Histopathology Workshop – Liver Pathology

Slide Seminar – Focal Liver Lesions

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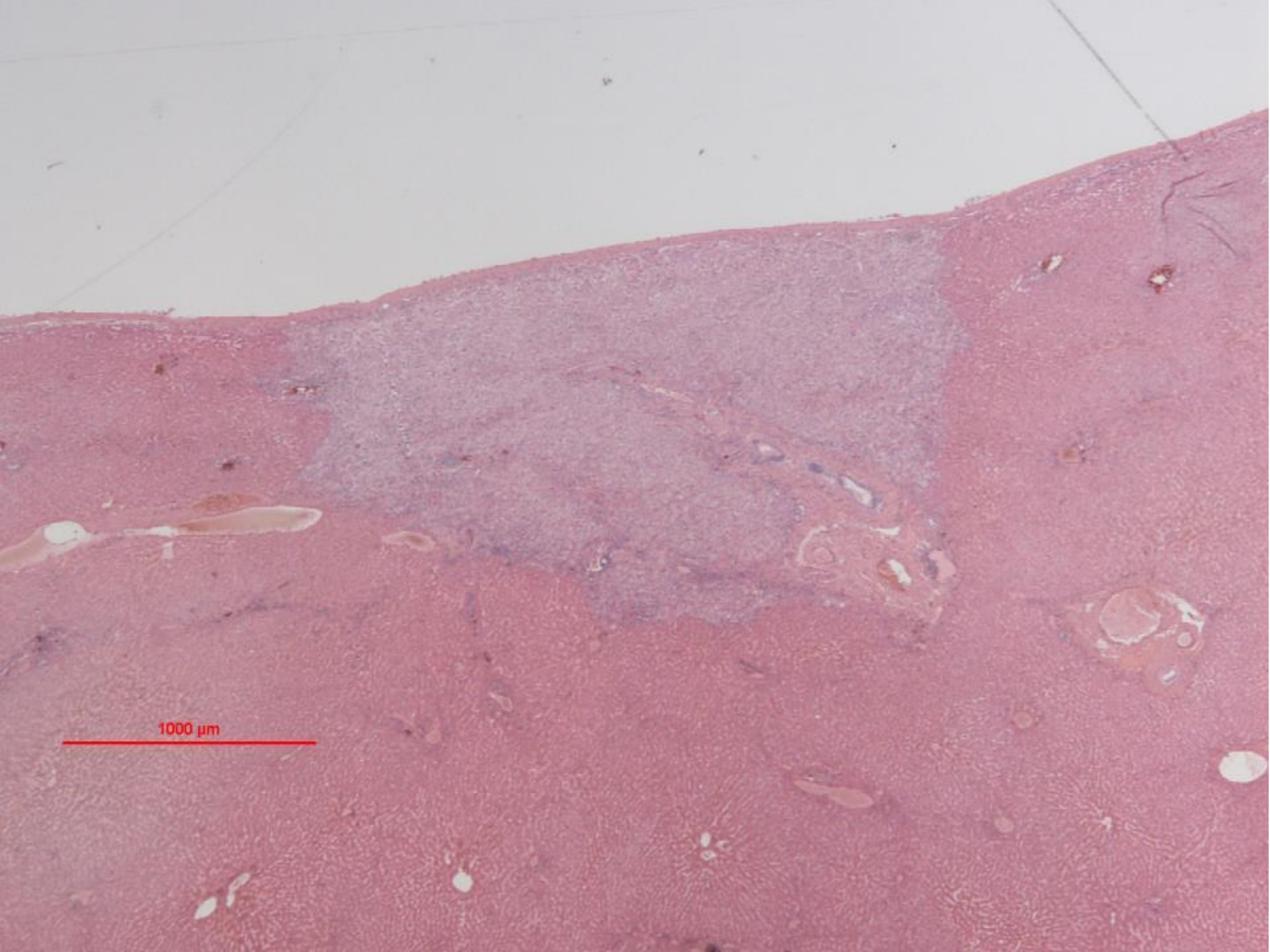
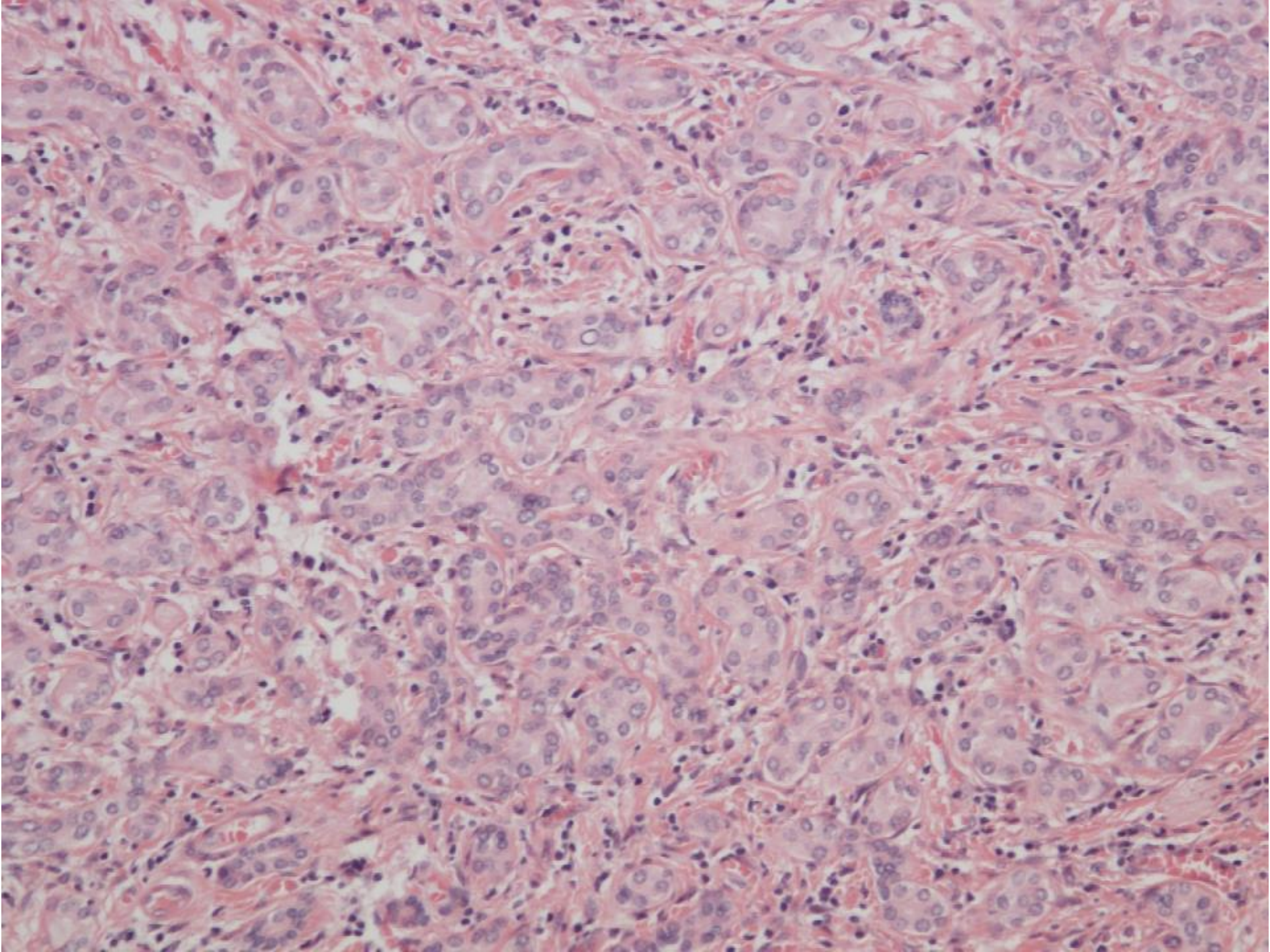
Case 1

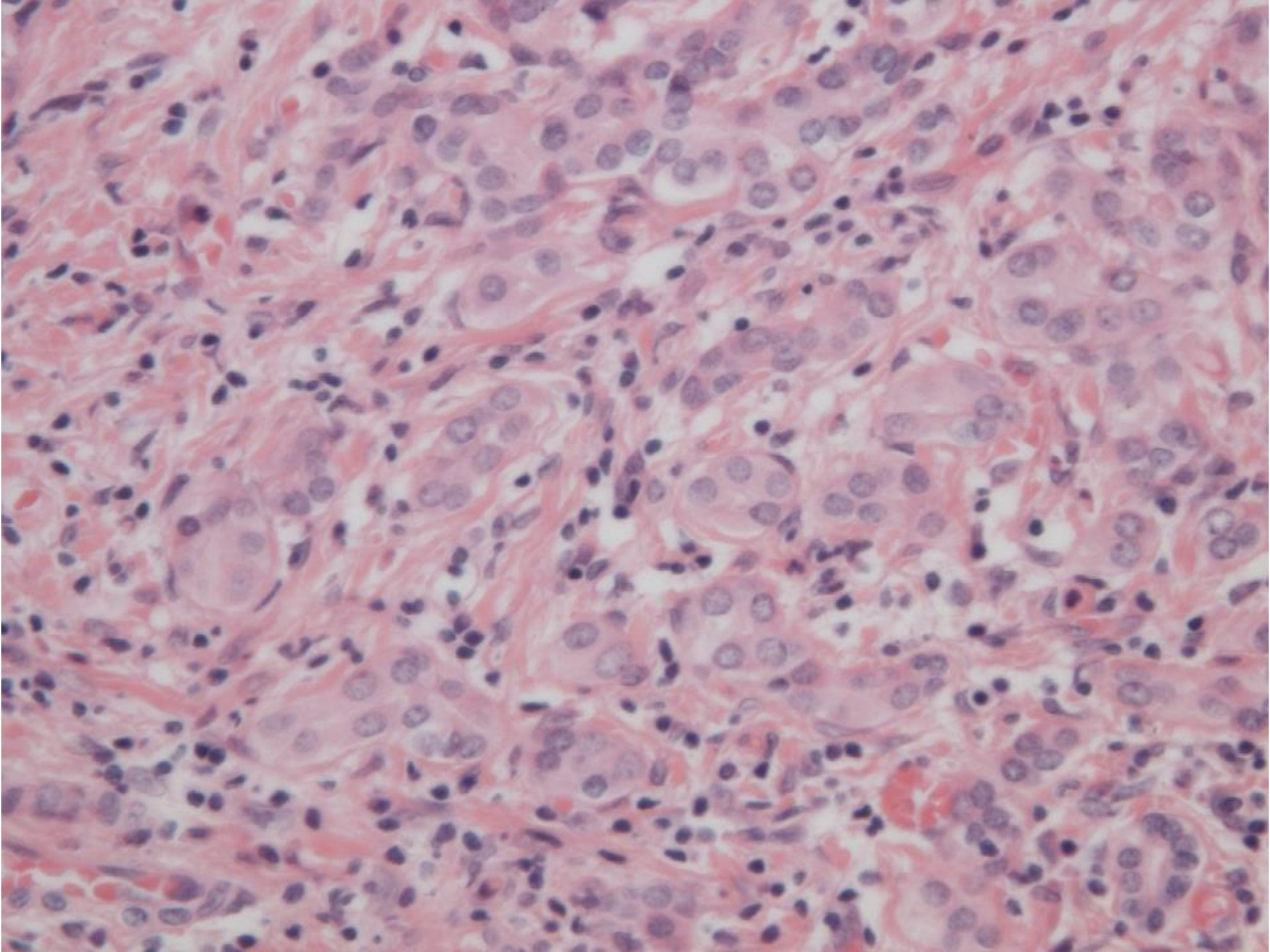
Case 1 - Clinical Summary

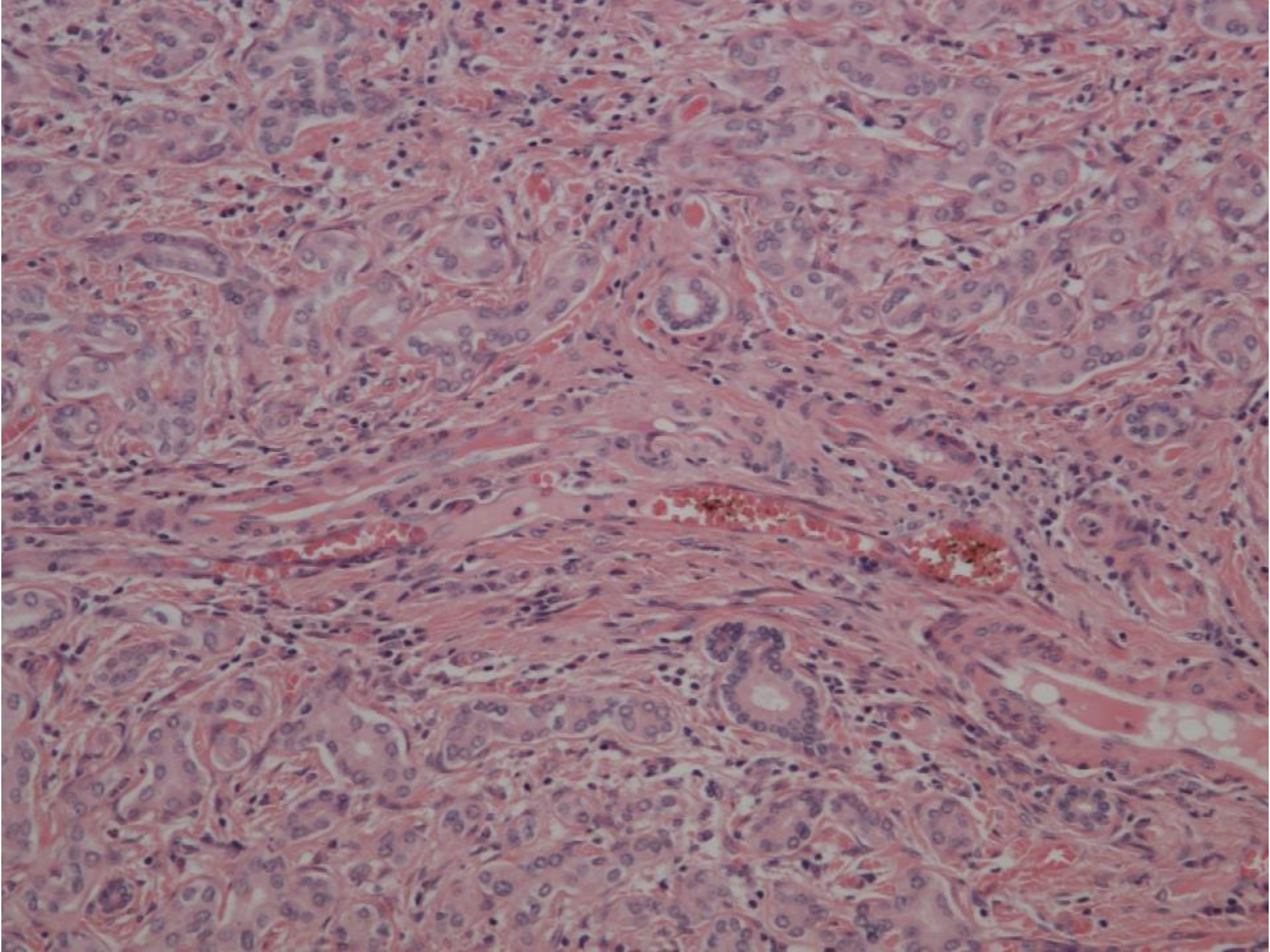
Male, age 56

- Liver resection for metastatic colorectal carcinoma.
- Incidental small subcapsular lesion 0.5cm diameter in segment 6.


1000 µm







Case 1 – Histological Findings

- Small, slightly irregular glands
- No cytological atypia
- Scanty fibrous stroma containing inflammatory cells
- Incorporated portal tract

Case 1 – Diagnosis

Peribiliary gland hamartoma
(bile duct adenoma)

Case 1 – Discussion Points

1. Nature of lesion (evidence for peribiliary gland origin)

- Topographic relationship to normal bile duct
- Immunohistochemical studies show phenotype of peribiliary glands rather than bile ducts (D10 & 1F6 positive) (Bhathal 1996)
- Similar changes may occur as reaction to localised area of parenchymal extinction (e.g. in cirrhotic livers)
  - "peribiliary gland hyperplasia"
- Minimal malignant potential

BUT

- Recent studies have shown *BRAF* V600E mutations in 55% of cases, suggesting bile duct adenoma is a neoplasm (Pujals Hepatology 2014 & Pujals Histopathology 2015)
- Similar mutations seen in 5% of intrahepatic cholangiocarcinomas

Case 1 – Discussion Points

2. Clinical Presentation

- incidental finding at abdominal surgery
- common indication for frozen section

Case 1 – Discussion Points

3. Features favouring a benign process

- small size
- lack of cytological atypia
- fibrous stroma dense & inflamed (but not desmoplastic)
  - ➢ Some lesions may have abundant hyalinised fibrous stroma with relatively scanty glands
- incorporated portal tracts

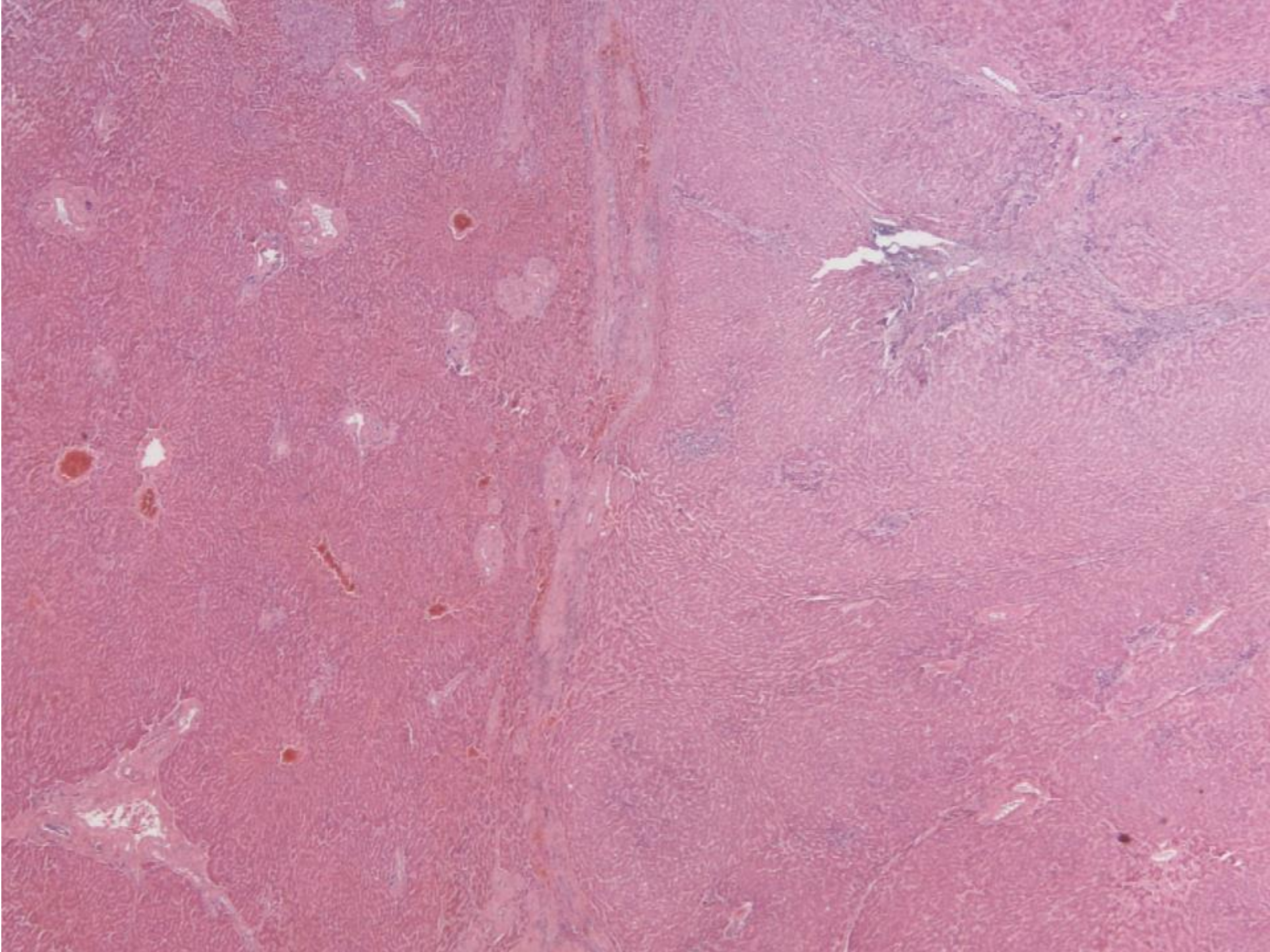
Case 2

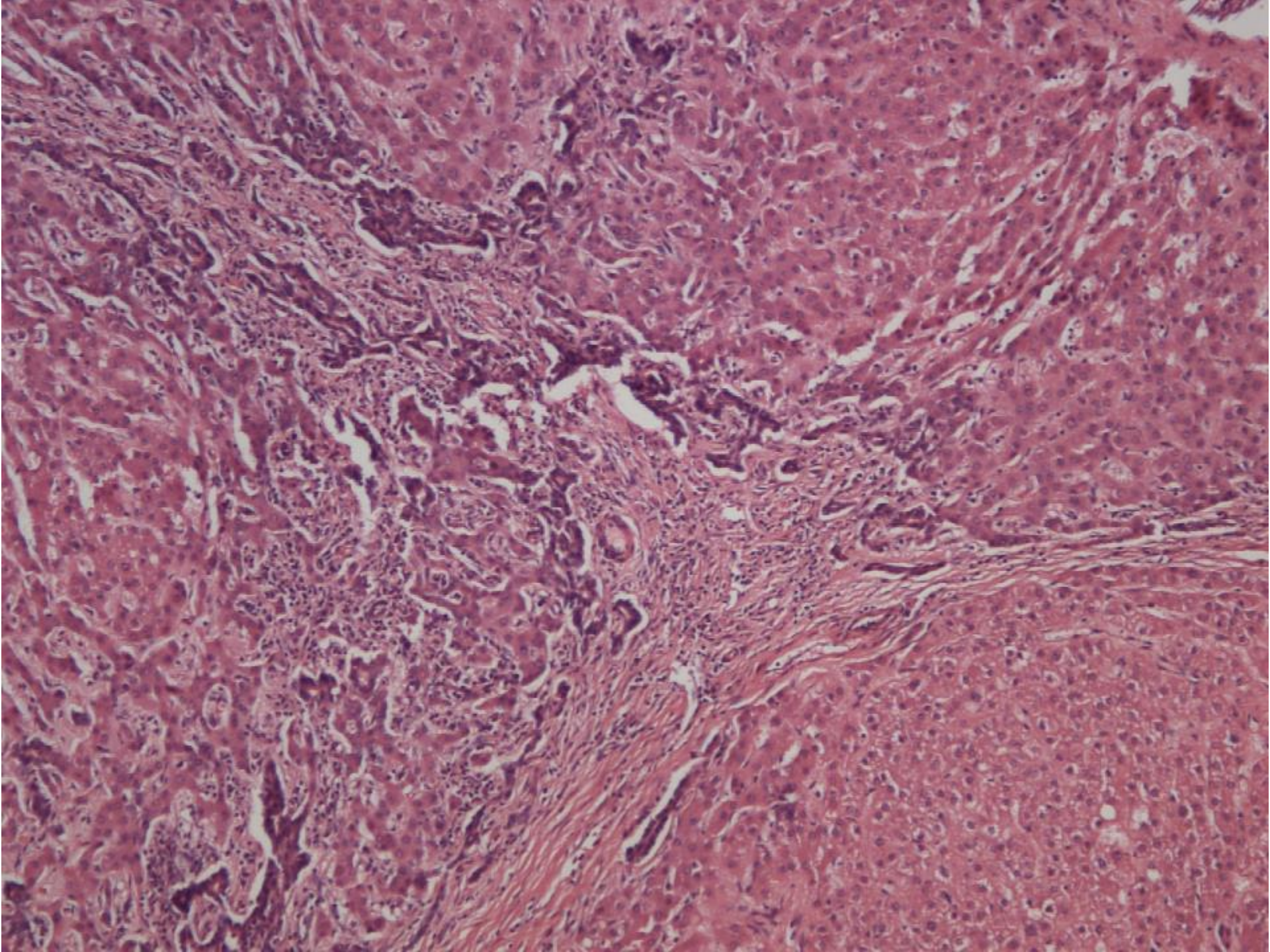
Case 2 - Clinical Summary

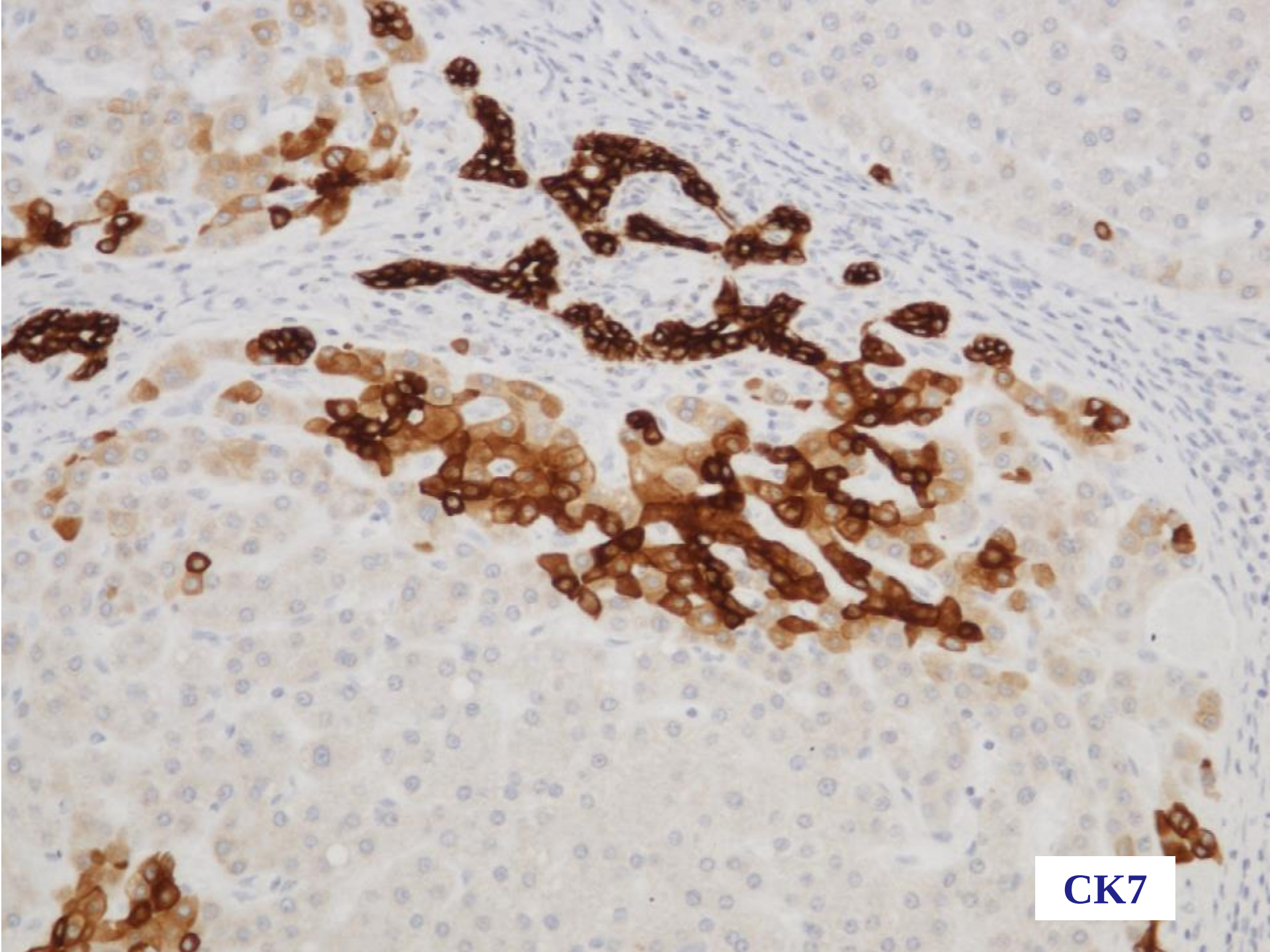
Female, age 51

- Liver resection for three lesions in left lobe.
- Main lesion 8cm
  - histology = hepatocellular adenoma
- Slide submitted is from a 4.5cm lesion, which had an irregular central scar
- (3rd lesion 1.5cm diameter had similar histological appearances to lesion 2, but lacked a central scar)

Case 2 – Macroscopic Findings



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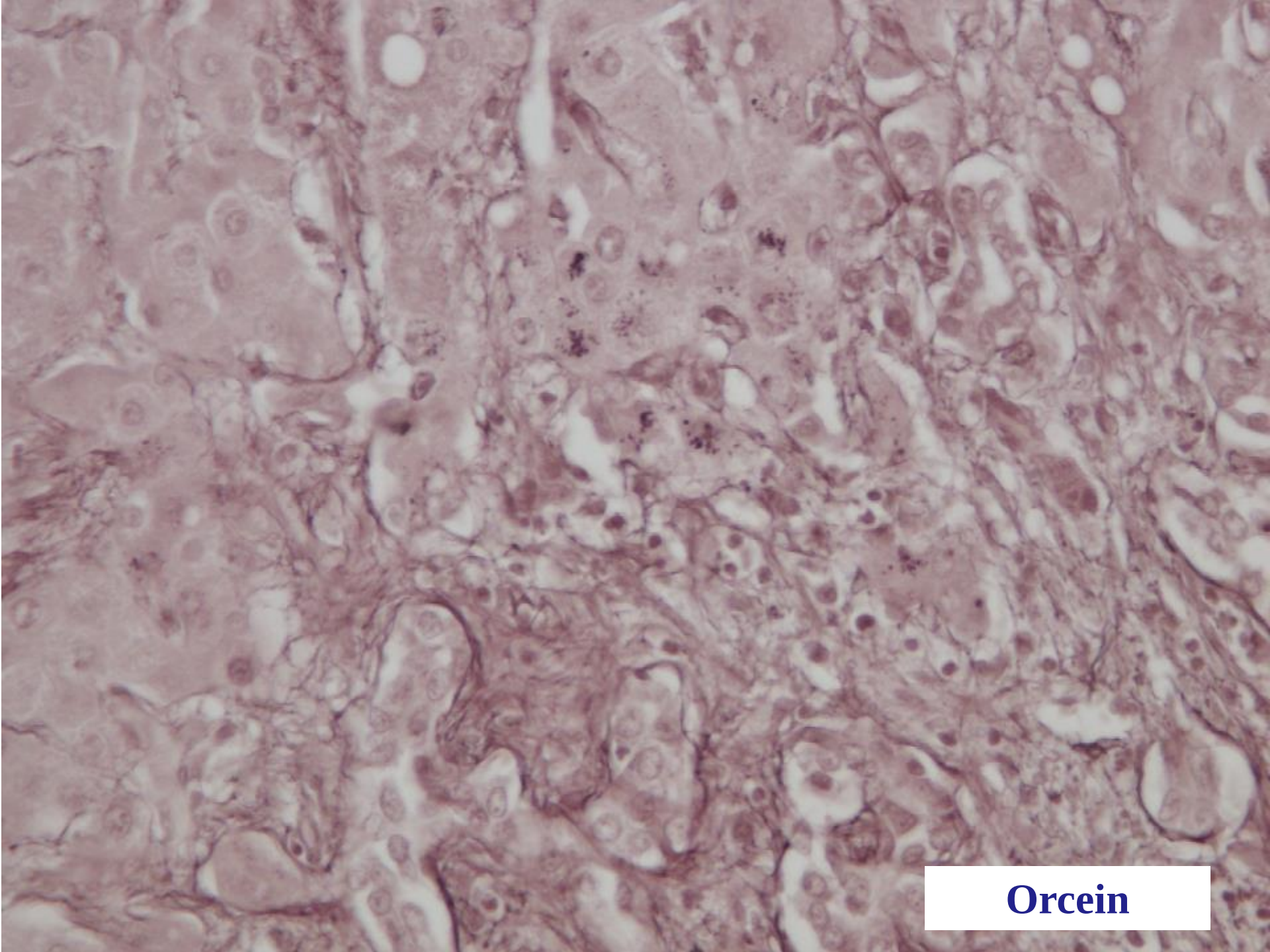
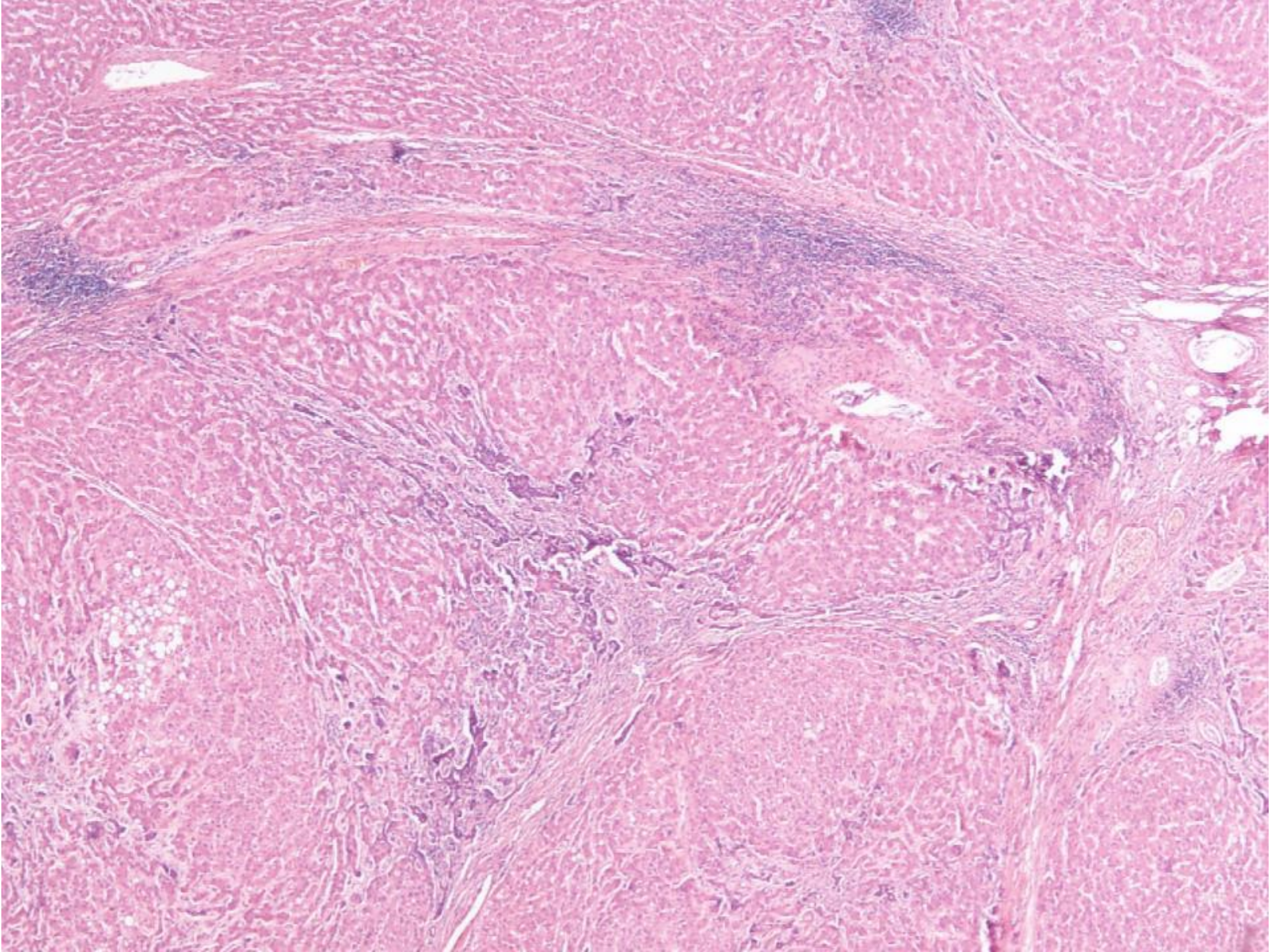
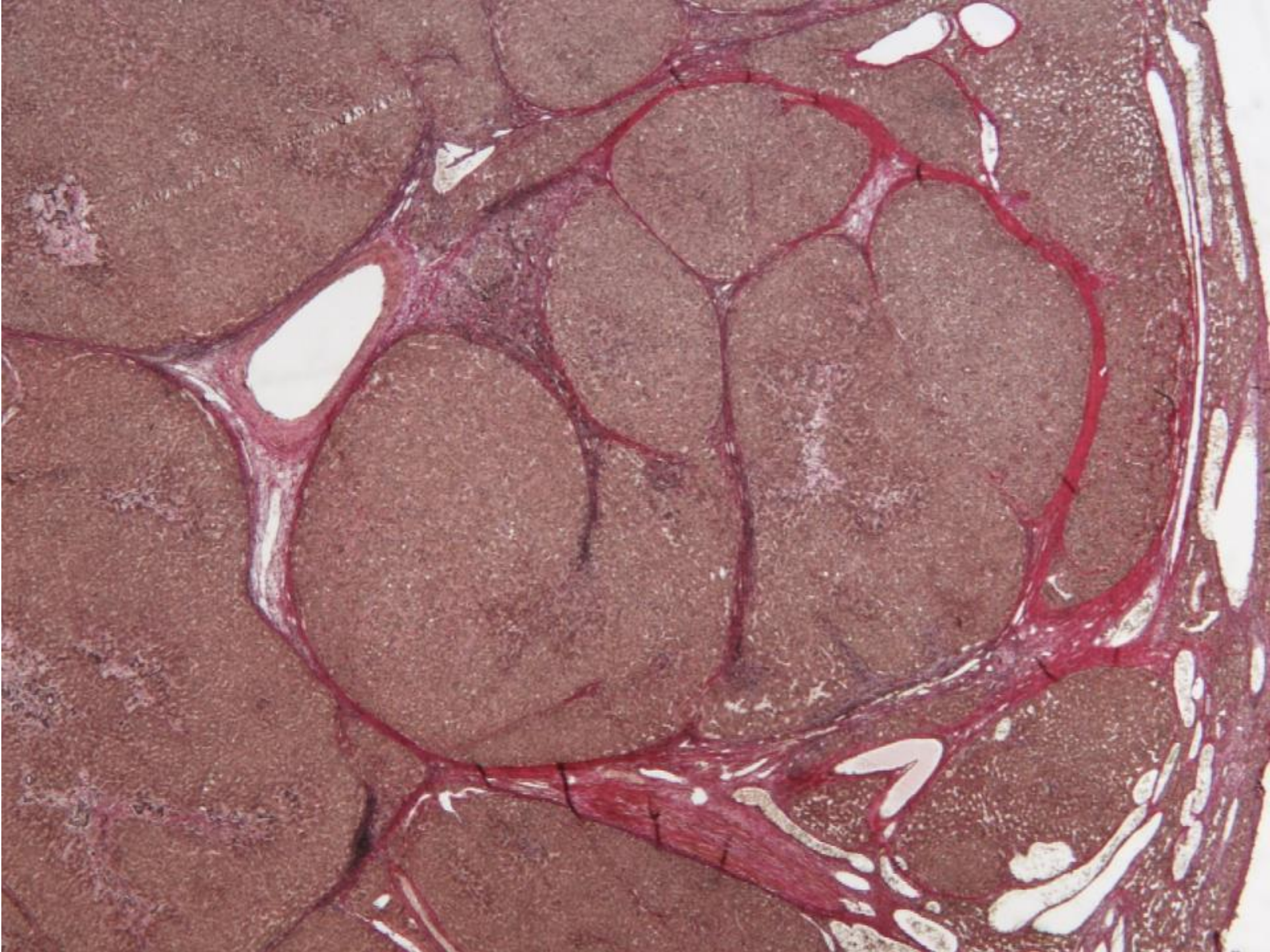
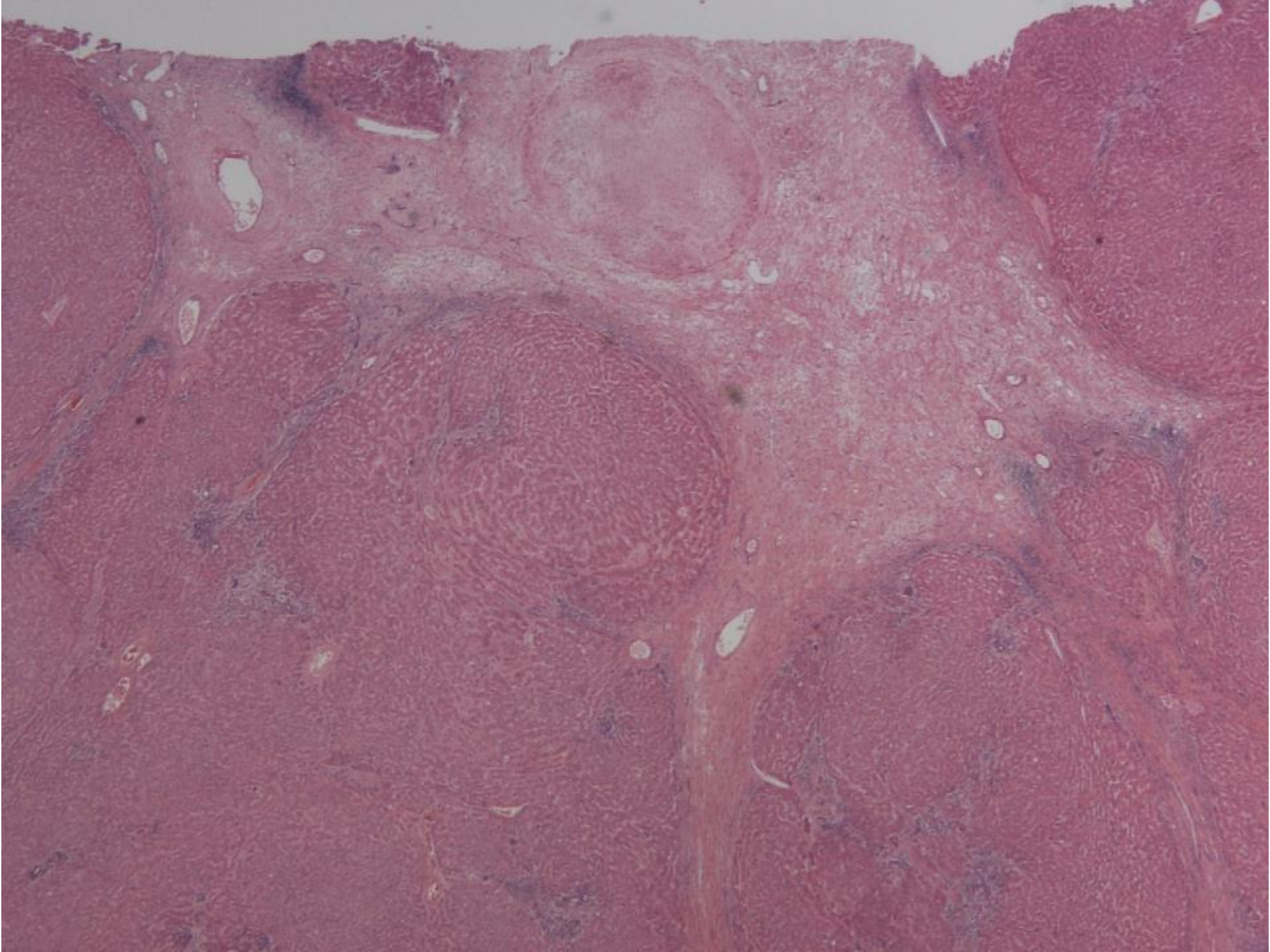
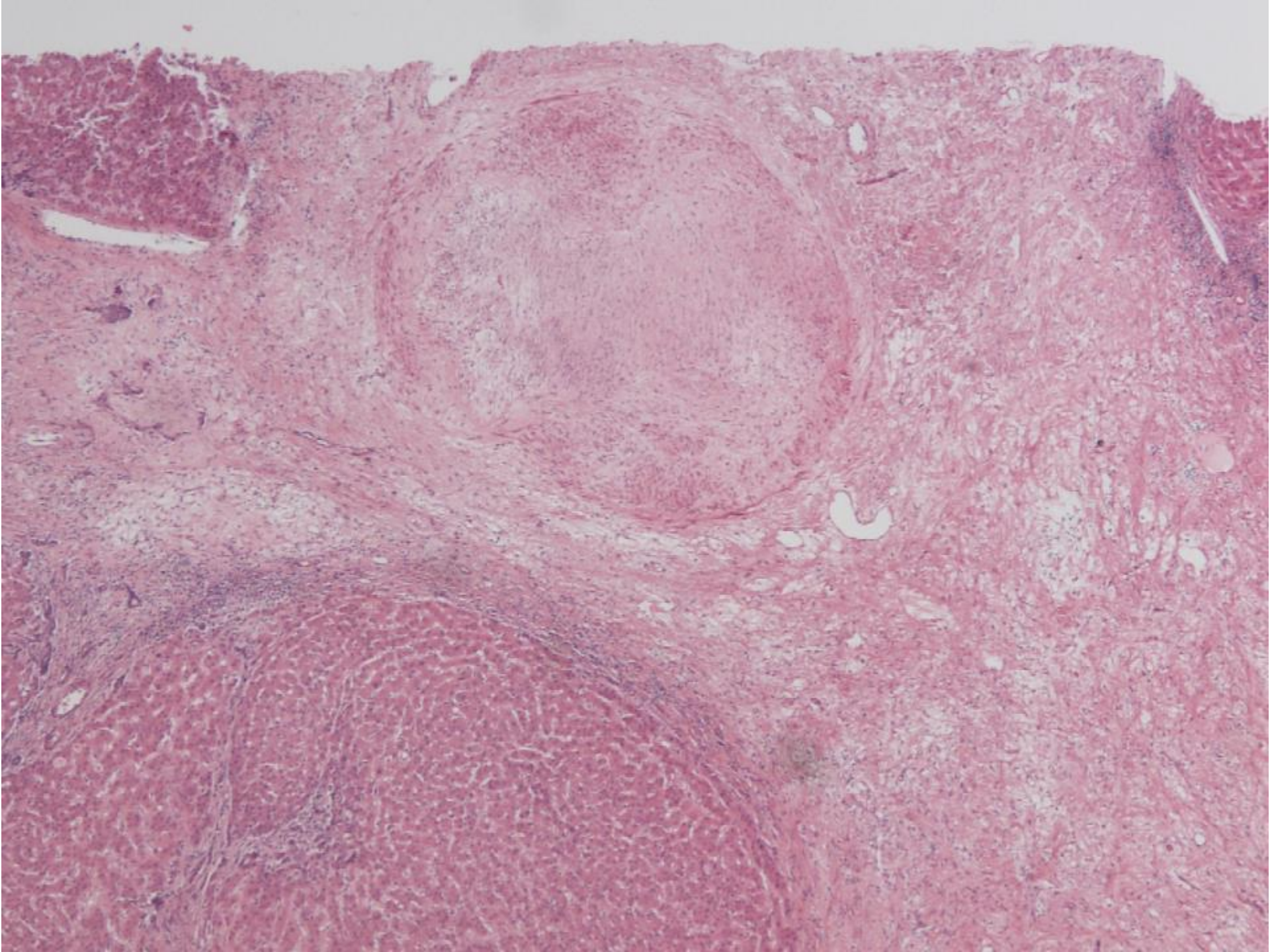
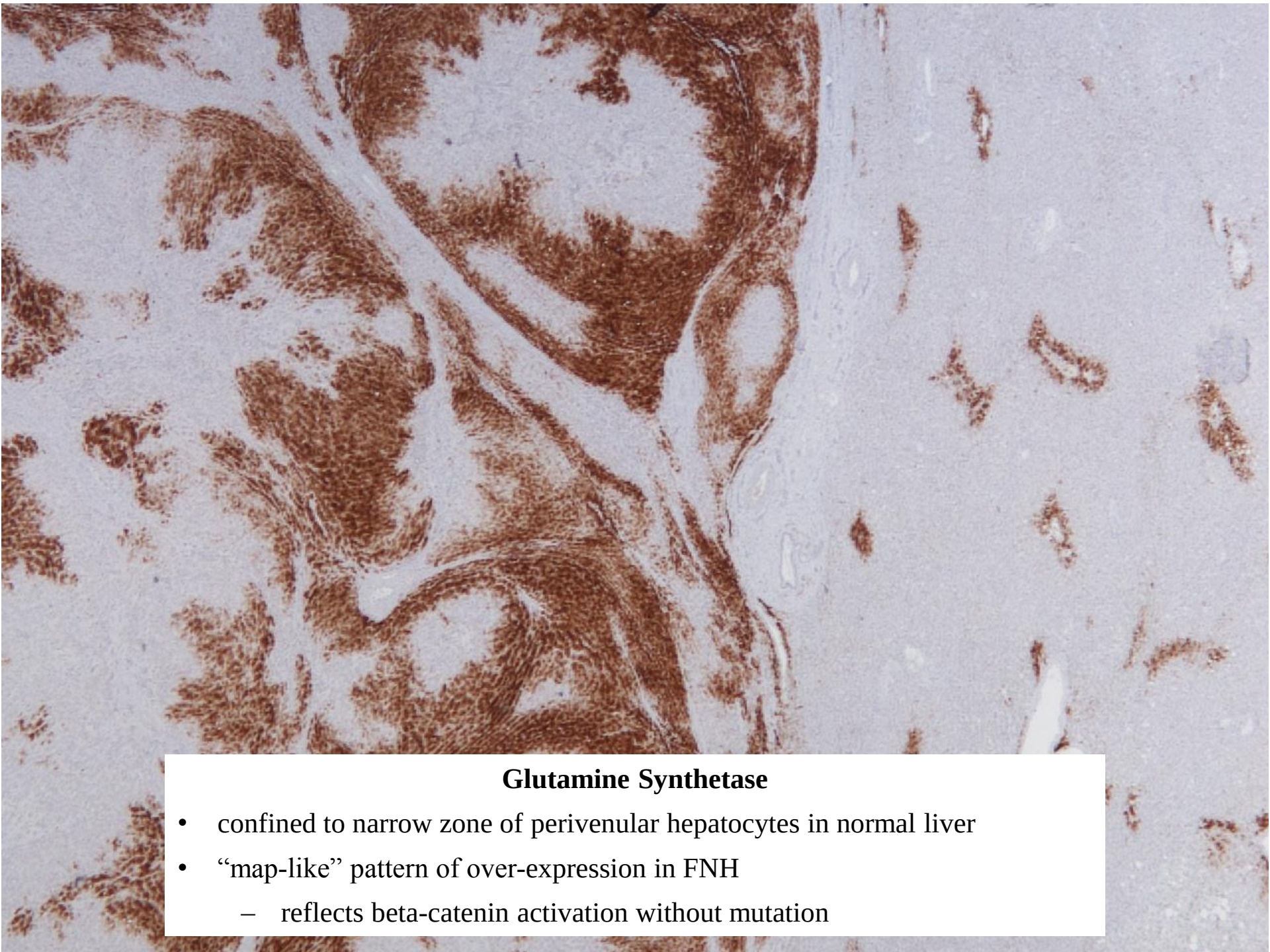

Orcein











Glutamine Synthetase

- confined to narrow zone of perivenular hepatocytes in normal liver
- “map-like” pattern of over-expression in FNH
  - reflects beta-catenin activation without mutation

Case 2 – Histological Findings

- Well-differentiated hepatocellular lesion, showing no cytological atypia
- Central fibrous scar containing abnormal blood vessels
- Radiating fibrous septa containing arteries (without bile ducts), inflammatory cells and marginal zones of ductular reaction
- “Map-like” overexpression of glutamine synthetase

Case 2 – Diagnosis

Focal Nodular Hyperplasia

Case 2 – Discussion Points

1. Pathogenesis of FNH

- Response to altered blood flow (increased arterial flow)
  - ? Hepatic or portal venous injury as primary event
  - Congestion and parenchymal collapse (fibrous septa)
  - Arterio-venous shunting and hyper-arterialisation (loss of portal veins and bile ducts)

- May be **primary** or **secondary**

Type	Pathogenesis / Histological Features
Primary	• Primary vascular abnormality (congenital or acquired) • Central scar with abnormal blood vessel(s)
Secondary	• FNH-like changes present in association with vascular abnormalities related to other liver diseases (focal or diffuse): – Focal lesions – e.g. haemangioma, hepatocellular adenoma – Diffuse disease – e.g . Cirrhosis, Budd-Chiari syndrome • May have different features to primary FNH (Rebouissou 2008)

Case 2 – Discussion Points

2. Problems with liver biopsy interpretation

- Features of FNH can mimic other liver diseases
  - Cirrhosis
  - Chronic biliary disease with bile duct loss
  - Nearby space-occupying lesion

Case 2 – Discussion Points

3. FNH versus Hepatocellular Adenoma

	FNH	HCA
Central Scar	Yes (contains abnormal blood vessels) Some FNH, especially small lesions, may lack clearly identifiable scar	No Foci of fibrosis related to old haemorrhage/necrosis
Nodular Growth Pattern	Typical	Indistinct
Ductular Reaction	Yes (related to fibrovascular septa, inflammatory cells often present)	Not usually (arterial branches +/- fibrous tissue present without ductules) Inflammatory sub-type may contain foci of DR & inflammation (previously classified as "telangiectatic FNH")
Glutamine synthetase expression	"Map-like" distribution adjacent to hepatic veins	Mostly negative or perivascular (diffusely positive in beta-catenin mutated HCA)

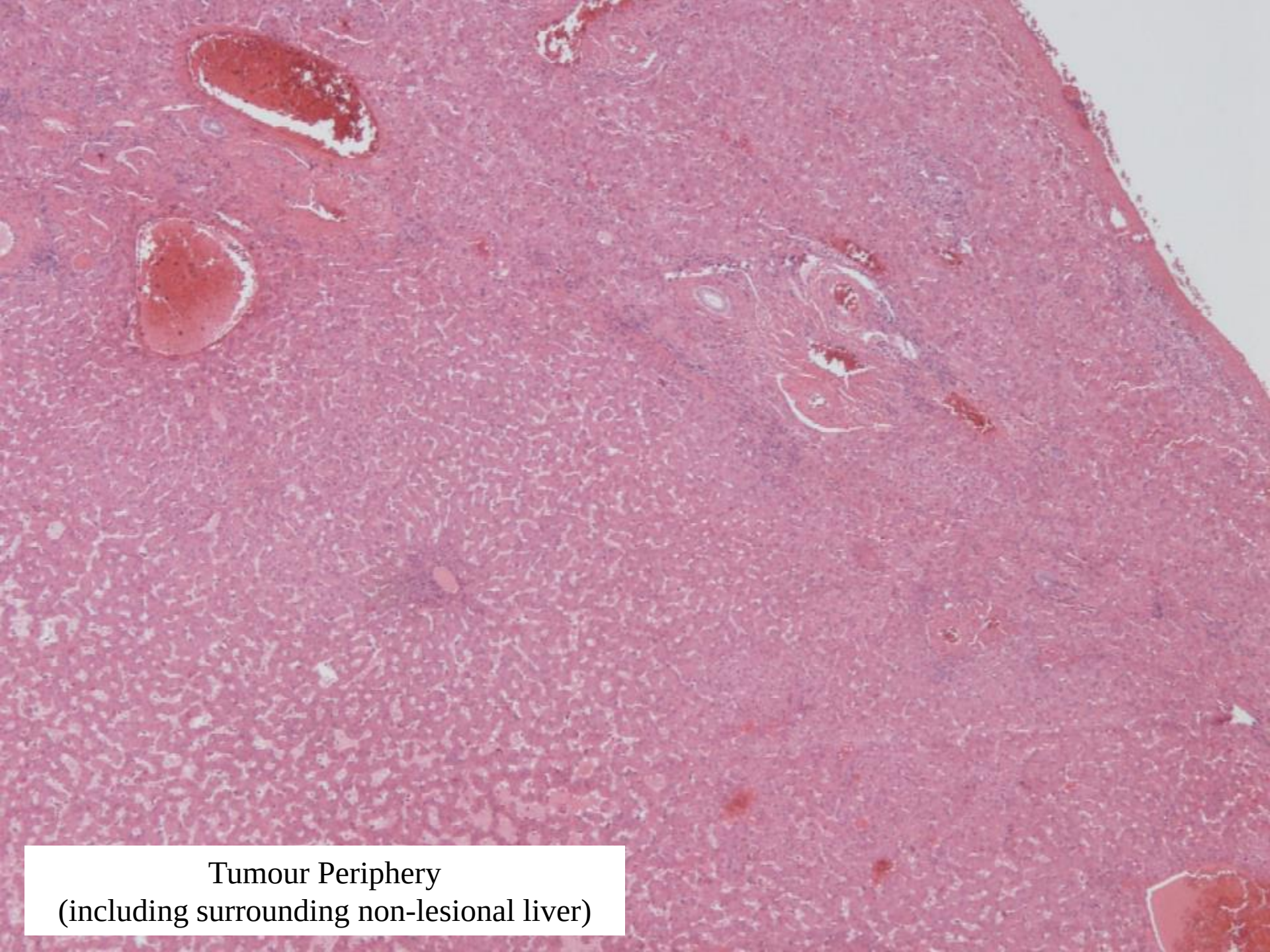
Case 3 - Clinical Summary

Female, age 37

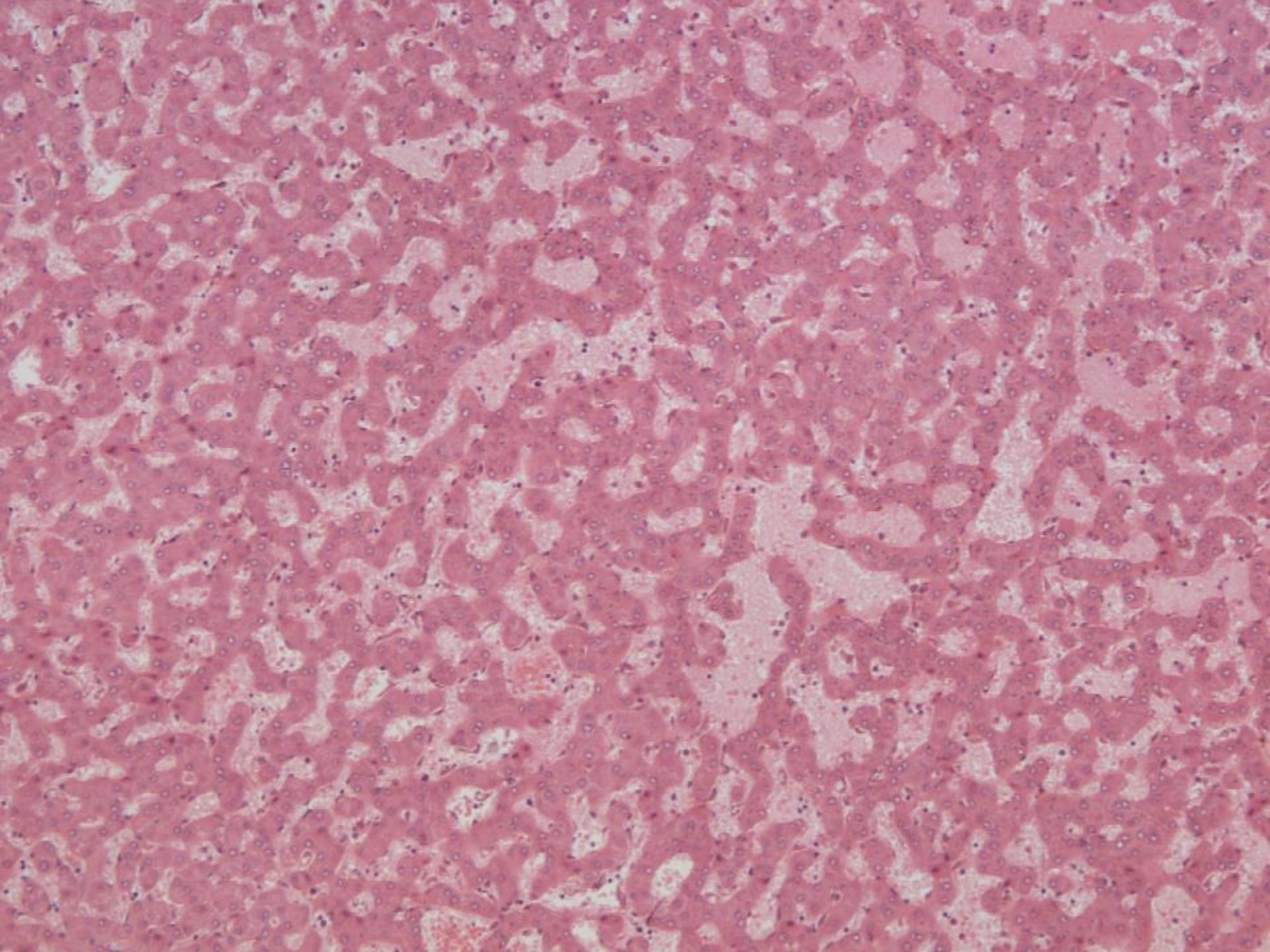
- Left lobe resection for 10 cm mass bulging from surface.
- Slide submitted is from periphery of lesion to include adjacent non-neoplastic liver tissue.

