# Speaker Declarations

BDIAP-UKLPG Liver Pathology Update Meeting,
Royal Institute of British Architects, Portland Place, London
22nd November 2018

Name of Speaker : **Stefan Hübscher**

**This presenter has the following declarations of relationship with industry**

- Personal payments/honoraria/fees – Dr Falk Pharma, ICON plc

22/11/2018

# Update from the 2018 Gnomes Meeting – Athens 2-5 May 2018

## Drug-induced Liver Injury
## Chief Gnome – Dina Tiniakos

Stefan Hübscher,
Institute of Immunology and Immunotherapy, University of Birmingham
Department of Cellular Pathology, Queen Elizabeth Hospital, Birmingham

# 50 years of Liver Pathology: A history of the Gnomes

## 1968-2018

Dina Tiniakos

Michael Torbenson

Valeer Desmet

Athens 2018

# Bernard Portmann

6 February 1940 – 22 April 2018

**Gnomes Meeting – Sesimbra, Portugal 1992**
Chief Gnome – Amelia Baptista

Bernard's first Gnomes meeting

**Gnomes Meeting – London 1999**
Chief Gnome – Bernard Portmann

Bernard hosted the 1999 Gnomes Meeting at 2 Carlton House Terrace (headquarters of the Royal College of Pathologists), during Roddy MacSween's tenure as President of RCPath

# Bernard Portmann

6 February 1940 – 22 April 2018


**Gnomes Meeting Paris 2010**
Chief Gnome – Pierre Bedossa

Bernard presenting the Kings College Hospital cases at his last Gnomes meeting

**Gnomes Meeting Paris 2010**
Chief Gnome – Pierre Bedossa

Bernard delivers a farewell speech to the Gnomes during the end of meeting dinner at the restaurant “La Grande Cascade”

Histopathology

*Histopathology* 2018, **73**, 543–544. DOI: 10.1111/his.13702

# Professor Bernard Portmann – Obituary

Alberto Quaglia[1] *MD PhD FRCPath*
Roger Williams[2] *CBE, MD, FRCP, FRCS, FRCPE, FRACP, FMedSci, FRCPI (Hon) FACP (Hon)*

Bernard Claude Portmann was born in Geneva, Switzerland on 6th February 1940. After completing his Maturité Classique at Collège Calvin, in Geneva in 1959, he joined Geneva Medical School where he obtained his MB, BS degrees in 1961 and subsequently the Swiss Confederation Medical Diploma with honours in June 1966. He then commenced training in histopathology, holding the position of chief resident between 1969 and 1973 in the Department of Pathology, of Geneva University Hospital under Professors Majno and Vassalli; he obtained his

> obtaining from the general histopathology department the high level of support required by a specialised Liver Unit. Ignoring the potential difficulties, Roger decided in late 1973 that the increasing number of liver biopsy specimens seen at that time should be processed in the Unit Lab."
> Bernard Portmann

He joined the liver unit at King's College Hospital in 1973, supported initially by a travelling fellowship from the Swiss Academy of Medicine. He was appointed Research Pathologist and Honorary Clinical Assistant in 1975. His research interests included the development and application of techniques to demonstrate secretory products, cell constituents, receptors and viral material in adult and paediatric liver tissue and liver allografts, the investigation of the enzymatic and phenotypic hepatocellular changes during carcinogenesis and the study of regeneration after severe liver necrosis in man. After obtaining his Membership of the Royal College of Pathologists by examination, in 1977 (becoming a Fellow in 1989), he was appointed Consultant Histopathologist with an interest in liver disease at King's in 1978. A travelling fellowship from the British Society of Gastroenterology in 1982 sponsored his visit to Dr Hans Popper at Mount Sinai Medical Centre in New York.

By creating King's unique dedicated liver histopathology laboratory, an integral part of the clinical department, Professor Portmann was critical in developing King's Liver Unit into one of the best hepatology centres in the world. His close collaboration with Professor Alex Mowat also laid the foundations

## Annual Meetings of the International Liver Study Group

- First meeting, July 1968, University of Zürich (Martin Schmid)
- Currently 15 circulating members (8 Europe, 5 North America, 2 Australia)

- Cases circulated prior to meeting (2/person) to cover particular theme
- Suggested diagnoses submitted prior to meeting and collated by local organiser

- Cases presented and discussed further at meeting (2 days)
- Aim to reach consensus and provide summary/guidelines
  - **2018 – "Drug-induced Liver Injury"**

# Drug-induced Liver Injury

## General Considerations

## Drug-induced Liver Disease - Causative Agents

1. At least 600 drugs have been implicated in causing liver damage

2. Most of the commonly prescribed drugs are potentially hepatotoxic

3. Some drugs available “over the counter” are potentially hepatotoxic (including serious reactions – e.g. paracetamol)

4. Many potentially hepatotoxic agents may not be recognised as drugs (e.g. herbal remedies, dietary supplements)

## Drug-induced Liver Disease - Patterns Of Liver Injury

(1) Most of the common morphological patterns of liver damage may be caused by drugs

(2) Histological distinction from other causes of liver damage is frequently difficult or impossible

(3) Drug-induced liver injury therefore diagnosed by exclusion.

(4) For some patterns of liver injury drugs should be considered near the top of the differential diagnosis

- e.g. pure/bland intrahepatic cholestasis
  (Liver EQA – Circulation LS, case LS8 = OCP induced cholestasis)

# DILI PATHOLOGY

PHILIP KAYE

November 2017

BSG Pathology
Winter Meeting

**Full version of talk available via UKLPG web pages (Virtual Pathology Leeds)**

**http://www.virtualpathology.leeds.ac.uk/eqa/specialist/liver/liver_update_2017.php**

# Summary of presented cases

(28 cases in total)

Gnomes 2018

Athens

# Gnomes Meeting 2018 Athens – Summary of Cases Presented (1)

| Type of drug | Pattern | Cases |
|---|---|---|
| **Anti- depressant** | Acute hepatitis<br>Hepatitis (AIH-like) + cholangiopathy | Adelaide-B (sertraline)<br>Heidelberg-B (sertraline) |
| **Anti-TNFα** | AIH-like features<br>Chronic hepatitis like | Basel-A (Infliximab)<br>Washington-A (Infliximab) |
| **Antibiotics** | Cholestatic hepatitis<br>Severe hepatitis with submassive necrosis<br>Severe hepatitis with submassive necrosis | Groningen-A (co-trimoxazole)<br>Paris-A (isoniazid)<br>Rochester-A (Bactrim) |
| **Immune check-point inhibitors** | Hepatitis, bile duct injury<br>Chronic hepatitis like<br>Centrilobular necrosis<br>Hepatitis, microgranulomas | Basel –A (ipilimumab & nivolomab)<br>Bethesda –A (pembrolizumab)<br>Birmingham-A (nivolumab)<br>Brisbane-B (ipilimumab & nivolomab) |
| **Oral contraceptives** | Sinusoidal dilatation<br>Bile duct injury (also MDR3 deficiency) | Adelaide-A<br>Brisbane-A |
| **Toxins/chemicals** | Periportal necrosis | Paris-B (phosphorus) |

# Gnomes Meeting 2018 Athens – Summary of Cases Presented (2)

| Type of drug | Pattern | Cases |
|---|---|---|
| **Anti-neoplastic drugs** | Sinusoidal obstruction syndrome<br>Sclerosing cholangitis<br>Vanishing BD syndrome | Halifax-A (oxaliplatin)<br>Rochester-B (FUDR)<br>Washington-B (6MP) |
| **Amiodarone (?)** | Acute hepatocellular injury | Bethesda-B |
| **Polypharmacy** | Glycogen ground-glass inclusions | Rome-A |
| **Azathioprine** | Cholestasis and ductopenia | Groningen-B |
| **Herbal/Dietary Supplements** | Acute hepatitis<br>Zonal/submassive necrosis<br>Acute hepatitis with submassive necrosis | Athens-A (multiple agents)<br>Vienna-A (nicotinamide = Vitamin B3)<br>Vienna-B (NONI juice) |
| **Corticosteroids** | Acute hepatitis with zone 3 necrosis | Rome-B (prednisolone) |
| **Anti-coagulant** | Hepatitis with bridging necrosis | Heidelberg-A (Phenprocoumon) |
| **Not drug-induced** | Epithelioid haemangioendothelioma<br>Sarcoidosis<br>Regressed HFE cirrhosis | Athens-B<br>Birmingham –B<br>Halifax-B |

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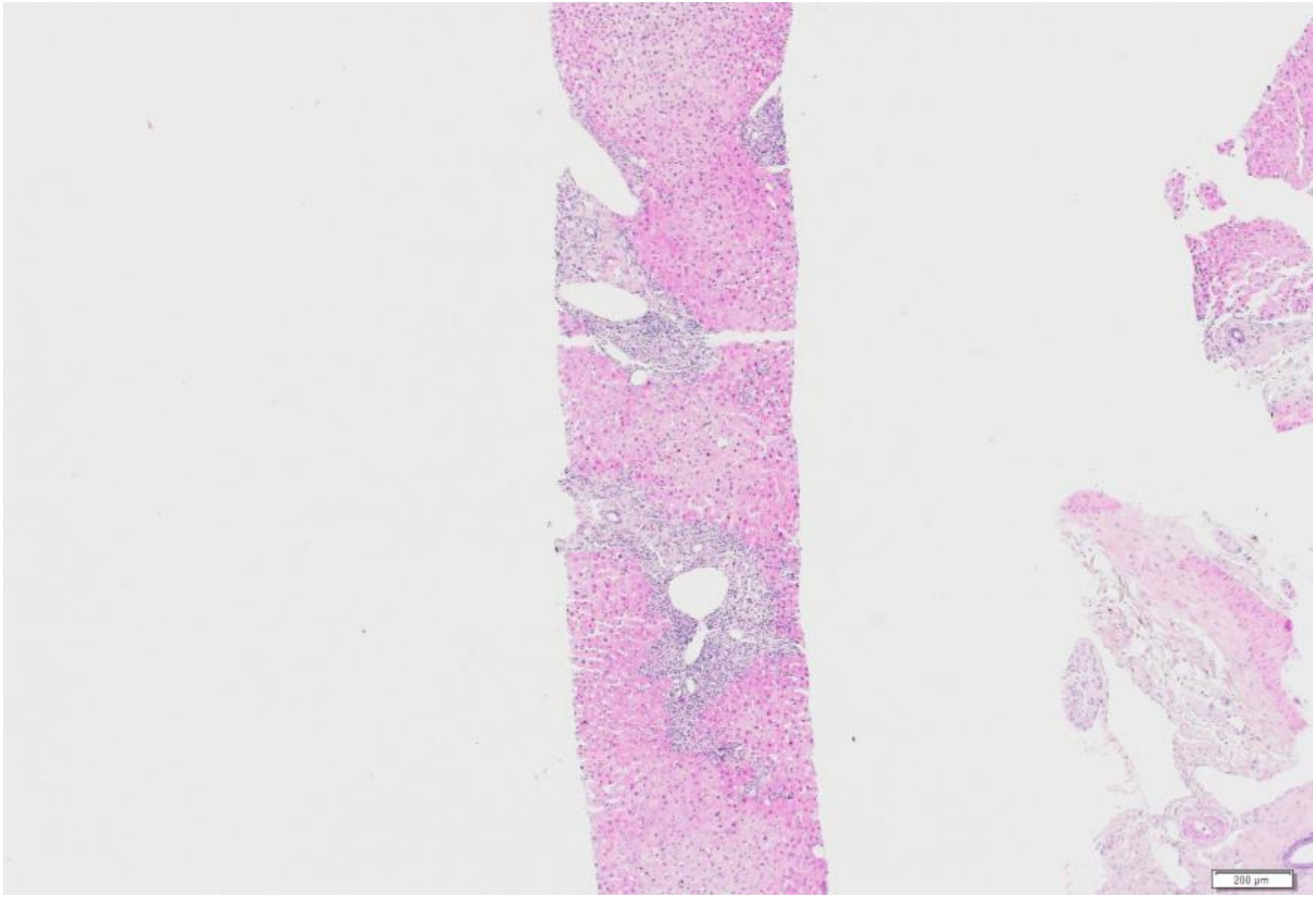
| **Toxins/chemicals** | Periportal necrosis | Paris-B (phosphorus) |

# Clinical history

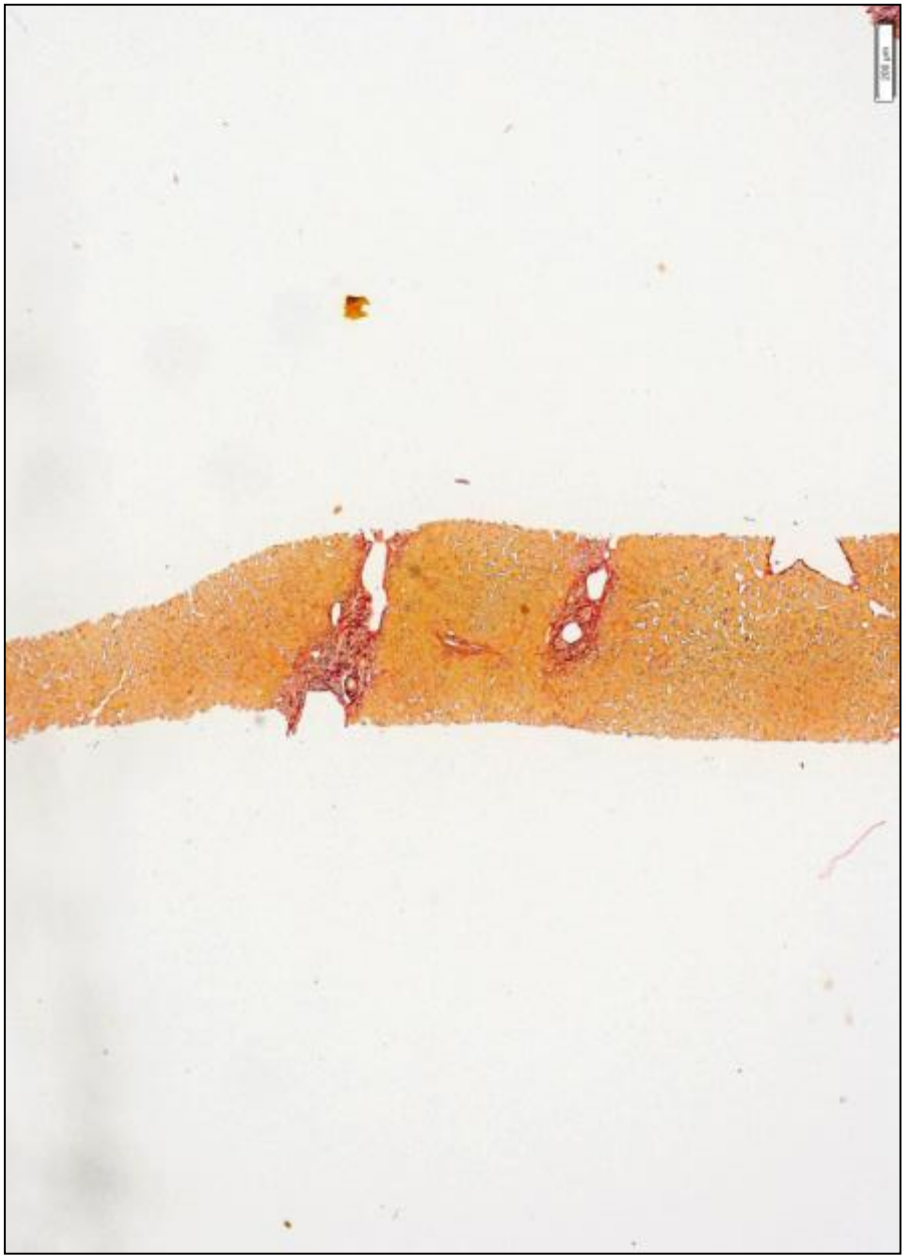
- A 66- year-old woman with rheumatoid arthritis started therapy with Infliximab.
- After three infusions developed an acute hepatopathy.
- Laboratory tests: ASAT 154 U/l, ALAT 229 U/l, gGT 60 U/l, ANA positivity 1:80.
- A liver biopsy was performed

