Drug Induced Liver Injury (DILI)

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Why is DILI important?

- A primary role of the liver is metabolism of drugs and toxins
  - Primary target for adverse drug reactions
- DILI is common and the clinical cases are probably the tip of the iceberg
- With new drugs coming on markt the incidence of DILI is on the increase

- DILI is the most common cause of market failure & market withdrawal of a drug

Diagnosis of DILI or ?DILI

Liver biopsies	Total	?Drug	%
2010	216	7	3.2%
2015	146	6	4.1%
2016	240	25	10.4%
2017	119	16	13.4%
2018	120	17	14.2%
2019*	94	18	19.1%

DILI in a liver biopsy

- Any pattern of liver injury can be caused by a drug/toxin
- A drug/toxin can cause any pattern of liver injury

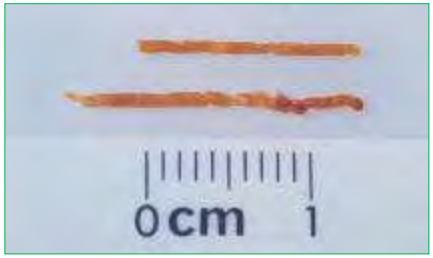
Conclusion: It is not possible to diagnose or exclude DILI with any degree of confidence on liver biopsy

BUT!

- Some drugs/toxins – specific patterns of injury
- Some patterns of injury are classically associated with a particular drug
- Good **clinico-pathological correlation** can sometimes provide a temporal association between a drug and liver dysfunction
- Removal of the drug results in resolution
- ?? Re-challenge

Clinico-pathological correlation

- DILI is a prime example of the importance of clinico-pathological correlation in the diagnosis of liver disease



Liver Biopsy

Drug History

Dx of DILI

Otherwise you run the risk of being:

- Unhelpful, ie the liver biopsy is wasted
- Misleading, ie the pt may receive inappropriate Tx

Clinical history is not always helpful

- The presentation and/or biochemistry is non-specific
- Routine liver screen is negative
  - Helpful in excluding other aetiologies

Drug history is not always helpful

- Patient is unreliable historian
- Patient may be on multiple medications
- Patient does not mention drugs
  - Naturopathic meds
  - Illicit drugs

When do we consider drug toxicity?

1. Clinical history indicates a suspect drug
2. The pattern of injury is typical of a particular drug
3. The pattern of injury is unusual
   - eg a mixed pattern
4. The pattern of injury is totally non specific
   - ie could be anything and DILI is in the DD

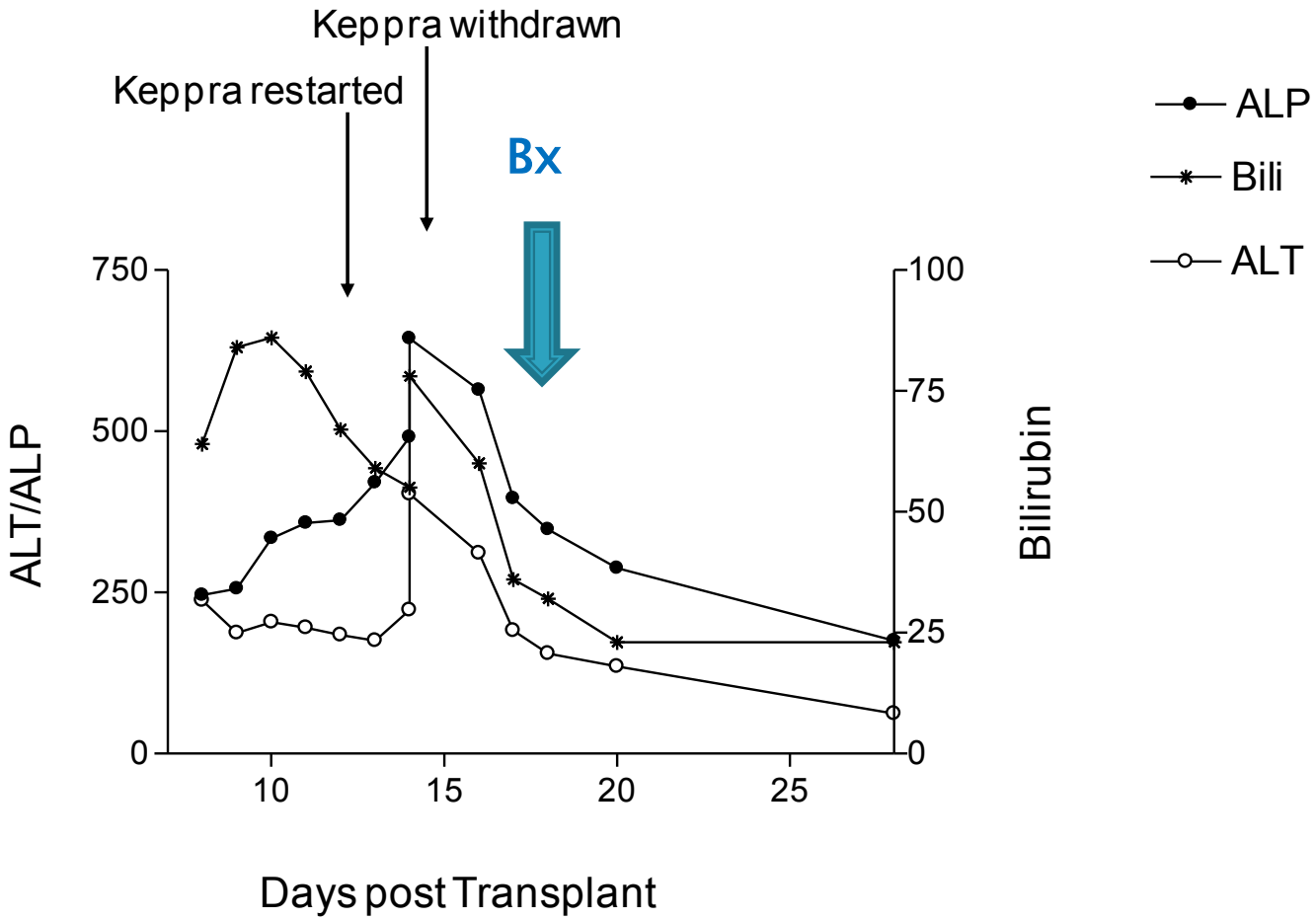
Clinical History: what do we want?

The clinician should contribute a comprehensive clinical history

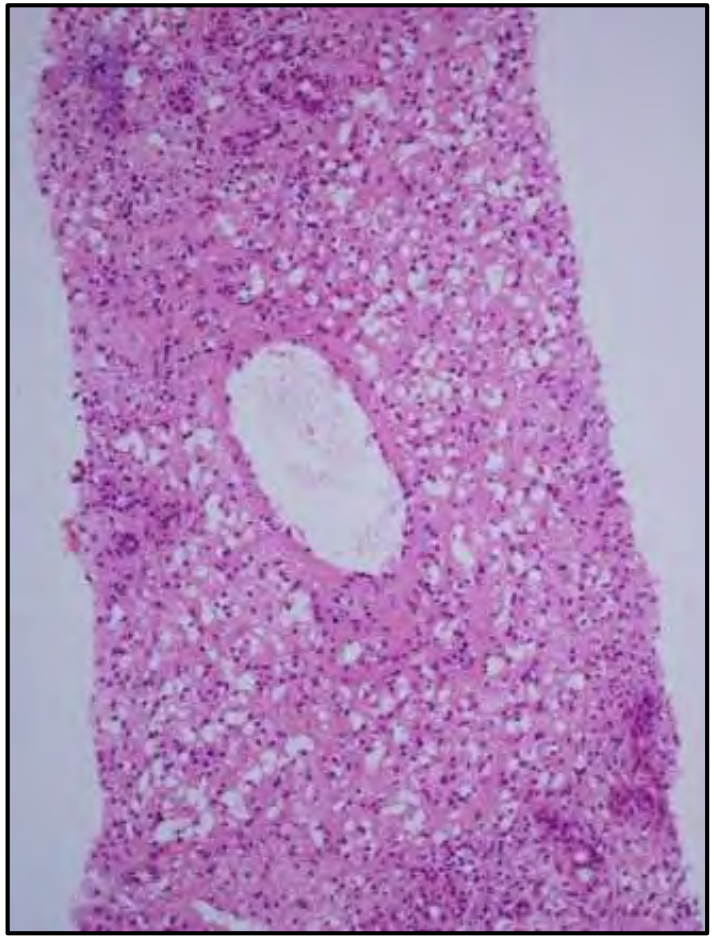
1. Drugs – Start, duration, cessation
2. Abnormal LFTs – Start, duration and course
3. Relationship between 1 and 2
4. Timing of biopsy

*Not all drug effects have a logical chronology

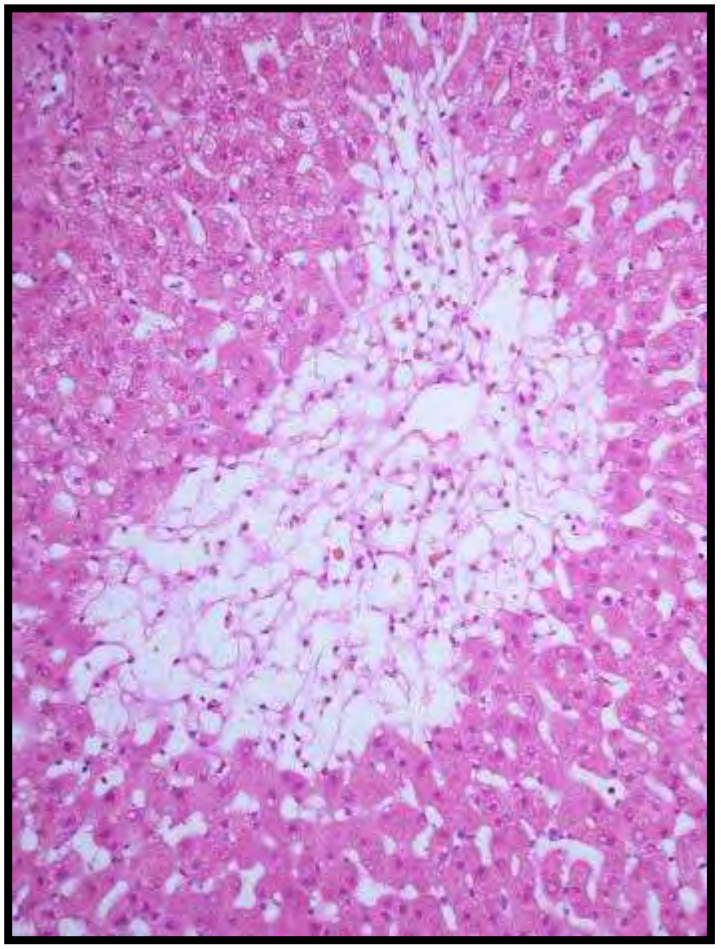
Restarting Keppra post liver OLTx



Massive necrosis: Keppra (levetericetum)



Core bx at presentation



Core bx day 19 post Tx

What are Drugs?

- Medications
- Illicit drugs

- Naturopathic substances
  - Herbal supplements
  - Body building supplements

- Toxins
  - Alcohol

Data base of hepatotoxic drugs

- https://livertox.nih.gov/

What patterns of damage?

DILI Network (DILIN) in USA

- Funded by National Institute of Health
- Database DILI cases across 12 US sites
- Recognise 14 common reaction patterns associated with DILI

http://www.dilin.org/

Histologic Pattern	Description	Example Drugs
Acute hepatitis	Predominantly lobular inflammation and damage that overshadows portal inflammation. No fibrosis.	Fluoroquinolones; nitrofurantoin and methyldopa (acute autoimmune)
Chronic hepatitis	Predominantly portal inflammation with varying degrees of lobular inflammation. No cholestasis. Variable degrees of portal fibrosis.	Nitrofurantoin, methyldopa
Acute cholestasis	Deposition of bile in either a hepatocellular or canalicular pattern with minimal inflammation.	Estrogens, androgenic steroids
Chronic cholestasis	Bile deposition with evidence of duct injury, such as ductular proliferation or ductopenia.	Floxuridine
Cholestatic hepatitis	A combination of hepatitic and cholestatic patterns.	Amoxicillin-clavulanate, fluoroquinolones
Granulomatous inflammation	Nonnecrotizing epithelioid granulomas.	Phenytoin
Macrovesicular steatosis	Variable degrees of accumulation of large fat droplets with peripheral displacement of the nucleus without significant inflammation or cholestasis or alternate pattern.	Methotrexate, tamoxifen
Microvesicular steatosis	Diffuse hepatocyte accumulation of small fat droplets maintaining a central placement of the nucleus without significant inflammation or cholestasis or alternate pattern.	Valproic acid, tetracycline
Steatohepatitis	Steatosis with hepatocyte ballooning, variable degrees of inflammation, and fibrosis.	Amiodarone, tamoxifen, methotrexate
Zonal necrosis	Coagulative hepatocyte necrosis within 1 of the 3 zones of the liver acinar unit (zone 3 is most common).	Acetaminophen
Massive or submassive necrosis	Confluent multiacinar necrosis with variable inflammation.	Isoniazid, nitrofurantoin, methyldopa
Sinusoidal obstruction syndrome/veno-occlusive disease	Sinusoidal dilatation and congestion, central venule occlusions, perisinusoidal fibrosis.	Chemotherapeutic agents, bone marrow transplant regimen
Mixed or unclassifiable injury	A combination of 2 or more other patterns or significant change that does not qualify for another pattern.	No specific associations
Minimal nonspecific changes	Minor changes such as minimal inflammation or steatosis that do not qualify as normal or for another pattern.	No specific associations

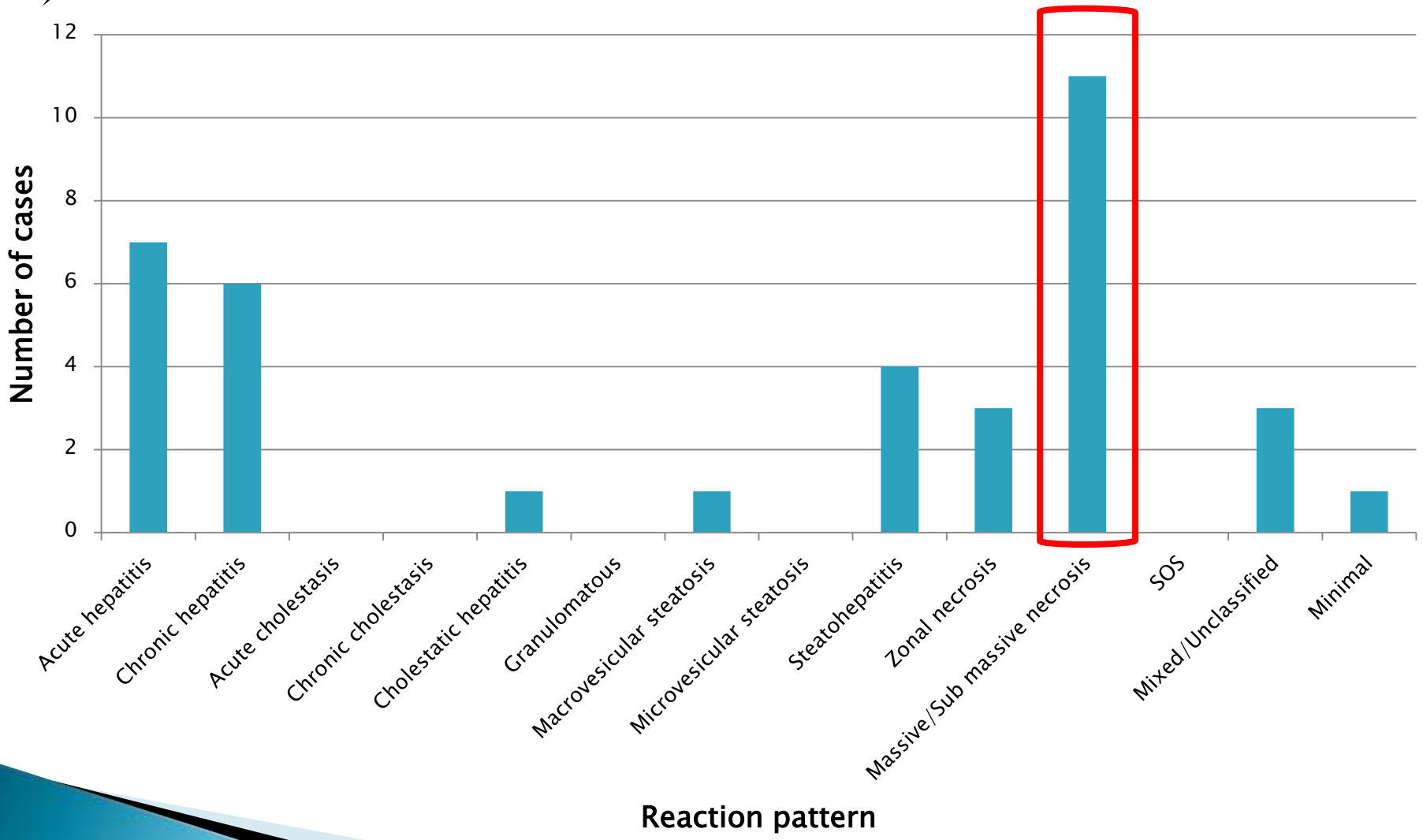
Fisher K, Vuppalanchu R, Saxena R. Drug-induced liver injury. Arch Pathol Lab Med. 2015 July:139: 876-87