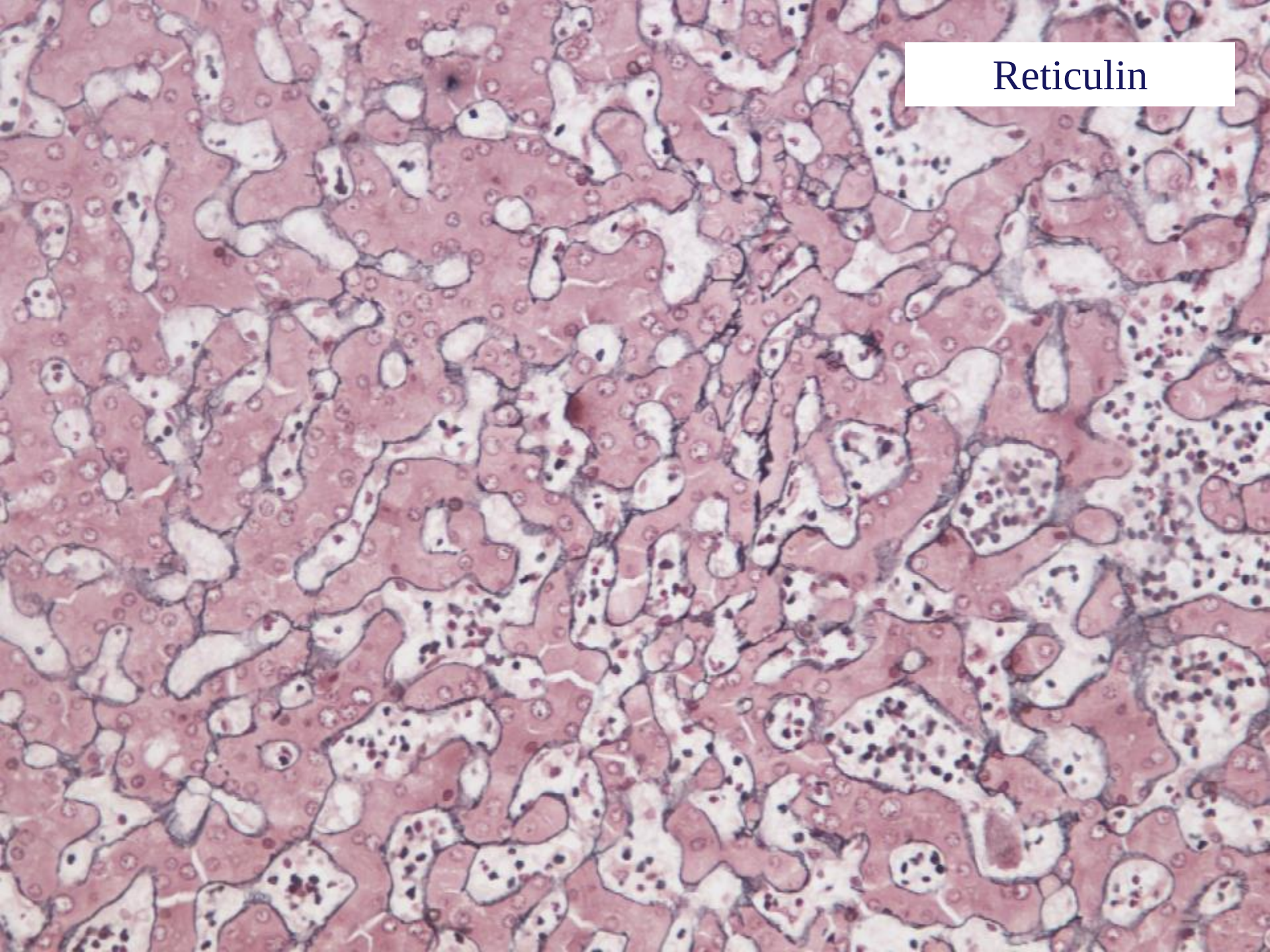

20 mm

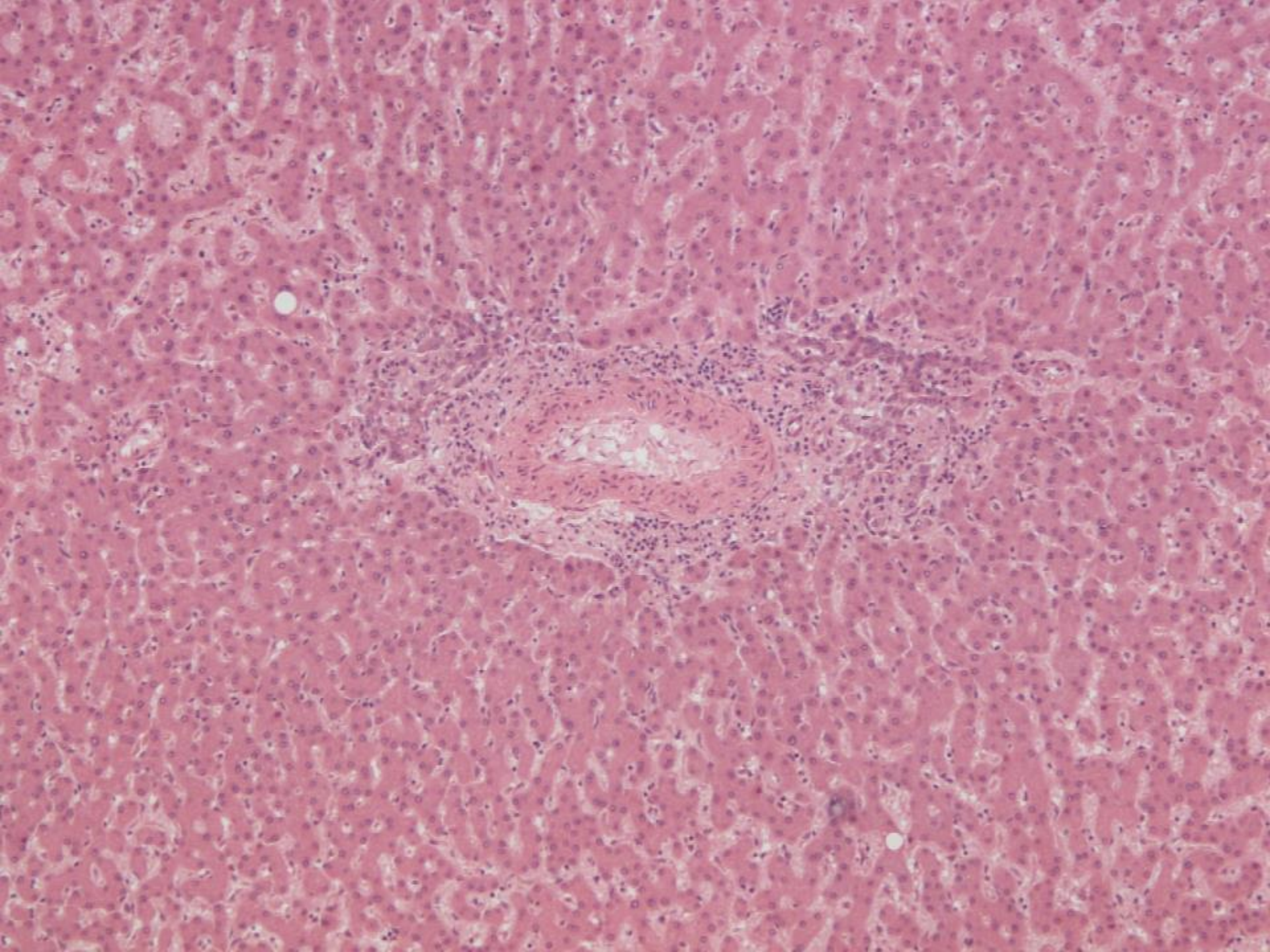

10 mm

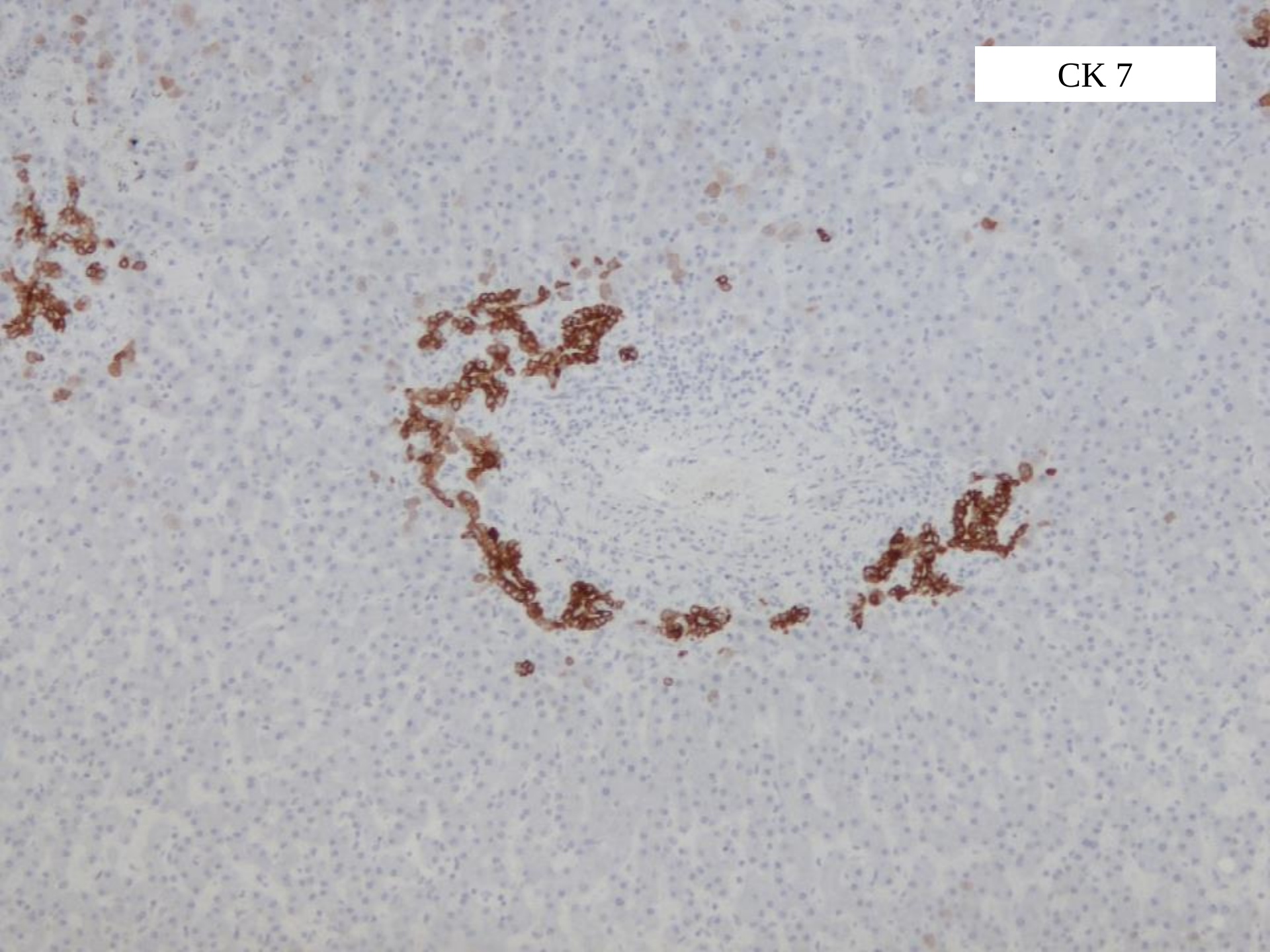


Tumour Periphery
(including surrounding non-lesional liver)




Reticulin

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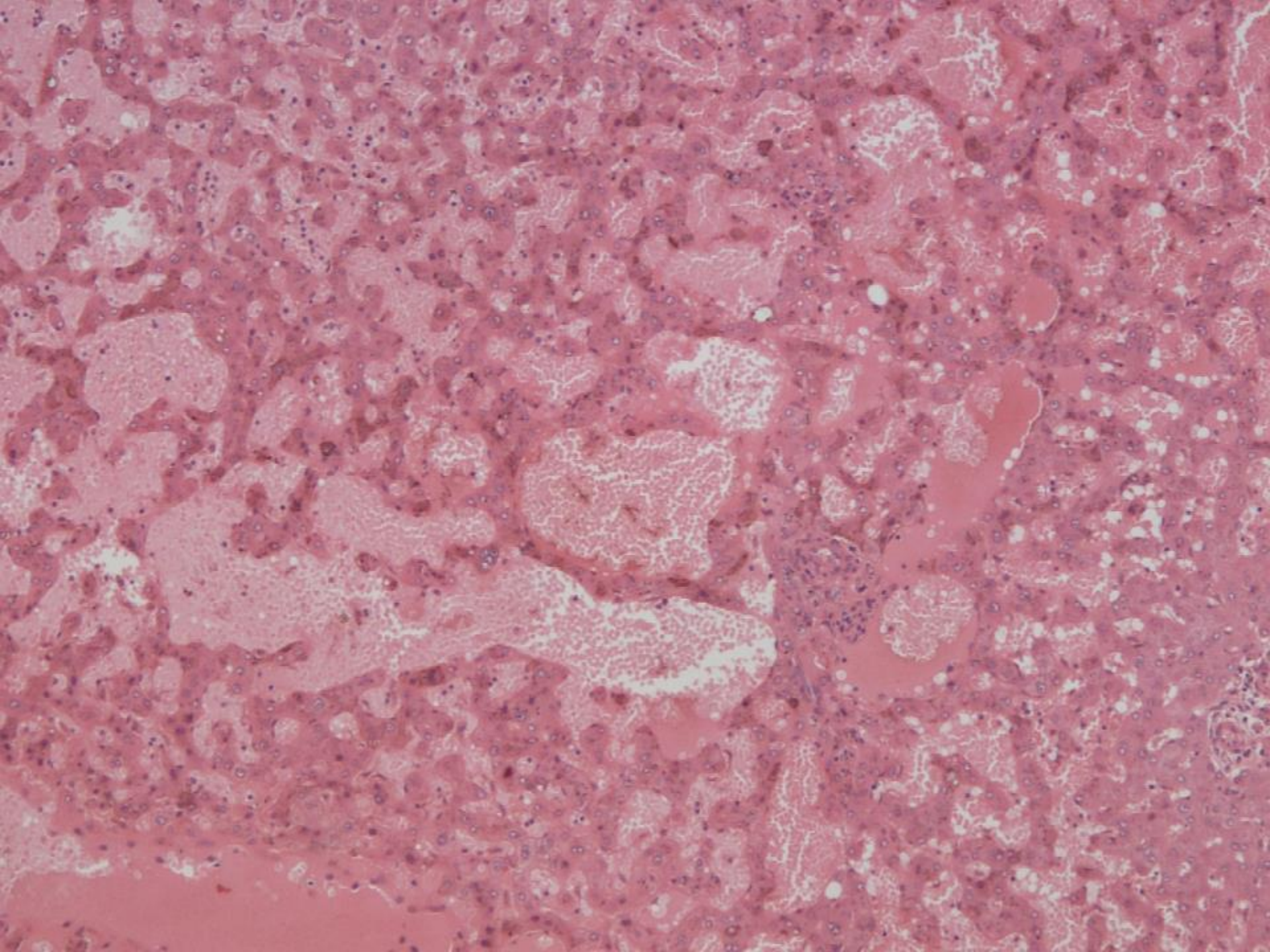
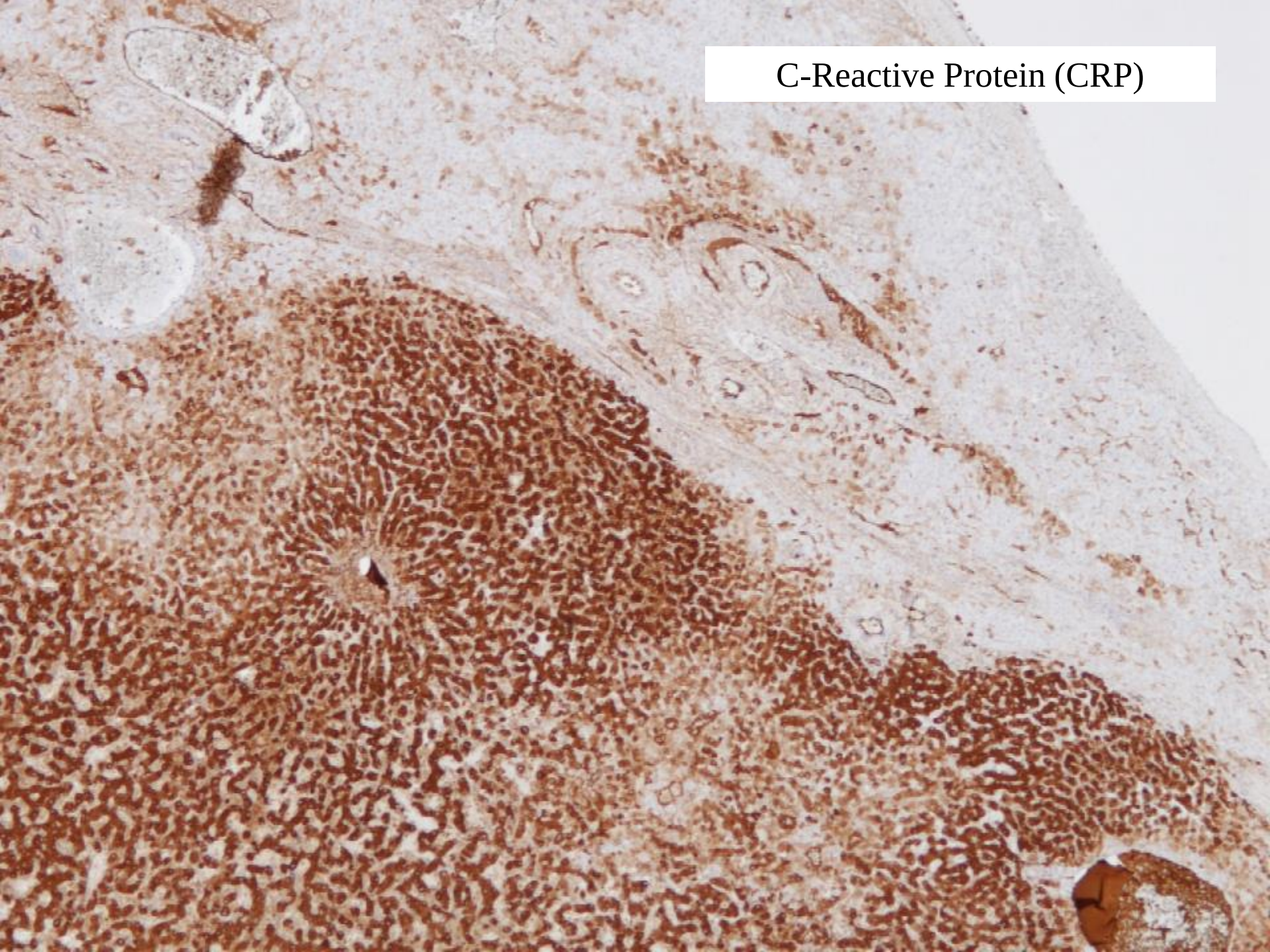
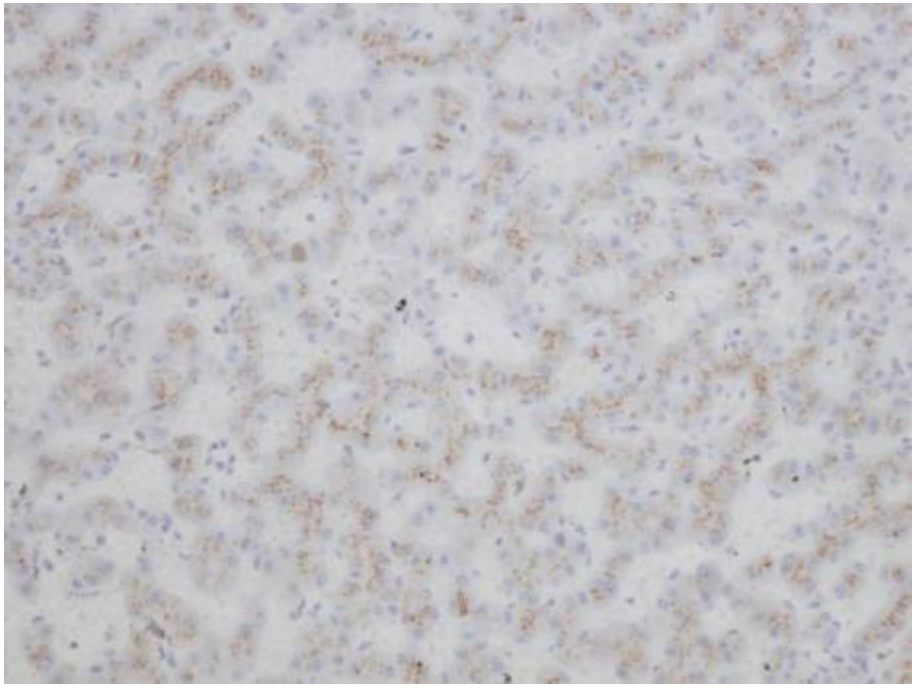
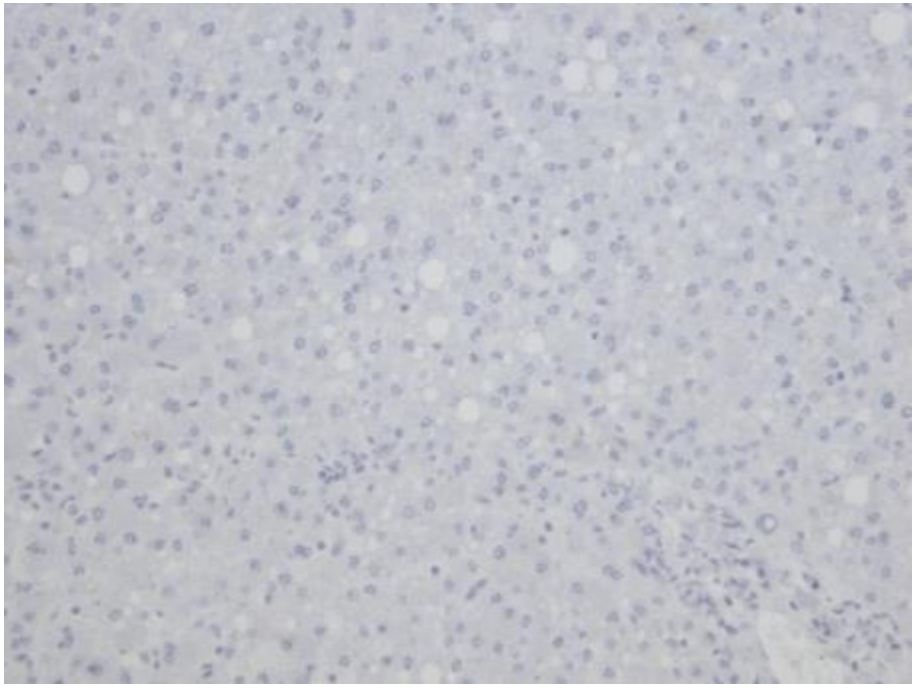



C-Reactive Protein (CRP)

Serum Amyloid A (SAA)

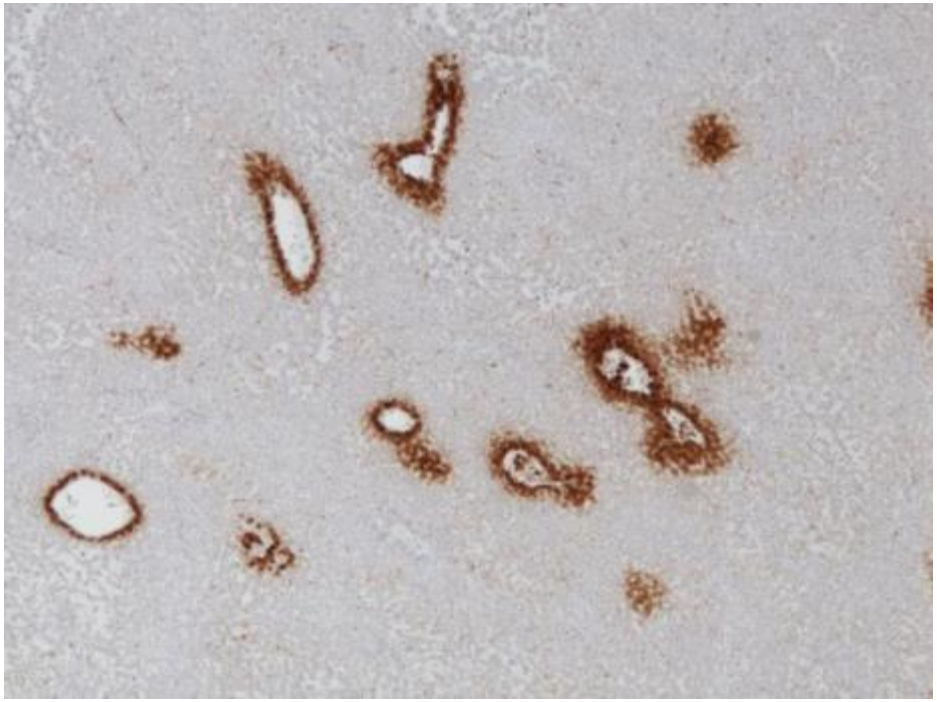


Tumour



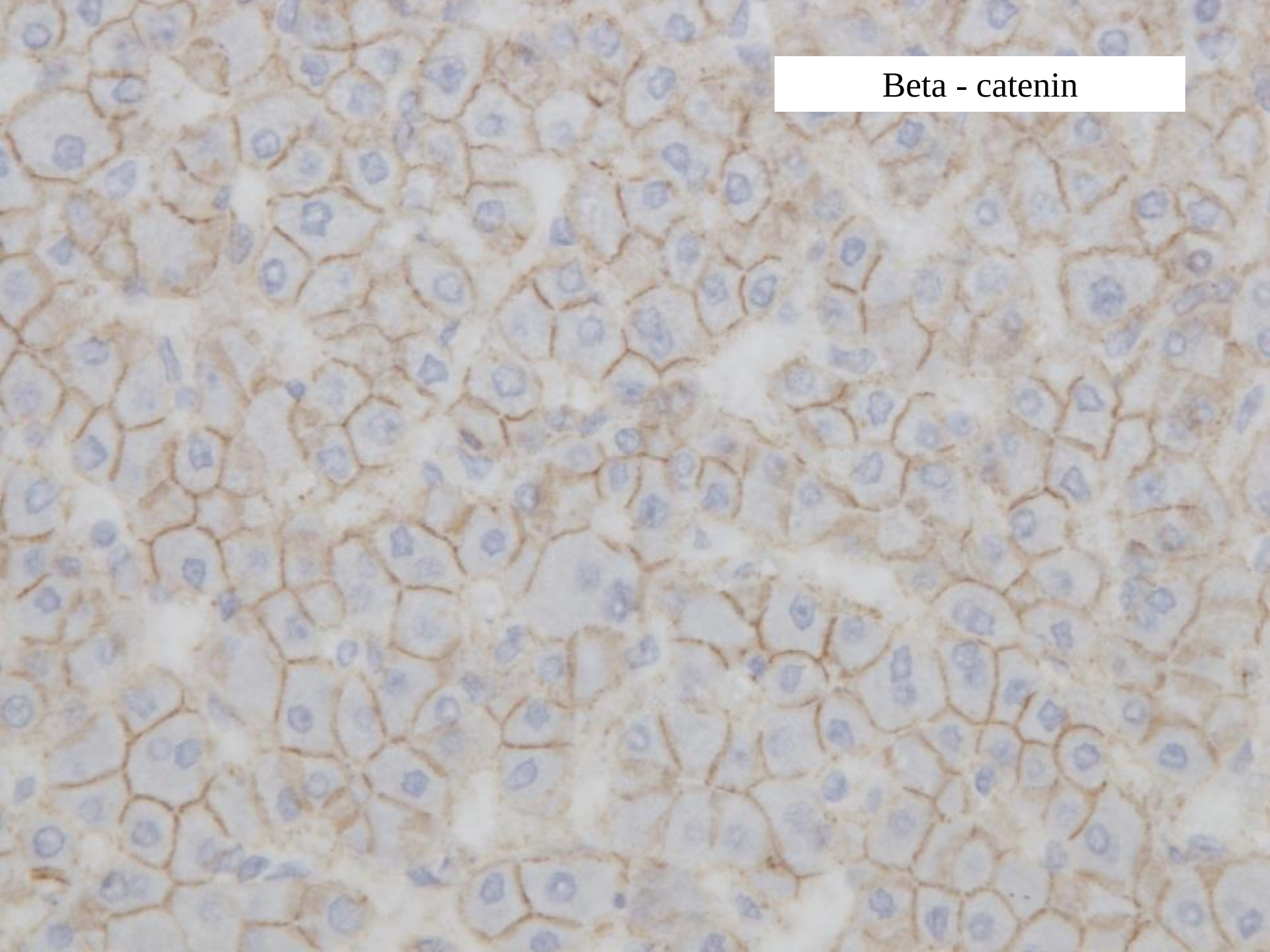
Non-lesional liver

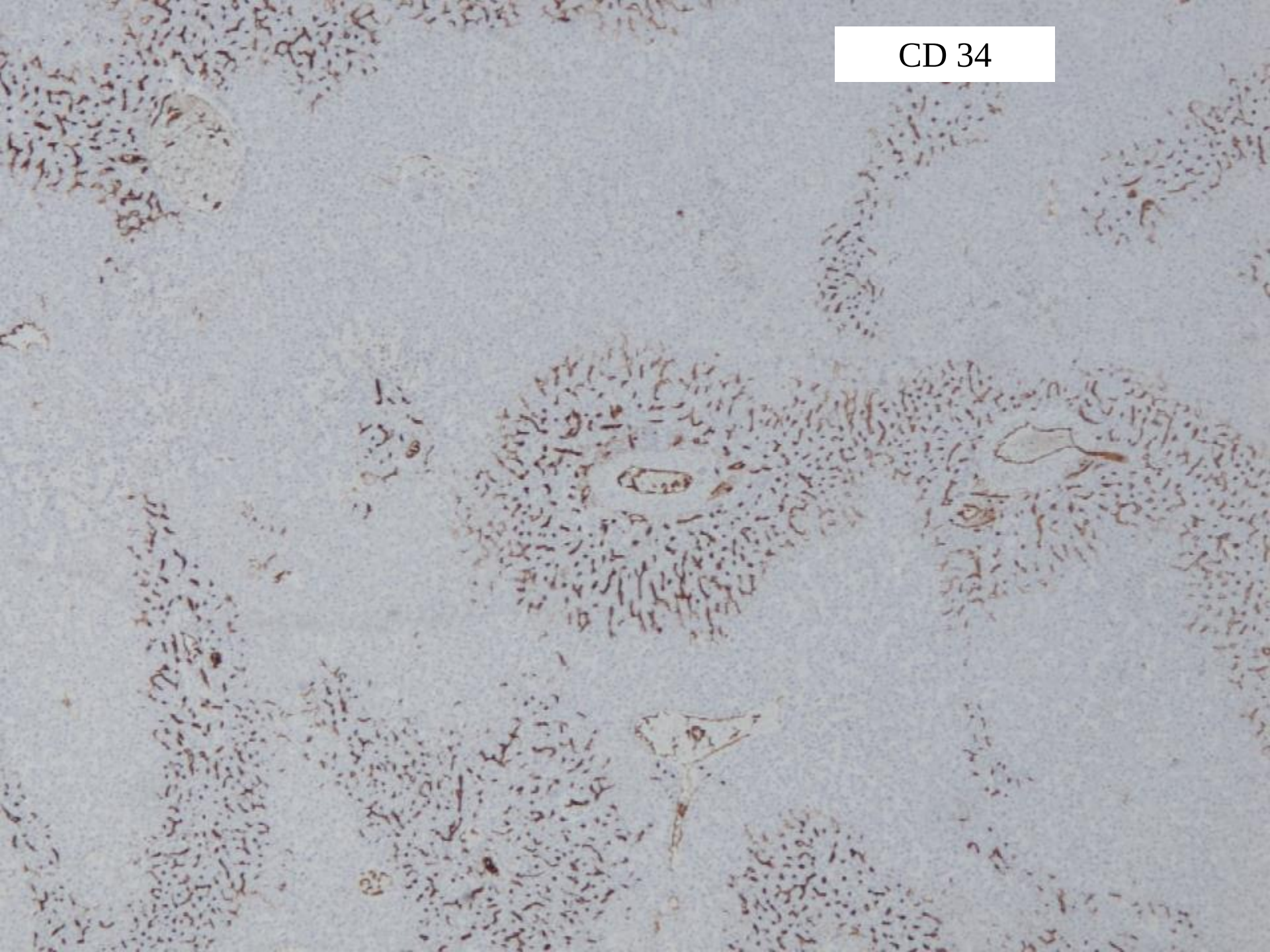
Glutamine Synthetase

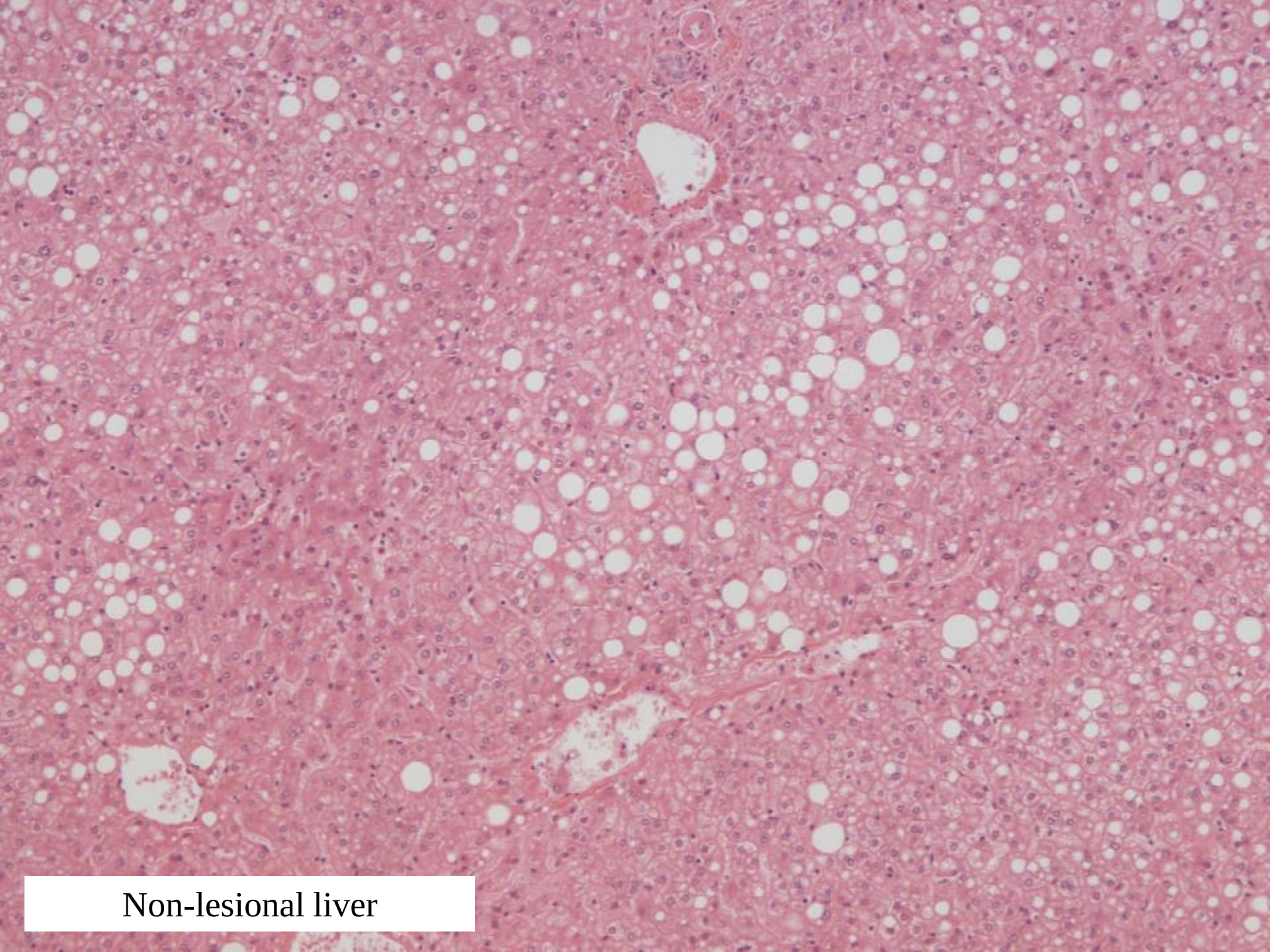


Tumour

Non-lesional liver


Beta - catenin


CD 34


Non-lesional liver

Case 3 – Histological Findings

- Well-differentiated hepatocellular lesion
- Fibrovascular structures containing foci of inflammation and ductular reaction
- Sinusoidal dilatation and peliosis
- No cytological atypia. Reticulin framework well preserved.

- Immunohistochemistry
  - Diffuse CRP and SAA expression favours inflammatory phenotype
  - No features to suggest beta-catenin mutation

- Uninvolved liver shows mild fatty change (probably NAFLD – BMI 33)

Case 3 – Diagnosis

- Hepatocellular adenoma (inflammatory subtype)
- No evidence of malignancy
- Arising in background of fatty liver (metabolic syndrome)

Hepatocellular Adenoma – Molecular Classification
(Bioulac-Sage et al)

1. Molecular studies have sub-classified HCAs according to different gene mutations

2. Subsequent studies, using resection specimens, have shown that these HCA subtypes have different clinico-pathological features and immunostaining profiles

3. Immunophenotypic characterisation may also be possible in liver biopsy specimens

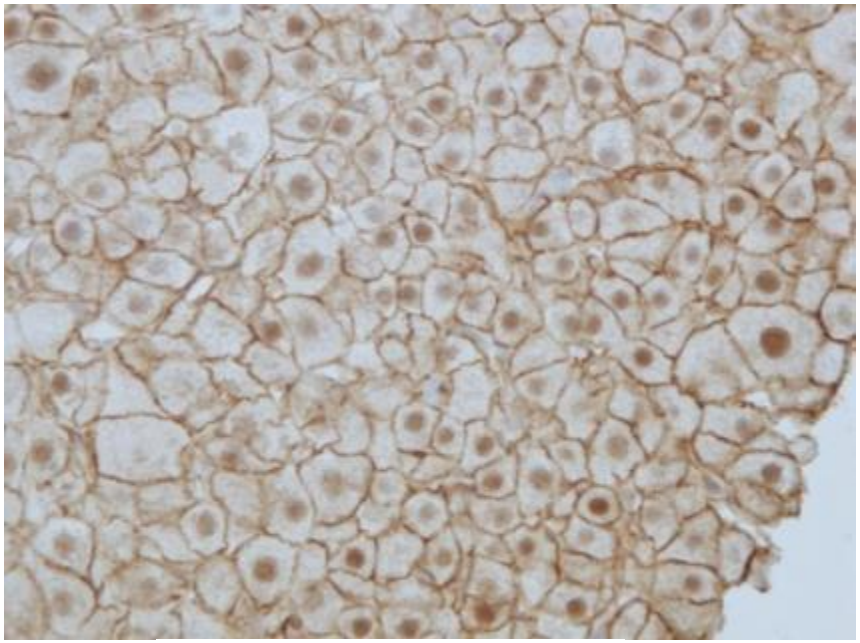
4. Findings may be relevant for clinical management – e.g. identifying lesions with an increased risk of haemorrhage or malignant transformation

Hepatocellular Adenoma
Recent Developments in Genotypic and Phenotypic Classification

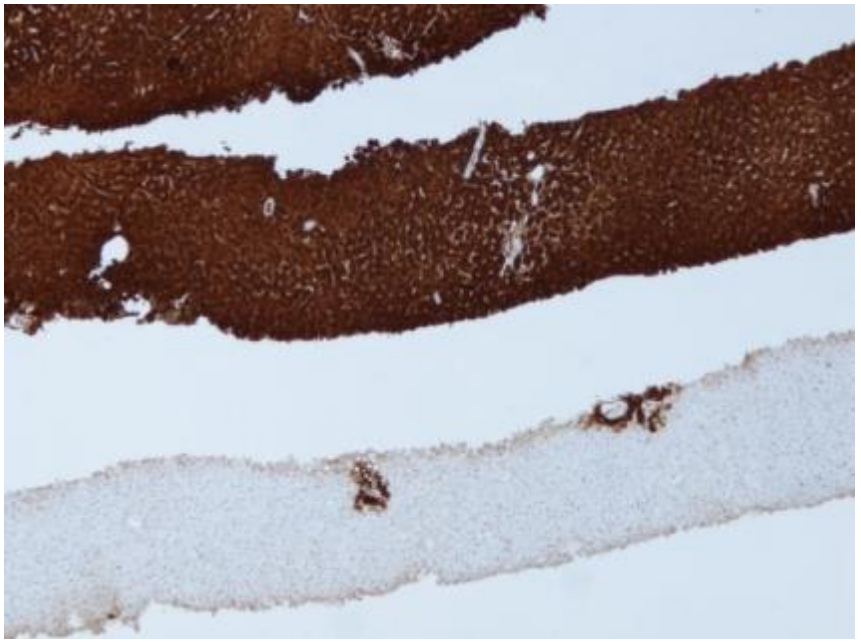
(Bioulac Sage 2011, Nault 2017)

Adenoma Subtype	**Frequency**	**Molecular Alterations**	**Immuno-phenotype**	**Clinico-pathological features**	**Malignant potential**
HNF1α Inactivated (H-HCA)	30-35%	Hepatocyte nuclear factor 1 α inactivation	Absent staining for liver fatty acid binding protein (LFABP)	Marked steatosis (due to lack of LFABP)	Very low
β–catenin activated (b-HCA)	5-10%	β–catenin activation	Nuclear β–catenin Glutamine synthetase	More common in men Cytological atypia, pseudoglandular formation	Up to 40%
Inflammatory (IHCA)	50-60%	IL-6 /STAT3 activation	Serum amyloid A C-reactive protein	Sinusoidal dilation (“telangiectatic”) & abnormal vessels Inflammatory infiltrates Ductular reaction (FNH-like) Associated with metabolic syndrome & steatosis in background liver β–catenin mutation in up to 10%	Low (increased in male patients, obesity , β–catenin activation)
Unclassified	< 10%				

Beta-Catenin Mutated Liver Cell Neoplasm



Beta – catenin
(nuclear expression)



Glutamine Synthetase
(Diffuse expression vs perivascular in non-lesional liver)

Male, age 31

- 11 cm mass in right lobe of liver
- Well differentiated hepatocellular lesion with no cytological atypia
- Presence of focal reticulin fibre loss, glypican 3 positivity, diffuse sinusoidal CD34 expression suggestive of well-differentiated HCC
- Some “atypical adenoma-like neoplasms” of uncertain malignant potential may be difficult to classify (Evason 2013, Bedossa 2014, Balabaud 2015)

Hepatocellular Adenoma – New Subtypes
Cases Previously Labelled as "Unclassified"

Sonic Hedgehog Activated HCA

(Nault Gastroenterology 2017, Henriet Hepatology 2017, Nault Hepatology 2018)

- 4% of all adenomas
- Associated with obesity and steatosis in non-lesional liver
- Clear cells and eosinophilic small cells
- Foci of congestion and peliosis
- Increased risk of bleeding (up to 80%)

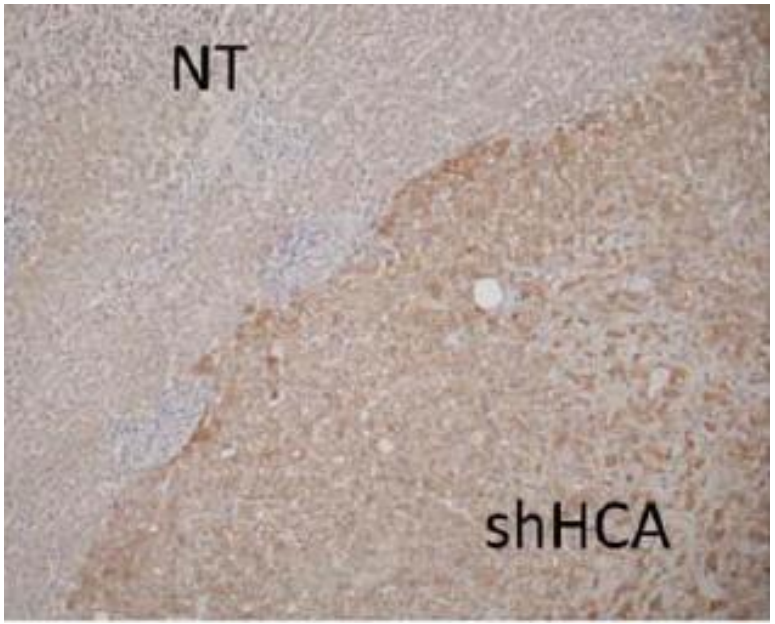
Hepatocellular Adenoma – New Subtypes
Cases Previously Labelled as "Unclassified"

Sonic Hedgehog Activated HCA

(Nault Gastroenterology 2017, Henriet Hepatology 2017, Nault Hepatology 2018)

- Argininosuccinate Synthase 1 (ASS1) as immunohistochemical marker

Non-Tumoral Liver
Staining confined to periportal hepatocytes



Sonic Hedgehog Activated HCA
Staining diffusely positive

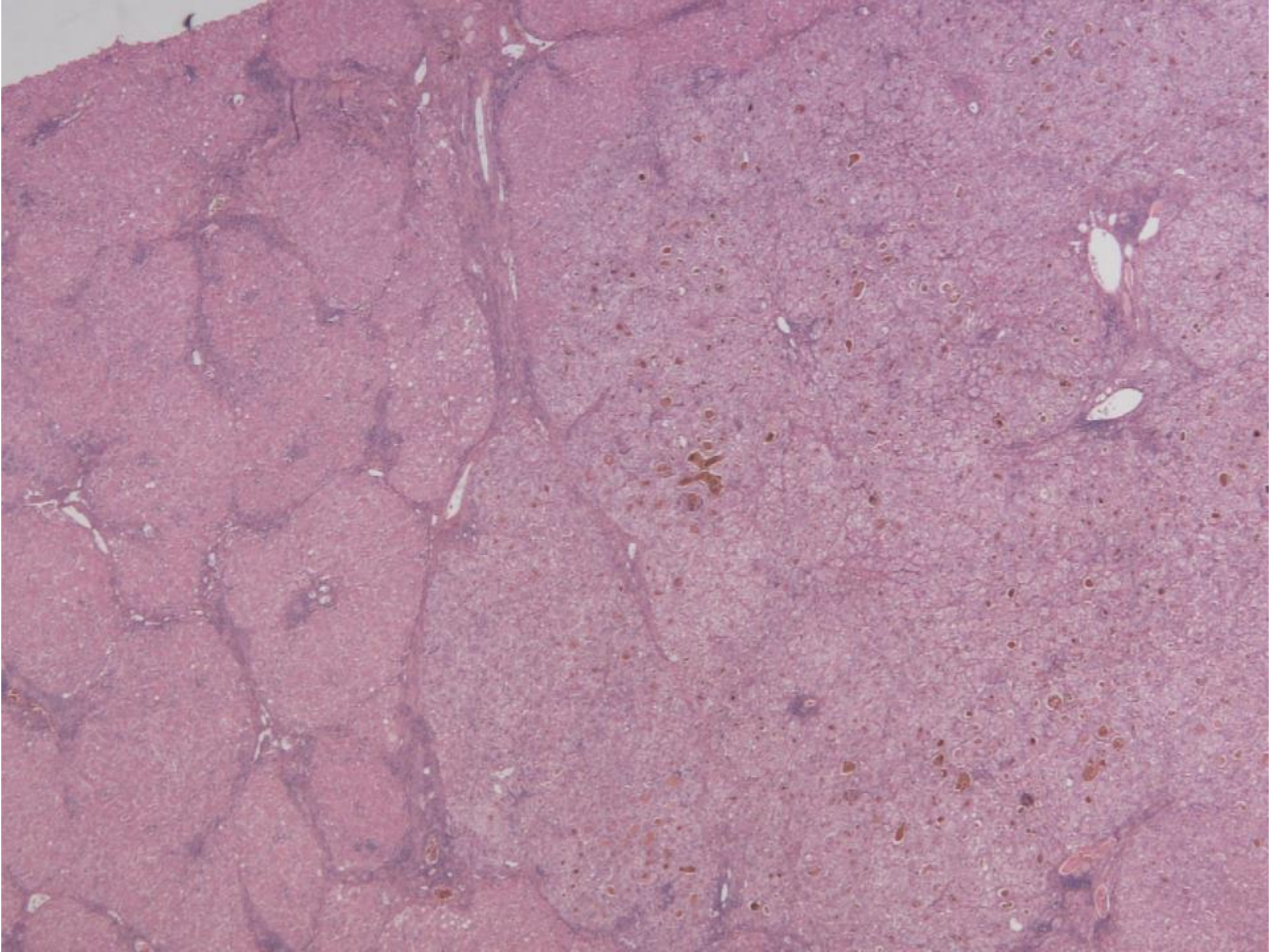
(from Nault, Hepatology 2018; 68: 964-976)

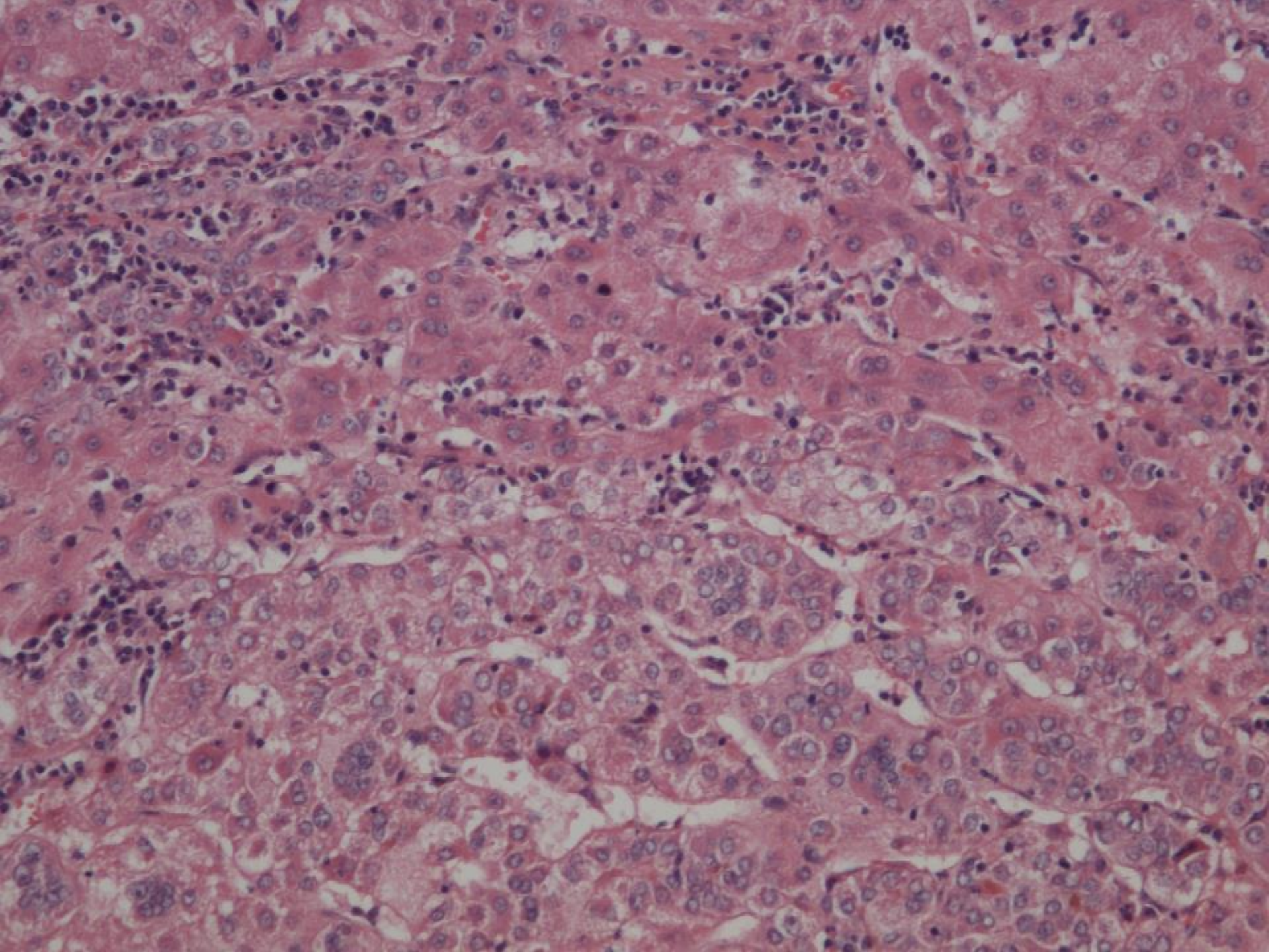
Case 4

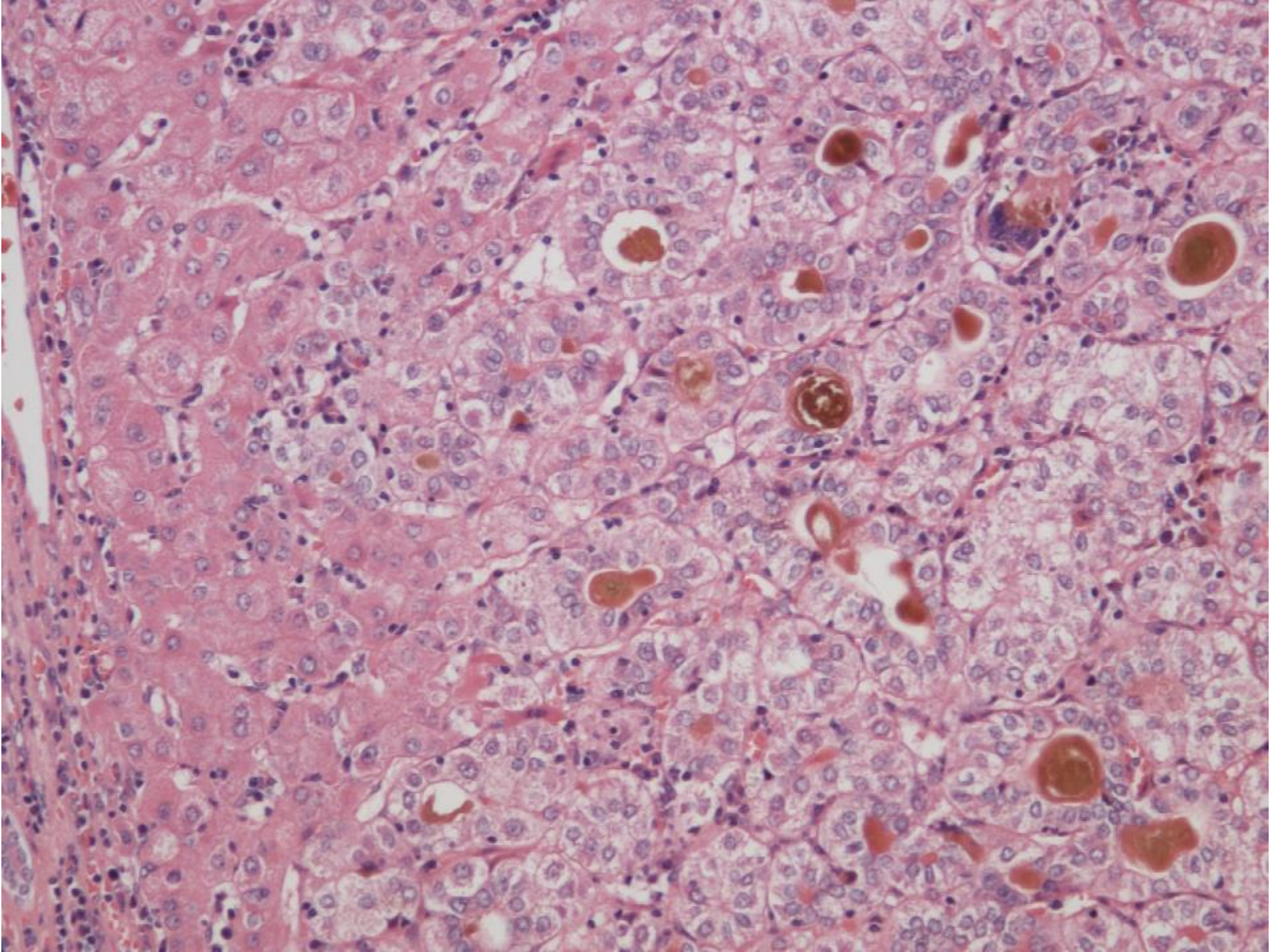
Case 4 – Clinical Summary

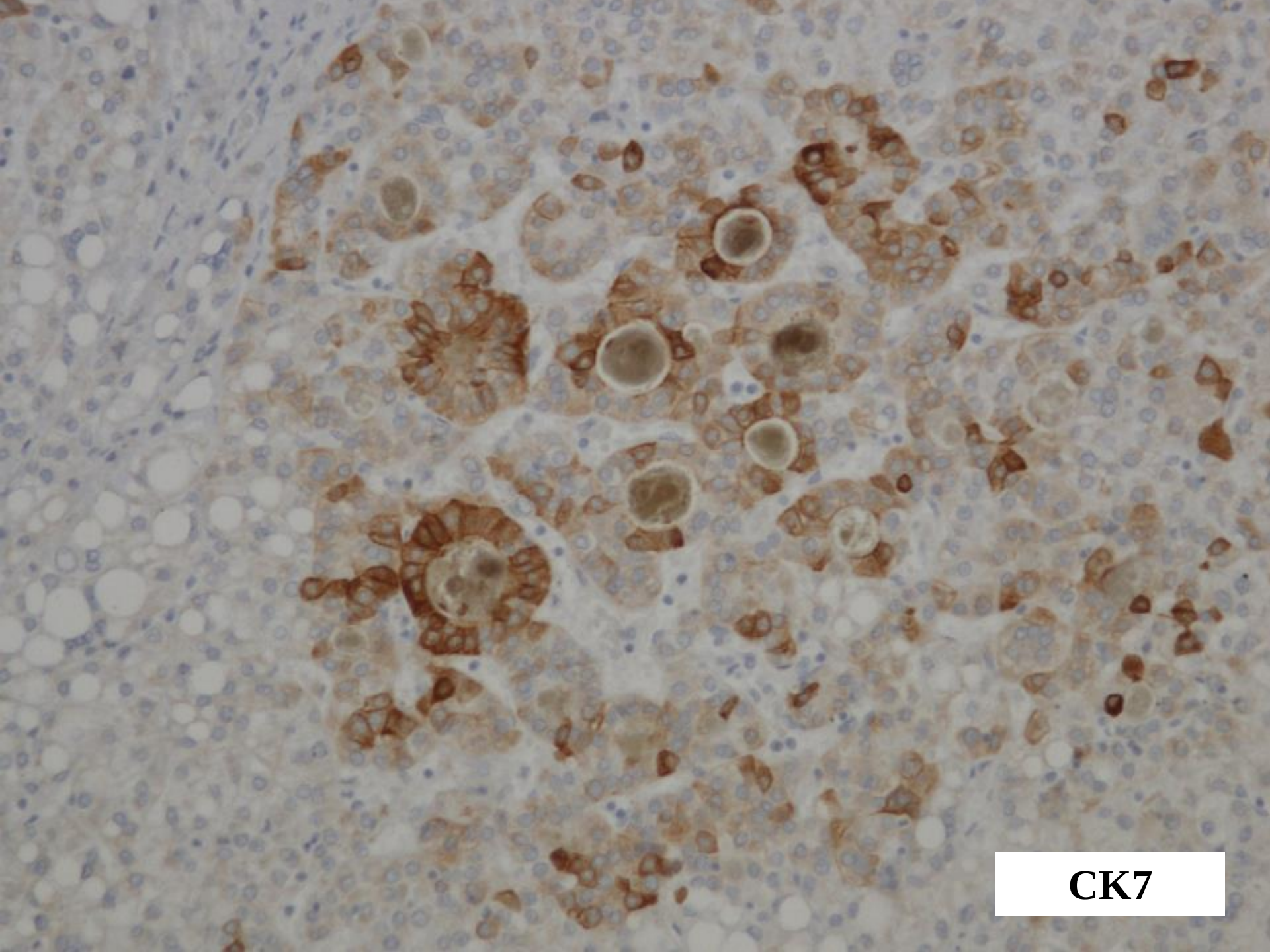
Male, age 45

- Liver transplantation for autoimmune hepatitis
- Incidental nodule 1.2cm diameter in right lobe of liver





