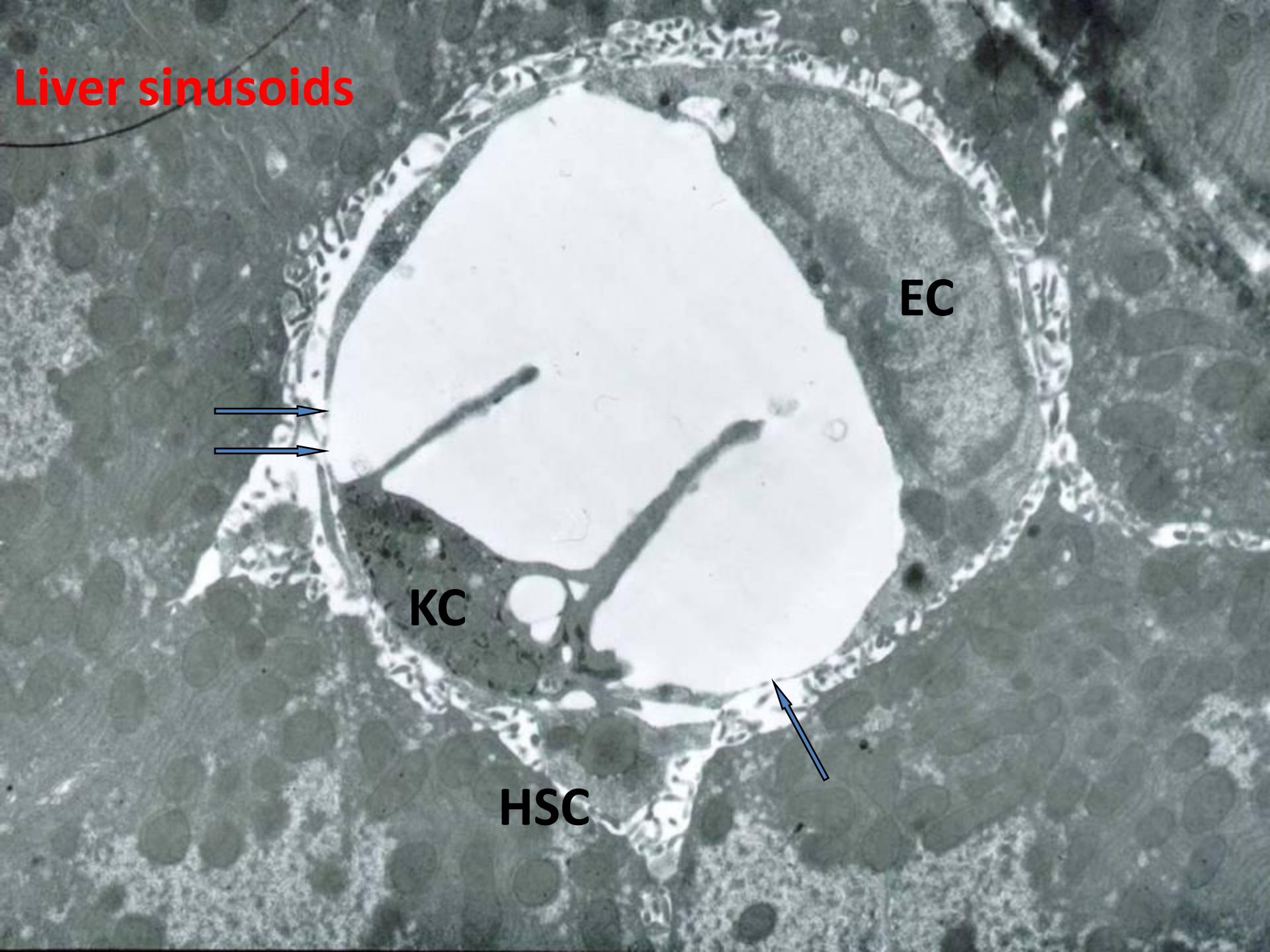
Update from the Gnomes meeting 2011

Sinusoidal lesions

Alastair Burt
Newcastle University


Liver sinusoids
EC
KC
HSC

Kupffer cells

- ‘Fixed’ tissue macrophages
- Recruitment from bone marrow-derived monocytes
- Clearance of viruses, fungi, bacteria and parasites
- Endotoxin clearance through TLRs
- Express endogenous peroxidase in RER in animal liver; human markers include CD68

Sinusoidal endothelial cells

- Fenestrated with sieve like plates
- No underlying basement membrane (although some collagen IV present)
- Filtration effect: role of white blood cells
- Endocytosis and scavenger function
- Normal human liver: minimal expression of Factor VIII RAg/CD31/CD34

Hepatic stellate cells

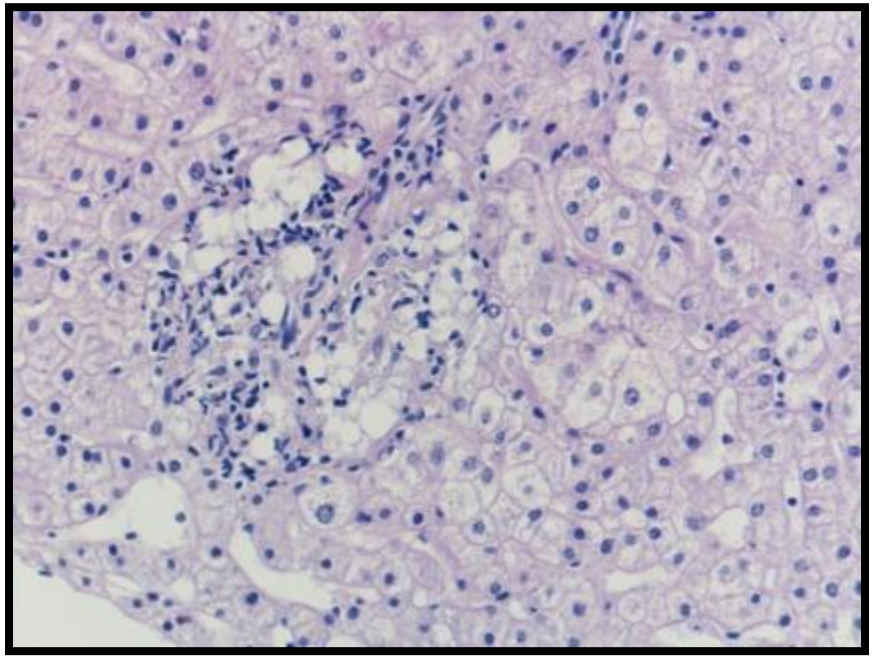
- Present in space of Disse
- Sinusoidal pericytes with long processes that surround SECs
- Contractile
- Produce matrix proteins and some metalloproteinases
- Storage of retinoids
- Activated to myofibroblasts: α SMA positive

Other sinusoidal components

- Second layer cells
- Liver associated lymphocytes
- Nerves
- Matrix proteins
- Lymph

Case study: Athens A

- 37 year old female
- Recurrent febrile episodes
- Lower limb subcutaneous nodules
- Symmetrical sensory neuropathy
- Arthralgia
- Diagnosis: Weber-Christian disease: treated with steroids
- Developed plaques on legs and ulcers on elbows; knees
- Abnormal LFTs



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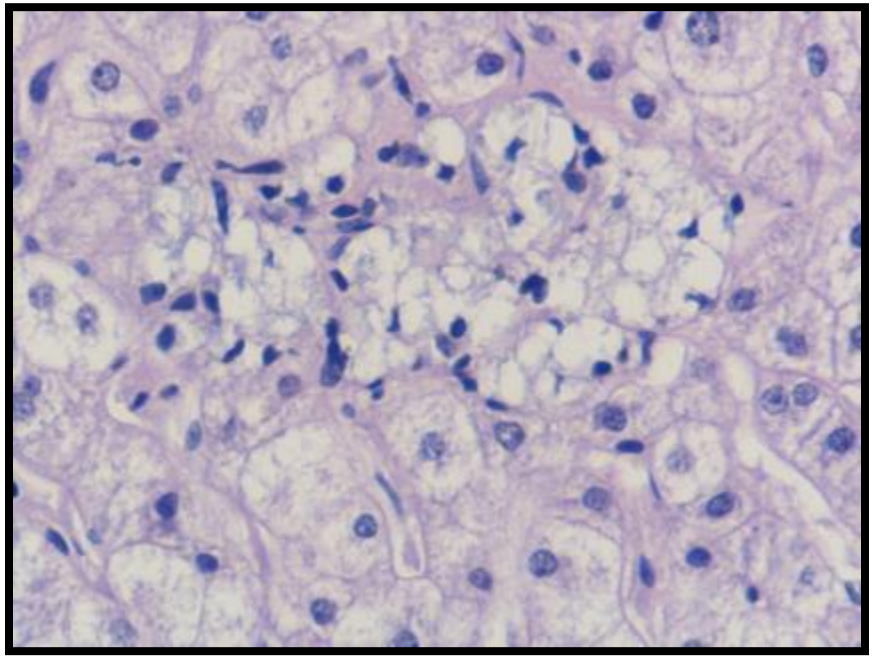

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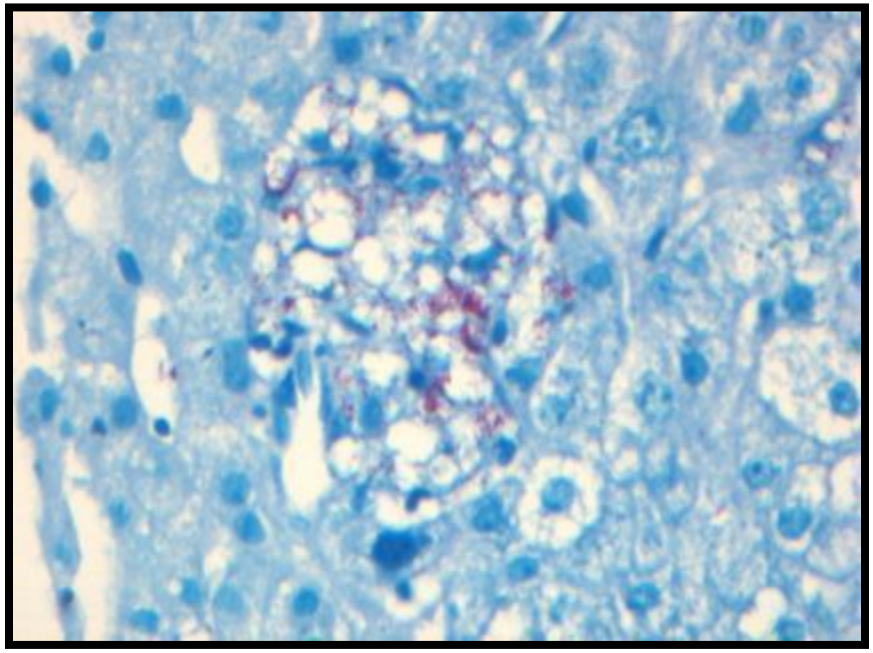
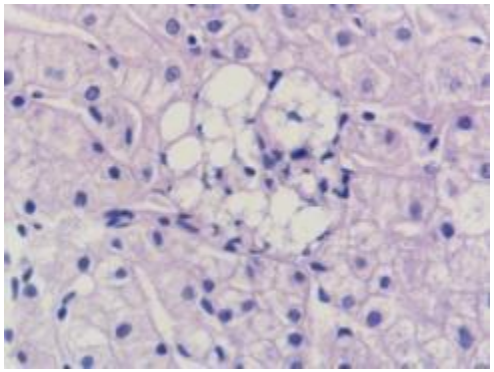


Foamy macrophages in lepromatous leprosy

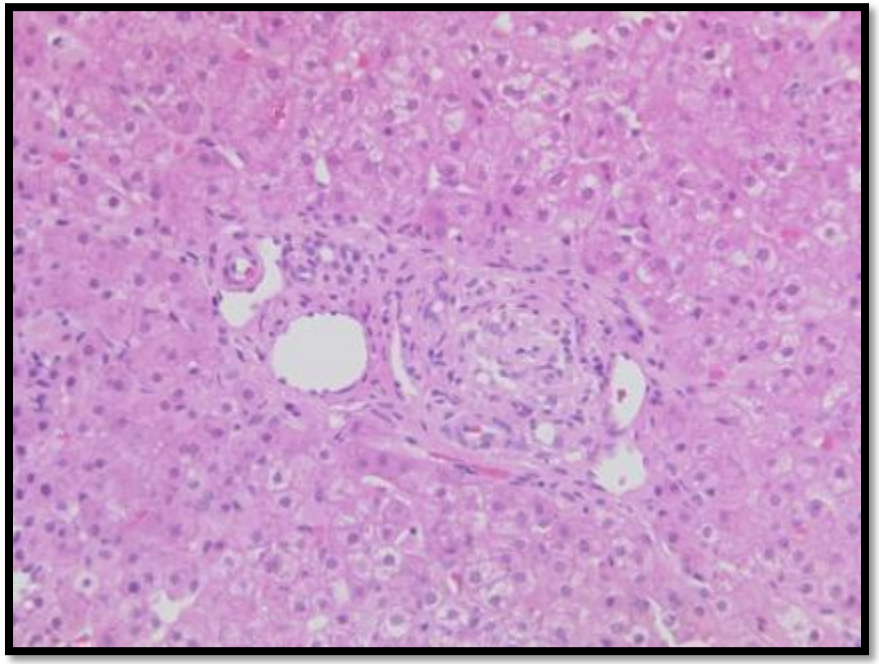


"In the fresh state they have one characteristic that is especially noteworthy, i.e., their tendency to form a sort of vacuole, apparently from taking up water, so that under the circumstances they acquire a wholly physaliferous appearance"

Virchow, R. (1863). Die krankhaften Geschwülste. August Hirschwald, Berlin.

