Leverpathologie

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1. Eosinofiele granulocyten zijn karakteristiek voor toxische hepatitiden (DILI).

Goed/fout

2. Naast de hoeveelheid fibrose is ook het patroon/ligging van de collageenvezels belangrijk bij het opstellen van de differentiaal diagnose van onderliggend leverlijden.

Goed/fout

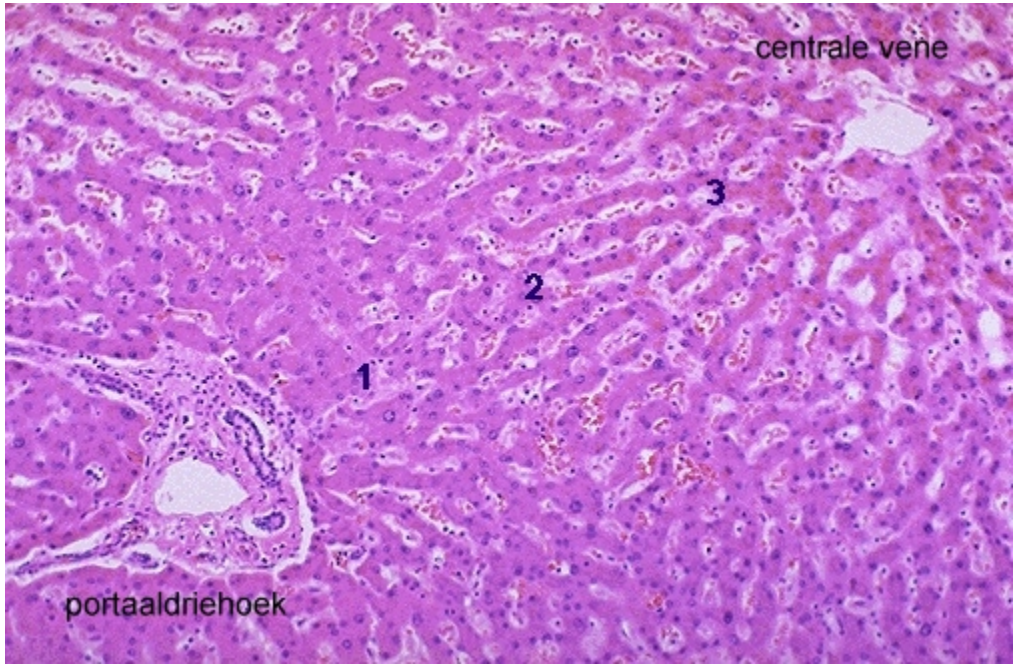
Interpretatie leverbiopt

Afwijkingen:

Waar ?

Wat ?

Klinisch correlaat !

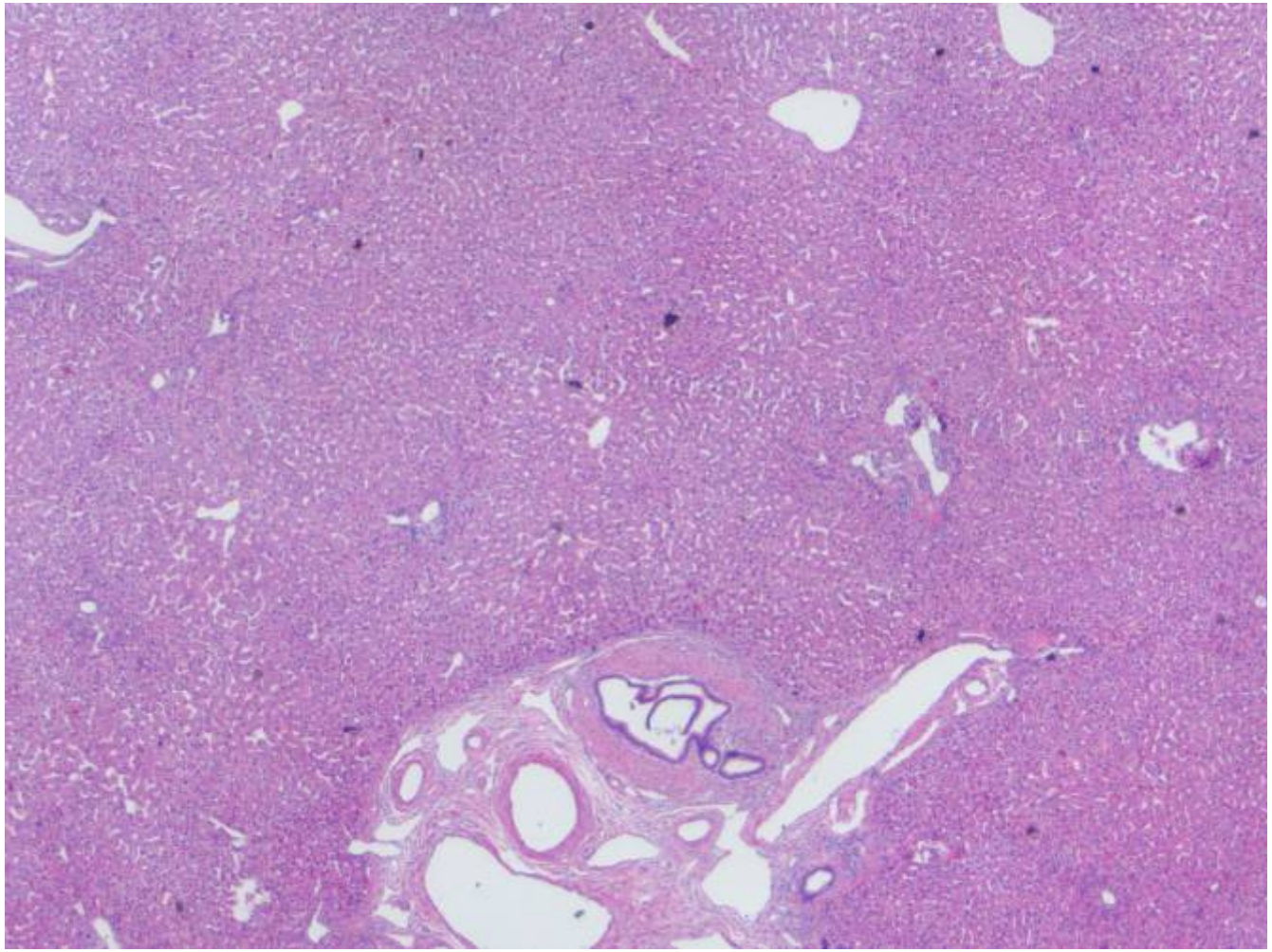


Liver acinus

Zone 1: surrounds portal tract
Zone 3: surrounds central vein

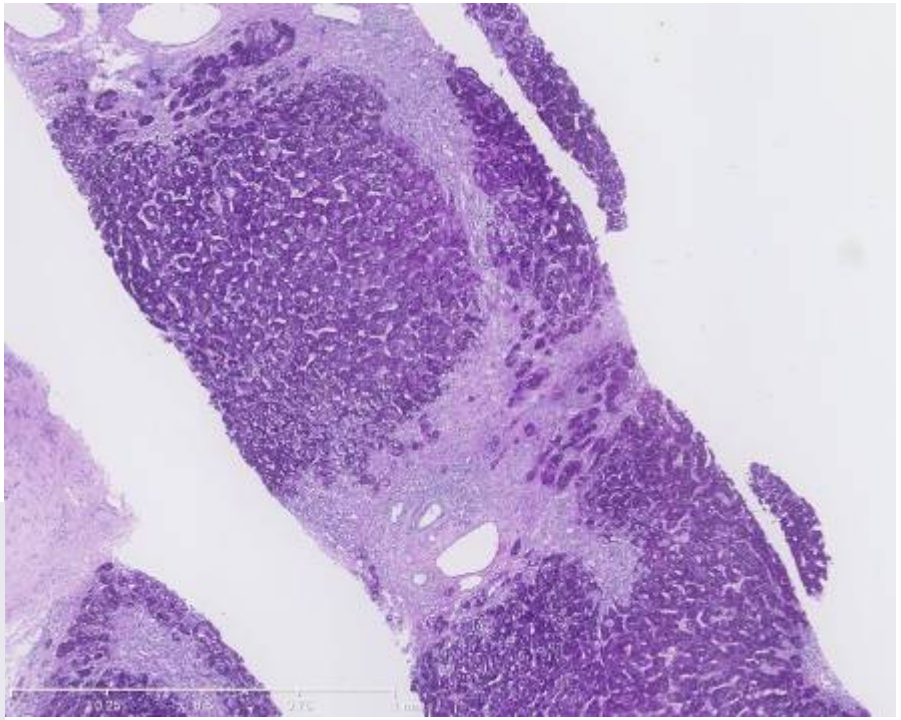
Stainings

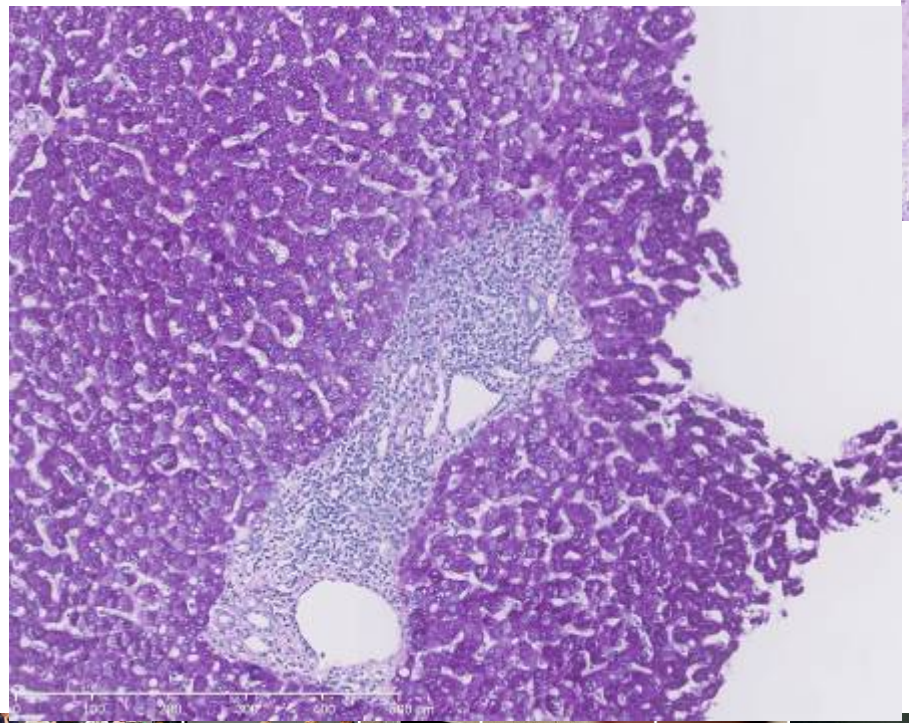
HE	overall architecture, inflammation, steatosis
PAS	stains glycogen, delineates limiting plate
PAS-D	ceroid-laden macrophages, α1-antitrypsin, copper binding protein, basal membrane