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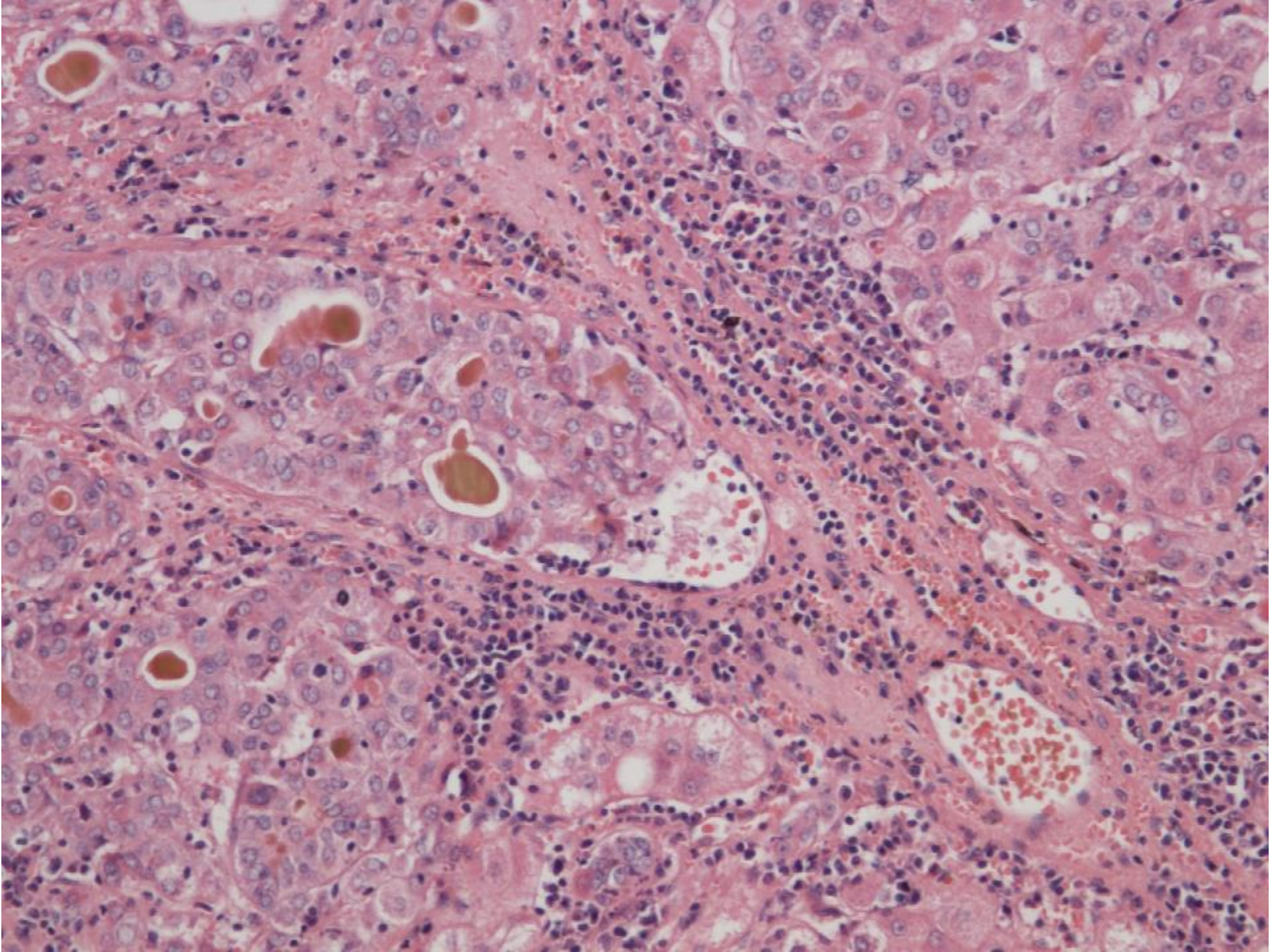


Case 4 – H & E findings

Well-differentiated hepatocellular lesion showing:

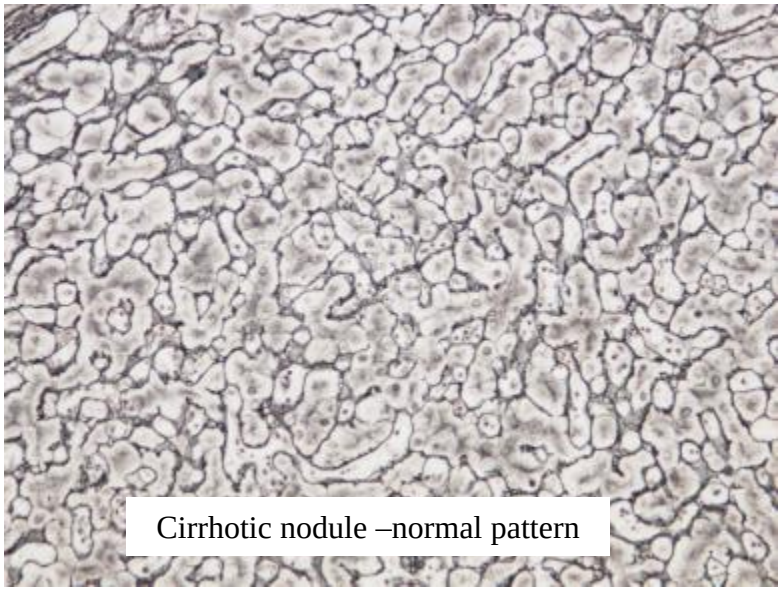
- Cytological atypia
  - increased N/C ratio, nuclear crowding, mild nuclear pleomorphism
- Architectural atypia
  - thick plates (> 3 cells thick), glandular structures
- Probable microvascular invasion

➢ Sufficient to warrant a diagnosis of well-differentiated HCC
(versus large cirrhotic nodule or dysplastic nodule)

What additional stains may be helpful in the biopsy diagnosis of early / well-differentiated HCC?

- Particularly applies to small lesions (1-2cm) where radiological findings are inconclusive

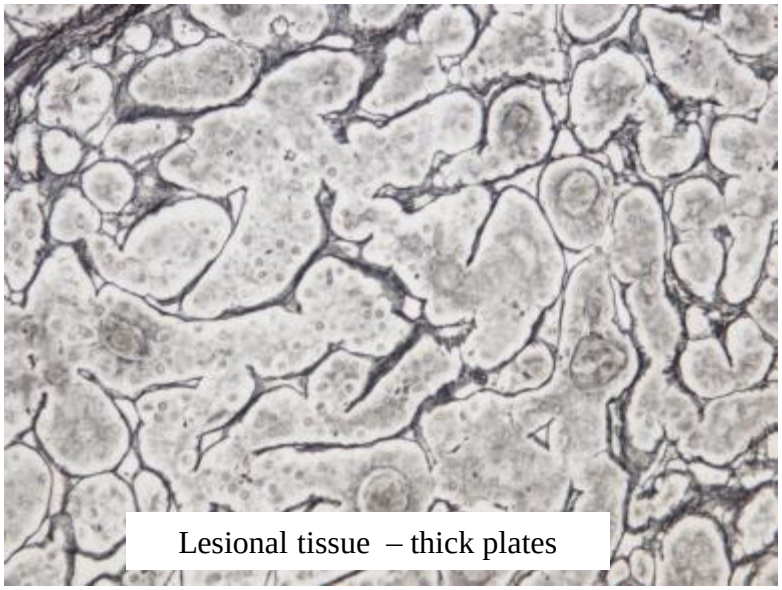
Assessment of Well-differentiated Hepatocellular Lesions - Reticulin Staining



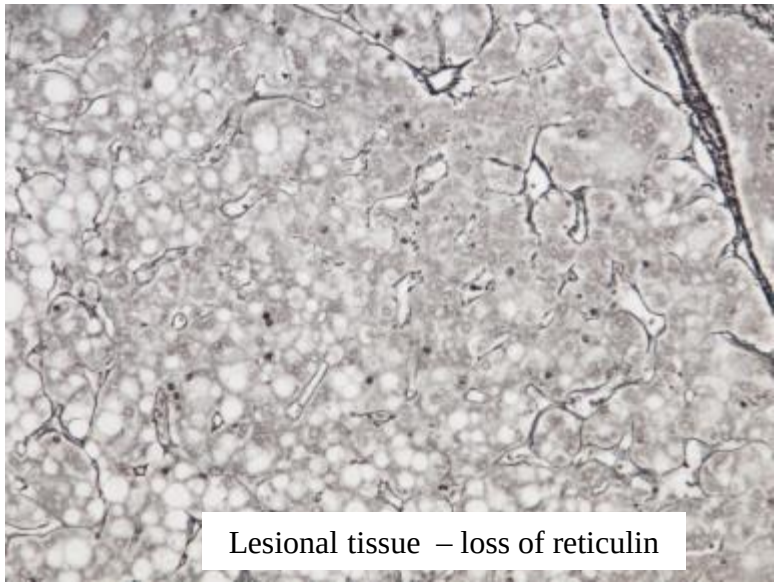
Cirrhotic nodule –normal pattern

Problems with Reticulin Staining in HCC

- Reticulin fibres may be preserved in well-differentiated/early HCC
- Focal reticulin fibre loss may occur in benign liver disease
  - e.g. Fatty liver disease (Singhi 2012)
  - Steatotic hepatocellular adenoma



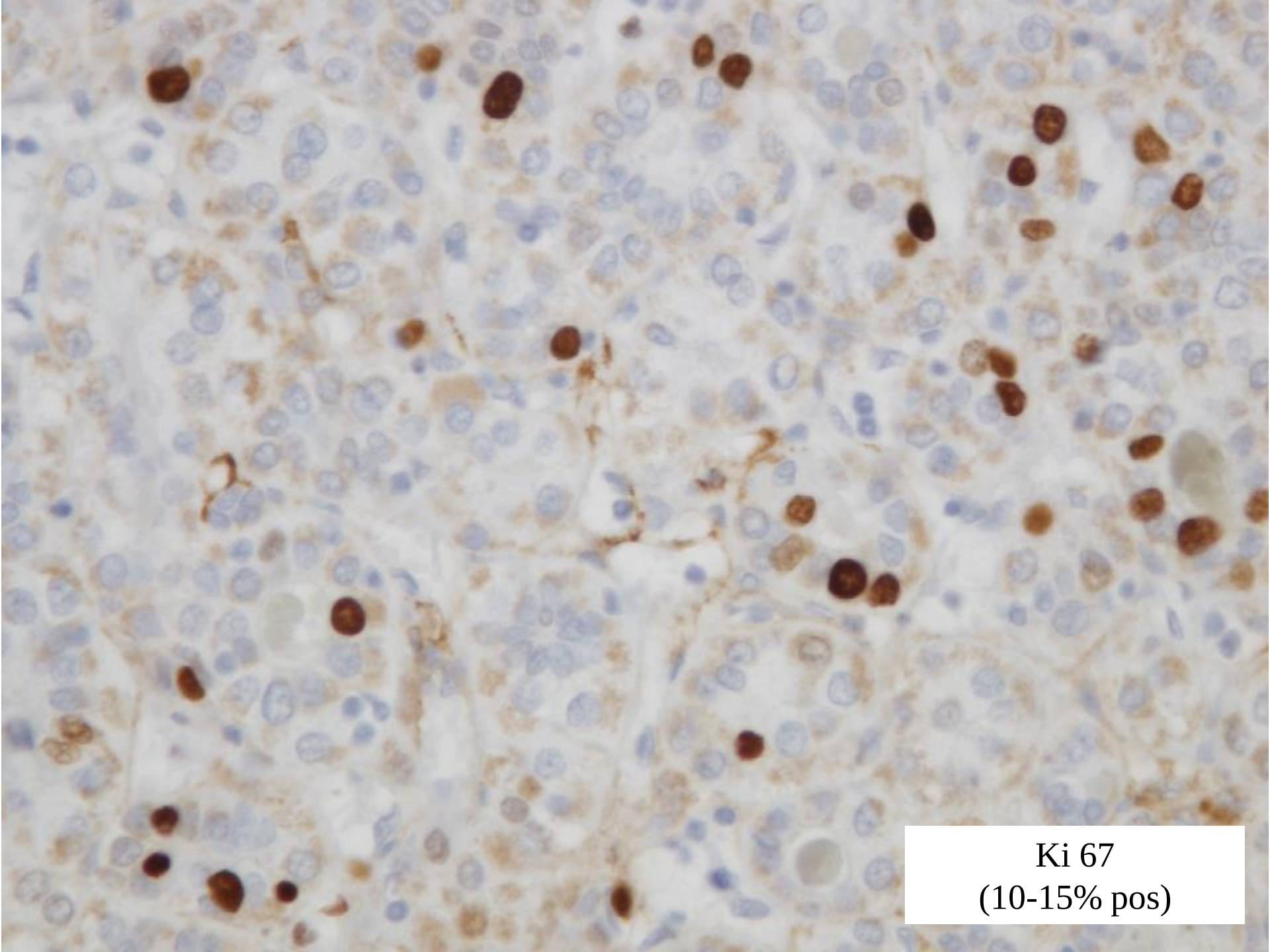
Lesional tissue – thick plates

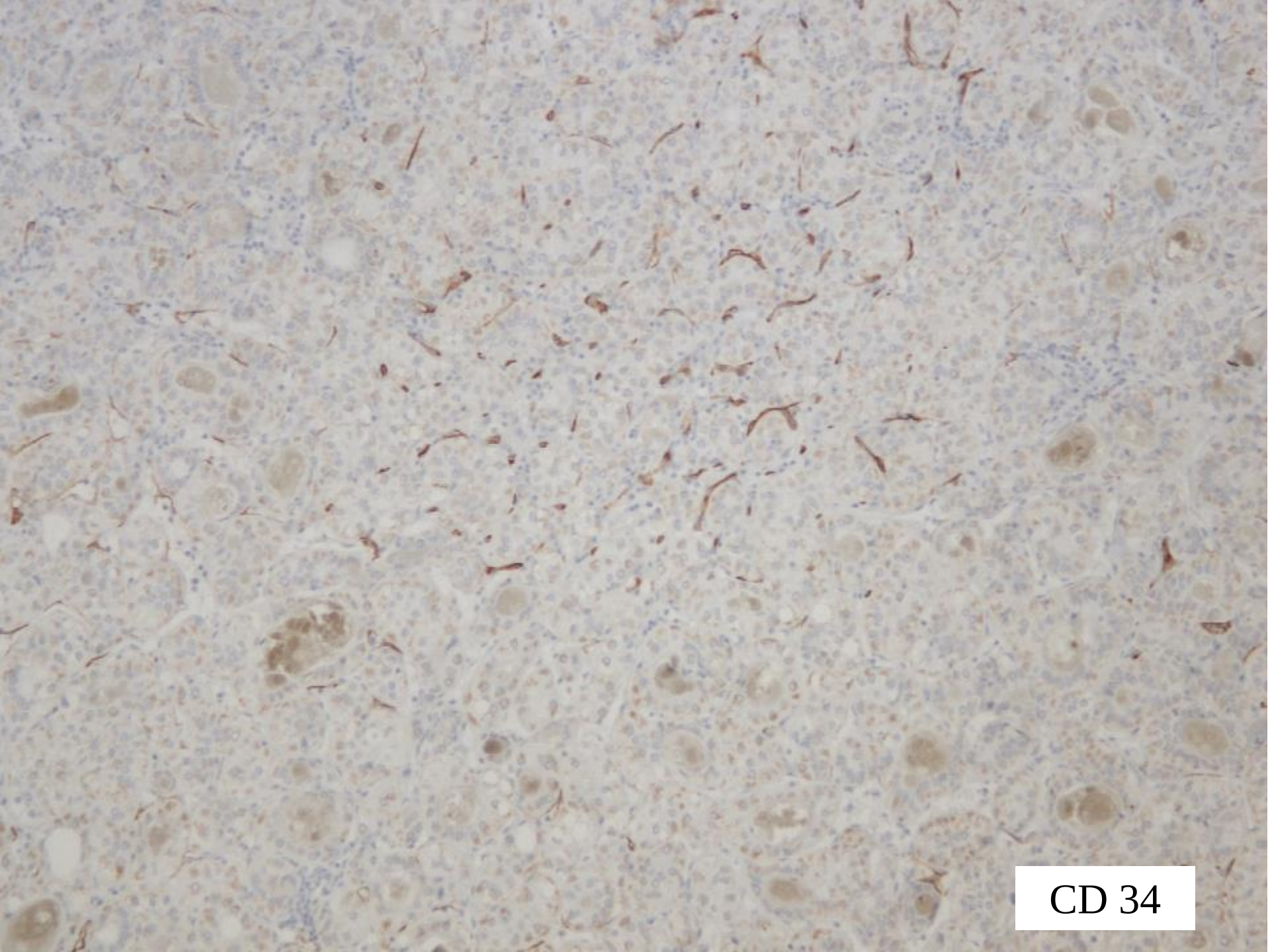


Lesional tissue – loss of reticulin

Benign Versus Malignant Nodules in Cirrhotic Livers
Features Favouring a Diagnosis of Malignancy
"Conventional" Immunohistochemical Markers

Antibody	Comment
Ki 67	Stepwise increase (cirrhotic nodule – dysplastic nodule – early HCC) No defined threshold for diagnosing HCC Rarely exceeds 5% in well-differentiated HCC
CD34	Diffuse capillarisation of sinusoids (vs focal in cirrhotic nodules) May also occur in high-grade dysplastic nodules (and in FNH & liver cell adenoma)
AFP	Rarely positive in early HCC


Ki 67
(10-15% pos)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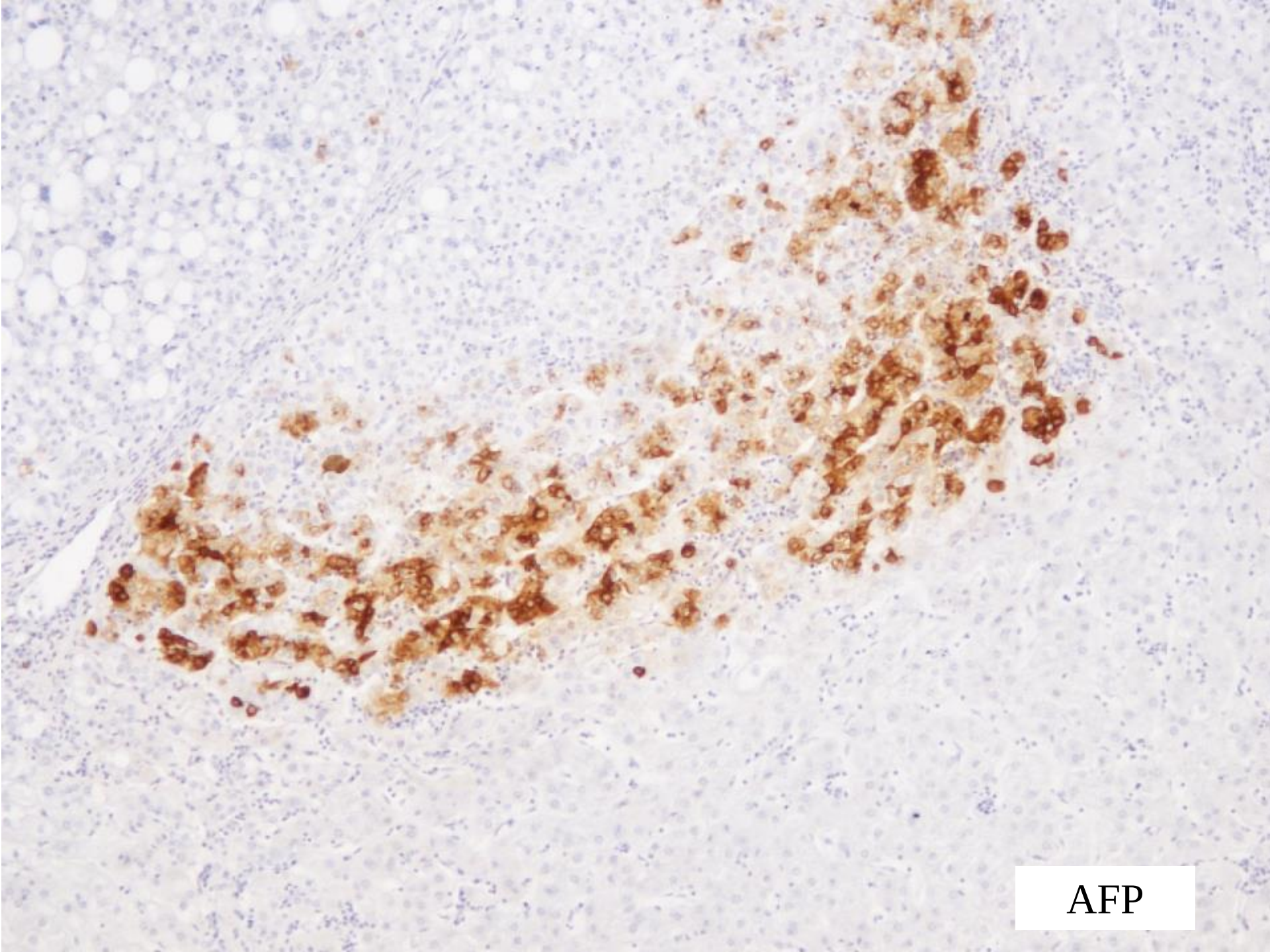
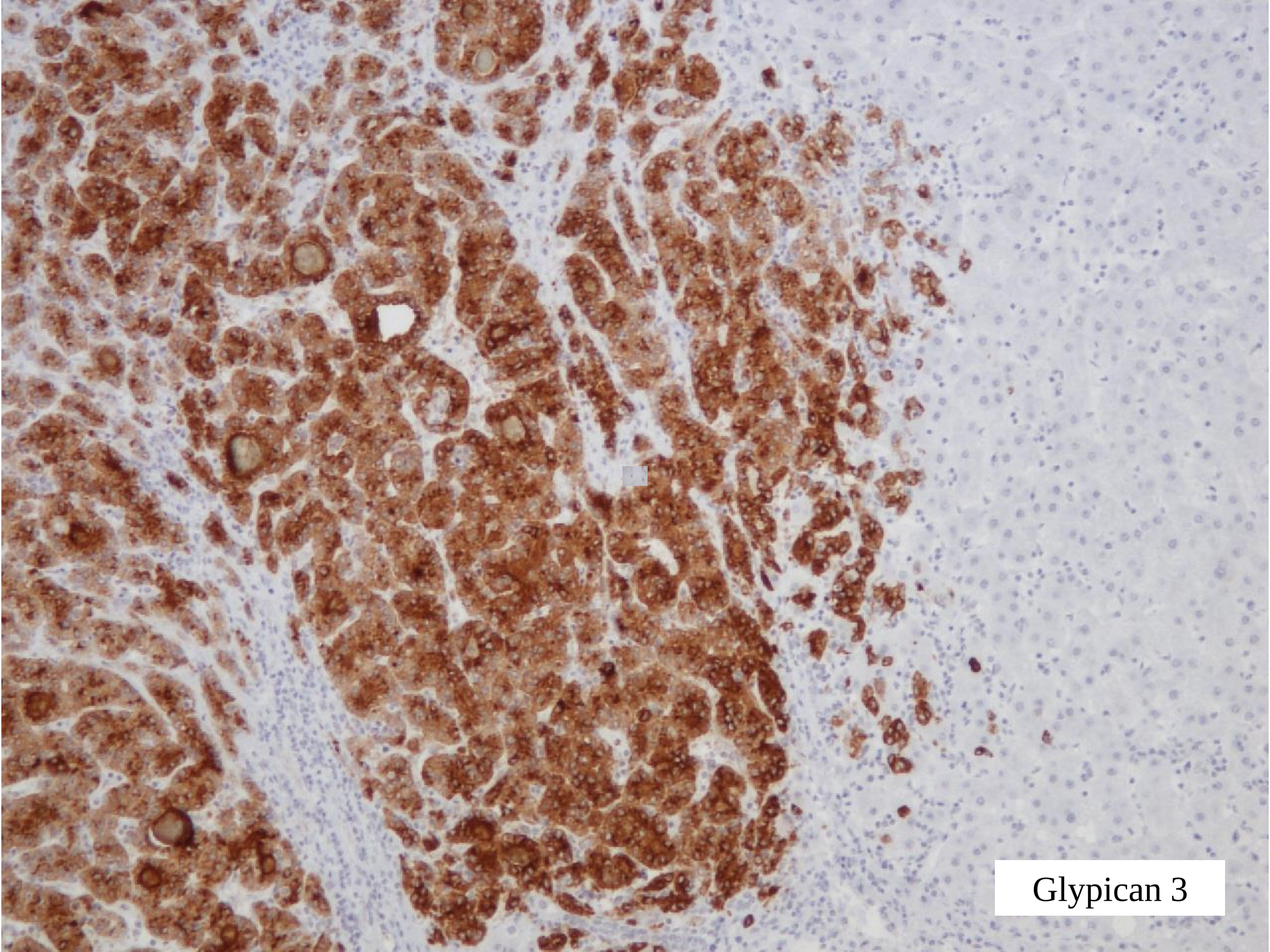

AFP

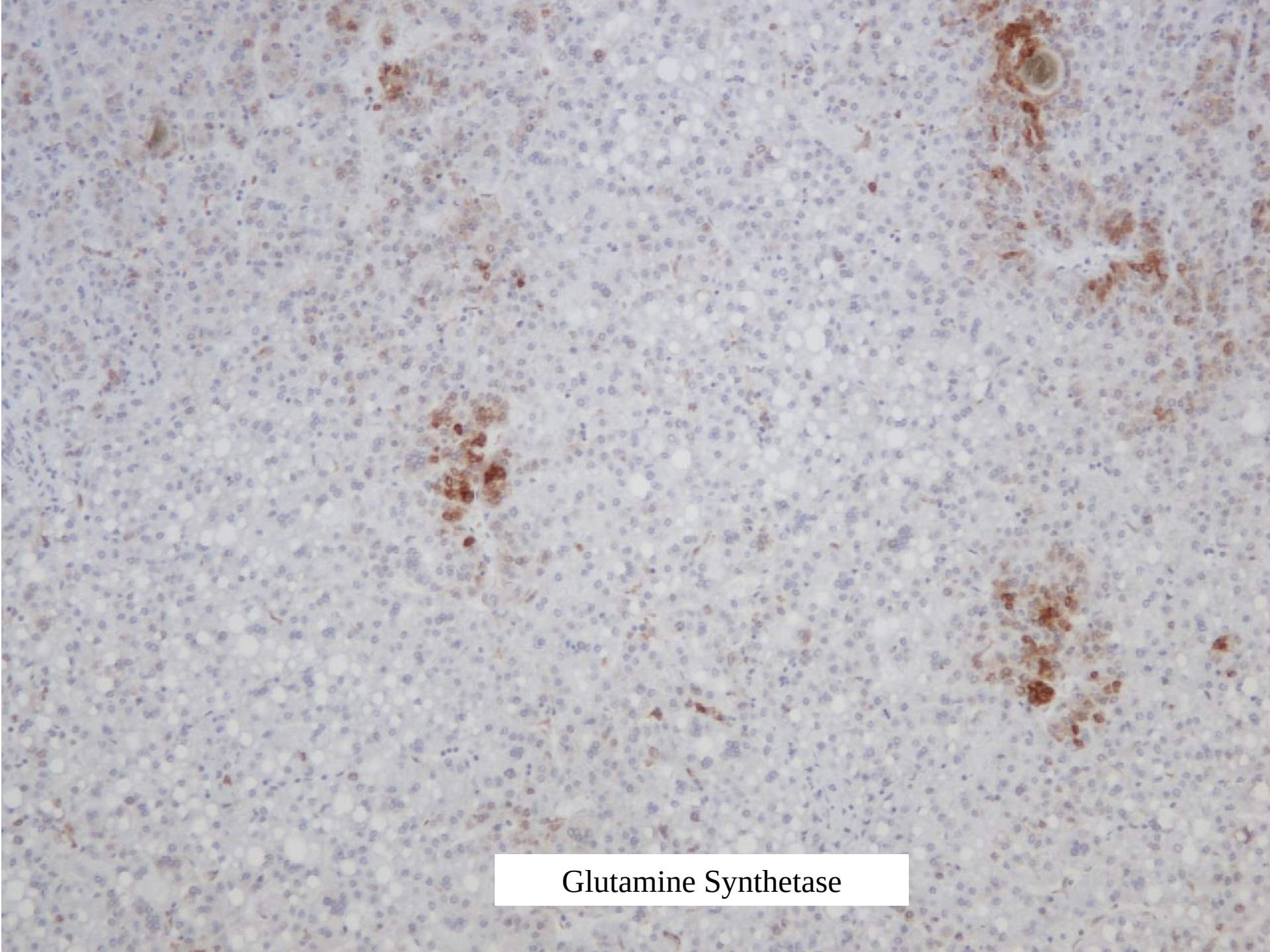
Benign Versus Malignant Nodules in Cirrhotic Livers
Features Favouring a Diagnosis of Malignancy
More Recent Immunohistochemical Markers

Molecular studies have identified many genes up-regulated in early HCC

Some have products can be demonstrated immunohistochemically:

Genes/Proteins Upregulated in Early HCC		**Immunohistochemistry** (criteria for positivity)
Glypican-3	Heparan sulphate proteoglycan Promotes growth of HCC by stimulating Wnt signalling	Cytoplasmic/membranous (> 5-10% of cells)
HSP 70	Chaperone stress protein Potent anti-apoptotic survival factor	Cytoplasmic/nuclear (> 5-10% of cells)
Glutamine Synthetase	Target gene for beta- catenin, GS overexpressed with activation/ mutation of beta-catenin, Involved with hepatocyte regeneration/proliferation	Cytoplasmic (diffuse >50%, unrelated to vessels)


Glypican 3


Glutamine Synthetase

Benign Versus Malignant Nodules in Cirrhotic Livers
Features Favouring a Diagnosis of Malignancy – Immunohistochemical Markers

Application (Glypican-3, HSP 70, Glutamine Synthetase)

- None has 100% specificity or sensitivity individually
- Panel of antibodies improves diagnostic accuracy
  - ≥ 2/3 positive - 100% specificity & 60-70 % sensitivity for HCC (Di Tommaso 2009, Tremosini 2012)

Limitations

1. Reproducibility of staining methods
2. Conventional histology remains the "gold standard"
   - Studies investigating new antibodies use routine histological assessments to define dysplastic nodules and early/well-differentiated HCC
   - Immunohistochemical panel should only be used as an adjunct to conventional histological assessment

Case 4 – Diagnosis

Hepatocellular carcinoma (well-differentiated)

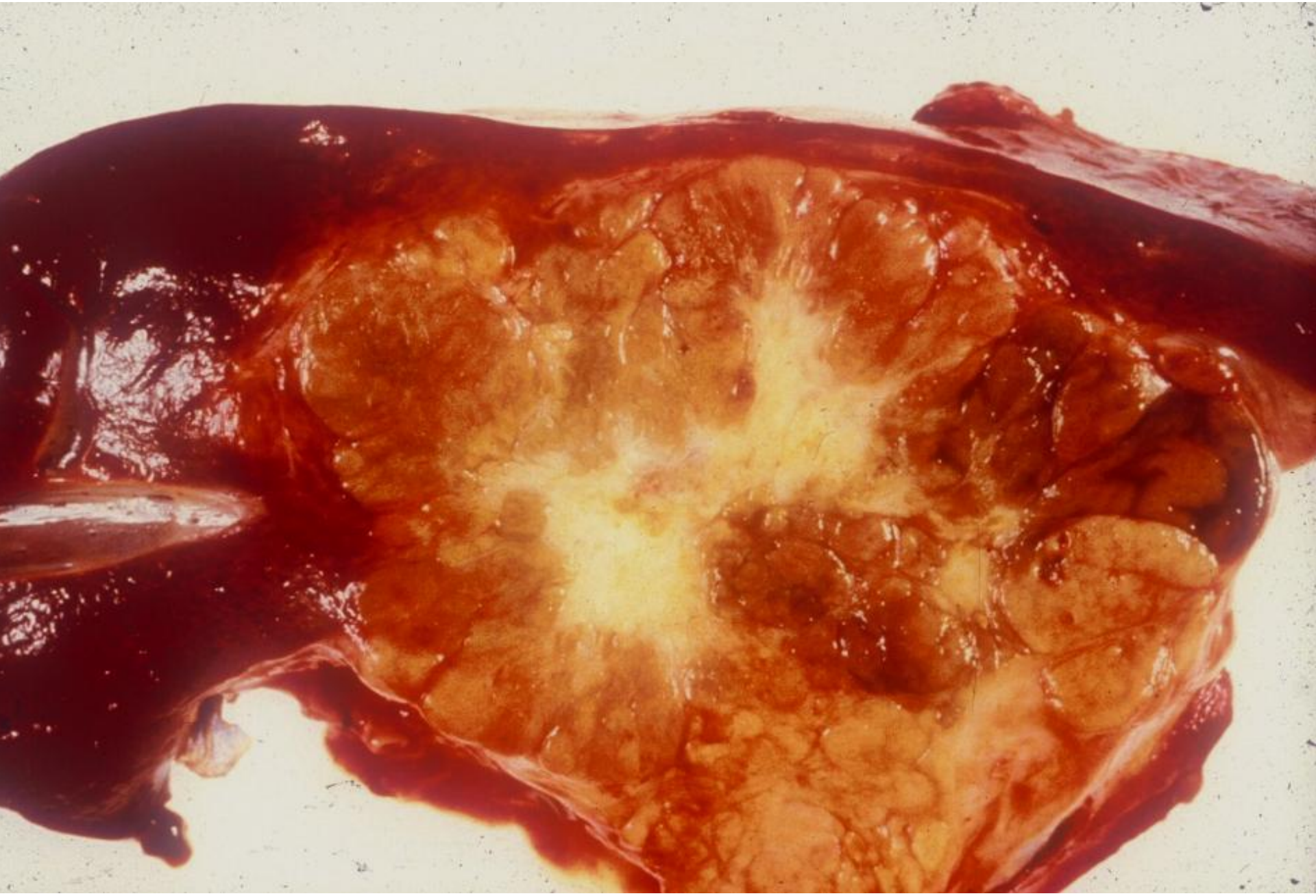
arising in a background of cirrhosis (AIH)

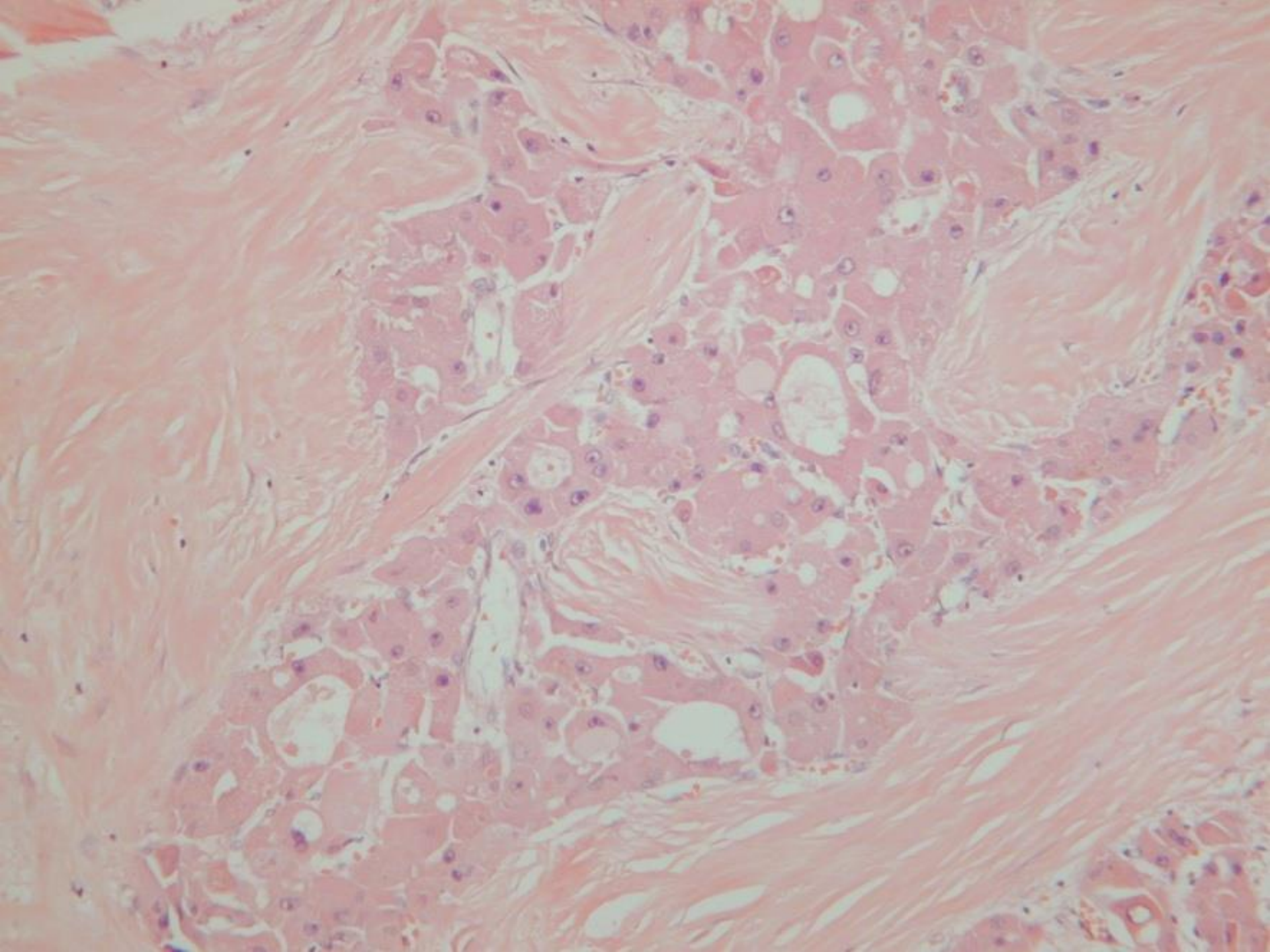
Case 5

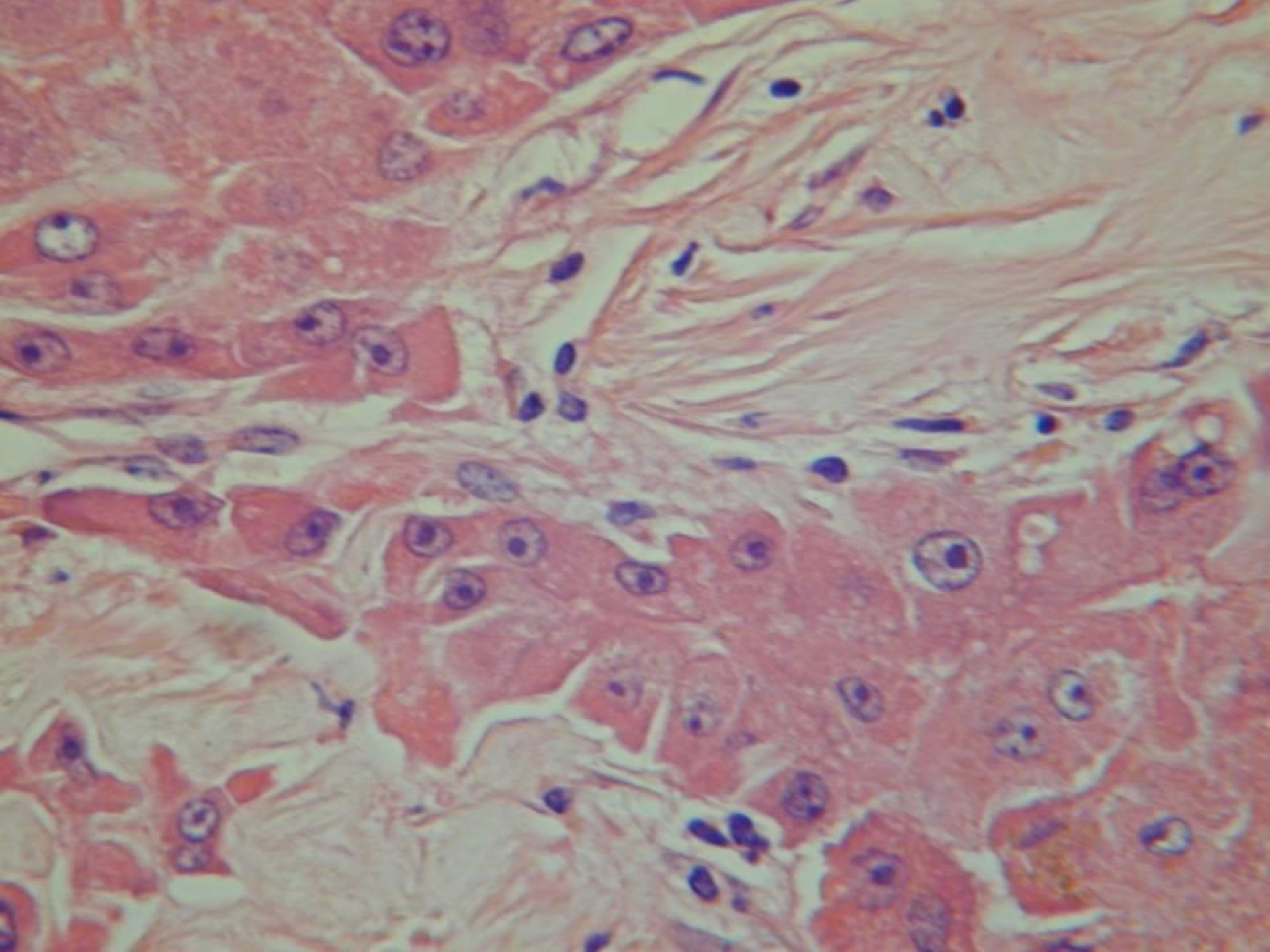
Case 5 - Clinical Summary

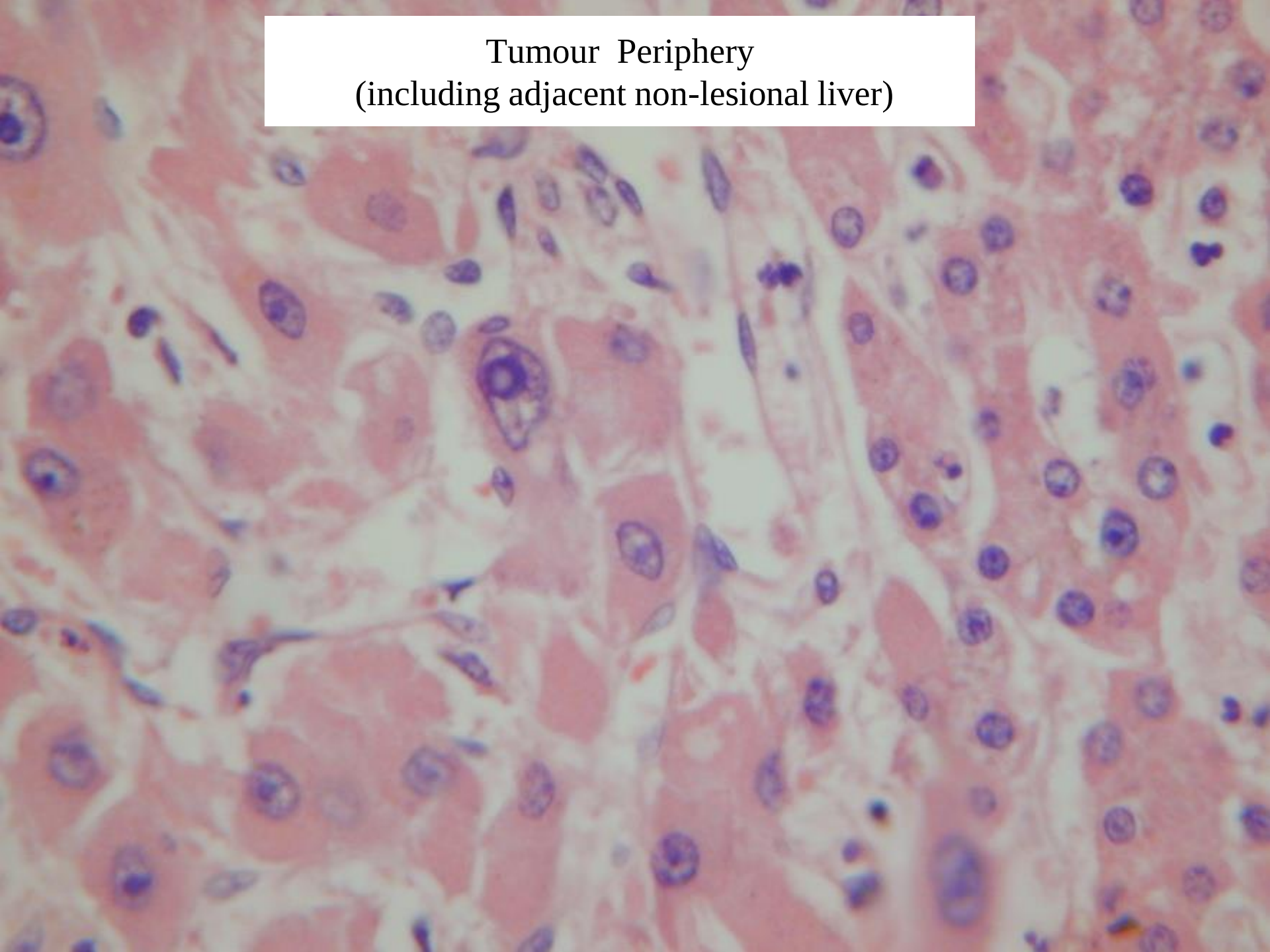
Female, age 26

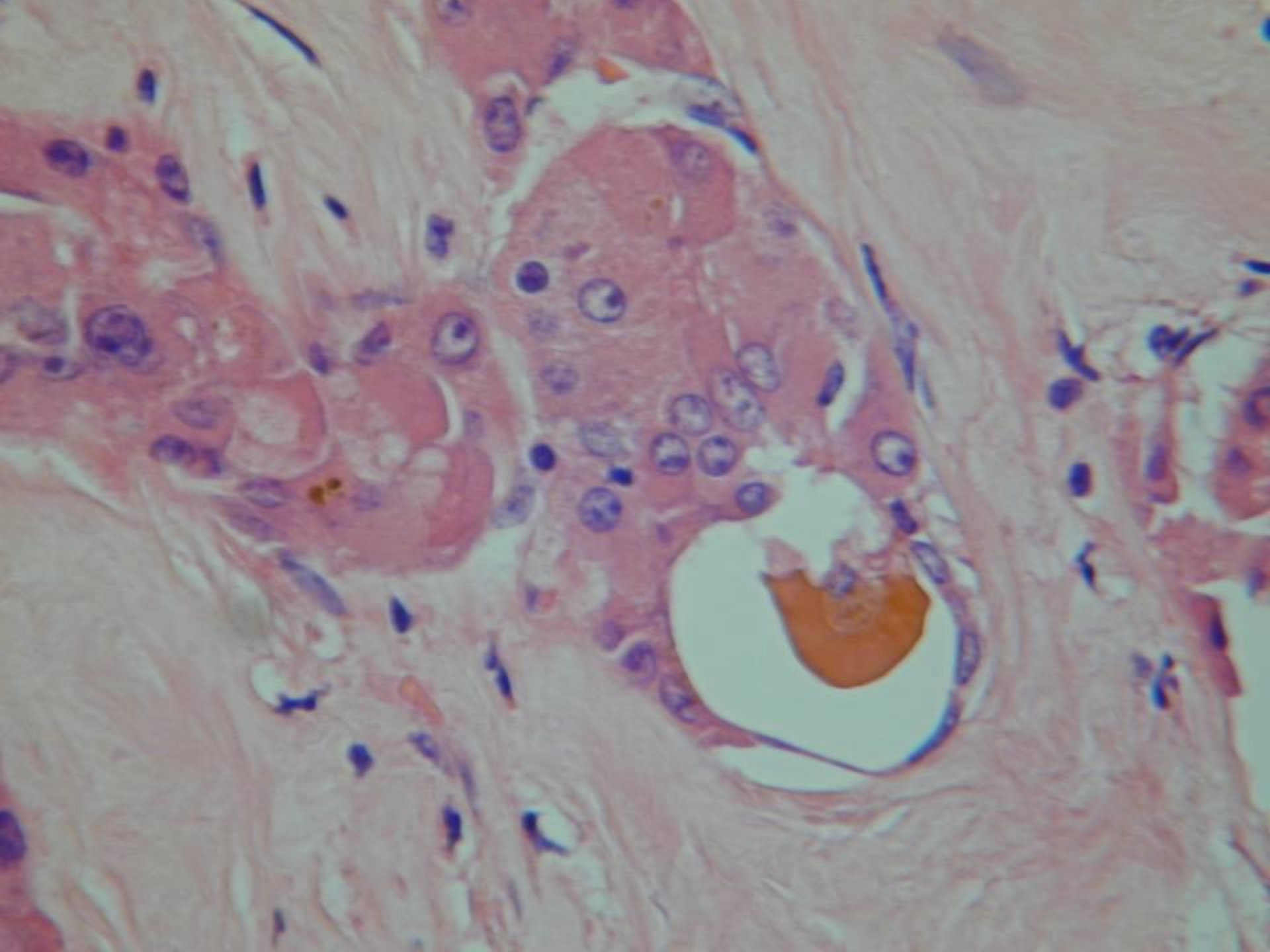
- Right hemi-hepatectomy specimen.
- Large mass 12 cm diameter with central scar. Enlarged perihilar and coeliac lymph nodes.
- Slide submitted is from periphery of lesion to include surrounding non-neoplastic liver tissue.

