Update from the 2017 Gnomes Meeting – Groningen, 10-13 May 2017

Vascular Liver Pathology (Non-neoplastic)
Chief Gnome – Annette Gouw

Stefan Hübscher,
Institute of Immunology and Immunotherapy, University of Birmingham
Department of Cellular Pathology, Queen Elizabeth Hospital, Birmingham

Annual Meetings of the International Liver Study Group

- First meeting, July 1968, University of Zürich (Martin Schmid)
- Currently 13 circulating members (6 Europe, 5 North America, 2 Australia)

- Cases circulated prior to meeting (2-3/ person) to cover particular theme
- Suggested diagnoses submitted prior to meeting and collated by local organiser

- Cases presented and discussed further at meeting (2 days)
- Aim to reach consensus and provide summary/guidelines
  - Usually a 2 year cycle – 2nd year focuses on specific areas of interest
  - **2017 – "Non-tumoral Vascular Diseases"**

Vascular Liver Diseases

Classification and Pathological Features

Vascular Diseases of the Liver – Aetiological Classification

Primary

- Diseases in which damage to hepatic vessels occurs as the primary event
  - Hepatic artery
  - Portal vein
  - Sinusoids
  - Hepatic vein

Secondary

- Diseases in which vascular changes occur as secondary event
  - Intrahepatic: Other primary liver diseases - e.g. vascular disturbances in liver fibrosis/cirrhosis, NRH in pre-cirrhotic PBC.
  - Extrahepatic : - e.g. venous outflow obstruction secondary to cardiac disease, “ischaemic hepatitis” secondary to hypotension.

Primary Hepatic Vascular Diseases - Pathological Changes and Clinical Syndromes

Site of vessel	Pathological changes	Clinical Syndromes
Hepatic artery	Inflammation, thrombosis	Ischaemic cholangiopathy
Portal vein (large)	Thrombosis	Portal vein thrombosis
Portal vein (small)	Obliteration/loss • possibly related to previous thrombosis	"Idiopathic" non-cirrhotic portal hypertension
Sinusoid	Endothelial injury • usually caused by toxins (dilatation/congestion)	"Sinusoidal obstruction syndrome"
Hepatic vein (small)	Endothelial injury • usually caused by toxins (luminal occlusion)	Hepatic veno-occlusive disease
Hepatic vein (large)	Thrombosis	Budd-Chiari syndrome

Gnomes Meeting, Groningen 2017 – Summary of Cases Presented
Primary Hepatic Vascular Diseases

Site of vessel	Pathological changes	Cases presented
Arteries	Thrombosis Fibrointimal hyperplasia	Adelaide B ; Brisbane A; Newcastle B; Rochester A
Portal vein (large)	Absence Thrombosis	Adelaide A; BirminghamA; St Louis A
Portal vein (small)	Obliteration/loss INCPH	Birmingham A; Groningen A; Groningen B; Halifax A; Paris A
Sinusoid	Endothelial injury/SOS	Basel A; Newcastle A; Paris B, Washington C
Hepatic vein (small)	Endothelial injury VOD	Basel B; Halifax A
Hepatic vein (large)	Thrombosis, Stenosis Extrahepatic obstruction	Birmingham B; Brisbane B St Louis B (cardiac)

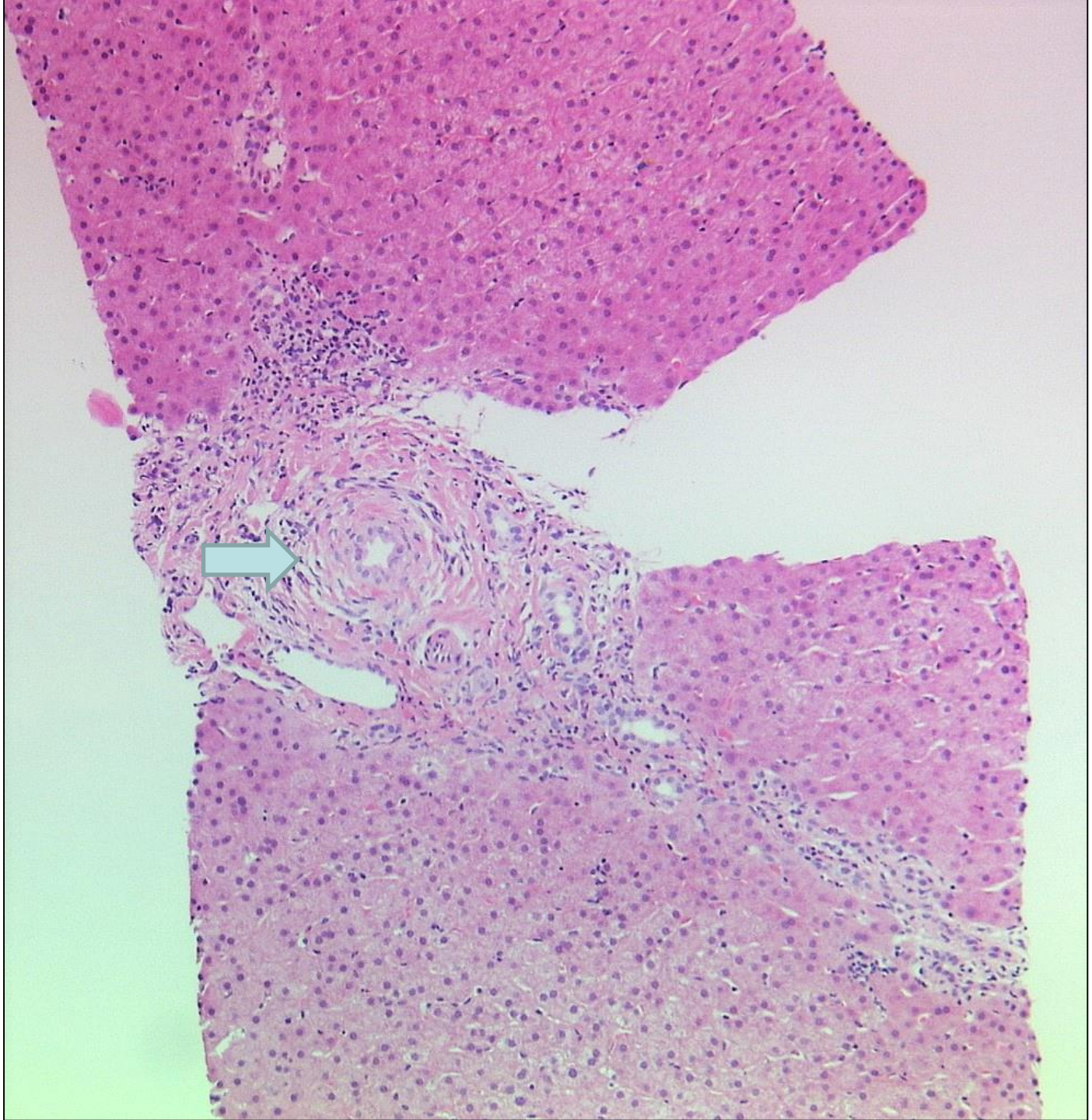
Arterial Lesions

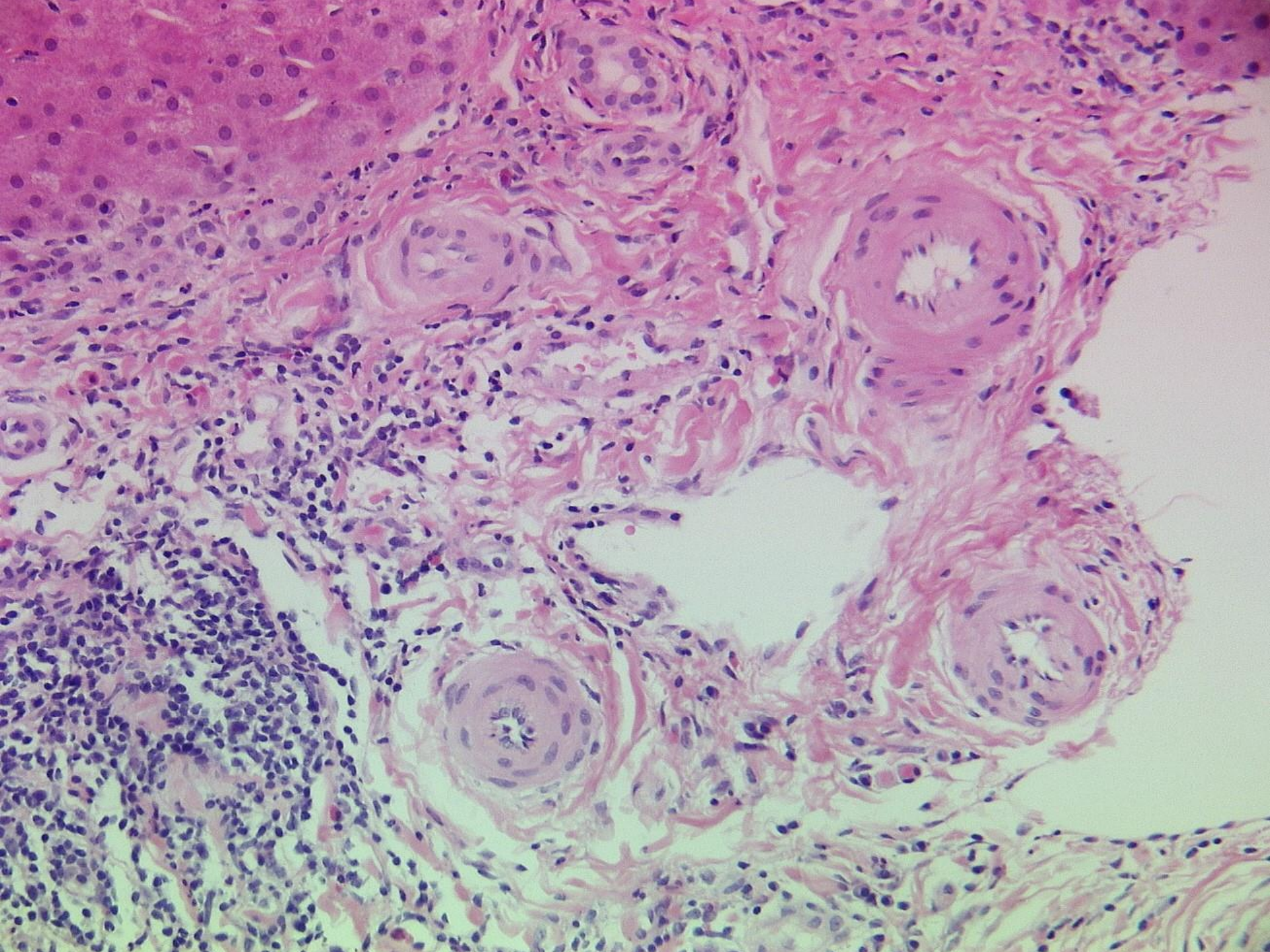
Newcastle Case B – Dina Tiniakos
Case History

- 8-year-old boy with ulcerative colitis diagnosed 7/2015
- In 8/2016 presented with deranged liver function tests

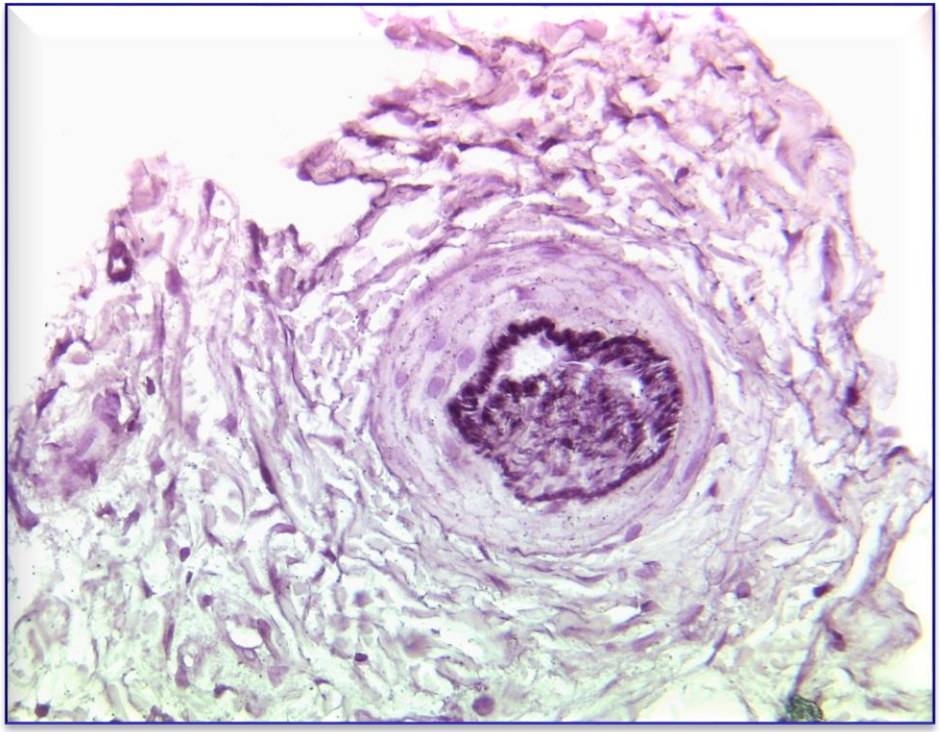
On admission:

- **ALT 106 U/L** (normal range ALT 7-56 U/L)
- bilirubin 7 µmol/L (normal range 3-25 µmol/L)
- **ALP 532 U/L** (normal range 30-130 U/L)
- **GGT 357 U/L** (normal range 10-71 U/L)
- viral screen negative (HAV, HBV, HCV, HEV, HIV, CMV)
- **IgG 25.3** (normal range IgG 7.0-16.0 g/L)
- **ANA positive 1:80, ASMA positive >1:640, AMA negative**

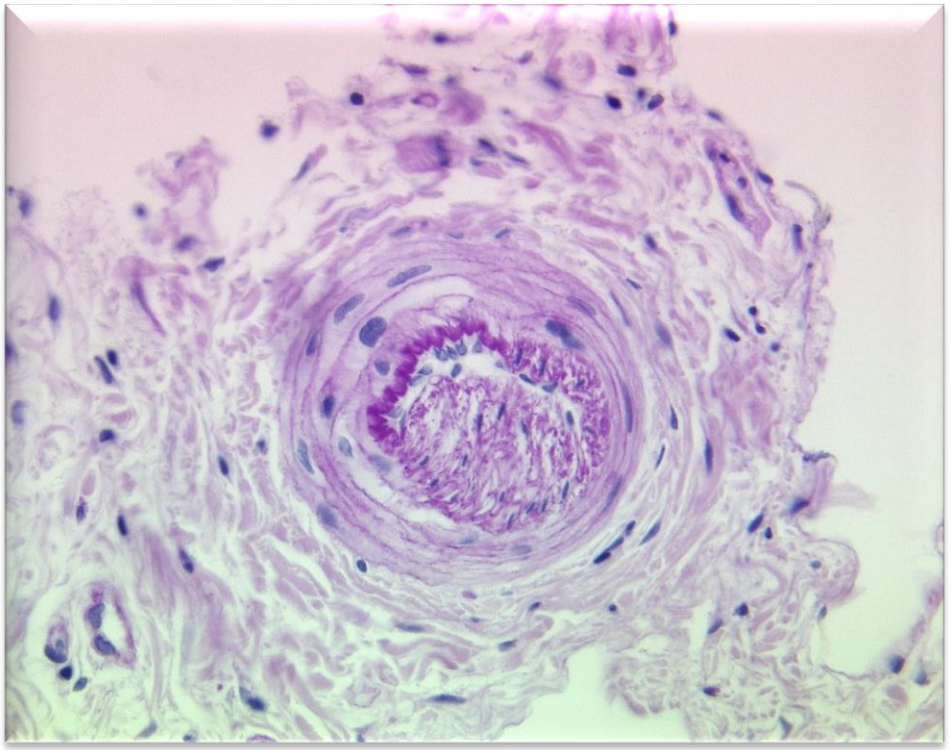




Fibrointimal Thickening of Hepatic Arterioles



Orcein



DPAS

Newcastle B

Autoimmune cholangitis with features of primary sclerosing cholangitis and arterial vasculopathy

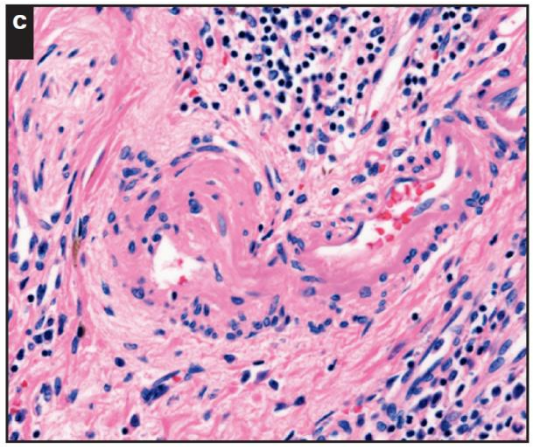
Hepatic Arterial Changes in Primary Sclerosing Cholangitis (PSC)

Primary Sclerosing Cholangitis

Am J Clin Pathol April 2015;143:505-513

Detailed Histologic Assessment and Integration Using Bioinformatics Highlights Arterial Fibrointimal Hyperplasia as a Novel Feature

Gonzalo Carrasco-Avino, MD,[1] Thomas D. Schiano, MD,[2] Stephen C. Ward, MD, PhD,[1] Swan N. Thung, MD,[1] and M. Isabel Fiel, MD[1]



- Arterial fibrointimal hyperplasia more frequent in PSC (75%) than controls – PBC, ALD, HCV (30%)

- Hepatectomy specimens obtained at liver transplantation – lesions involving medium-sized and small arteries
- Unclear if these are a primary or secondary event
- Could contribute to bile duct injury (similar bile duct lesions in ischaemic cholangiopathy)

Gnomes Meeting, Groningen 2017 – Summary of Cases Presented
Arterial Lesions

Case No	Arterial Lesion
Adelaide B	Epithelioid haemangioendothelioma with focal necrosis ?related to arterial compromise
Brisbane A	Hyaline arteriolosclerosis (hypertension and renal impairment) • Similar changes also seen in diabetes
Newcastle B	PSC with fibrointimal hyperplasia
Rochester A	Hereditary lymphoedema (with secondary arterial changes)

Portal Vein Lesions

(large and small)

