LUDWIG INSTITUTE FOR CANCER RESEARCH

Imperial College London

BSG Winter Pathology Meeting:

What's new in inflammatory liver disease?

Rob Goldin

r.goldin@imperial.ac.uk

@UKLiverPath

@robdgol

Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD

Rinella ME, Tacke F, Sanyal AJ, Anstee QM.

Journal of Hepatology. 2019 Jul 9.

Table 2. Suggested endpoints for NASH trials across the development

	Precirrhotic NASH
Early phase development	ALT, AST Hepatic fat (MRI-PDFF) Note: Consider mechanism of action of drug when choosing
Phase 2b	NASH resolution without worsening of fibrosis or at least one stage reduction in fibrosis At least a 2-point reduction in NAFLD NAS: At least a 1-point reduction in either lobular inflammation or hepatocellular ballooning AND no worsening of fibrosis stage
Phase 3	NASH resolution* with no worsening of fibrosis AND/OR At least a 1-point improvement in fibrosis with no worsening of NASH
Phase 4	Confirmatory clinical benefit trials Composite of: – Histological progression to cirrhosis – All-cause mortality – Liver transplant† – Hepatic decompensation events – Increase of MELD score from below 12 to ≥15

* Disappearance of ballooning and disappearance or persistence of minimal, lobular inflammation that do not qualify for the diagnosis of NASH.

Improvements in histologic features and diagnosis associated with improvement in fibrosis in NASH: results from the NASH Clinical Research Network Treatment Trials

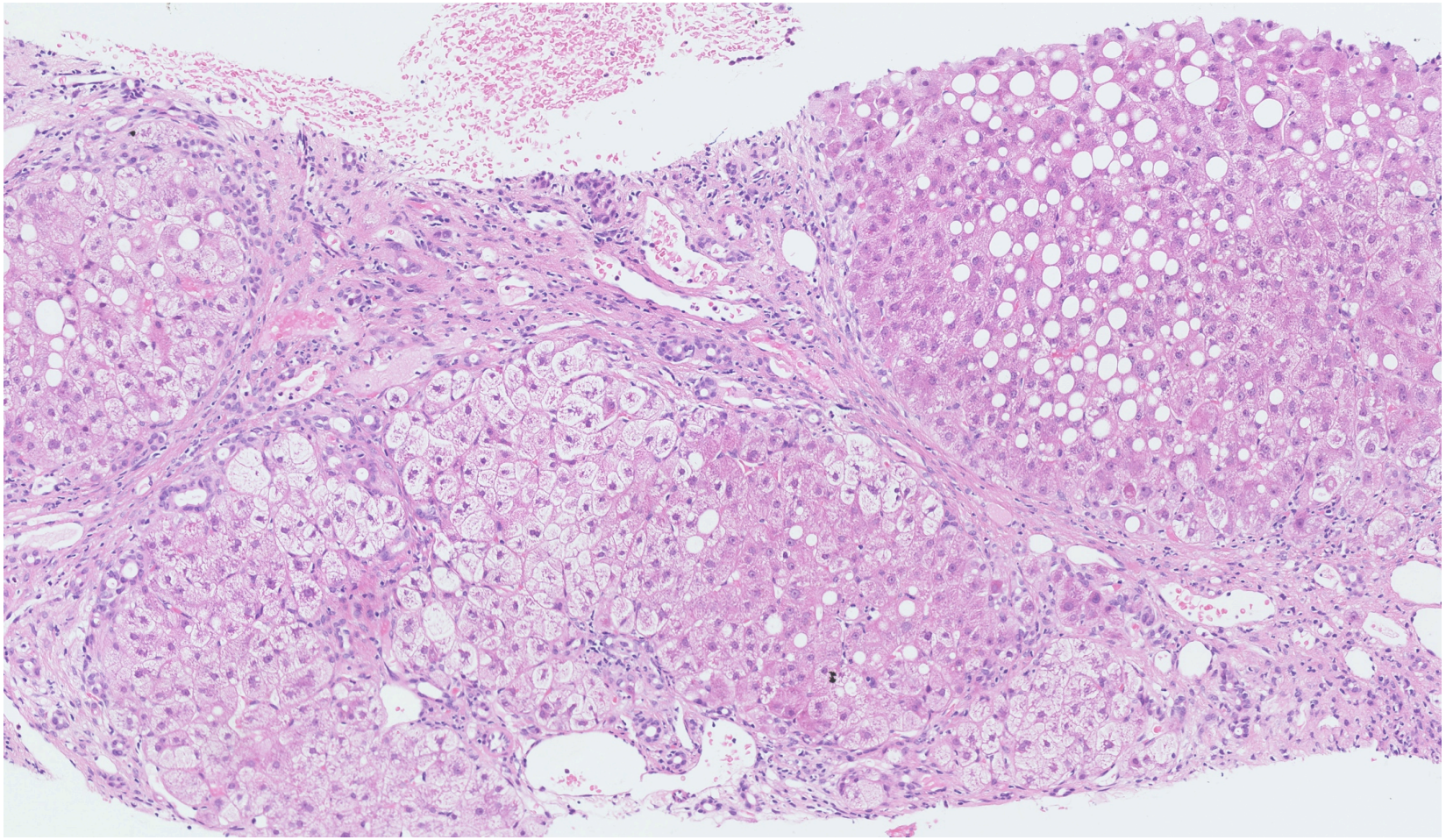
Brunt EM, Kleiner DE, Wilson LA.

Hepatology. August 2019.

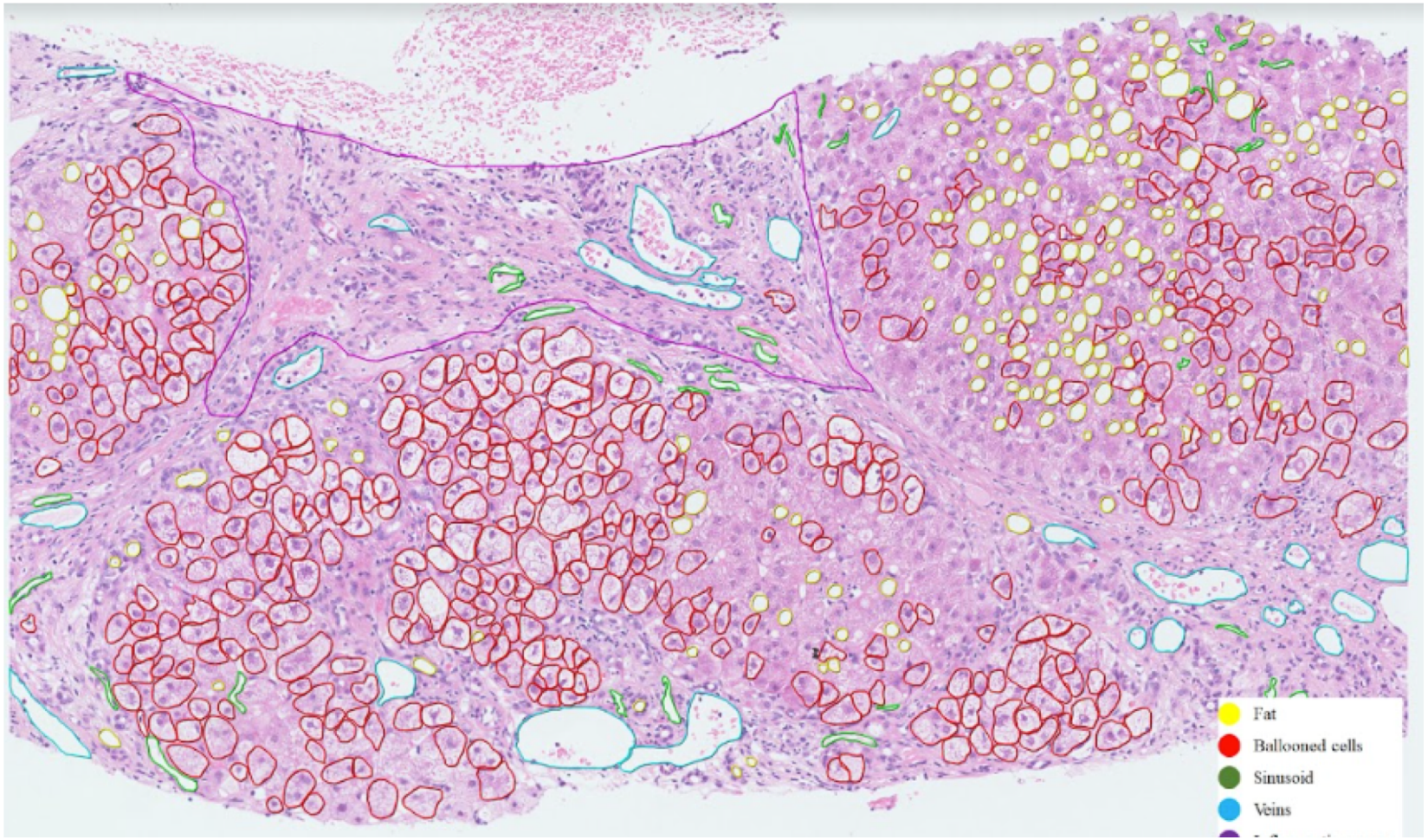
What do you need to diagnose a fatty liver hepatitis?