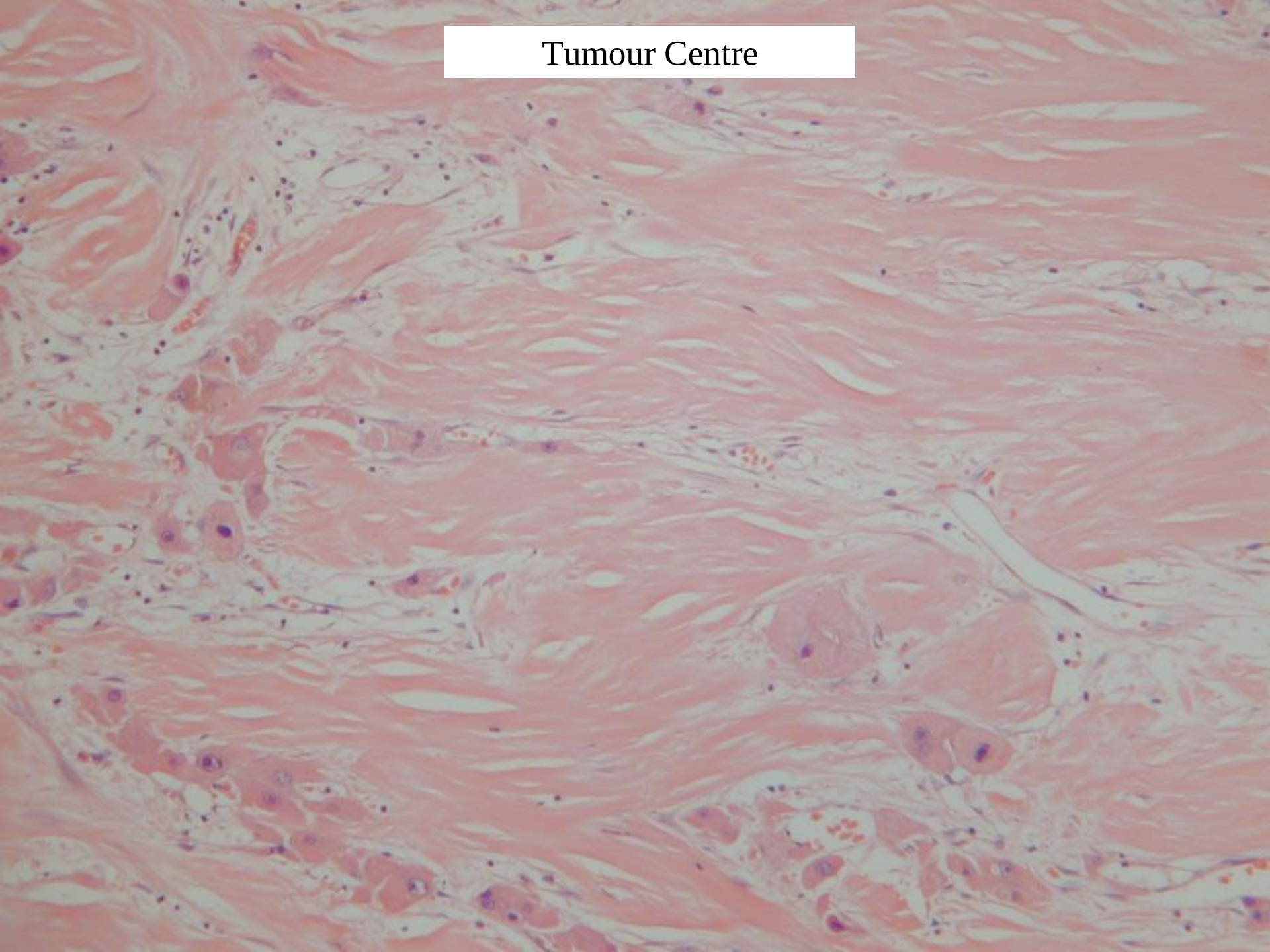


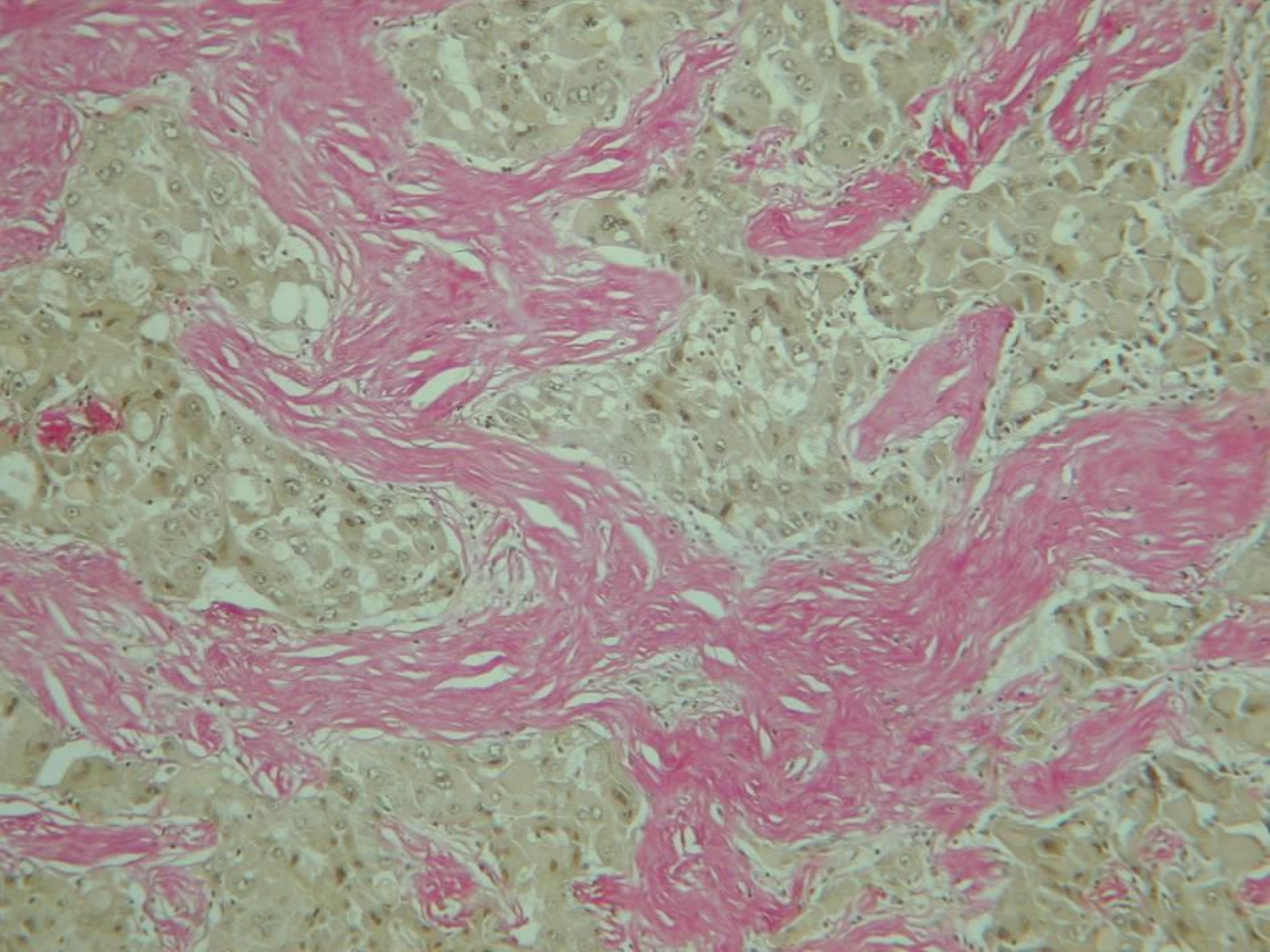




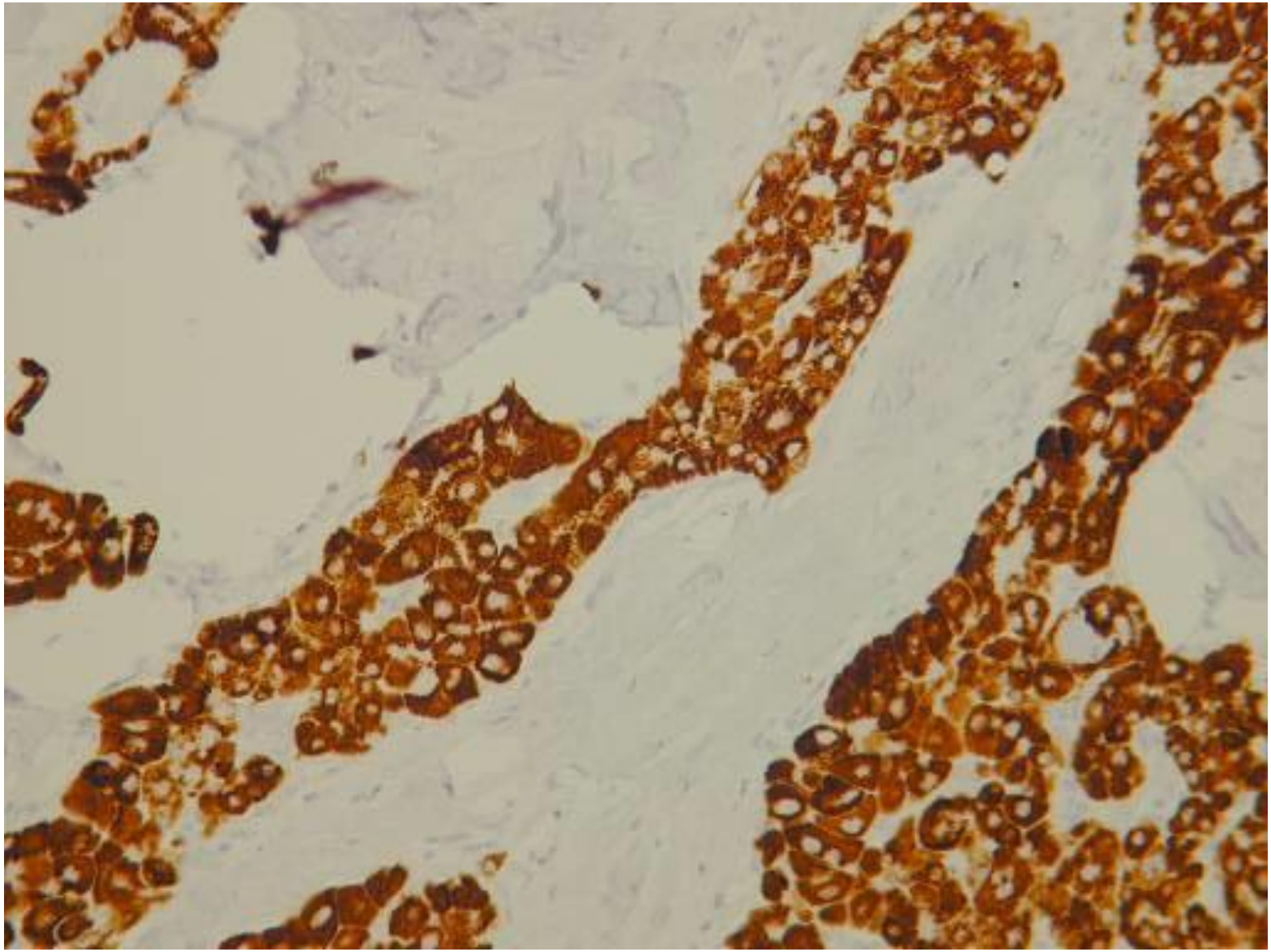

Tumour Periphery
(including adjacent non-lesional liver)



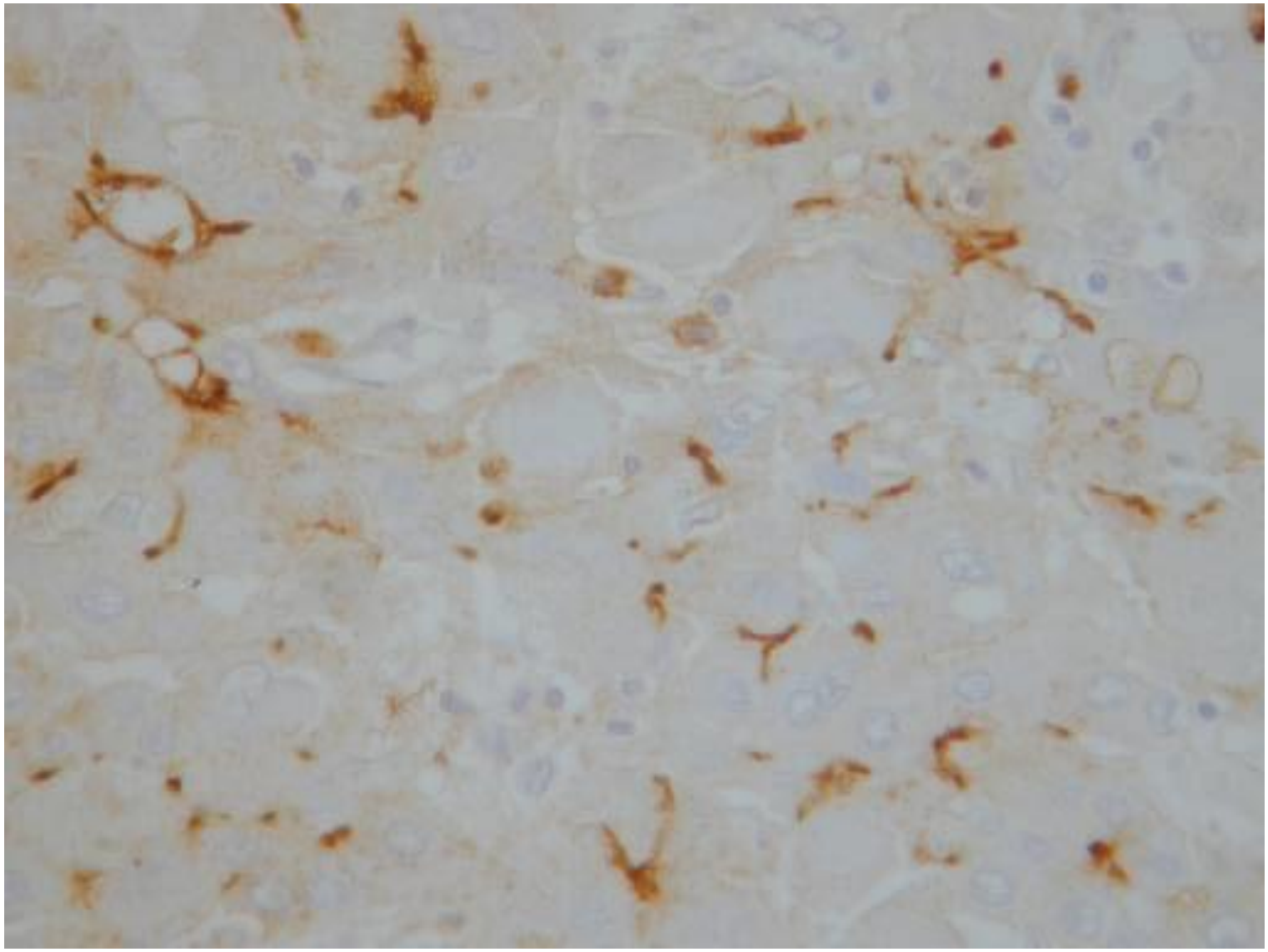

Tumour Centre



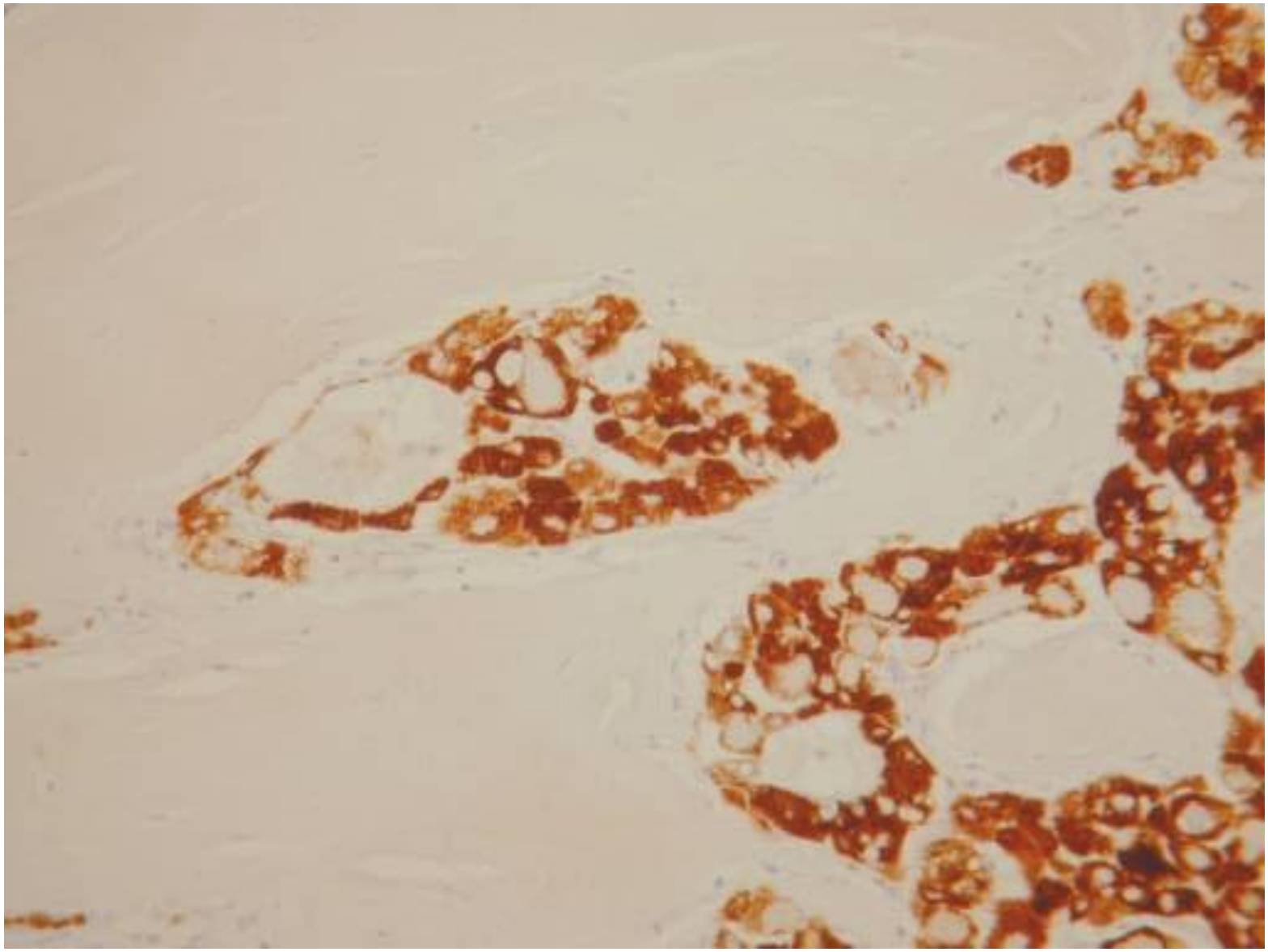
Hep Par 1



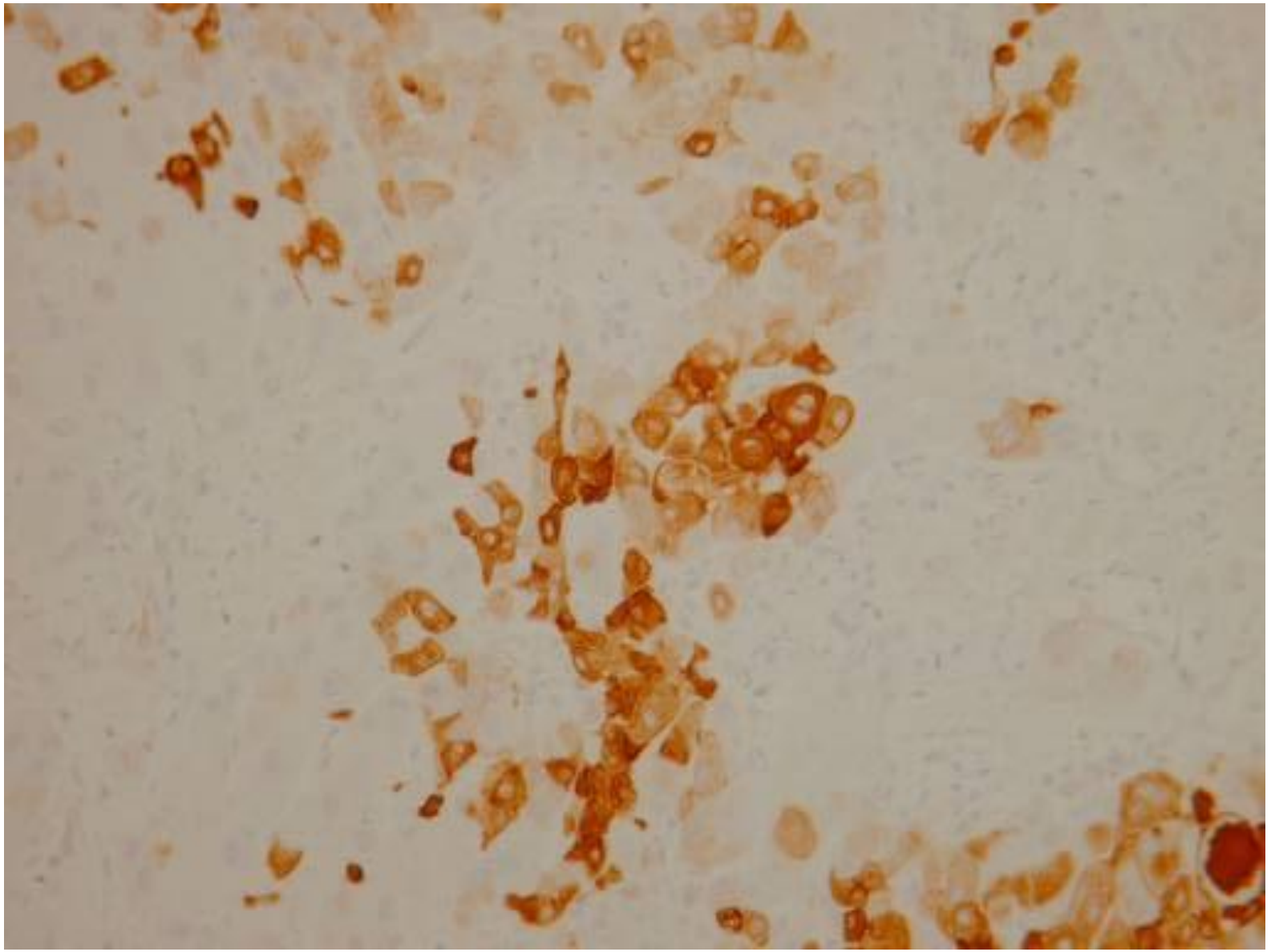
Polyclonal CEA

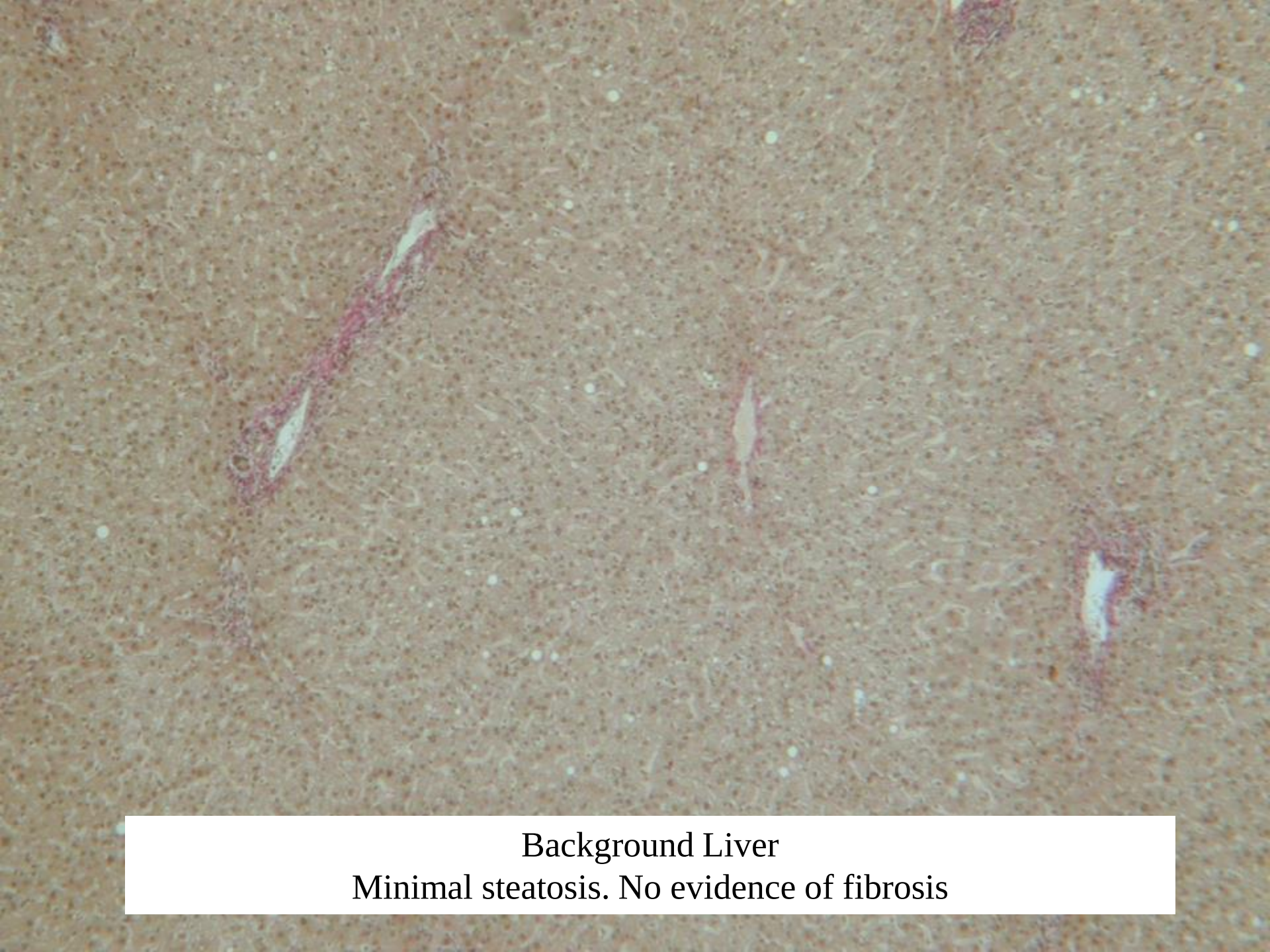


Mitochondria



CK7





Background Liver
Minimal steatosis. No evidence of fibrosis

Case 5 – Histological Findings

- Well-differentiated hepatocellular lesion
- Large cells with abundant granular eosinophilic cytoplasm
  - "Oncocytic-like" appearance (due to presence of numerous mitochondria)
- Large nuclei and nucleoli
- Dense stroma arranged as parallel lamellae
  - Most abundant centrally
- Immunostaining positive for Hep Par 1, pCEA (canalicular), mitochondria and CK7

Case 5 – Diagnosis

Fibrolamellar hepatocellular carcinoma

Case 5 – Discussion Points

Fibrolamellar carcinoma versus conventional HCC

1. Clinico-pathological features
2. Tumour biology
3. Problems with histological diagnosis

Fibrolamellar versus Conventional HCC
Clinico-pathological Features

	Fibrolamellar HCC	Conventional HCC
Age	5-35 years (median 20) (second peak, age 60-70 – Eggert 2013)	Most > 50 years
Sex	M=F	M>F
Aetiology	Unknown	HBV, HCV, alcohol, haemochromatosis
Uninvolved liver	Normal	Usually cirrhotic (Cases occurring in non-cirrhotic liver usually have risk factors for chronic liver disease and pre-cirrhotic fibrosis)
Location	2/3rds in left lobe	No preferential location

Fibrolamellar versus Conventional HCC
Tumour Biology

1. Molecular pathology

- Differences in gene mutations and molecular signalling pathways
  - e.g. FLC not associated with p53 or beta-catenin mutations , elevated AFP or elevated survivin expression (Liu 2009, Malouf 2012)

- Recent studies have identified a chromosome 19 –linked fusion product involving exon 1 from *DNAJB1* gene and exons 2-10 of *PRKACA* gene (Honeyman , Science 2014: Cornella, Gastroenterology 2015: Graham, Mod Pathol 2015, Graham Mod Pathol 2018)
  - Present in 79-100% of cases of FLC
  - Not seen in other types of primary hepatic neoplasm (including conventional and sclerosing/scirrhous HCC)
  - Not reported previously in any other type of cancer (Andersen, Gastroenterology 2015)
  - FISH- *PRKACA* positivity present in 102/103 “typical” FLC cases (Graham2018)

Fibrolamellar versus Conventional HCC
Tumour Biology

2. **Immunohistochemical phenotype** (Malouf 2009, Vivekanandan 2009, Abdul-Al 2010, Ward 2010, Zenali 2010, Patonai 2011, Ross 2011, Goodman 2012, Patonai 2013, Limaiem 2015)

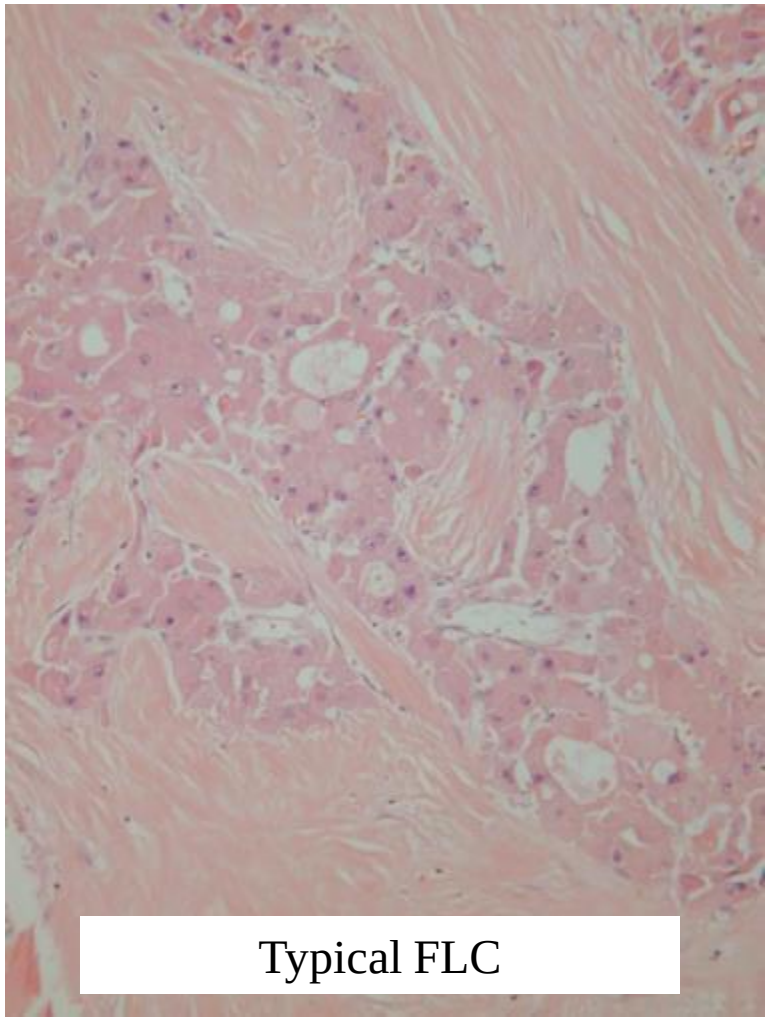
- FLC more frequently expresses CK 7, EMA, CD68, CD56
- FLC less frequently expresses AFP, beta –catenin, CK 19
- Hep Par 1, pCEA (canalicular) and CD34 (sinusoidal) typically present in both FLC and conventional HCC

Fibrolamellar HCC - Problems with Histological Diagnosis

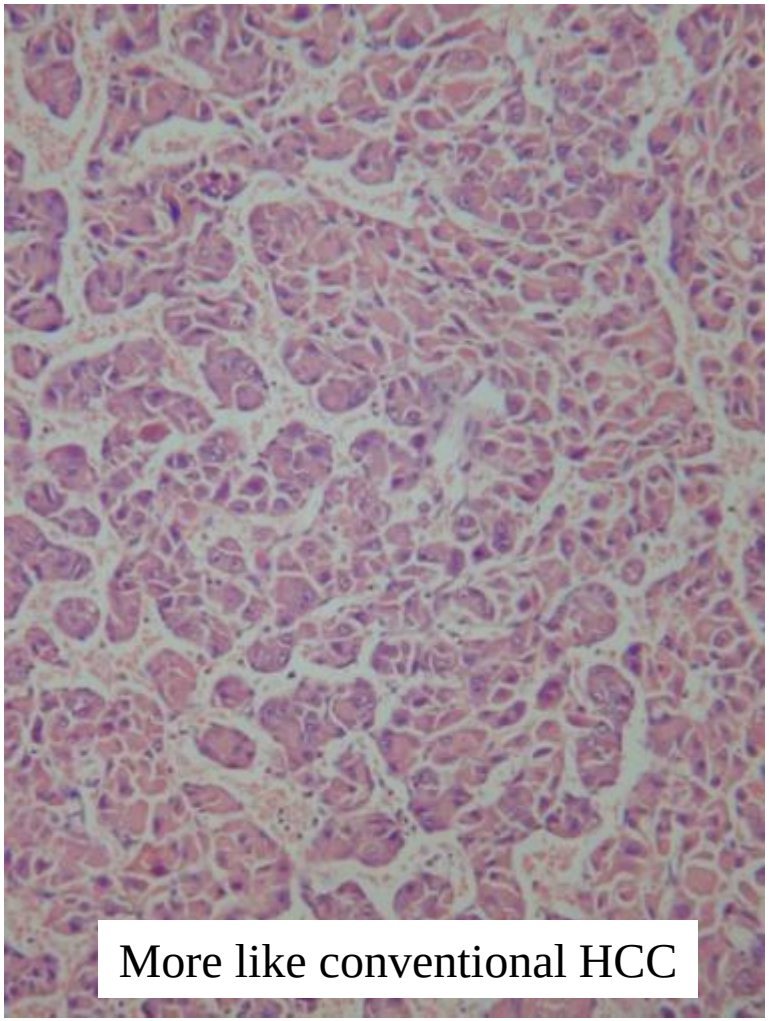
1. **FLC may contain areas resembling conventional HCC**

- Mixed features of FLC and HCC present in up to 25% cases initially diagnosed as FLC (Malouf 2012)
- Cases of "mixed FLC" more frequently occur in older people, have higher AFP levels and worse prognosis .
- Different patterns of recurrence /metastases (mixed FLC – intrahepatic, pure FLC – extrahepatic)

Mixed features of fibrolamellar and conventional HCC



Typical FLC



More like conventional HCC

Fibrolamellar HCC - Problems with Histological Diagnosis

2. Conventional HCC may contain areas with a resemblance to FLC (sclerosing or scirrhous HCC)

a. Cases of HCC occurring in non-cirrhotic liver may be variant of intrahepatic cholangiocarcinoma (or mixed HCC/CC)

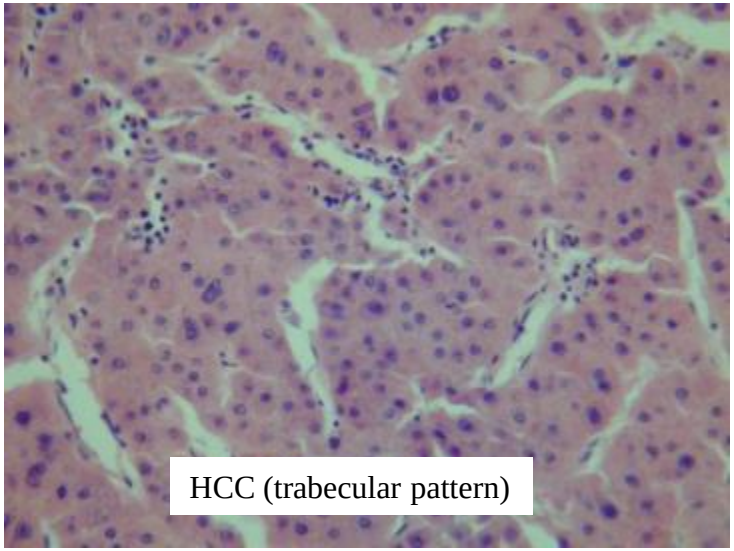
- Stroma loose and cells smaller than in FLC

b. Typical HCCs in cirrhotic liver may contain foci with cytological features and/or stroma resembling FLC

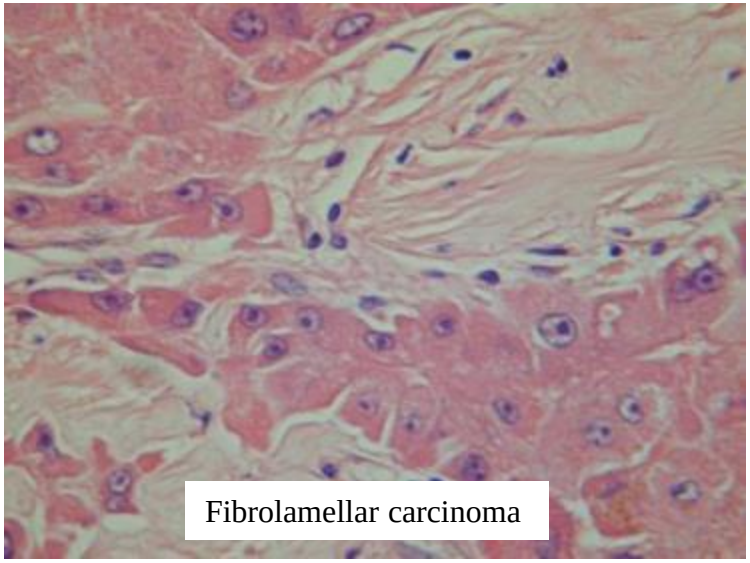
- Infrequent case reports
- Functional significance uncertain

HCC with Foci of FLC

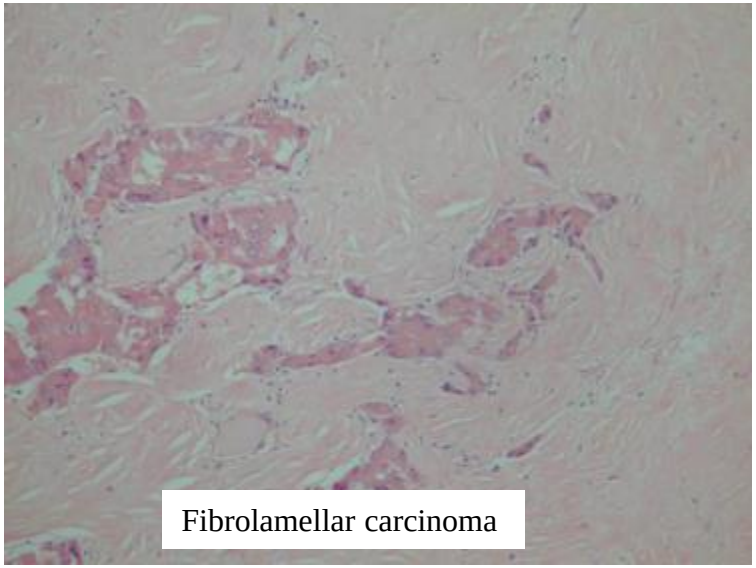
Female, age 67. Liver transplant for NASH. 3.5cm nodule in right lobe



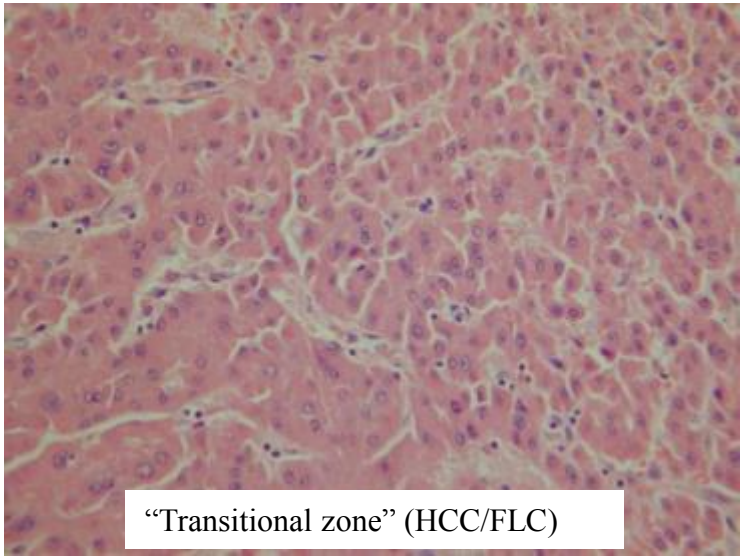
HCC (trabecular pattern)



Fibrolamellar carcinoma



Fibrolamellar carcinoma



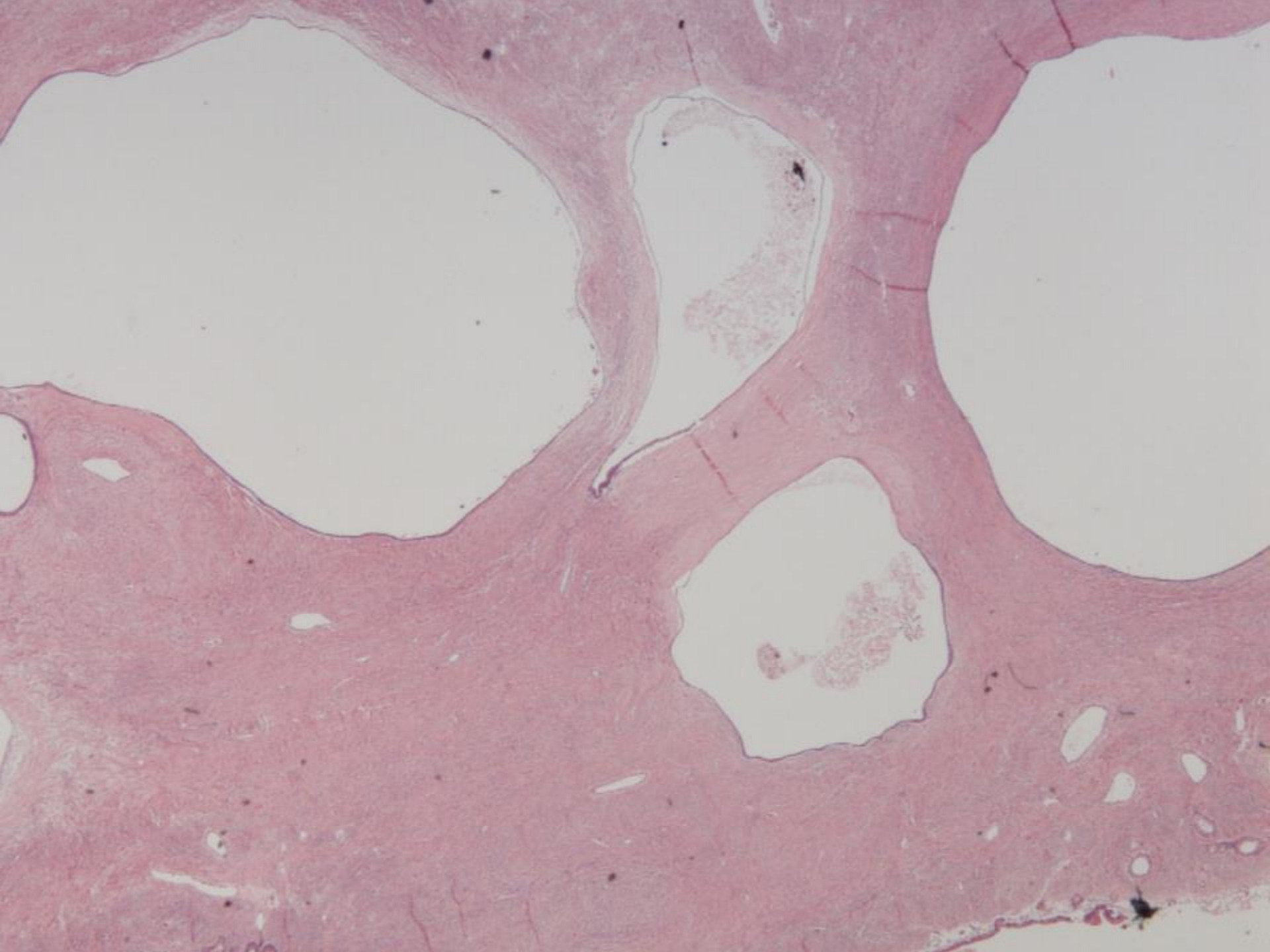
“Transitional zone” (HCC/FLC)

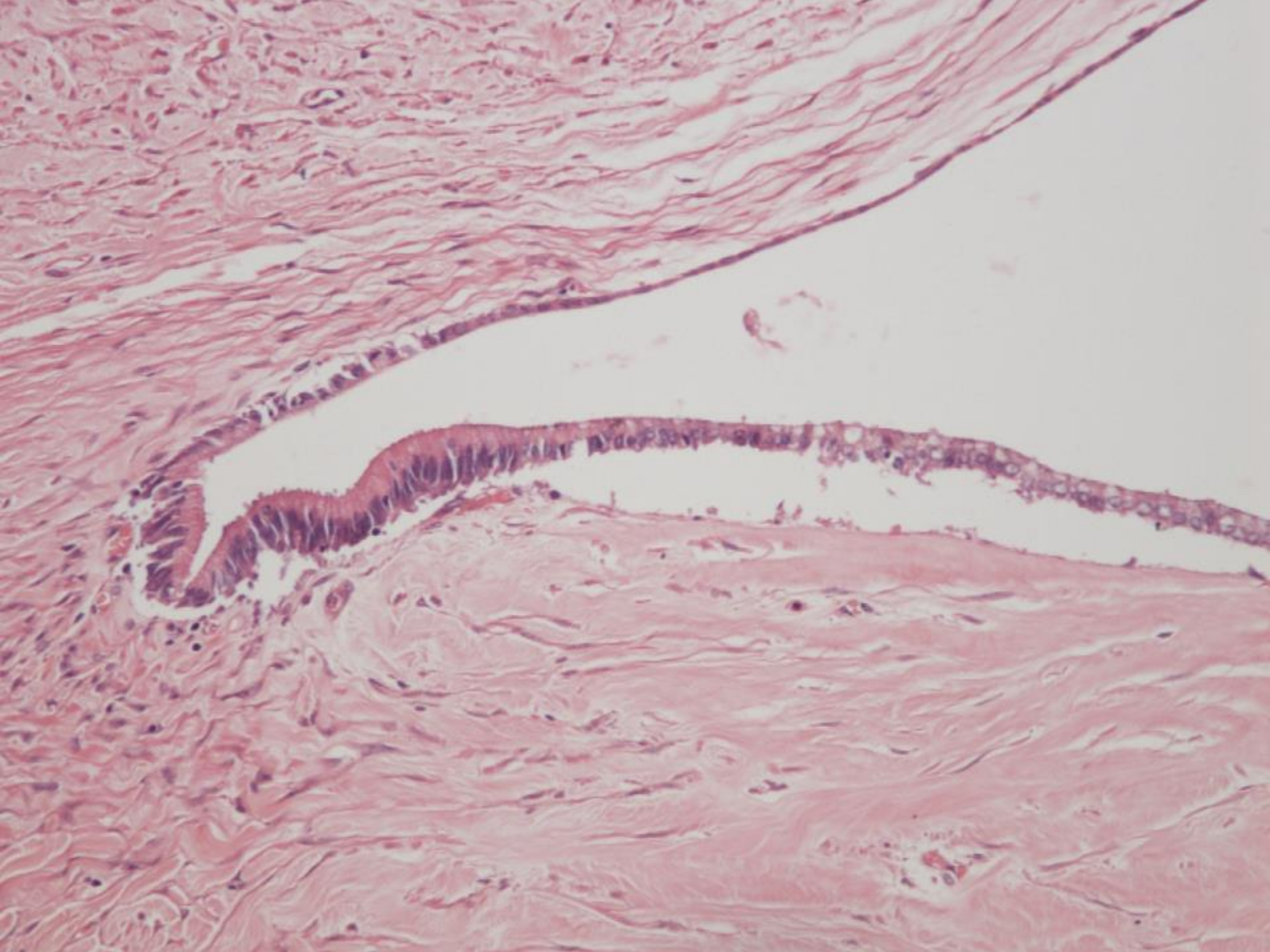
Case 6

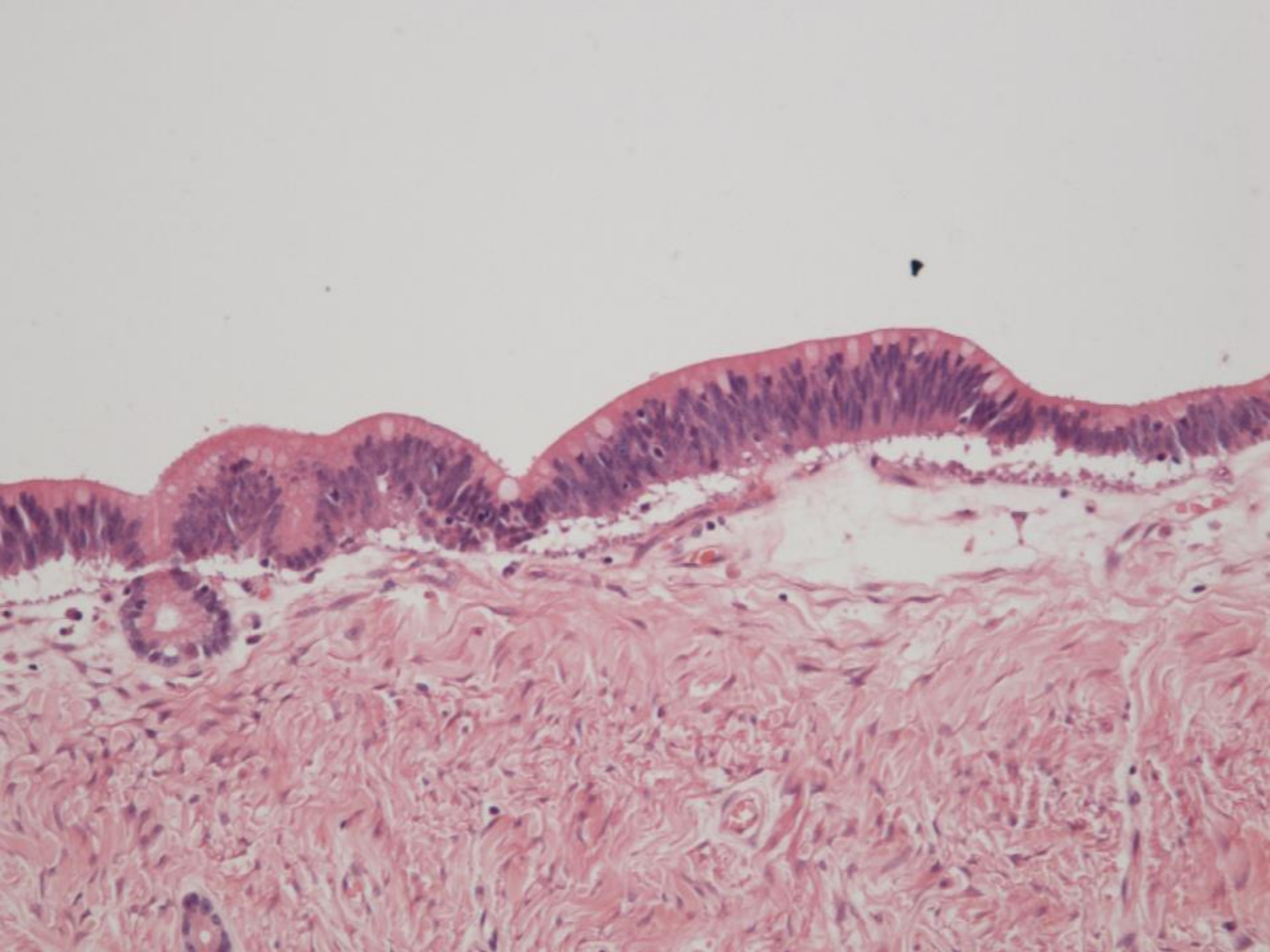
Case 6 – Clinical Summary

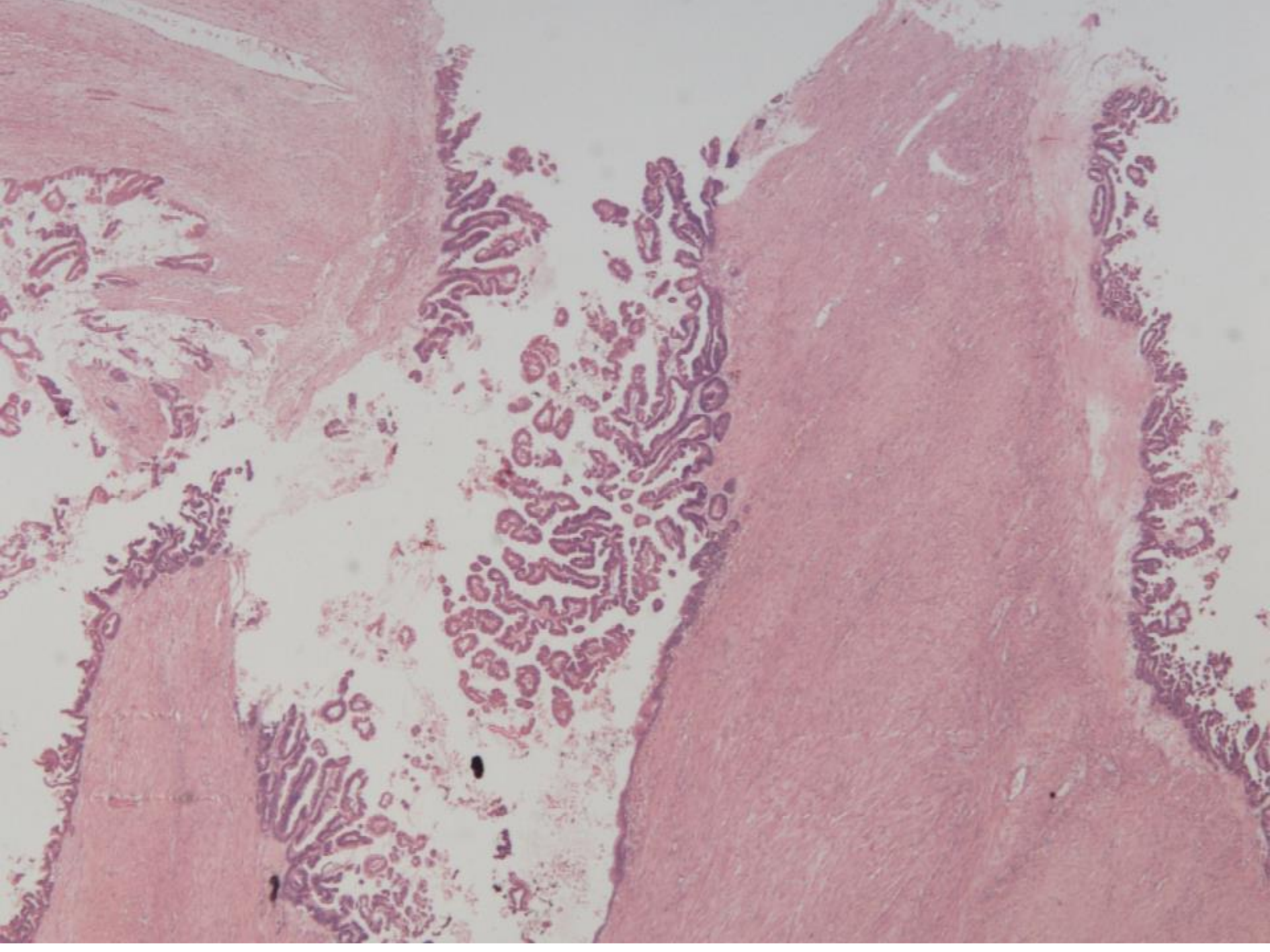
Female, age 55

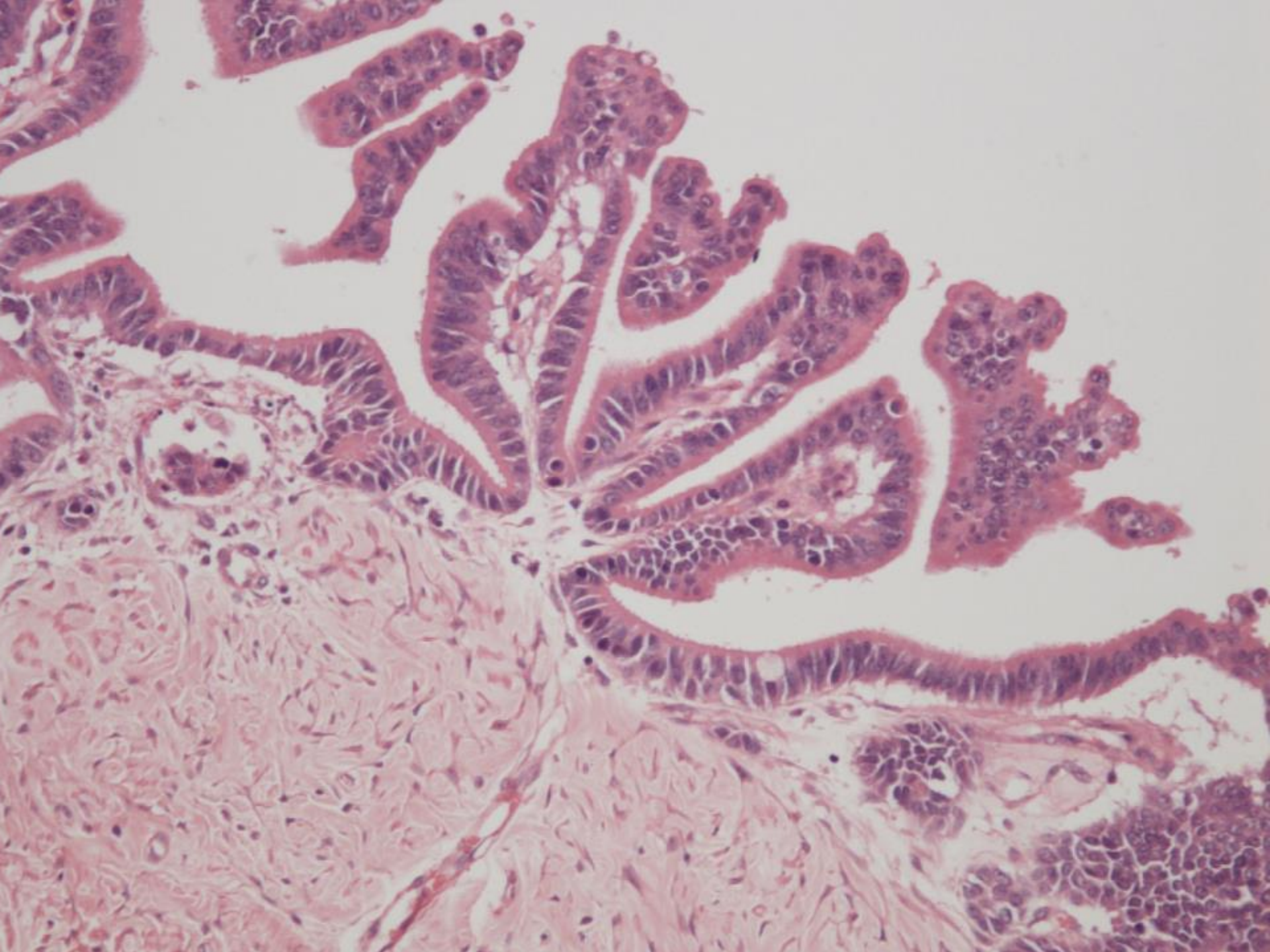
- Liver resection.
- Large multiloculated cyst 18 cm maximum dimension in left lobe.