Case study: Newcastle A

- 9 month old female
- Referred to Tertiary Immunodeficiency Unit with Severe Combined Immune Deficiency
- BMT performed with successful engraftment
- Post transplant noted to have abnormal LFTs with ALT > 1000
- All viral screening negative apart from HHV6



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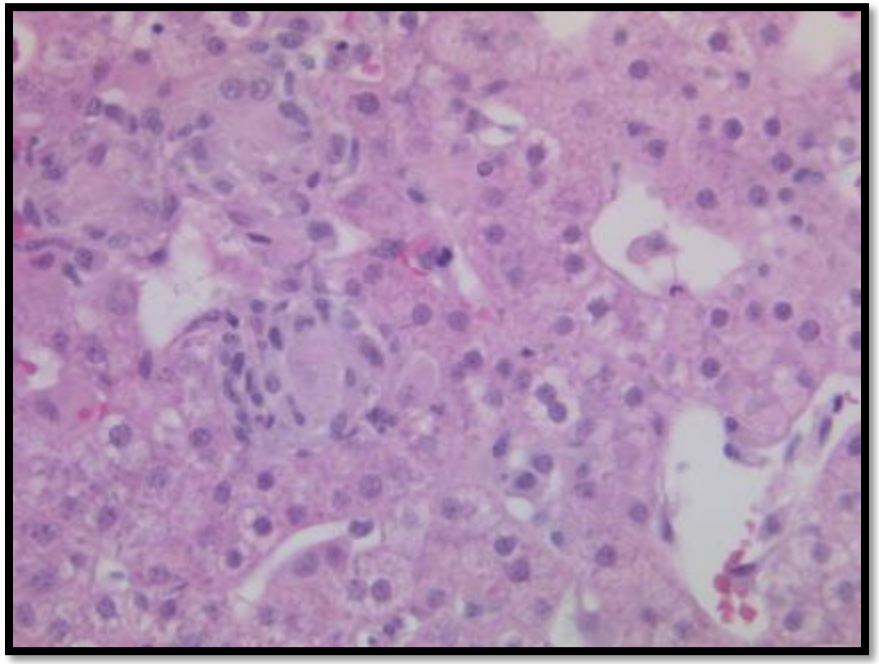

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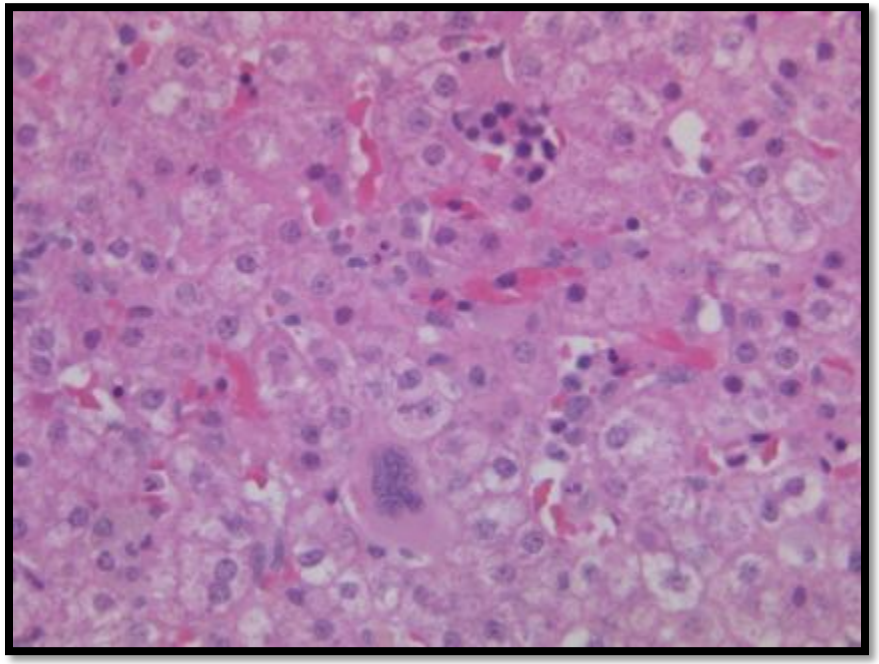
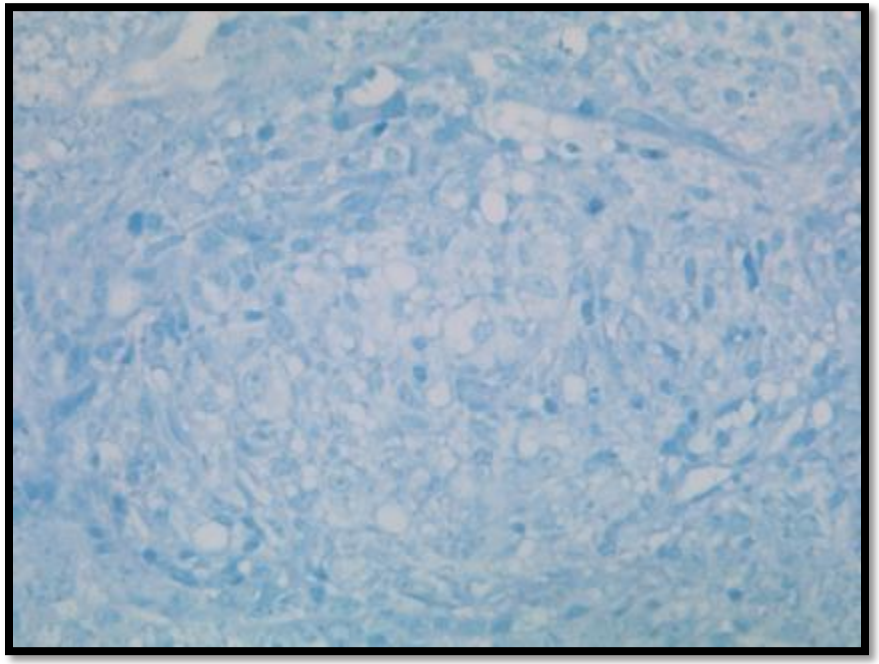
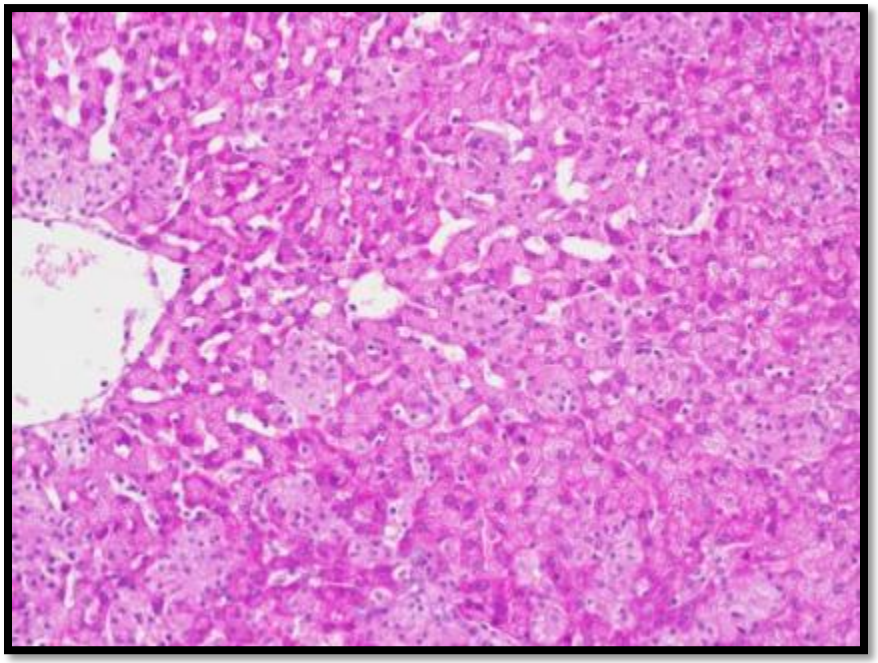


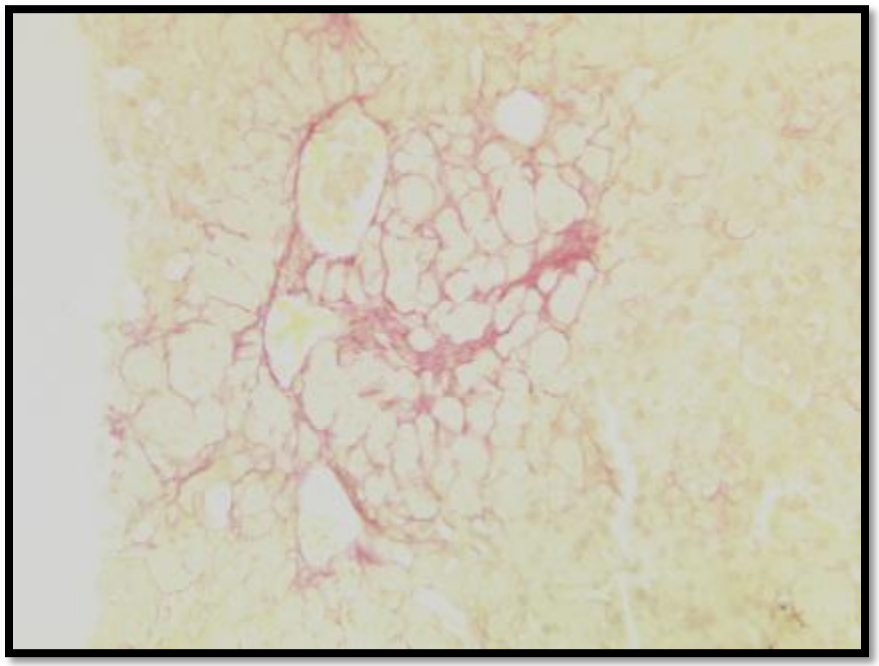
Case study: Newcastle A

- Aged 5 months presented with skin ulcers: BCG abscesses
- Treated with anti-tuberculous therapy
- SCID: mutation not known: NK indeterminate
- Allograft from father: CD3/CD10 depleted
- Episodes of fever post BMT: immune reconstitution? HHV6?
- Liver injury: ? All BCG or superimposed HHV6 and/or immune reconstitution



Newcastle A: differential diagnosis





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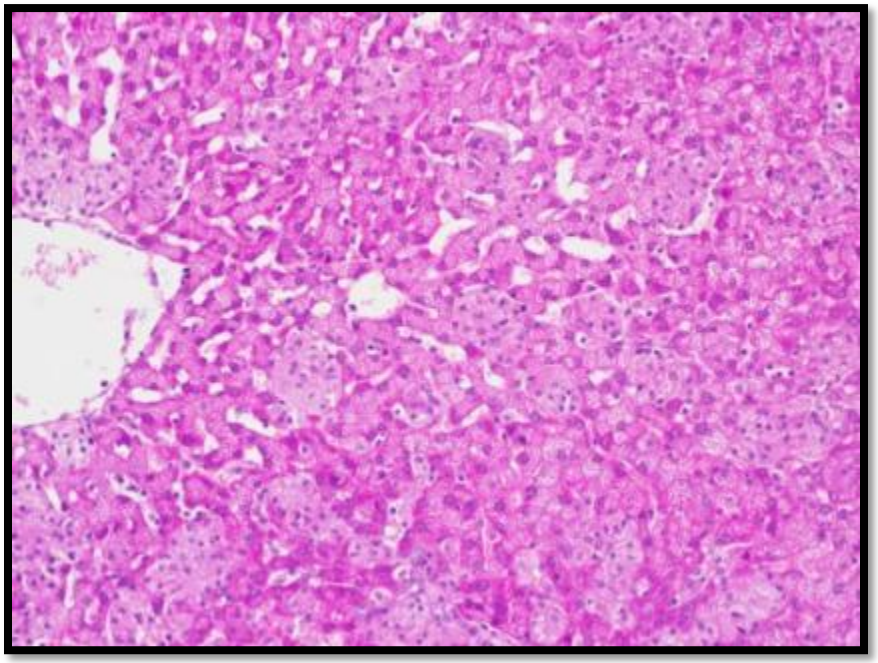
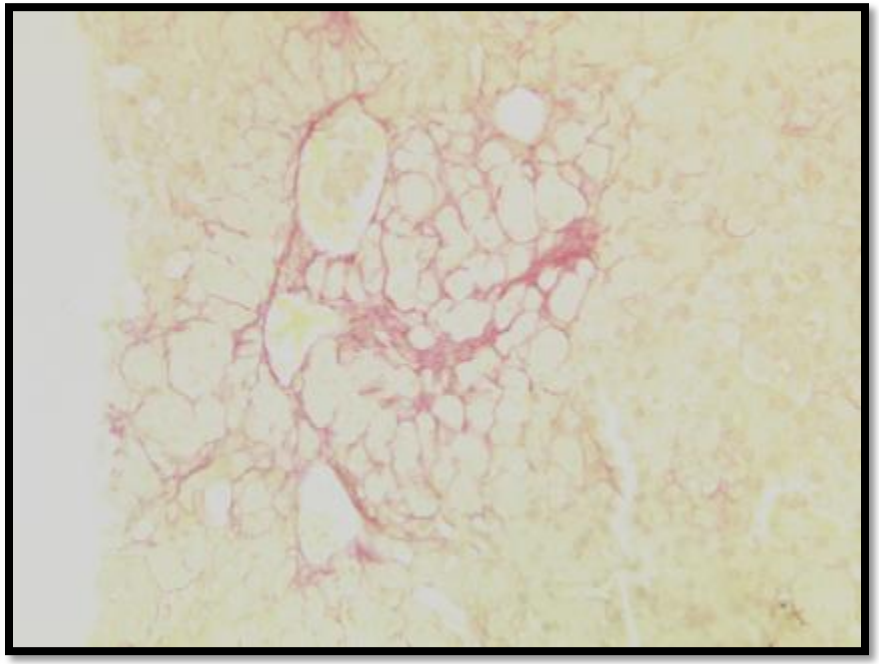




