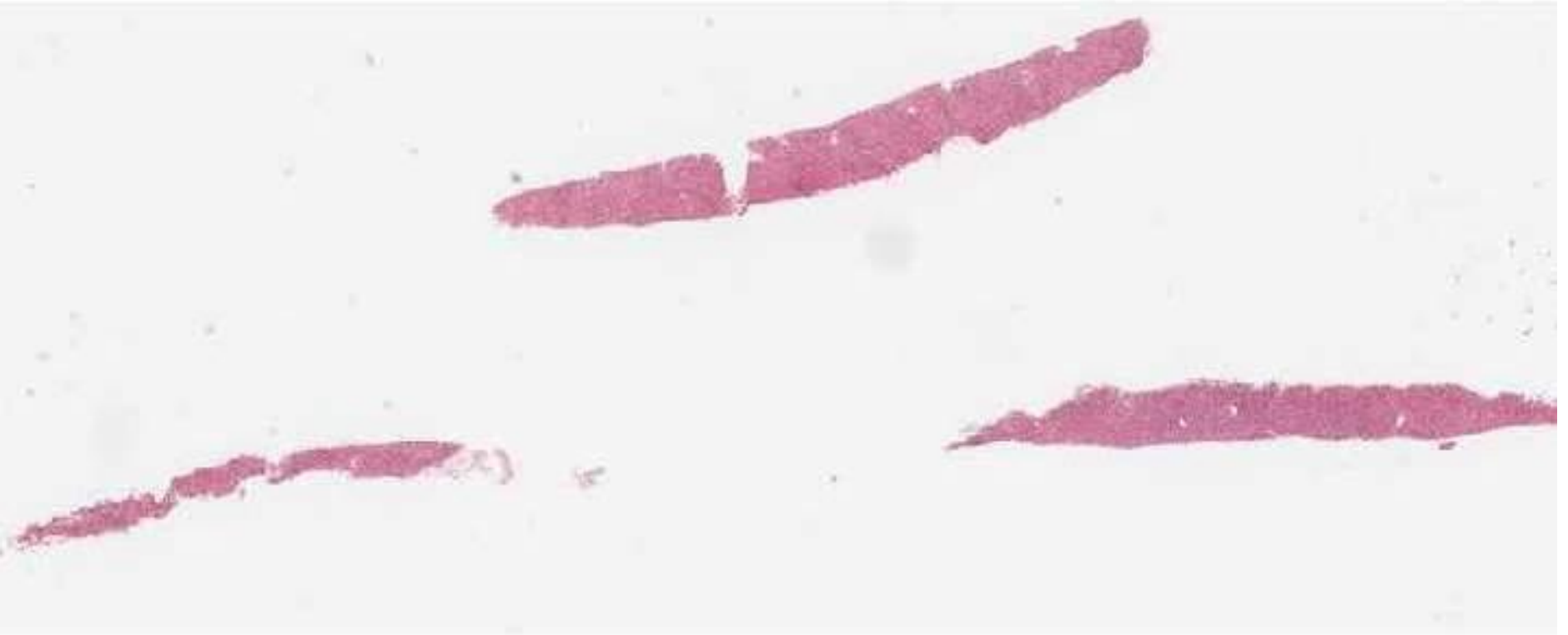
Discussion: The clinicians should have already checked for anti-mitochondrial antibodies, and included the result on the request form - if present biopsy may not be required.

Case 270

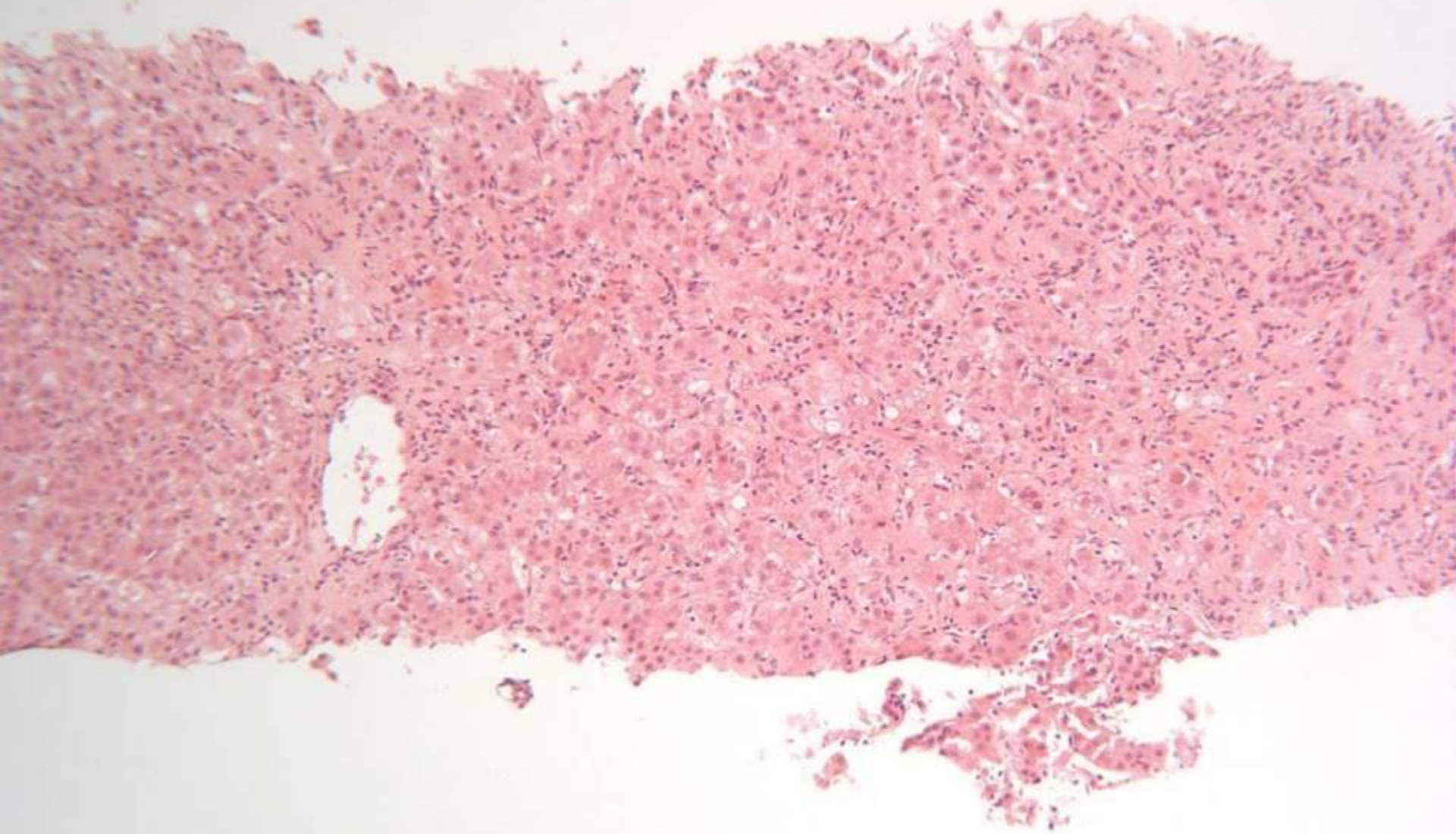
62F. Jaundice, ?cause. US normal,
?AI, bil 264, ALP 307, ALT 494,
HAV, HBV, HCV neg,
neg - autoimmune profile,

Reticulin collapse,
elastin - not increased. DPAS ceroid++. No
increase in CAP.