“You need more than a few ballooned cells.”

Raw image



Annotated image



Fatty Liver Disease: A Practical Approach.

Mostafa M, Abdelkader A, Evans JJ, Hagen EG, Hartley CP.

Arch Pathol Lab Med. 2019 Oct 11. doi: 10.5858/arpa.2019-0341-RA.

Cryptogenic cirrhosis: Old and new perspectives in the era of molecular and genomic medicine

Nalbantoglu I, Jain D.

Seminars in Diagnostic Pathology 2019 Jul 24. WB Saunders.

Cryptogenic Cirrhosis

Less than 10% of cases of cirrhosis.

Isn’t it all burnt out fatty liver disease?

Patient’s with NASH cirrhosis are more likely to be:

White, women, 60 years+, have Type 2 diabetes

Cryptogenic Cirrhosis: Conditions to exclude

Table 1
Histologic patterns that can be observed in cryptogenic cirrhosis and their main differential diagnosis.

Histologic pattern	Possible etiologies
Hepatitis	Occult hepatitis C Occult hepatitis E Occult autoimmune hepatitis Alpha-1 antitrypsin deficiency Celiac disease Wilson disease Familial Mediterranean fever Others[1]
Steatotic	Non-alcoholic fatty liver disease Alcoholic liver disease Wilson disease Lysosomal acid lipase deficiency Others[1]
Biliary	Primary biliary cholangitis Primary sclerosing cholangitis Secondary sclerosing cholangitis Progressive familial intrahepatic cholestasis syndromes (MDR3)
Bland (patternless)	Wilson disease Burned-out non-alcoholic fatty liver disease Burned-out alcoholic liver disease Others[1]

[1] May include several other unlisted causes.

In cases defined clinically, a histopathological examination can make a diagnosis in 85%

Cryptogenic Cirrhosis: Conditions to think about

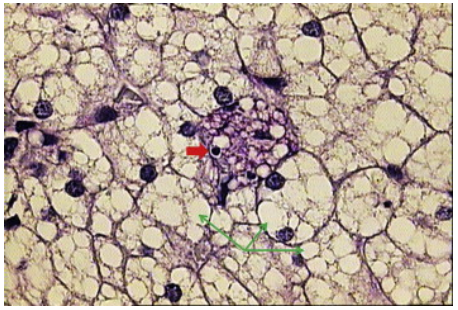
- **Hepatitic pattern:**

Occult HCV (in 10% of cases)

Seronegative AIH

Chronic HEV (in immunocompromised people)

Coeliac disease



- **Rare causes of a fatty liver hepatitis:**

Wilson's Disease, lysosomal acid lipase deficiency

- **Rare causes of a biliary pattern:**

Progressive Familial Intrahepatic Cholestasis in adults

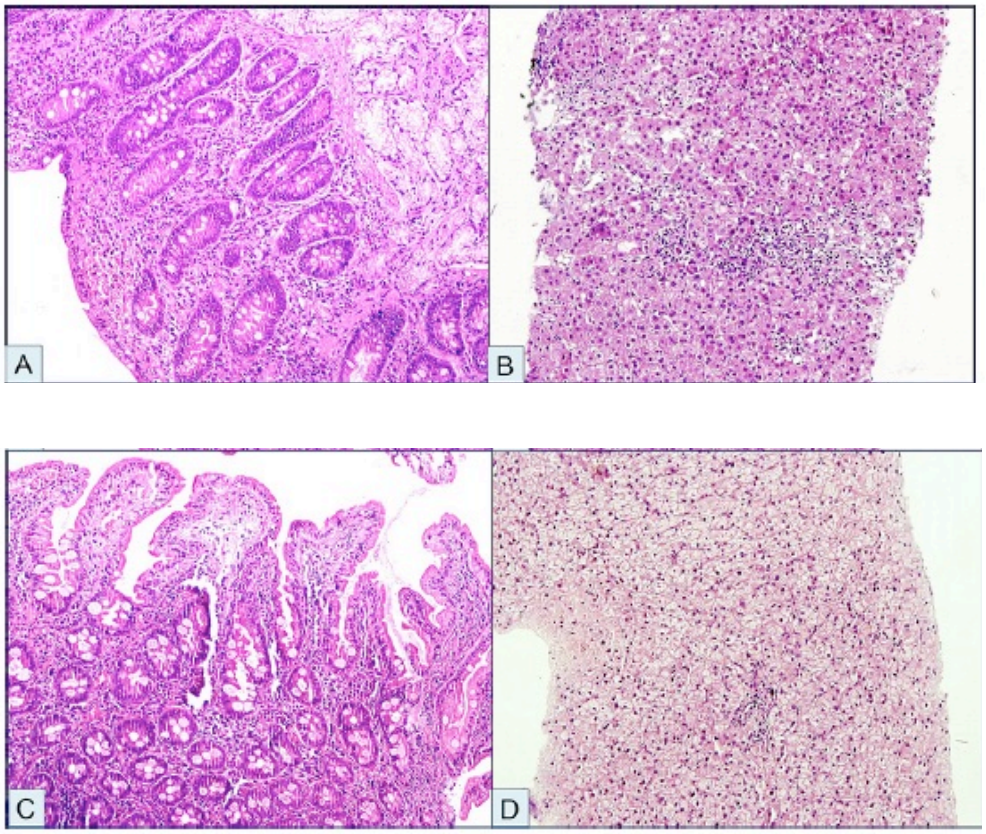
Celiac disease and liver disorders: from putative pathogenesis to clinical implications.

Hoffmanová I, Sánchez D, Tučková L, Tlaskalová-Hogenová H.
Nutrients. 2019 Jul;10(7):892.

Liver Disease in patients with Coeliac Disease: Types

1. “Coeliac hepatitis”
2. Associated autoimmune liver diseases
3. Co-existing liver diseases

Resolution of small intestinal and liver changes on a gluten free diet



Coeliac hepatitis

- Celiac hepatitis is characterized by the presence of liver injury that resolves after introduction of a gluten free diet.
- The histologic picture varies from normal liver architecture with minimal portal inflammation to cirrhosis.
- Non-specific reactive hepatitis is the mostly described lesion.
- Inflammatory alterations of the bile ducts have not been described

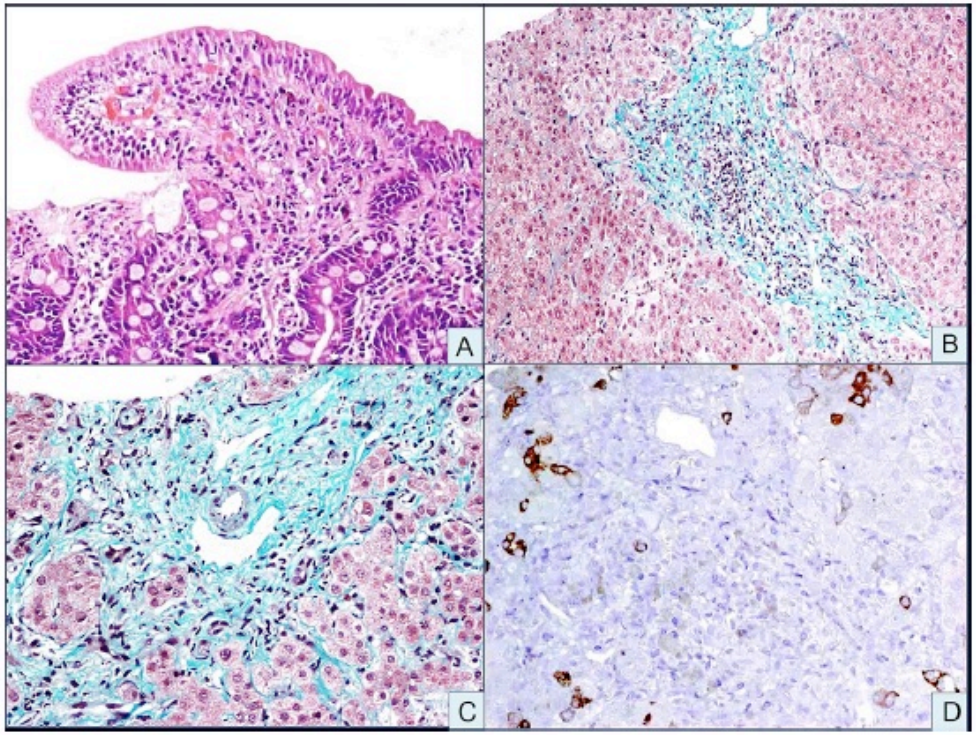
CD associated autoimmune liver diseases

- autoimmune hepatitis
- primary biliary cholangitis
- primary sclerosing cholangitis