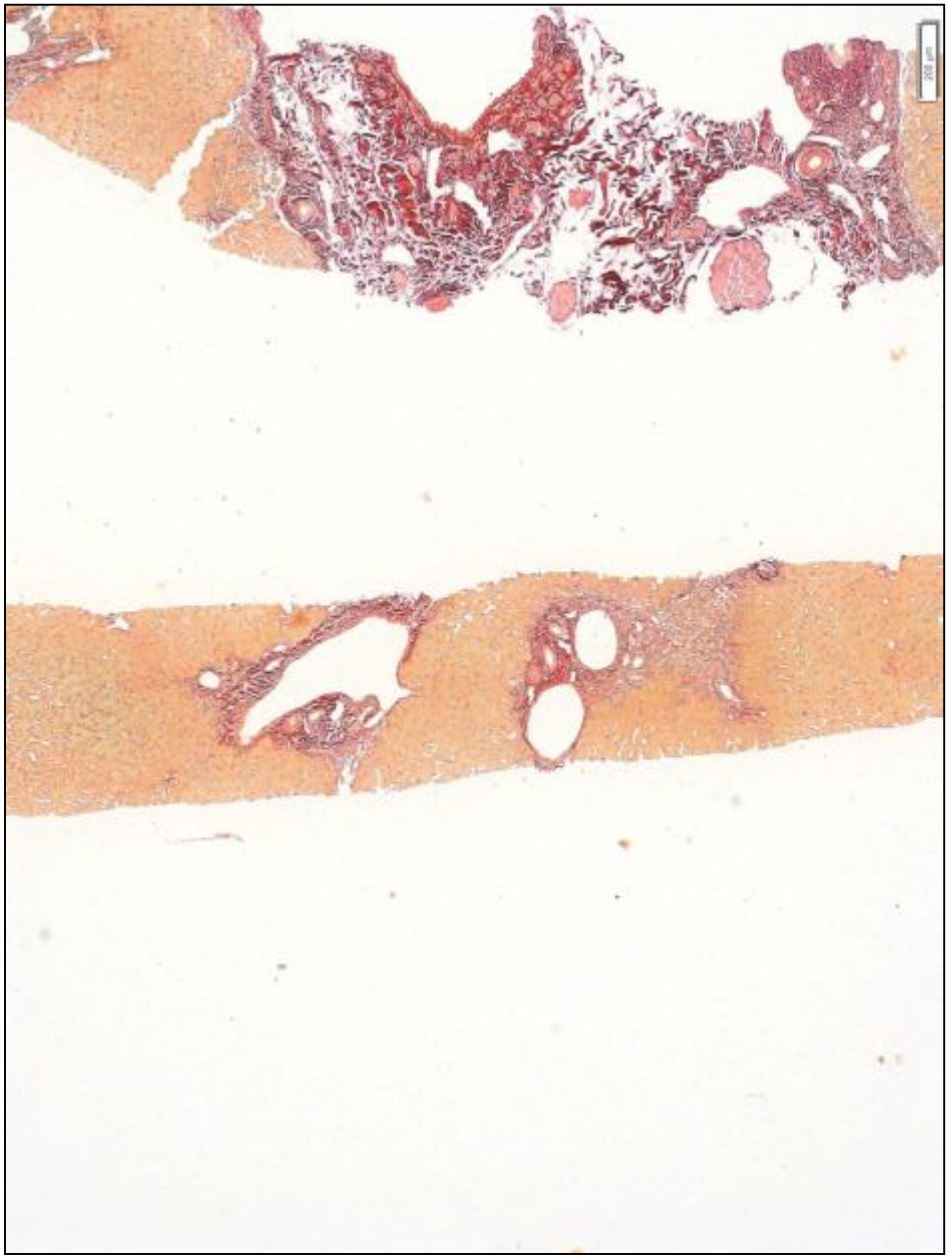



Universitätsspital Basel

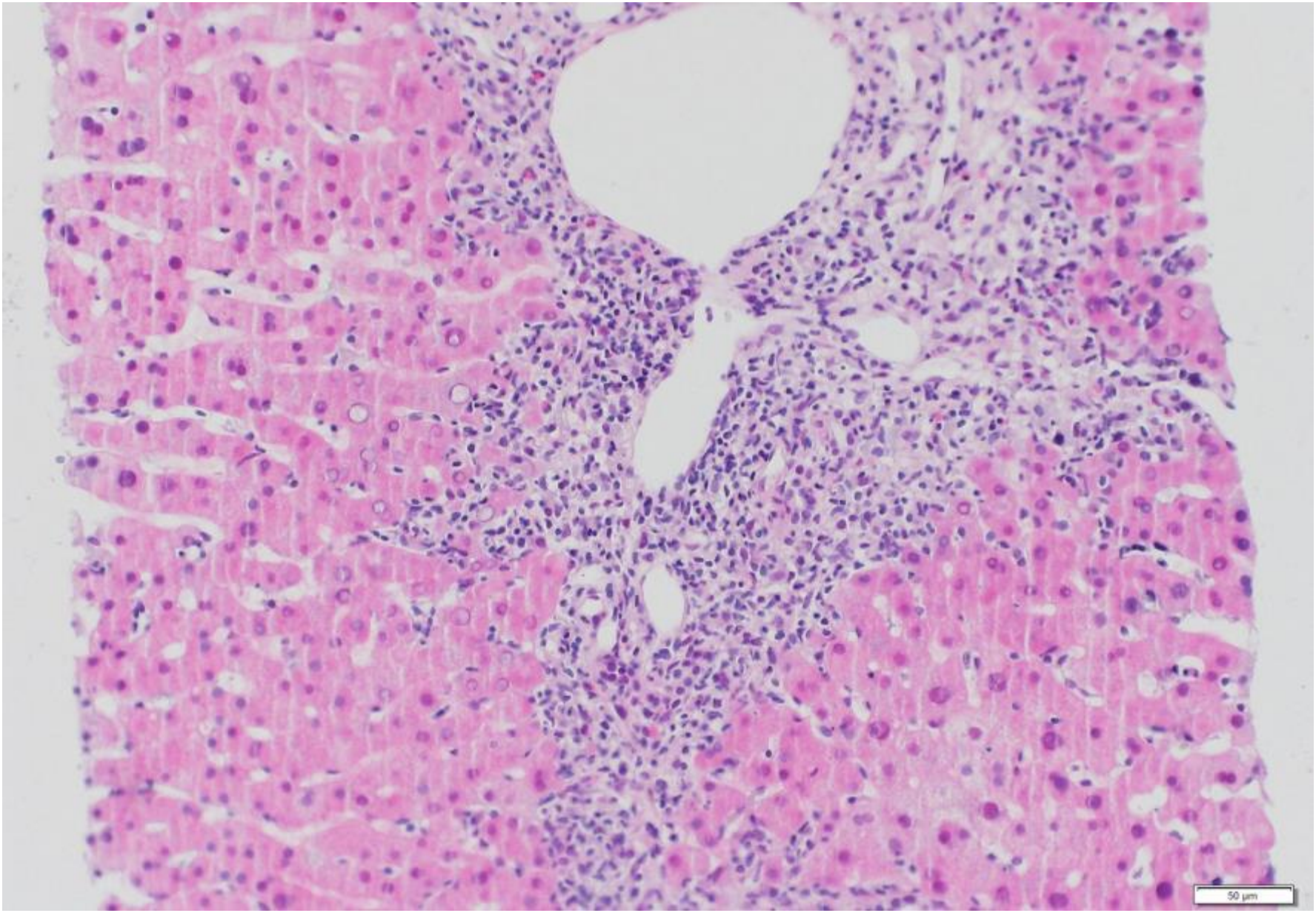
Preserved lobular architecture and marked inflammation of portal tracts

B10.38339





Preserved lobular architecture




Universitätsspital Basel

Lymphoplasmacytic portal inflammation & interface hepatitis

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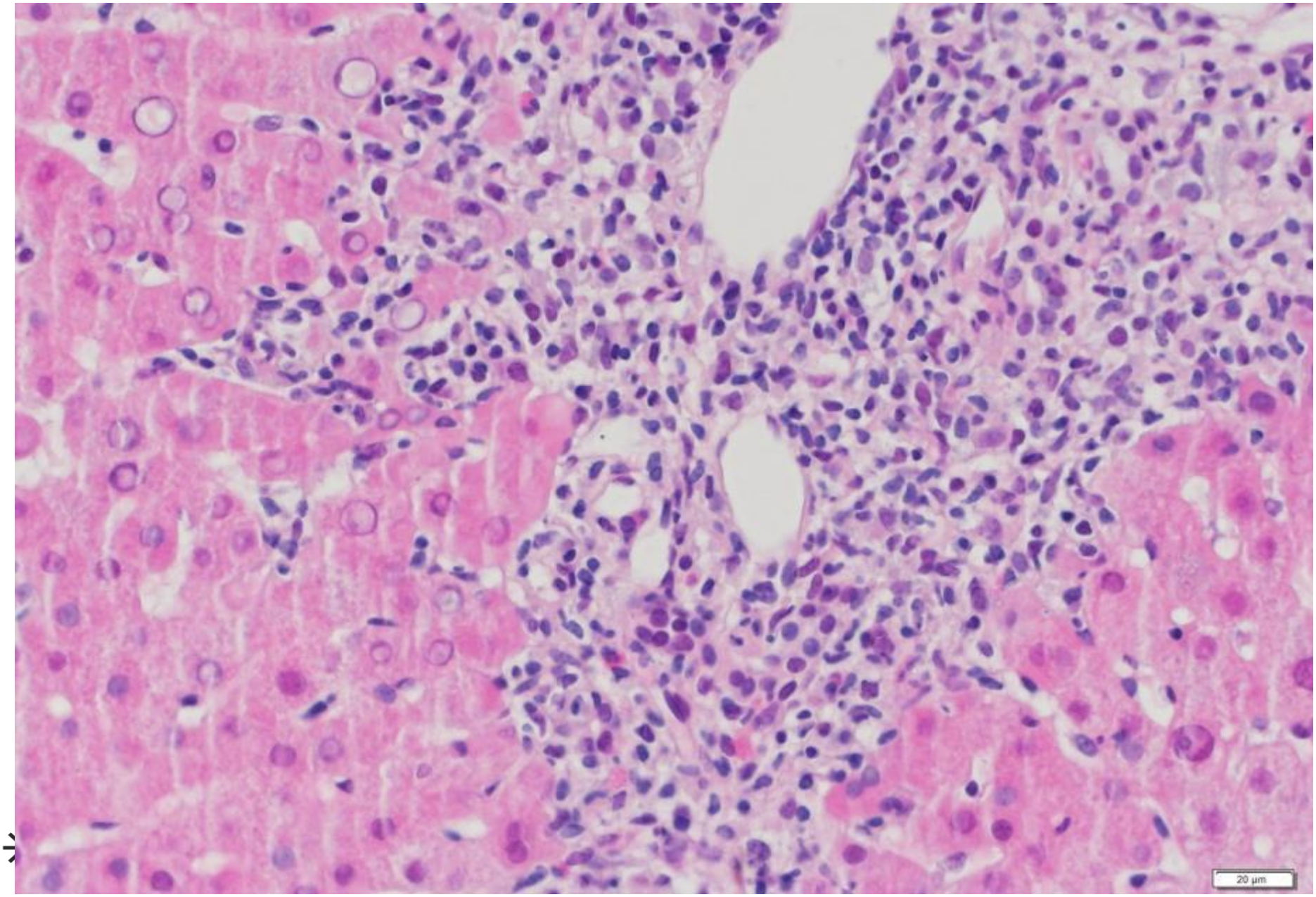


Universitätsspital Basel

Lymphoplasmacelluar infiltrates with some eosinophils

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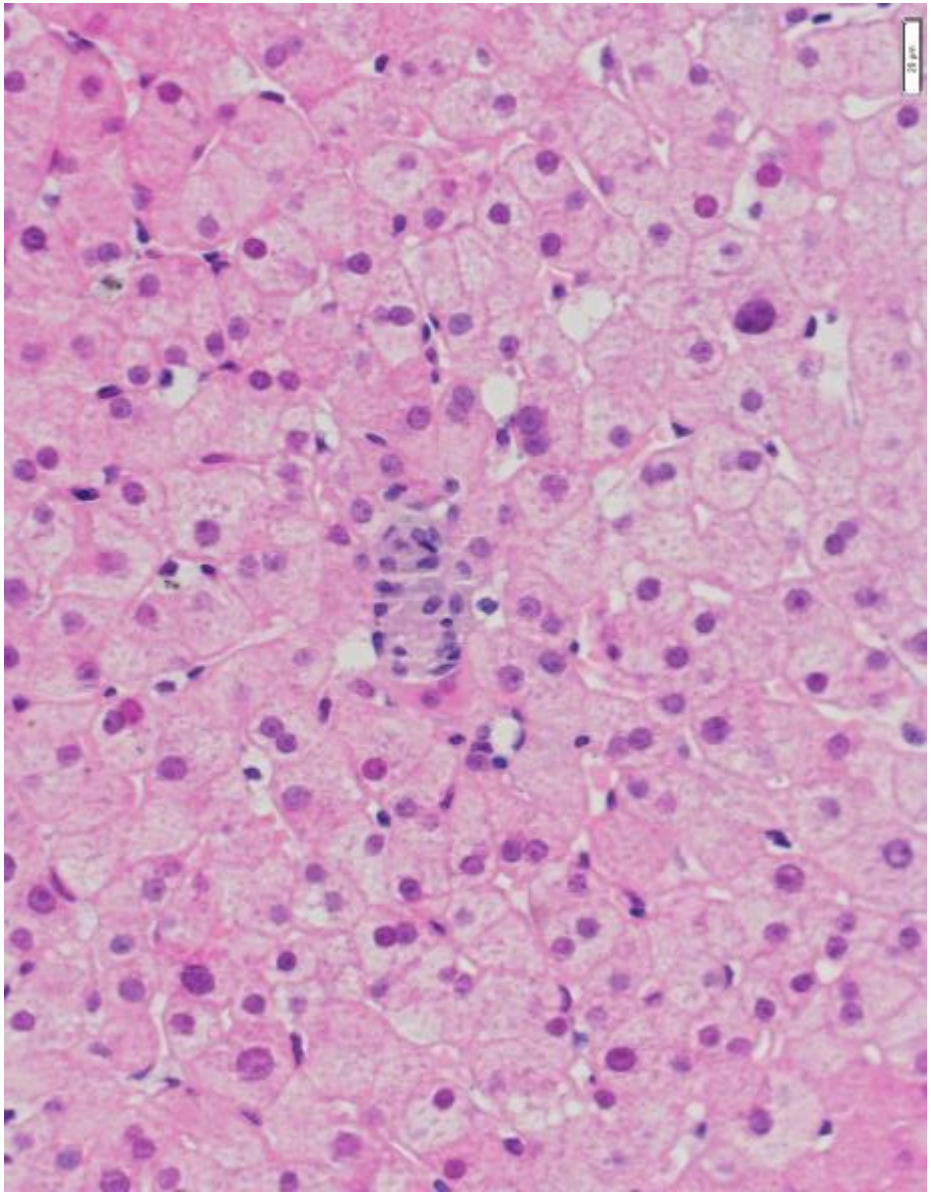

