Beyond A, B, and C:
Emerging & Re-Emerging Infections in the Liver

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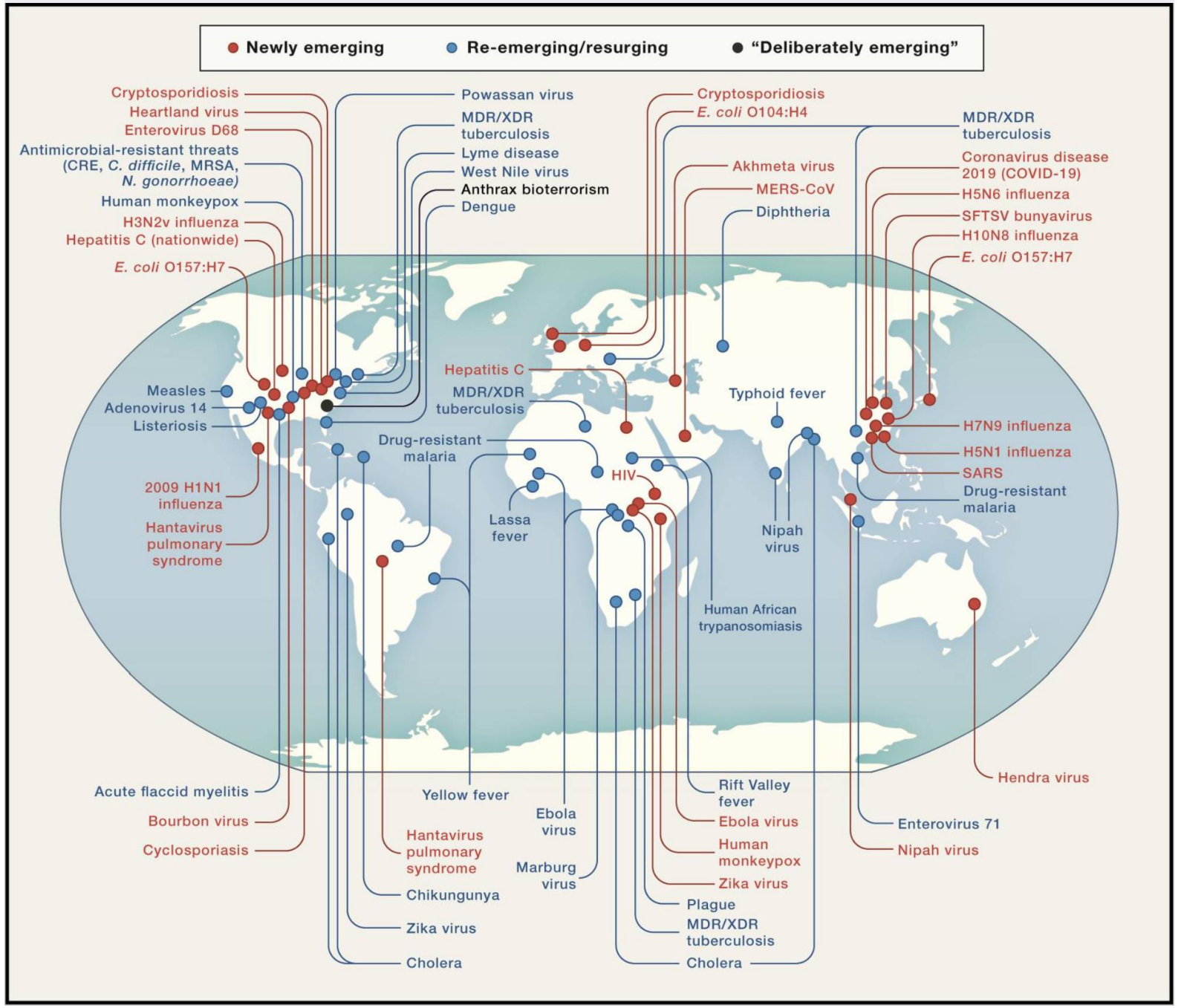
No Disclosures

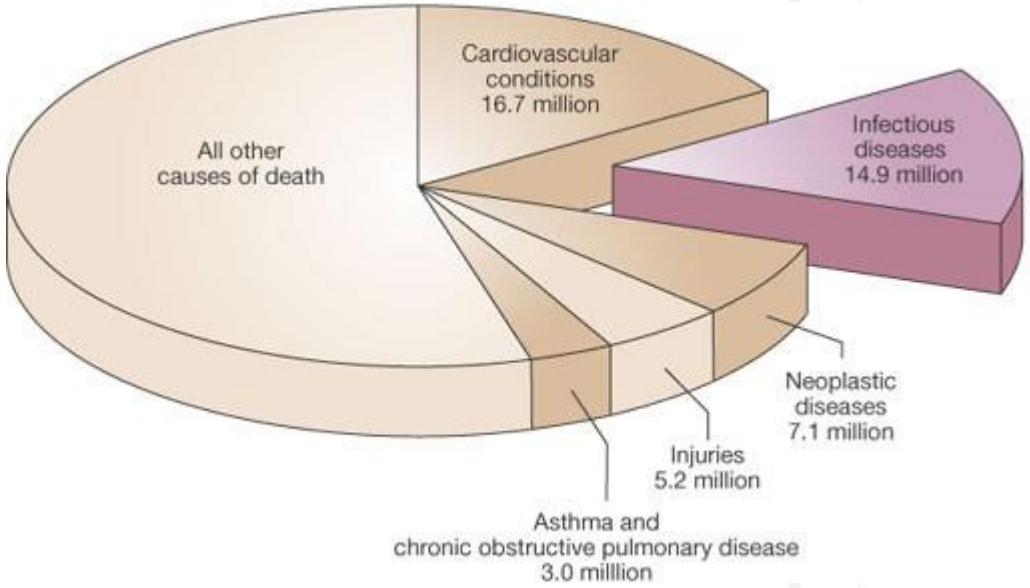
Emerging and Re-emerging Infectious Diseases

- **Emerging**: Infections that have *newly* appeared in a population (ex. COVID-19)
- **Re-emerging**: infections that are *resurging* in incidence or geographic range (ex. measles).

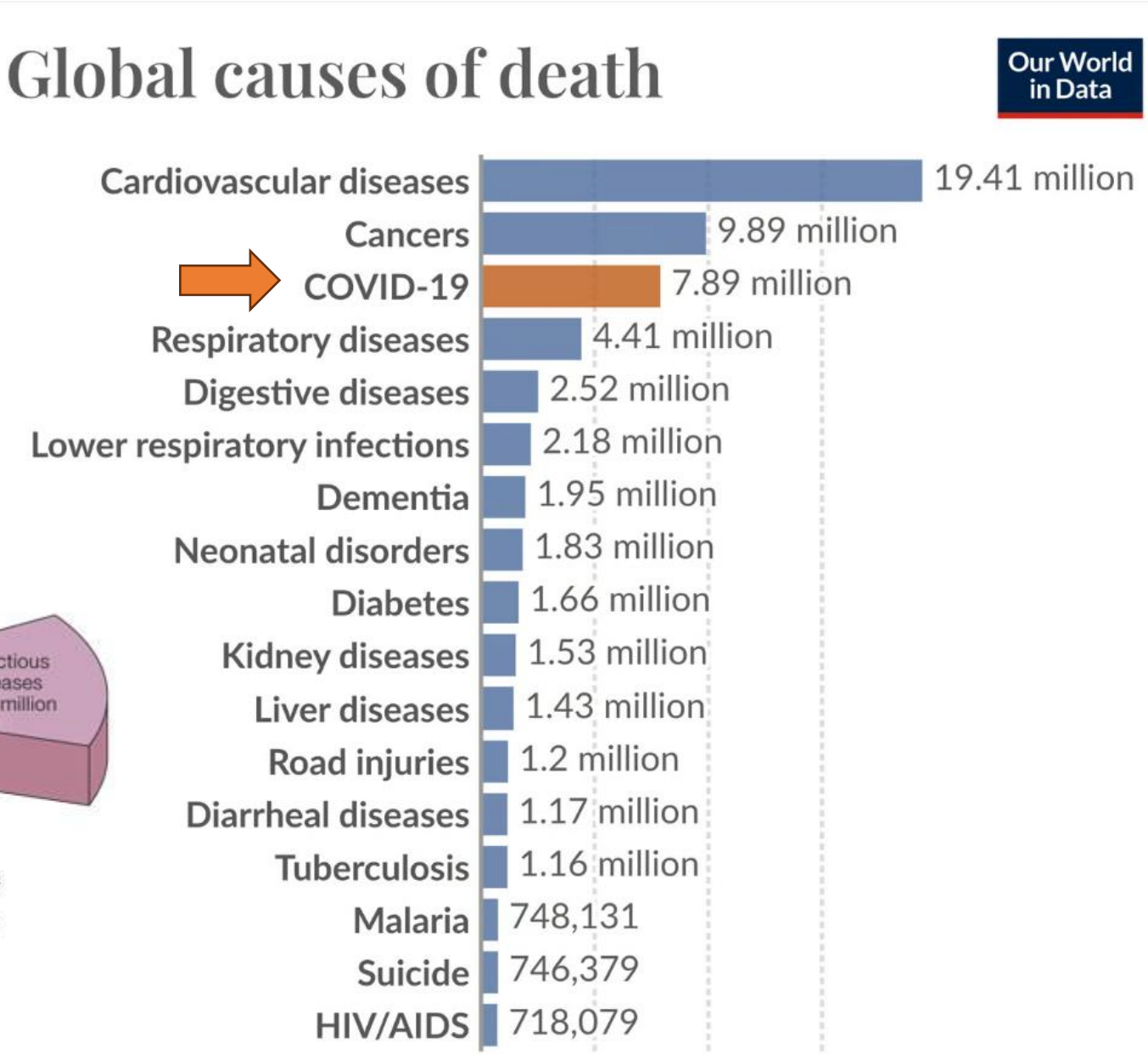


Morens DM, Fauci AS. Emerging Pandemic Diseases: How We Got to COVID-19. Cell. 2020 Sep 3;182(5):1077-1092

COVID-19 was the 3rd largest cause of death in 2021 and infections surpassed cancers



https://www.nature.com/articles/nature02759/figures/2



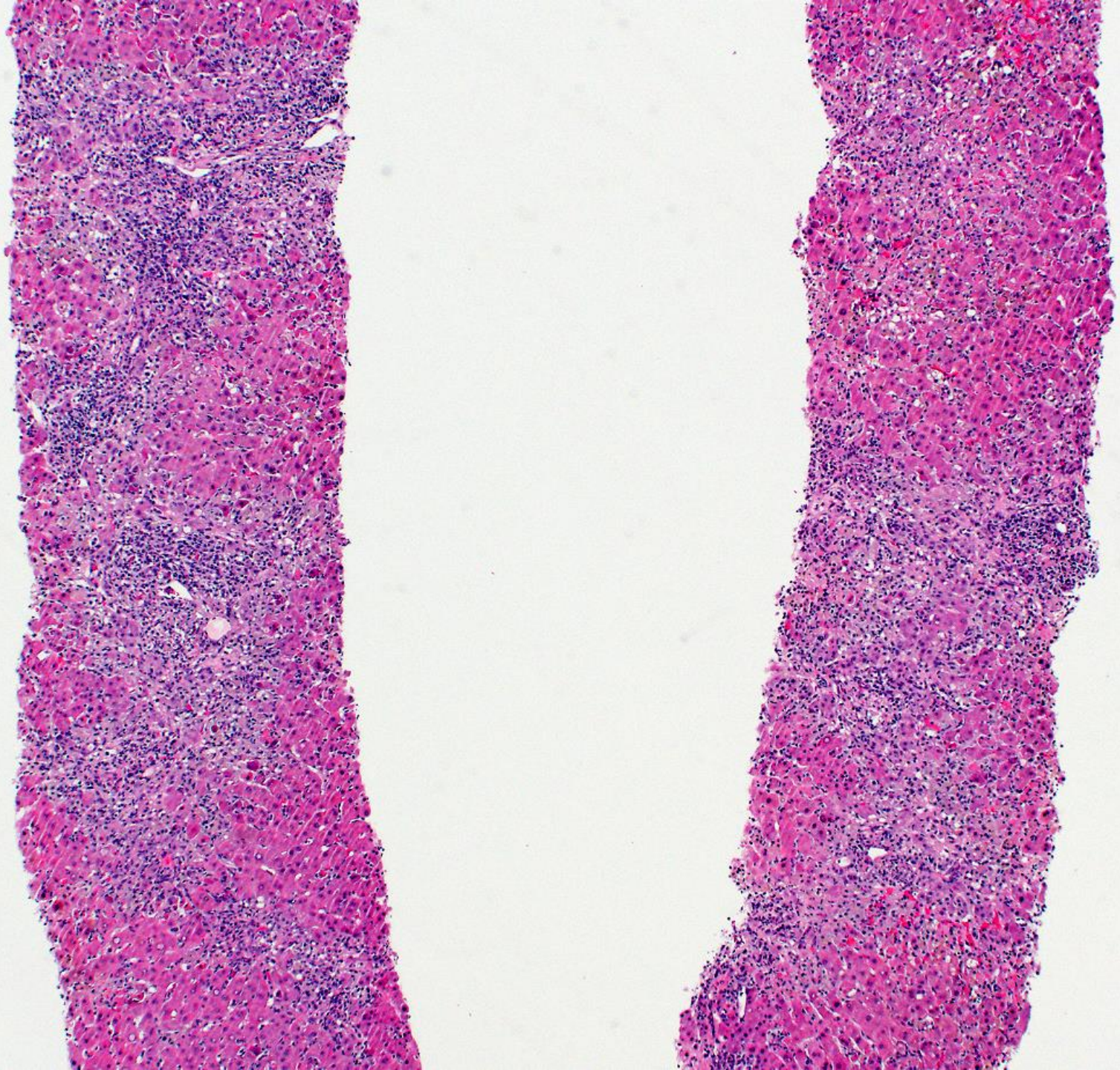
Objectives
In 3 clinical cases…

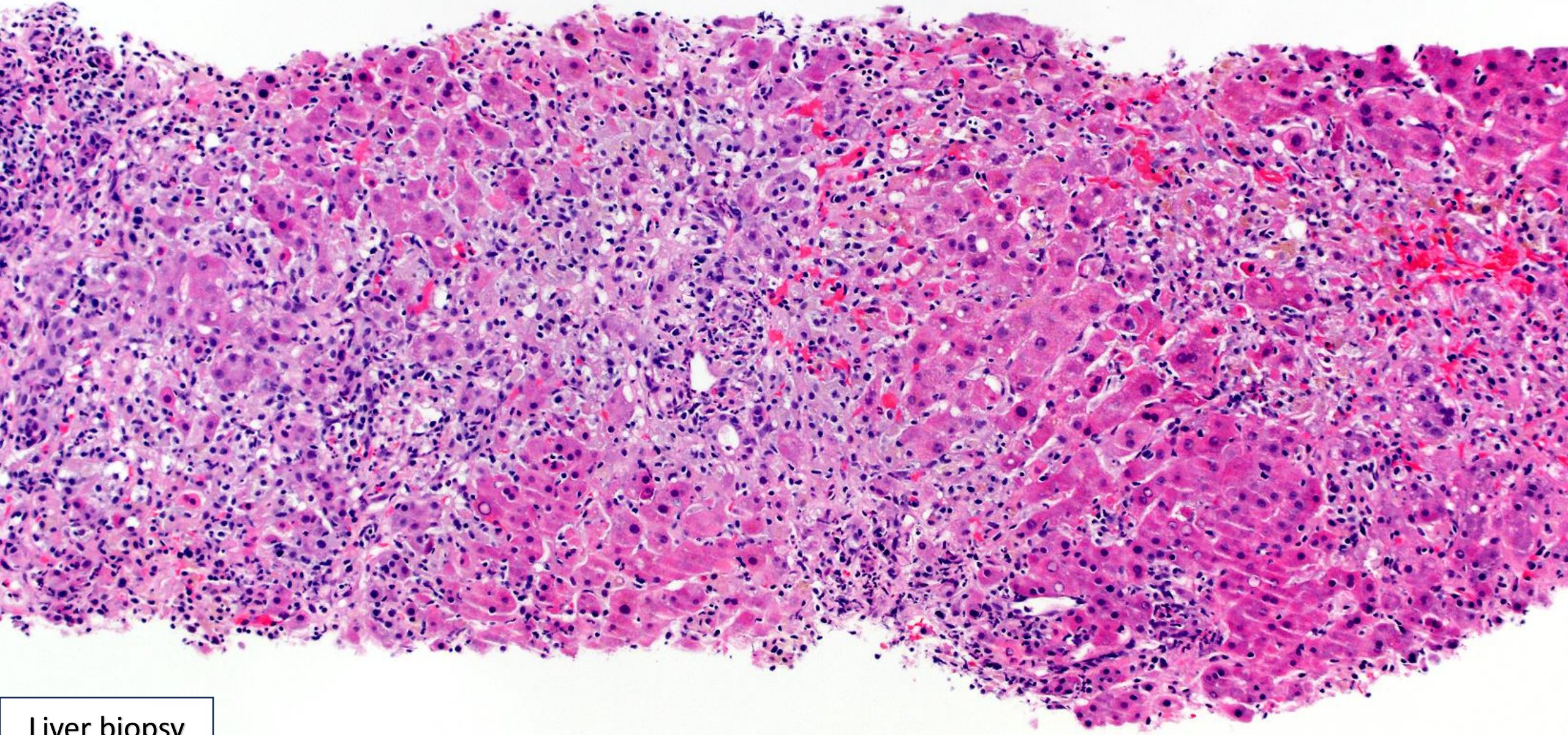
- Recognize patterns of inflammation in the liver that aid in the diagnosis of emerging and re-emerging infectious diseases
- Synthesize clinical and laboratory data to narrow the differential diagnosis and help determine the etiology of hepatitis
- Utilize and interpret special and immunohistochemical stains in the diagnosis of liver infections in tissue sections

Case 1

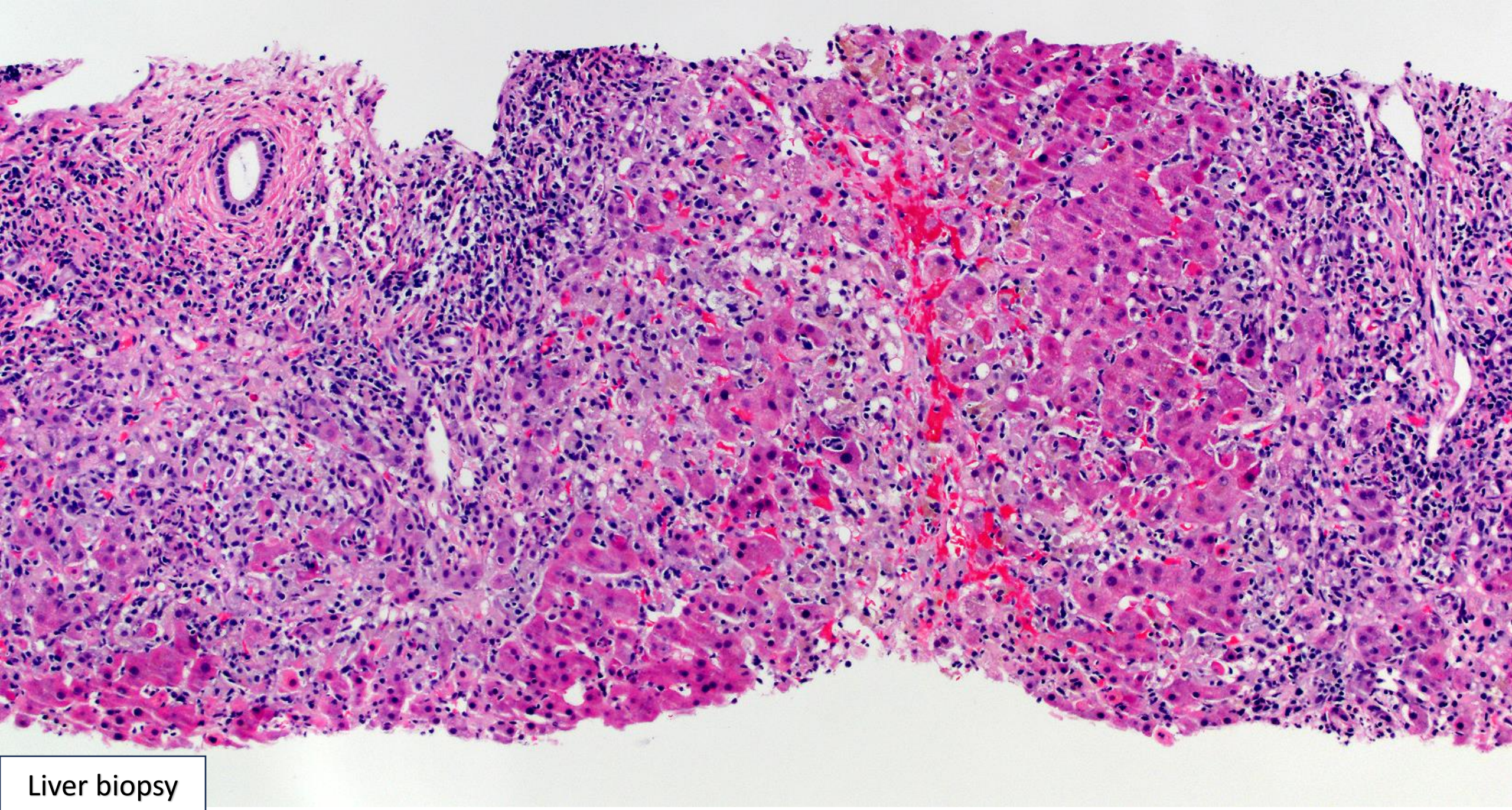
- 67-year-old male worked as a truck driver and had a history of coronary artery disease and type 2 diabetes mellitus, developed nausea and vomiting while driving in WY
- Hospitalized for diabetic ketoacidosis (DKA), treated with IV antibiotics and discharged from hospital
- On follow-up with primary care provider 4 days later **AST and ALT were in the 3000s**, **ALK 302, bilirubin 8.4**
- He reported jaundice and dark urine; denies abdominal pain, nausea, vomiting, diarrhea, alcohol or acetaminophen use
- ALT rose from 3000 to 4800 and AST went from 3700 to 6000; he was transferred to U
- Viral hepatitis panel (A, B, C) was negative, ANA screen for autoimmune hepatitis and HIV testing were negative
- Abdominal imaging ruled out portal vein thrombosis, hepatic vein thrombosis, and biliary duct obstruction
- Suspected drug-induced liver injury from prior antimicrobial therapy for DKA