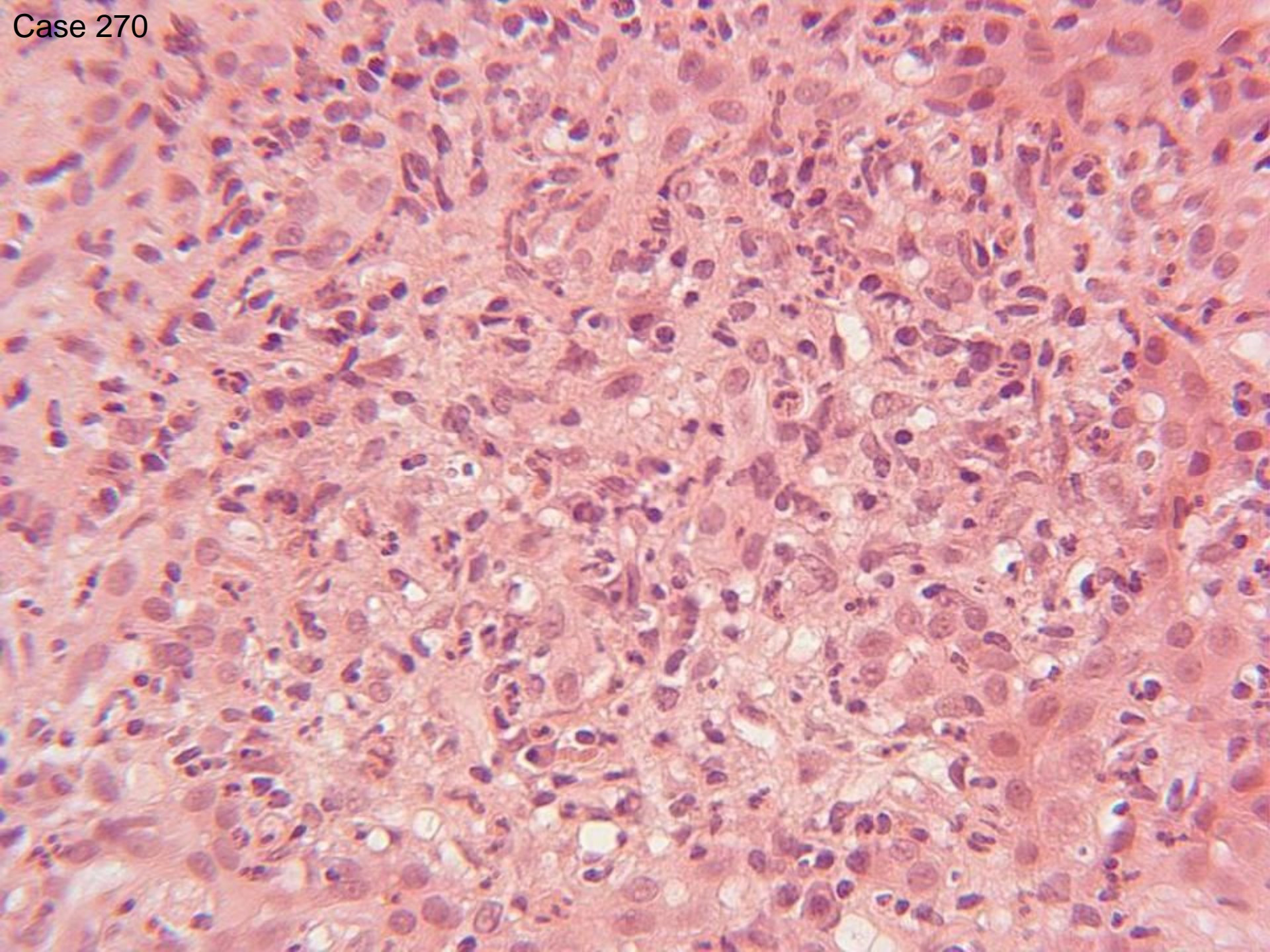
Case 270



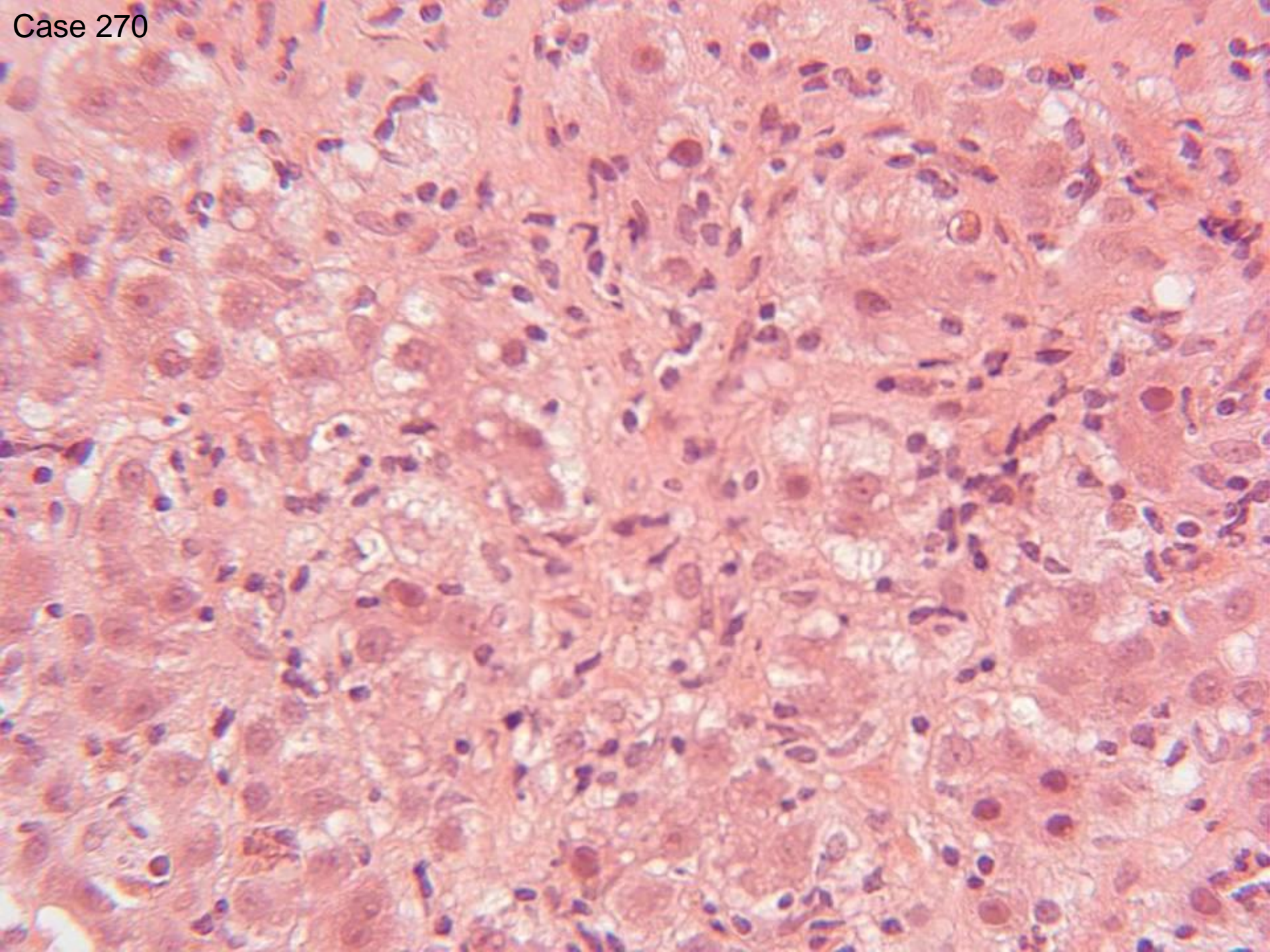
Case 270



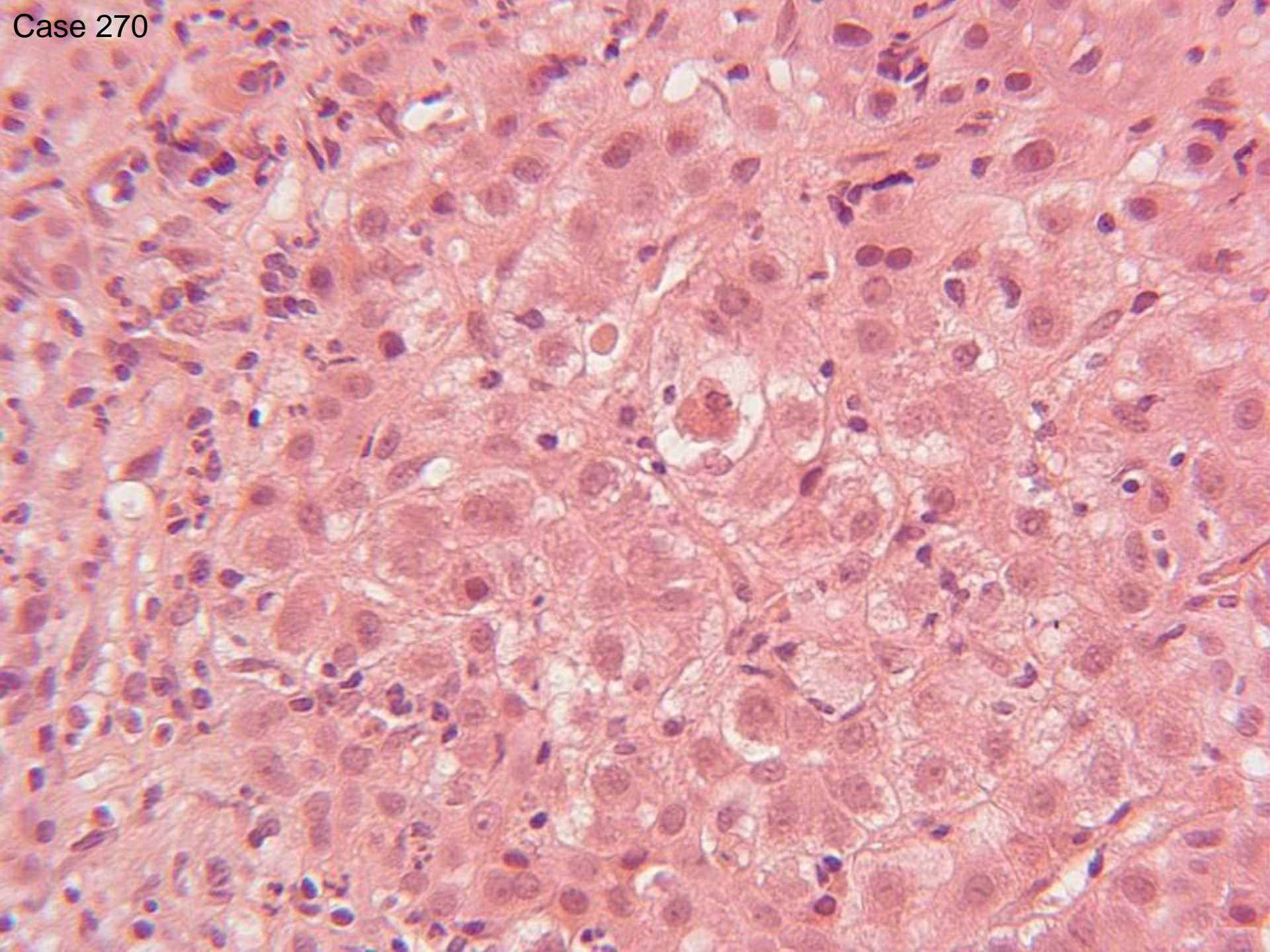
Case 270



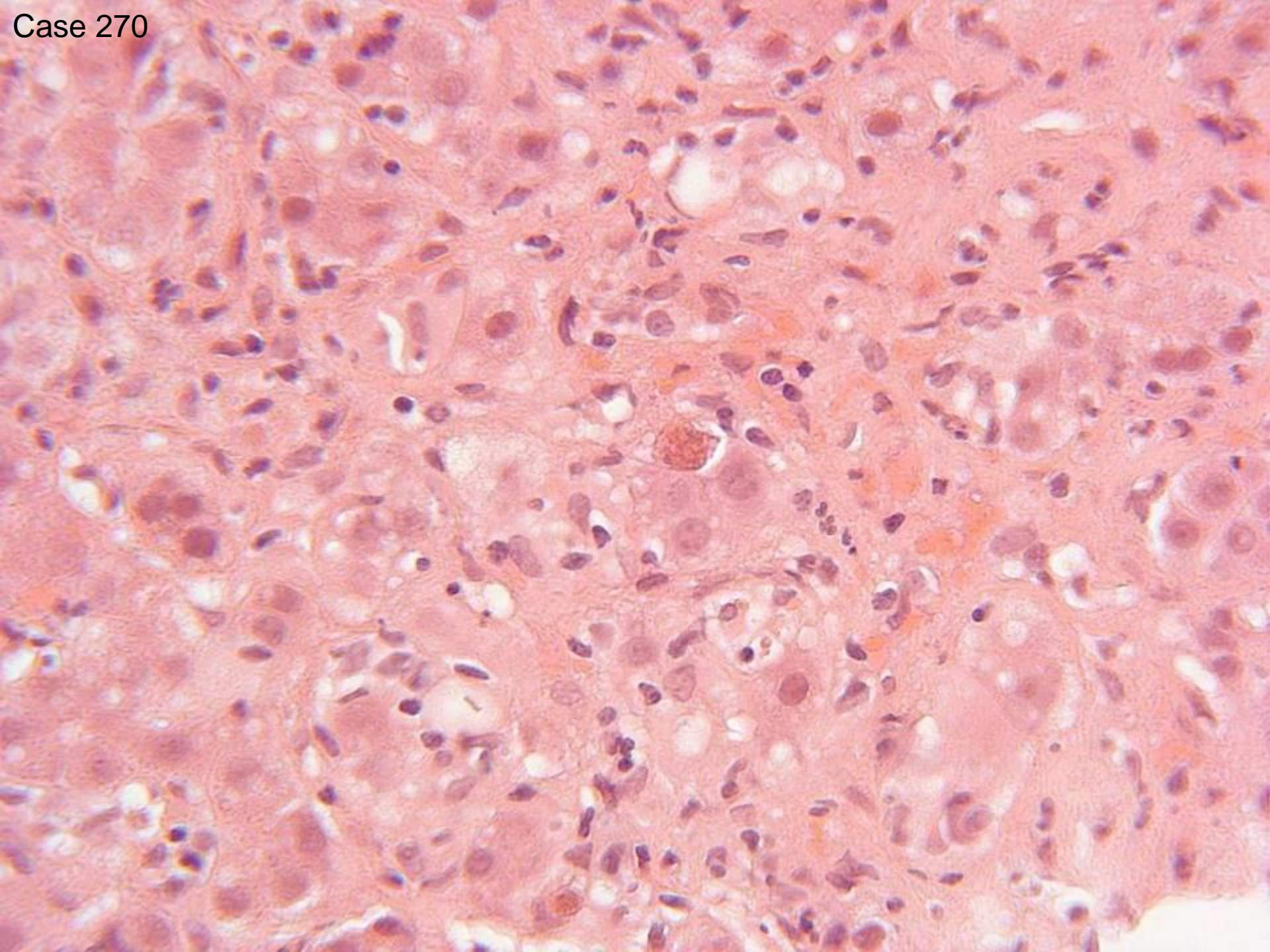
Case 270



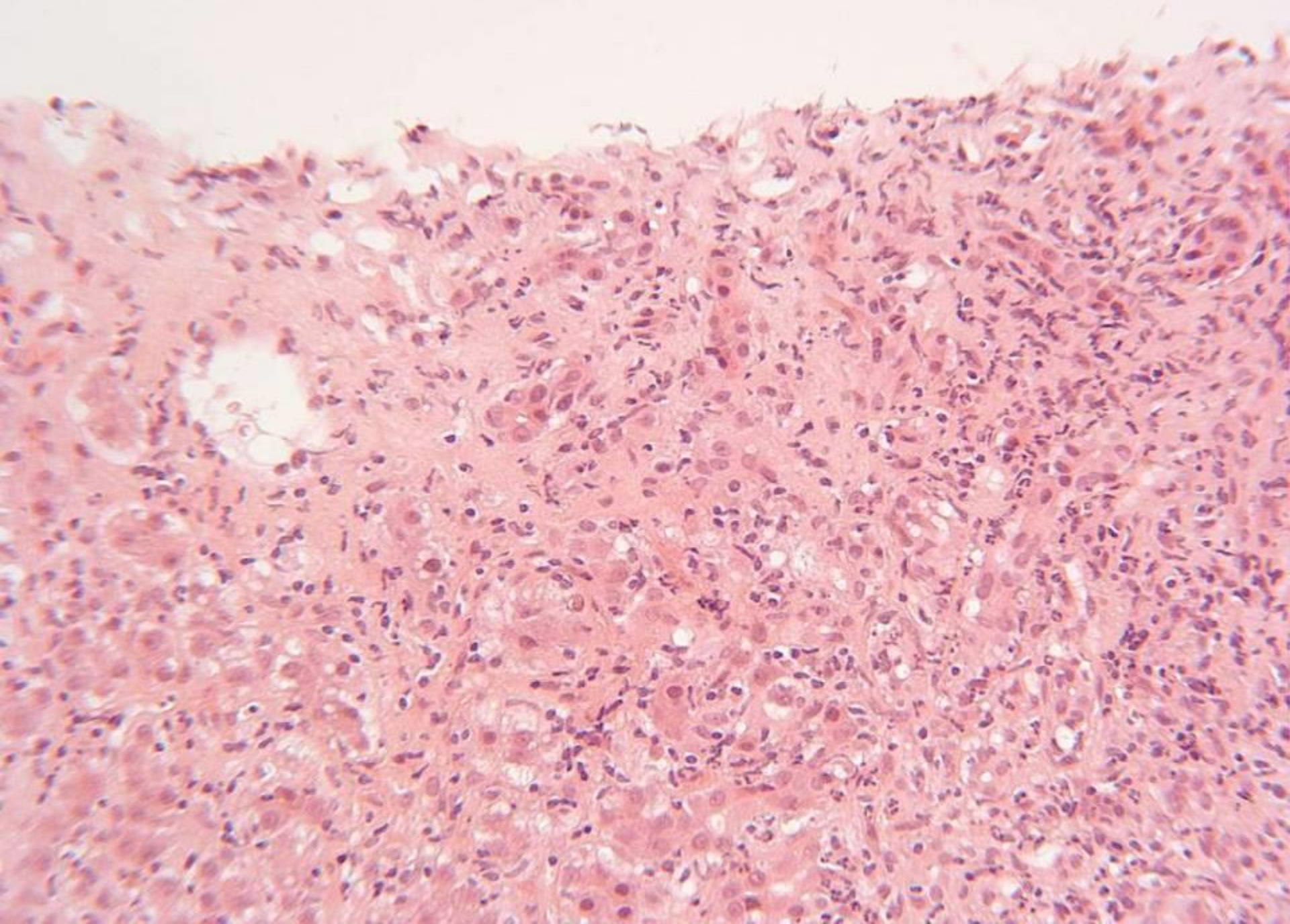
Case 270



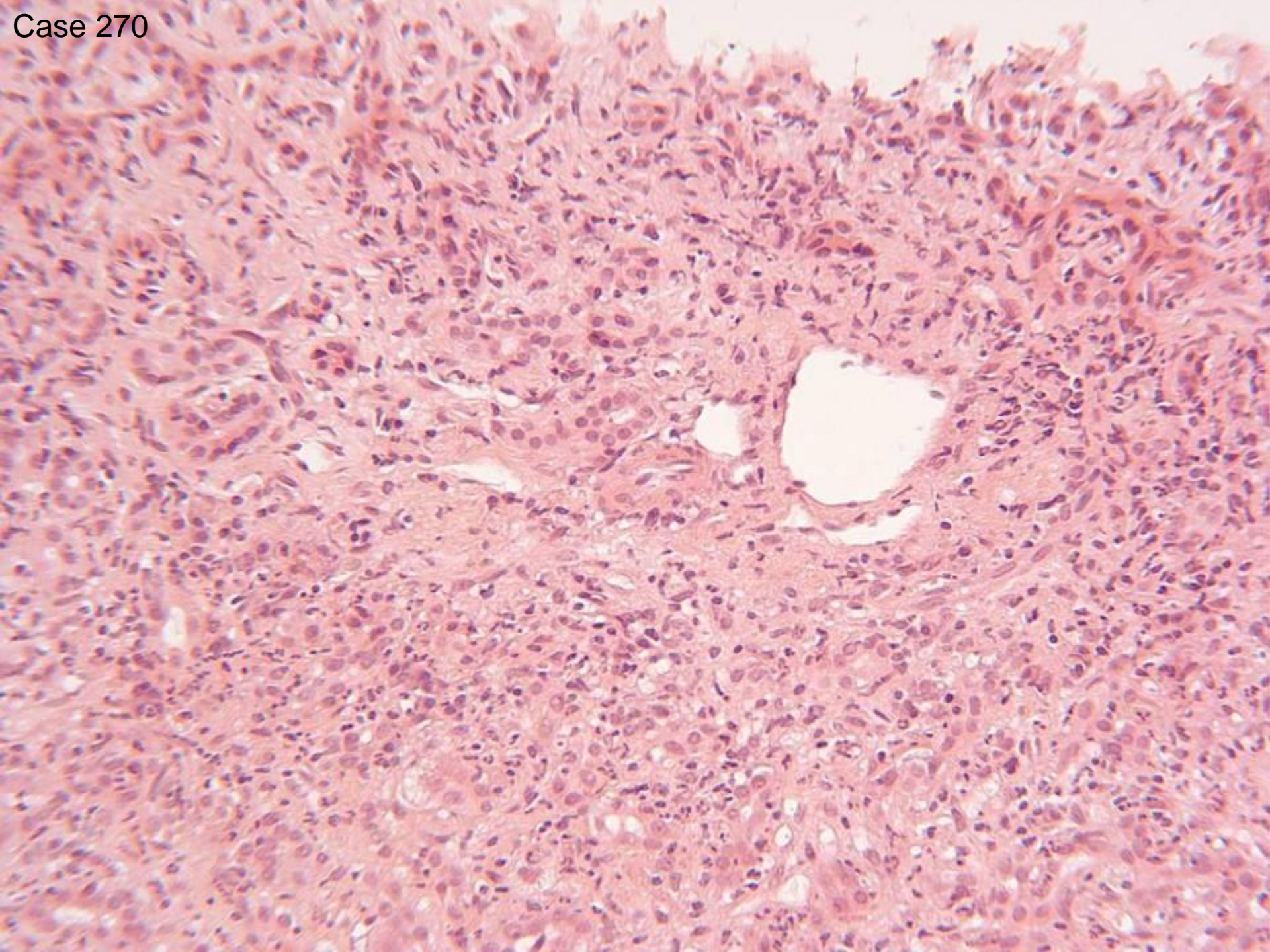
Case 270



Case 270



Case 270



Case 270

- 31 acute hepatitis with confluent necrosis, and differential
- 11 acute hepatitis, no mention of confluent necrosis, with differential

- 1 acute hepatitis with cholangitis
- 1 acute viral hepatitis, no differential
- 1 acute hepatitis, drugs no differential
- 1 cholestatic hepatitis, ? drugs
- 1 acute hepatitis with ascending cholangitis, obstruction, secondary biliary cirrhosis
- 1 cholestatic jaundice, due to sepsis/drugs/LBDO

- 3 chronic active hepatitis
- 1 widespread necrosis with chronic active inflammation, ?drug/other
- 1 ductular reaction with polys etc. ?LBDO
- 4 acute alcoholic hepatitis
- 1 veno-occlusive disease
- 2 description only, no mention of 'hepatitis'

Case 270

Scoring: A diagnosis of acute hepatitis with appropriate differential of possible causes required for full marks.

The presence of confluent necrosis is important in indicating the severity of the hepatitis, and should be included when reporting such a case (but if required here the case could not be included in scoring).

Responses indicating a single aetiology scored half marks. Other diagnoses scored 0.

Case 270

Discussion: In biopsies of acute hepatitis, it is important clearly to indicate that this is acute and not chronic disease, and the severity of the necrosis (spotty, confluent, zonal, bridging, panacinar).

Recognised causes include acute presentation of autoimmune hepatitis, drugs, and viral hepatitis; histology is rarely able to indicate the cause. In practice about 75% cases of severe acute hepatitis requiring transplant are seronegative (i.e. no clinically recognised cause).

Case 270

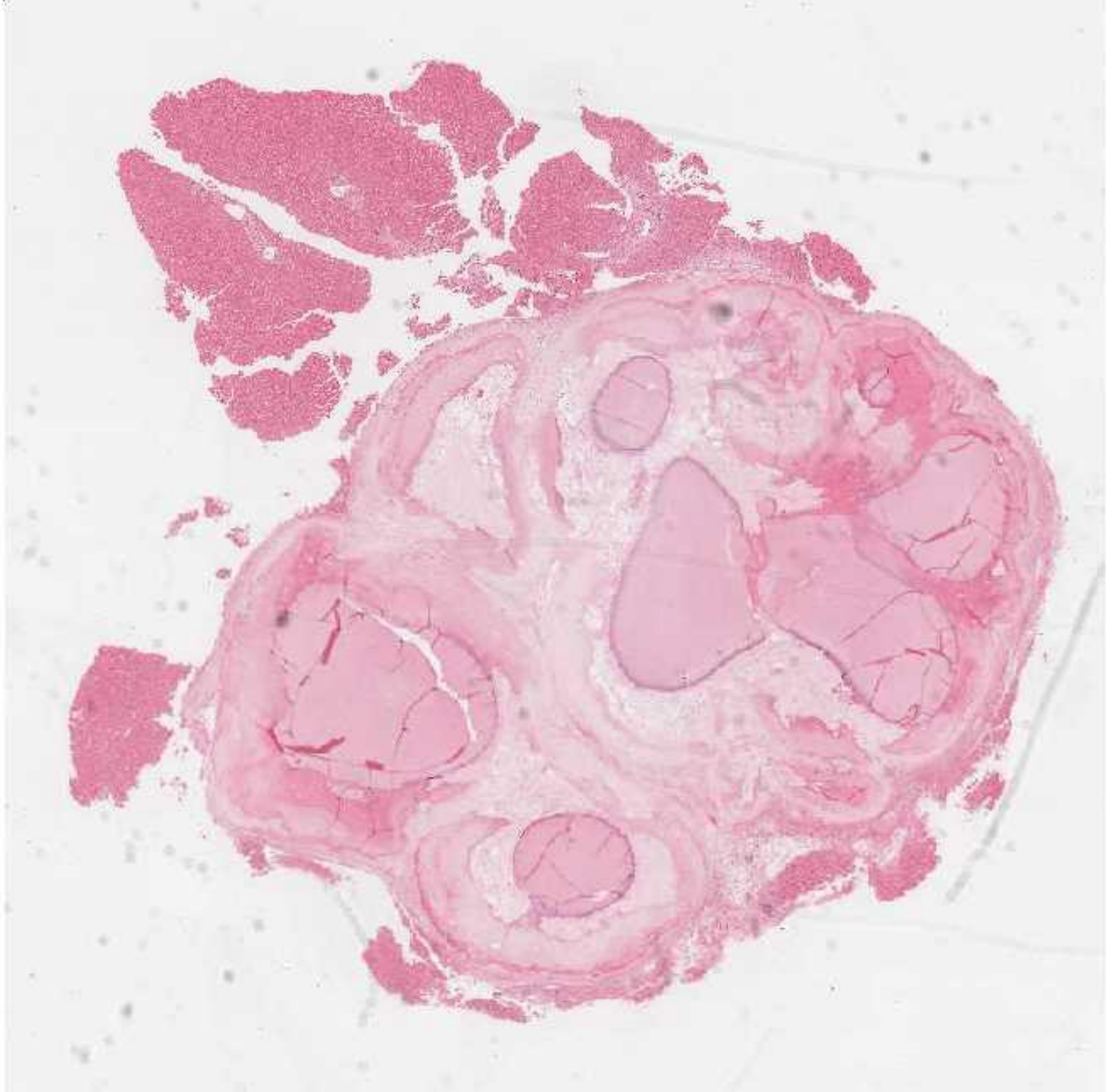
Original diagnosis: acute hepatitis, cause unknown.

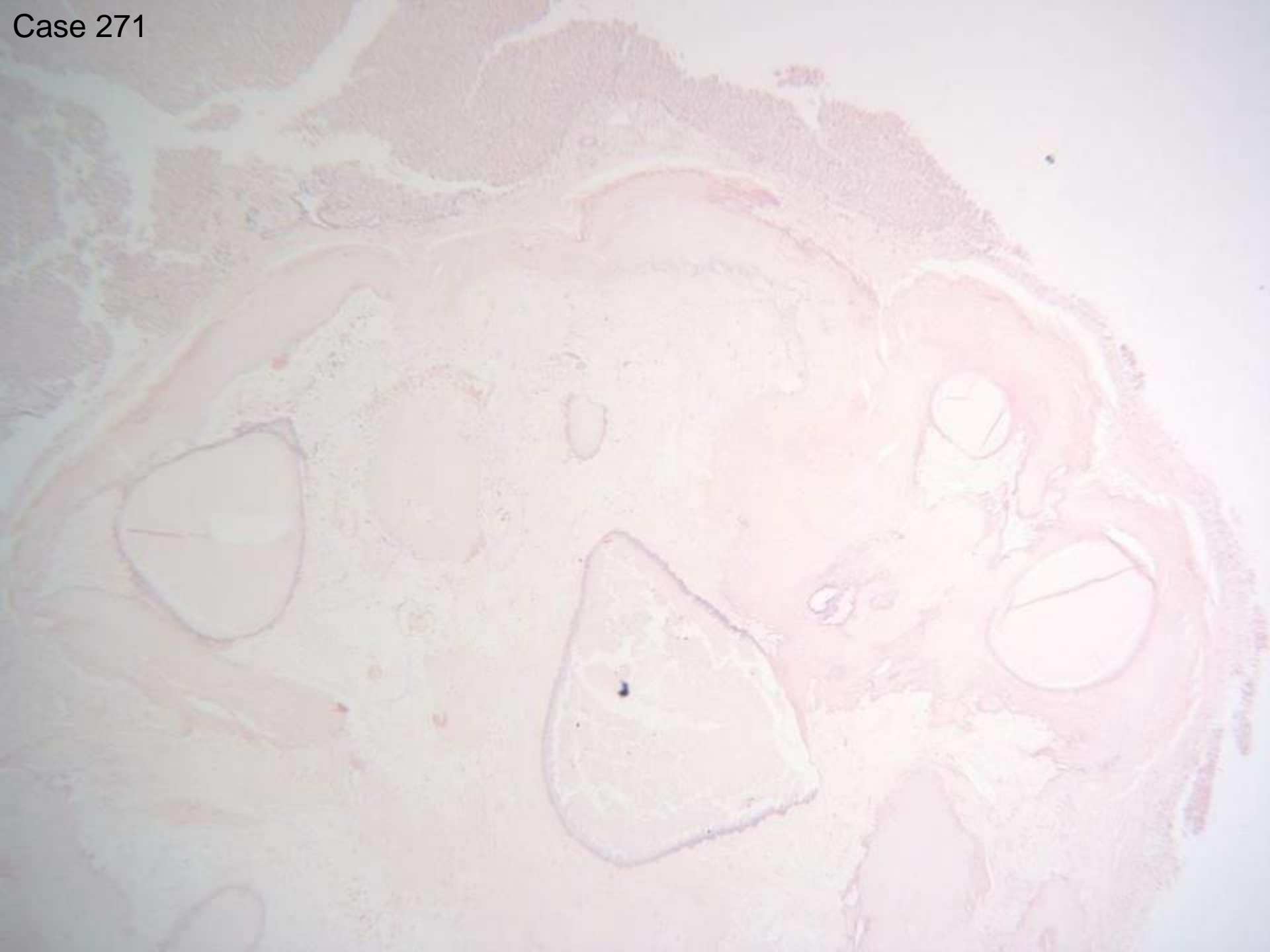
Follow up information: resolved over 4-6 months. Repeat biopsy normal, (although still raised enzymes).

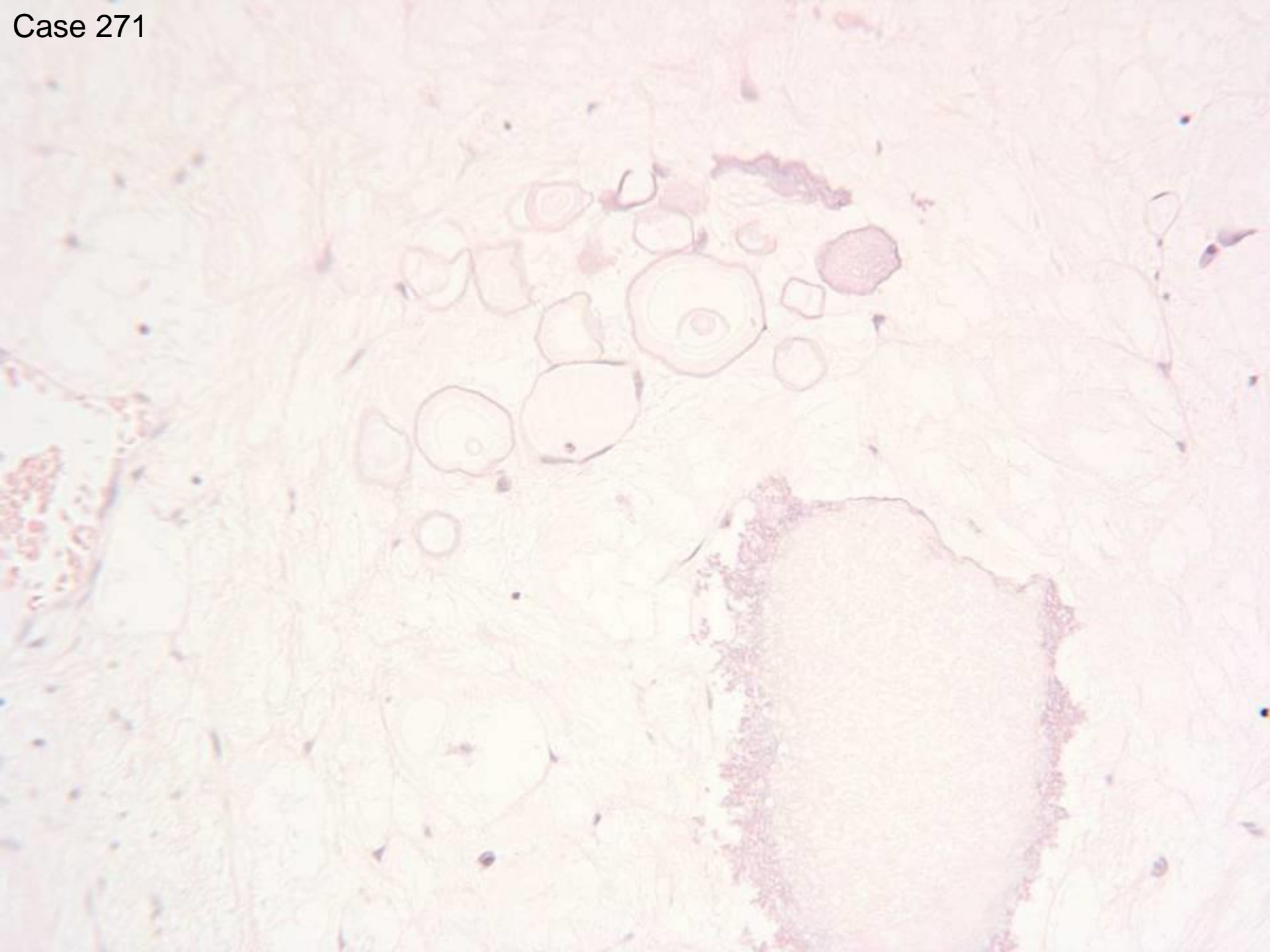
Case 271

58M.