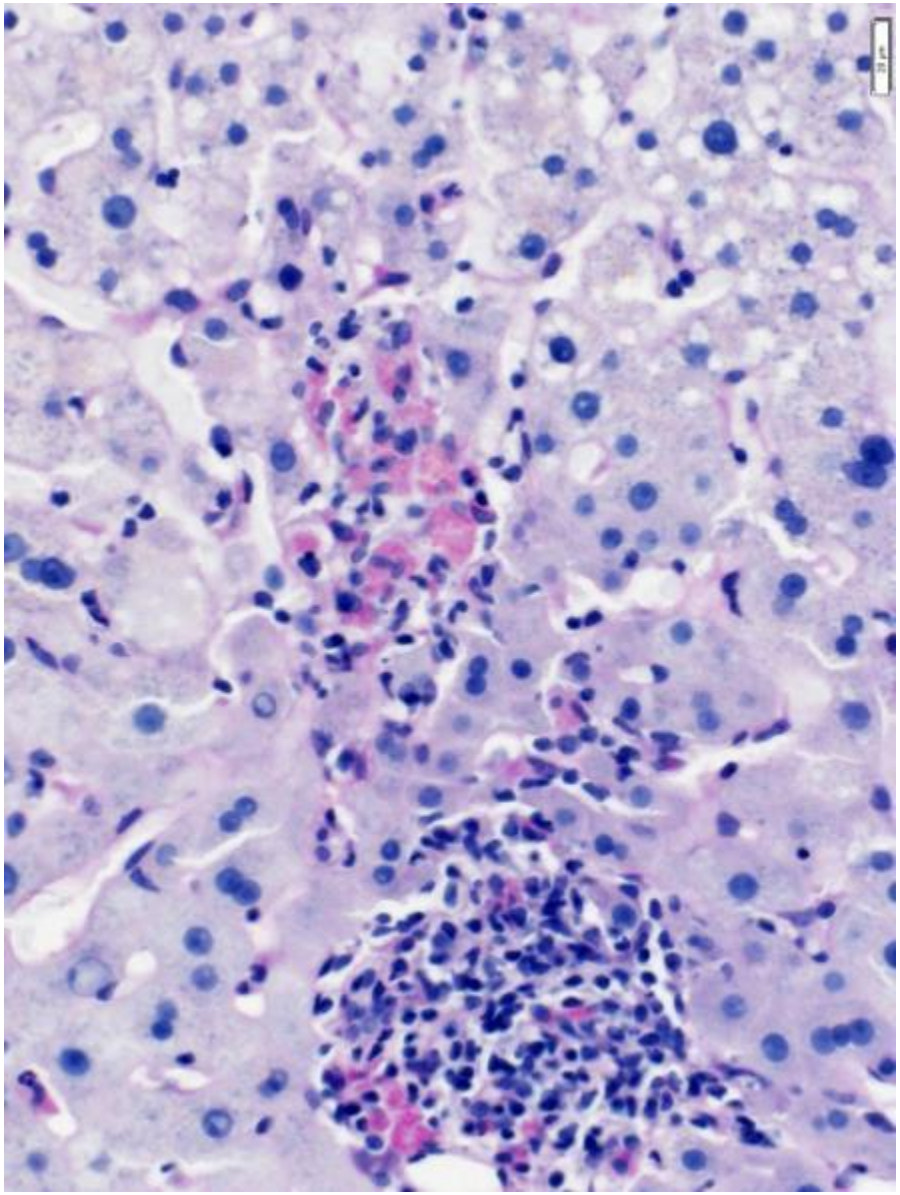

Universitätsspital Basel

Rare histiocytic microgranuloma with ceroid pigment

B10.38339

# Histological features

- Portal lymphoplasmacellular infiltrates with some eosinophils
- Interface hepatitis
- Mild mononuclear lobular infiltration with scattered ceroid pigmented macrophages
- Absence of fibrosis

## BASEL-B, 2018

### Diagnosis

Infliximab related-hepatitis with AIH-like features

### Follow-up

- ✓ No other cause of liver disease was identified
- ✓ Prednisone was started and and liver enzymes fell into the normal range within 3 weeks.
- ✓ Prednisone was tapered and stopped after 3 months
- ✓ Serum ANA reverted to negative
- ✓ No recurrence after 7 years

# TNF-α antagonists

- 34 cases of DILI (6 new cases + 28 previously reported cases)
- Infliximab (n=26), etanercept (n=4) , adalimumab (n=4)
- Median latency: 13 wks (2-104)
- 67% ANA positivity (> infliximab, ≥ 1:80)
- Prognosis usually good
  - Occasional cases develop liver failure

Ghabril M, Clin Gastroenterol Hepatol, 2013

# TNF-a antagonists DILI
# Histology – Cases with AIH-like Features

- Portal and lobular mixed inflammation
- Interface hepatitis, occasionally with plasma cells and rosettes
- Bridging / centrilobular necrosis
- Ddx : AIH !

# Drug-induced Autoimmune-like Hepatitis

(Czaja A, Dig Dis Sci, 2011)

**Table 1** Etiological agents proposed for autoimmune-like hepatitis

| Definite drug association ($n = 7$) | Probable drug association ($n = 6$) | Possible drug association ($n = 14$) | Possible supplements/ toxins ($n = 6$) |
|---|---|---|---|
| Dihydralazine [99, 127] | Atorvastatin [75, 223] | Adalimumab [87] | Black cohosh [91, 93] |
| Halothane [101, 224] | Clometacine [225, 226] | Benzarone [66] | Dai-saiko-to [90] |
| Methyldopa [118, 227] | Diclofenac [67, 148, 228] | Cephalexin [27] | Germander [94, 95] |
| Minocycline [107, 108, 110, 229] | Infliximab [84, 230–232] | Fenofibrate [68] | Hydroxycut [89] |
| Nitrofurantoin [113, 114, 233] | Isoniazid [234] | Indometacin [82] | Ma huang [92, 235] |
| Oxiphenisatin [97] | Propylthiouracil [73, 74] | Imatinab [83] | Trichloroethylene [96] |
| Tienilic acid [122, 125] | | Meloxicam [69] | |
| | | Methylphenidate [70] | |
| | | Papaverine [71] | |
| | | Pemoline [72] | |
| | | Phenprocoumon [80] | |
| | | Prometrium [27] | |
| | | Rosuvastin [79] | |
| | | Terbinafine [81] | |

*Numbers in brackets* are references

# Drug-induced Autoimmune-like Hepatitis

- Female predominance (> 80%)
- Autoantibodies: ANA and ASMA; anti-LKM2 and antiP450 2C9 (tienilic acid) ; antib. to P450 1A2 (dihydralazine)
- Most cases resolve within 1 month after discontinuation of the incriminated drug

# Drug-induced Autoimmune-like Hepatitis

## Histological features

- Classical (inflammatory) features of autoimmune hepatitis
- Fibrosis rarely prominent at presentation
- No progression to cirrhosis

Czaja A, Dig Dis Sci, 2011

Bjornsson E, Hepatology, 2010

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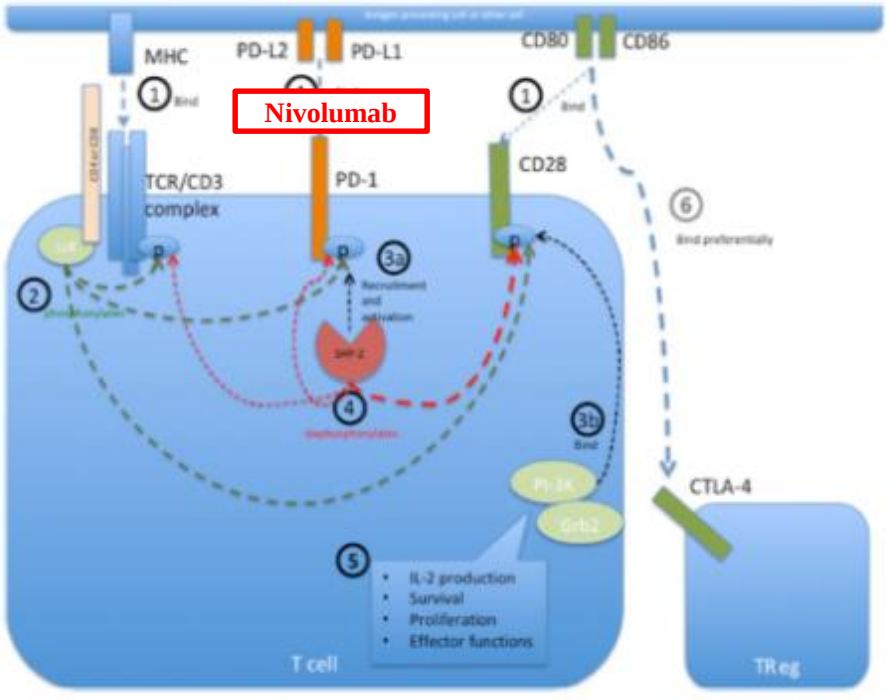
# Immune Checkpoint Inhibitors

- Increasingly used to treat advanced/disseminated malignancy, when other treatments have failed
- Effective in treating cancer
- Side effects common and may be serious

# Pathways of Immune Checkpoint Inhibition

| Signalling Pathway | Examples of Antibodies Used |
|---|---|
| **PD-1/PD-L1** | **PD-1 inhibitors:** Nivolumab, Pembrolizumab, Pidilizumab. **PD-L1 inhibitors:** Atezolizumab |
| **CTLA4** | Ipilimumab, Tremelimumab |




**Factors Regulating Activation of T Cells by Antigen Presenting Cells**
(from Seidel, Frontiers in Oncology, March 2018)

**Mechanism of Action:**

- Drugs block signalling pathways normally regulating T cell activation
- Facilitate T cell-mediated destruction of tumour cells

**BUT:**

- May result in systemic T cell activation leading to a range of immune related adverse events
- Commonly affected organs include skin, gastrointestinal tract, liver, lung, endocrine glands and kidney.

# Immune Checkpoint Inhibitors in Treatment of Cancer



**Table 1.** Indications and dates of approval of ICIs by US FDA and EMA updated to January 2018.

| ICI and *mechanism of action* | Indication | Approval by US FDA | Approval by EMA |
|---|---|---|---|
| Nivolumab<br>*Anti-PD-1 antibody* | Metastatic melanoma | Dec 2014 | Jun 2015 |
| | Advanced non-small cell lung cancer | Mar 2015 | Jul 2015 |
| | Metastatic renal cell carcinoma | Nov 2015 | Apr 2016 |
| | Classical Hodgkin lymphoma | May 2016 | Nov 2017 |
| | Head and neck cancer | Nov 2016 | Apr 2017 |
| | Locally advanced or metastatic urothelial carcinoma | Feb 2017 | Jun 2017 |
| | Microsatellite instability-high metastatic colorectal cancer | Aug 2017 | — |
| | Hepatocellular carcinoma | Sep 2017 | — |
| | Adjuvant treatment for stage III or IV completely resected melanoma | Dec 2017 | — |

*Ther Adv Med Oncol*

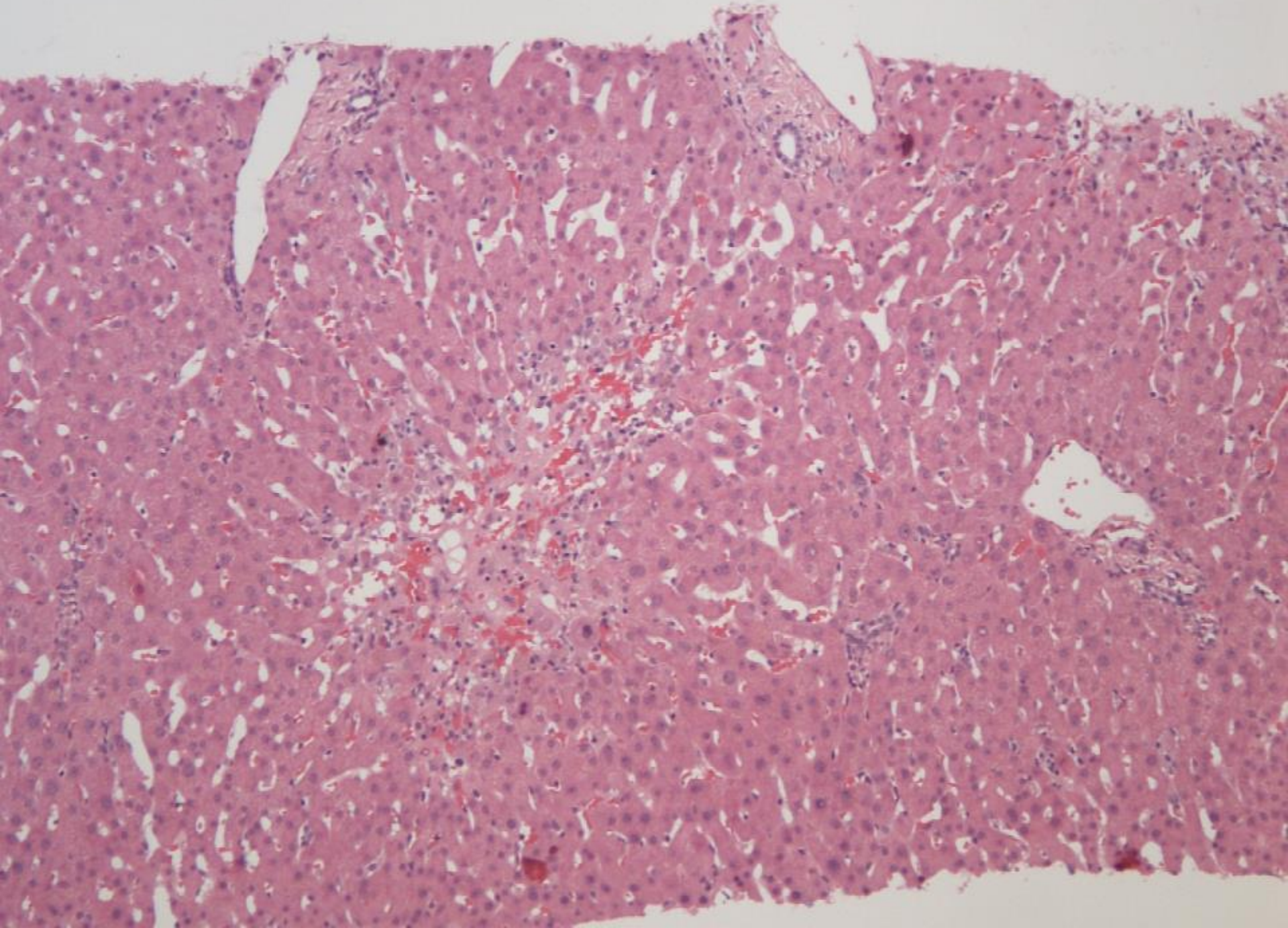
2018, Vol. 10: 1–11

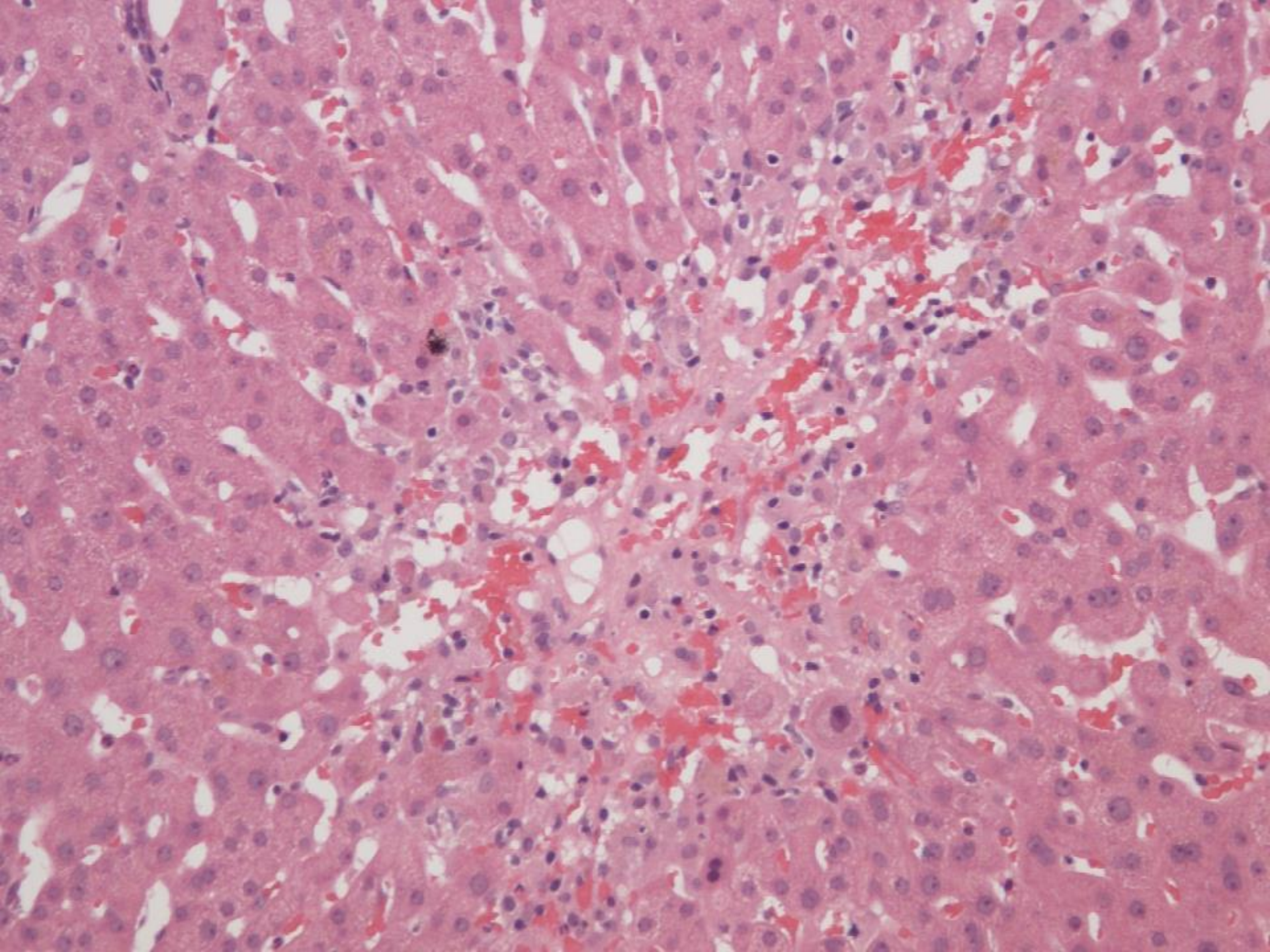
# **Birmingham A/2018** (Stefan Hübscher)