- A few patients with newly diagnosed coeliac diseaese and suffering from liver failure due to autoimmune hepatitis,
- A gluten free diet was able to reverse hepatic dysfunction

e.g. Gastroenterology 2002, 122, 881–888.

PBC associated with CD



Co-existing liver disease in coeliac disease

- The prevalence of CD in patients with NAFLD is 10%.
- CD seem to be at increase risk (5X) of NAFLD

Something old, something new: liver injury associated with total parenteral nutrition therapy and immune checkpoint inhibitors

Meyerson C, Naini BV.

Human Pathology. 2019 Oct 26.

Intestinal Failure Associated Liver Disease (IFALD)

- Abnormal liver histology is not mandatory for a diagnosis of IFALD and the decision to perform a liver biopsy should be made on a case-by-case basis.
- Hyperbilirubinaemia in the absence of radiological obstruction.

Histopathology

- **In infants:**

Canalicular cholestasis is the most common finding

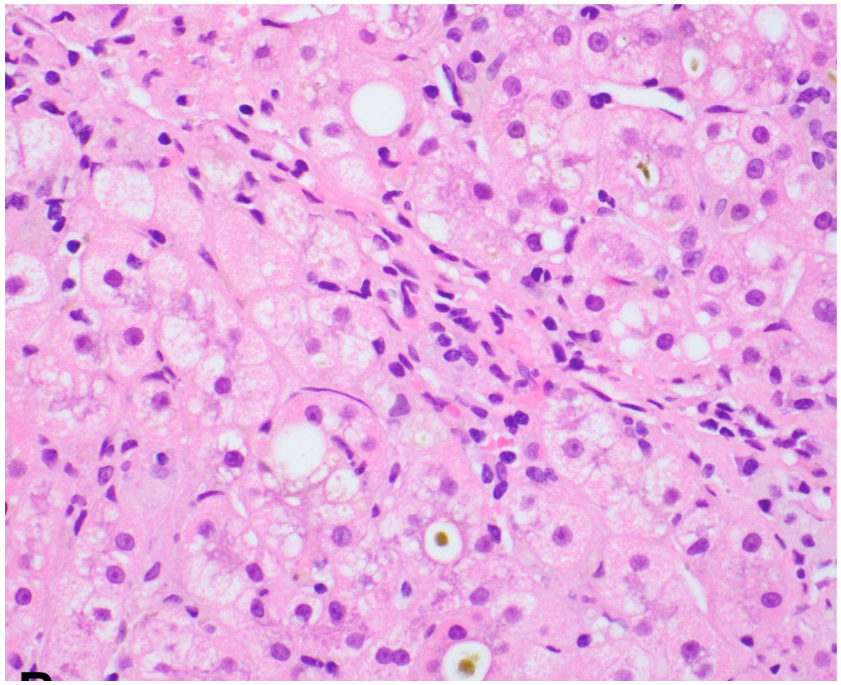
There may be biliary obstructive features which can lead to cirrhosis.

Hepatocellular carcinoma have been reported

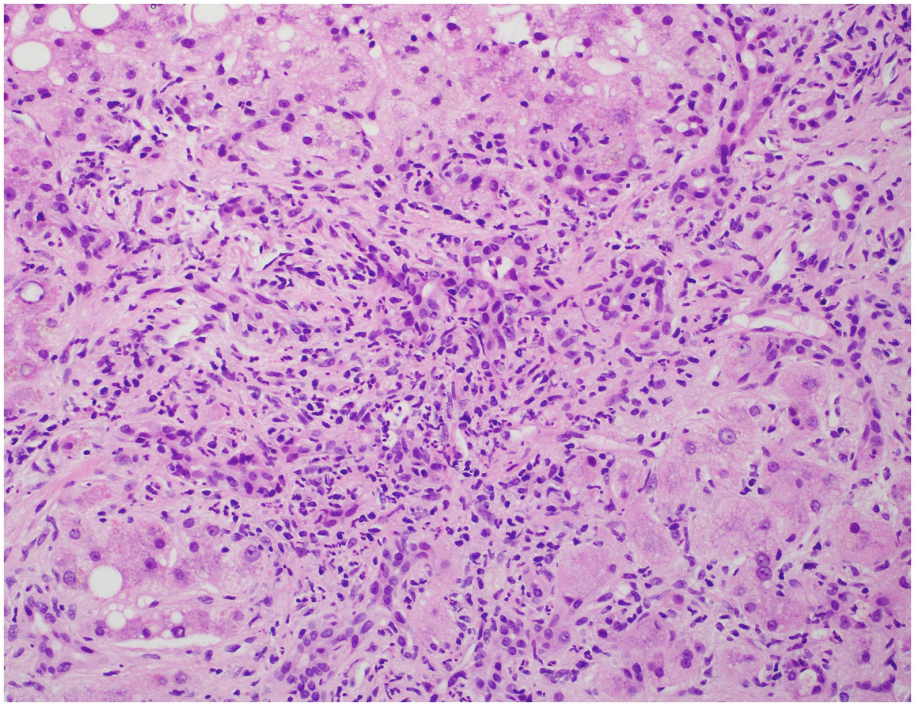
- **In adults:**

steatosis and steatohepatitis are more commonly seen

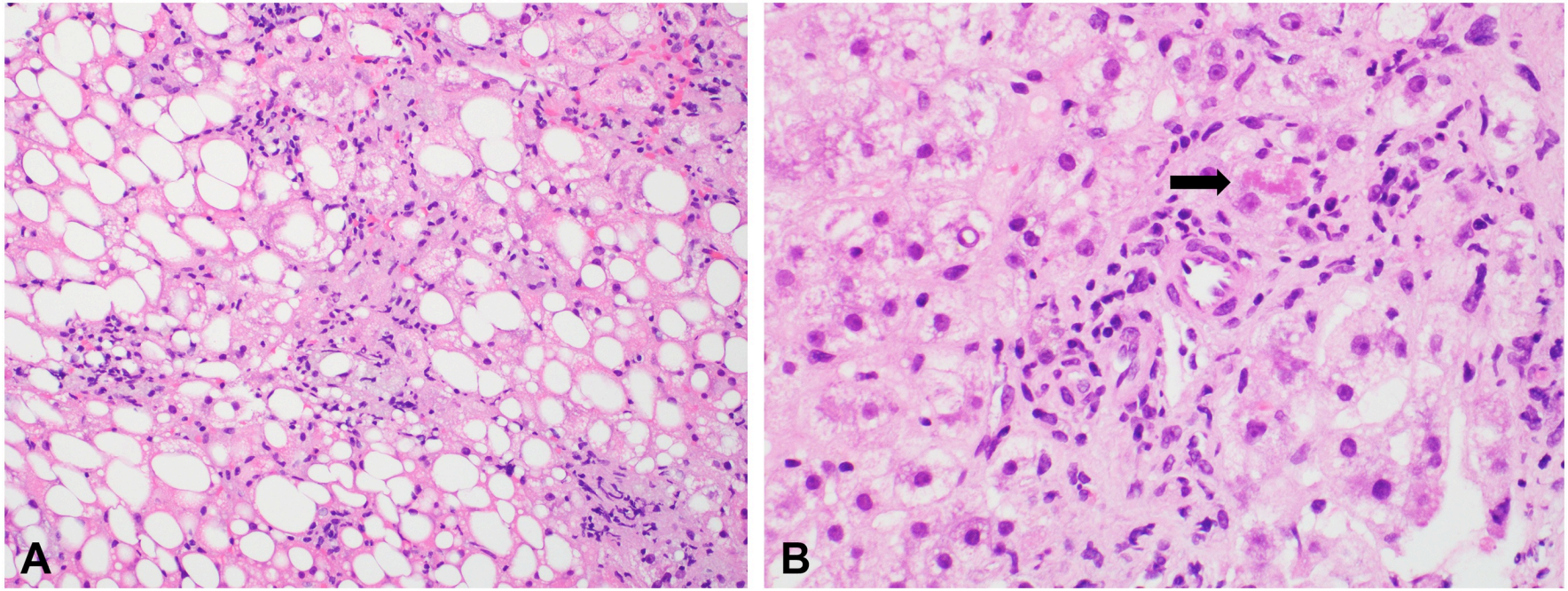
IFALD in infants: Canalicular cholestasis