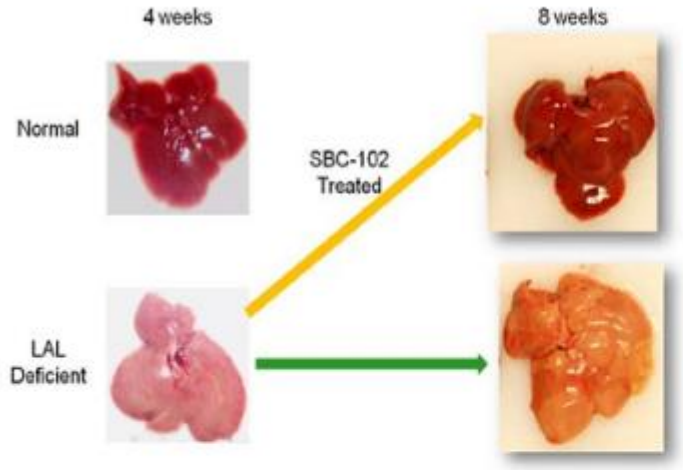
RECOMBINANT LYSOSOMAL ACID LIPASE NORMALIZES LIVER WEIGHT, TRANSAMINASES AND HISTOPATHOLOGICAL ABNORMALITIES IN AN *IN VIVO* MODEL OF CHOLESTERYL ESTER STORAGE DISEASE

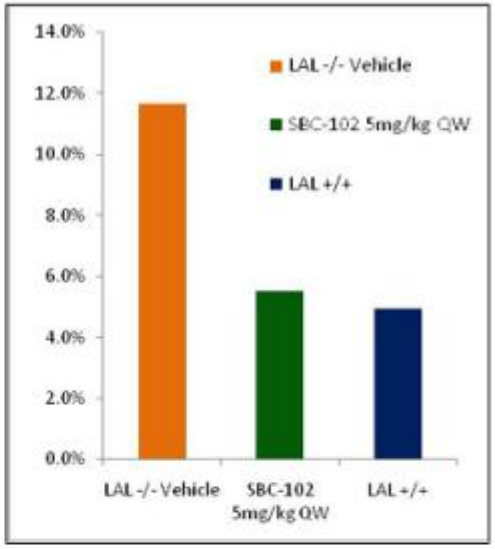
M Leavitt[1], AD Burt [2], W Hu[1], D Canty[1], M Gray[1], A Bray[1], A Harvey[1], CP Day[3], AG Quinn[1]

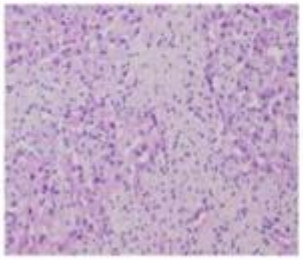
[1] Synageva BioPharma Corp., Lexington, MA; [2] Institute of Cellular Medicine & [3] Faculty of Medical Sciences Newcastle University, Newcastle upon Tyne, UK

Pharmacodynamic effects of SBC-102

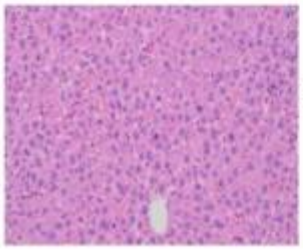
SBC-102 5mg/kg once weekly (4 doses)



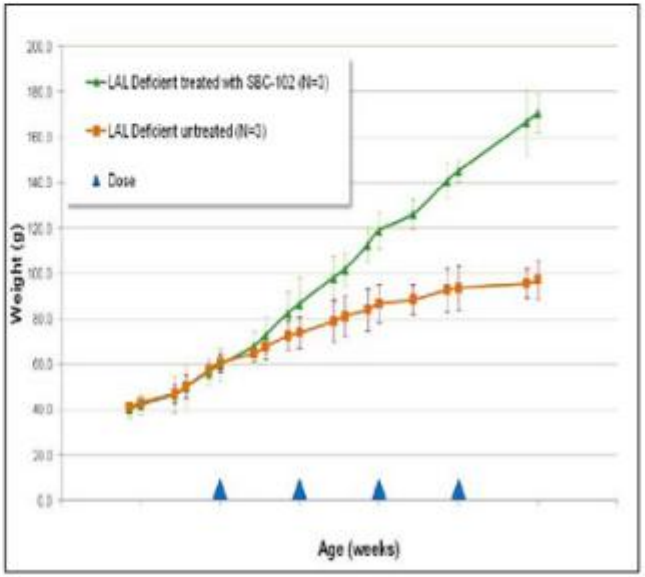




LAL
Deficient



SBC-102
Treated



Kupffer cell aggregates and accumulation

Foamy

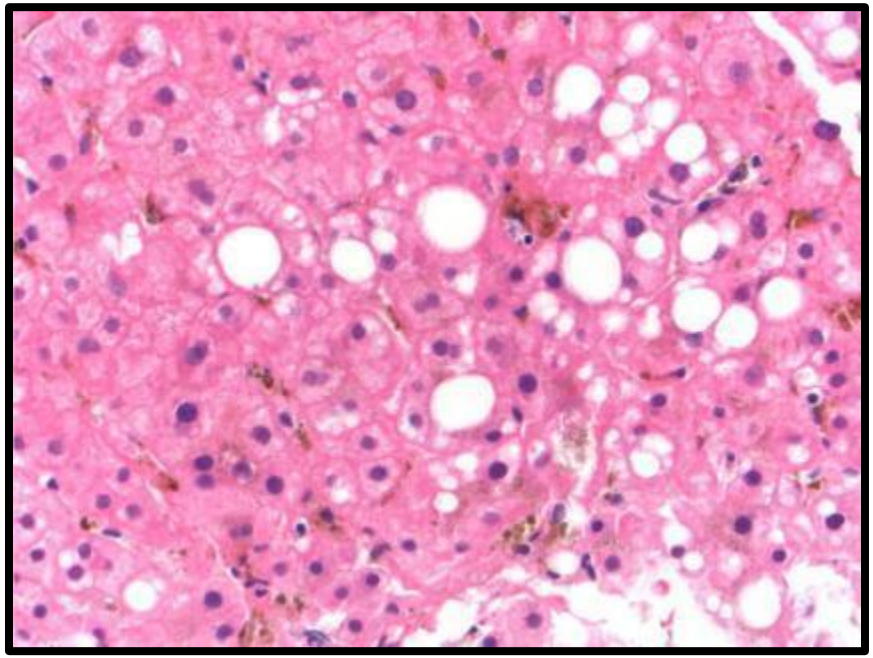
- CESD
- Cystinosis
- GM1 gangliosidosis type III
- Fabry disease
- Metachromatic leukodystrophy
- Niemann-Pick disease
- Atypical mycobacterial diseases

Non-foamy

- Ceroid-pigment
- Ceroid lipofuscinosis
- Other pigments (malaria, schistosmiasis, thorotrast, gold, iron)
- Gaucher disease
- Non-Langerhans cell histiocytosis
- Whipple disease

Case study: Brisbane A

- 36 year old female
- Normal BMI
- Physical exam normal
- Raised serum ferritin (3340 ug/L)
- Transferrin saturation normal (29%)
- HFE: no mutations (C282Y, H63D, S65S)
- Iron
  - HIC 96 umol/g (NR 5-35)
  - HII 2.1 (N < 1.1)
- No thalassaemia, anaemia, PCT, CLD



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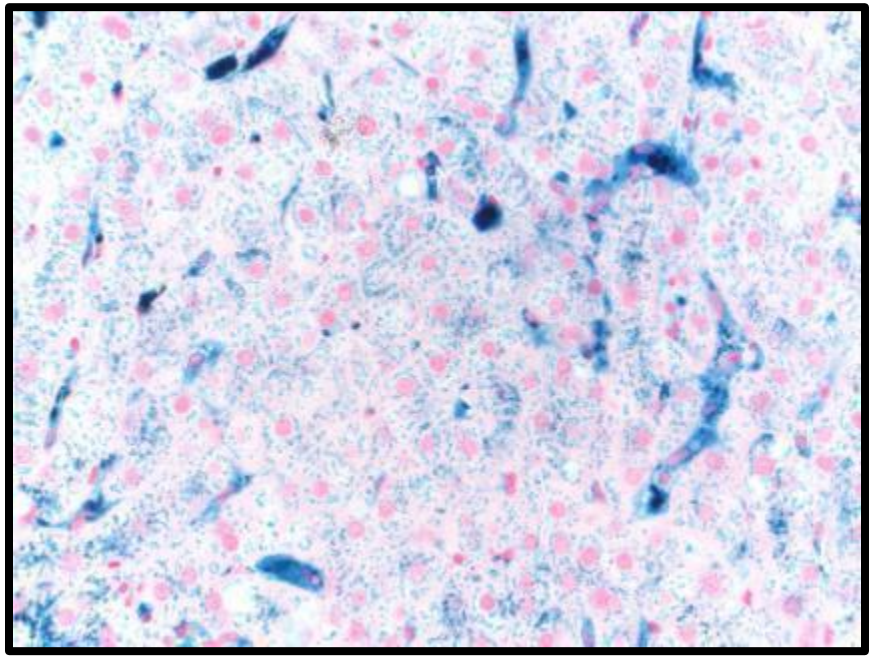

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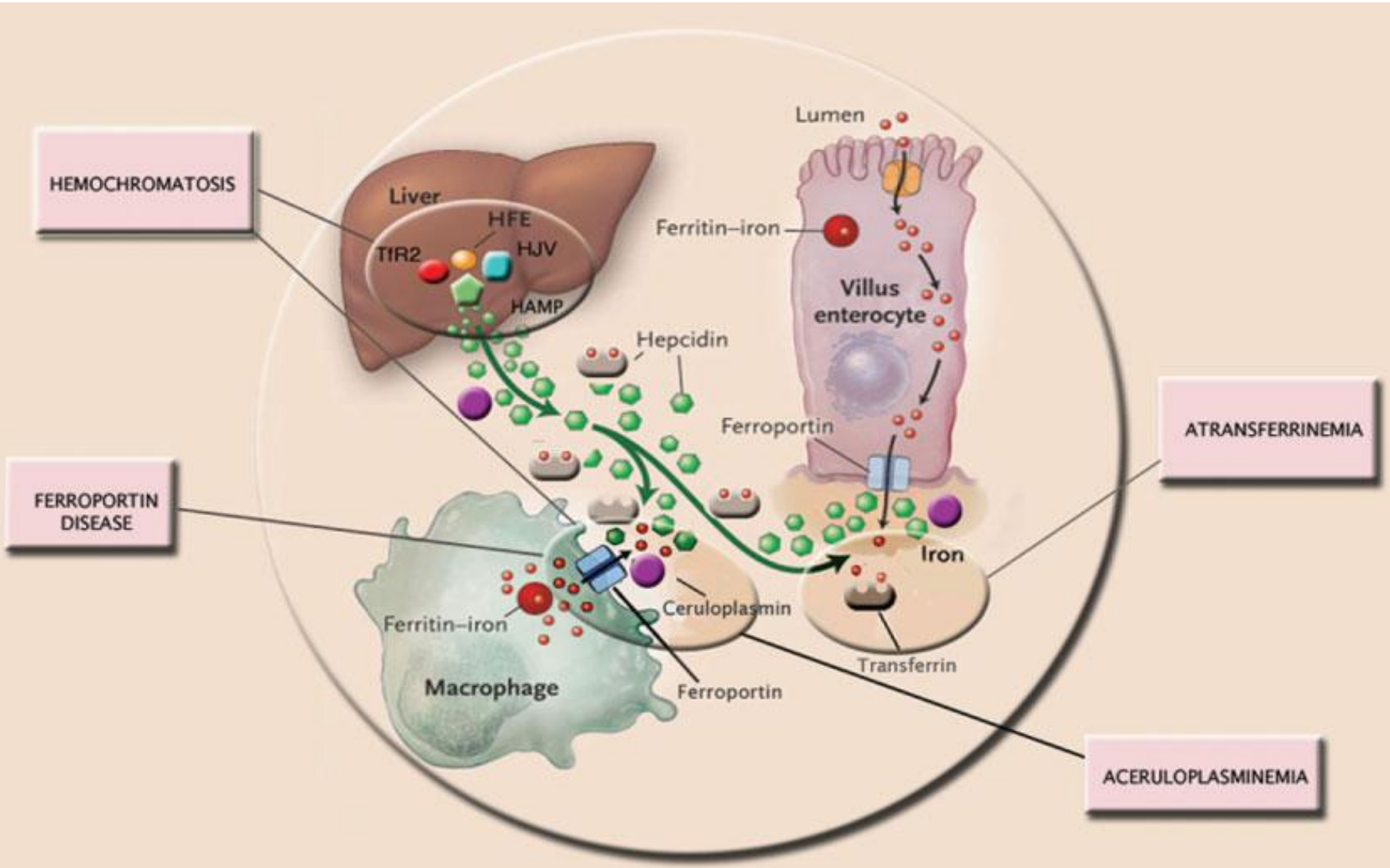
- Ferroportin gene (*SLC40A1*) coding region & splice sites sequenced
- Alanine to aspartic acid substitution
  - A77D
  - inactivating