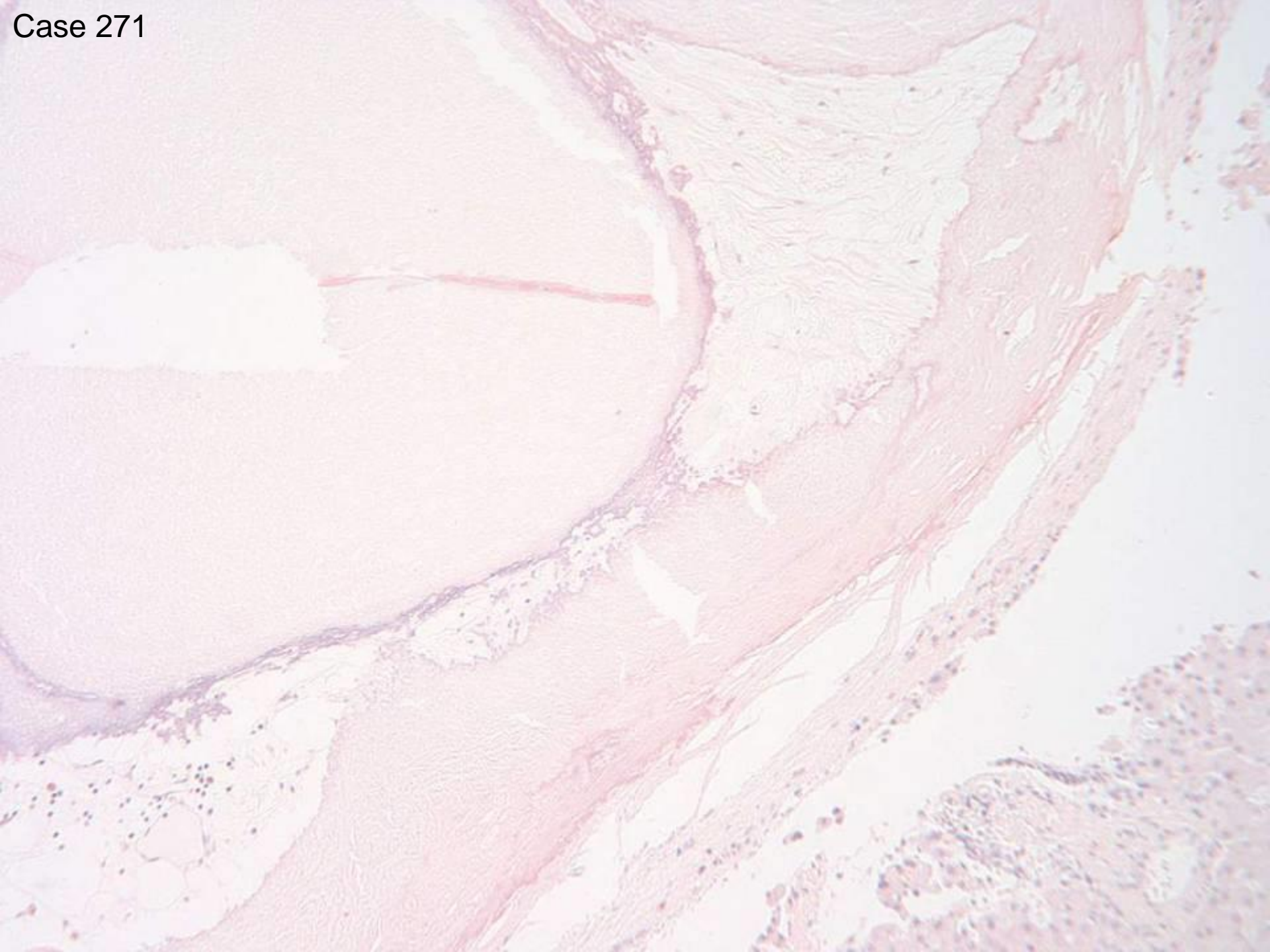
Incidental finding of liver nodule at time
of abdominal aortic aneurysm repair







Case 271



Case 271

- 17 solitary necrotic nodule
- 29 solitary fibrous/calcified nodule
- 5 sclerosed haemangioma
- 2 pseudotumour
- 1 echinococcus or other infectious agent (as only diagnosis)
- 1 amorphous ghost material, geographic layering, ? infective
- 1 amyloid

comment: 13 mentioned parasites - hydatid, worms, larva, eggs, echinococcus, capillariasis, pentastoma, cysticercosis

Original diagnosis: sclerosed haemangioma (based on architecture and lack of necrosis). Focal metaplastic bone noted.

Case 271

Scoring: no points for amyloid, echinococcus or other infectious, or pseudotumour as the main diagnosis, as this suggests inflammatory pseudotumour.

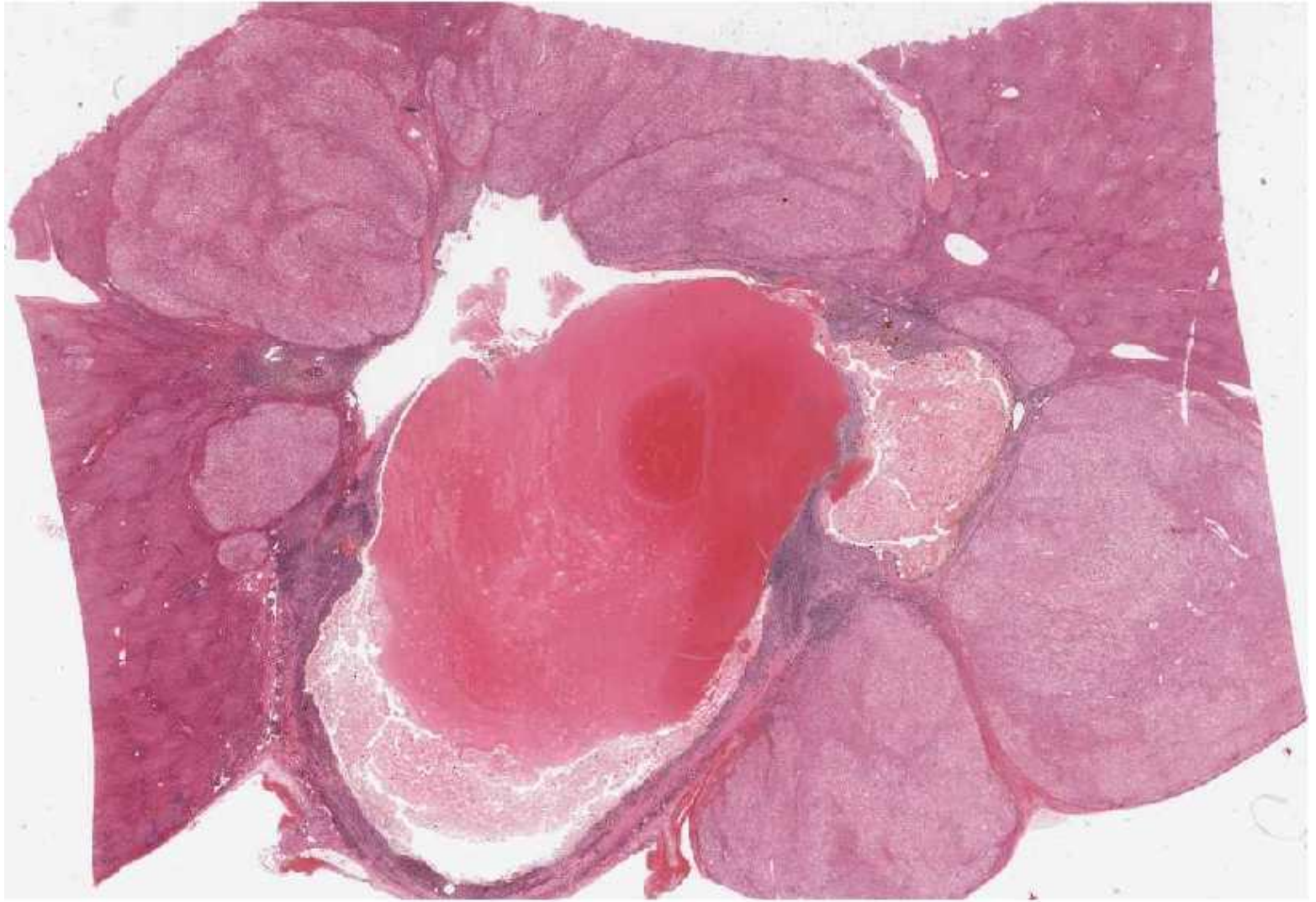
Discussion: Fibrotic/calcifying nodules represent the end stage of focal necrotic lesions in the liver; the original cause - e.g. inflammatory/ parasitic infection or sclerosed haemangioma, can no longer be identified.

Case 272

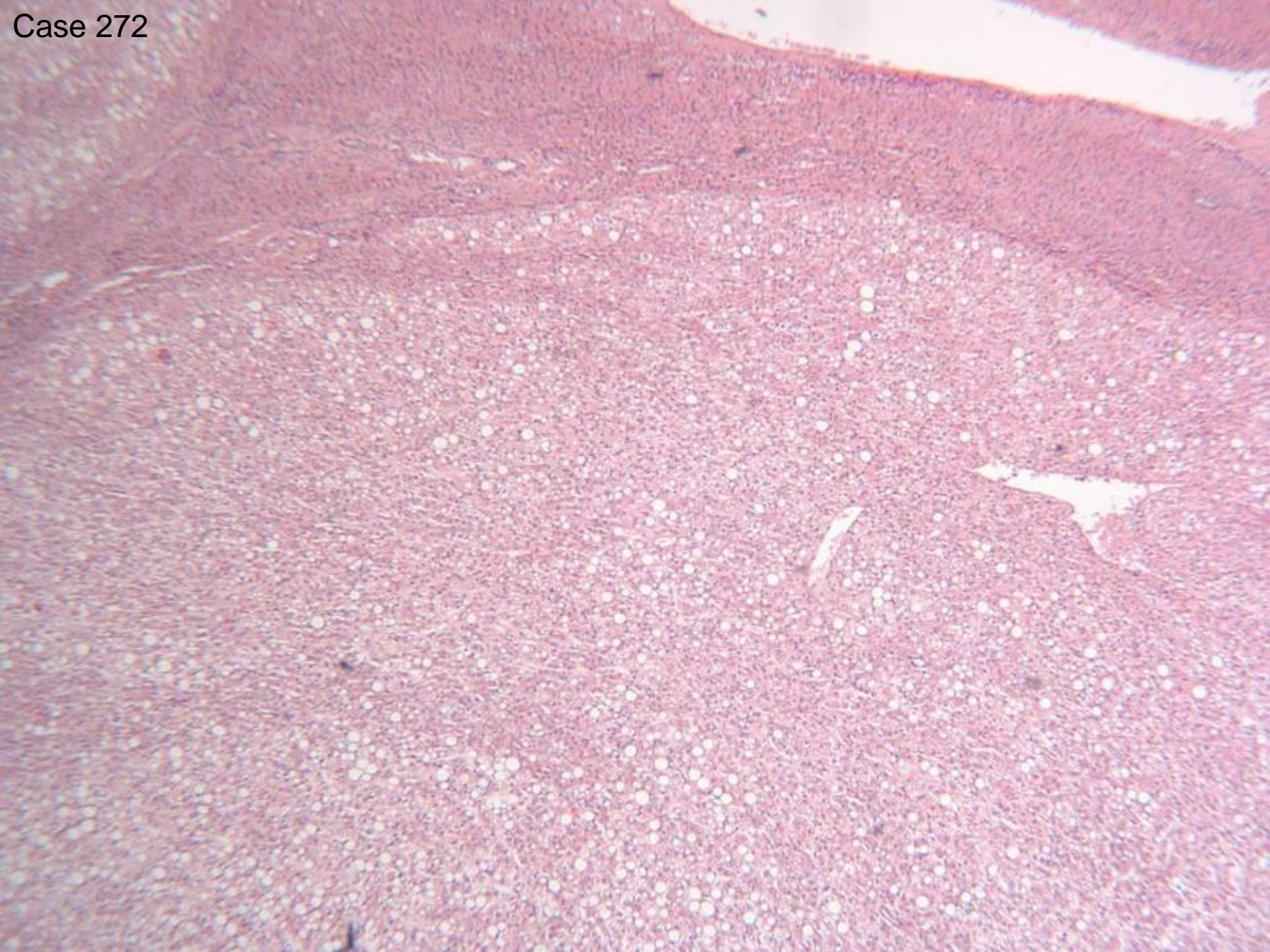
50F.