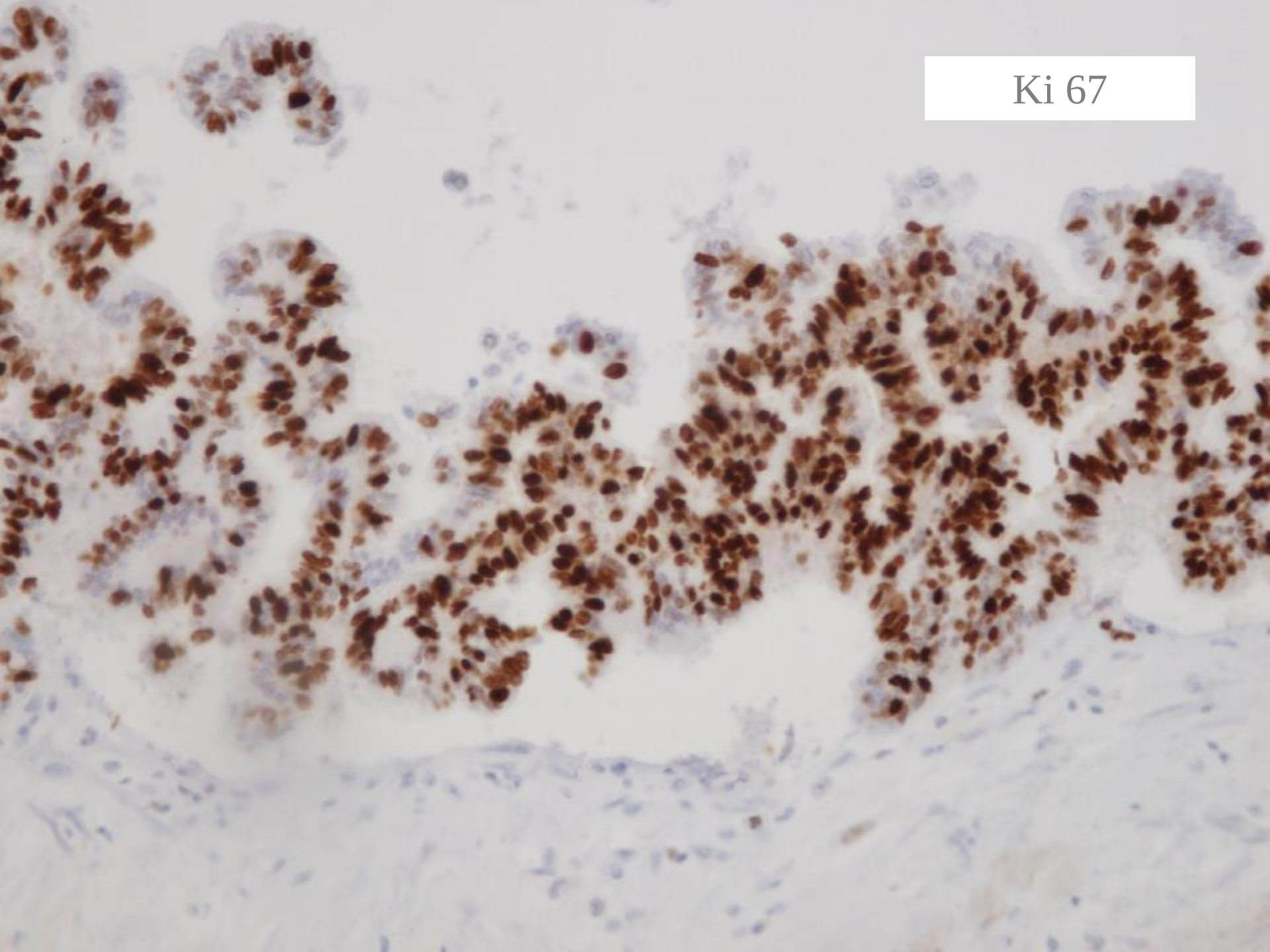


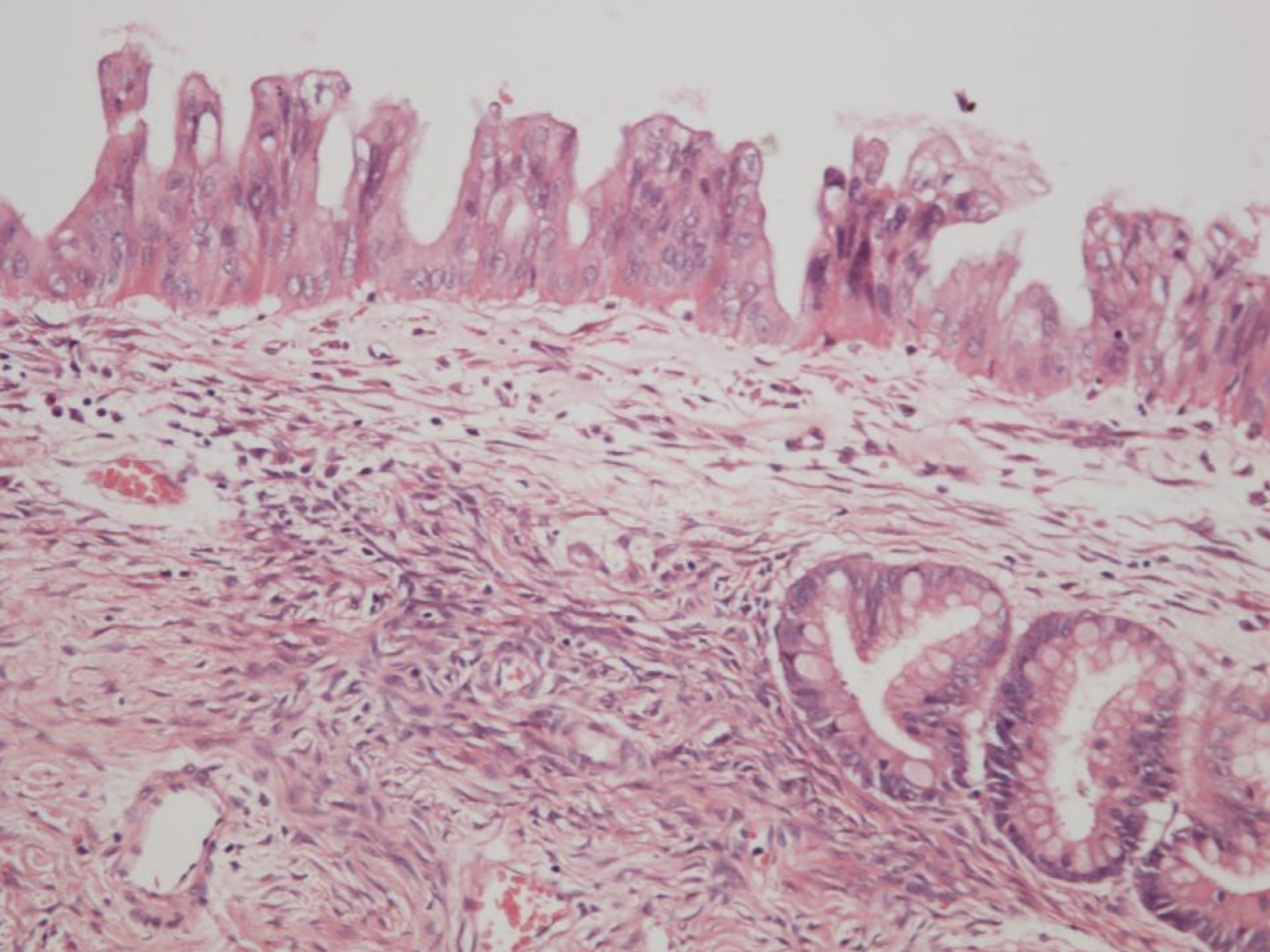


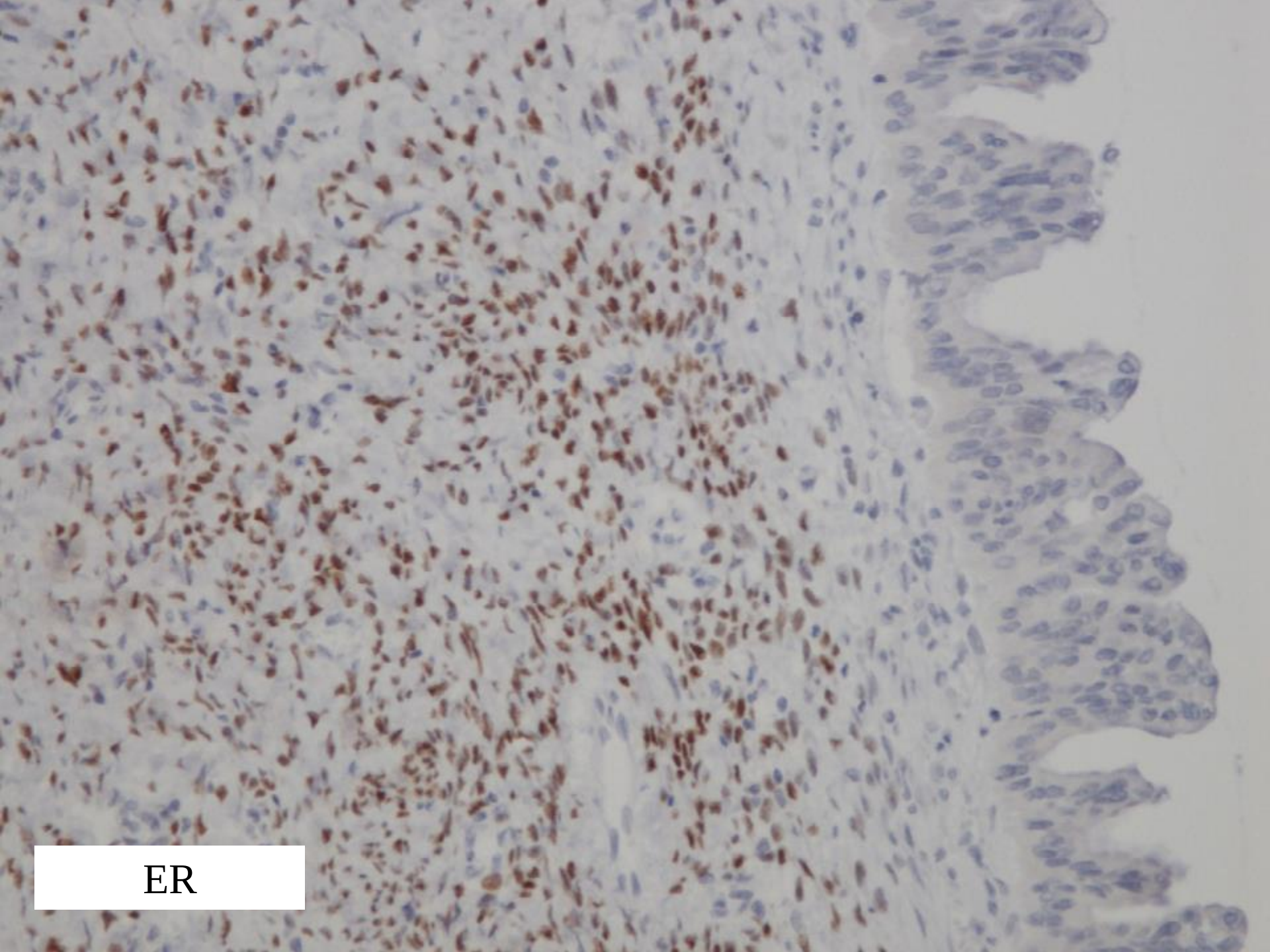







Ki 67

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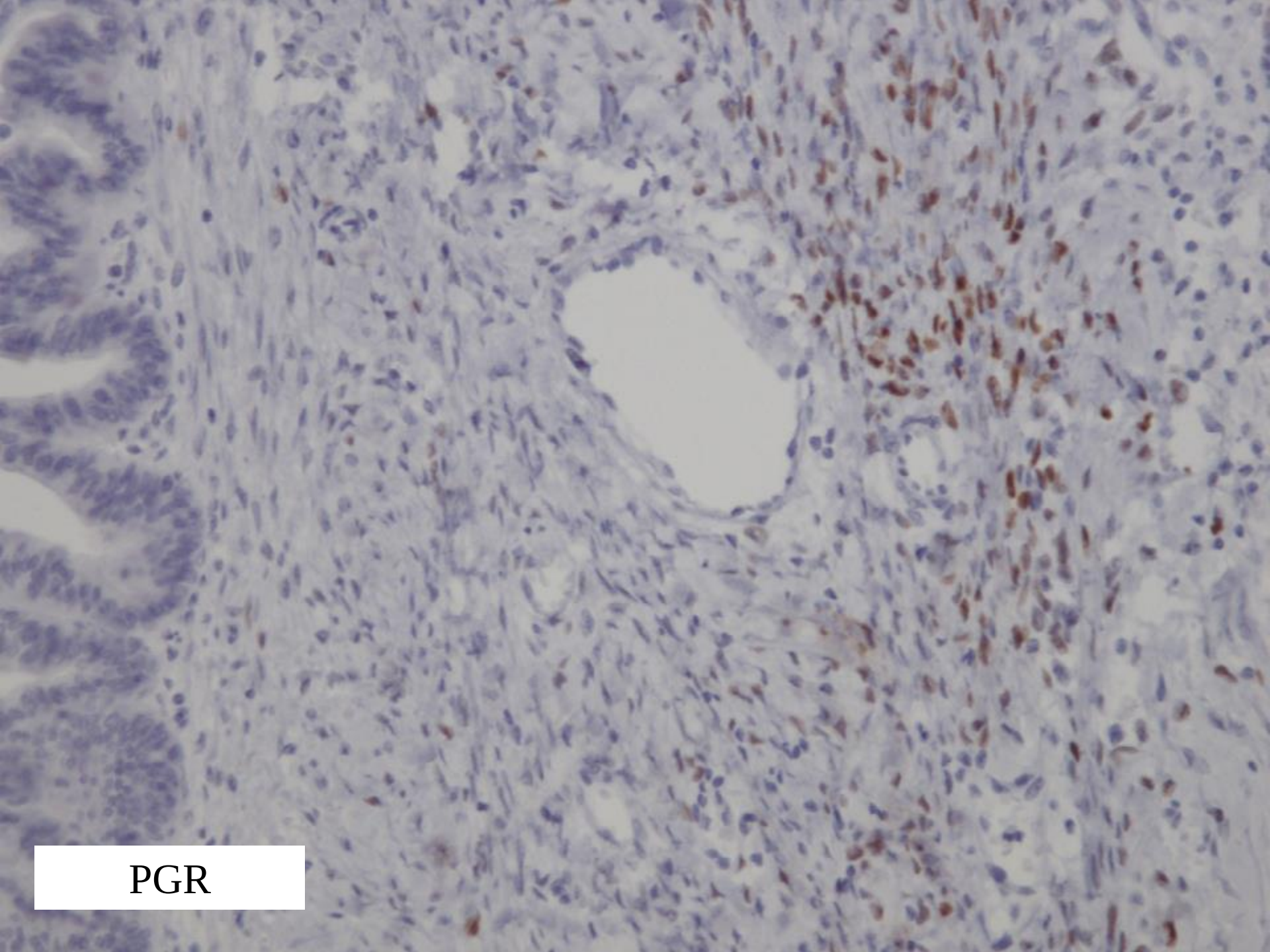
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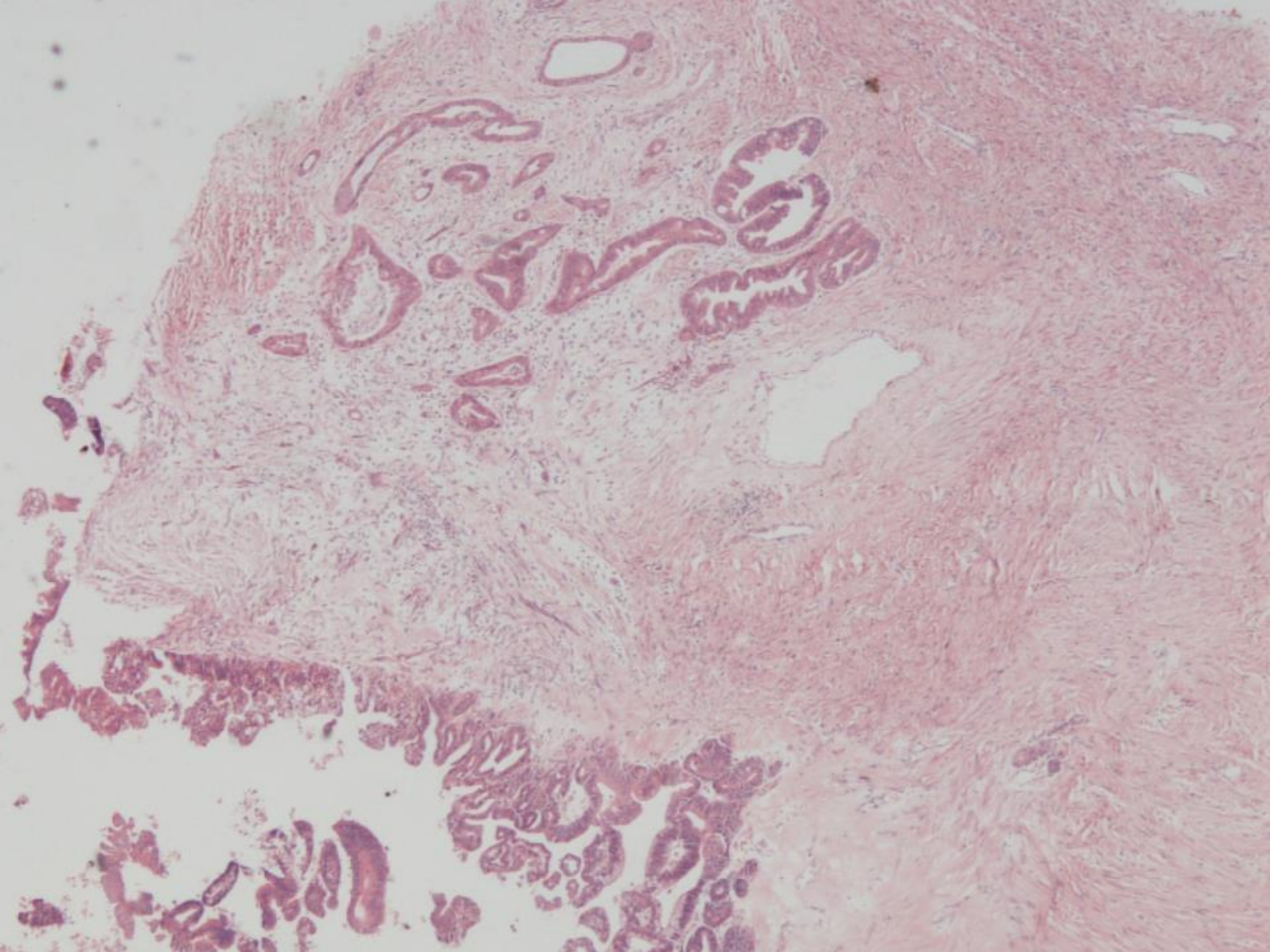
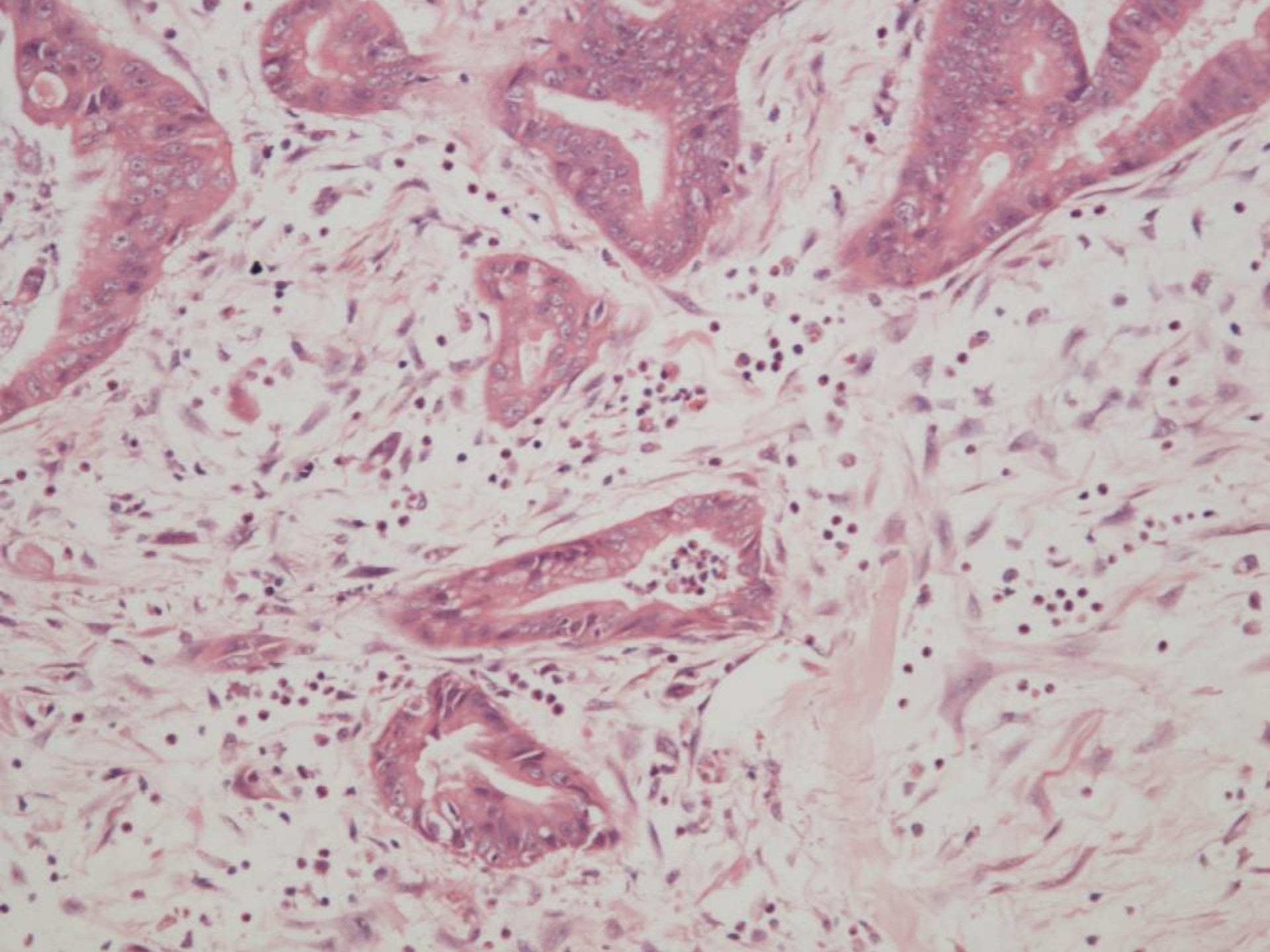
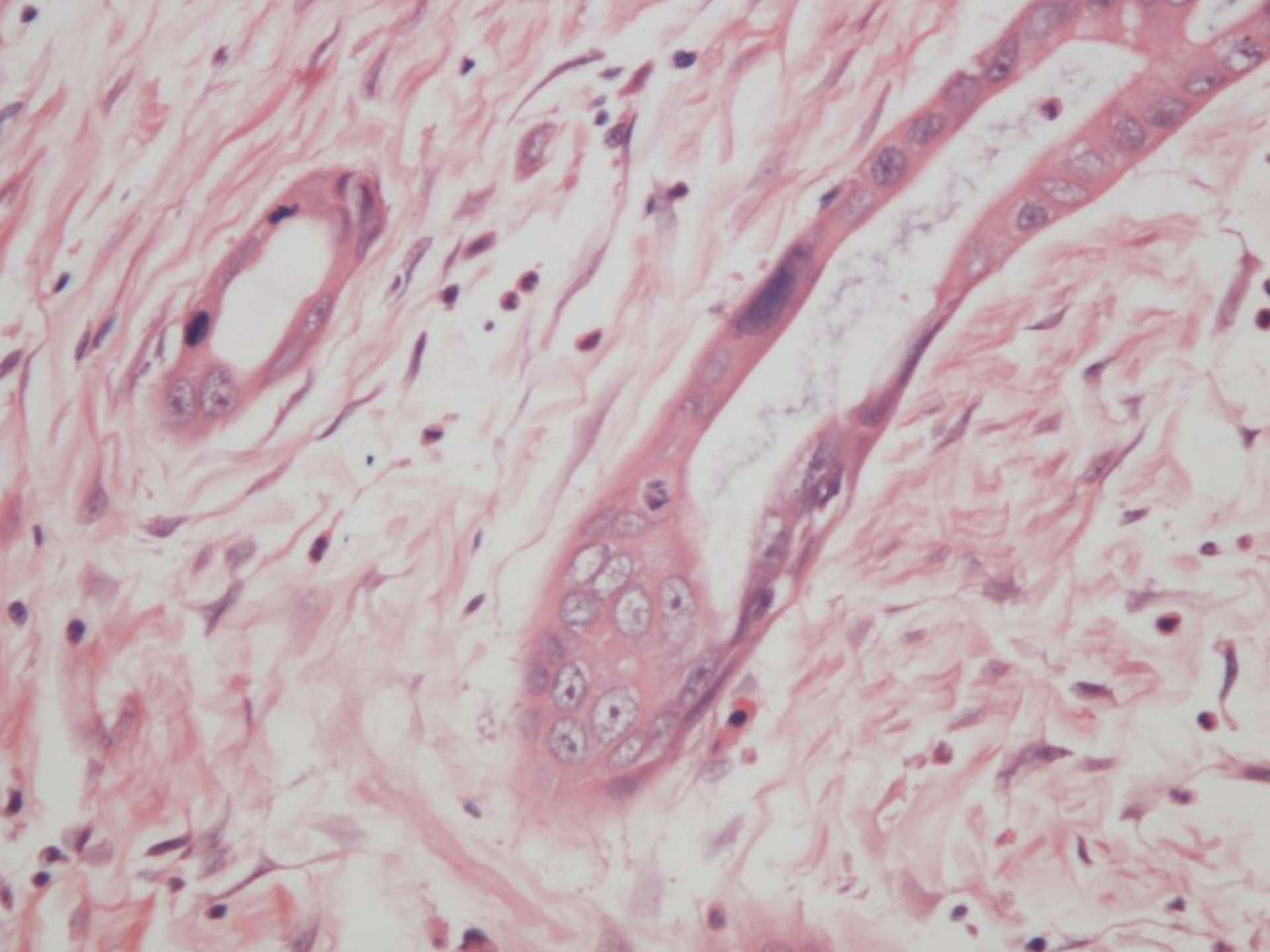






Case 6 – Histological Findings

- Multiloculated cystic neoplasm
- Mucinous epithelium showing varying degrees of dysplasia, focally high-grade
- Ovarian-like subepithelial mesenchymal stroma
- Occasional foci of invasive adenocarcinoma

Case 6 – Diagnosis

Current Terminology:

- Mucinous cystic neoplasm with foci of invasive adenocarcinoma
  - MCN terminology used in WHO 2010 Classification

Previous Terminology

- Hepatobiliary cystadenoma with foci of invasive carcinoma (cystadenocarcinoma)

Case 6 – Discussion Points

1. Is hepatic mucinous cystic neoplasm the counterpart of mucinous cystic neoplasms arising in pancreas?

- Both tumours have female preponderance (> 95% of cases)
- Histological features similar (including ovarian-like stroma)
- Similar pathogenetic mechanisms postulated (to account for ovarian like stroma)
  - Epithelial cells covering embryonic gonads in early foetal life lie close to developing embryonic foregut ? derived from ectopic ovarian tissue
  - Majority of hepatic MCNs arise in segment 4, which lies close to embryonic gonads

Case 6 – Discussion Points

2. Is the presence of a mesenchymal stroma an essential pre-requisite to make a diagnosis of hepatic mucinous cystic neoplasm ?

- Some pancreatic pathologists suggest that mucinous cystic neoplasms can only be diagnosed if an ovarian-like stroma is present
  - Mainly done to aid in the distinction from other cystic lesions (especially intraductal papillary mucinous neoplasm -IPMN)
  - Intraductal papillary neoplasm (IPN) of bile duct can also present as a cystic lesion in liver
- This approach would mean that hepatic mucinous cystic neoplasm could only be diagnosed in women

Case 6 – Discussion Points

3. What is the risk of malignant transformation?

- No prospective studies
- Detection of focal malignant change requires extensive sampling

- Cases of cystic hepatobiliary neoplasms undergoing resection (Devaney 1994, Li 2009, Song 2011, Zen 2011, Martel 2013)
  - 39/158 (25%) had foci of malignancy or were classified as cystadenocarcinoma (range 0 -42%)
  - Wide range in reported prevalence may reflect differences in diagnostic criteria

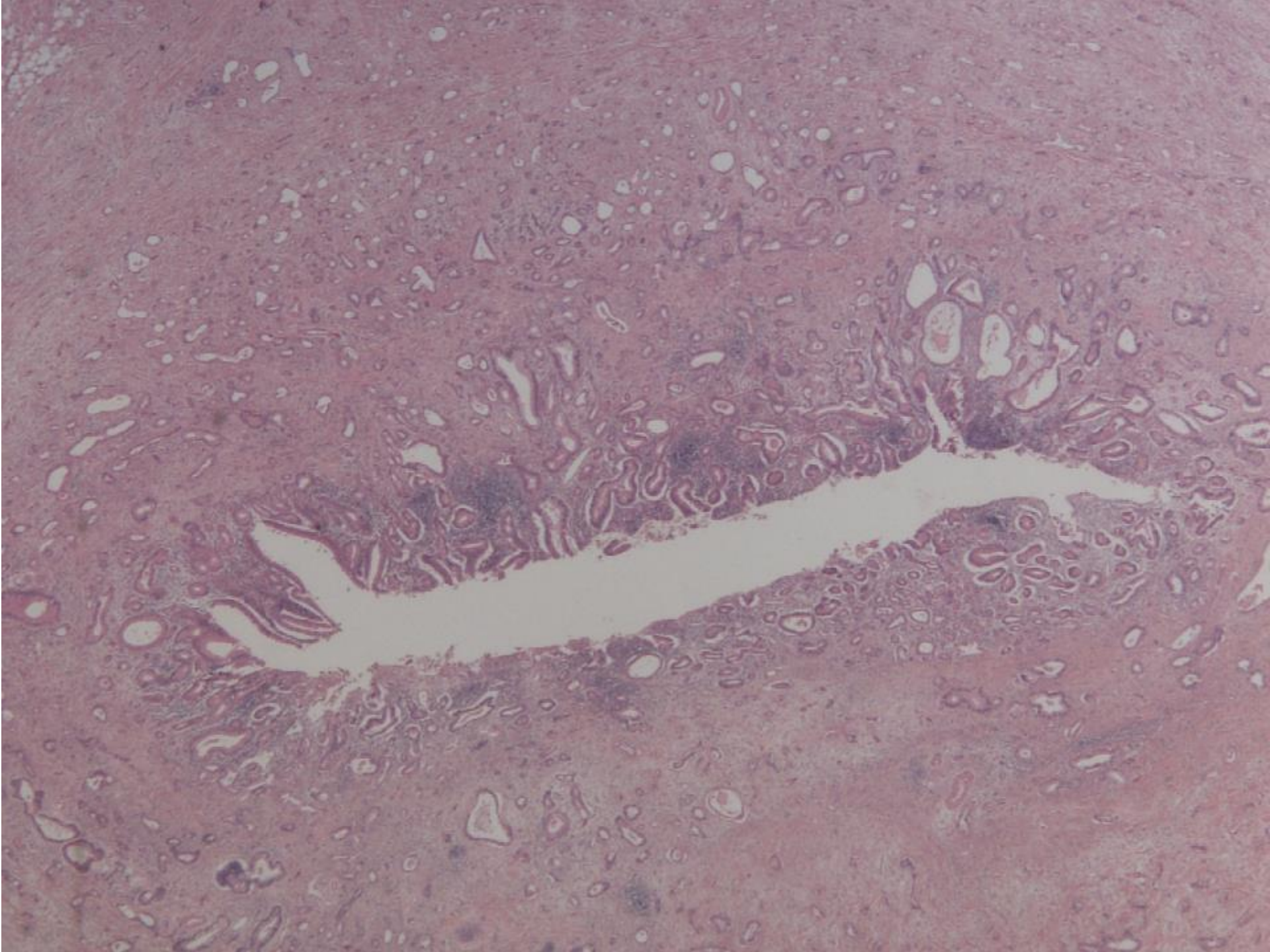
- Mucinous cystic neoplasms in pancreas
  - 7 - 36% have areas of invasive carcinoma
  - Size (>4cm) and presence of solid areas correlate with malignancy

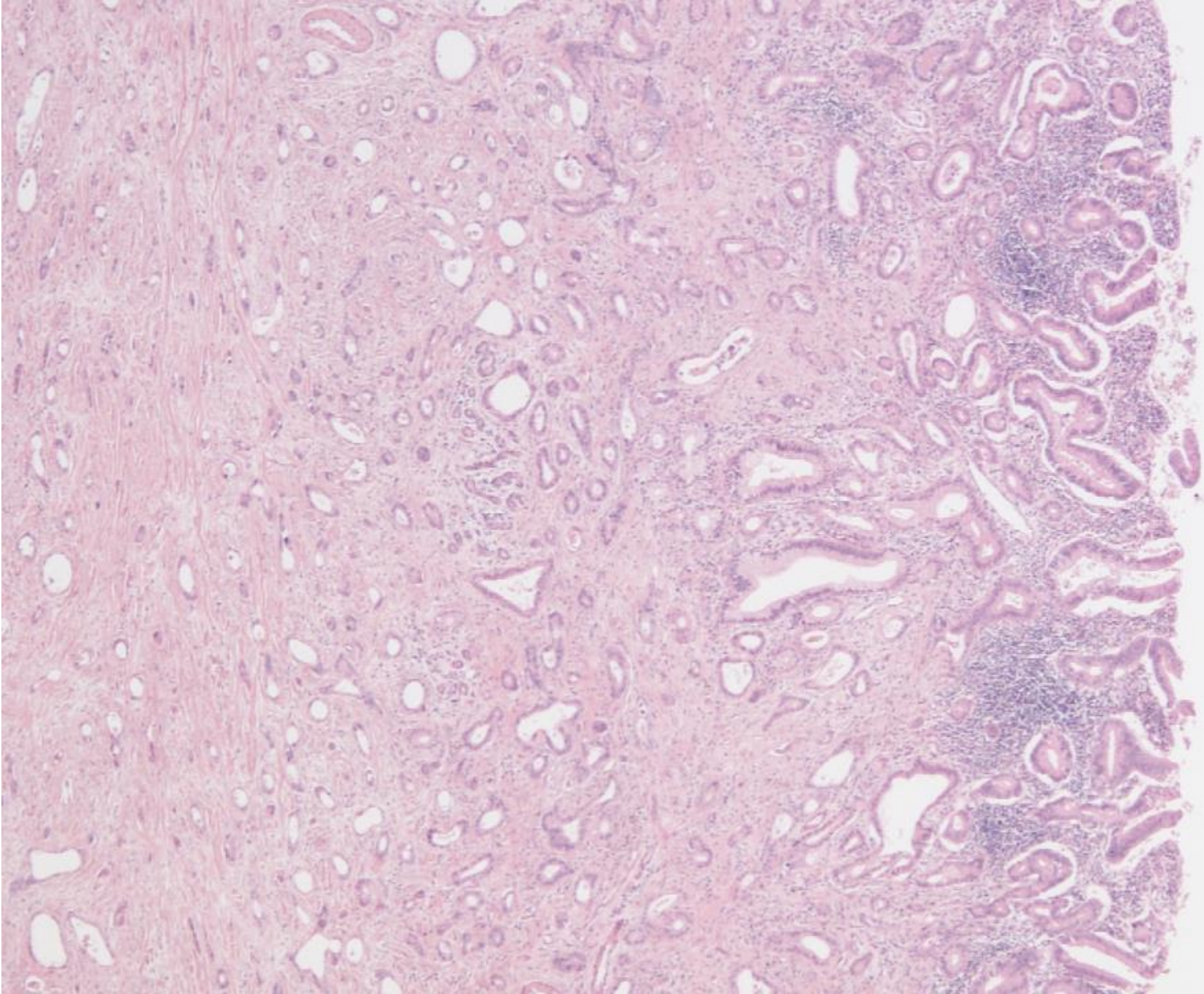
Case 7

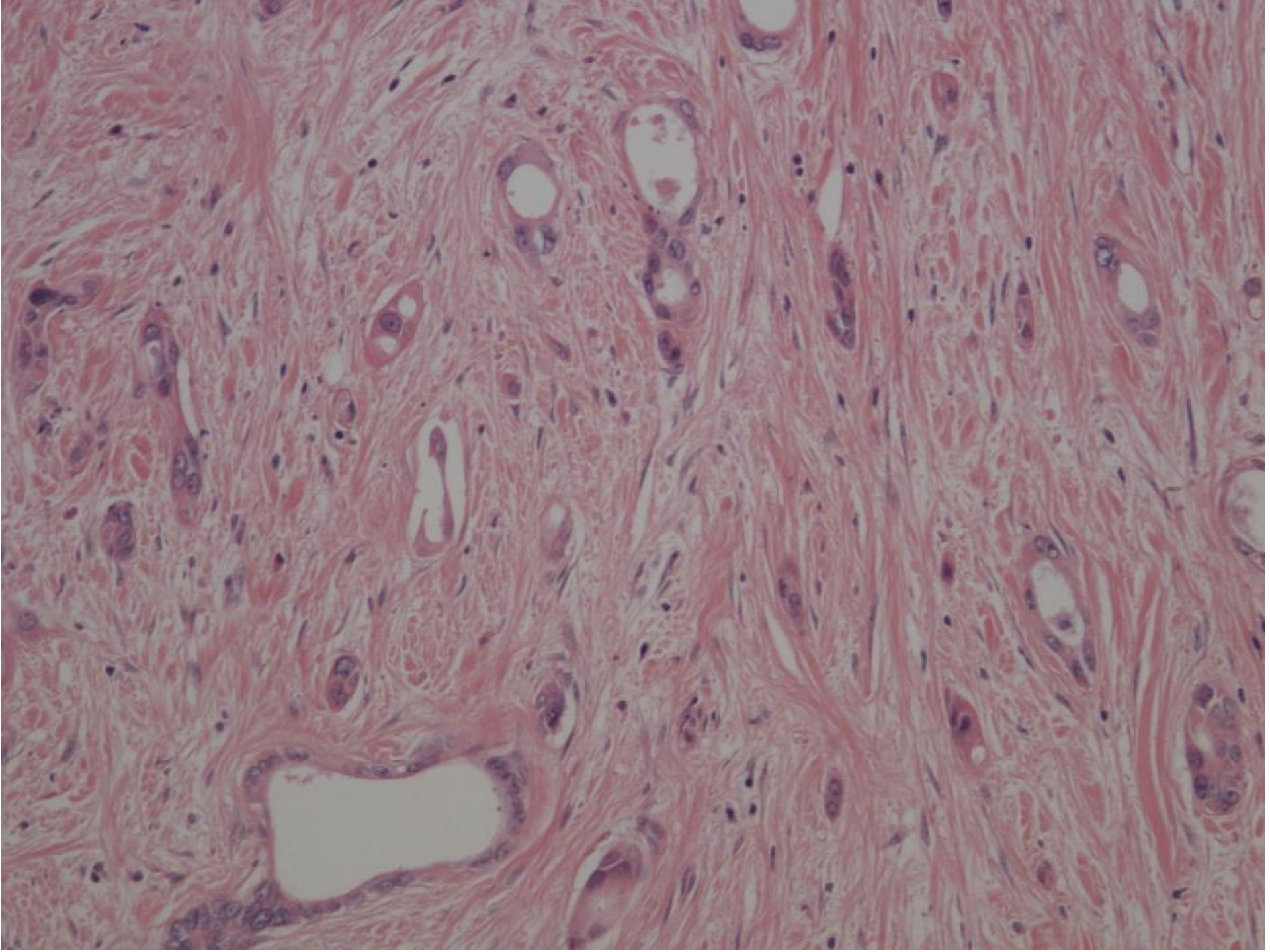
Case 7 - Clinical Summary

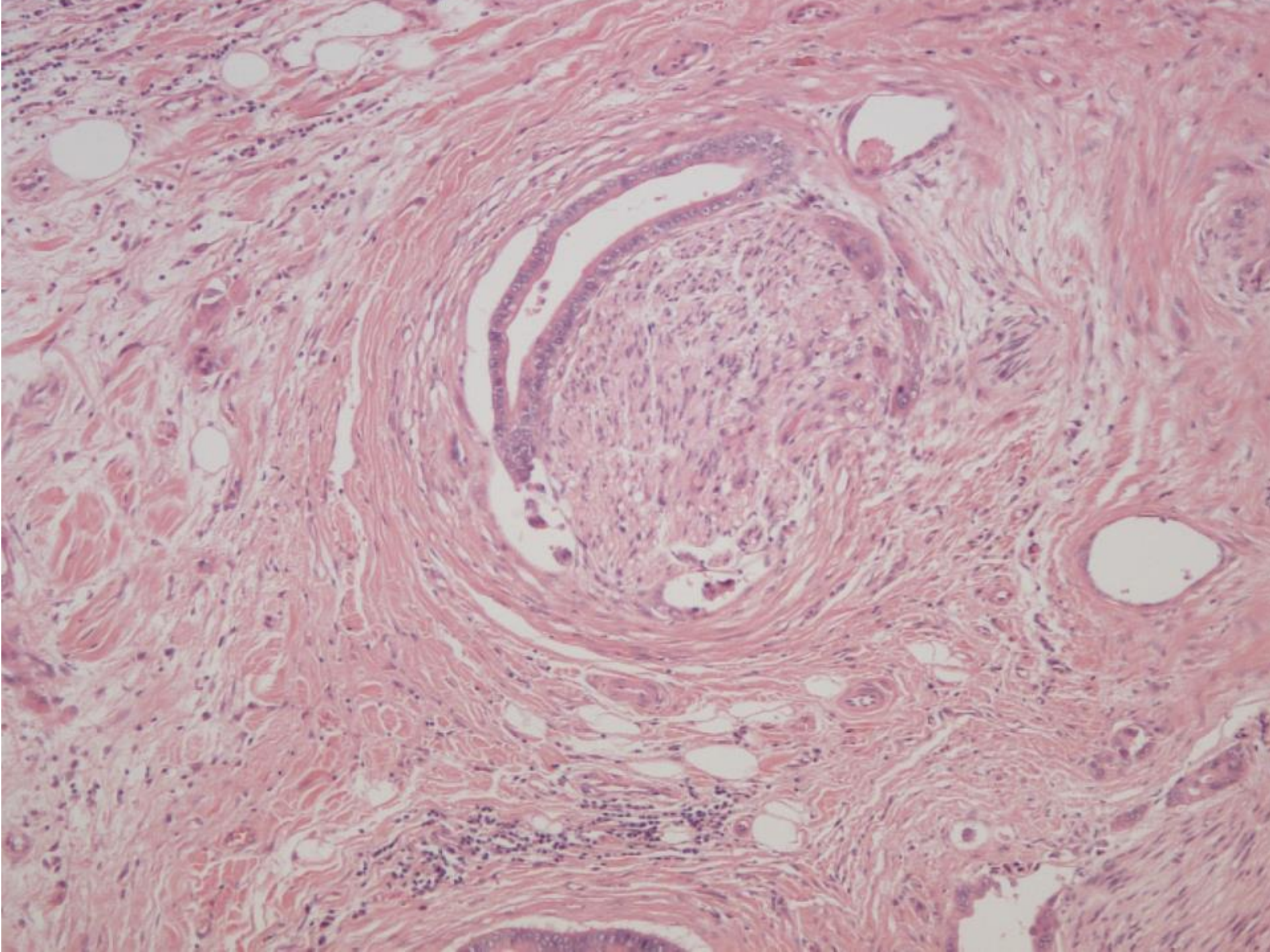
Male, age 67

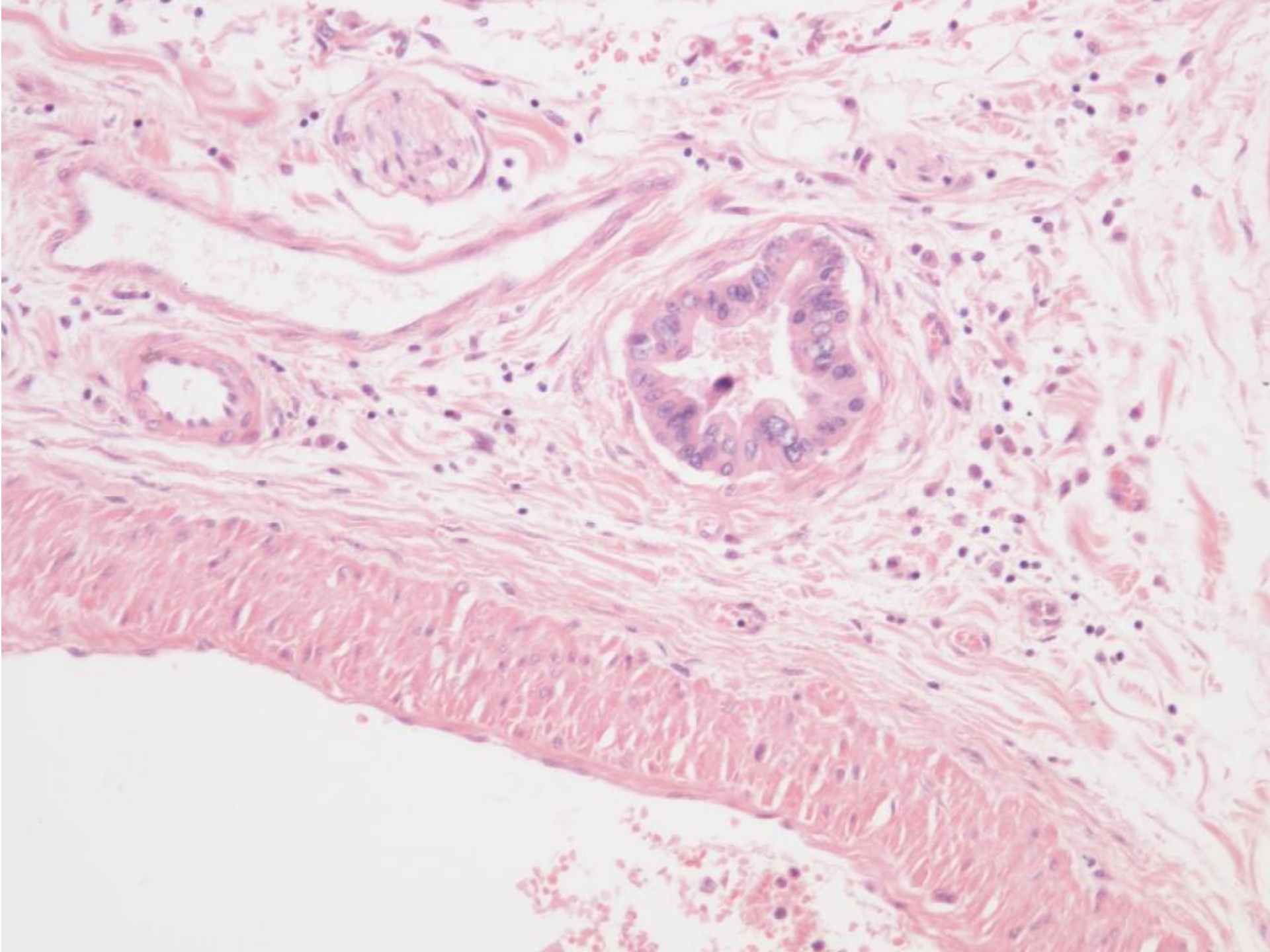
- Extended right hemi-hepatectomy for hilar lesion causing obstructive jaundice.
- Slide submitted is from extrahepatic segment of bile duct.
- Macroscopy showed thickened segment of bile duct 2cm long, extending from hilum towards junction with cystic duct



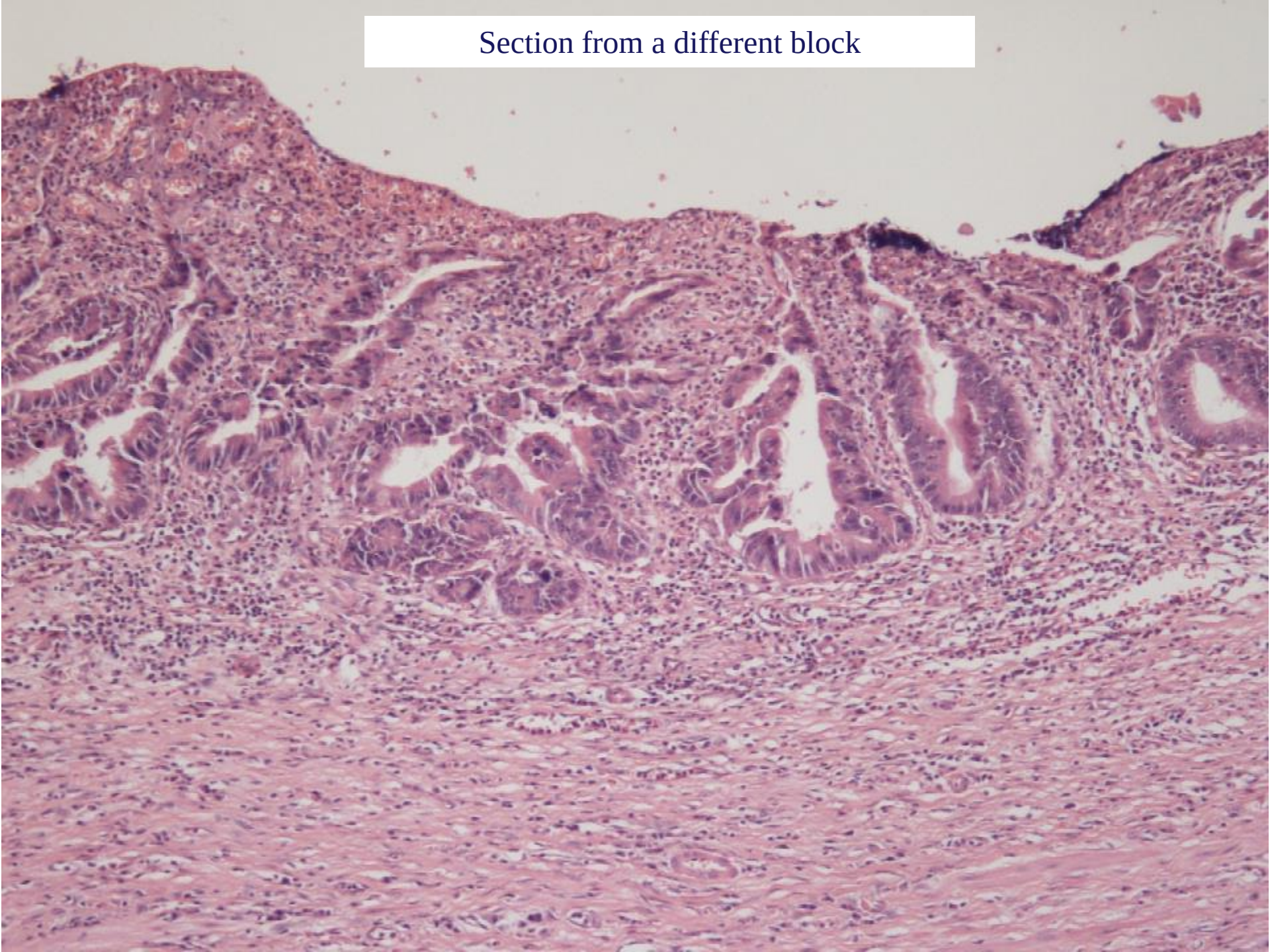


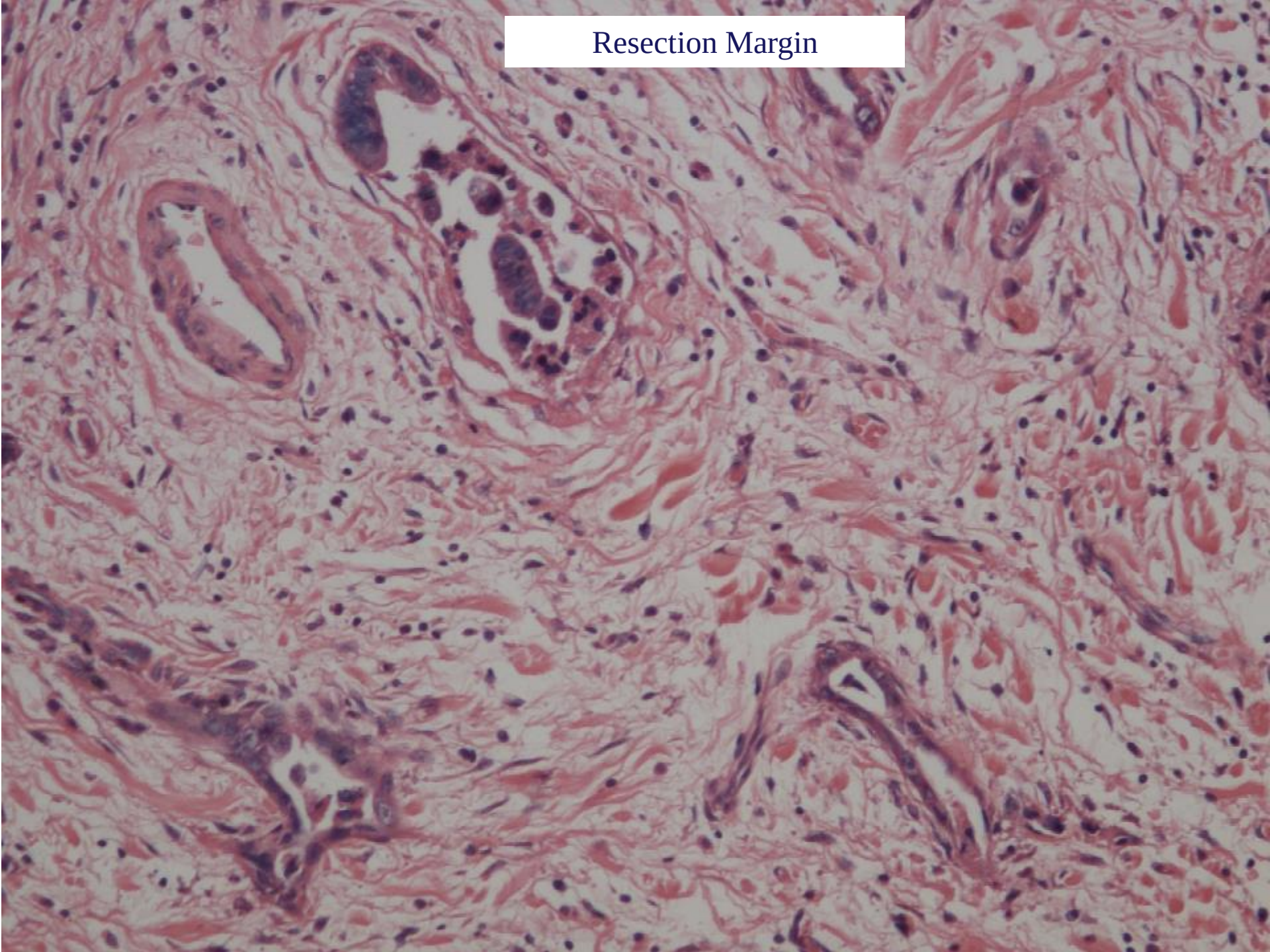






Section from a different block




Resection Margin

Case 7 – Histological Findings & Diagnosis

Histological Findings

- Malignant glands invading full thickness of bile duct wall
- Foci of perineural and vascular invasion
- Occasional foci of intramucosal carcinoma
- Tumour present at resection margin

Diagnosis

- Perihilar Cholangiocarcinoma

Case 7 – Discussion Points
1. Macroscopic Classification of Cholangiocarcinoma

	Hilar / perihilar	**Peripheral (intrahepatic)**
Site of origin	Large ducts (proximal to cystic duct origin) • ? May arise from peribiliary glands	Small bile ducts/bile ductules Progenitor cells (in canals of Hering)
Growth Pattern	Periductal	Mass forming
Risk Factors	Chronic inflammatory bile duct disease • e.g. PSC, hepatolithiasis, parasitic diseases	Chronic inflammatory bile duct disease Also chronic parenchymal liver disease (e.g. HCV, ALD, NAFLD)
Premalignant lesions	Biliary intra-epithelial neoplasia (Bil-IN) Intraductal papillary neoplasm (IPN)	Less clearly defined
Histology	Adenocarcinoma	Mostly adenocarcinoma • Morphological spectrum from pure HCC to pure CC (intermediate lesions with mixed features of HCC and CC)
Clinical presentation	Biliary obstruction	Liver mass
Problems with histological assessment	Distinction from inflammatory causes of bile duct stricture (including IgG4-associated disease)	Distinction from other hepatic neoplasms (primary or metastatic)

Case 7 – Discussion Points
2. Hilar Cholangiocarcinoma versus Inflammatory Stricture

Features supporting a diagnosis of malignancy

- Subtle nuclear atypia, mitoses
- Infiltrative growth pattern (including perineural invasion)
- Immunohistochemistry
  - Ki67
  - EMA/K7 (to identify individual cells in inflamed stroma)
  - (bcl-2, p53, k-ras)
- Other approaches (mainly used for brush cytology specimens)
  - digital image analysis (DIA) to assess aneuploidy
  - fluorescence in-situ hybridization (FISH) to assess chromosomal abnormalities

Case 7 – Discussion Points
3. Assessment of Perineural/Vascular Invasion

- Typically present in outer wall of bile duct
- Often extends beyonds macroscopically visible tumour
  - Important mechanism for tumour recurrence following resection
- Isolated malignant glands may be present some distance from periphery of main lesion identified microscopically
- Importance in assessment of margins from resection specimens
  - Including peri-operative frozen section assessment