IFALD in infants: Biliary fibrosis



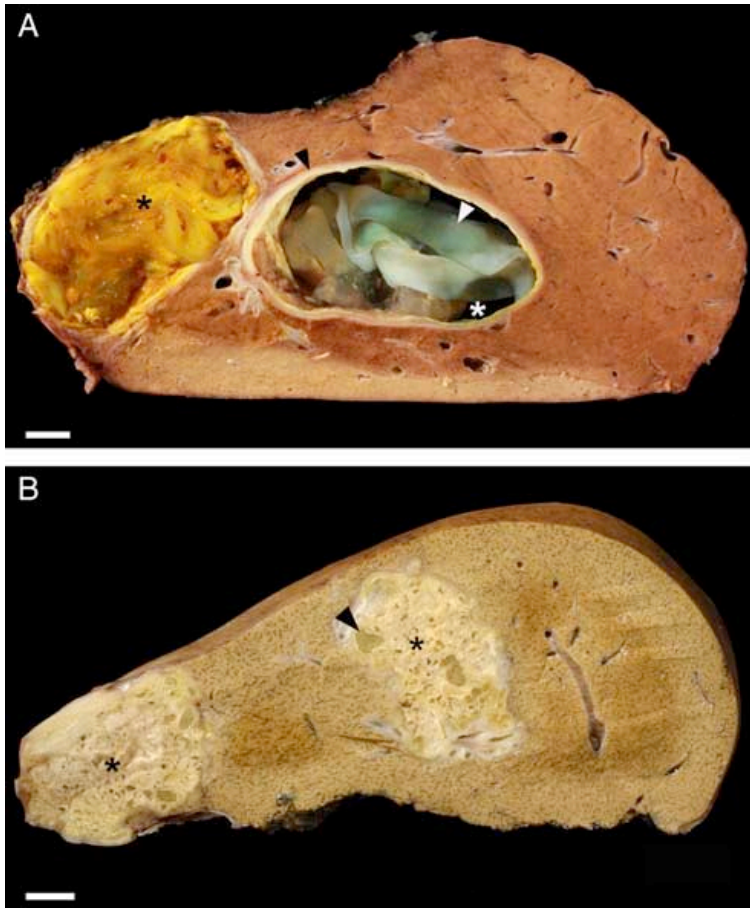
IFALD in adults: Steatohepatitis



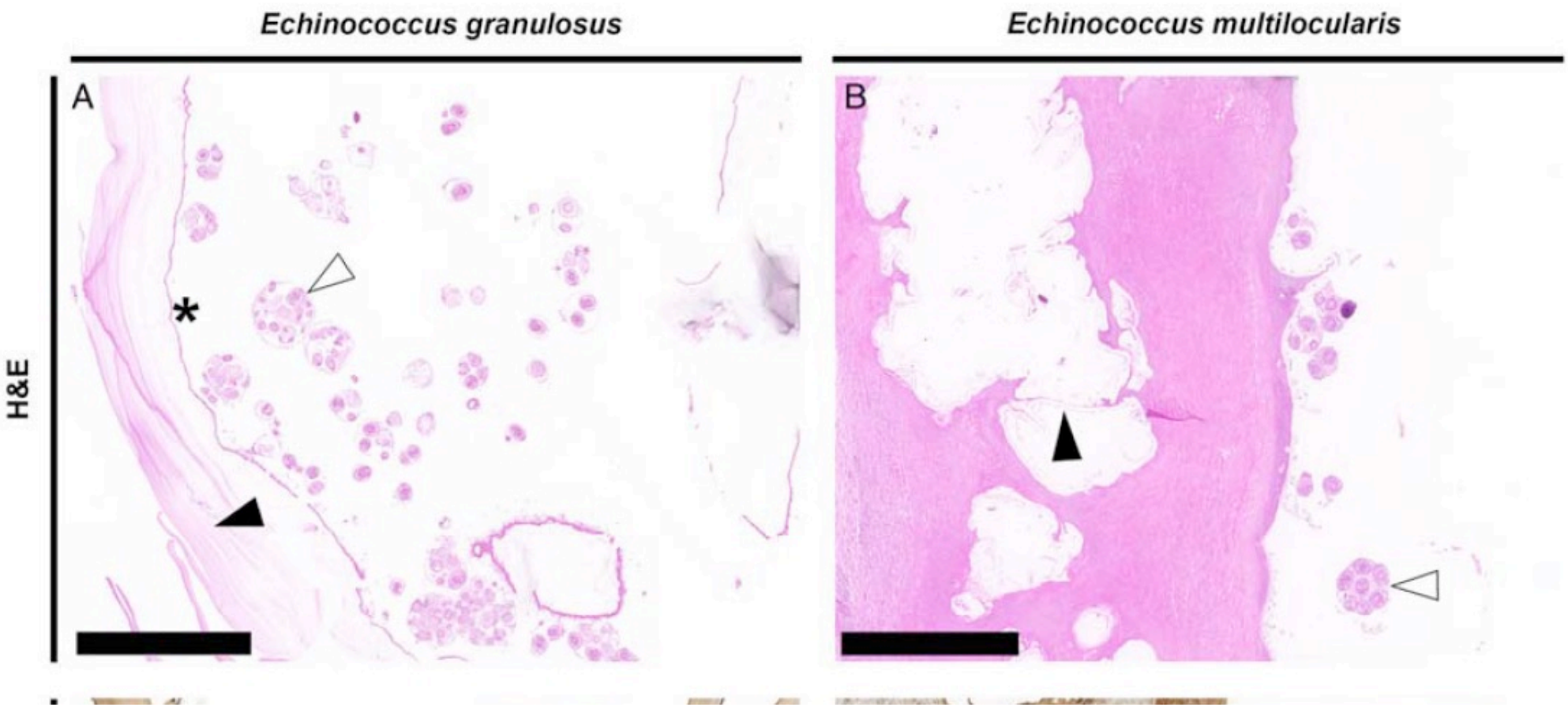
Pathology of Echinococcosis: A Morphologic and Immunohistochemical Study on 138 Specimens With Focus on the Differential Diagnosis Between Cystic and Alveolar Echinococcosis.

Reinehr M, Micheloud C, Grimm F, Kronenberg PA, Grimm J, Beck A, Nell J, zu Schwabedissen CM, Furrer E, Müllhaupt B, Barth TF.

The American Journal of Surgical Pathology. 2019 Oct 22.



1. Cystic echinococcosis (alias unilocular echinococcosis) is caused by Echinococcus granulosus sensu lato.
2. Alveolar hydatid disease (alias multilocular echinococcosis) is caused by Echinococcus multilocularis, and


Echinococcus granulosus
Echinococcus multilocularis
H&E
A
B
*

Six morphologic criteria sufficiently discriminated between Echinococcus granulosus (EG) and Echinococcus multilocularis (MG)

1. size of smallest cyst (EG/EM: >2/≤2 mm)
2. size of the largest cyst (EG/EM: >25/≤25 mm),
3. thickness of laminated layer (EG/EM: >0.15/≤0.15 mm)
4. pericystic fibrosis (EG/EM: >0.6/≤0.6 mm),
5. striation of laminated layer (EG/EM: moderate-strong/weak)
6. number of cysts (EG/EM: ≤9/>9).