Ultrasound detected abnormal area on
liver, localised abnormality, ?adenoma

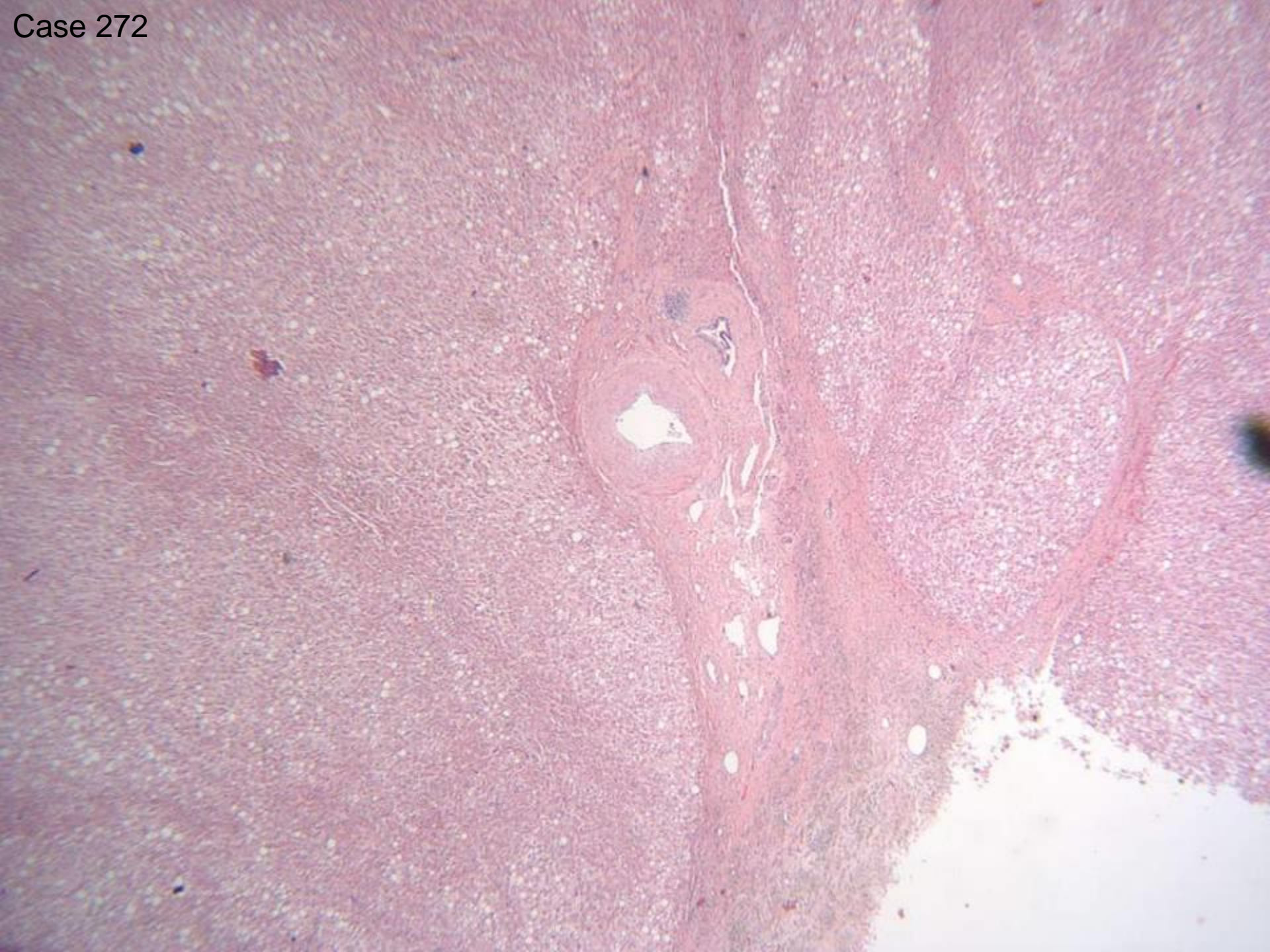
Case 272



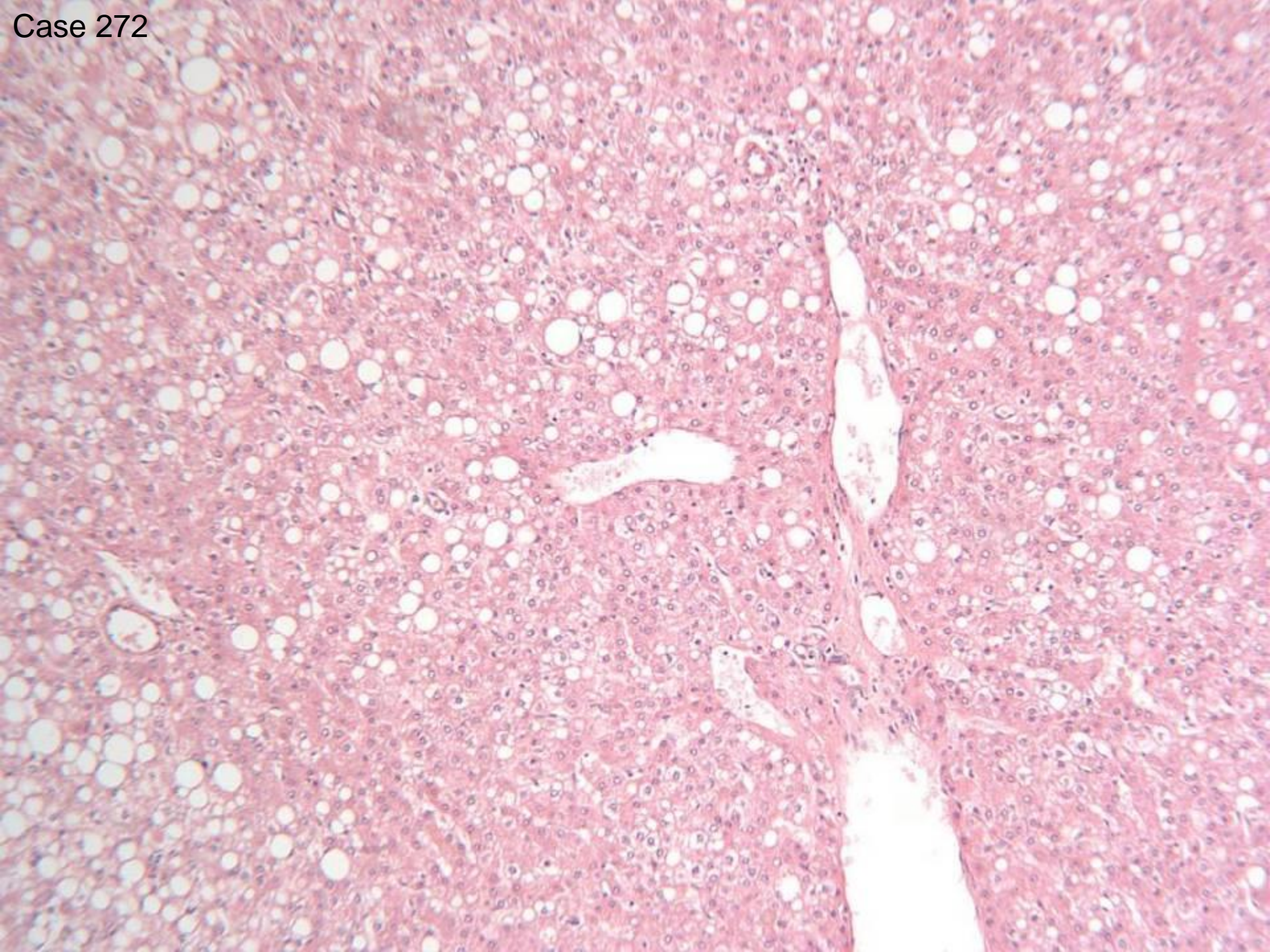
Case 272



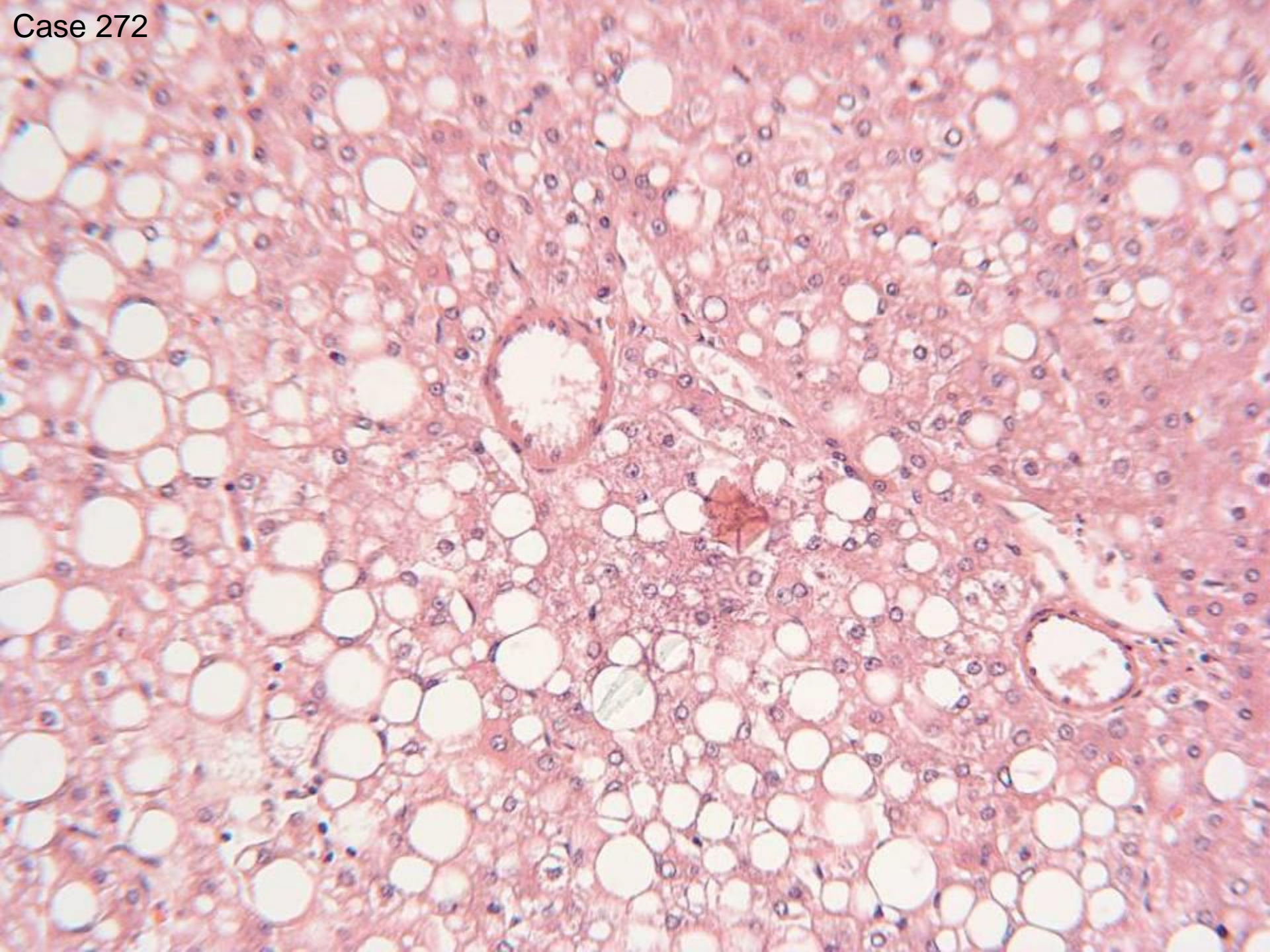
Case 272



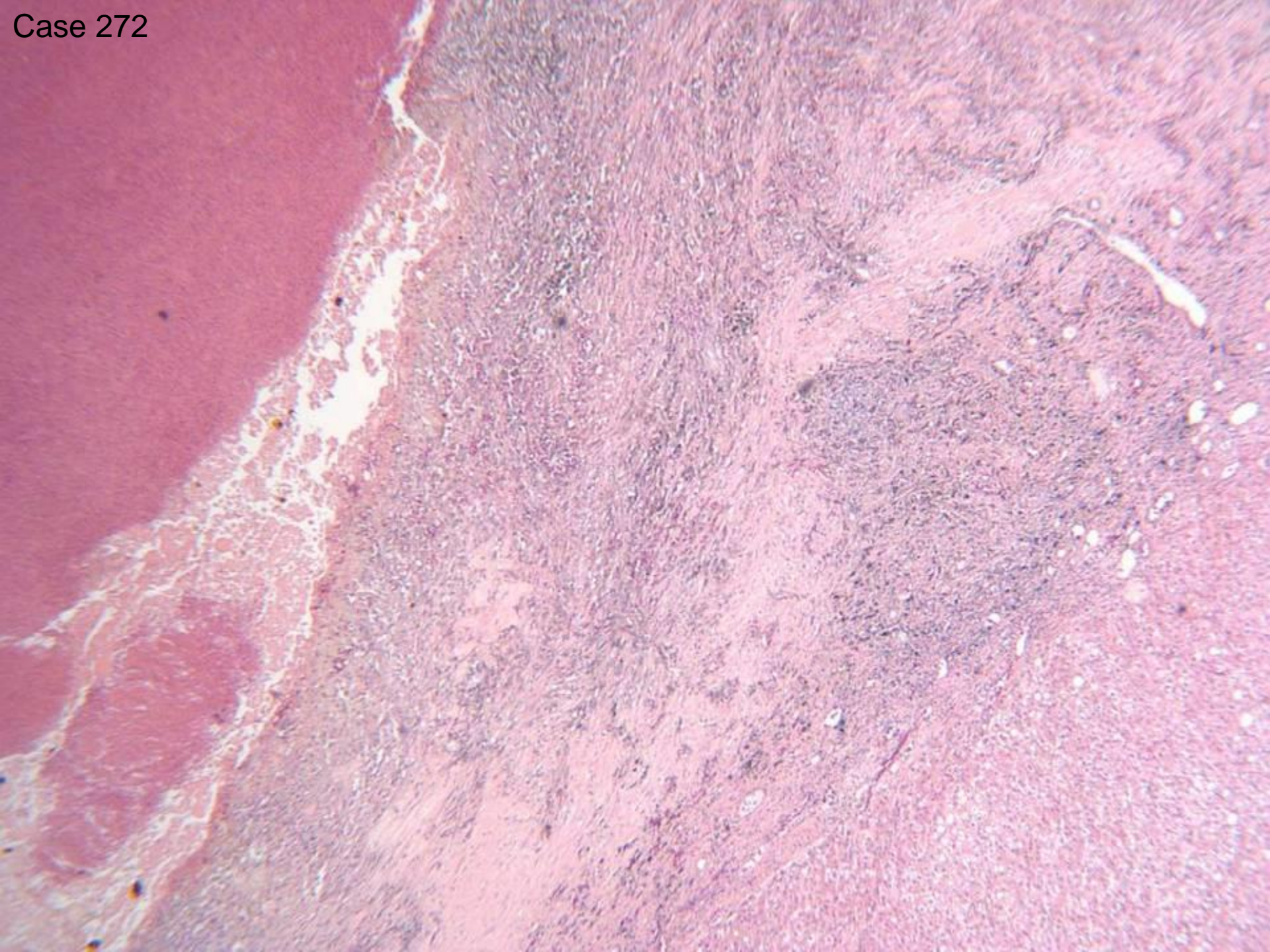
Case 272



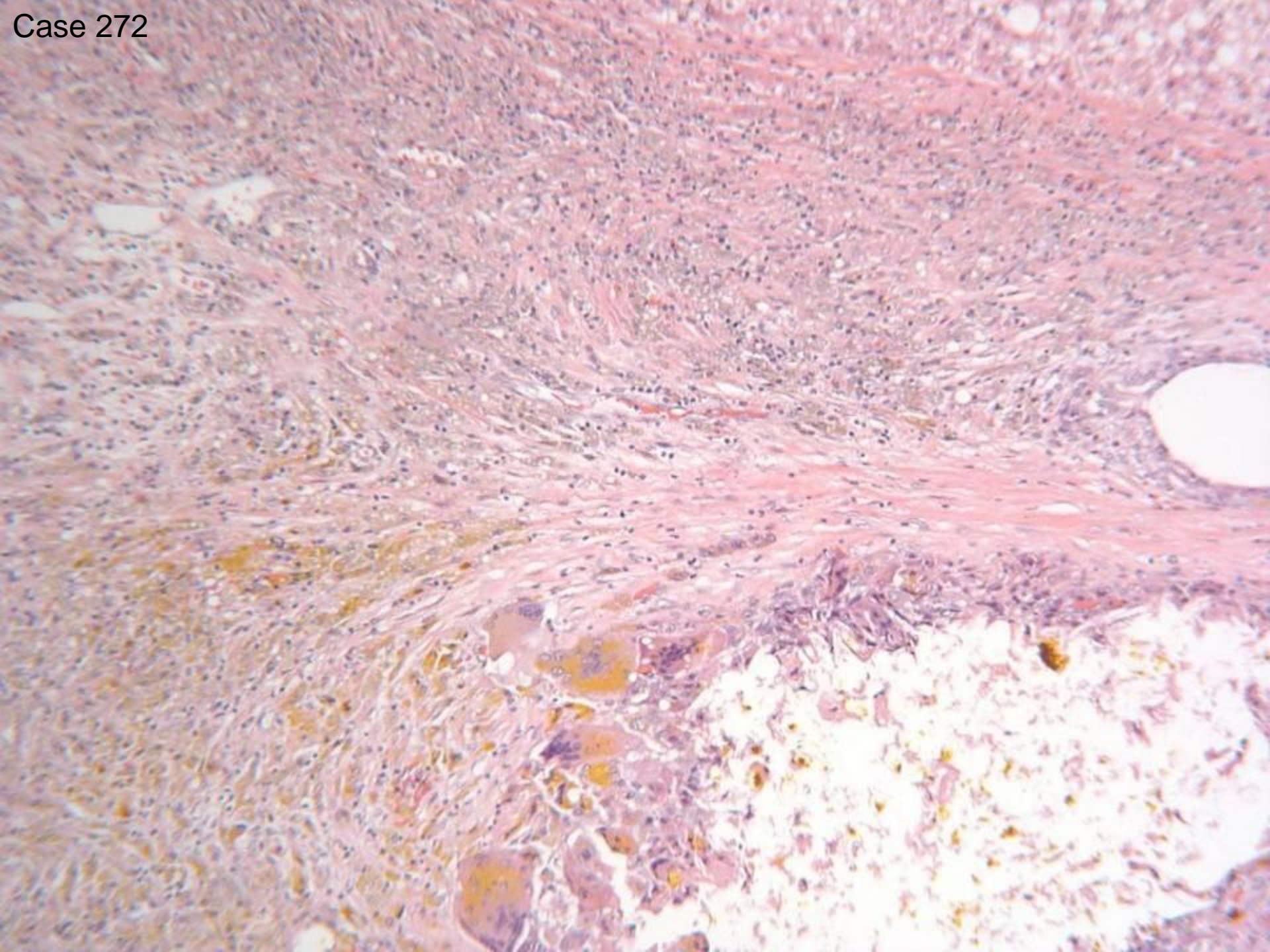
Case 272



Case 272



Case 272



Case 272

- 19 focal nodular hyperplasia, no differential
- 17 adenoma, no differential

- 15 favour adenoma with differential
- 4 favour FNH with differential

- 3 FNH or adenoma, no preference
- 1 combined FNH/adenoma

The above include 10 responses with HCC in the differential diagnosis, but none gave HCC as main diagnosis.

Original diagnosis: focal nodular hyperplasia

Case 272

Scoring: all diagnoses scored 10.

Discussion: this is a benign hepatocellular nodular lesion in which the unaccompanied arteries and absence of fibrous septa with ductular reaction or inflammation indicate adenoma rather than FNH. The haemorrhage is attributable to the previous biopsy - without this the presence of haemorrhage would be a feature of adenoma rather than FNH. The distinction is more important in biopsy specimens where resection is indicated unless a clear diagnosis of FNH can be made.

There is diffuse fatty change in this adenoma. This has been described by the French as a feature of the subset of adenomas with hepatocyte nuclear factor 1alpha (Bioulac P et al, J Hepatol 2007;46:521-527) although such categorisation is immunohistochemistry/molecular pathology is not currently in use in UK.

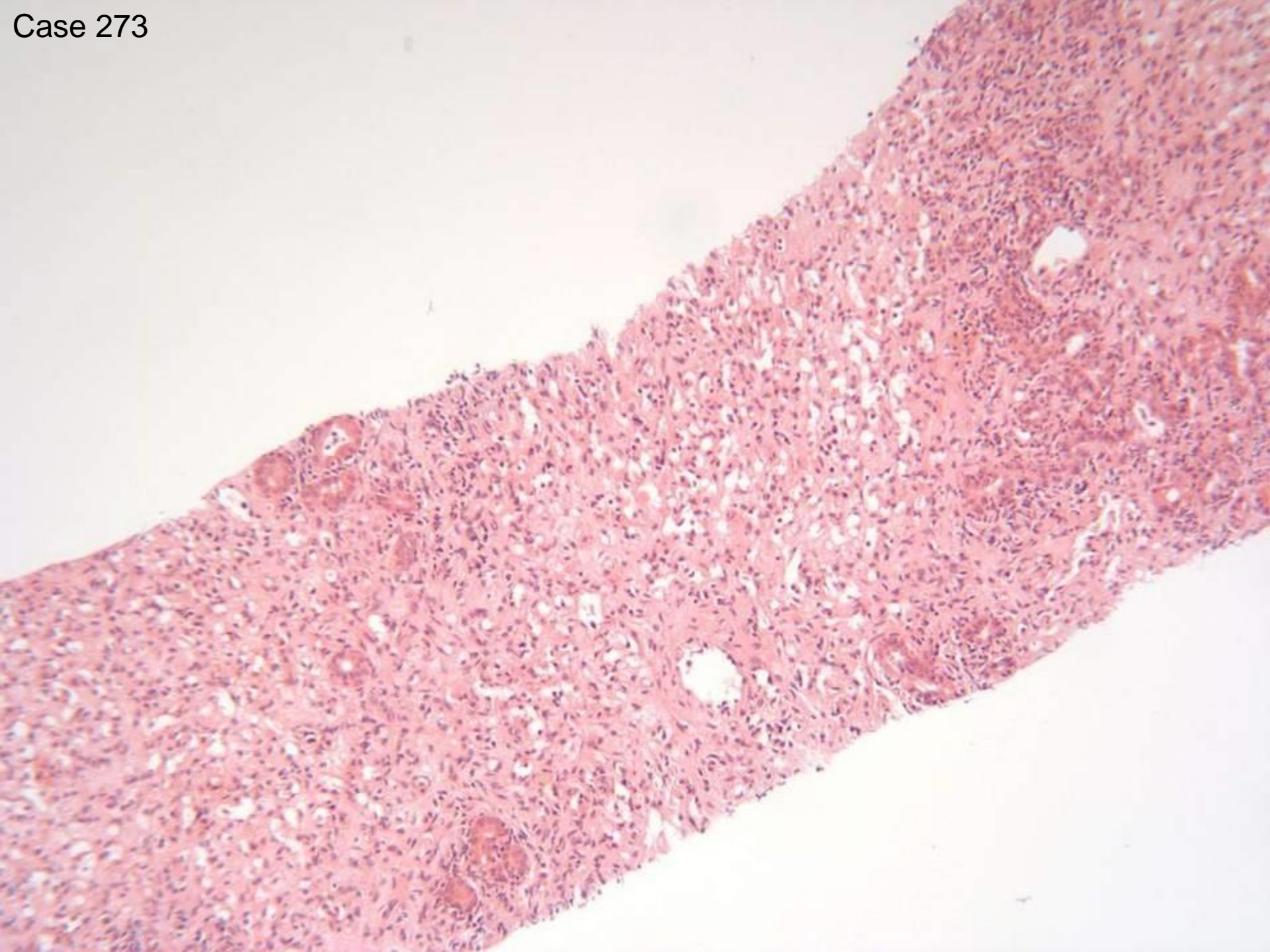
Case 273

55F.

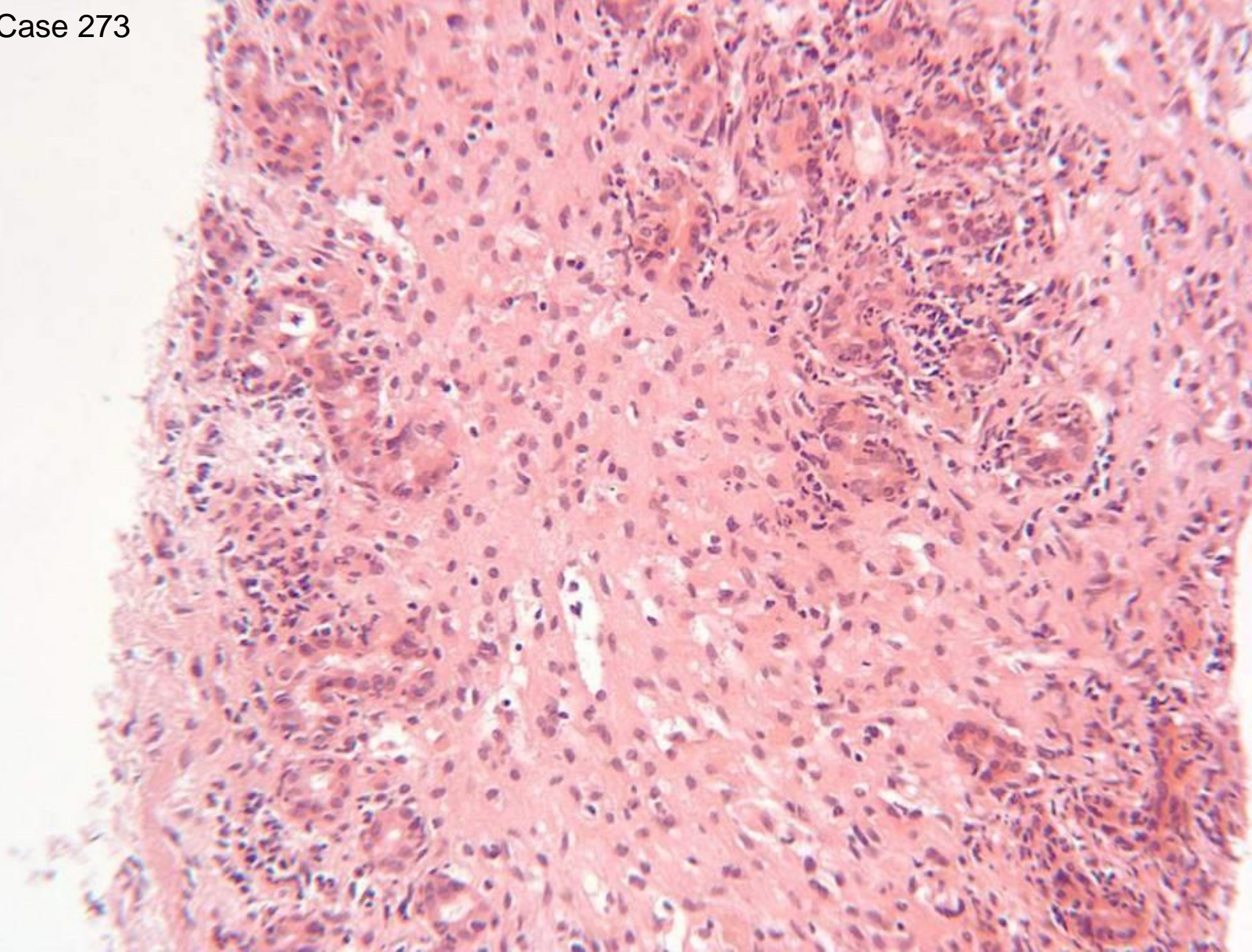
For transjugular biopsy, Acute renal failure,
cirrhotic liver, liver failure



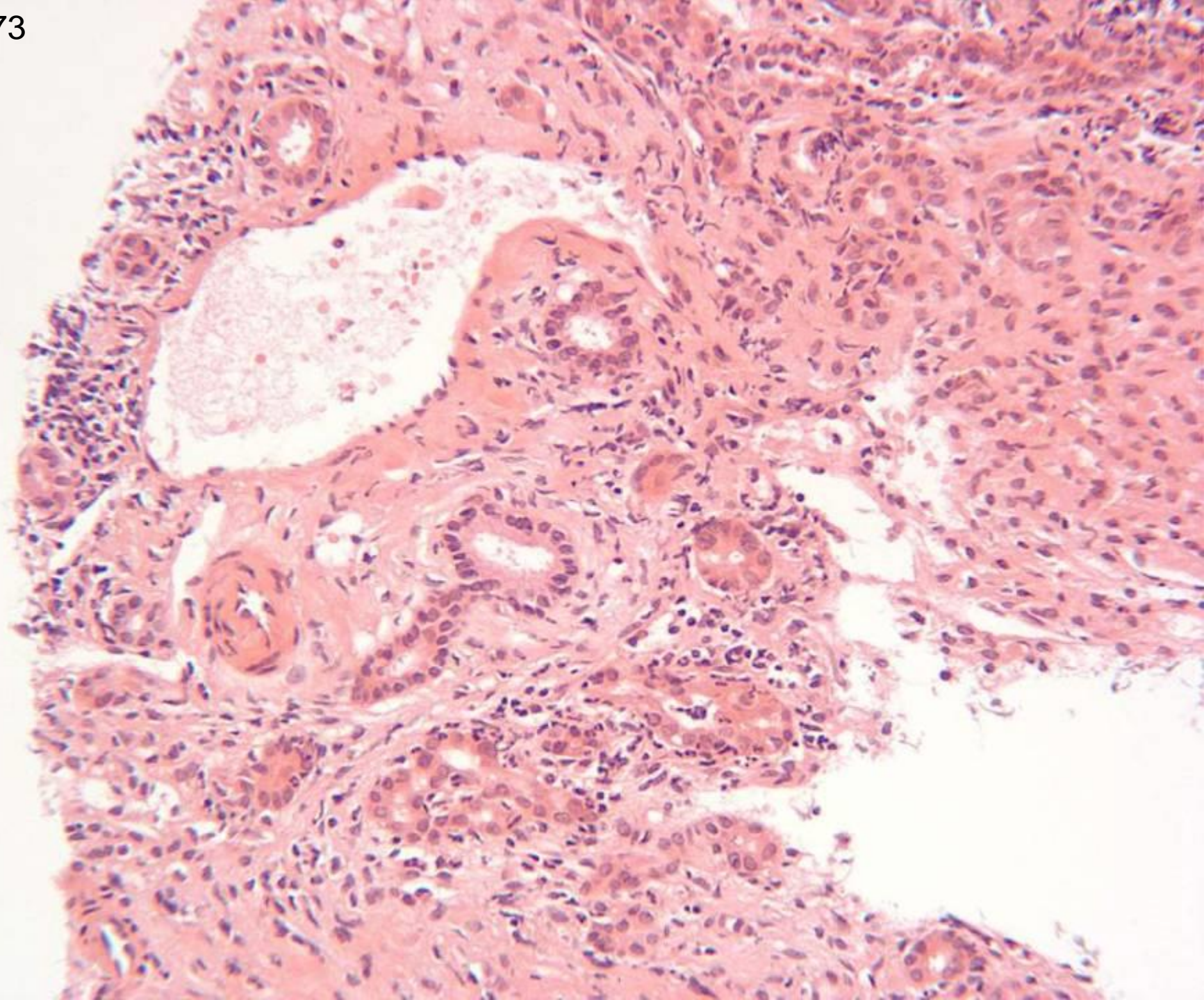
Case 273



Case 273



Case 273



Case 273

38 massive necrosis

13 cirrhosis, of which

5 cause suggested

7 cirrhosis ? cause, with cholangitis

1 cirrhosis, cholangitis, ductular reaction ?PSC

1 cirrhosis + acute necrosis

1 active cirrhosis with neutrophils ? sepsis/alcohol

1 end stage liver with acute hepatitis, ? autoimmune

3 biliary obstruction/cholangitis

3 description only - not including hepatitis or cirrhosis, or specific diagnosis

Case 273

Scoring: not scored: insufficient concensus. Case of educational importance.

Discussion: This case represents an important diagnostic pitfall, of misinterpreting confluent multiacinar necrosis as chronic liver disease.

The diagnosis of acute hepatitis/necrosis is indicated by the retained relative position of portal tracts/efferent veins, the loose arrangement of collapsed reticulin where the hepatocytes used to be, and presence of Kupffer cells. This represents a more severe acute hepatitis than was seen in case 270.

Case 273 discussion contd.