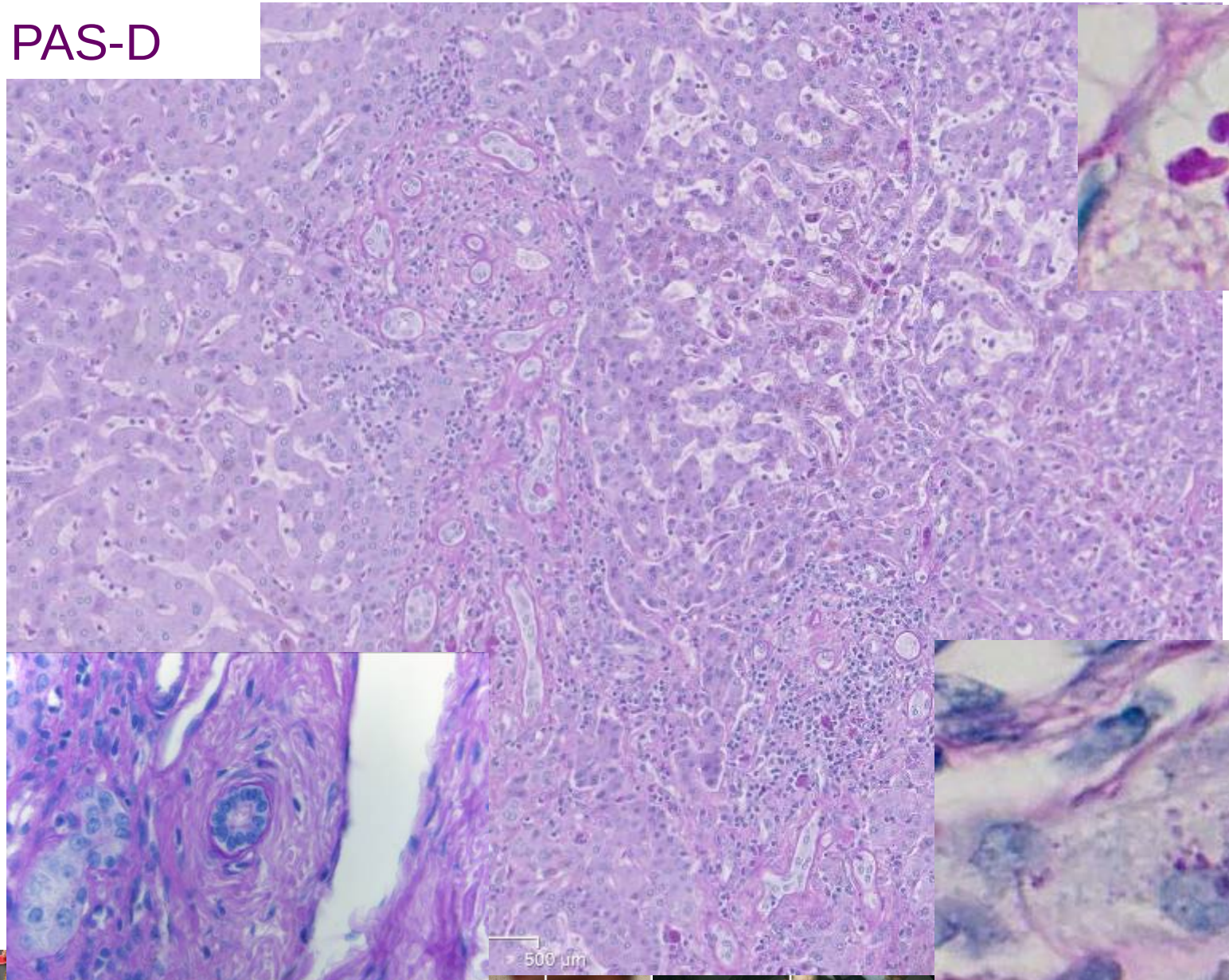
HE; hematoxylin eosin

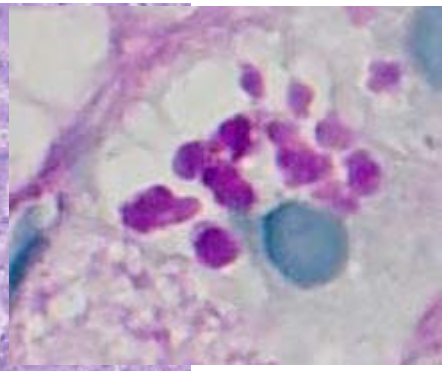
PAS

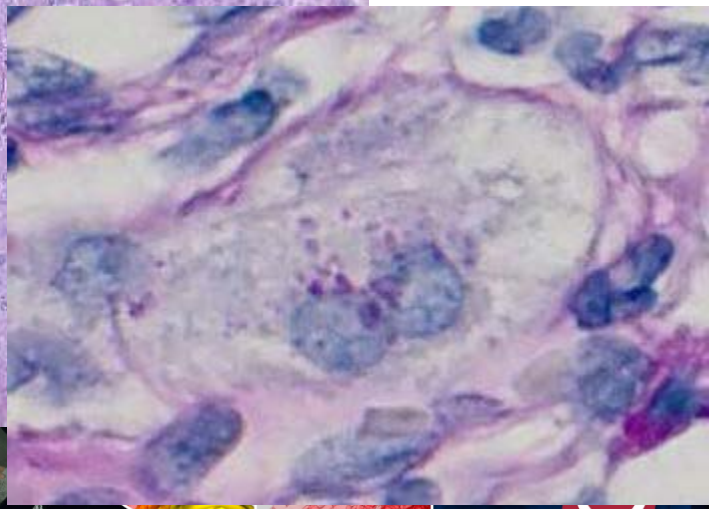


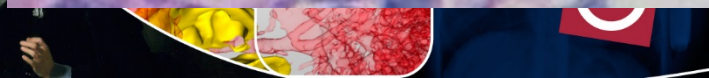


PAS-D





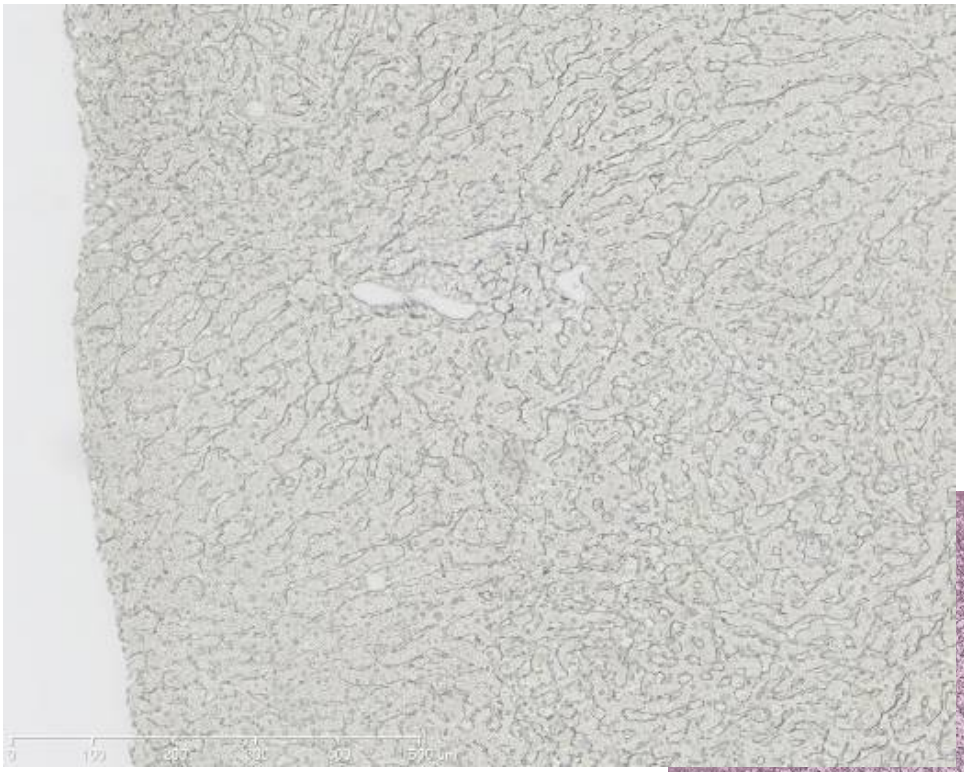


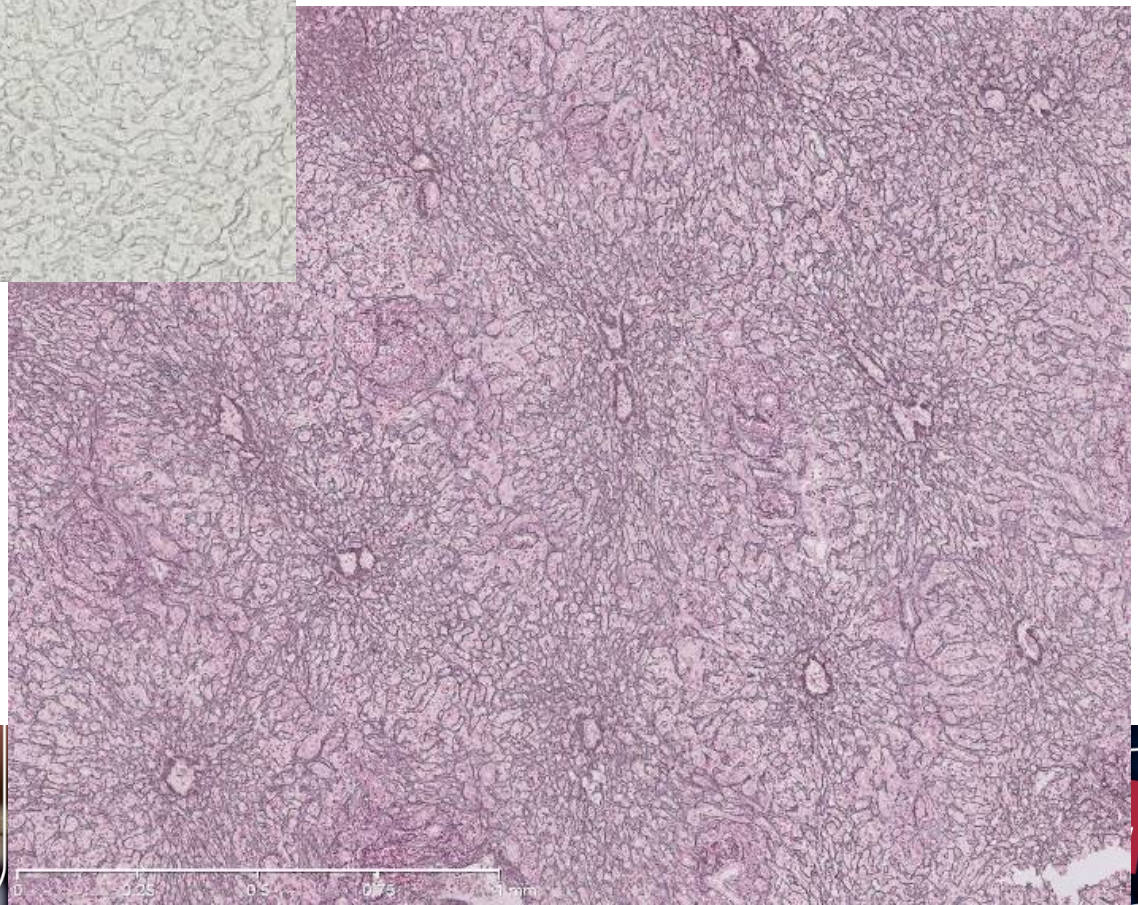


Stainings

Reticulin	structure of liver cell cords, subtle fibrosis
EVG/SR	collagen deposition
CU/FE	copper/iron
CK7	bile ducts, ductular reaction, CK7 expression on hepatocytes (~ biliary phenotype)

Reticulin





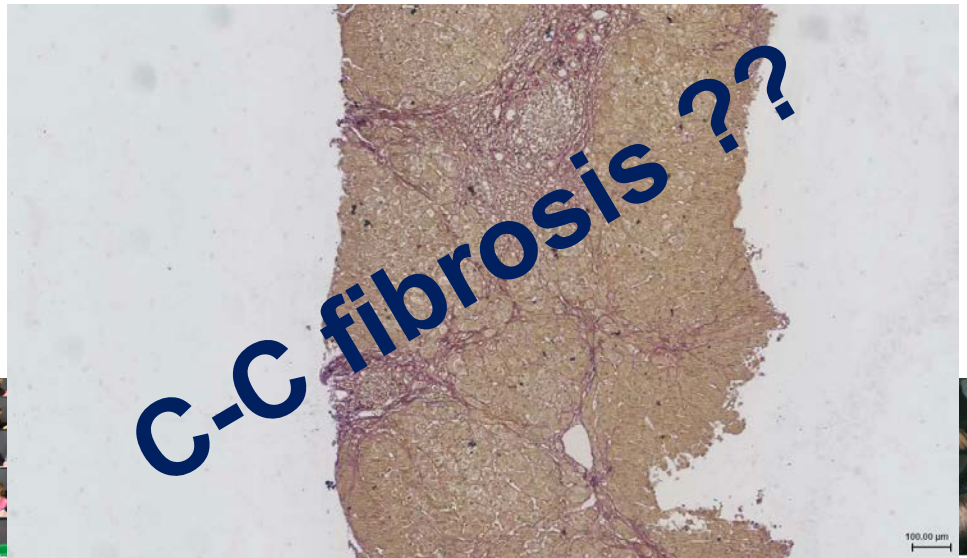
Collagen stainings

Patterns of necrosis and fibrosis

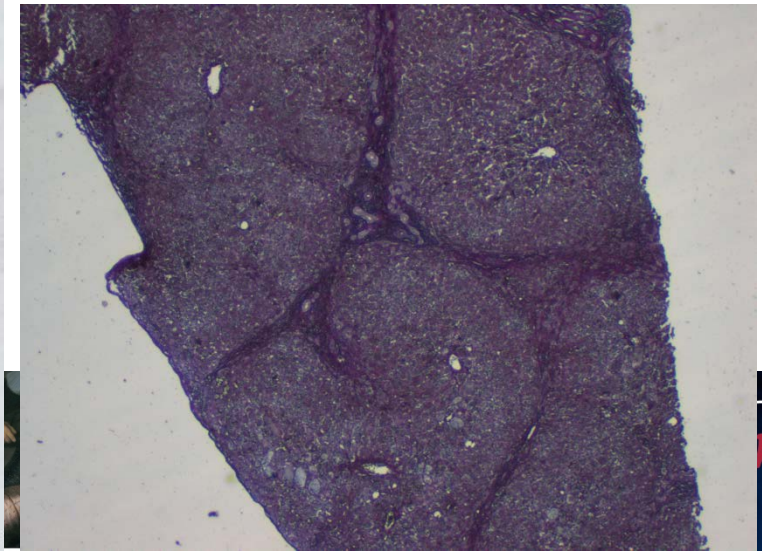
Confluerent P-C necrosis : acute viral hepatitis and/or exacerbation of chronic hepatitis