Liver biopsy
H+E stain

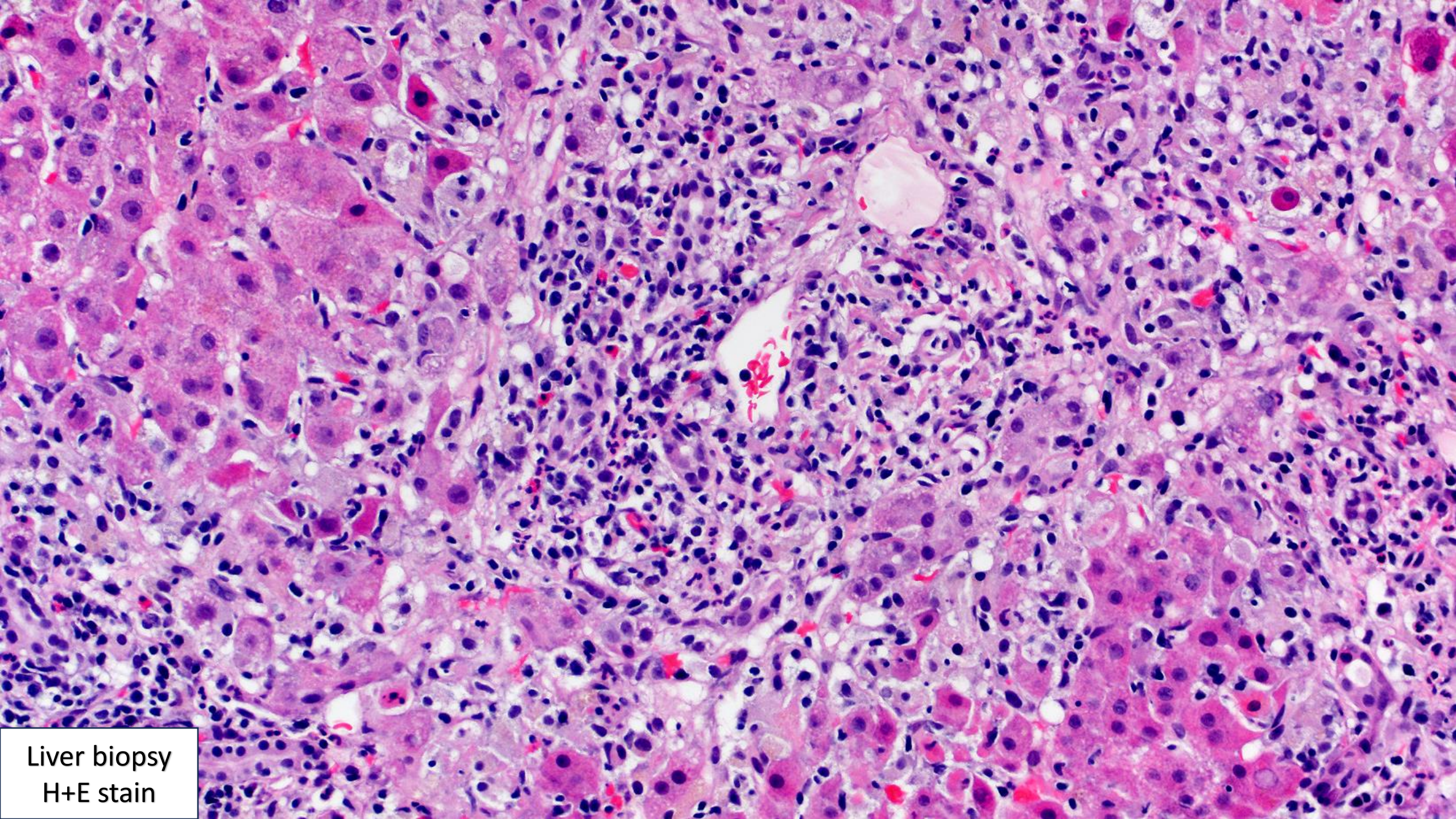


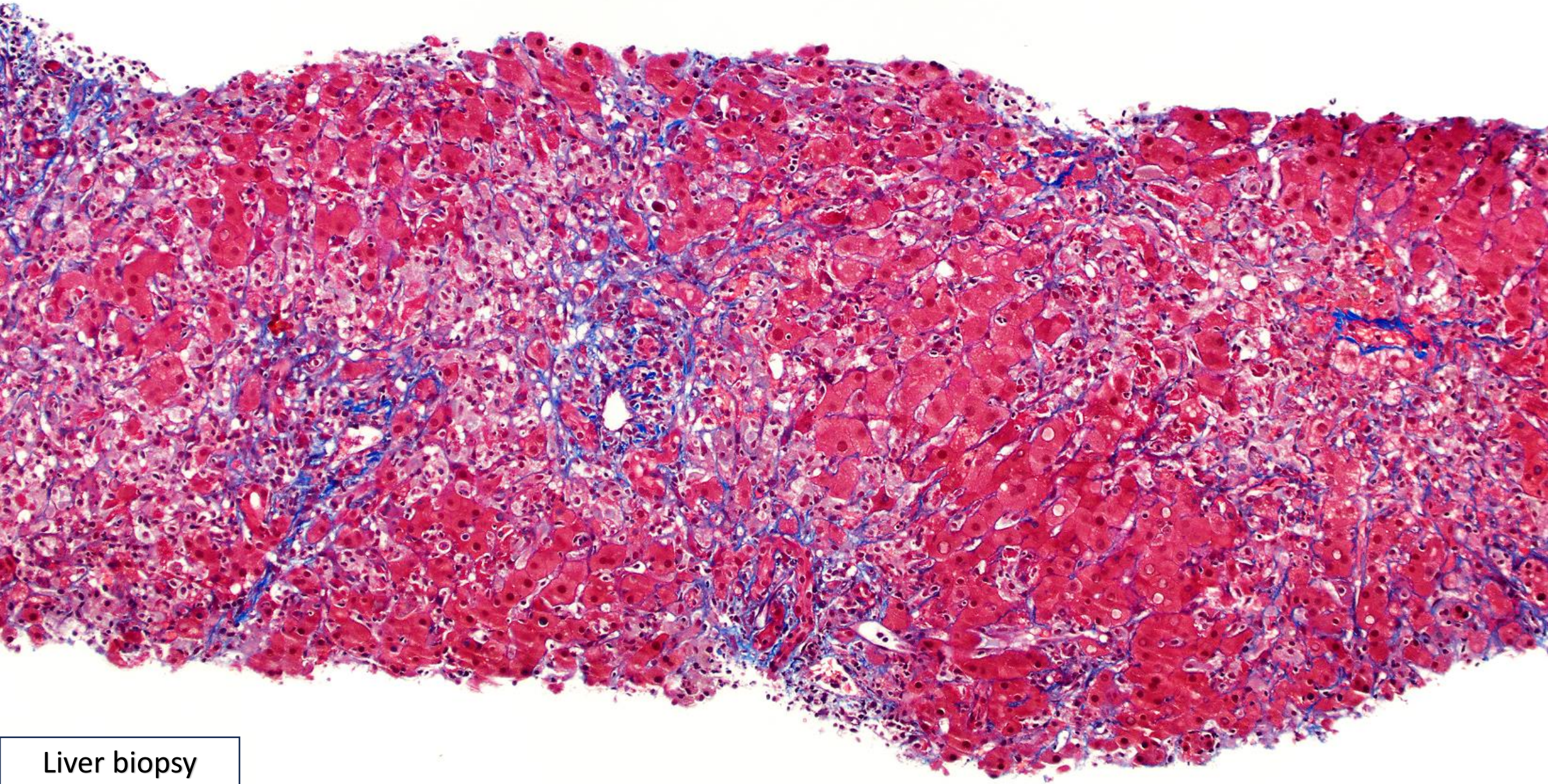


Liver biopsy
H+E stain



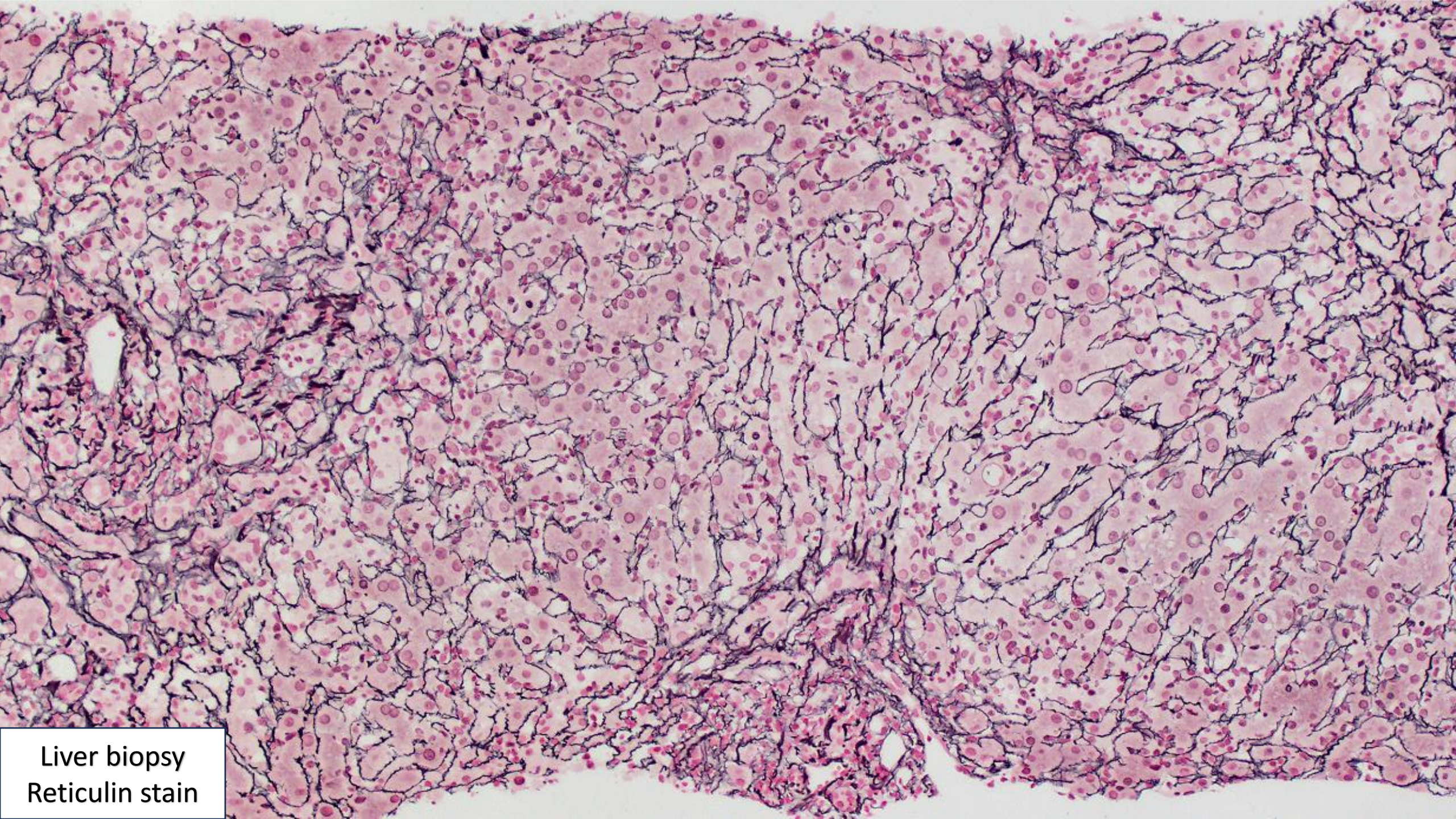
Liver biopsy
H+E stain


Liver biopsy
H+E stain



Liver biopsy

Trichrome stain


Liver biopsy
Reticulin stain

What is your differential diagnosis for active hepatitis with bridging necrosis?

Case continued…

- Liver biopsy indicates severe active hepatitis with bridging necrosis: AIH versus infection versus drug?
- No evidence of HSV 1/2 or adenovirus, Hepatitis A, B, C were clinically excluded, ANA was negative
- Clinical c/f drug-induced liver injury - recent use of piperacillin-tazobactam for a week during admission for DKA
- Patient acutely worsens with chest pain, abdominal pain, encephalopathy, and asterixis

- Liver enzymes: AST 9813, ALT 7057
- Transplantation considered, but after decompensation, patient was transitioned to comfort care and passed away
- Autopsy was performed and showed fulminant hepatic failure…

And then some additional test results became available

Hepatitis E Virus by Quantitative PCR

Status: **Final result** Visible to patient: **No (not released)** Dx: **Acute hepatitis**

0 Result Notes

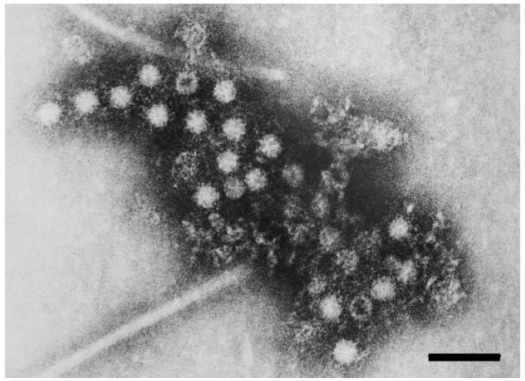
	Ref Range & Units	5 mo ago
Hepatitis E Quant by PCR, Source		Plasma
Hepatitis E Quant by PCR, IU/mL		4,560,000
Hepatitis E Quant by PCR, Log IU/mL		6.7
Hepatitis E Quant by PCR, Interp	Not Detected	**Detected !**

Comment: INTERPRETIVE INFORMATION: Hepatitis E Virus by Quantitative PCR

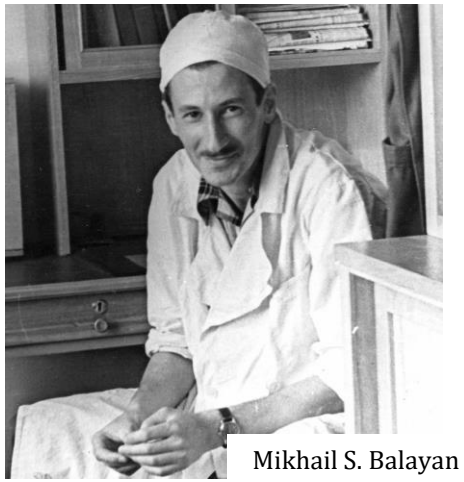
Further testing revealed Genotype 3

Which of the following statements is TRUE about HEV?

A. Limited to developing countries
B. Humans are the only known reservoir
C. Easily transmitted by casual contact
D. Travelers have the highest risk of acquiring HEV



Hepatitis E Virus



Mikhail S. Balayan

- Small RNA virus in family *Hepeviridae*
- Worldwide 20 million annual infections and 3.3 million symptomatic cases, 6% seroprevalence in U.S.
- First described in mid-1950's – outbreak in Delhi with 30,000 cases of jaundice
- Not identified until 1980's by self-inoculated Russian virologist, Mikhail Balayan, from pooled fecal samples of Soviet troops in Afghanistan
- Variable incubation period, 15-60 days
- Most patients are asymptomatic with mild elevations in liver enzymes

- Serology (enzyme immunoassay) IgM, IgG – not reliable in immune suppression
- HEV RNA nucleic acid amplification test (NAAT) – detect conserved domains of genome
- Male gender, diabetes and heavy alcohol use associated with increased risk of symptomatic infections
- Chronic HEV infection – persistence of HEV RNA in blood or stool for at least 3 months
- Chronic infections in 20-50% of transplant patients exposed to HEV & can progress to cirrhosis
- Treatment: Ribavirin

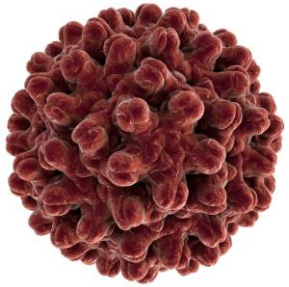
https://www.who.int/news-room/fact-sheets/detail/hepatitis-e

Pisano MB, et al. Hepatitis E virus infection in the United States: Seroprevalence, risk factors and the influence of immunological assays. PLoS One. 2022 Aug 5;17(8):e0272809.

Lemon SM, Walker CM. Enterically Transmitted Non-A, Non-B Hepatitis and the Discovery of Hepatitis E Virus. Cold Spring Harb Perspect Med. 2019 Aug 1;9(8):a033449.

Dalton HR et al. Host risk factors and autochthonous hepatitis E infection. Eur J Gastroenterol Hepatol. 2011 Nov;23(12):1200-5

Songtanin B et al. Hepatitis E Virus Infections: Epidemiology, Genetic Diversity, and Clinical Considerations. Viruses. 2023 Jun 17;15(6):1389.



Hepatitis E Viral Genotypes

4 mammalian genotypes 1 serotype

Genotypes 1 and 2 (humans)

- Humans are the reservoir
- Fecal-oral transmission
- Endemic to and epidemics in Asia, Africa, Central America
- Waterborne outbreaks associated with heavy flooding
- Infrequent person-to-person transmission (unlike HAV)
- HEV-1 is associated with high maternal morbidity and mortality

Genotypes 3 and 4 (zoonotic infections)

- Animals are the reservoir: pigs, wild boars, goats, sheep, deer
- Worldwide, North and South America
- Fecal contamination of water and consumption of contaminated meat

Aslan AT, Balaban HY. Hepatitis E virus: Epidemiology, diagnosis, clinical manifestations, and treatment. World J Gastroenterol. 2020 Oct 7;26(37):5543-5560. PMID: 33071523.

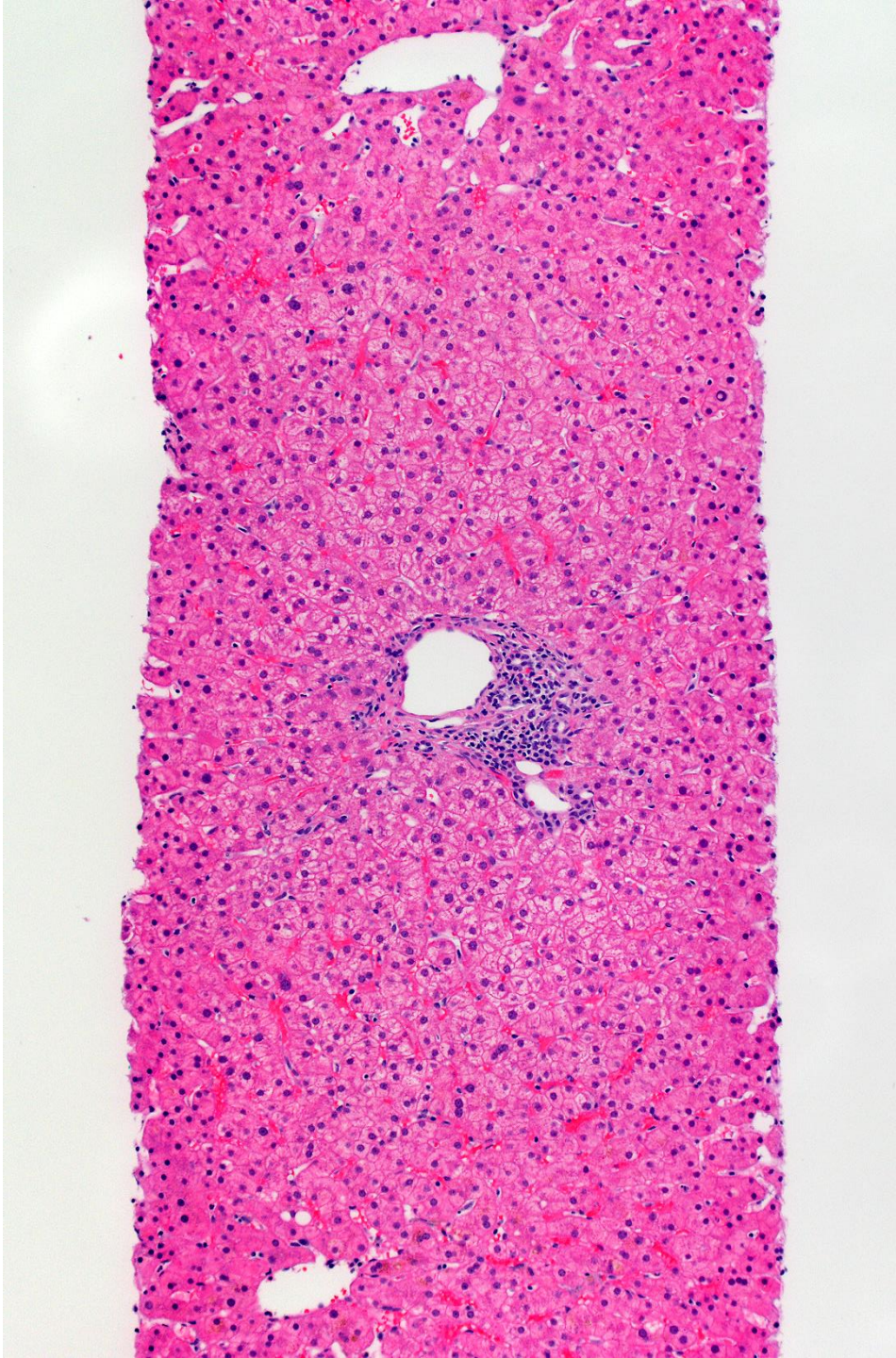
Case 1
The Clinical Team Asks Questions…What's the Exposure?

- The patient's wife mentioned they ate bison at home in late July
- The bison was bought at a store and cooked thoroughly per her report

- There was still another package of bison in her freezer and she was asked to keep it until further notice…

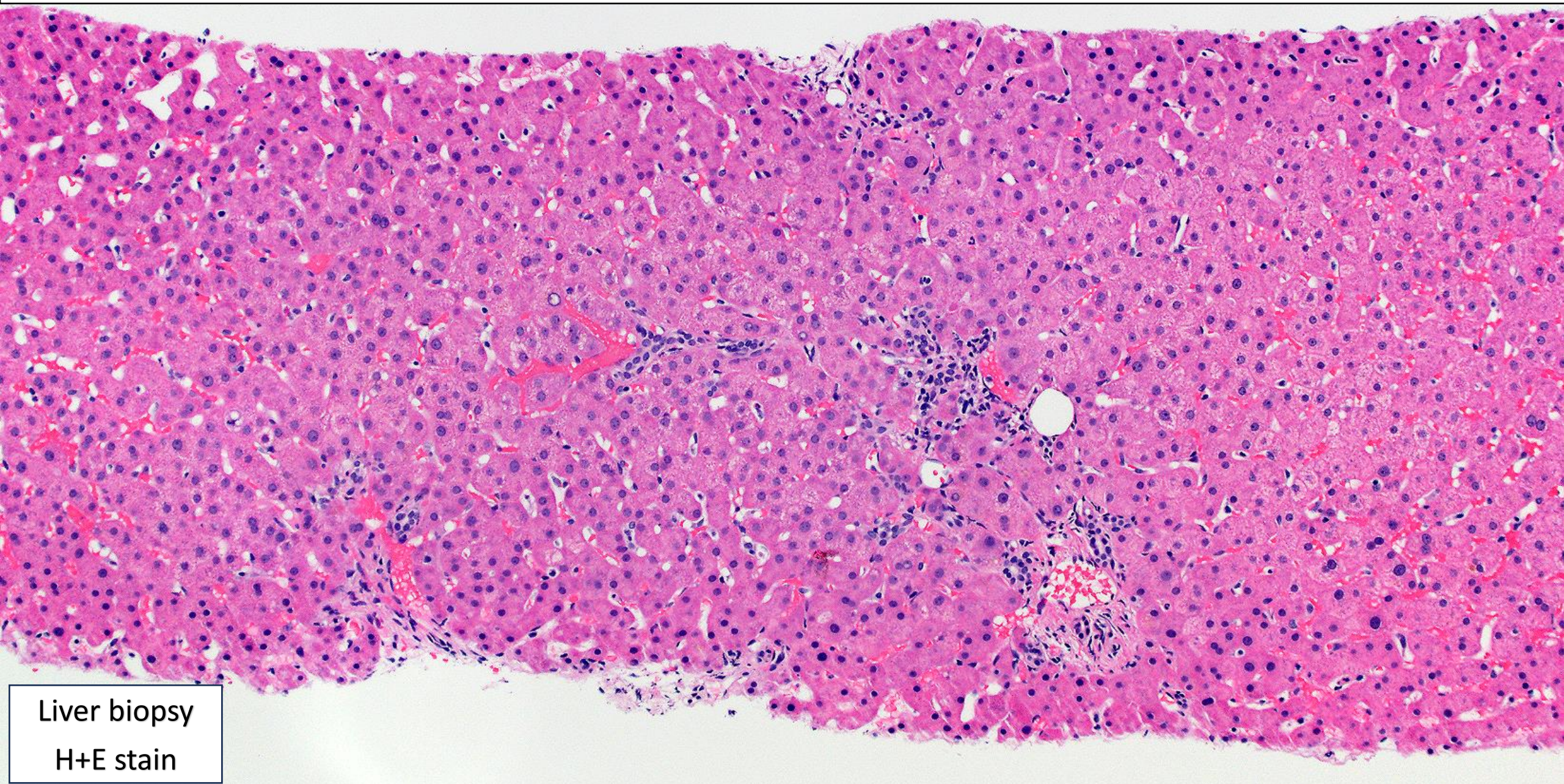
A Second Case of Hepatitis E Virus!

- 47-year-old male with obesity and type 2 diabetes **status post liver transplant** for cirrhosis due to steatohepatitis
- 3-months post transplant has elevated LFTs: **AST 92, ALT 240, ALK 150**
- Treated with prednisone for presumed acute cellular rejection
- After an initial response to treatment, ALT increased: **AST 69, ALT 311, ALK 107**



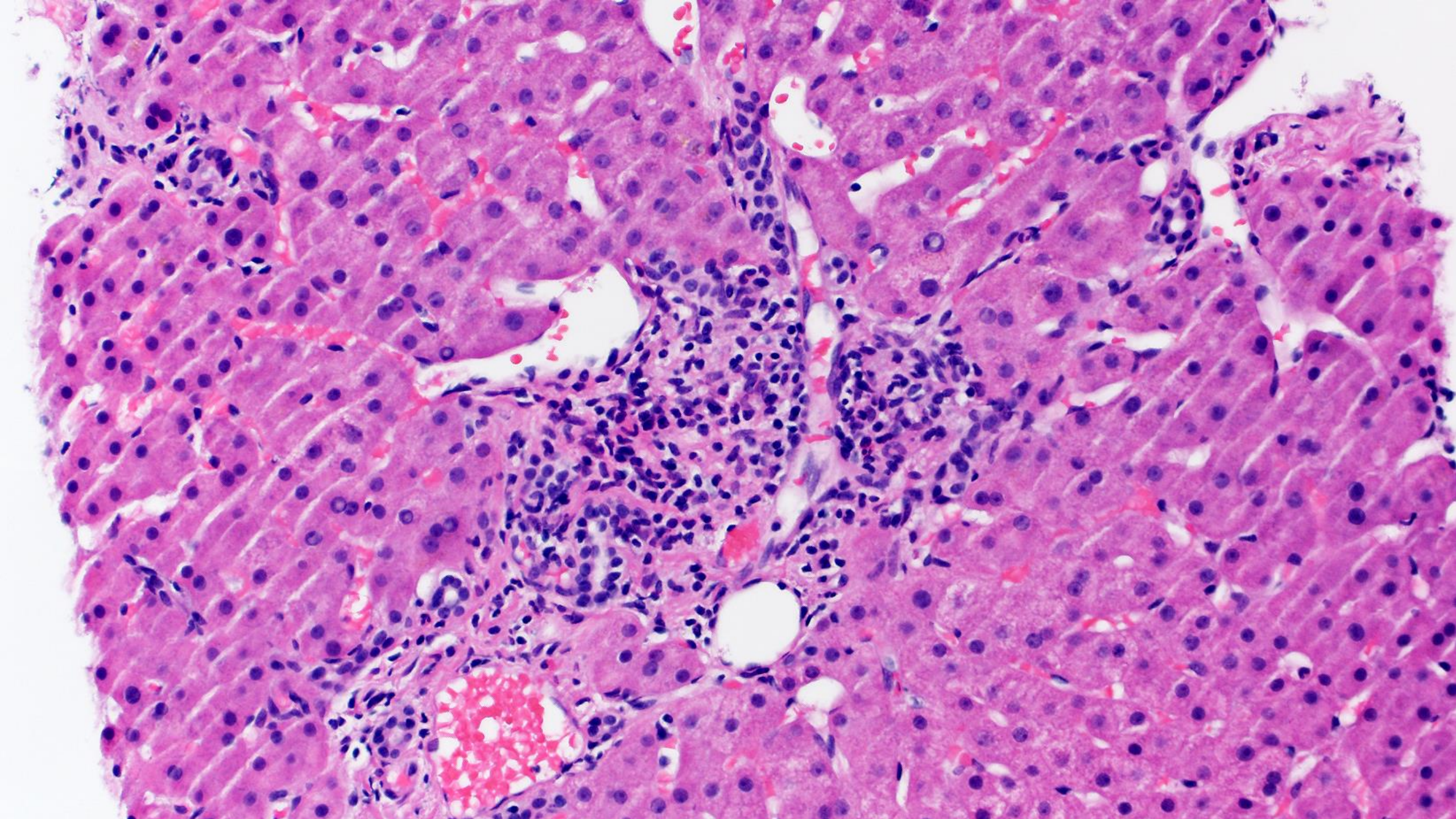
Enzymes continue to rise after this 2nd liver biopsy over 2 weeks