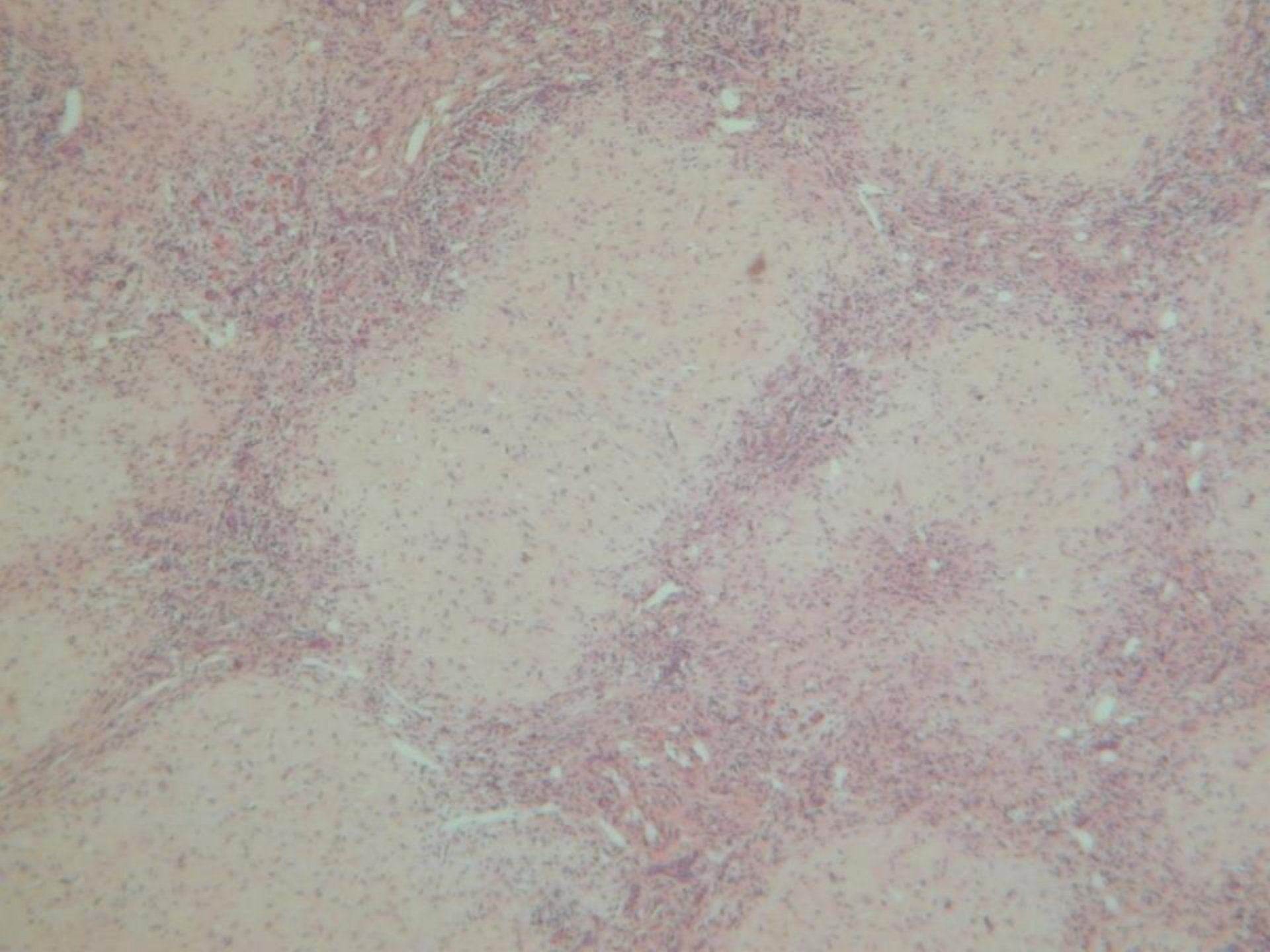
Case 8

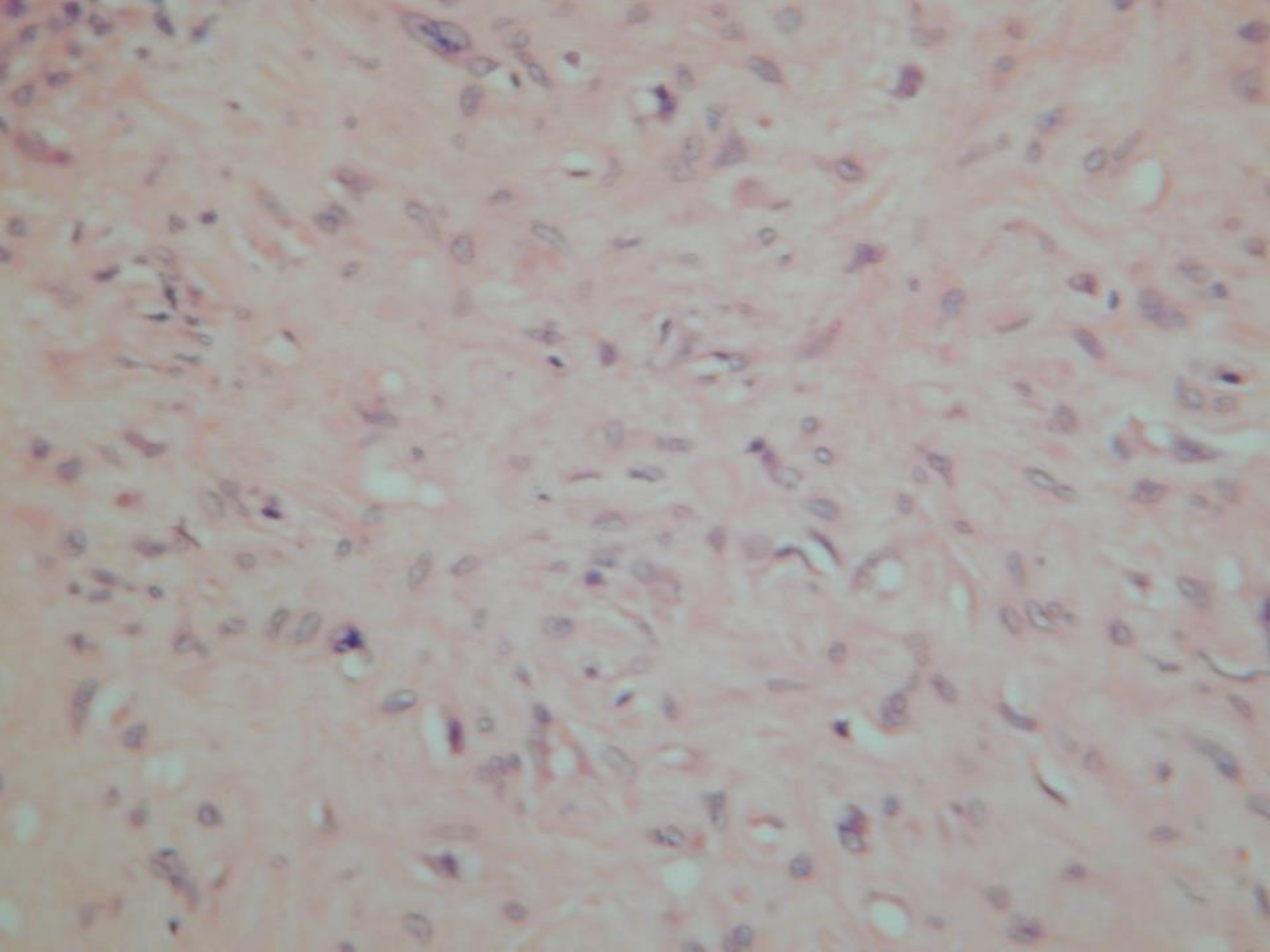
Case 8 - Clinical Summary

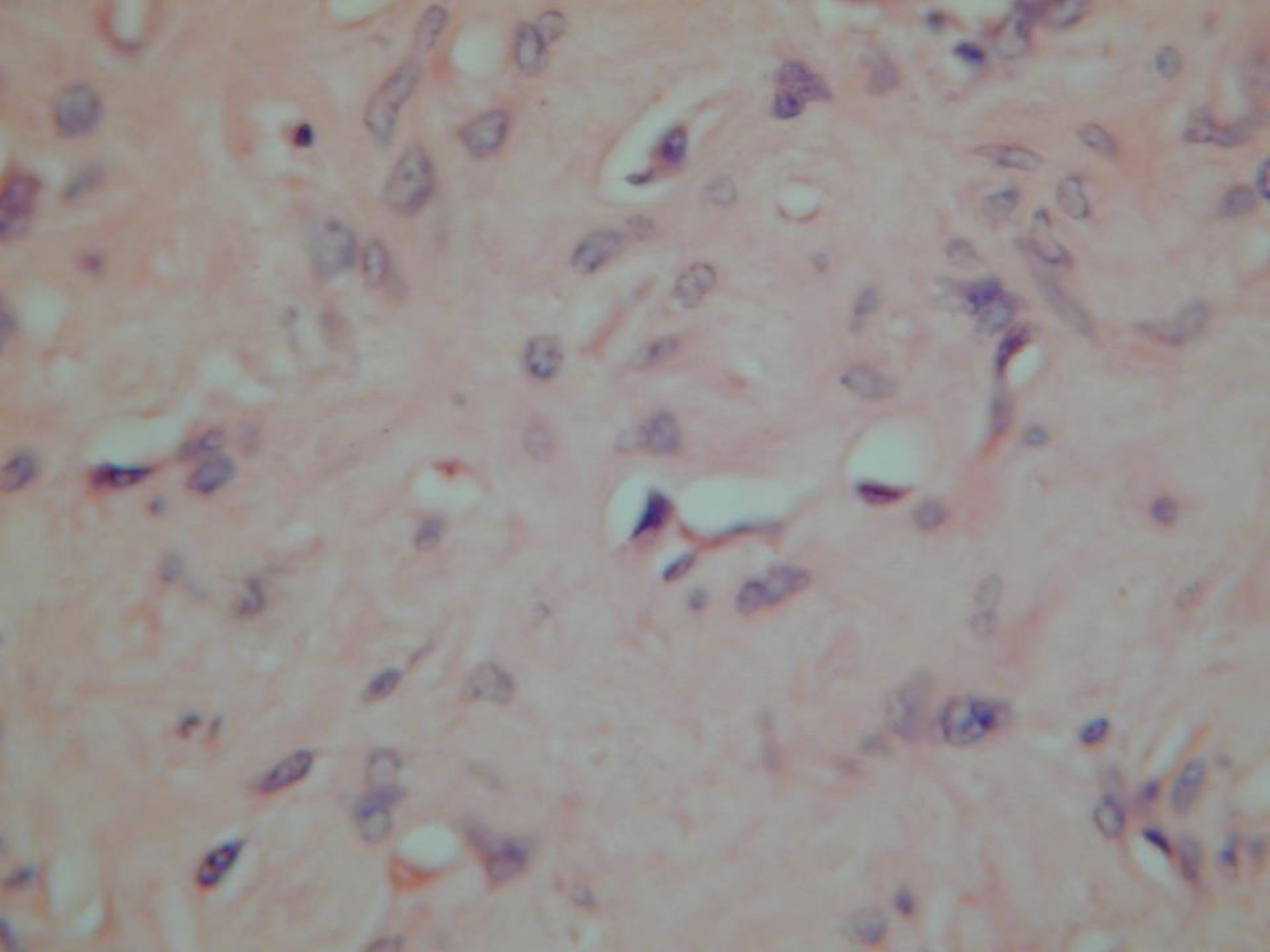
Female, age 25

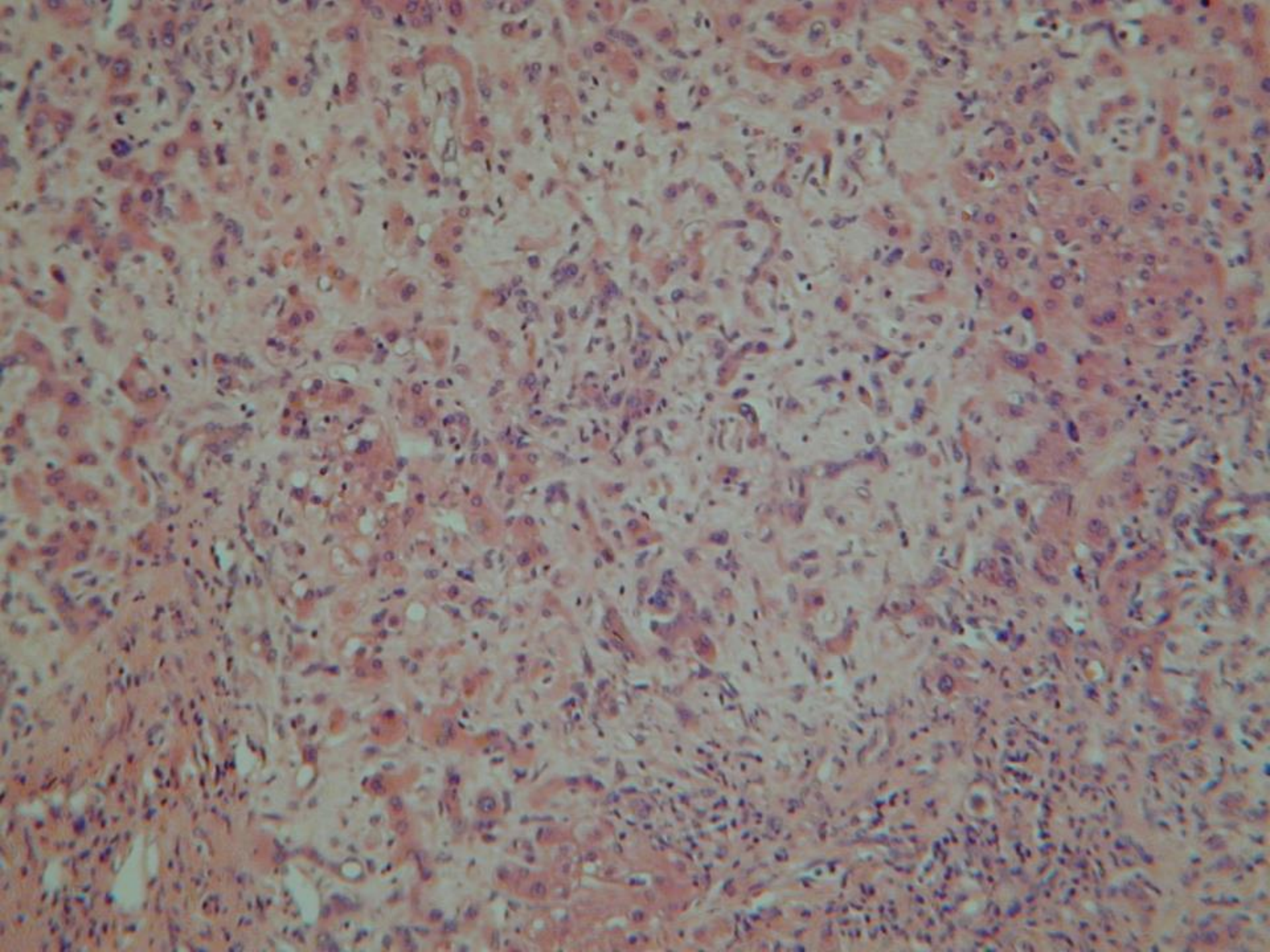
- Liver transplantation.
- Multiple nodules 1-6 cm diameter composed of firm white tissue throughout liver.
- Previous biopsy elsewhere reported as showing fibrosis ? cause

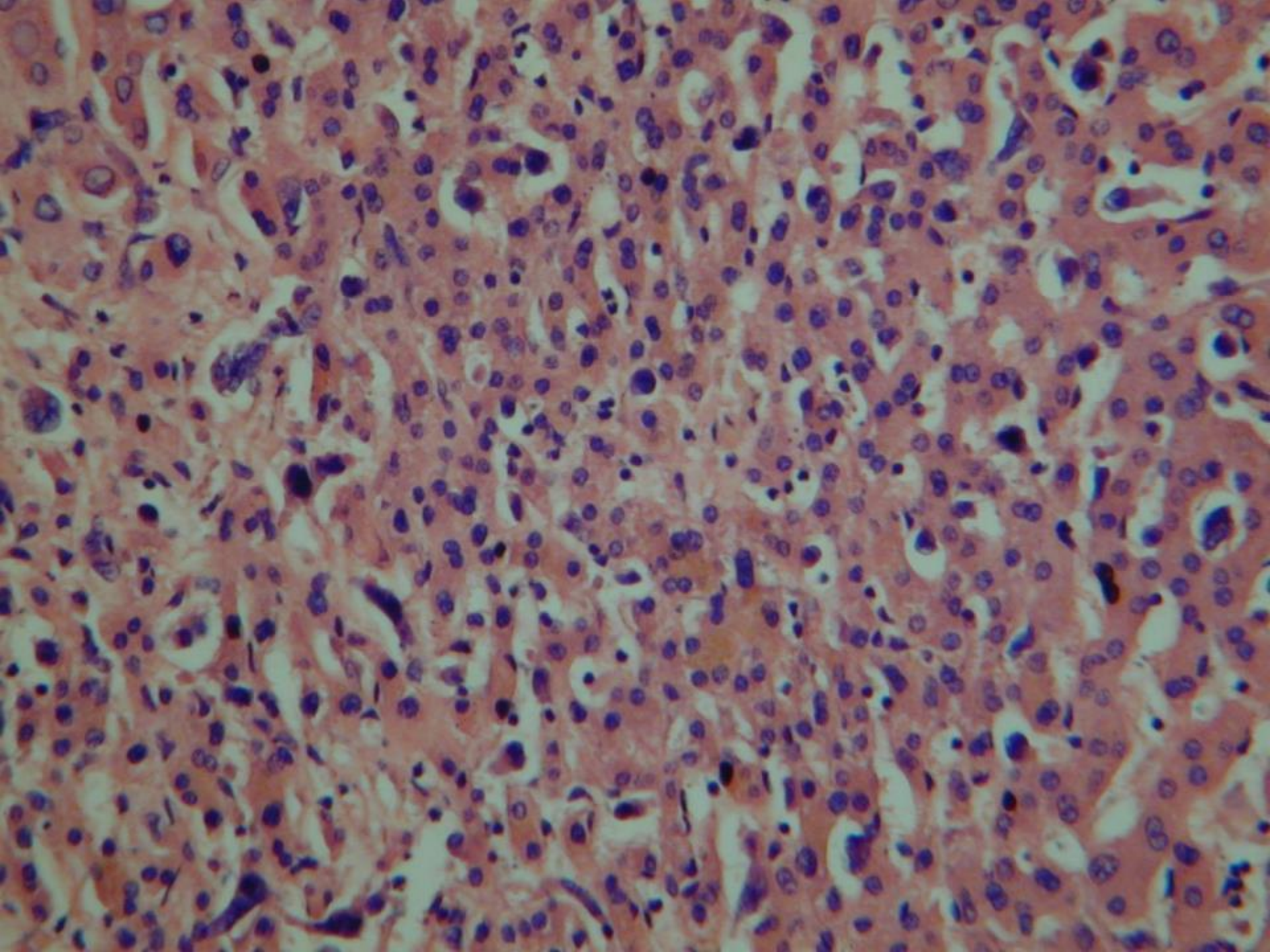

CM 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
NON-SLIP
STEEL RULER

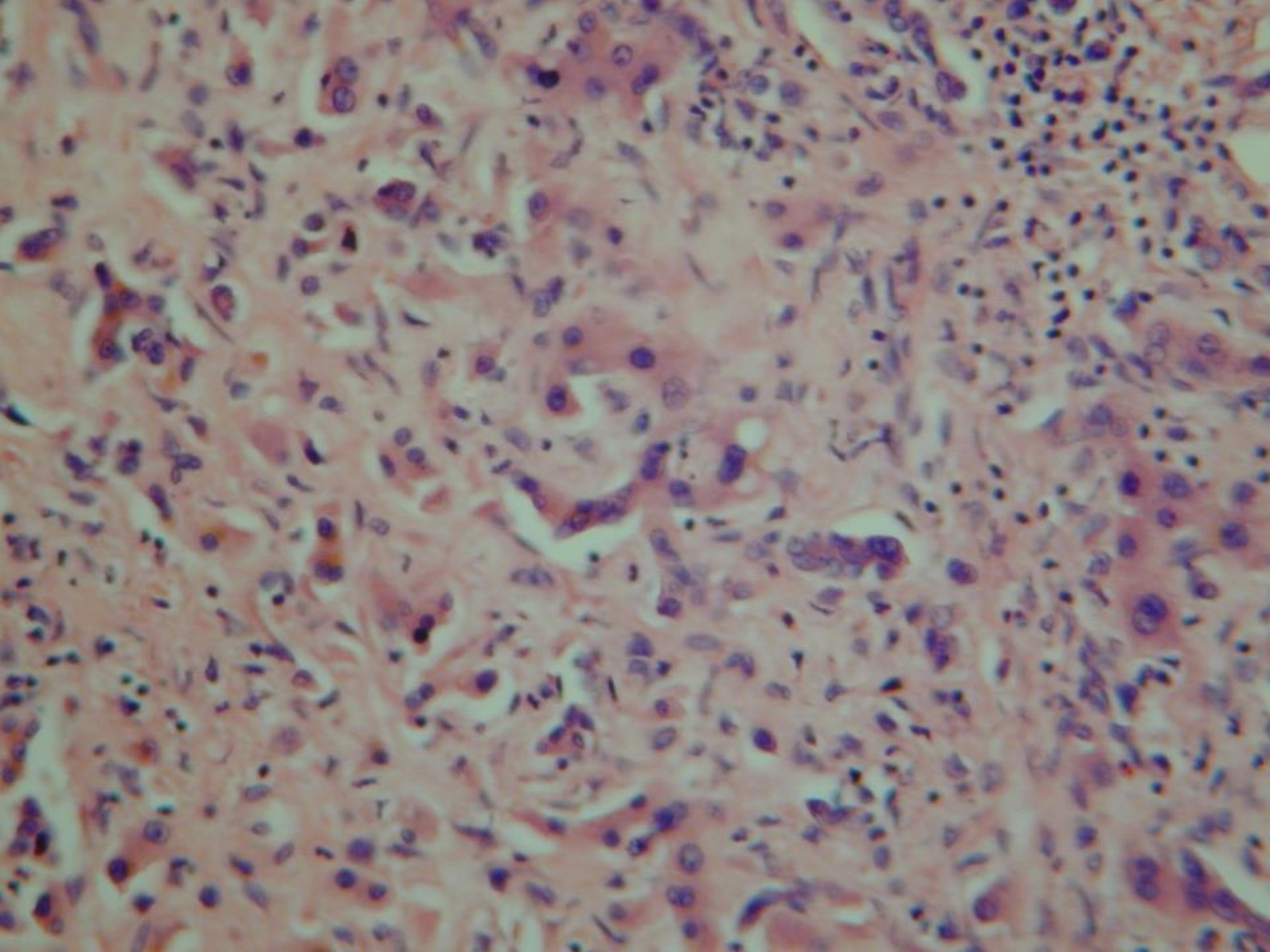


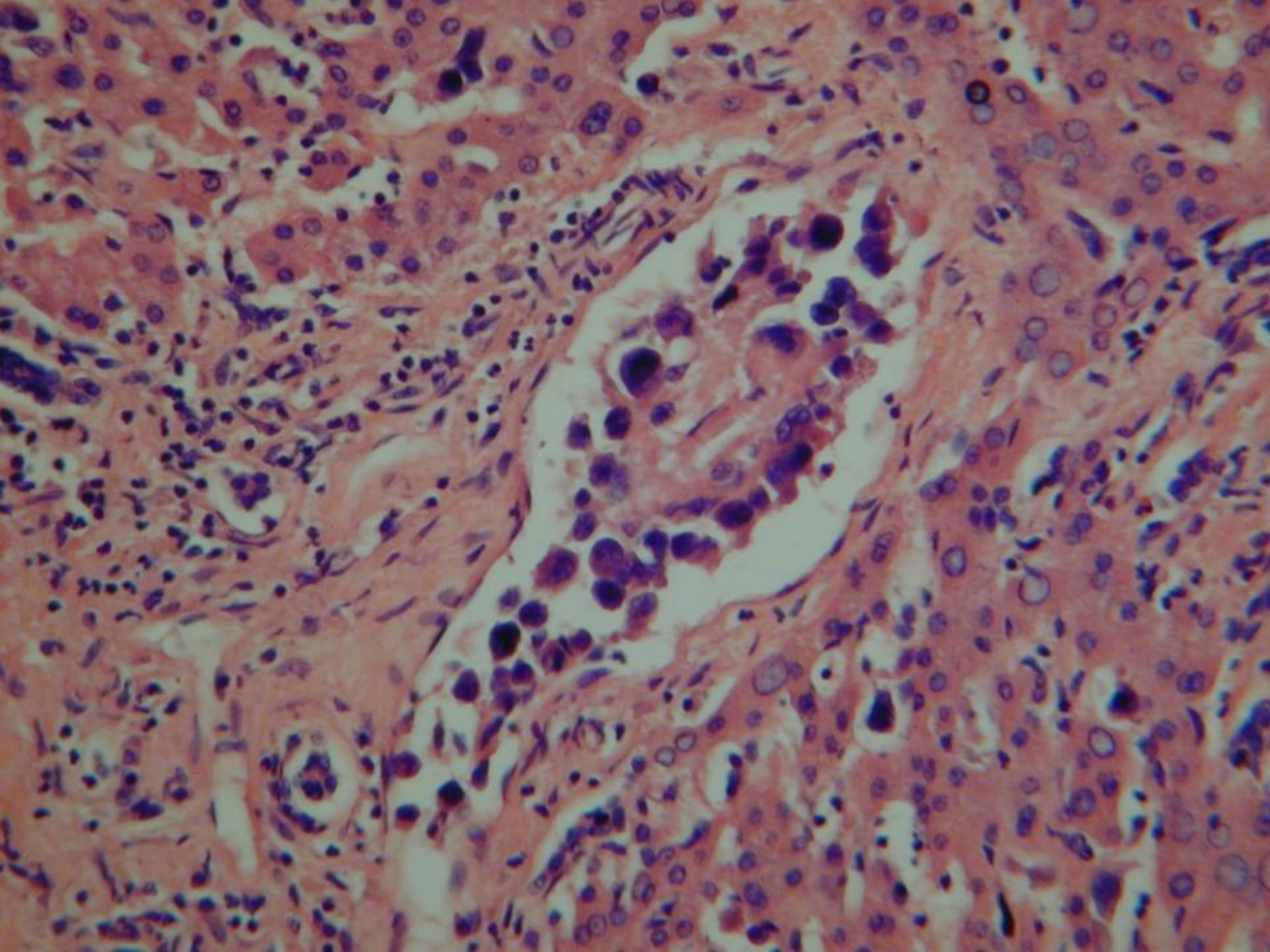


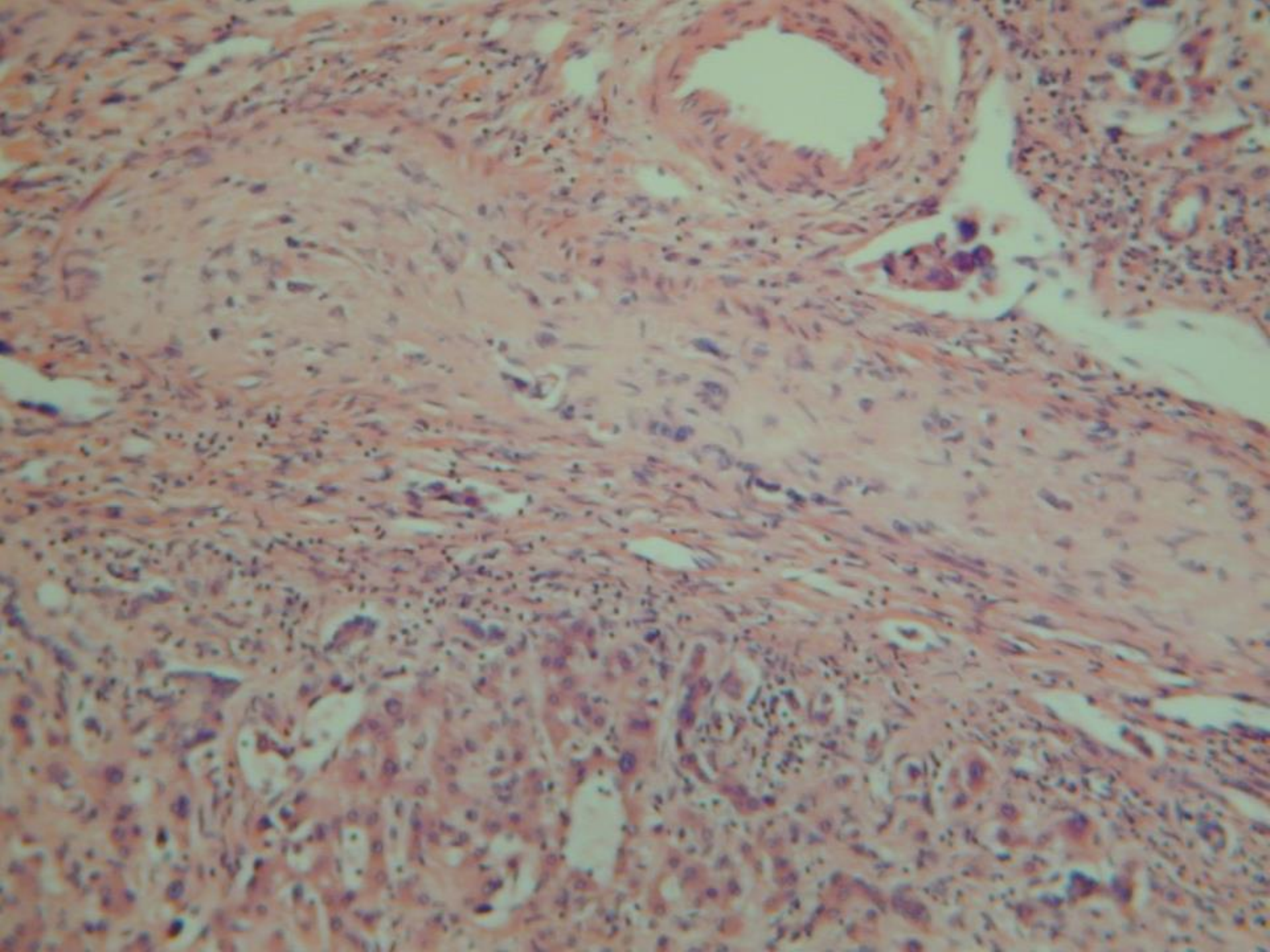


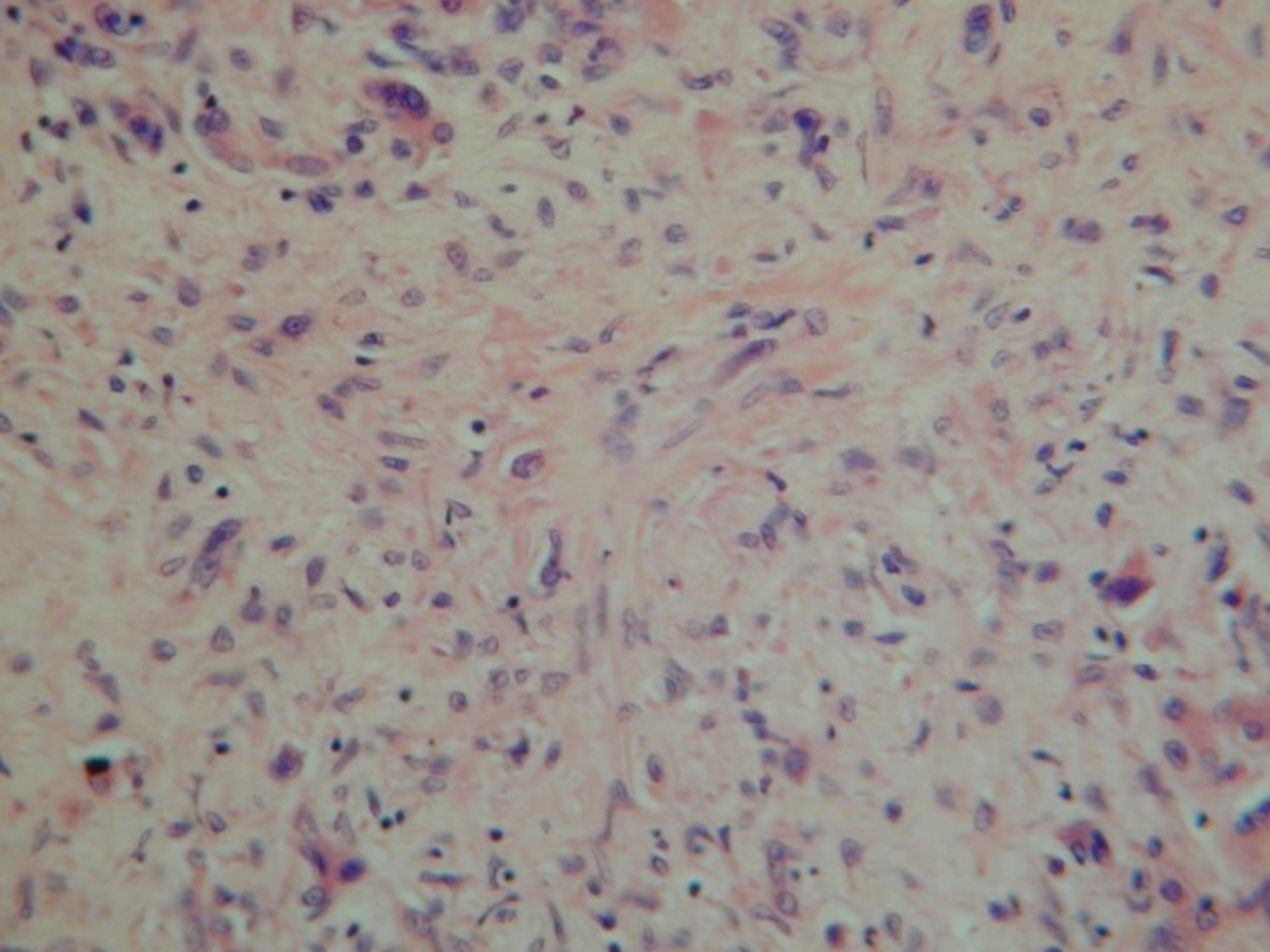


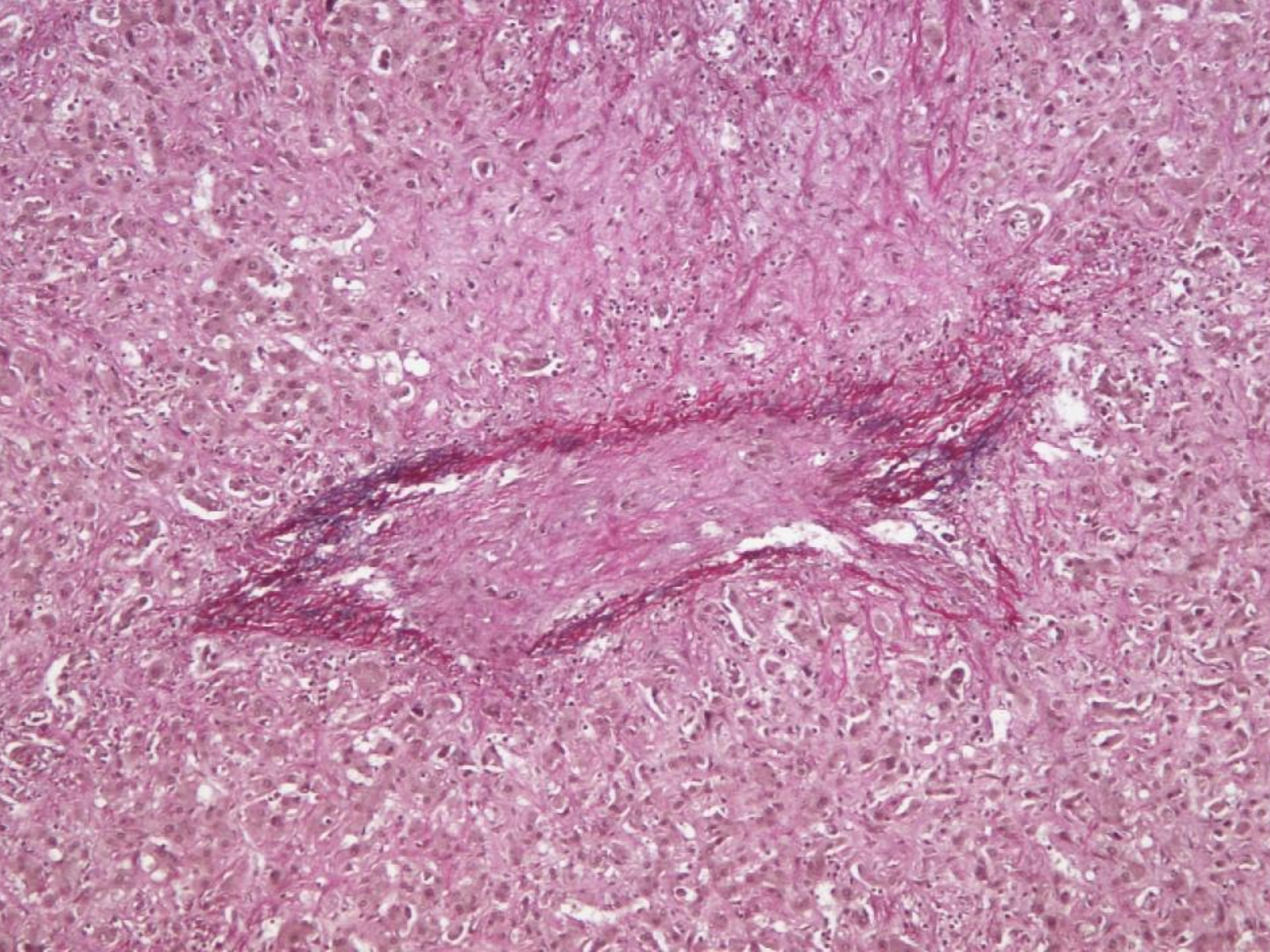


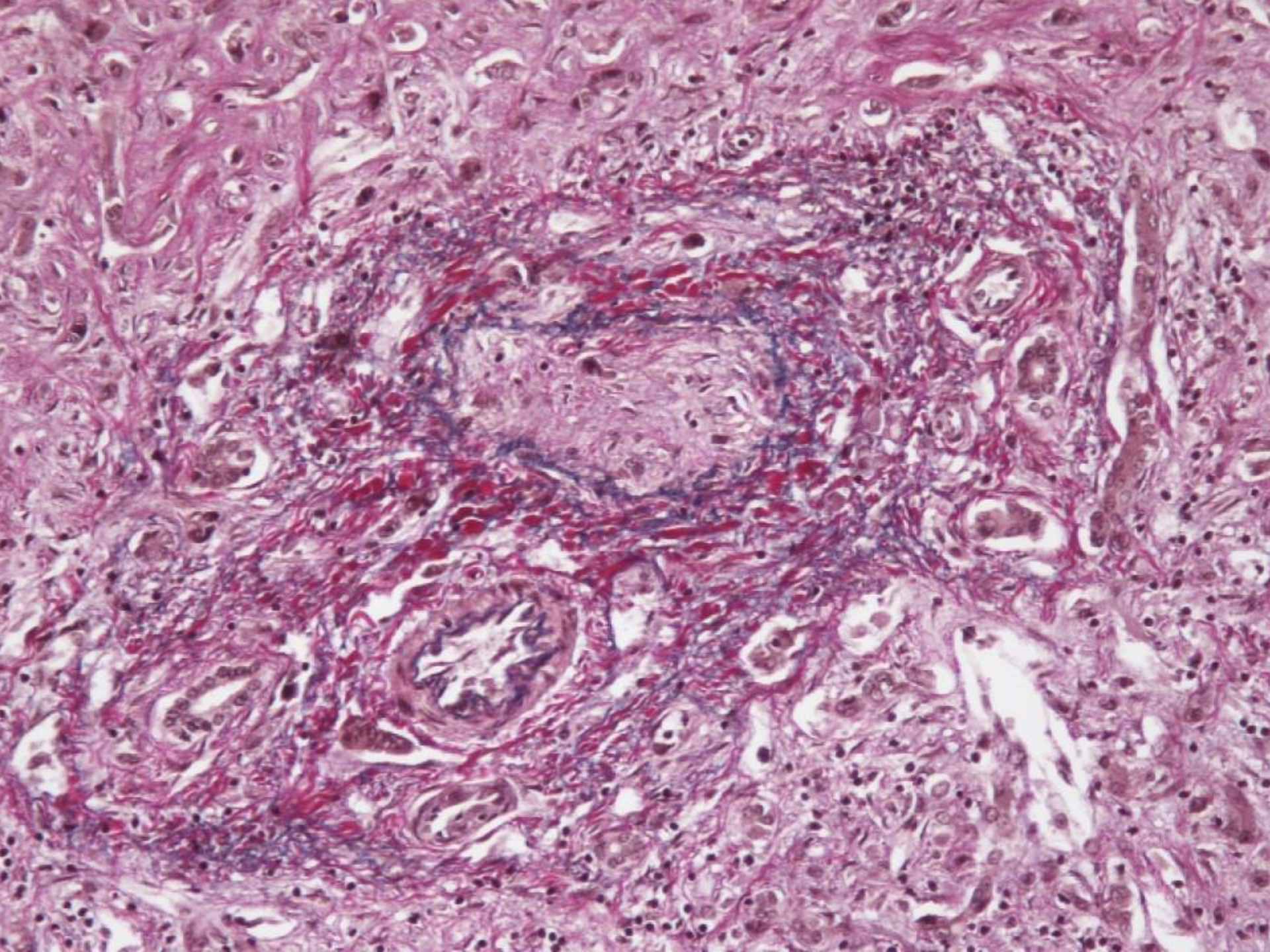


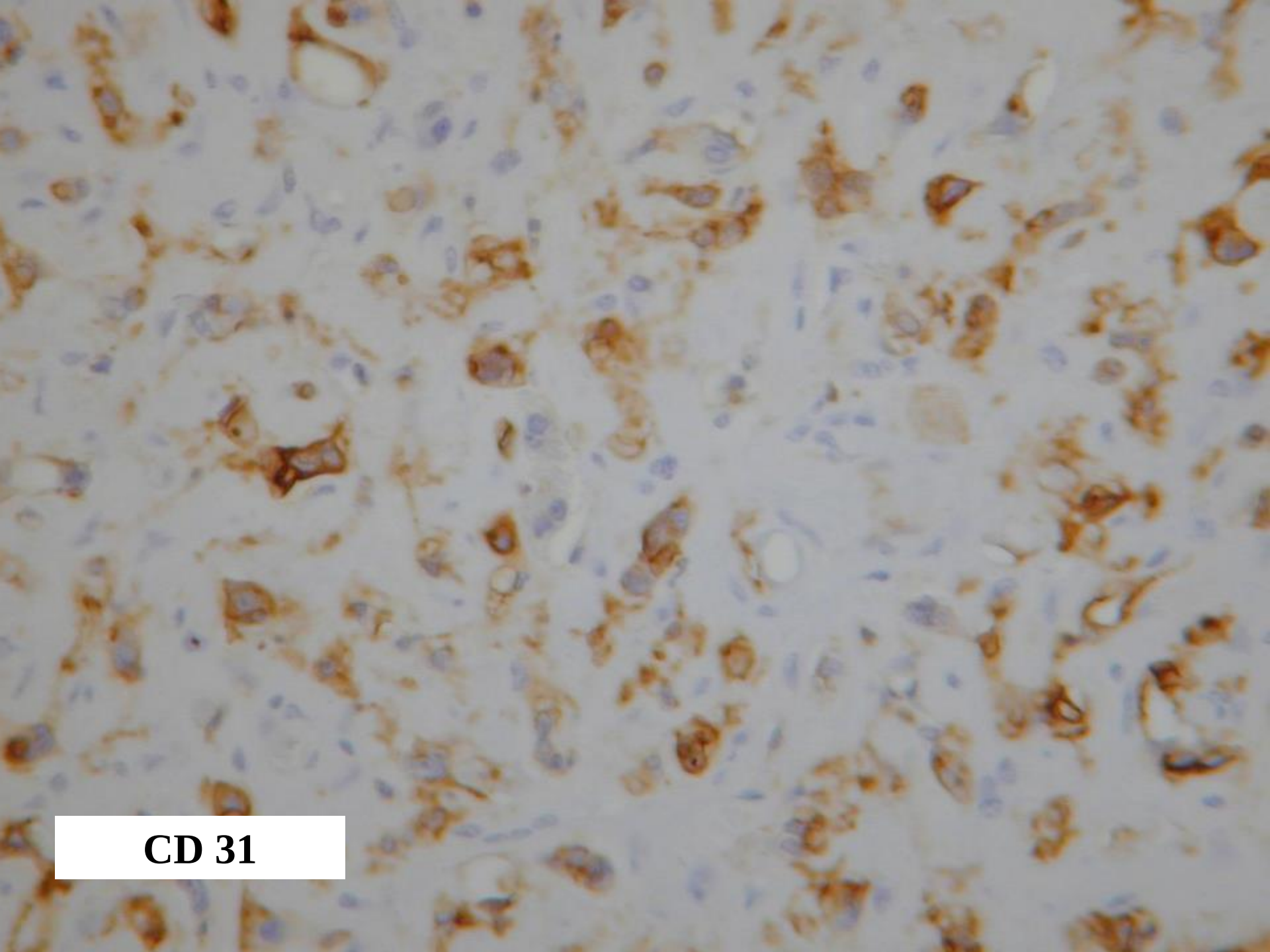








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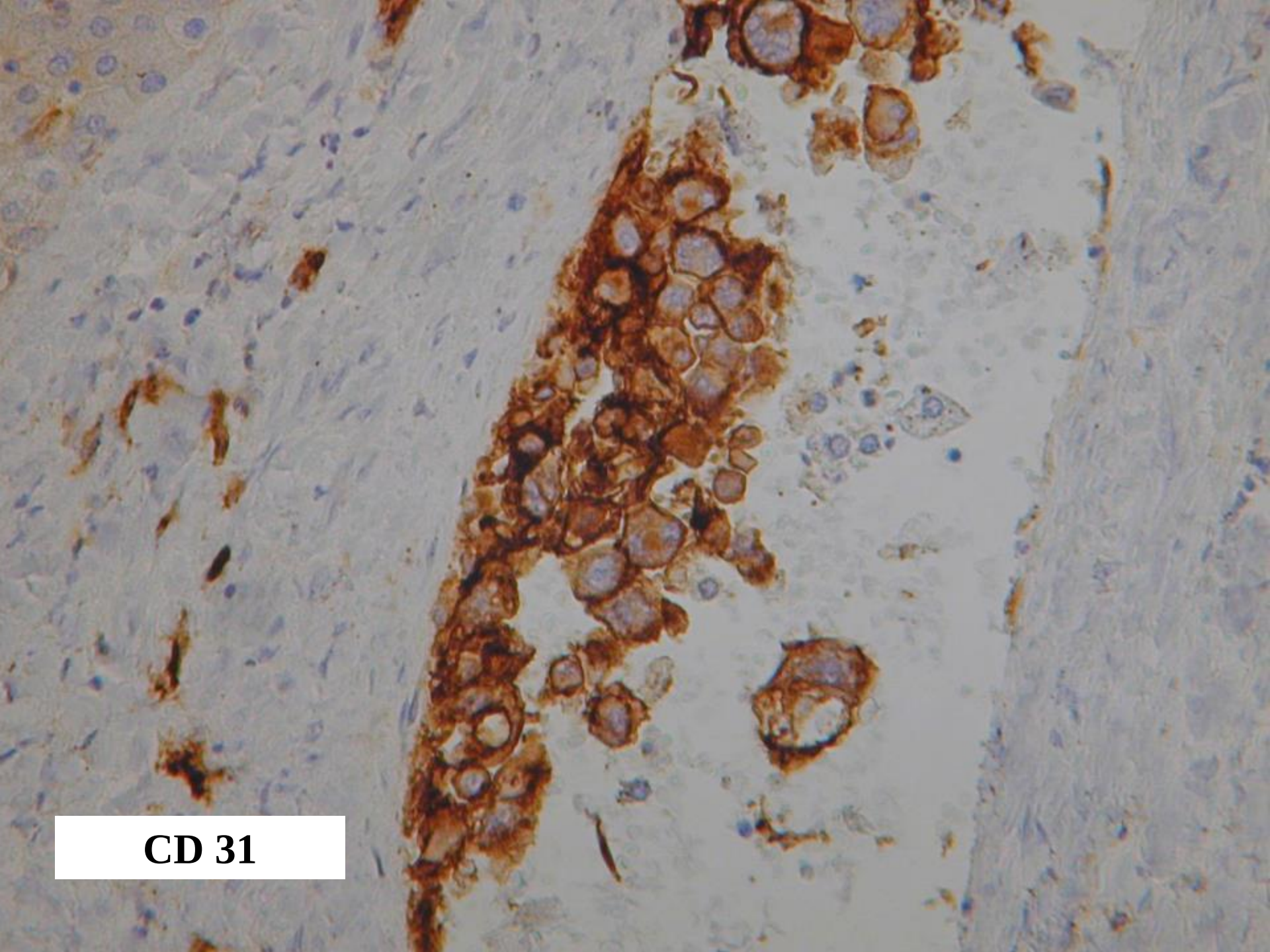
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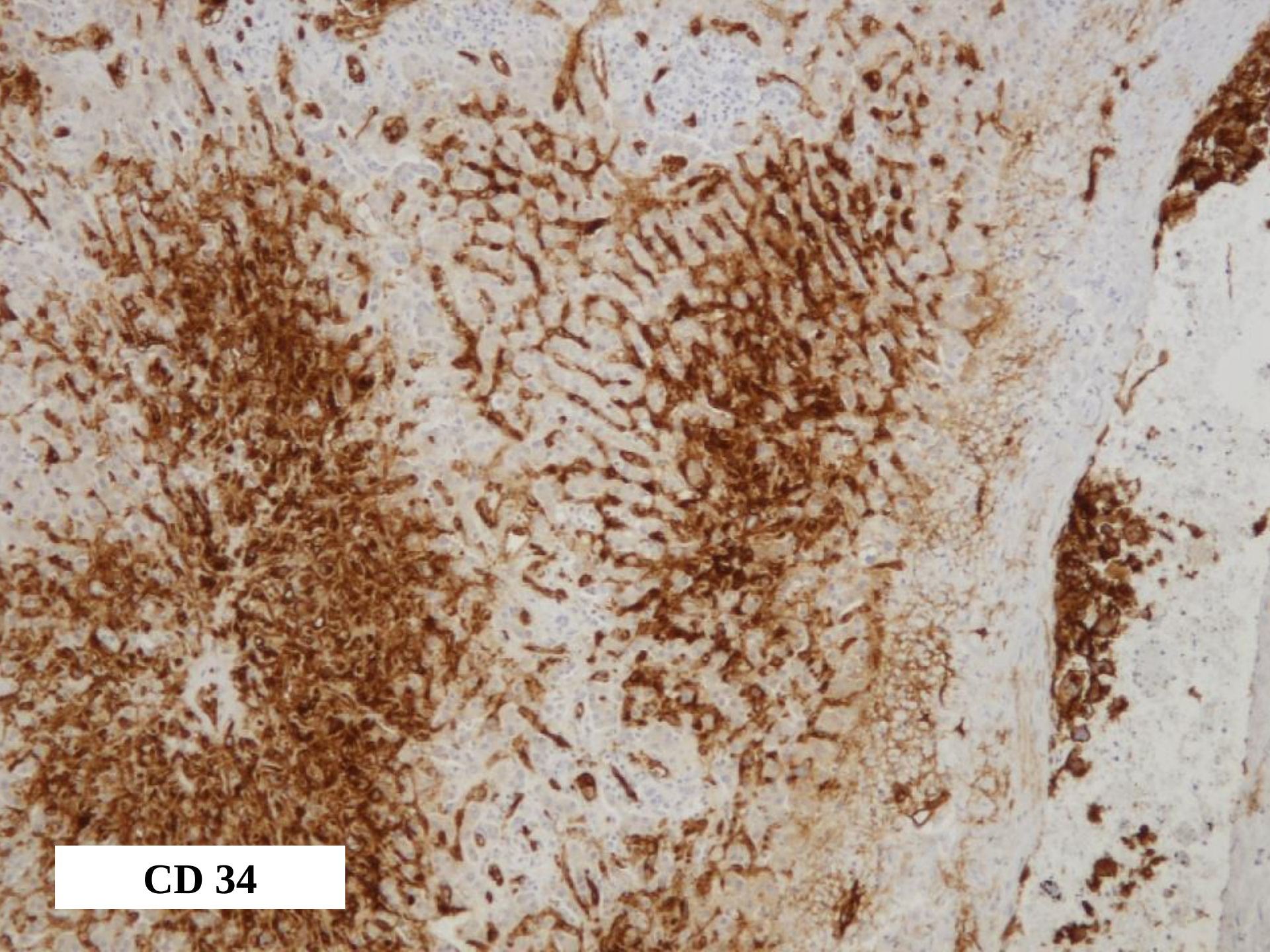
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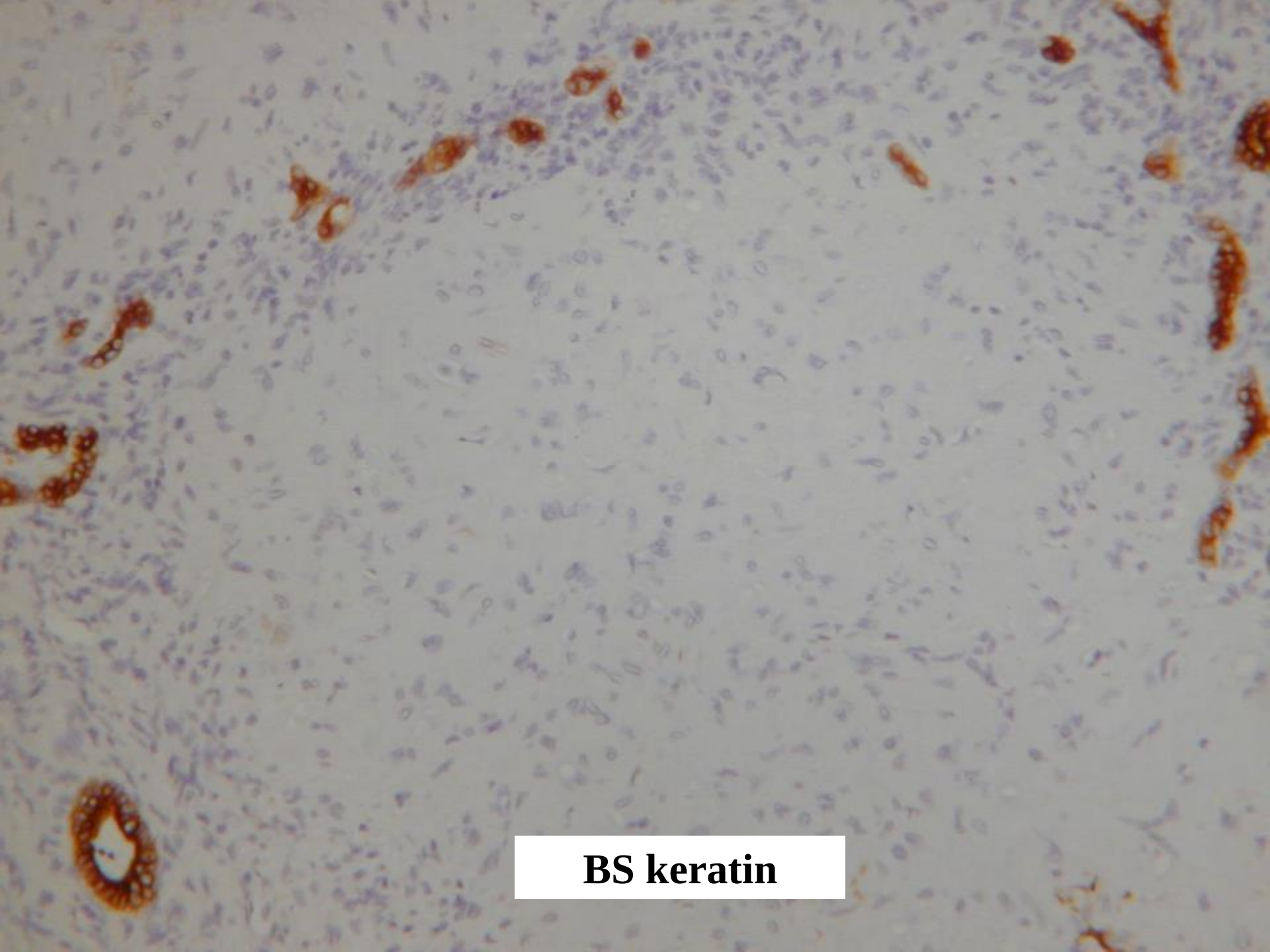
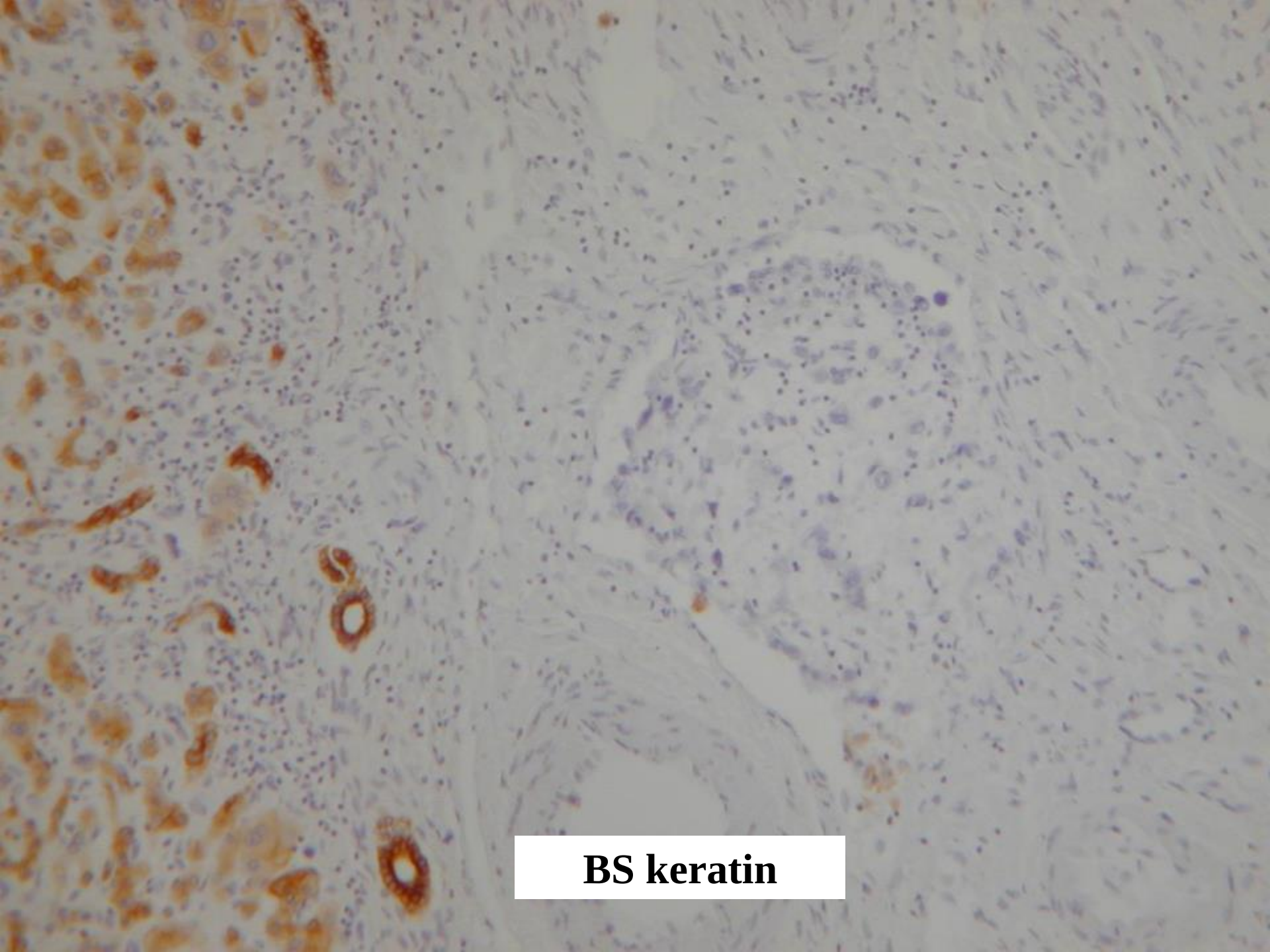