Confluerent P-P necrosis : chronic hepatitis and biliary tract disease

HCV: P-C; P-P

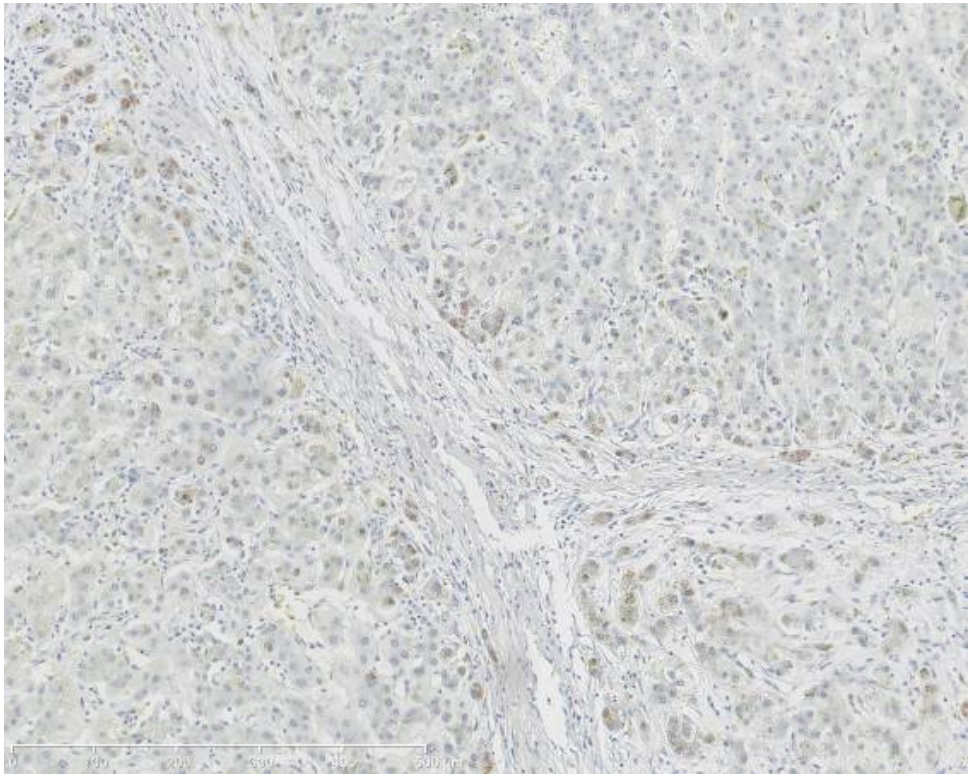


EHBDA: P-P

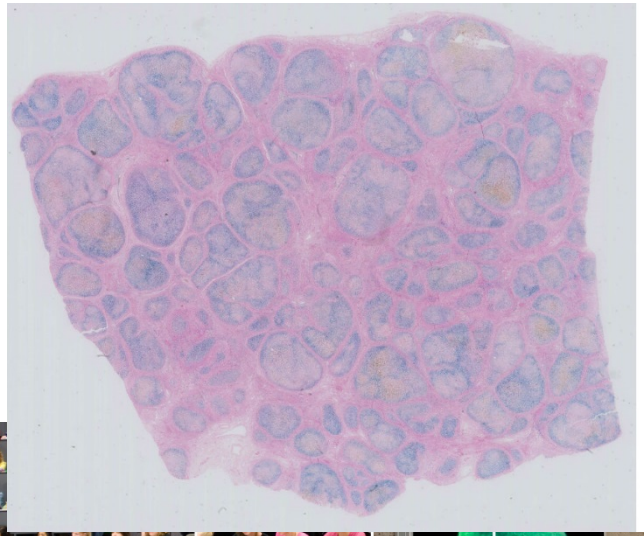


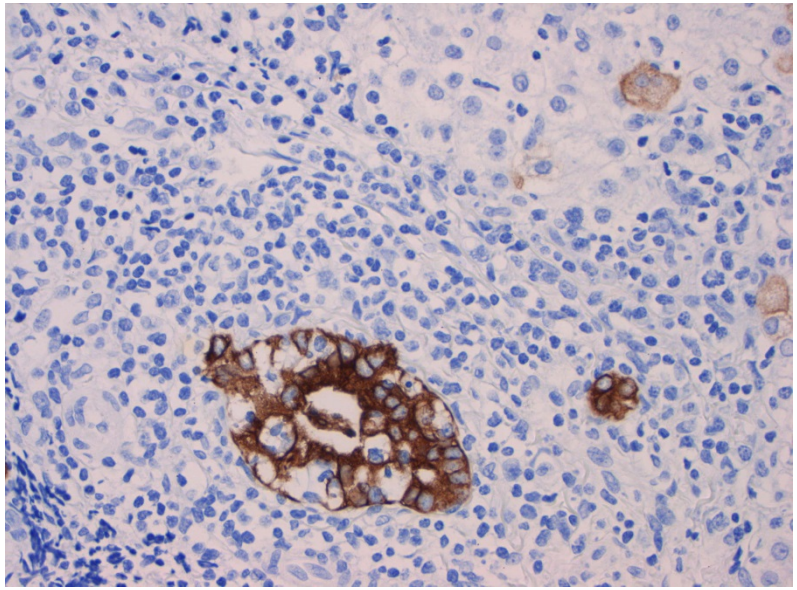
Copper

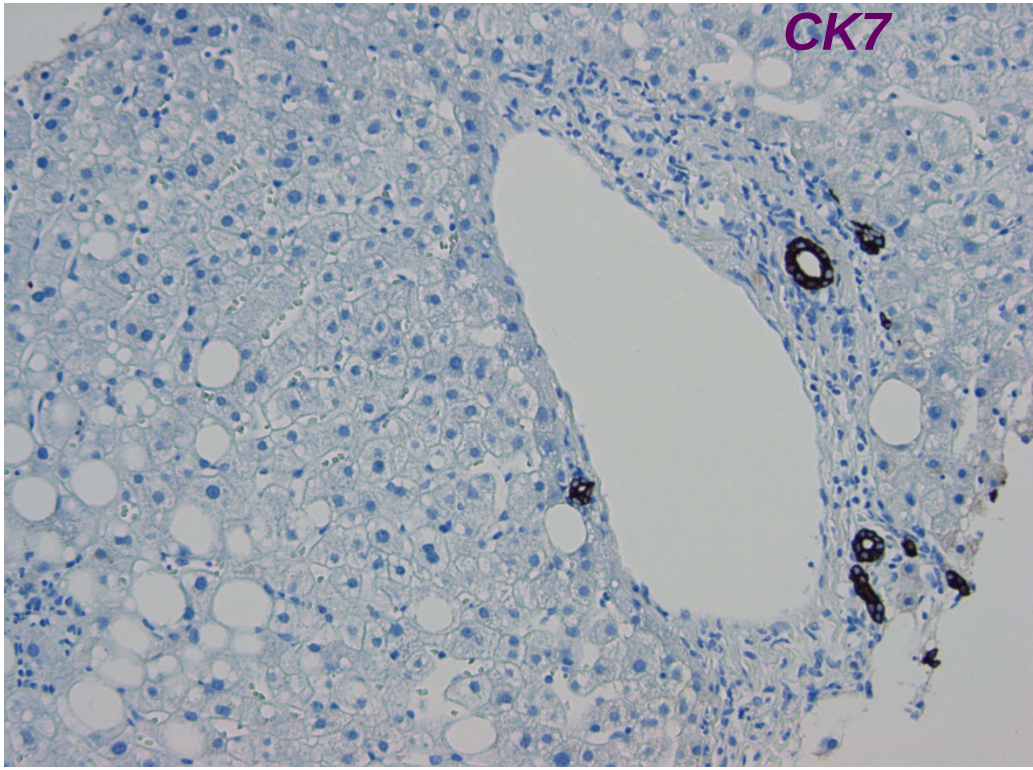
~ normally secreted in bile

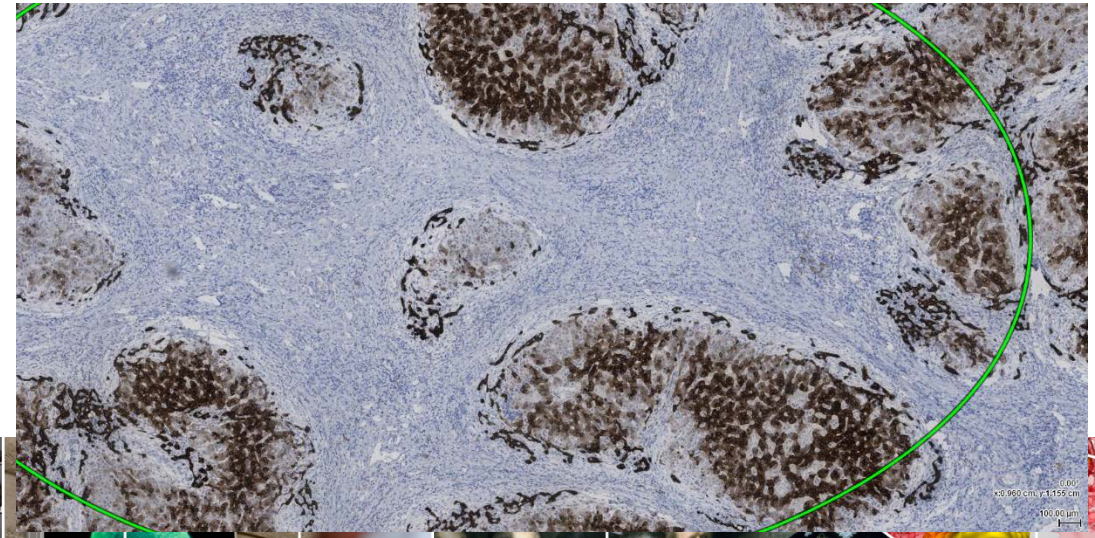


Fe






CK7

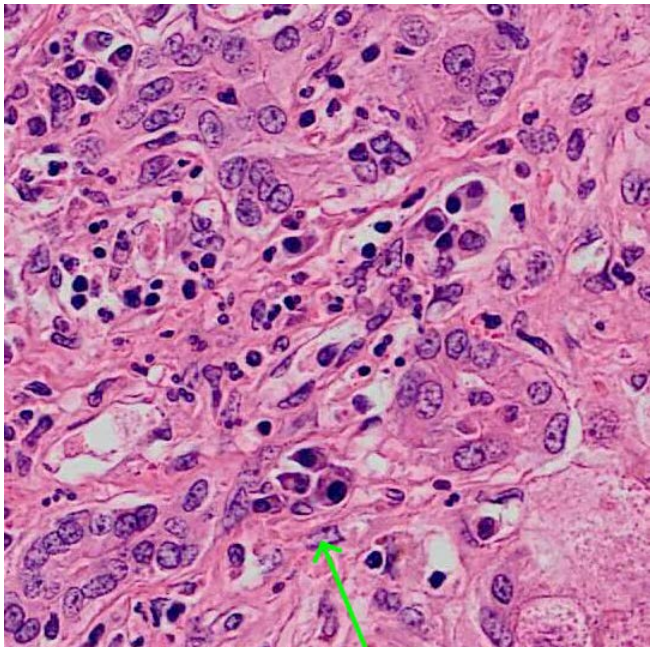



amc

Liver diseases

Diagnostic clues

Inflammatory cells

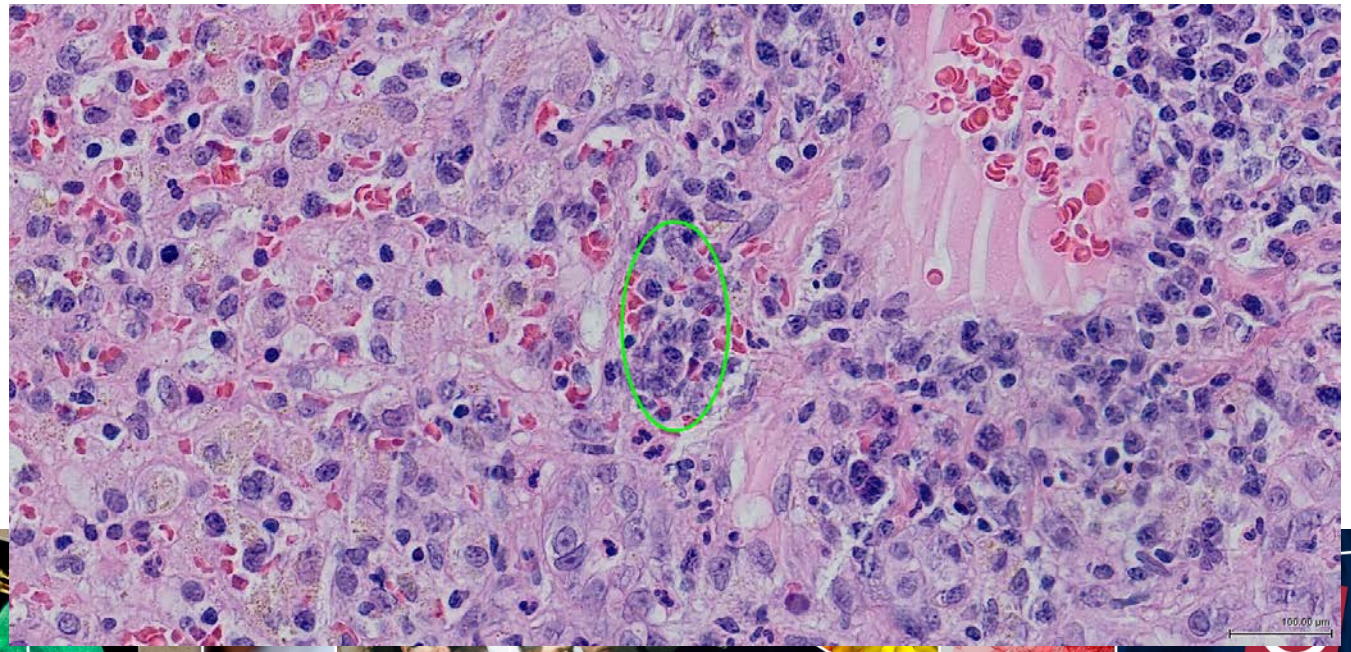


2 verschillende patiënten met acute hepatitis:

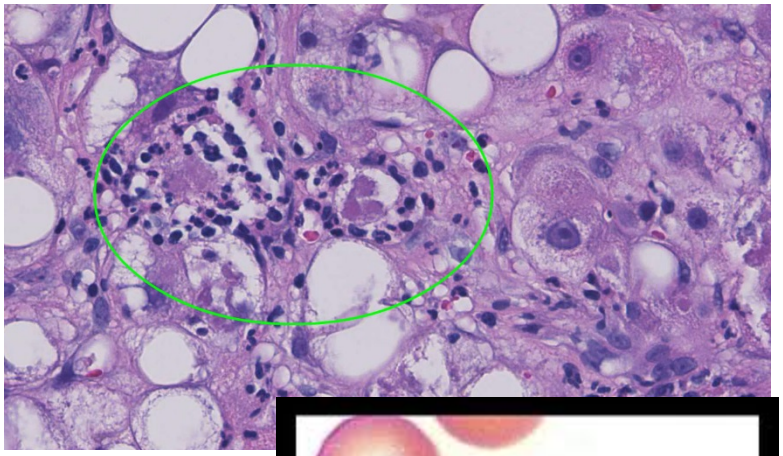
A. 2 x AIH

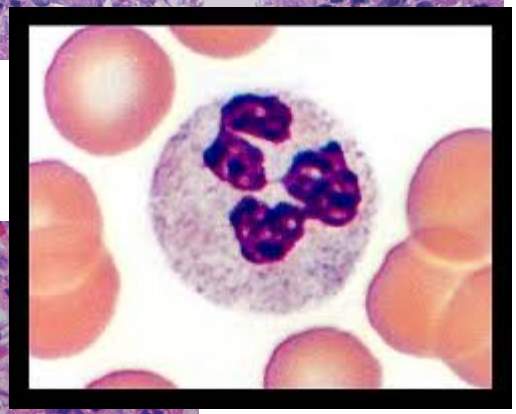
B. 1 x AIH, 1 x AIH-like drug reaction

C. 1 x AIH, 1 x virale hepatitis

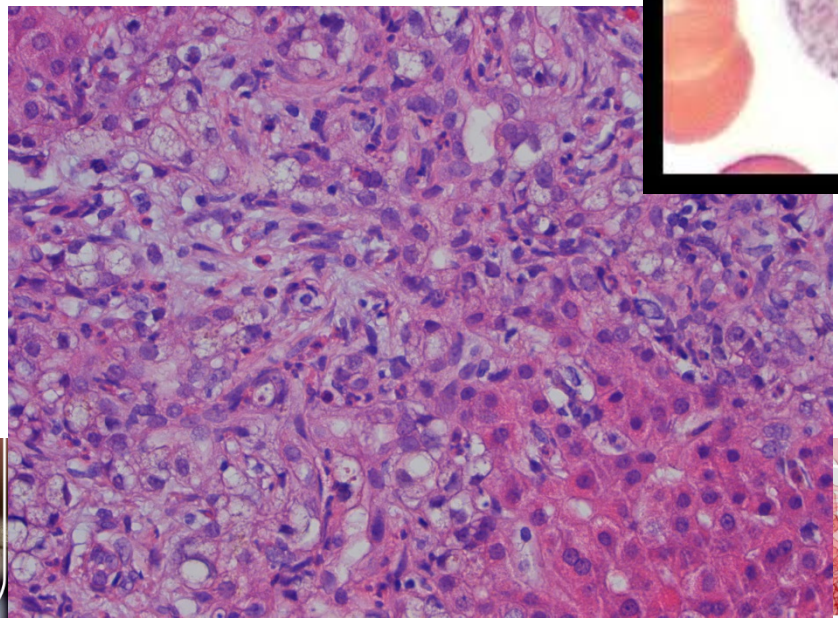


Polymorphs/neutrophils:



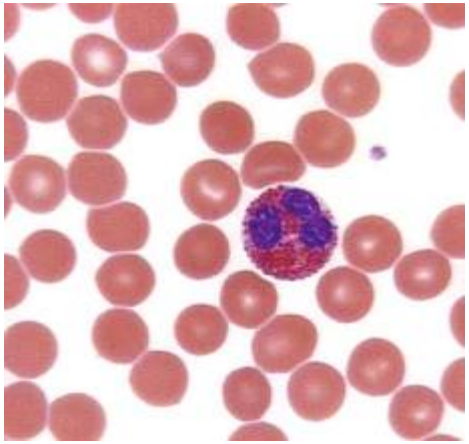


Steatohepatitis
Ductular reaction
Drugs



Microabcesses ~ CMV
Perfusion damage
Surgical necrosis

Eosinophilic granulocytes:



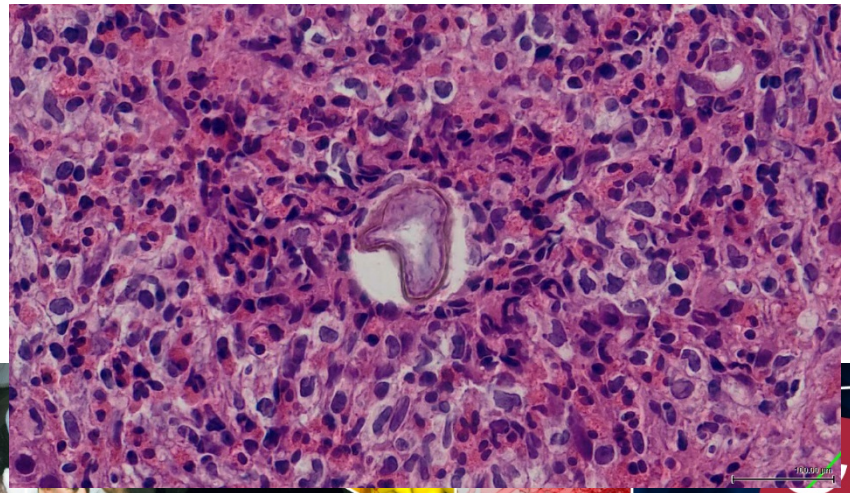
Parasites

Drugs

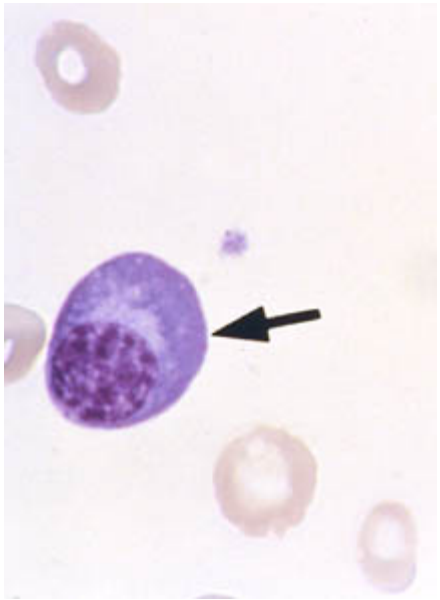
Primary biliairy cholangitis (PBC)/AIH

IgG4 disease

Cellular rejection



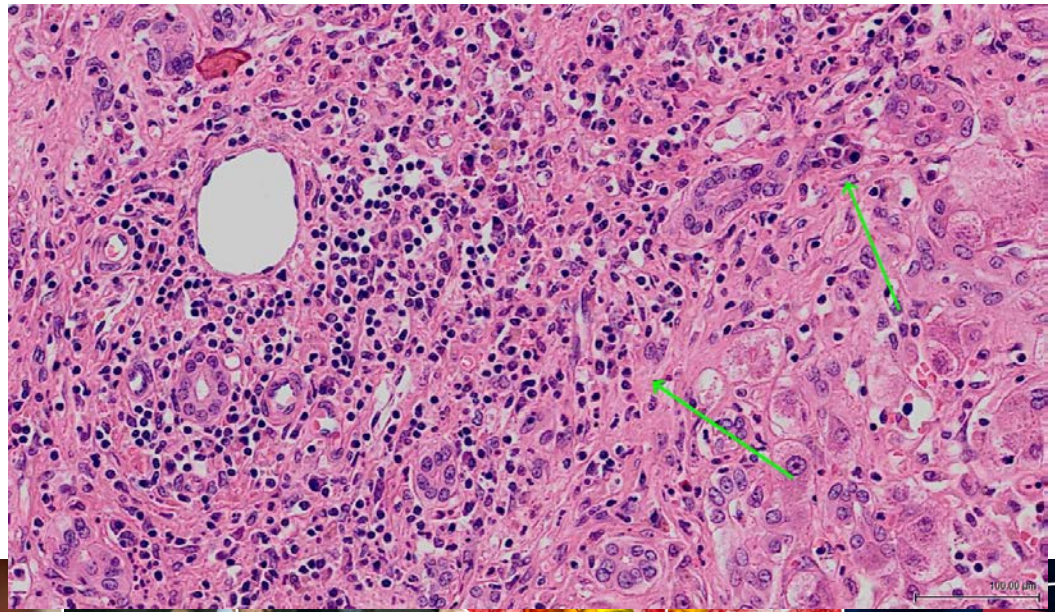
Plasma cells:



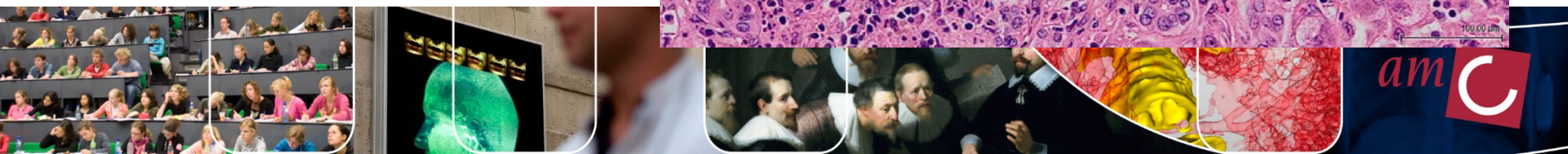
Auto Immune Hepatitis (AIH)

Viral hepatitis

PBC



Drugs



Lymphoid aggregates:

Hepatitis C (or B)

PBC

AIH

Lymphoma

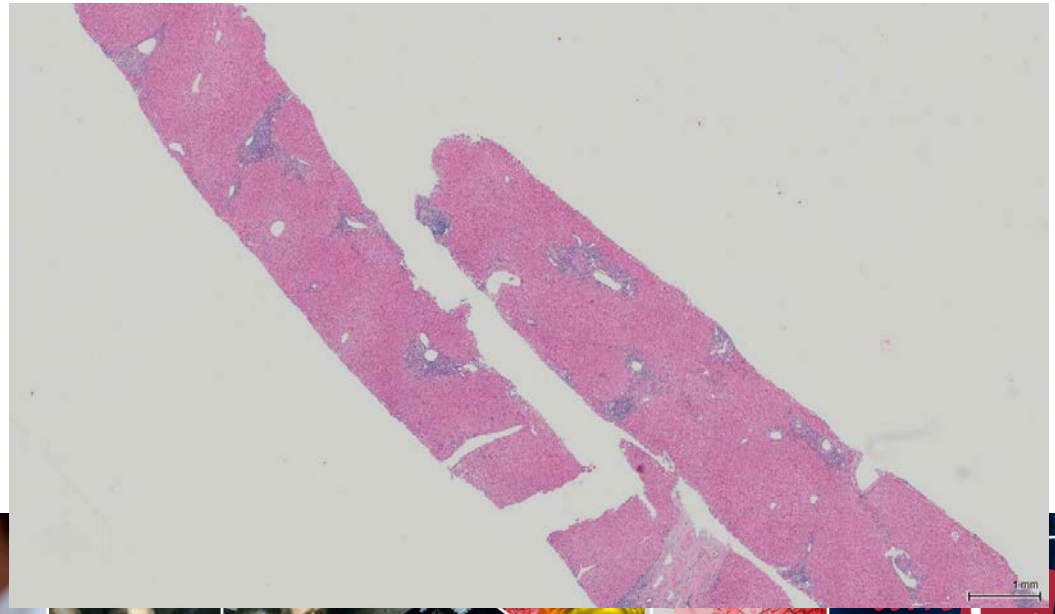
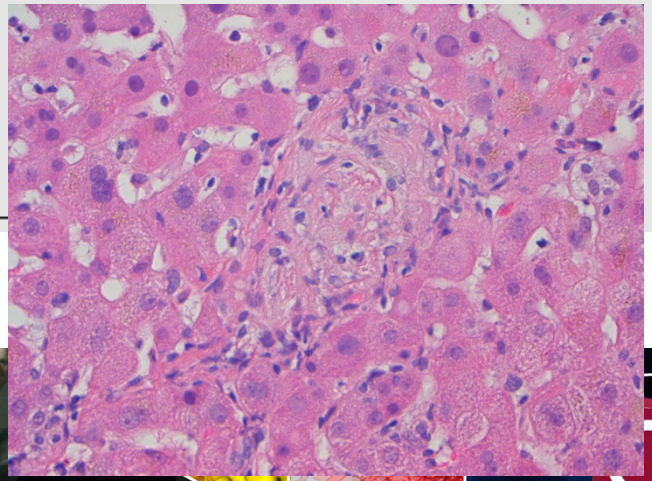


Table 2 Granuloma etiologies and characteristics.