AST 186, ALT 559, ALK 174, total bili 1.8



Liver biopsy

H+E stain

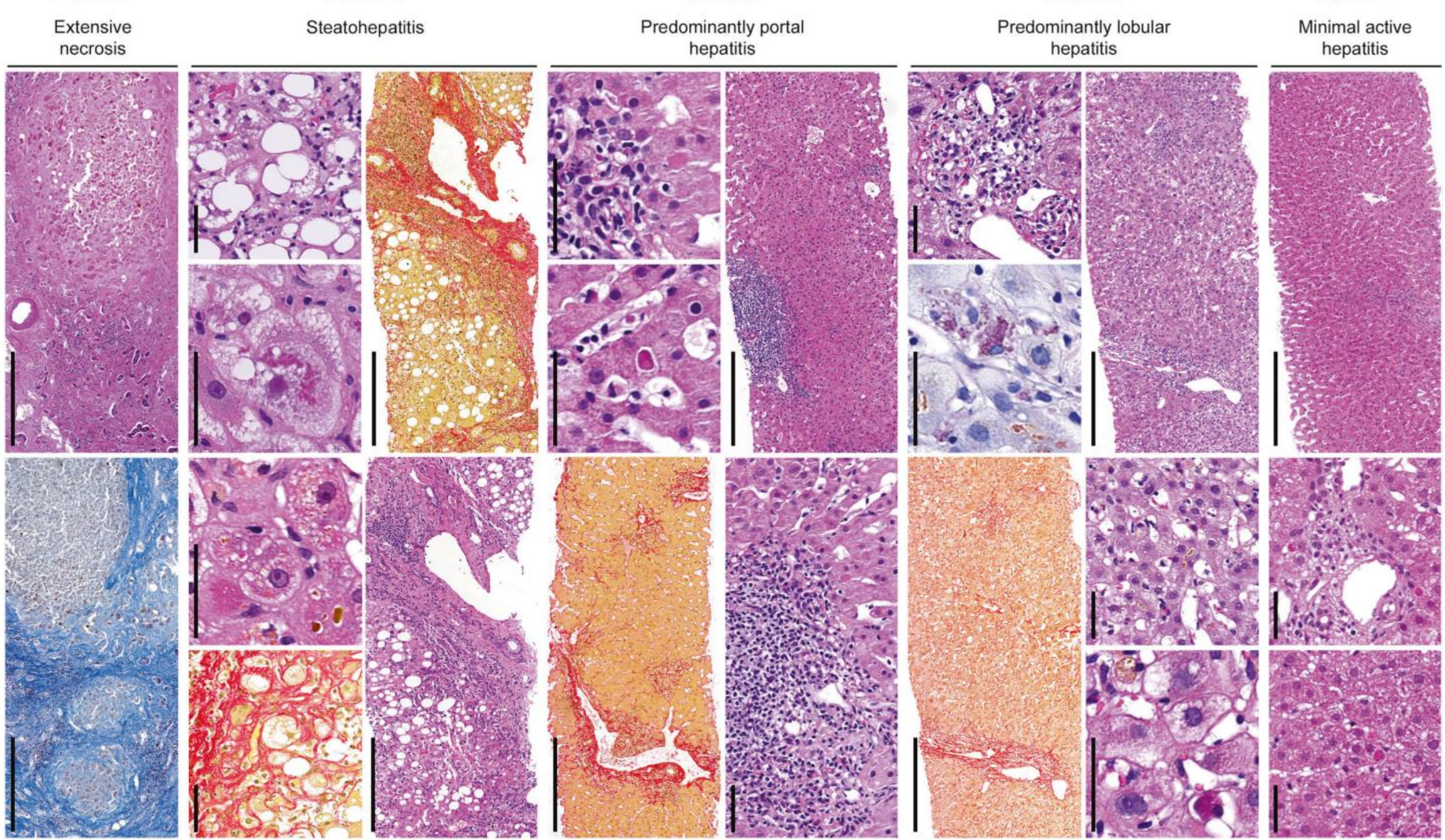


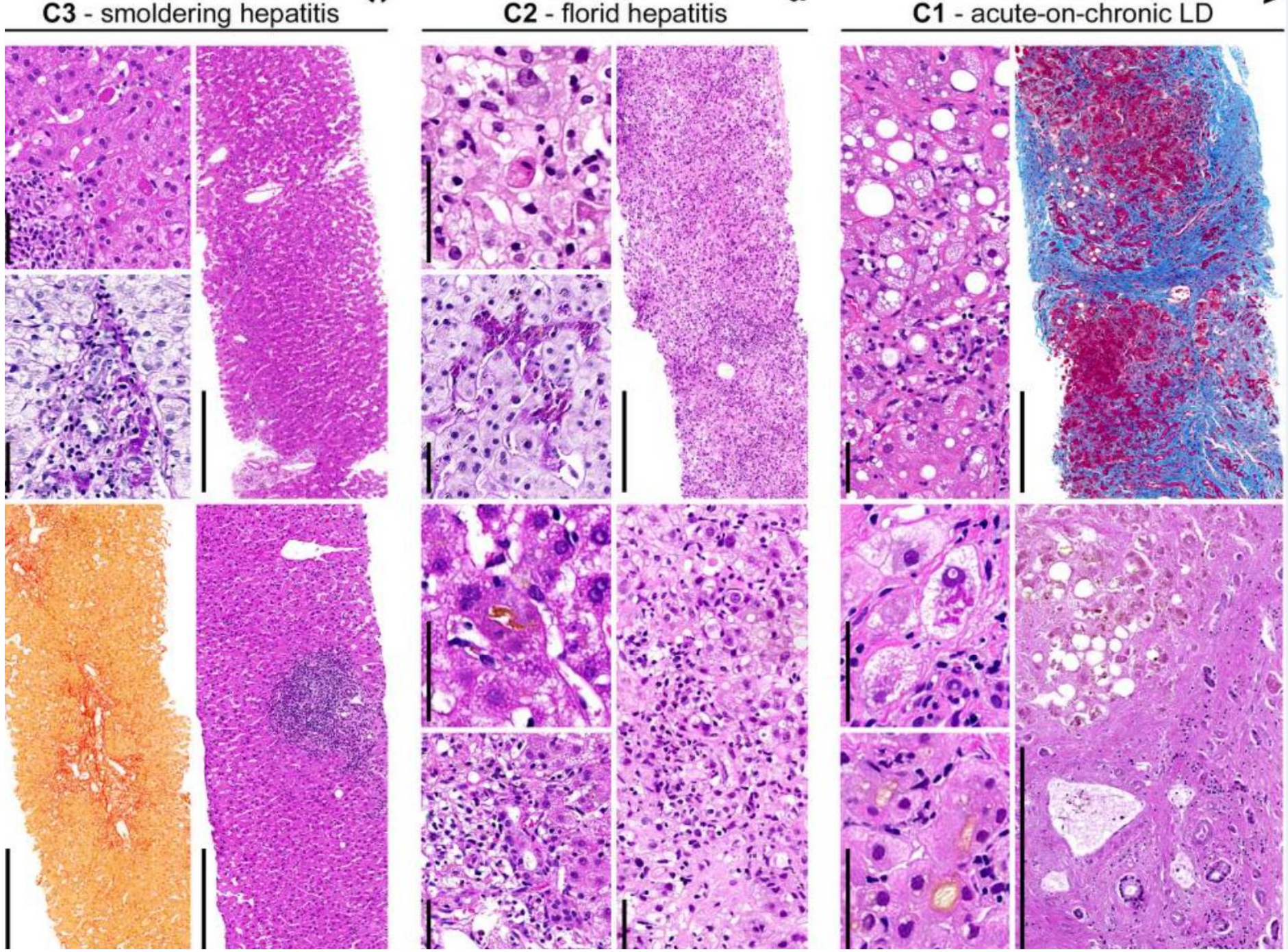
HEPATITIS E VIRUS BY QUANTITATIVE PCR

Status: **Final result** Visible to patient: **Yes (seen)** Dx: **Immunosuppression (HCC); Liver transp...**

Component Ref Range & Units	1 mo ago (12/16/24)	1 mo ago (12/2/24)	2 mo ago (10/28/24)	3 mo ago (10/14/24)	3 mo ago (9/27/24)
Hepatitis E Quant by PCR, Log IU/mL log IU/mL	**Not Quantified**	Not Quantified CM	3.7	4.8	6.7
Comment: Not Quantified - Hepatitis E Virus RNA was detected, but at a level below 3.3 log IU/mL (1,800 IU/mL). Virus detected at a level below 3.3 log IU/mL cannot be accurately quantified by this assay.					
Hepatitis E Quant by PCR, Interp Not Detected	Detected !	Detected ! CM	Detected ! CM	Detected ! CM	Detected ! CM
Comment: INTERPRETIVE INFORMATION: Hepatitis E Virus by Quantitative PCR The quantitative range of this assay is 3.3- 8.3 log IU/mL (1,800- 180,000,000 IU/mL). One IU/mL of HEV RNA is approximately 2.25 copies/mL.					

What accounts for the drastically different presentations of HEV?

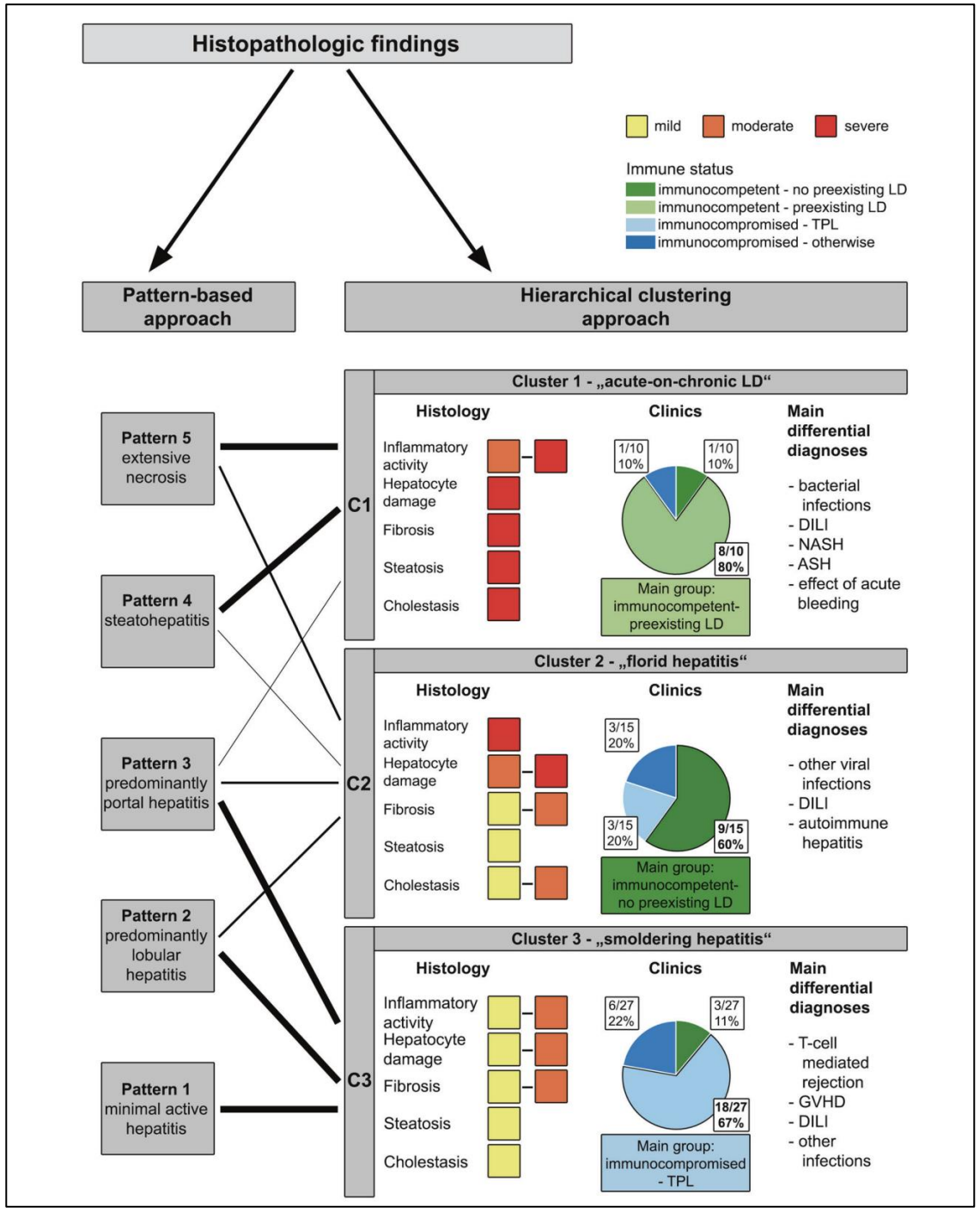

Extensive necrosis
Steatohepatitis
Predominantly portal hepatitis
Predominantly lobular hepatitis
Minimal active hepatitis



Lenggenhager D, et al. The histologic presentation of hepatitis E reflects patients' immune status and pre-existing liver condition. Mod Pathol. 2021 Jan;34(1):233-248

Heterogeneous Manifestations of HEV in Liver Biopsy

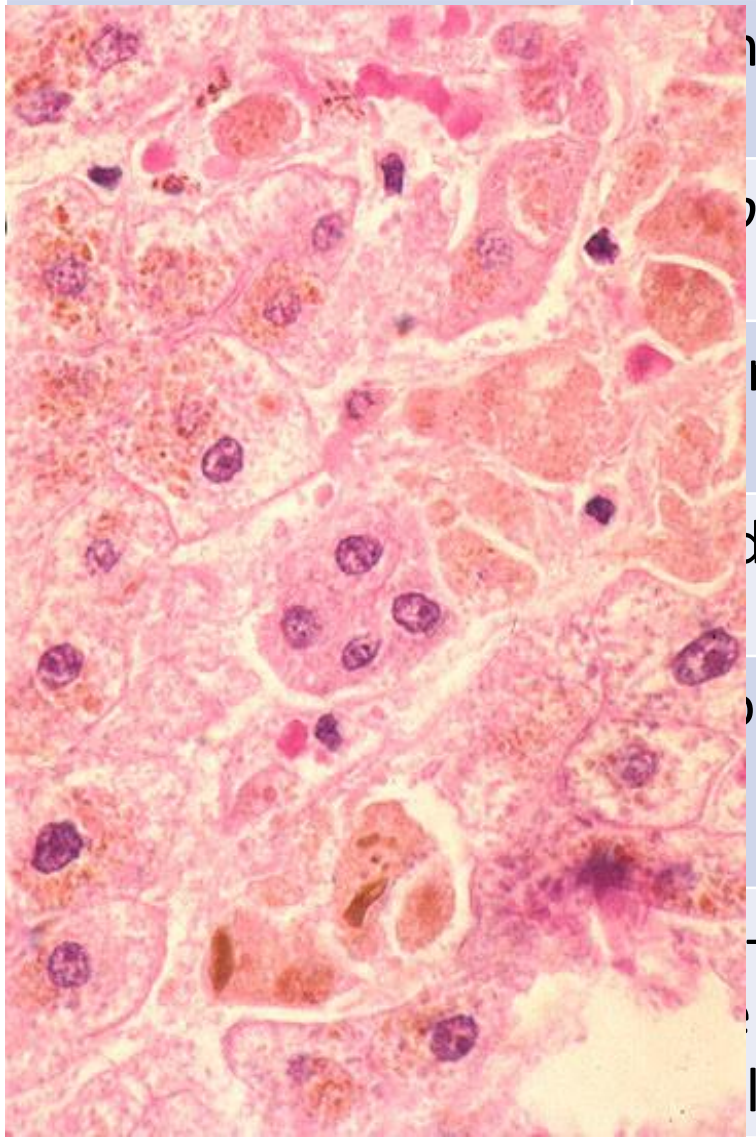
- Acute on chronic infection
  - Extensive necrosis and steatohepatitis
- Immunocompetent
  - Florid hepatitis
- Immunosuppressed
  - Minimal active hepatitis

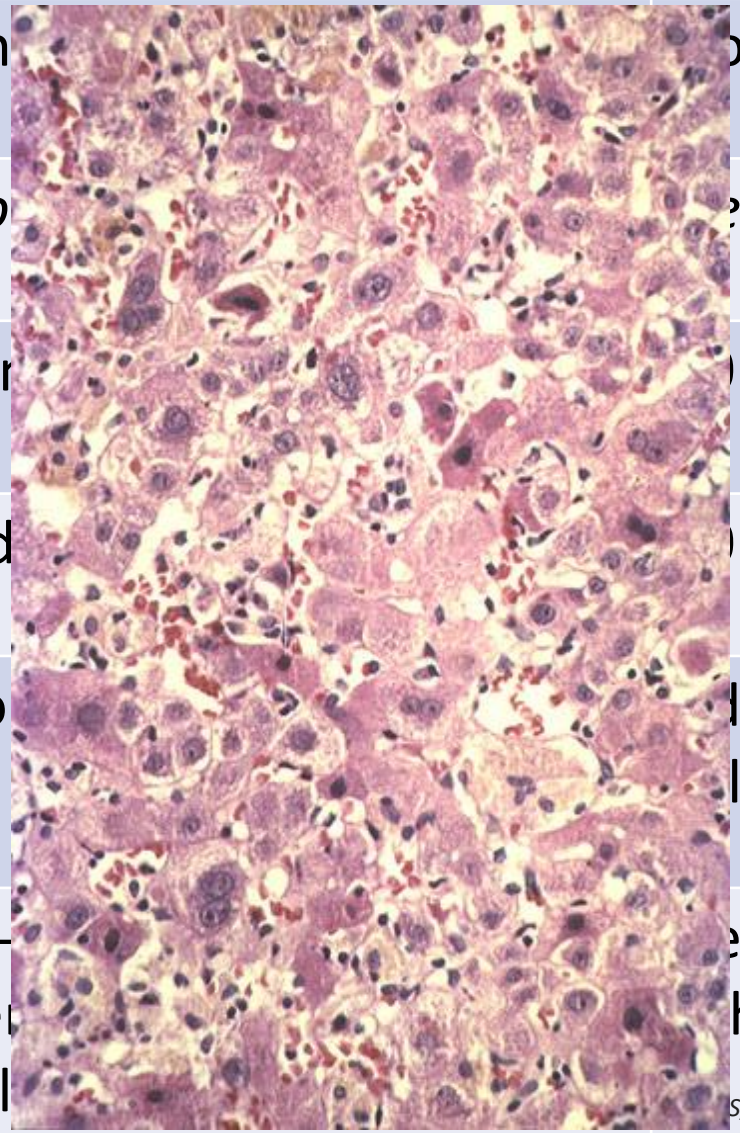


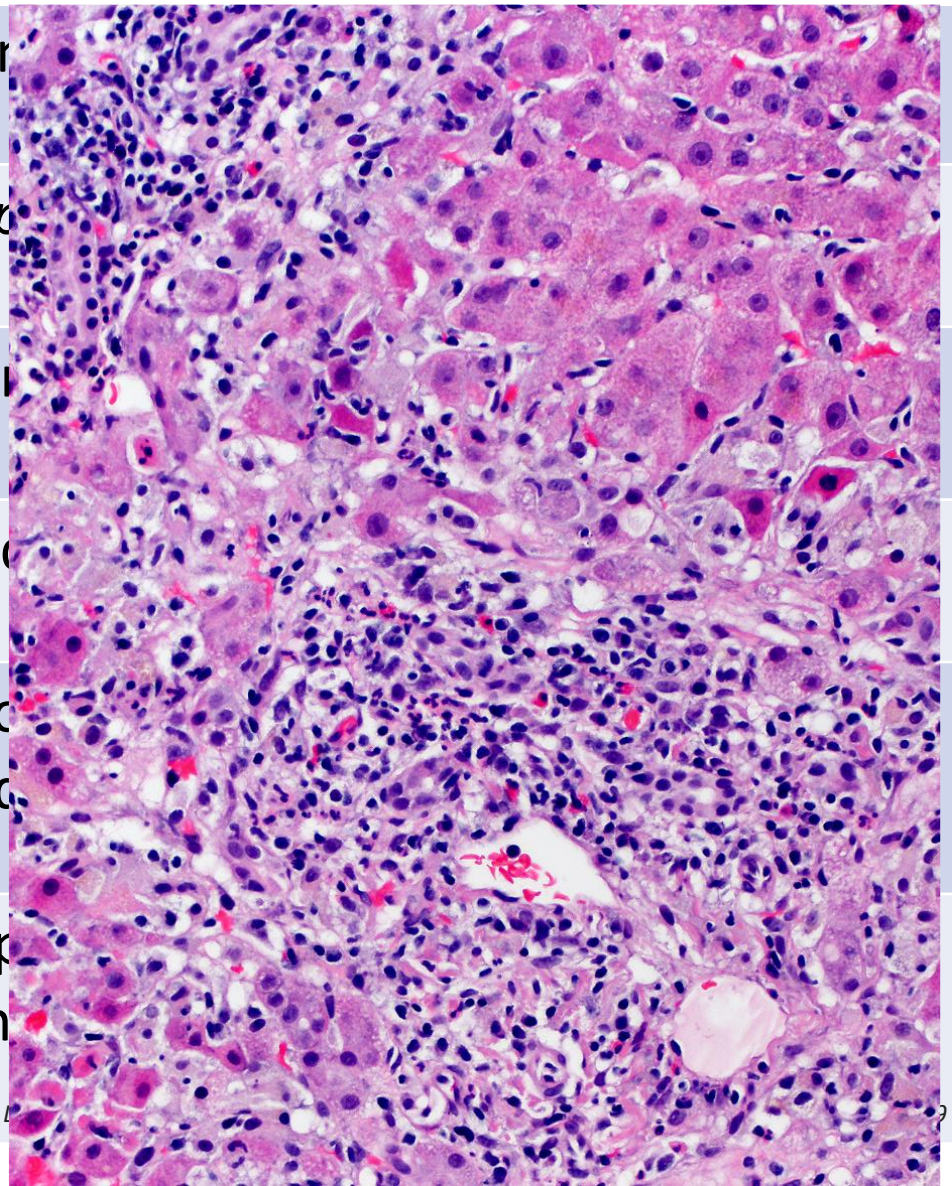
Lenggenhager D, et al. The histologic presentation of hepatitis E reflects patients' immune status and pre-existing liver condition. Mod Pathol. 2021 Jan;34(1):233-248

Comparing Viral Hepatitis A and Hepatitis E

	Hepatitis A virus	Hepatitis E virus







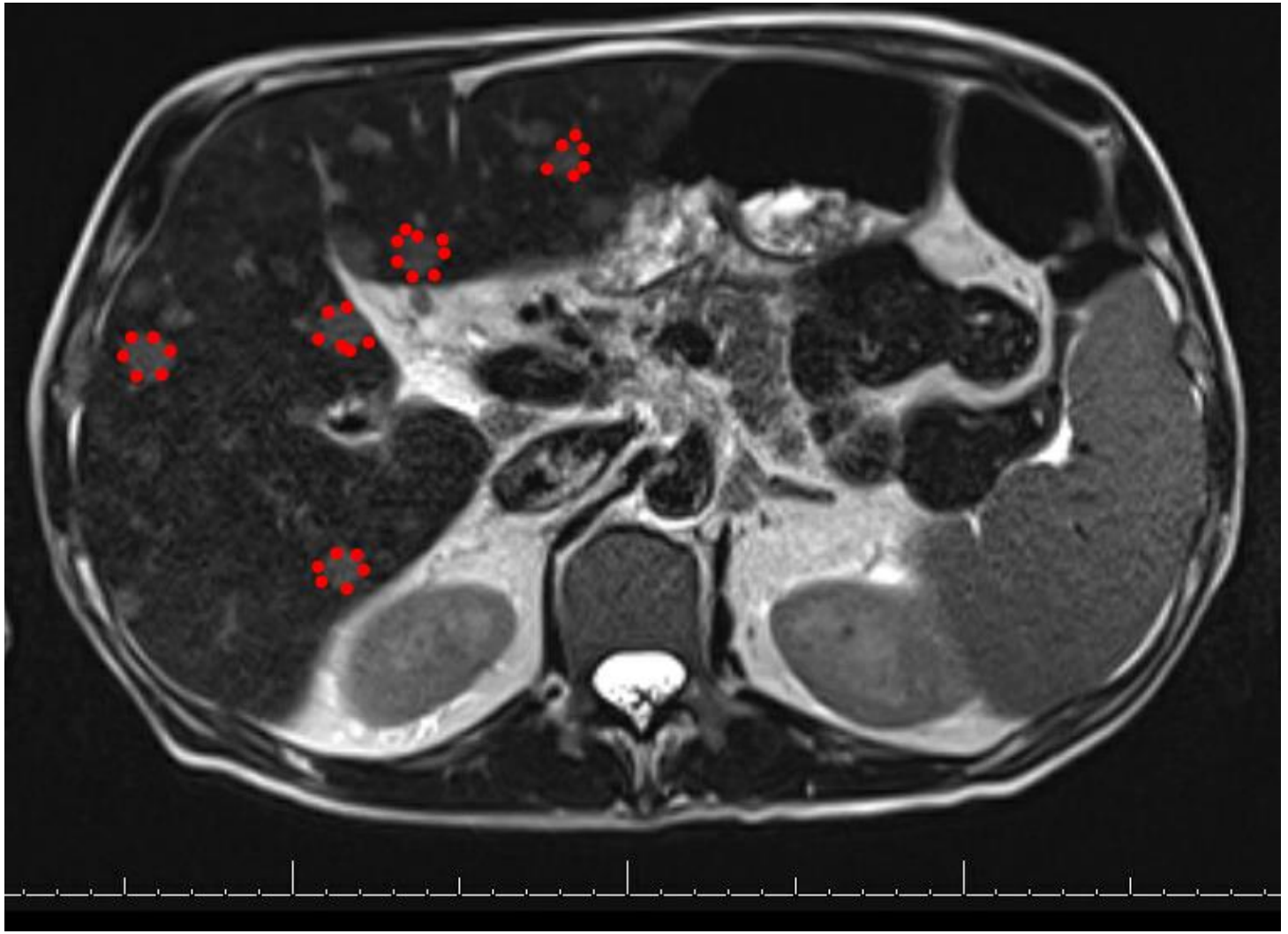
https://www.meddean.luc.edu/lumen/meded/orfpath/virhepa.htm

Case 1 Summary

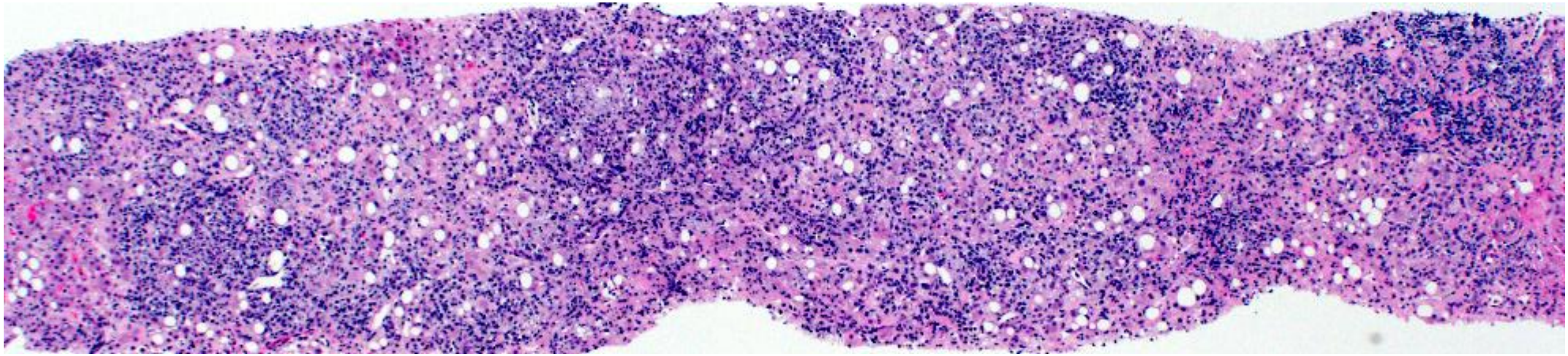
- The manifestations of HEV infection are heterogeneous and depend upon the **immune status** of the host
- HEV should be included in the differential diagnosis of active hepatitis in immunocompetent patients and mild portal & lobular hepatitis in immunosuppressed patients
- There is no widely available immunostain, so the infection could be included in the differential and HEV PCR testing recommended

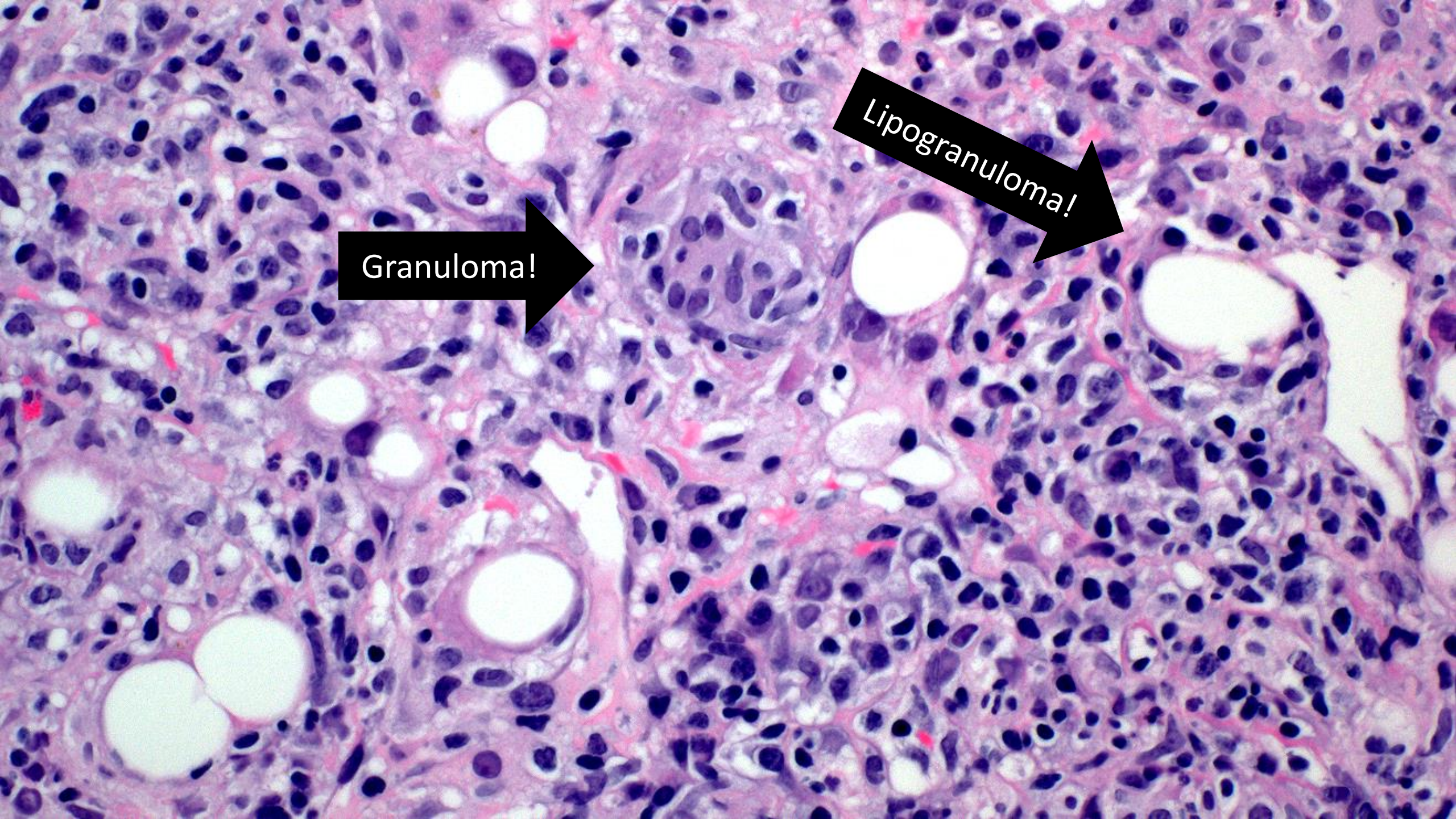
Case 2: A 60-year-old male with failure to thrive