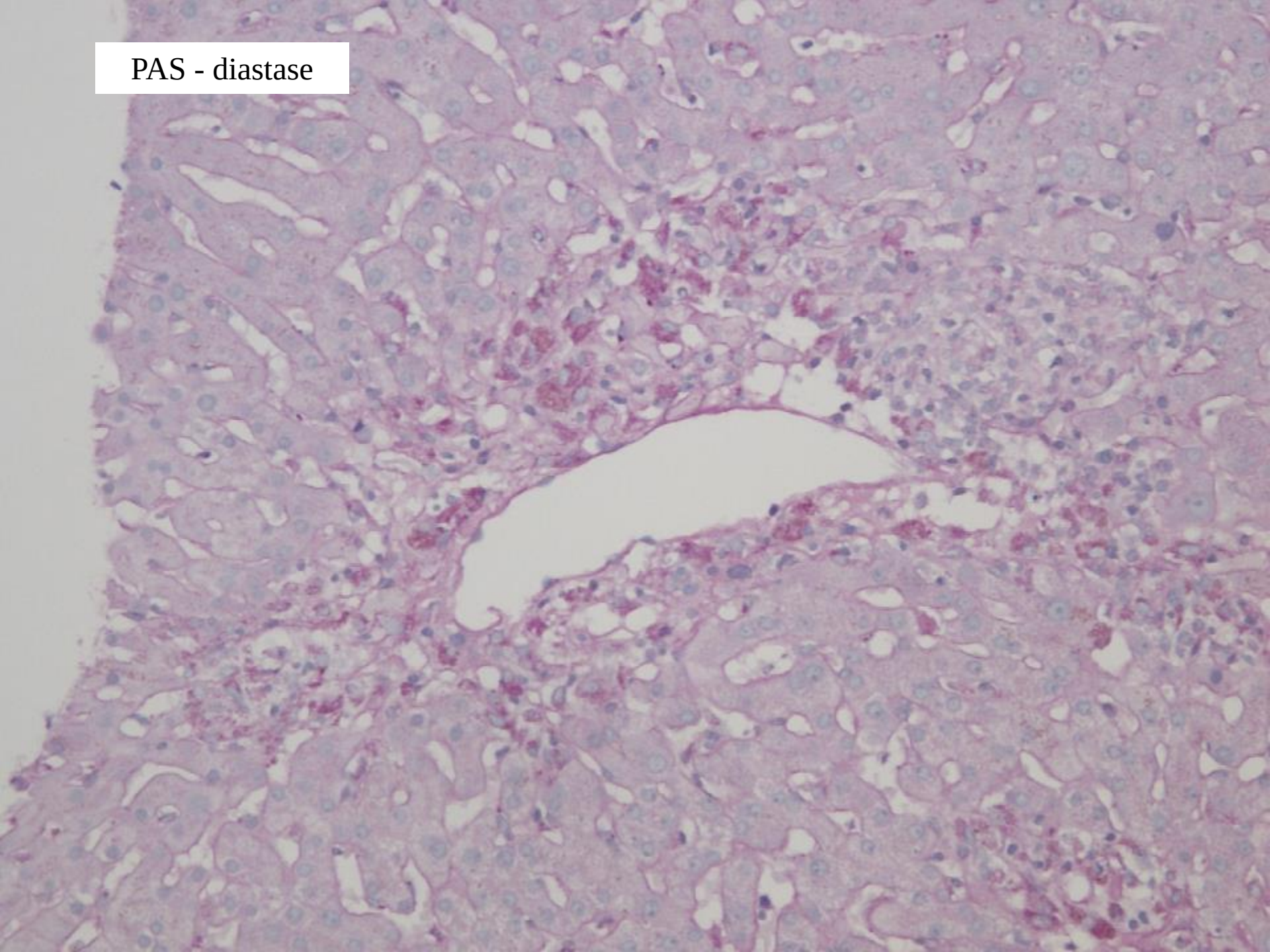
**Bham A/2018. Female, age 66**

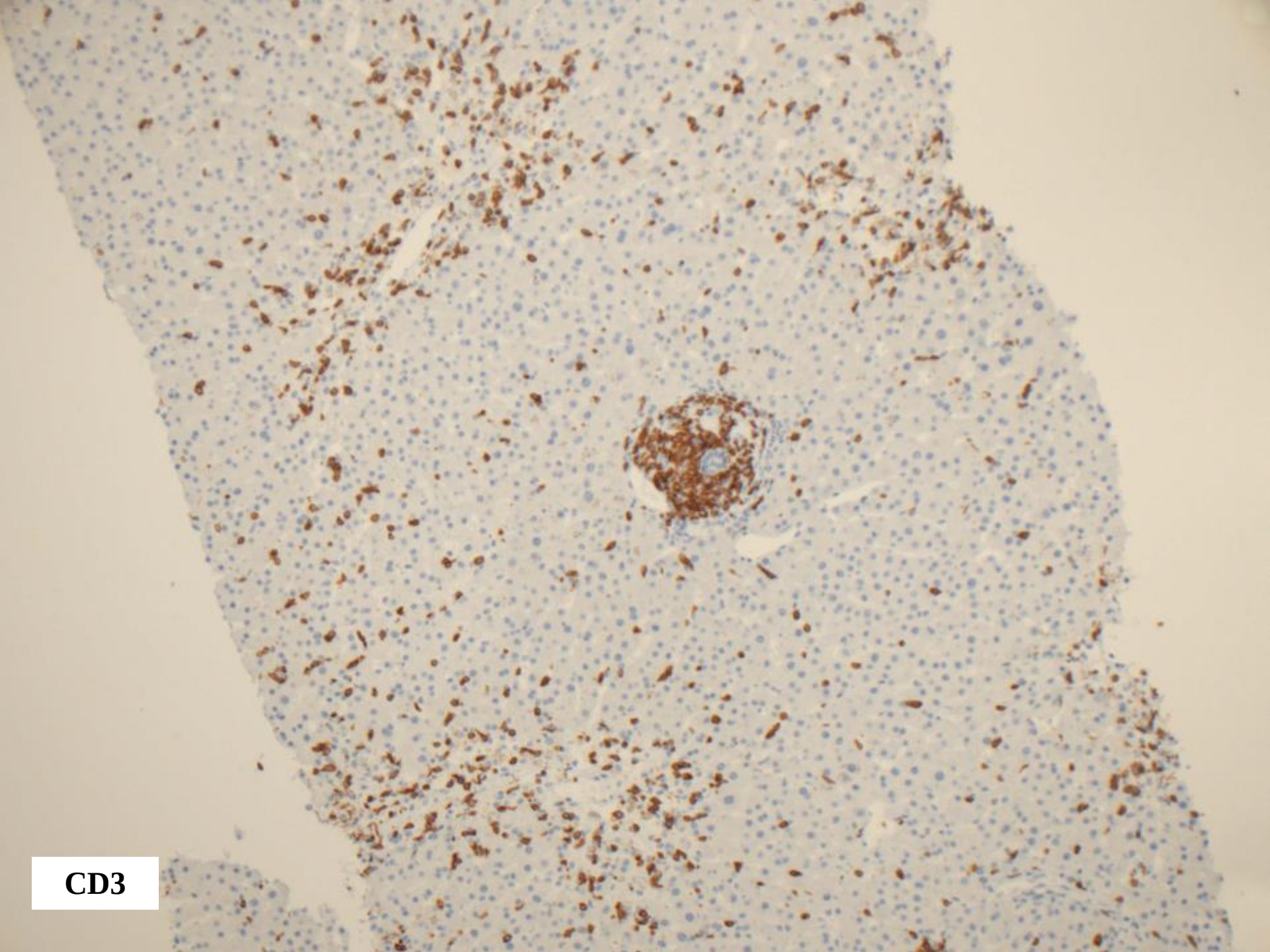
- Metastatic malignant melanoma – lesions in skin, lungs, adrenal gland and bone.
- Treated with Nivolumab (immune checkpoint inhibitor blocking PD-1)

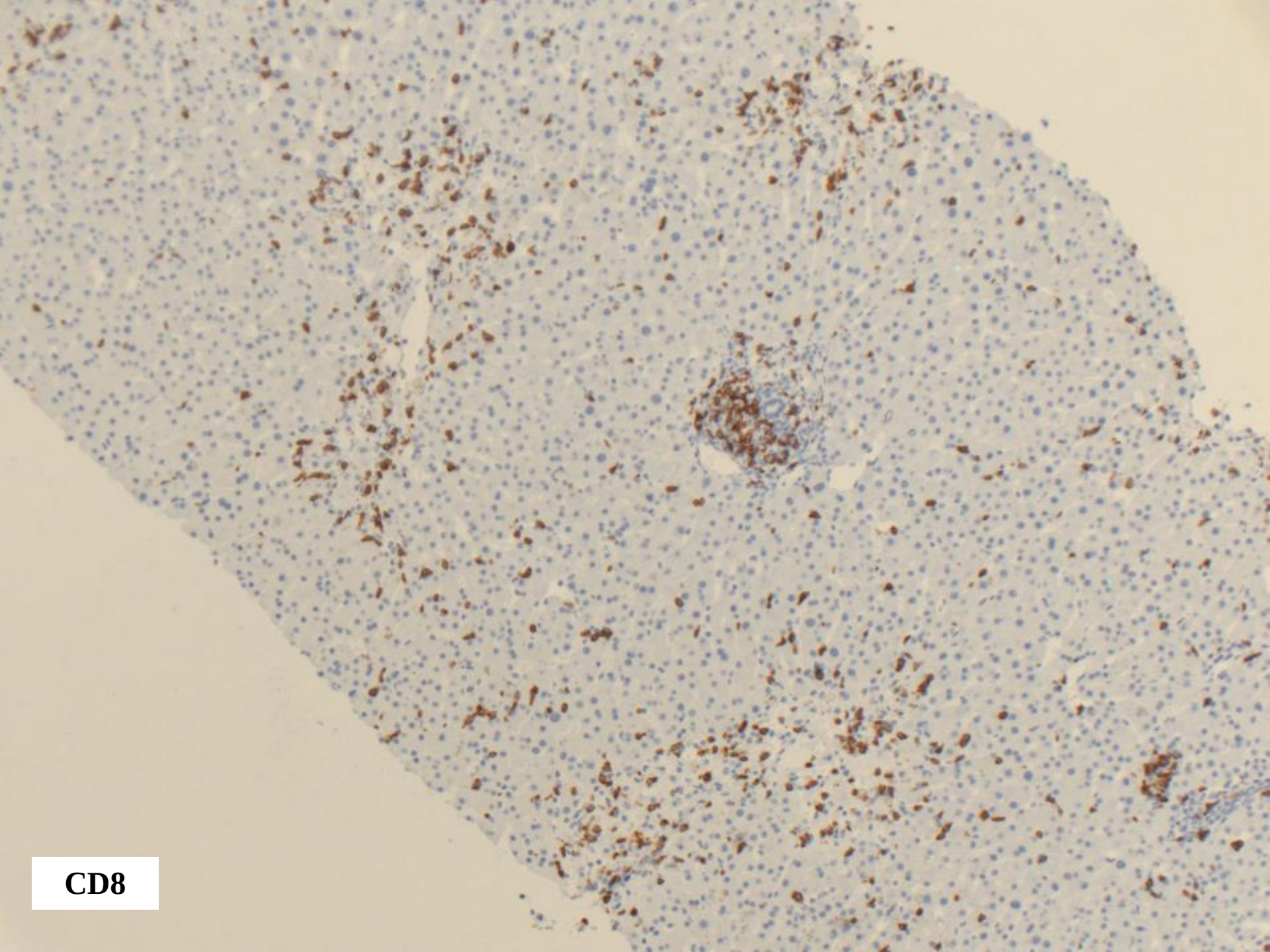
- Treatment stopped because of immunotherapy-related adverse events.
- Recently diagnosed with collagenous colitis, chronic diarrhoea and weight loss
- On the most recent bloods found to have deranged ALT which is worsening, now 426. Bilirubin normal.
- Liver biopsy to rule out immunotherapy related hepatitis (slide A/2018).