Granuloma etiologies	Granuloma characteristics
Autoimmune	
Sarcoid	Noncaseating epithelioid granulomas
Primary biliary cirrhosis	Noncaseating granulomas near portal triads
Infectious	
Mycobacterium tuberculosis	AFB inside epithelioid granulomas and giant cells often with ring of lymphocytes and histiocytes
M avium intracellulare	Aggregates of foamy macrophages in parenchyma and portal triads with +AFB stain
M leprae	Foamy histiocytes in portal tracts and lobules with multiple AFB found
Brucella	Noncaseating granulomas
Rickettsia	Fibrin ring surrounding vesicle of fat
Francisella	Suppurative microabscesses with surrounding macrophages
Listeria	Microabscesses with small granulomas
Bartonella henselae	Stellate abscesses with three distinct zones
Tropheryma whipplei	Epithelioid granulomas
Histoplasma	Macrophages and lymphocytes with histoplasma and epithelioid cells in center
Schistosoma	Eosinophils with fibrosis and collagen deposition in peri-portal and peri-sinusoidal areas often with egg at the center
Leishmania	Fibrin ring or epithelioid granulomas
Hepatitis C	Epithelioid granulomas
Drugs and Chemicals	Granulomas with eosinophils
Malignancy	Non-necrotic granulomas



Drug-induced hepatitis

Table 2 Overview of drug-induced liver injury patterns

Histological pattern	Differential diagnosis	Common drugs involved
Acute hepatitis and cholestatic hepatitis	Viral hepatitis, autoimmune hepatitis, Wilson disease, idiopathic	See table 3
Acute liver failure		
Necrosis with marked inflammation	Autoimmune hepatitis, viral hepatitis, Wilson disease	Isoniazid, monoamine oxidase inhibitors, anticonvulsants (phenytoin, valproate), antimicrobials (sulfonamides, cotrimoxazole, ketoconazole)
Necrosis with little or no inflammation	Herpes simplex or adenoviral hepatitis, Wilson disease, malignant infiltration	Acetaminophen, cocaine, MDMA (ecstasy), carbon tetrachloride
Microvesicular steatosis with little or no inflammation	Acute alcohol intoxication, Reye syndrome, fatty liver of pregnancy	Tetracycline, nucleoside analogues
Chronic hepatitis		
Autoimmune marker-negative	Autoimmune hepatitis. chronic viral hepatitis, Wilson disease	Lisinopril, sulfonamides, trazodone, uracil, tegafur, tamoxifen, methotrexate
Drug-induced autoimmune hepatitis	Autoimmune hepatitis	Minocycline, nitrofurantoin, methyldopa, clometacin
Cholestasis		
Bland cholestasis	Sepsis, cardiac failure, shock, large duct obstruction, benign intrahepatic cholestasis, intrahepatic cholestasis of pregnancy	Anabolic/androgenic steroids, oestrogenic steroids, NSAIDs (nimesulide, piroxicam)
Cholestatic hepatitis (cholangiolitic or hypersensitivity cholestasis)	Viral hepatitis, large duct obstruction	Chlorpromazine, clarithromycin
Granulomatous hepatitis	Infections, sarcoidosis, primary biliary cirrhosis, talc, metal toxicity	Isoniazid, interferon, phenytoin, allopurinol (also see box 2)
Steatosis/steatohepatitis		
Macrovesicular steatosis	Diabetes, obesity, Wilson disease, hepatitis C	Alcohol, steroids, total parenteral nutrition, gold, chlorinated hydrocarbons, chemotherapeutic agents (5-fluorouracil)
Microvesicular steatosis	Fatty liver of pregnancy, carnitine deficiency, Reye syndrome	Cocaine, tetracycline, valproic acid, zidovudine
Steatohepatitis	(See macrovesicular steatosis differential)	Amiodarone, chemotherapeutic agents (irinotecan), perhexiline
Vascular abnormalities		
Sinusoidal obstruction syndrome	Myeloablation, venous outflow obstruction, right heart disease	Oxaliplatin, pyrrolizidine alkaloids, chemotherapy for ALL

ALL, acute lymphoblastic leukaemia; MDMA, 3,4-methylenedioxymethylamphetamine; NSAID, non-steroidal anti-inflammatory drug.

J Clin Pathol 2009;**62**:481–492. doi:10.1136/jcp.2008.058248

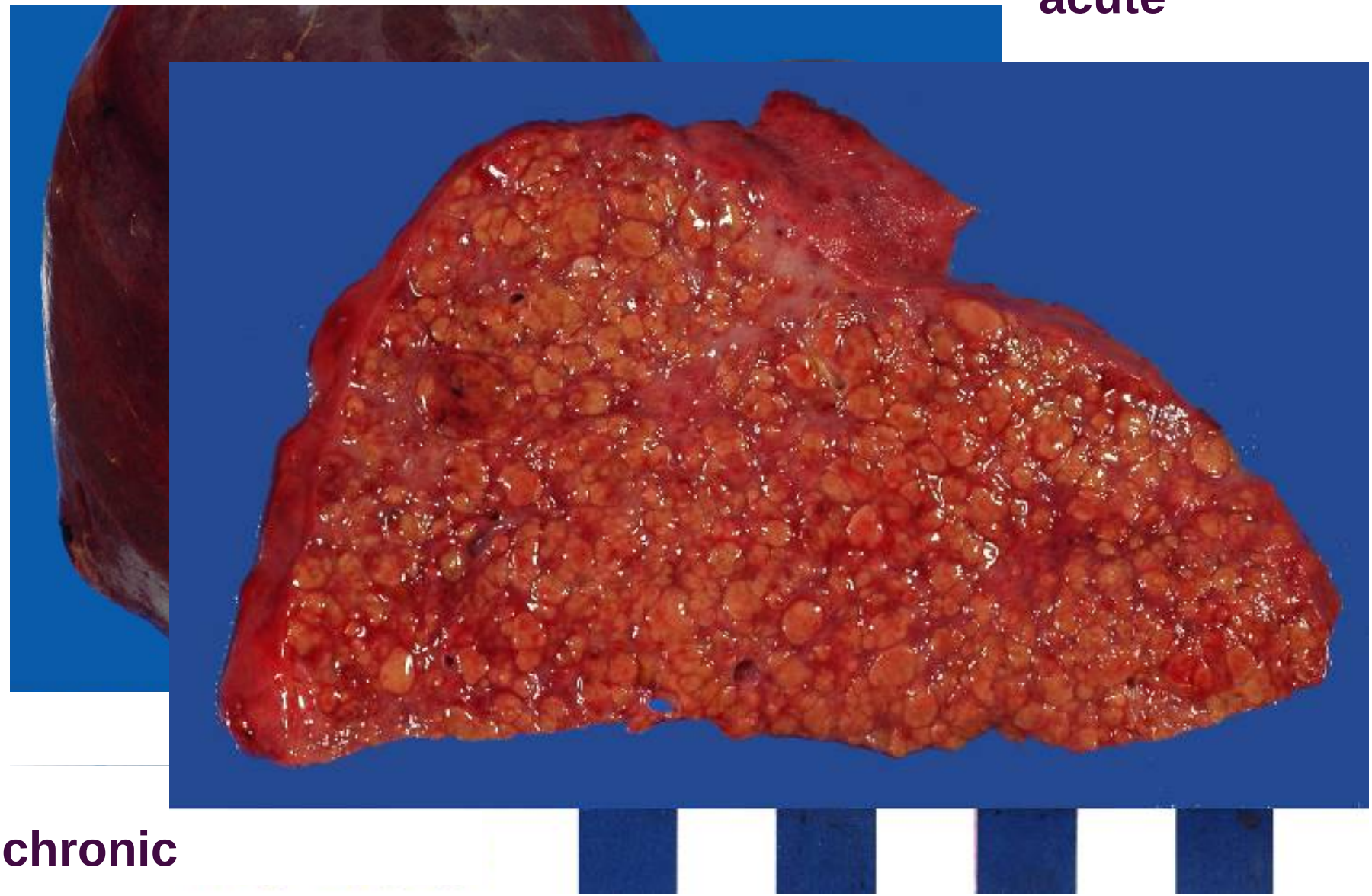
Drug-induced hepatitis

Altijd in de DD!!!

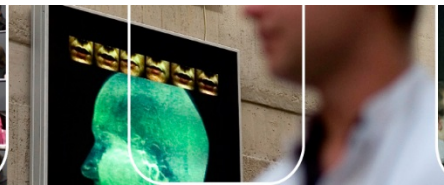
Hepatitis

Acute vs chronic

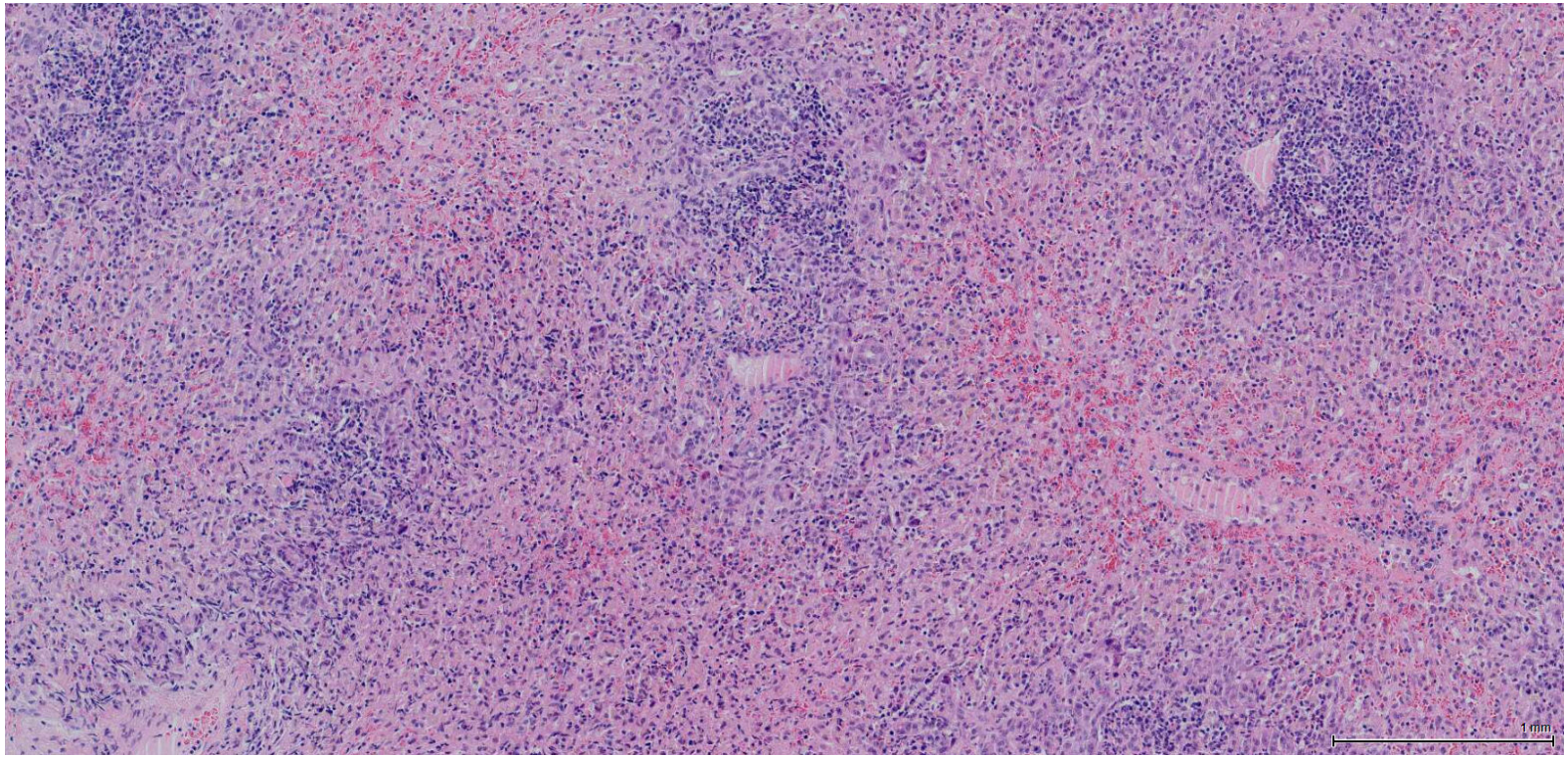
acute



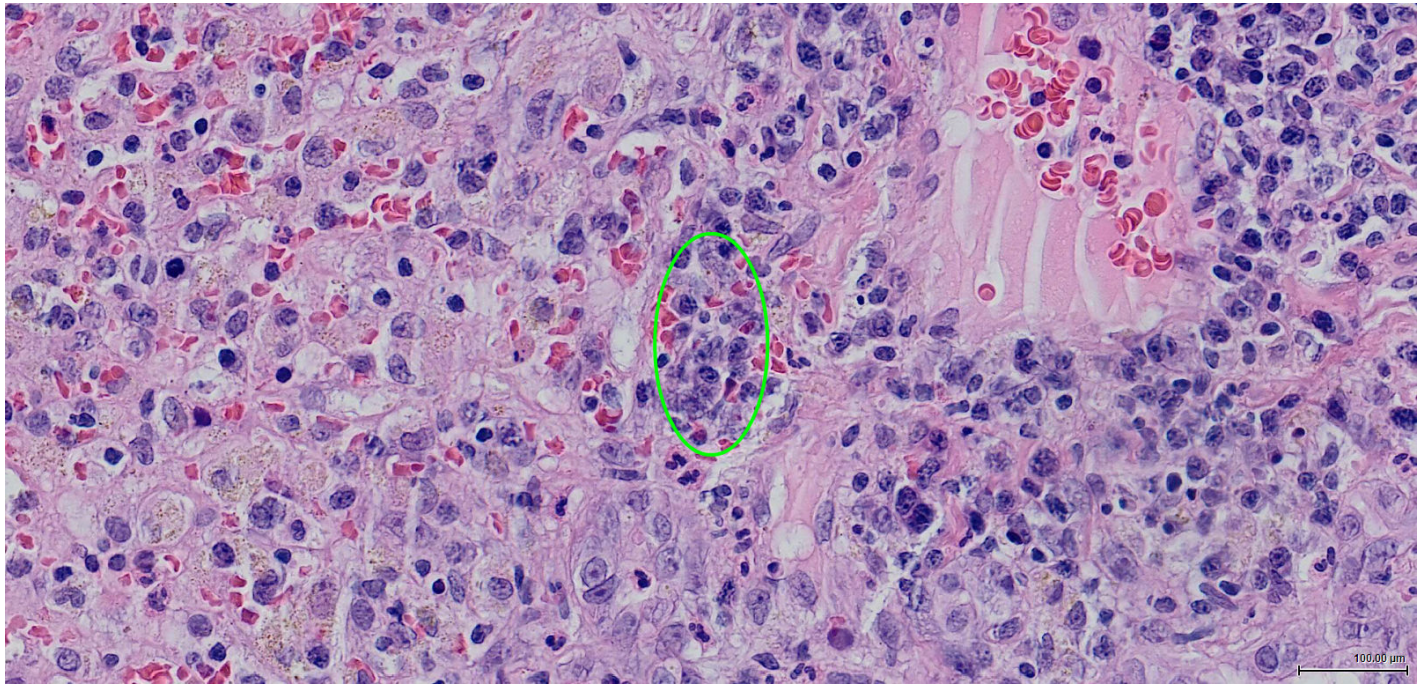
chronic

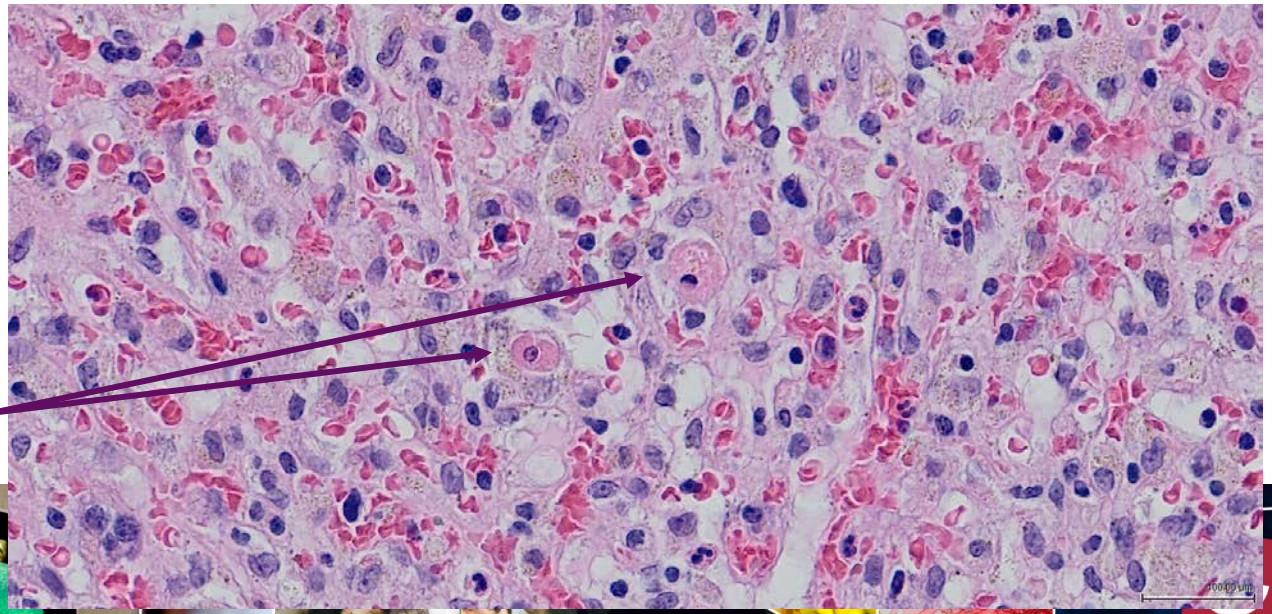


Acute HBV



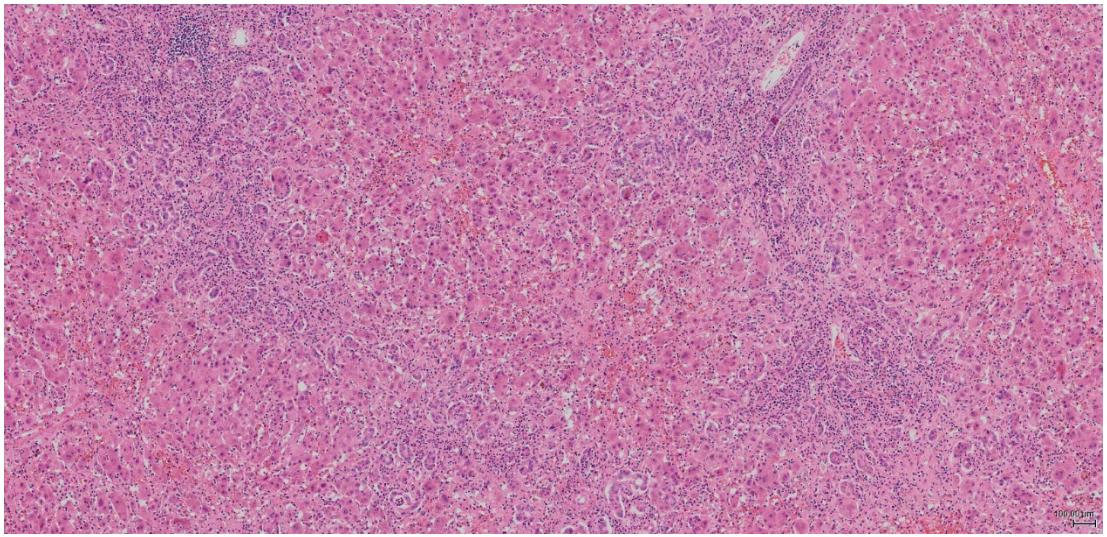
HbS en HbC (-)