Ferroportin



Pietrangelo J Hepatol 2010

Ferroportin disease

Classical

Inactivating
Macrophage accumulation

- A77D
- D157G
- V162del
- others

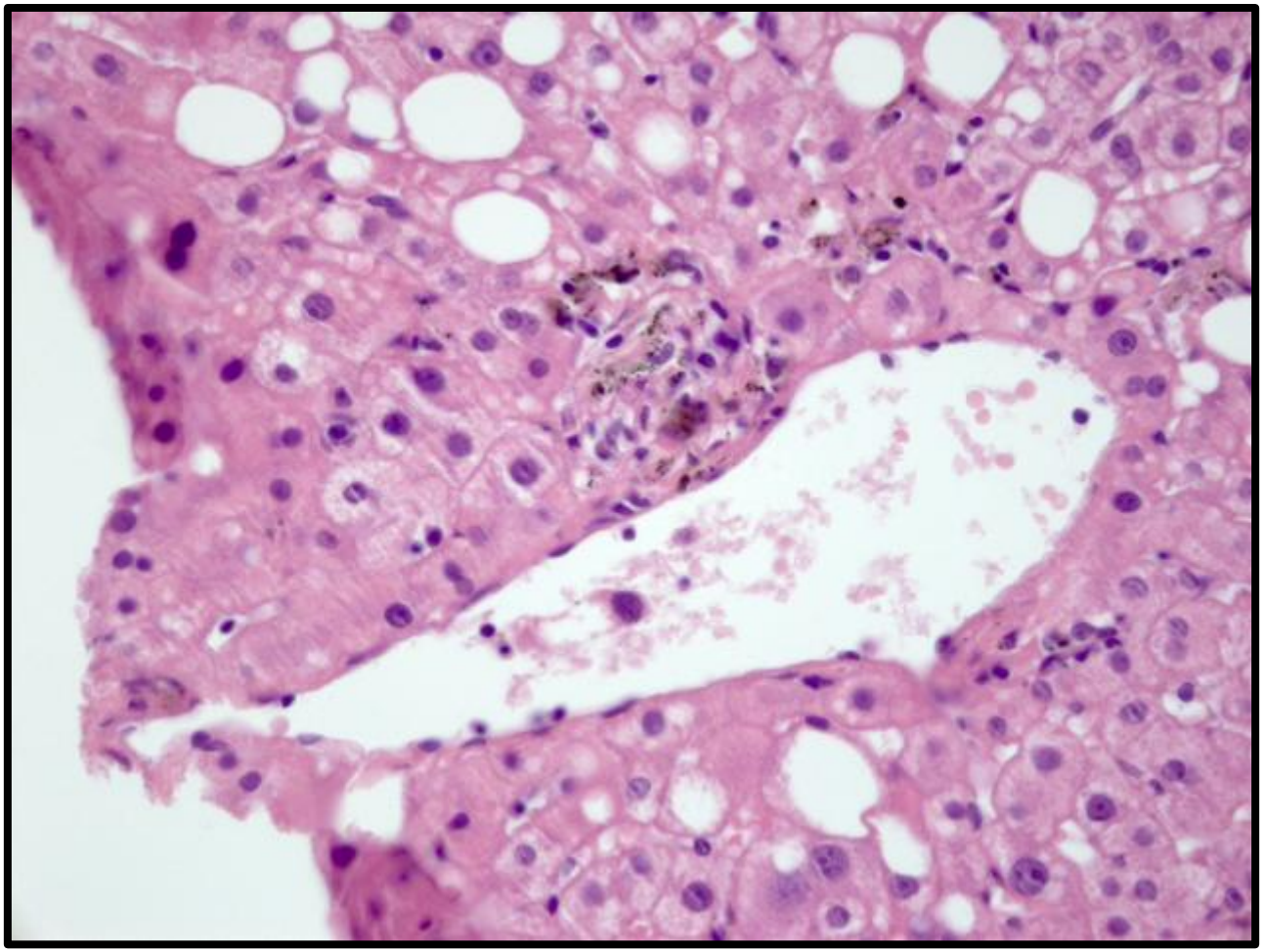
Non-classical

Activating

Distribution like genetic haemochromatosis

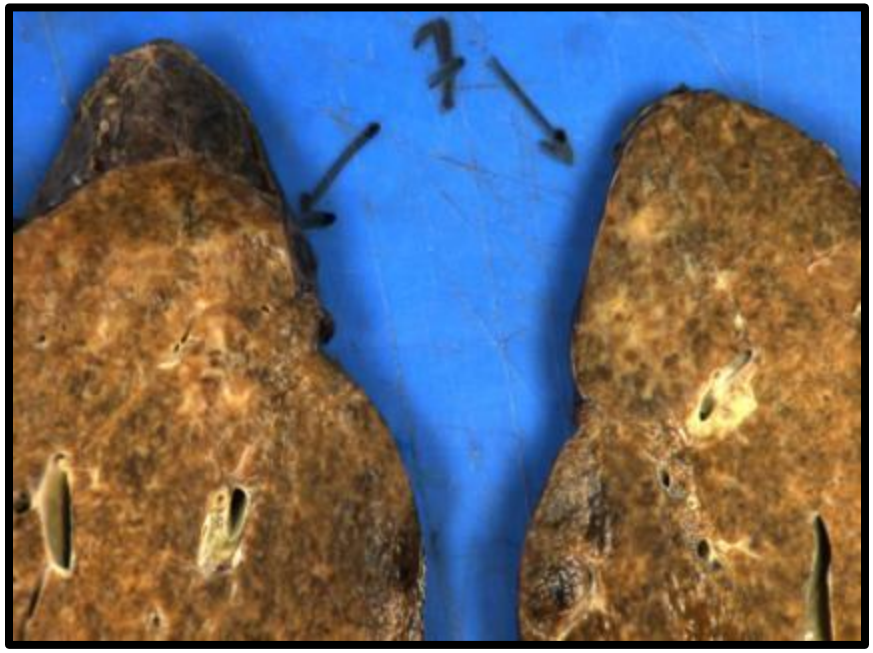
- N144H
- Y64N
- C326Y/S
- others

Cologne B



Case study: Groningen A

- Male 30yrs
- 2007: diagnosis of cirrhosis elsewhere
  - Oesophageal varices splenomegaly
  - Years of alcohol and cocaine abuse
- 2008: admission for OLT
  - jaundice, portal gastropathy, obesity (BMI 37), DM II, HIV/HBV/HCV neg
  - AP 200, LDH 392, ALT 68, Bil 550, albumin 24, GGT 22
  - CT: non-homogenous liver but no focal lesion



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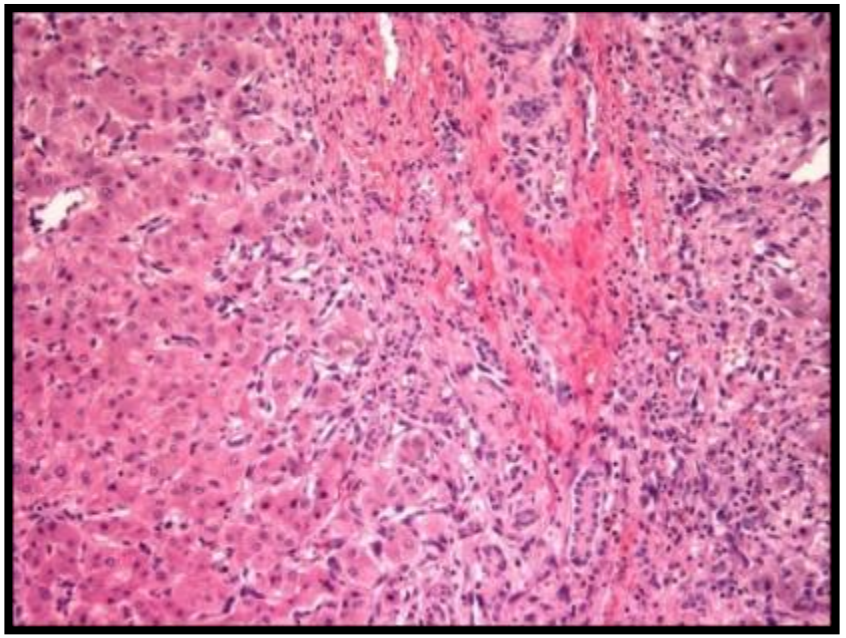

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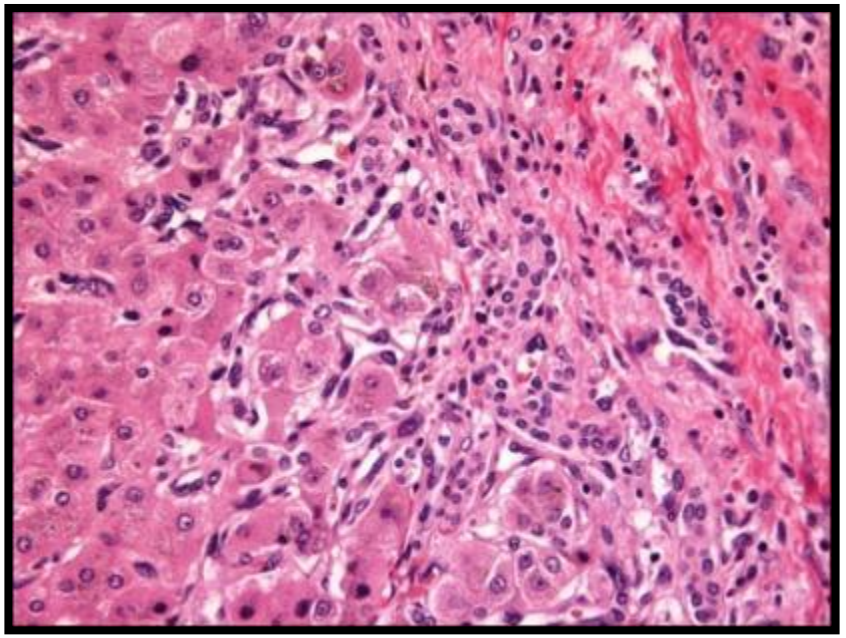

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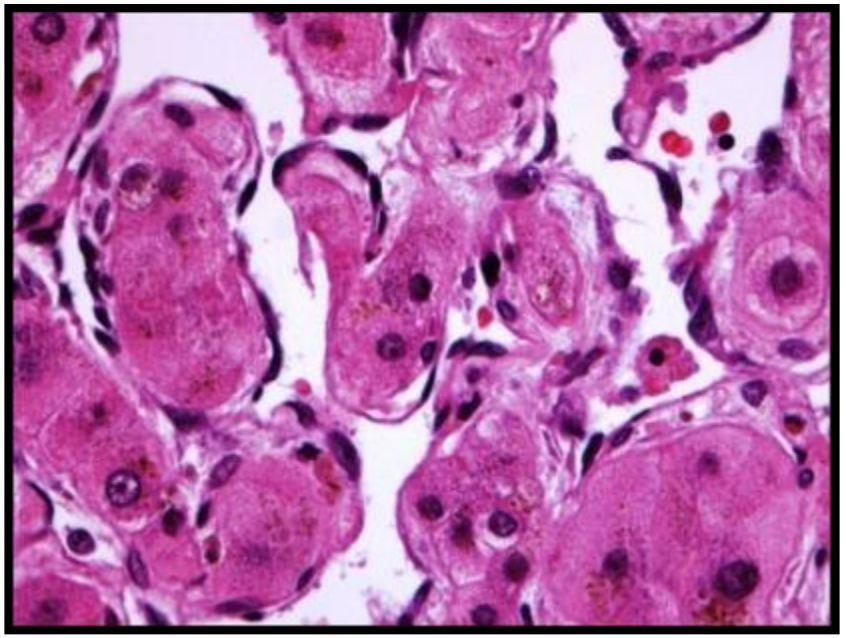

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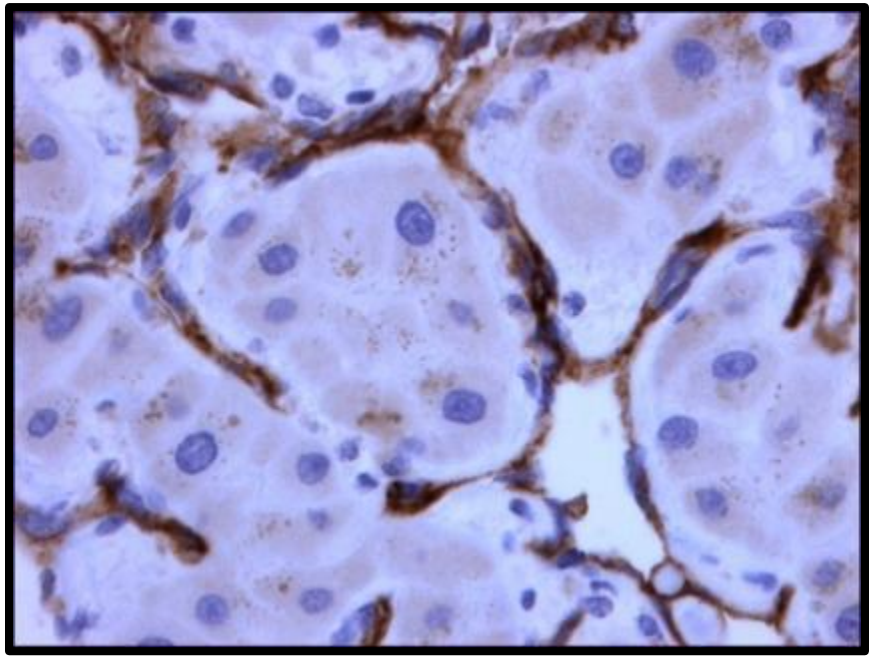