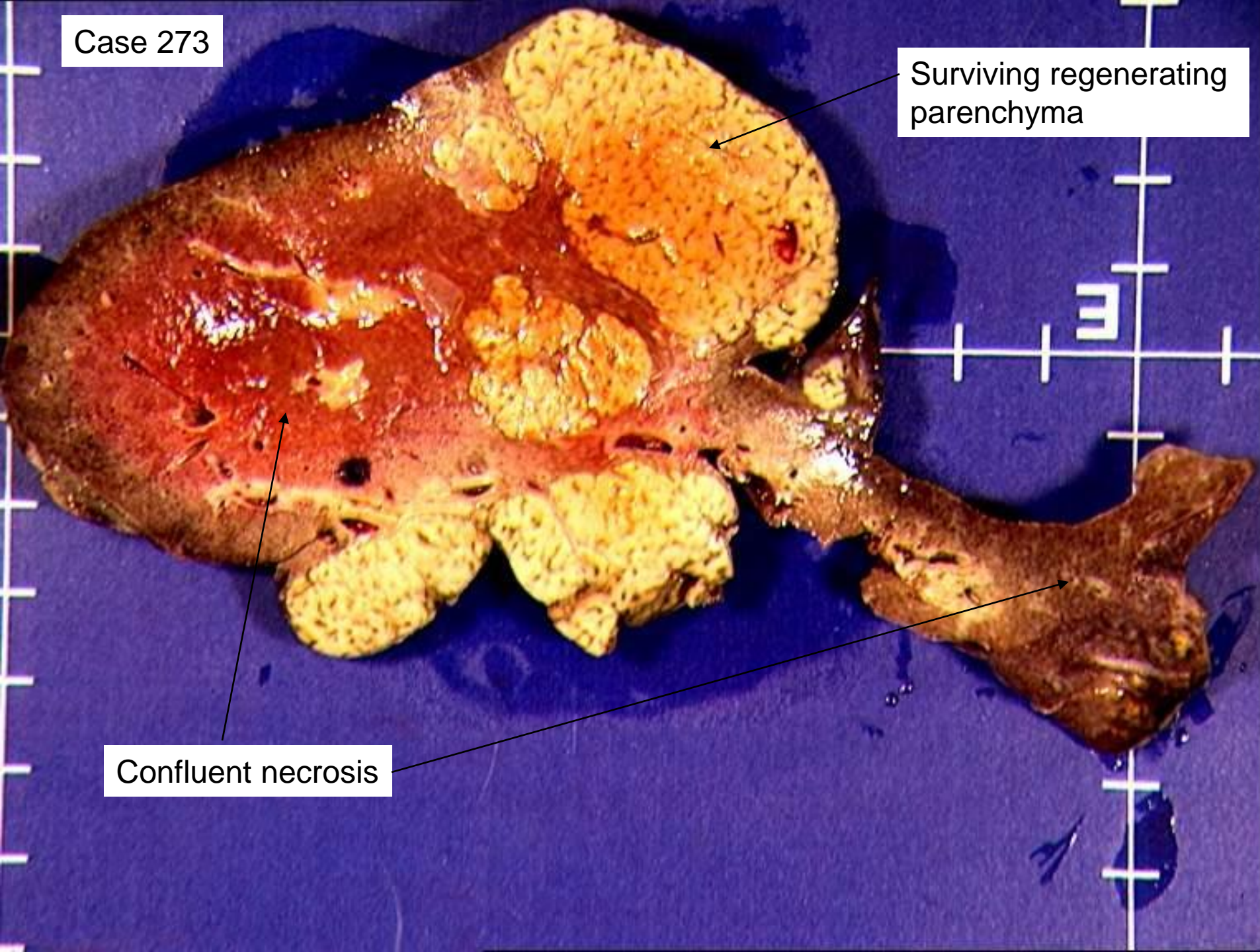
Misdiagnosing this as chronic liver disease has very important clinical consequences, since correct management of acute liver failure would not be instituted. Liver biopsy is done in patients presenting with acute hepatic failure to confirm the diagnosis of acute hepatitis/necrosis and exclude chronic liver disease, alcoholic hepatitis, and Paracetamol toxicity. Wilson's disease may be seen on biopsy, but requires other tests for exclusion.

This patient required an urgent liver transplant. (Photographs of the gross appearance and histology of the explant in the next slide). Regenerative nodules evolve quickly (few weeks) in this situation, and explain the cirrhotic appearance of the liver on ultrasound. Acute renal failure develops in 30% patients with acute liver failure not due to paracetamol.

Case 273

Surviving regenerating
parenchyma

Confluent necrosis



Case 273

Original diagnosis: confluent necrosis, consistent with subacute liver failure

Follow up information:

Full history = 8 weeks of jaundice, more recently coagulopathy and encephalopathy.

Negative for viruses and autoantibodies. Deteriorated despite steroids, super-urgent liver transplant.

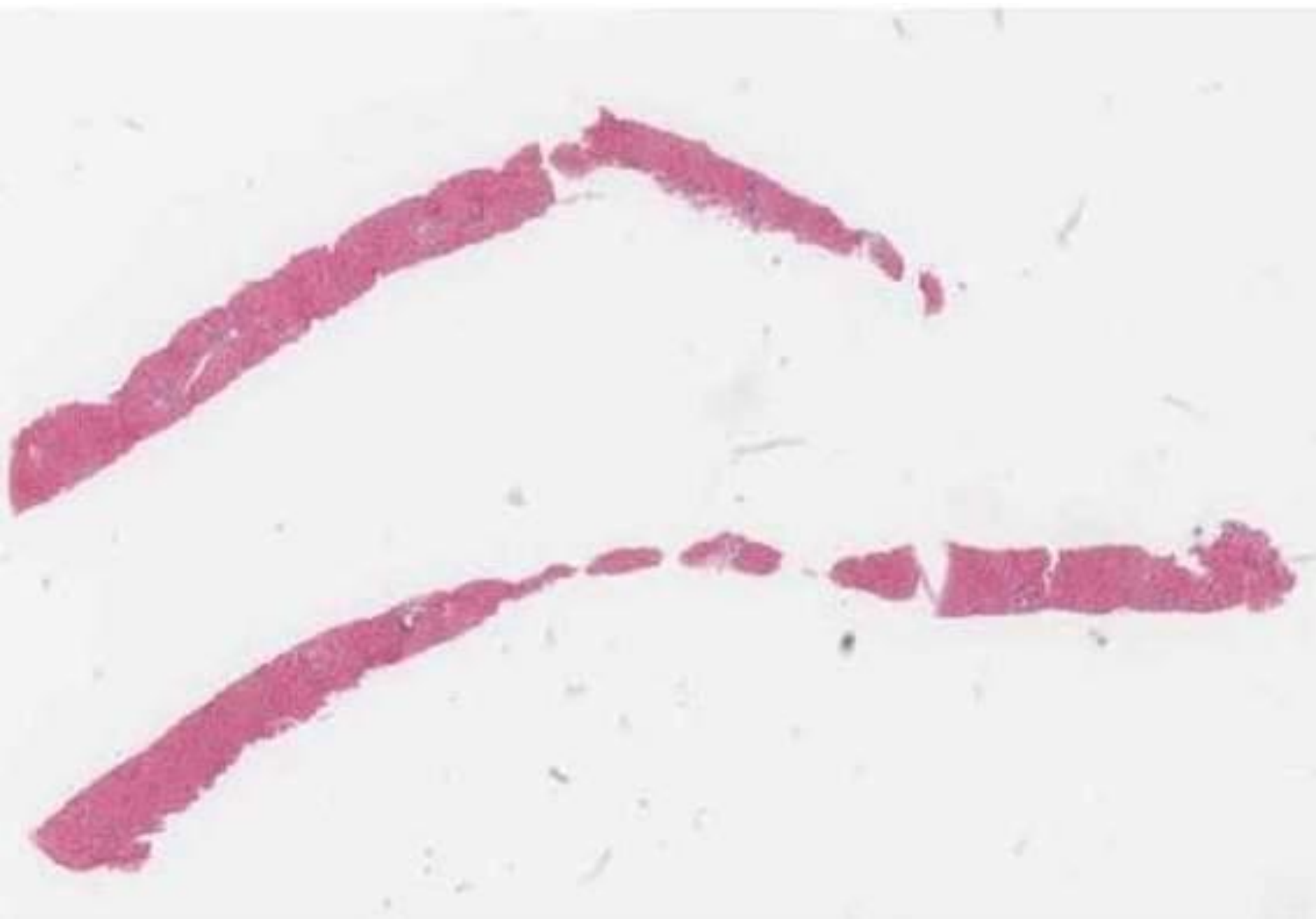
Liver 610g, shrunken, wrinkled capsule, with some regenerative nodules. Good early recovery, renal function returned to normal.

Case 274

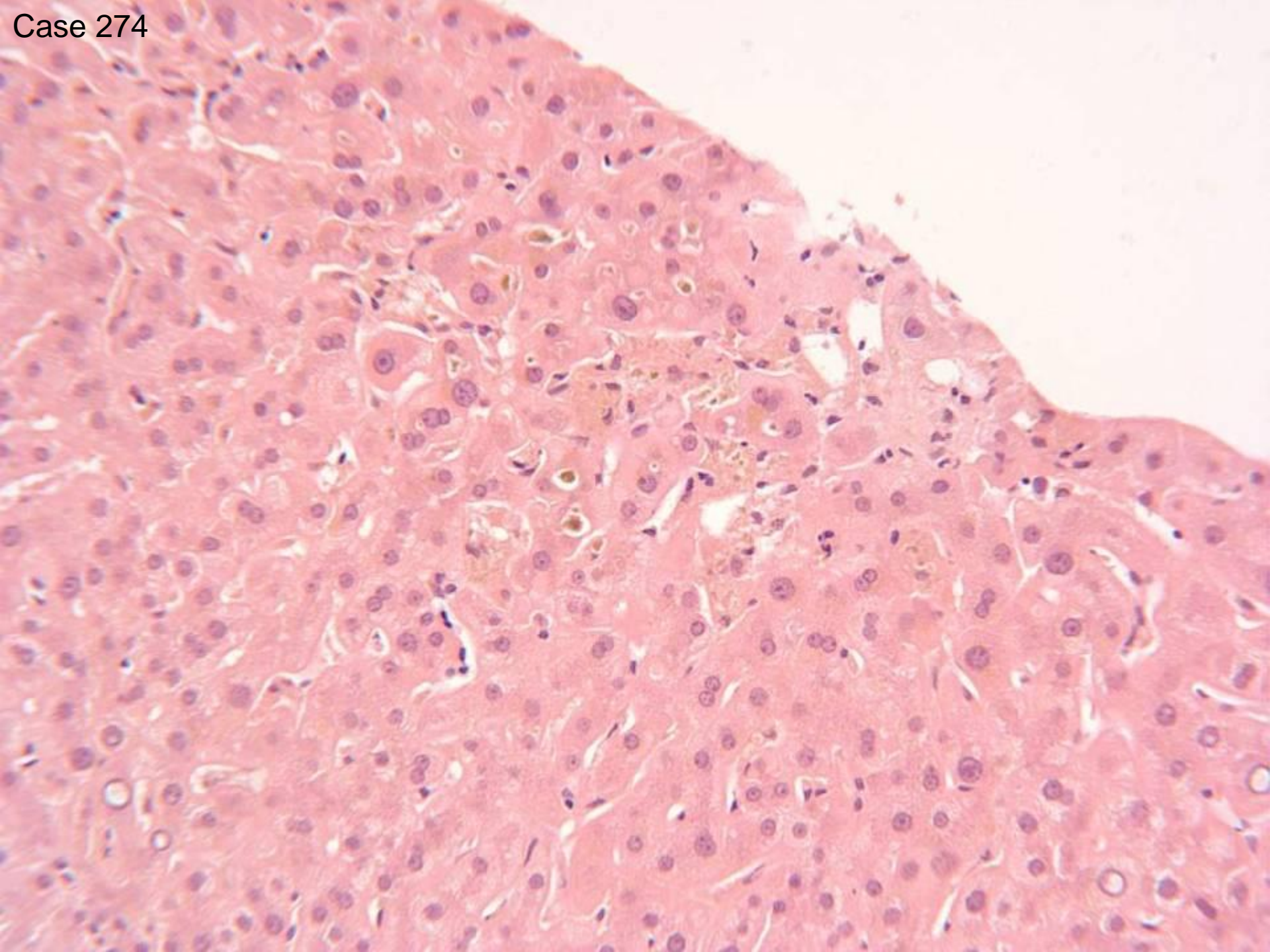
62M.

Jaundice, ?cause.

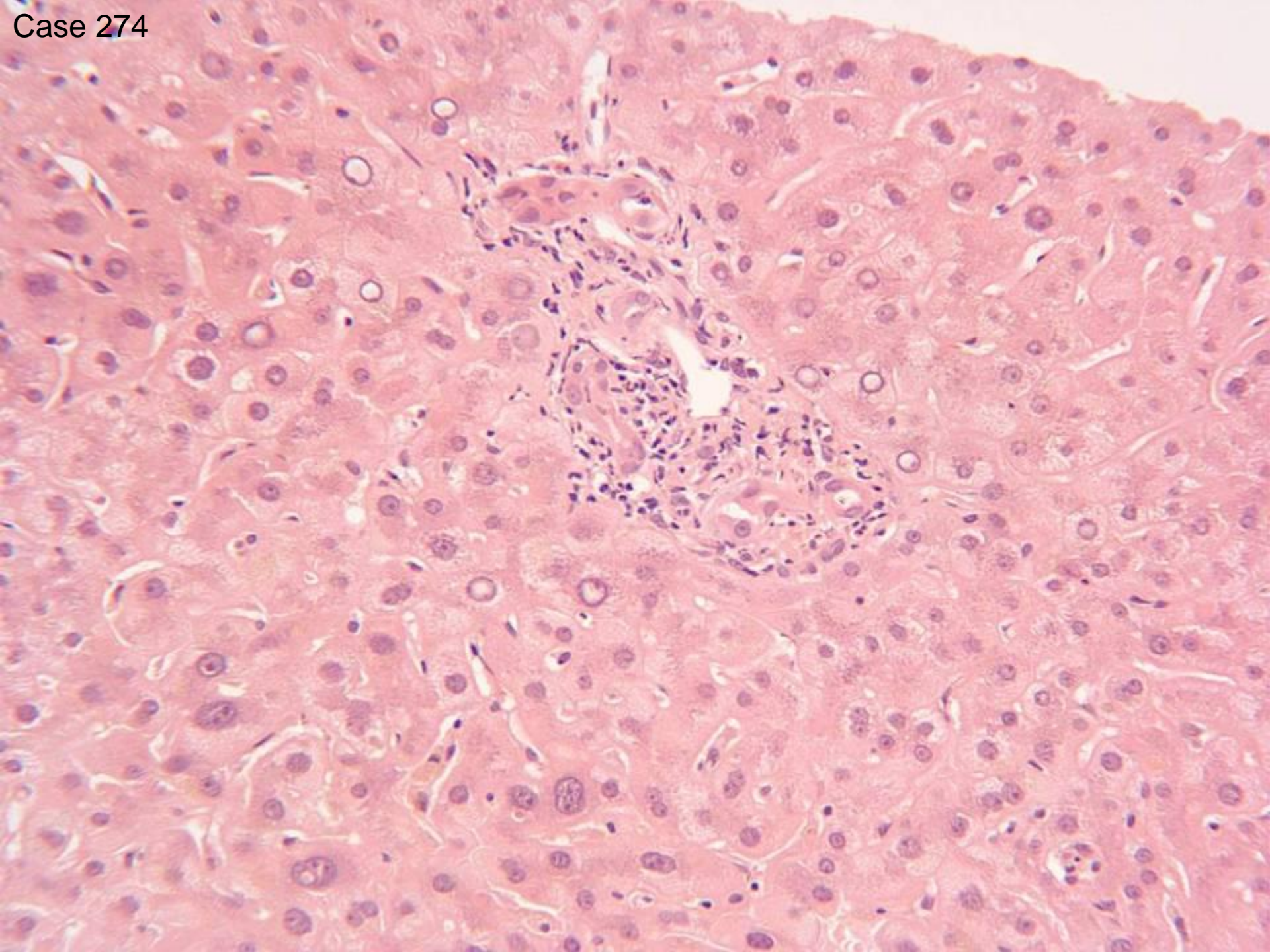
Allograft for lymphoma in September 2005. After cyclosporin withdrawn, jaundiced. ?G-v-HD.



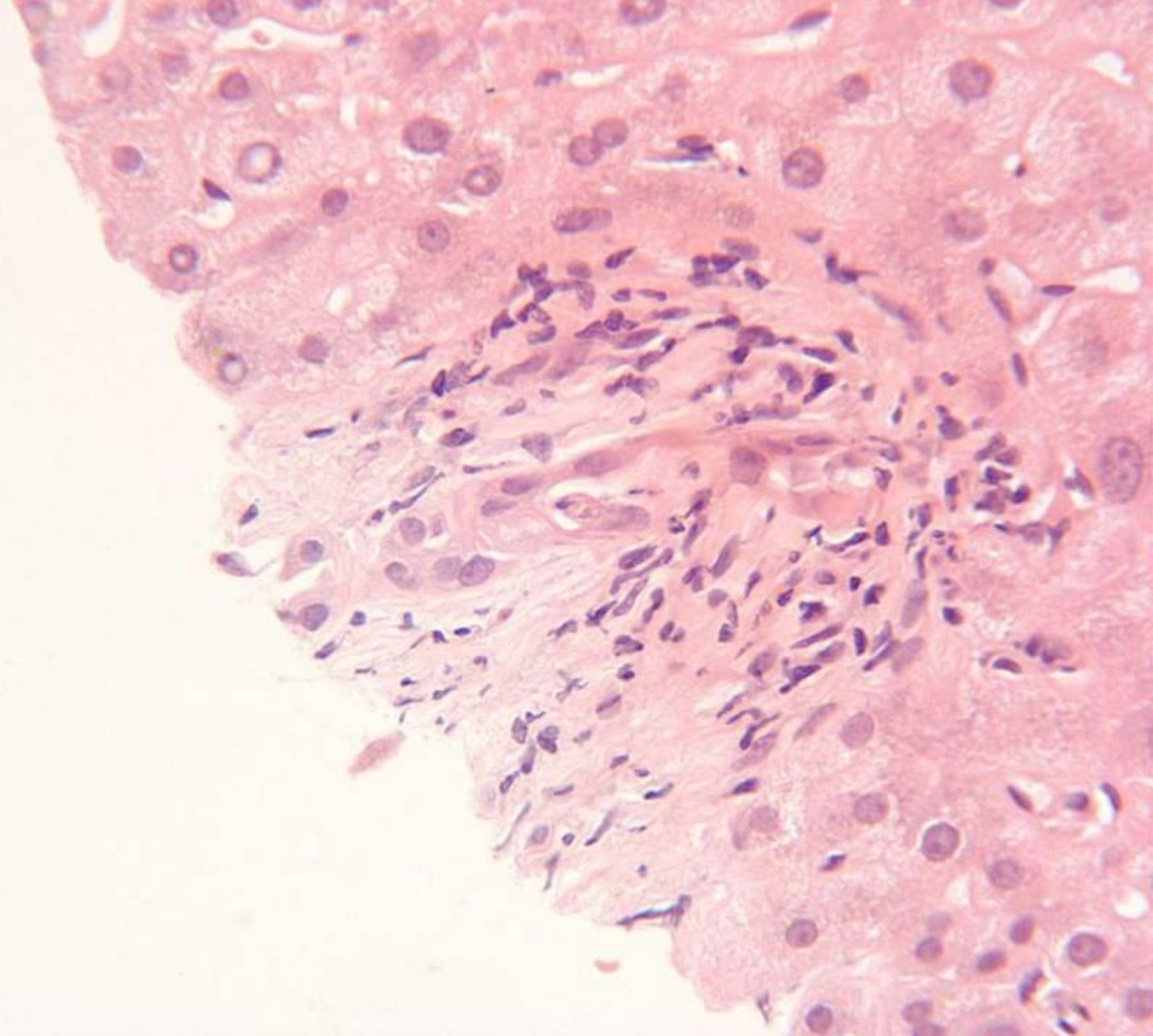
Case 274



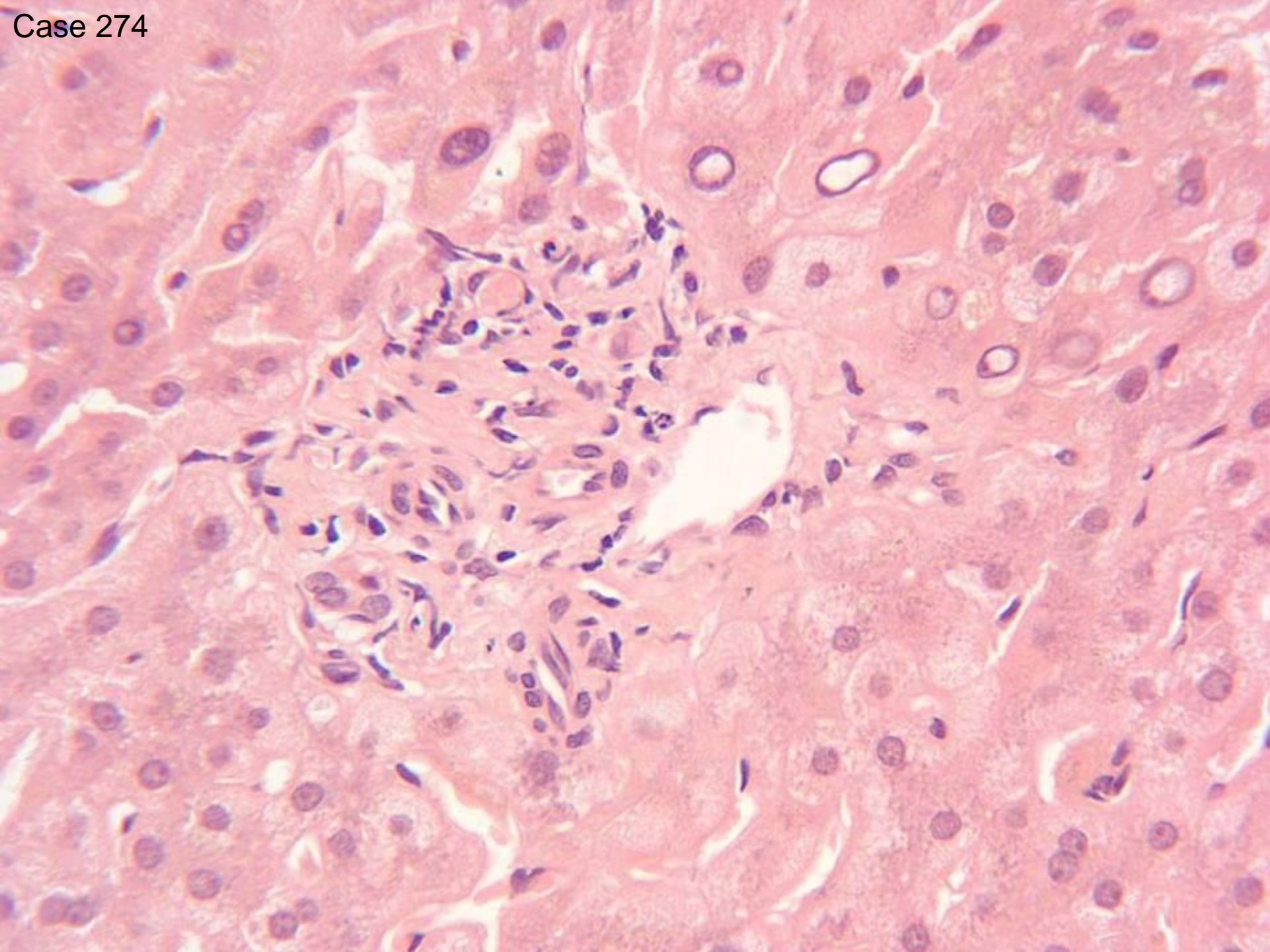
Case 274



Case 274



Case 274



Case 274

51 GVHD

- 1 c/w GVHD, exclude drugs
- 1 could be GVHD, ? Cholangitis

- 2 c/w large bile duct obstruction
- 1 LBDO, not GVHD
- 1 no convincing GVHD, early chronic hepatitis ? Drugs

- 2 chronic rejection (answer suggests misinterpreted as liver transplant, not BMT)

- 1 sclerosing cholangitis, ?primary or secondary

Original diagnosis: features typical of GVHD

Case 274

- *Scoring: Score 10 for GVHD, 0 for responses indicating that this was not GVHD, and 5 for could be GVHD ? cholangitis.*
- Discussion: This was a very good example of well developed bile duct changes in graft versus host disease. GVHD is often a clinical diagnosis, and liver biopsies are taken when there is clinical uncertainty. In practice, the bile duct changes are usually less apparent than seen here, and often very subtle. The diagnosis is then dependent on the combination of subtle histological changes and clinical circumstances, (jaundice developing when immunosuppression is reduced as in this case), with the role of the biopsy mainly to exclude other causes. (Quaglia A et al, Histopathology. 2007;50:727-38).