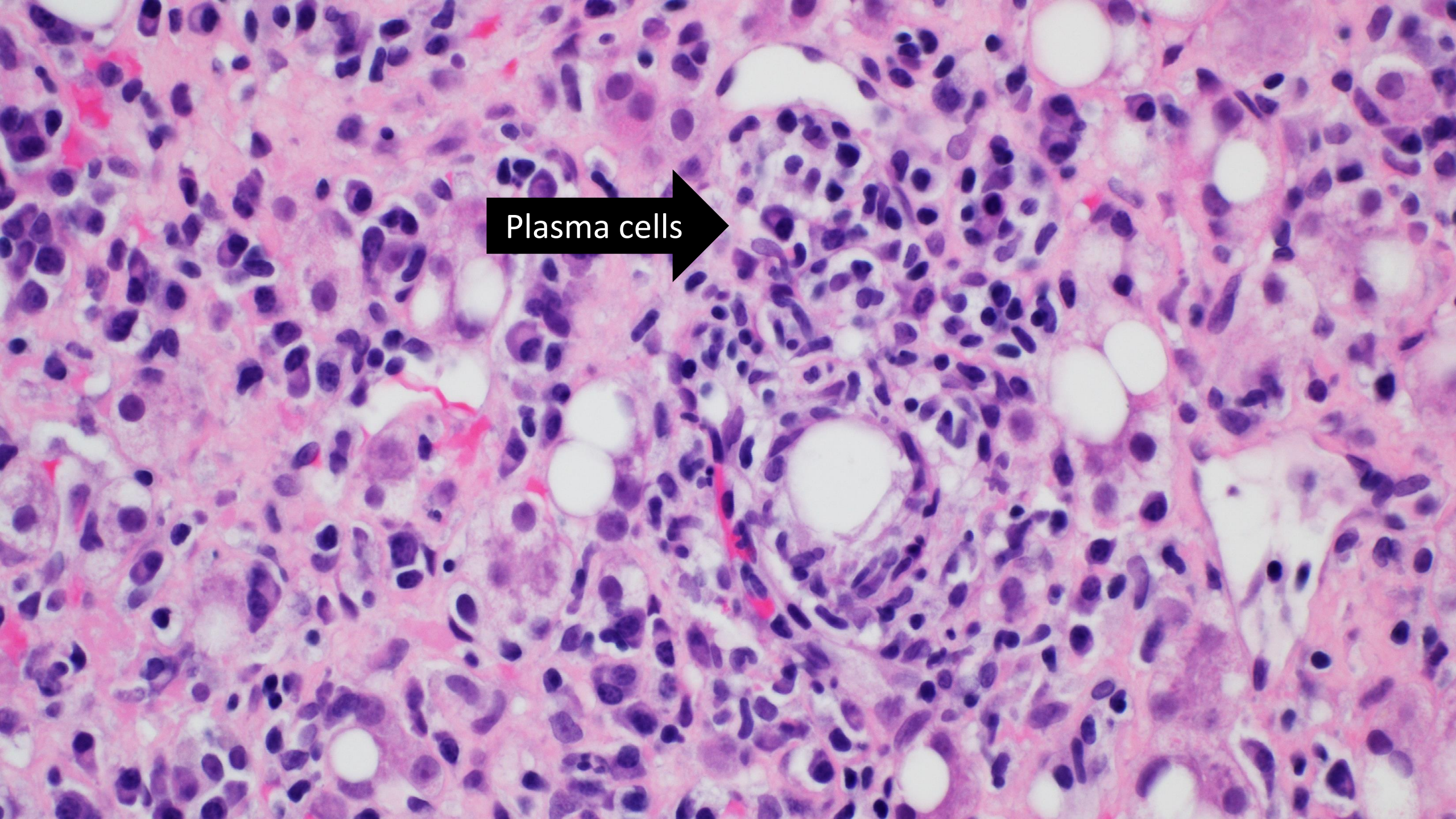
- 60 yo M undergoing workup for failure to thrive, & unintentional 45 lbs weight loss
- Liver Enzymes:
  - AST 37, ALT 36, **ALK 338**
- MRI shows innumerable, scattered, arterially enhancing liver lesions – concerning for metastatic disease
- 3 cm liver lesion targeted for tissue biopsy

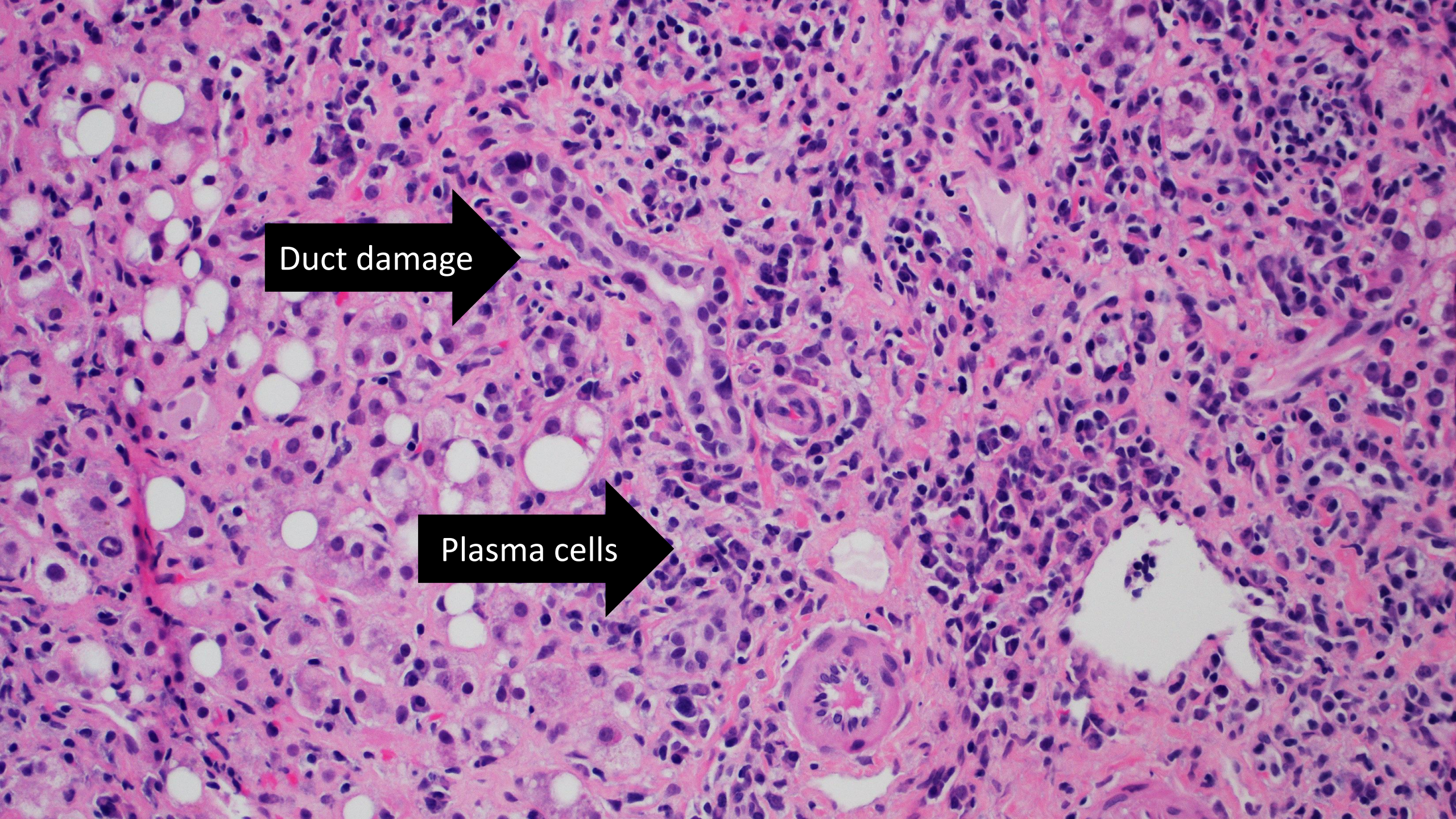


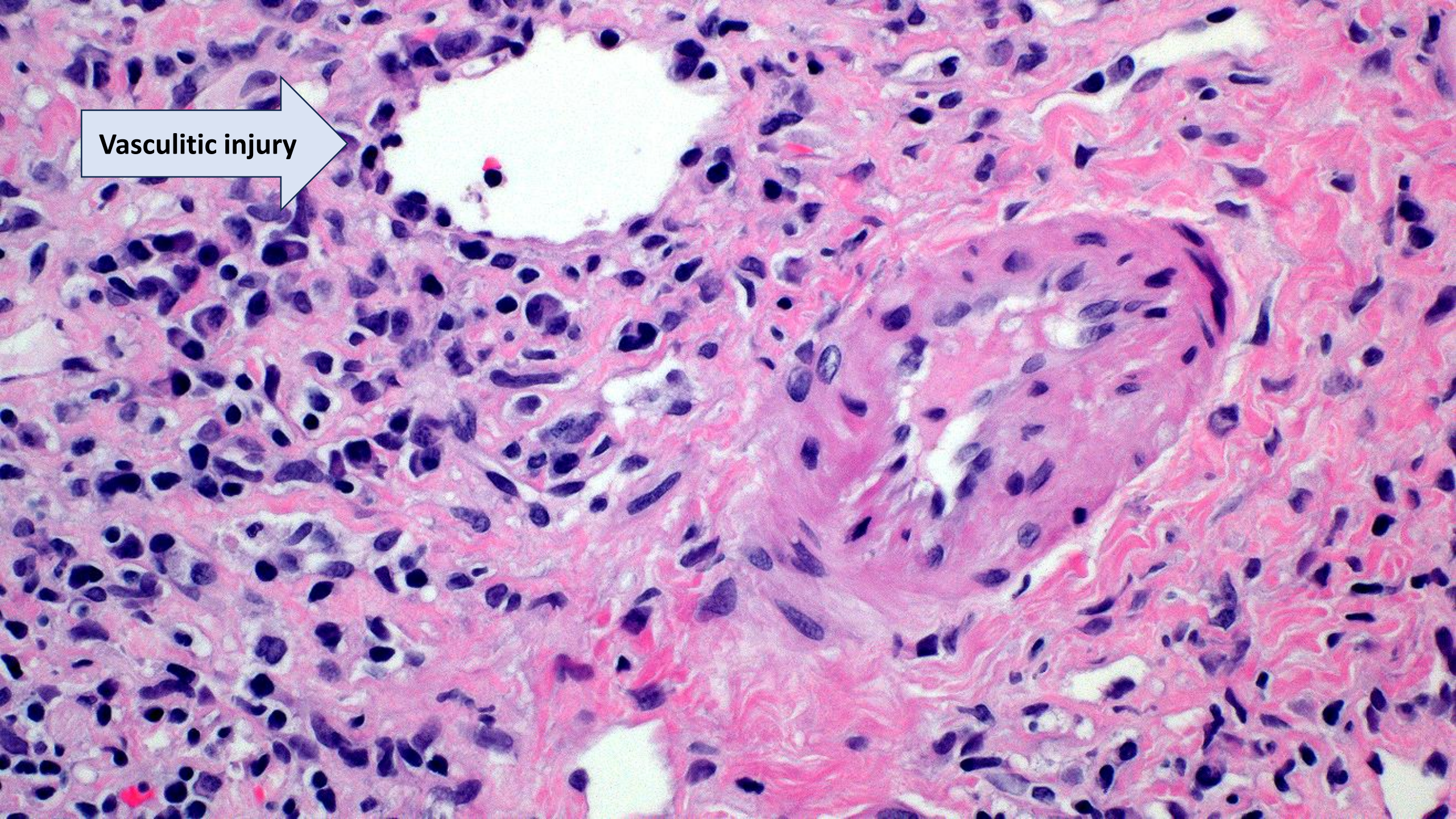
Liver H+E stain
0.7 cm core

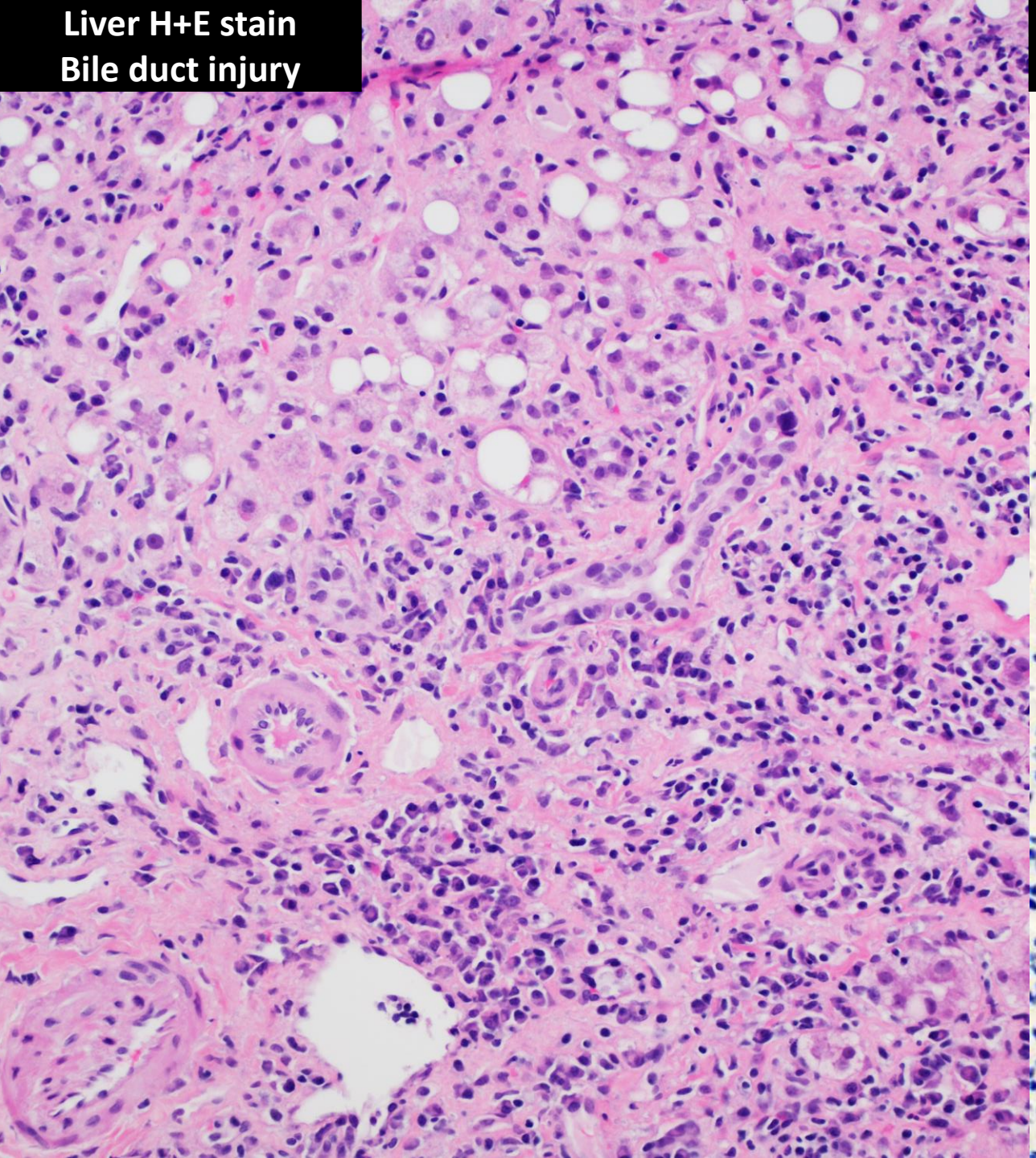


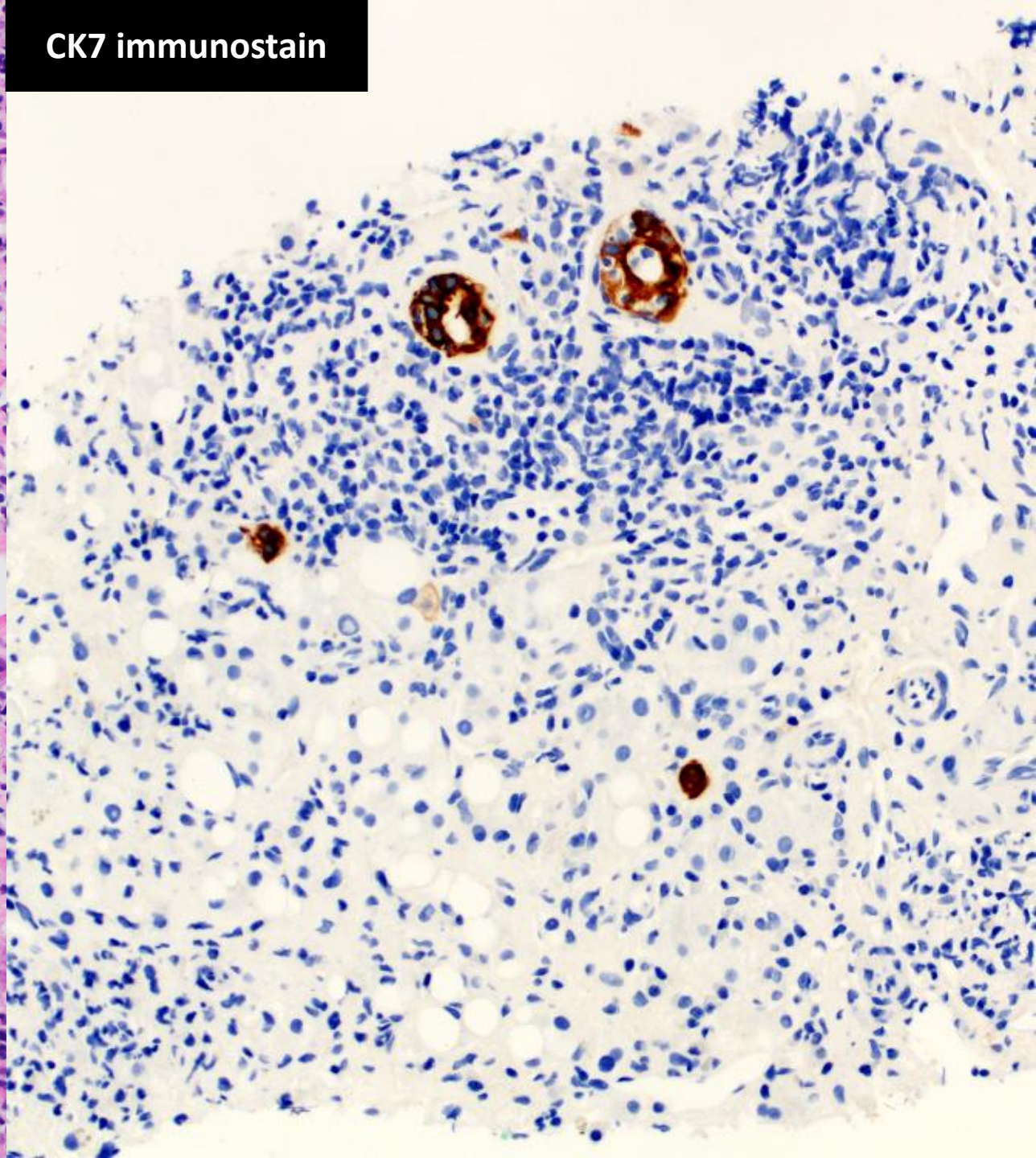

Granuloma!
Lipogranuloma!


Plasma cells


Duct damage
Plasma cells


Vasculitic injury

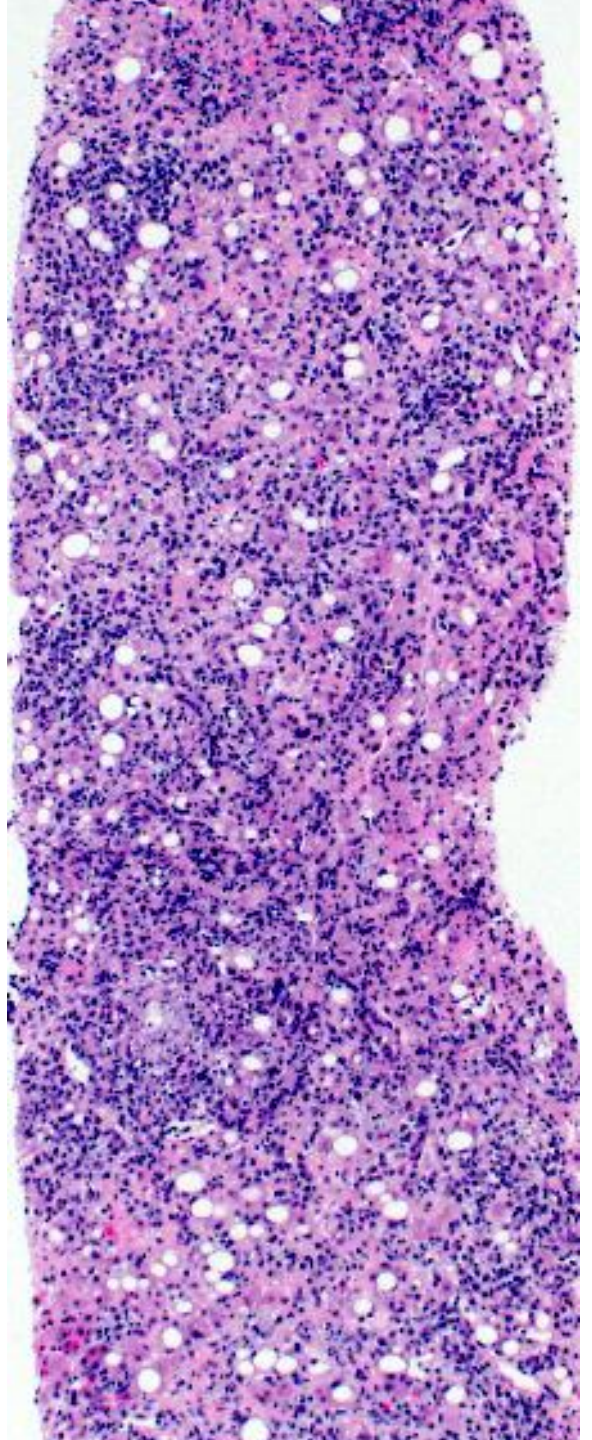

Liver H+E stain
Bile duct injury


CK7 immunostain

Summarize the Morphologic changes

- Active hepatitis
- Lobular disarray
- Granulomatous inflammation
  - Lymphocytes, plasma cells, histiocytes
  - Non necrotizing lipogranulomas
- Vasculitic injury
- Bile duct injury

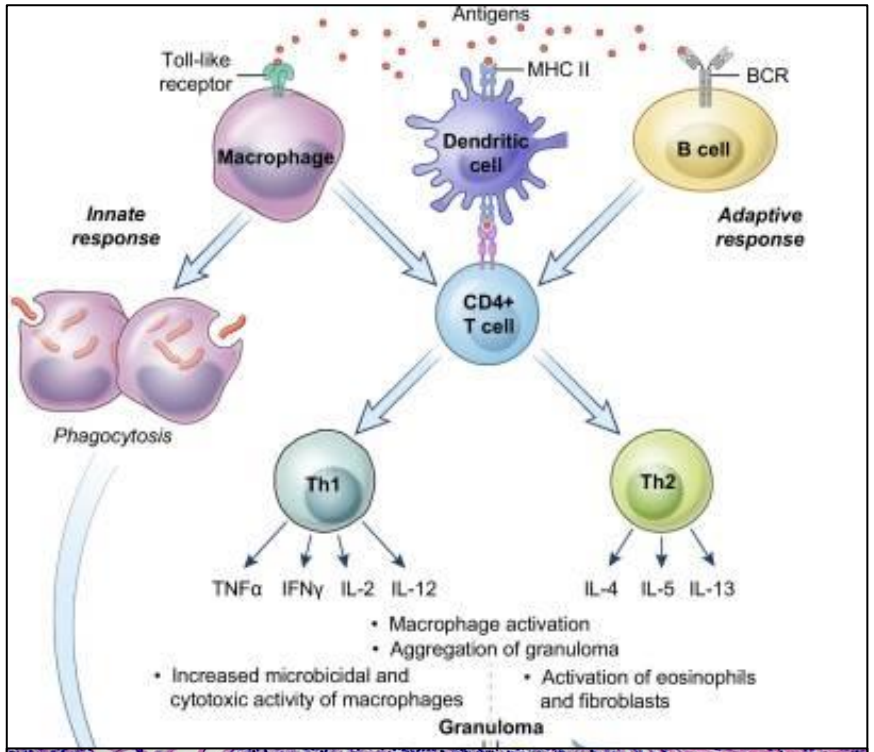
- Etiology?
  - Bacteria
  - Viral
  - Fungal

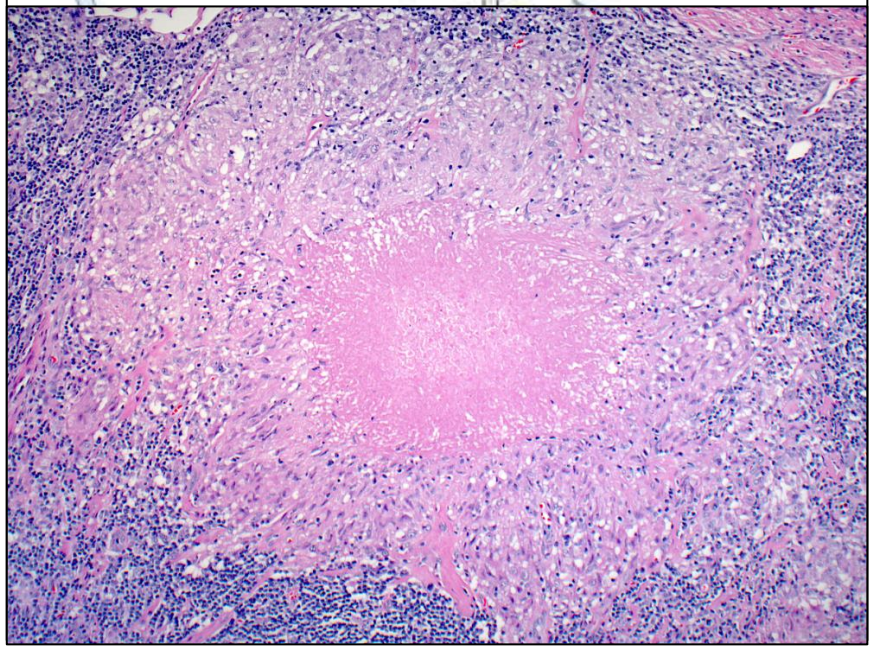


Granulomatous hepatitis

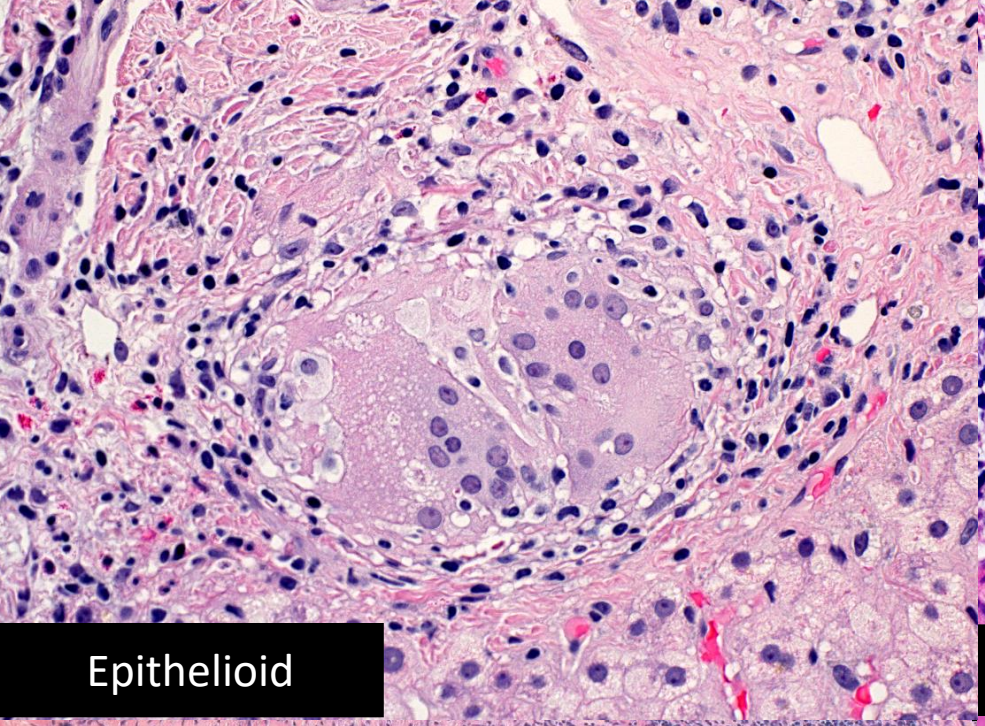
Granulomatous Hepatitis

- Liver has largest proportion of resident tissue macrophages (Kupffer cells) & hepatic sinusoidal endothelial cells
  - **Reticuloendothelial system**
- Granulomas in 1-15% of liver biopsies performed for increasing LFTs or eval for systemic disease
- Broad differential diagnosis: drug, infection, autoimmune, foreign body, idiopathic
- **Etiologies**
  - Western world: idiopathic, sarcoid, primary biliary cholangitis (non-infectious)
  - Middle East and Asia: Infections, particularly tuberculosis
- Type & Location: Where are the granulomas and how are they characterized?