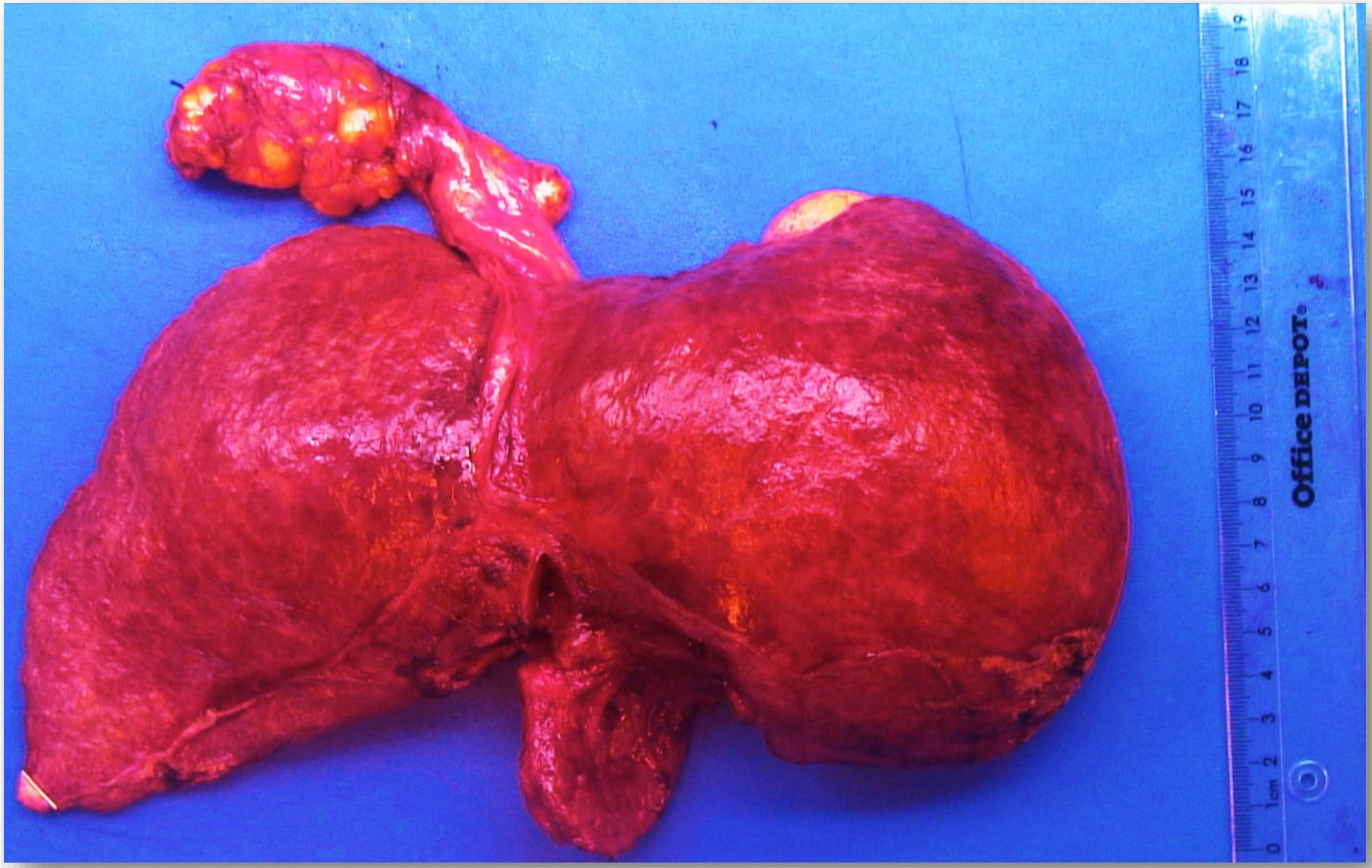
Groningen - Case A
(Annette Gouw)

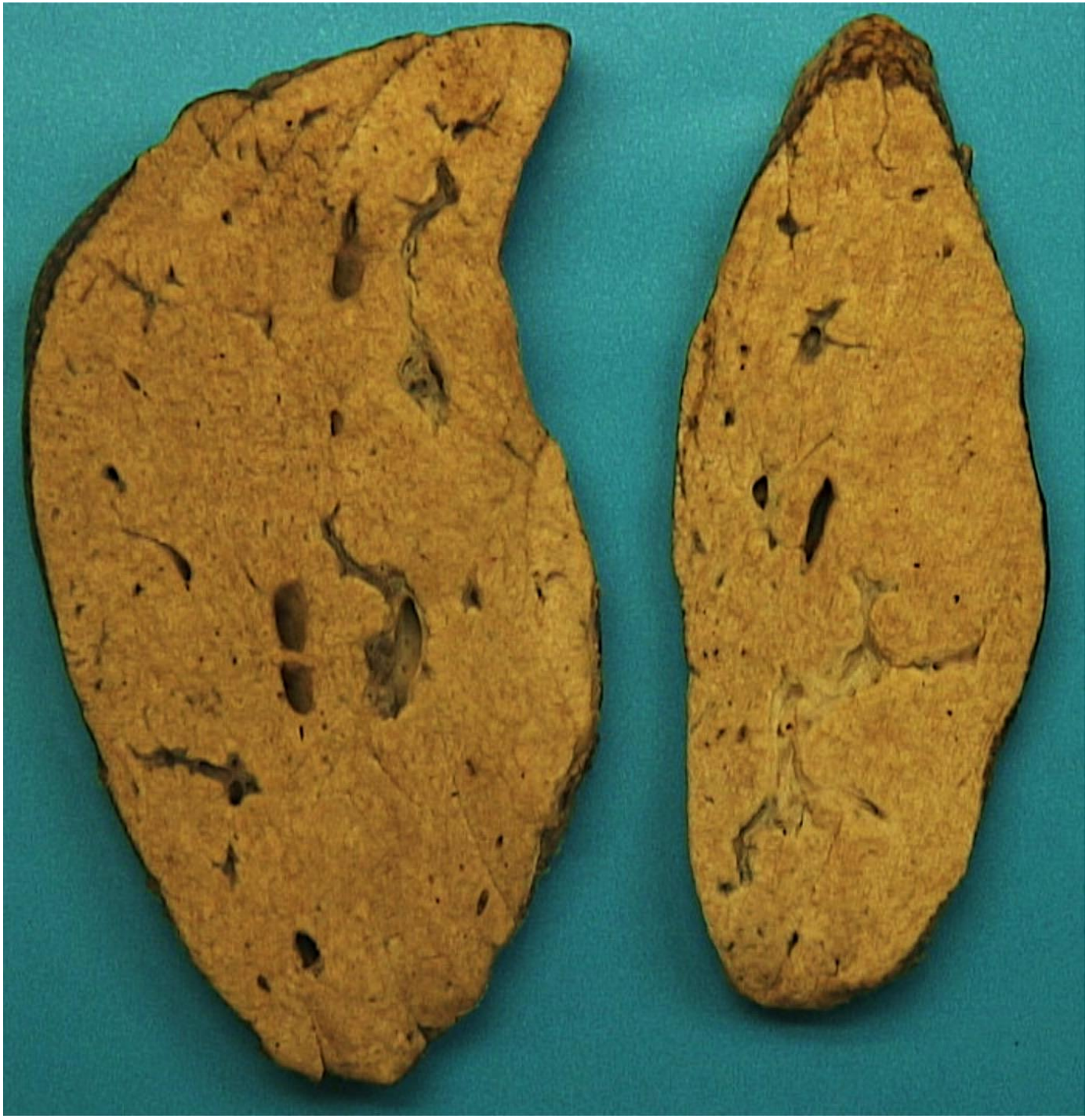
- Male; 53 yr, LT in 2014: NASH related cirrhosis (BMI 33).
  (no pre-transplant liver biopsy)

Medical history:

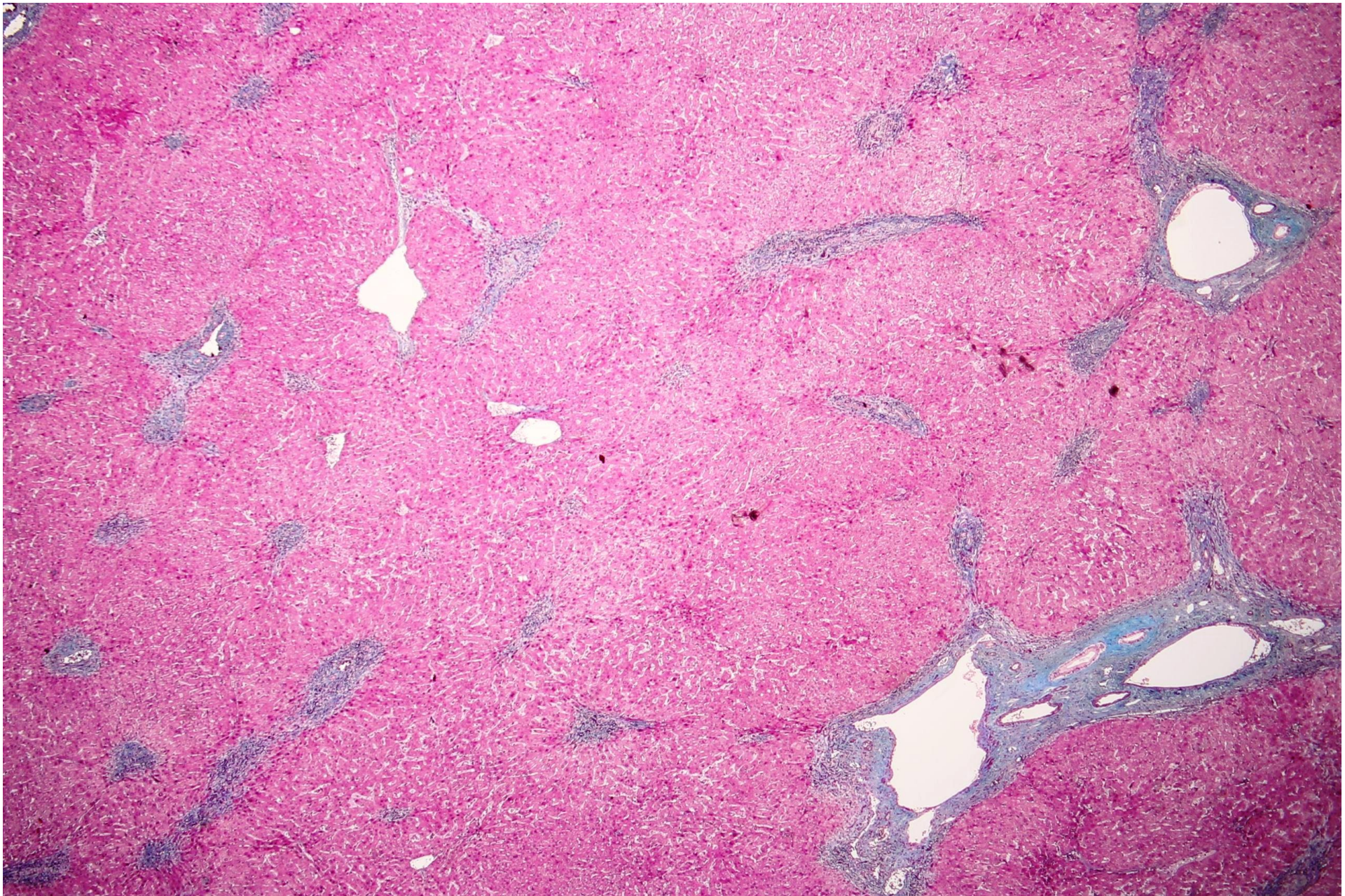
- Since 1994: normocytic anemia and thrombopenia of unknown cause.
- 2008: therapy for idiopathic hypopituitarism (hypothyroidism, adrenal insufficiency, hypogonadism)
- 2010: pulmonary embolism. Malaise and dyspnea ever since.
- 2011: cardiological evaluation: no cardial abnormalities.
- 2013: ascites, splenomegaly, recanalization of umbilical vein, portal hypertension.

Case A Groningen

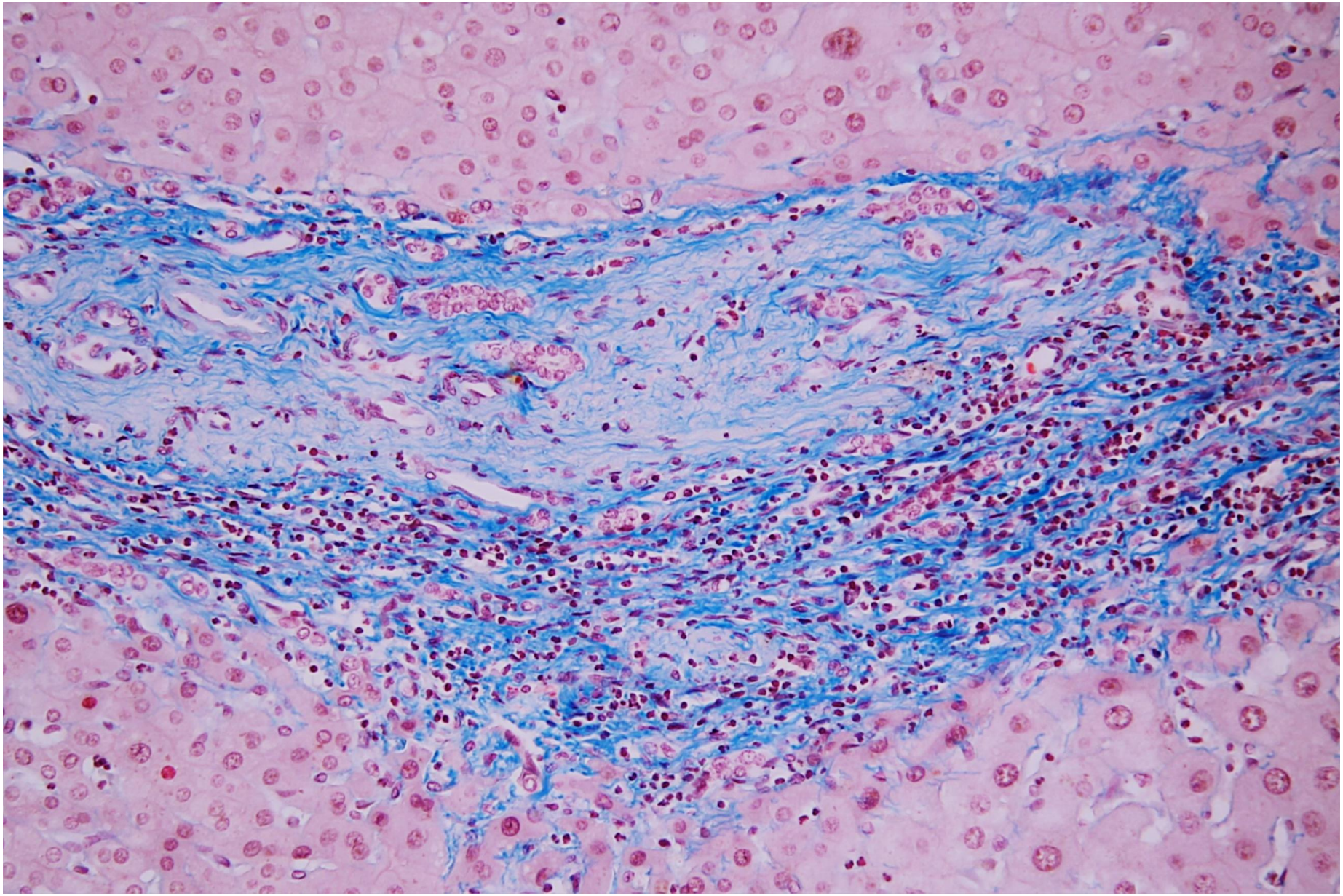




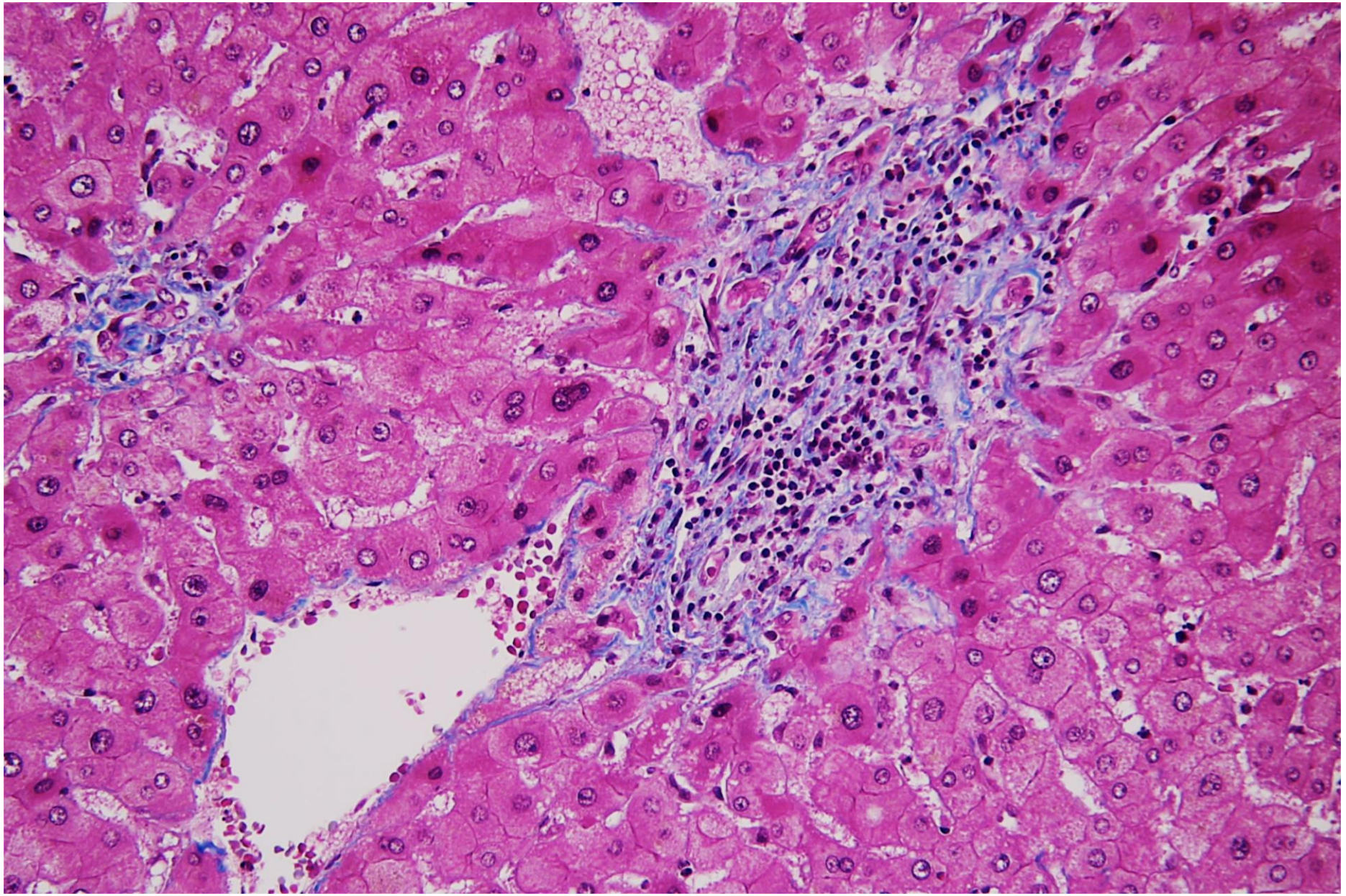
Periportal fibrosis, non-bridging fibrous septa