PathWest review

- Reports of all liver biopsies coded as DILI over 5 year period.
- Classified into:
  - Definite – culprit drug with compatible histology
  - Possible – often multi-drug with compatible histology
  - Unlikely – drug history unknown and other aetiologies not excluded – (DVA)

- Review slides & categorise into 14 reaction patterns

Results


Number of cases
12
10
8
6
4
2
0
Acute hepatitis
Chronic hepatitis
Acute cholestasis
Chronic cholestasis
Cholestatic hepatitis
Granulomatous
Macrovesicular steatosis
Microvesicular steatosis
Steatohepatitis
Zonal necrosis
Massive/Sub massive necrosis
SOS
Mixed/Unclassified
Minimal
Reaction pattern

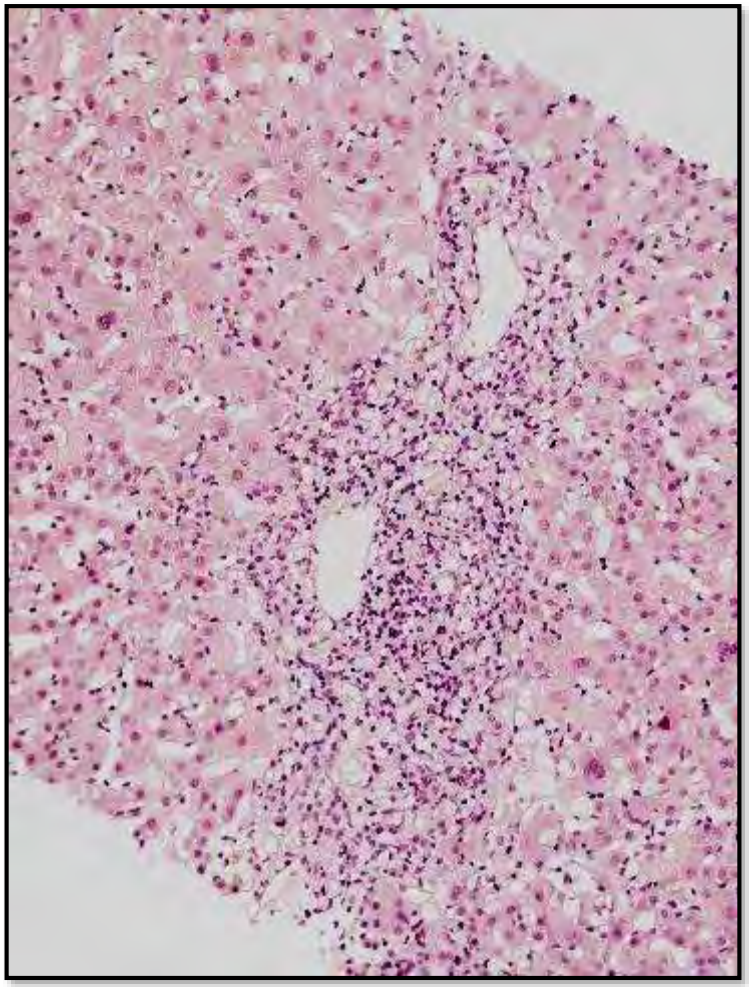
Reaction patterns

- Acute/chronic hepatitis
- Acute/chronic cholestasis
- Cholestatic hepatitis
- Granulomatous
- Macro/microvesicular steatosis
- Steatohepatitis
- Zonal or sub-massive/massive necrosis
- SOS
- Mixed/unclassified
- Minimal change

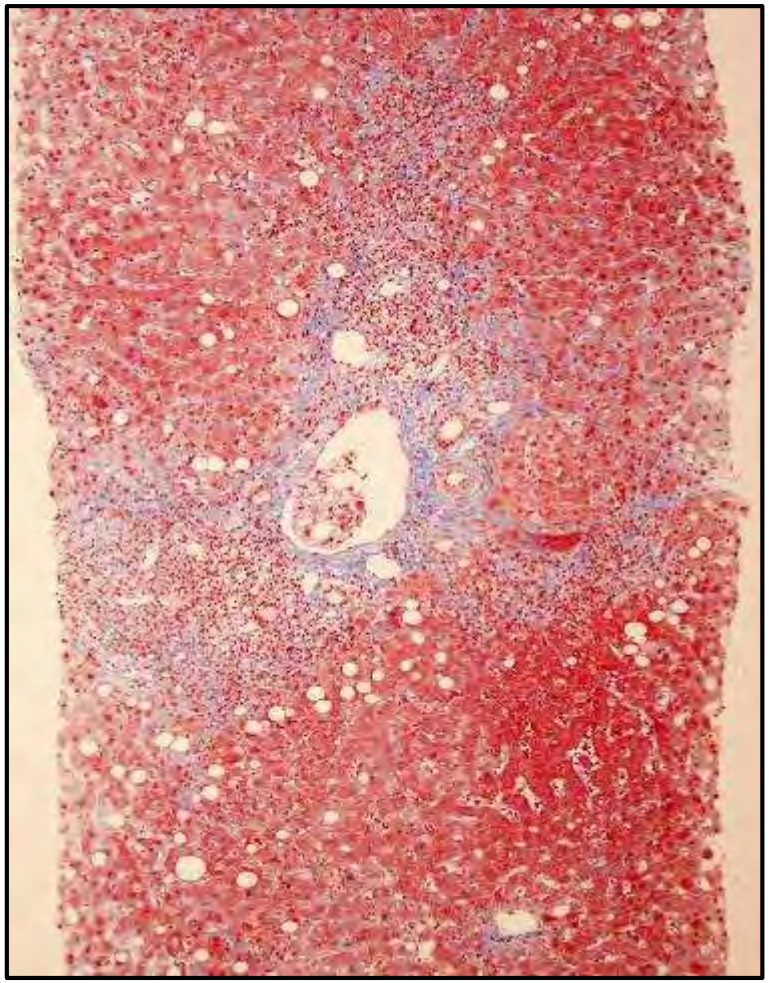
Pattern: acute vs chronic hepatitis

- Clinical history – duration of:
  - Symptoms
  - Abnormal LFTs
- ?? Type of inflammatory cells present
- Presence of fibrosis

Pattern: acute vs chronic hepatitis



Herbal supplements



Sulphasalazine

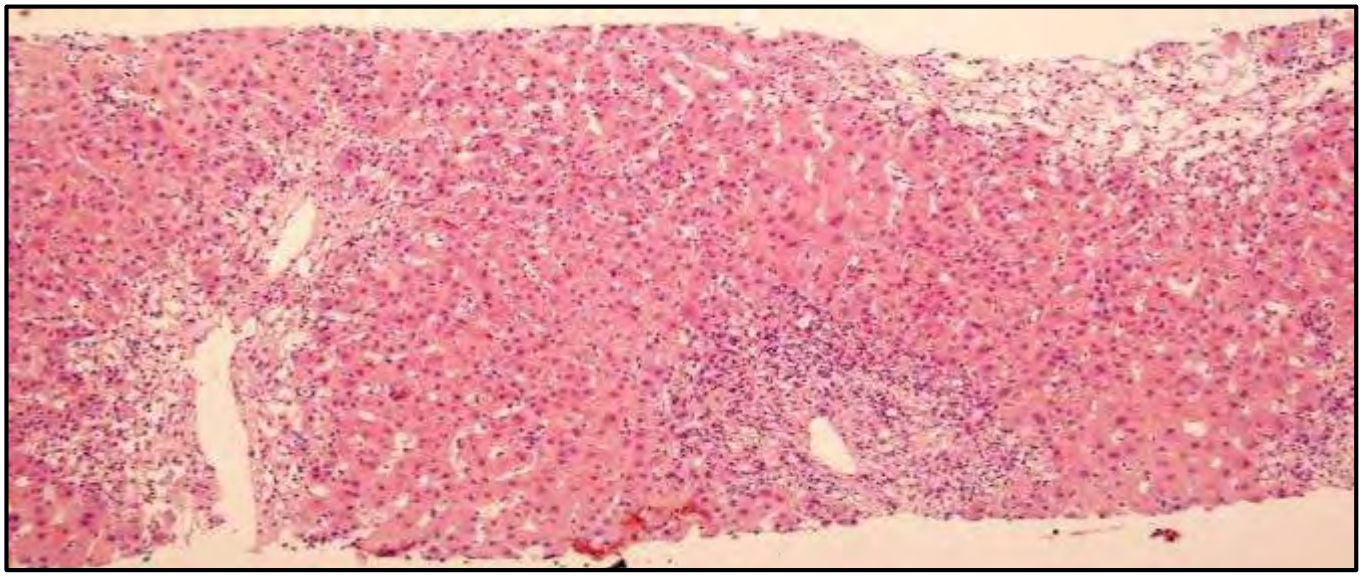
Pattern: Necrosis – terminology

- **Single cell**
- **"Spotty" or patchy**: *small* clusters of cells
- **Confluent**: *substantial* number of hepatocytes
  - **Zonal**: affecting zones 1, 2 or 3 of lobule
  - **Bridging**: central-portal and central-central
- **Sub-massive**: *global* necrosis of 30-70% of liver
- **Massive**: *extensive* diffuse panlobular and multilobular necrosis

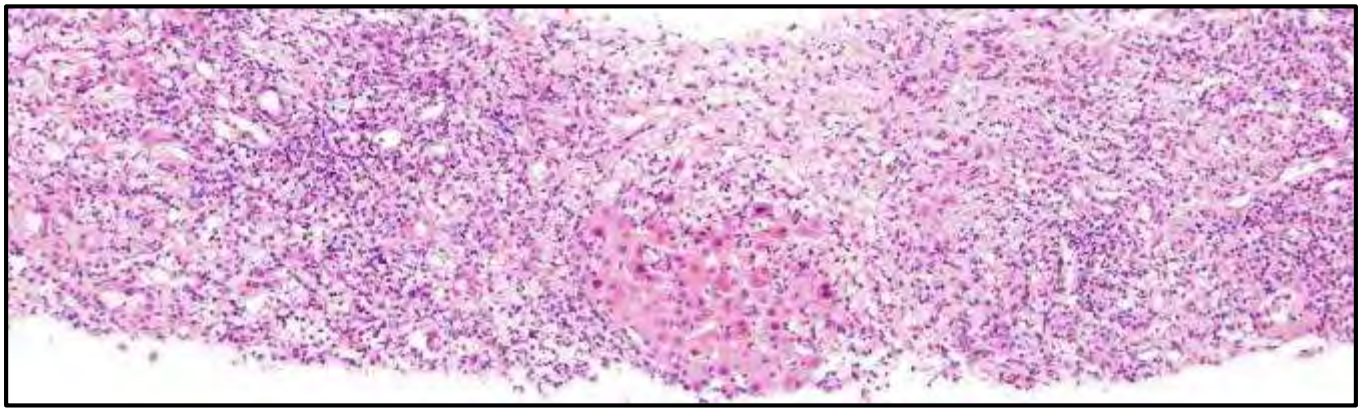
- Should not use fulminant or sub-fulminant
  - they are clinical terms