Case 275

64F.

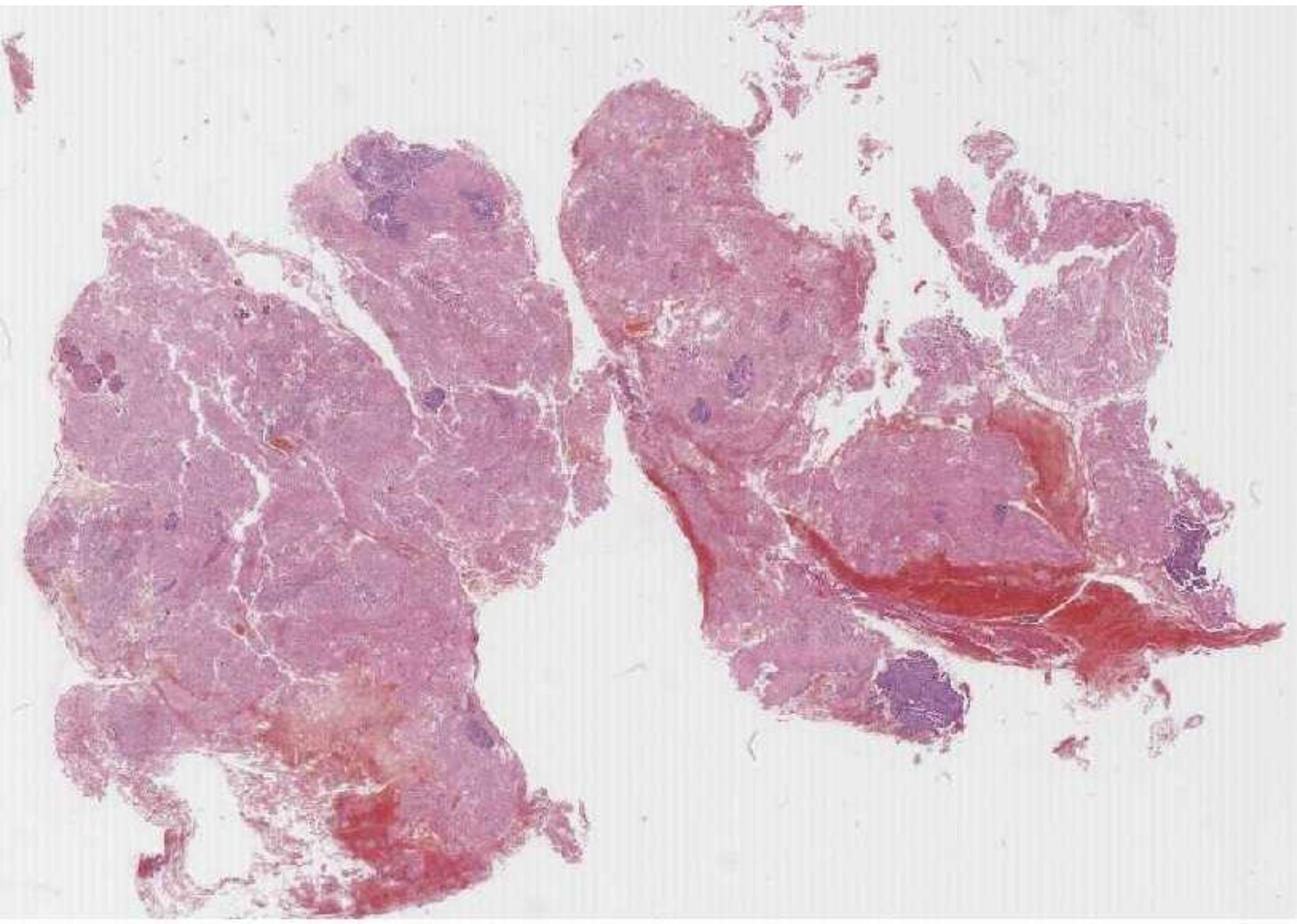
Lady of Indian origin with diabetes and HCV infection.

Presented with pyrexia and signs of peritonitis.

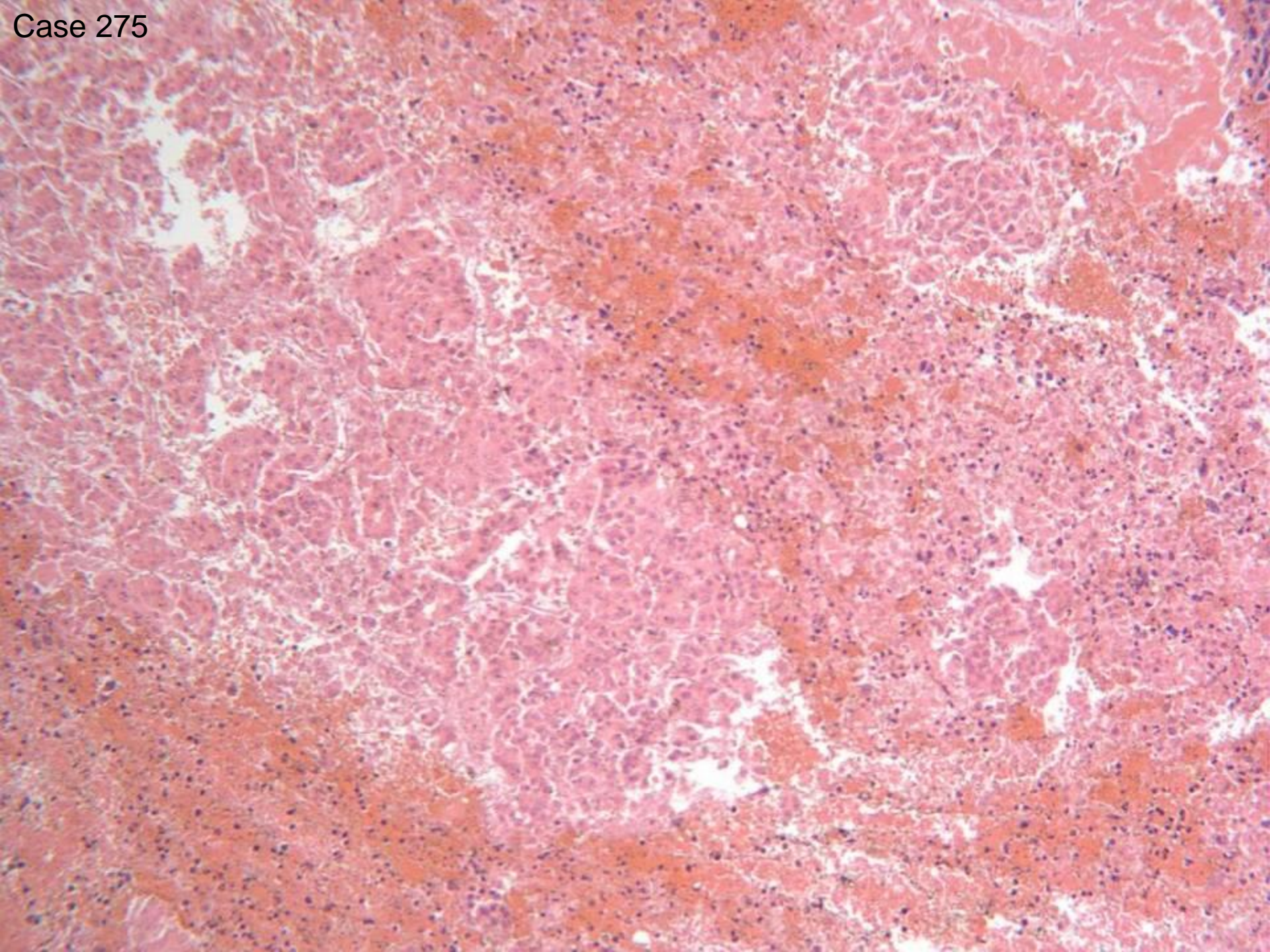
CT suggested cirrhosis and liver abscess.

At laparotomy abscess confirmed and drained.

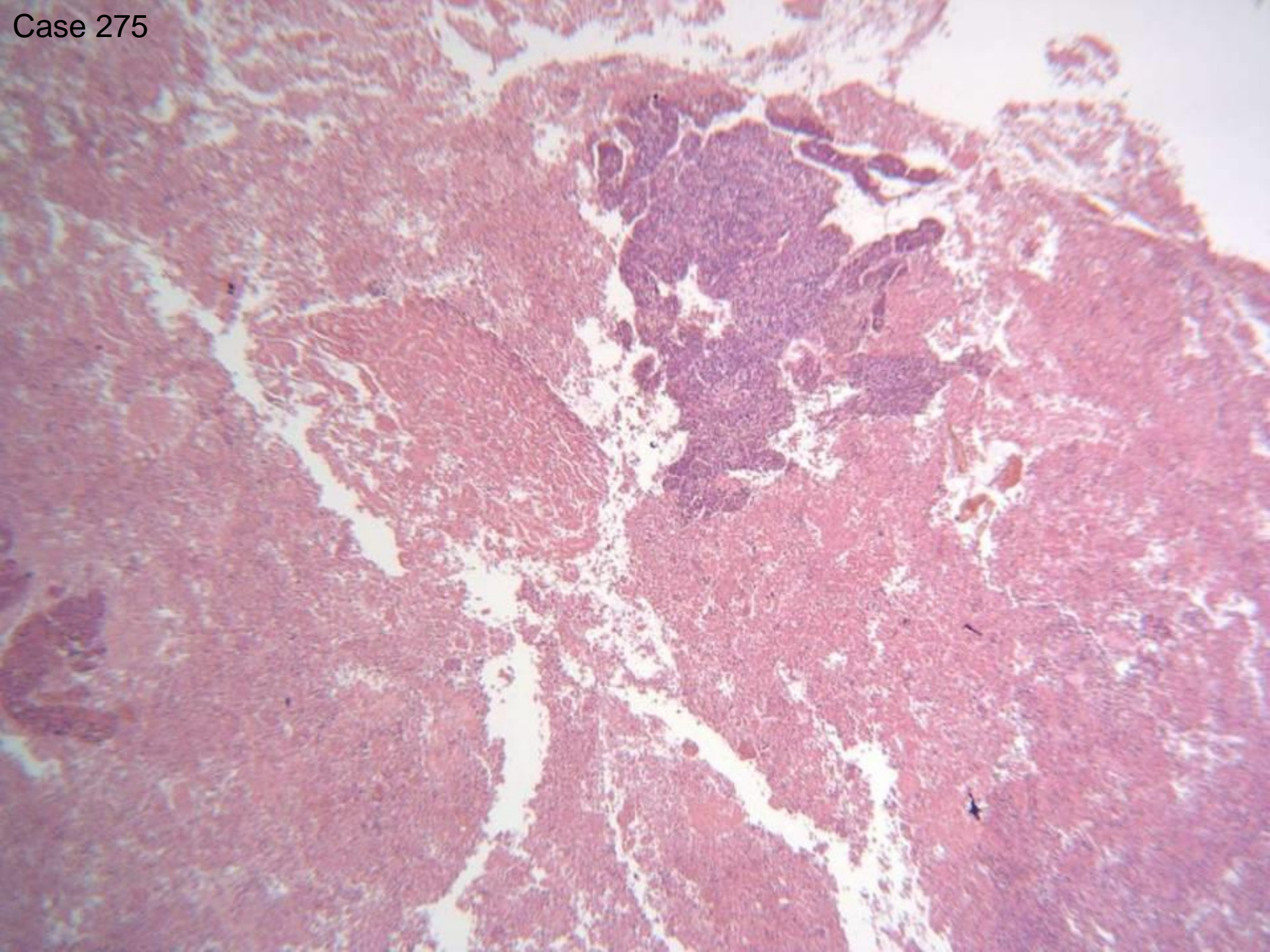
Case 275



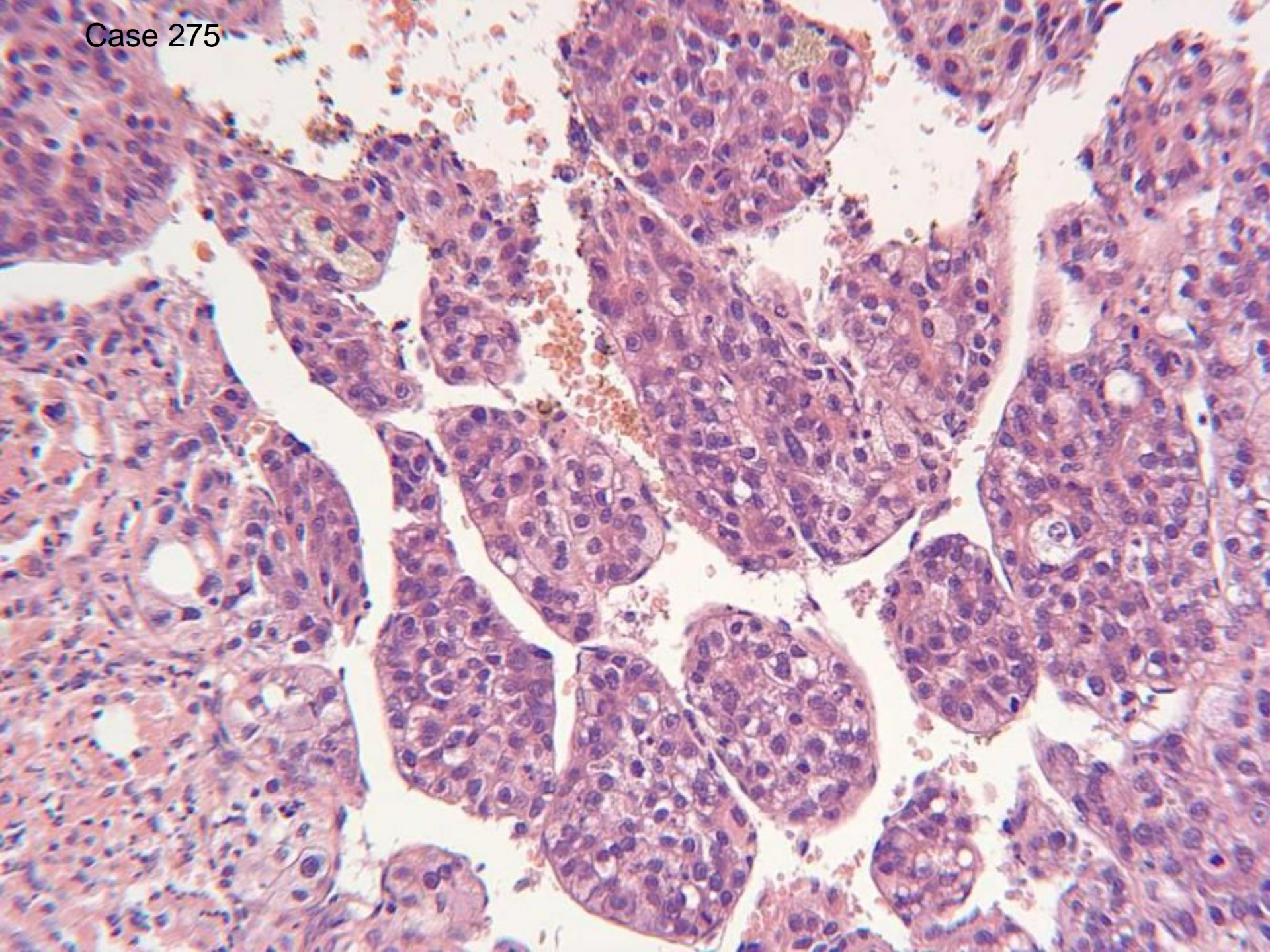
Case 275



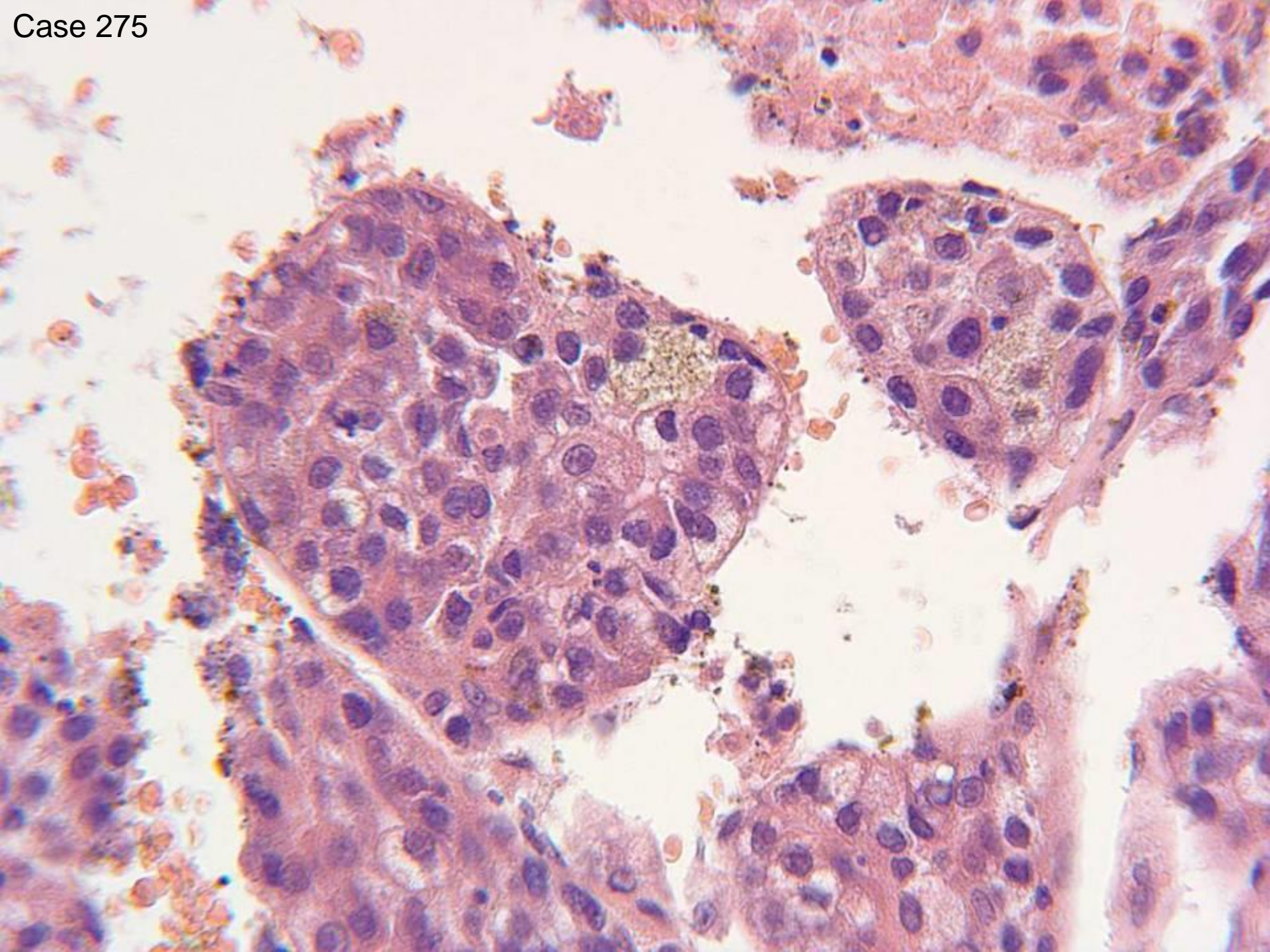
Case 275



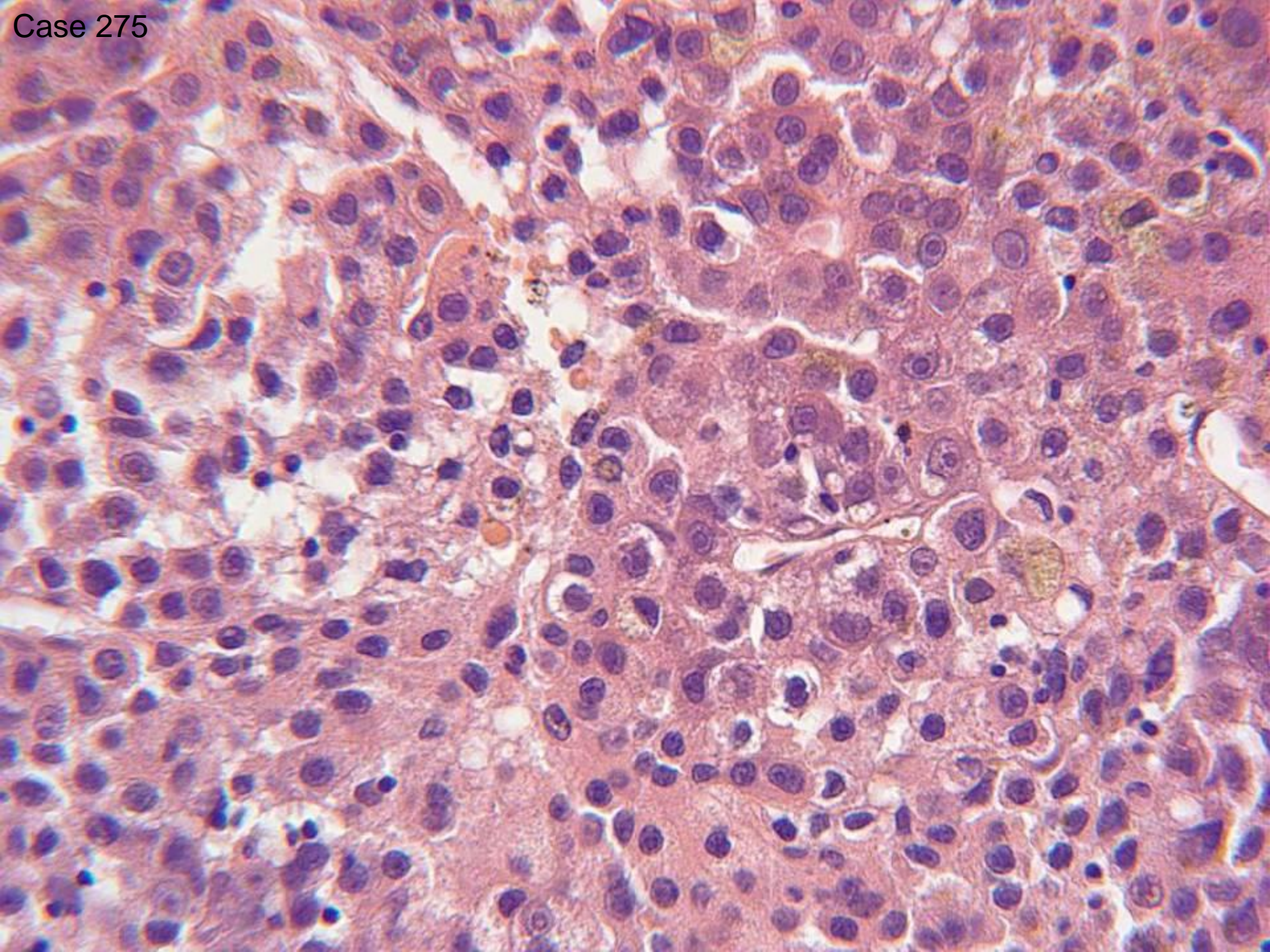
Case 275



Case 275



Case 275



Case 275

- 18 HCC - as definite diagnosis, no immunohistochemistry in answer
- 35 HCC - as likely or definite diagnosis, answer includes immunohistochemistry
- 6 malignant tumour, differential includes HCC, immunohistochemistry required
- 1 metastatic carcinoma (HCC not mentioned)

Original diagnosis: hepatocellular carcinoma

Case 275

- *Scoring: Score 10 for diagnoses of HCC, and 0 for metastatic carcinoma (HCC not mentioned).*
- Discussion: The need for immunohistochemistry was discussed. HCC is the most likely diagnosis in this setting, but the possibility of metastasis may need exclusion by IHC, especially if the liver was not seen to be cirrhotic at surgery.