Human Pathology (2019) 87, 75–82

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PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Identification of key challenges in liver pathology: data from a multicenter study of extramural consults☆,☆☆

Michael S. Torbenson MD[a,*], Christina A. Arnold MD[b], Rondell P. Graham MBBS[a], Dhanpat Jain MD[c], Sanjay Kakar MD[d], Dora M. Lam-Himlin MD[e], Bita V. Naini MD[f], Tsung-Teh Wu MD, PhD[a], Matthew Yeh MD, PhD[g]

Table 3 Receipt of relevant information with consults

	Received N (% of total)	Not received but not relevant N (% of total)	Cases missing relevant information N (% of total)
All cases, N = 541			
Laboratory test results	303 (56%)	82 (15%)	156 (29%)
Clinical information	433 (80%)	18 (3%)	90 (17%)
Imaging findings	168 (31%)	140 (26%)	233 (43%)
Medical consults, N = 328			
Laboratory test results	261 (80%)	3 (1%)	64 (20%)
Clinical information	276 (84%)	5 (2%)	47 (14%)
Imaging findings	70 (21%)	126 (38%)	132 (40%)
Tumor consults, N = 213			
Laboratory test results	43 (20%)	79 (37%)	91 (43%)
Clinical information	158 (74%)	13 (6%)	42 (20%)
Imaging findings	98 (46%)	14 (7%)	101 (47%)

- A preliminary diagnosis was provided by the referring pathologist in 65% of cases.
- The most common questions in medical liver pathology were:

1. general classification of a hepatitic pattern of injury (37%),
2. primary biliary cirrhosis (14%)
3. fatty liver disease (13%)
4. autoimmune hepatitis (12%)
5. aetiology of cirrhosis (10%).

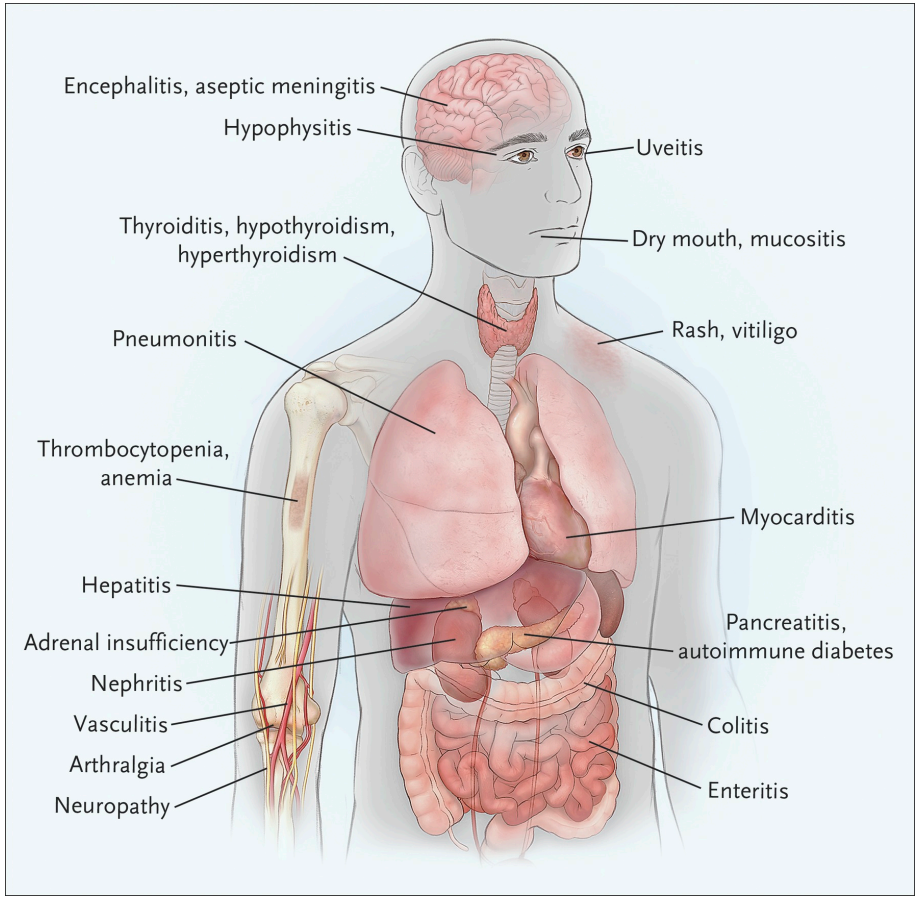
Table 6 Types of questions in the setting of autoimmune hepatitis and PBC

Basic question	Main diagnosis considered by referring pathologist	
	Autoimmune hepatitis N	PBC N
Confirm diagnosis	20	17
Overlap, AIH and PBC	8	9
Overlap with PSC	1	3
NAFLD with possible AIH	10	NA
NAFLD with possible PBC	0	1
DILI *vs* AIH	2	NA
DILI *vs* PBC	NA	0

Abbreviations: AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; NAFLD, Non-alcohol fatty liver disease; DILI, drug-induced liver injury; NA, not available.

Checkpoint Hepatitis

Organs Affected by Immune Checkpoint Blockade.



Postow MA et al. N Engl J Med 2018;378:158-168

immune-related Adverse Events (irEMs): Frequency

Table 1. Percentage ranges of all-grade immune-related common adverse events by checkpoint inhibitor class.

Class of Immune Checkpoint Inhibitors	Approved Agents	Rash	Diarrhea	Colitis	Elevated ALT	Hypothyroidism	Hypophysitis	Citations
Anti CTLA-4	Ipilimumab, Tremelimumab	12–68%	31–49%	7–11.6%	3–9%	4–4.2%	4–6%	[9–14]
Anti PD-1	Nivolumab, Pembrolizumab	11.7–24%	2.9–11.5%	1.3–2.9%	1.8–7.1%	3.4–8.5%	0.25%	
Anti PD-L1	Atezolizumab, Durvalumab, Avelumab	7.4%	11.6–23%	0.7–19.7%	0.9–4.0%	5.0–9.6%	0.2%	

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY 2019, VOL. 15, NO. 3, 231–244

immune-related Adverse Events: Timing

1. skin: 2-3 weeks
2. gastro-intestinal tract: 4-7 weeks
3. liver: 4-8 weeks
4. endocrine: 9 weeks

1/3rd of patients with liver involvement have preceding or concurrent involvement of other sites

immune-related Adverse Events:
Patterns of liver damage

1. Panlobular hepatitis (65%)
2. Isolated zone 3 necrosis (20%)
3. Granulomatous hepatitis (5%)
4. Bile duct damage (5%)
5. Others e.g. fatty liver hepatitis (5%)