Patterns: Necrosis: Zonal vs sub-massive/massive

Cyproterone acetate



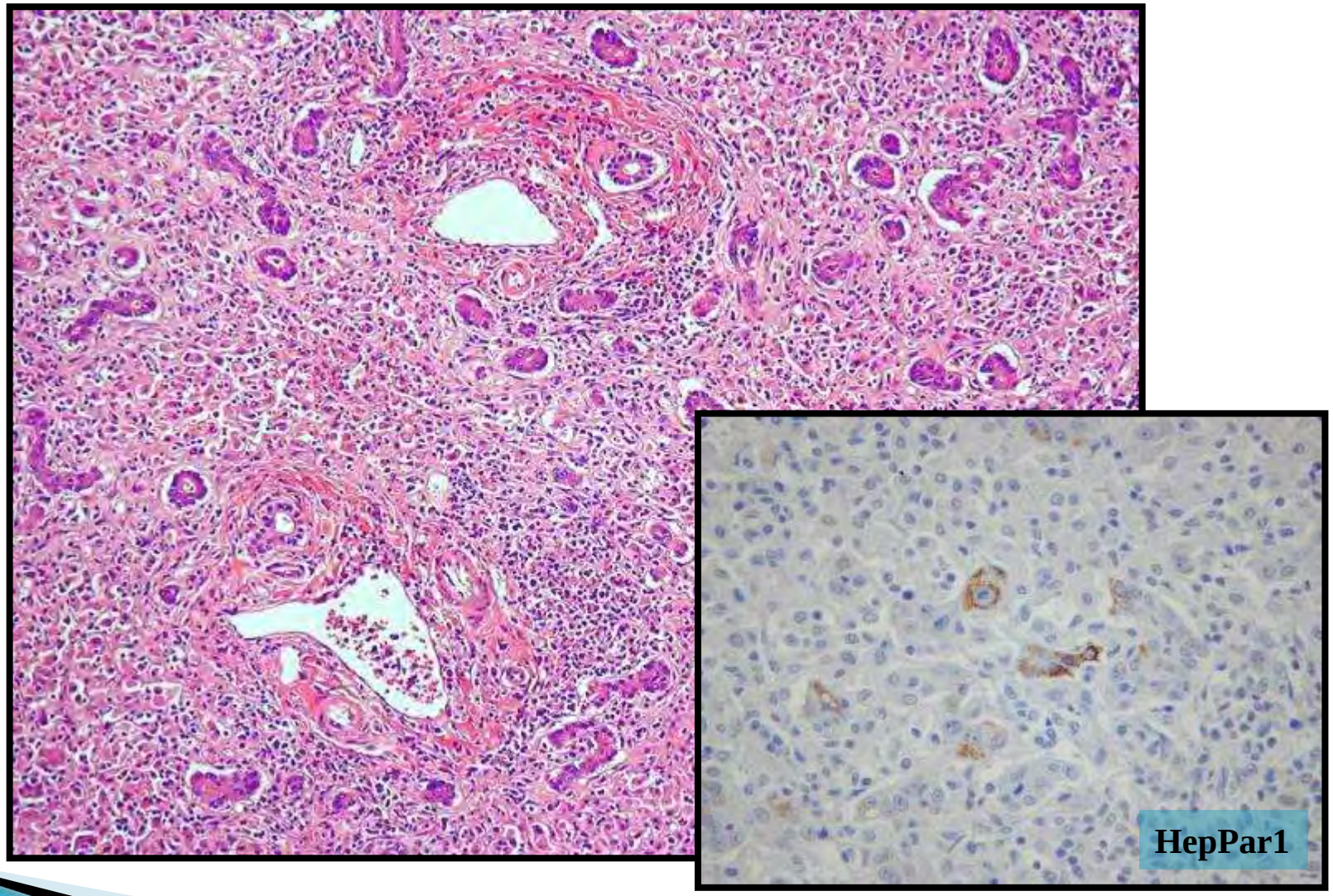
?Drug



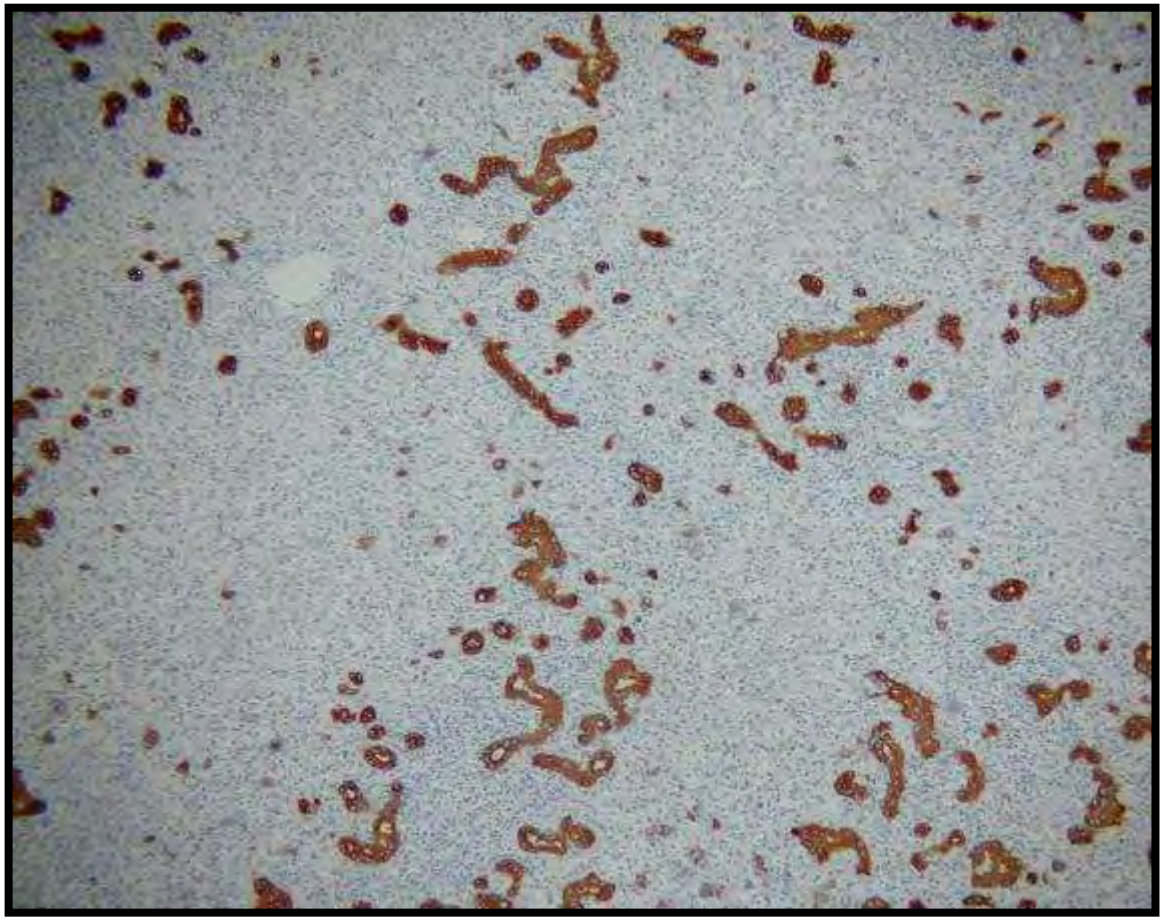
Pattern: Necrosis

- Necrosis is non-specific
- Massive/sub massive necrosis usually wipes out any diagnostic clues
- DD includes;
  - Drugs/Toxins
  - Fulminant viral hepatitis
  - Other infections
  - AIH
  - Wilson's disease