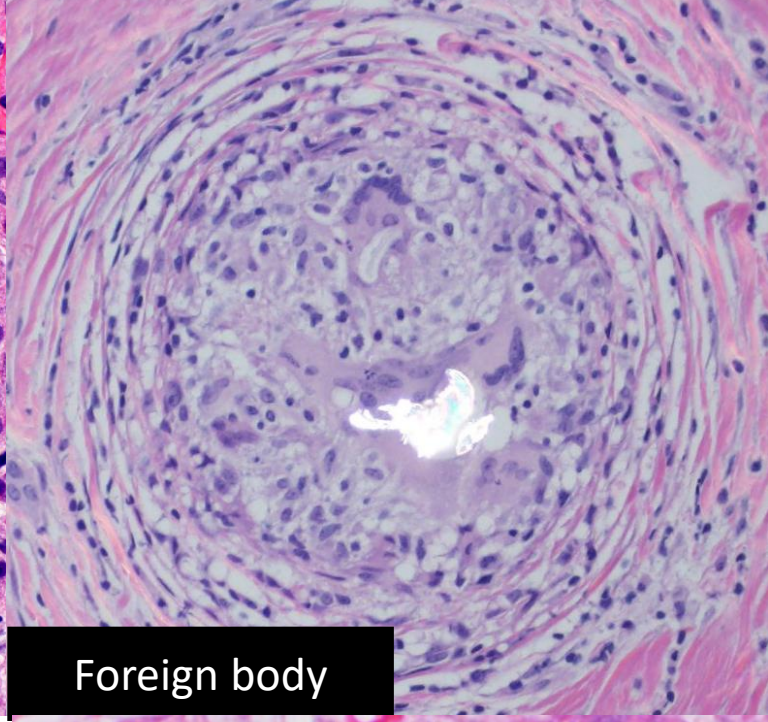


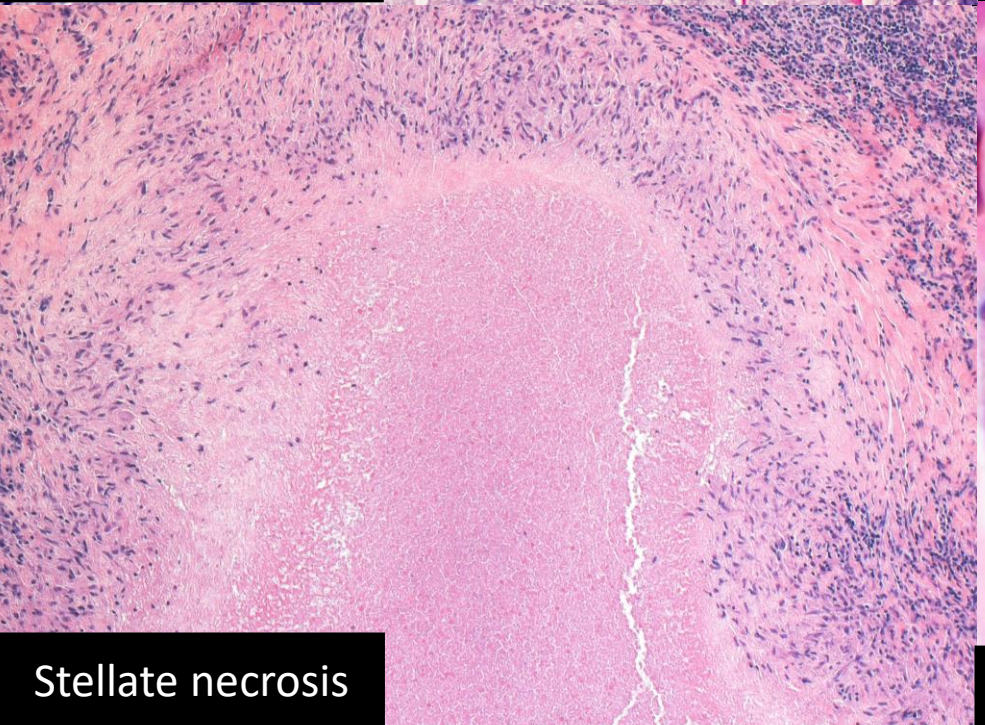


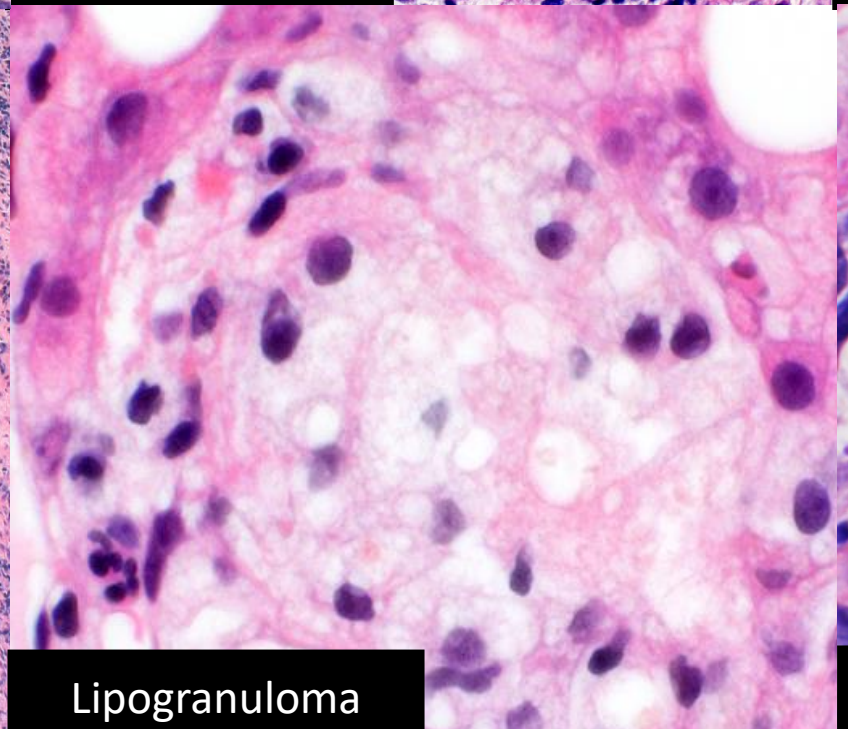
Mironova M, et al. Granulomatous liver diseases. Hepatol Commun. 2024 Mar 18;8(4):e0392.
Sartin JS, Walker RC. Granulomatous hepatitis: a retrospective review of 88 cases at the Mayo Clinic. Mayo Clin Proc. 1991 Sep;66(9):914-8.

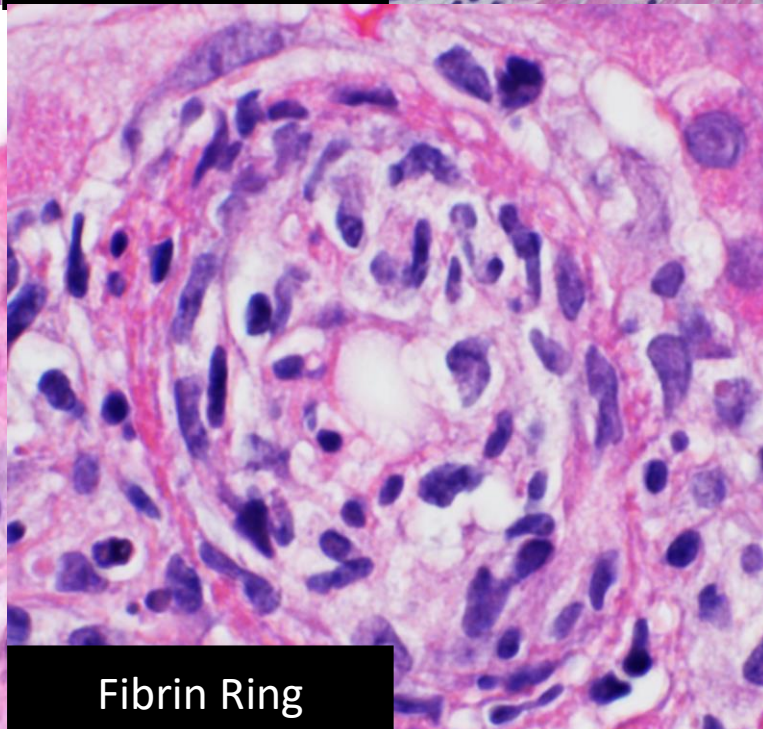

Epithelioid


Duct centric


Foreign body

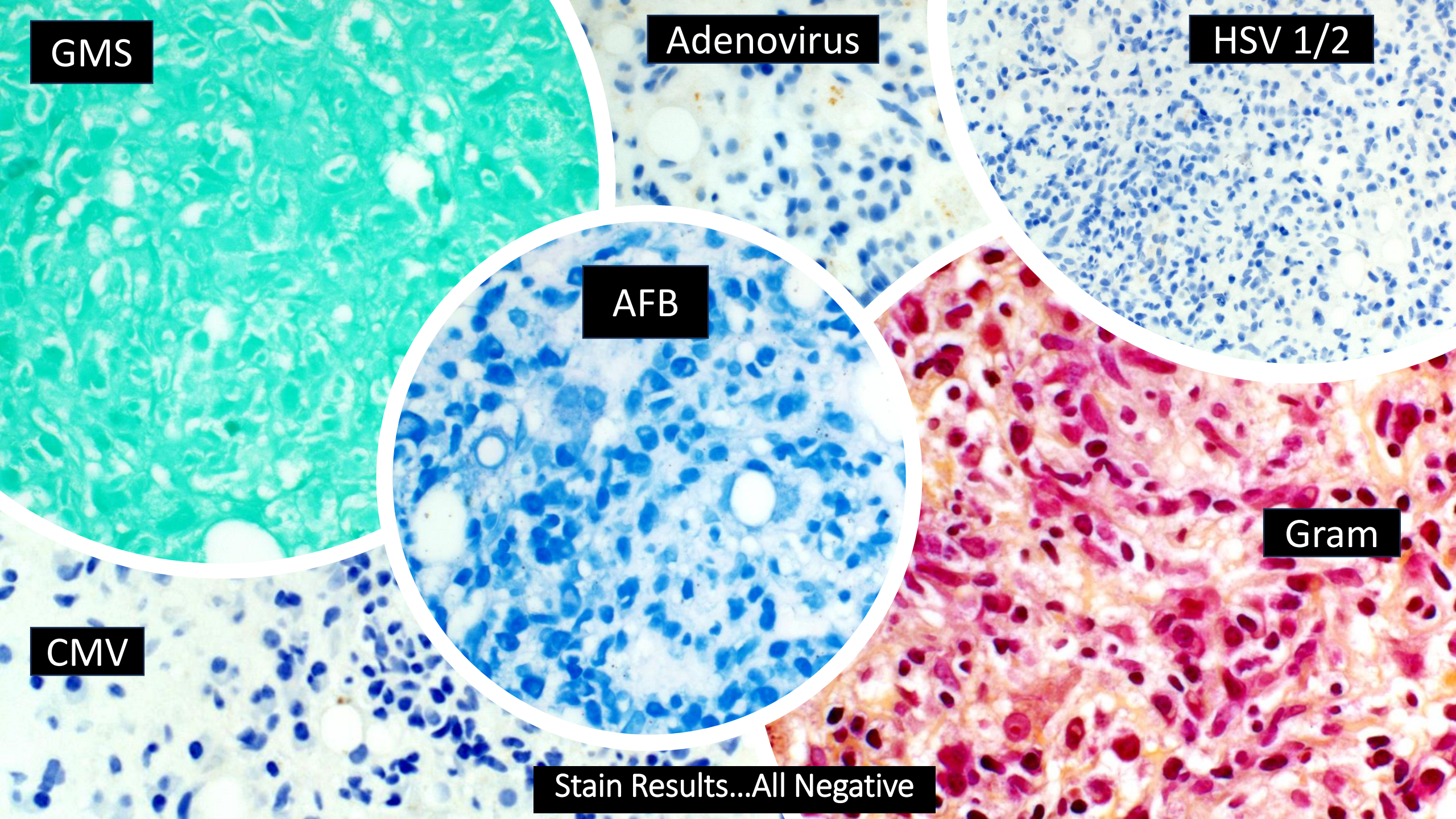

Stellate necrosis


Lipogranuloma

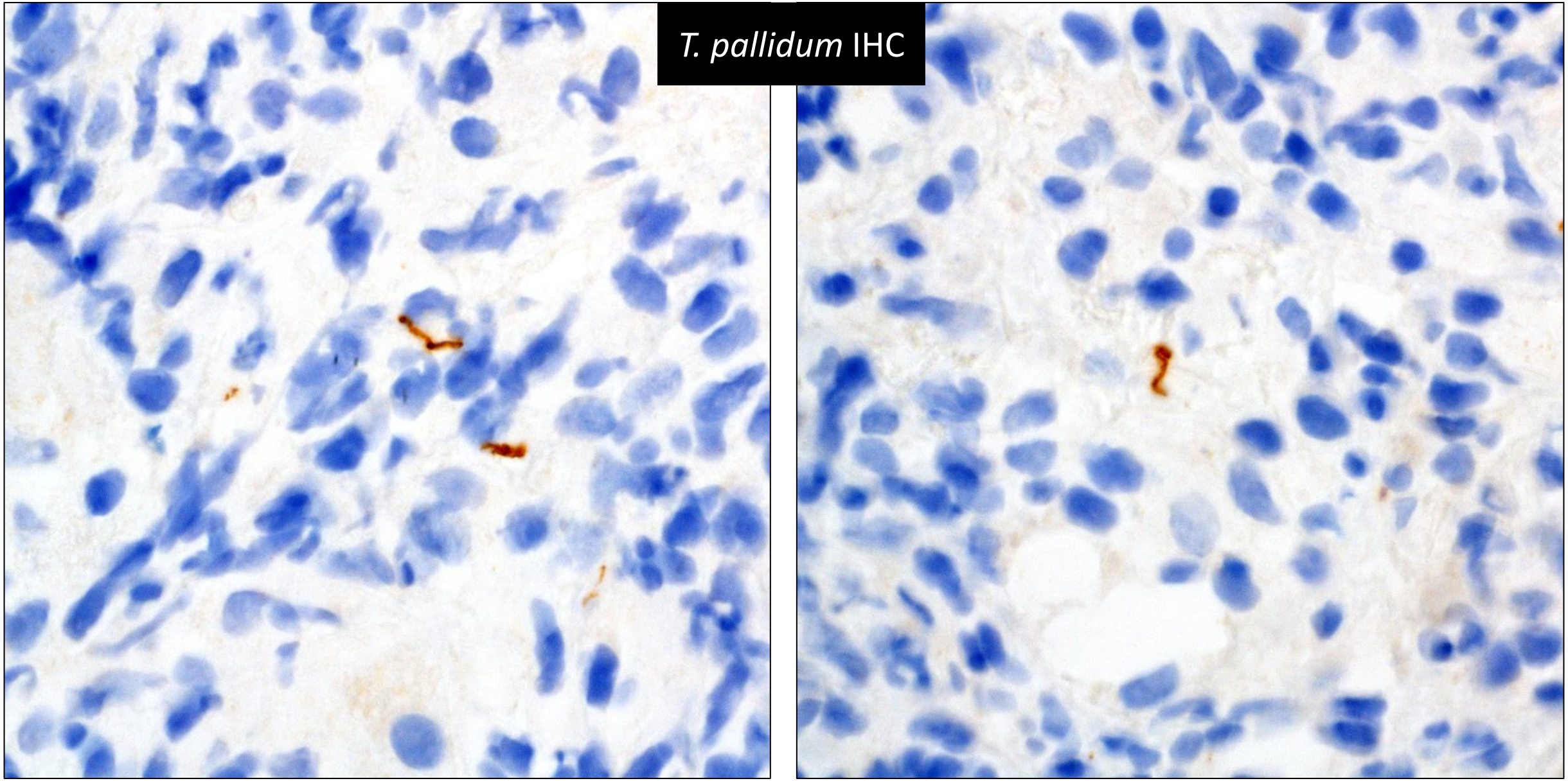

Fibrin Ring

What stains do you want to order for the granulomatous inflammation in the liver?

A. AFB
B. Fungal stain (GMS or PAS)
C. AFB and fungal stain (GMS or PAS)
D. AFB, fungal and others


GMS
Adenovirus
HSV 1/2
AFB
Gram
CMV
Stain Results…All Negative

Any other ideas?


T. pallidum IHC

Patient's history of syphilis infections

2012

- HIV diagnosed
- Incidental: Syphilis RPR 1:32, treated IM

	2018	2019	2020	2021	2022
RPR	Reactive	Reactive	Non-reactive	No data	**Reactive**
Titer	1:2	1:2	-	-	**1:2048**
Sx	Diffuse maculopapular rash	-	-	-	**Failure to thrive**

What does the liver involvement signify in this case?

A. Primary syphilis
B. Secondary syphilis
C. Tertiary syphilis (“gumma”)
D. Unusual manifestation of secondary syphilis

Stages & Manifestations of Syphilis

- **Primary**
  - Painless chancre at site of contact
  - 3-6 weeks, resolves
- **Secondary**
  - Dissemination, including to liver – ****High Alk Phos is typical****
  - Maculopapular rash
  - Mucosal ulcers
  - ****Lues Maligna****
- **Latent**
  - No visible signs or symptoms
- **Tertiary**
  - Heart, blood vessels, brain
  - 10-30 years post-infection

Pareek, S.S. Liver involvement in secondary syphilis. Digest Dis Sci **24**, *41–43 (1979). https://doi.org/10.1007/BF01297236*

https://phil.cdc.gov/Details.aspx?pid=14966

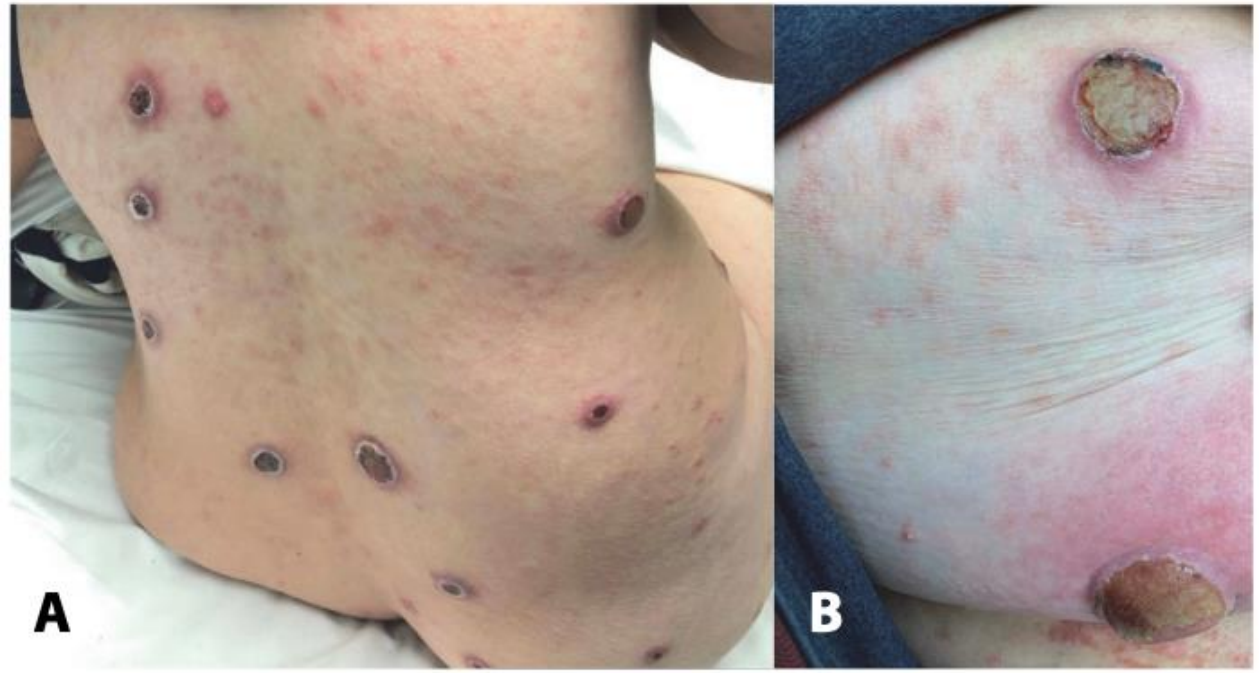
Lues Maligna: Extremely rare form of secondary syphilis

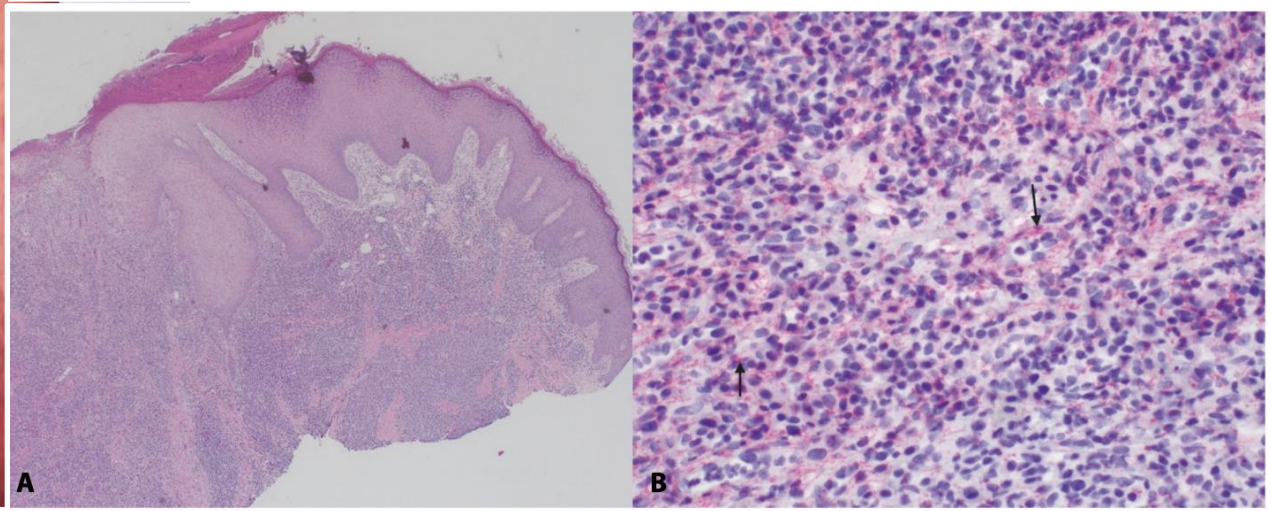
- Originally described as *tertiary* syphilis in 1859, but later reclassified as *secondary* syphilis
- 'Malignant' form of secondary syphilis associated with ulceronodular skin lesions
- Small series and case reports
- May be associated with immunosuppression
  - Chronic alcohol use
  - HIV/AIDs
- Can involve the mucosa, lymph node, liver and spleen
- Pathologic features of skin lesions
  - Epidermal ulceration
  - Plasma cell-rich inflammation
  - Perivascular inflammation
  - Obliteration of small venules
- Rapidly responds to penicillin

Don PC, Rubinstein R, Christie S. Malignant syphilis (lues maligna) and concurrent infection with HIV. Int J Dermatol. 1995 Jun;34(6):403-7.

Tucker JD, Shah S, Jarell AD, Tsai KY, Zembowicz A, Kroshinsky D. Lues maligna in early HIV infection case report and review of the literature. Sex Transm Dis. 2009 Aug;36(8):512-4.

Dermatologic Manifestation of Lues Maligna



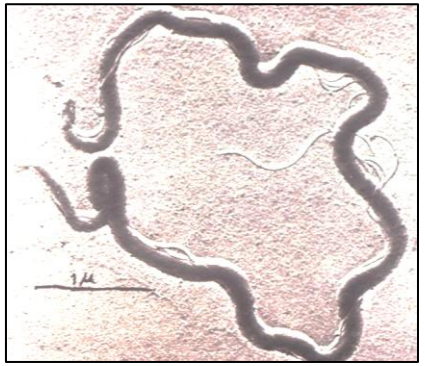


Bayramgürler D, Bilen N, Yildiz K, Sikar A, Yavuz M. Lues maligna in a chronic alcoholic patient. J Dermatol. 2005 Mar;32(3):217-9.

Nguyen CN, Shaw FM, Li MM, Blalock TW. A rare case of lues maligna in an HIV-negative woman. Dermatol Online J. 2022 Oct 15;28(5).