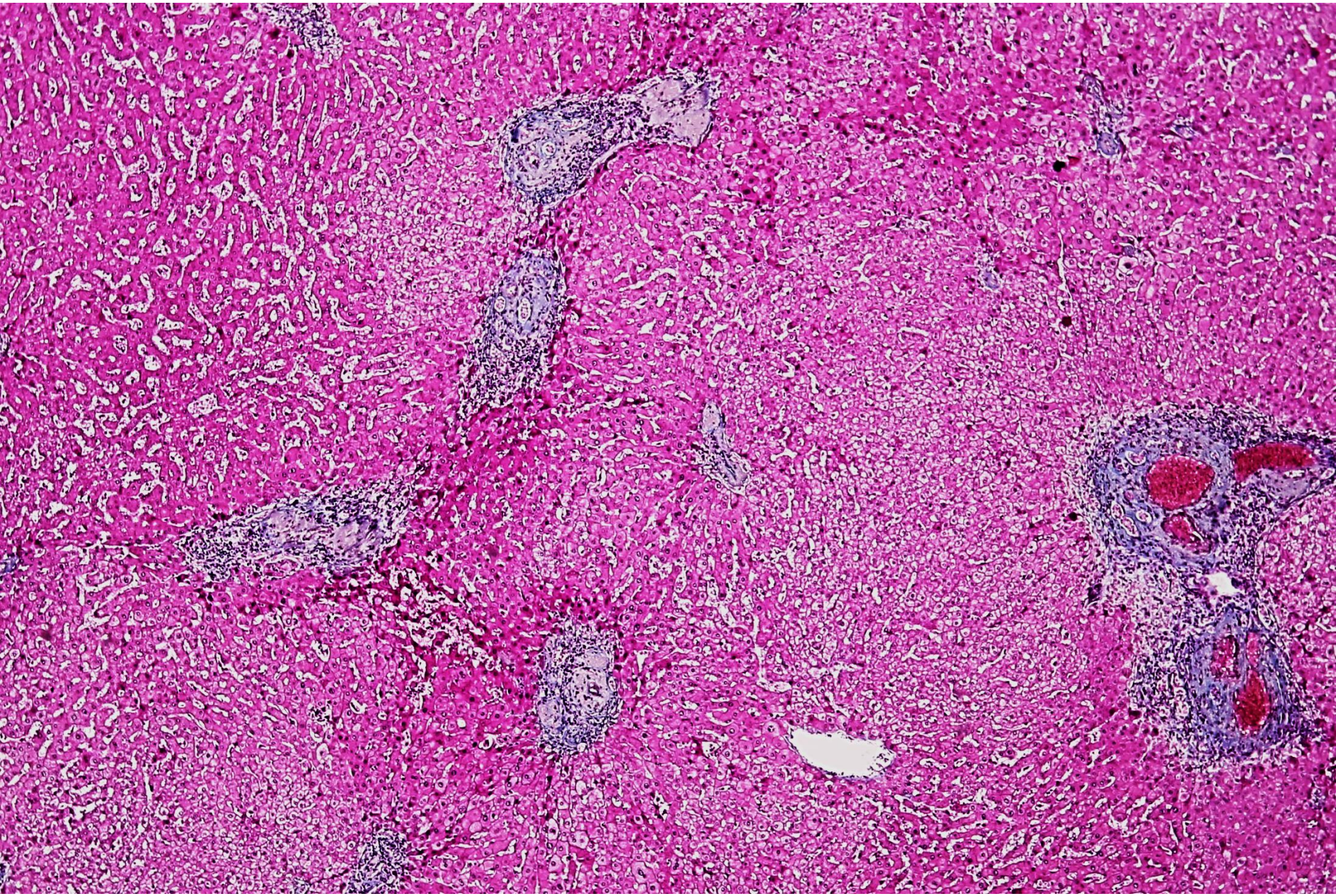
Sclerotic portal tract, no portal vein



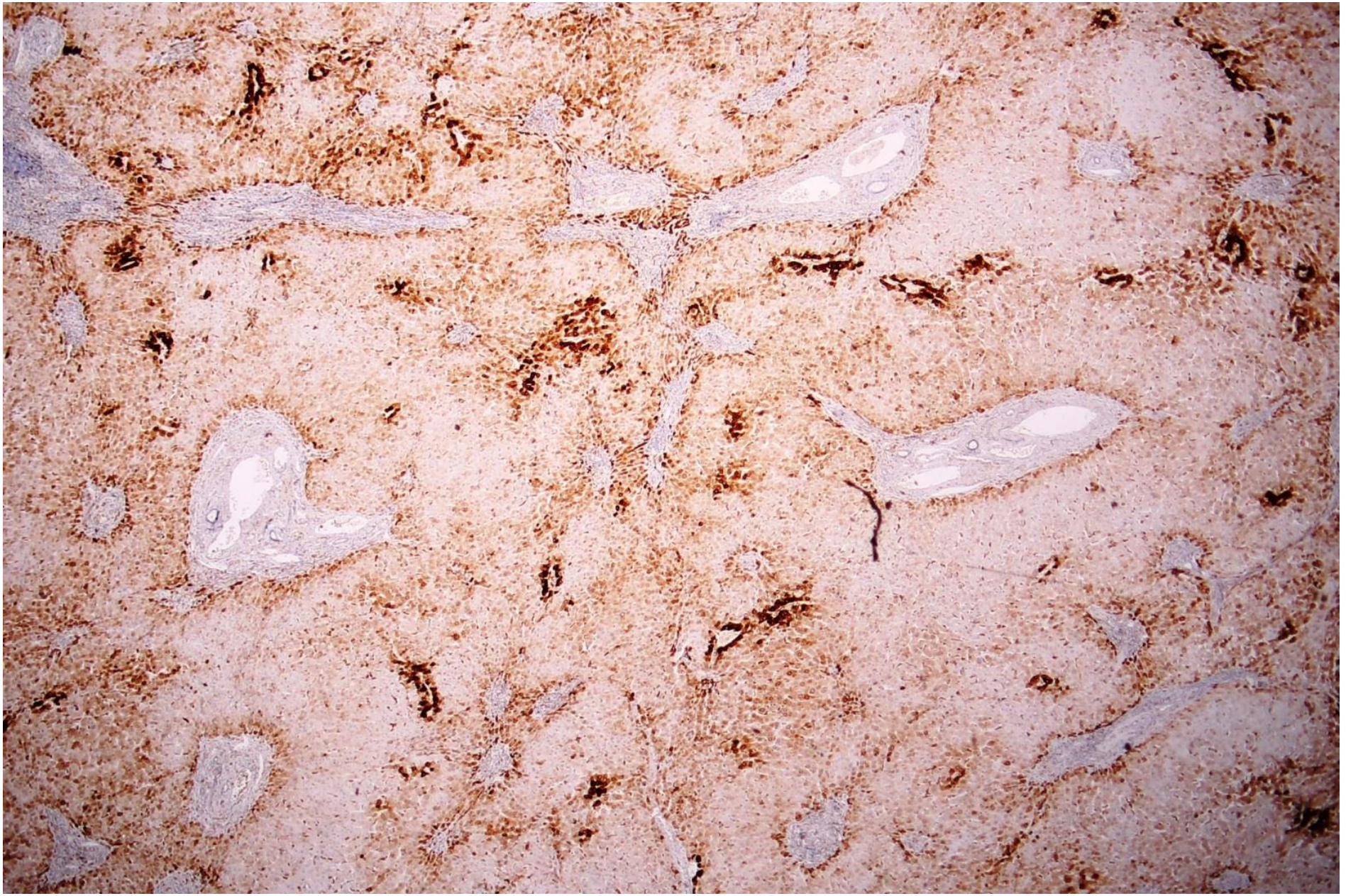
Sclerotic portal tract, dilated periportal vessels



Portal tracts abnormally closely apposed



Glutamine Synthetase – Normal Zonation



Histological findings

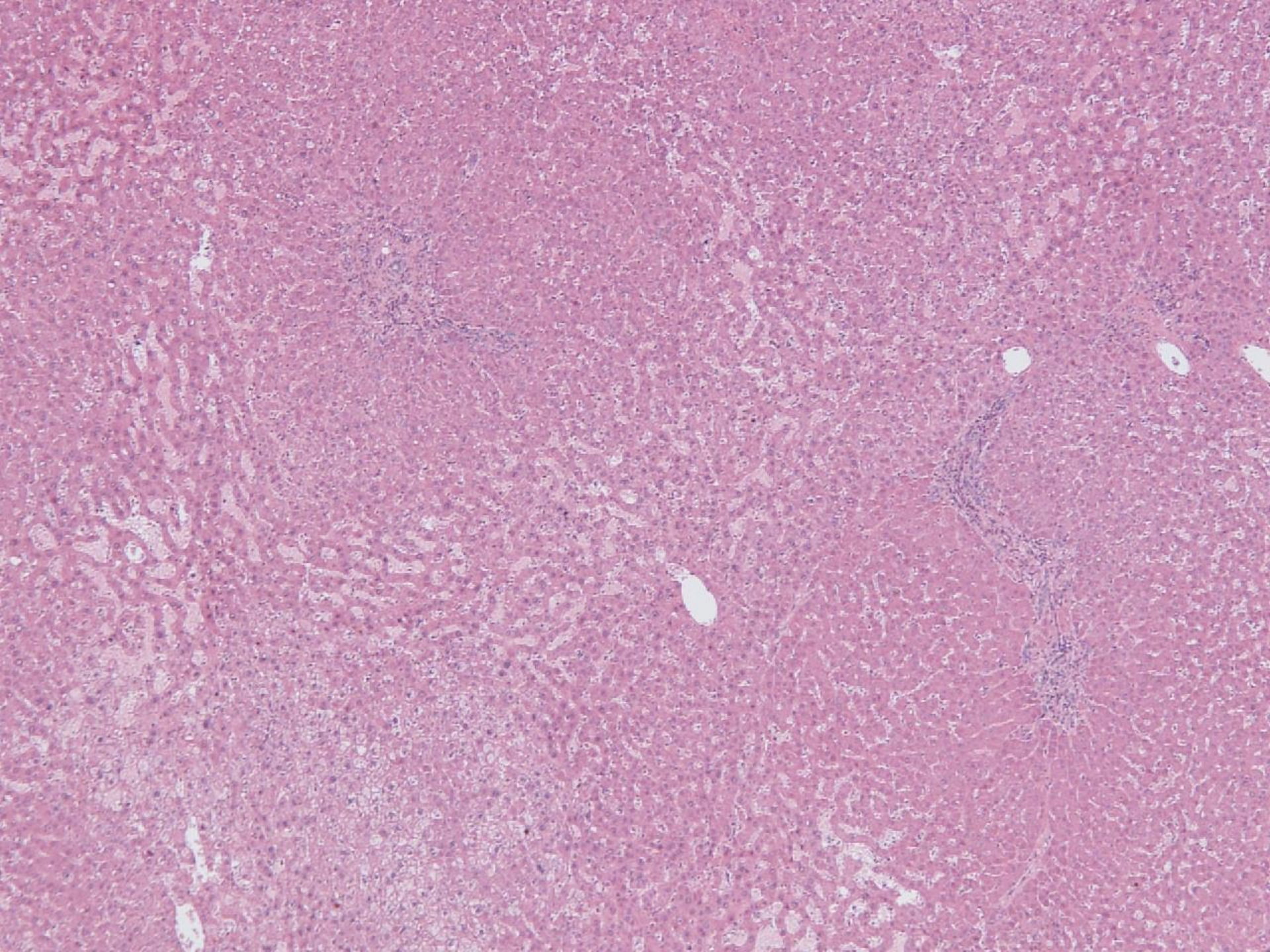
- No cirrhosis; no steatosis
- Abnormal portal tracts and portal veins
  - Incomplete Septa
  - Portal sclerosis
  - Obliterated or dilated portal veins
  - Dilated shunt-vessels
- **Histological Dx:**
  - **Obliterative Portal Venopathy (“idiopathic” non-cirrhotic portal hypertension)**

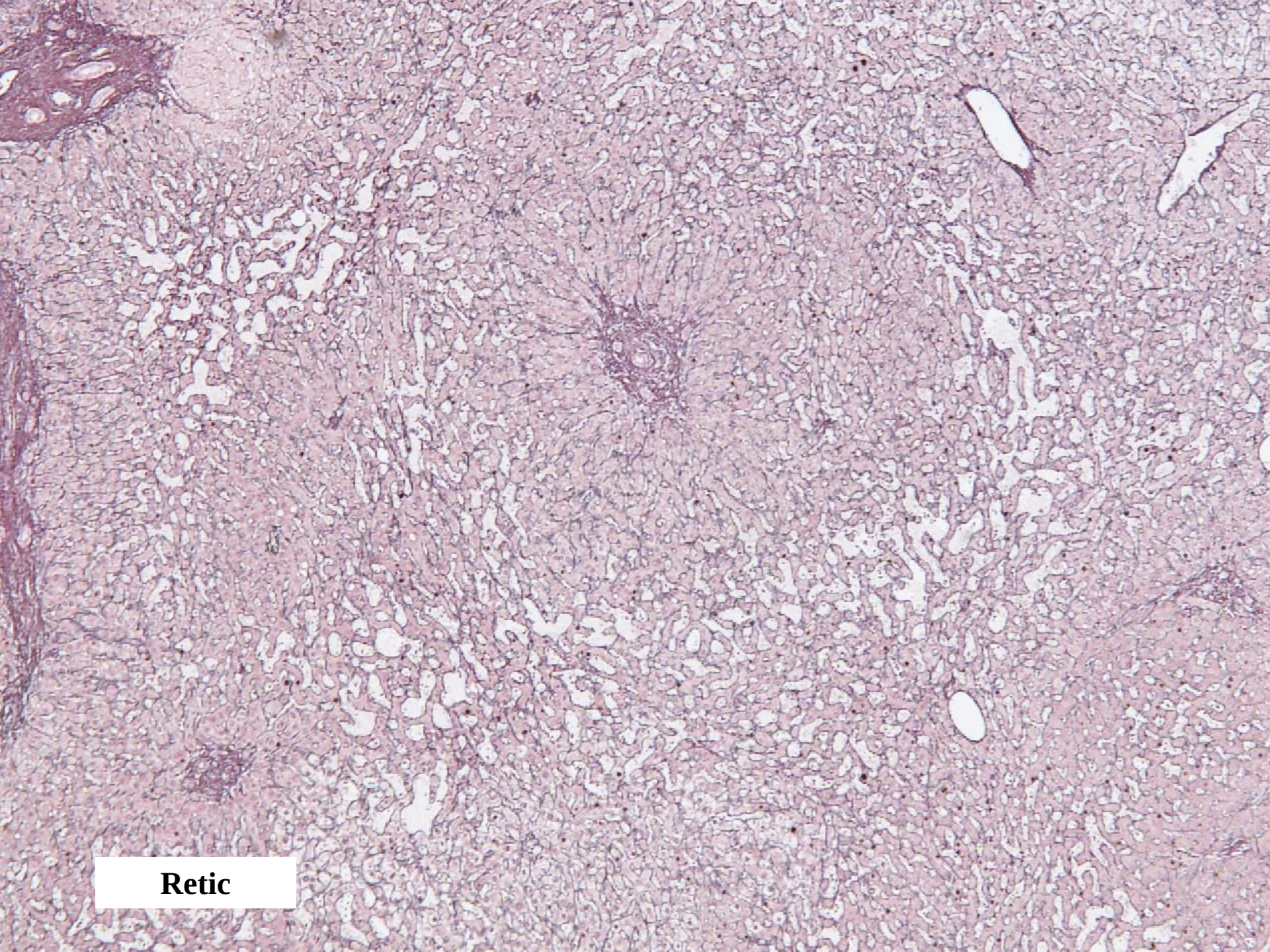
Birmingham A/2017

Male, age 70.