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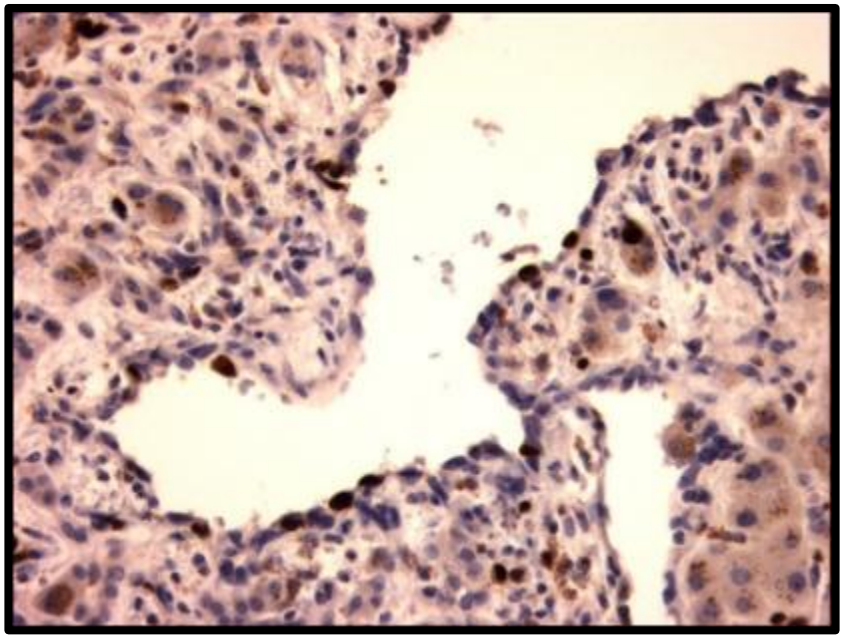
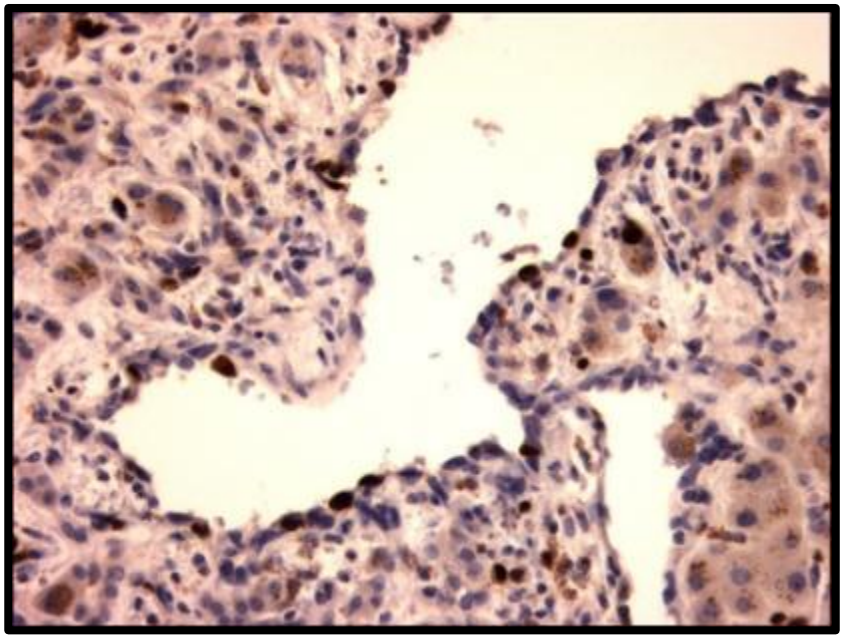


Groningen A: angiosarcoma

- Rare; < 1% primary malignant liver tumors
- About 25 cases/yr USA
- M:F = 3:1; Age: 50-60 yr
- Aetiology:
  - Carcinogenic agents: thorotrast, pvc, arsenic, anabolic steroids, cyclophosphamide
- Symptoms: abdominal pain, weight loss, weakness



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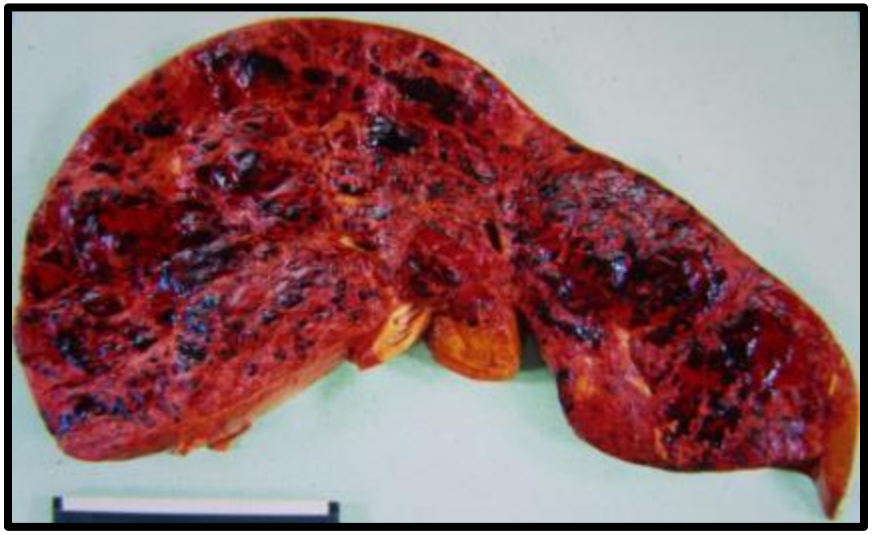
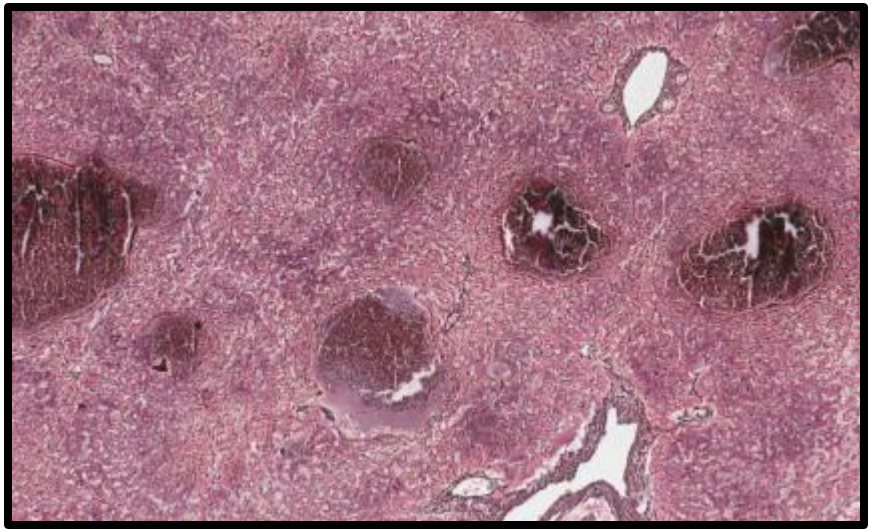
- 4 days post OLT: ReTx due to PNF
- Complicated post LT course: infections
- 4 months post OLT: lung and bone-marrow metastasis (BM biopsy proven)