Dermatologic findings in our Case

Syphilitic Hepatitis - “luetic jaundice”



~150 published cases in adults

- Largest systematic review (2018) 144 cases
- 1951 - Earliest published case

Epidemiology

- 40 years old (mean age)
- 90% Male
- 61% Concurrent HIV infection

Clinical features

- 78% Rashes –maculopapular, soles, palms
- 57% Fatigue or poor appetite
- 35% Icterus
- 26% Fever

Laboratory data (mean values)

- ALT 314 AST 684
- **ALK 684** **GGT 561**

Exam

- 54% Hepatomegaly
- 31% Lymphadenopathy
- 14% Splenomegaly

Histopathologic features

- 35% (55/144) Patients had liver biopsy done
- 87% Portal and lobular inflammation
- 49% Cholestasis
- **20% Granuloma**

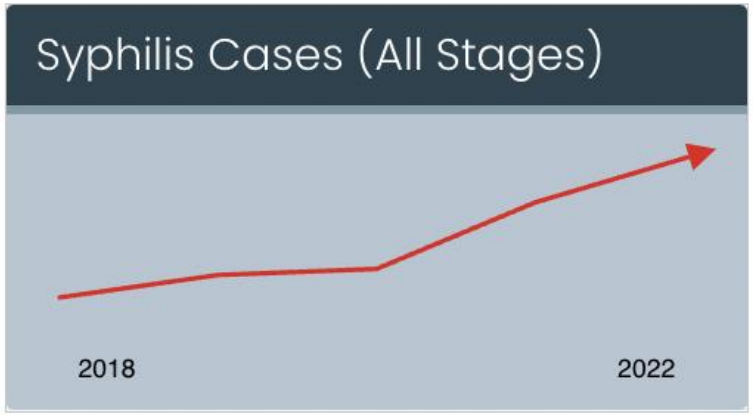
Ancillary stains

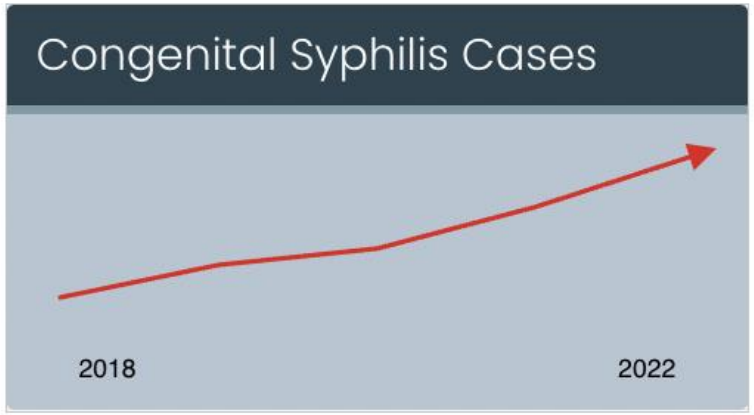
- Spirochetes identified in 19/28 (68%) of cases that were stained
- 15 by *T. pallidum* immunostain
- 4 by Warthin Starry

Huang J, Lin S, Wan B, Zhu Y. A Systematic Literature Review of Syphilitic Hepatitis in Adults. J Clin Transl Hepatol. 2018 Sep 28;6(3):306-309

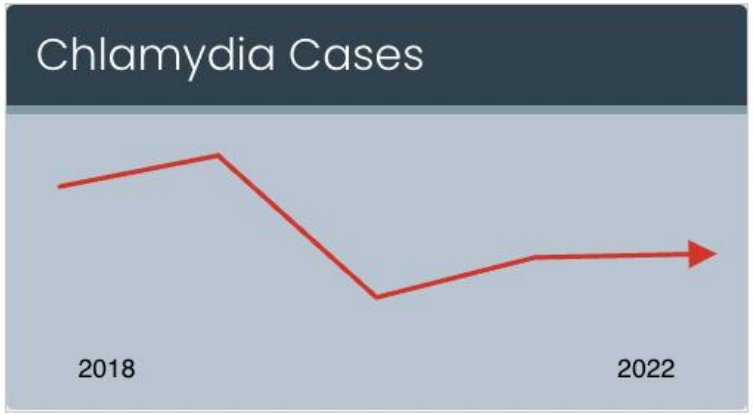
Syphilis is *still* on the Rise!

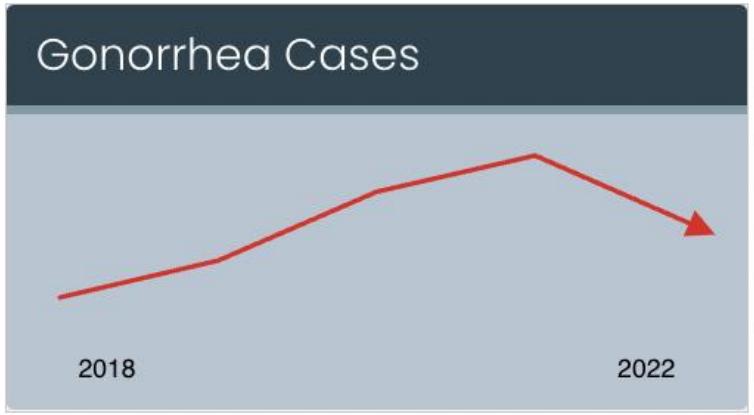
Since 2018 syphilis cases have increased 80%





Over 207,000 cases of syphilis reported in 2022
- Highest number reported since 1950.

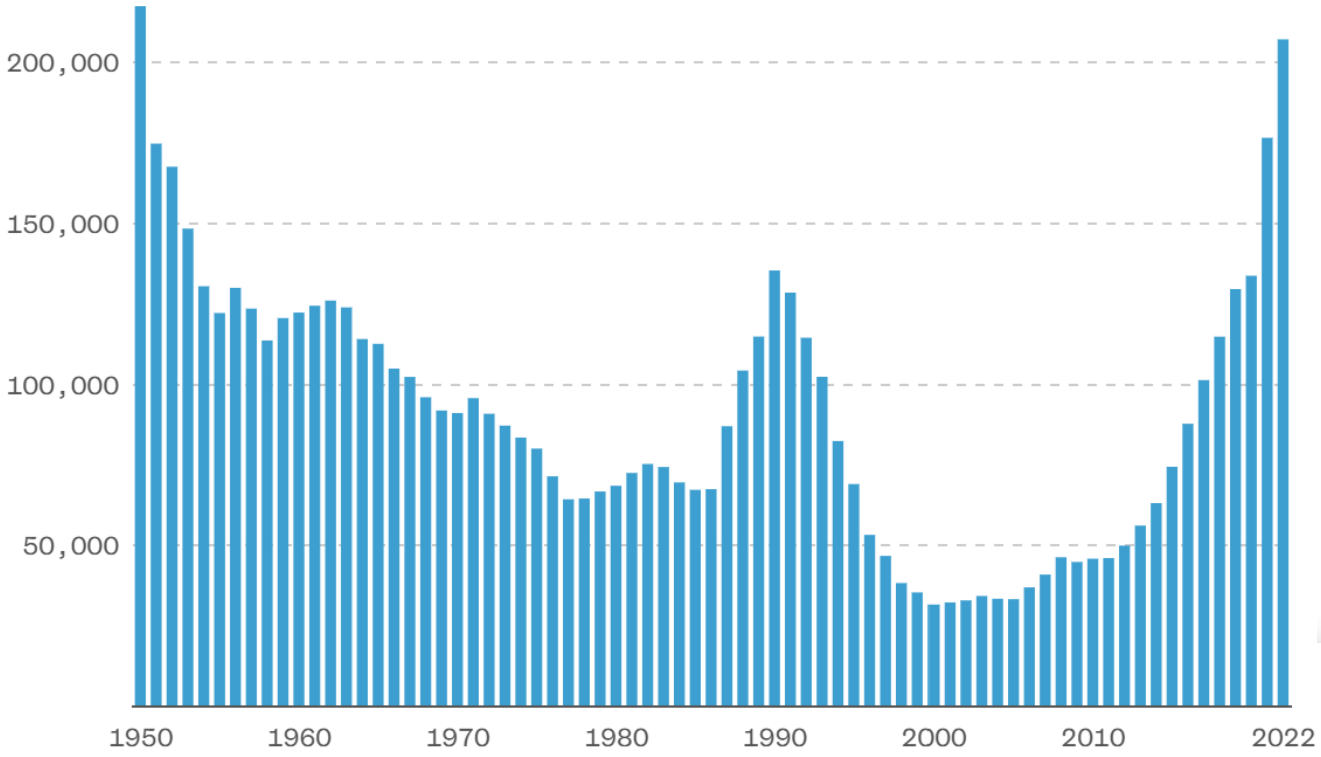




https://www.cdc.gov/std/statistics/2022/default.htm

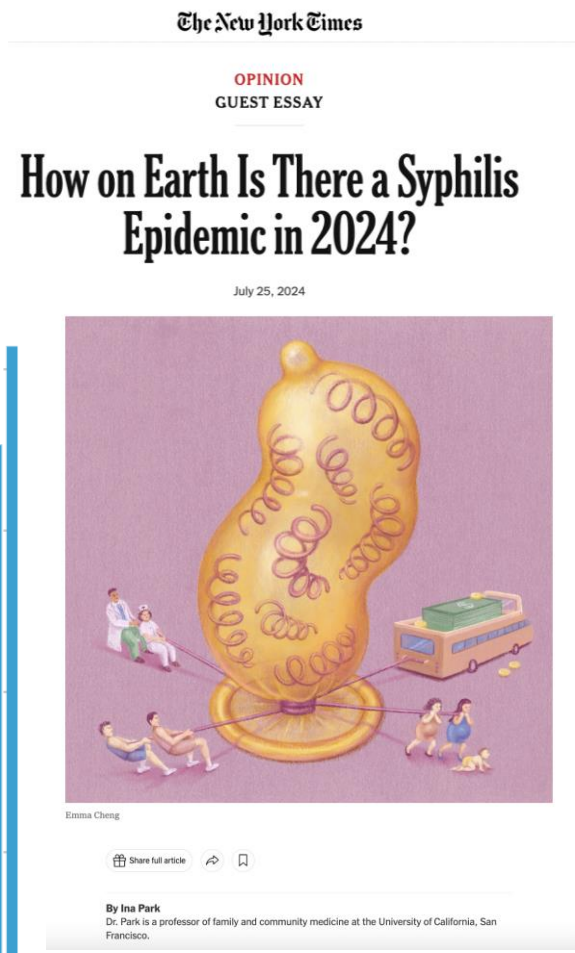
Syphilis in the U.S.

More than 200,000 cases were reported in 2022, the most since 1950.



Source: Centers for Disease Control and Prevention

Graphic: Joe Murphy / NBC News



The New York Times

OPINION

GUEST ESSAY

How on Earth Is There a Syphilis Epidemic in 2024?

July 25, 2024

Emma Cheng

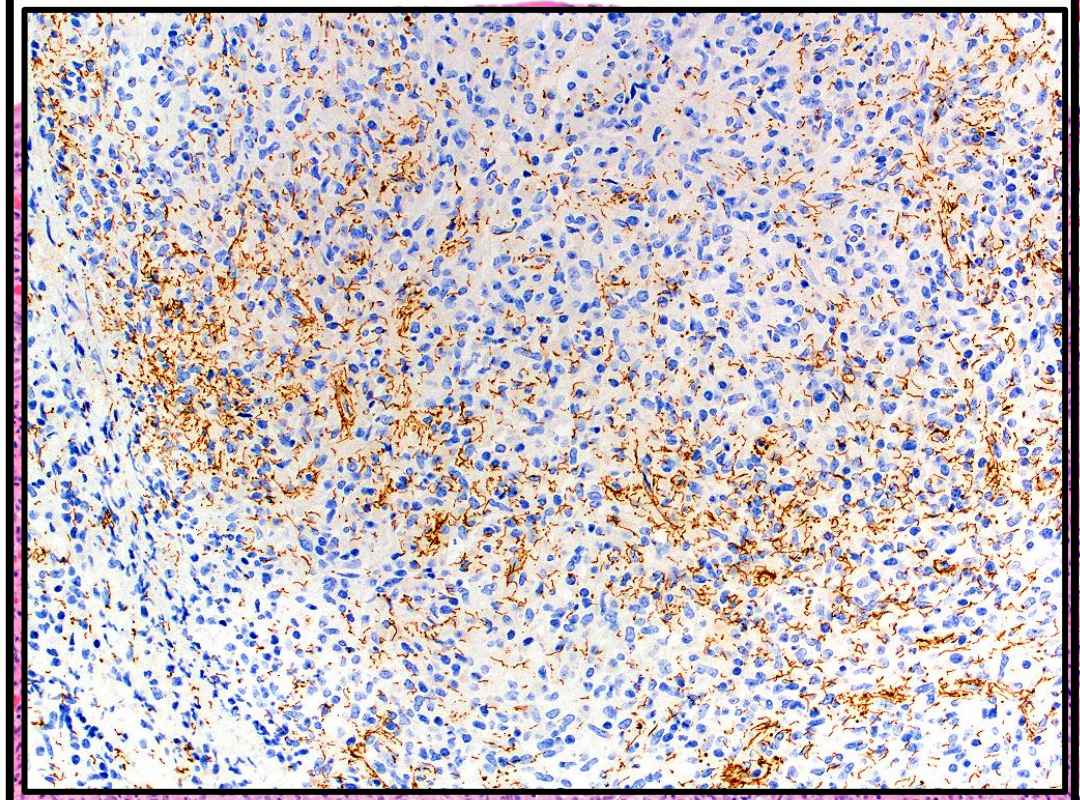
Share full article

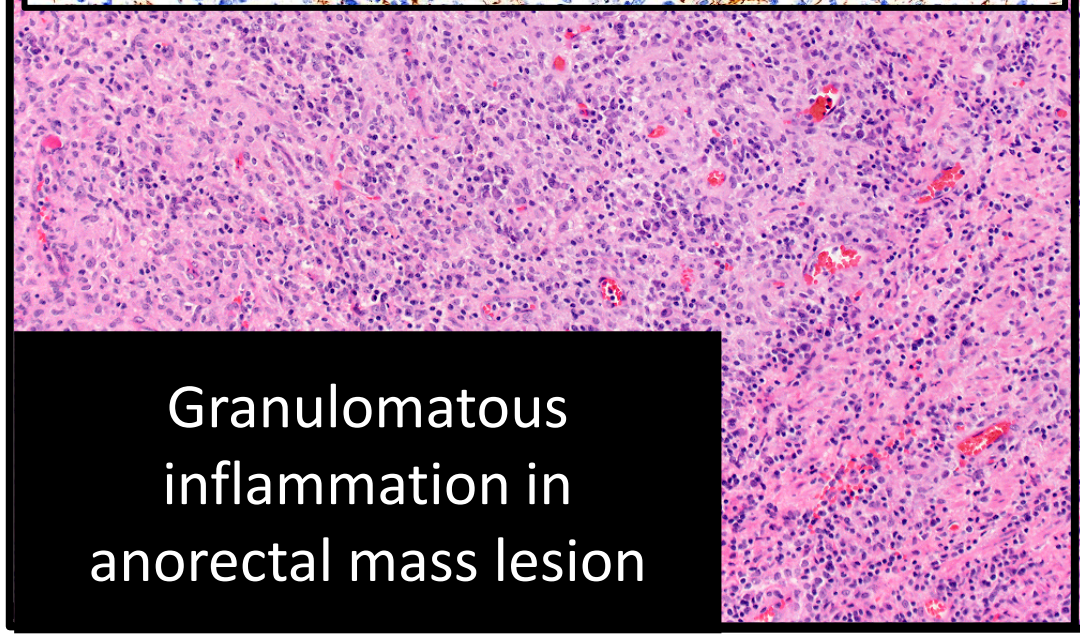
By Ina Park

Dr. Park is a professor of family and community medicine at the University of California, San Francisco.

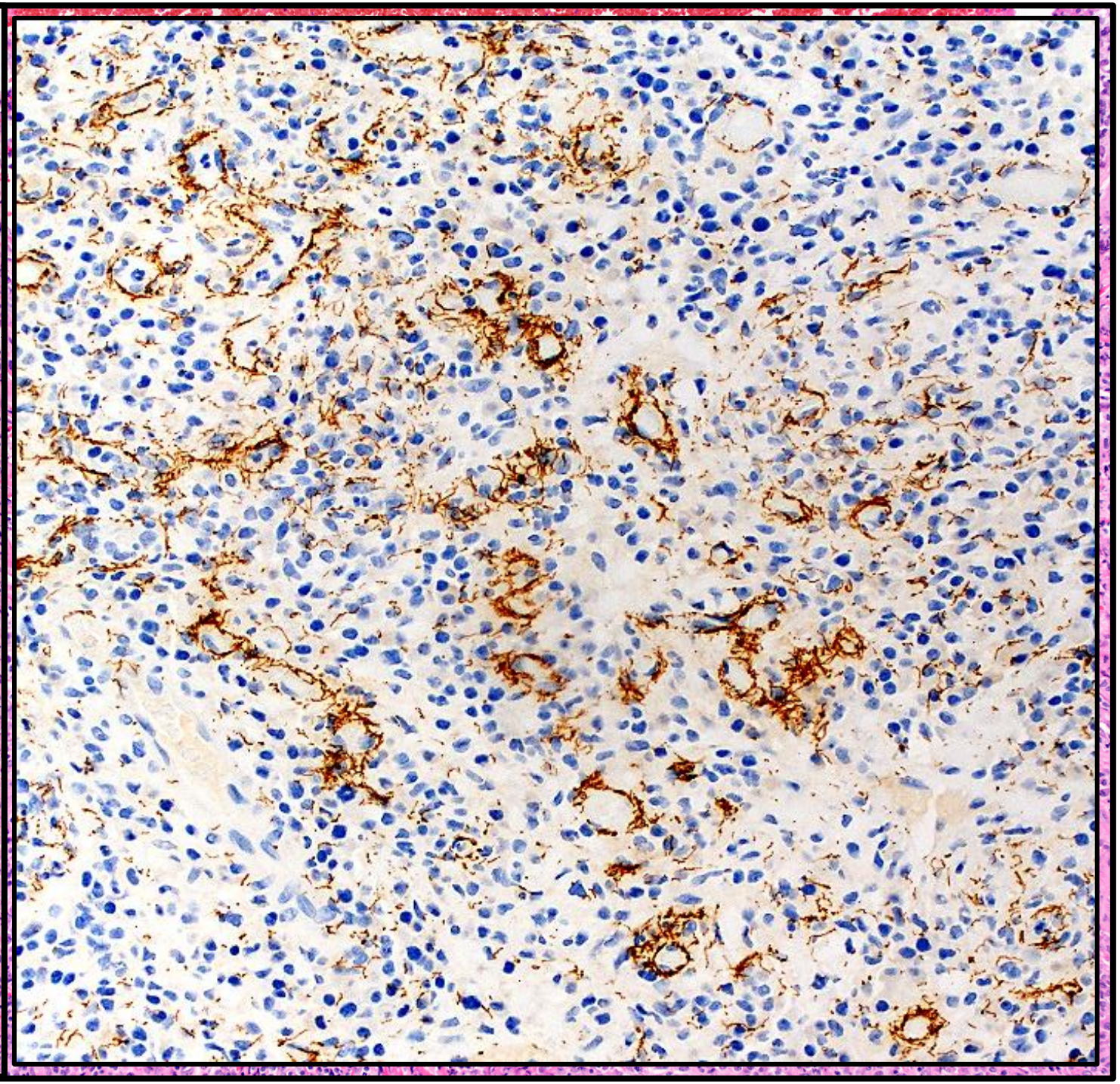
Retrospective Search of University of Utah Syphilis Cases

Case	Gender	Age	Clinical features	Tissue, sample	Pathologic features	Clinically Suspected
1	M	55	Perianal skin lesion	Perianal mass, biopsy	Ulcerated skin with granulation tissue & lymphoplasmacytic inflammation	Yes, considered in differential diagnosis
2	M	31	Inguinal LAD Rectal mass	Rectum, biopsy	Mixed lymphocytes, plasma cells, eosinophils neutrophils	No
3	M	39	Multiple painful tongue lesions with weight loss	Left lateral tongue, biopsy	Band-like subepithelial lympho-plasmacytic infiltrate	No
4	M	41	HIV positive with rectal mass	Rectal mass, biopsy	Acute inflammation with a prominent lymphoid infiltrate	Yes, positive screening RPR before path review
5	M	53	Hemorrhoids, tenesmus, and ulcerated lesion	Anal lesion, excision	Florid lympho-plasmacytic inflammation	No
6	M	62	Multiple liver lesions, anemia, and weight loss	Liver, biopsy	Florid lympho-plasmacytic and histiocytic inflammation	Yes, found on routine screening
7	F	46	Tonsil/soft palate chancre. Classic skin rash	Tongue/soft palate, biopsy	Superficial neutrophils, marked plasma cells	No

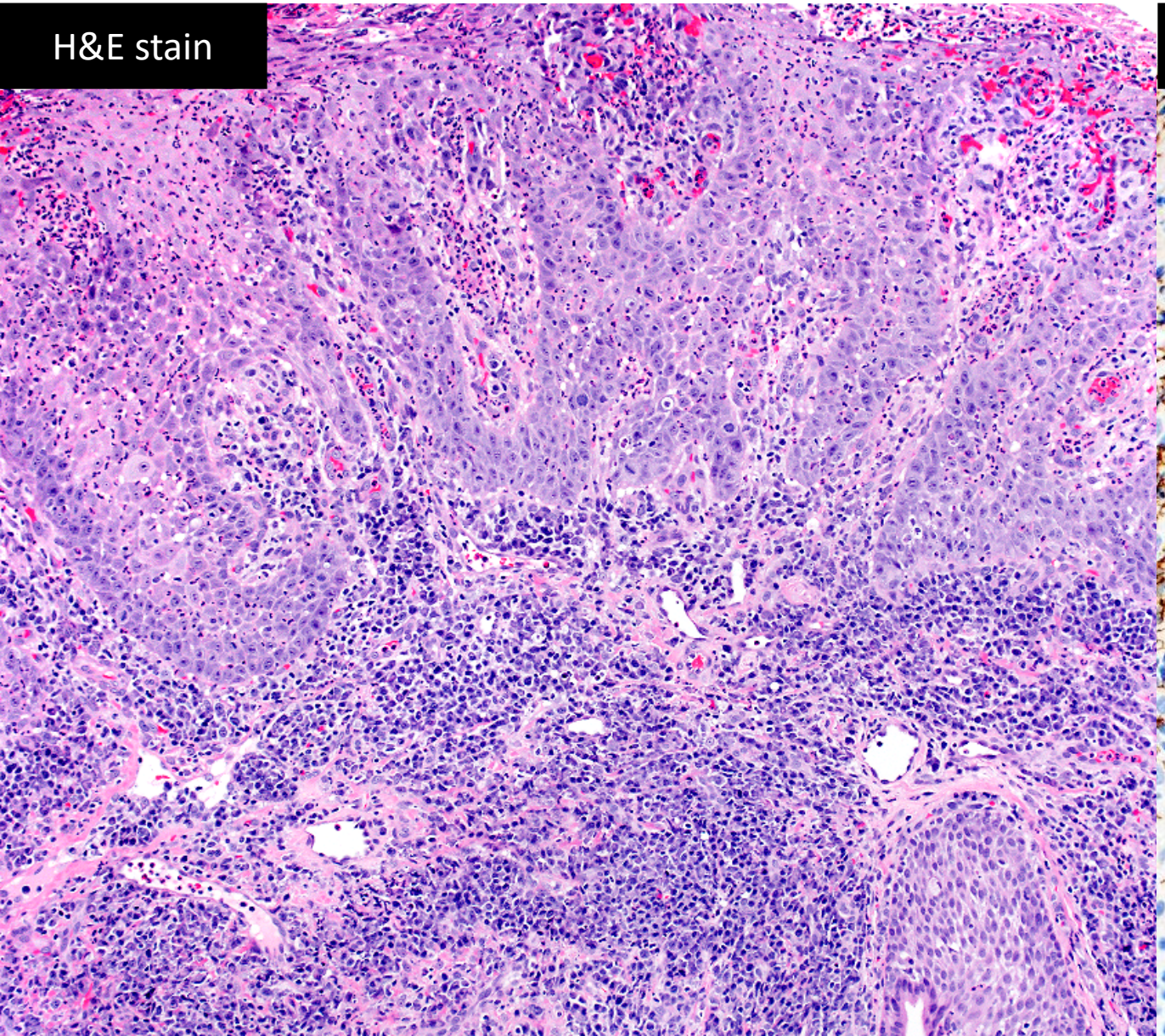


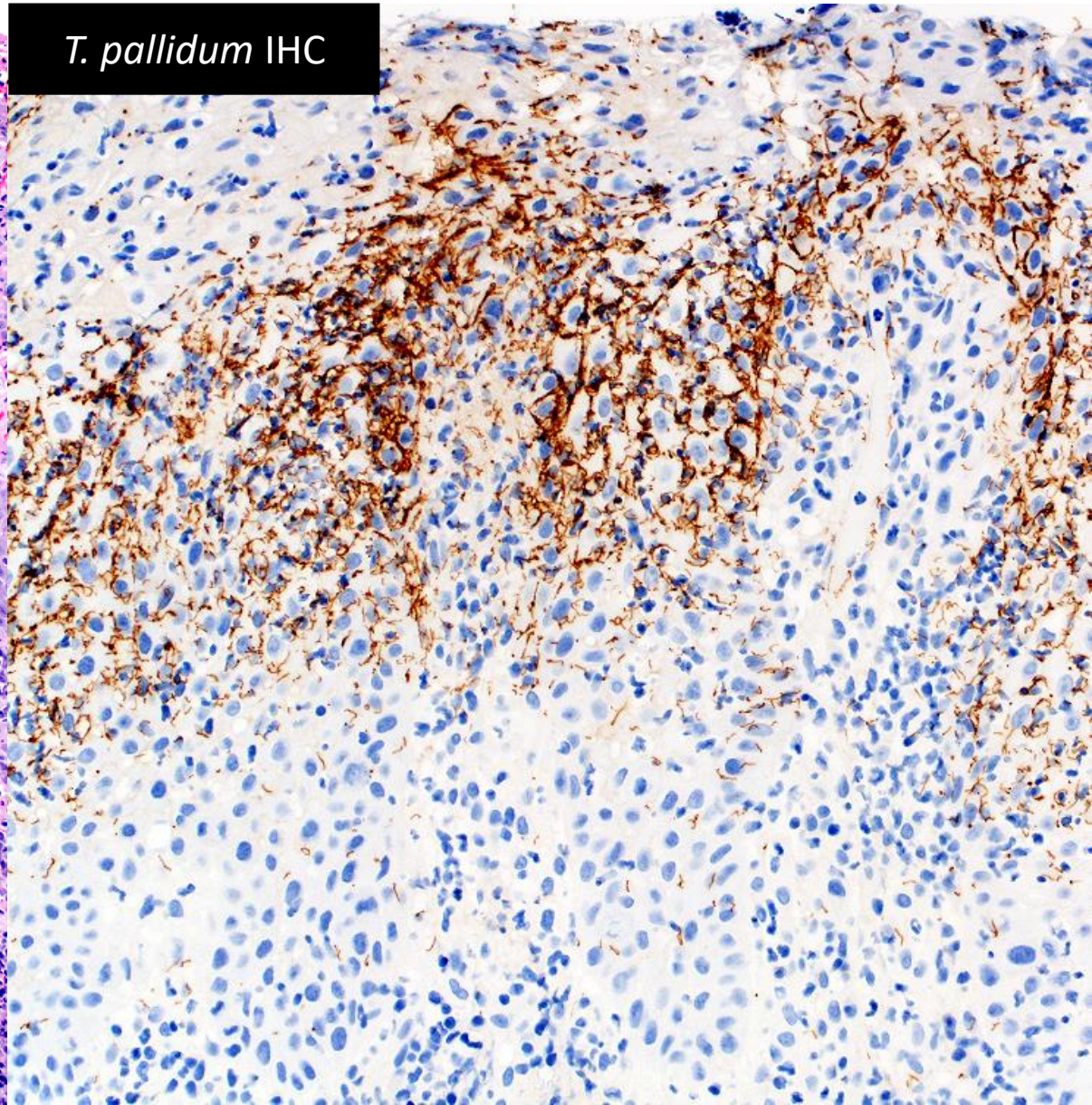


Granulomatous inflammation in anorectal mass lesion



46 yo F - Left tonsil biopsy





Syphilis - The “Great Mimicker”

