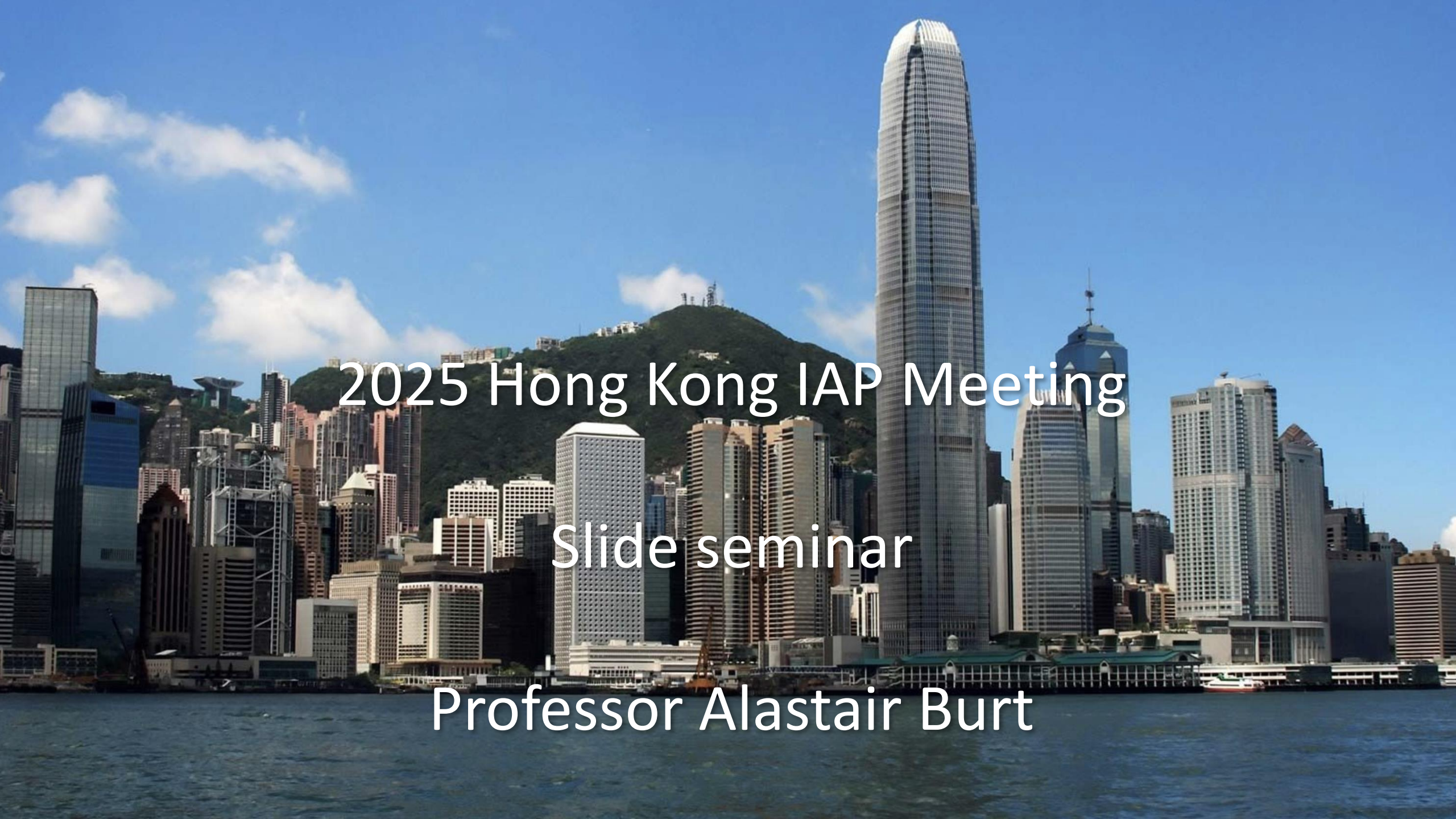


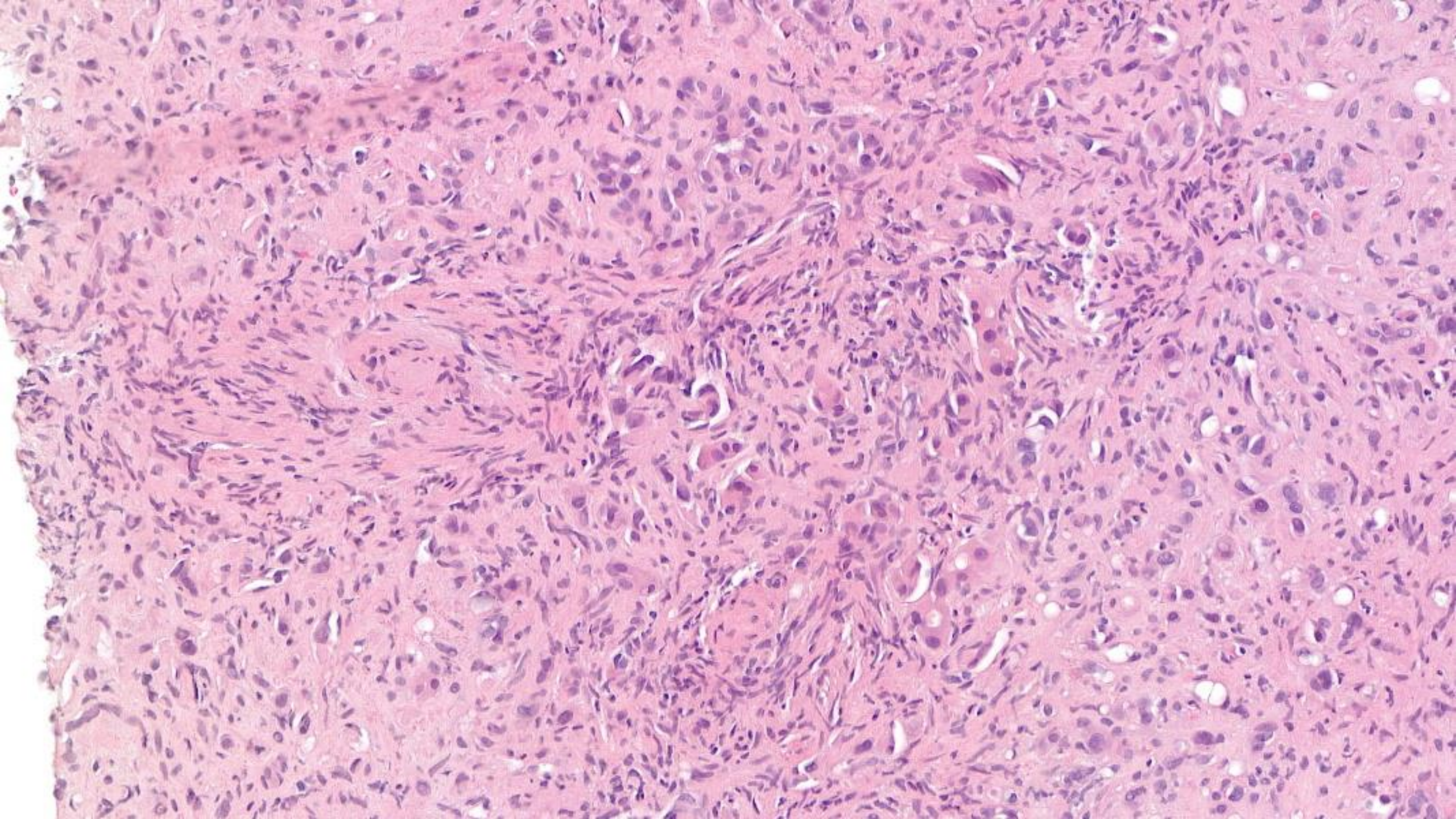
2025 Hong Kong IAP Meeting

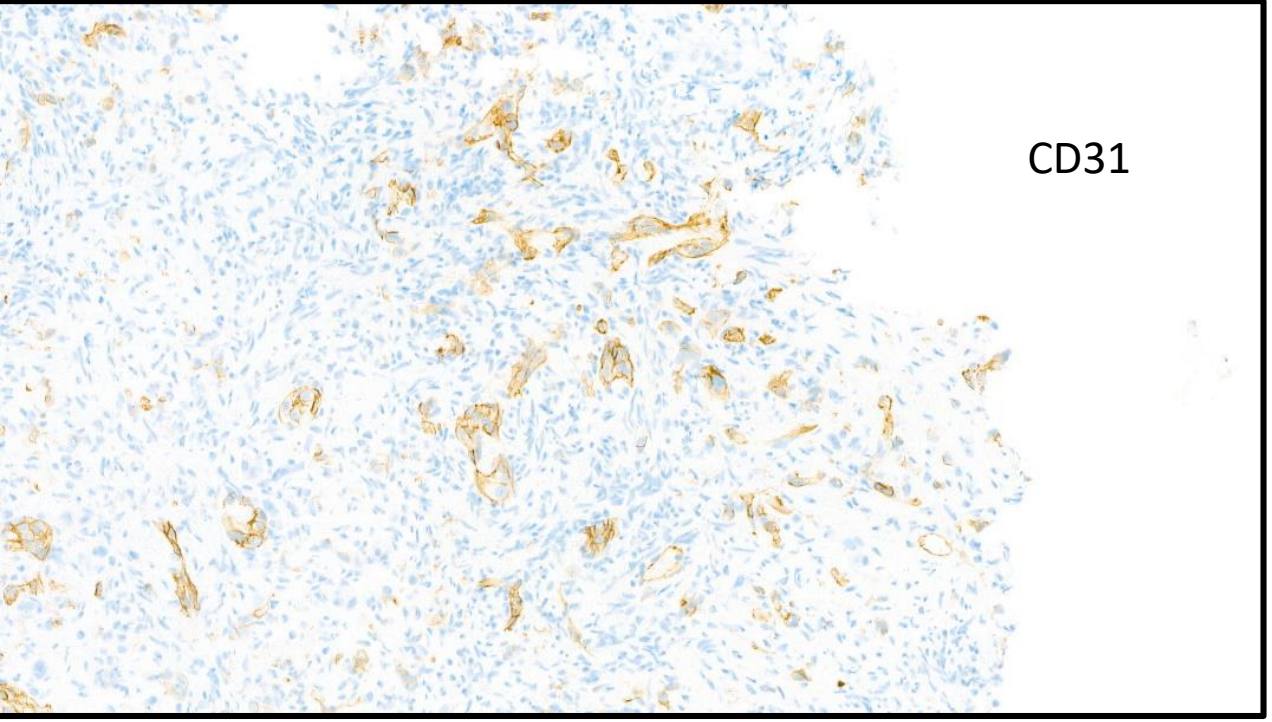
Slide seminar

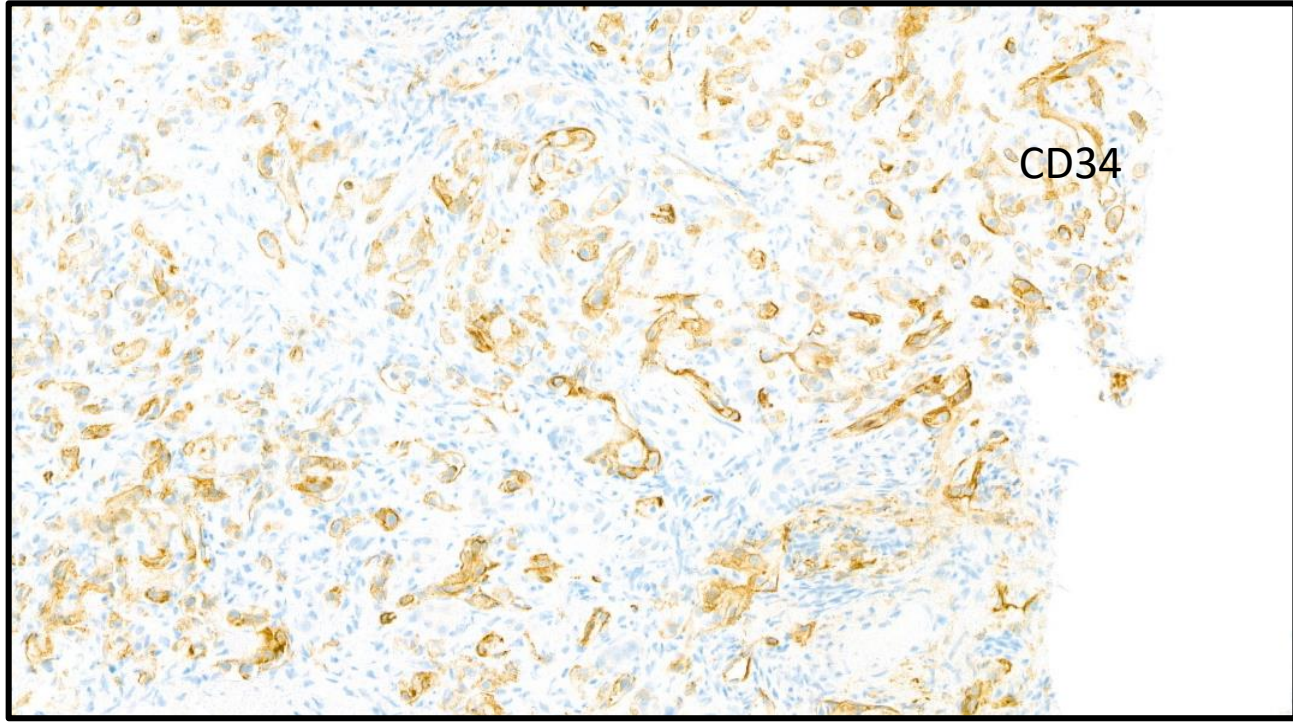
Professor Alastair Burt

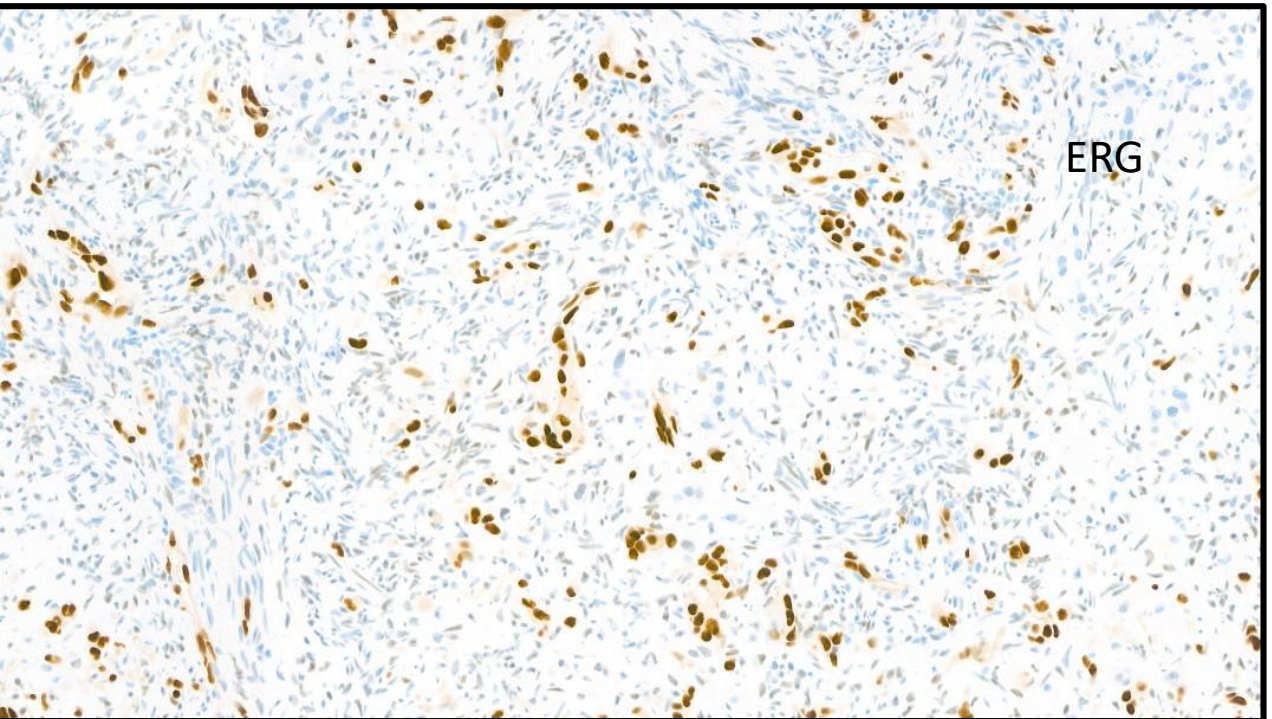
CASE A

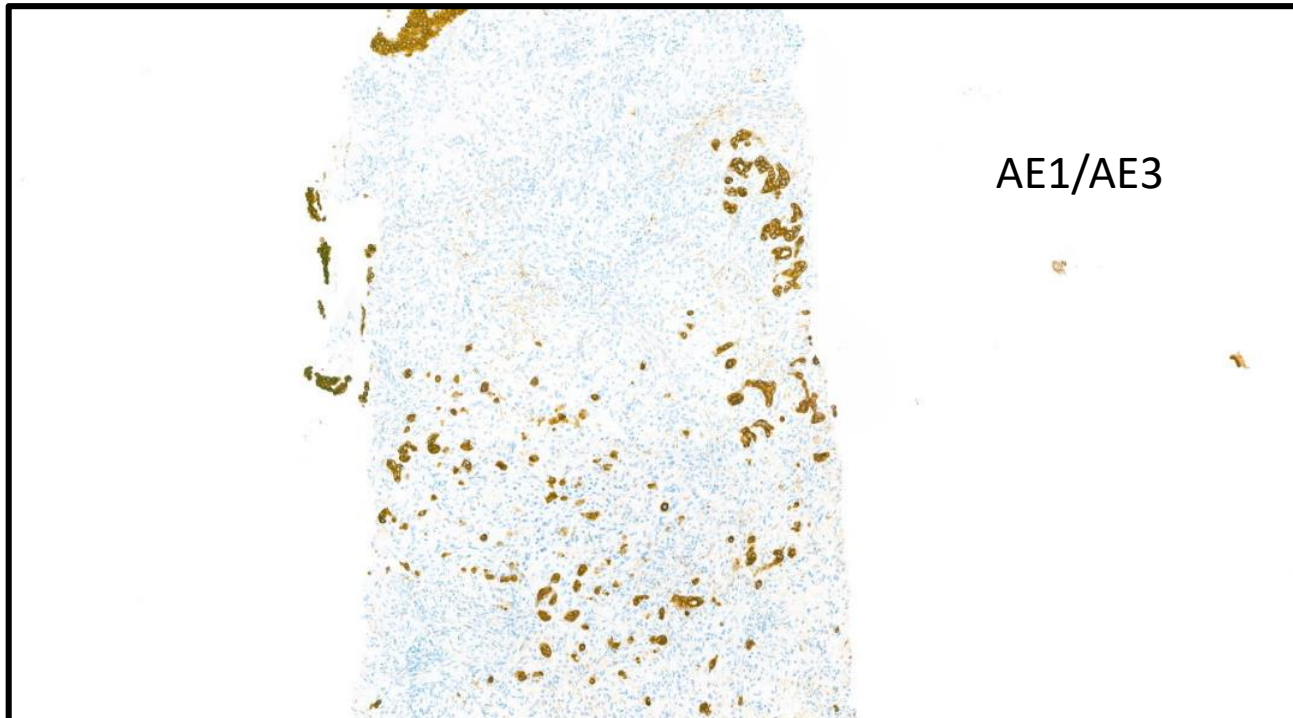
30 year old female with weight loss and malaise. On imaging multiple liver lesions noted. Main differential diagnosis clinically was (i) neuroendocrine tumours and (ii) other metastatic disease.