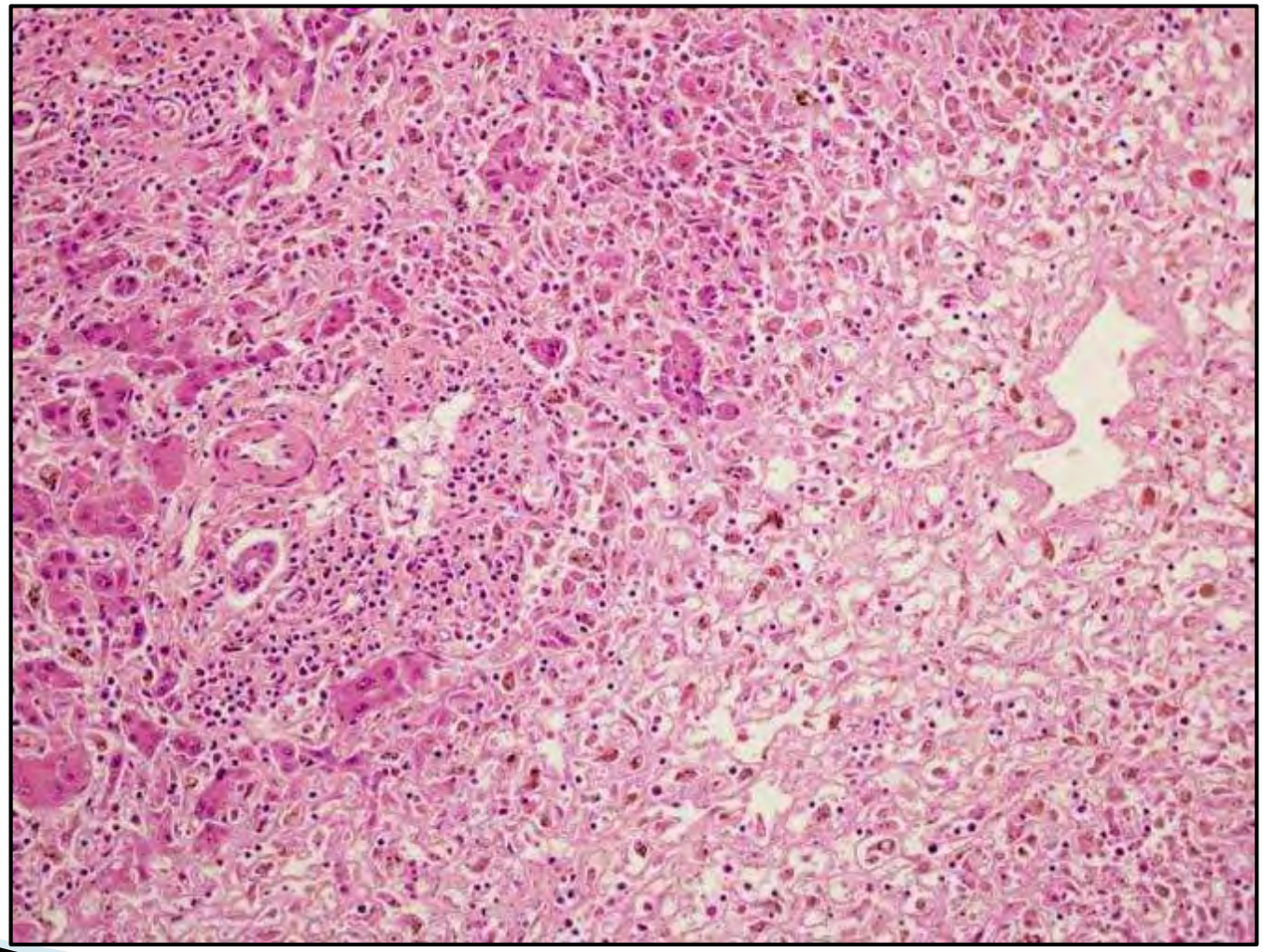
Massive necrosis: Methoxyflurane



Massive or sub-massive necrosis: ductular reaction

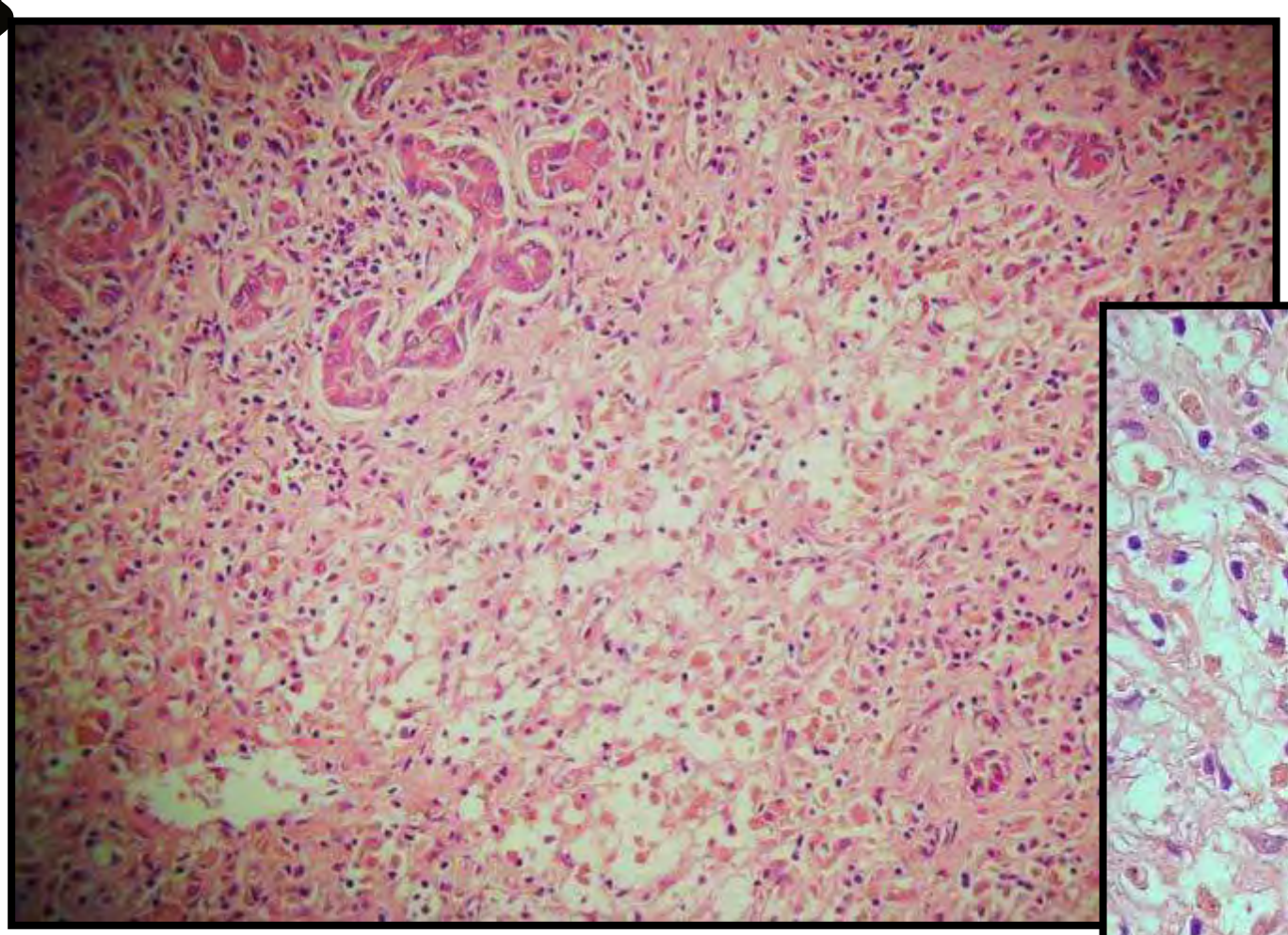


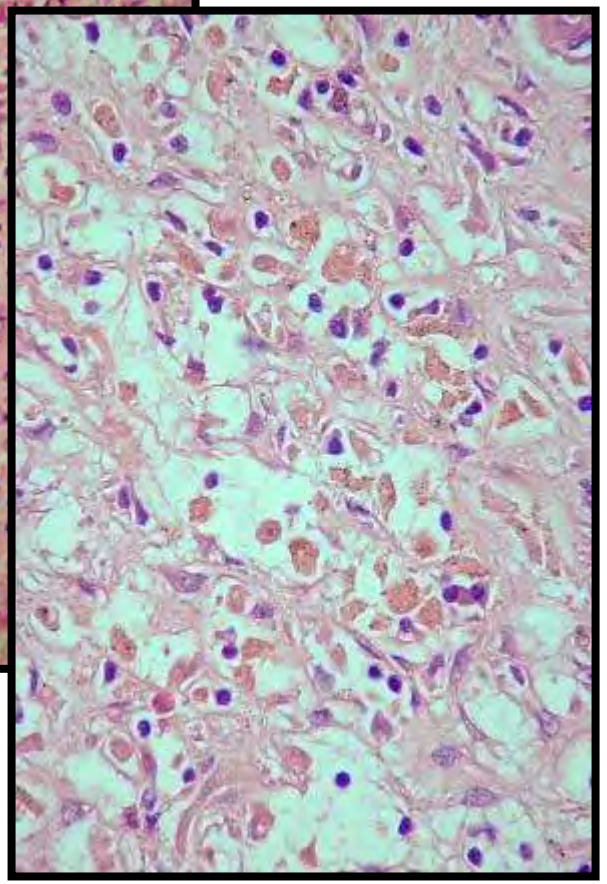
Massive necrosis: empty trabeculae



Augmentin

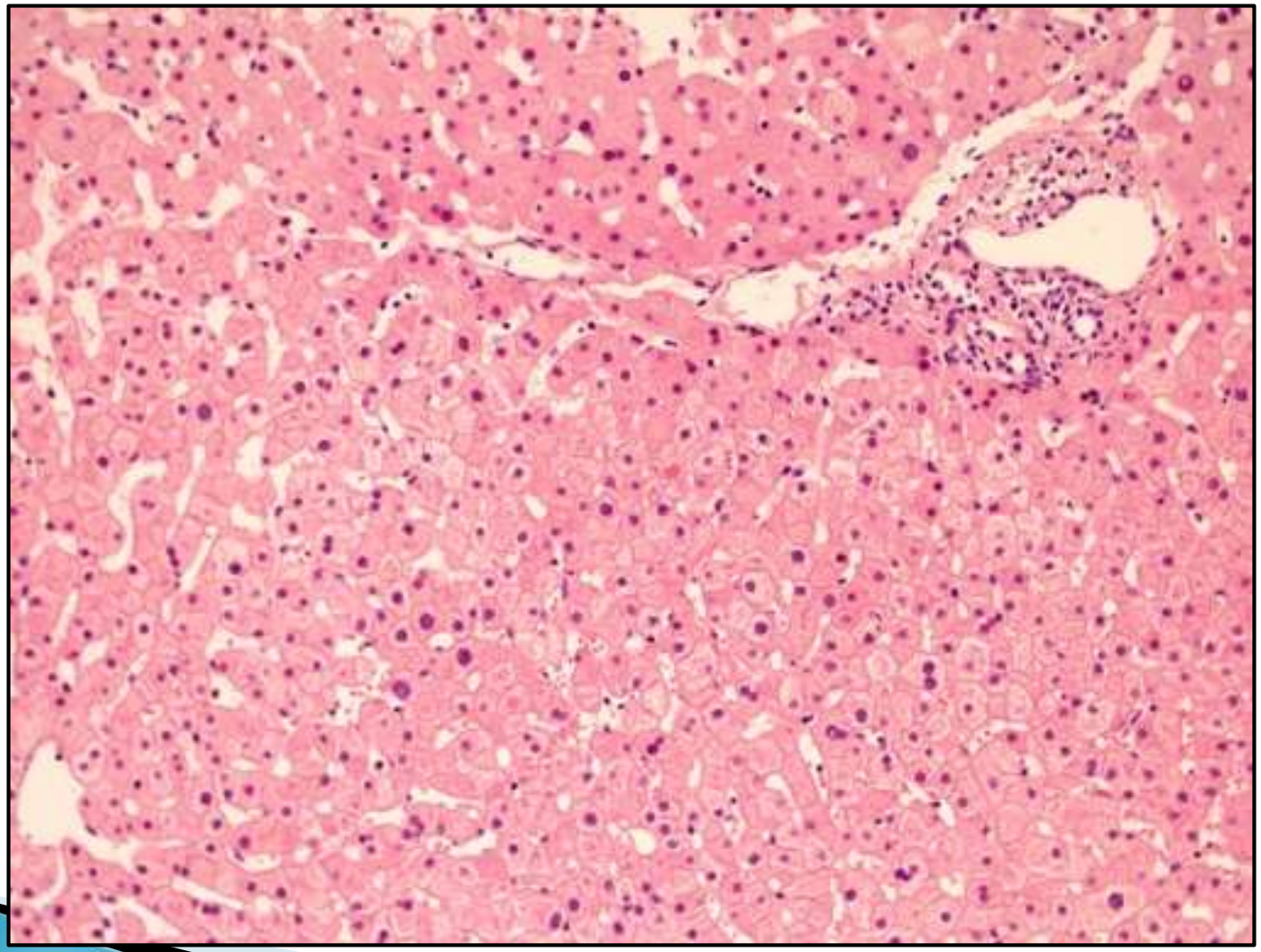
Massive or sub-massive necrosis



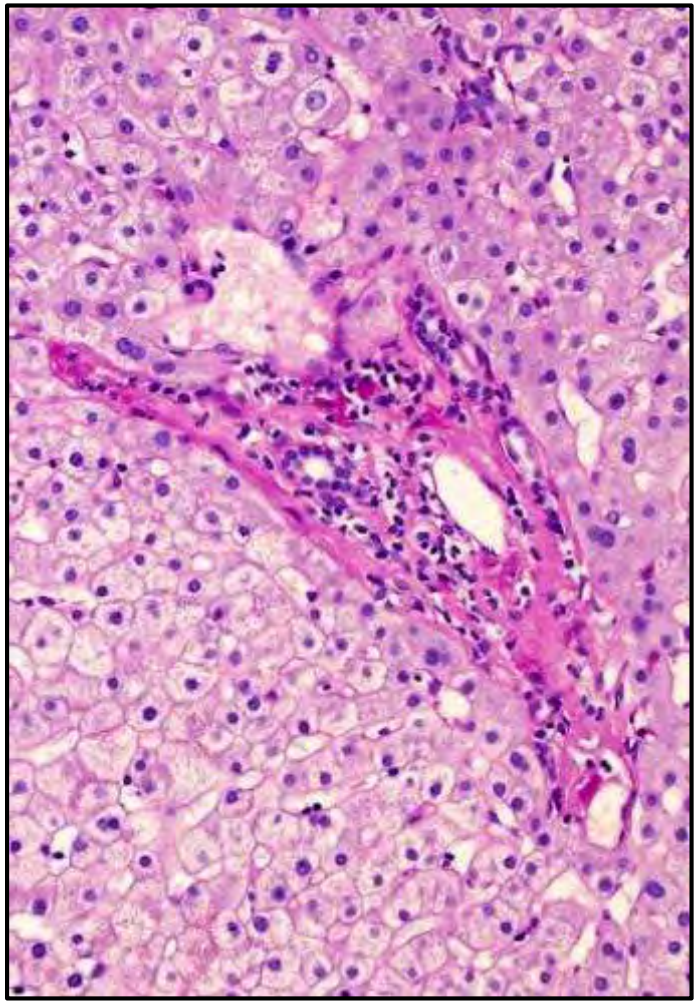


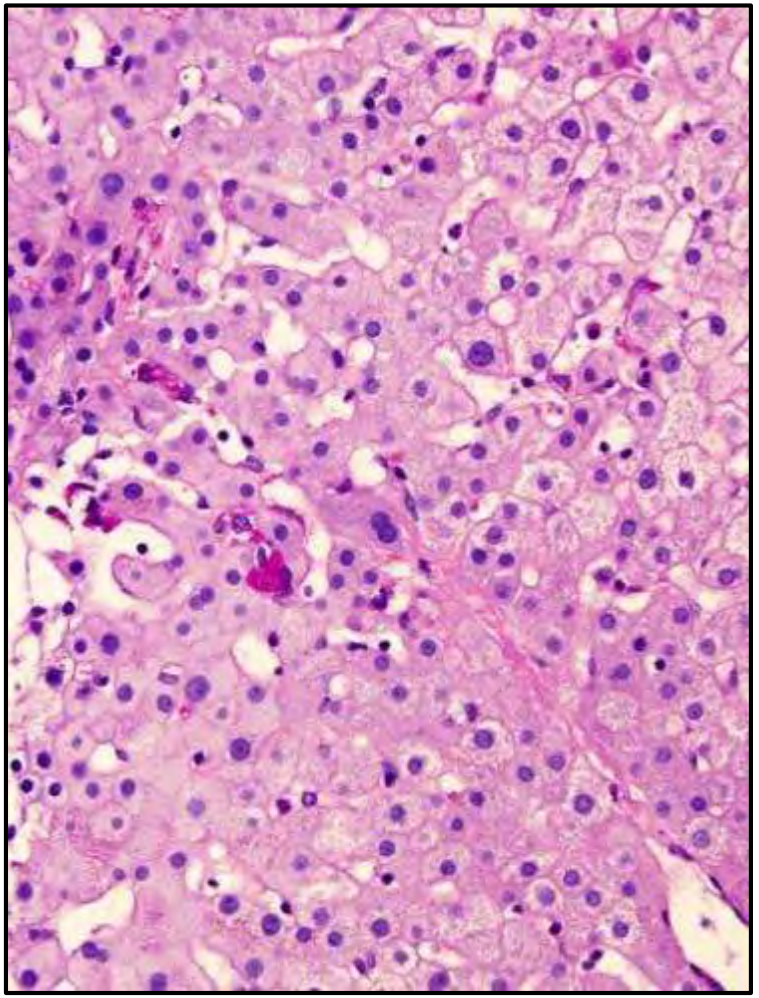
Fulminant HBV

Pattern: Minimal non-specific changes



Pattern: Minimal non-specific changes





Patterns: Minimal non-specific changes

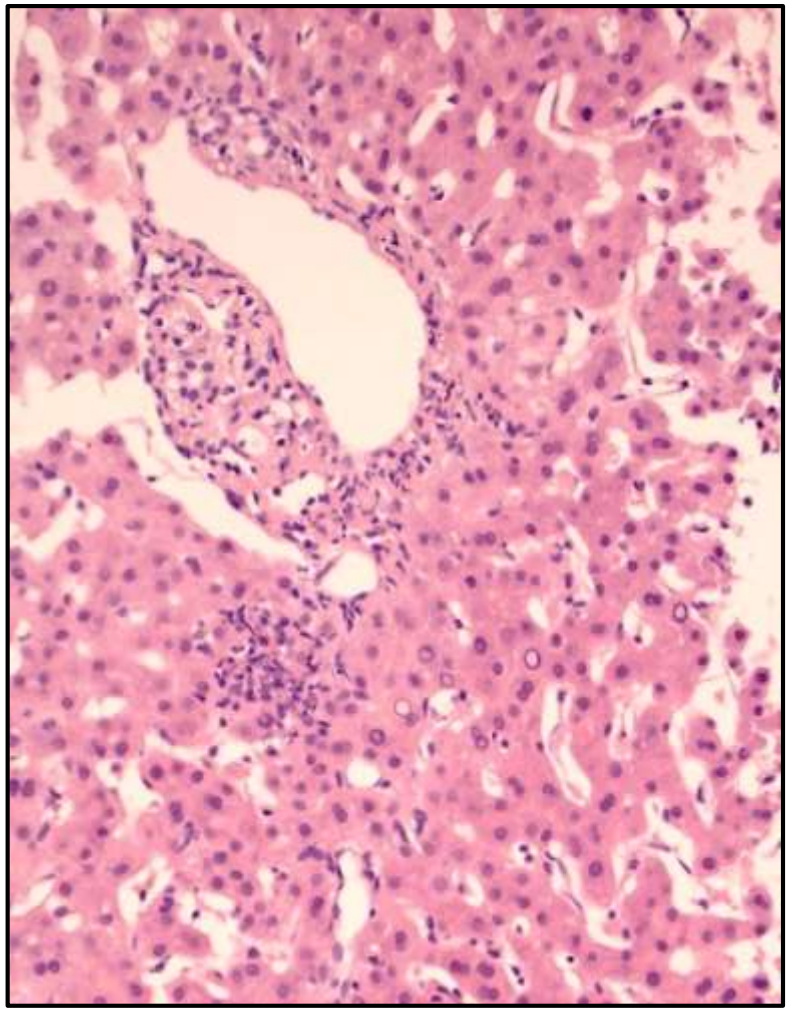
- The presence of pigment laden macrophages suggests a resolving acute hepatitis.
- Often the liver biopsy has been performed some weeks after the initiating consultation.
- Sometimes the LFTs have returned to normal.

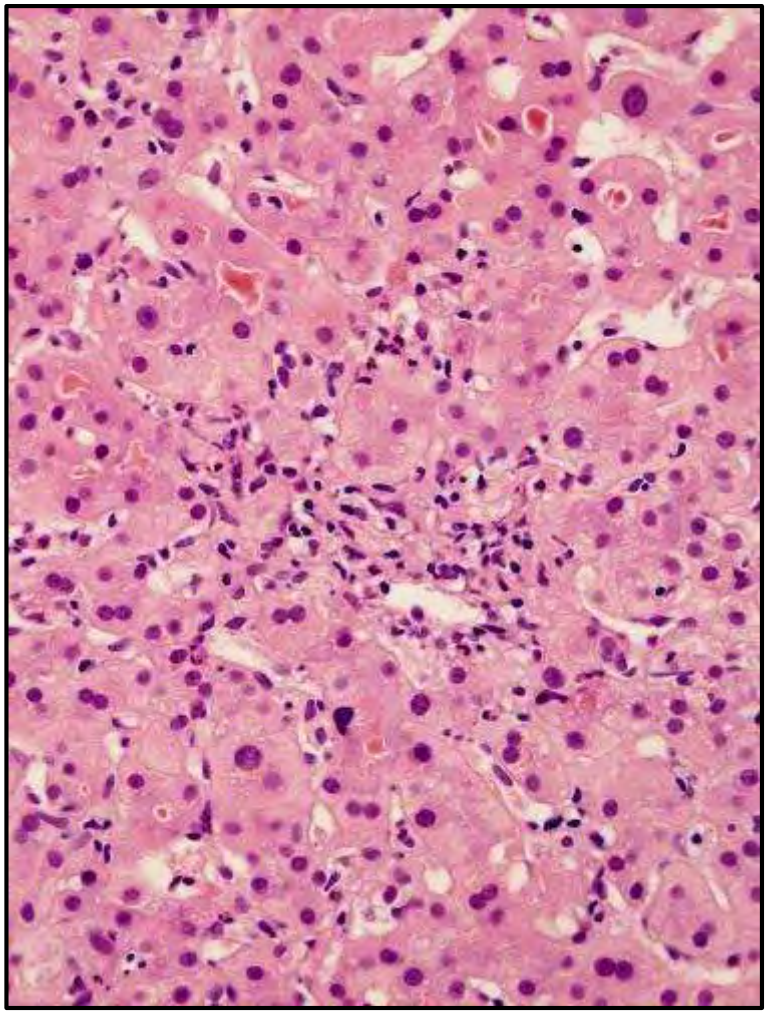
Specific Drugs

TKI	Acute hepatitis	Chronic hepatitis	Macrovesicular steatosis	Zonal necrosis	Massive/ Sub massive necrosis	Mixed/ Unclassified	Minimal
Antibiotic/Antifungal	2	1			1		
Azathioprine						1	
Cisplatin							1
Cyproterone acetate						1	
Disulfuram					1		
Fingolimod	1						
Herbal medication	1				4		
Imatinib					1		
Levetiracetam					1		
Metformin					1		
Methotrexate			1	1			
Paracetamol				1	1		
Rivaroxiban		1					
Statin	1						
Sulfasalazine				1			

Herbal Supplements/illicit drugs

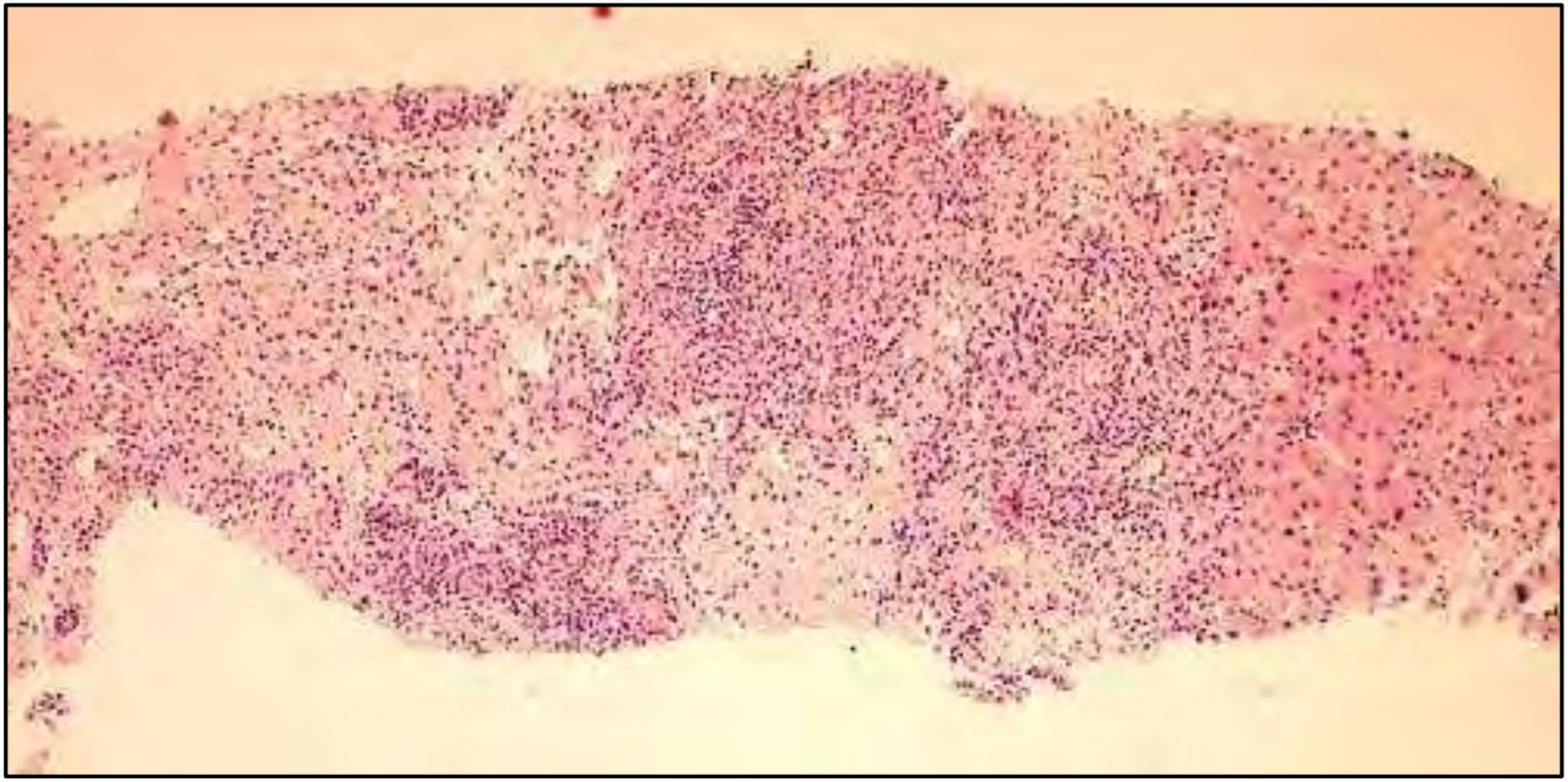
35yo M: cholestatic jaundice:





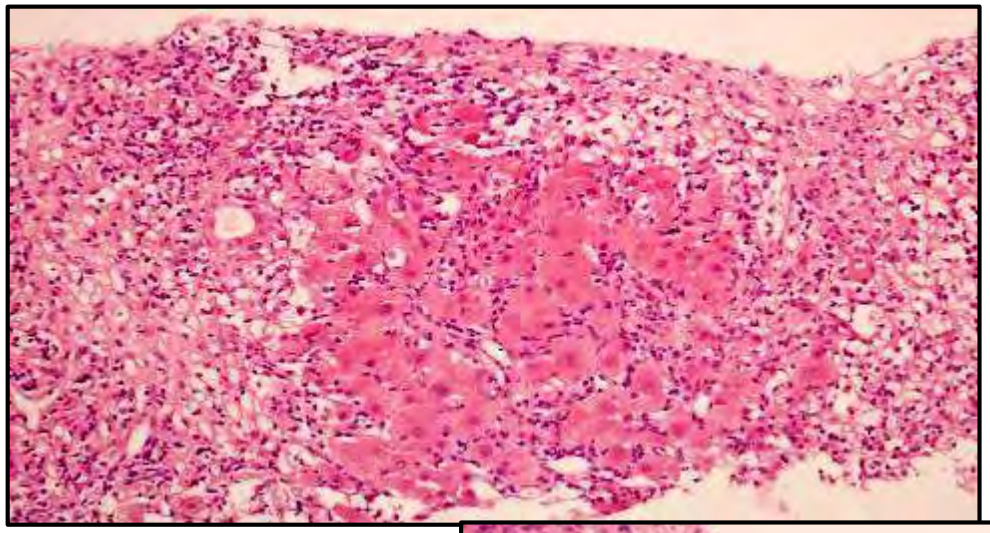
herbal supplements

27yo M: acute liver failure

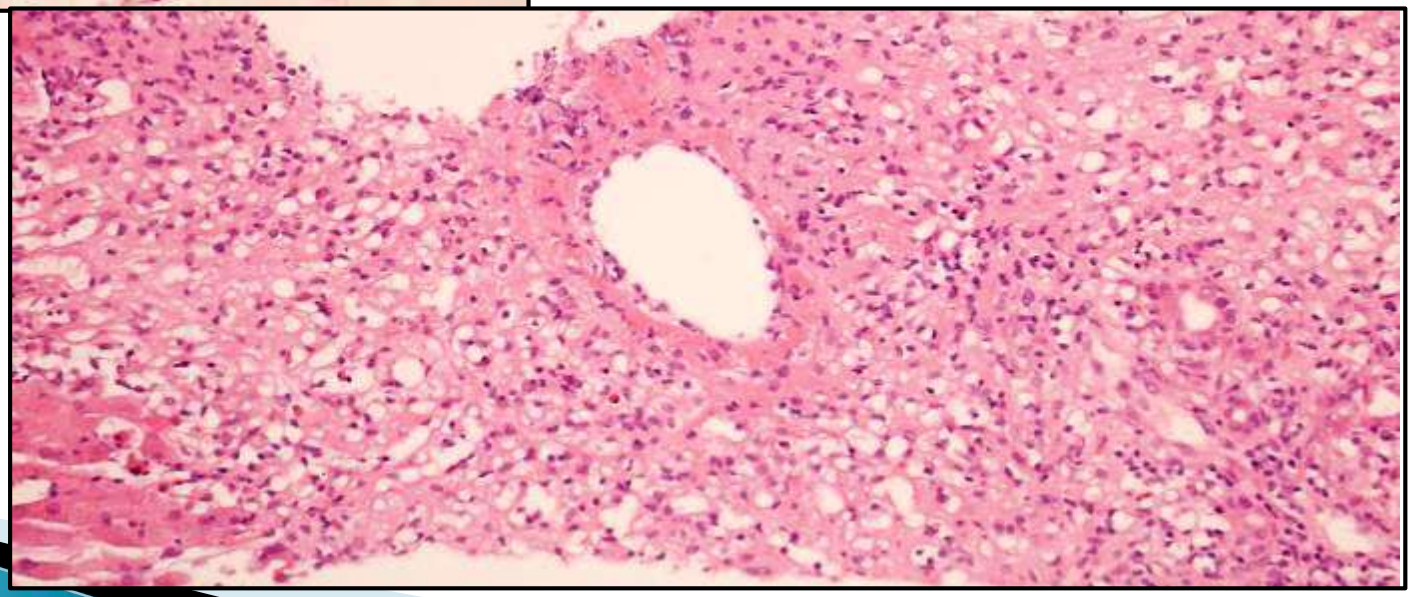


green tea extract or garcinia cambogia (Malabar tamarind)

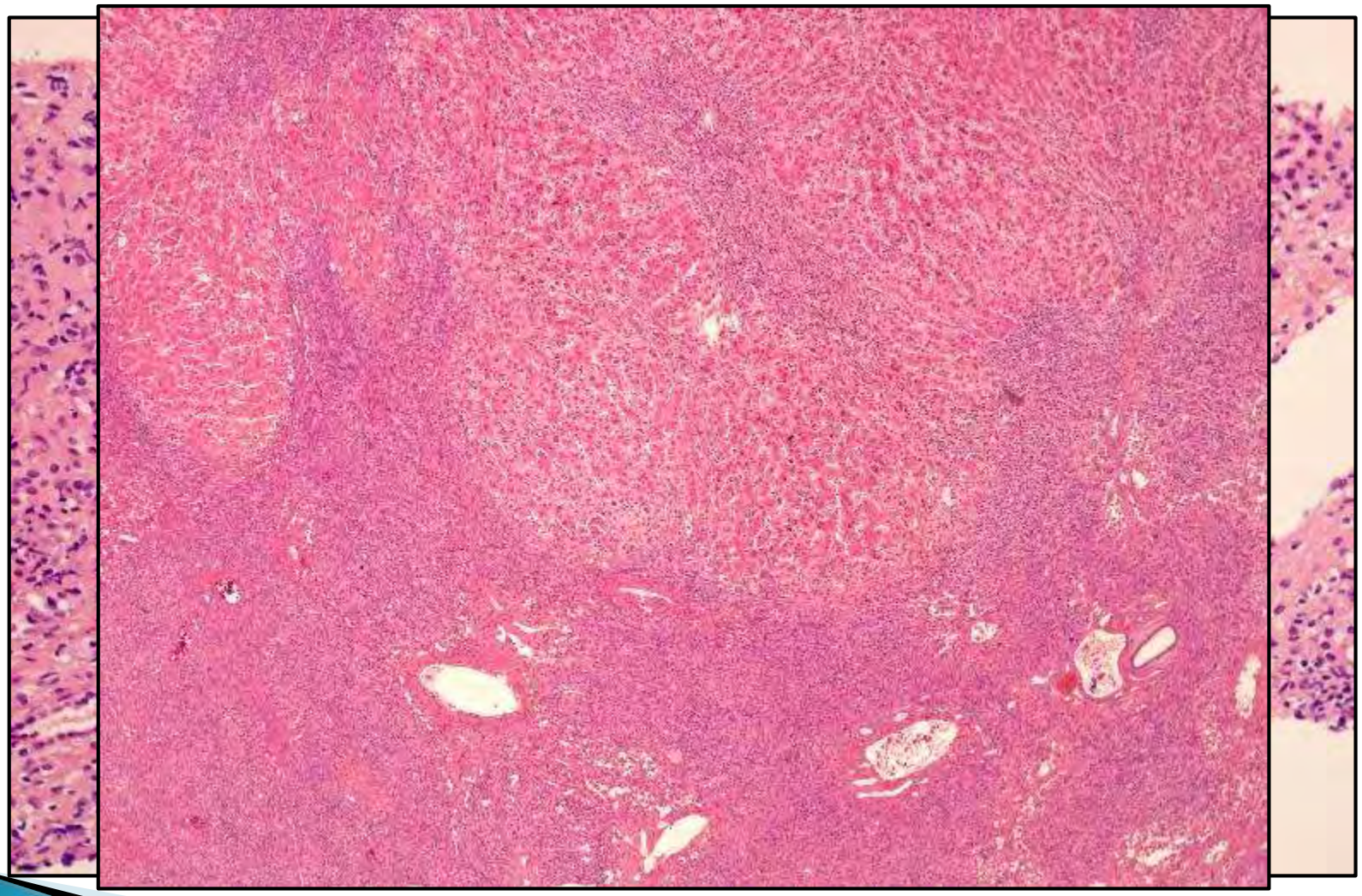
26yo – acute liver failure



1 tablet Ecstasy, 4/52 prior to presentation

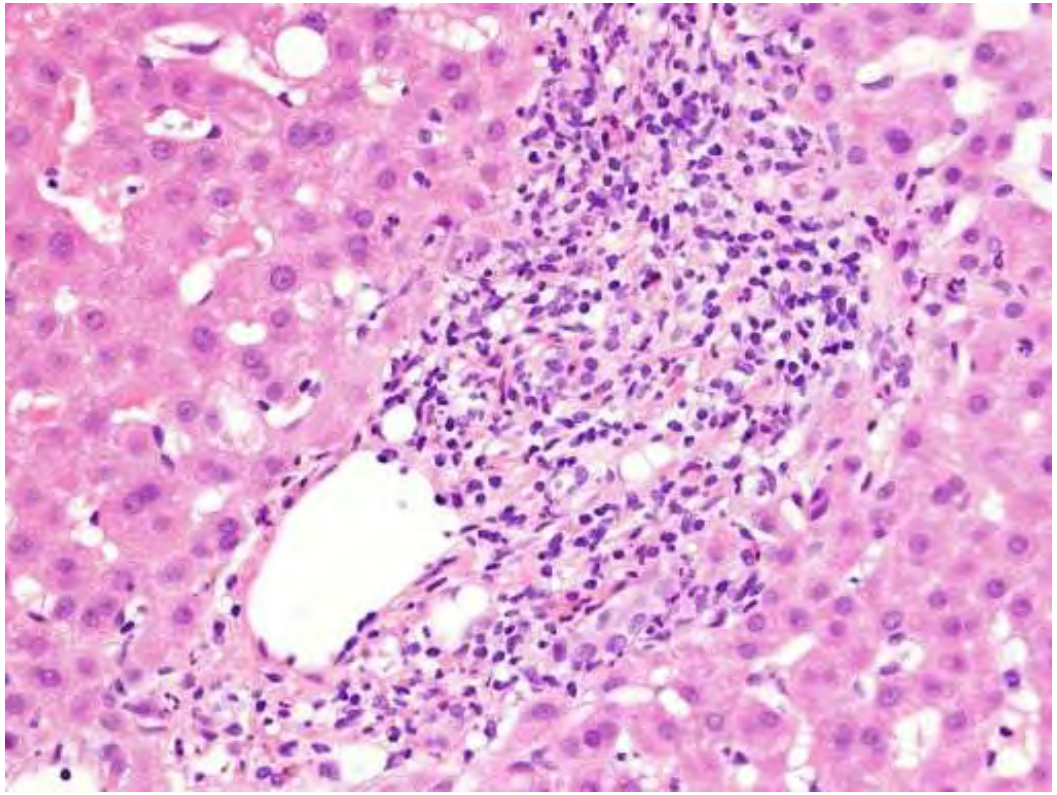


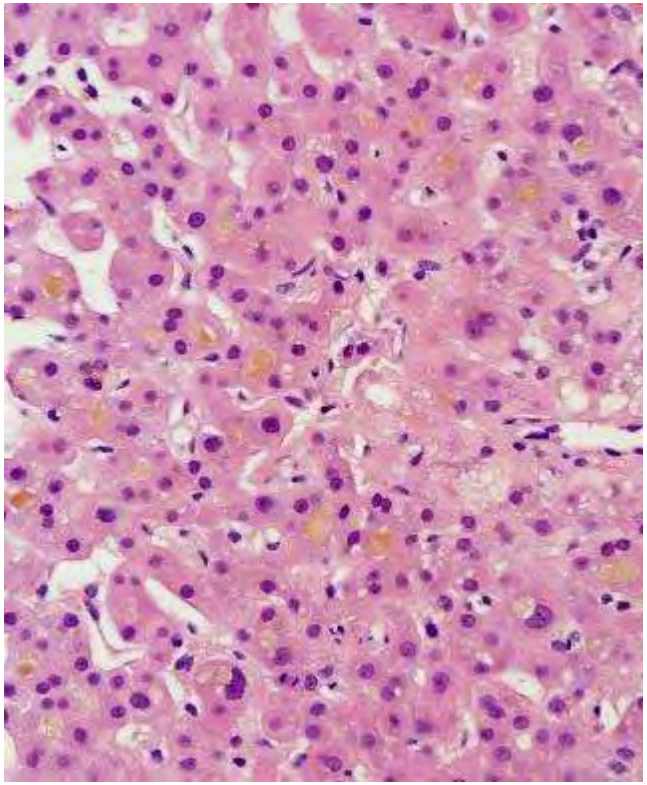
30yo M (Somalia) – acute liver failure



Chewing Khat leaf

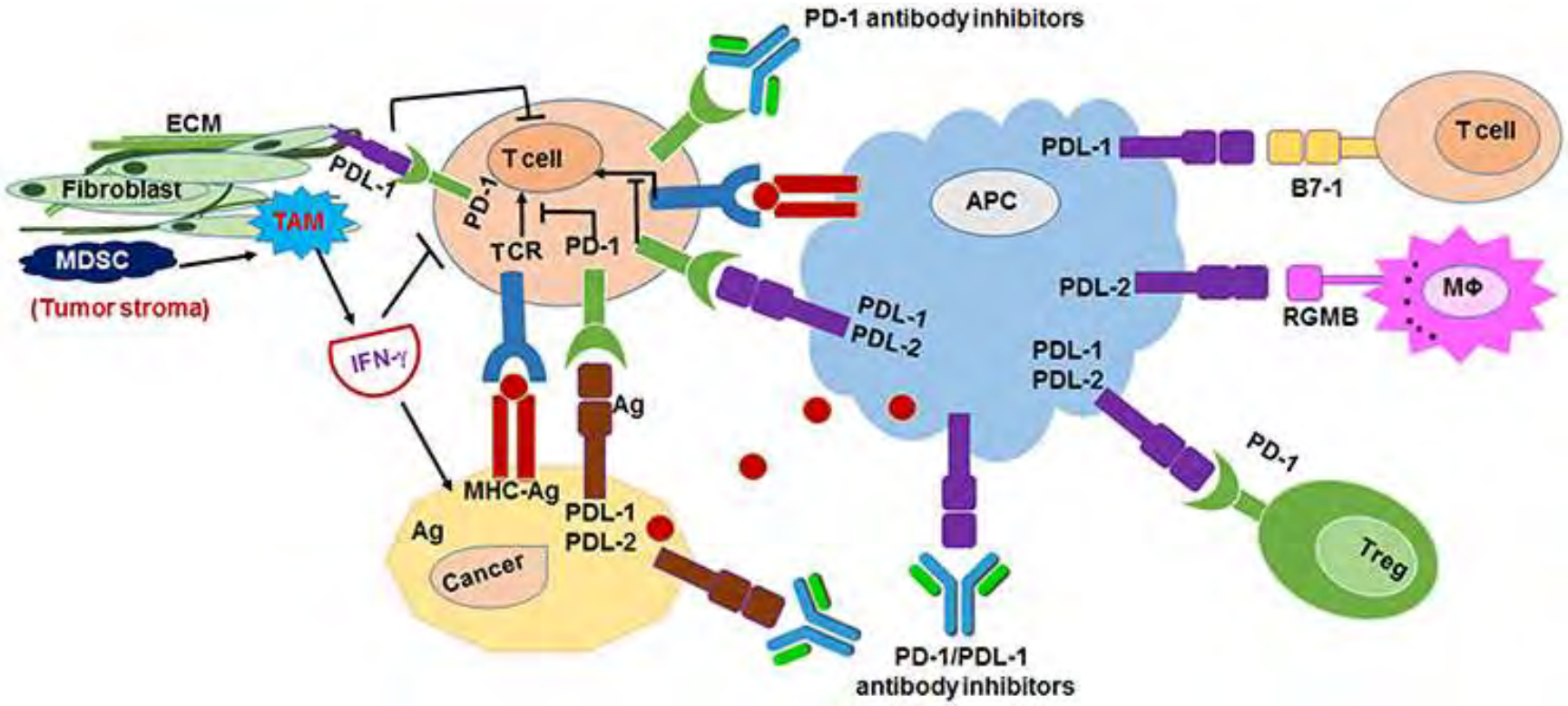
44yo M: acute hepatitis,
ALT 250, AST 104, ALP 200, Bili 831