Journal of Clinical Pathology 2018;**71:**665-671

Seminars in Diagnostic Pathology, https://doi.org/10.1053/j.semdp.2019.07.009

Patterns of Liver Damage:
1. Panlobular Hepatitis

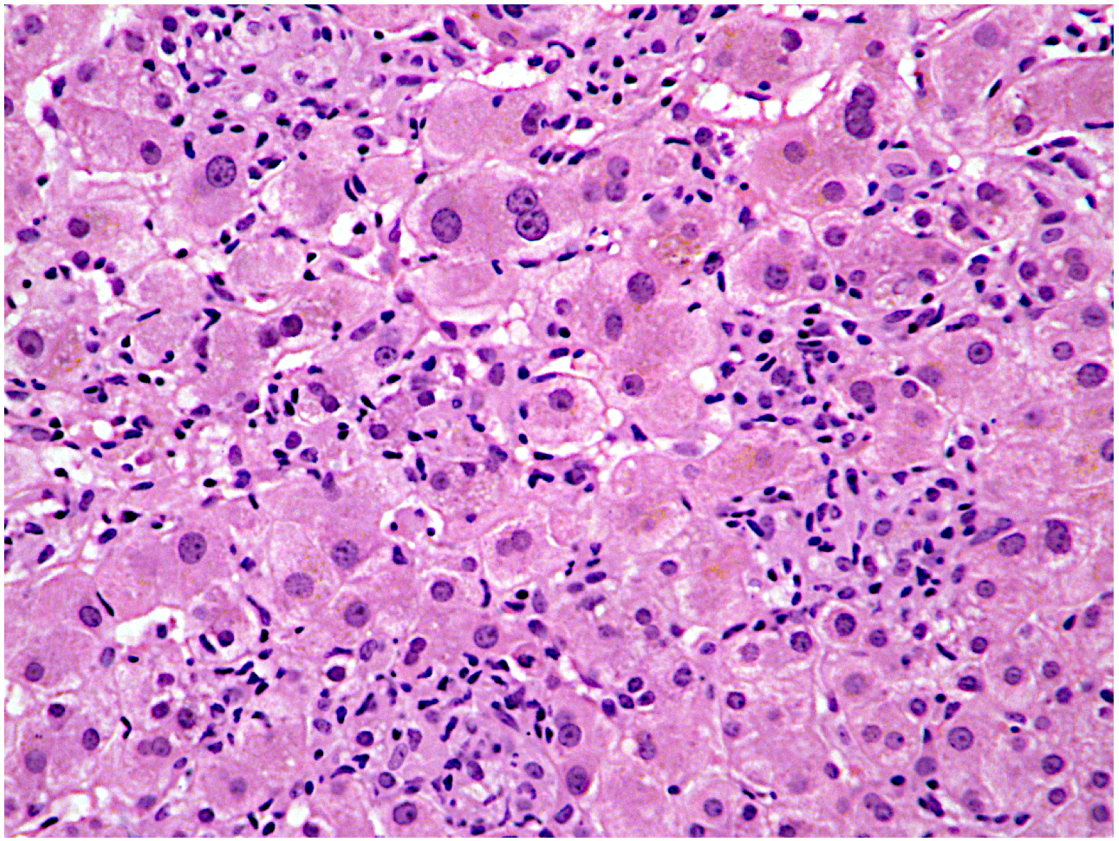
- **Portal tract changes:** Mild

1. Lymphocytic infiltrate – interface hepatitis, if severe
2. Ductular reaction

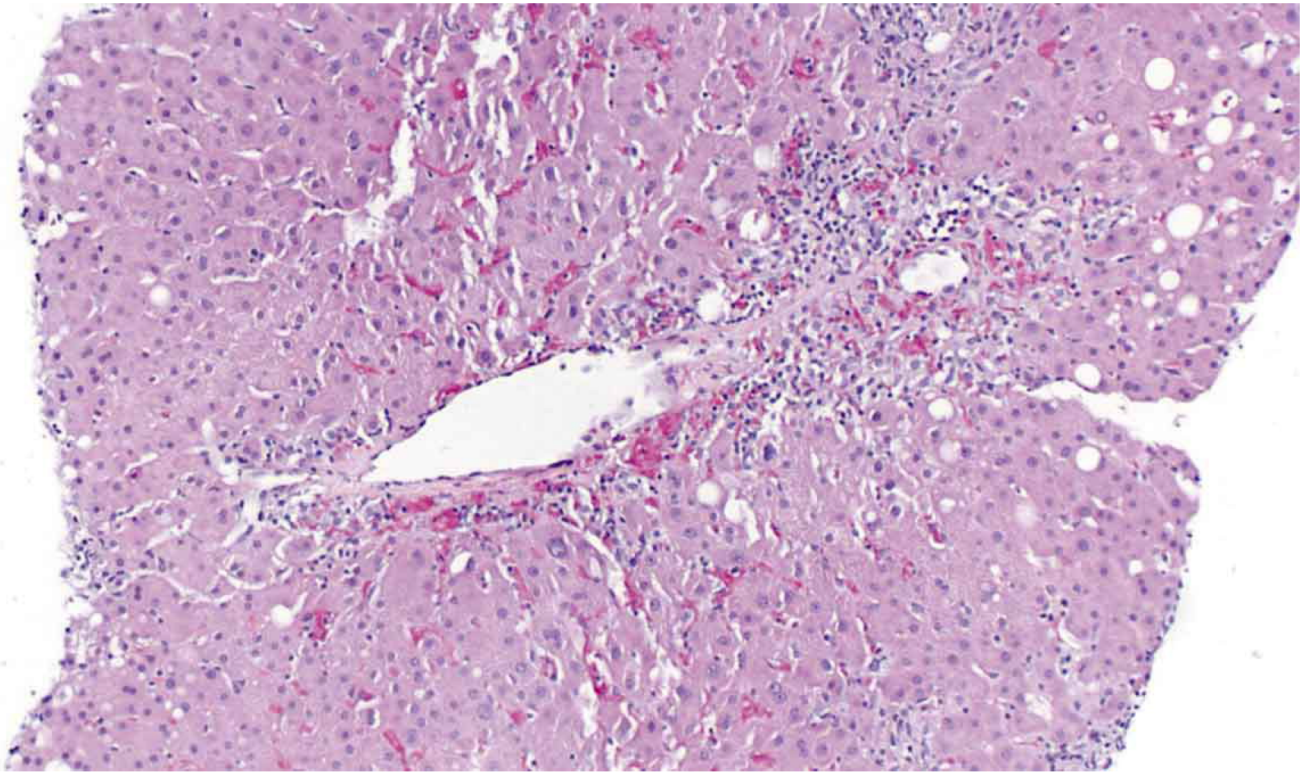
- **Lobules:** Marked

1. Focal necrosis and apoptosis
2. Mainly lymphocytes - eosinophils may be prominent
3. Activated macrophages – may form microgranulomas
4. Regenerative hepatocyte changes
5. Endothelialits

Patterns of Liver Damage:
1. Panlobular Hepatitis



Patterns of Liver Damage:
2. Isolated Zone 3 necrosis



Differences between Checkpoint inhibitor hepatitis and Auto-immune hepatitis

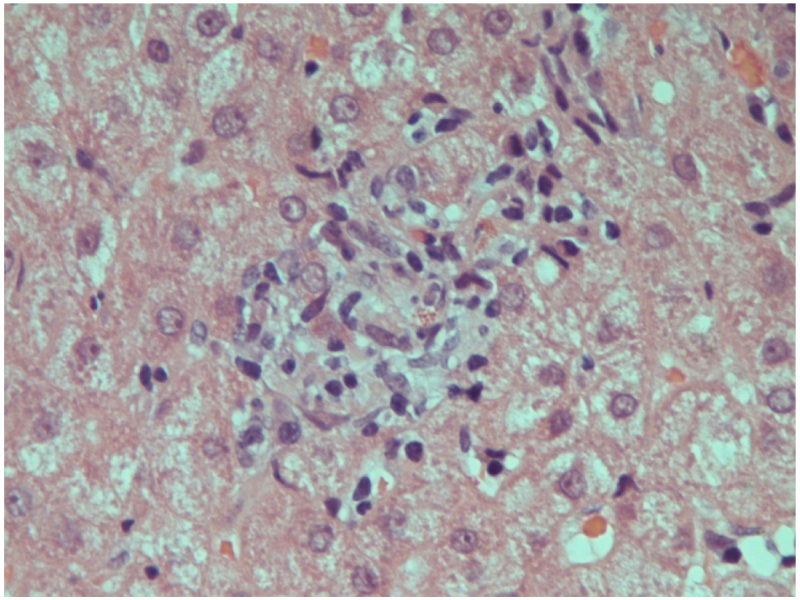
1. Low levels of auto-antibodies
2. No HLA association
3. Less portal and interface inflammation.
4. Plasma cells not conspicuous, eosinophils less common
5. Infiltration mainly be CD3+ CD8+ T-lymphocytes
   (as compared with CD20+ B cells and CD3 + CD4+ T lymphocytes in AIH)
6. Confluent necrosis, rosettes, emperipolesis and bile plugs less common

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY 2019, VOL. 15, NO. 3, 231–244