- Liver transplantation for “cryptogenic cirrhosis.”.
- Problems with recurrent bleeding from oesophageal varices. TIPSS inserted August 2014
- No previous liver biopsy

- Hepatectomy specimen showed features of obliterative portal venopathy/idiopathic non-cirrhotic portal hypertension
- Large portal vein thrombosis (presumed secondary)

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“Idiopathic” Non - Cirrhotic Portal Hypertension

Definition (EASL Guidlines, J Hepatol 2016)

1. Evidence of portal hypertension (e.g. varices, splenomegaly)
2. Patent (large) portal and hepatic veins on imaging
3. No cirrhosis (or significant fibrosis) on liver biopsy
4. No risk factors for chronic liver disease (e.g. alcohol, viral hepatitis)
5. Exclusion of other non-cirrhotic liver diseases associated with portal hypertension (e.g. Congenital hepatic fibrosis, sarcoidosis, schistosomiasis)

"Idiopathic" Non- Cirrhotic Portal Hypertension

(Lee, J Pathol & Translational Medicine 2016)

Alternative Terms

- Idiopathic portal hypertension
- Non-cirrhotic portal hypertension
- Non-cirrhotic intrahepatic portal hypertension
- Hepatoportal sclerosis (Mikkelsen 1965)
- Non-cirrhotic portal fibrosis (Boyer 1967)
- Obliterative portal venopathy (Nayak 1969)

Other Related Histopathological Entities

- Nodular regenerative hyperplasia (Ranstrom 1953)
- Incomplete septal cirrhosis (Popper 1966)
- Partial nodular transformation (Sherlock 1966)

Above studies suggest that these are distinct clinico-pathological entities

The Spectrum of Non-Cirrhotic Portal Hypertension

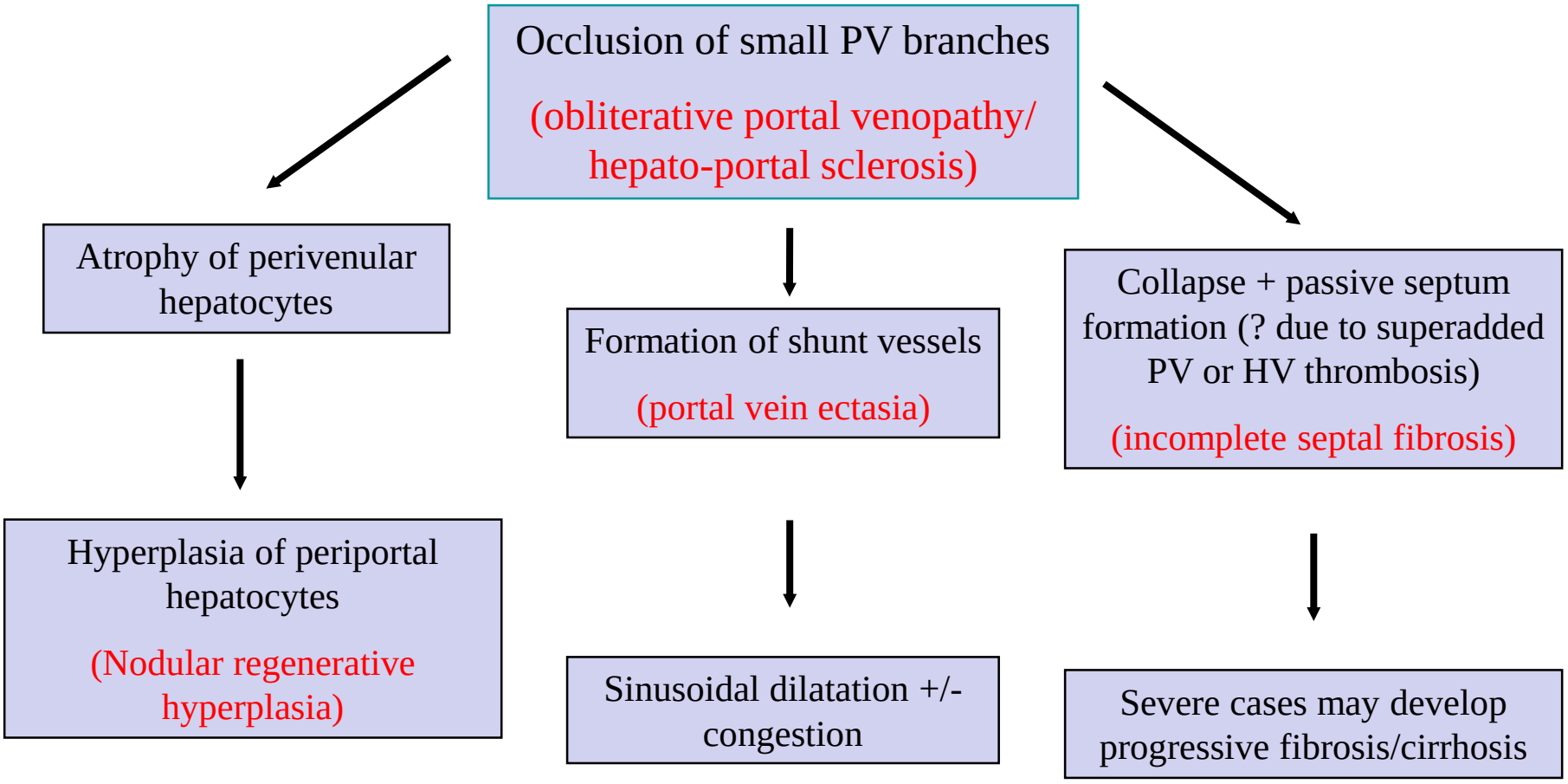
Nakanuma, Histopathology 1996; 28: 195-204

	Idiopathic portal hypertension (n=66)	**Nodular regenerative hyperplasia (n=14)**	**Partial nodular transformation (n=2)**	**Incomplete septal cirrhosis (n=25)**
Portal fibrosis/ venous obliteration	100%	100%	100%	100%
Nodular hyperplasia without fibrosis	41%	100%	100%	32%
Intralobular fibrous septa	94%	86%	100%	100%

- Importance of obliterative portal venopathy confirmed in more recent studies (Nayak 2011, Cazals-Hatem 2011, Saigal 2011, Guido 2016)

Non-cirrhotic portal hypertension (obliterative portal venopathy)
Pathogenesis + Histological Features

(from Hübscher, Diagnostic Histopathology 2011; 17: 530-538)



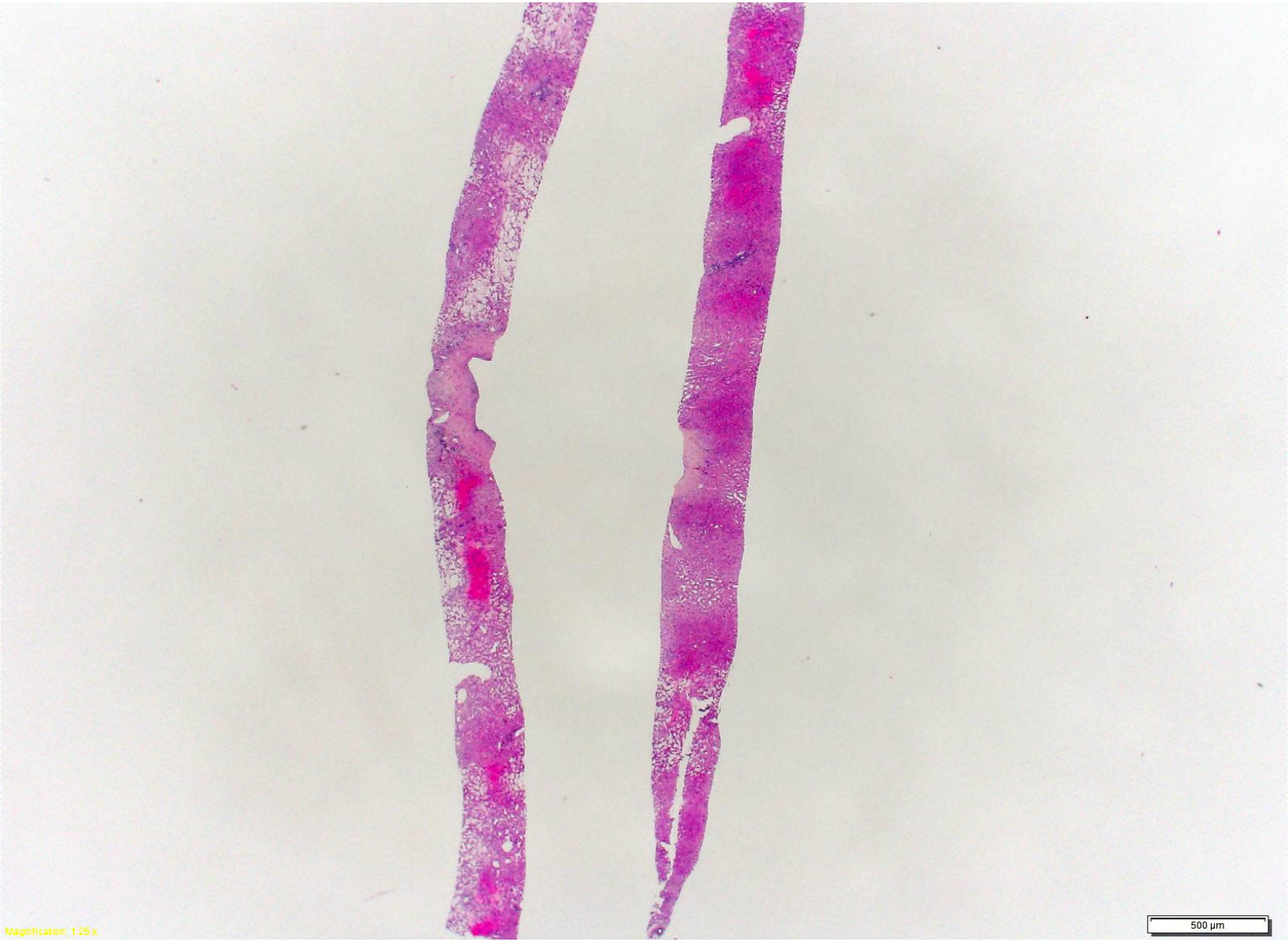
Gnomes Meeting, Groningen 2017 – Summary of Cases Presented
Portal Vein Lesions

Case No	Portal Vein Lesion
Adelaide A	HCV cirrhosis. Right lobe atrophy/extinction complicating TIPPS-related portal vein occlusion
Birmingham A	Obliterative portal venopathy (NCPH) with secondary large portal vein thrombosis
Groningen A	Obliterative portal venopathy
Groningen B	Nodular regenerative hyperplasia/obliterative portal venopathy - MGUS and Von Meyenburg complexes
Halifax A	Monoclonal gammopathy with fibro-obliterative portal venopathy
Paris A	Incomplete septal cirrhosis in cystic fibrosis
St Louis A	Abernethy syndrome – splanchnic vascular malformation • associated with absent portal vein and liver lesions (FNH, HCA, HCC)

Sinusoidal (+ Small Hepatic Vein) Lesions

BASEL A/2017- Luigi Terracciano
Clinical history

- A 47- year-old man was admitted to our hospital because of cholestatic hepatopathy with increase of cholestatic parameters and transaminases.
- At ultrasonography no evidence of mechanical obstruction.
- Because of diabetes mellitus type I and end-stage renal failure he underwent pancreas and renal transplanation 13 years before.
- He was under treatment with Azathioprine, Prednisone, Tacrolimus, Amlodipine, Bisoprolol, Torasemide.
- Search for causes of liver disease including HBV, HCV, hemochromatosis and autoantibodies, was negative.
- A liver biopsy was performed.


Magnification: 1.25 x
500 µm

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Lobular architecture preserved, except for areas of liver cell dropout

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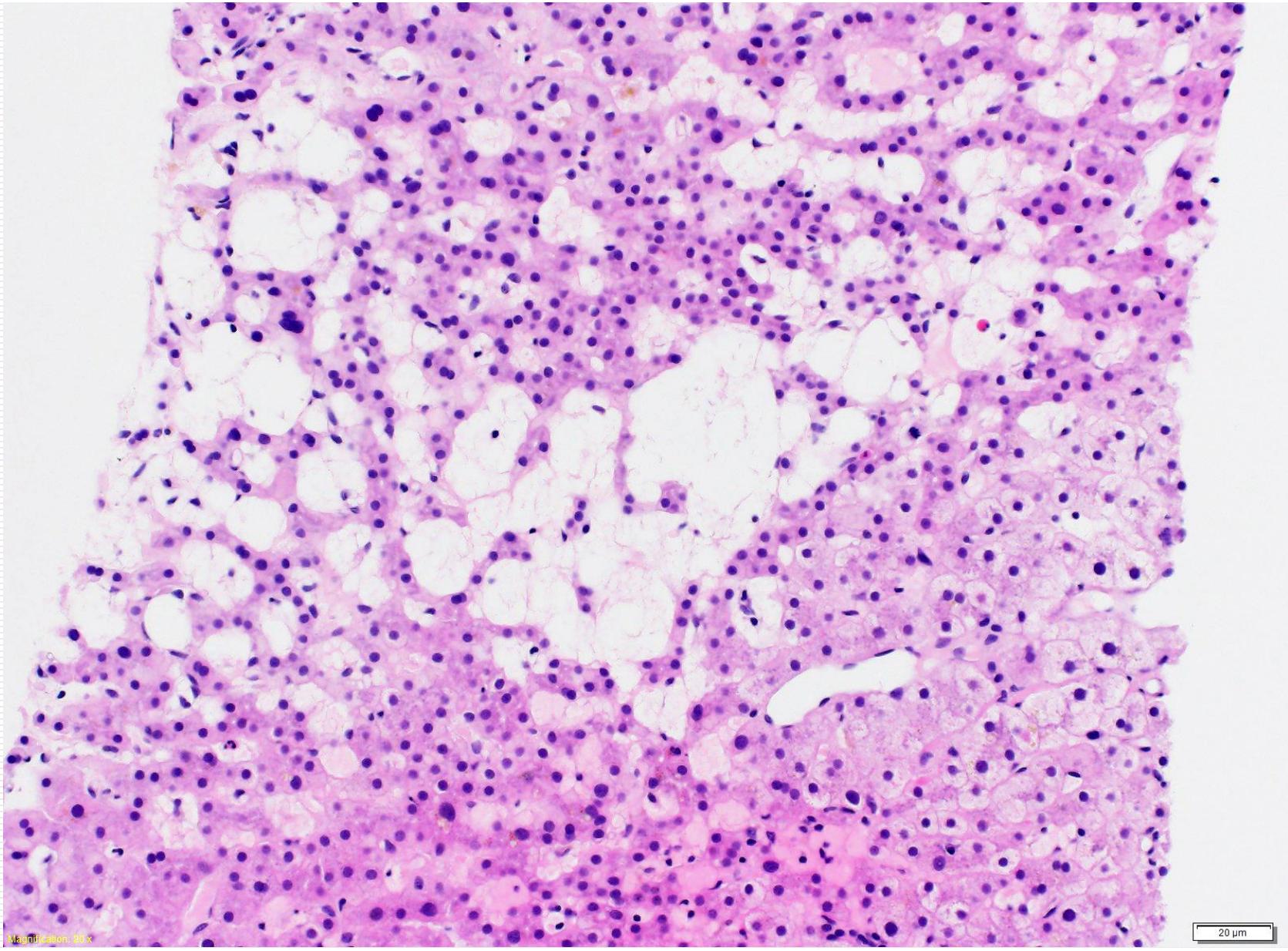

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Sinusoidal dilatation

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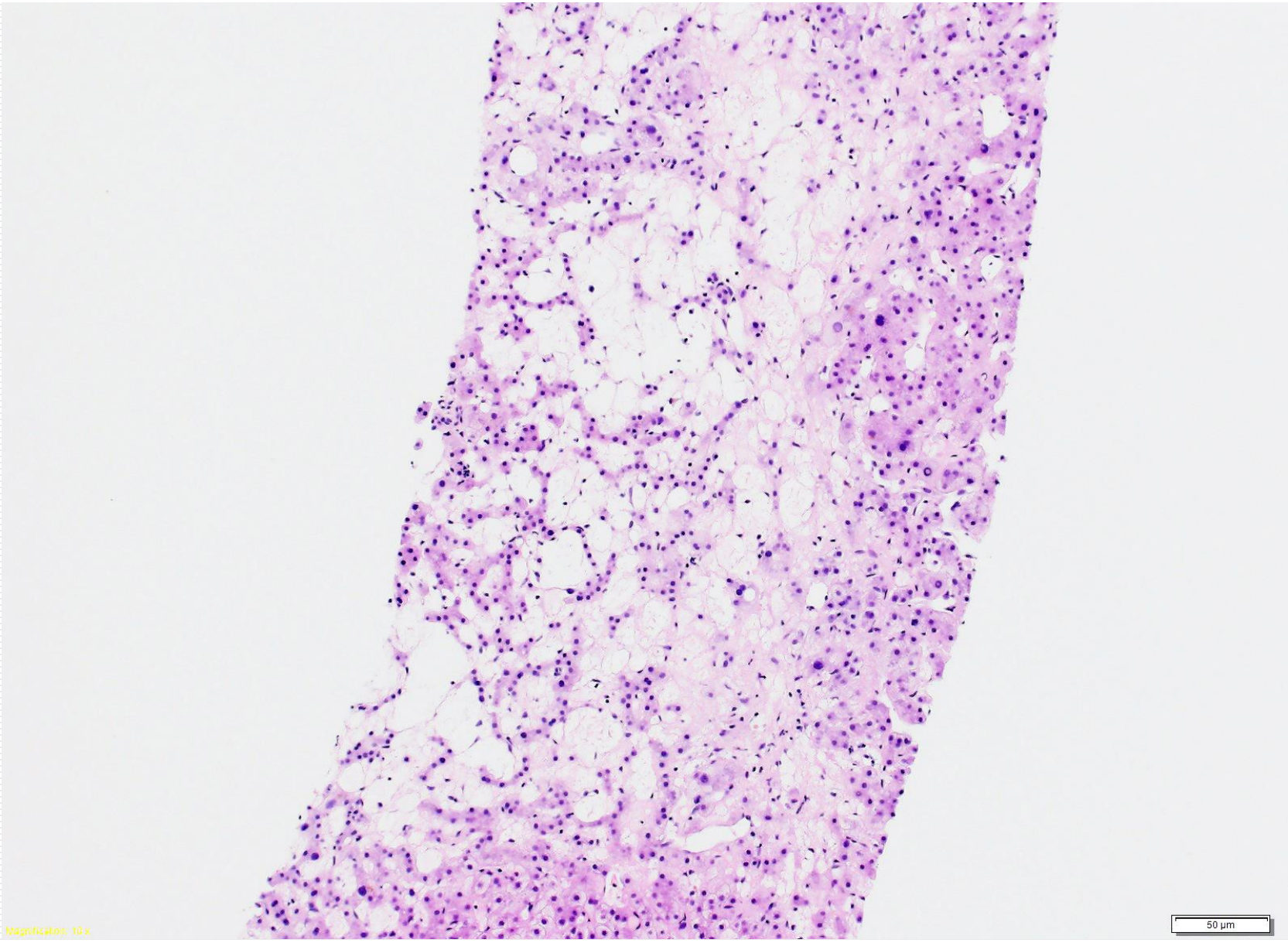

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Liver cell dropout with disruption of hepatic laminae