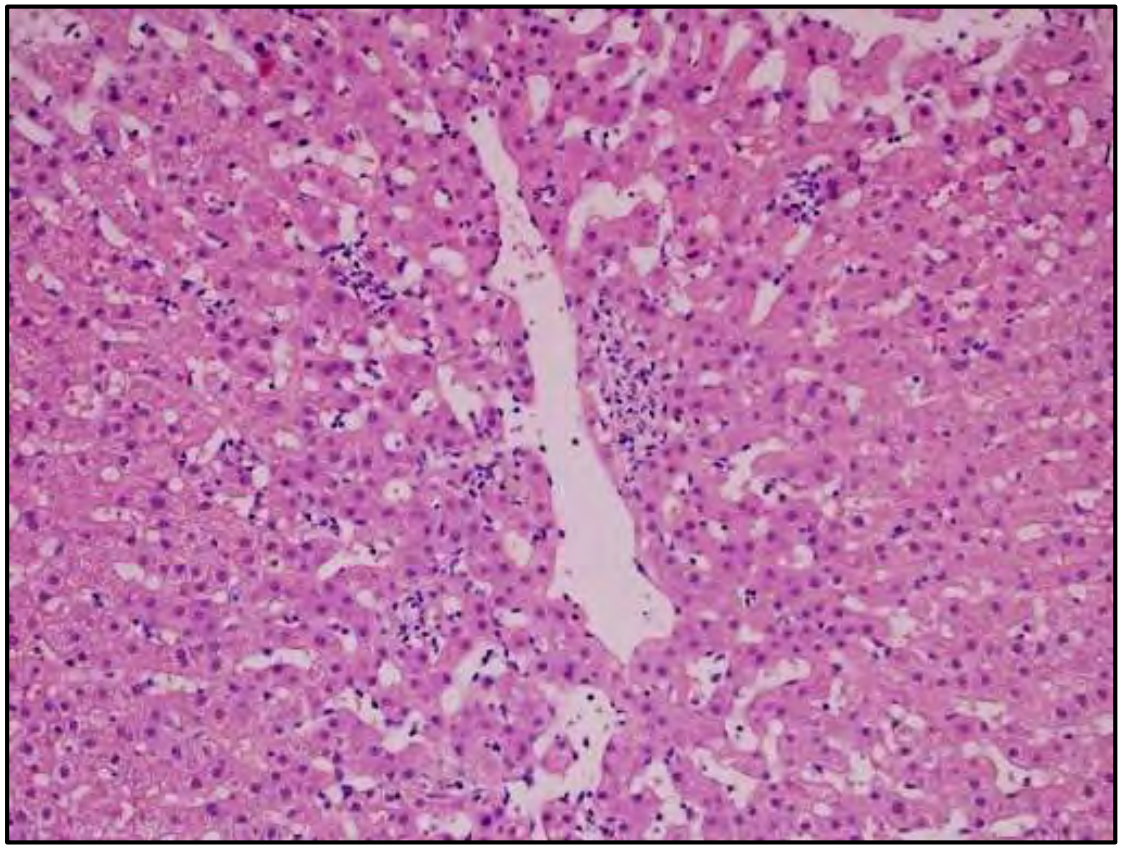


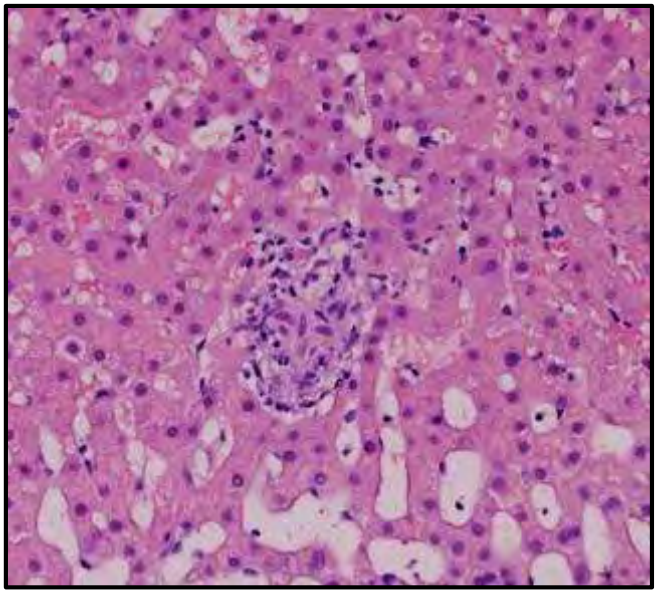
Selective Androgen Receptor Modulator (SARM)

Mabs/ Immunomodulating agents



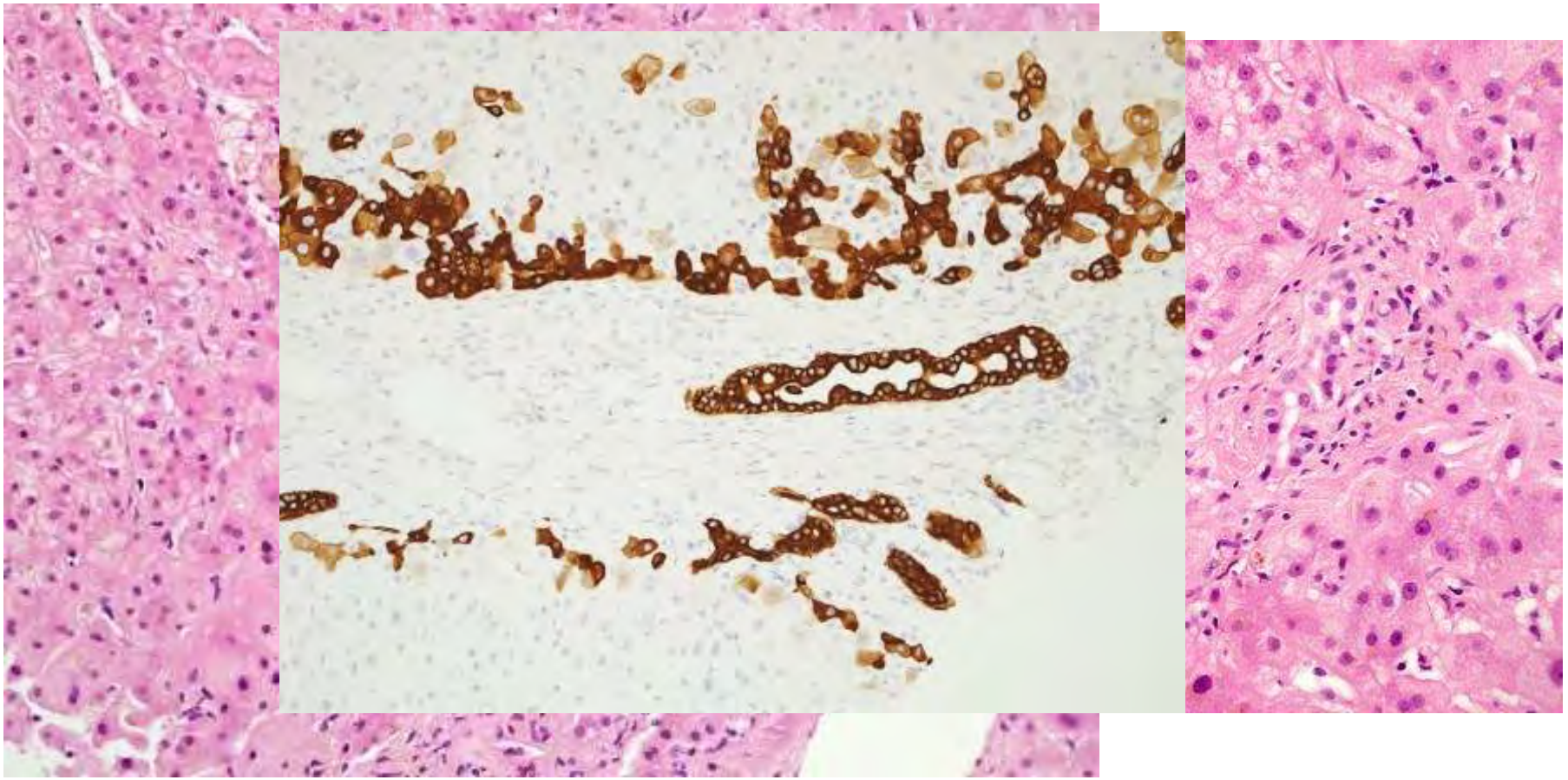
Drugs: 20yo F, abnormal LFTs





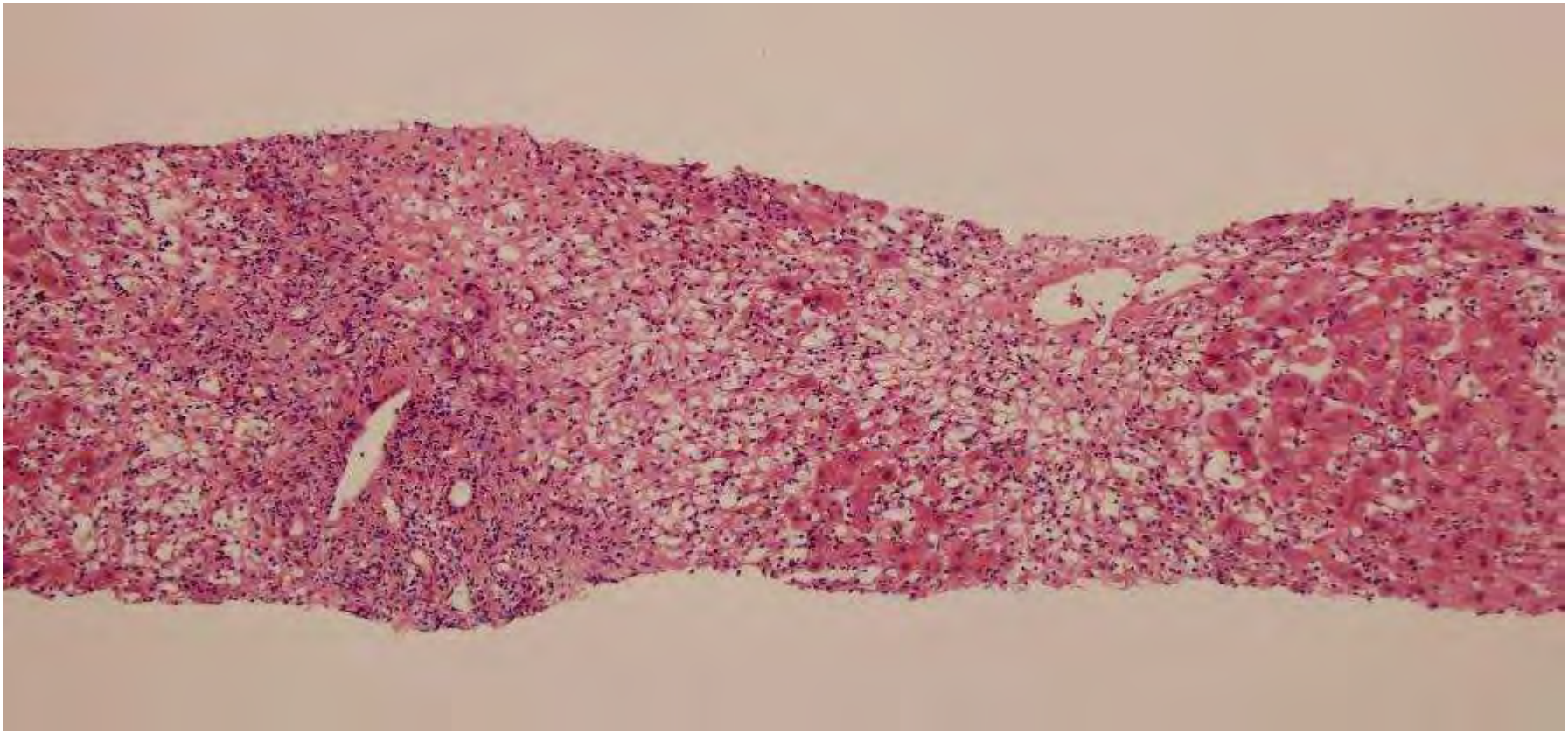
Metastatic melanoma - Dabrafenib/trametinib

82yo M, cholestatic LFTs – AP 1490, GGT 1620, ALT 75

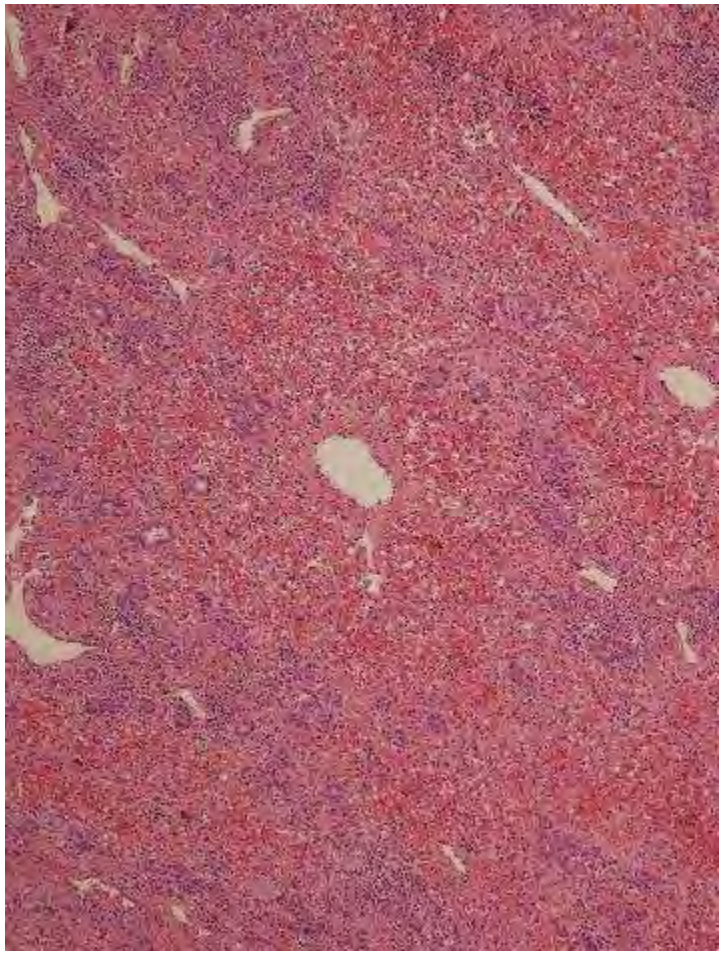


metastatic melanoma – pembolizumab

30yo F: Acute liver failure, 5/12 hx of CML



30yo F: Acute liver failure, 5/12 hx of CML



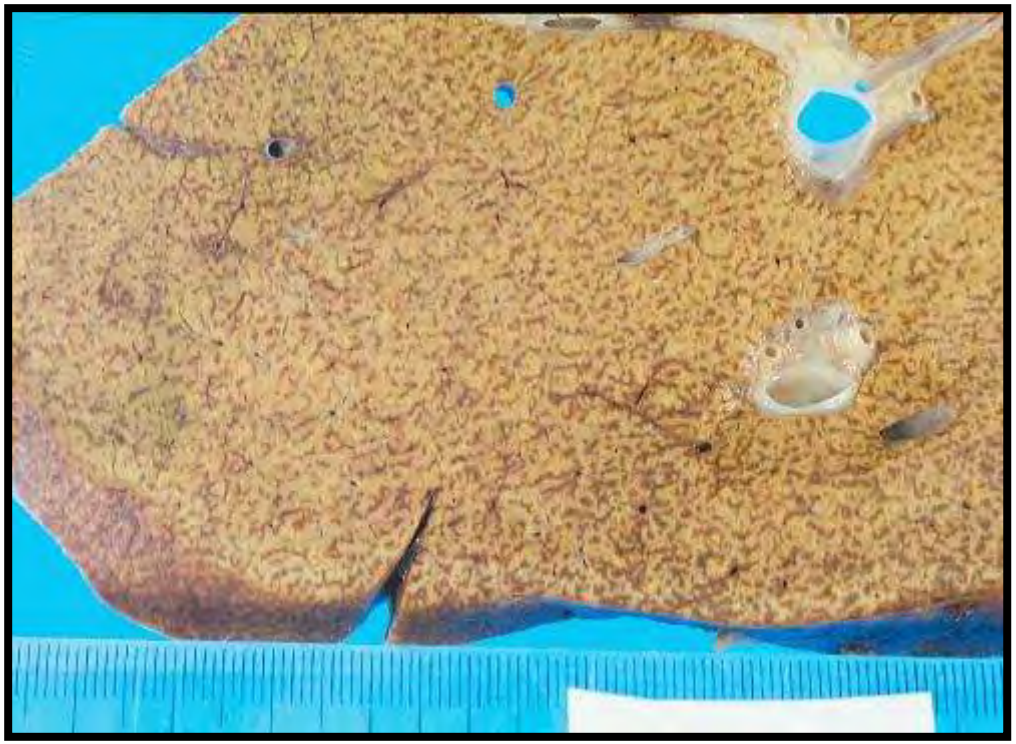
Imatinib (Gleevec)