BS keratin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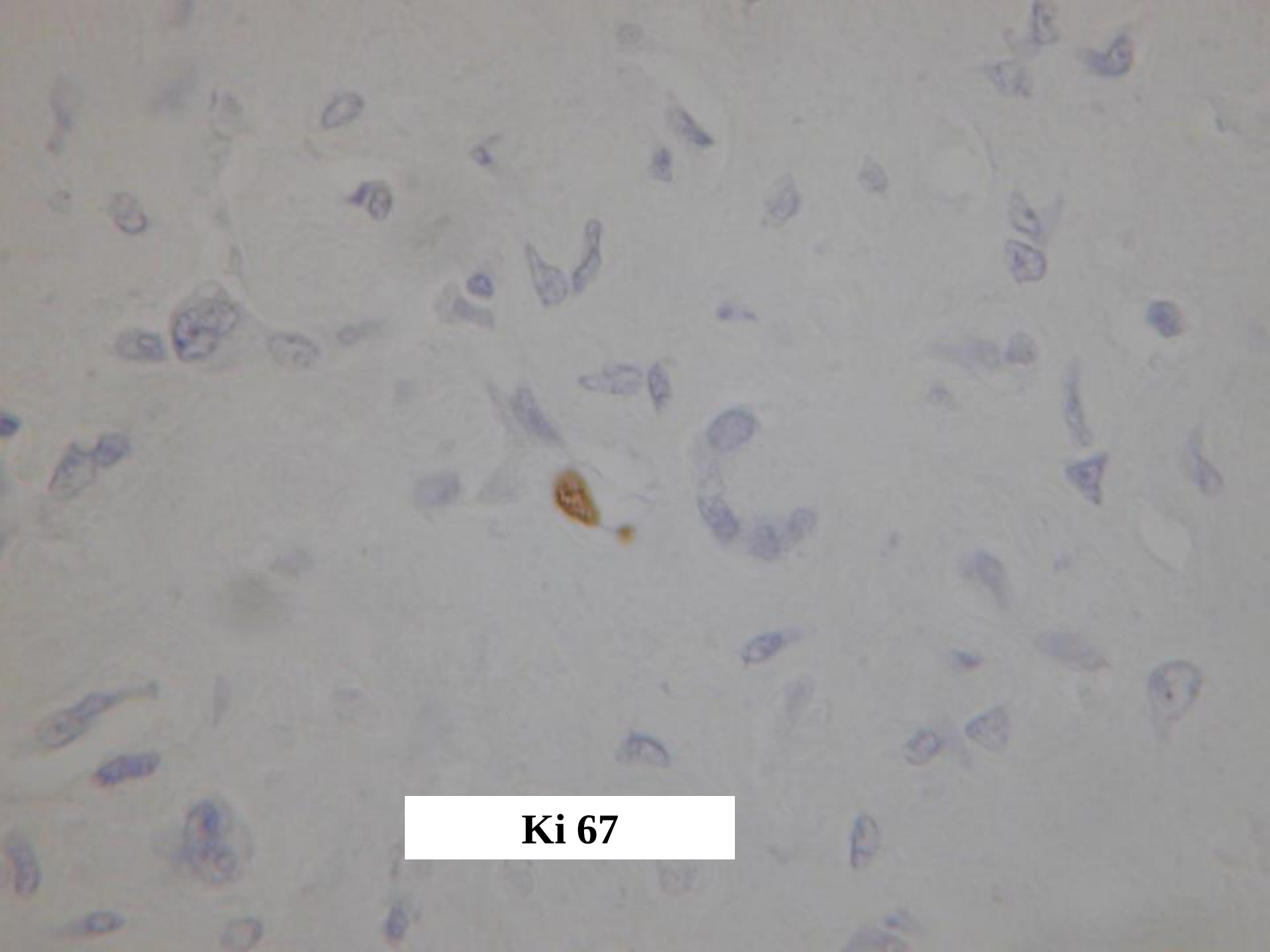
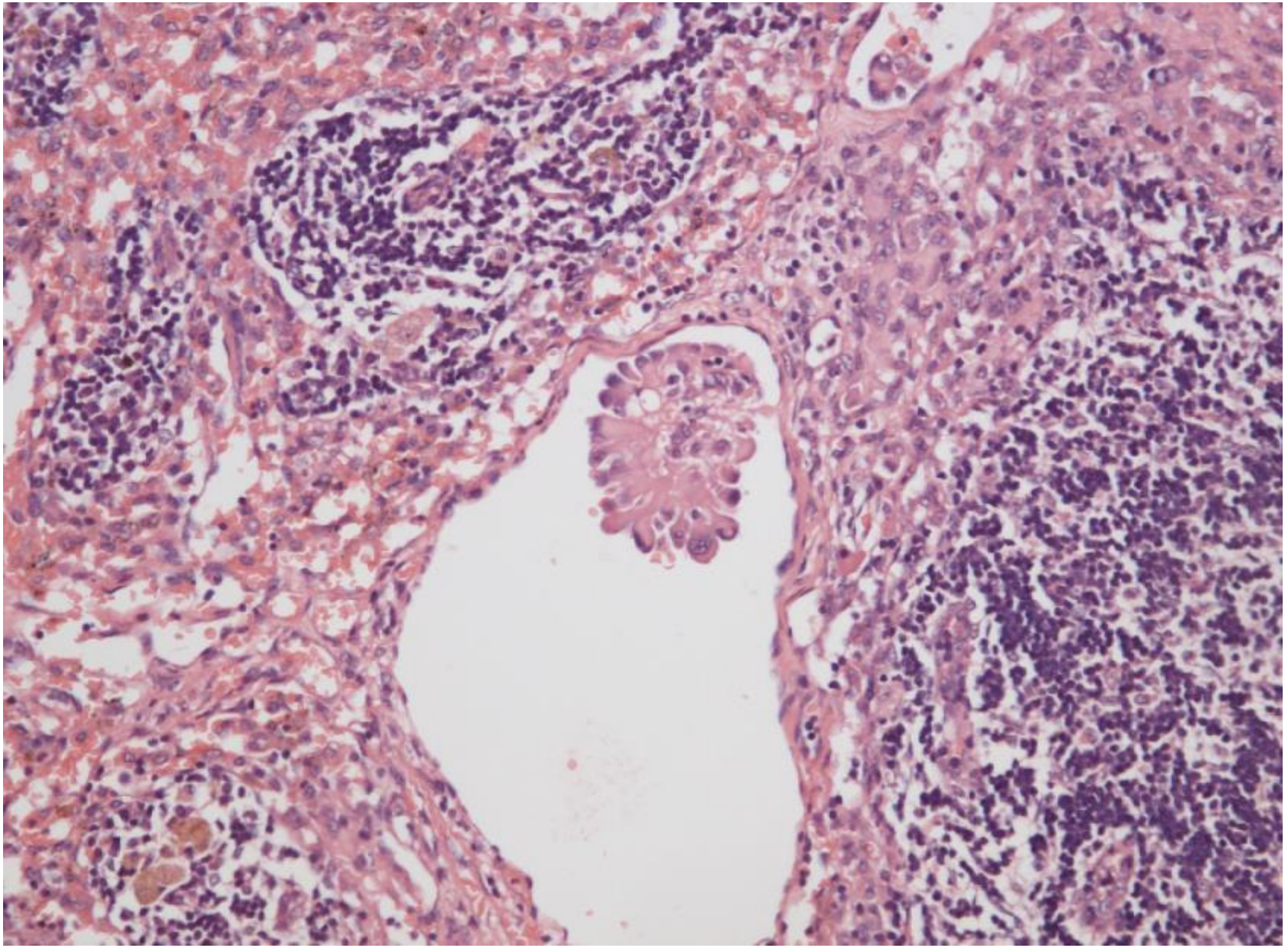

Ki 67

Hilar Lymph Node



Case 8

Diagnosis

Epithelioid haemangioendothelioma

Lymph node metastasis

Epithelioid Haemangioendothelioma - Discussion Points

1. **Characteristic "zonation"** (Dietze 1989)

- highest cellularity at periphery
  - "tectorial" growth pattern along sinusoids
  - intravascular "sprouts"

- obliteration of sinusoids and vessels associated with increasing fibrosis centrally
  - myxoid stroma, scanty tumour cells

Epithelioid Haemangioendothelioma - Discussion Points

2. Usually multifocal

- > 80% of cases, both lobes
  - Implications for surgical resection
  - Liver transplantation as treatment option

- Extrahepatic disease in 30-40% of cases
  - Lung commonest site
  - Other sites include lymph nodes, peritoneum, spleen & bone (Mehrabi 2006)
  - ? Metastatic disease, ? Multifocal primary sites

- Recent molecular studies have shown identical WWTR1-CAMTA1 fusion product in different nodules from 2 patients with multi-centric hepatic EHE (Errani 2012)
  - Suggests metastatic implants from same neoplastic clone

Epithelioid haemangioendothelioma - Discussion Points

3. **Differential Diagnosis**
   - other neoplasms (esp sclerosing carcinoma)
   - reactive conditions with fibrosis (including Budd-Chiari syndrome)

- Overall 60-80% incorrect initial diagnosis (Makhlouf 1999, Mehrabi 2006)
  - Most common cholangiocarcinoma (29%), angiosarcoma (10%), HCC (6%), metastatic carcinoma (6%), sclerosing haemangioma (6%)

Epithelioid haemangioendothelioma - Discussion Points

4. Behaviour unpredictable

- Low grade malignancy (40-50 % 5 year survival)
- High cellularity associated with poor outcome (Makhlouf 1999)
- Size & number of nodules, number of segments involved also prognostic (Grotz 2010)

Case 9

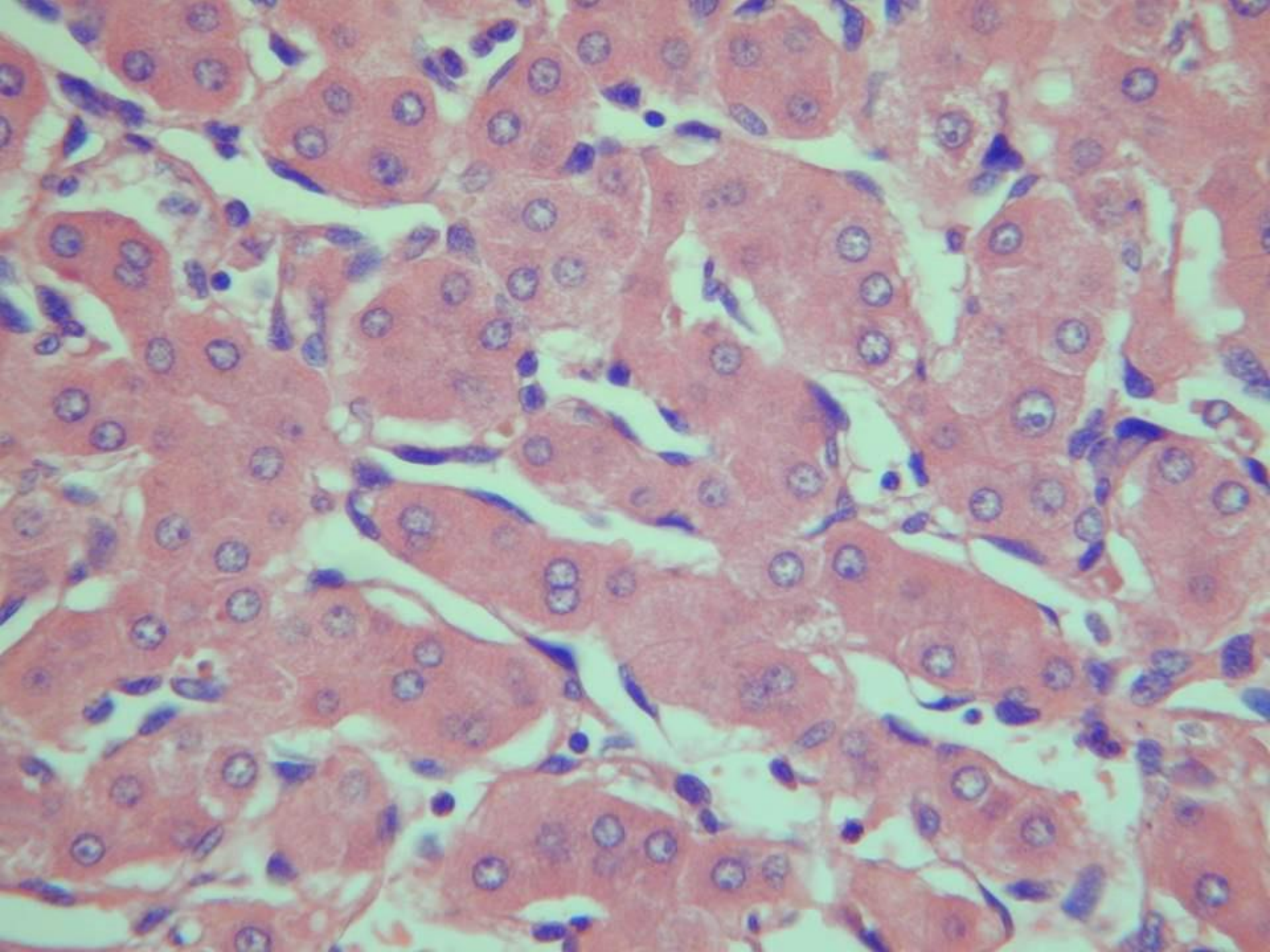
Case 9 - Clinical Summary

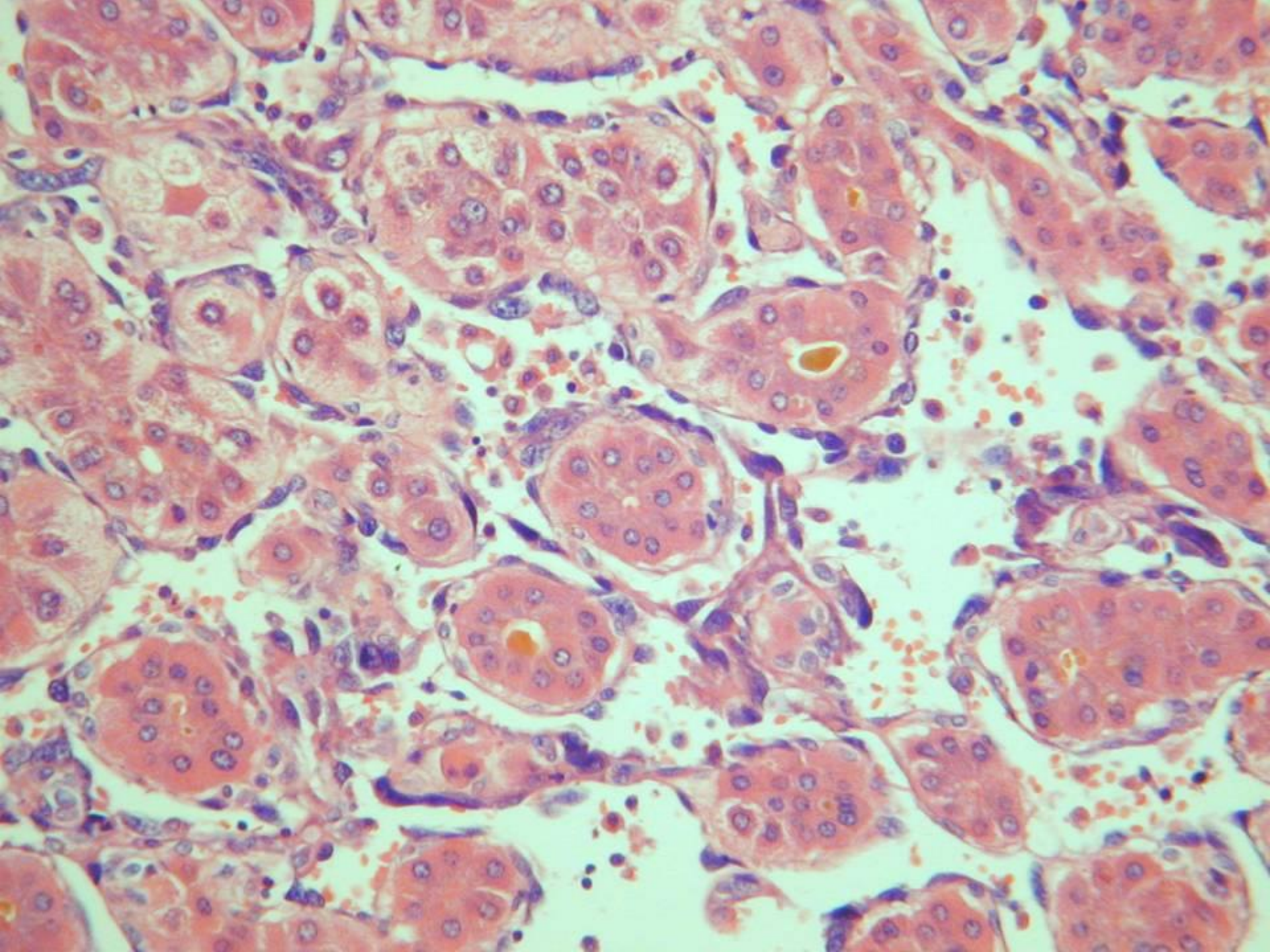
Male, age 37

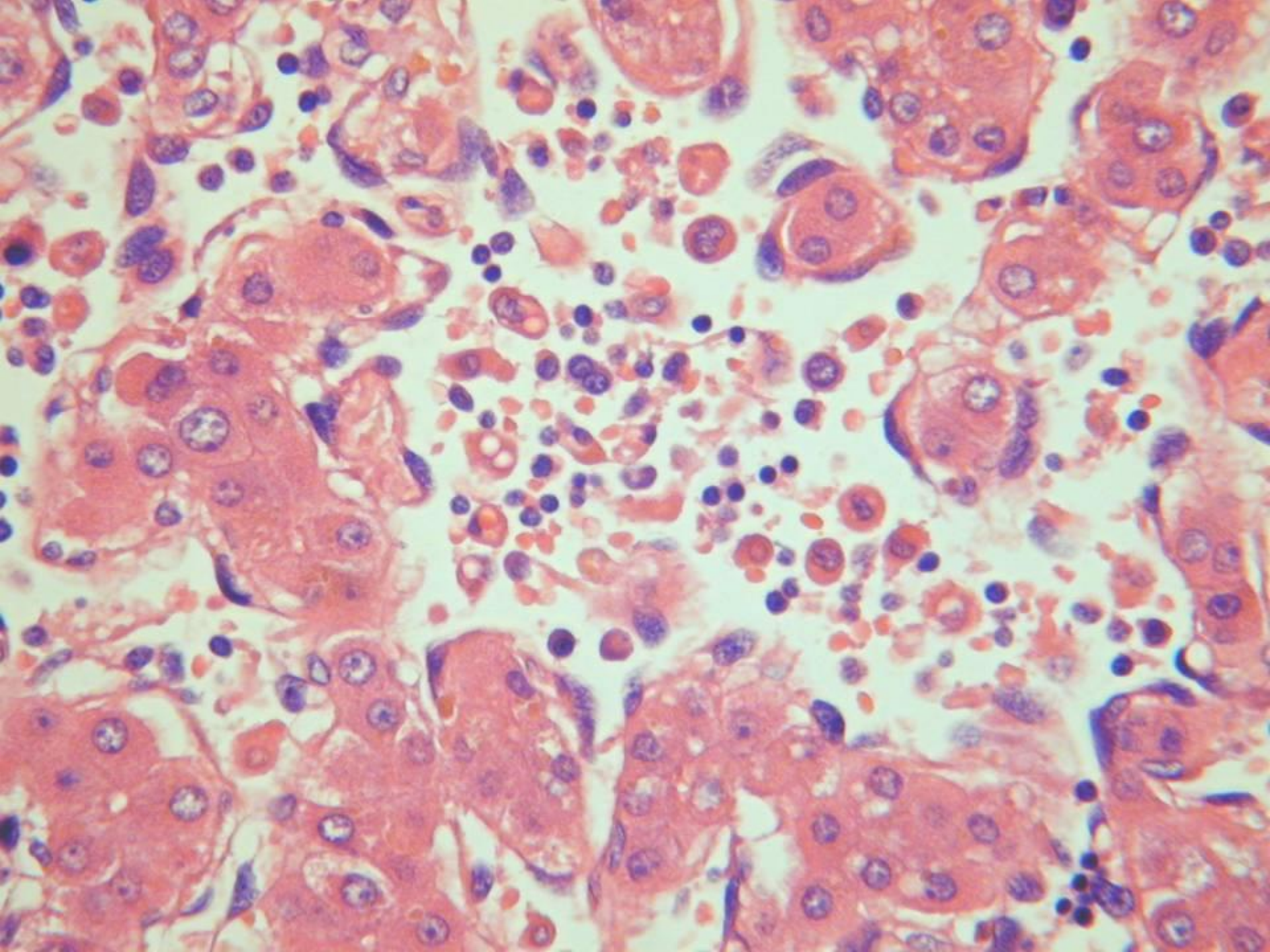
- Liver transplantation
- Multiple haemorrhagic nodules throughout the liver

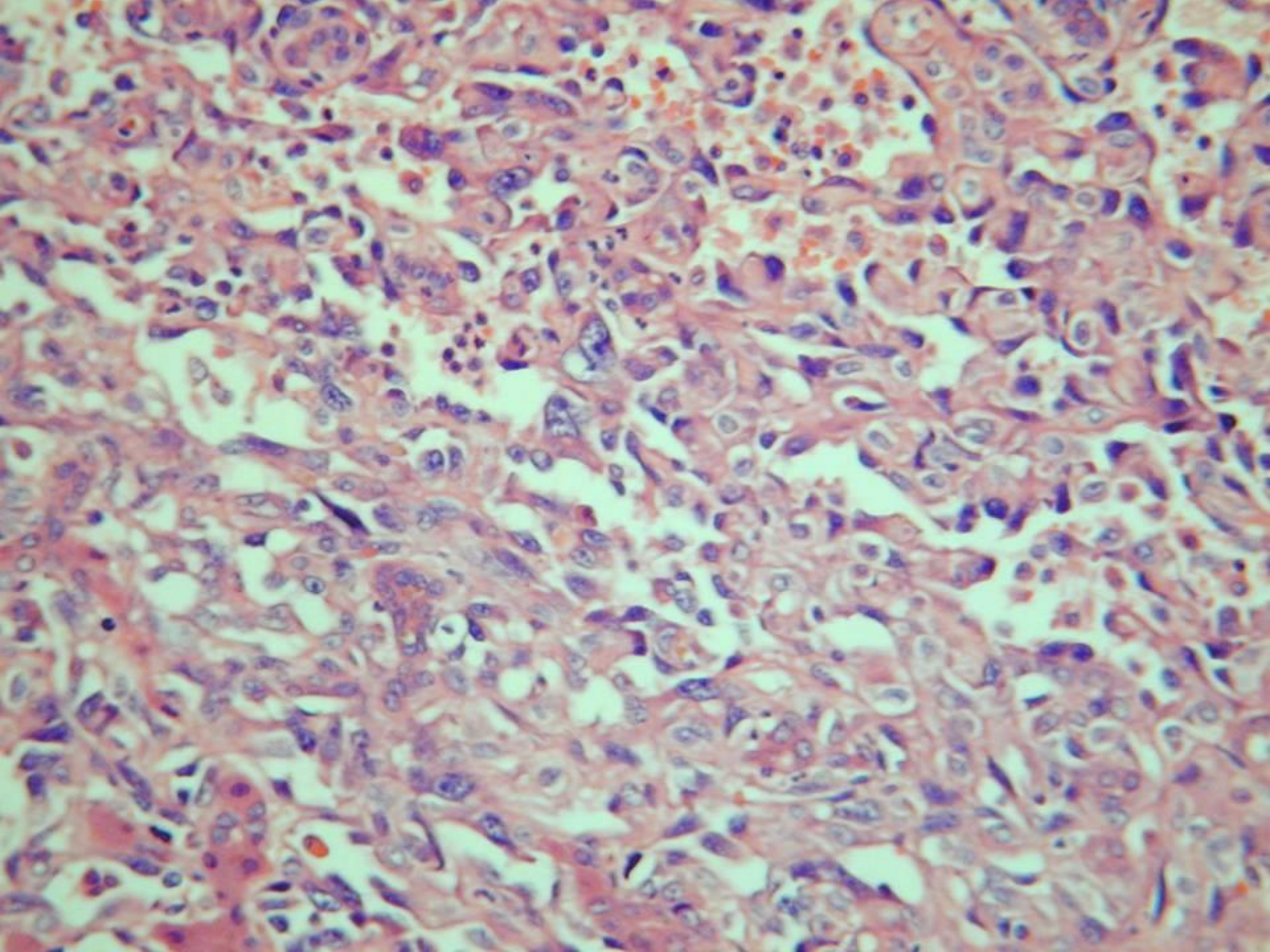
Further Clinical Information

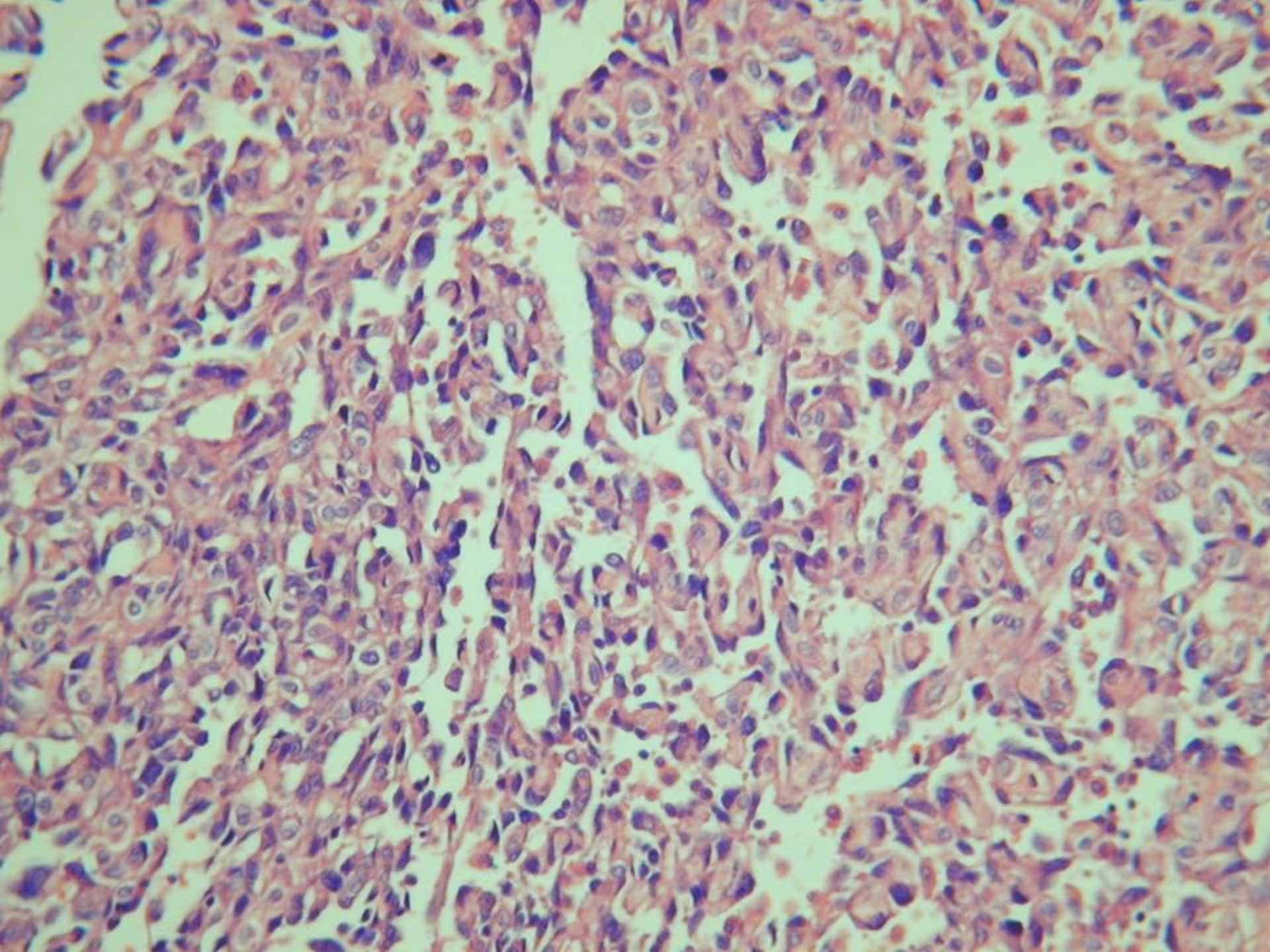
- Presented Dec 1988 with signs of decompensated liver disease (suspected ALD)
- Liver biopsy (at referring hospital) – extensive fibrosis ("pattern not typical of alcoholic cirrhosis")
- Review of liver biopsy – occasional atypical endothelial cells ? angiosarcoma
- Repeat liver biopsy – vasoformative neoplasm, in keeping with angiosarcoma
- Liver transplantation, March 1989

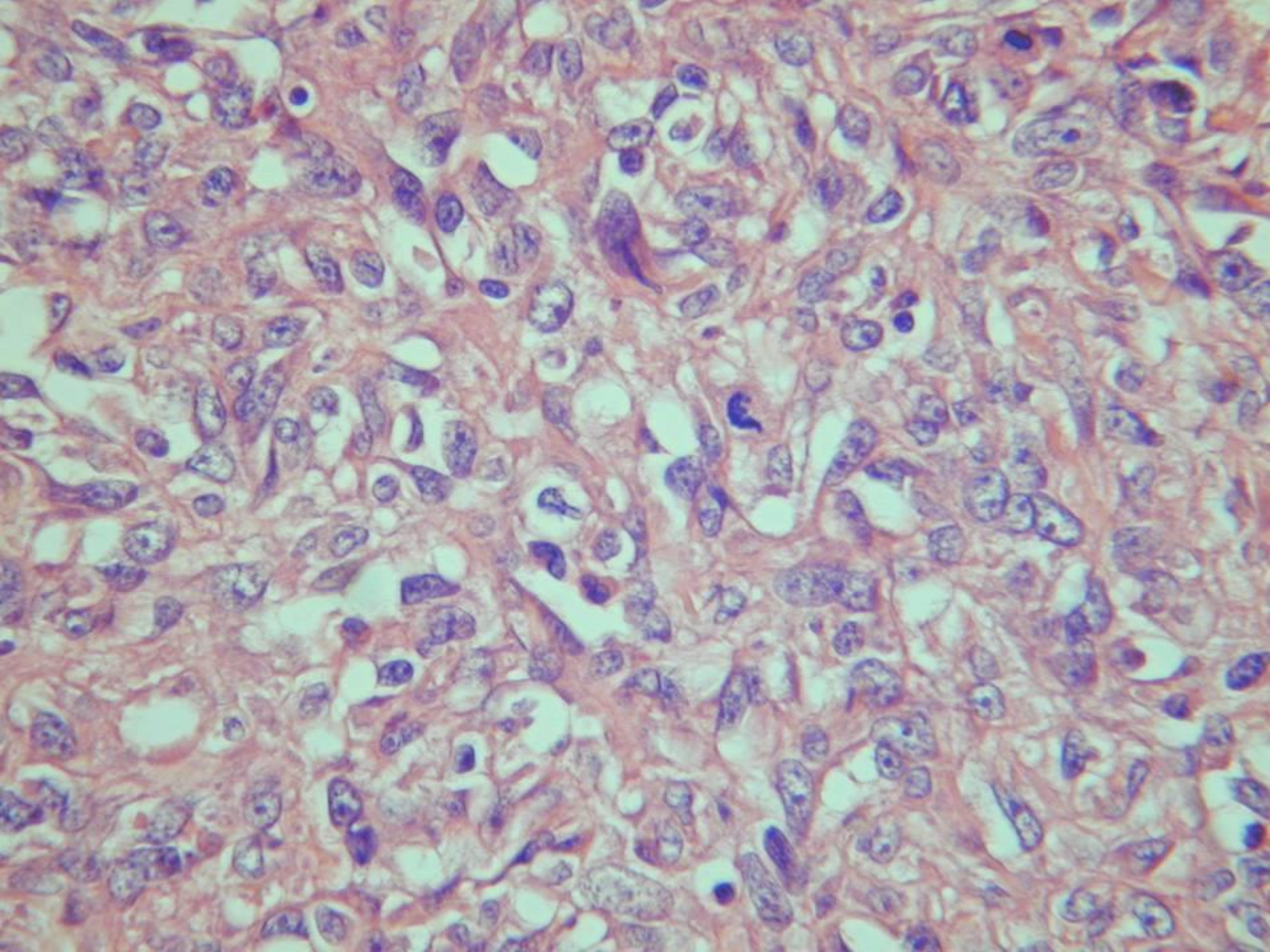


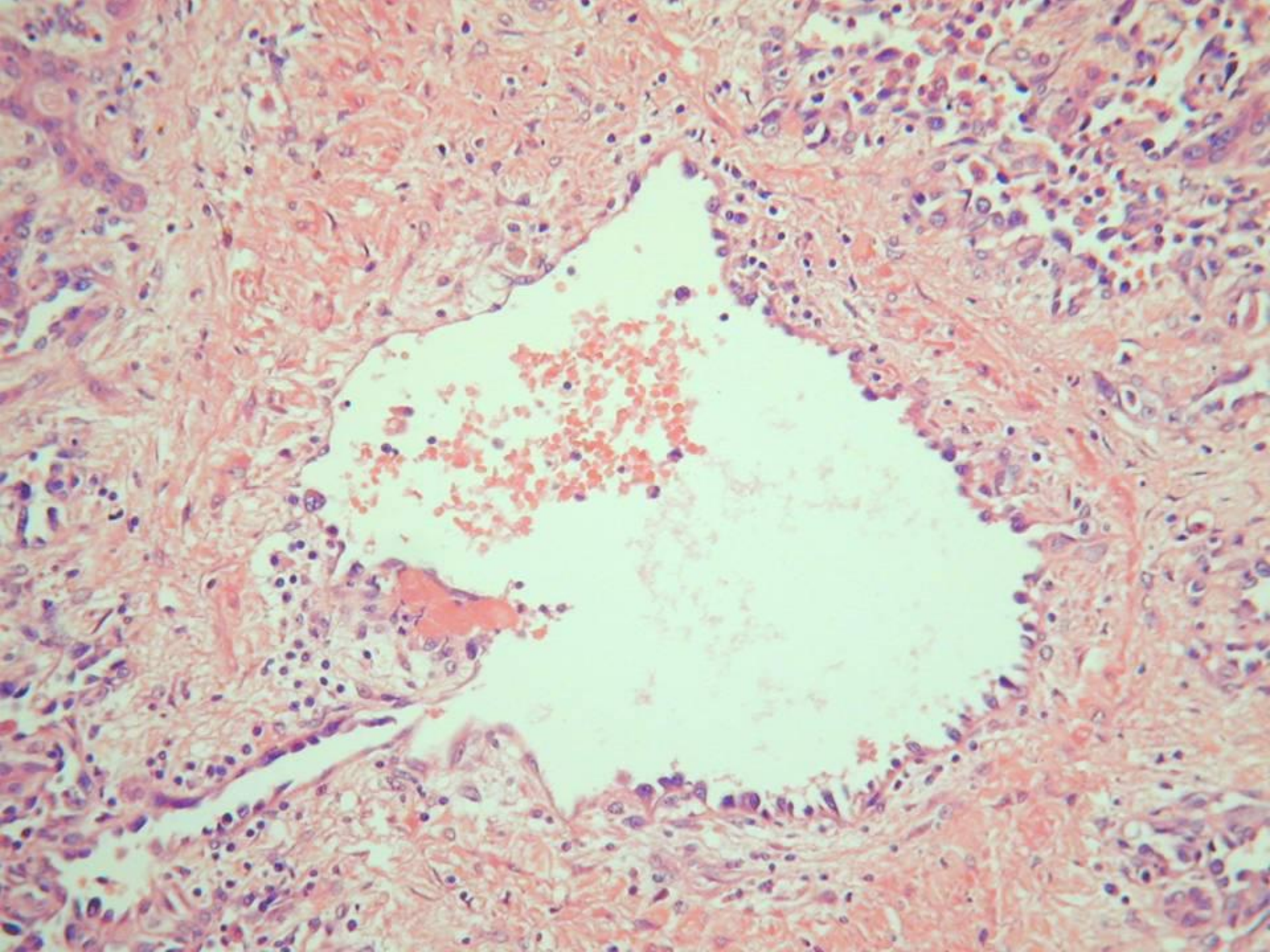


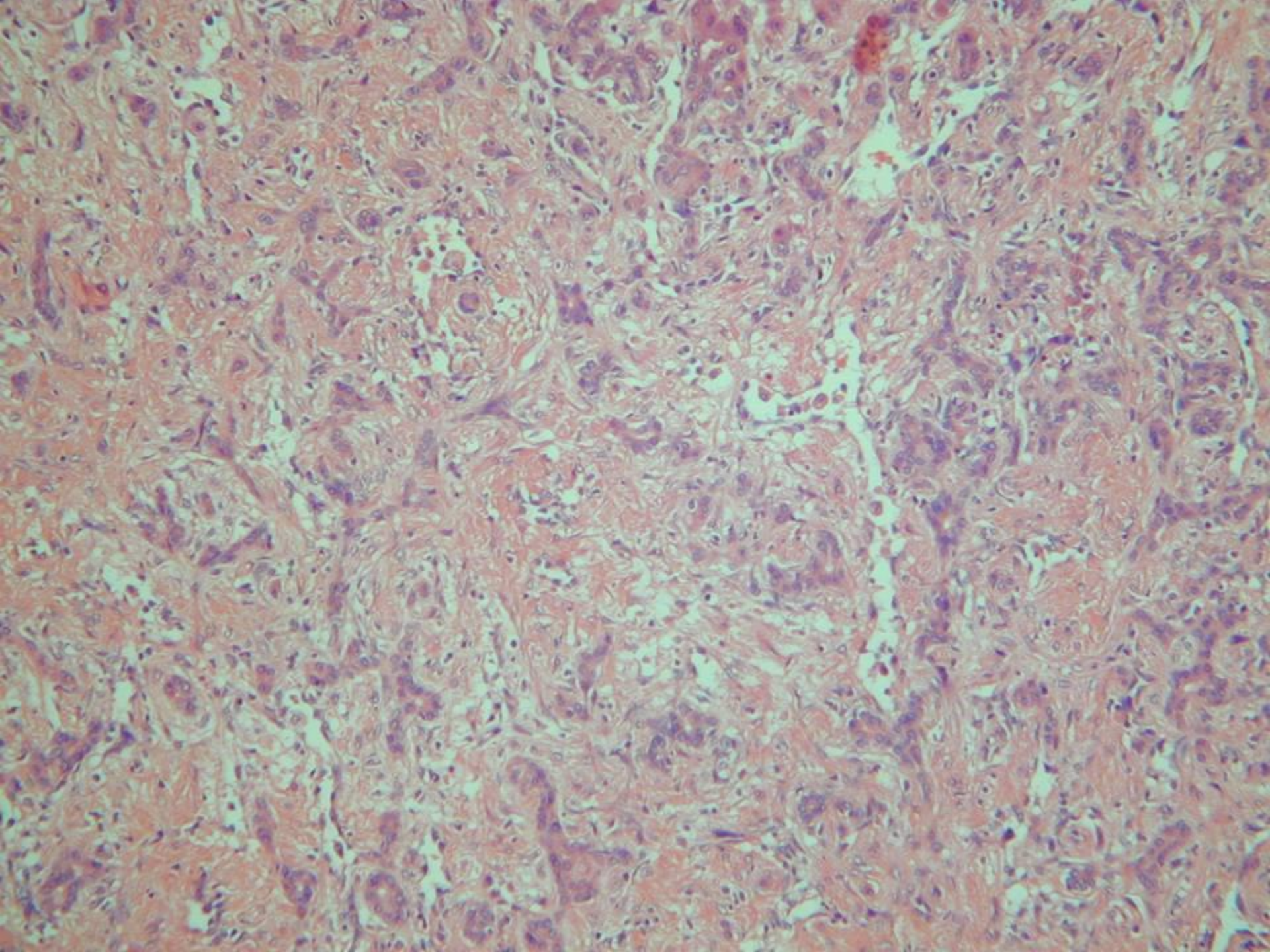


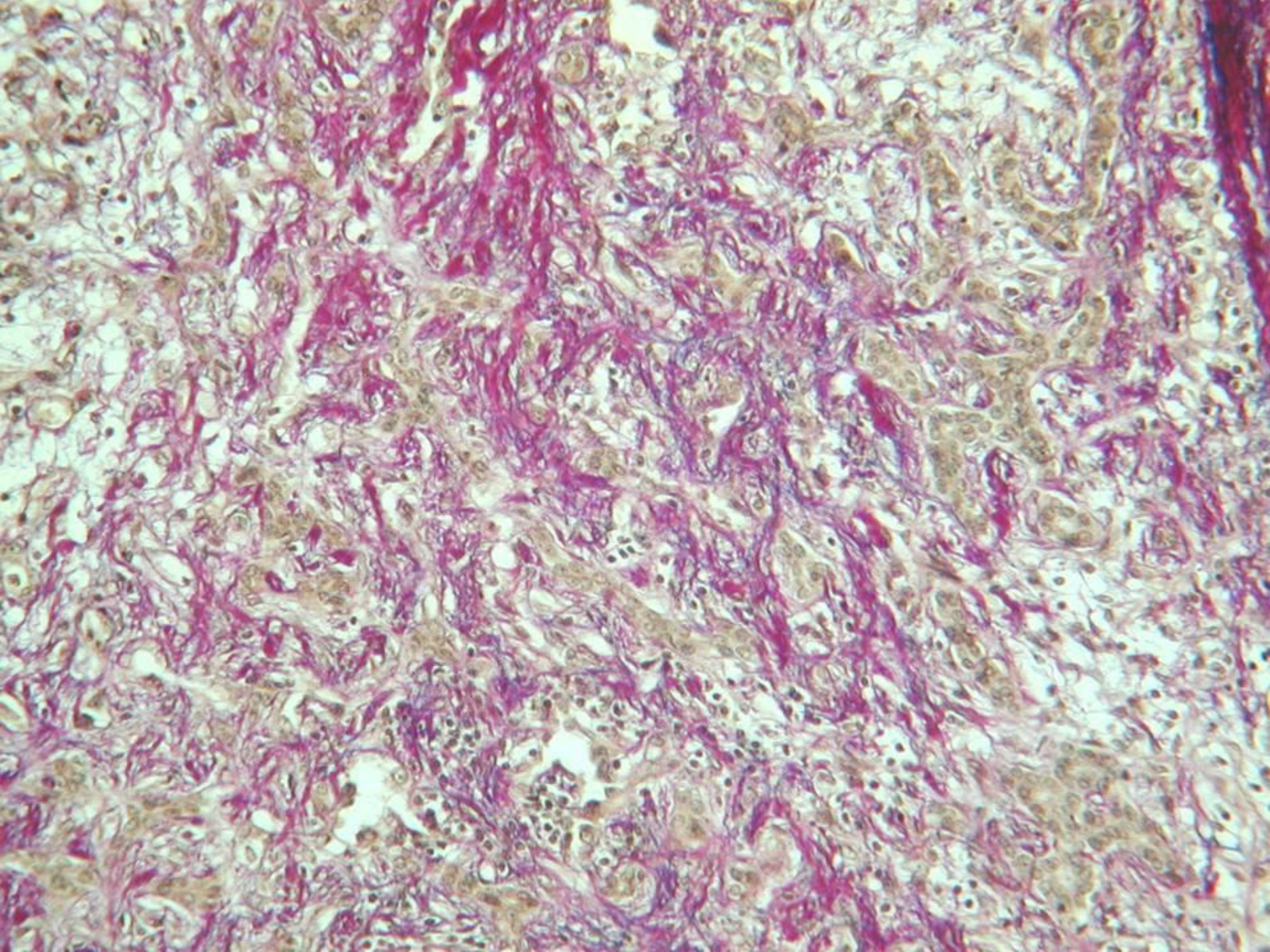


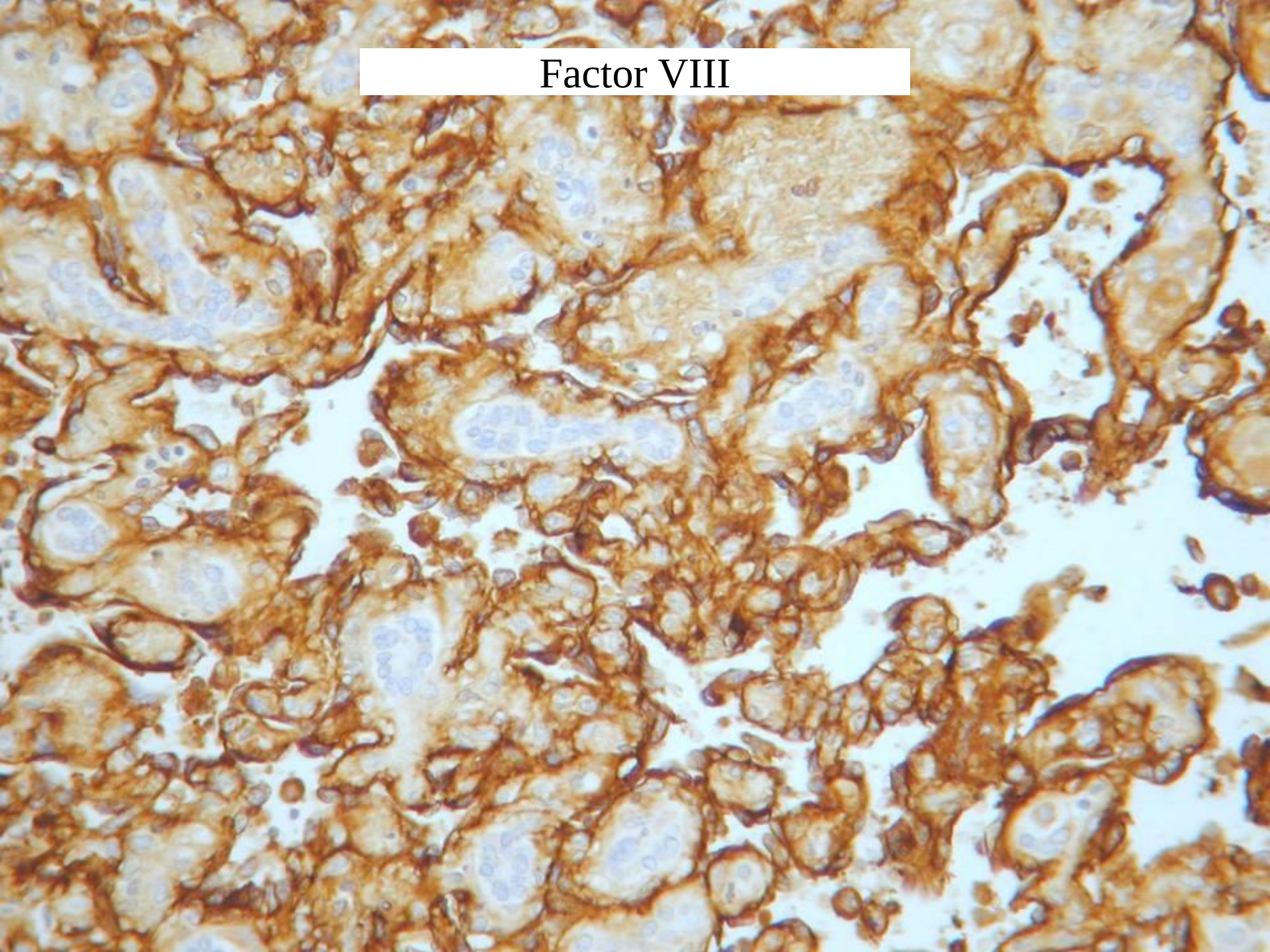








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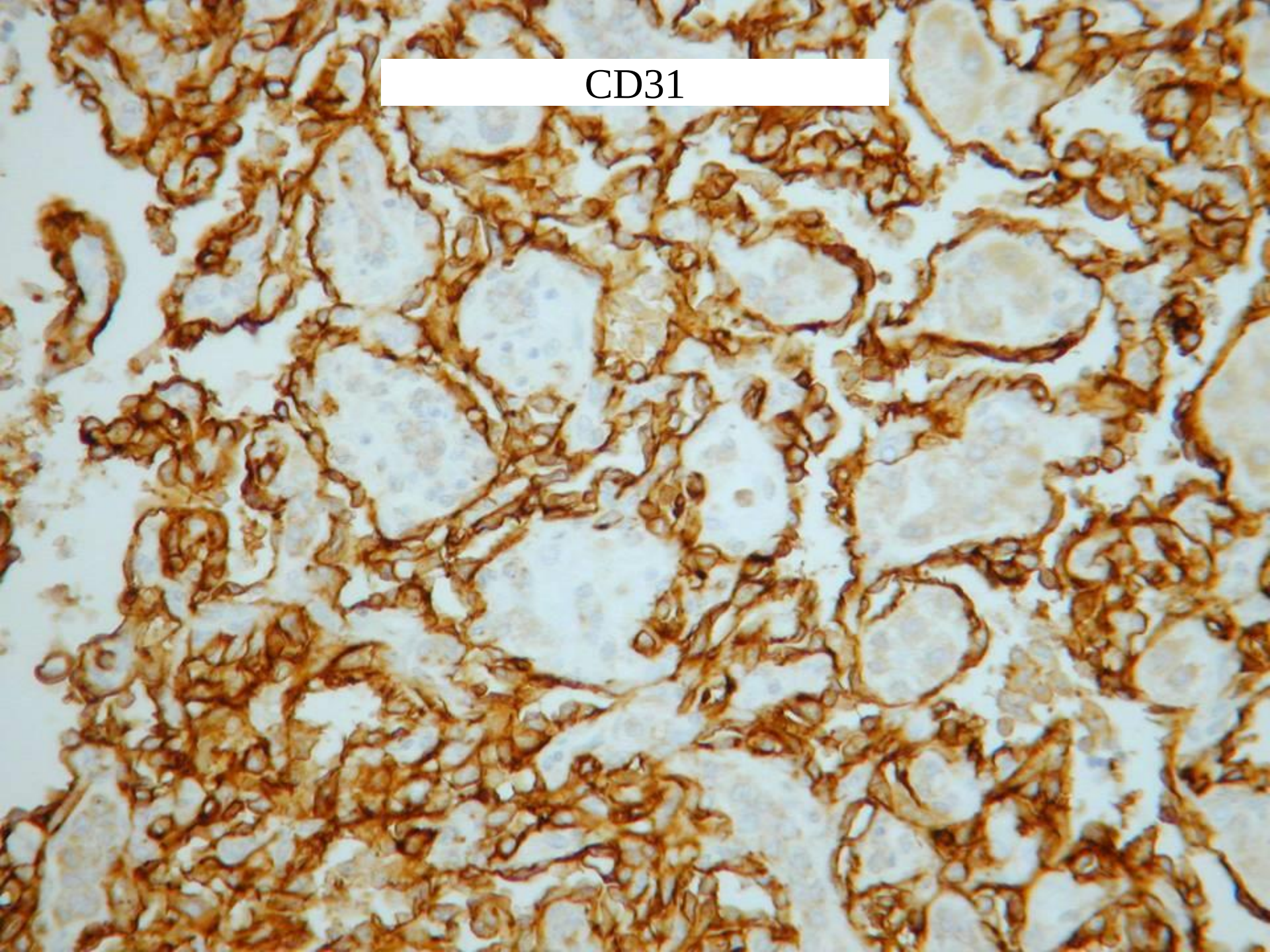
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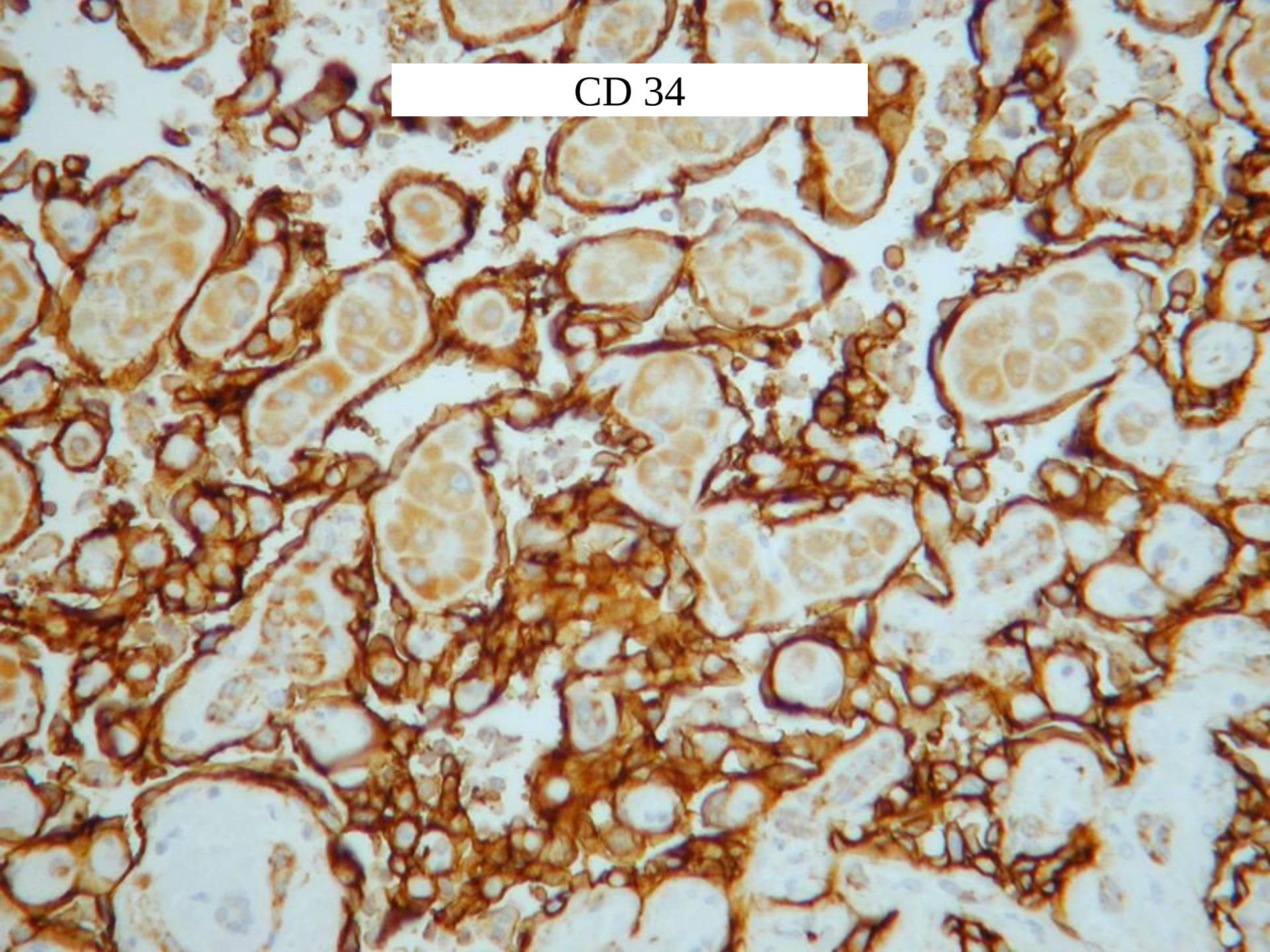
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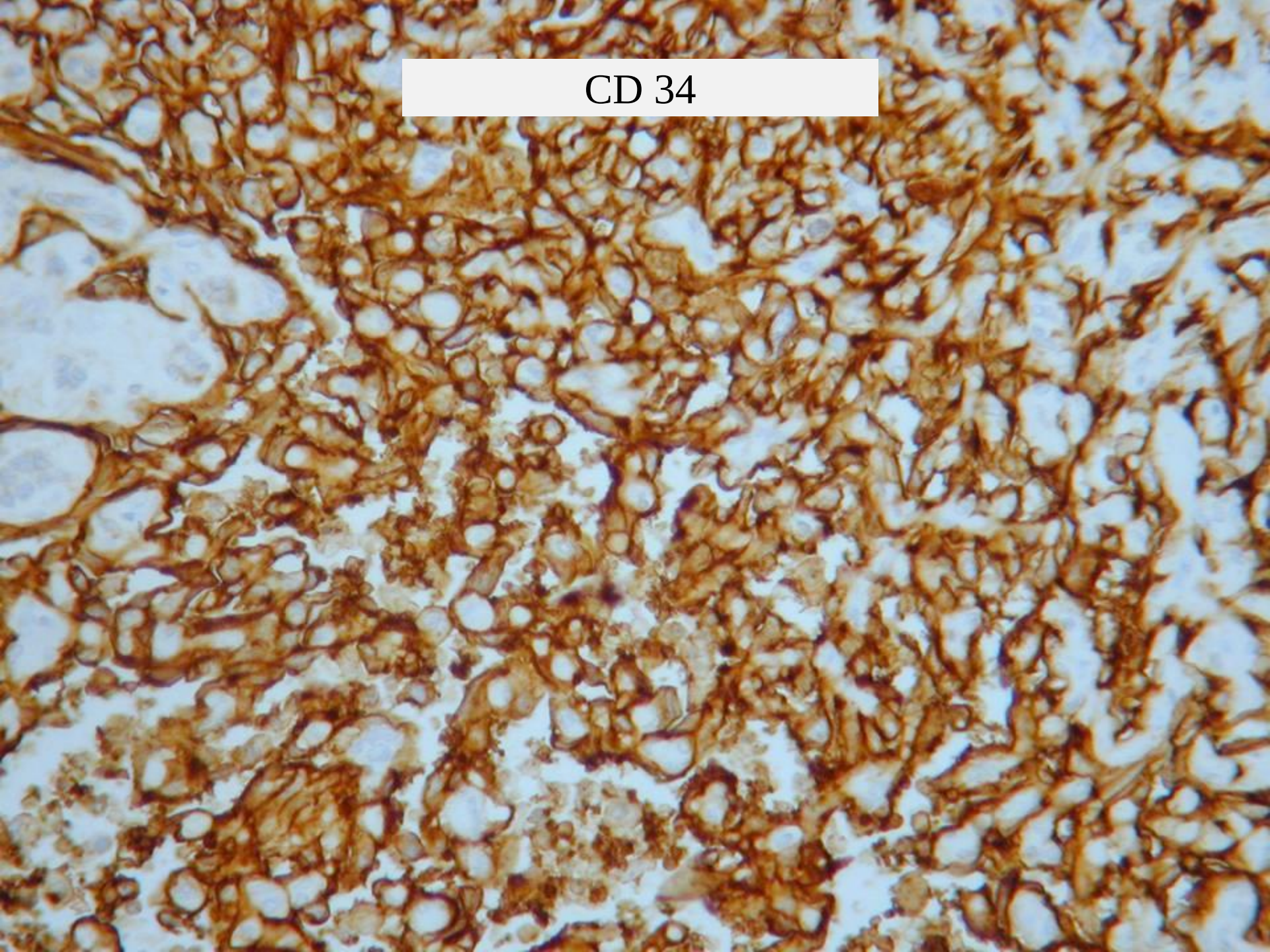
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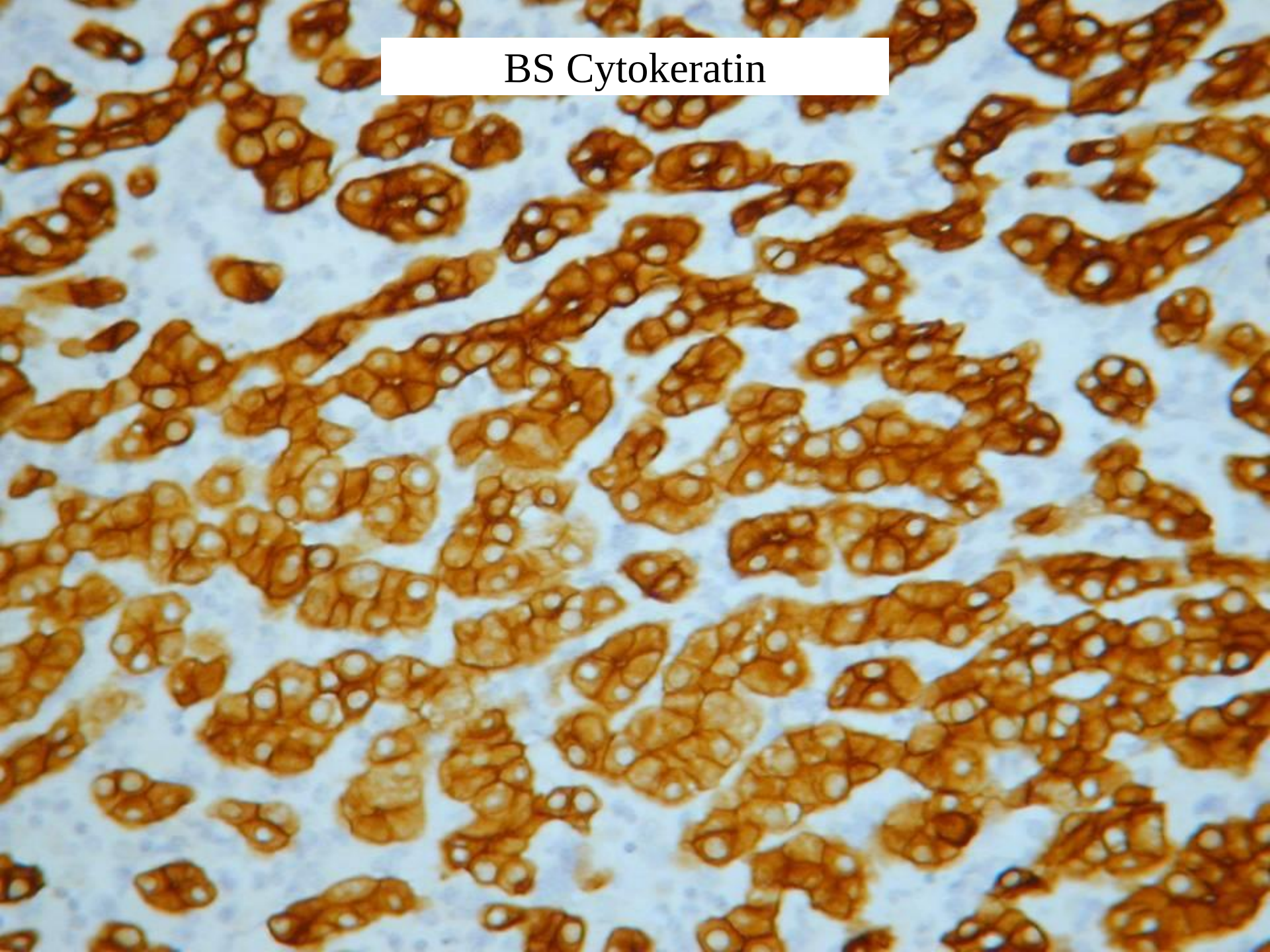
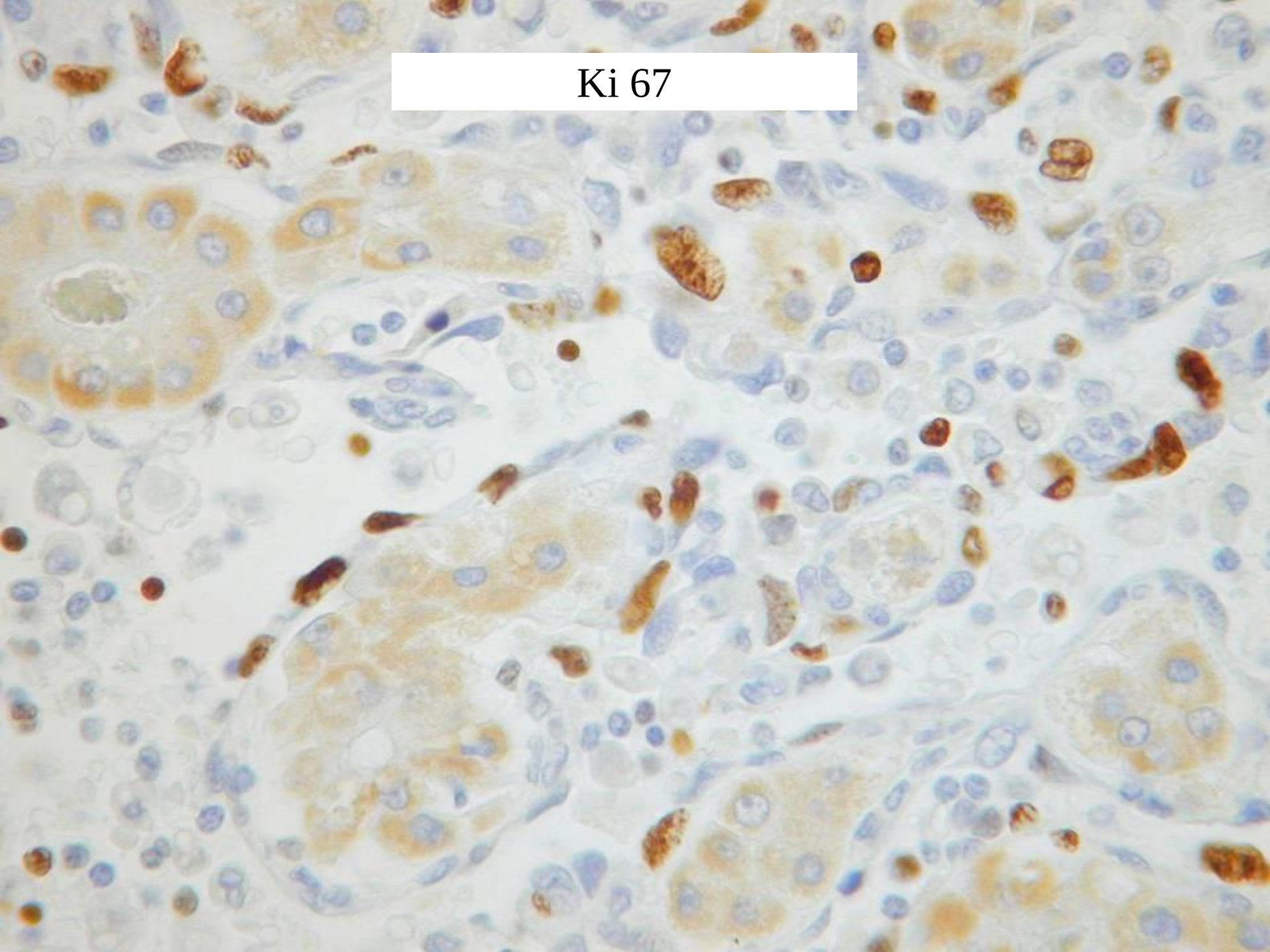
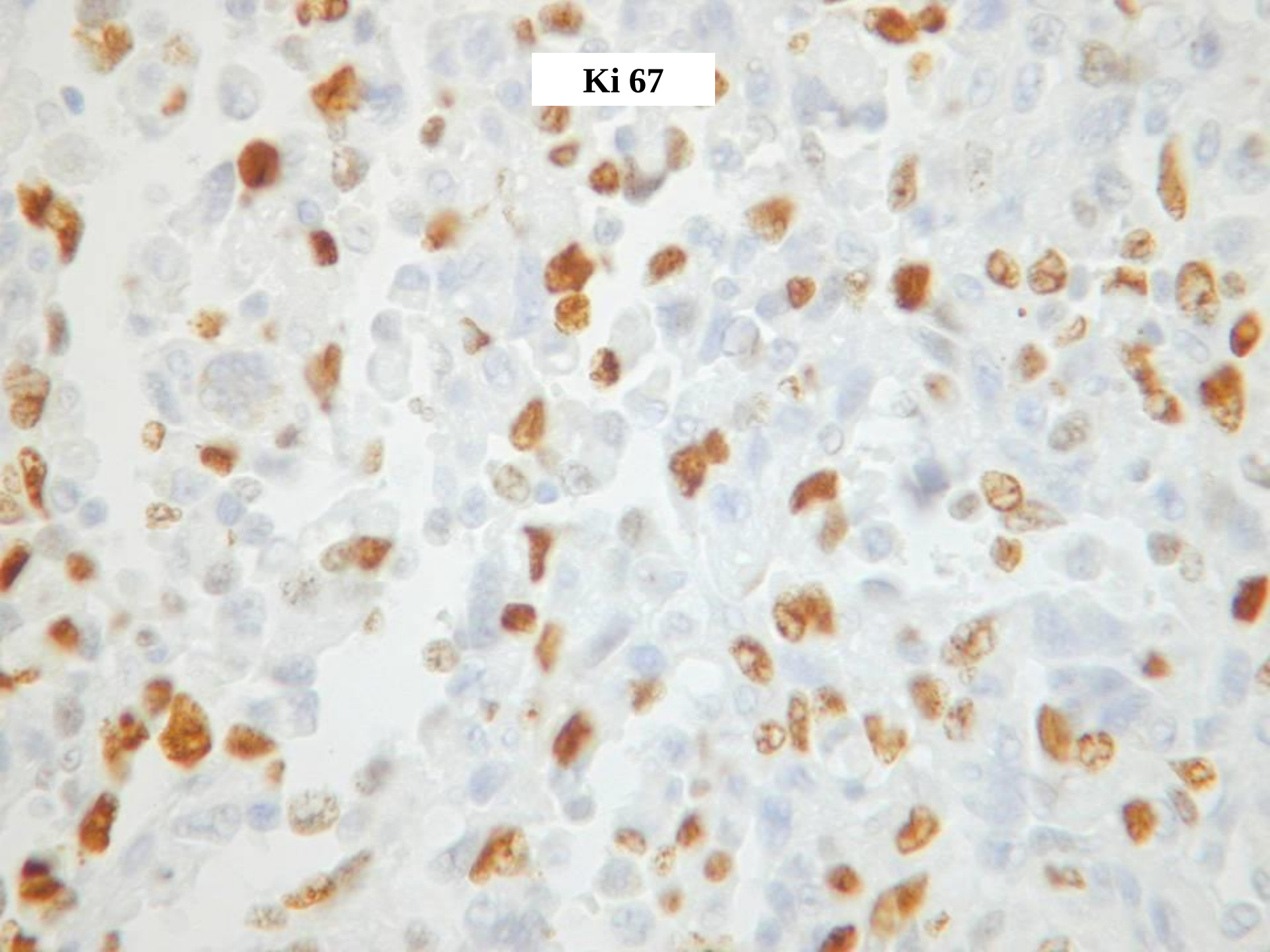