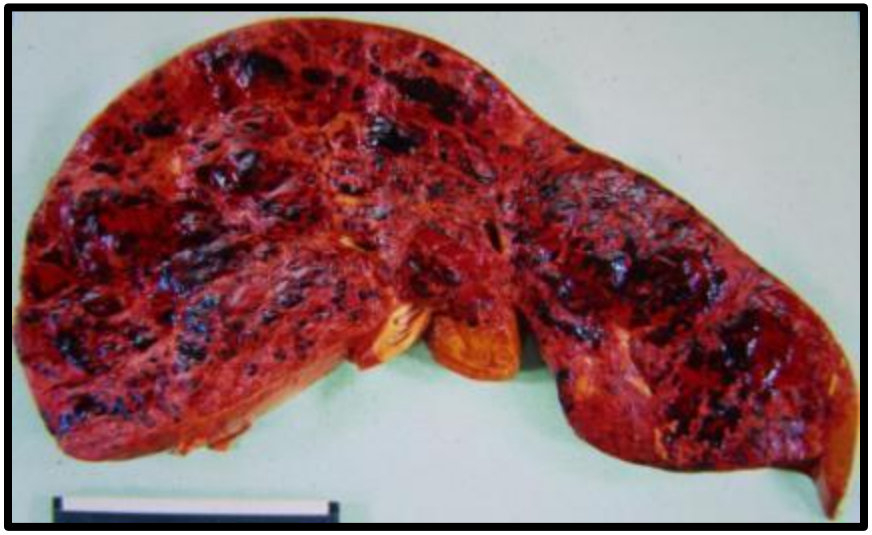
† 9 months post OLT

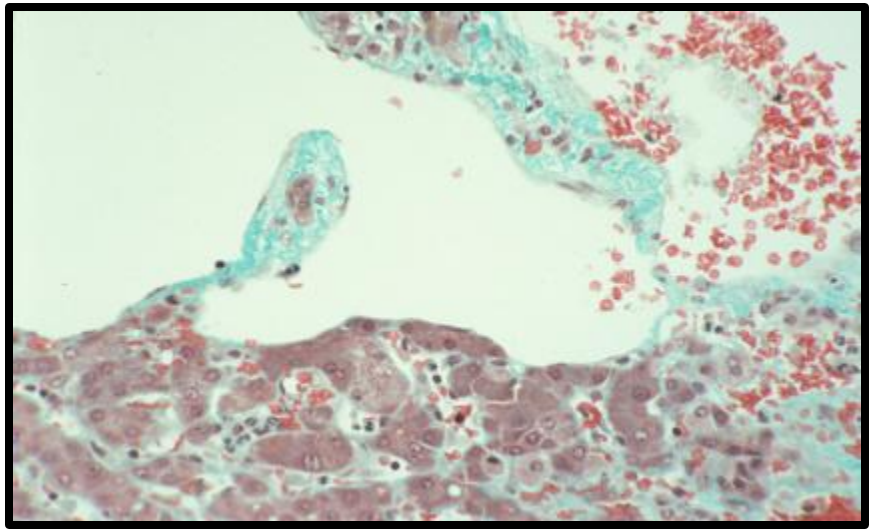
Halifax A

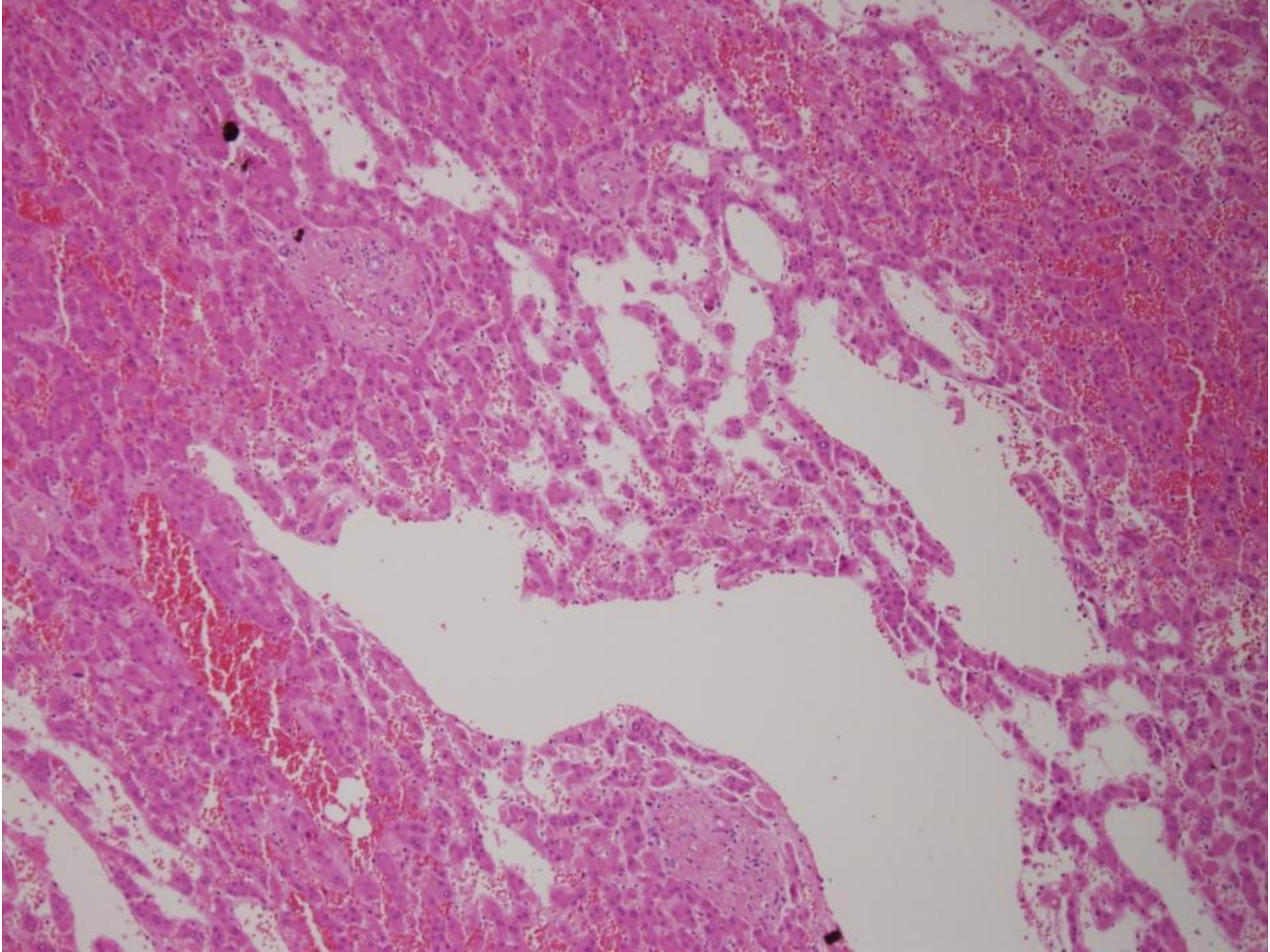




Halifax A: peliosis hepatis

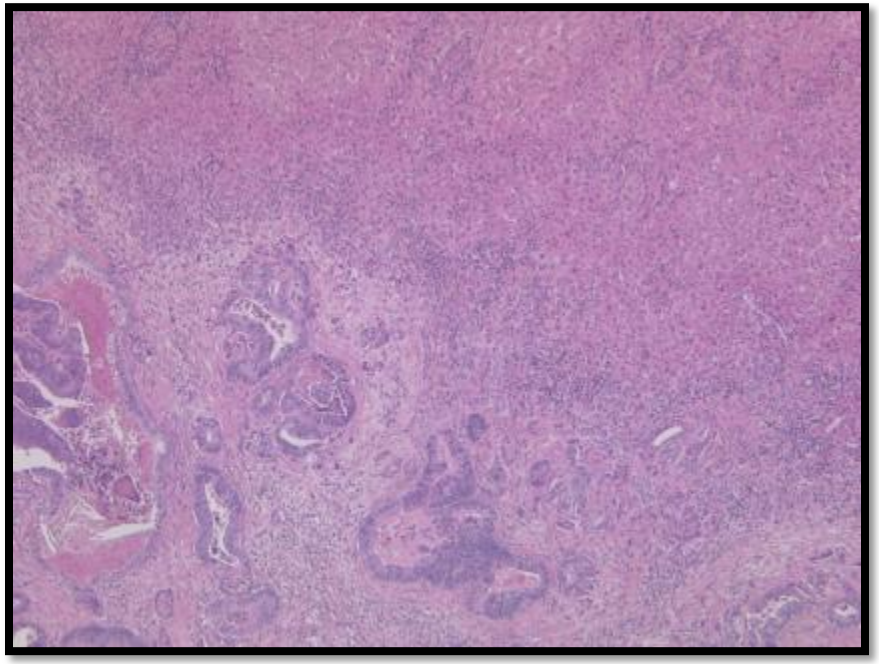






Case study: Newcastle B

- 65 year old male
- T3N1 upper rectal carcinoma with liver metastases
- Pre-operative chemo-radiotherapy (including oxaliplatin)
- AP resection and right hemihepatectomy



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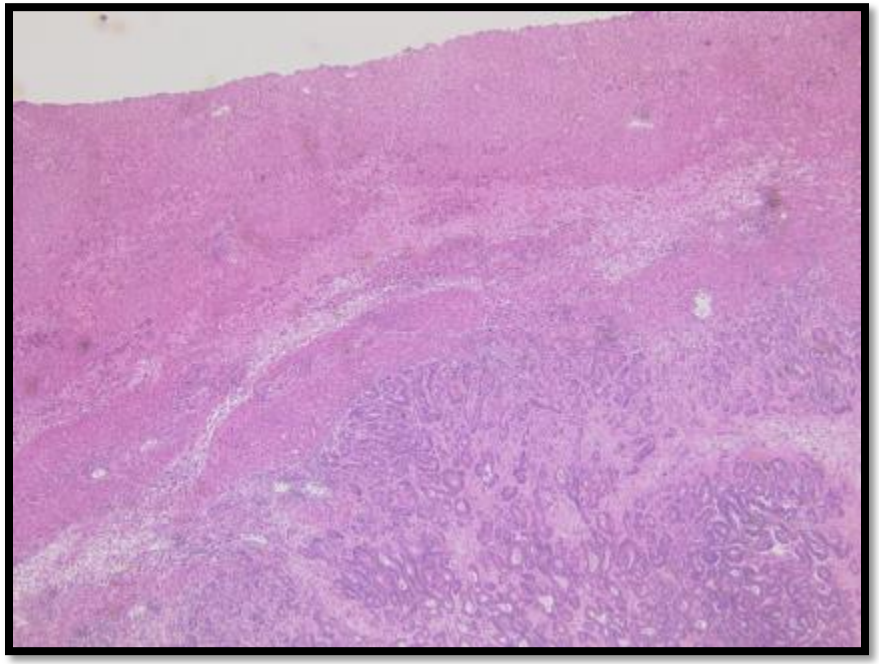

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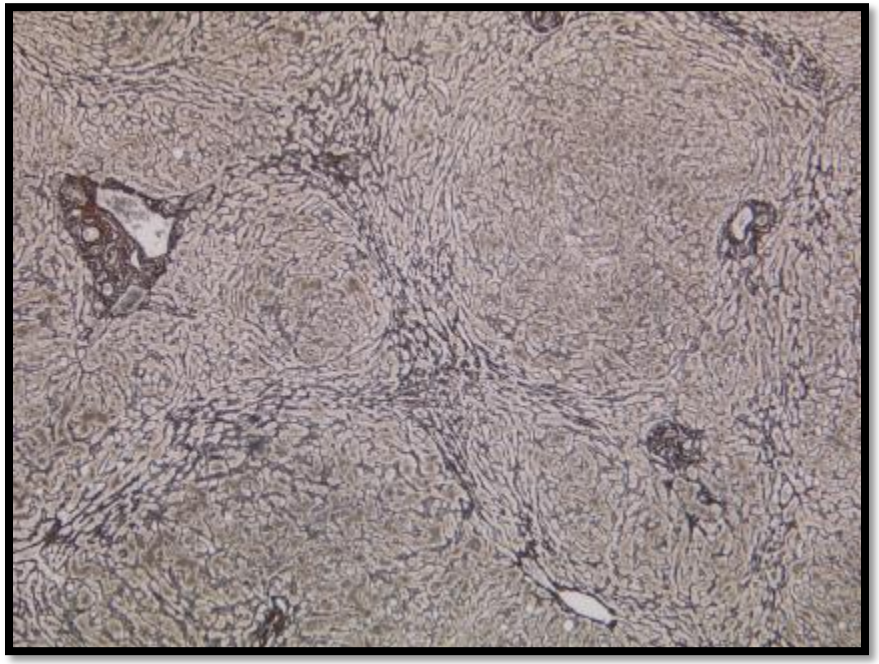

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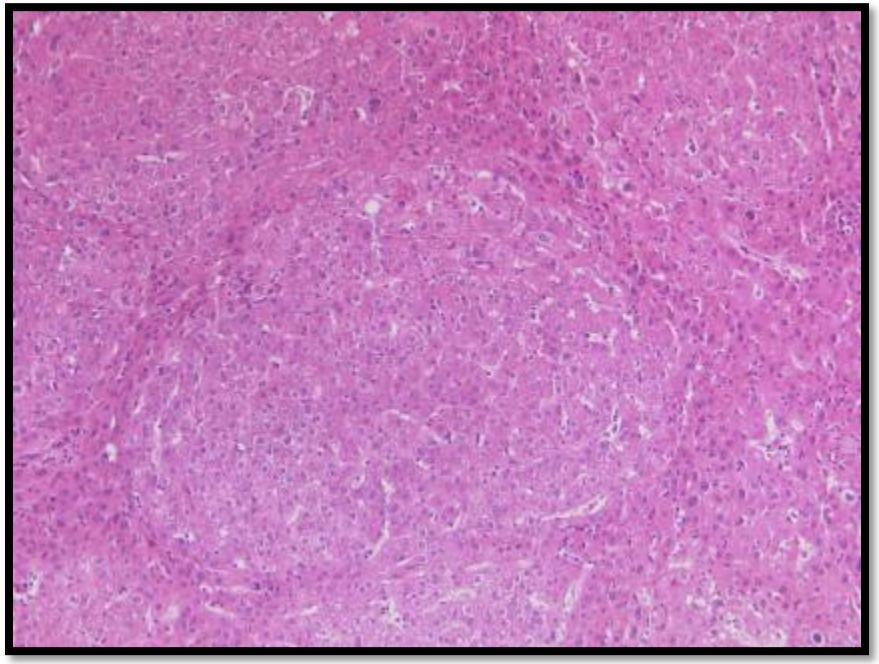
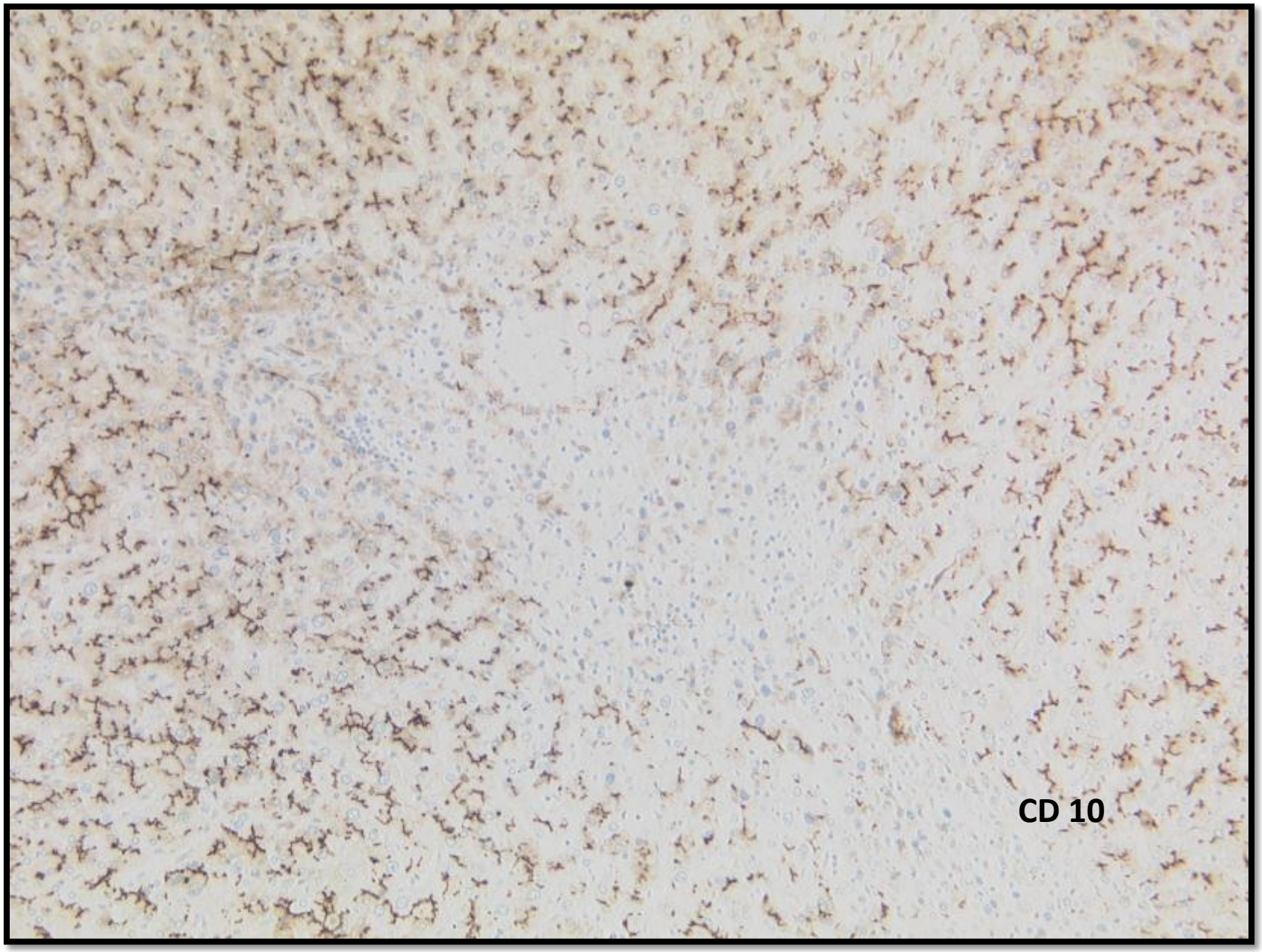
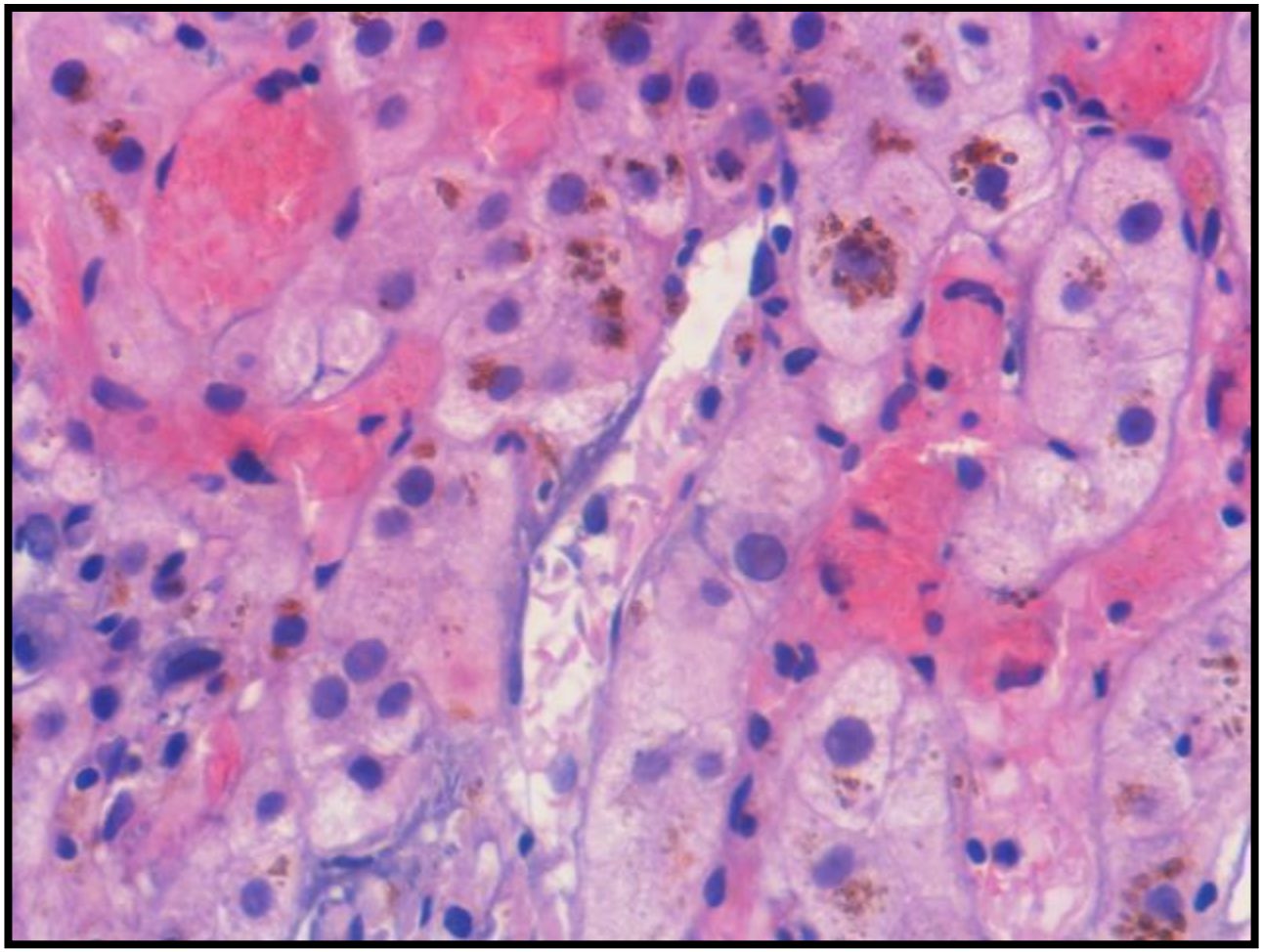