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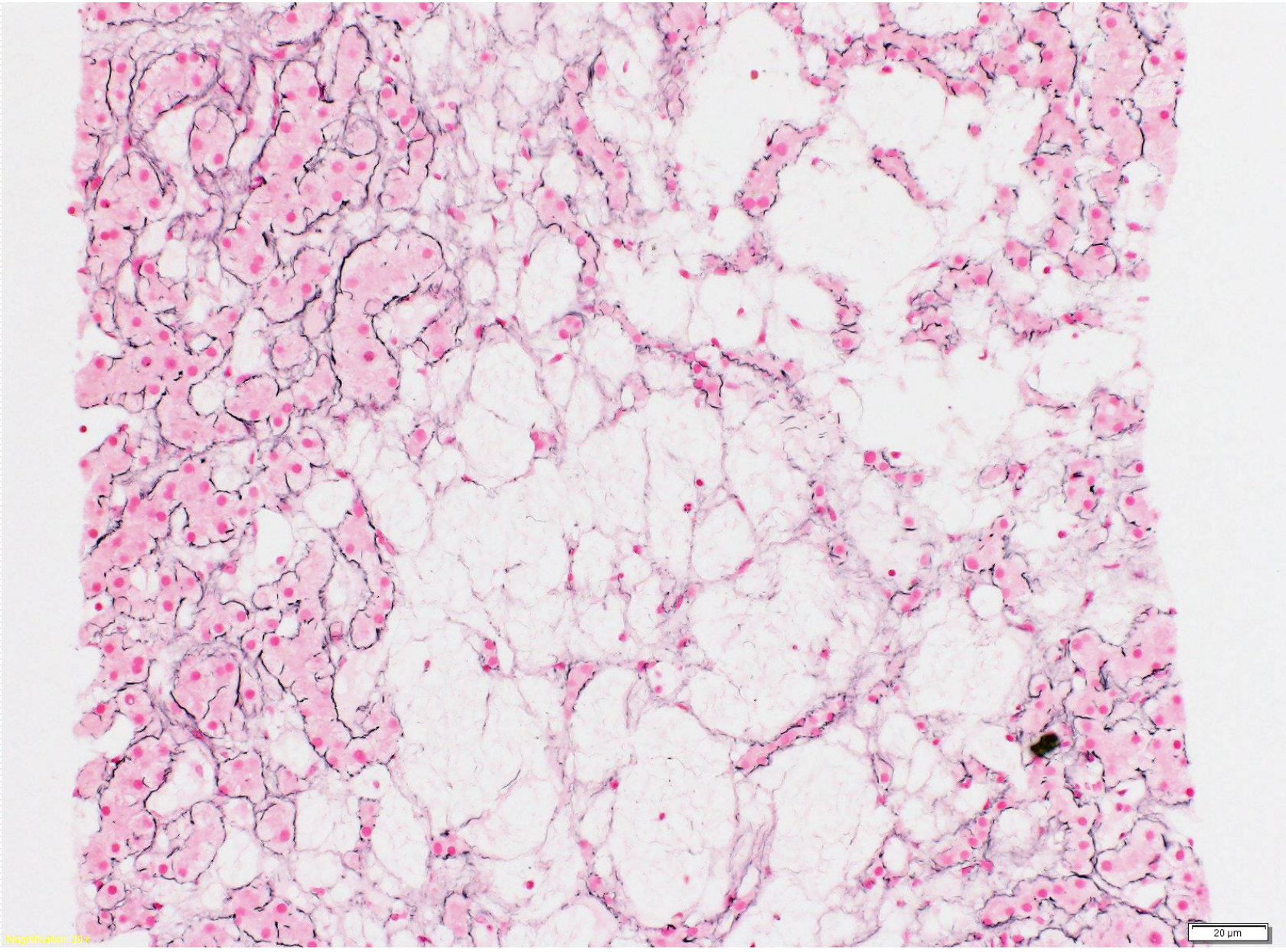

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Loss of reticulin

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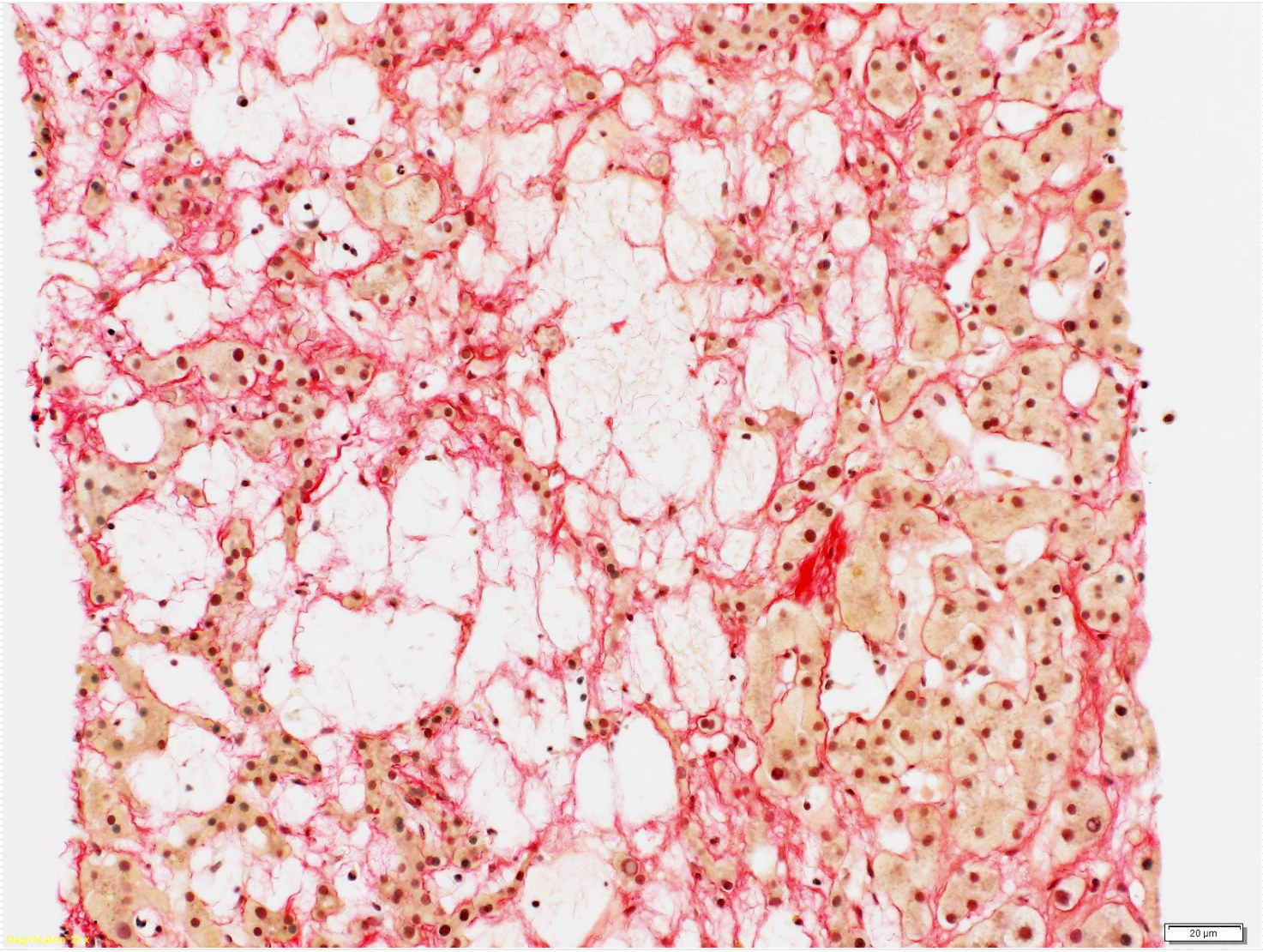

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Perisinusoidal fibrosis

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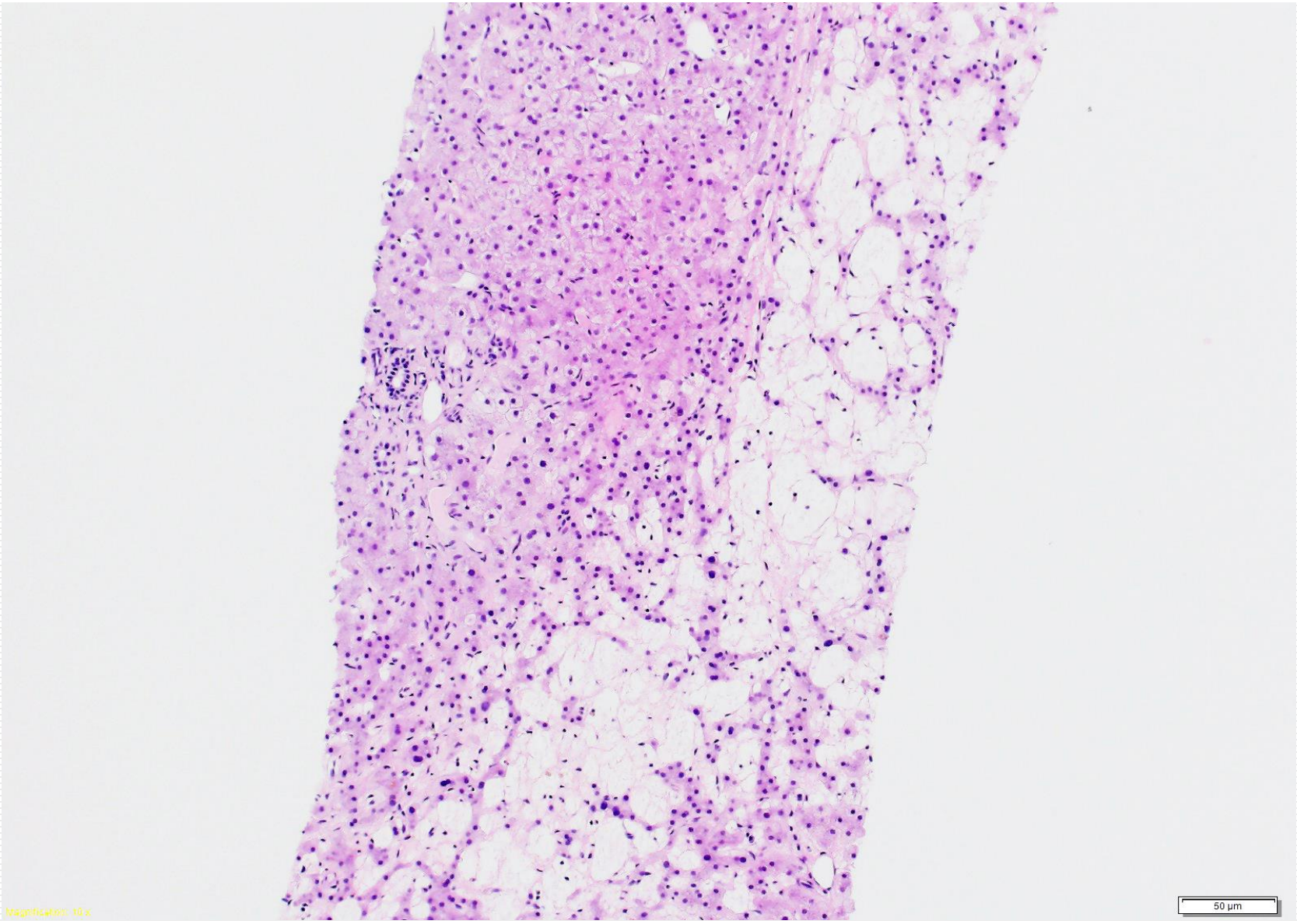

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Absence of portal as well as lobular inflammation

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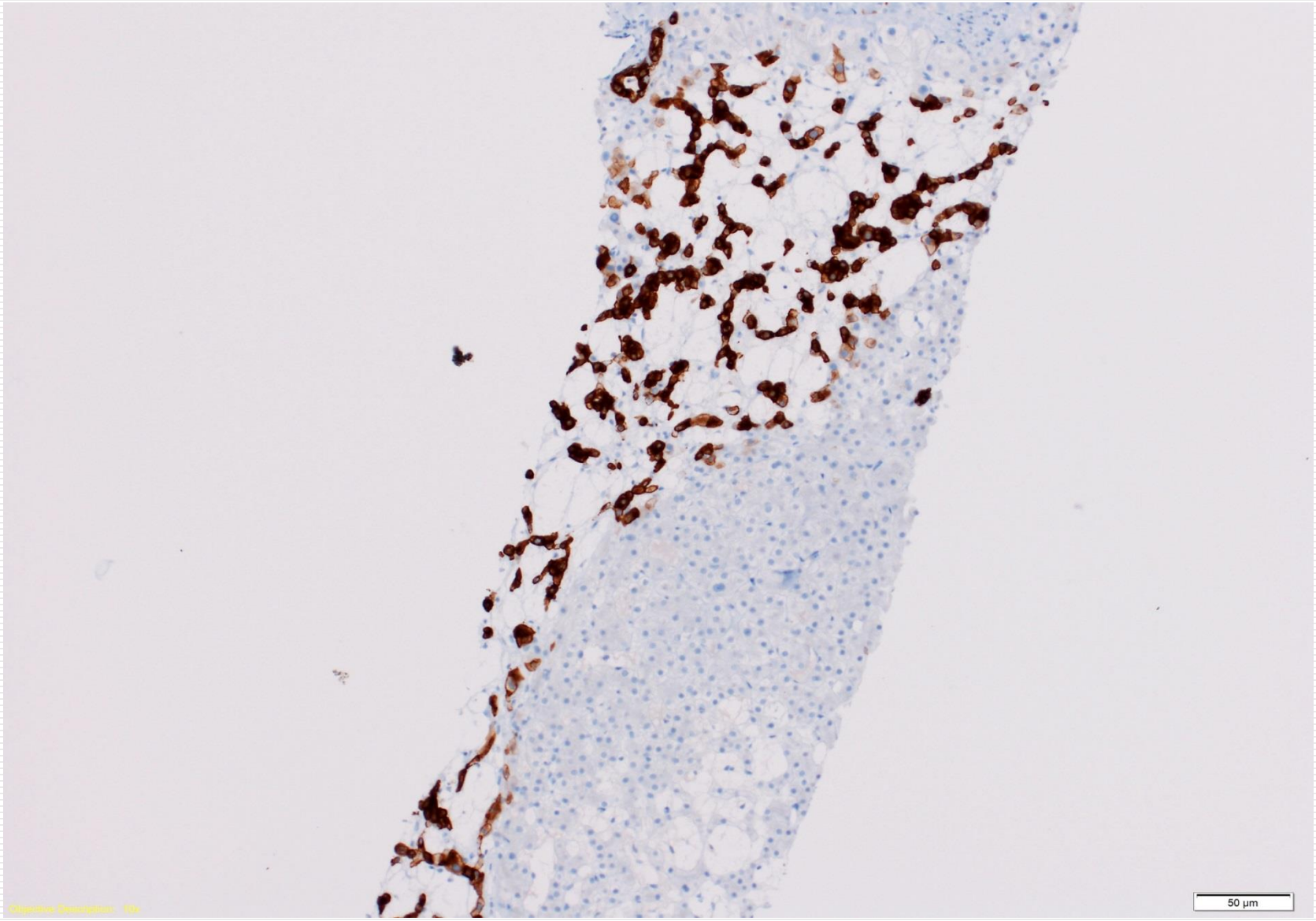

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CK7 expression

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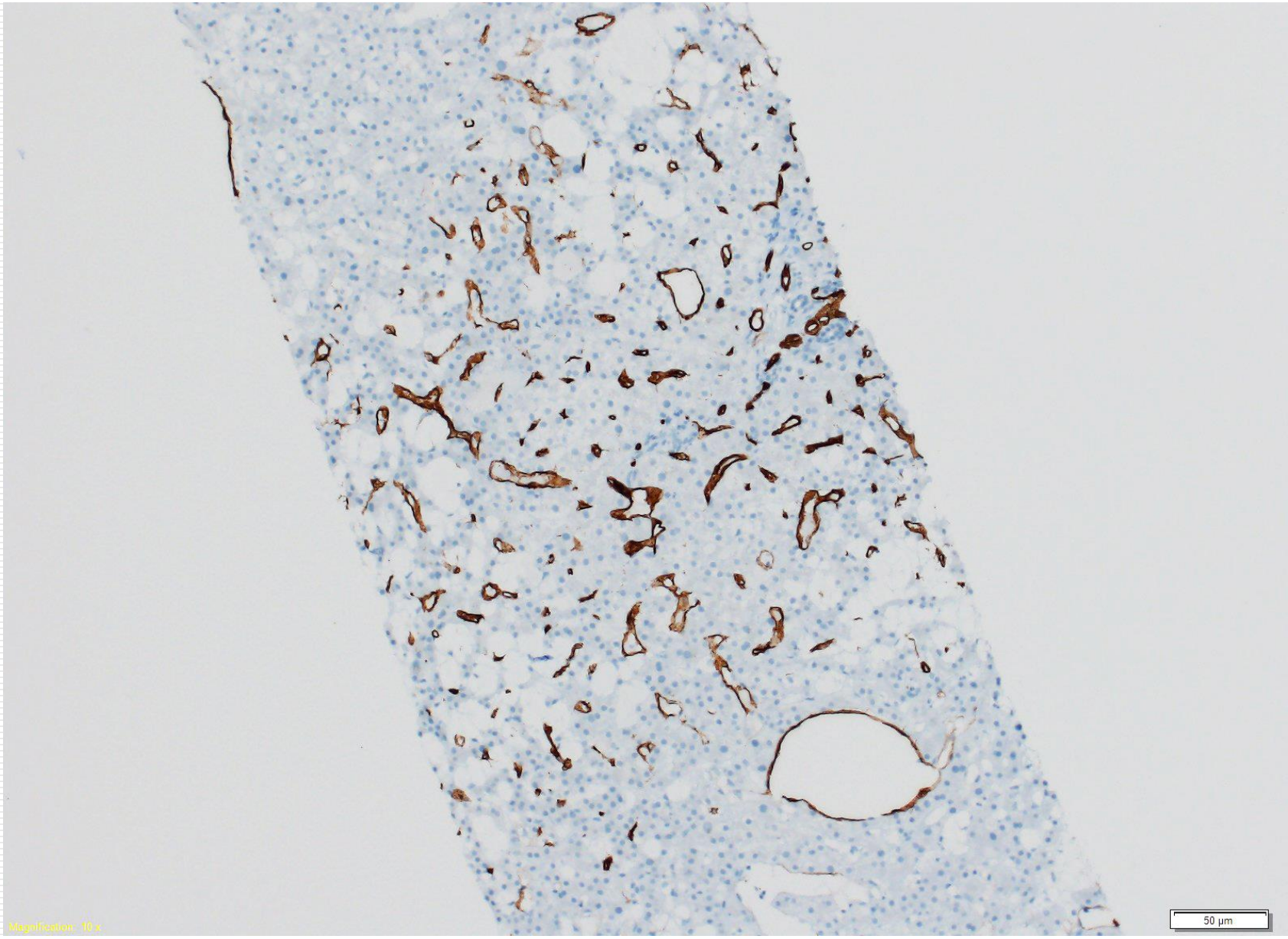