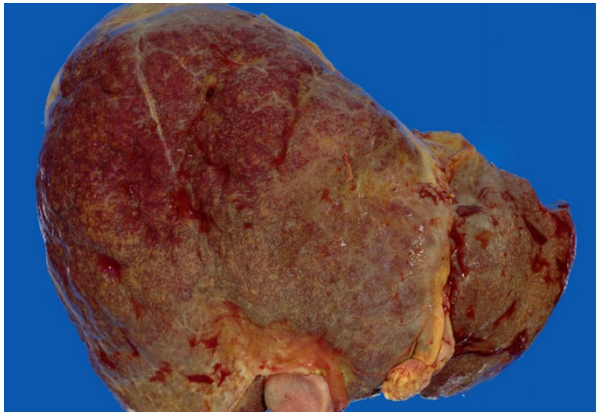


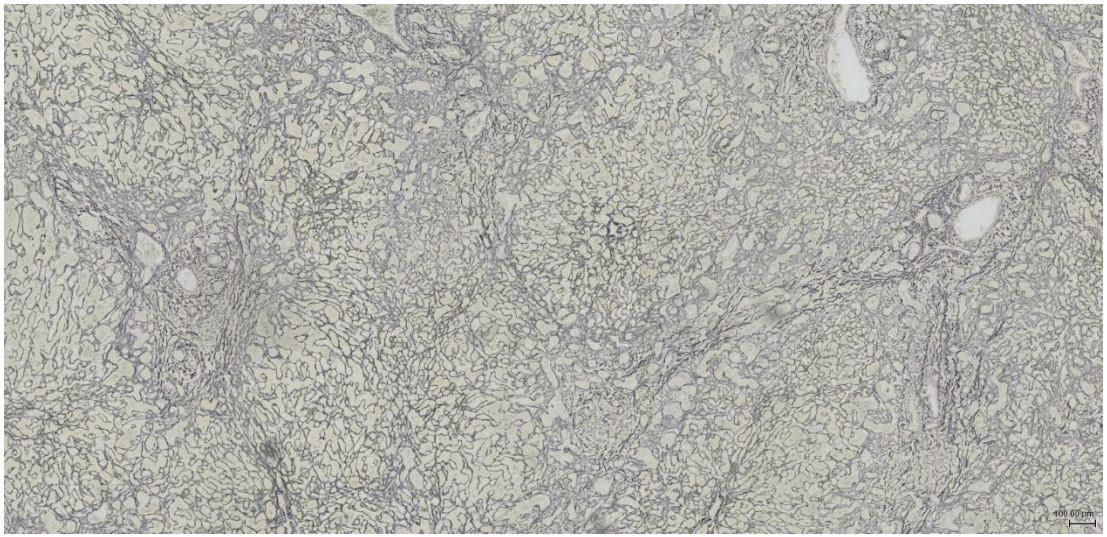


Councilman bodies

Acute AIH







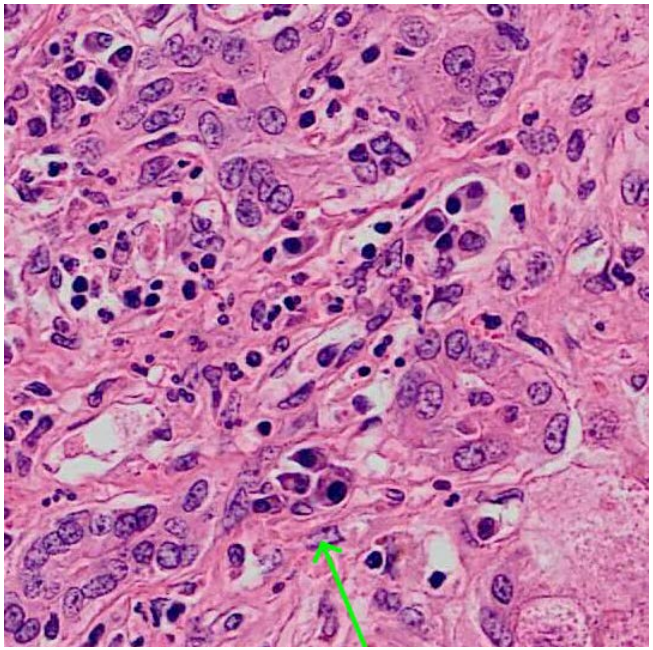


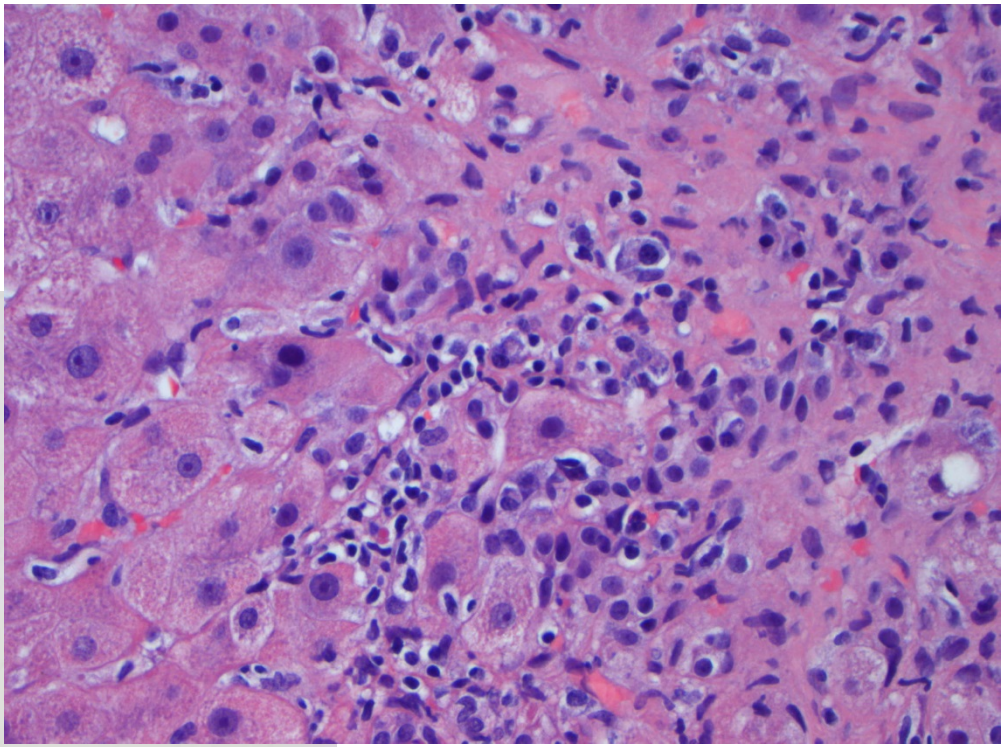
Table 2. Simplified Diagnostic Criteria for the Diagnosis of AIH

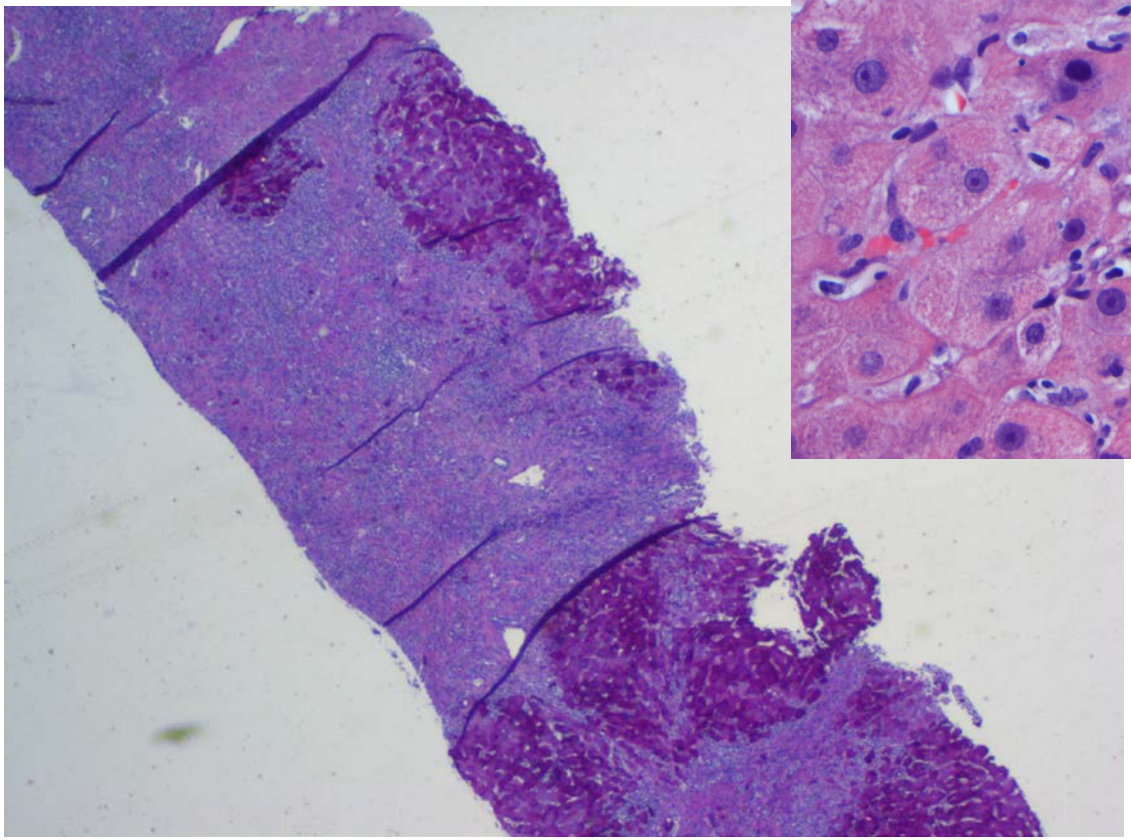
Parameter	Discriminator	Score
ANA or SMA +	≥1:40	+1
ANA or SMA +	≥1:80 or	+2
LKM +	≥1:40 or	+2
SLA	Positive	+2
IgG Level	>Upper limit of normal	+1
	>1.1× Upper limit of normal	+2
Liver Histology	Compatible with AIH	+1
	Typical of AIH	+2
Absence of Viral Hepatitis	No	0
	Yes	+2

Adapted from Hennes et al.[8]
≥6 points: Probable AIH
≥7 points: Definite AIH

Yeoman AD, Westbrook RH, Al-Chalabi T, Carey I, Heaton ND, Portmann BC, Heneghan MA. Diagnostic value and utility of the simplified International Autoimmune Hepatitis Group (IAIHG) criteria in acute and chronic liver disease. Hepatology. 2009 Aug;50(2):538-45.

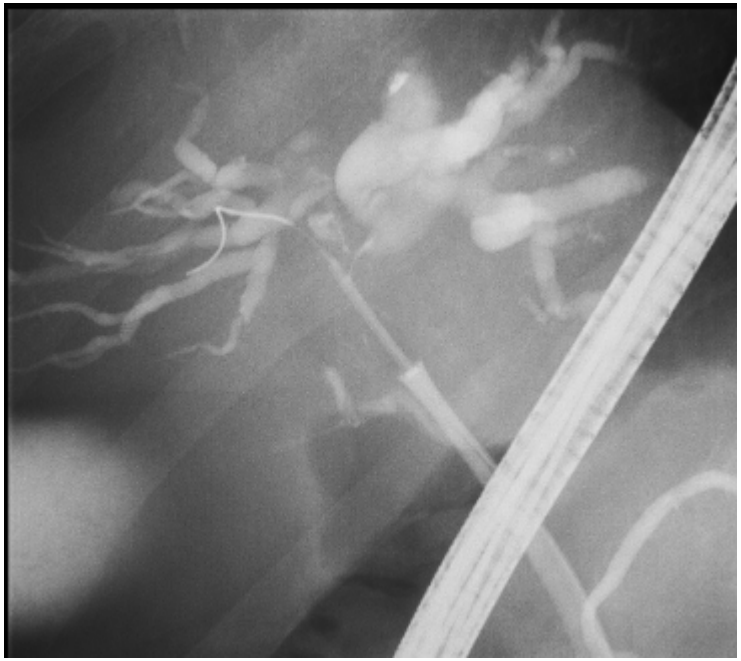
Vrouw, 78 jaar



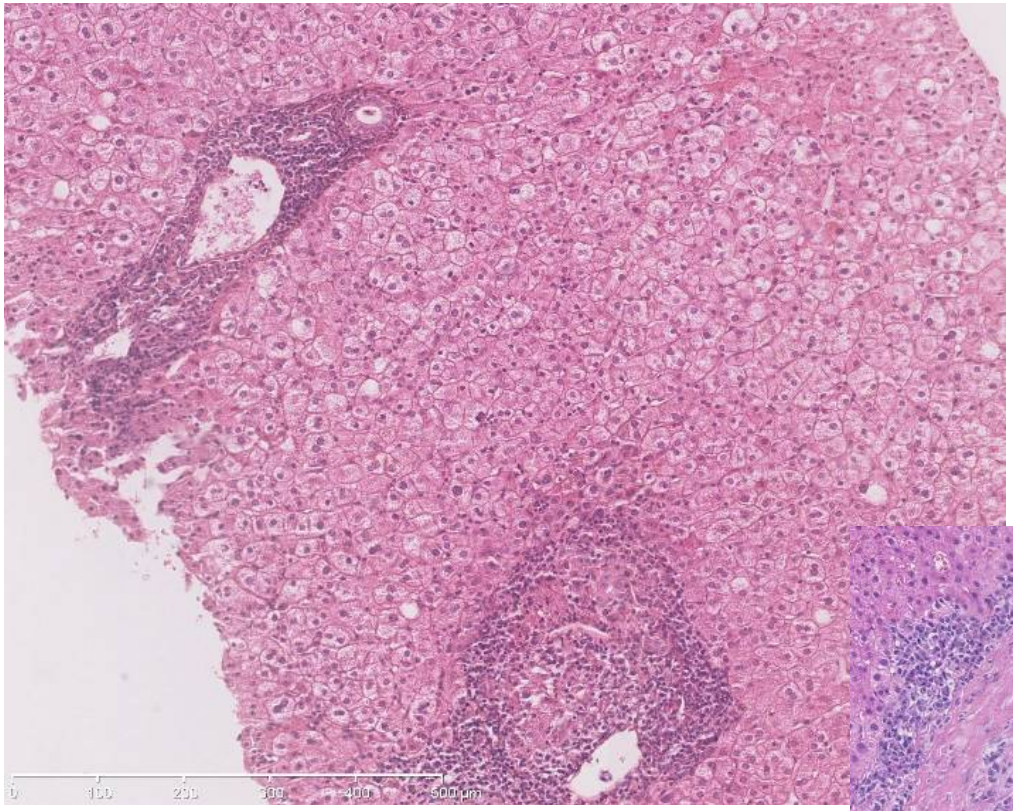


R/ Nitrofurantoine

Bjornsson et. Drug-Induced Autoimmune Hepatitis: Clinical Characteristics and Prognosis. Hepatology 2010