CD 10

Athens B



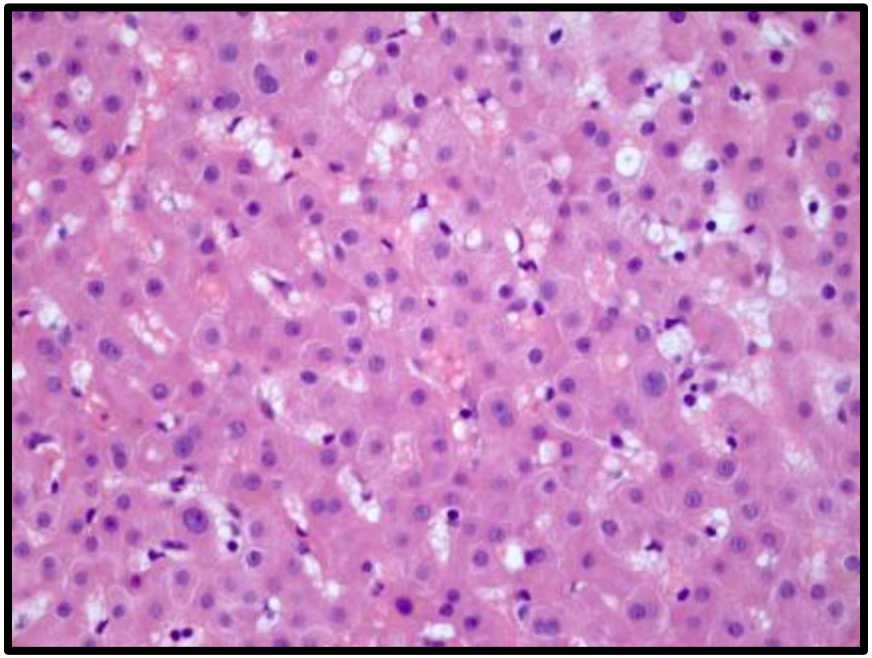
Hepatic histological findings in SCD

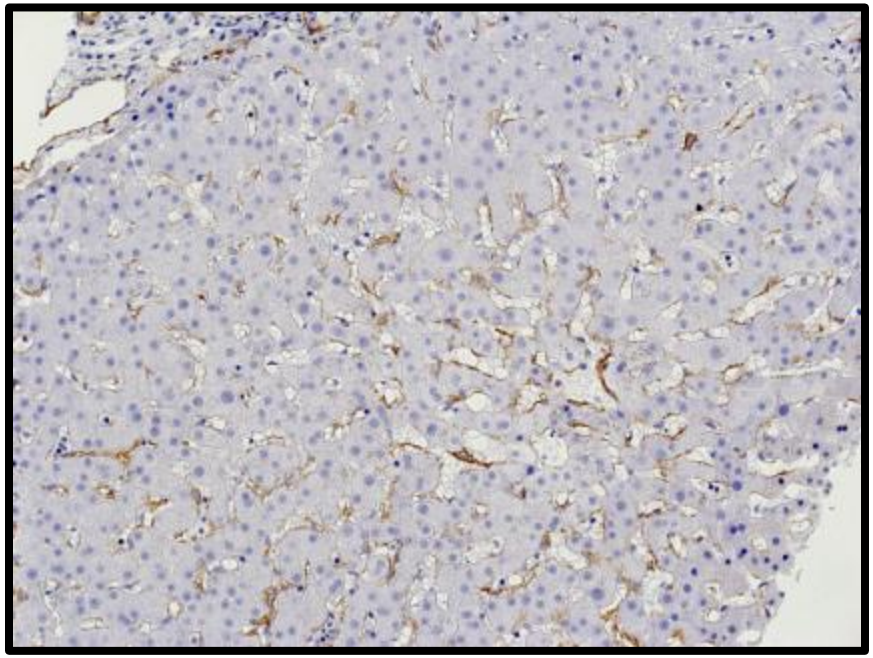
- Severe fibrosis/cirrhosis (16%-29%)
  - associated with the presence of
    viral infection (20%-50% HCV or HBV)
    markers of autoimmune disease

  - due to SCD alone

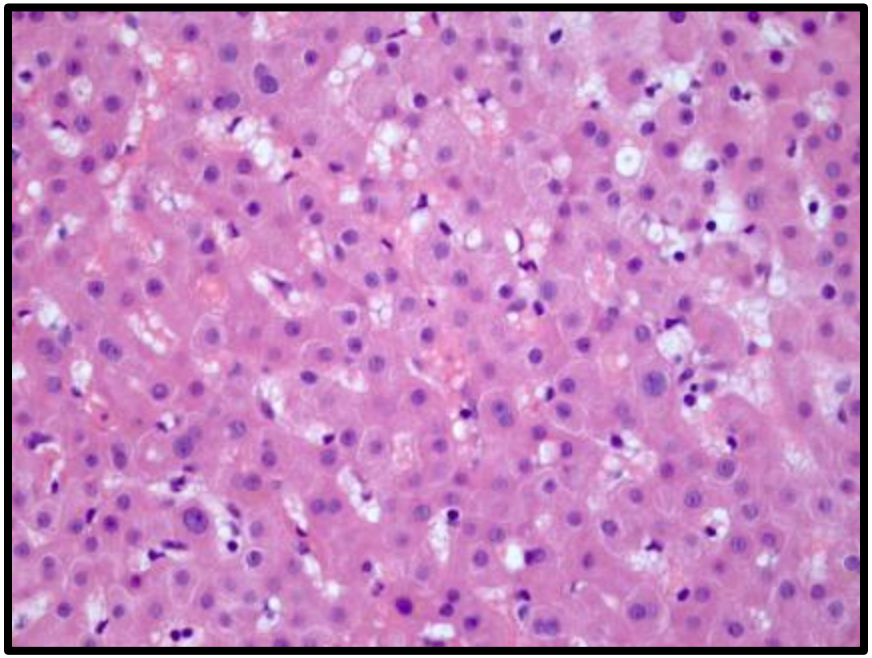
- Secondary iron overload
- Erythrophagocytosis
- Extramedullary haemopoiesis
- NRH
- Cholangiopathy
- Sickle cell intrahepatic cholestasis (very rare)