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CD34

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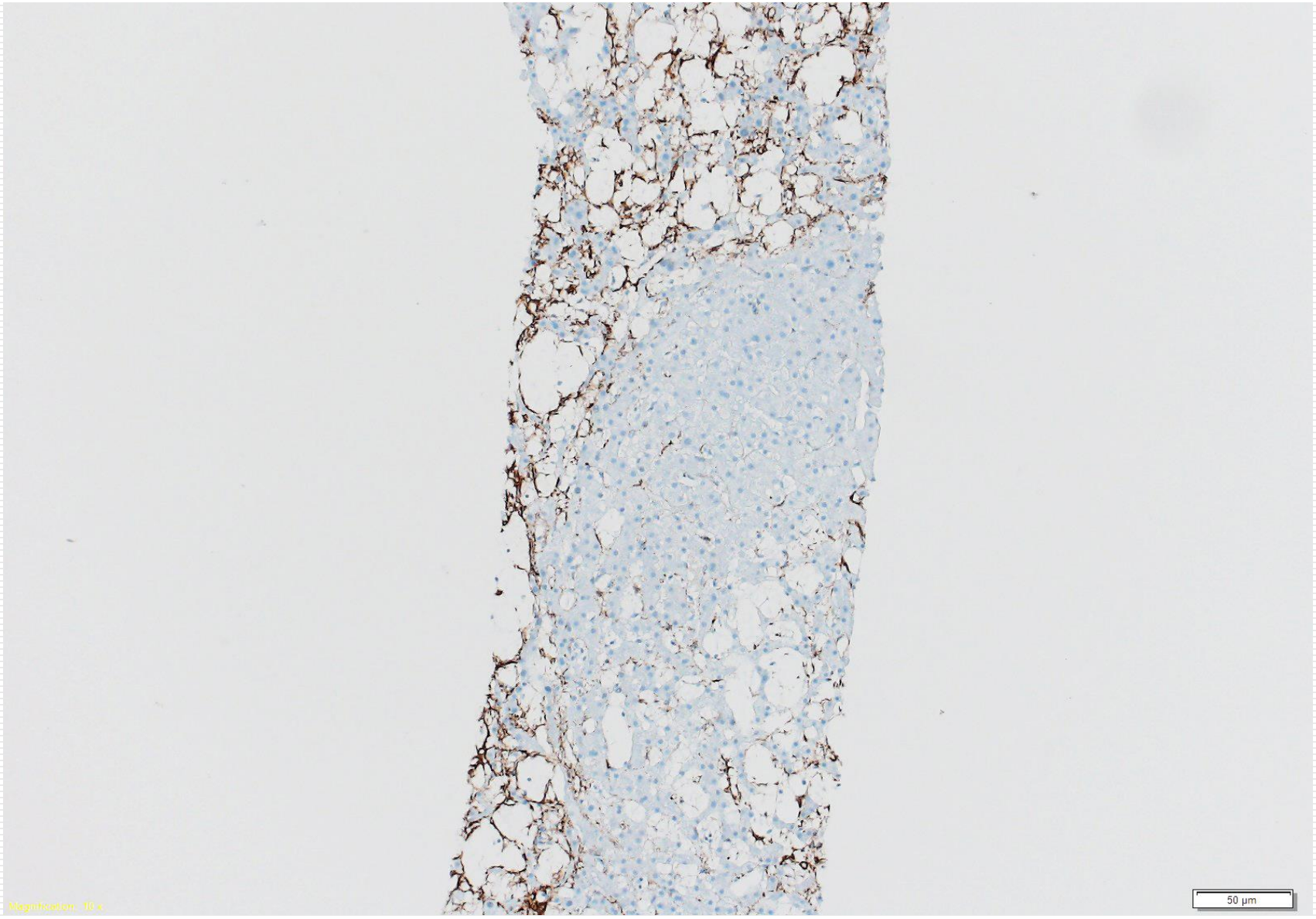

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SMA

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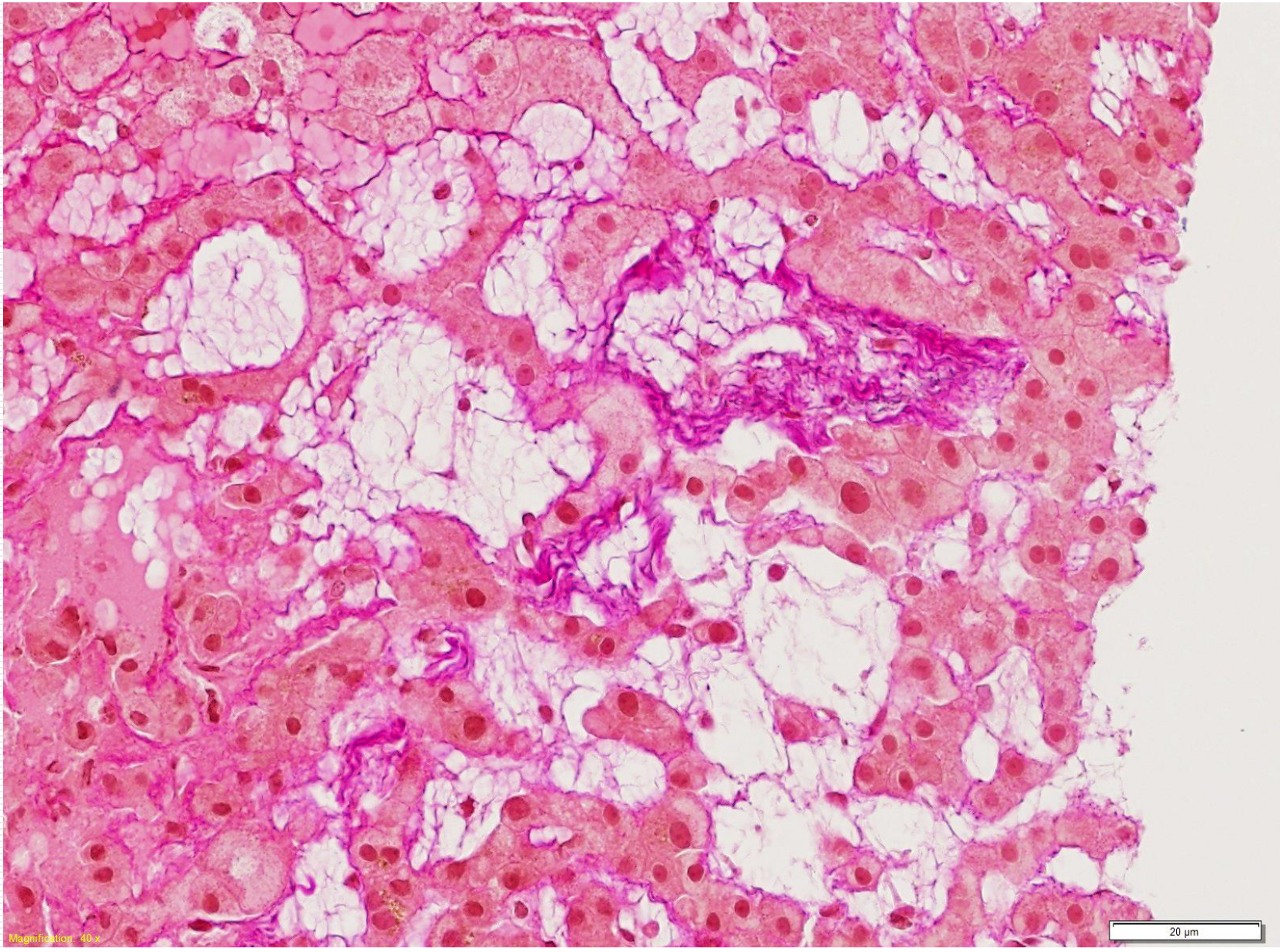

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A single central vein with luminal narrowing

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Histological features

- ✓ Sinusoidal dilation, congestion and peliosis-like areas
- ✓ Strong CK7 expression around cell dropout areas
- ✓ Occasional luminal narrowing of central veins
- ✓ No significant lobular inflammation
- ✓ No significant portal fibrosis

Diagnosis

Sinusoidal congestion, peliosis and luminal narrowing of central veins in keeping with Sinusoidal Obstruction Syndrome, probably related to azathioprine intake

Sinuosoidal obstruction syndrome (SOS) (hepatic veno-occlusive disease)

Causes / Associated Conditions:

1. Herbal (bush) teas or food sources containing pyrrolizidine alkaloids (*Crotolaria, Heliotropium, Senecio, Symphytum*)
2. Drugs:
   - chemo-irradiation-induced-injury: gemtuzumab ozogamicin, actinomycin, dacarbazine, cytyosine arabinoside, mithramycin, 6-thioguanine, urethane,
   - Myeloablative condition therapy: cyclophosphamide, busulfan + total body irradiation (TBI)
   - Adjuvant or neoadjuvant chemotherapy with hepatectomy for metastatic liver disease (oxaliplatin)
   - Azathioprine
3. Radiation-induced liver disease
4. Liver transplantation
5. VOD with immunodeficiency (VODI)

Gnomes Meeting, Groningen 2017 – Summary of Cases Presented
Sinusoidal /Small Hepatic Vein Lesions

Case No	Sinusoidal /Small Hepatic Vein Lesion
Basel A	Sinusoidal obstruction syndrome (azathioprine-induced)
Basel B	Sinusoidal obstruction syndrome (complicating haemopoietic stem cell transplantation)
Halifax B	Perisinusoidal fibrosis (residual collagen from incomplete merging of buds within cirrhotic septum)
Newcastle A	Perisinusoidal fibrosis (type 1 diabetes with diabetic hepatosclerosis)
Washington C	Sinusoidal infiltration (EBV-associated haemophagocytic lymphohistiocytosis)

Diseases of Liver Sinusoids
Theme of Gnomes Meetings in 2011 (St Louis) and 2012 (Mwanza)

Histopathology

Histopathology 2014, **64**, 907–920. DOI: 10.1111/his.12364

REVIEW

Pathology of the liver sinusoids*

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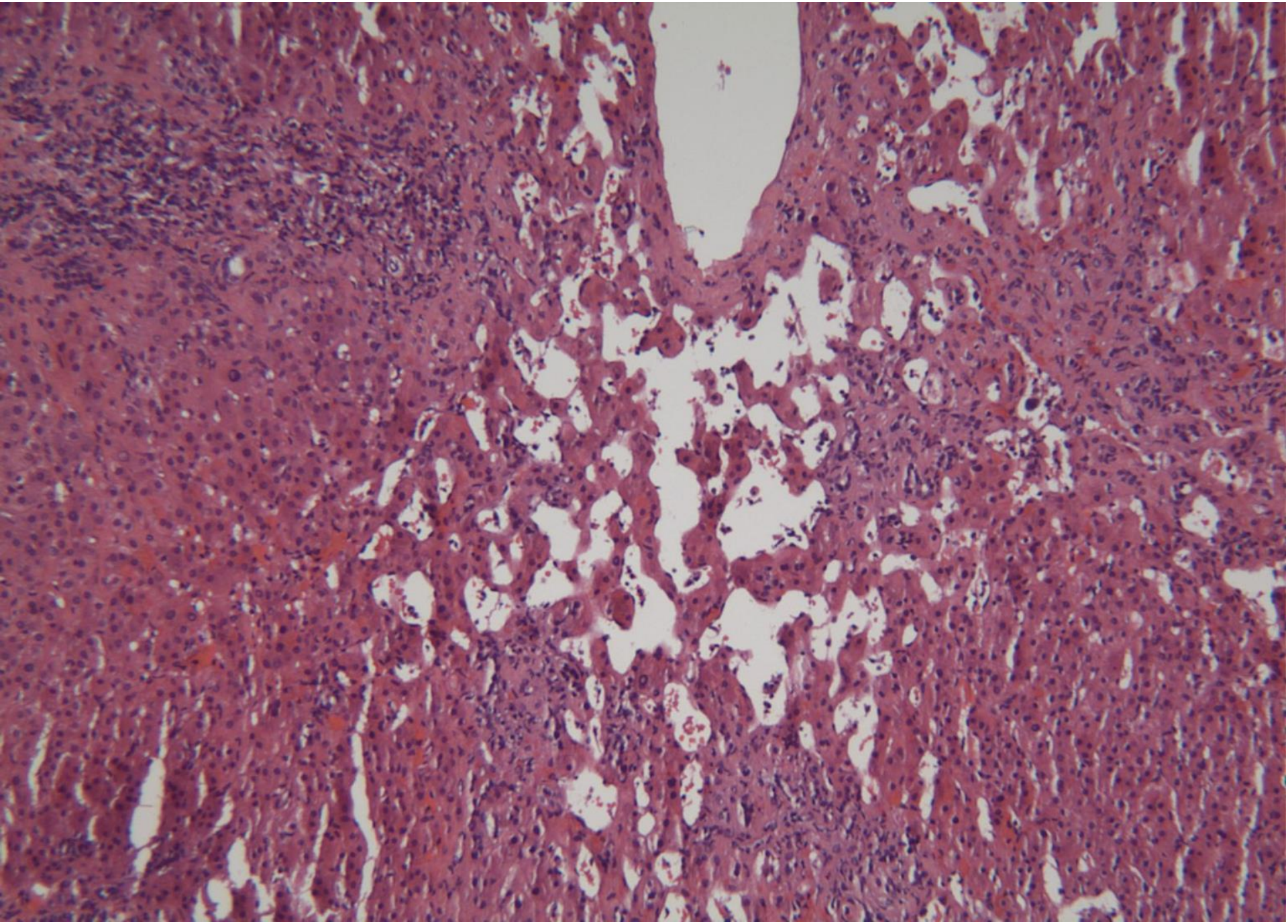
Large Hepatic Vein Lesions (including Hepatic Venous Outflow Obstruction)