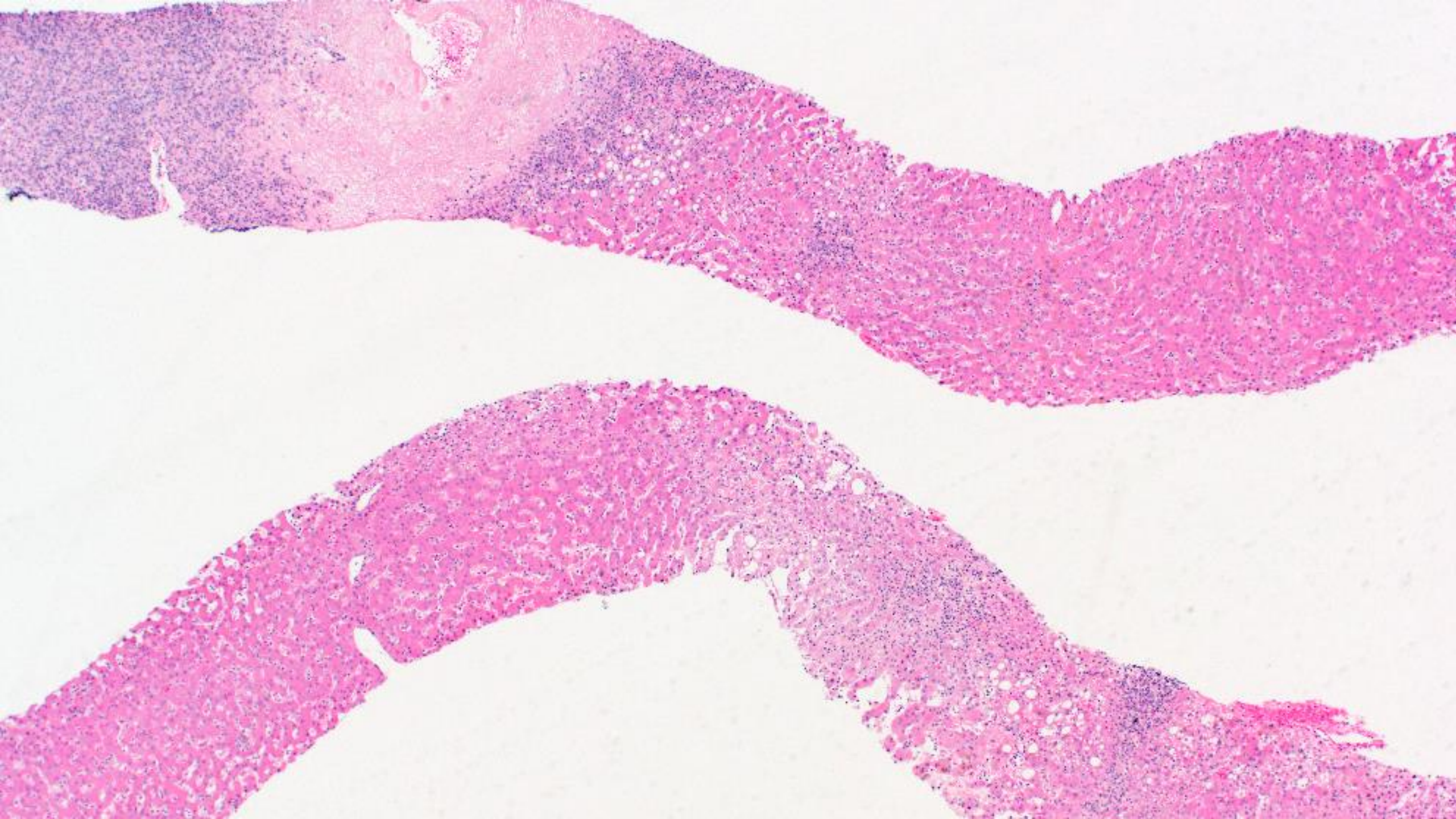
- 46 yo F with rash on her abdomen, spine, neck, back of head, proximal lower extremities; not itchy
- Multiple coin-sized lesions, almost completely faded.
- Swollen joints (elbows, shoulders, knees, ankles)
- Stiffness in wrists, MCPs, PIPs, elbows, shoulders, knees
- Tender LAD on the neck and axillae occasionally
- Change in voice and swollen tongue:
- Labs: negative ANA & RF, elevated ESR, CRP
- Prominent hair loss
- Photosensitivity w/ immediate sunburn on chest and face
- **Painful mouth sores on inner lip for 2 months (biopsied)**

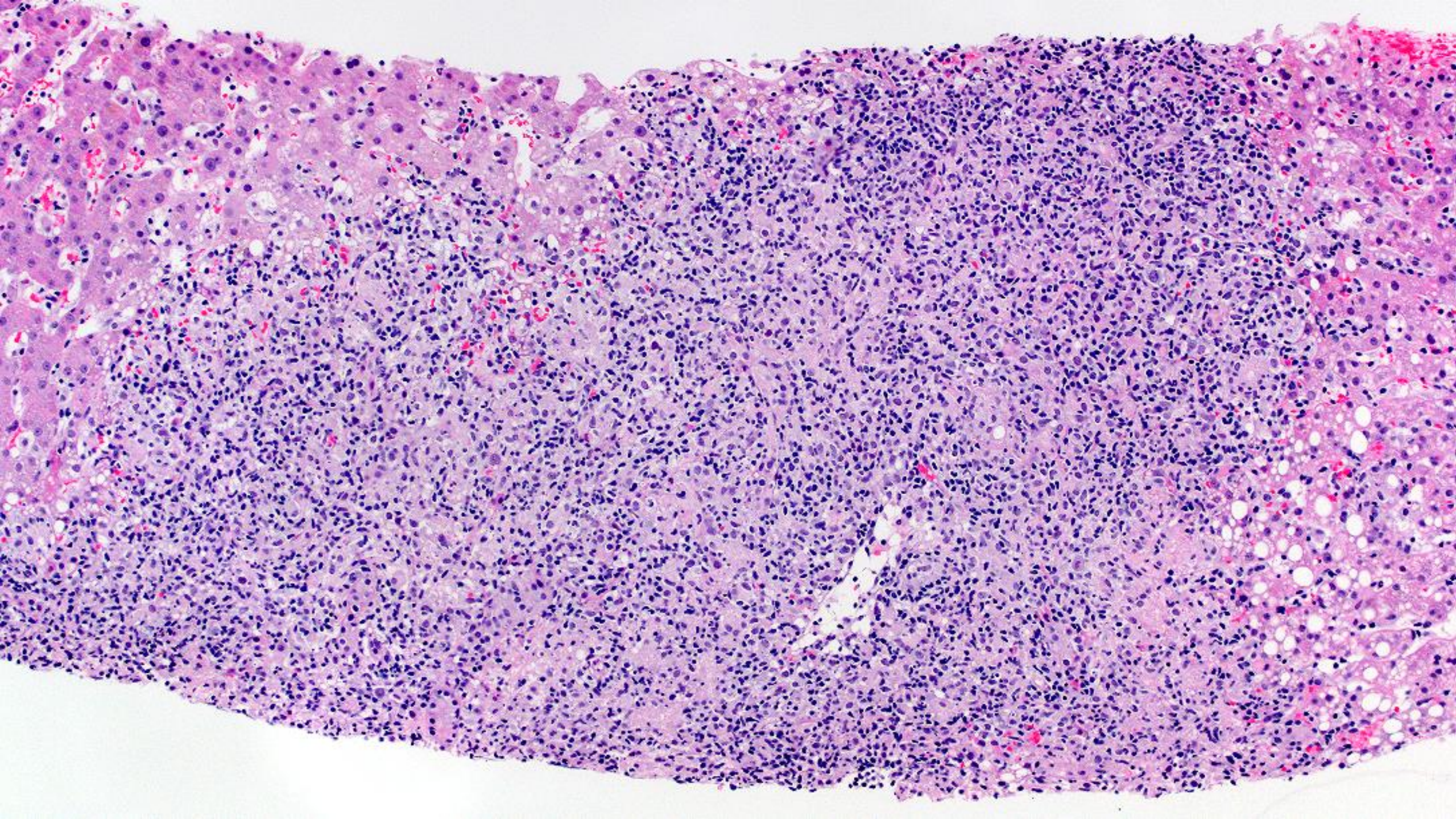
He *(or she)* who knows syphilis, knows medicine.

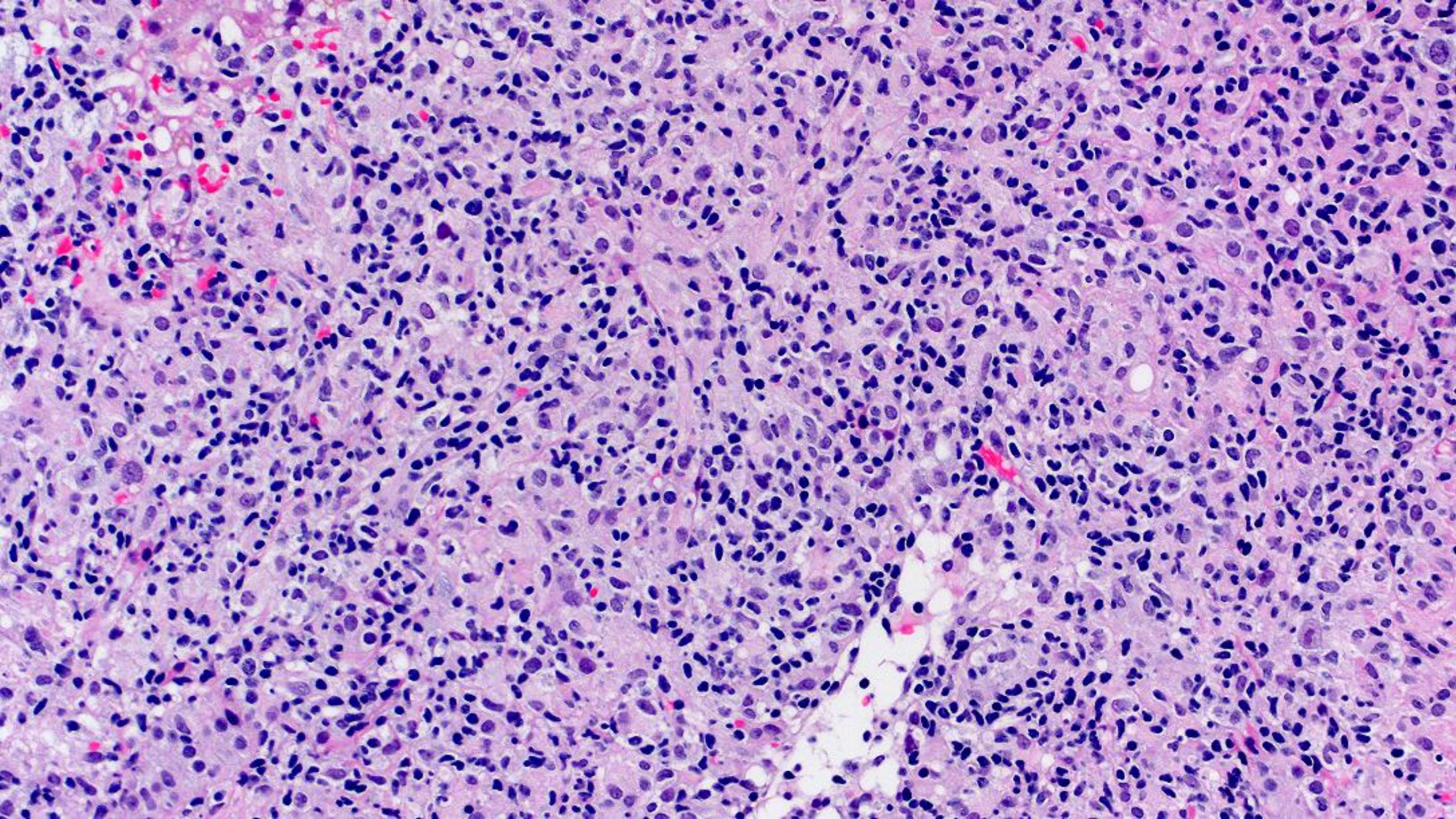
– William Osler

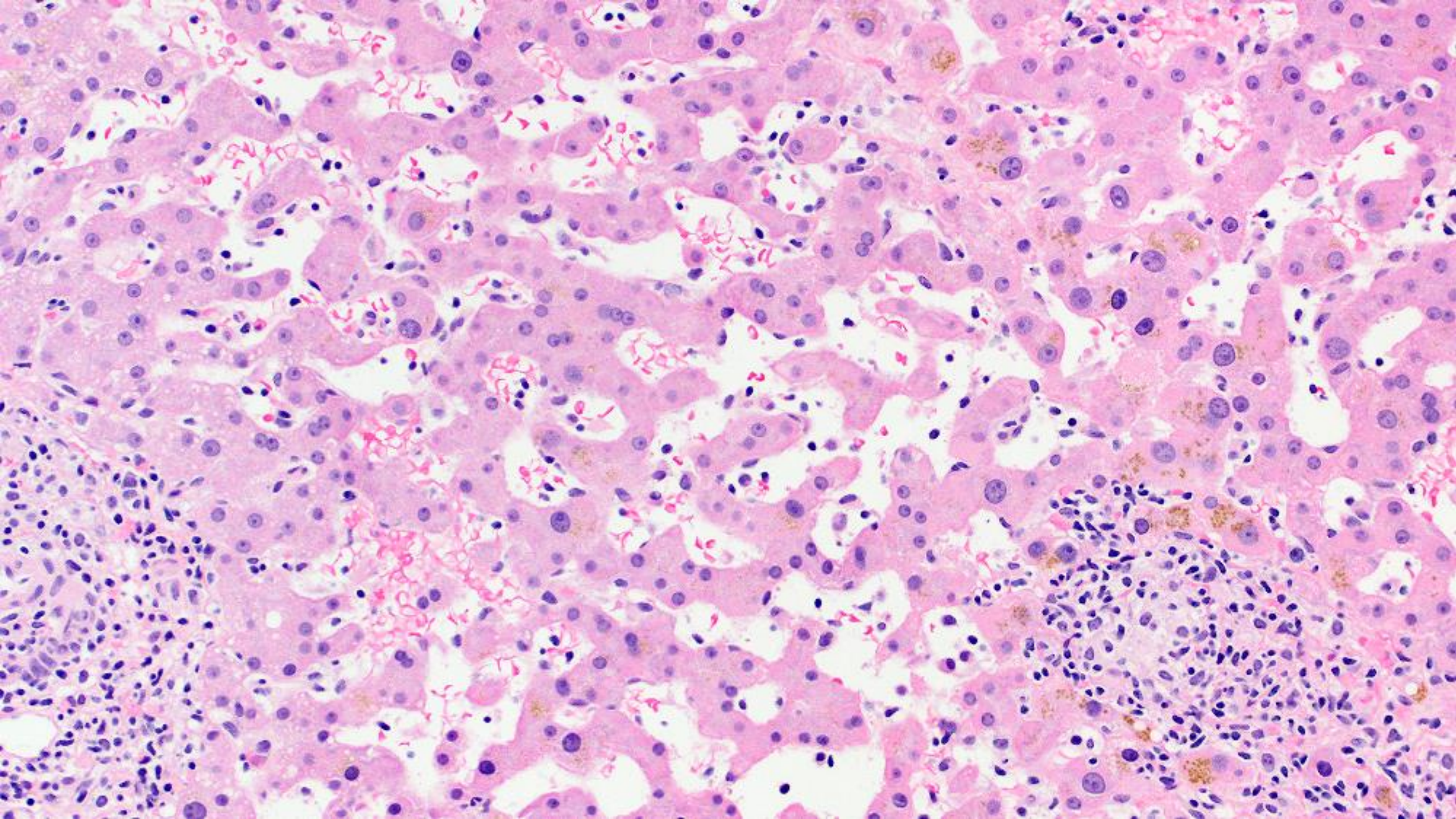
Case 3: 56-year-old female with disseminated *Mycobacterium haemophilum* & LGL lymphoma

- **Disseminated *Mycobacterium haemophilum*** diagnosed 2021 now on azithromycin prophylaxis
- **LGL lymphoma** dx 2 years earlier, treated with methotrexate for 6 mos, **not currently on therapy**
- More recently, she developed persistent shortness of breath and cough, fever, weight loss, loss of appetite, and night sweats
- Presents to ED with similar symptoms and 2 days of confusion with short term memory loss
- Labs on presentation:
  - AST 178, ALT 139, **Alk 495**, T bili 0.8
- **CT shows diffusely enlarged liver with numerous ill-defined hypodense lesions** throughout, the largest measuring up to 6.8 cm
  - Splenomegaly with splenic lesions
  - Retroperitoneal LAD
  - New bilateral solid and ground glass pulmonary nodules









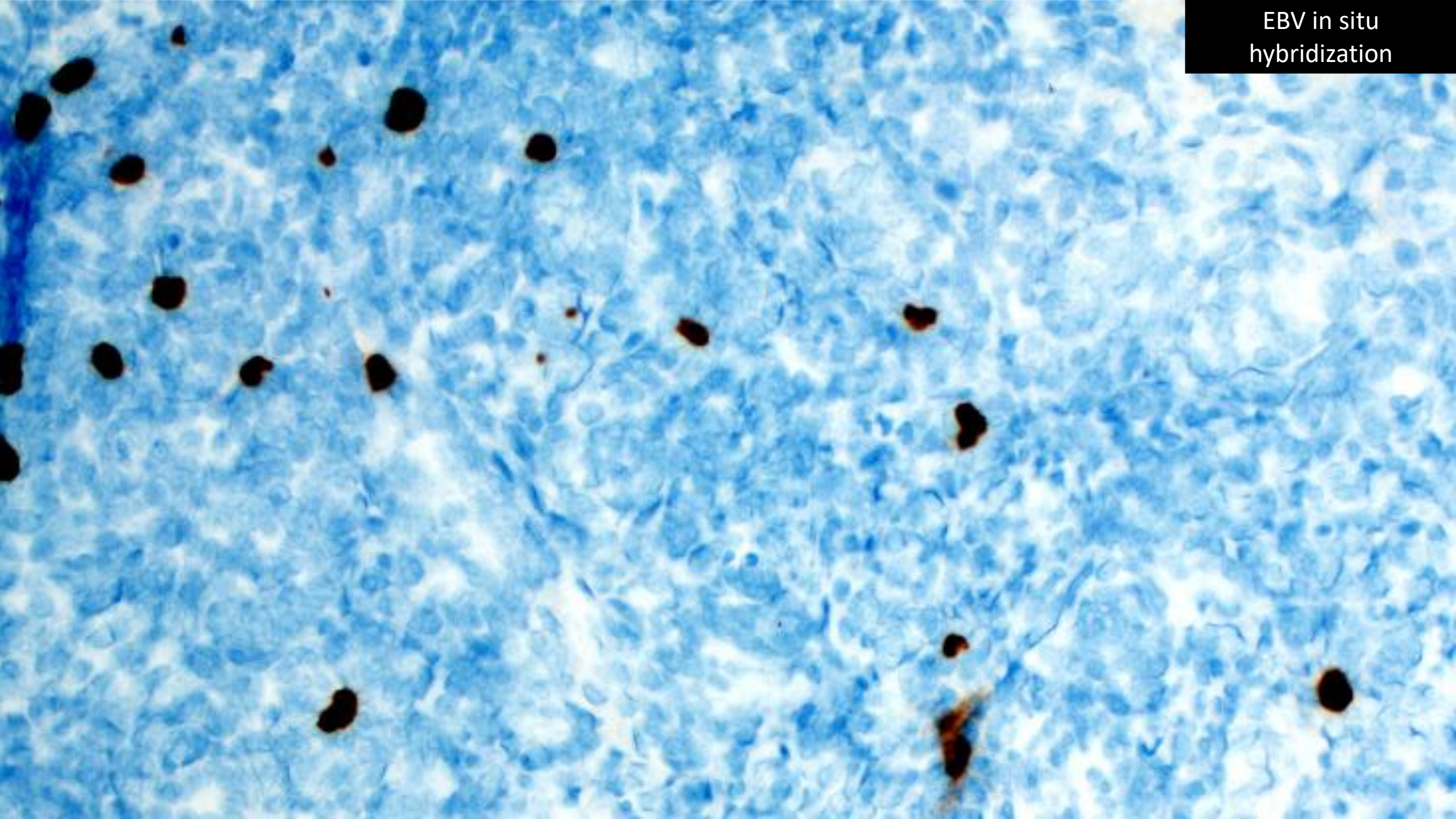
What infectious disease stains should we get?

A. AFB and GMS
B. Full court press: AFB, GMS, Gram, HSV, CMV, Adenovirus…
C. This is not infectious

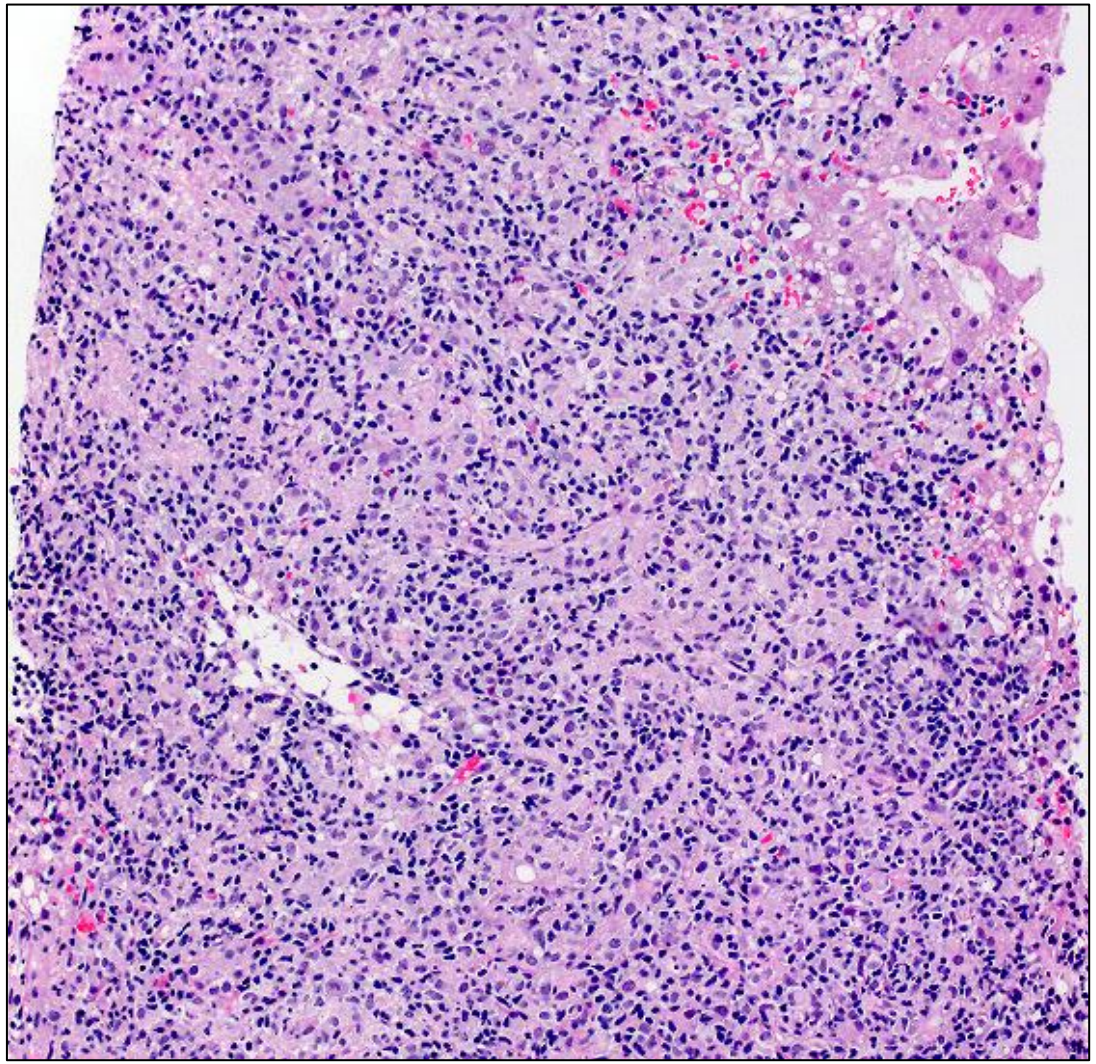
These stains were negative

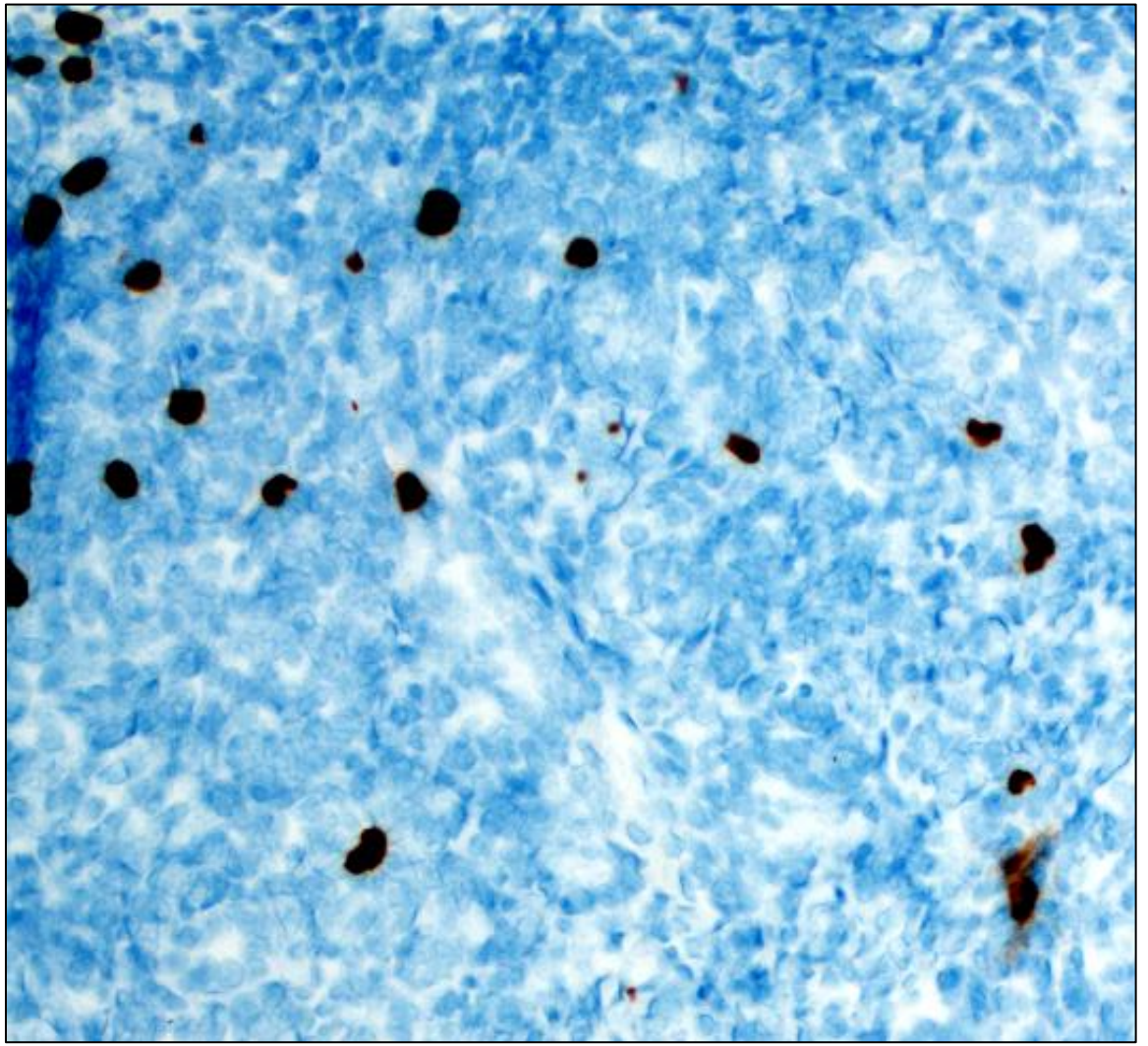
- AFB
- MTB IHC
- GMS
- *T. pallidum*
- CMV
- Adenovirus
- HSV 1/2