Modern Pathology (2018) 31:965–973

Patterns of Liver Damage:
3. Granulomas

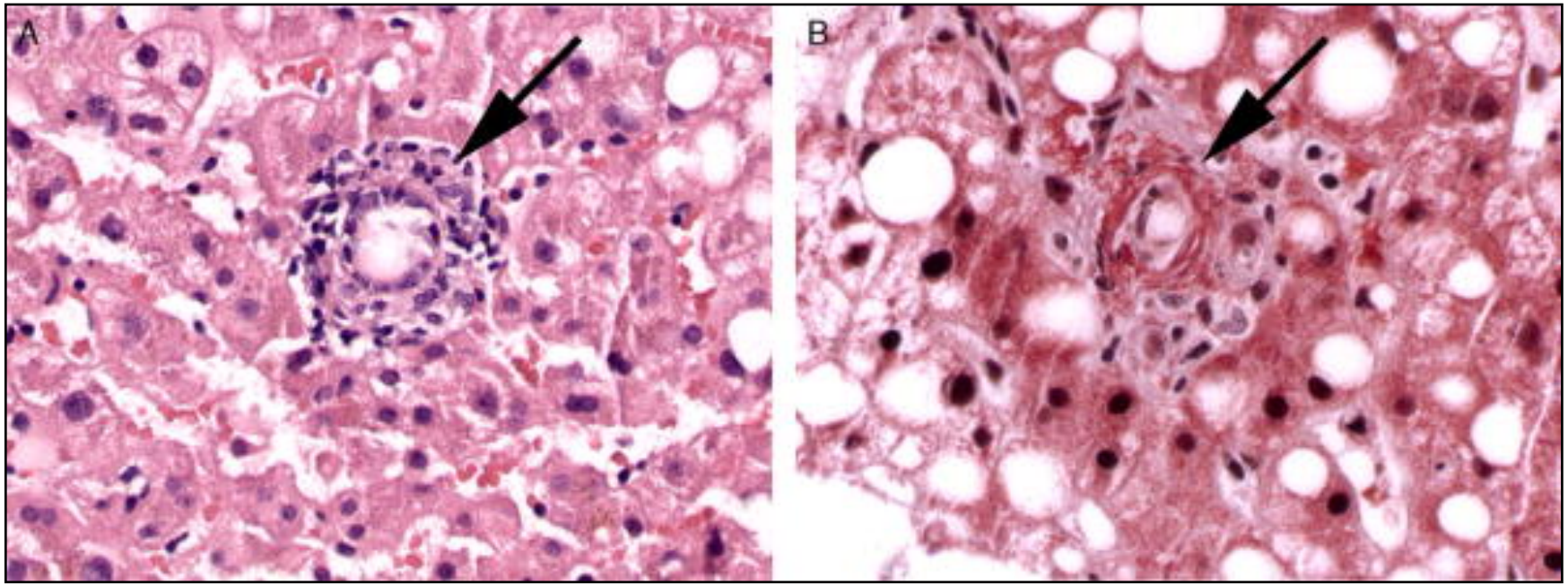
- Seen with ipilimumab +/_ nivolumab.



Fibrin Ring Granulomas in Checkpoint Inhibitor-induced Hepatitis.
Everett, Jamie; Srivastava, Amitabh; Misdraji, Joseph

American Journal of Surgical Pathology. 41(1):134-137, January 2017.
DOI: 10.1097/PAS.0000000000000759

FIGURE 2 . Case 2: A, Small fibrin ring granuloma (arrow). B, Trichrome stain highlights the red fibrinous ring (arrow) within the fibrin ring granuloma. Note the presence of steatosis in hepatocytes around the fibrin ring granuloma.

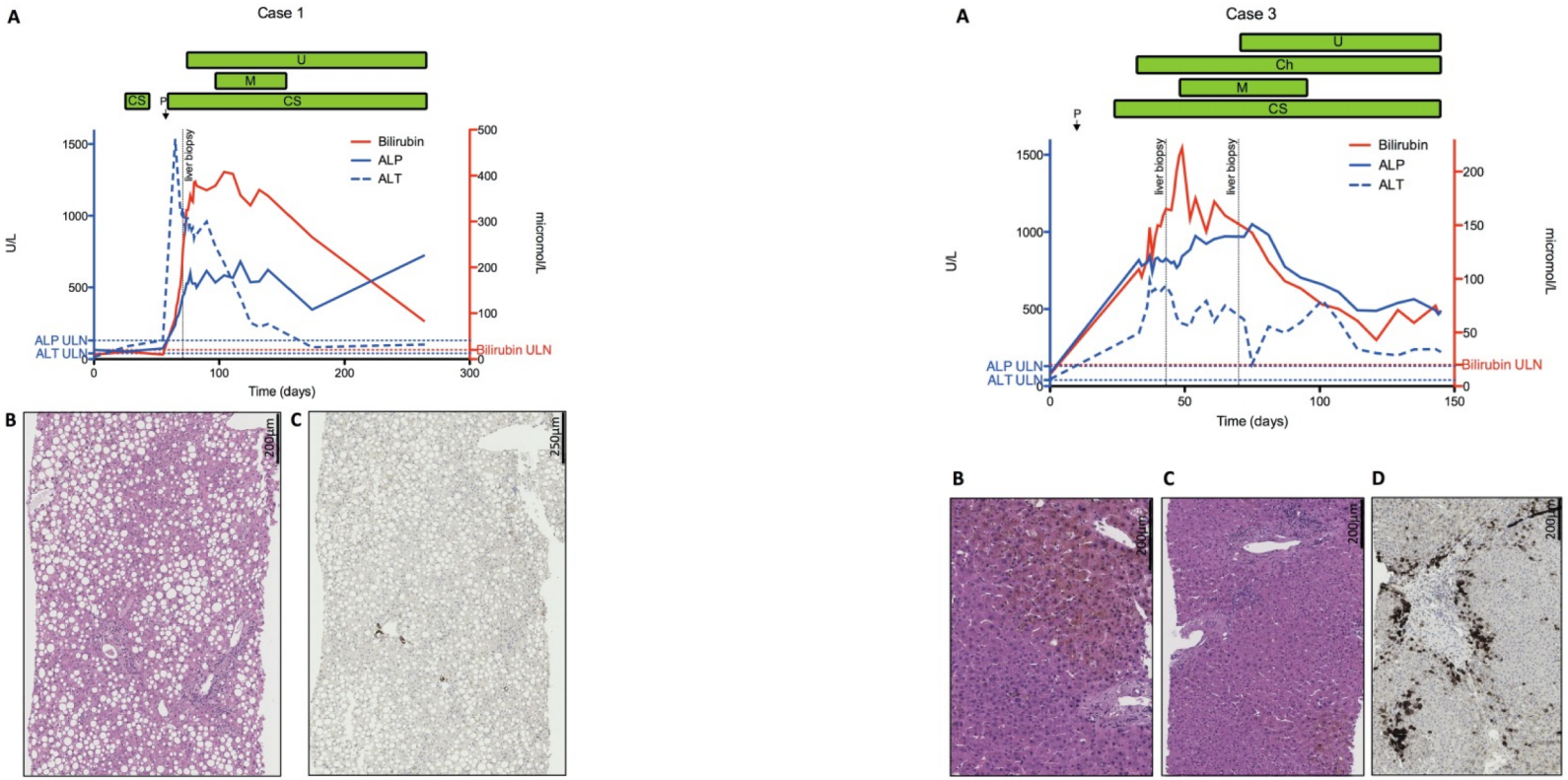


Patterns of Liver Damage:
4. Bile duct damage

- Intrahepatic and extrahepatic bile ducts may be involved.
- PSC and PBC – like histology has been described

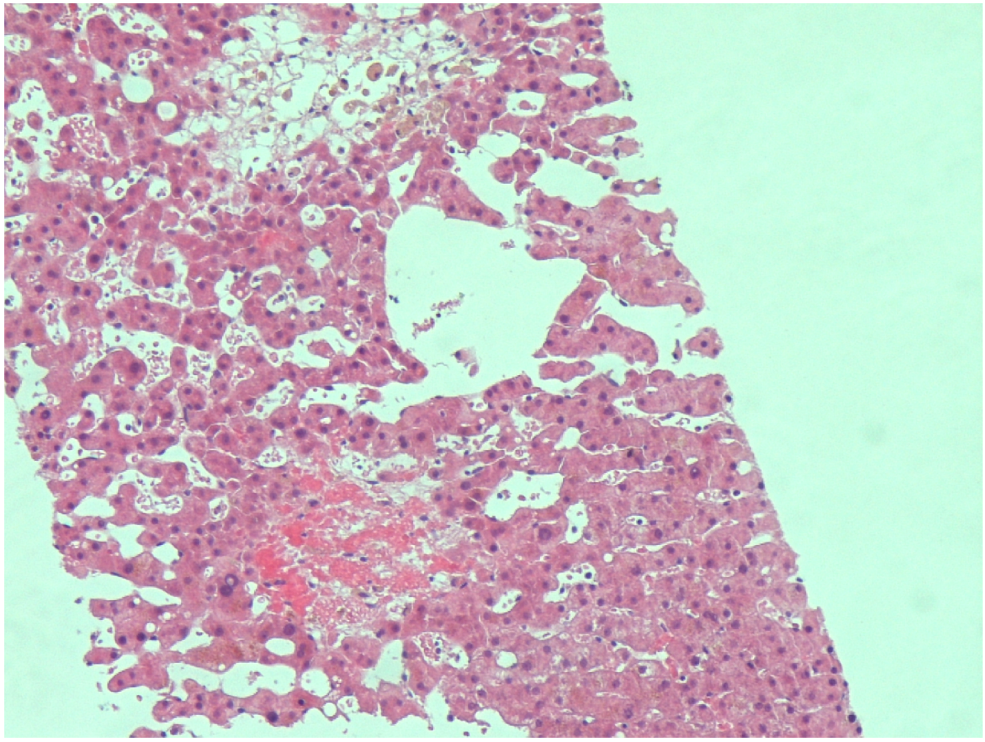
Investigational New Drugs. 2017 Aug 1;35(4):529-36
Intern Med 58: 1747-1752, 2019
Seminars in Diagnostic Pathology, https://doi.org/10.1053/j.semdp.2019.07.009

Patterns of Liver Damage:
4. Bile duct damage



ESMO open. 2017 Oct 1;2(4):e000268.