Primary Biliary Cholangitis (PBC)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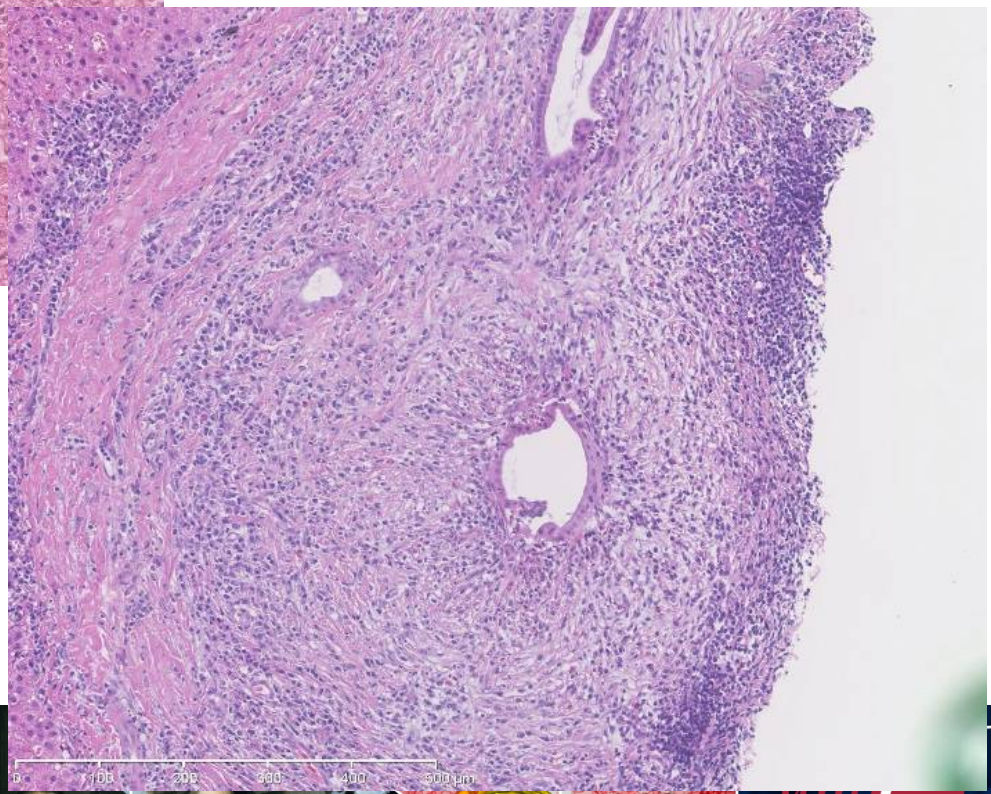
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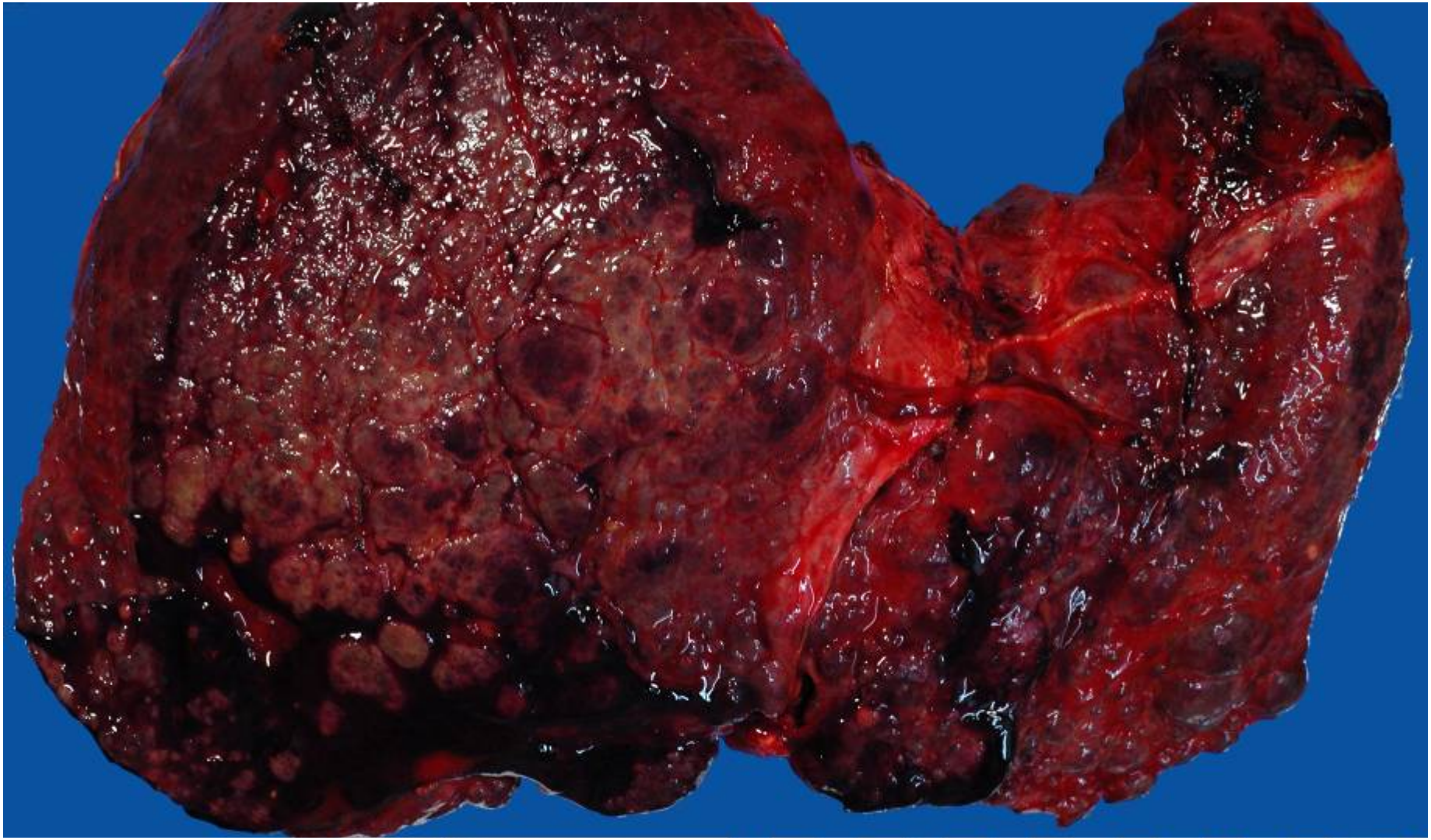


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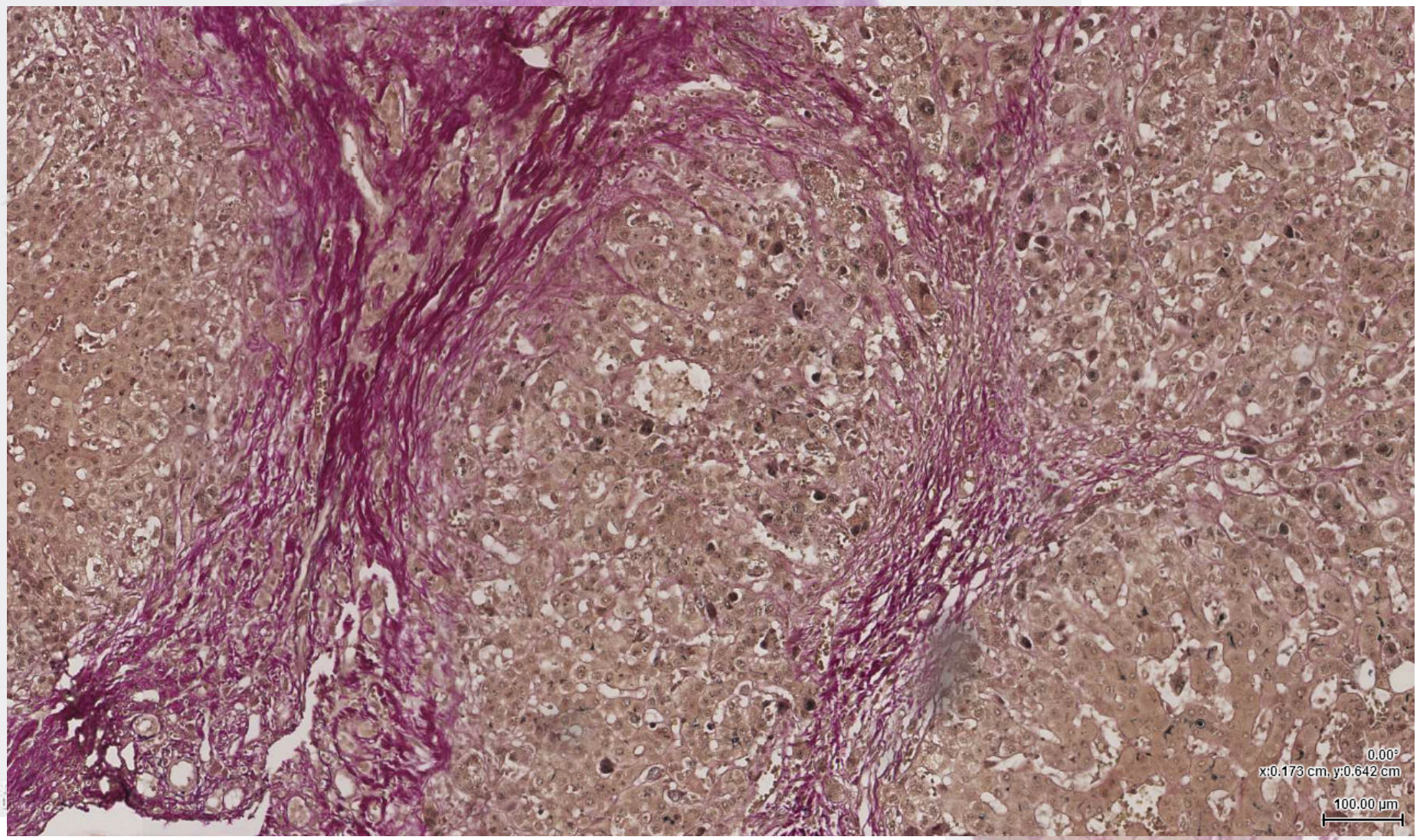
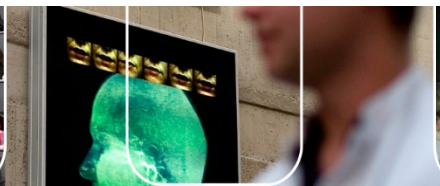
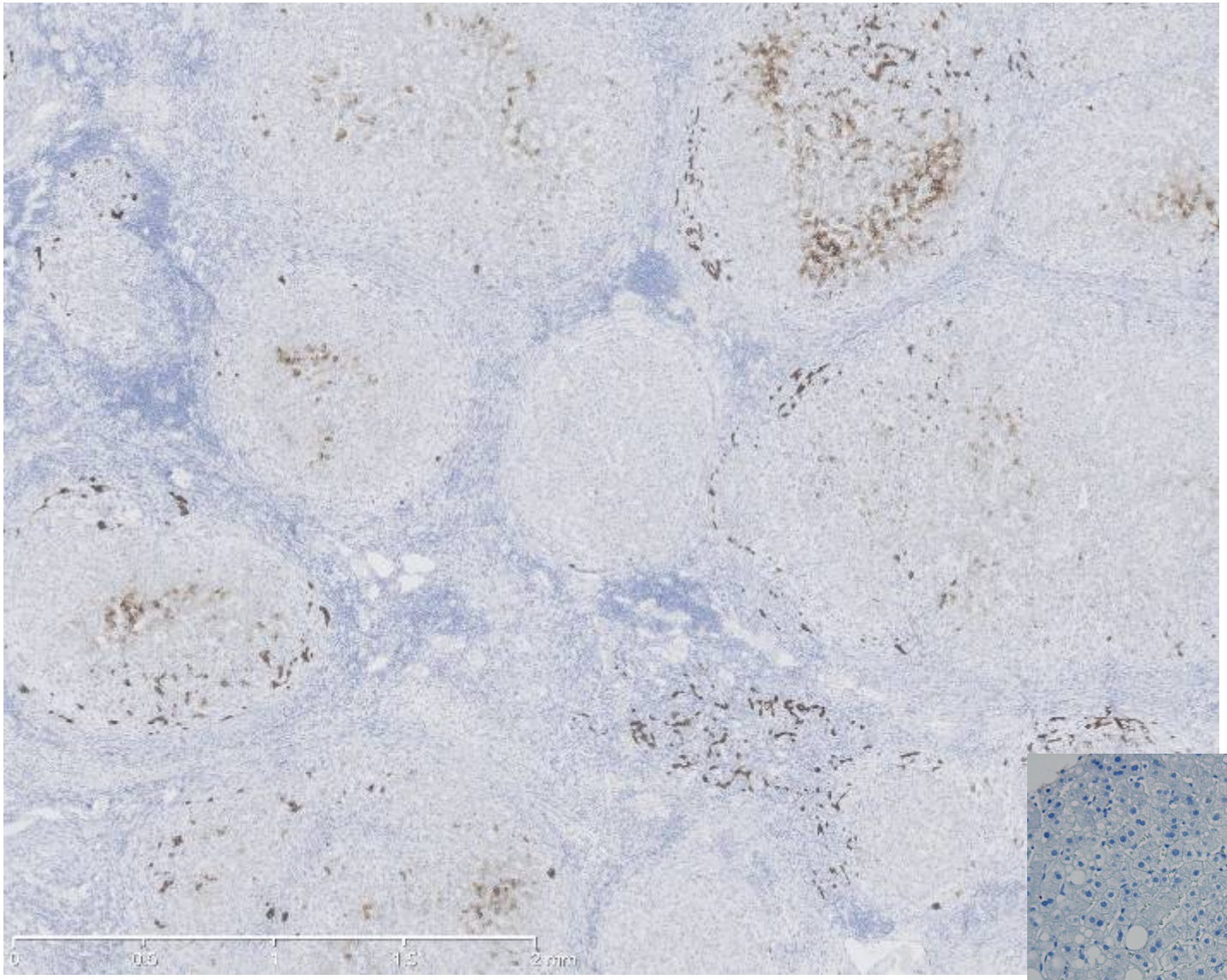
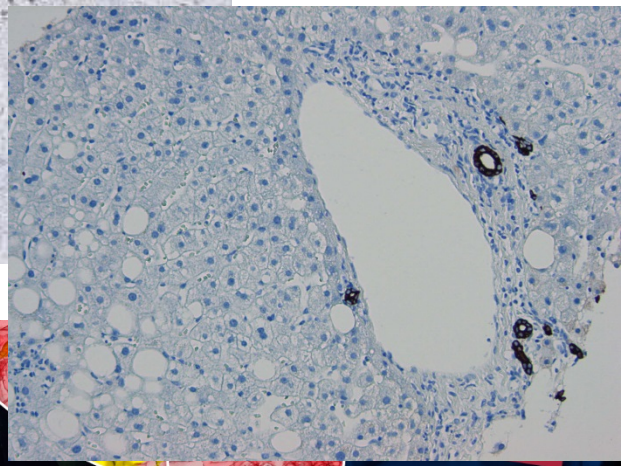
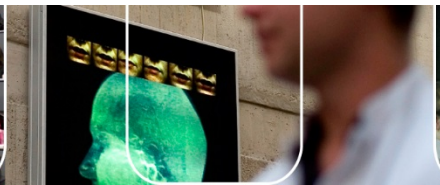
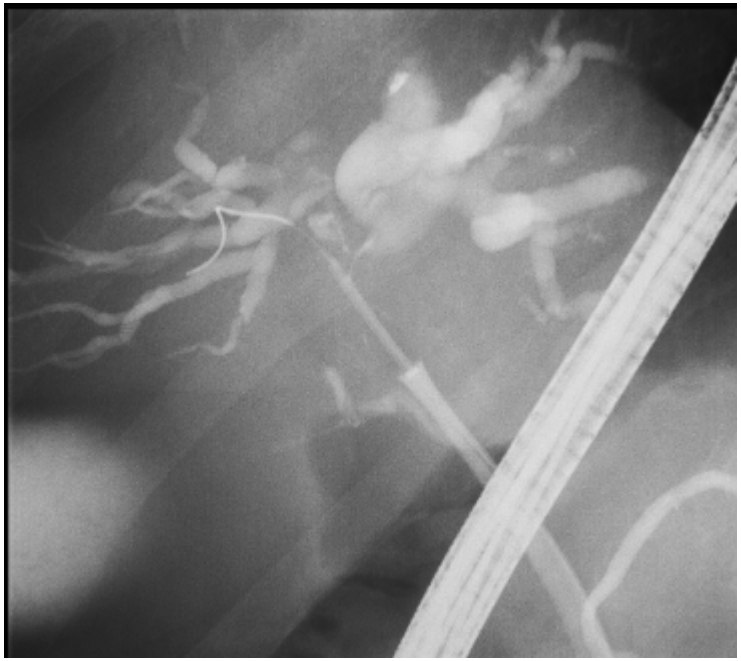

0.00°
x:0.173 cm, y:0.642 cm
100.00 µm




0
0.5
1
1.5
2 mm







Primary Sclerosering Cholangitis (PSC)

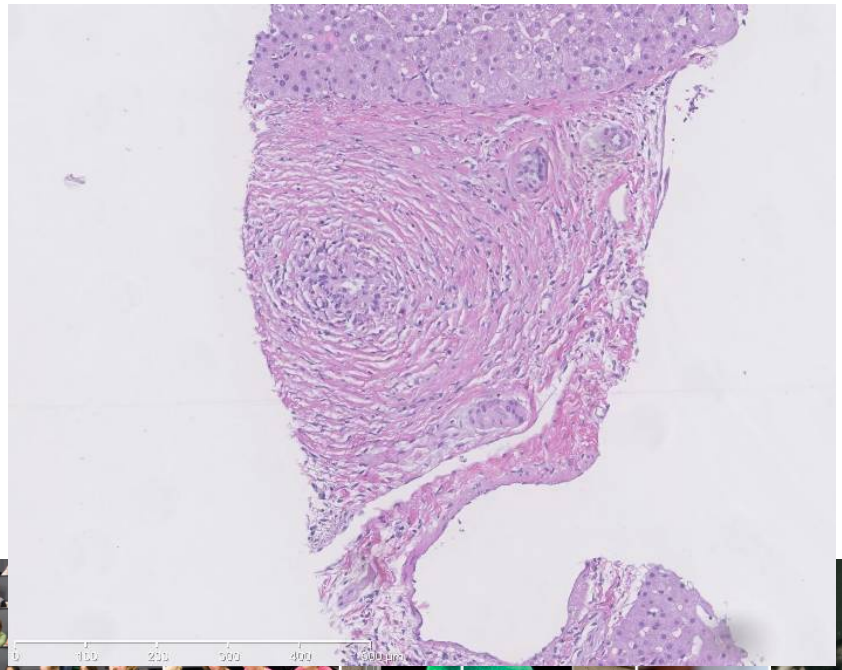
Table 11.5 Disorders leading to secondary sclerosing cholangitis

Infectious	
	Cryptosporidiosis and/or CMV infection
	Primary immunodeficiency (CD40 ligand, combined immunodeficiency)
	Secondary immunodeficiency (AIDS cholangiopathy)
	Hydatid cysts (rupture)
Ischaemic	
	Liver allograft: thrombotic or foam cell arteriopathy
	Intra-arterial infusion chemotherapy
	Radiation injury
	Recurrent pyogenic cholangitis
Toxic (caustic)	
	Scolicidal hydatic cyst injection
Neoplastic	
	Langerhans cell histiocytosis
	Malignant infiltration (rare)
Mechanical	
	Choledochal varices (portal vein block, cavernous transformation)