BS Cytokeratin


BS Cytokeratin


Ki 67


Ki 67

Case 9 – Diagnosis

Hepatic Angiosarcoma

Case 9 – Discussion Points

1. Broad spectrum of changes

- May reflect different stages in evolution
- Problems with liver biopsy diagnosis
  - Subtle intrasinusoidal changes in early lesions ("tectorial growth pattern")
  - Fibrous stroma may replace/obscure neoplastic cells (may be mistaken as a reactive/fibrotic process)

2. "Bland" cytology versus aggressive clinical course

- Even areas with early lesions (lack of mitoses) have high Ki 67 labelling index

3. Aetiology – role of occupational/environmental factors?

Angiosarcoma – Aetiological Factors

Recognised Risk Factors (long latent period, up to 50 years)

- Vinyl chloride monomer
  - Incidence declining, no new cases in Europe in people first exposed after 1972
- Thorotrast
- Arsenical compounds
- Radiation
- Organophosphates (e.g.pesticides)
- Androgenic/anabolic steroids

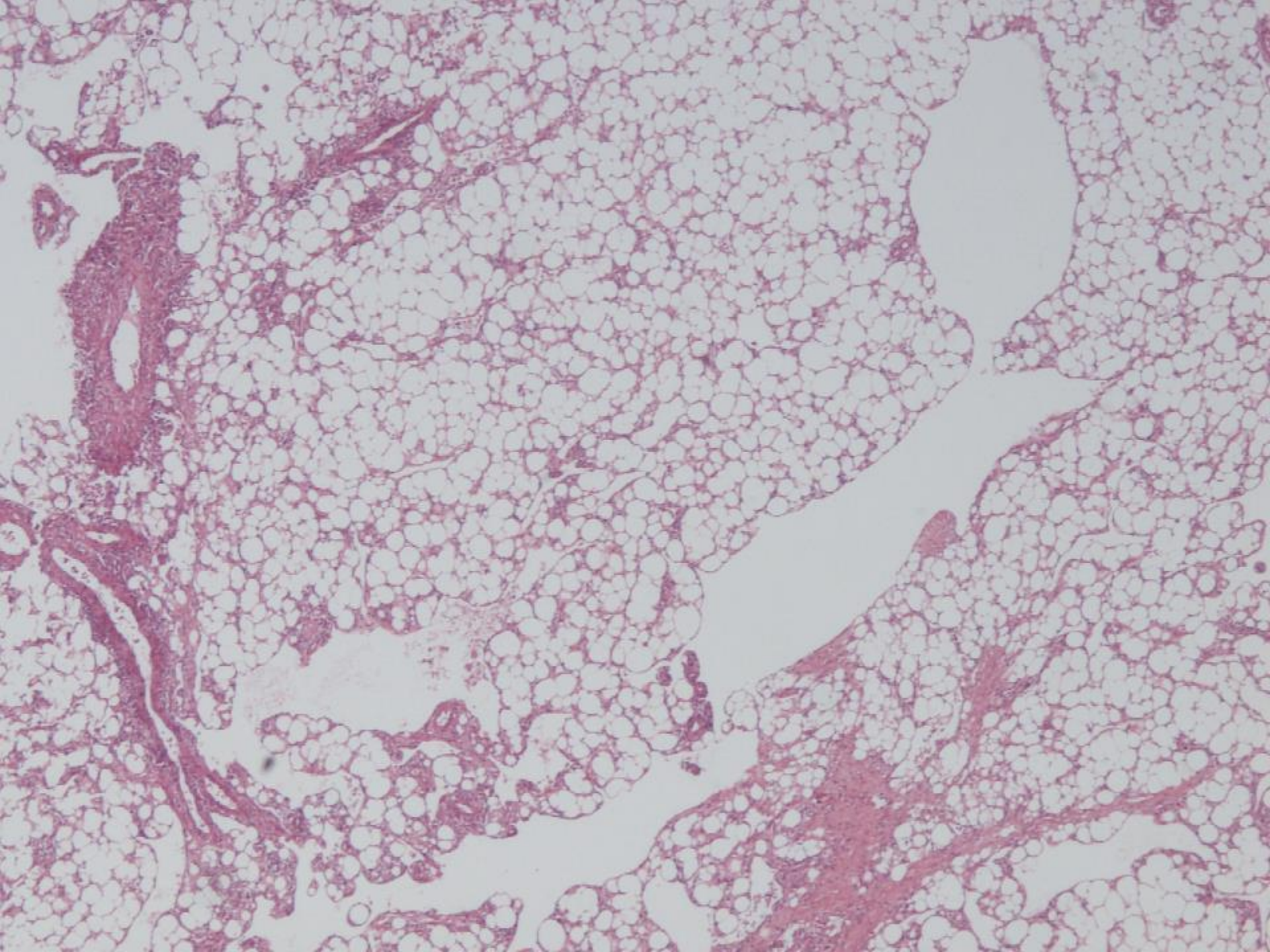
Most cases (>80%) no obvious cause identified

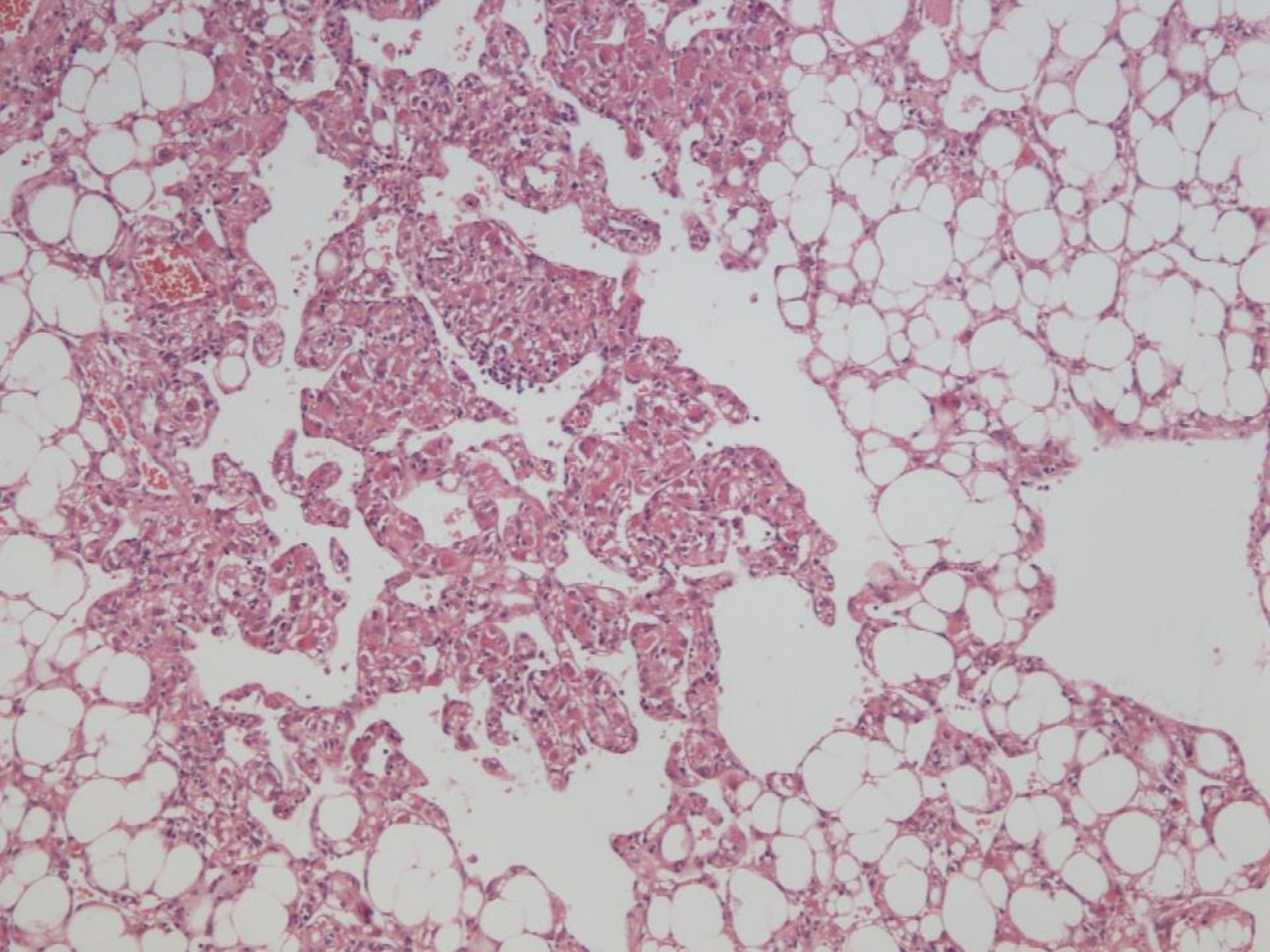
Case 10

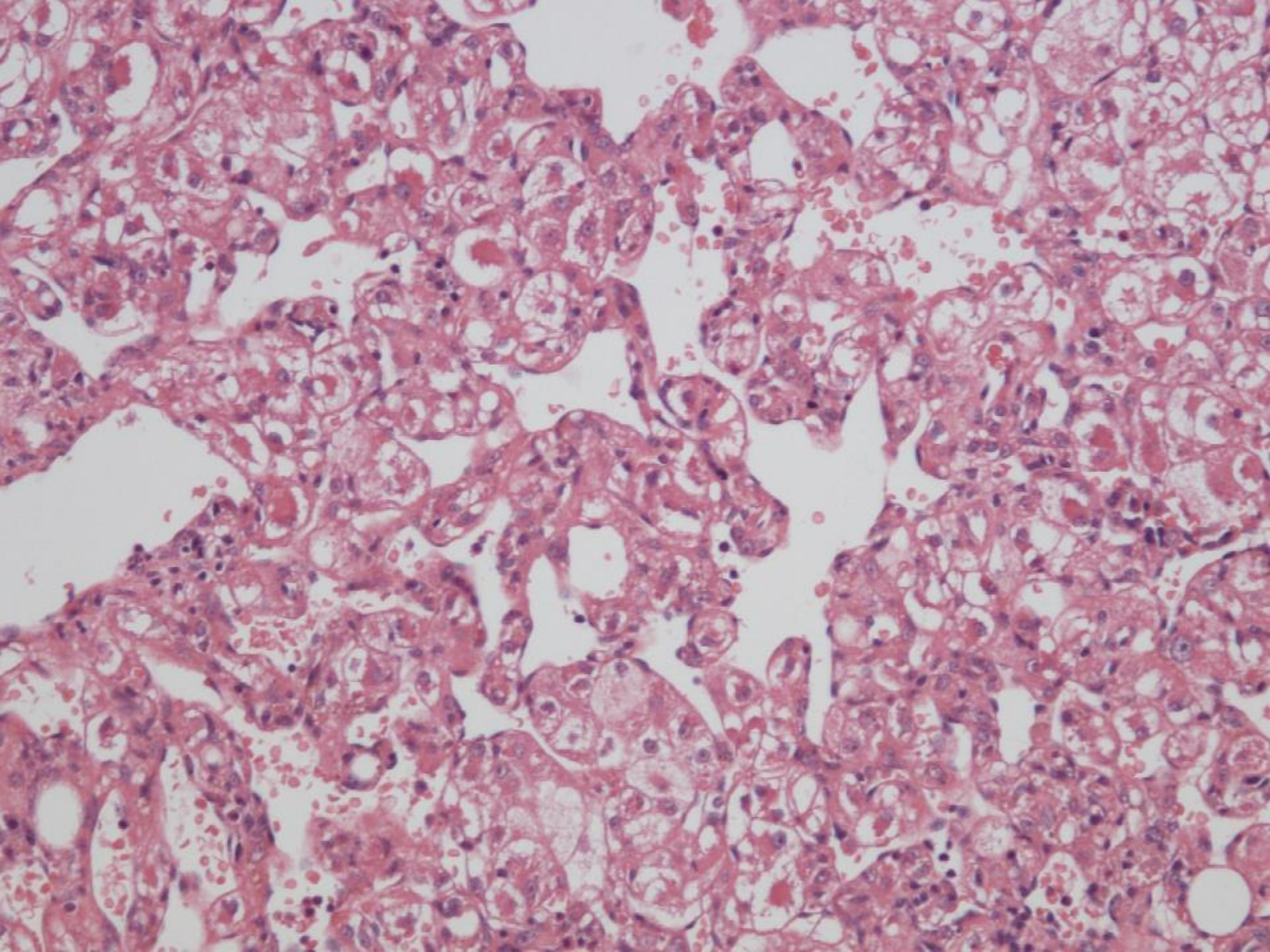
Case 10 - Clinical Summary

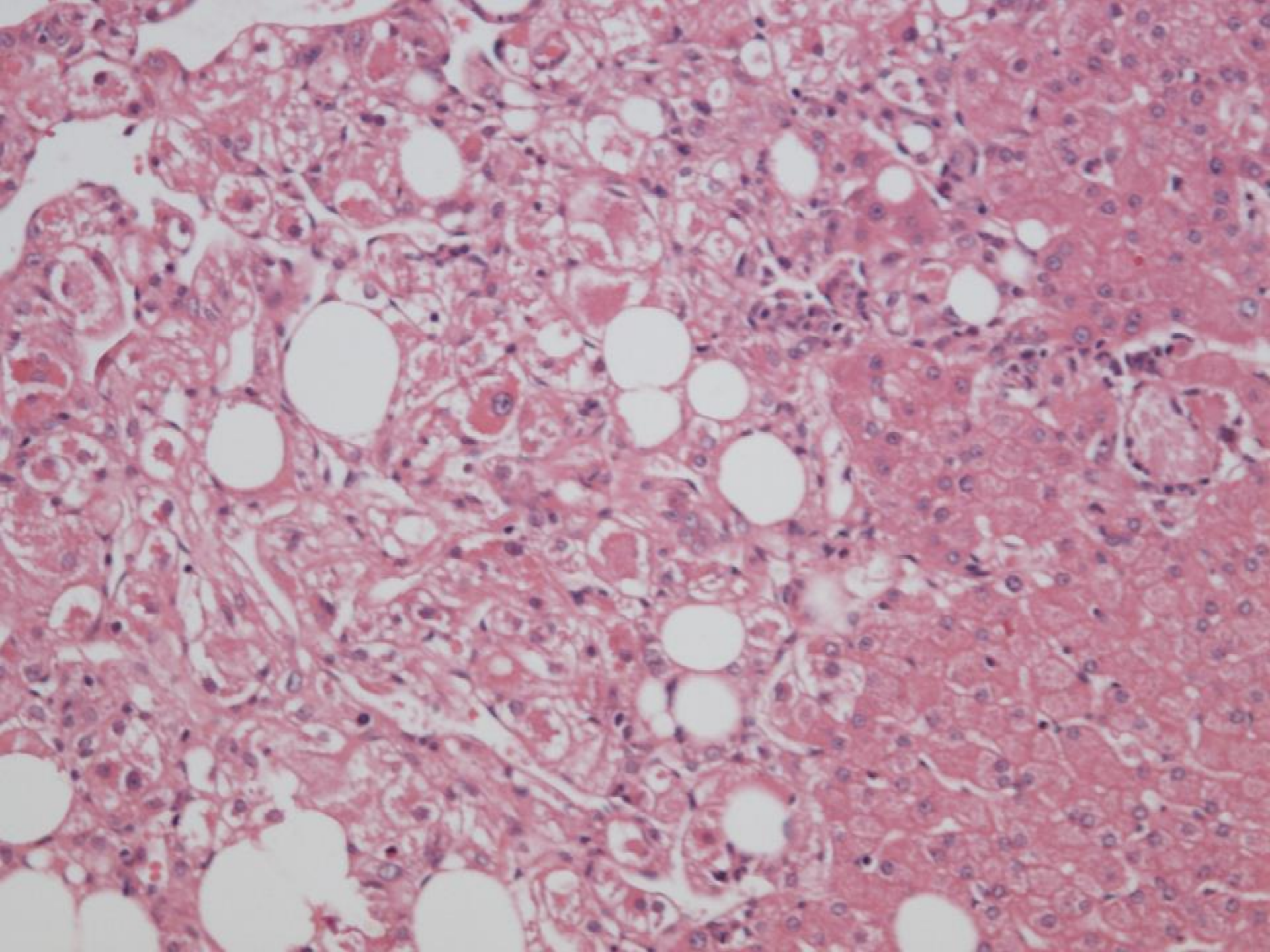
Female, age 28

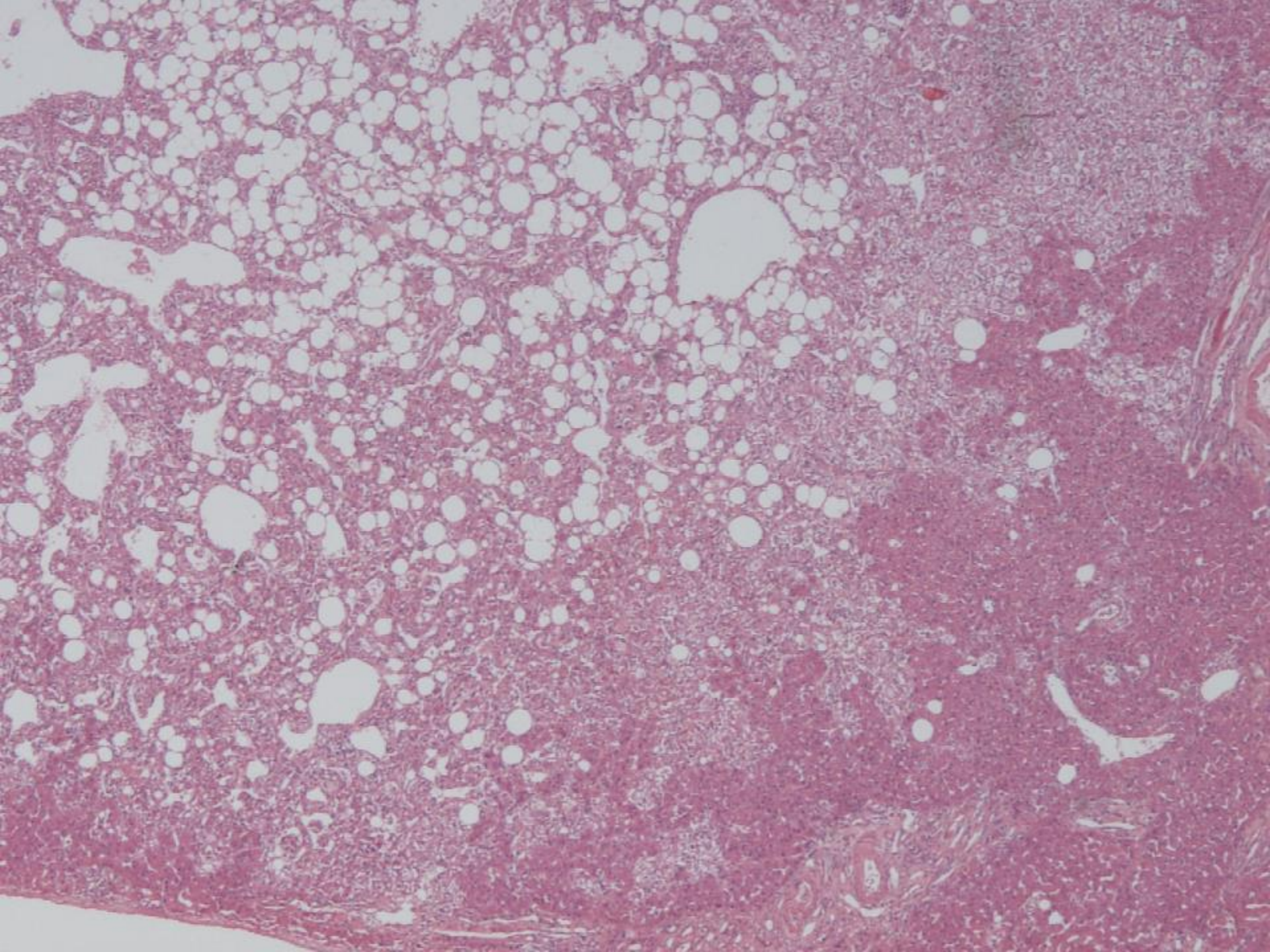
- Lesion 2.5cm diameter in left lobe
- Liver resection

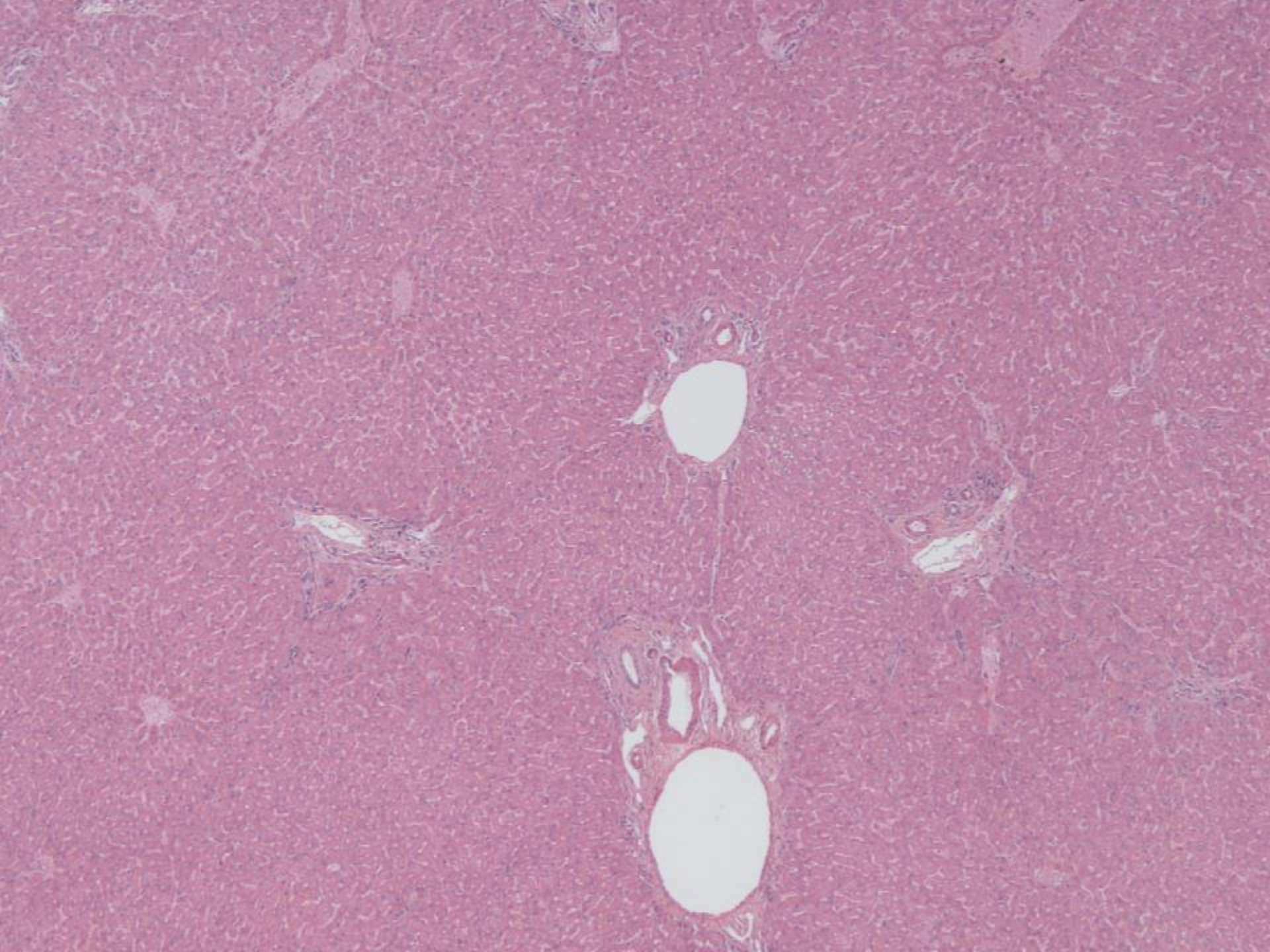


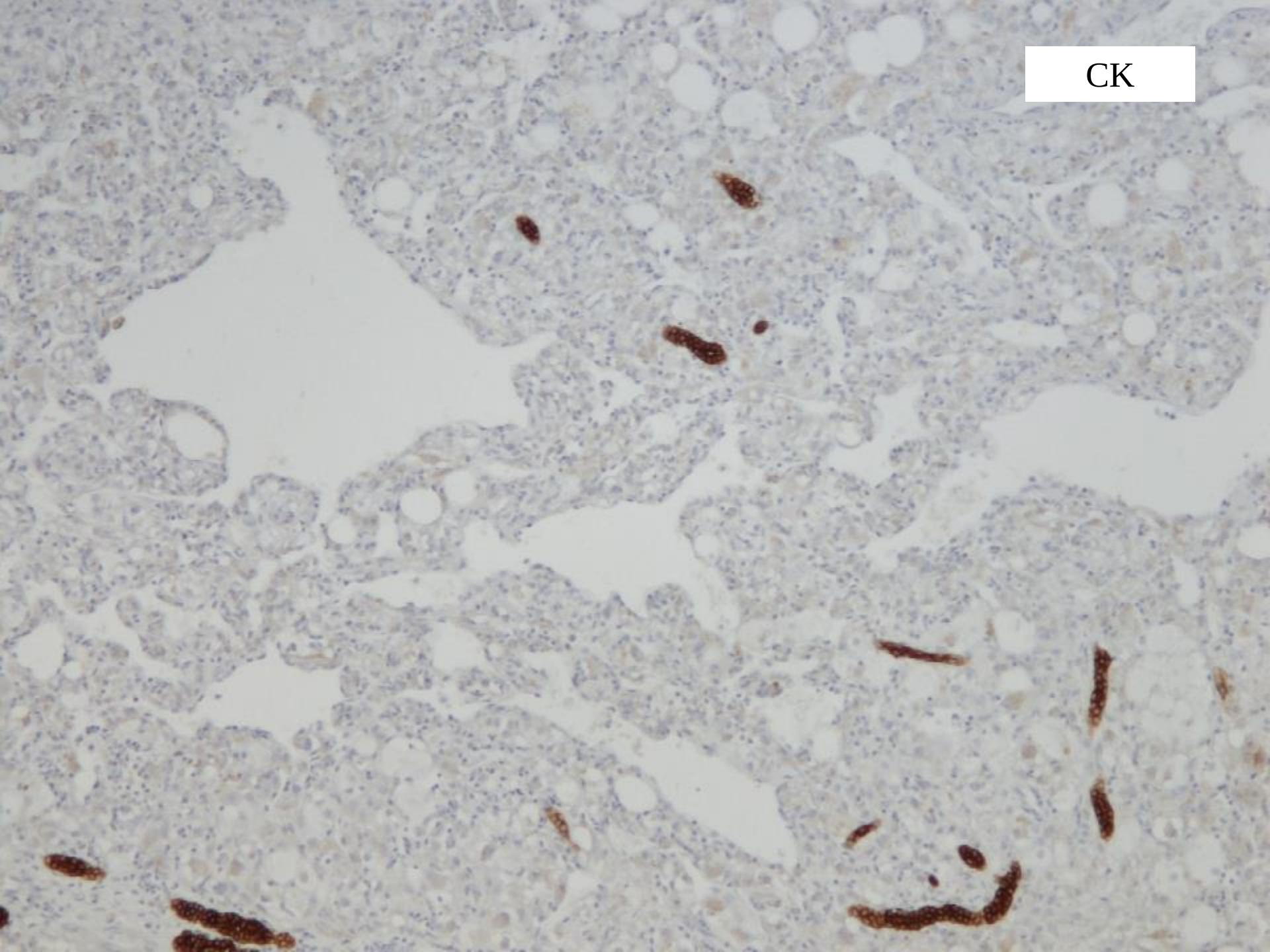








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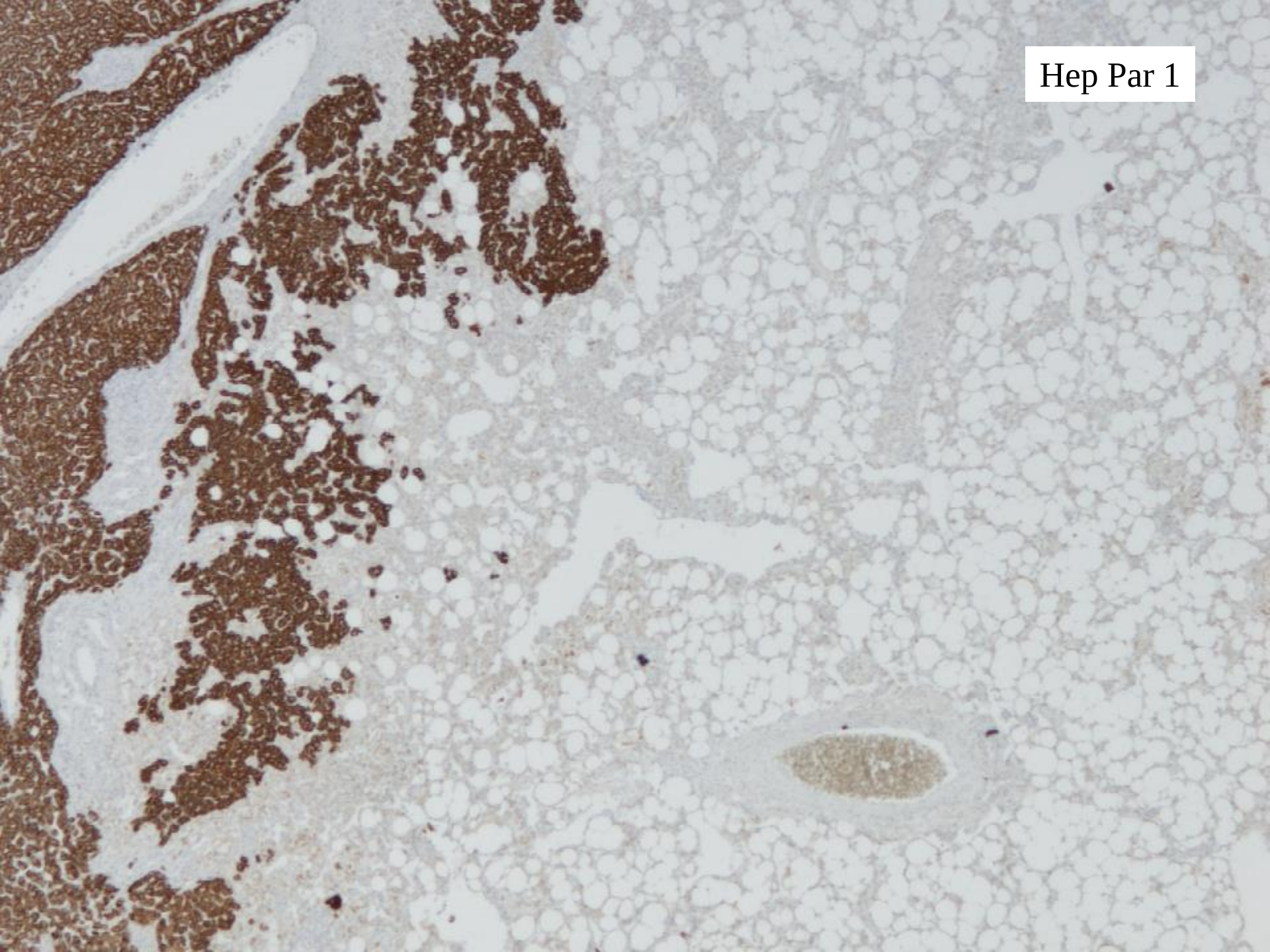
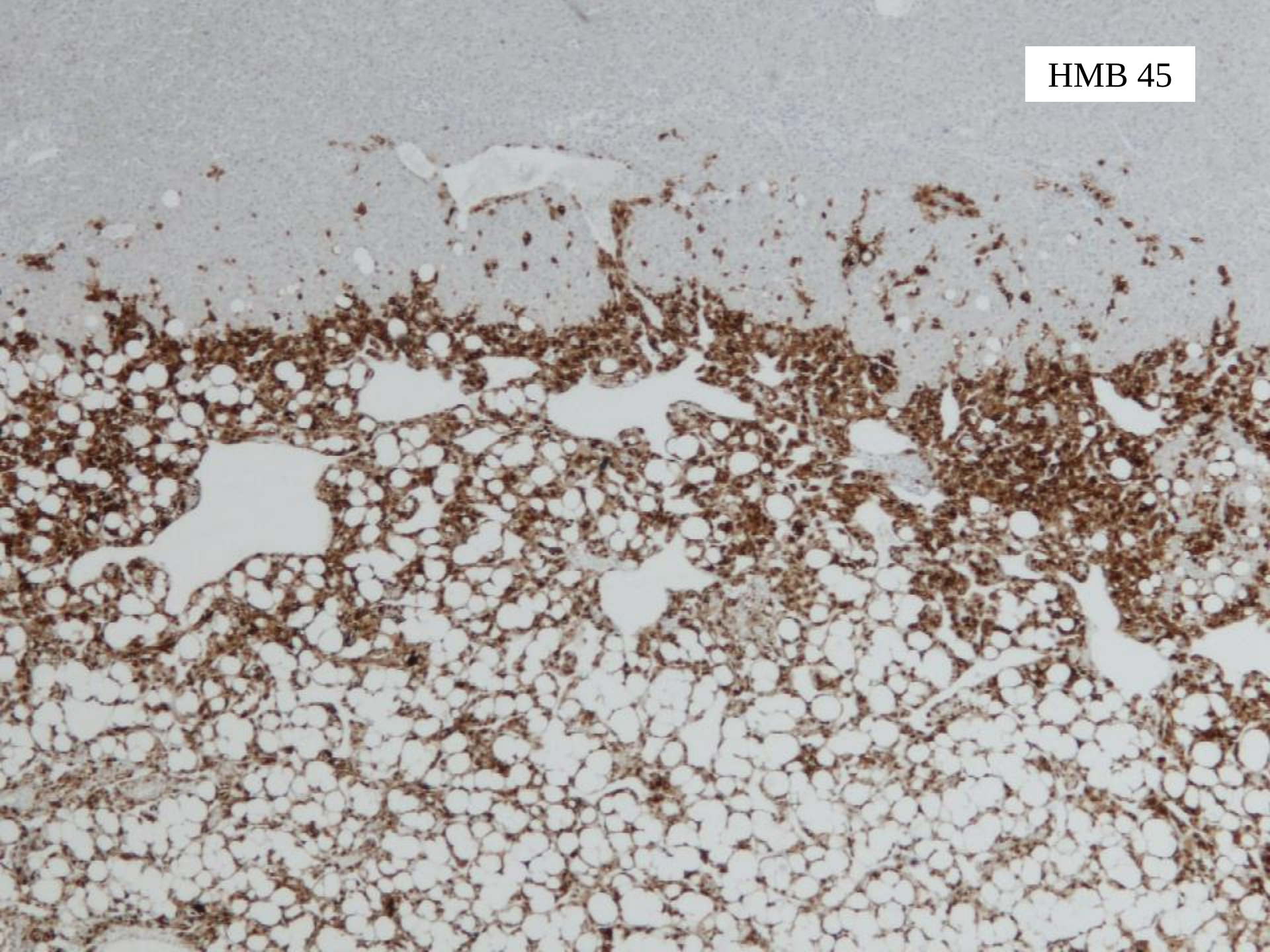
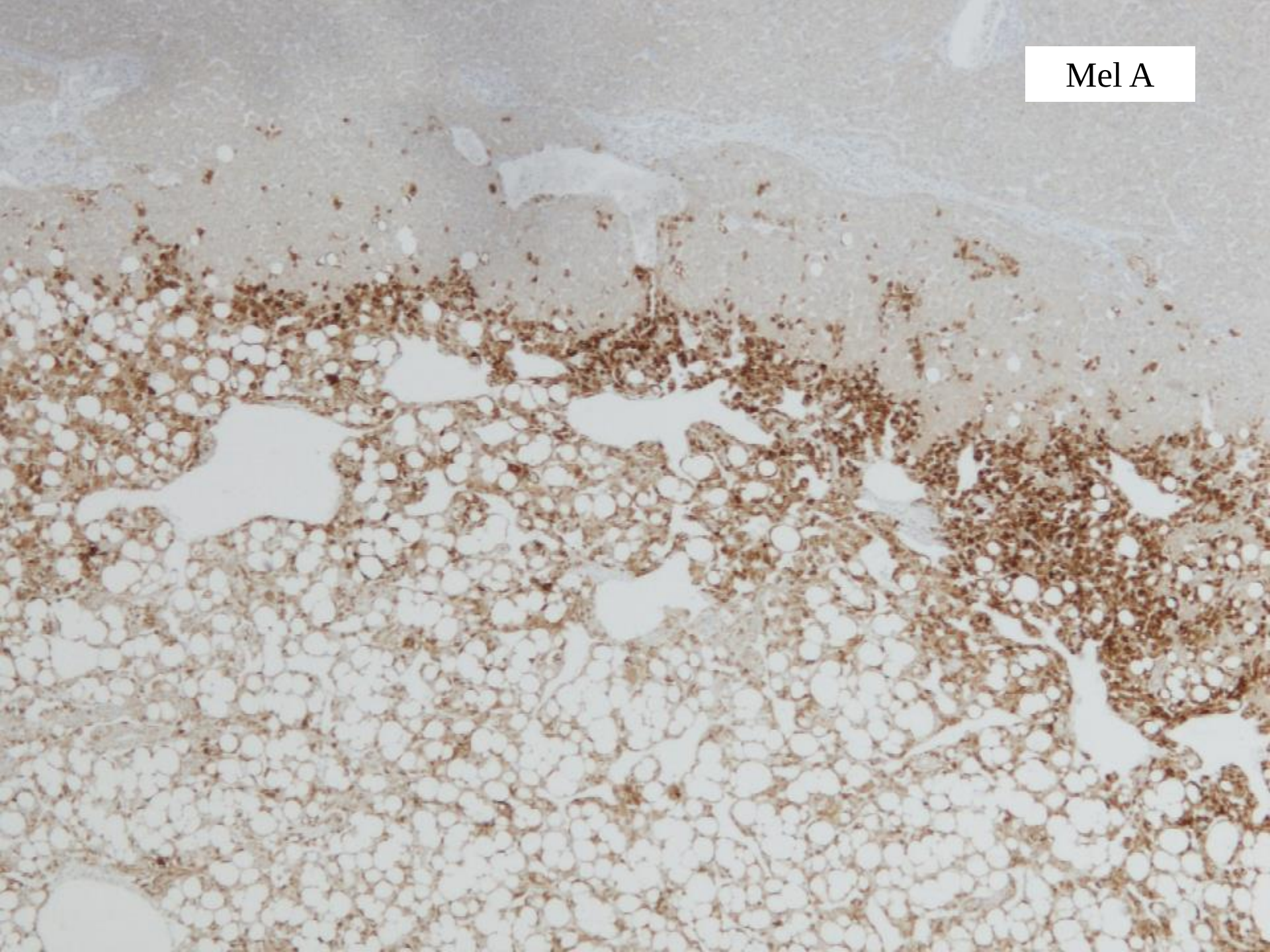
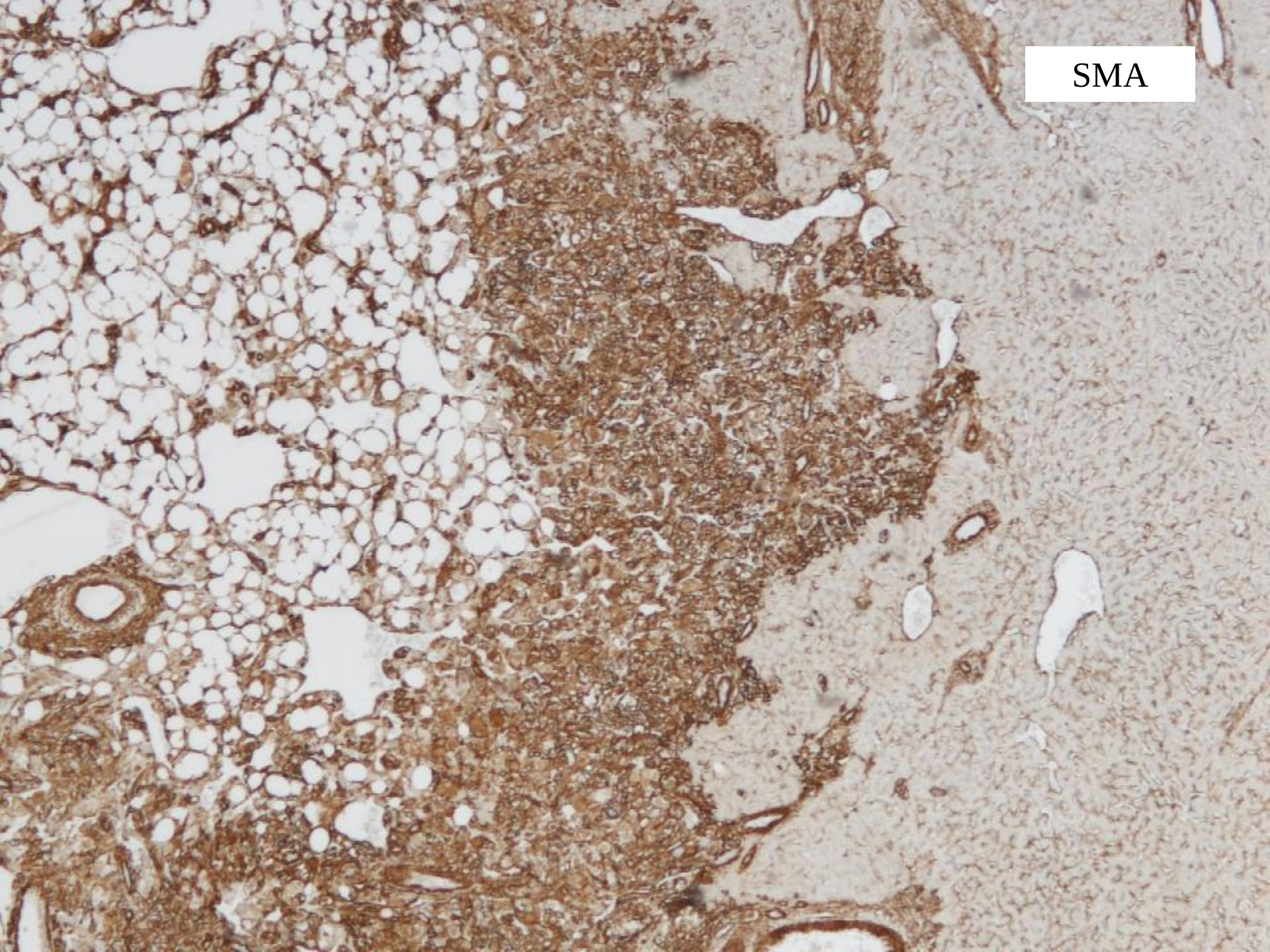
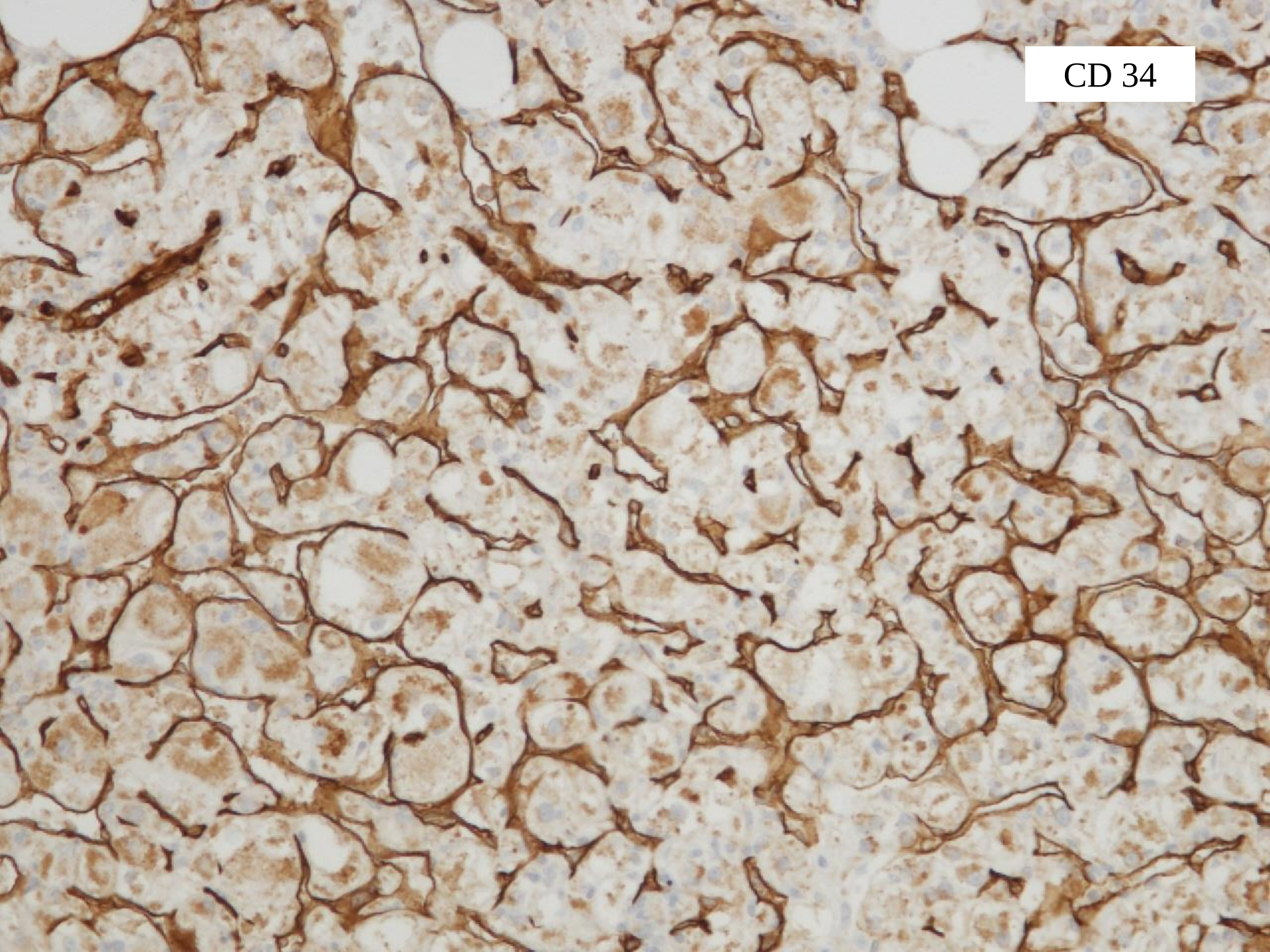

Hep Par 1


HMB 45


Mel A


SMA


CD 34

Case 10 – Histological Findings

- Complex lesion containing adipose tissue, blood vessels, spindle cells and epithelioid cells
- Epithelioid cells focally have trabecular arrangement
- Irregular margins
- Immunostaining positive for HMB 45, Mel-A and SMA

Case 10 – Diagnosis

Hepatic Angiomyolipoma

Case 10 – Discussion Points

1. Histiogenesis

2. Heterogenous morphological patterns

3. Potential for malignant behaviour

Angiomyolipoma - Histiogenesis

- Part of the spectrum of perivascular epithelioid cell neoplasms (PEComas) - derived from perivascular epithelioid cells (Rao, Histopathology 2013)

- Members of PEComa family include:
  - Angiomyolipoma (AML) of kidney and liver (liver = 2nd commonest site)
  - Clear cell sugar tumour (CCST) of lung
  - Lymphangioleiomyomatosis
  - Lymphangiomyoma
  - Clear cell myomelanocytic tumor (skin, falciform ligament/ligamentum teres)
  - Non-specified PEComas (soft tissue, visceral organs, bone,skin)

- Variable association with tuberous sclerosis ("tuberous sclerosis complex")
  - Hepatic AML rarely associated (unlike renal AML)

Angiomyolipoma – Heterogeneous Histological Appearances

Most lesions contain a mixture 3 main components

1. Mature adipose tissue
2. Blood vessels – often tortuous and thick-walled
3. Smooth muscle - spindle cell or epithelioid (most specific & diagnostic)

- May be classified as lipomatous, angiomatous, myomatous if one component predominates (>80%) or otherwise as mixed (Nonomura 2012)
- Rare inflammatory subtype (Agaimy 2013)
  - May resemble inflammatory pseudotumour (IgG4 positive)

Angiomyolipoma – Heterogeneous Histological Appearances

Problems with histological diagnosis

- Cases with a predominance of one pattern may be mistake as lipoma, vascular lesion or smooth muscle neoplasm
- Problems with needle biopsy diagnosis (sampling variability)
- Most hepatic AML (65%) have a predominantly myomatous pattern (Nonomura 2012)
  - Epithelioid smooth muscle components may have a trabecular pattern and can mimic hepatocellular neoplasms (adenoma or HCC)
  - 25/48 (52%) surgically resected cases of AML had pre-operative diagnosis of HCC (Nonomura 2012)

Epithelioid Angiomyolipoma versus Liver Cell Adenoma / HCC
Immunohistochemistry

Antigens expressed by AML (and not by liver cell neoplasms)

- SMA
- HMB 45, Melanoma-associated antigen
- Other : CD 117, S100 (focal), cathepsin K (Rao 2013)

Antigens expressed by liver cell neoplasms (and not by AML)

- Hep Par 1
- Cytokeratin

Angiomyolipoma – Potential for Malignant Behaviour

- Great majority behave in a benign fashion

- Cytological atypia and infiltrative margins commonly present, but do not indicate malignancy

- 4 cases of malignant AML reviewed by Nguyen (Nguyen 2008)
  - 3 metastasized, one death from aggressive local diease
  - Generally larger than benign hepatic AML (all 4 > 10cm)
  - All 4 had foci of coagulative necrosis
  - No other distinguishing features

Histopathology

Histopathology 2012, **61**, 863–880. DOI: 10.1111/j.1365-2559.2012.04306.x

Angiomyolipoma of the liver: a reappraisal of morphological features and delineation of new characteristic histological features from the clinicopathological findings of 55 tumours in 47 patients

Akitaka Nonomura, Yasunori Enomoto, Maiko Takeda, Masato Takano, Kohei Morita & Takahiko Kasai

Department of Diagnostic Pathology, Nara Medical University School of Medicine, Nara, Japan

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AFIP ATLAS OF TUMOR PATHOLOGY
Series 4

Tumors of the Liver

Michael Torbenson, MD
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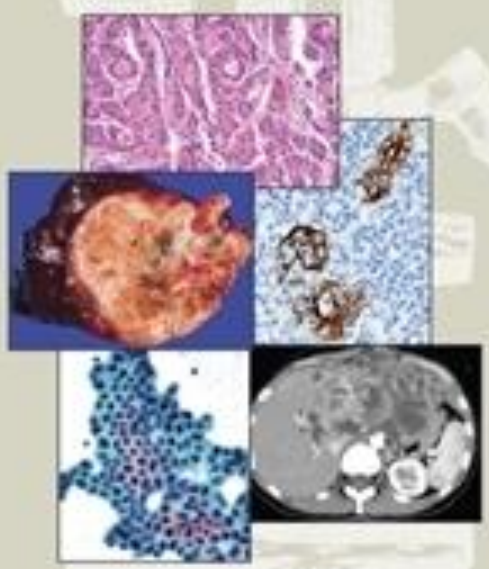
Matthew M. Yeh, MD, PhD



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ARP


The End……..