A few old favourites

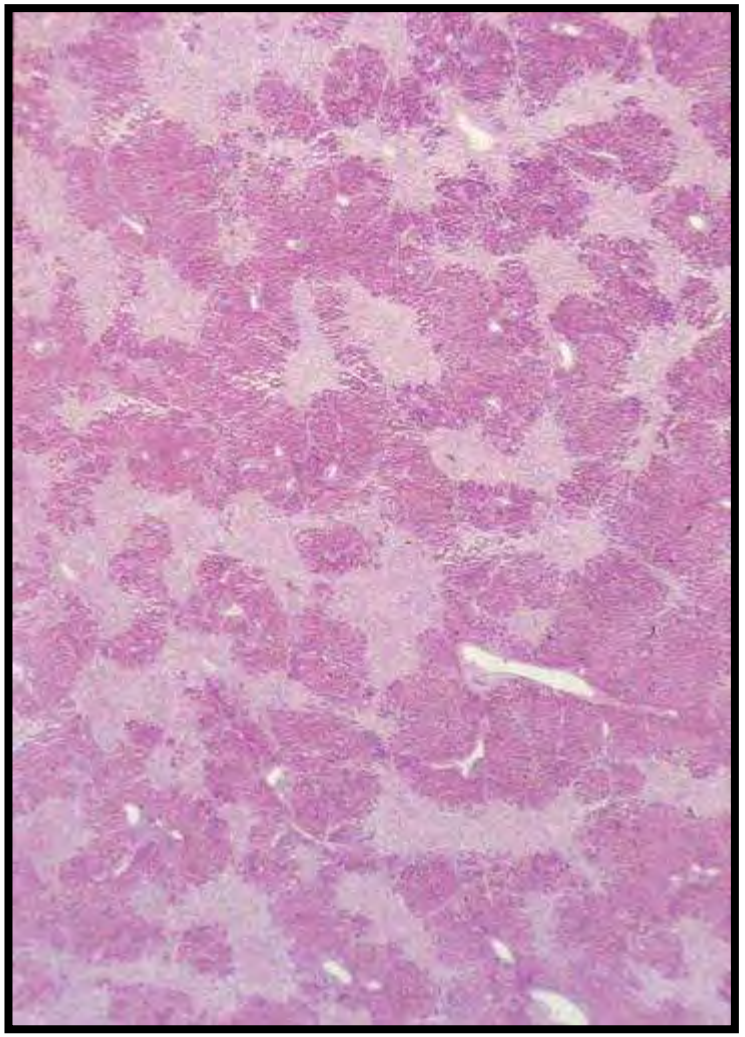
- Paracetamol
- Flucloxicillin
- Azathioprine

- Celebrex

Drugs: Paracetamol (Acetaminophen)

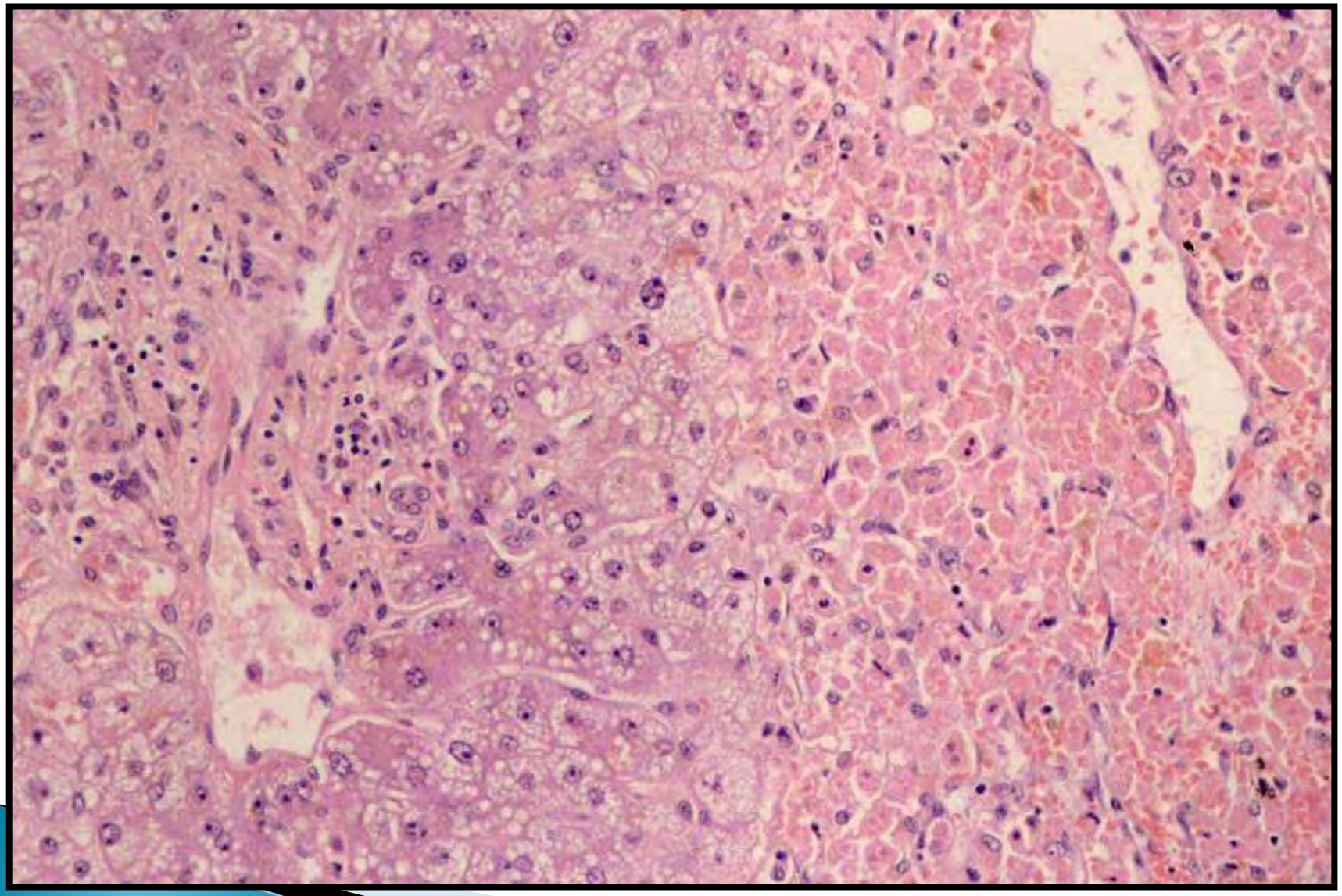


Nutmeg liver

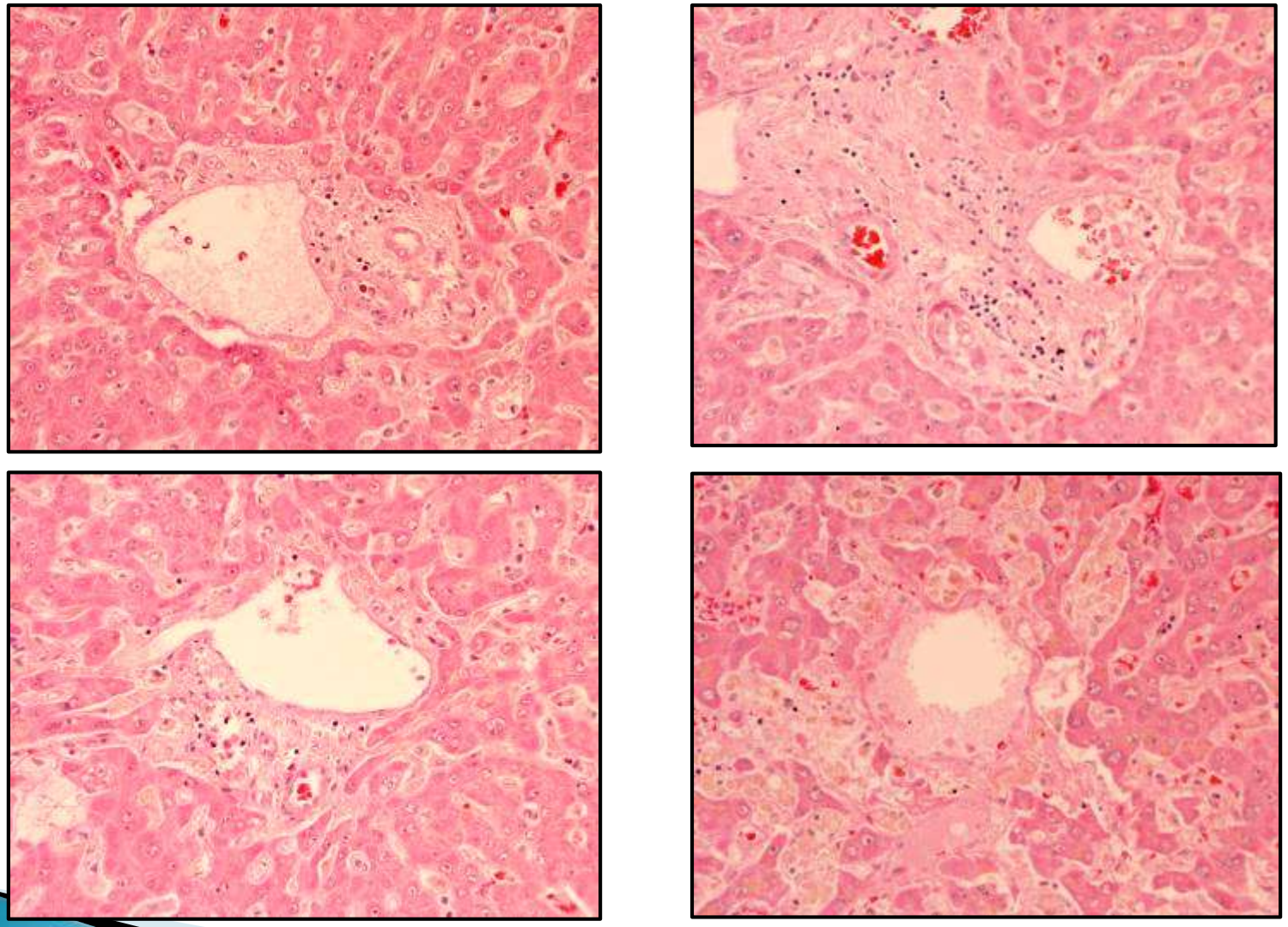


peri-central necrosis

Drugs: Paracetamol (Acetaminophen)