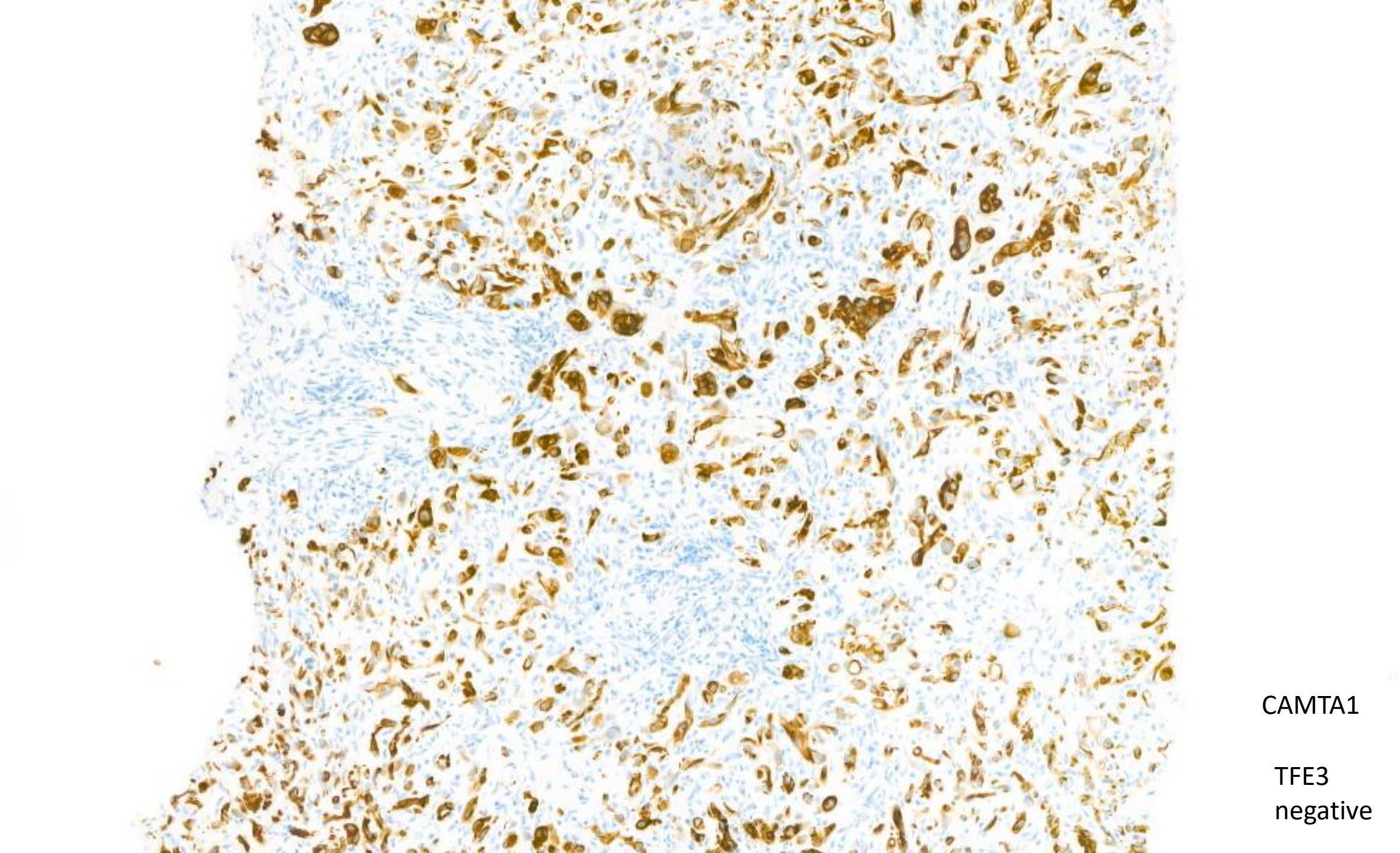



CD31


CD34


ERG


AE1/AE3

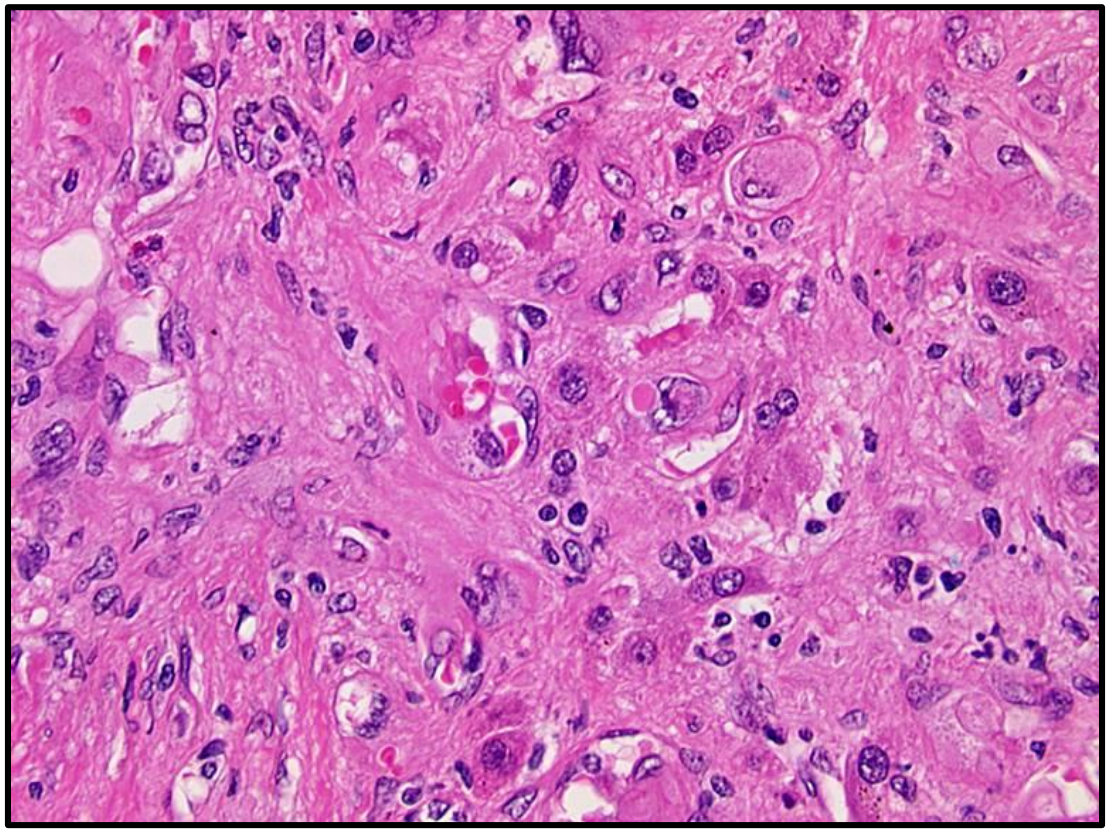


CAMTA1

TFE3
negative

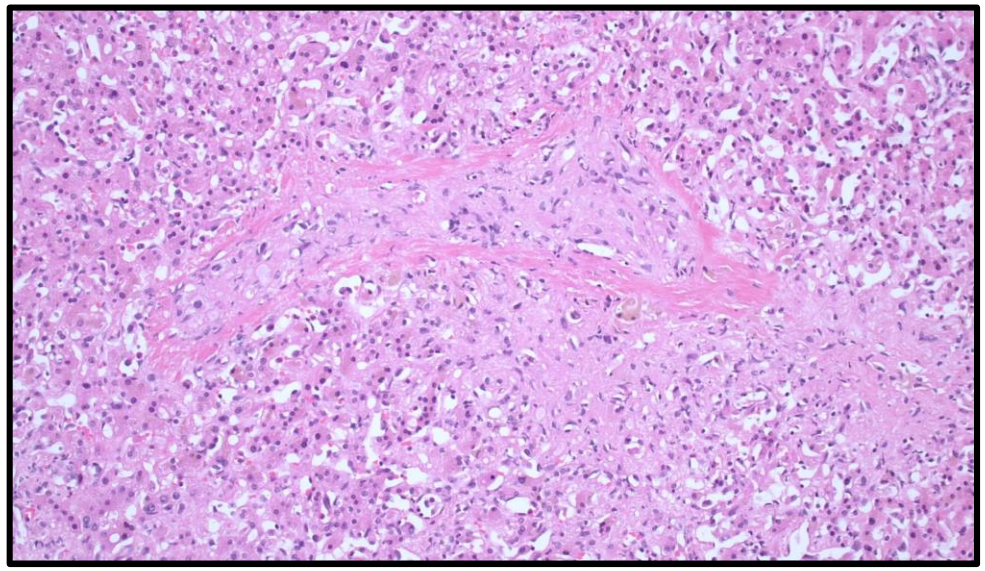
Epithelioid haemangioendothelioma

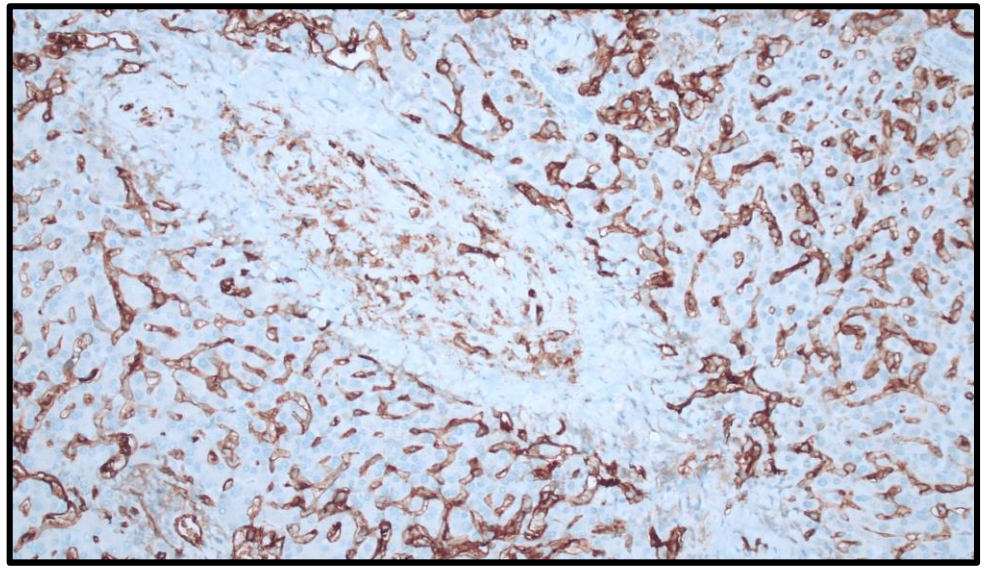
- Described in a variety of sites: skin, bone, lung (+ many others!)
- Previously misdiagnosed as sclerotic CC
- F>M 2:1
- Mean age = 50
- Malaise; weight loss; pain
- May produce Budd Chiari syndrome
- Metastases in 30%
- 43% 5YS
- Approx 50% die of disease



Epithelioid haemangioendothelioma

- Frequently multiple
- White, firm
- 0.2-14cm diameter.
- Fibrous stroma with obliteration of vessels
- Dendritic and epithelioid cells
- Intracytoplasmic lumina
- Factor VIIIRAg (CD 31/CD34) +ve
- May also be CK +ve





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› Cancer. 1999 Feb 1;85(3):562-82.
doi: 10.1002/(sici)1097-0142(19990201)85:3<562::aid-cncr7>3.0.co;2-t.

Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases

H R Makhlouf [1], K G Ishak, Z D Goodman

Epithelioid haemangioendothelioma

- Frequently multiple
- White, firm
- 0.2-14cm diameter.
- Fibrous stroma with obliteration of vessels
- Dendritic and epithelioid cells
- Intracytoplasmic lumina
- Factor VIIIRAg (CD 31/CD34) +ve
- May also be CK +ve
- *WWTR1-CAMTA1* translocation
- CAMTA + by IHC
- 5% *YAP1-TFE3* fusion gene (TFE3 +)

Translocation t(1;3)(p36.3;q25) Is a Nonrandom Aberration in Epithelioid Hemangioendothelioma

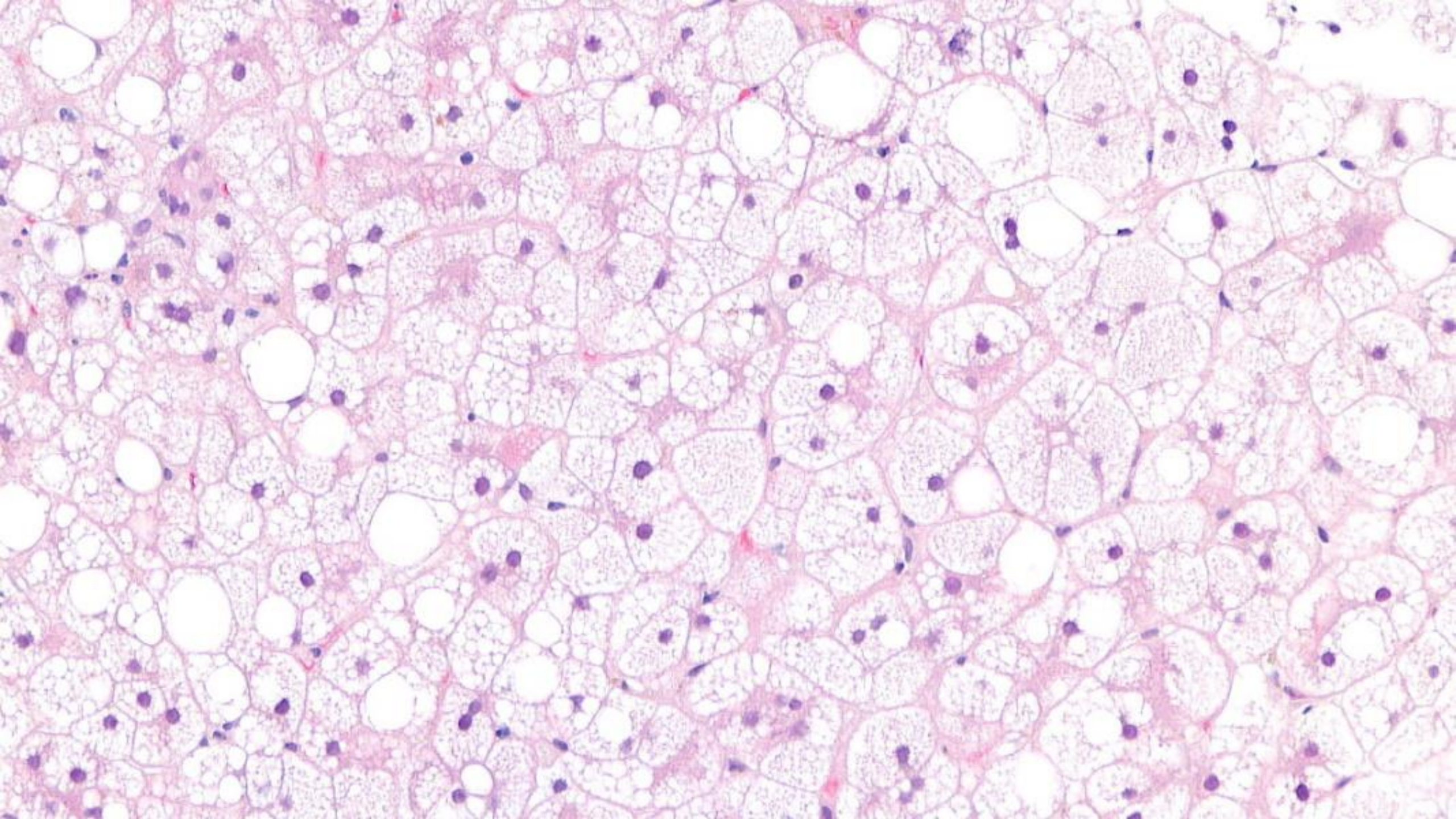
Mendlick, Matthew R. B.A.; Nelson, Marilu B.S., CLSp (CG), CLSp (MB); Pickering, Diane B.S., CLSp (CG); Johansson, Sonny L. M.D., Ph.D.; Seemayer, Thomas A. M.D.; Neff, James R. M.D.; Vergara, Gerardo M.D.; Rosenthal, Howard M.D.; Bridge, Julia A. M.D.

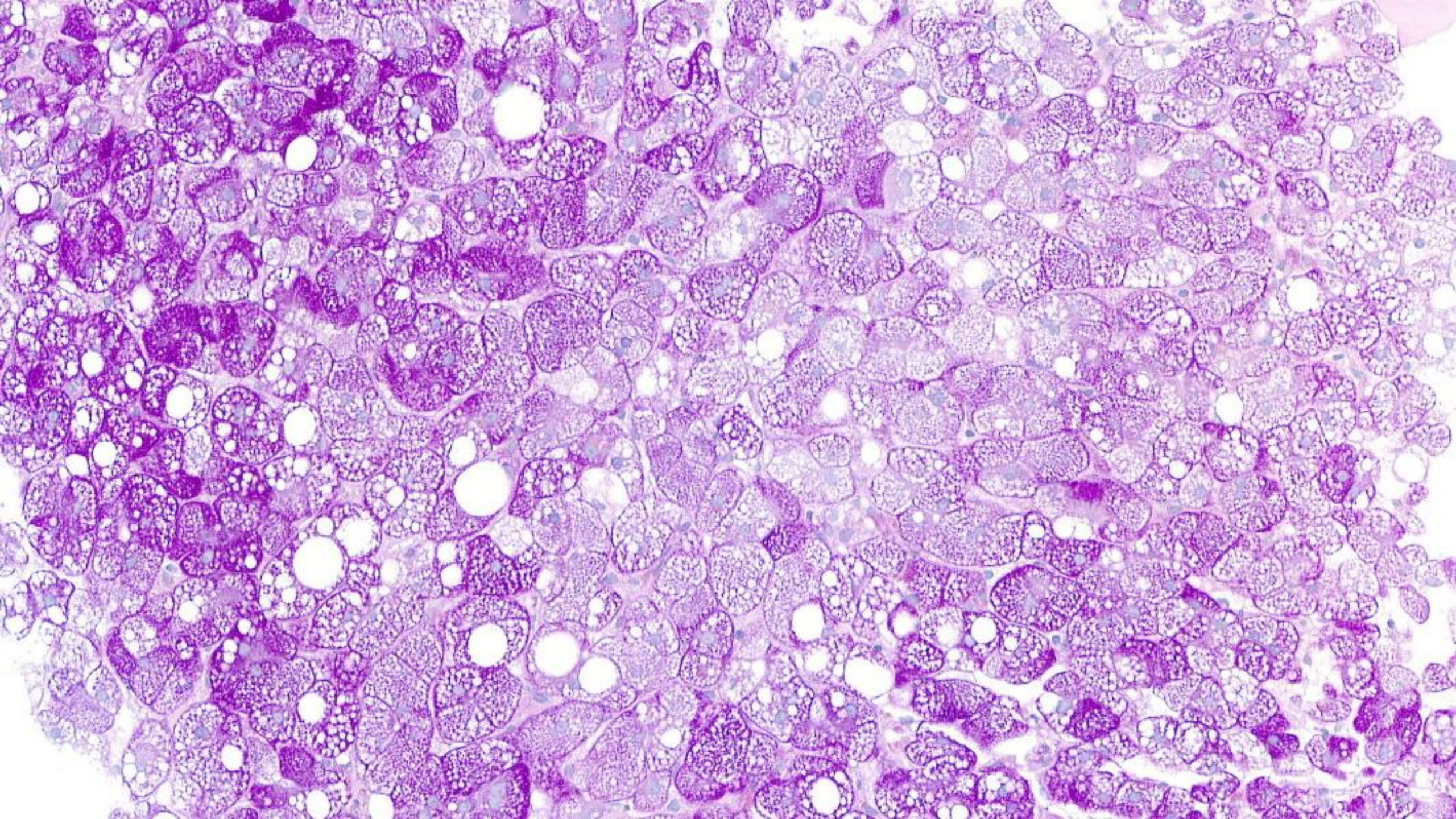
Author Information

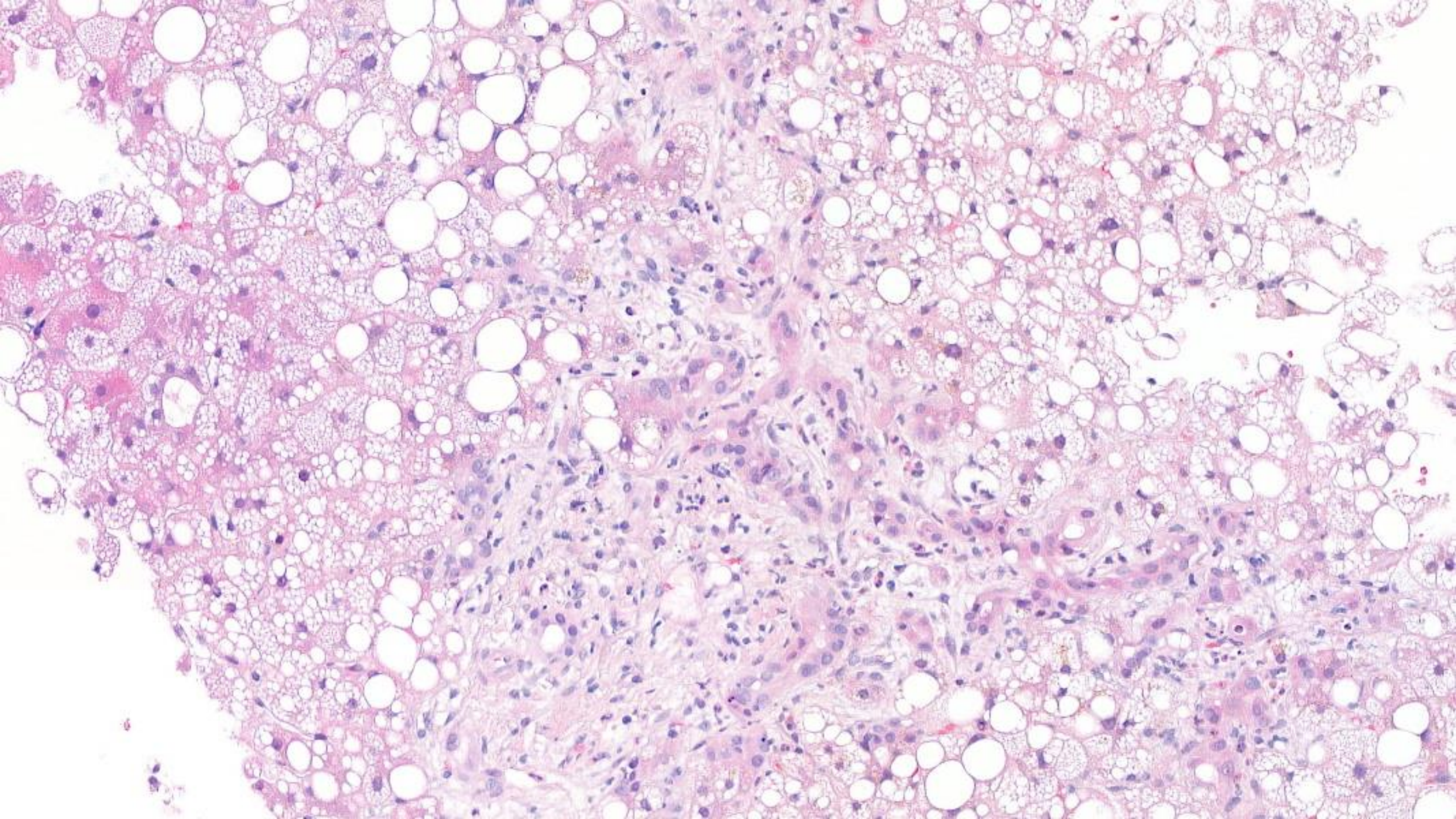
The American Journal of Surgical Pathology 25(5):p 684-687, May 2001.