Case 276

66M.

Request form details - ?drug related hepatitis.

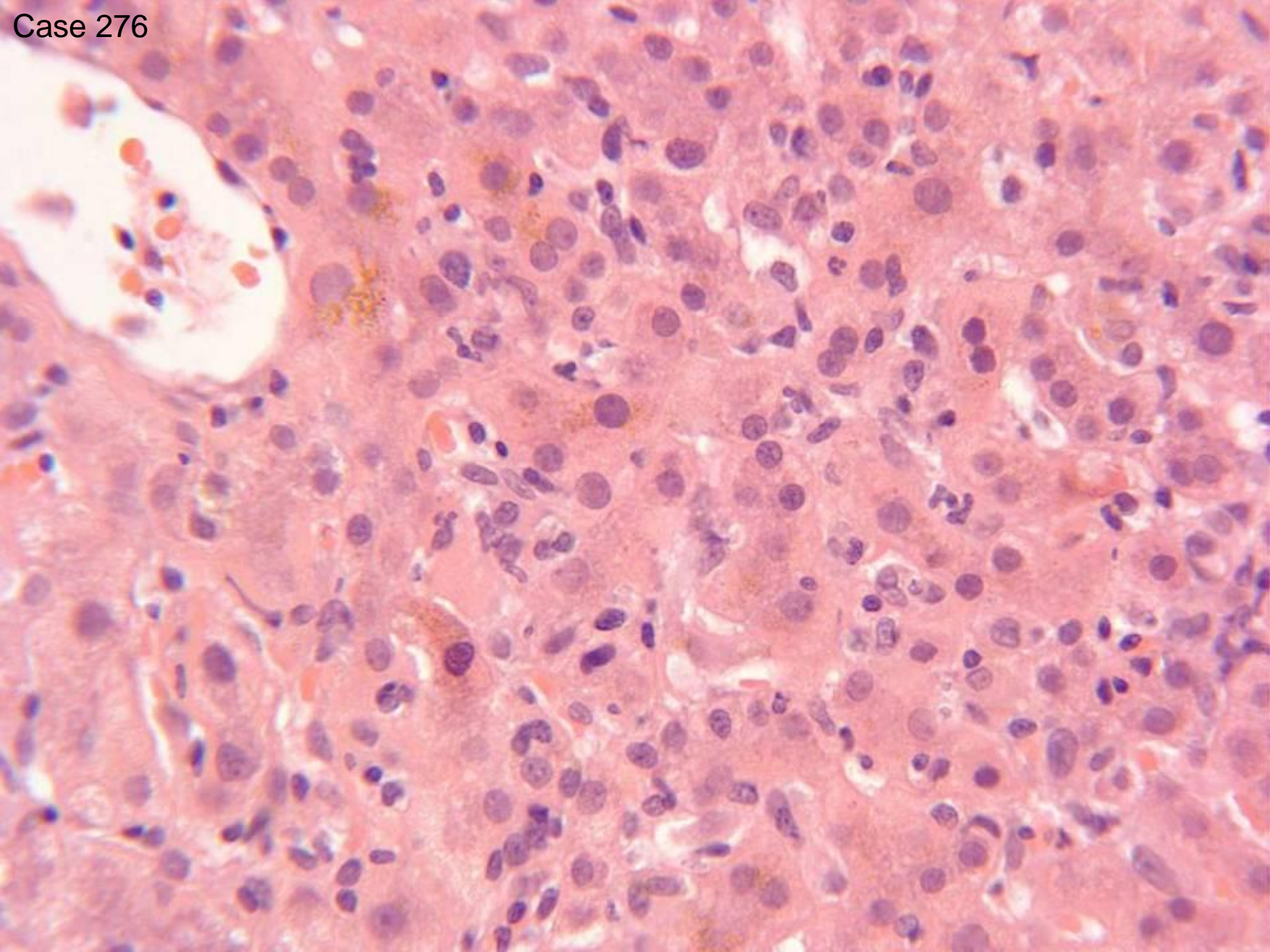
Further information - autoimmune profile
negative. Hepatitis A, B & C negative.

Metabolic screen negative.

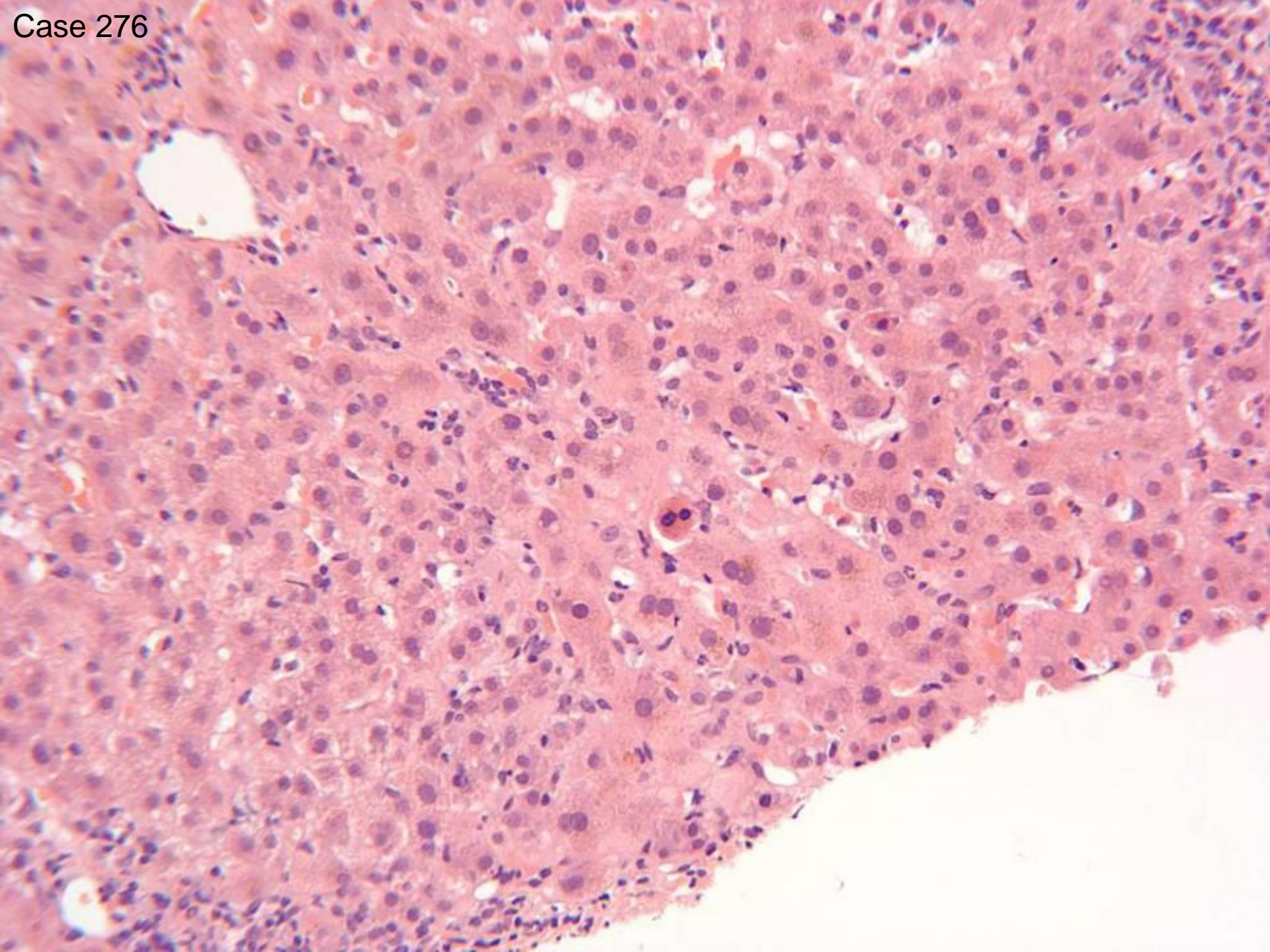
um



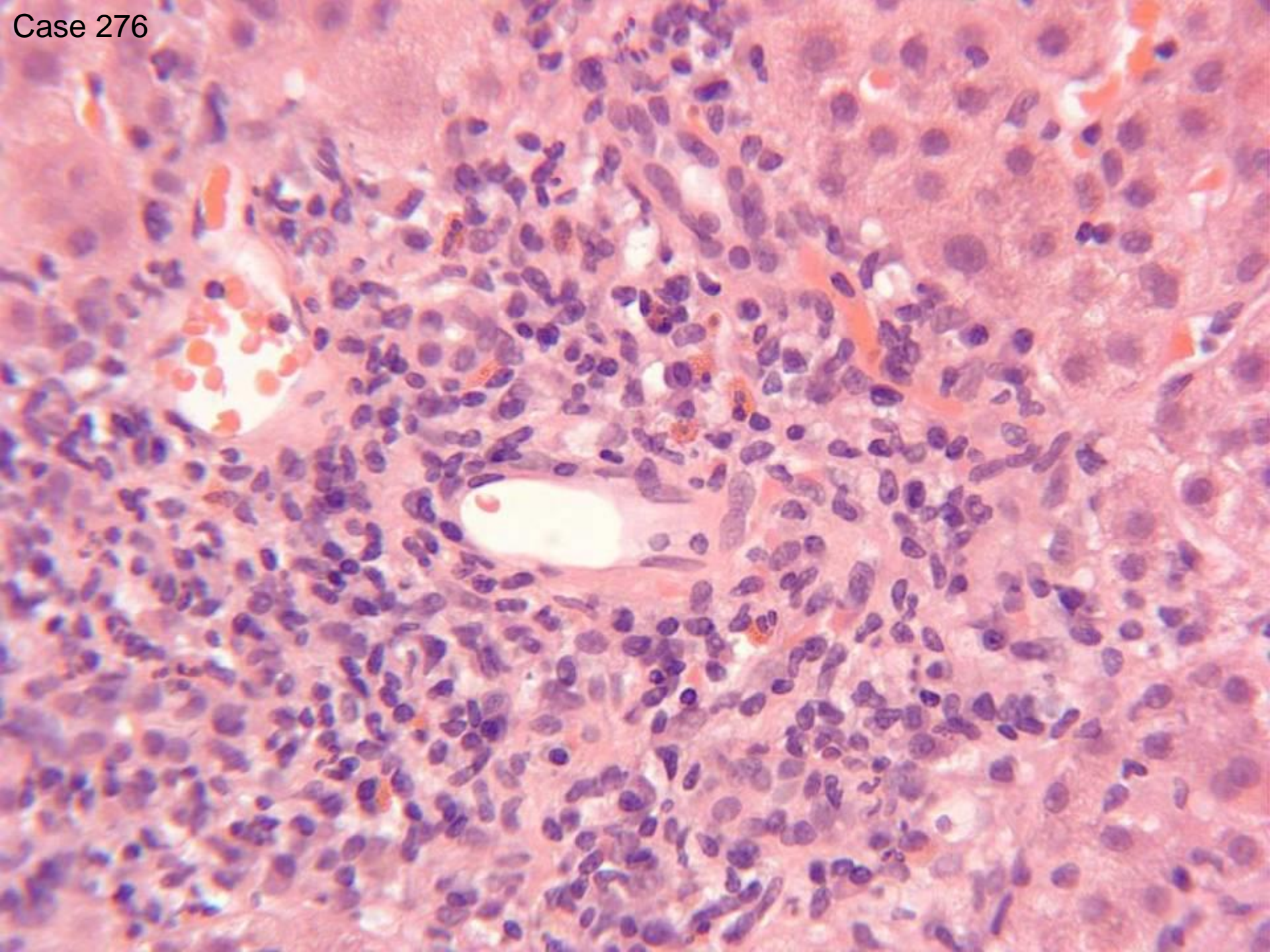
Case 276



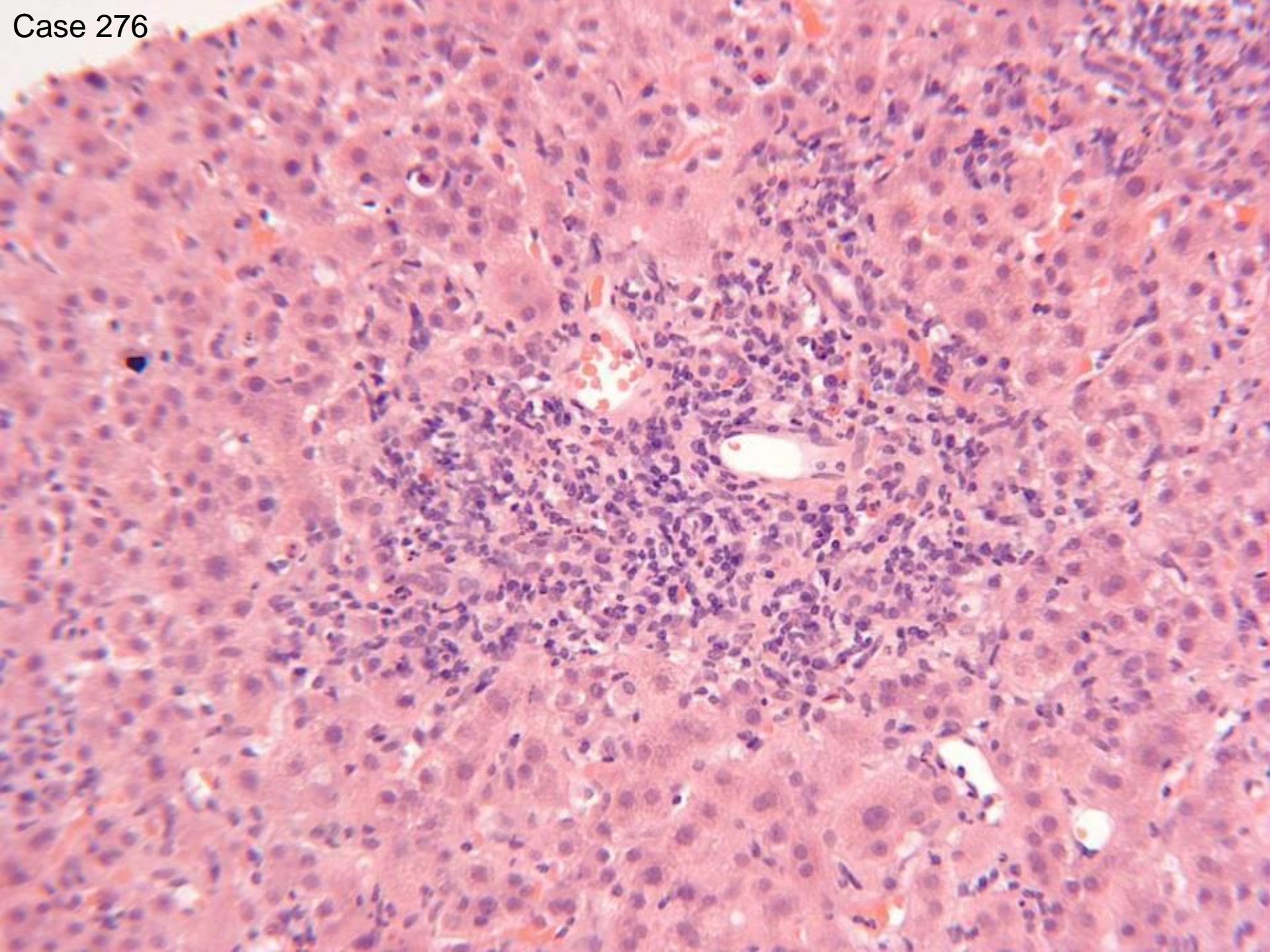
Case 276



Case 276



Case 276



Case 276

48 hepatitis, c/w drugs

(of which 18 specified acute hepatitis, and rest did not include acute or chronic)

7 chronic hepatitis, c/w drugs

2 chronic hepatitis ? drug or seronegative/autoimmune

1 severe acute hepatitis, most likely AIH, r/o drugs, HEV

1 active chronic hepatitis - autoimmune (drugs not mentioned)

1 cholestatic acute liver necrosis

most answers included the need for an actual drug history to make the diagnosis

Case 276

- *Scoring: Hepatitis consistent with drugs scored 10, whether or not acute hepatitis was specifically stated. Responses specifically stating chronic hepatitis c/w drugs were scored 5. Score 0 for responses not mentioning drug aetiology.*

Case 276

Discussion: Most commented on the need for a more detailed drug history to support the diagnosis, with appropriate differentials.

Follow up information - drug history obtained: following a stroke, treated with statin, and placed in a trial involving aspirin / clopidogrel / telmisartan / placebo.

No other risk factors for liver disease - assumed to be drug induced hepatitis. Started on IV steroids with good response. Subsequently found to have antibodies to Hepatitis E (both IgG and IgM). No foreign travel or links with either pigs or eating undercooked meat.

The IgG and IgM against hepatitis E indicates that this is most likely acute hepatitis E - (Peron JA et al, *Virchows Arch.* 2007 Apr;450(4):405-10). The literature suggests that hepatitis E may be associated with marked lobular necroinflammatory activity, associated with neutrophils, cholestasis and cholangitis. (*Malcolm P et al Histopathology 2007*).

Case 276

Original diagnosis: cholestatic hepatitis, ? Drug-related or other seronegative hepatitis.

Follow up information: following a stroke, treated with statin, and placed in a trial involving Asasantin / clopidogrel / telmisartan / placebo.

No other risk factors for liver disease - assumed to be drug induced hepatitis. Started on IV steroids with good response.

Subsequently found to have antibodies to Hepatitis E (both IgG and IgM). No foreign travel or links with either pigs or eating undercooked meat.

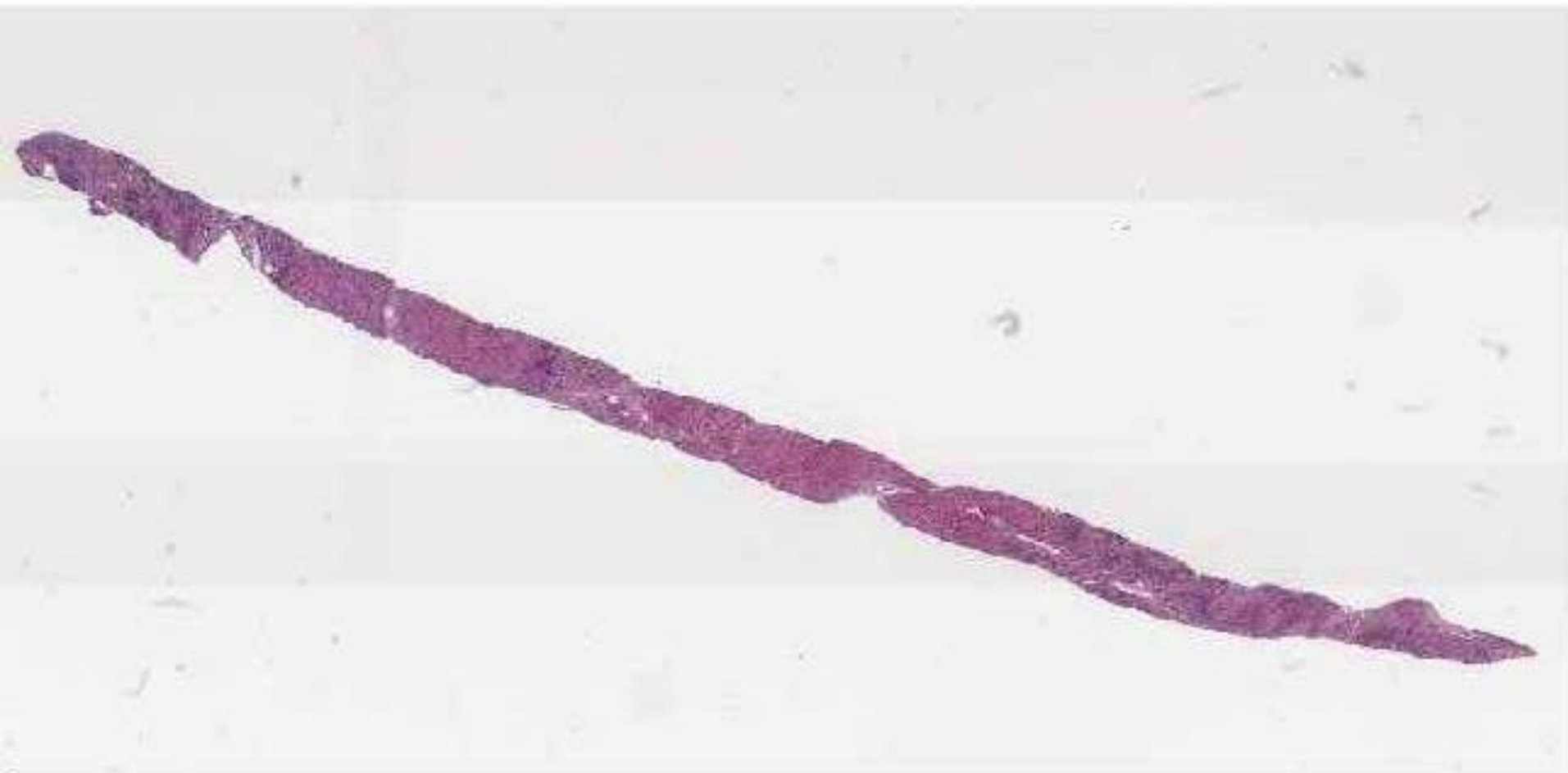
Case 277

34M.