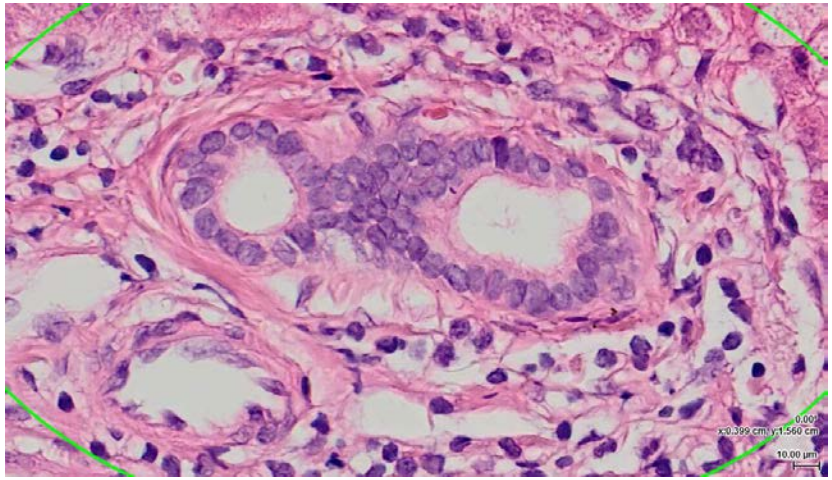
Histopathology

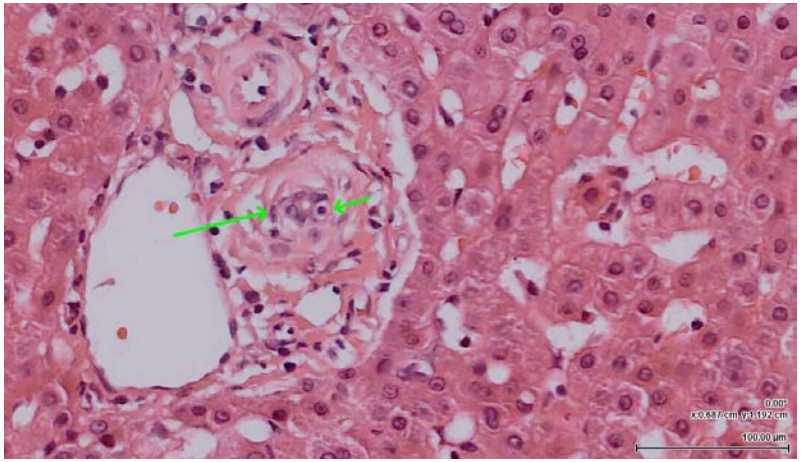
Major bile ducts frequent site of injury… upstream non-specific features of obstruction (dd small duct PSC)

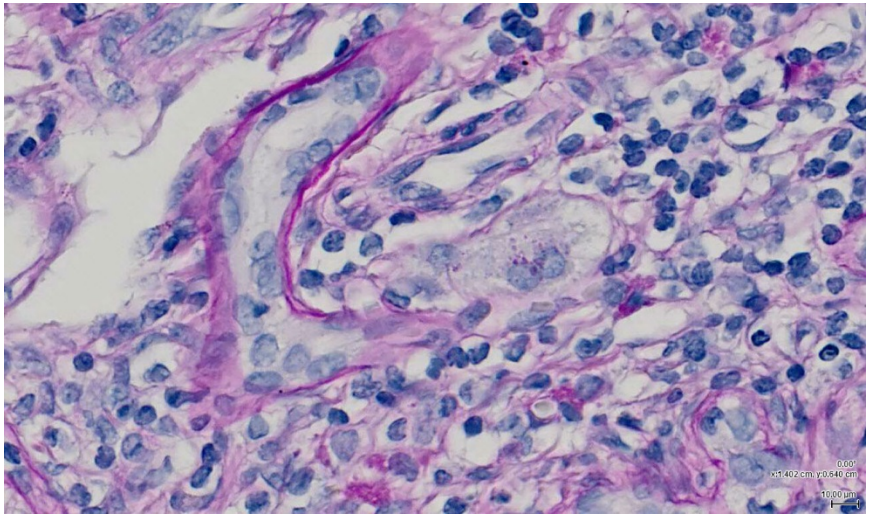
Fibro-obliterative ductal lesions with ‘onion-skin’ type, periductal fibrosis → destruction of bile ducts and ductopenia.

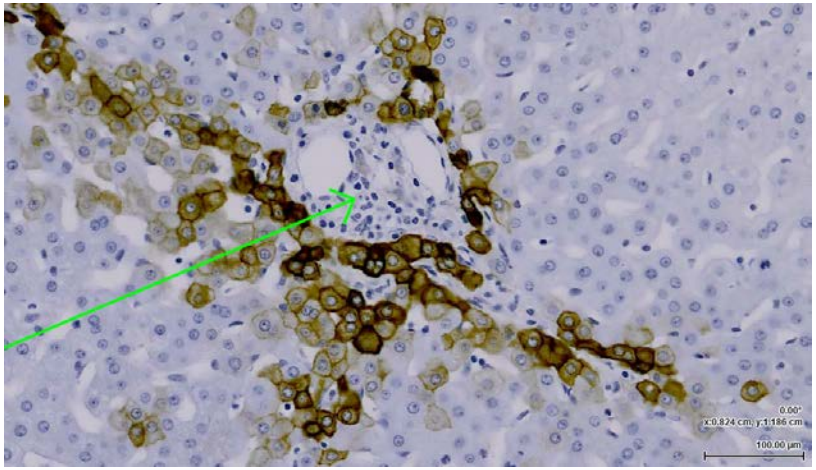


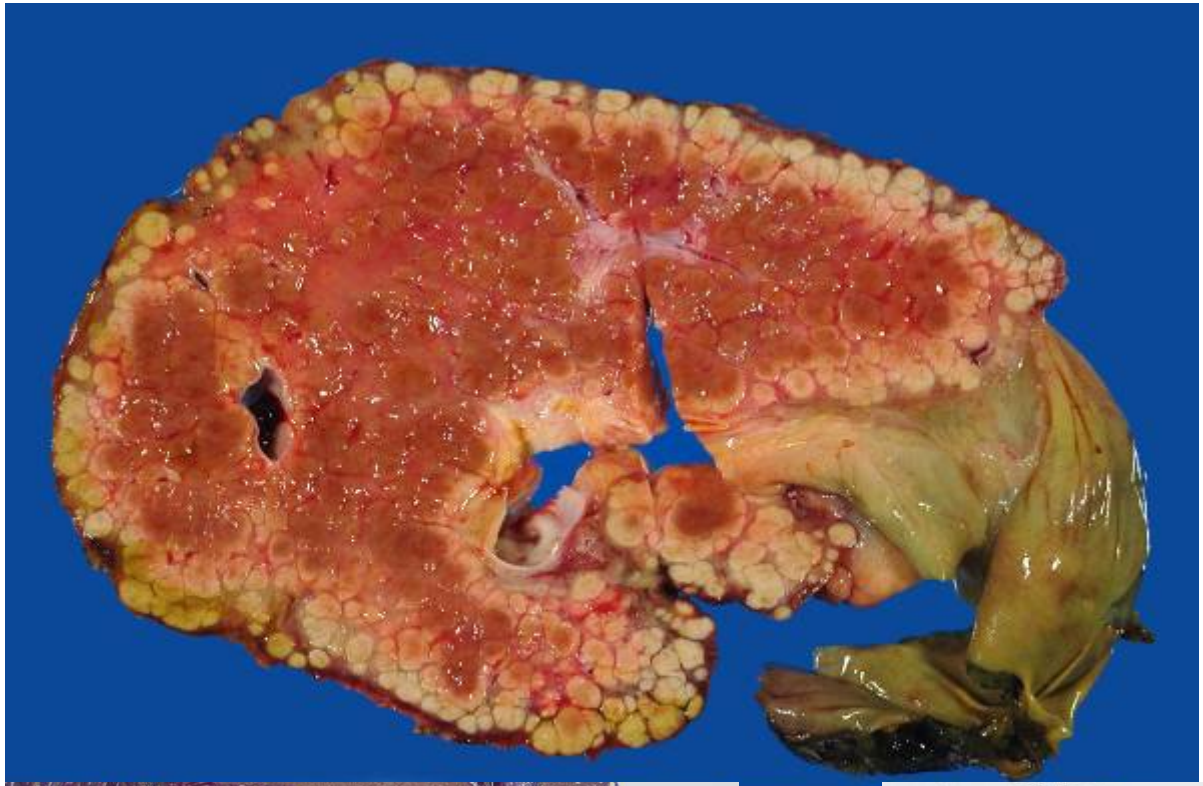
Association with IBD (50-**80**%)