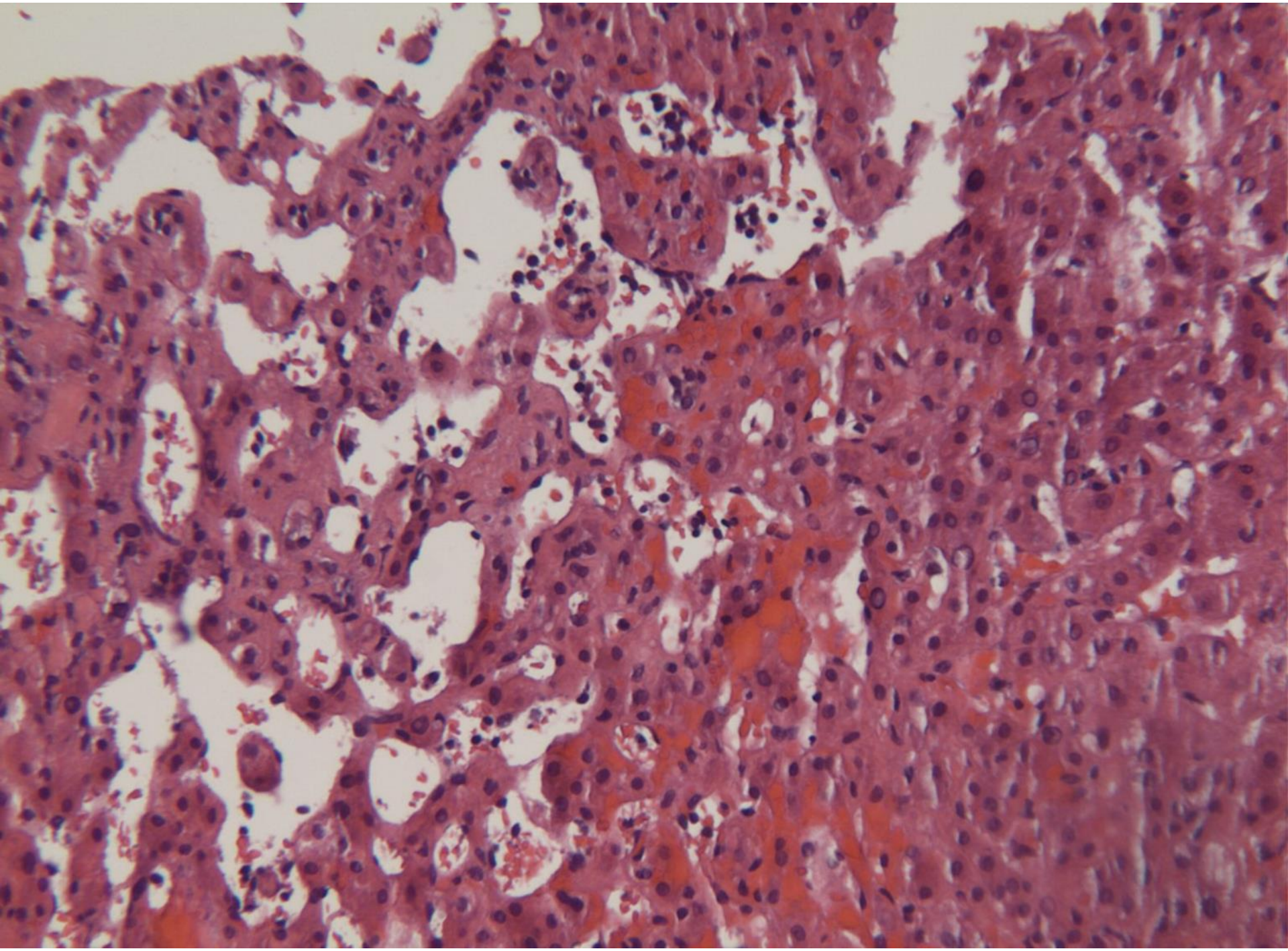
St Louis B/2017 – Beth Brunt

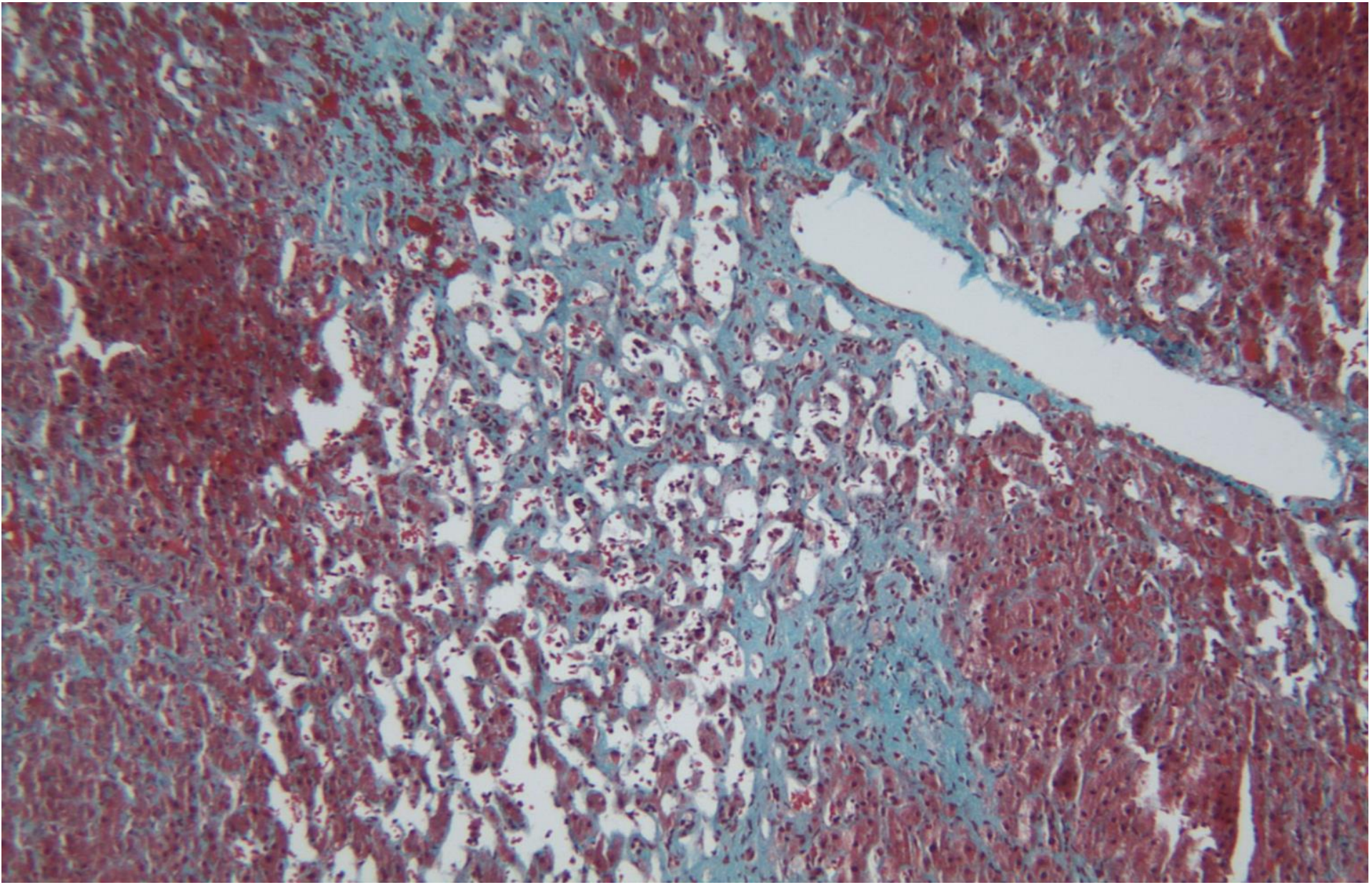
- 52 yM
- Morbid obesity, DM
- Congestive heart failure, Afib
- Undergoing gastric bypass surgery

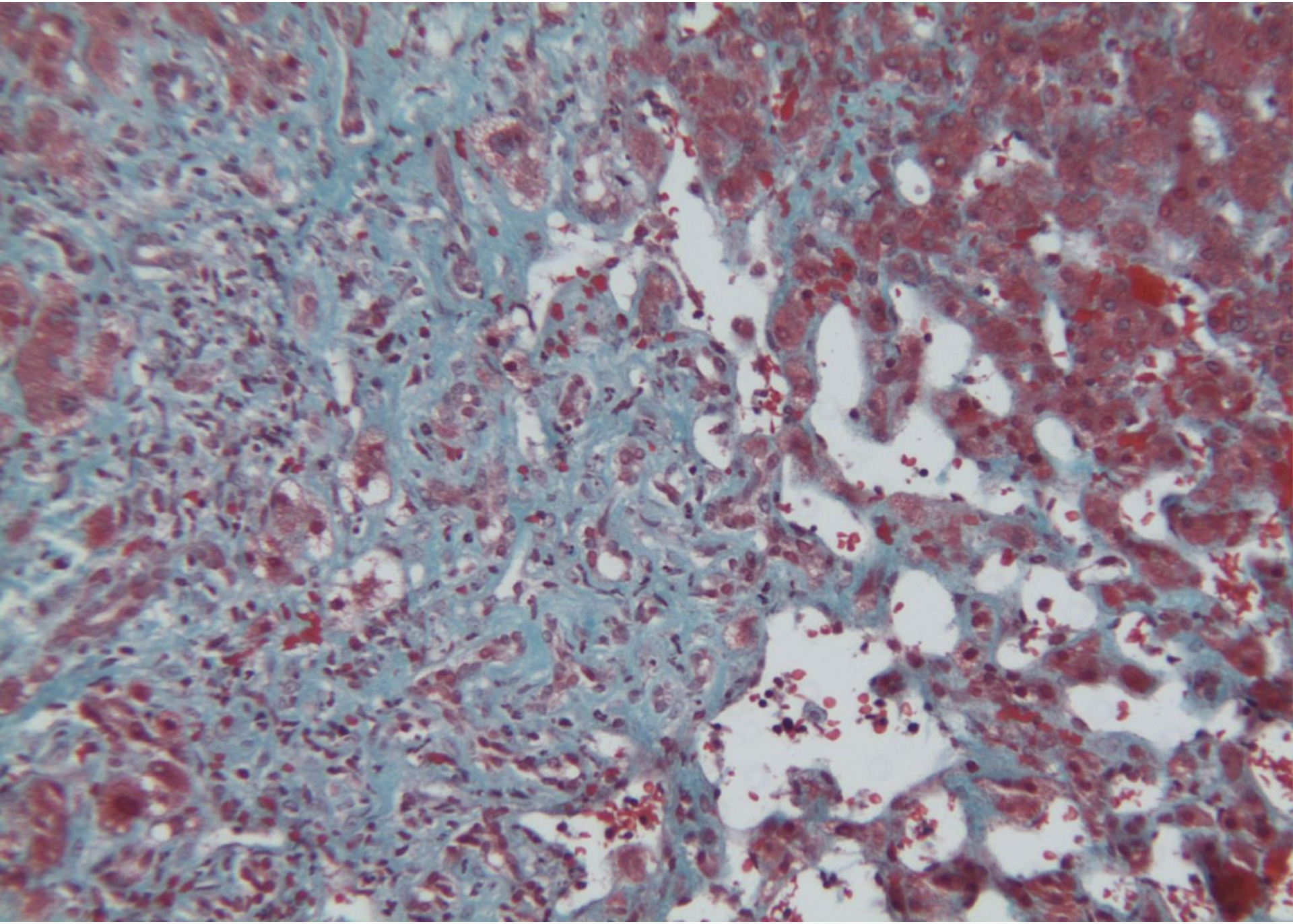
- Surgeon: "Liver looked funny"….biopsy done…disbelief!

- Sent for 2nd opinion







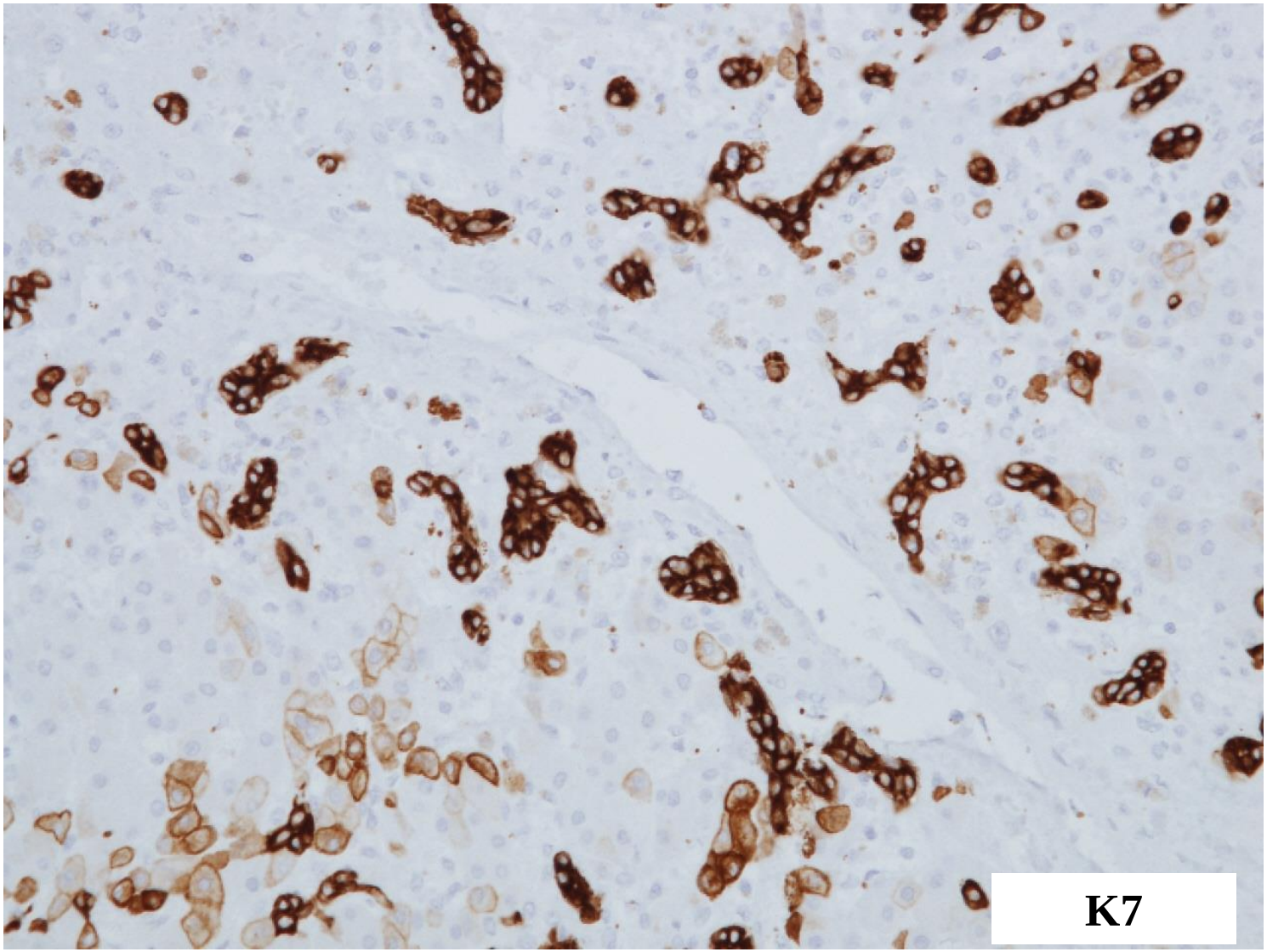


STL B - Diagnosis

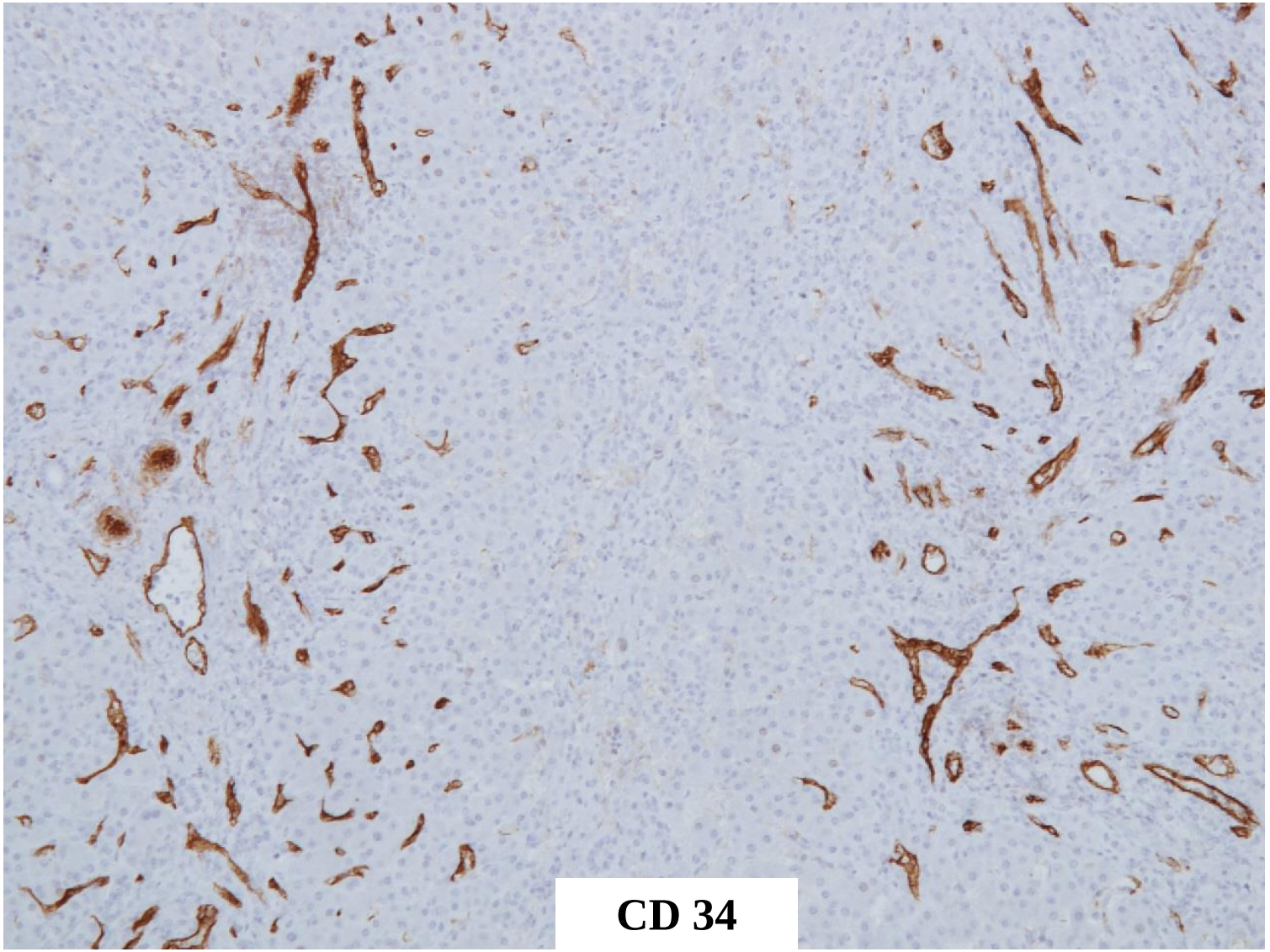
- Venous outflow obstruction secondary to right-sided heart failure
- No evidence of fatty liver disease

- Centrilobular changes may mimic biliary disease

Budd-Chiari Syndrome
Centrilobular ductular reaction (& CK7+ intermediate hepatobiliary cells)
(Birmingham Case B/2017)



Sinusoidal Capillarisation in Budd-Chiari Syndrome
(Birmingham Case B/2017)



Venous Outflow Obstruction
Centrilobular Changes Mimicking Biliary Disease

	No of cases	Causes of centrilobular injury	Changes seen in centrizonal regions
Krings 2014	61	Cardiac -29, BCS – 18, VOD – 2, unknown – 9	Ductules – 72% K7+ hepatocytes (intermed phenotype) – 93% Arterioles – 82% CD34+ microvessels – 93% CD34 + sinusoids – 96%
Delladetsima 2016	18	Hep venous congestion -15 NRH -1, other -2	K7+ atrophic hepatocytes CD34+ sinusoids
Matsukuma 2017	32	Hep venous congestion – 19 NAFLD – 7, ALD - 6	K7+ hepatocytes – 69% CD34+ vessels – 91%

- Presence/extent of biliary/microvascular changes correlates with severity of fibrosis
- Probably a response to centrilobular hypoxia
- Similar changes described in another study of NAFLD (Gill 2011)

Gnomes Meeting, Groningen 2017 – Summary of Cases Presented
Large Hepatic Vein Lesions (including extrahepatic venous outflow obstruction)

Case No	Large Hepatic Vein Lesion
Birmingham B	Budd-Chiari syndrome (acute-on-chronic)
Brisbane B	Hepatic vein stenosis (complicating liver transplantation)
St Louis B	Hepatic venous outflow obstruction (secondary to cardiac failure)

Architectural Disturbances in Vascular Liver Diseases

- Nodular regenerative hyperplasia
- Perisinusoidal fibrosis
- Incomplete septal fibrosis/cirrhosis