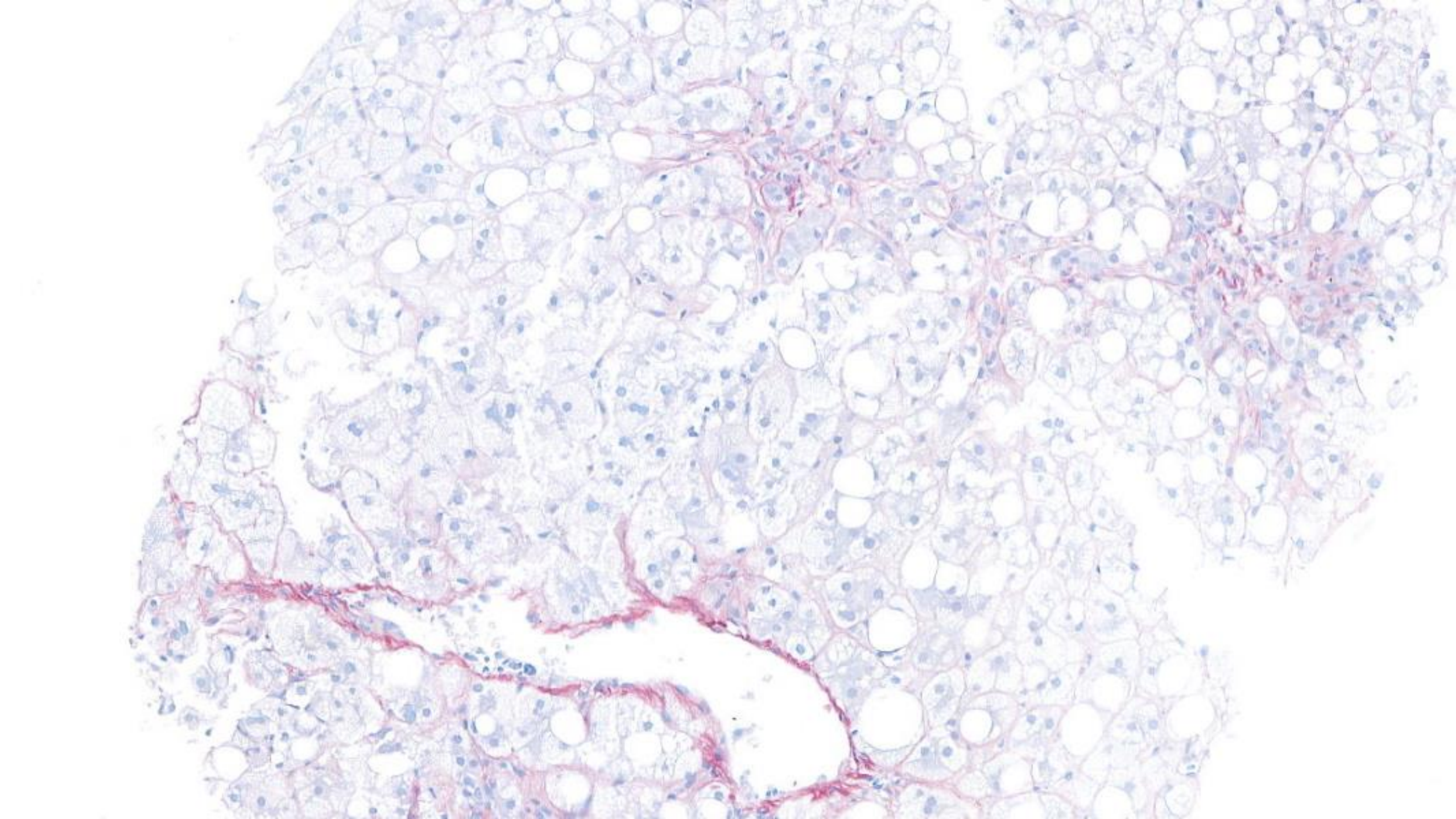
CASE B

65 year old male. Fibroscan suggestive of significant fibrosis. Mild elevation of AFP. ALT > 400, ALP borderline elevation. Clinical differential: (i) autoimmune hepatitis, (ii) MetALD steatotic liver disease.









GASTROENTEROLOGY 1983;84:683–92

Alcoholic Foamy Degeneration—A Pattern of Acute Alcoholic Injury of the Liver

TOSHIKAZU UCHIDA, HENRY KAO, MARIA QUISPE-SJOGREN, and ROBERT L. PETERS
University of Southern California School of Medicine, Department of Pathology, Liver Unit, Rancho Los Amigos Hospital, Downey, California

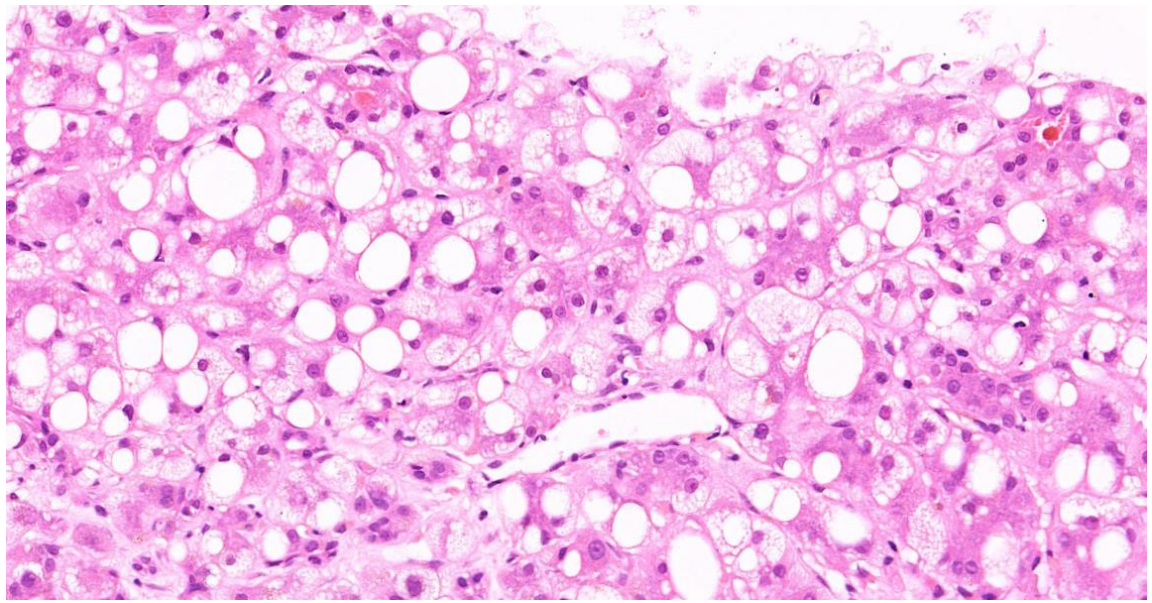


Table 1. Summary of Symptoms and Signs of Alcoholic Foamy Degeneration in Comparison With Acute Sclerosing Hyaline Necrosis

	AFD[a] (*n* = 21)	ASHN[b] (*n* = 13)
Symptoms		
Nausea	12/19	5/12
Vomiting	11/19	5/12
Weight loss	11/15	4/9
Abdominal pain	10/17	6/12
Fatigue	10/15	7/9
Signs		
Jaundice	19/21	8/13
Hepatomegaly	19/21	8/13
High fever (> 101°F)	3/21	3/13
Significant ascites	1/21	7/13
Significant peripheral edema	1/19	9/13
Esophageal varices	3/13	8/11
Complications		
Encephalopathy	1/19	1/13
Gastrointestinal bleeding	2/20	4/13
Renal failure	0/21	0/13

Patient numbers with this finding/patient numbers evaluated. [a] AFD = alcoholic foamy degeneration. [b] ASHN = acute sclerosing hyaline necrosis.

REVIEW

Alcoholic Foamy Degeneration and Alcoholic Fatty Liver With Jaundice: Often Overlooked Causes of Jaundice and Hepatic Decompensation That Can Mimic Alcoholic Hepatitis

Nitzan Roth M.D., Ph.D.,* Gary Kanel M.D.,† Neil Kaplowitz M.D.*

Clinical Liver Disease, Vol 6, No 6, December 2015

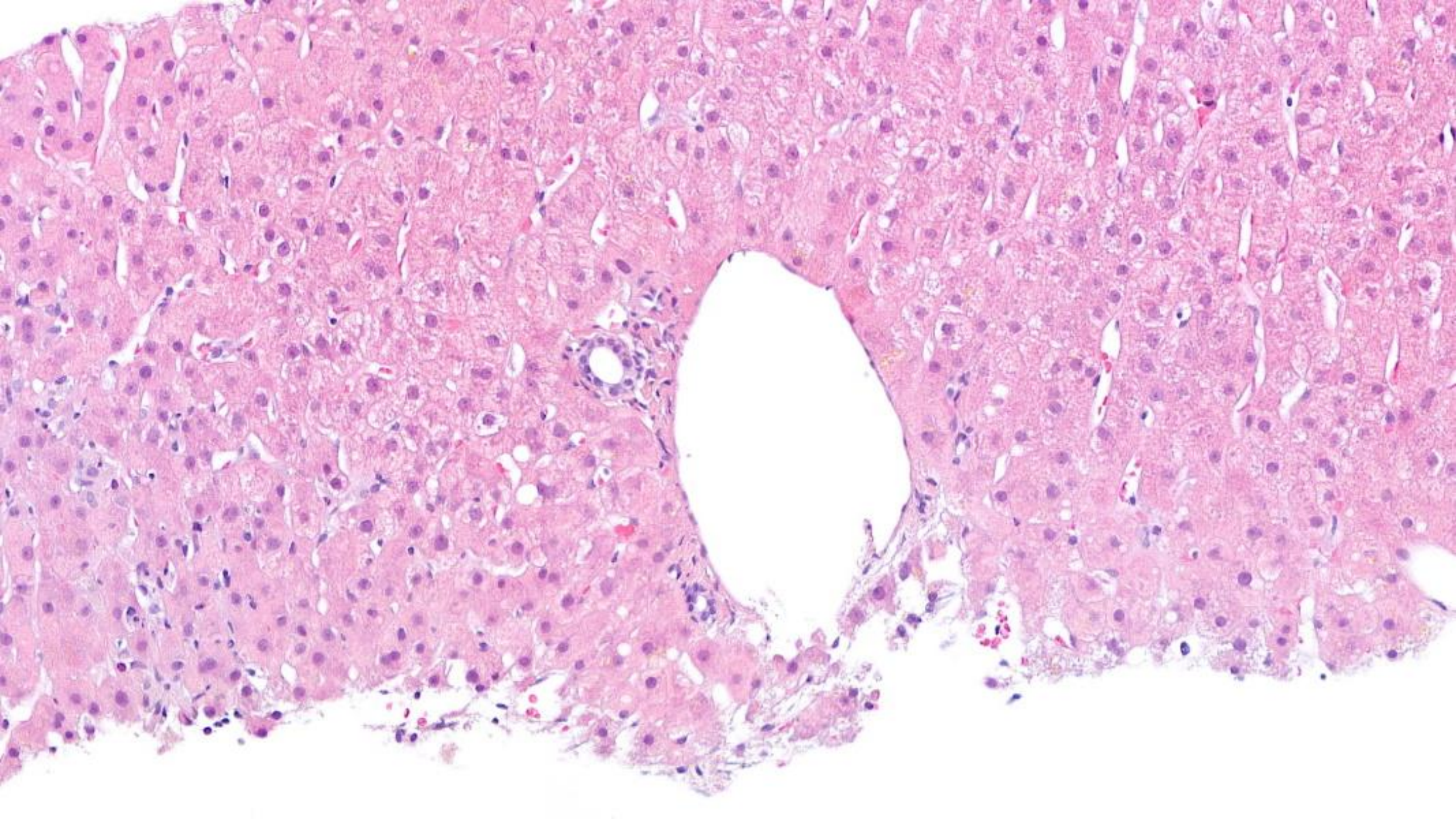
TABLE 1 Typical Histological Features of Alcoholic Fatty Liver With Jaundice, Alcoholic Foamy Degeneration, Alcoholic Hepatitis, and Alcoholic Hepatitis With Coexisting Alcoholic Foamy Degeneration[1,4,5,7]

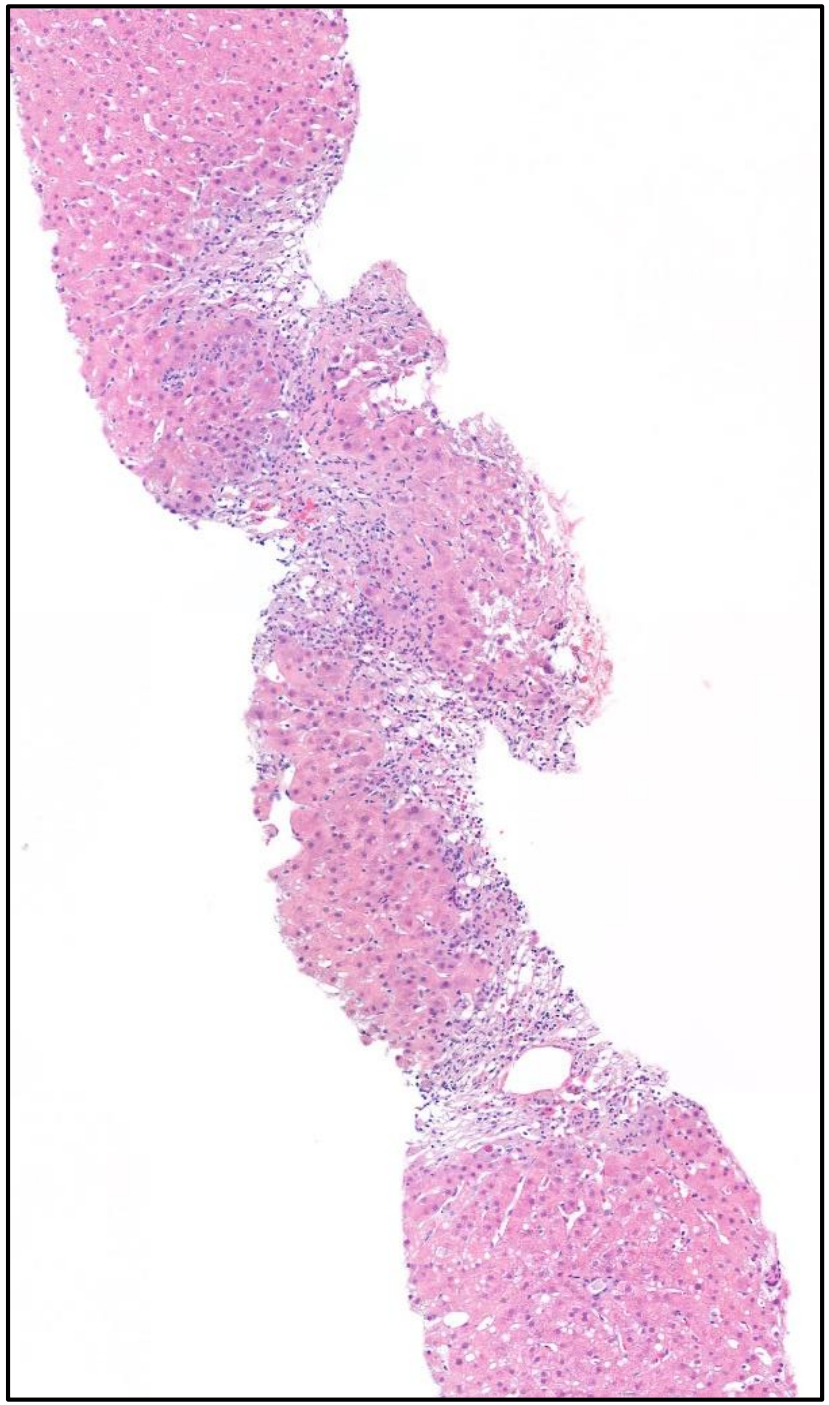
	AFLJ	AFD	AH	AH-AFD
Macrovesicular fatty change	++	+	+	+
Microvesicular fatty change	−	++	−	+
Portal fibrosis	− to ++	− to ++	+ to ++	+ to ++
Neutrophilic lobular inflammation	−	−	++	++
Mallory-Denk bodies	−	−	+	+
Sinusoidal collagen deposition	−	−	+	+

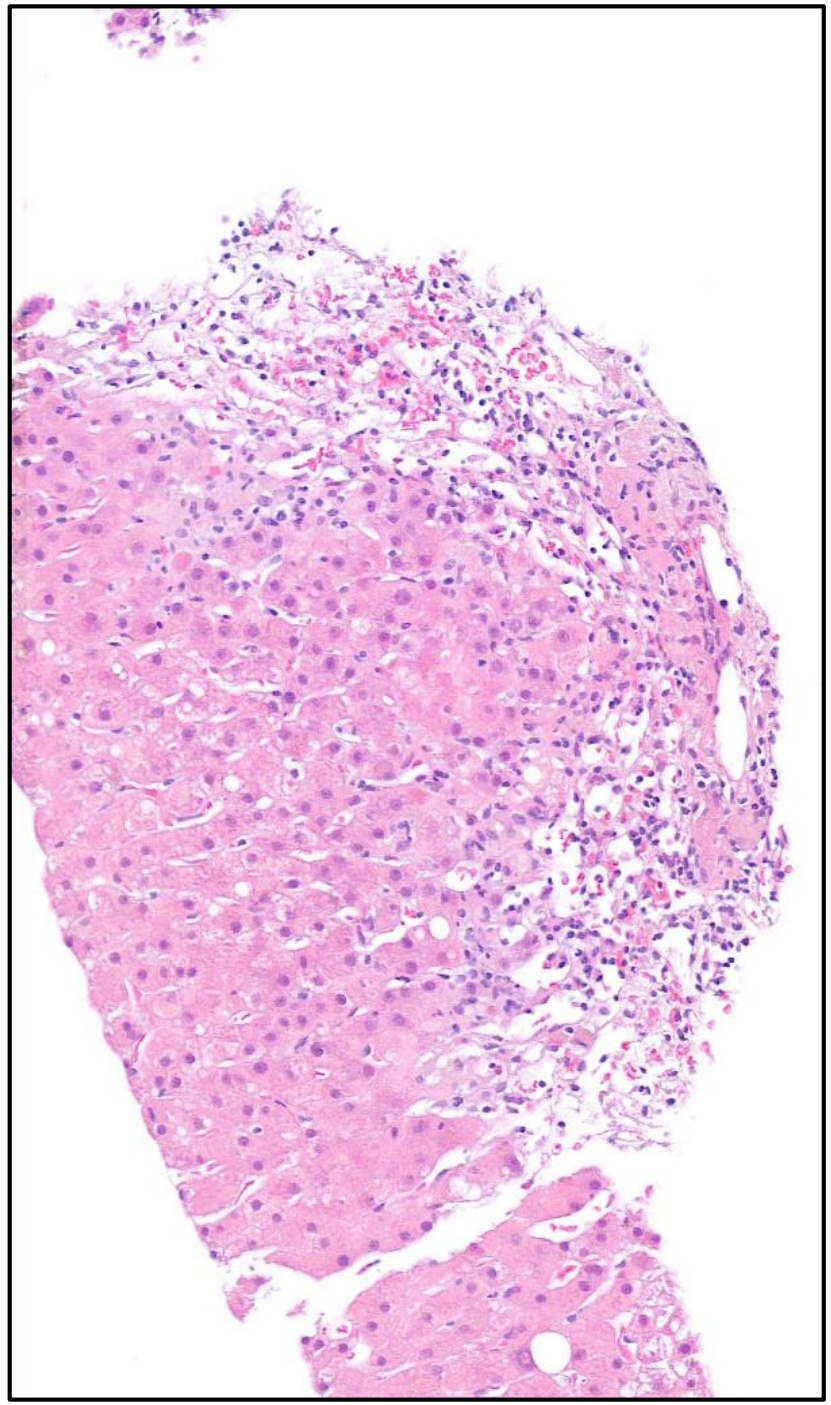
++, prominent; +, present, −, absent or minimal.