- But wait, there's one more…


EBV in situ
hybridization

Hemophagocytic Lymphohistiocytosis



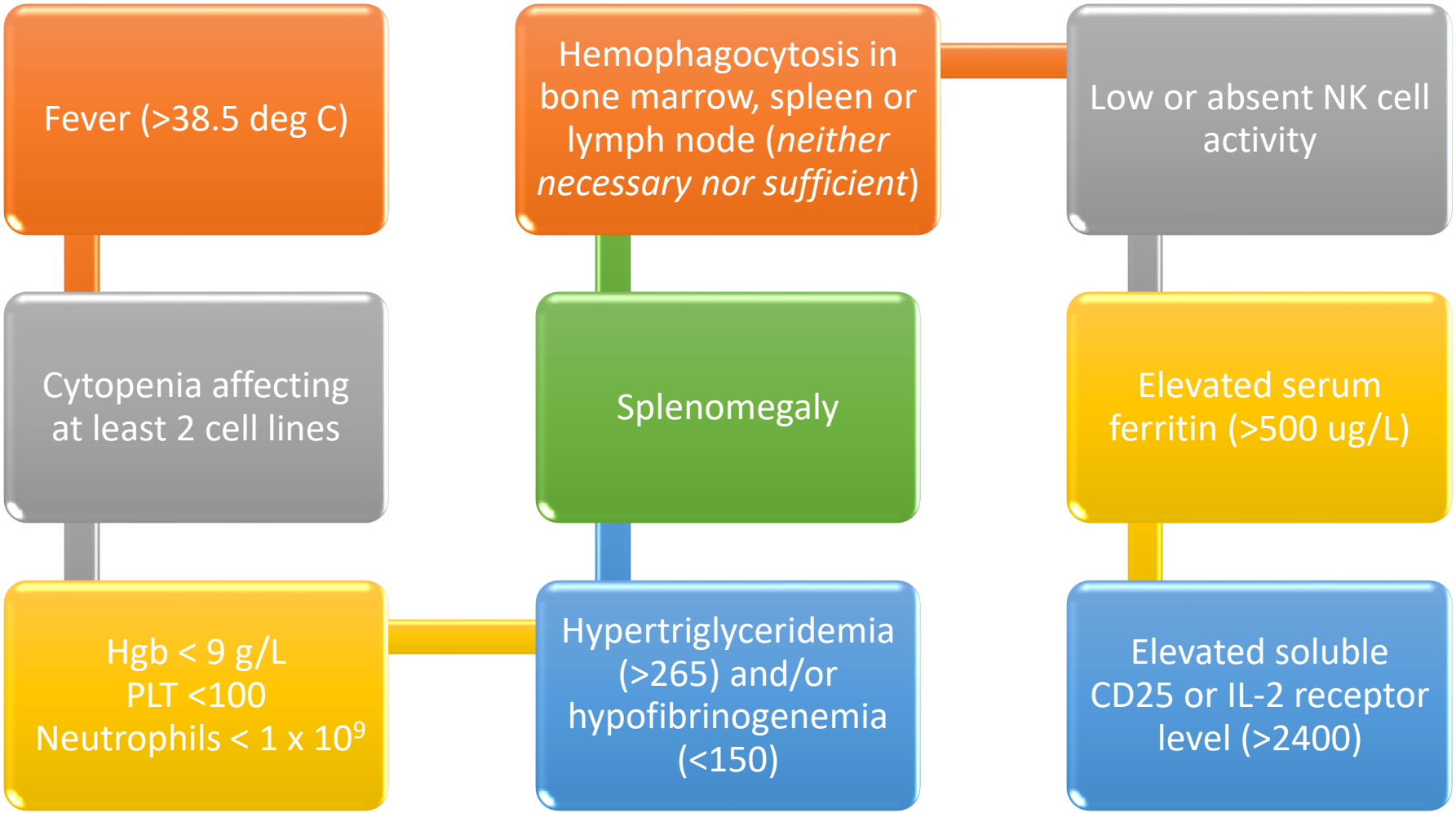


Epstein-Barr Virus by Quantitative NAAT, Plasma

EBV Quantitative by NAAT, Plasma	7050	IU/mL
Epstein-Barr Virus Antibody Panel I		
EBV Av To Early (D) Ag IgG	>150.0 ▲	
EBV VCA IgG Ag	>750.0 ▲	
EBV VCA IgM Ag	13.3	
EBV Ab To Nuclear Ag IgG	21.2	

Laboratory tests performed after the biopsy results identify EBV Viremia

HLH Diagnostic Criteria



Griffin G, Shenoi S, Hughes GC. Best Pract Res Clin Rheumatol. 2020 Aug;34(4):101515. doi: 10.1016/j.berh.2020.101515. Epub 2020 May 7.

Hemophagocytic Lymphohistiocytosis (HLH)

- Exuberant & sustained histiocytic proliferation, hemophagocytosis, cytokine-mediated life-threatening tissue injury and organ failure
- Different underlying mechanisms
  - Genetic – occurs in first year of life for 70-80% of cases
    - Familial – autosomal recessive due to mutations in NK/T-cell cytotoxic pathway (ie. perforin defects, genes in packaging, transport, release of cytotoxic granules)
    - Primary immunodeficiency syndrome (ex. X-linked proliferative syndrome)
  - Secondary/acquired
    - Infection, autoimmune conditions, immunosuppression
    - Underlying pathogenesis remains poorly understood
- High mortality – up to 73% when associated with EBV

Griffin G, Shenoi S, Hughes GC. Best Pract Res Clin Rheumatol. 2020 Aug;34(4):101515.
Maakaroun NR, Moanna A, Jacob JT, Albrecht H. Rev Med Virol. 2010 Mar;20(2):93-105.
Rosado FG, Kim AS. Am J Clin Pathol. 2013 Jun;139(6):713-27.

Reported Pathologic Features of HLH in Liver

<u>Not specific</u>

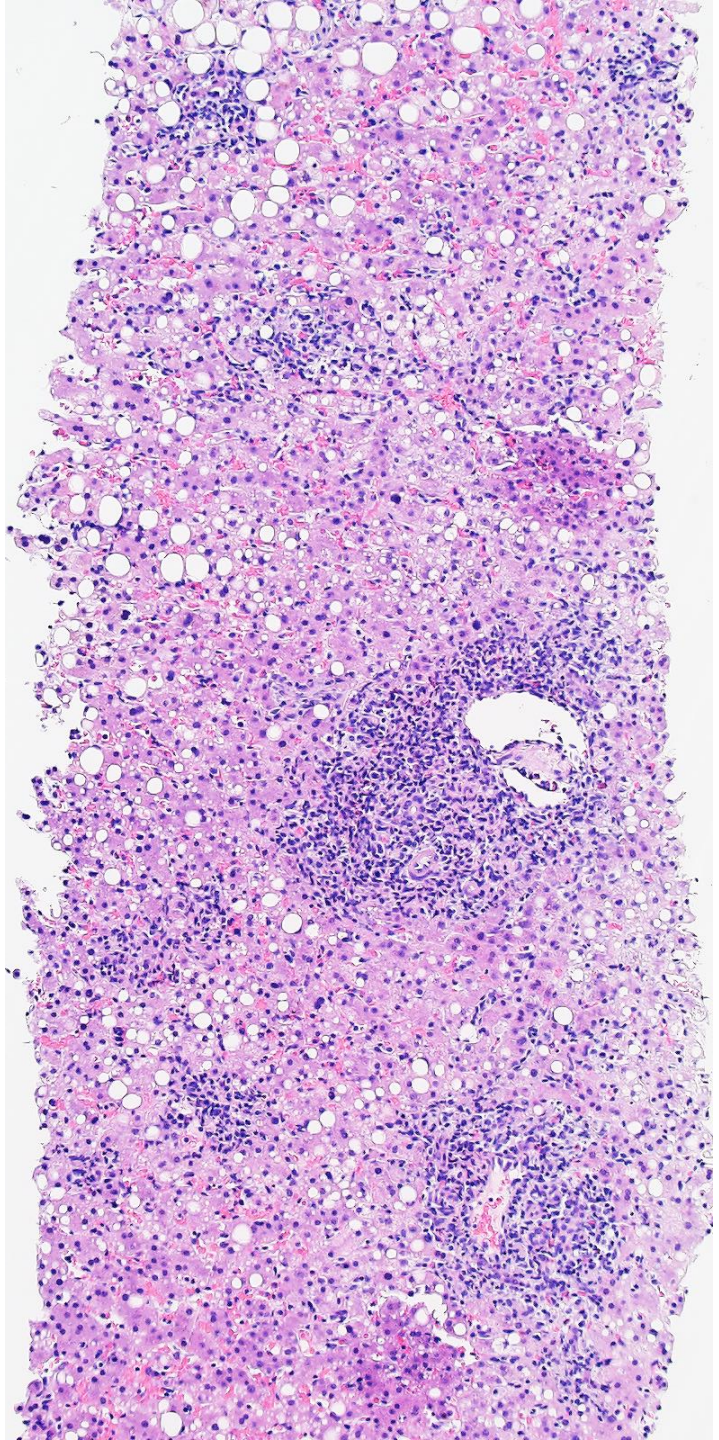
- Severe cholestasis
- Ductular reaction
- Hemophagocytosis
- Endothelialitis
- Sinusoidal dilatation
- Massive hepatic necrosis in acute liver failure

Schneier A, Stueck AE, Petersen B, Thung SN, Perumalswami P. An Unusual Cause of Acute Liver Failure: Three Cases of Hemophagocytic Lymphohistiocytosis Presenting at a Transplant Center. Semin Liver Dis. 2016 Feb;36(1):99-105.

Lin S, Li Y, Long J, Liu Q, Yang F, He Y. Acute liver failure caused by hemophagocytic lymphohistiocytosis in adults: A case report and review of the literature. Medicine (Baltimore). 2016 Nov;95(47):e5431

EBV hepatitis

- Classic mononucleosis syndrome
  - Triad: fever, pharyngitis, cervical lymphadenopathy
- EBV is typically diagnosed clinically and with characteristic lab evidence
  - Lymphocytosis
  - Serologic testing
- Liver involvement is common (>90%), but typically self-limited with mildly elevated enzymes (2-3 times upper limit of normal)
  - Enzymes normalize over ~ 3 weeks



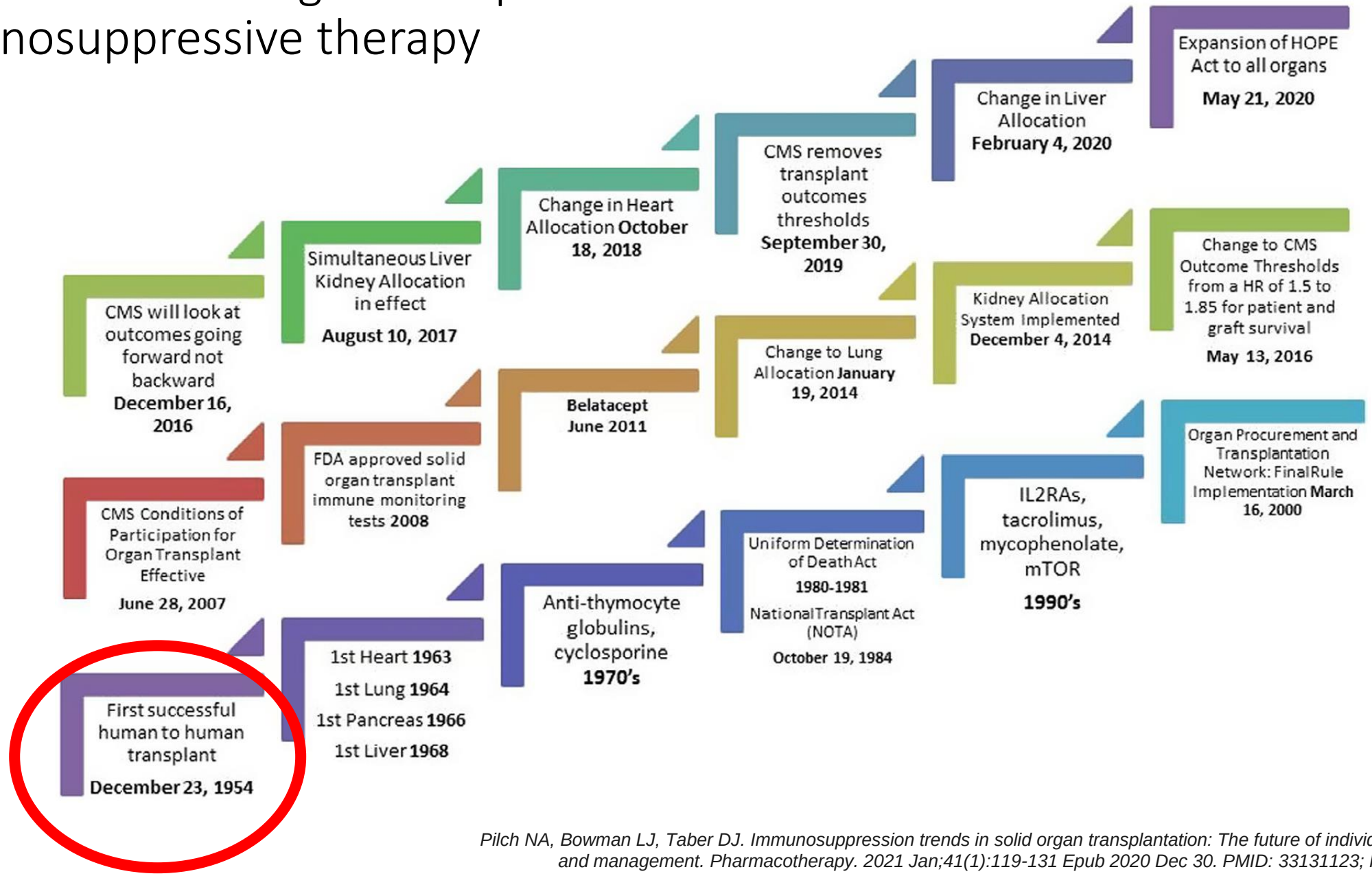
Schechter S, Lamps L.. Arch Pathol Lab Med. 2018 Oct;142(10):1191-1195.
Suh N, Liapis H, Misdraji J, Brunt EM, Wang HL. Am J Surg Pathol. 2007 Sep;31(9):1403-9.

Histopathologic Features of EBV Hepatitis

- 8 patients with acute EBV from 3 institutions
- Characteristic features
  - Portal inflammation (predominately lymphocytes) with few admixed plasma cells, neutrophils, eosinophils
  - Mild bile duct damage
  - Endophlebitis of portal veins
  - Beaded sinusoidal lymphocytic infiltration
  - **Small epithelioid granulomas in 3/8 cases**
  - Spotty necrosis; no confluent necrosis
  - Positive EBER ISH and PCR for EBV DNA

Schechter S, Lamps L. Arch Pathol Lab Med. 2018 Oct;142(10):1191-1195.
Suh N, Liapis H, Misdraji J, Brunt EM, Wang HL. Am J Surg Pathol. 2007 Sep;31(9):1403-9.

Advances in solid organ transplantation & immunosuppressive therapy

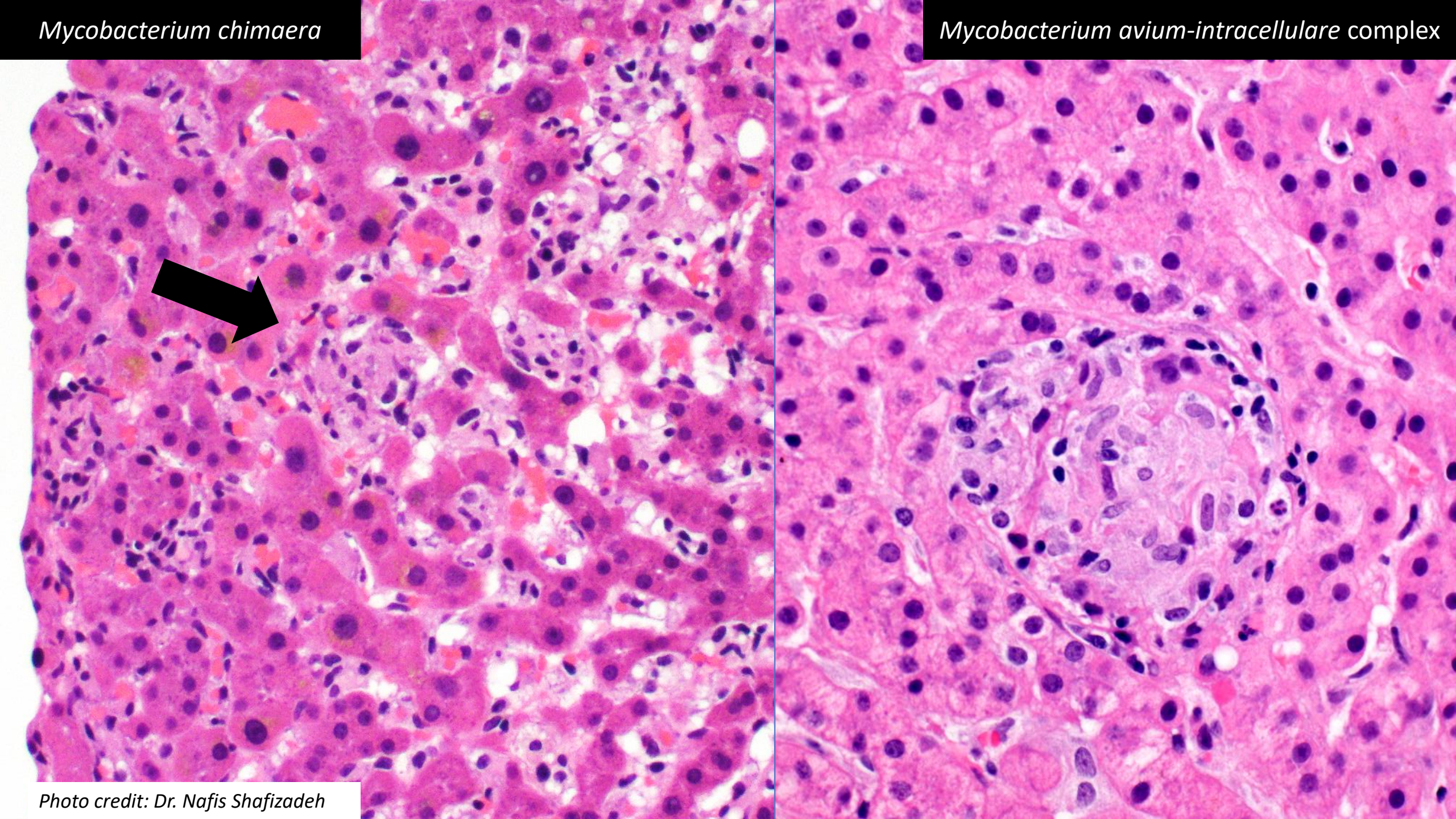


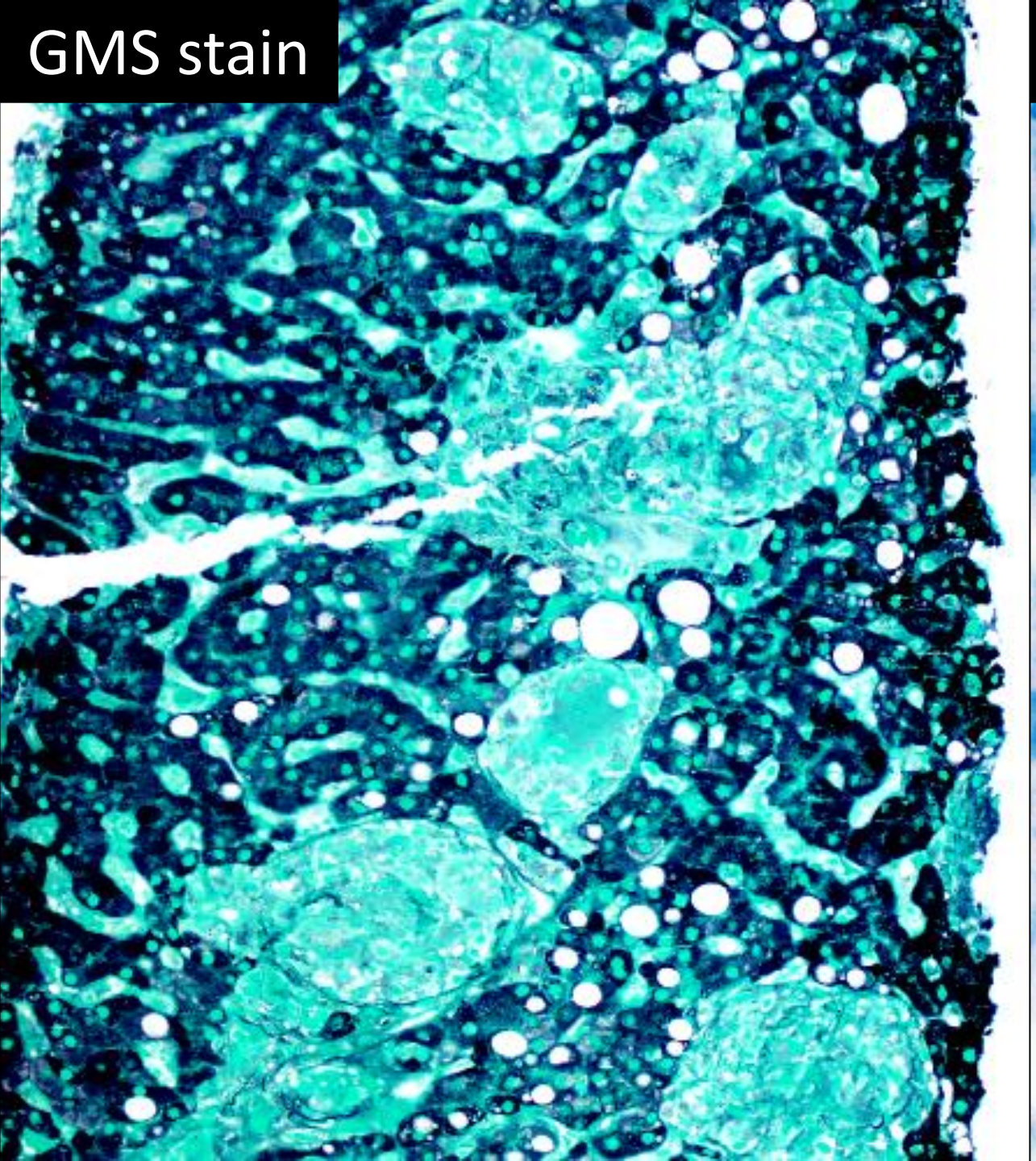
Pilch NA, Bowman LJ, Taber DJ. Immunosuppression trends in solid organ transplantation: The future of individualization, monitoring, and management. Pharmacotherapy. 2021 Jan;41(1):119-131 Epub 2020 Dec 30. PMID: 33131123; PMCID: PMC8778961.

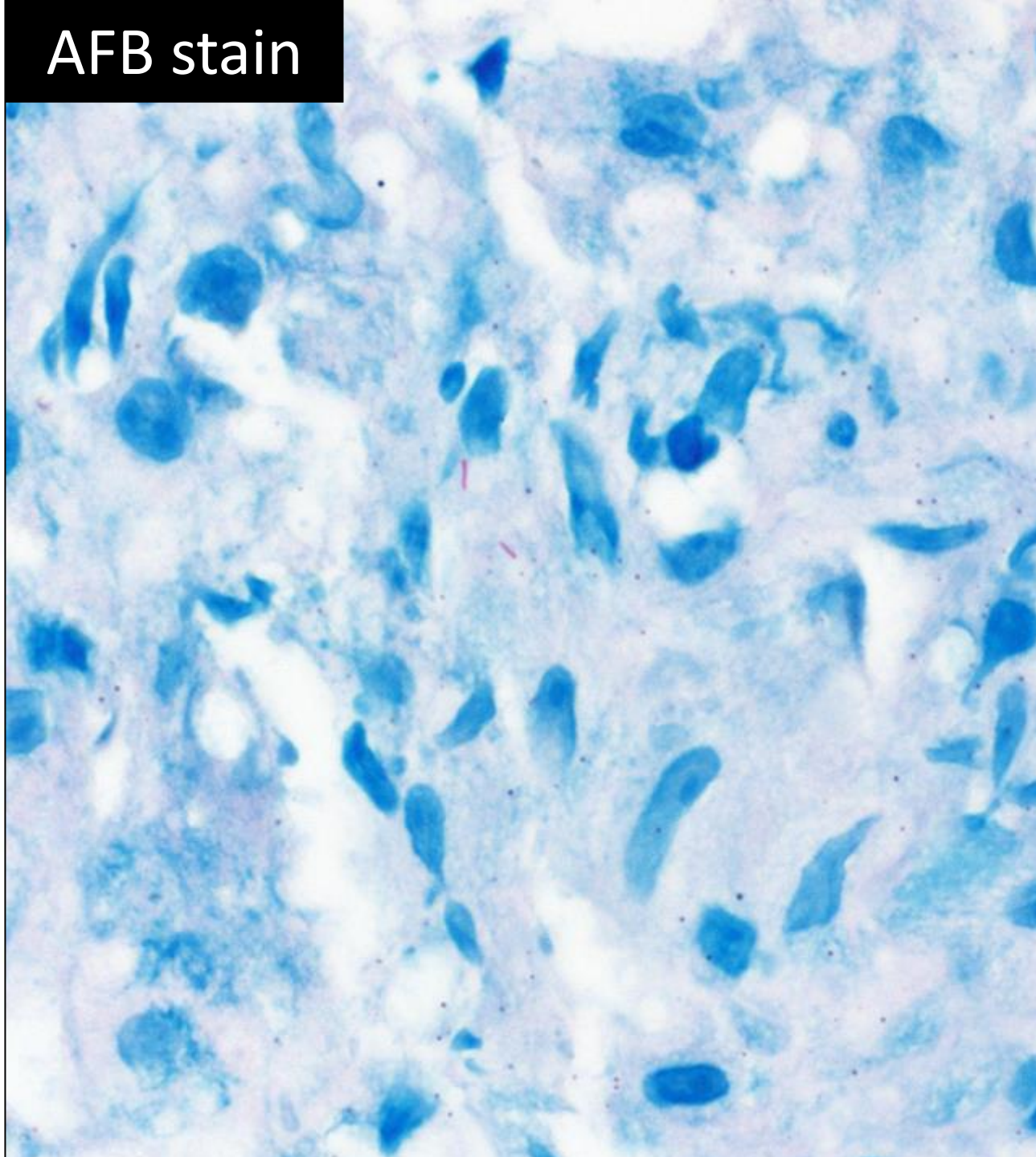
Summary

- 3 cases of emerging or reemerging active hepatitis
  - Hepatitis E virus
  - Lues maligna (secondary syphilis)
  - EBV-associated Hemophagocytic Lymphohistiocytosis (HLH)
- Syphilitic hepatitis and EBV-associated HLH have *granulomatous inflammation;* and also *elevations in ALK* which would initially suggest biliary or outflow obstructive process
- Pathology (histopathologic eval and ancillary stains) played an important role in determining the underlying etiology of each case


Thank you!


Mycobacterium chimaera
Mycobacterium avium-intracellulare complex
Photo credit: Dr. Nafis Shafizadeh


GMS stain


AFB stain