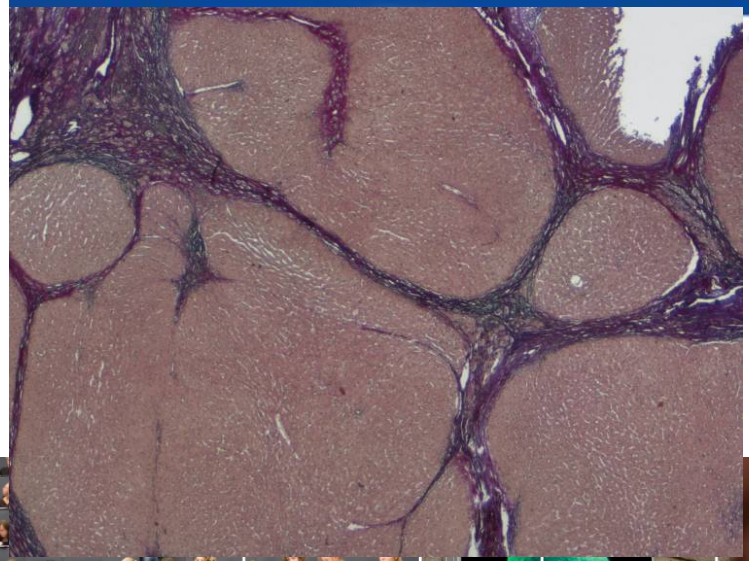


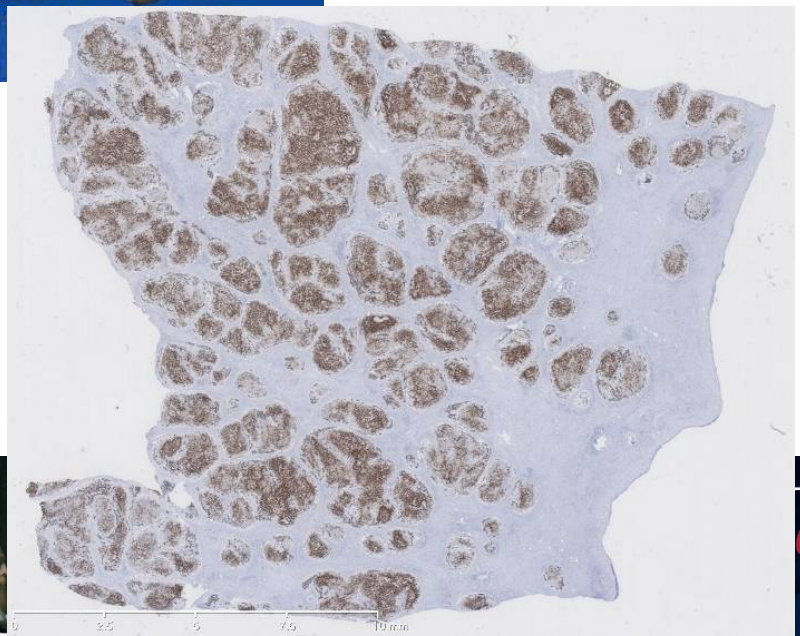






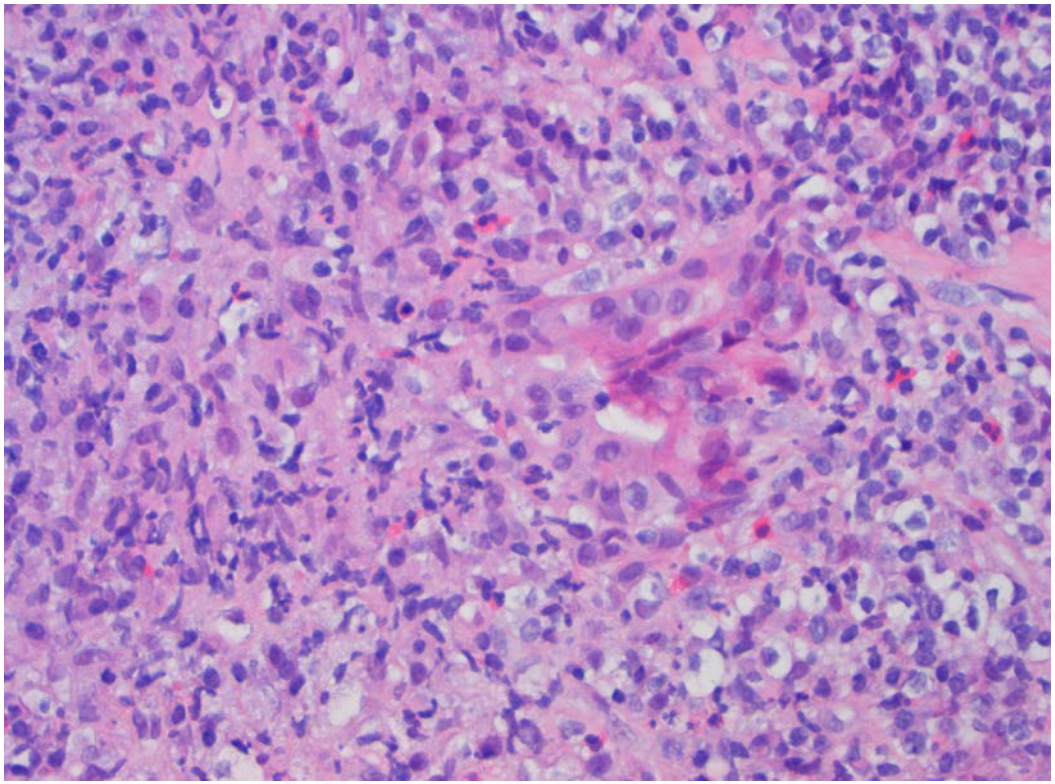




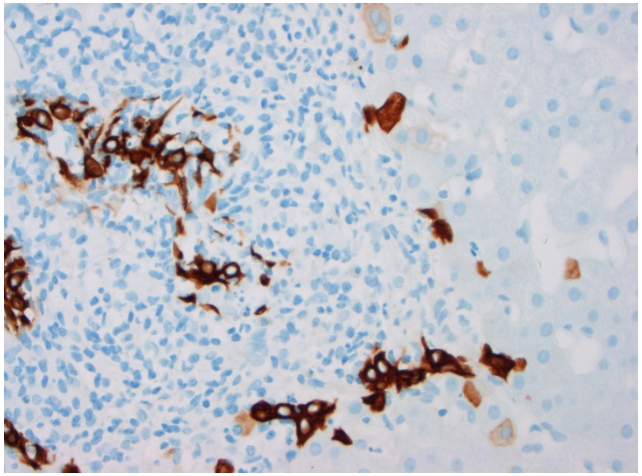

0
2.5
5
7.5
10 mm

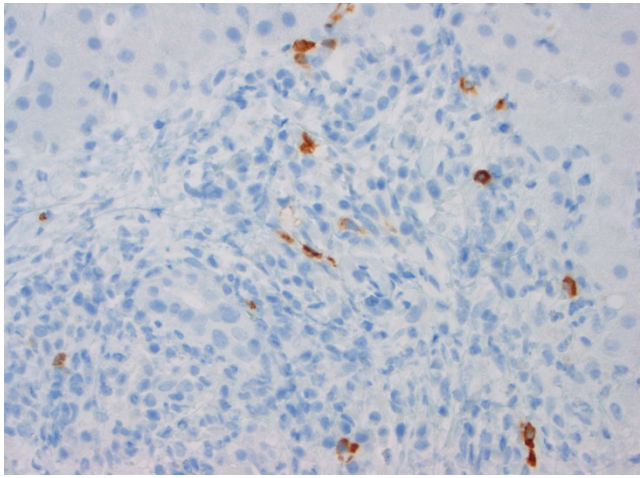

am

IgG4 cholangiopathie



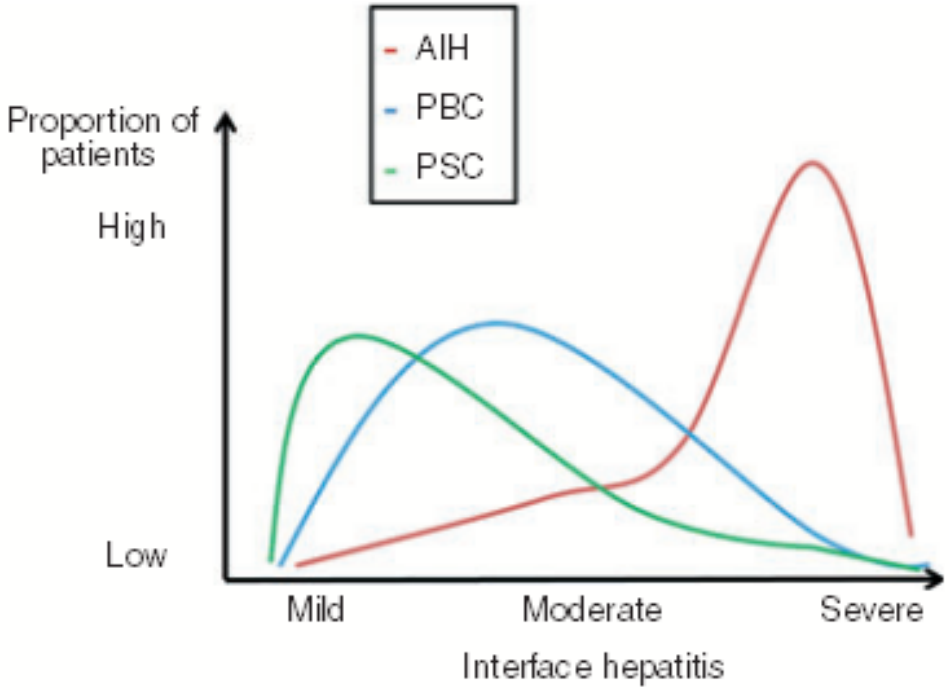
CK7





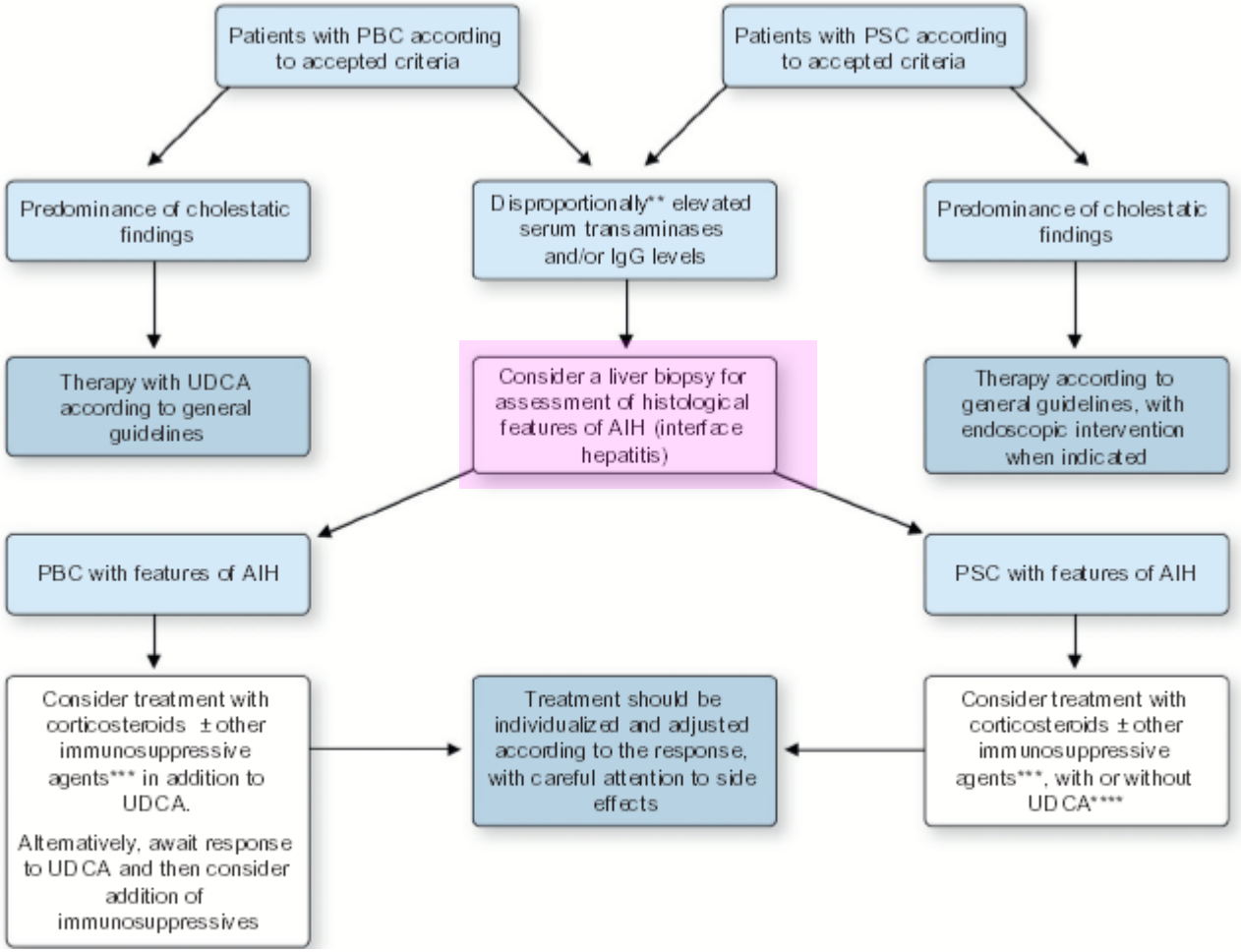
IgG4

Bile duct injury/overlap syndrome



Presence of severe interface hepatitis in primary biliary cirrhosis portends a worse prognosis

Trivedi PJ, Hirschfield GM.
Aliment Pharmacol Ther. 2012 Sep;36(6):517-33



Overlap syndromes: The International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue

Kirsten Muri Boberg[1,*], Roger W. Chapman[2], Gideon M. Hirschfield[3], Ansgar W. Lohse[4], Michael P. Manns[5], Erik Schrumpf[1], on behalf of the International Autoimmune Hepatitis Group

Journal of Hepatology 2011 vol. 54 | 374–385

Chronic hepatitis

- ***6 months***

Inflammation and scarring

(grading and staging)

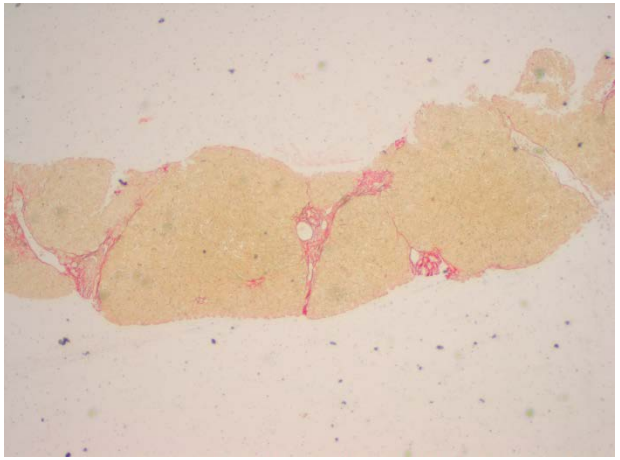
Grading and staging

Chronic (viral) hepatitis: Metavir (F1-F4), Ishak (F1-F6)

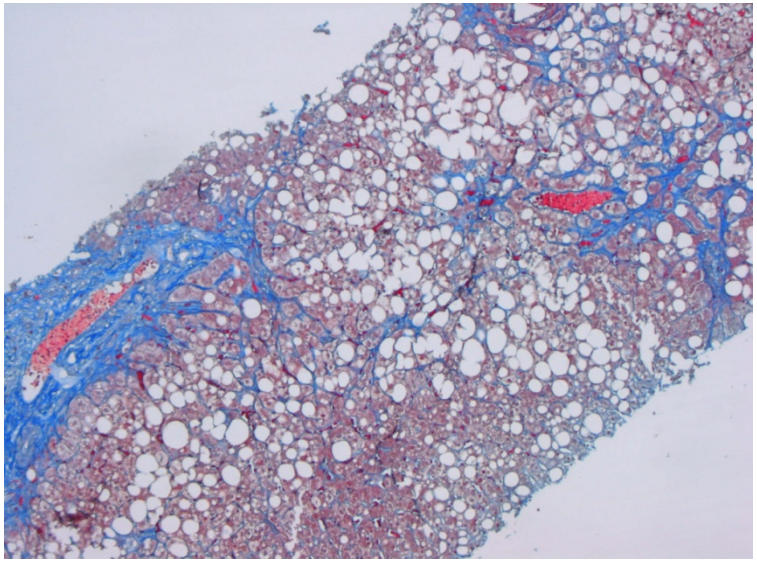
NASH: Kleiner-Brunt, SAF score

Biliary disease (PBC): Ludwig staging system, Nakanuma

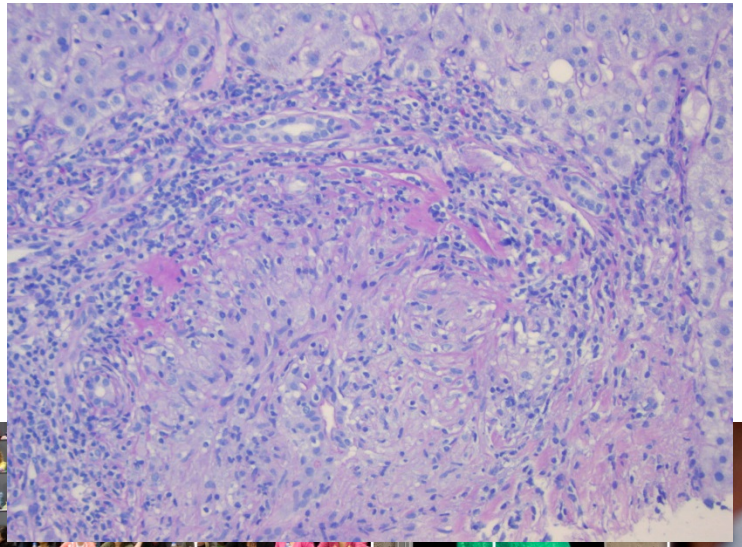
Grading and staging



HBV: Metavir F2, Ishak F3

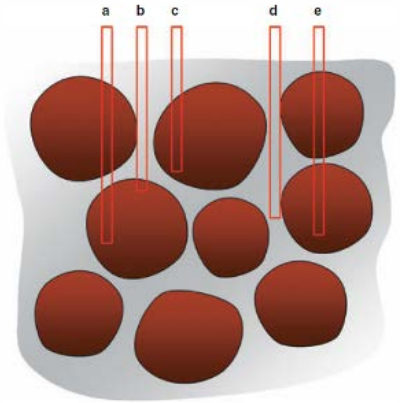


NASH, Brunt F2



PBC, Ludwig stadium 2

Attention



Patchy distribution of some diseases

adequate biopsy

Interobservariability

double reading, consensus

validation ~ clinical relevancy

CIRROSE

René Laënnec (1781-1826) in "*De l'auscultation médiate ou Traité du Diagnostic des Maladies des Poumons et du Coeur*"(1819).

"Le foie réduit au tiers de son volume se trouvait caché dans la région qu'il occupe; incisé, il paraissait entièrement composé d'une multitude de grains de la grosseur d'un frain de chènevis ou de millet, de couleur jaune ou jaune roux."

Cirrhosis histology and Laennec staging system correlate with high portal pressure

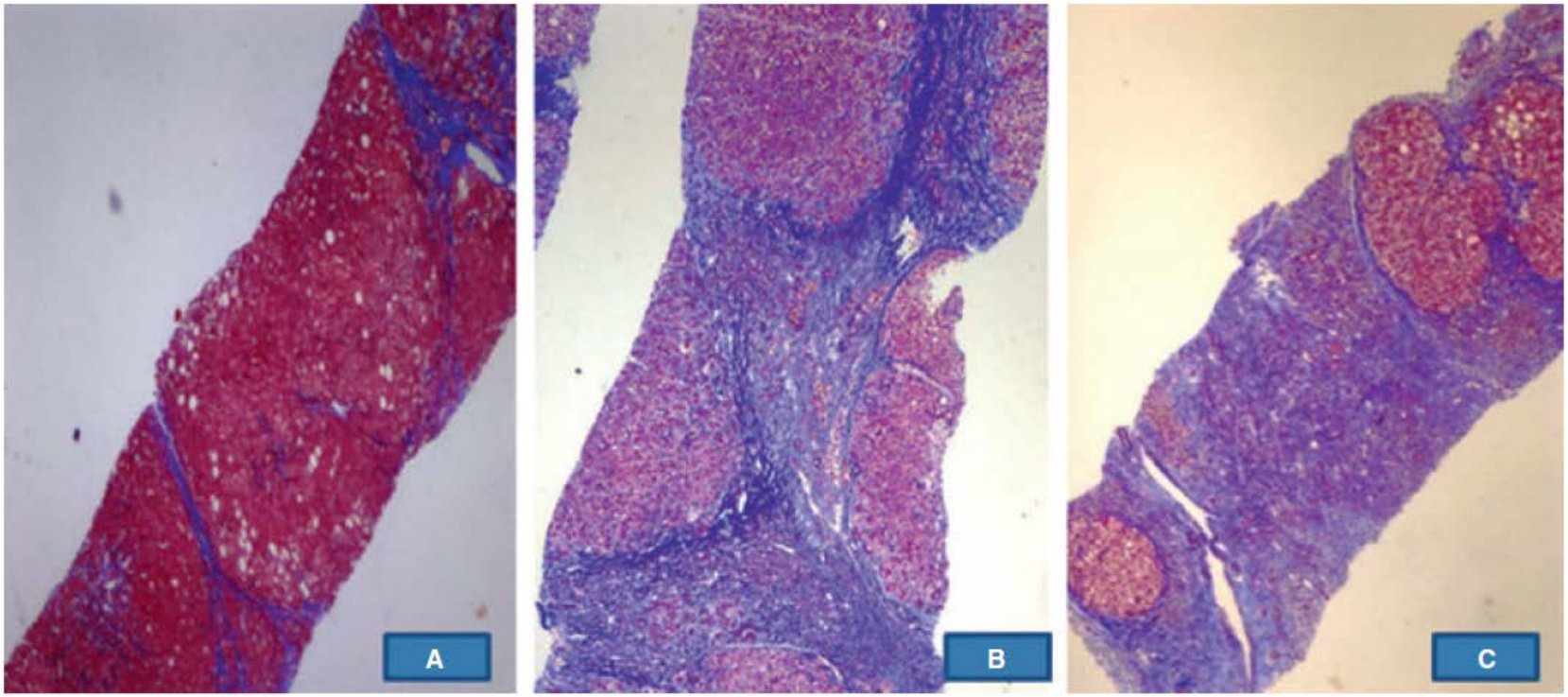
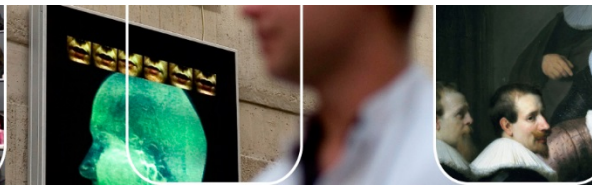
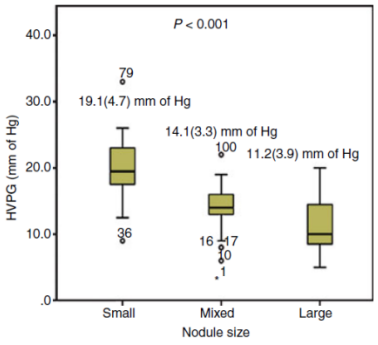
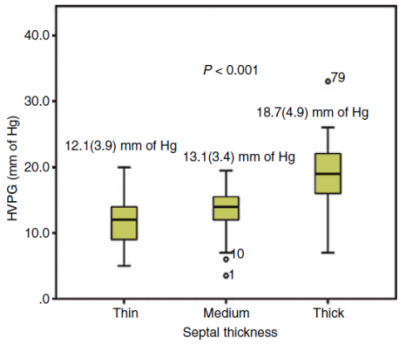


Figure 1. A–C, Laennec stages of cirrhosis: 4A (showing visible nodules with thin fibrous septa), 4B (showing three broad fibrous septa), and 4C (showing very broad septa with more than half of the biopsy comprising micronodules).

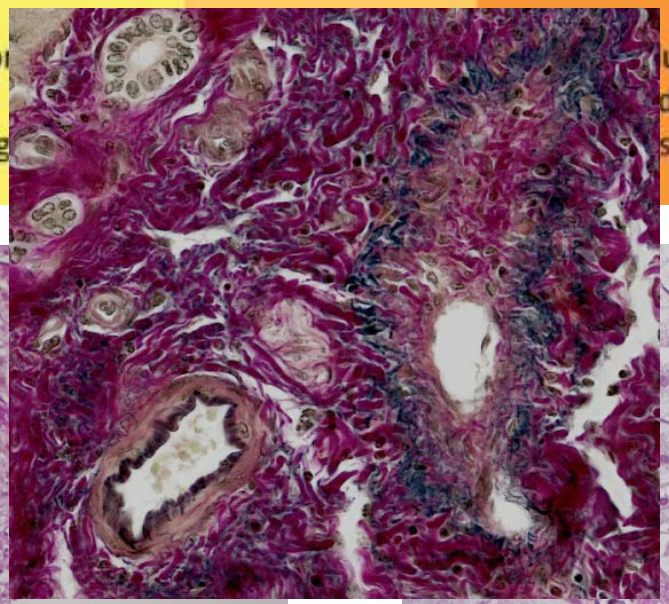
Histopathology, April 2013







Histological	F1-F3		F4 (Cirrhosis)	
Clinical	*Non-cirrhotic*	*Compensated*	*Compensated*	*Decompensated*
Symptoms	None	None (no varices)	None (varices present)	Ascites, VH, Encephalopathy
Sub-stage	-	Stage 1	Stage 2	Stages 3 and 4
Hemodynamic (HVPG, mmHg)		>6	>10	>12
Biological	Fibr		ular)	Insoluble scar
	Ang		s	



REVIEW

Role of aetiology in the progression, regression, and parenchymal remodelling of liver disease: implications for liver biopsy interpretation

Alberto Quaglia,[1] Venancio A Alves,[2] Charles Balabaud,[3] Prithi S Bhathal,[4] Paulette Bioulac-Sage,[5] James M Crawford,[6] Amar P Dhillon,[7] Linda Ferrell,[8] Maria Guido,[9] Prodromos Hytiroglou,[10] Yasuni Nakanuma,[11] Valerie Paradis,[12] Dale C Snover,[13] Neil D Theise,[14] Swan N Thung,[15] Wilson M S Tsui,[16] Dirk J van Leeuwen[17,18]
The International Liver Pathology Study Group

Conclusion

New concepts on the reversibility of the pathological changes in advanced chronic liver diseases are having a major impact on patient management and, in turn, on the role of the liver pathologist, which evolves from the traditional grading and staging task to a more sophisticated investigation of tissue biology dynamics, gauging of disease severity, progression or regression, hepatic regeneration and functional recovery. The chronological and topographical variability of the disease process depends very much upon the underlying aetiology and needs to be taken into account, particularly when interpreting liver biopsy

Liver biopsy

Exclusion of concomitant disease

For diagnosis and/or confirmation of (suspected) disease

Confirmation of tumor and tumor type

Grading and staging of disease, taking into account specific patterns of damage

Morphological classification of cirrhosis based on quantitative/morphometric methods able to provide more precise prognostic information?

Aanvraag leverbiopt

GARBAGE IN……

GARBAGE OUT!!!!

Overige bijzonderheden .....

Vraagstelling/DD .....

.....

.....


am

Interpretation liver biopsy

It takes two to tango..

www.leverpathologie.nl