- Lobar/segmental atrophy

Washington Cases A/2017 & B/2017 – Zack Goodman

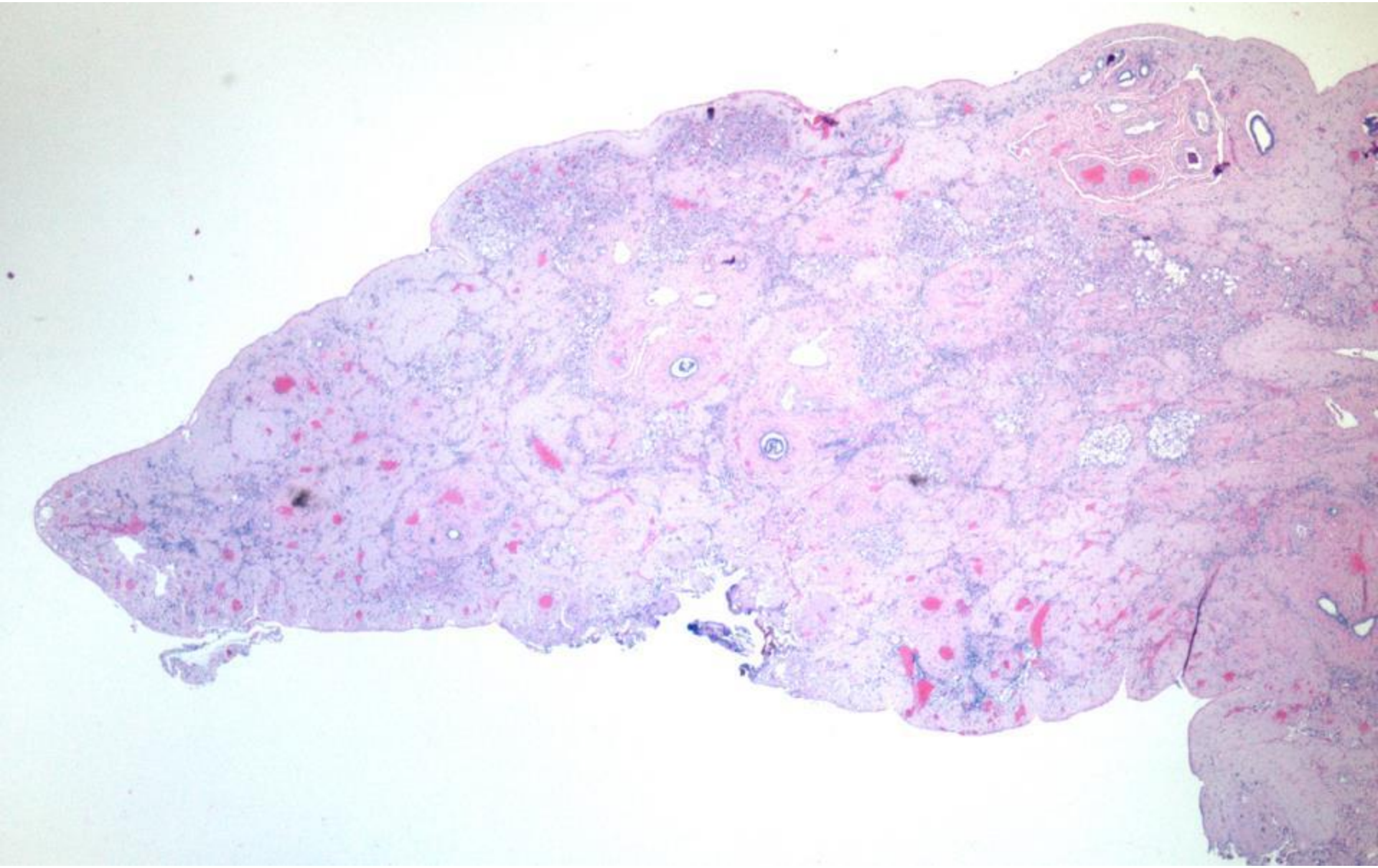
Washington A 59 F

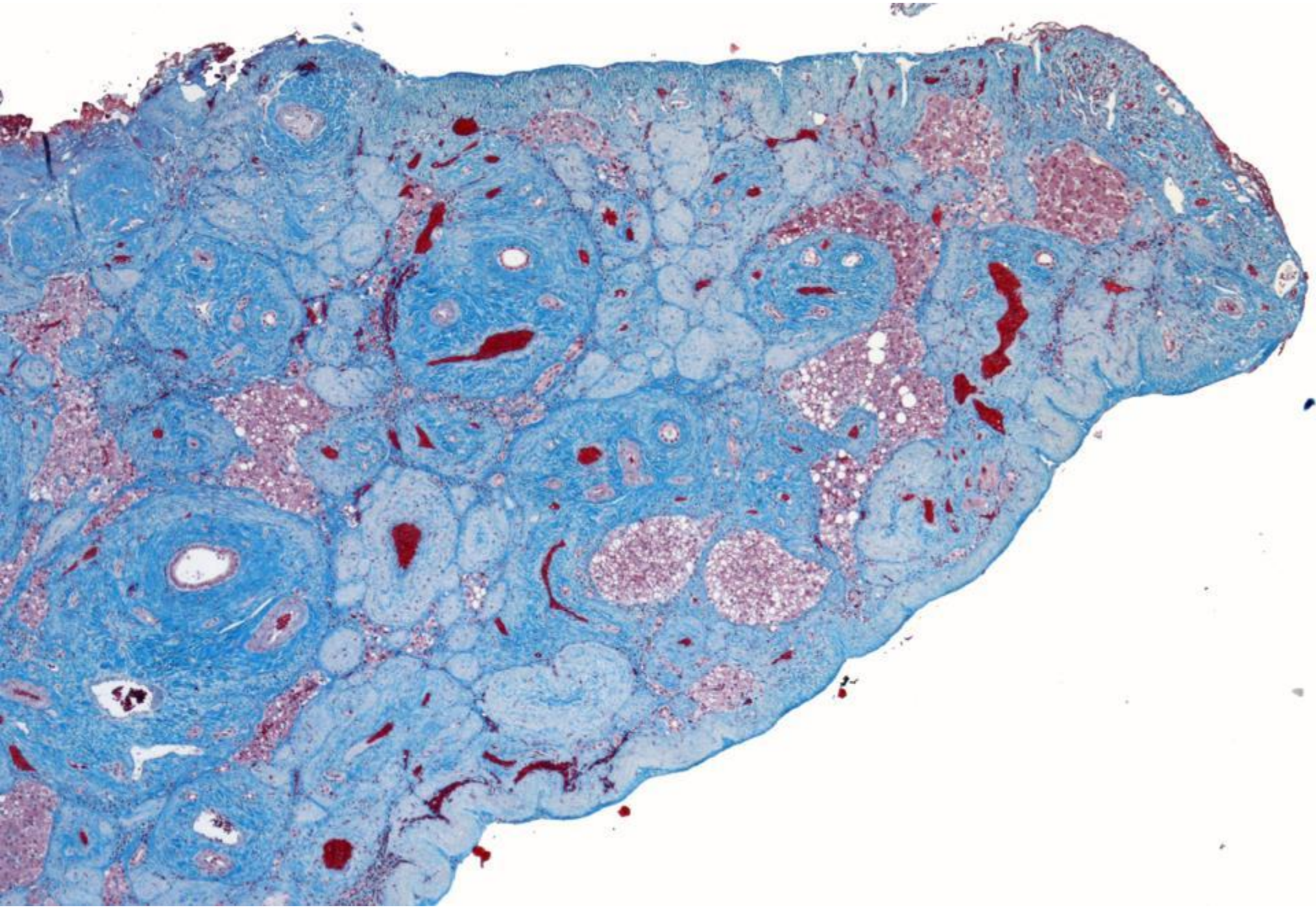
- Abnormal area on right anterior edge of liver
- Incidental finding during surgery for ovarian carcinoma

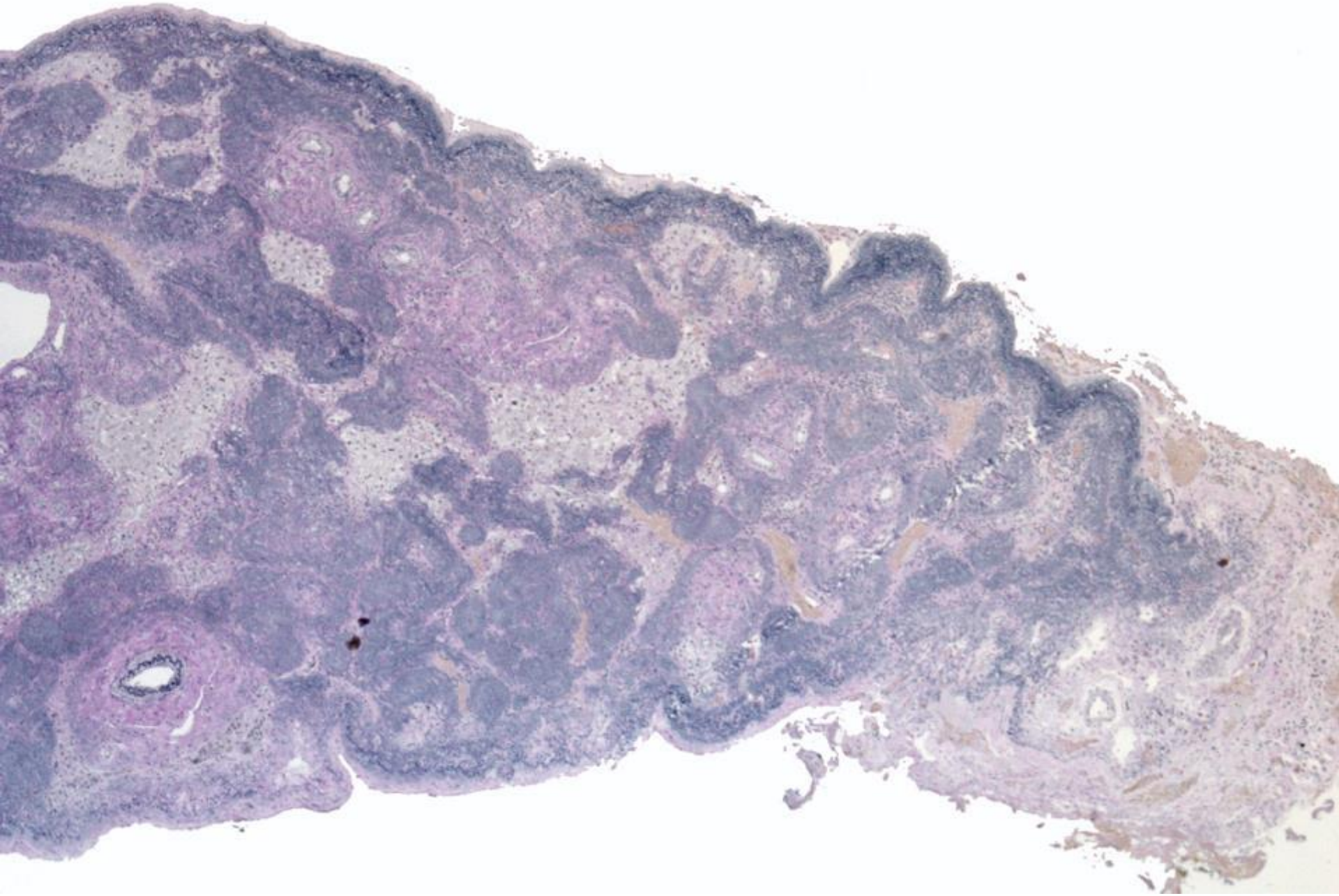
Washington B 58 F

- White plaque on surface of liver
- Incidental finding during laparoscopic cholecystectomy

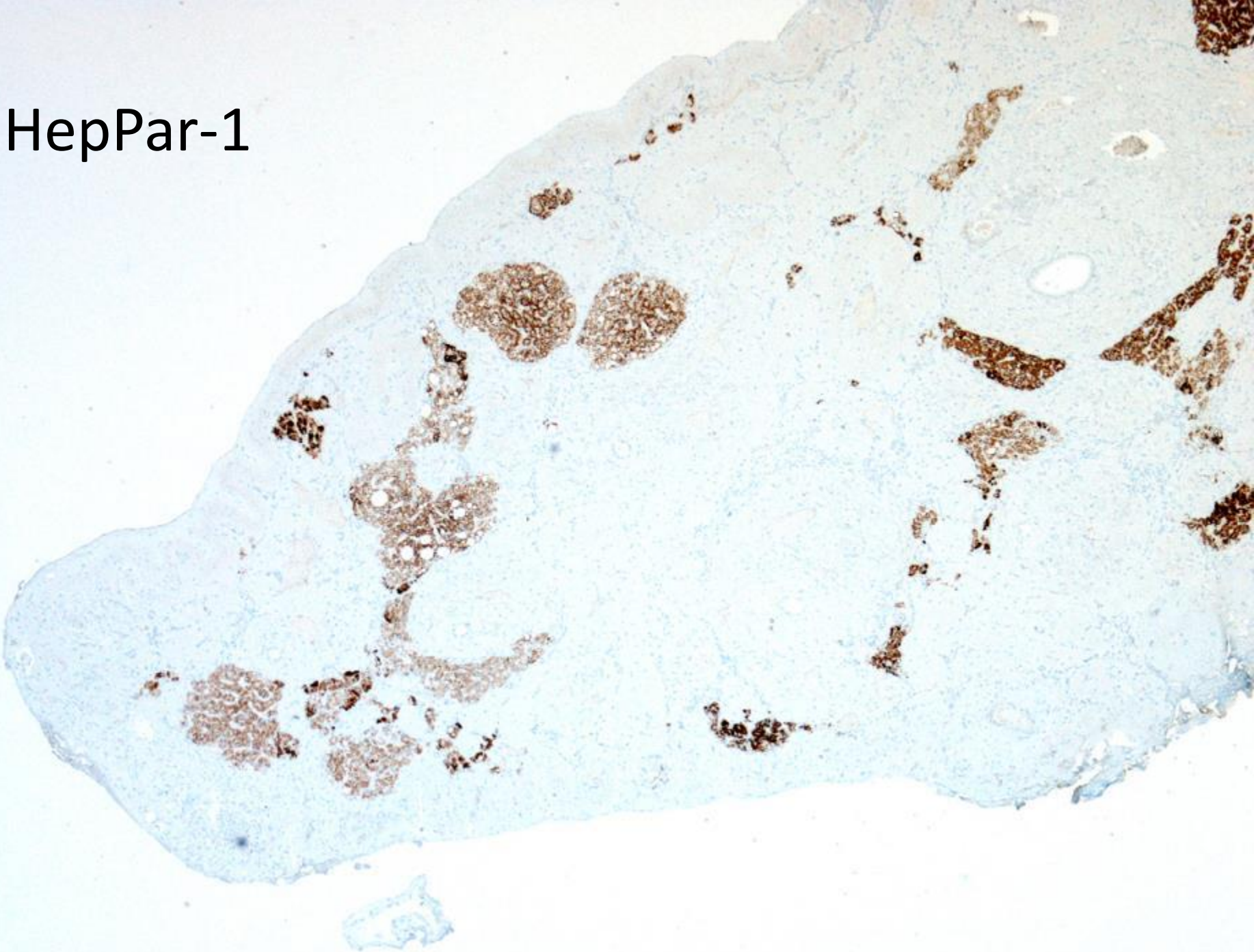
Washington A

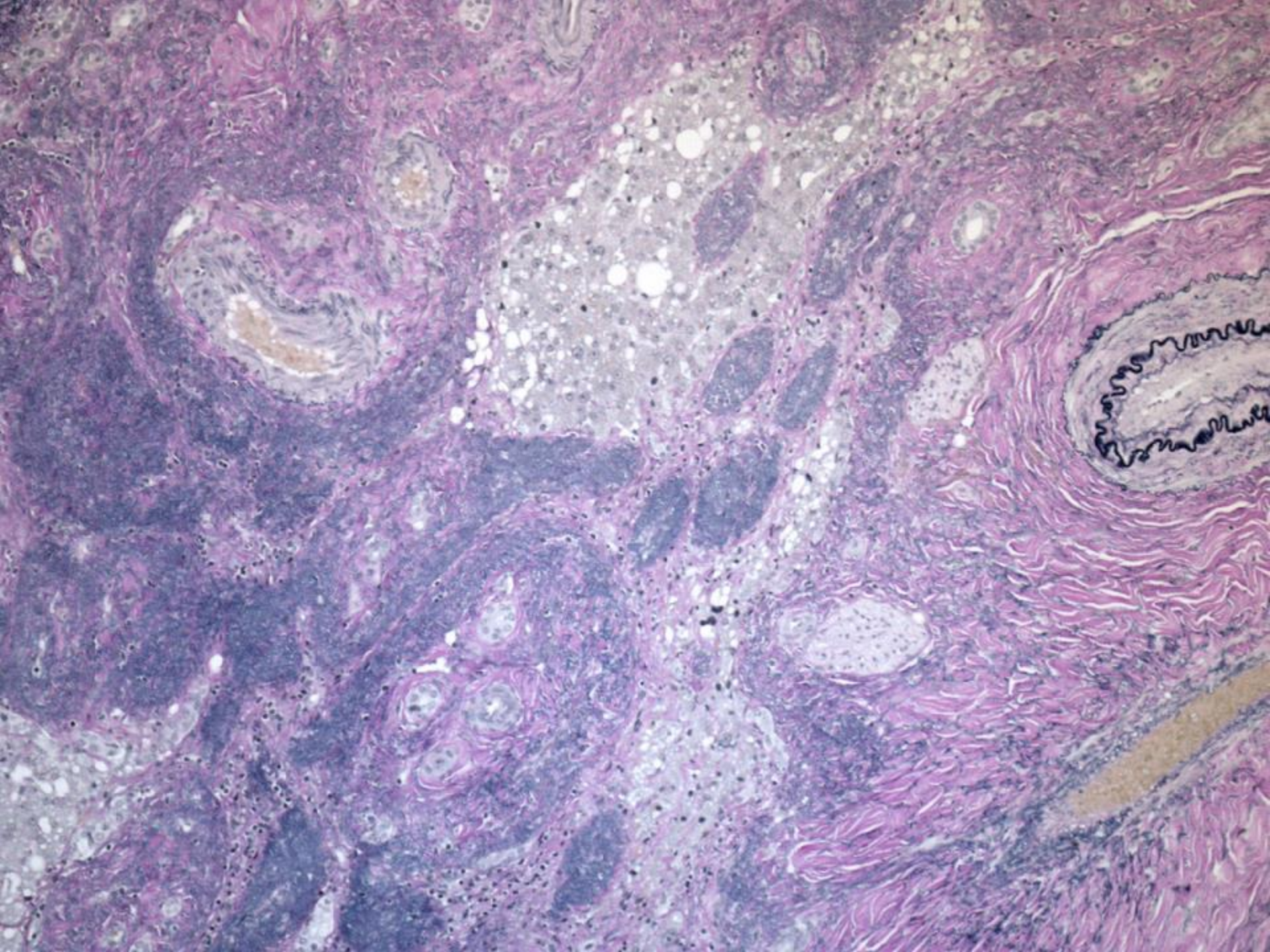






HepPar-1





Washington A
Histologic Findings

- **Loss of hepatocytes**
- **Stromal collapse**
- **Preservation of portal tracts and acinar landmarks**
- **Vascular occlusions**
- **Dx – Segmental atrophy**

Segmental Atrophy of the Liver: A Distinctive Pseudotumor of the Liver With Variable Histologic Appearances

Aatur D. Singhi, MD, Hala R. Maklouf, MD, PhD,† Anupamjit K. Mehrotra, MD,‡ Zachary D. Goodman, MD, PhD,‡ Uta Drebber, MD,§ Hans P. Dienes, MD,§ and Michael Torbenson, MD**

(*Am J Surg Pathol* 2011;35:364–371)

- 18 cases
  - 5 M:13F
  - Ages 14-91
  - Size 1.8-10.0 cm

- Histology
  - Vascular thickening or occlusion (arteries and veins) – 100%
    - ? Ischemic injury leading to localised atrophy
  - Early lesions (n=4) – parenchymal collapse, ductular reaction & inflammation
  - Later lesions (n=10) increasing elatosis
  - Advanced lesions (n=4) mostly elastosis

What Next?

Theme for 2018 Circulation

- Normally a 2 year cycle
- Many of the cases presented in 2017 overlapped with previous discussions related to liver sinusoidal diseases (2011 & 2012 meetings)
- Theme for 2018 will be “Drug-induced liver injury”

Gnomes Meeting 2018 – 50th Anniversary
Athens 2nd – 6th May 2018
Chief Gnome – Dina Tiniakos