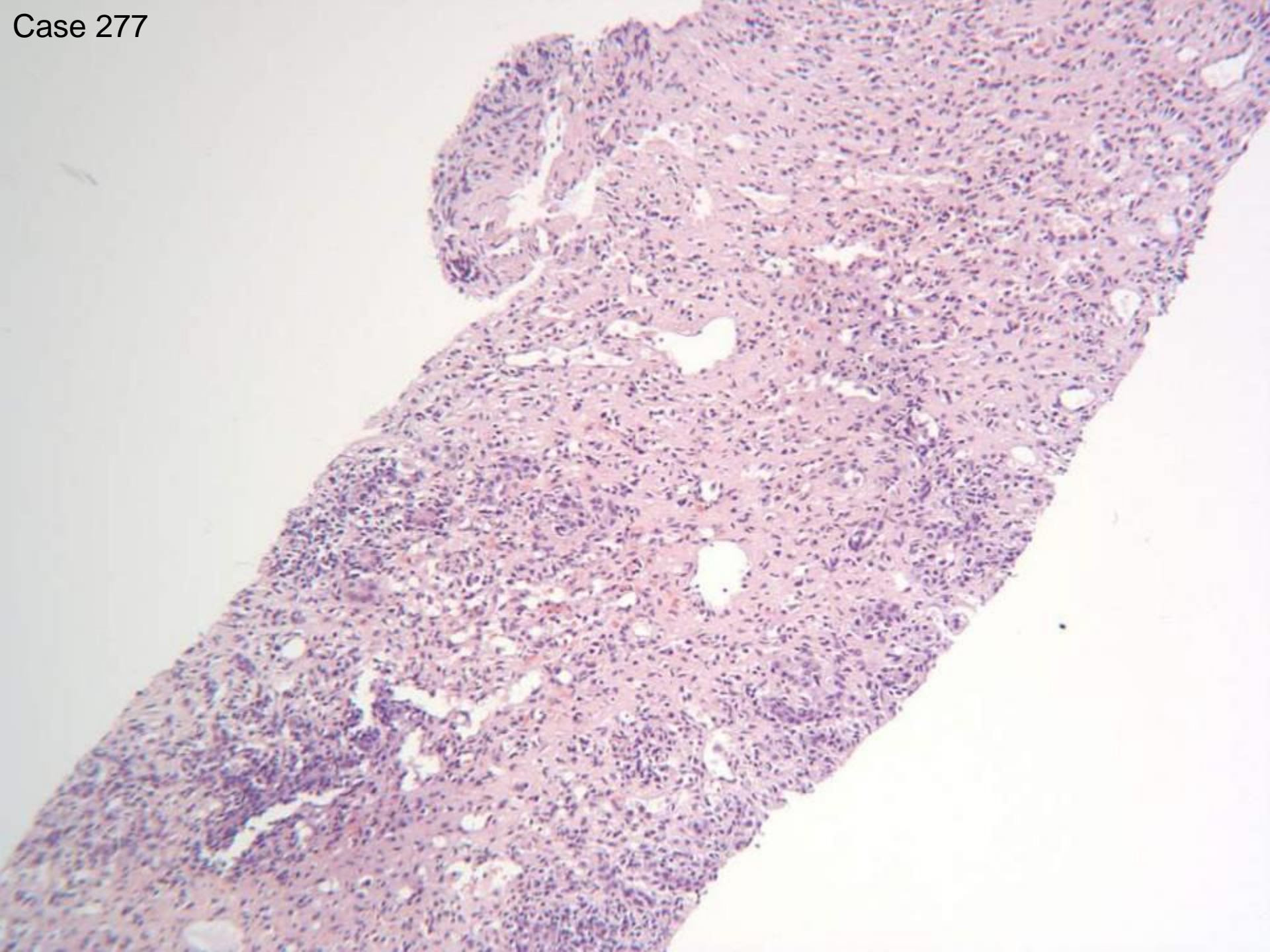
Epigastric pain and jaundice.

Deranged clotting, plugged liver biopsy.

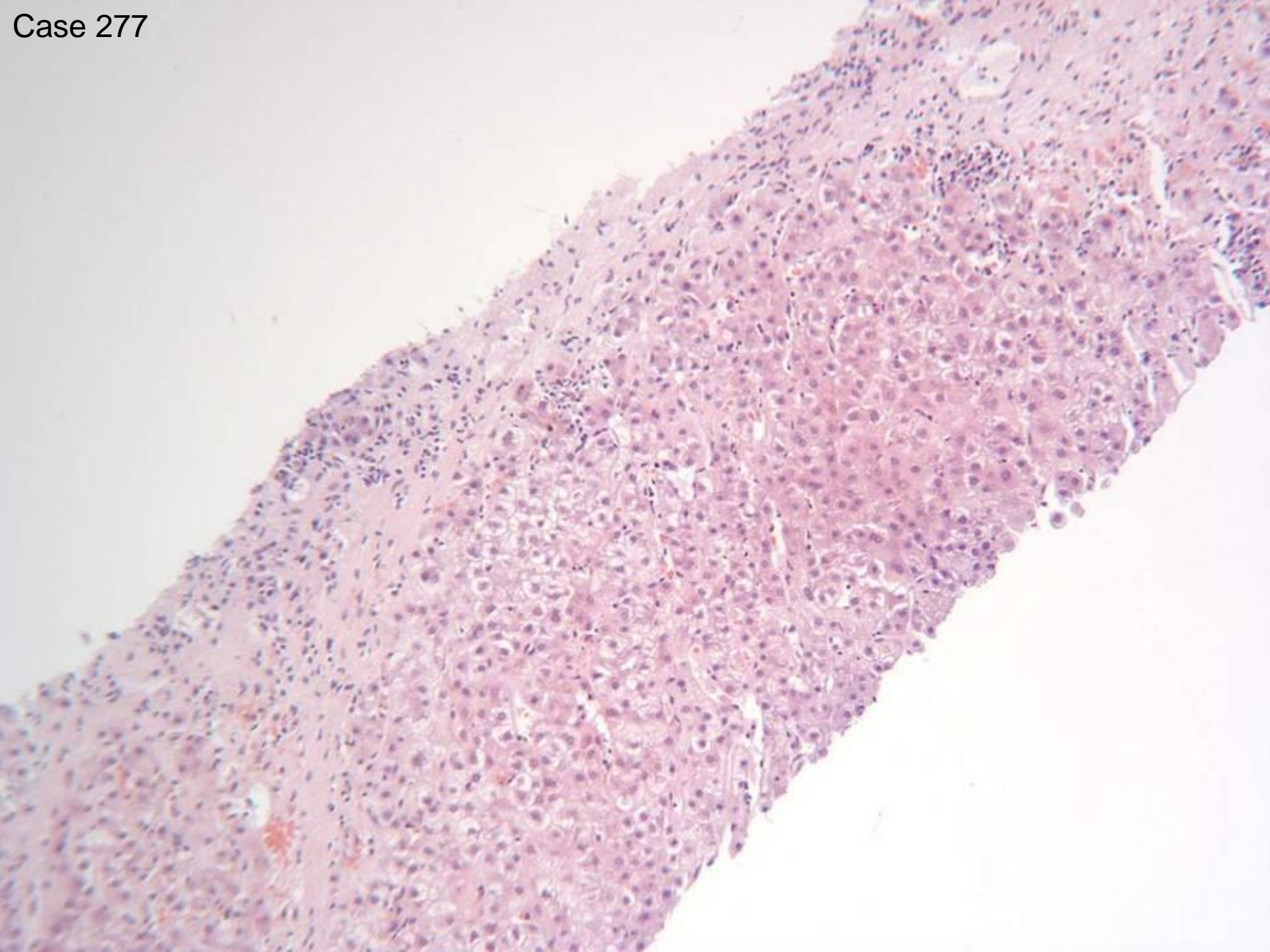
Case 277



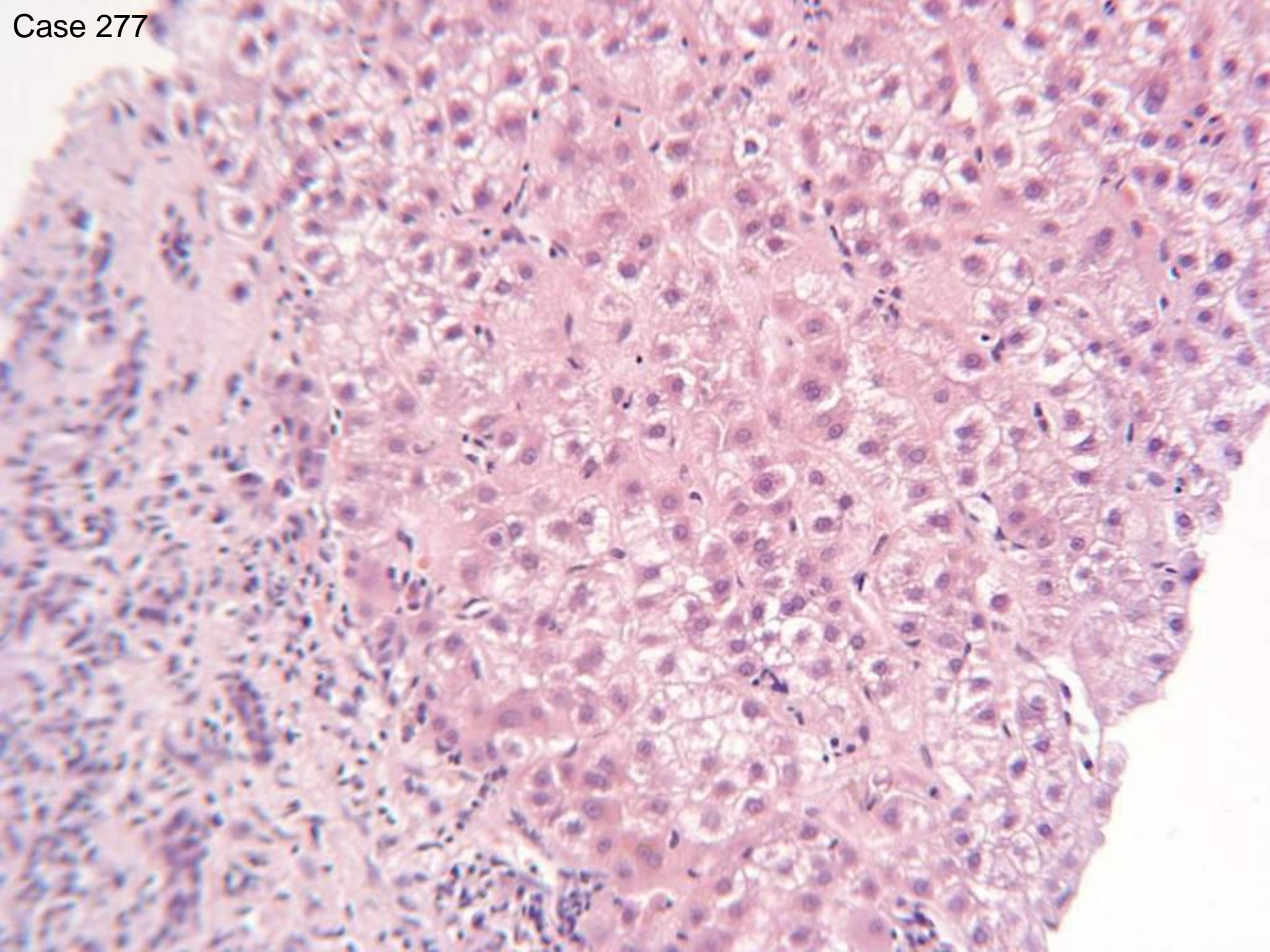
Case 277



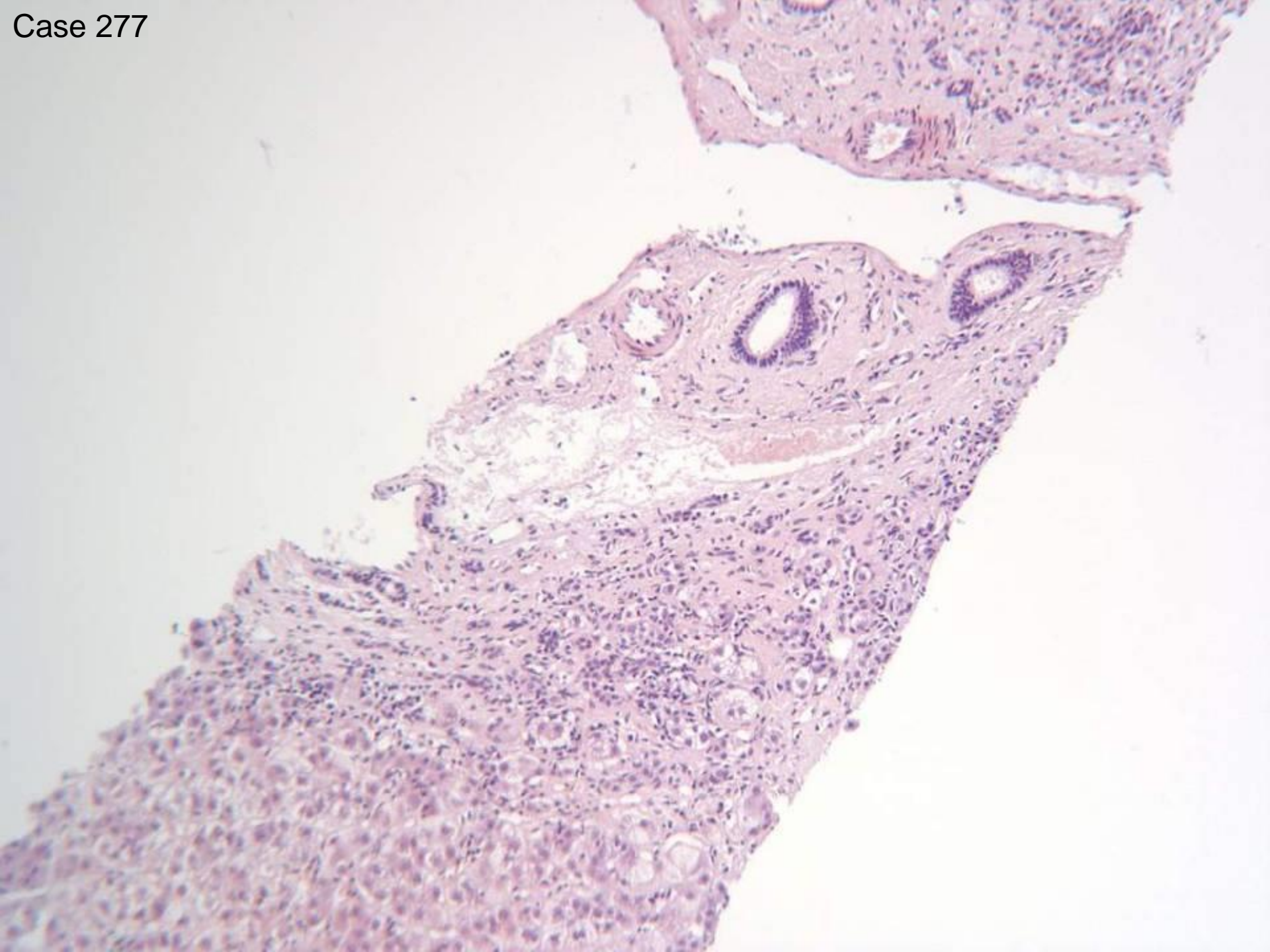
Case 277



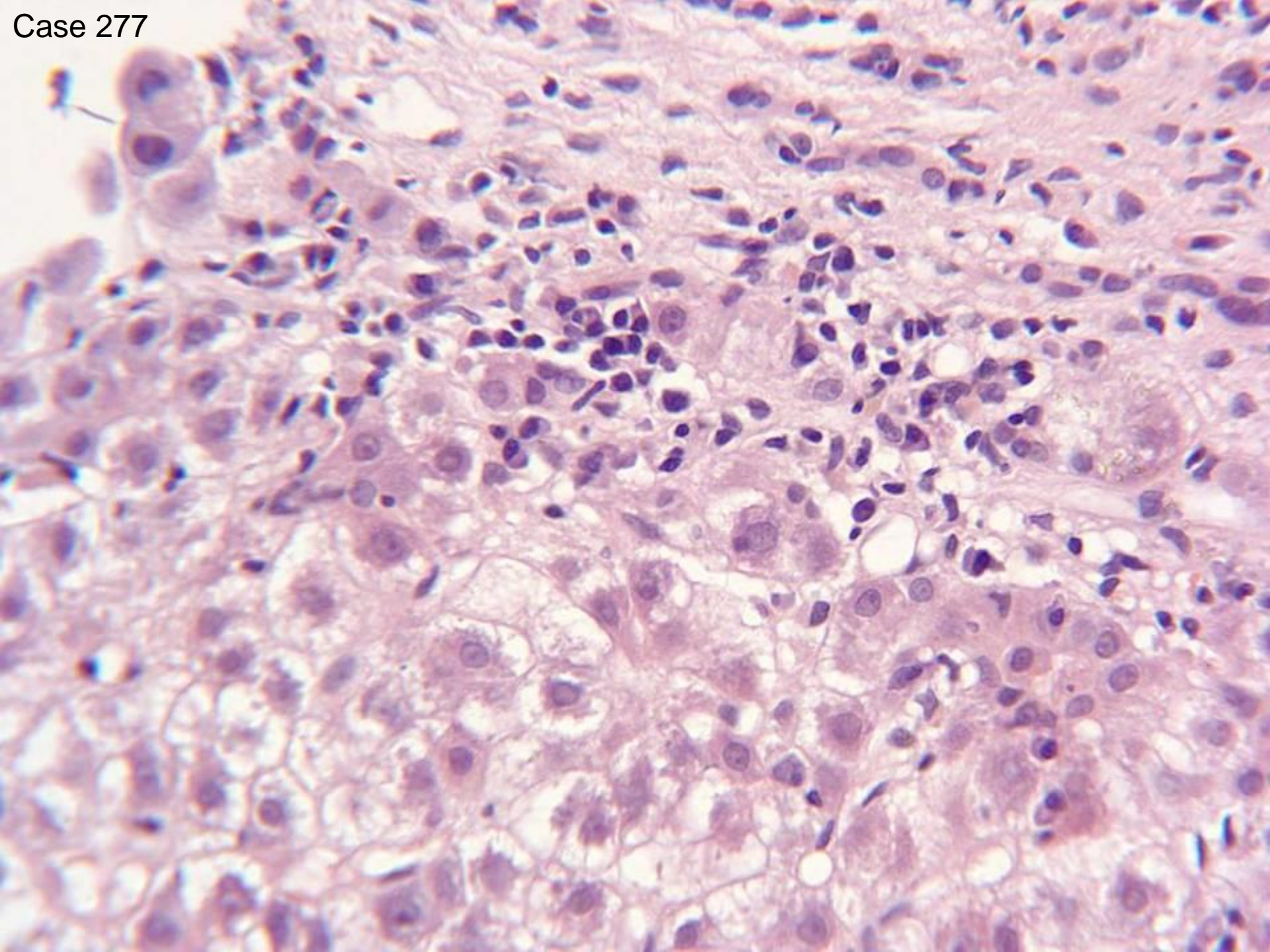
Case 277



Case 277



Case 277



Case 277

- 24 severe hepatitis with confluent necrosis
- 1 severe hepatitis, confluent necrosis not mentioned
- 1 massive liver cell necrosis with cholestasis

- 1 acute toxic hepatic injury, ? drug
- 1 acute/chronic viral hepatitis
- 1 ? ascending cholangitis/sepsis

- 7 answers suggest chronic hepatitis /post necrotic, evolving into cirrhosis
- 16 cirrhosis NOS
- 1 cirrhosis, ?biliary obstruction
- 2 alcoholic cirrhosis
- 3 no slide received.

Case 277

Scoring: not suitable for scoring.

Discussion: Another case of severe hepatitis, with confluent multiacinar necrosis affecting about 50% of the biopsy.

This is later in the evolution of the disease than case 273, with more mature collapse and no residual spaces in the area of necrosis. The recognition of the position of portal/central areas is characteristic.

There is also bridging necrosis (third image) and regenerative areas of parenchyma with mild ongoing necroinflammatory activity. Connective tissue stains help to assess the duration in such cases.

Case 277

Original diagnosis: acute hepatitis with confluent pan acinar necrosis.

Follow up information: 1 week history of jaundice. Hep A/B/C/EBV/CMV negative. ALT 545, bilirubin 215, INR 2.3, PT 27 secs. CT: small liver. Treated with steroids. Became encephalopathic, but then recovered.

Later found to have ANA 1/640, IgG 83.