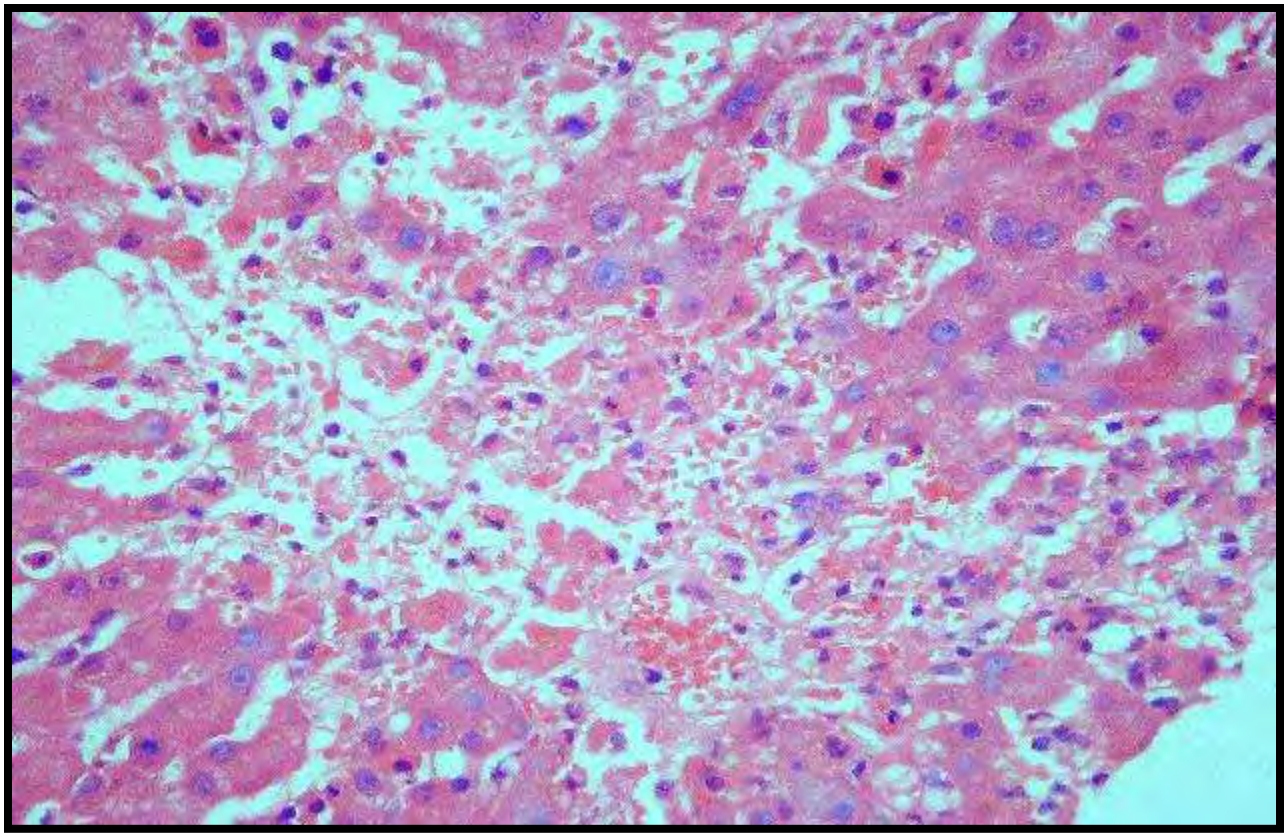


72yo F, 2x flucloxicillin – skin infection



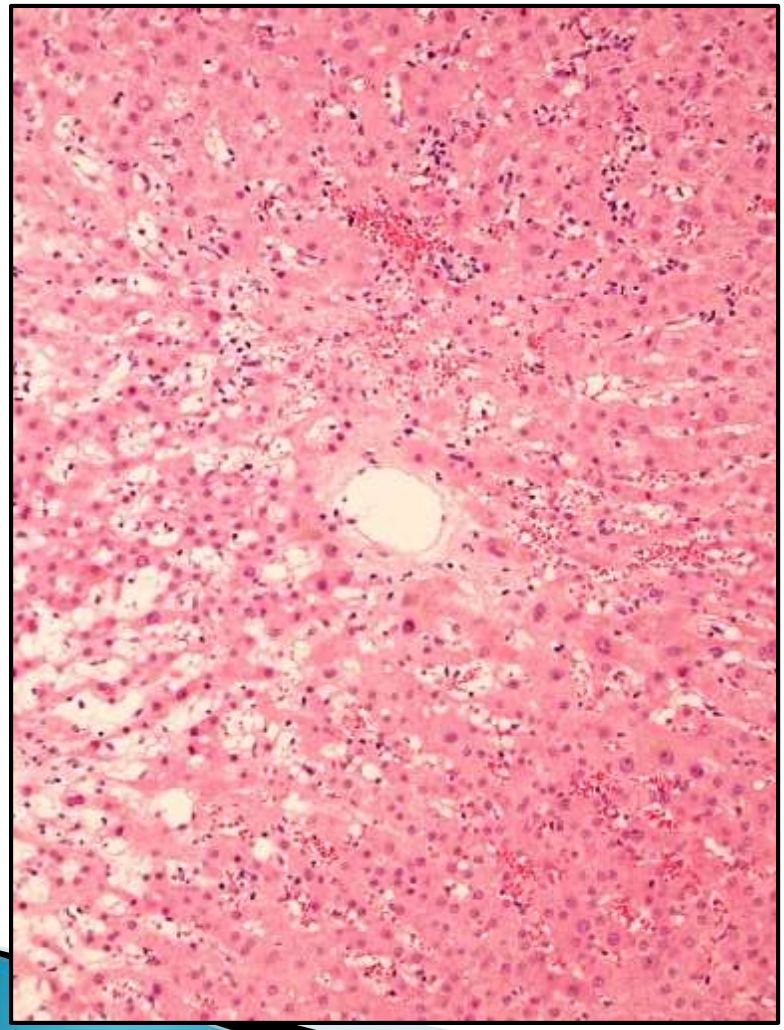
Vanishing bile duct syndrome

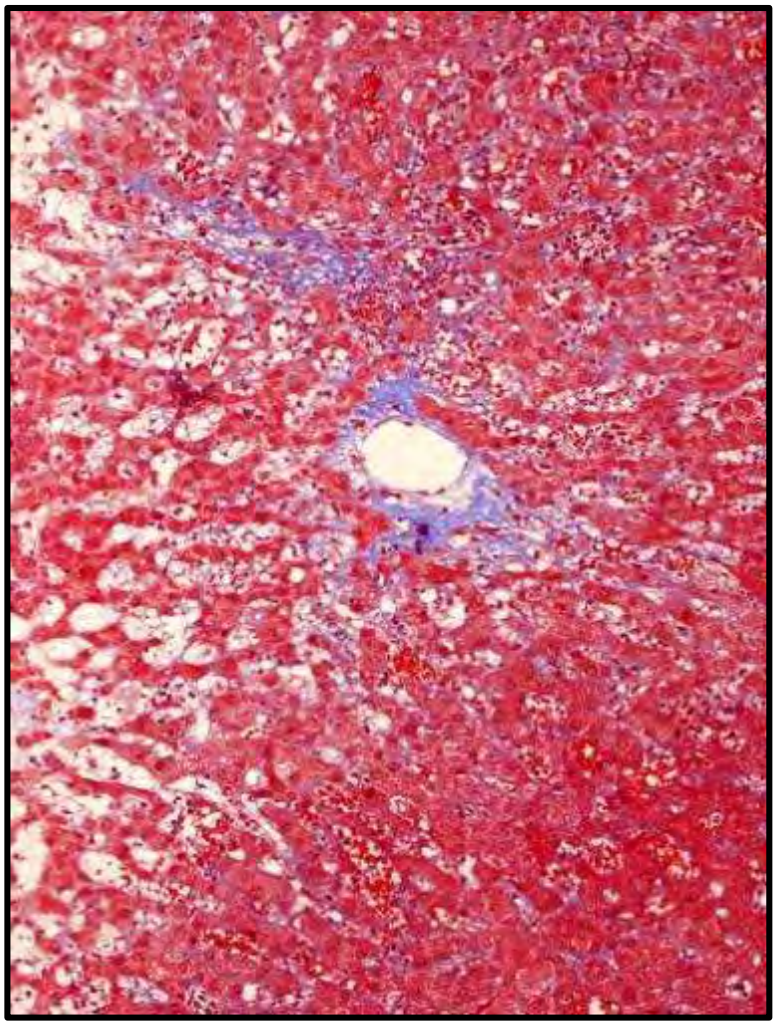
Drugs – Azothioprine



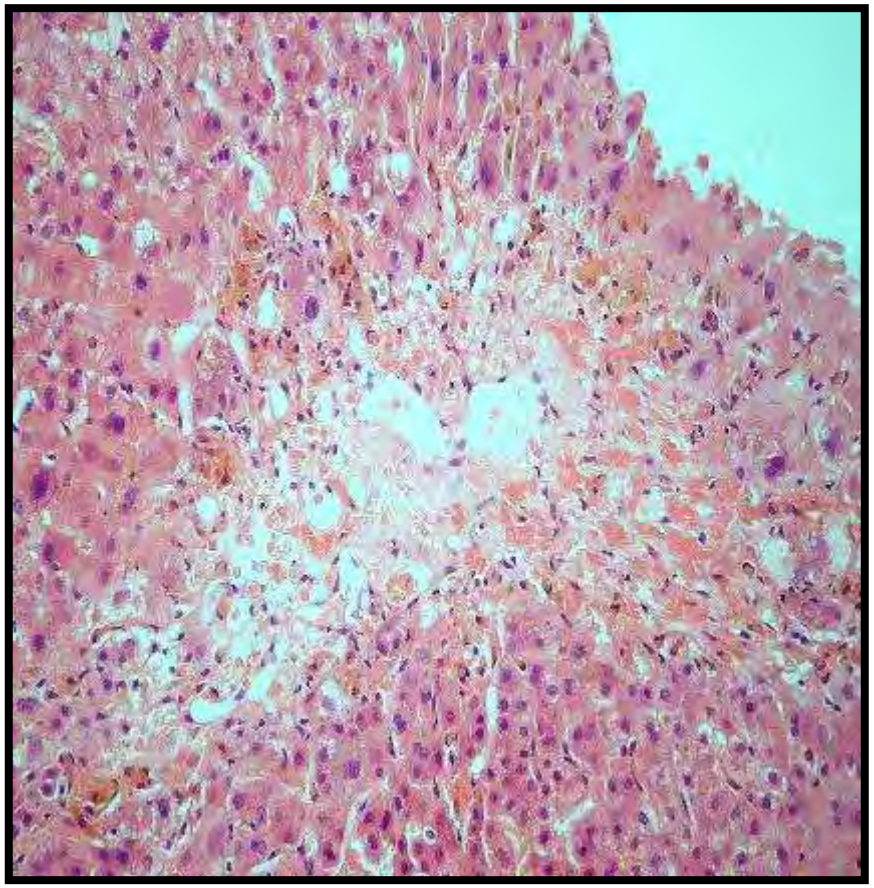
A veno-occlusive disease-like picture

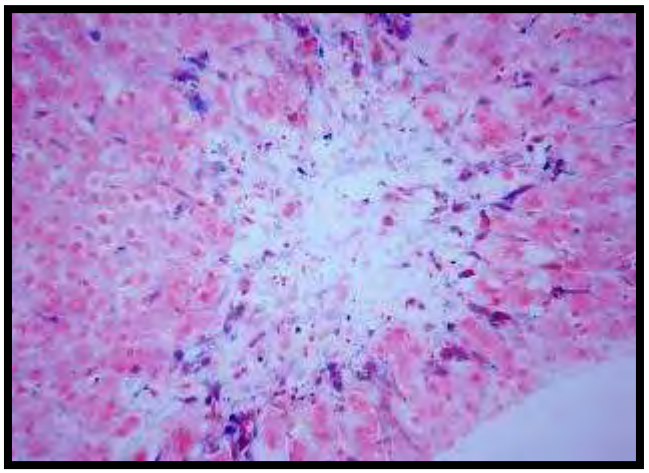
Drugs – 51yo F: liver Tx 6/12 for PBC, ongoing abn LFTs: Azothioprine

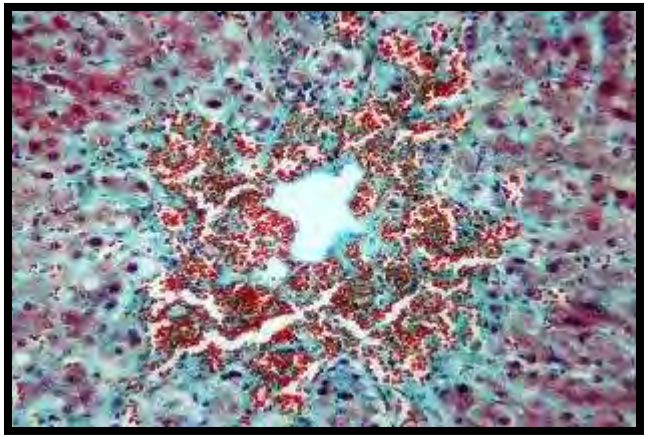




Drugs – Azothioprine

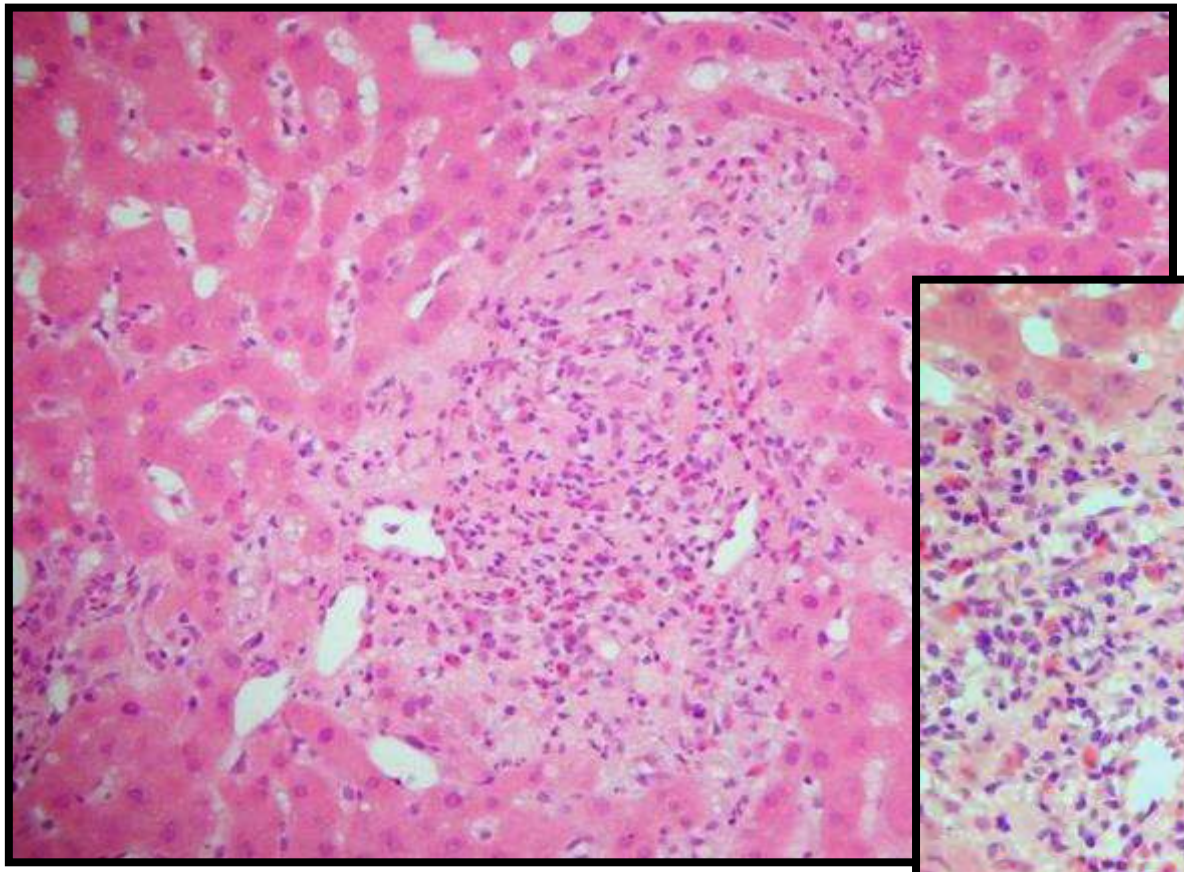


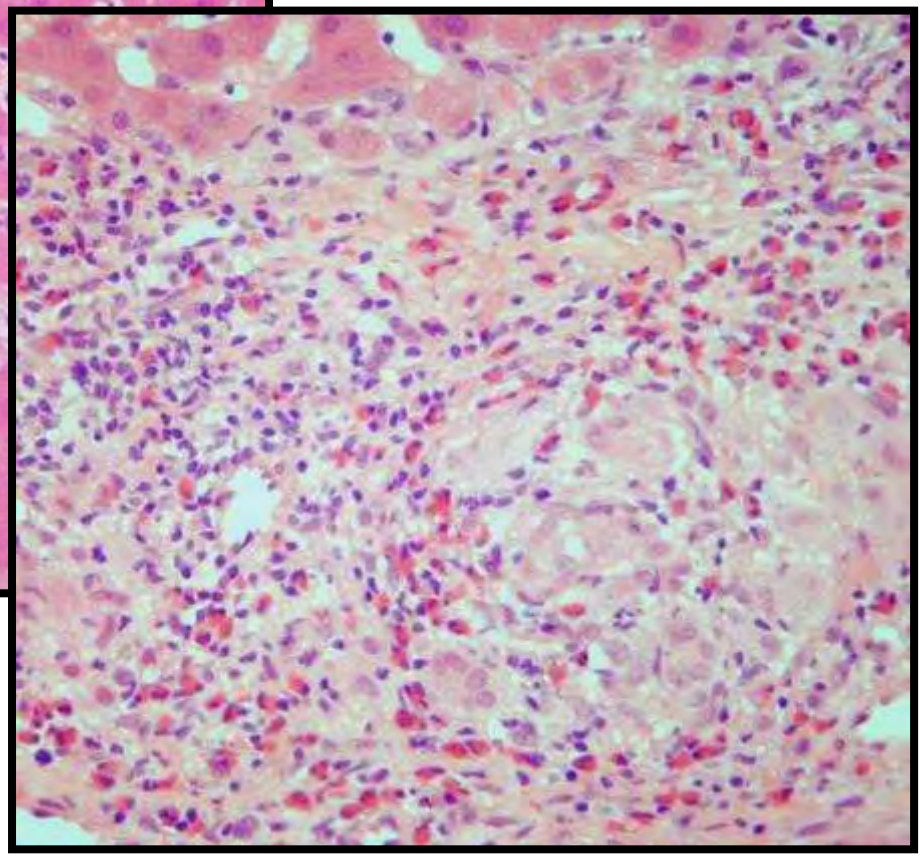




Hepatocyte dropout leading to central fibrosis

Mixed pattern – prominent eosinophils





Celebrex

DILI in a liver biopsy

- Any pattern of liver injury can be caused by a drug/toxin
- A drug/toxin can cause any pattern of liver injury

Good **clinico-pathological correlation** is essential

Make the clinicians go back and ask, particularly illicit and naturopathic substances

Pathologists role

- To recognise patterns typical of drug injury
  - Correlate with clinical history
  - Alert the clinician
- To raise the differential of drug injury when a pattern is unusual
- Document injury patterns associated with new drugs

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The End