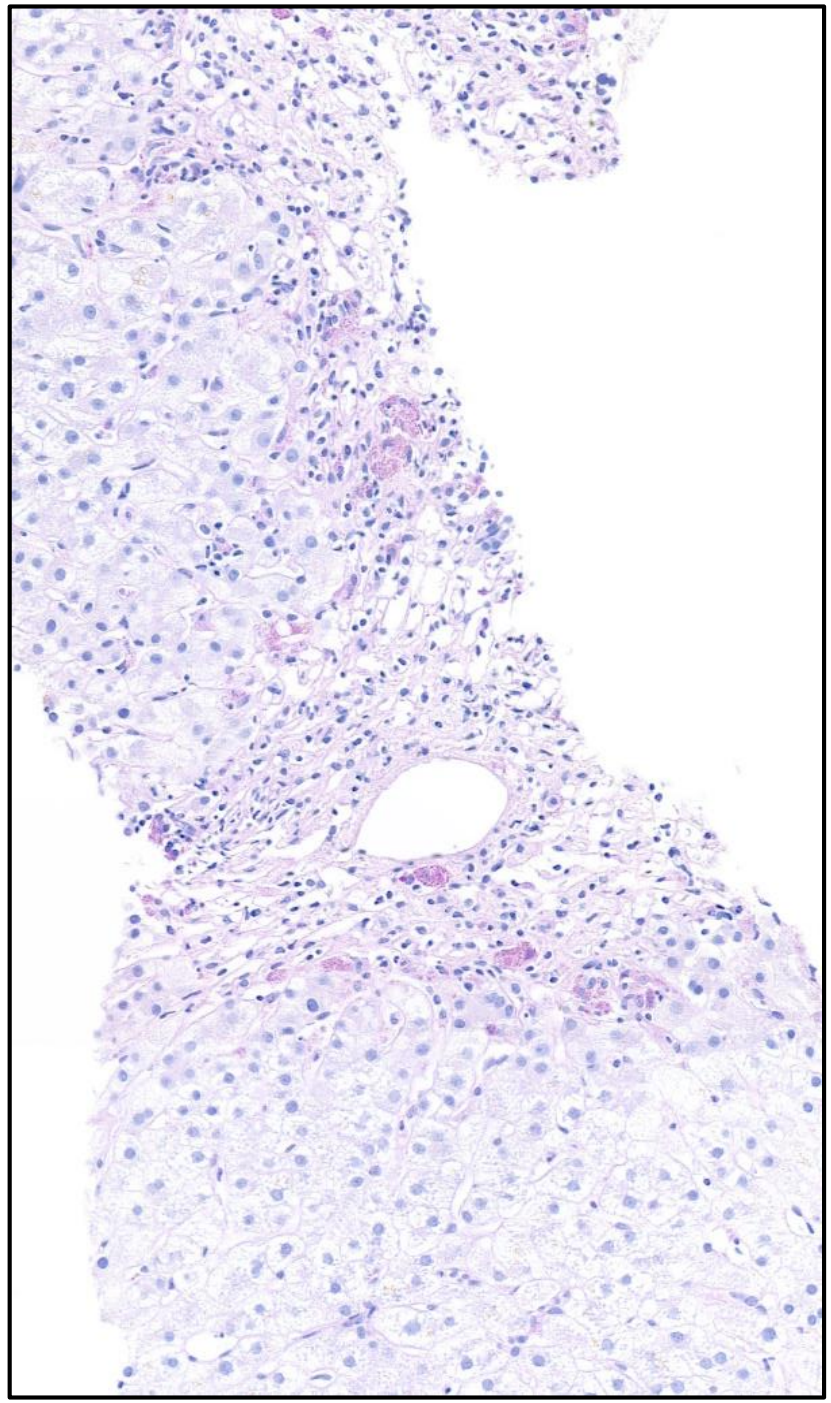
CASE C

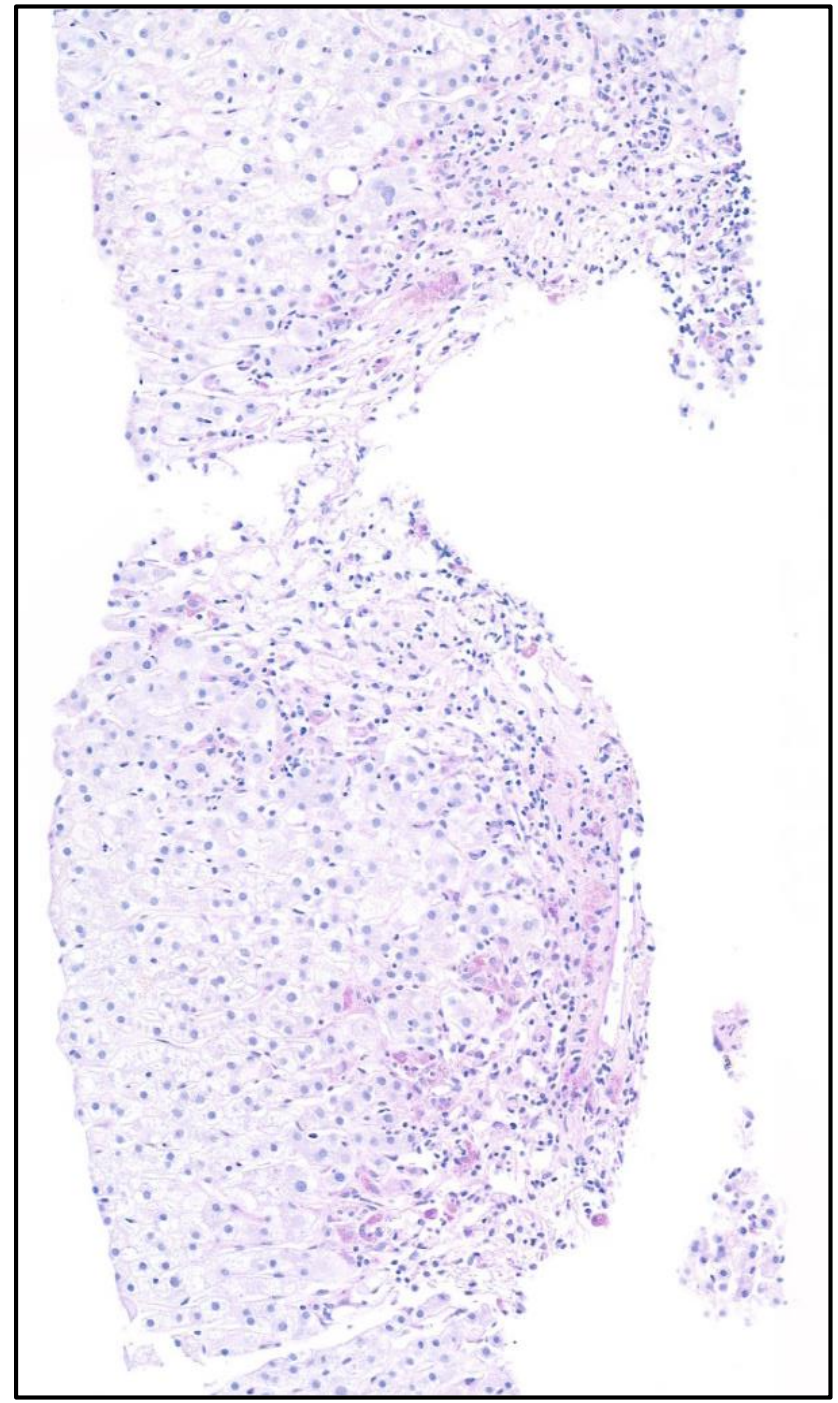
61 year old recently treated for stage 3 malignant melanoma. Viral screen negative. No autoantibodies. Normal immunoglobulins. ALT > 100.? Cause.