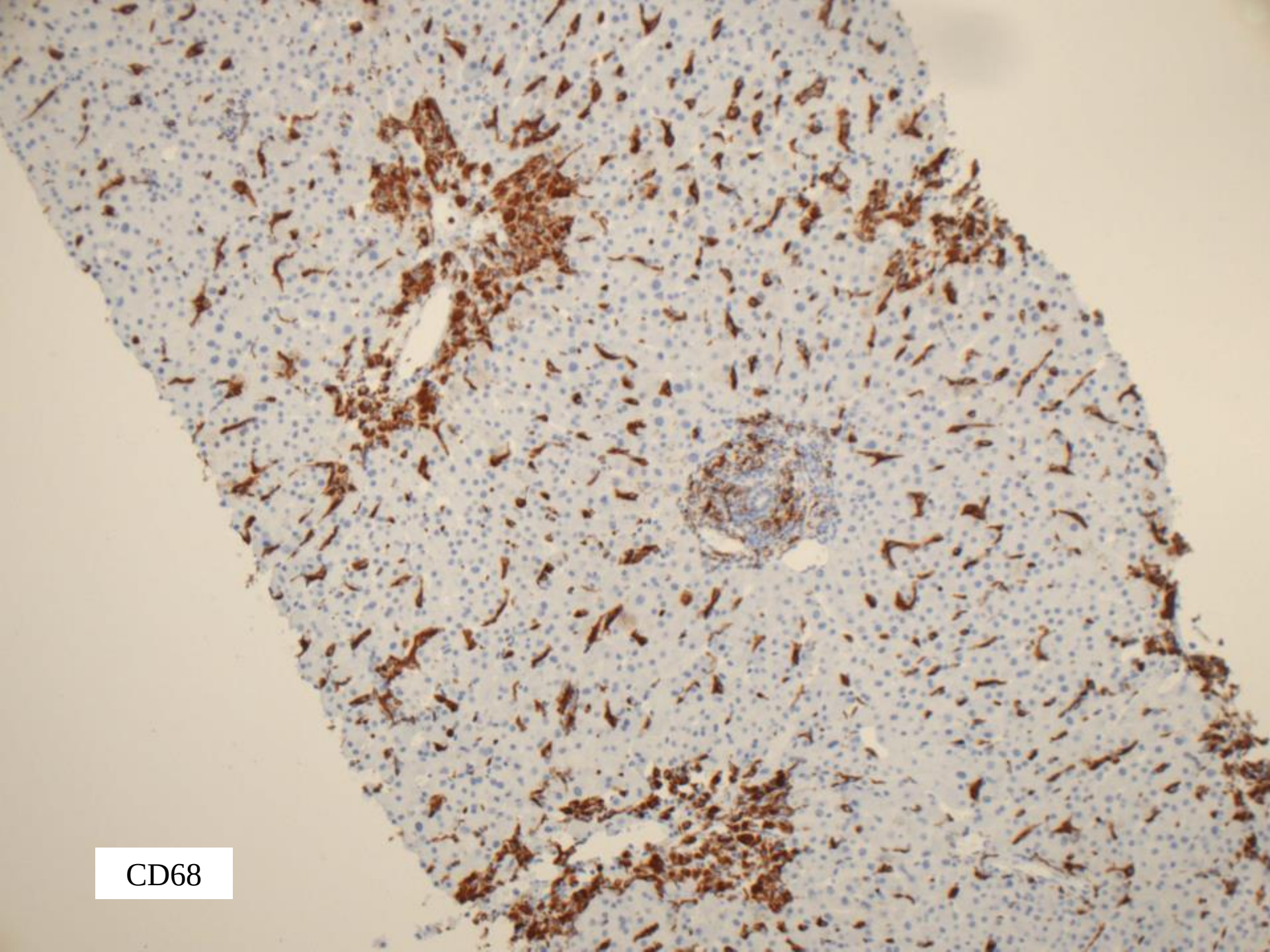


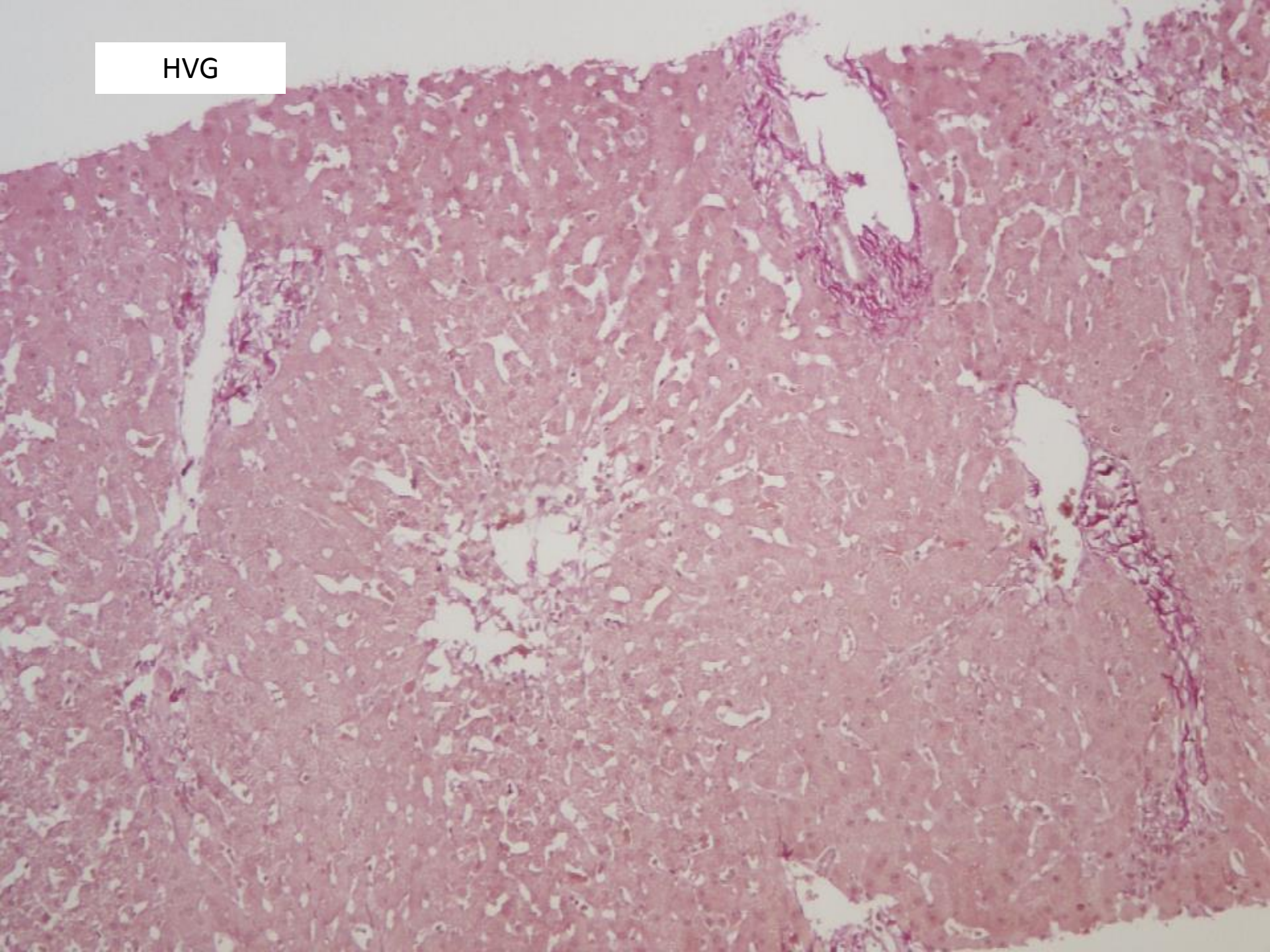



PAS - diastase


CD3


CD8


CD68


HVG

# Birmingham A/2018 - Diagnosis

- Acute injury with centrilobular inflammation + confluent necrosis (“central perivenulitis”)
- In keeping with drug-induced liver injury related to Nivolumab

## Birmingham A/2018 – Follow-up

- Started on IV methylprednisolone on the day before the biopsy
- Switched to prednisolone on day 3 after the biopsy
- ALT rapidly settled and has remained normal since

**Histological Findings in Immune Checkpoint Inhibitor Induced Liver Injury**

(Johncilla 2015, Doherty 2017, Gelsomino 2017, Kawakami 2017, Zen 2018, De Martin 2018)

**41 cases studied**

- Drugs implicated include inhibitors of PD-1/PD-L1 (nivolumab, pembrolizumab) and CTLA-4 (ipilimumab) – individually or in combination

**Main histological findings:**

- Diffuse lobular hepatitis, variable confluent centrilobular necrosis
- Lobular inflammatory cells mainly CD8+ T lymphocytes, plasma cells generally few
- Variable portal inflammation and interface hepatitis (generally mild)

  (localised centrilobular necro-inflammation uncommon)

**Other Findings:**

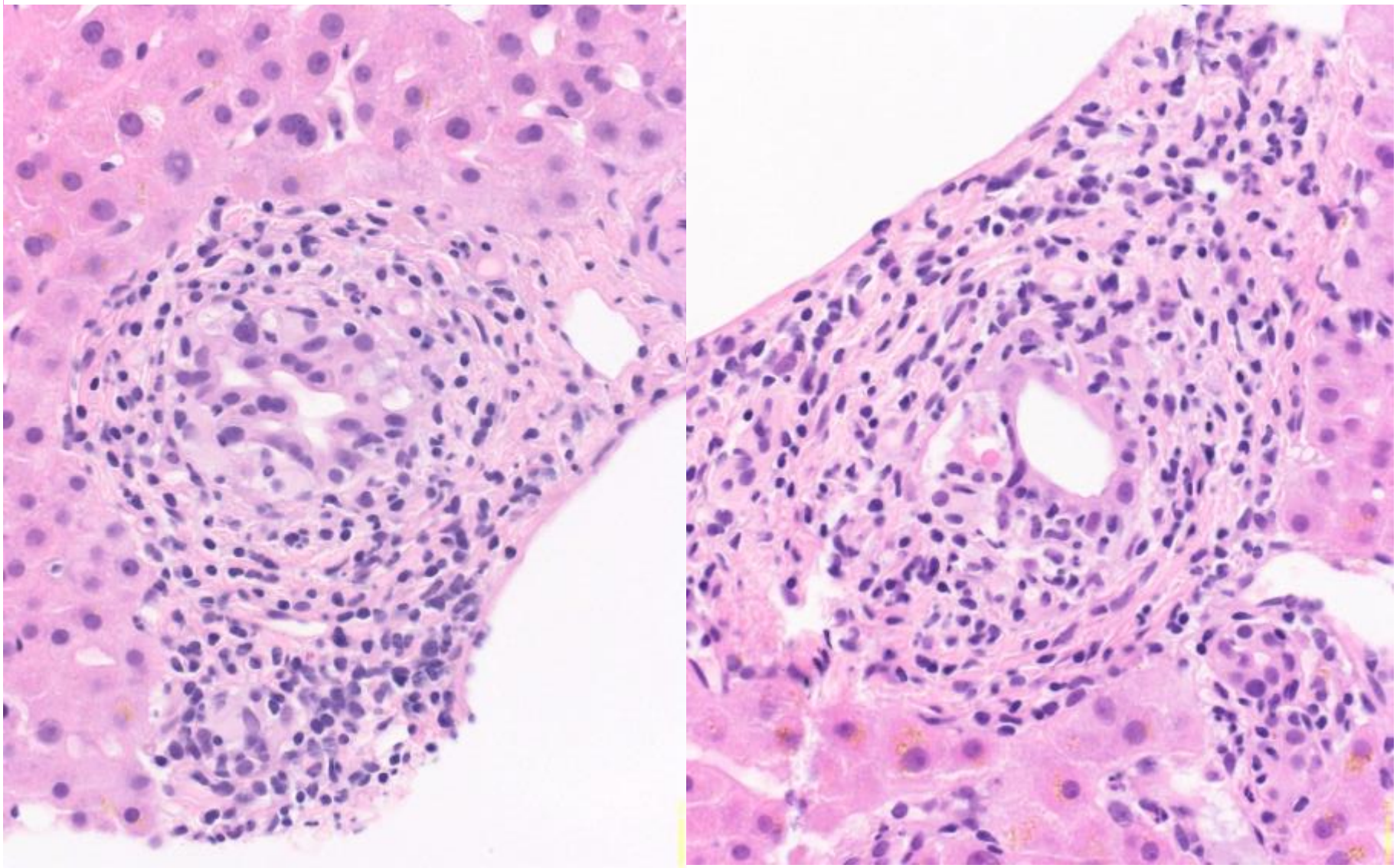
- Bile duct inflammation +/- bile duct loss
- Lobular granulomas/microgranulomas - mainly anti-CTLA4 cases (de Martin 2018)
- Fibrin ring granulomas - anti-CTLA4 cases only (de Martin 2018)
- Central vein endothelial inflammation – mainly anti-CTLA4 cases (de Martin 2018)
- Portal fibrosis

# Immune Checkpoint Inhibitors - Liver Toxicity

Other Patterns of Liver Injury
Seen in Circulated Cases

**Basel-A (Luigi Terracciano)**

57 year old woman with malignant melanoma – treated with ipilimumab and nivolumab



Universitätsspital Basel

Bile duct lesions in most portal tracts

B17. 2315

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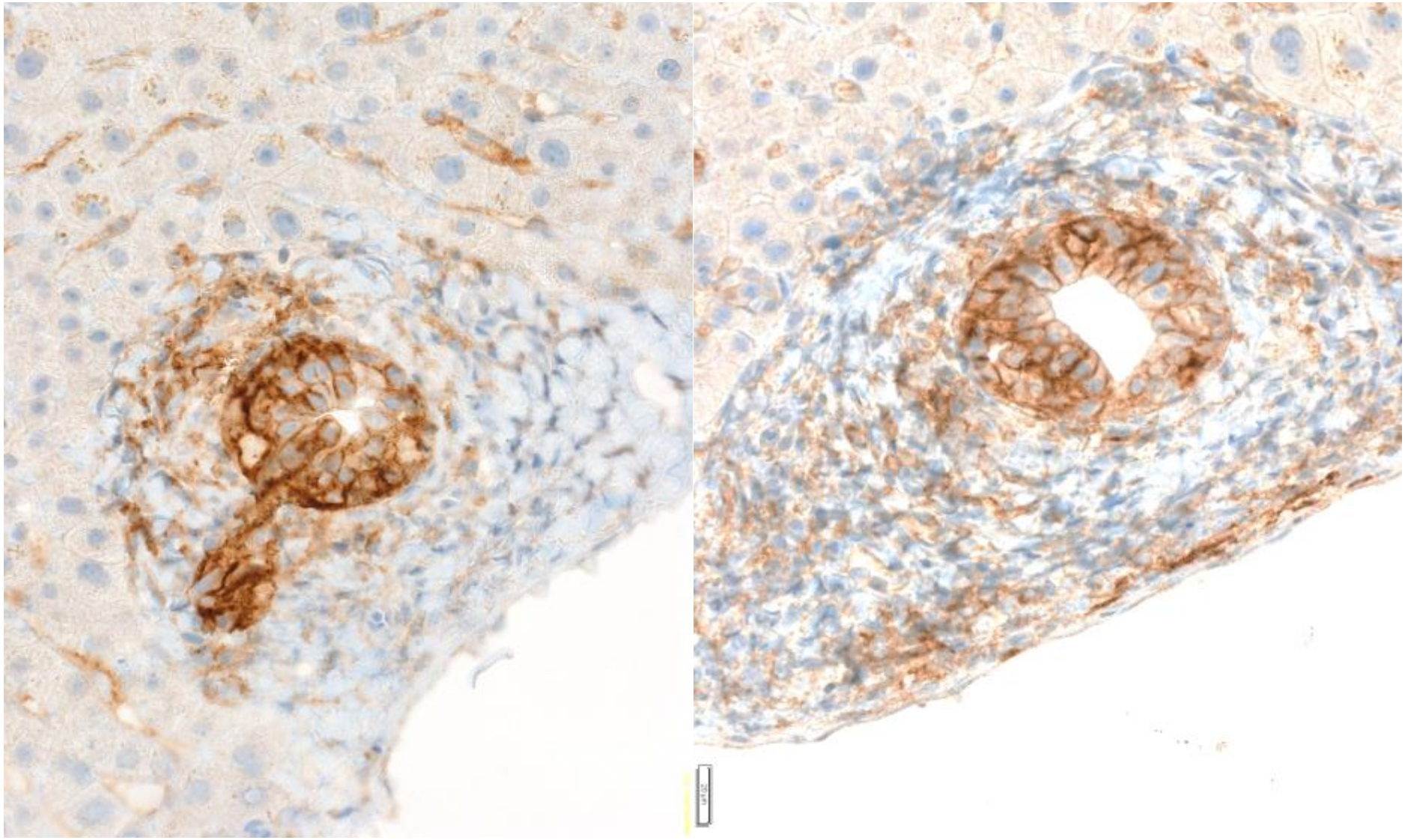