Patterns of Liver Damage 4. Others:
Vascular damage



Patterns of Liver Damage 4. Others: Unmasking underlying liver disease

- **Auto-immune hepatitis**

  case report rare

  Journal of Hepatology. 2017 Mar 1;66(3):657-9.

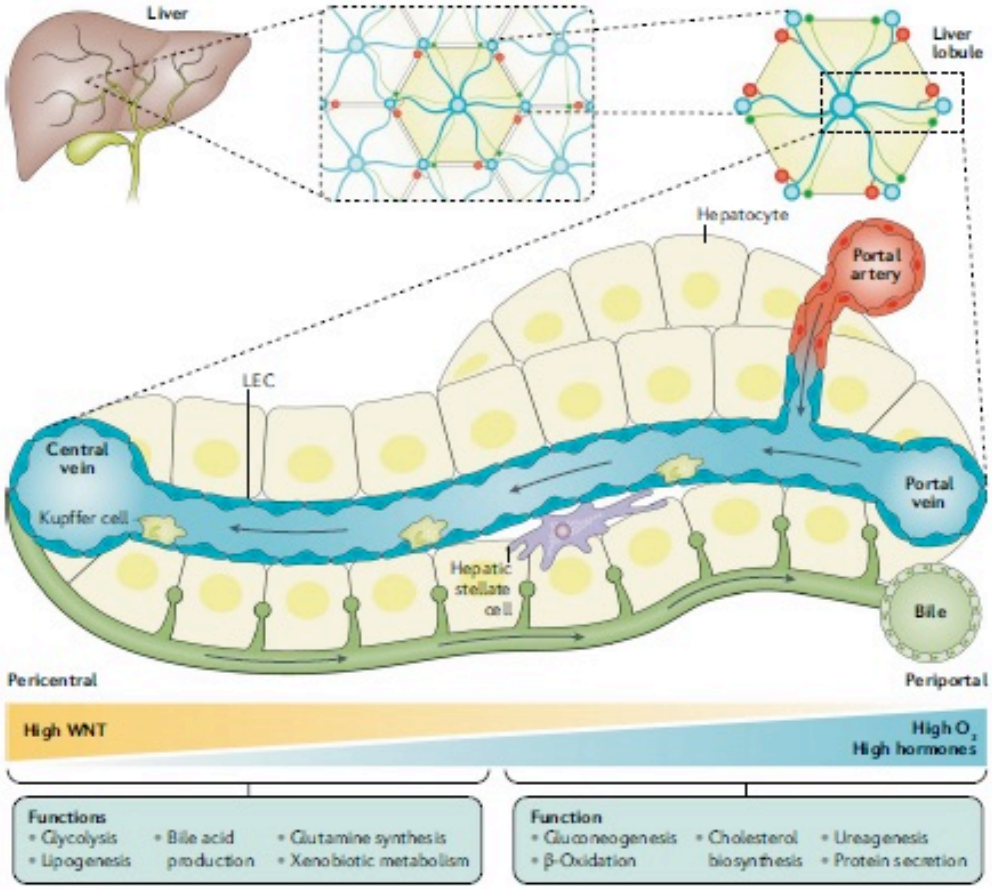
- **Underlying viral hepatitis in patients with HCC**

  must be very uncommon

Spatial heterogeneity in the mammalian liver.

Ben-Moshe S, Itzkovitz S.

Nature Reviews Gastroenterology & Hepatology. 2019 Apr 1:1.


Liver
Liver lobule
Hepatocyte
Portal artery
LEC
Central vein
Kupffer cell
Portal vein
Hepatic stellate cell
Bile
Pericentral
Periportal
High WNT
High O_2
High hormones
Functions
• Glycolysis
• Lipogenesis
• Bile acid production
• Glutamine synthesis
• Xenobiotic metabolism
Function
• Gluconeogenesis
• β-Oxidation
• Cholesterol biosynthesis
• Ureagenesis
• Protein secretion

Box 2 | **Liver zonation in pathological states**

Pericentral predominance

- Drugs and compounds
  - Acetominophen[105]
  - Carbon tetrachloride (CCl_4)[106]
  - Ethanol[104]
- Fatty liver disease[107]
- *Plasmodium* parasite infection (malaria)[114]

Periportal predominance

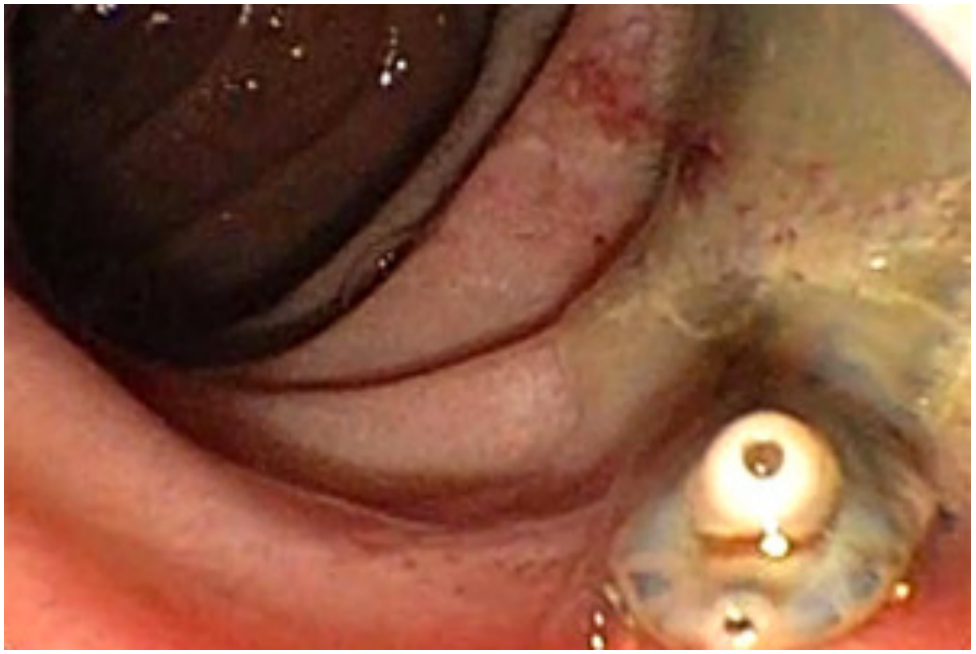
- Drugs and compounds
  - Doxorubicin[102]
  - Galactosamine[105]
  - Allyl alcohol[108]
- Autoimmune hepatitis[111]
- Primary biliary cirrhosis[121]

Zonation of drug damage

- The pericentral expression of P450 enzymes results in increased exposure to toxic intermediates.
- CYP2E1 and CYP1A2 are P450 enzymes that convert paracetamol into the toxic intermediate N-acetyl-p-benzoquinoneimine.

- Doxorubicin can lead to liver damage, predominately in the periportal zones.
- This zonal hepatotoxicity is attributed to the redox cycling of the drug in the more oxygenated portal zones.

Liver fluke



Video

LUDWIG INSTITUTE FOR CANCER RESEARCH

Imperial College London

BSG Winter Pathology Meeting:

What's new in inflammatory liver disease?

Rob Goldin

r.goldin@imperial.ac.uk