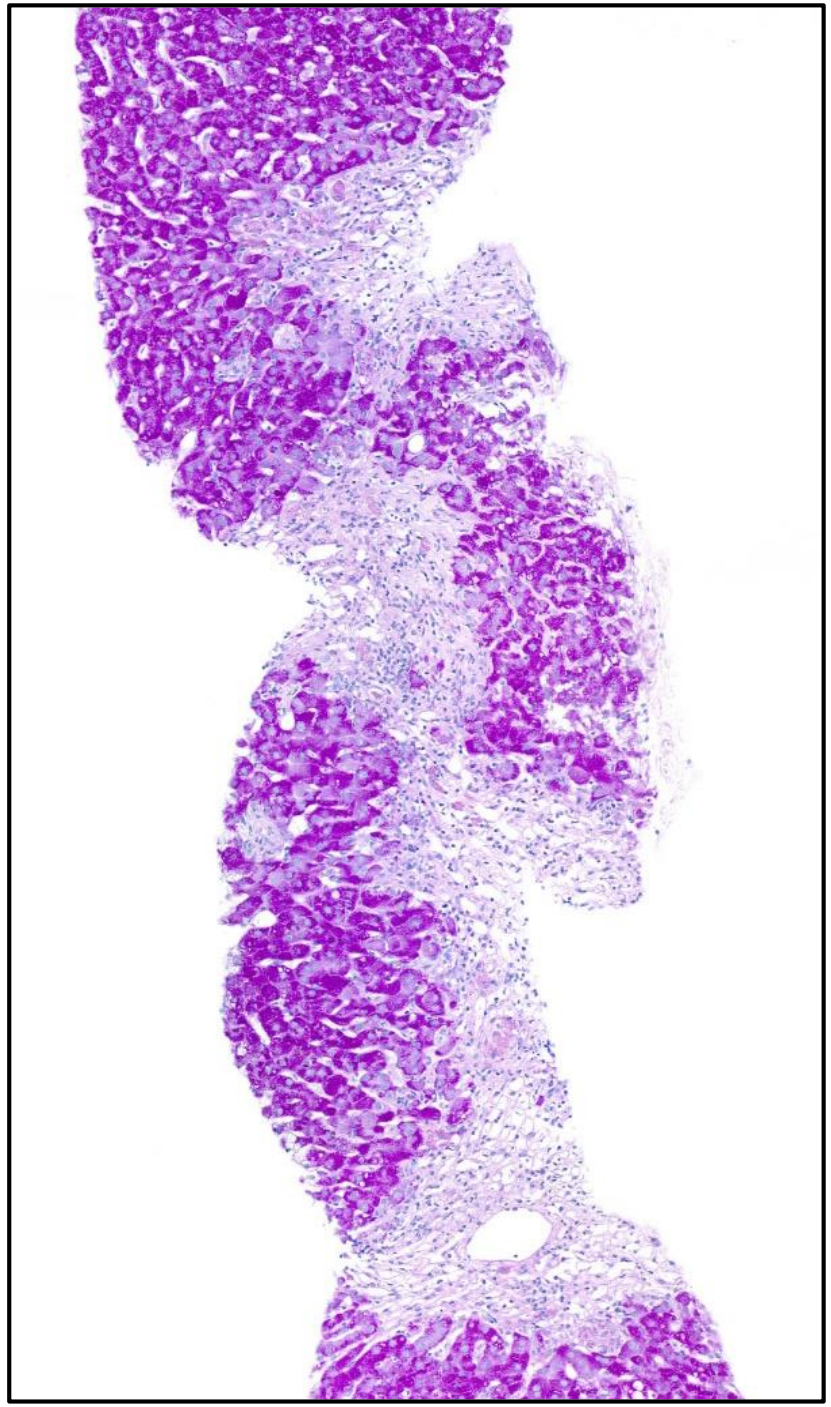


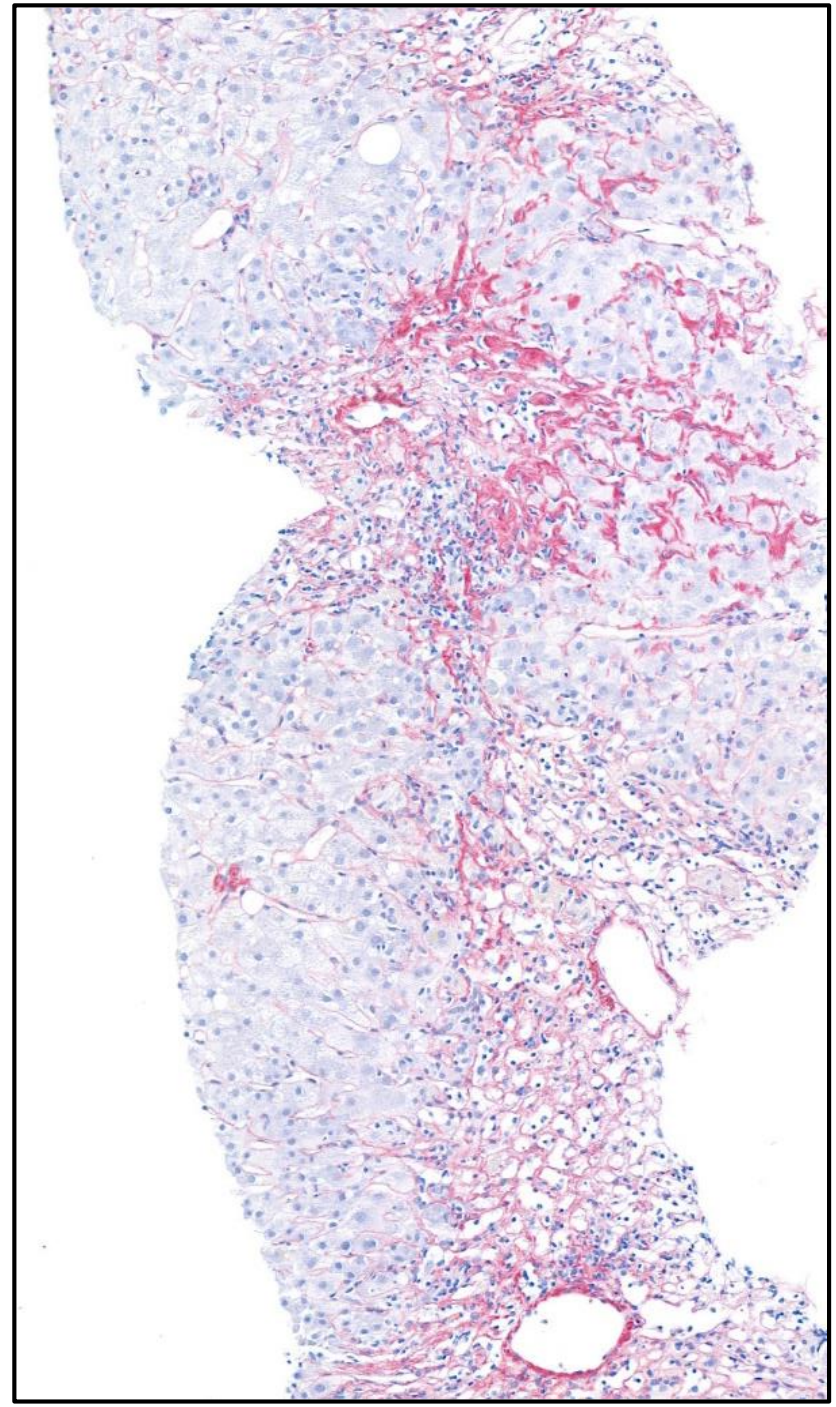


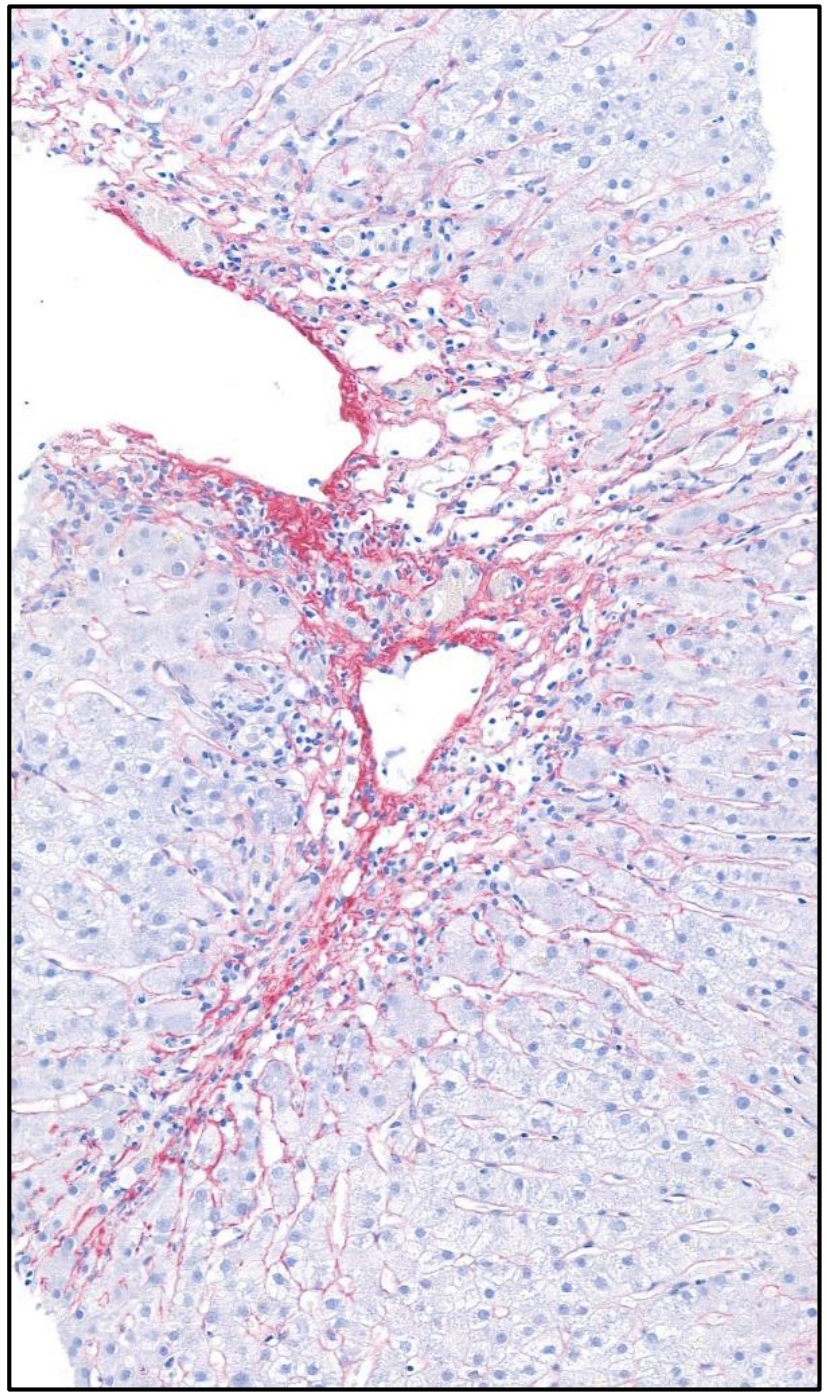


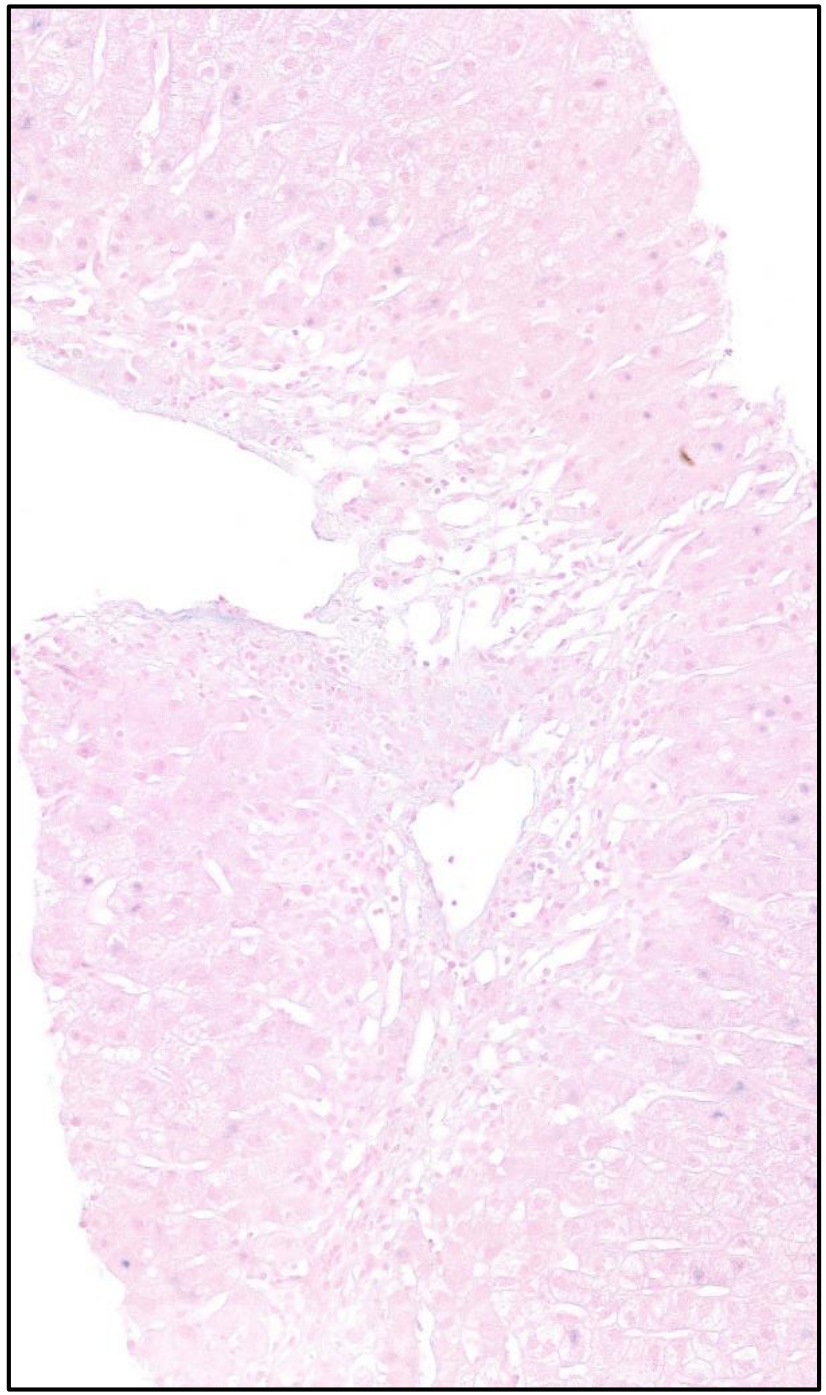












Dig Dis Sci. 2012 August ; 57(8): 2233–2240. doi:10.1007/s10620-012-2140-5.

Pathologic Changes in Ipilimumab-related Hepatitis in Patients with Metastatic Melanoma

David E. Kleiner, MD, PhD* and **David Berman, MD, PhD†**

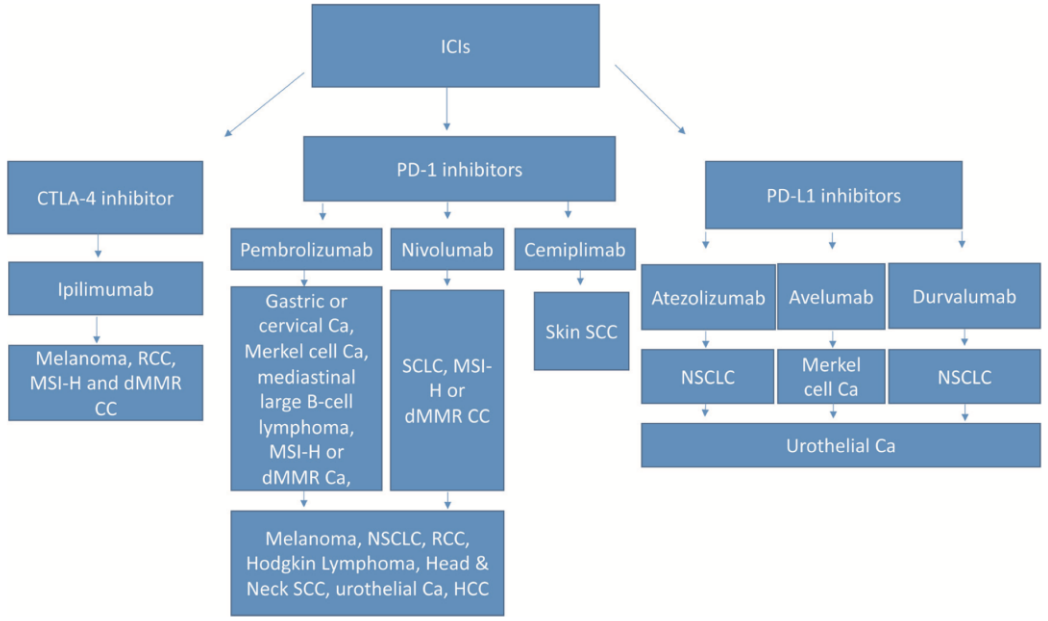
*Laboratory of Pathology, National Cancer Institute, Bldg 10, Room 2B50, MSC 1500, 10 Center Drive, Bethesda, MD, USA 20892. Phone: 301-594-2942. Fax: 301-480-9488. kleinerd@mail.nih.gov

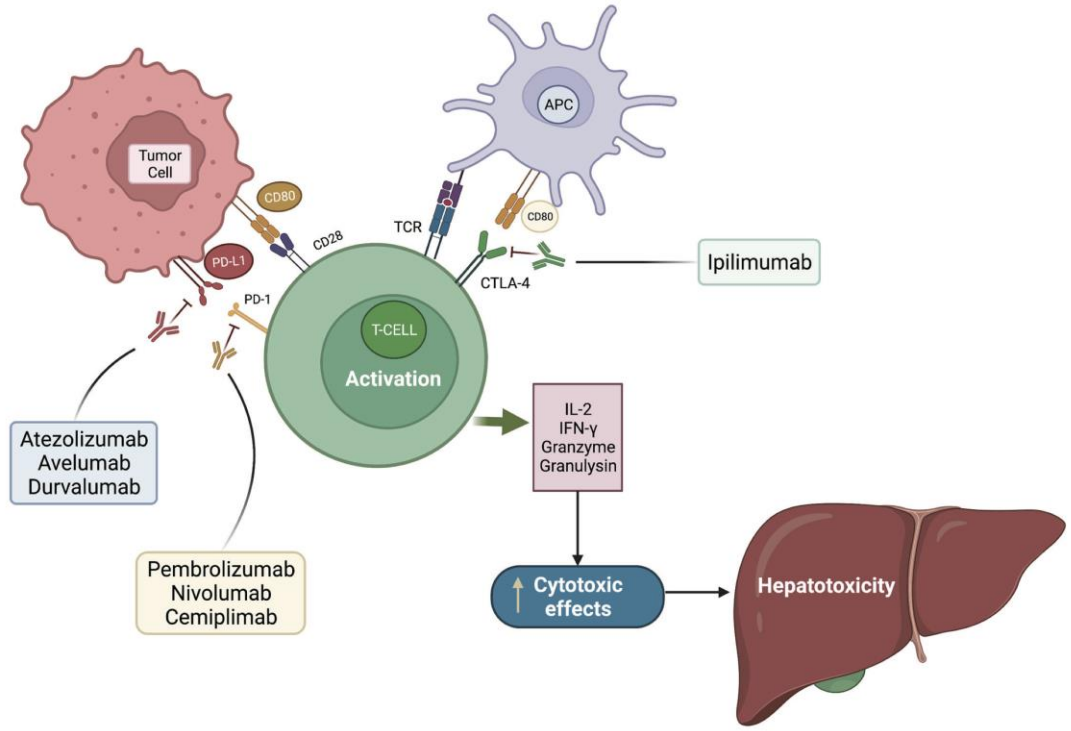
(*Am J Surg Pathol* 2015;39:1075–1084)

Ipilimumab-associated Hepatitis

Clinicopathologic Characterization in a Series of 11 Cases

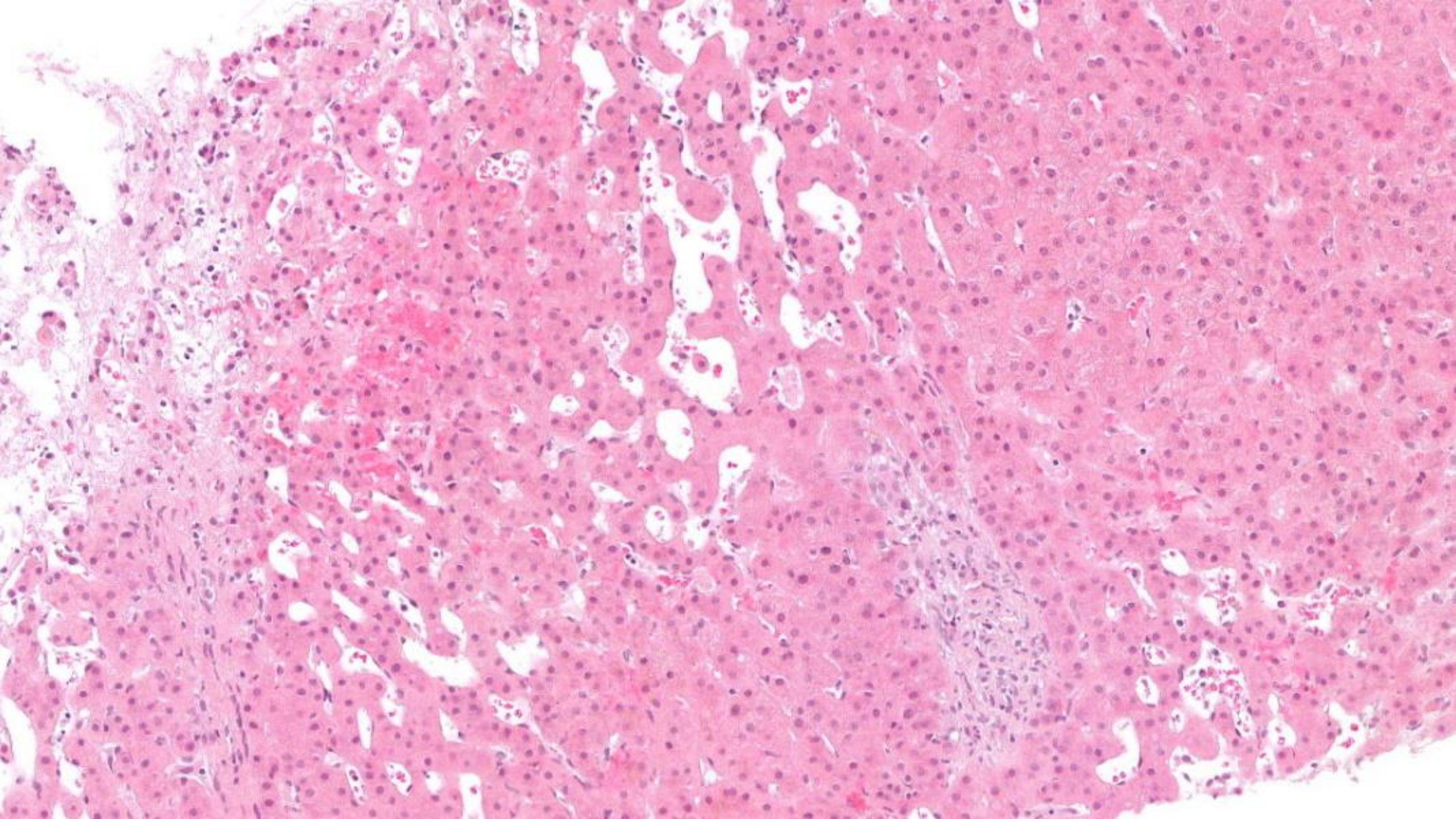
Melanie Johncilla, MD, Joseph Misdraji, MD,† Daniel S. Pratt, MD,‡ Agoston T. Agoston, MD, PhD,* Gregory Y. Lauwers, MD,† Amitabh Srivastava, MD,* and Leona A. Doyle, MD**

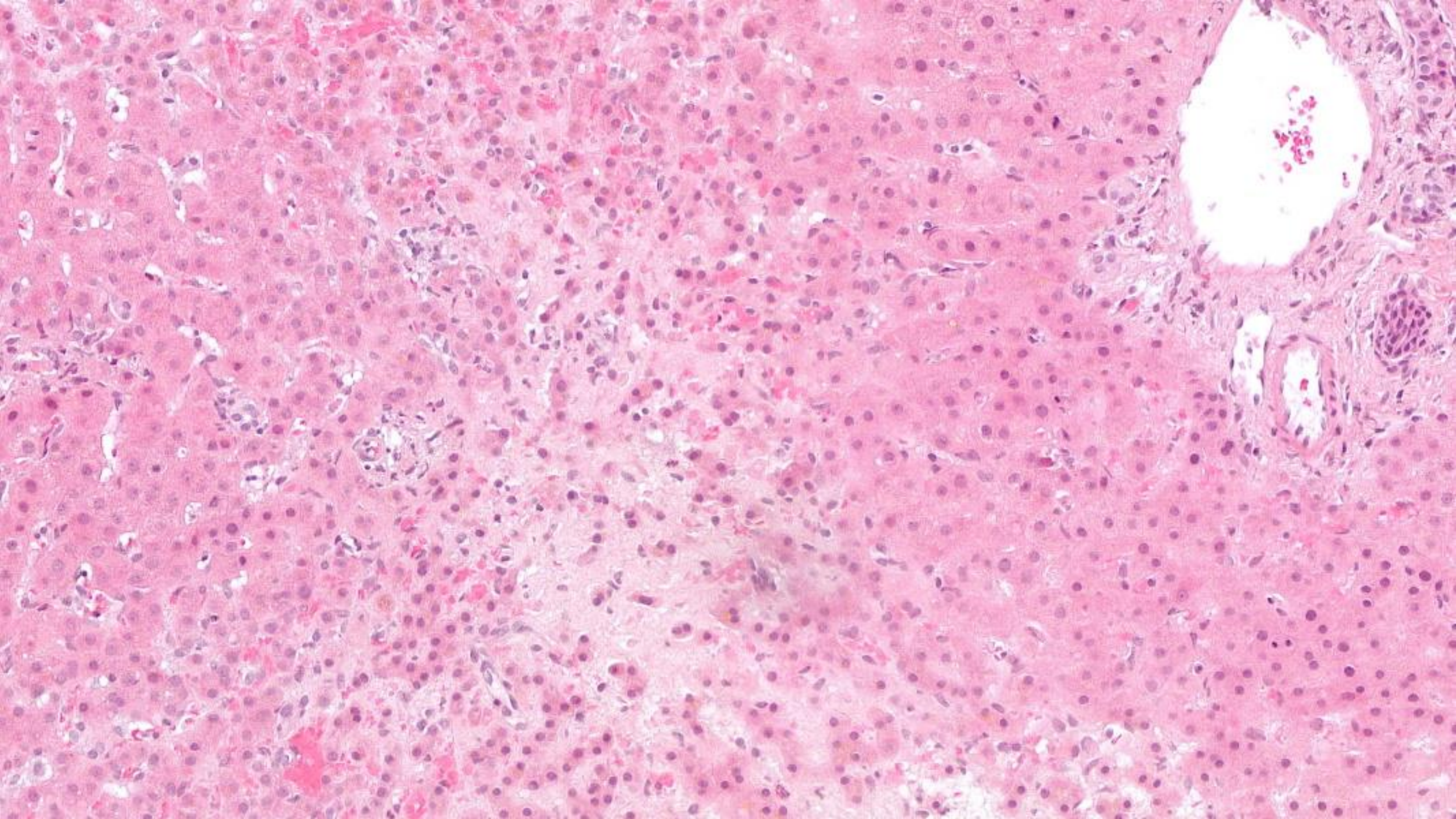

ICIs
CTLA-4 inhibitor
PD-1 inhibitors
PD-L1 inhibitors
Ipilimumab
Pembrolizumab
Nivolumab
Cemiplimab
Atezolizumab
Avelumab
Durvalumab
Melanoma, RCC, MSI-H and dMMR CC
Gastric or cervical Ca, Merkel cell Ca, mediastinal large B-cell lymphoma, MSI-H or dMMR Ca,
SCLC, MSI-H or dMMR CC
Skin SCC
NSCLC
Merkel cell Ca
NSCLC
Urothelial Ca
Melanoma, NSCLC, RCC, Hodgkin Lymphoma, Head & Neck SCC, urothelial Ca, HCC

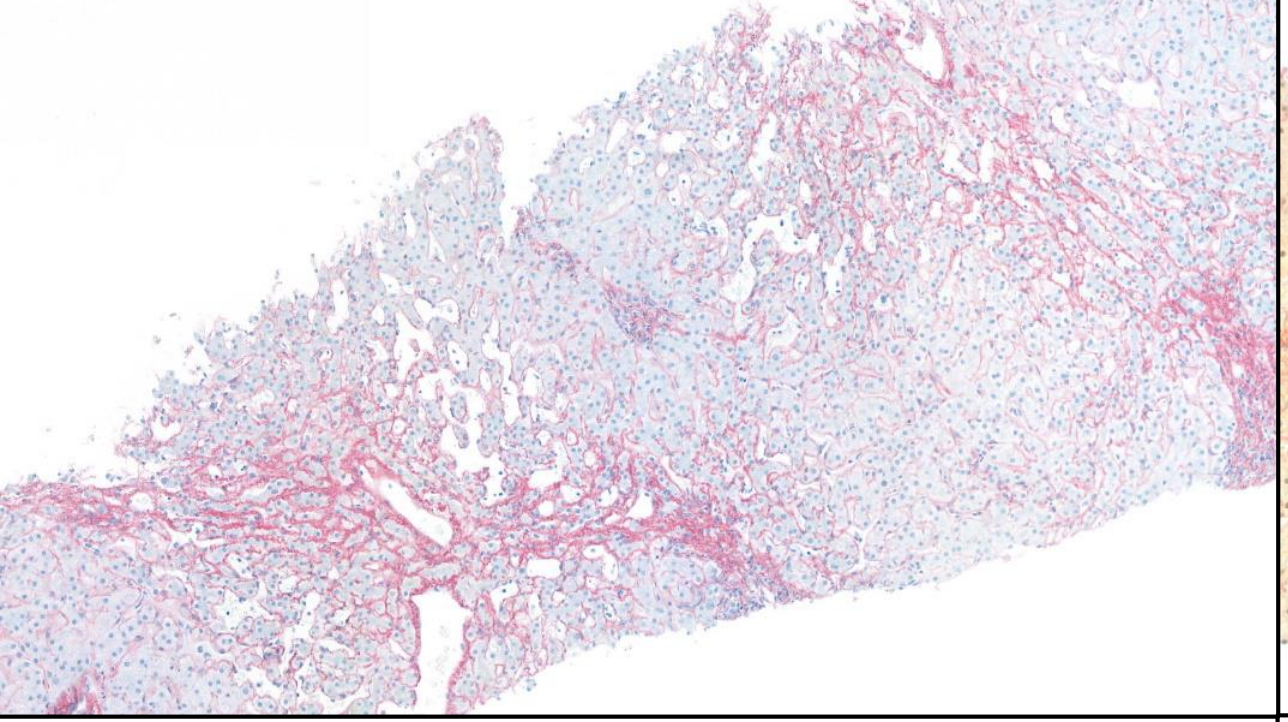

Tumor Cell
APC
CD80
CD80
PD-L1
CD28
TCR
CTLA-4
Ipilimumab
PD-1
T-CELL
Activation
Atezolizumab
Avelumab
Durvalumab
IL-2
IFN-γ
Granzyme
Granulysin
Pembrolizumab
Nivolumab
Cemiplimab
Cytotoxic effects
Hepatotoxicity