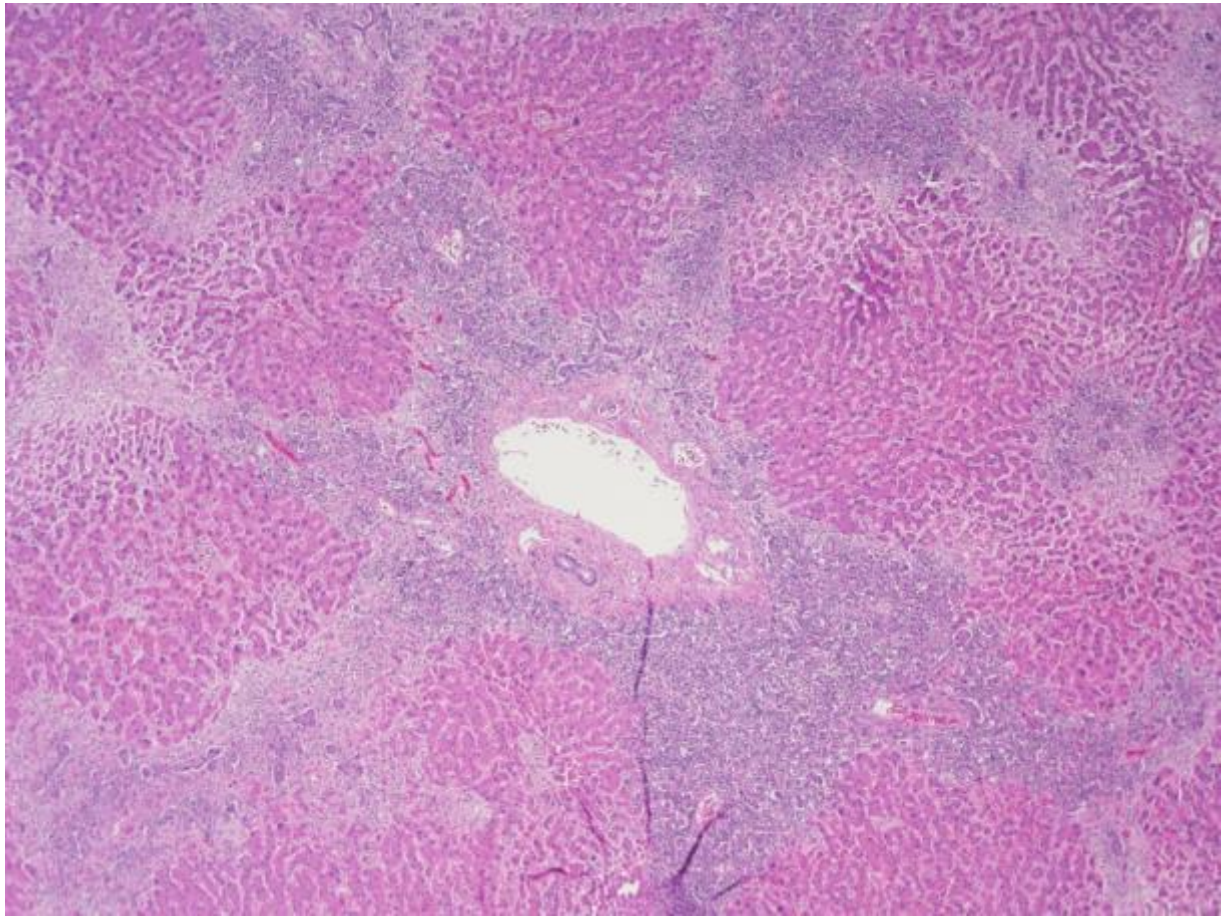
Universitätsspital Basel

**PD-L1**

B17. 2315

**Bethesda-B (David Kleiner)**

80 year old man with pleural mesothelioma – received one dose of pembrolizumab

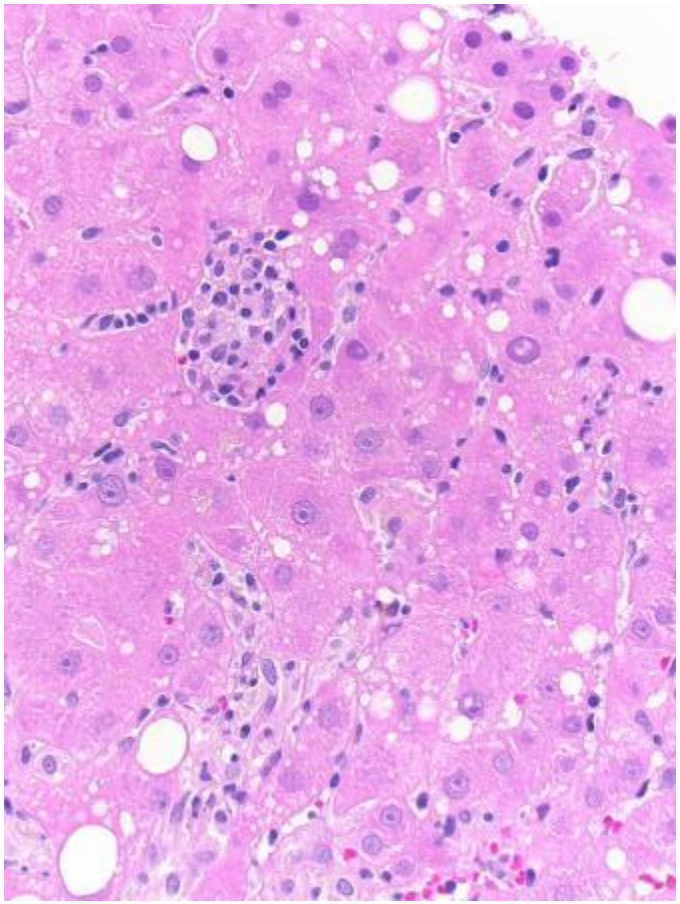


Autopsy Liver Wt: 2300 g

- Chronic hepatitis like picture with portal expansion and portal/periportal inflammation

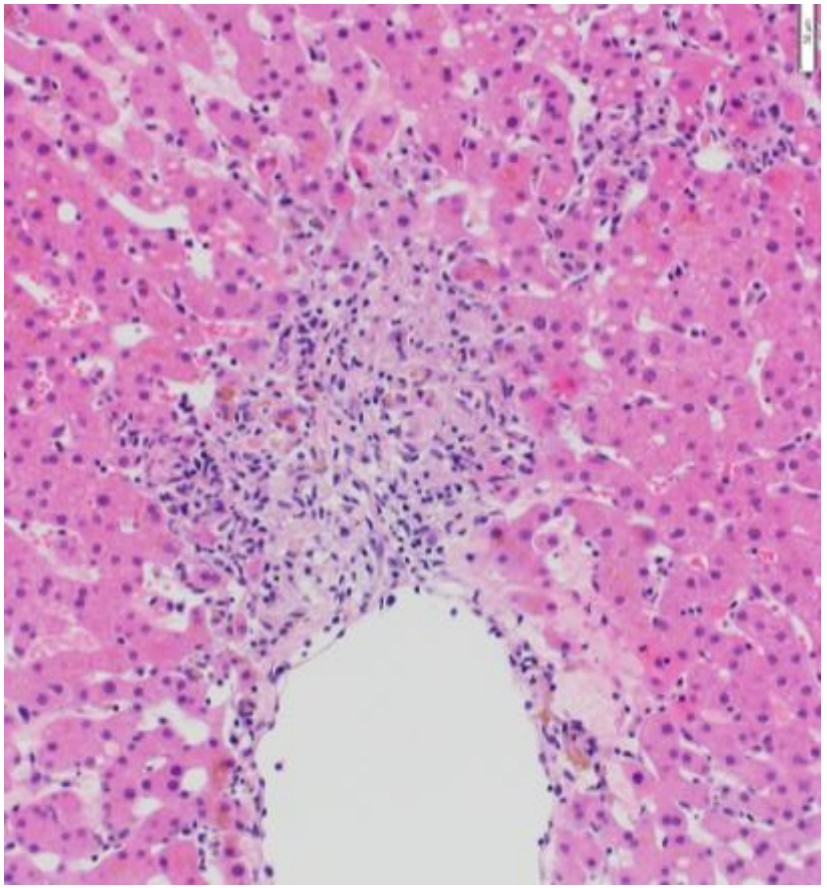
# Lobular Microgranulomas / Granulomas

**Brisbane-B (Andrew Clouston)**



**Ill-defined small histiocytic aggregates**
Ipilimumab and Nivolumab

**Basel-A (Luigi Terracciano)**



**Well formed granuloma**
Ipilimumab and Nivolumab0

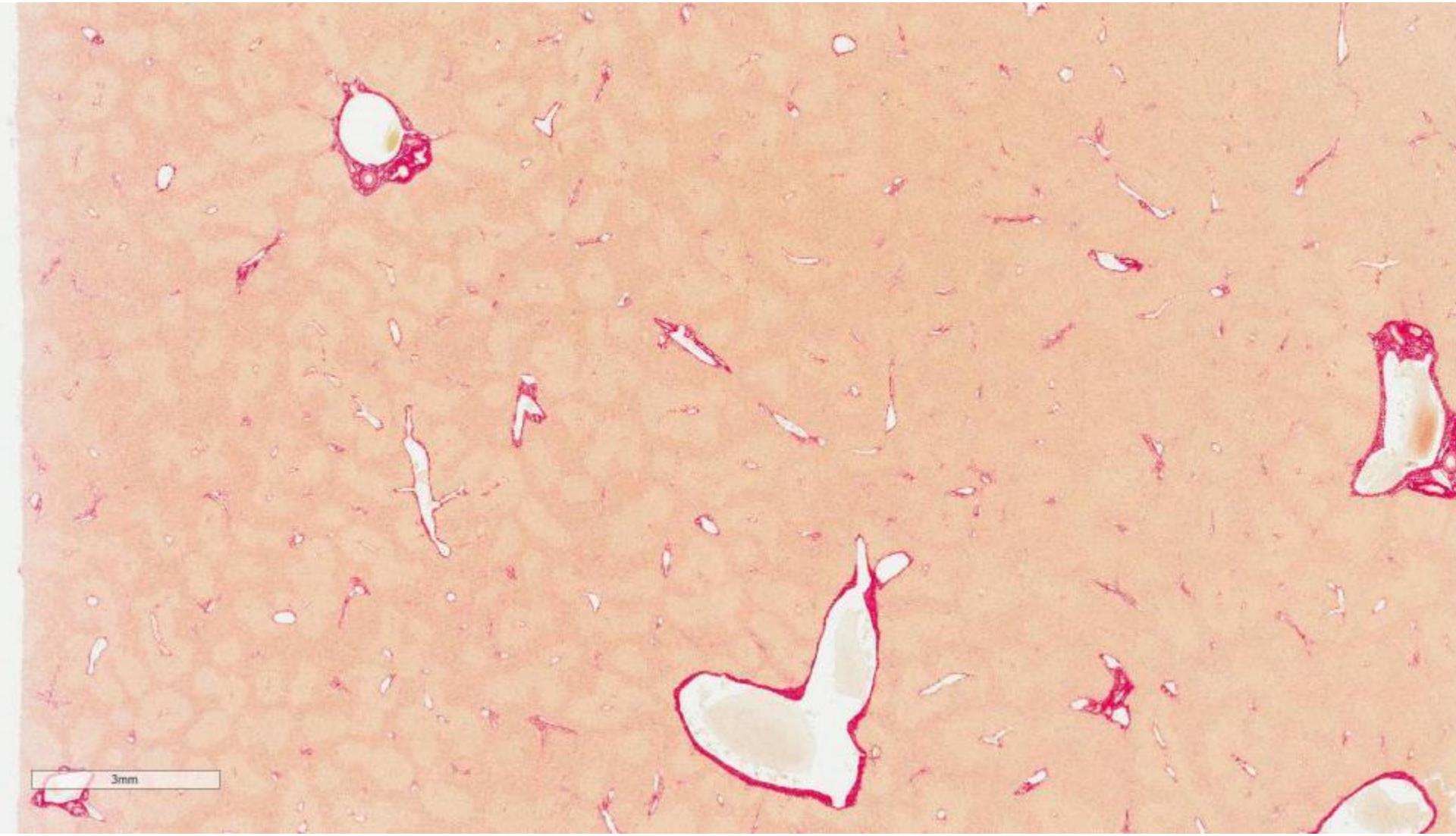
# Gnomes Meeting 2018 Athens – Summary of Cases Presented (1)

| Type of drug | Pattern | Cases |
|---|---|---|
| **Anti- depressant** | Acute hepatitis<br>Hepatitis (AIH-like) + cholangiopathy | Adelaide-B (sertraline)<br>Heidelberg-B (sertraline) |
| **Anti-TNFα** | AIH-like features<br>Chronic hepatitis like | Basel-A (Infliximab)<br>Washington-A (Infliximab) |
| **Antibiotics** | Cholestatic hepatitis<br>Severe hepatitis with submassive necrosis<br>Severe hepatitis with submassive necrosis | Groningen-A (co-trimoxazole)<br>Paris-A (isoniazid)<br>Rochester-A (Bactrim) |
| **Immune check-point inhibitors** | Hepatitis, bile duct injury<br>Chronic hepatitis like<br>Centrilobular necrosis<br>Hepatitis, microgranulomas | Basel –A (ipilimumab & nivolomab)<br>Bethesda –A (pembrolizumab)<br>Birmingham-A (nivolumab)<br>Brisbane-B (ipilimumab & nivolomab) |
| **Oral contraceptives** | Sinusoidal dilatation<br>Bile duct injury (also MDR3 deficiency) | Adelaide-A<br>Brisbane-A |
| **Toxins/chemicals** | **Periportal necrosis** | **Paris-B (phosphorus)** |

# Paris - Case 2 (17AG00481)

(Pierre Bedossa)

- A 3-years-old girl was admitted in the ICU for major acute liver failure.
- The general status of the baby deteriorated within hours and she undergo liver transplantation.
- The baby was from a very poor migrant family, living in the backyard of a shop of fireworks and firecrackers where the children was often left alone for several hours.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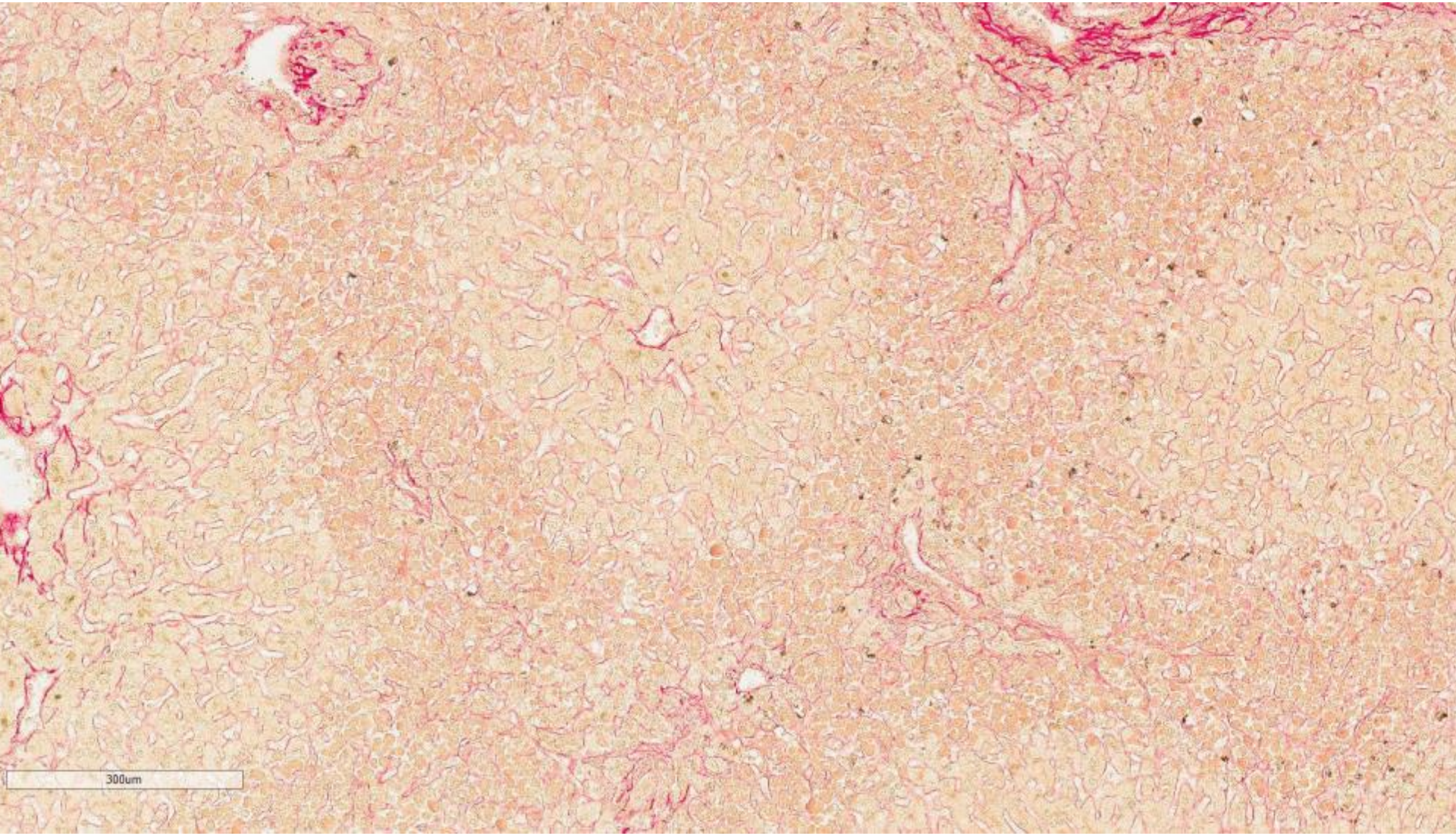
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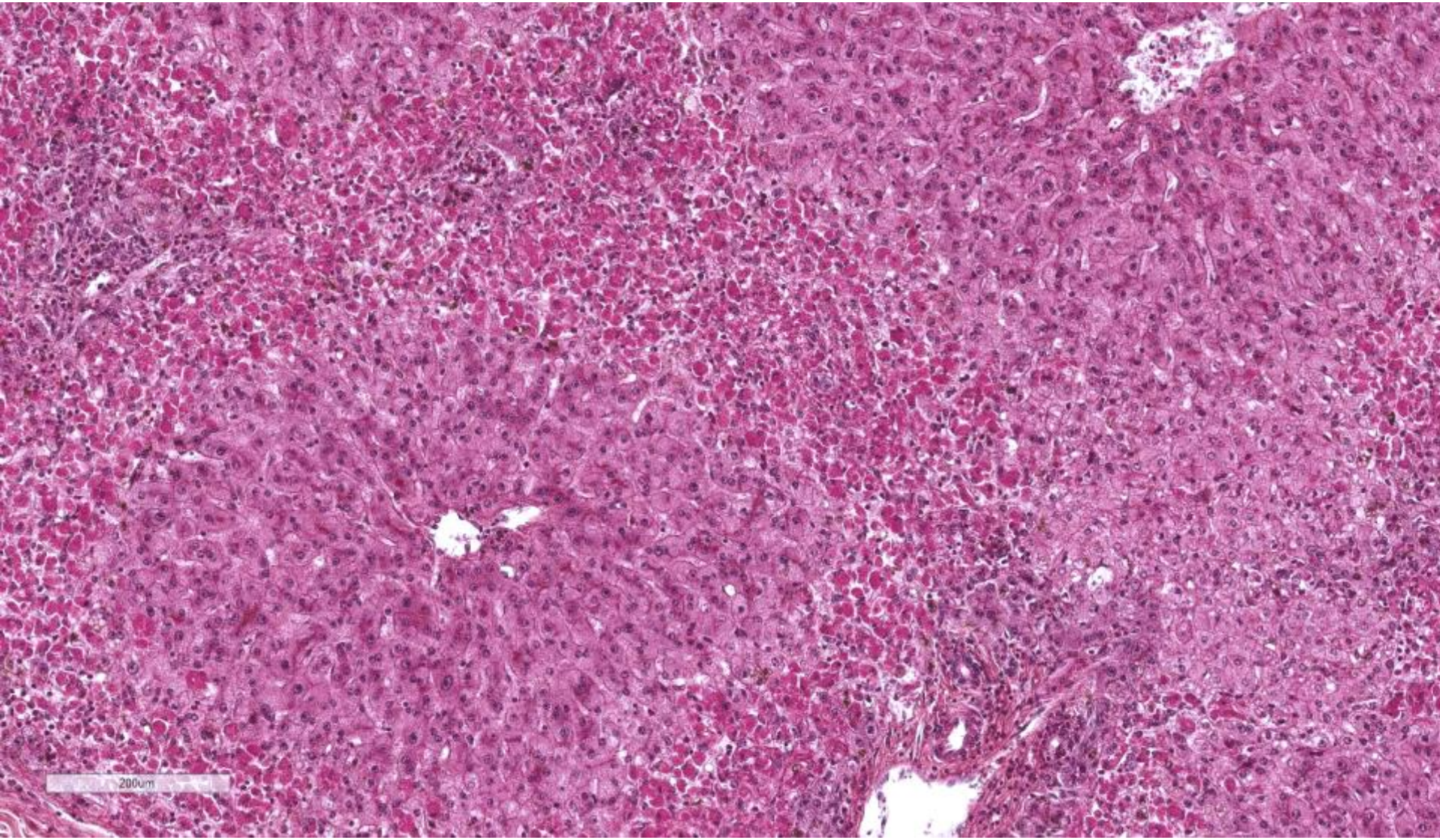
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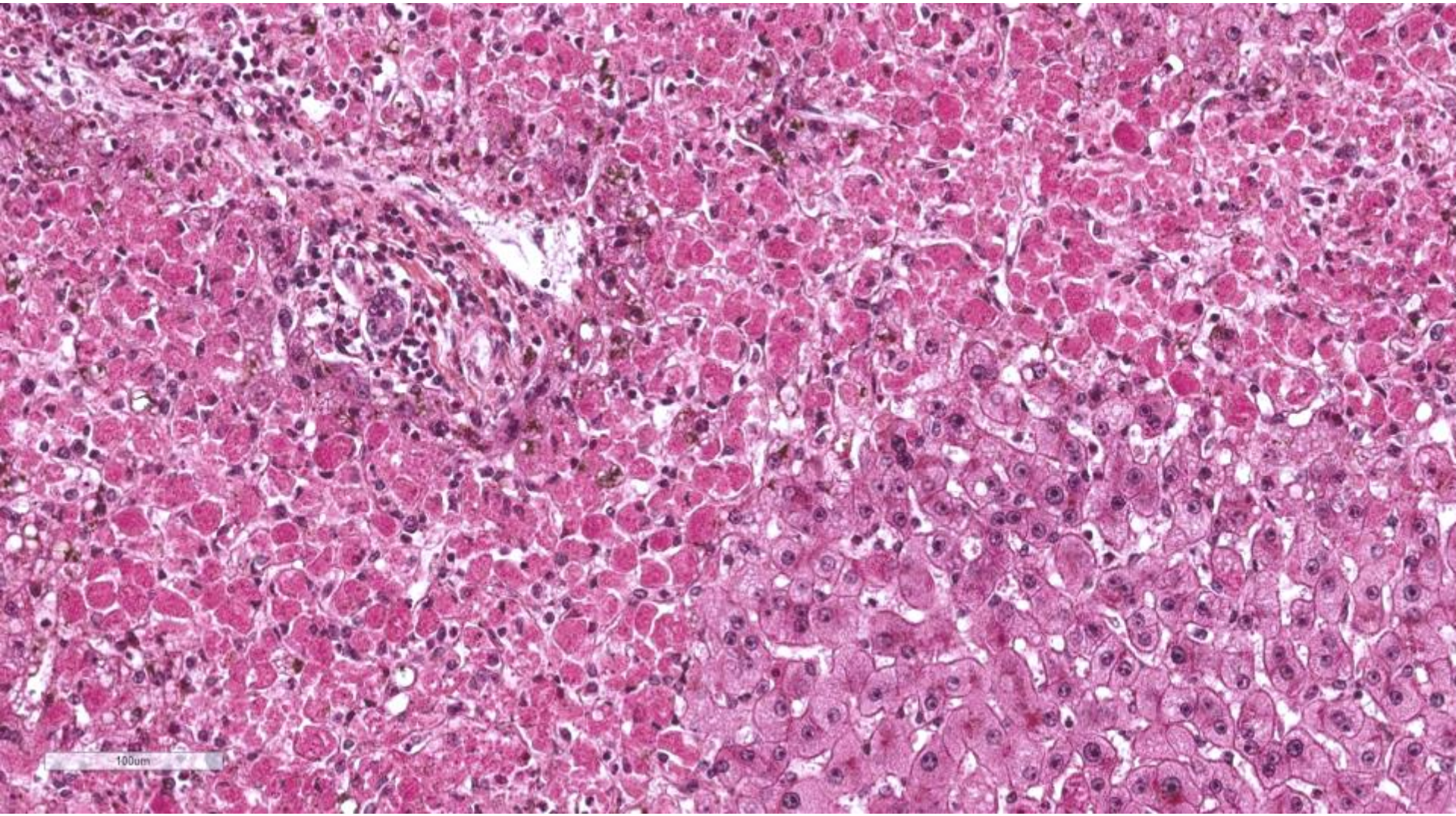
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# CASE 2. ACUTE ZONAL (PERIPORTAL) NECROSIS DUE TO PHOSPHORUS TOXICITY

# Zonal necrosis in DILI

- Usually Zone 3 (acetominophen, mushroom, CCl4) because of zonal location of most cytochromes that metabolize innocuous drugs into a potent hepatotoxic intermediate metabolite
- Extension from zone 3 to full lobule with confluent necrosis
- Periportal zonal necrosis is a rare feature : highly direct hepatotoxic drug invading the liver through portal vein → higher concentration of toxic drug in zone 1

**Kleiner DE, Drugs and Toxins – Chapter 12 in MacSween's Pathology of the Liver, 7th Edition, 2018**

**TABLE 12.6** Agents associated with zonal and diffuse necrosis

| Chemicals | Drugs |
|---|---|
| 2-Chloropropane (Z3) | Acetaminophen (paracetamol) (Z3) |
| 2-Nitropropane (D) | Amodiaquine (Z3) |
| Aflatoxins (Z1, Z3) | Anastrozole (Z3) |
| Albitocin (Z1) | Benorylate (ZN) |
| Alloxan (Z1) | Chloroform (Z3) |
| Allyl compounds (Z1) | Chlorzoxazone (Z3) |
| Amanitin (Z3) | Ciprofloxacin (Z3) |
| Aniline (D) | Citalopram (Z3) |
| Arsenic compounds (Z3, D) | Desipramine (ZN) |
| *Bacillus cereus* toxin (Z2) | Duloxetine (Z3) |
| Beryllium (Z2) | Ebrotidine (Z3) |
| Bromobenzene (Z3) | Enflurane (Z3) |
| Carbon tetrachloride (Z3) | Ethionamide (Z3) |
| Chlorinated Benzenes (Z3, D) | Ferrous sulphate (Z1) |
| Chlorinated diphenyls (D) | Fluroxene (Z3) |
| Chlorinated naphthalene (D) | Halothane (Z3) |
| Chloroprene (Z3) | Hycanthone (ZN) |
| Cocaine (Z1, Z3) | Imatinib mesylate (Z3) |
| Copper sulphate (Z3) | Imipramine (ZN) |
| DDT (Z3) | Indomethacin (ZN) |
| Dichloropropane (Z3) | Infliximab (Z3) |
| Dimethylnitrosamine (Z3) | Iodoform (Z3) |
| Dinitrobenzone (Z3, D) | Iproniazid (Z3) |
| Dinitrotoluene (Z3, D) | Isoflurane (Z3) |
| Dioxane (Z2, D) | **Isoniazid** (ZN) |
| Diptheria toxin (Z3) | Ketoconazole (Z3) |
| Ethylene dibromide (Z3) | Labetalol (Z3) |
| Ethylene dichloride (Z3) | Lamotrigene (Z1,Z3) |
| Galactosamine (D) | Levetiracetam (Z3) |
| Halogenated hydrocarbons (Z3, D) | Levofloxacin (Z3) |
| Luteoskyrin (Z3) | Lisinopril (Z3) |
| Manganese compounds (Z1) | Lovastatin (Z3) |
| Mushrooms (Z3, D) | Mesalamine (mesalazine) (Z1) |
| Naphthalene (Z3) | Methoxyflurane (ZN) |
| Ngaione (Z2) | Methyldopa (Z3) |
| Pemphigus vulgaris endotoxin (Z1) | Mithramycin (plicamycin) (Z3) |
| Paraquat (Z3) | Nefazodone (Z3) |
| Phalloidin (Z3) | Nevirapine (Z3) |
| Phosphorus (Z1) | Norfloxacin (Z3) |
| Rubratoxin (Z3) | Nortriptyline (Z3) |
| Selenium (D) | Olanzapine (Z3) |
| Sporidesmin (Z1) | Piroxicam (D) |
| Tetrachloroethane (Z3, D) | Propylthiouracil (Z3) |
| Tetrachloroethylene (Z3) | Quetiapine (Z3) |
| Thioacetamide (Z3) | Quinidine (ZN) |
| Trichloroethylene (Z3) | Rifampin (ZN) |
| Trinitrotoluene (Z3, D) | Roxithromycin (Z3) |
| | Sulfasalazine (ZN) |
| | Sulindac (ZN) |
| | Synthaline (Z1) |
| | Tacrine (Z3) |
| | Tacrolimus (Z3) |
| | Telithromycin (Z3) |
| | Ticrynafen (tienilic acid) (Z3) |
| | Tocilizumab (Z3) |
| | Tolazamide (ZN) |
| | Toloxatone (Z3) |
| | Troglitazone (Z3) |
| | Trovafloxacin (Z3) |
| | Urethane (ethyl carbamate) (Z3) |
| | Valproic acid (Z3) |
| | Venlafaxine (Z3) |

= Agents which preferentiaaly cause zone 1 (periportal) necrosis

# Acute liver failure after Phosphorus ingestion

- Ingestion of Fireworks: Rare Cause of Poisoning in Children. Yuksekkaya H, et al. Pediatr Emerg Care. 2018 Mar 12.
- Acute Yellow Phosphorus Poisoning Causing Fulminant Hepatic Failure with Parenchymal Hemorrhages and Contained Duodenal Perforation. Ravikanth R, et al. Indian J Crit Care Med. 2017 Apr;21(4):238-242.
- Clinical spectrum of yellow phosphorous poisoning in a tertiary care centre in South India: a case series. Mishra AK, Devakiruba NS, Jasmine S, Sathyendra S, Zachariah A, Iyadurai R. Trop Doct. 2017 Jul;47(3):245-249.
- Living donor liver transplantation for acute liver failure in pediatric patients caused by the ingestion of fireworks containing yellow phosphorus. Ates M et al. Liver Transpl. (2011)

# Gnomes Meeting 2018 Athens – Summary of Cases Presented (2)

| Type of drug | Pattern | Cases |
|---|---|---|
| **Anti-neoplastic drugs** | Sinusoidal obstruction syndrome<br>Sclerosing cholangitis<br>Vanishing BD syndrome | Halifax-A (oxaliplatin)<br>Rochester-B (FUDR)<br>Washington-B (6MP) |
| **Amiodarone (?)** | Acute hepatocellular injury | Bethesda-B |
| **Polypharmacy** | Glycogen ground-glass inclusions | Rome-A |
| **Azathioprine** | Cholestasis and ductopenia | Groningen-B |
| **Herbal/Dietary Supplements** | Acute hepatitis<br>Zonal/submassive necrosis<br>**Acute hepatitis with submassive necrosis** | Athens-A (multiple agents)<br>Vienna-A (nicotinamide = Vitamin B3)<br>**Vienna-B (NONI juice)** |
| **Corticosteroids** | Acute hepatitis with zone 3 necrosis | Rome-B (prednisolone) |
| **Anti-coagulant** | Hepatitis with bridging necrosis | Heidelberg-A (Phenprocoumon) |
| **Not drug-induced** | Epithelioid haemangioendothelioma<br>Sarcoidosis<br>Regressed HFE cirrhosis | Athens-B<br>Birmingham –B<br>Halifax-B |

## Liver Injury due to Herbal Medicines and Dietary Supplements

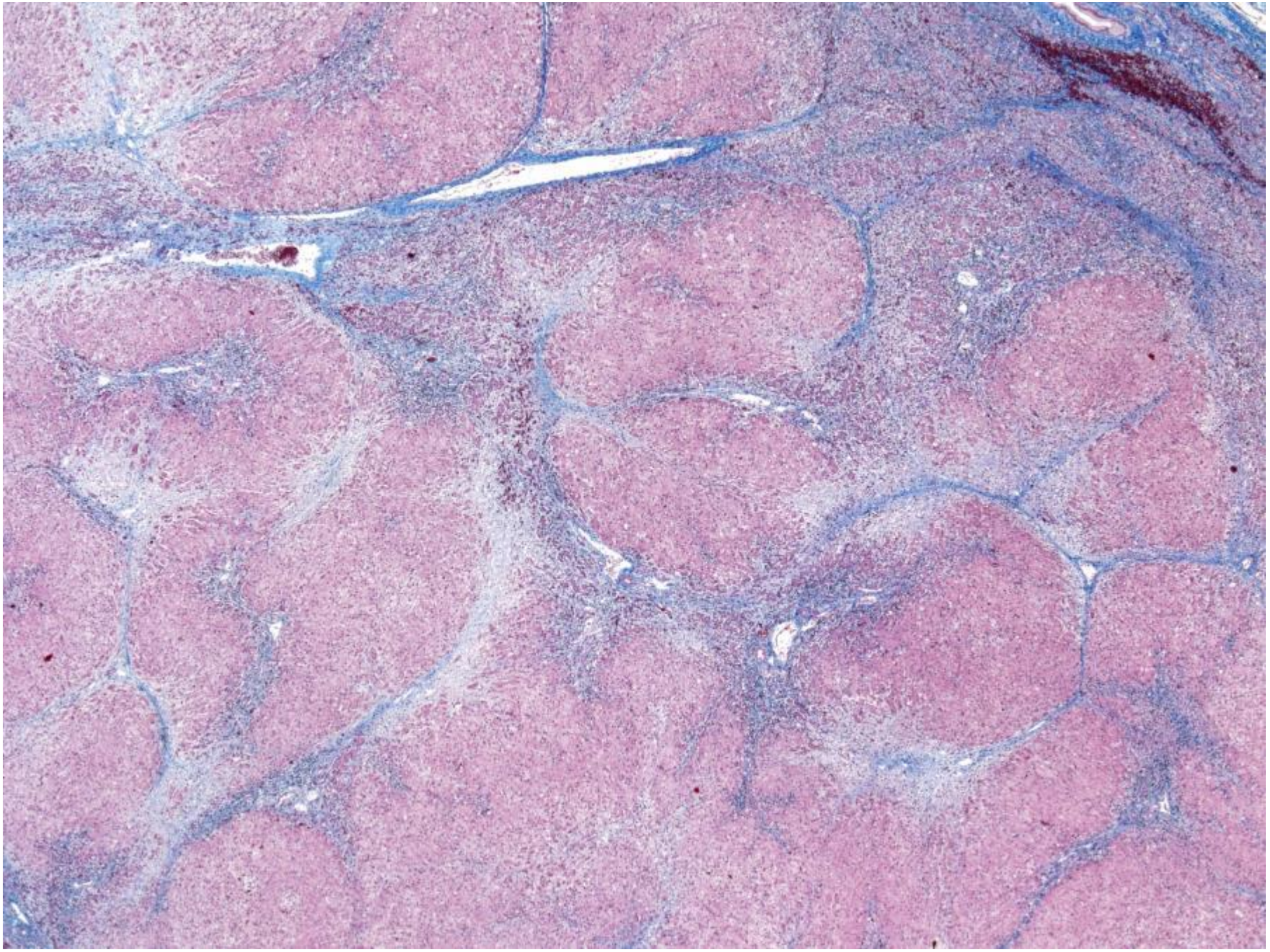
- Review of 185 publications identified at least 60 herbal agents with potential hepatotoxicity (Teschke, Liver International 2012)