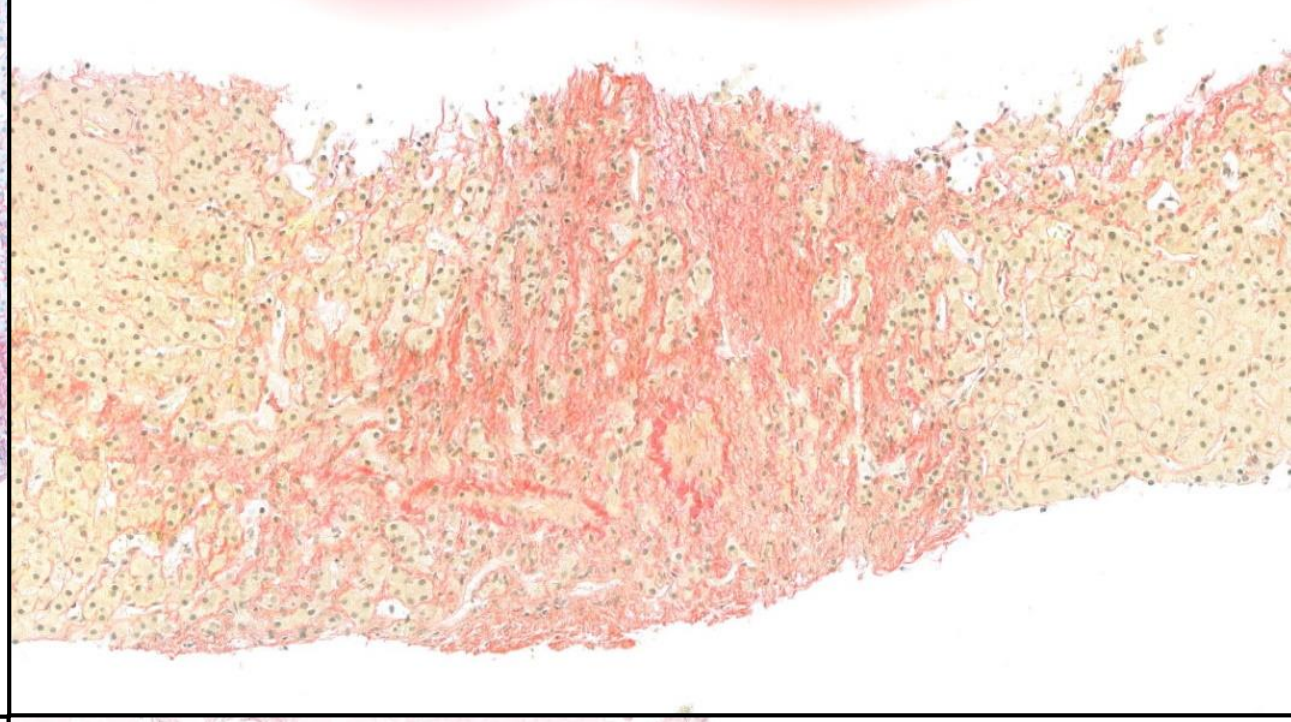
CASE D

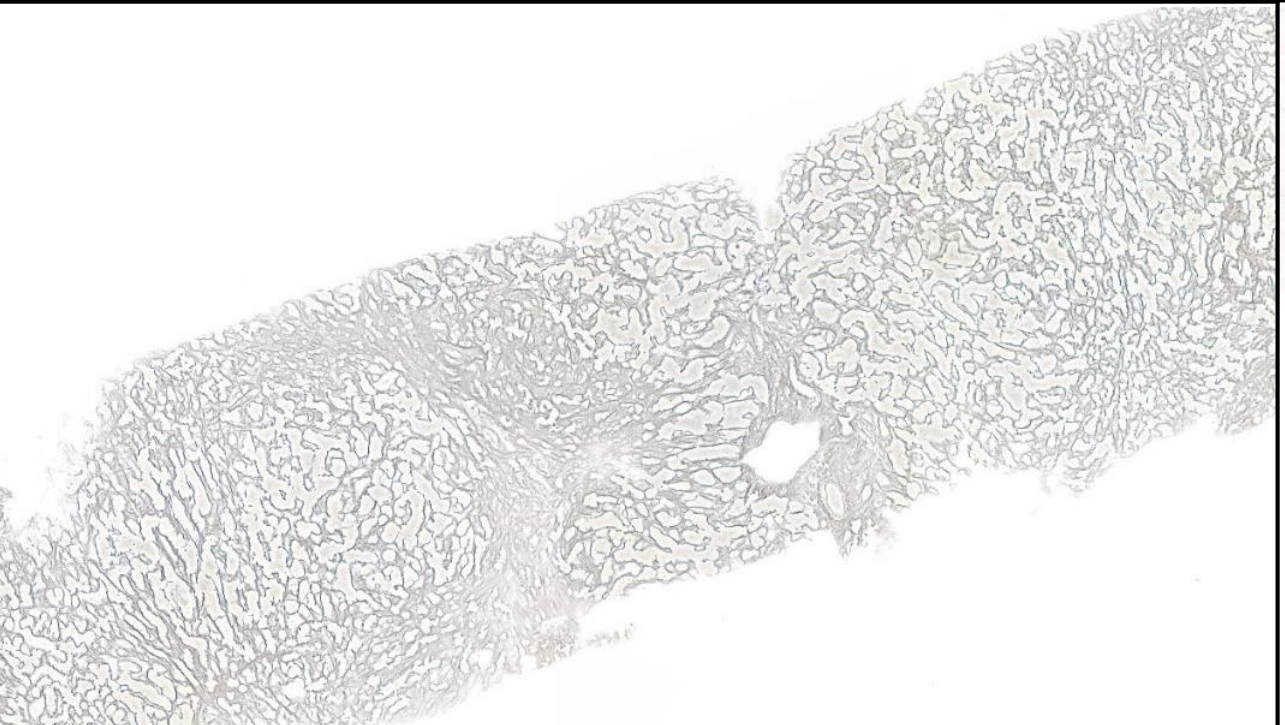
21 year old male with known complex congenital heart disease including transposition of the great vessels and double outlet right ventricle. Multiple palliative surgical interventions including Fontan procedure. Normal LFTs. Under consideration for cardiac transplantation.

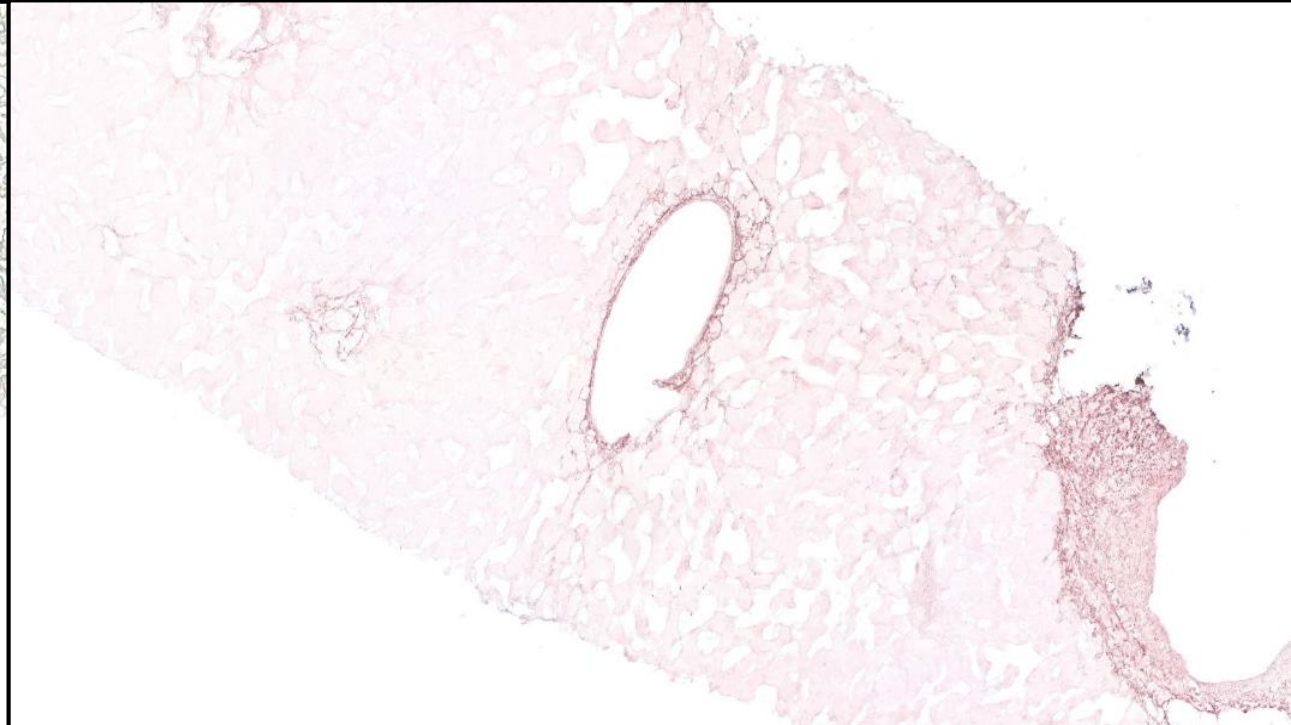




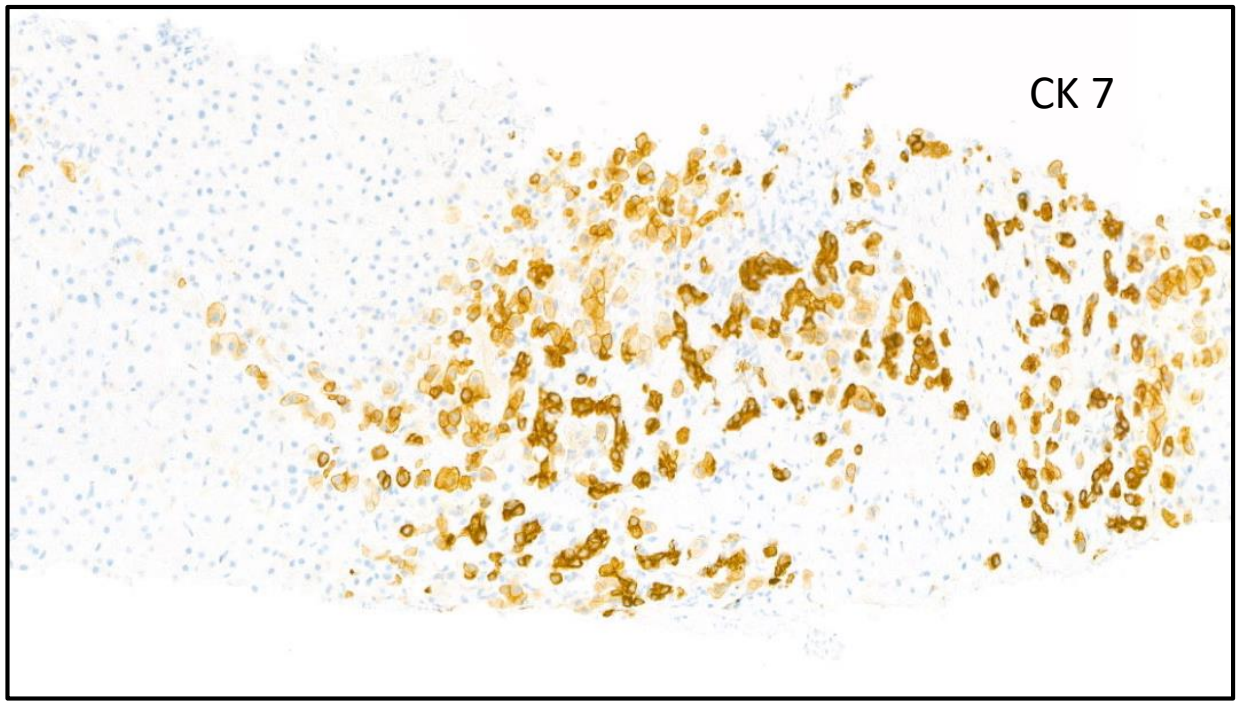


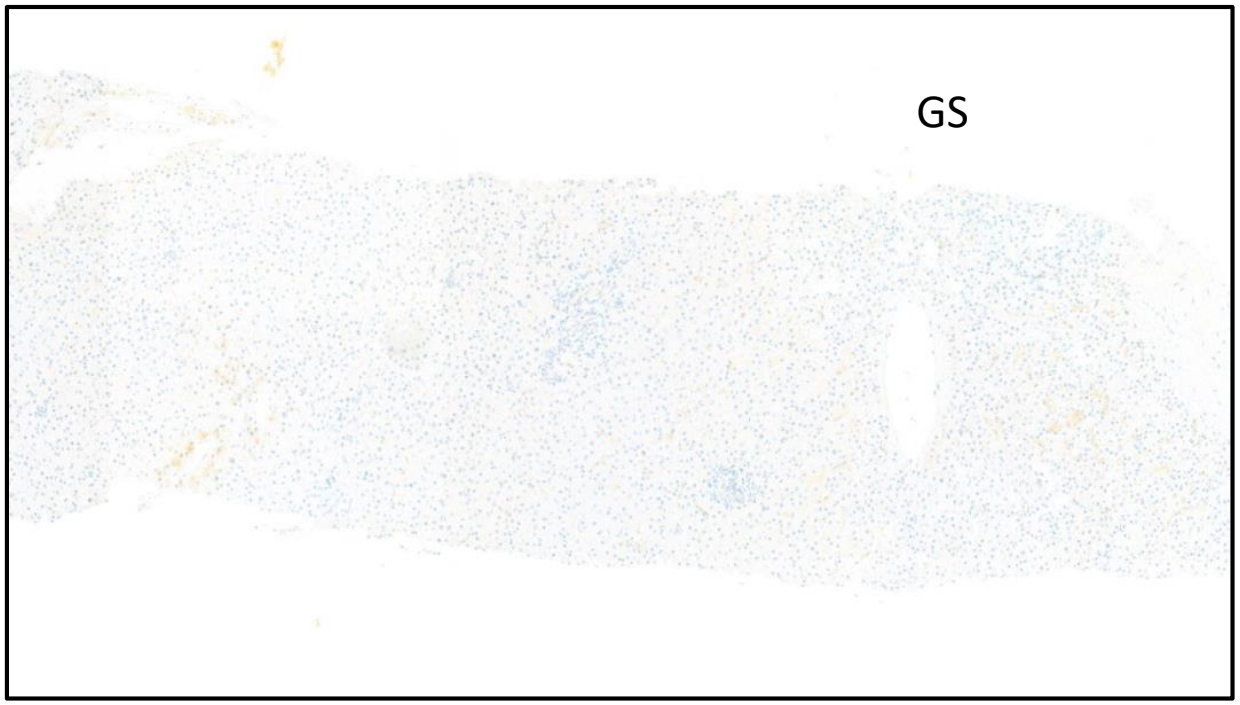






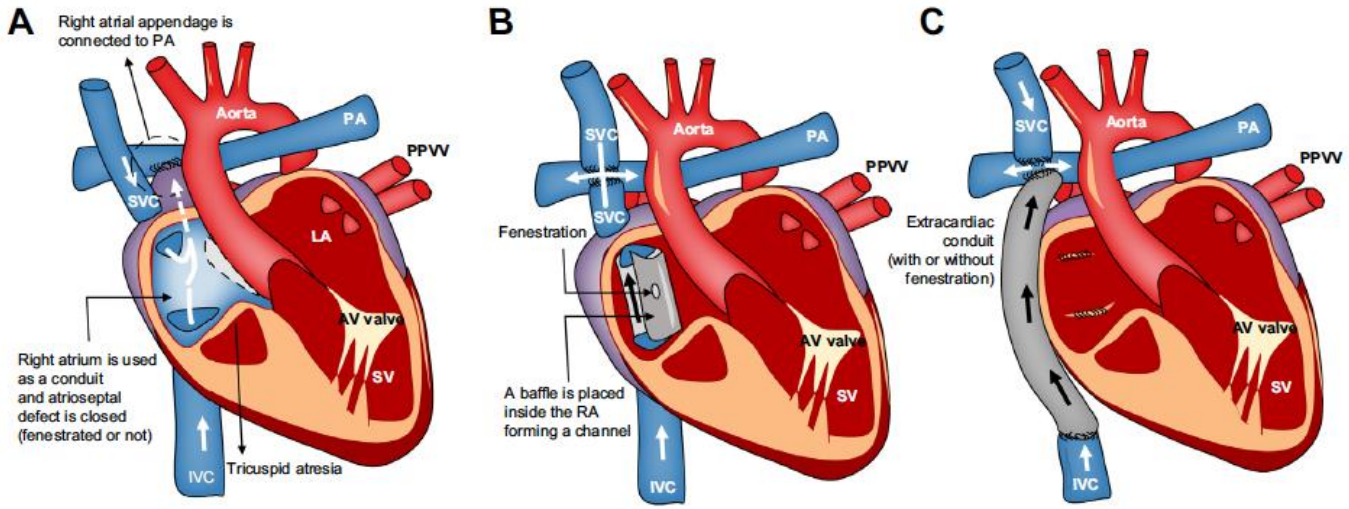
Case D





Pathophysiology of Fontan circulation

- Pulmonary and systemic circulations in parallel as in normal heart
- However, no sub-pulmonary ventricle
- Higher CVP > 10mmHg
- Cardiac output at rest < 80%
- Systemic venous congestion



Pathophysiology of Fontan circulation

- Pulmonary and systemic circulations in parallel as in normal heart
- However, no sub-pulmonary ventricle
- Higher CVP > 10mmHg
- Cardiac output at rest < 80%
- Systemic venous congestion

- Chronic renal disease
- Protein losing enteropathy
- Pleural effusion and hypoxia: intrapulmonary shunts
- Neurocognitive disorders
- Chylothorax
- Thromboembolism, peripheral oedema

Pathophysiology of Fontan circulation

- Pulmonary and systemic circulations in parallel as in normal heart
- However, no sub-pulmonary ventricle
- Higher CVP > 10mmHg
- Cardiac output at rest < 80%
- Systemic venous congestion

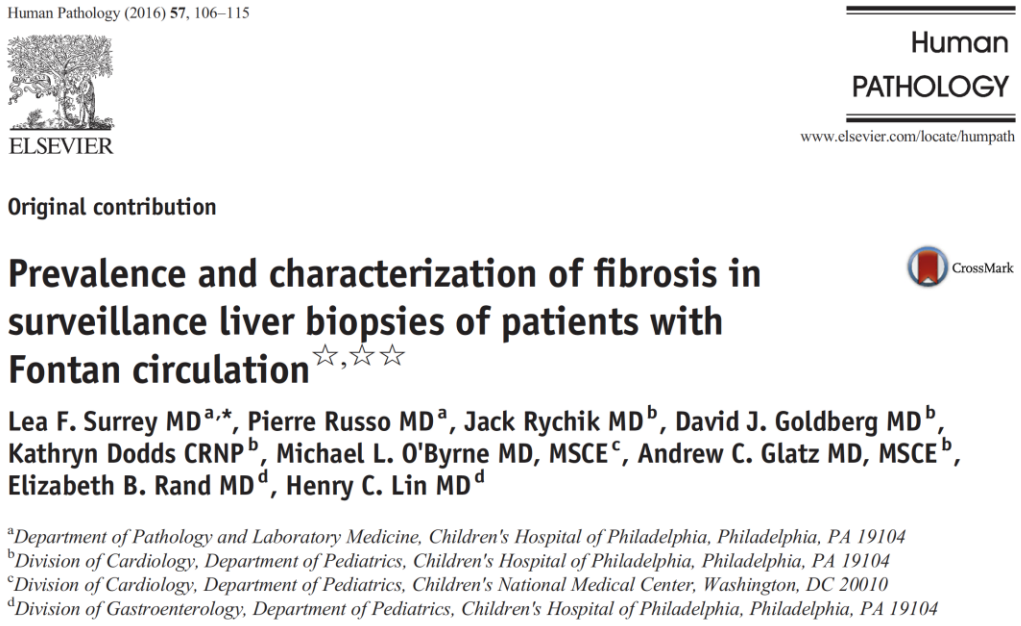
J THORAC CARDIOVASC SURG 86:757-760, 1983

Liver fibrosis (cardiac cirrhosis) five years after modified Fontan operation for tricuspid atresia

A 15-year-old girl was found to have severe liver fibrosis on liver biopsy at the time of cholecystectomy, 5½ years following a modified Fontan procedure (right atrial–right ventricular conduit) for tricuspid atresia. Postoperative right atrial pressures were consistently elevated above 13 mm Hg and this, in part, may have been due to progressive mild conduit stenosis. Because of increasing symptoms, the patient underwent successful revision of the conduit at the age of 15 years. It is suggested that sustained systemic venous hypertension caused the striking morphologic changes in the liver and that this serious complication may significantly affect the long-term prognosis of patients surviving the Fontan procedure.