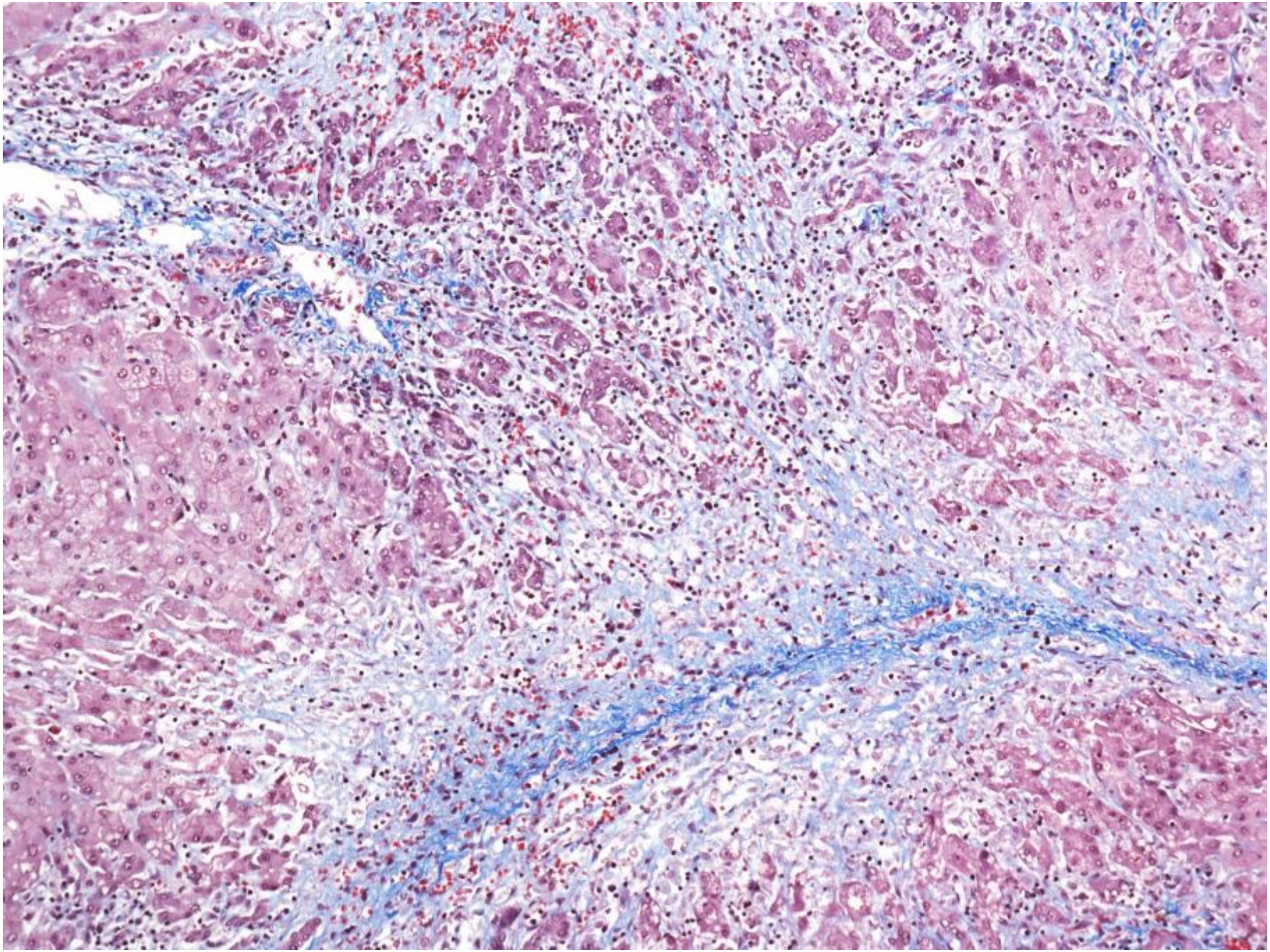
- Rising prevalence as cause of liver injury
  - 20% of DILI in US now attributed to herbs/dietary supplements (HDS) (Navarro, Hepatology 2014)
  - >70% of DILI in Singapore and Korea due to HDS (Wai 2007, Suk 2012)

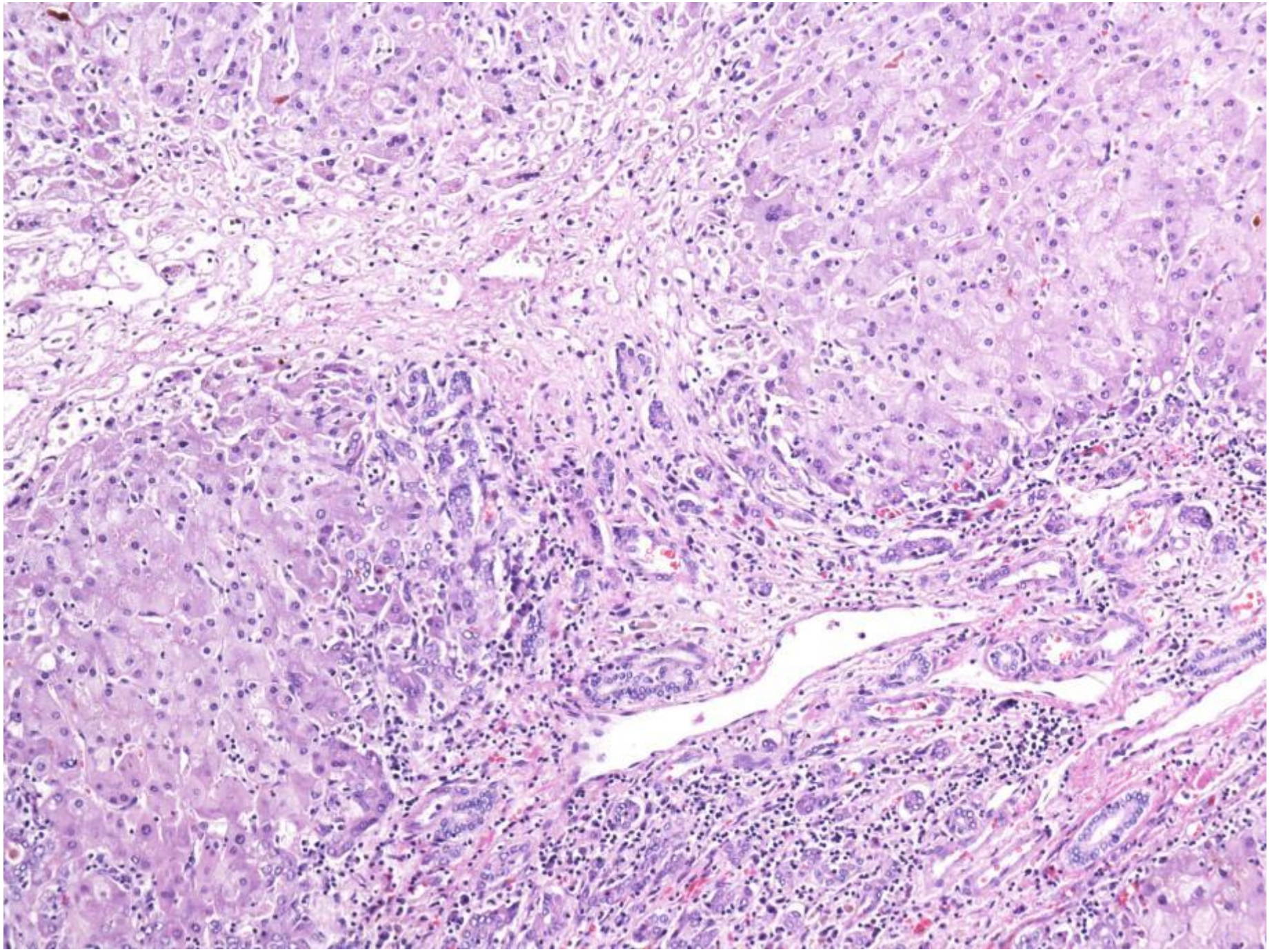
- **Patterns of injury ascribed to herbal hepatotoxicity**
  - Fatty change
  - Acute hepatitis (including rare severe cases with acute liver failure)
  - Chronic hepatitis
  - Fibrosis

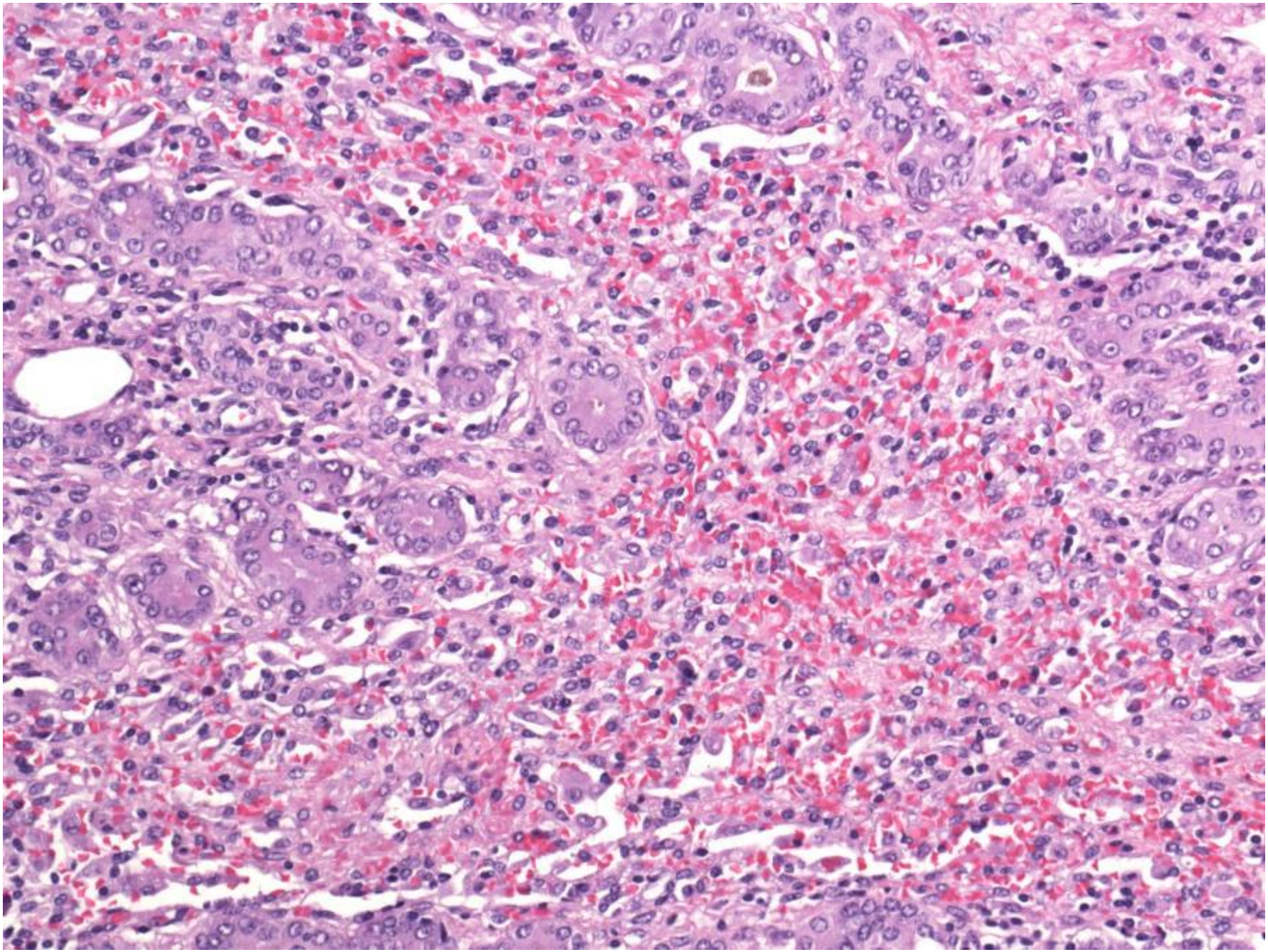
# **Vienna Case 2** (Hans Dienes)

- 29 year old patient was admitted to the hospital with symptoms and signs of acute hepatitis after receiving treatment with paracetamol for upper respiratory tract infection. He received a total dose of 40g and reduced his food intake due to an impaired appetite.
- Laboratory findings showed bilirubin values of 26.3 mg/dl, ASAT 2926 U/l, ALAT 2665 U/l, gGT 75 U/l, AP 209 U/l. Autoantibodies were negative as well as tests for viral hepatitis A-E. A Wilsons disease was ruled out.
- Clinical diagnosis was made as low dose paracetamol toxicity facilitated by fasting.
- However his health deteriorated and he developed liver failure which necessitated a liver transplantation.
- After extensive questioning, he admitted in an interview that he had ingested 1.5 liter of **NONI juice** per day for weeks that contained Morinda citrifolia (anthraquinone) from Tahiti, a **“wellness drink”.**









# Vienna case 2 – 2018
# Diagnosis:

Severe hepatitis with panacinar necrosis
(submassive hepatic necrosis)

Liver Failure due to NONI Juice

(Morinda Citrifolia, Anthraquinone)

**Noni Juice (Morinda Citrofolia)**

(from LiverTox - https://livertox.nlm.nih.gov/Noni.htm)

- Morinda citrofolia is a tropical fruit tree also known as Noni or Indian Mulberry
- Noni juice, roots, stems, bark, leaves and flowers have been used as medicinal remedies in Polynesia for centuries
- Now widely advertised as Western herbal medicine for a wide range of disorders including cancer, diabetes, depression, chronic fatigue and AIDS.
- Marketed in US since 1996
- Approved as a “novel food” by European Commission in 2003
- Also available in UK via internet (e.g. Amazon) and health food stores

**Noni Juice (Morinda Citrofolia)**
(from LiverTox - https://livertox.nlm.nih.gov/Noni.htm)

**Hepatotoxicity**

- Several case reports
- Latency 2 – 8 weeks
- Clinical features resemble acute hepatitis with hepatocellular pattern of serum enzyme elevations
- Mechanism uncertain – likely idiosyncratic rather than direct toxicity
- Causative agent also uncertain – possibly anthraquinones


And, finally…….

# Group Photograph by the Parthenon

# Private Tour of the New Acropolis Museum

# Dinner at the New Acropolis Museum

# Ceremonial Transfer of the Gnomes Hat

**Gnomes Meeting, Rochester 19th - 22nd June 2019**
**Chief Gnome – Mike Torbenson**
**Theme: "Primary malignant epithelial tumours of the liver"**


**Granulomas**