John H. Lemmer, M.D.,* Arnold G. Coran, M.D.,** Douglas M. Behrendt, M.D.,*** Kathleen P. Heidelberger,**** and Aaron M. Stern, M.D.,***** *Ann Arbor, Mich.*

Histology of FALD



Human Pathology (2016) 57, 106–115

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

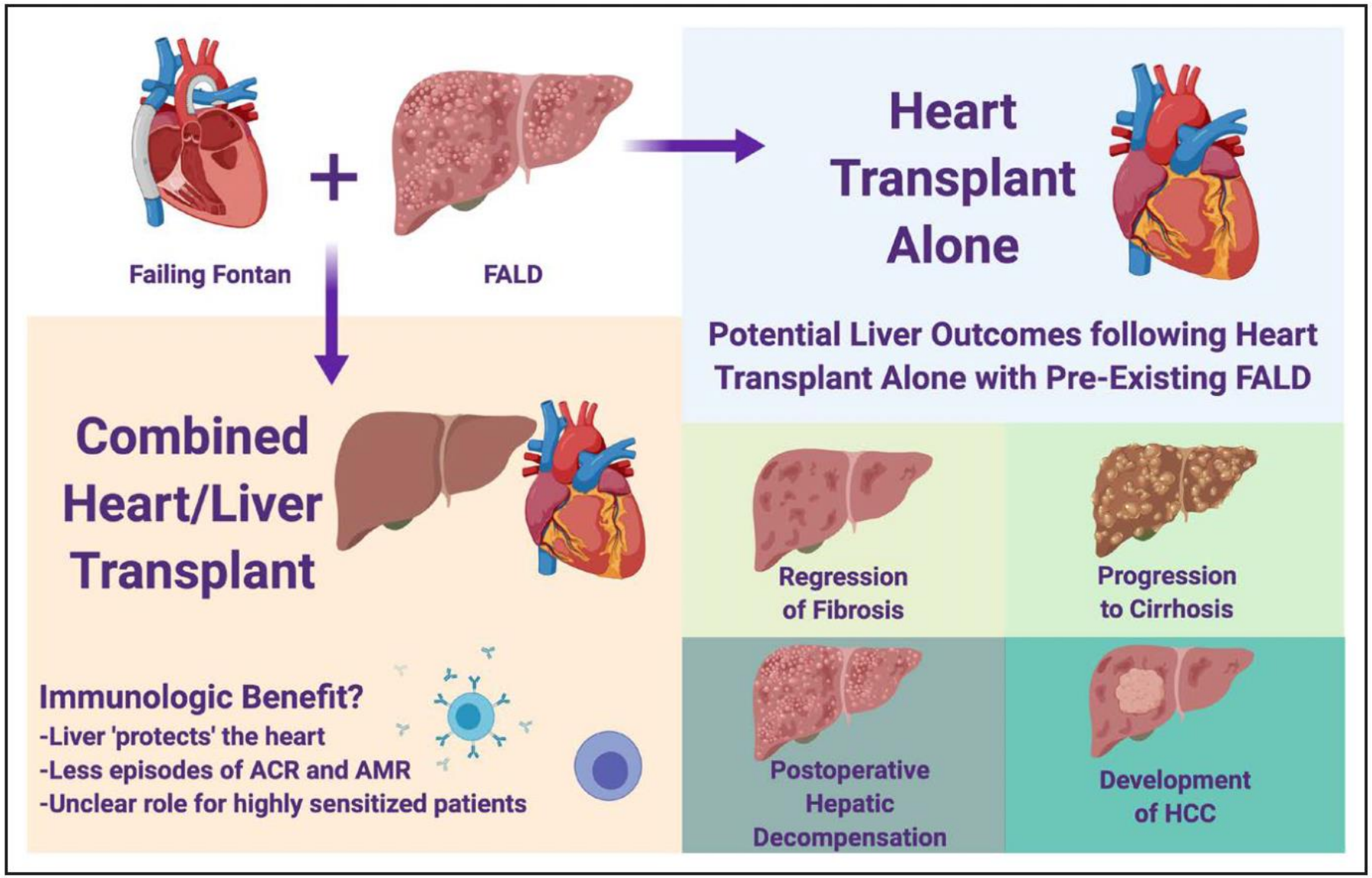
Original contribution

Prevalence and characterization of fibrosis in surveillance liver biopsies of patients with Fontan circulation☆,☆☆

Lea F. Surrey MD[a,*], Pierre Russo MD[a], Jack Rychik MD[b], David J. Goldberg MD[b], Kathryn Dodds CRNP[b], Michael L. O'Byrne MD, MSCE[c], Andrew C. Glatz MD, MSCE[b], Elizabeth B. Rand MD[d], Henry C. Lin MD[d]

[a]*Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Philadelphia, PA 19104*
[b]*Division of Cardiology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA 19104*
[c]*Division of Cardiology, Department of Pediatrics, Children's National Medical Center, Washington, DC 20010*
[d]*Division of Gastroenterology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA 19104*

- 74 biopsies from Fontan patients
- Collagen proportionate area
- METAVIR
- CHFS
- Sinusoidal fibrosis score (0-3)
- Sinusoidal dilatation score (0-3)
- 39% with ‘high grade; fibrosis
- Only blood parameter to correlate was mildly elevated PT/INR


Failing Fontan
FALD
Heart Transplant Alone
Potential Liver Outcomes following Heart Transplant Alone with Pre-Existing FALD
Combined Heart/Liver Transplant
Regression of Fibrosis
Progression to Cirrhosis
Immunologic Benefit?
-Liver 'protects' the heart
-Less episodes of ACR and AMR
-Unclear role for highly sensitized patients
Postoperative Hepatic Decompensation
Development of HCC

Freeman experience in Fontan CHL transplant

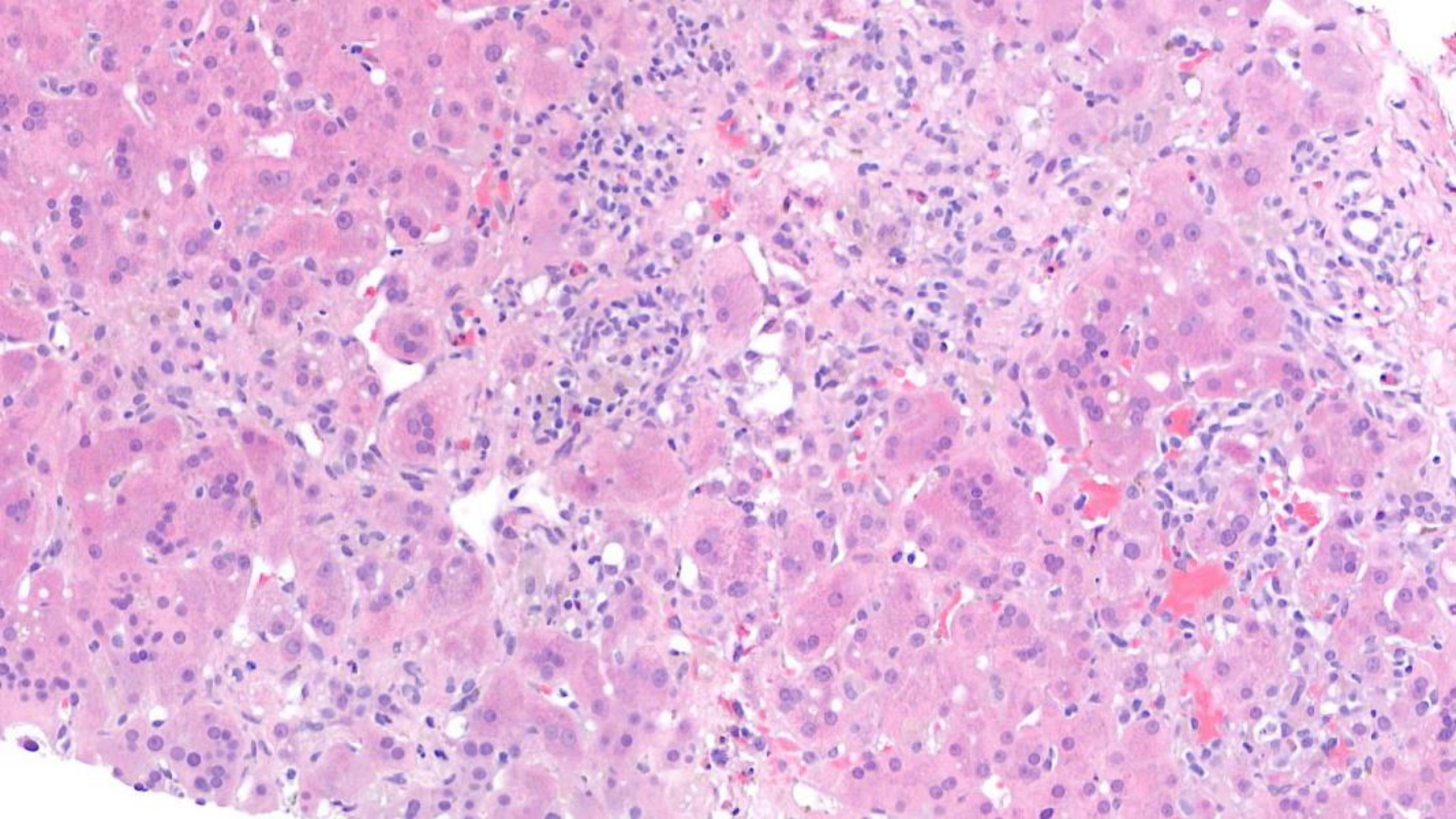
Patient	Anatomy	Type of Fontan	Reason for CHLT	Age at Tx	Tx date	Complications	Survival up to date	Outcome
1.	DORV, hypoplastic RV	AP	Fontan failure and liver cirrhosis	50	2015	Prolonged postoperative course due to sepsis, multiorgan failure and rehabilitation	8 years	Alive
2.	ccTGA, multiple VSDs, CoA	TCPC	HCC	24	2019	No major	4 years	Alive
3.	TA	AP	Fontan failure and liver cirrhosis	40	2020	No	3 years	Alive
4.	TA , PA	AP	Fontan failure and liver cirrhosis	37	2021	Heart graft failure (long cold ischaemic time, major intraop bleed), multiorgan failure including liver injury, extensive toxic epidermal necrolysis	12 days	Death
5. A	DILV, Sub-PS	AP	Fontan failure and liver cirrhosis	49	2023	Liver graft failure due to ischaemia (small hepatic donor artery and tight HA anastomosis) and profound muscle weakness	150 days	Alive
5. B	HTx	-	-	49	2023	Re-do liver transplant	76 days	Alive

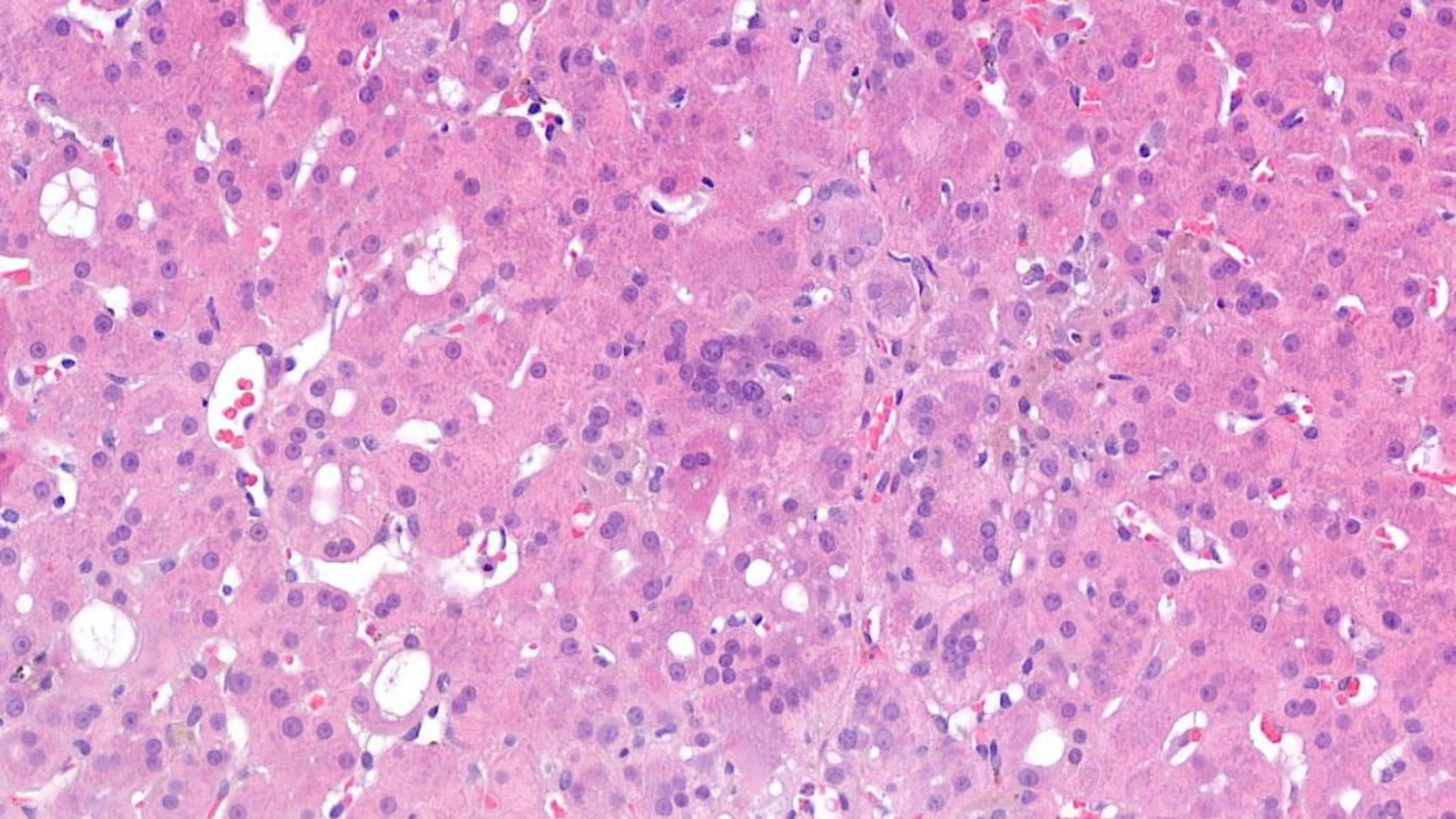
CASE E

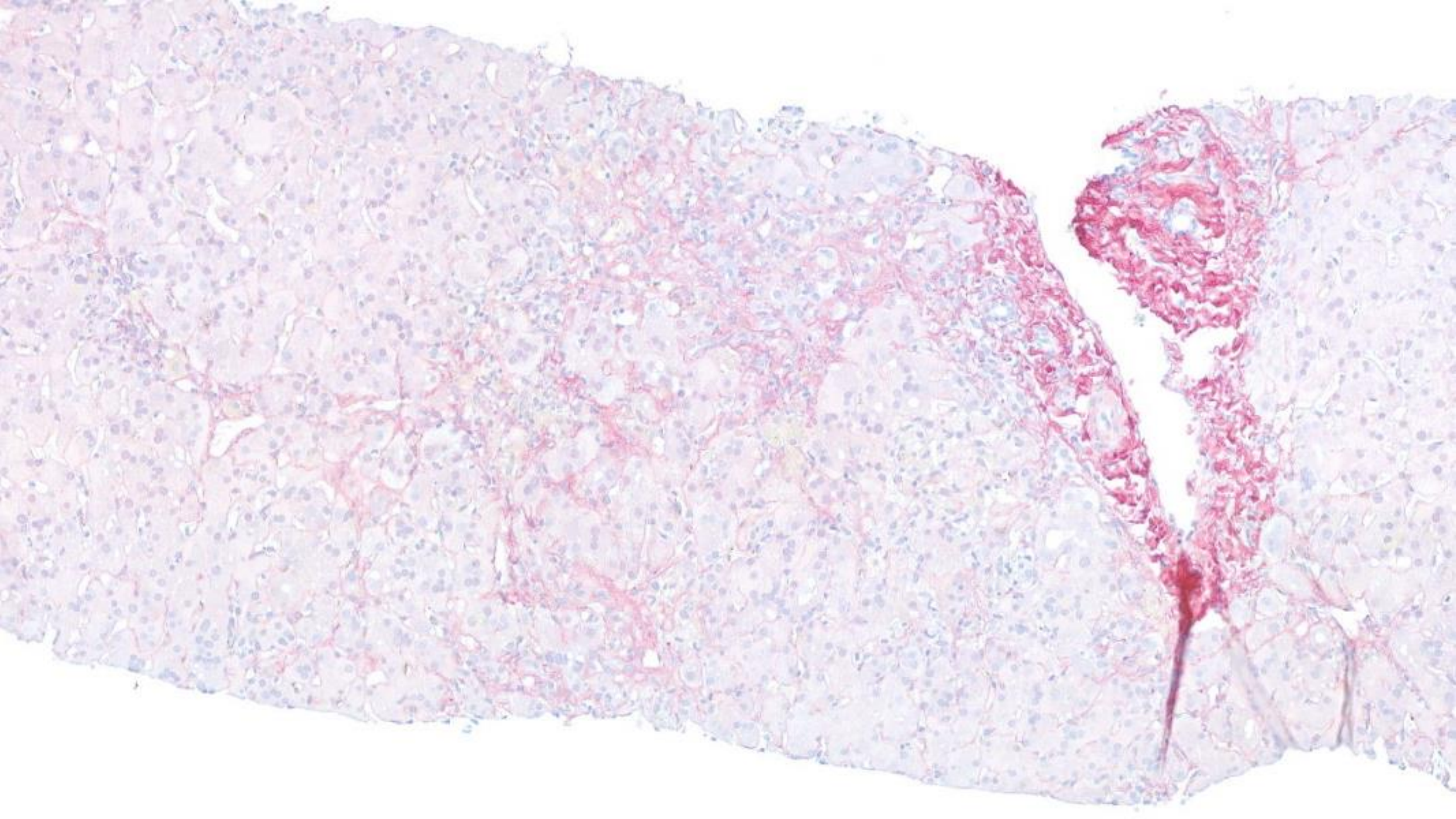
2 year old child who presented with acute liver failure. Transplanted elsewhere. Noted to be profoundly anaemic. At 6 months, found to have abnormal LFTs: clinical suspicion of T cell mediated rejection.

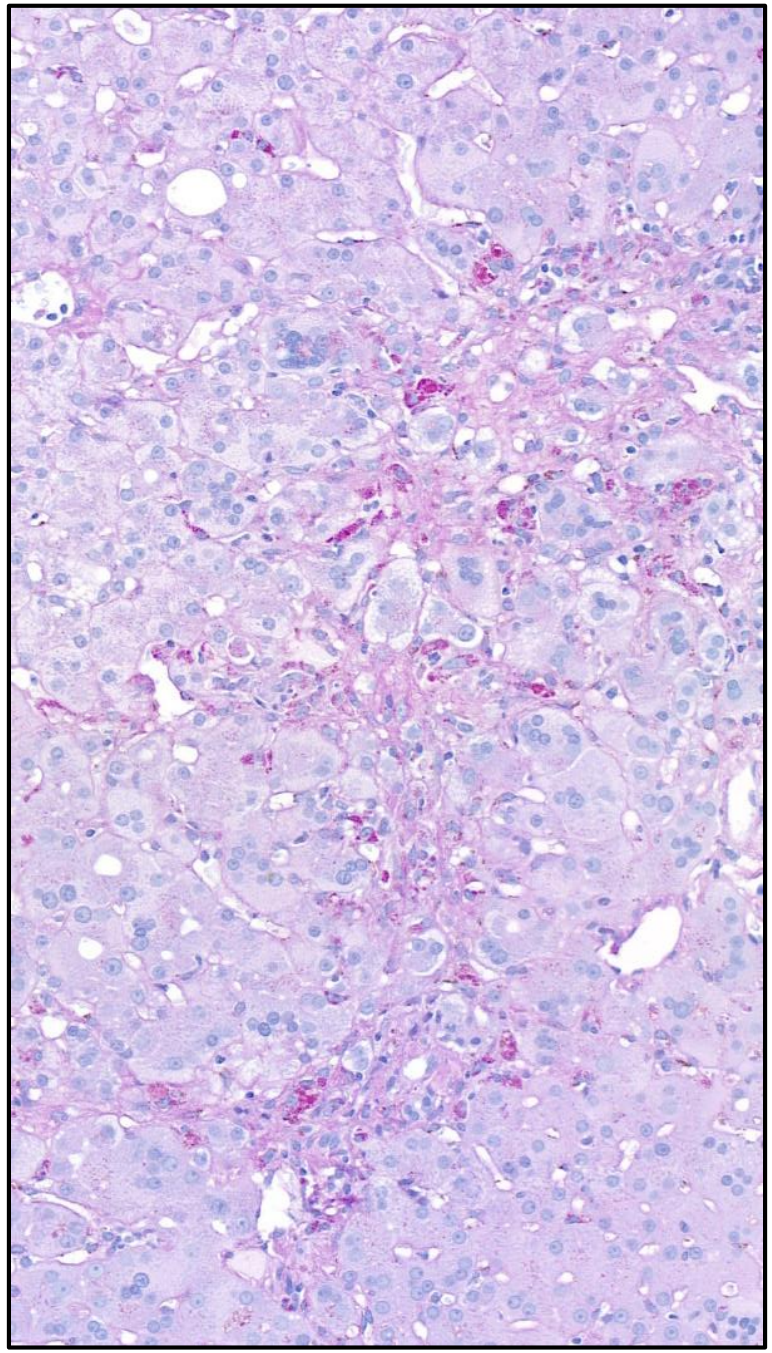
CASE E

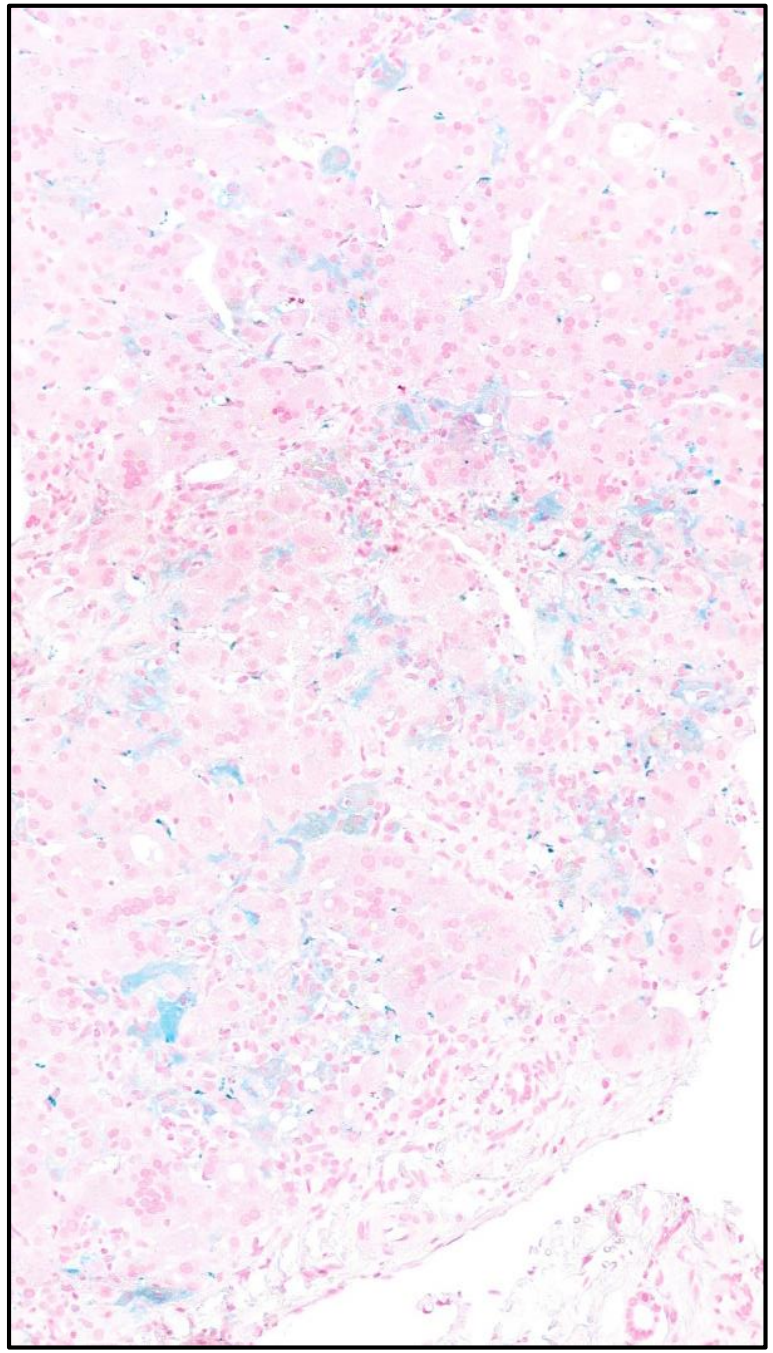
- 2 year old girl that presented with acute liver failure in 2022
- Transferred to Leeds for altruistic donor liver transplant
- Found to be markedly anaemic requiring multiple transfusions
- Represented to Newcastle hospital in December 2022 with further synthetic dysfunction and jaundice
- At that time, she had difficult to treat epileptic seizures
- Percutaneous liver biopsy undertaken





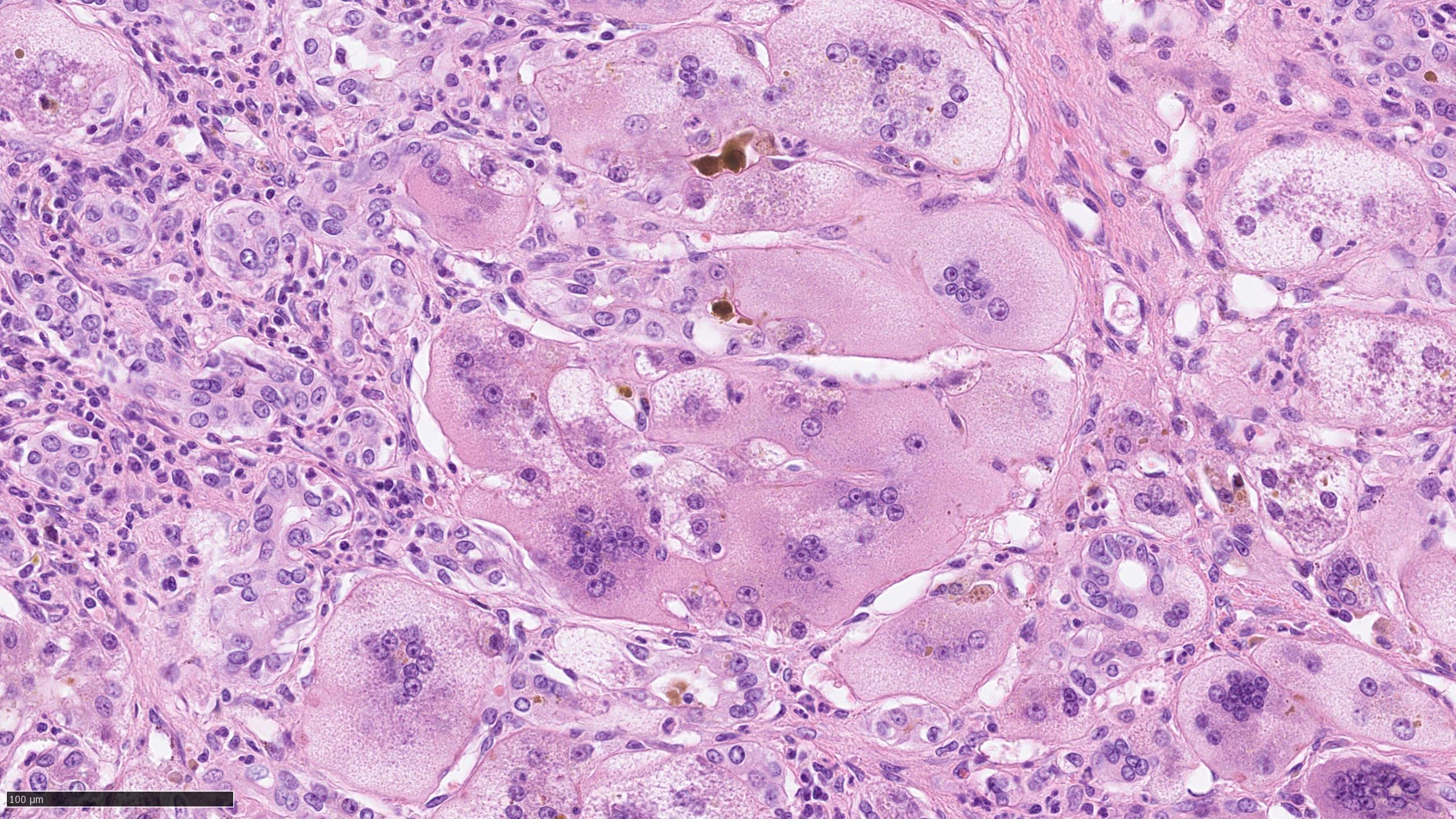






CASE E

- Diagnosis of giant cell hepatitis-autoimmune haemolytic anaemia made after original explant
- Treated with intravenous immunoglobulin, rituximab, steroids and MMF
- Developed malnutrition and gut failure – disseminated adenovirus and norovirus
- No circulating B cells and hypogammaglobulinaemia
- Central line infections: port cultures grew Lactobacillus and Candida
- Developed multi-organ failure and died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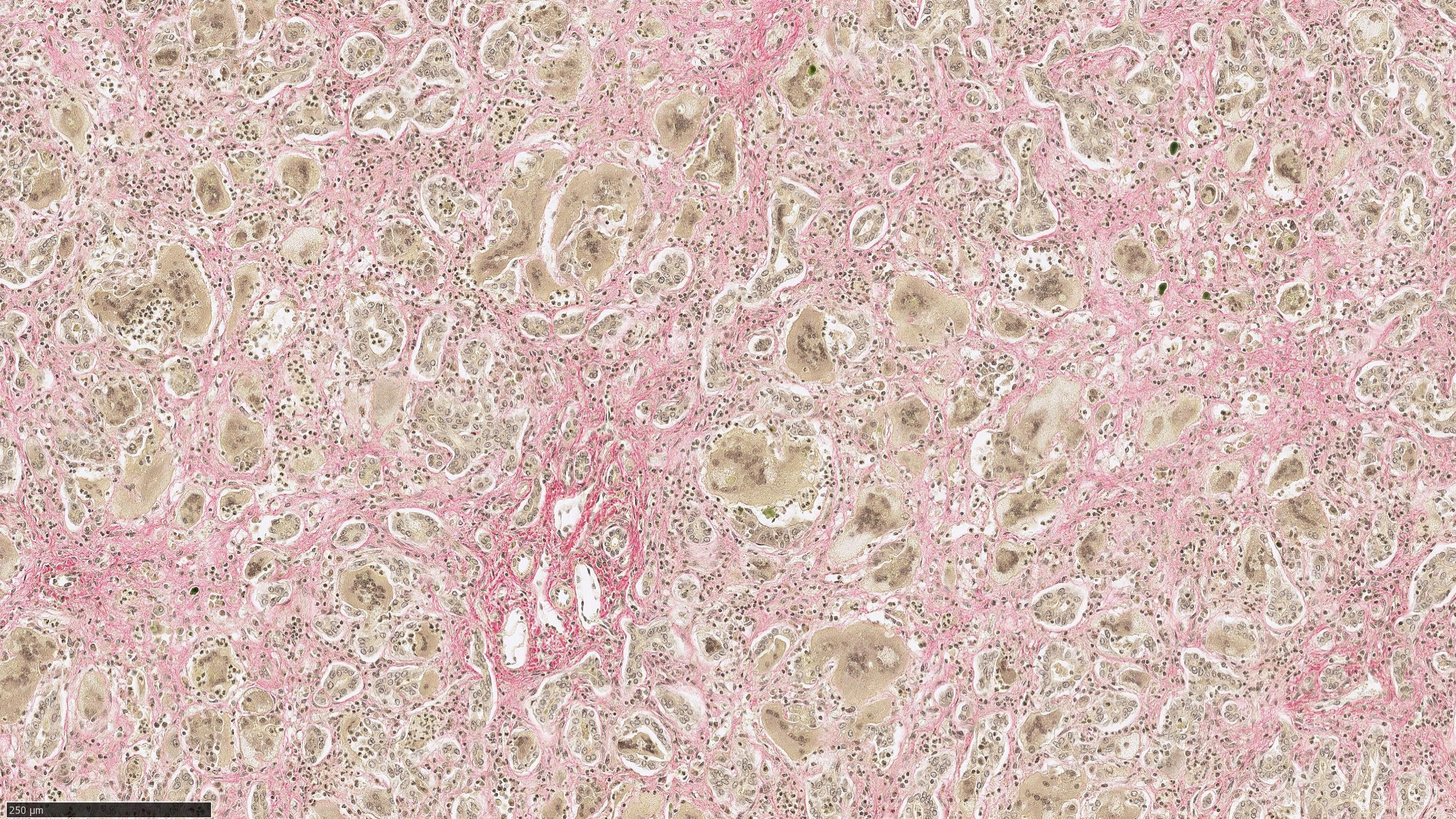
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Neonatal Giant Cell Hepatitis: Histological and Etiological Findings

Torbenson, Michael MD[*]; Hart, John MD[†]; Westerhoff, Maria MD[†]; Azzam, Ruba K. MD[‡]; Elgendi, Abeer MD[‡]; Mziray-Andrew, Haikaeli C. MD[‡]; Kim, Grace E. MD[§]; Scheimann, Ann MD, MBA[‖]

Author Information

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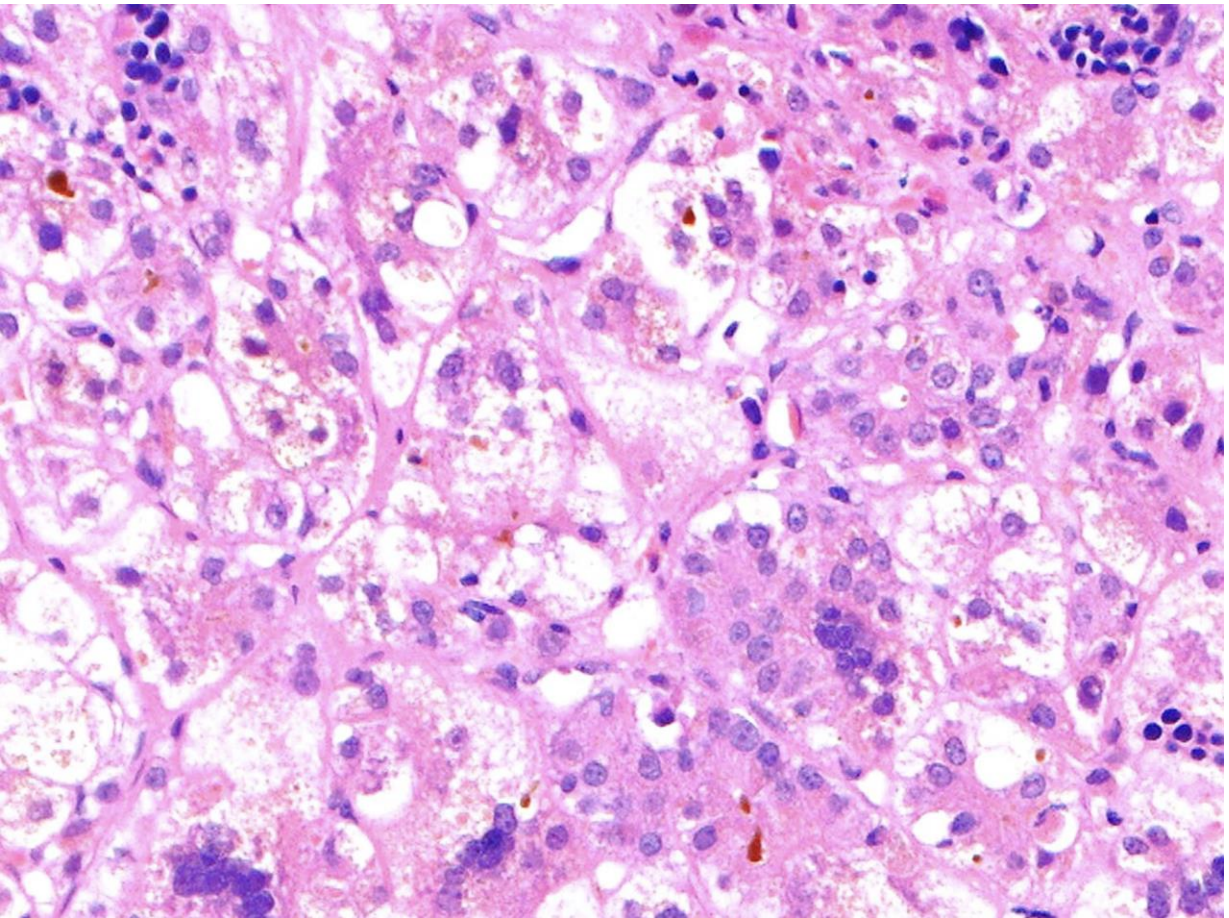

- Two centre retrospective study of 62 cases
- Average age at biopsy: 2 months
- Giant cell transformation involved average of 36% of hepatocytes
- Portal and lobular inflammation mild or absent in 95% cases
- Frequent bilirubinostasis and EMH
- Advanced fibrosis in only 8%
- Causes
  - Idiopathic 49%
  - Biliary disorders 20%
  - Hypopituaritism 16%

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ORIGINAL ARTICLE

Retrospective Study

Post-infantile giant cell hepatitis: A single center's experience over 25 years

Bassem Matta, Ricardo Cabello, Mordechai Rabinovitz, Marta Minervini, Shahid Malik

Table 3 Predisposing factors, *n* (%)

Predisposing factors	GCH on native liver	GCH on allograft
AIH	13 (32)	3 (30)
Drug induced	6 (15)	0
No factor identified	12 (30)	3 (30)
UC	2 (5)	3 (30)
PSC	3 (7)	1 (10)
HCV	2 (5)	1 (10)
CMV	1 (2)	1 (10)
SLE	2 (5)	0
Lymphoma	2 (5)	0
HAV	1 (2)	0
HBV	1 (2)	0
EBV	1 (2)	0
Sjogren	1 (2)	0
Autoimmune hemolytic anemia	1 (2)	0
CLL	1 (2)	0
Peripheral eosinophilia	1 (2)	0
SCC	1 (2)	0
Celiac disease	1 (2)	0

The Journal of Pediatrics
Volume 99, Issue 5, November 1981, Pages 704-711

Original article

Severe giant cell hepatitis with autoimmune hemolytic anemia in early childhood

M.D. O. Bernard, M.D. M. Hadchouel, M.D. J. Scotto, M.D. M. Odièvre, M.D. D. Alagille

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https://doi.org/10.1016/S0022-3476(81)80388-5

Four children, aged 6½ months to 2 years, presented with liver disease and autoimmune hemolyticanemia. Clinical signs included fever, jaundice, firm or hard hepatomegaly, and splenomegaly. Direct Coombs test results were of the mixed (IgG+C) type. Liver function tests showed high direct bilirubin, transaminase, and serum gamma globulin values, and a prolonged prothrombin time. The liver histology was characterized by marked lobular fibrosis and giant cell transformation. The course of the disease was severe, resulting in the death of three patients from liver failure. However, the liver disease seemed responsive to corticosteroid treatment, which in one patient was clearly beneficial.

GCH-AHA

- One of Bernard's patient cohort responded to steroids: ?possible autoimmune basis
- Responses less consistent than juvenile AIH
- Strong family history of autoimmune disorders
- Whitington et al (2014) hypothesized that it may be related to a humoral immune mechanism similar to GALD given the presence of giant cel transformation in both (?!)
- Demonstrated C5b-9 complex binding in hepatocytes
- Has led to B cell depletion therapies