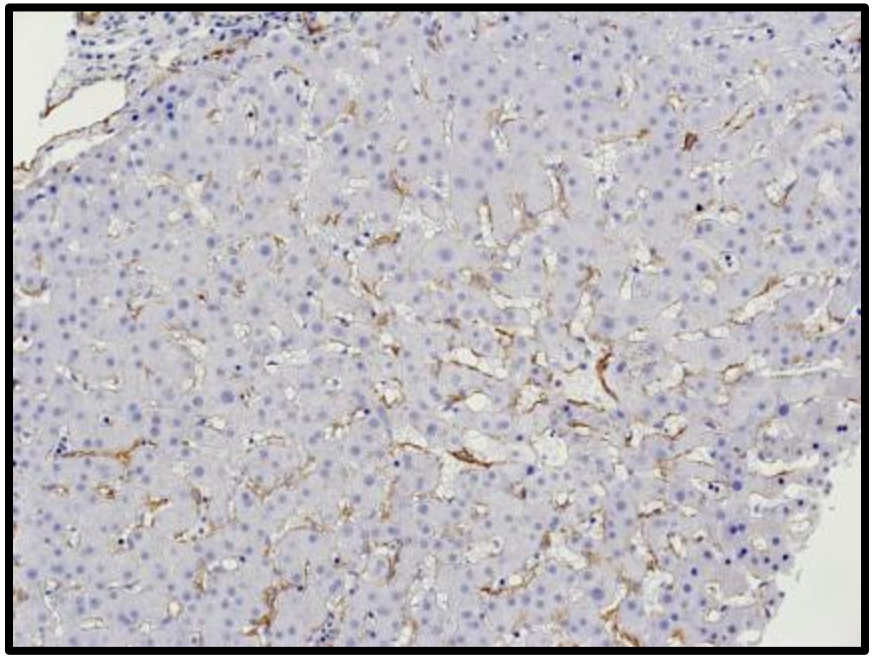
Cologne C



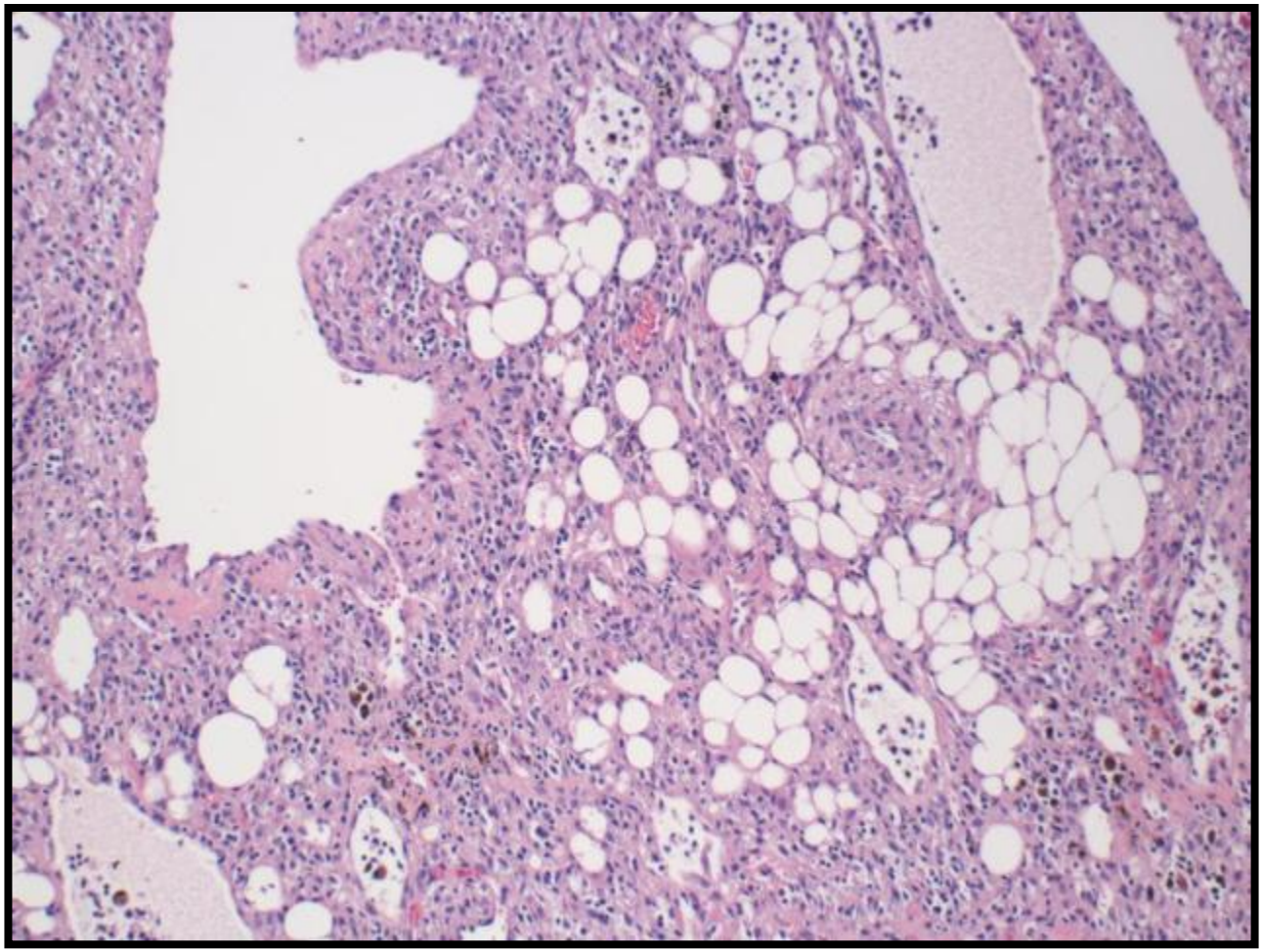


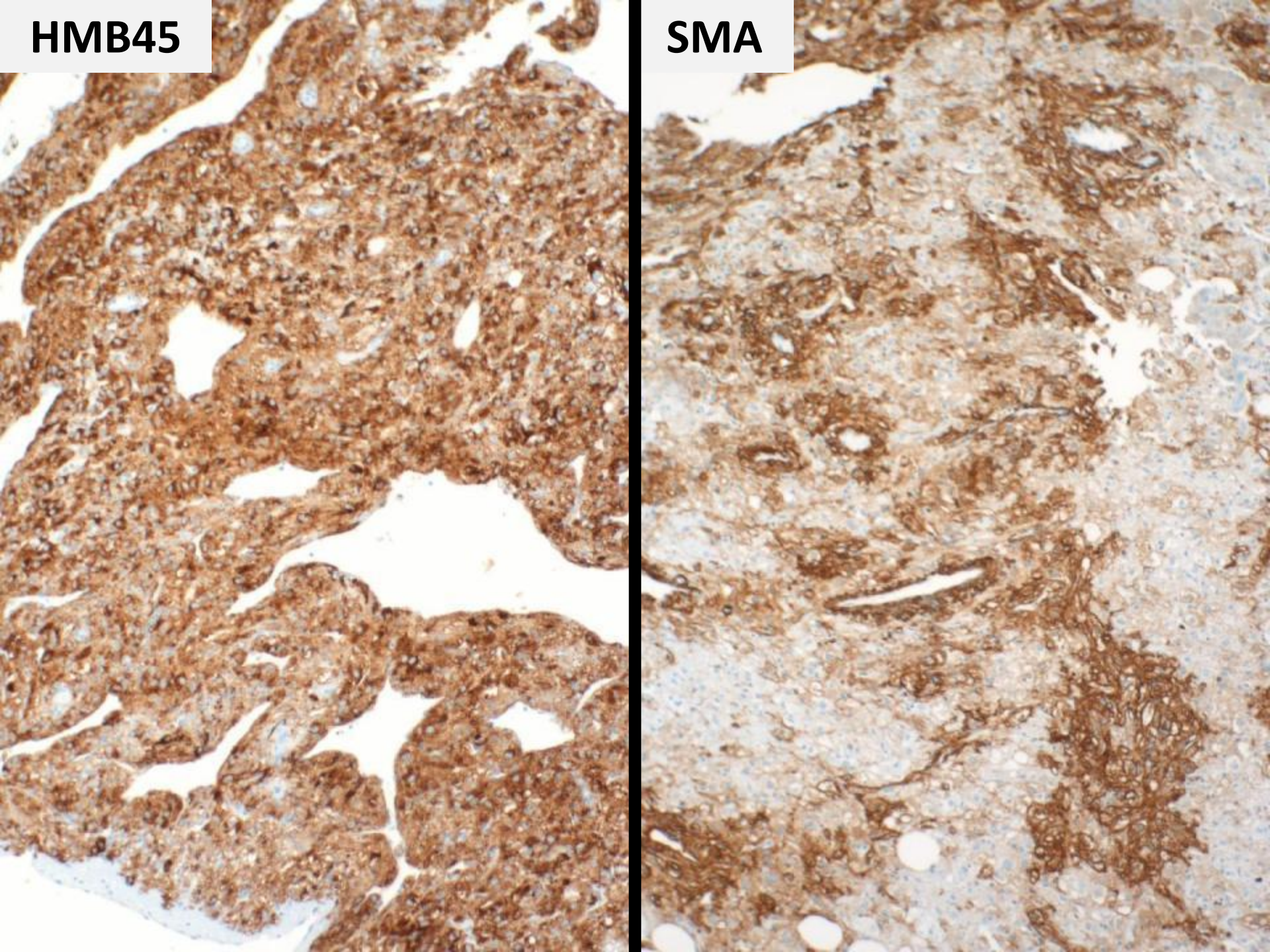
Hypervitaminosis A

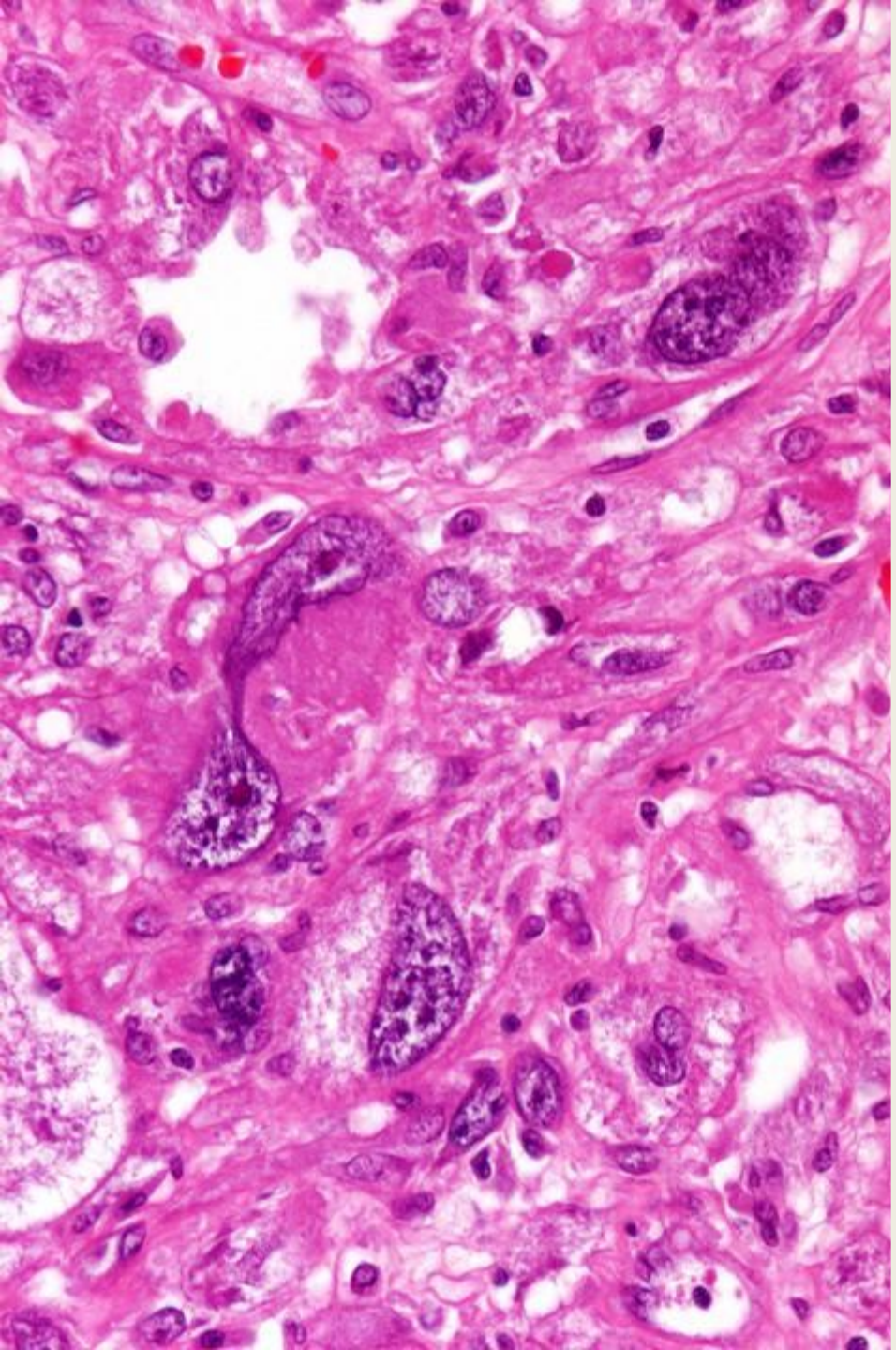
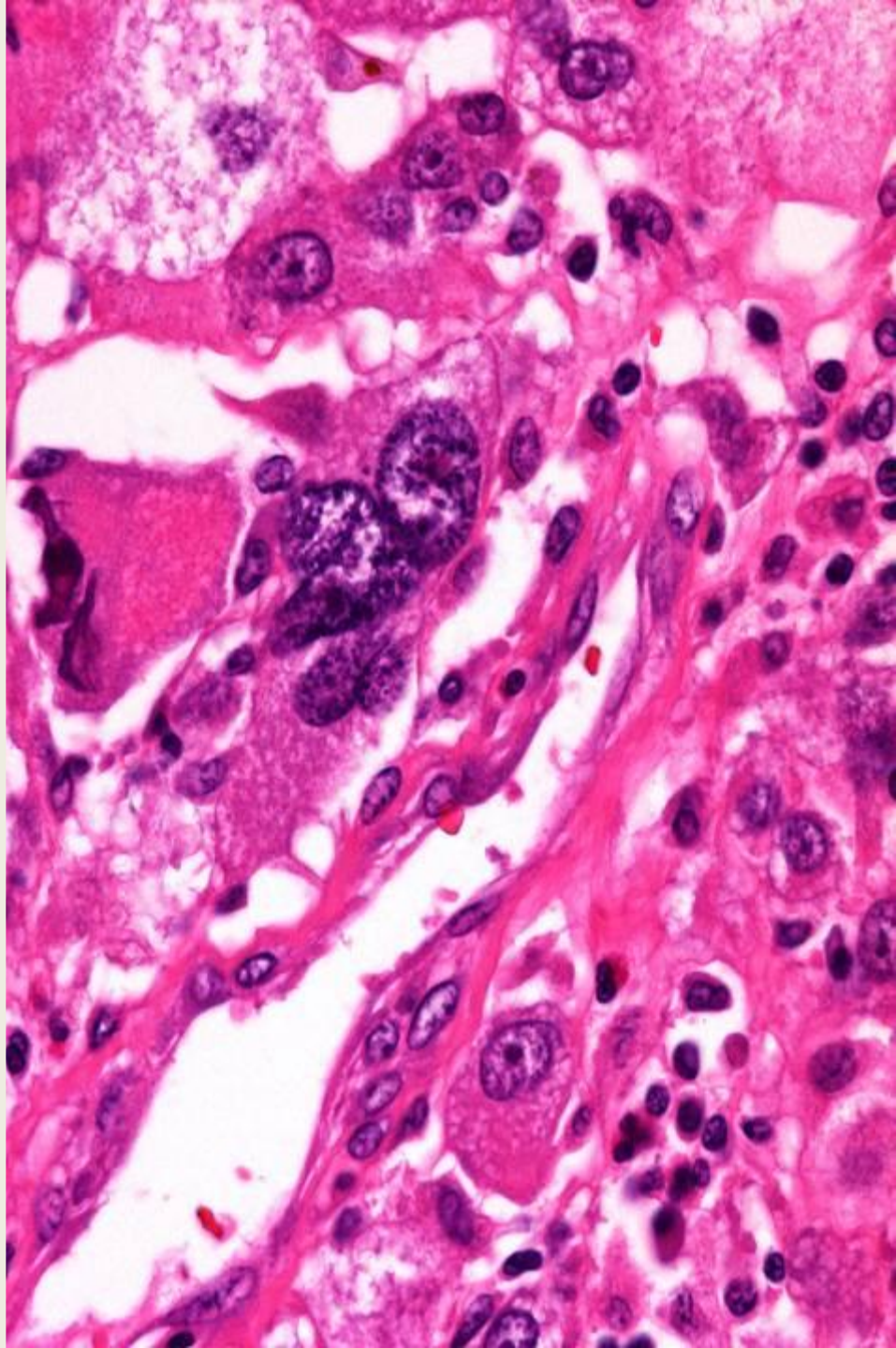




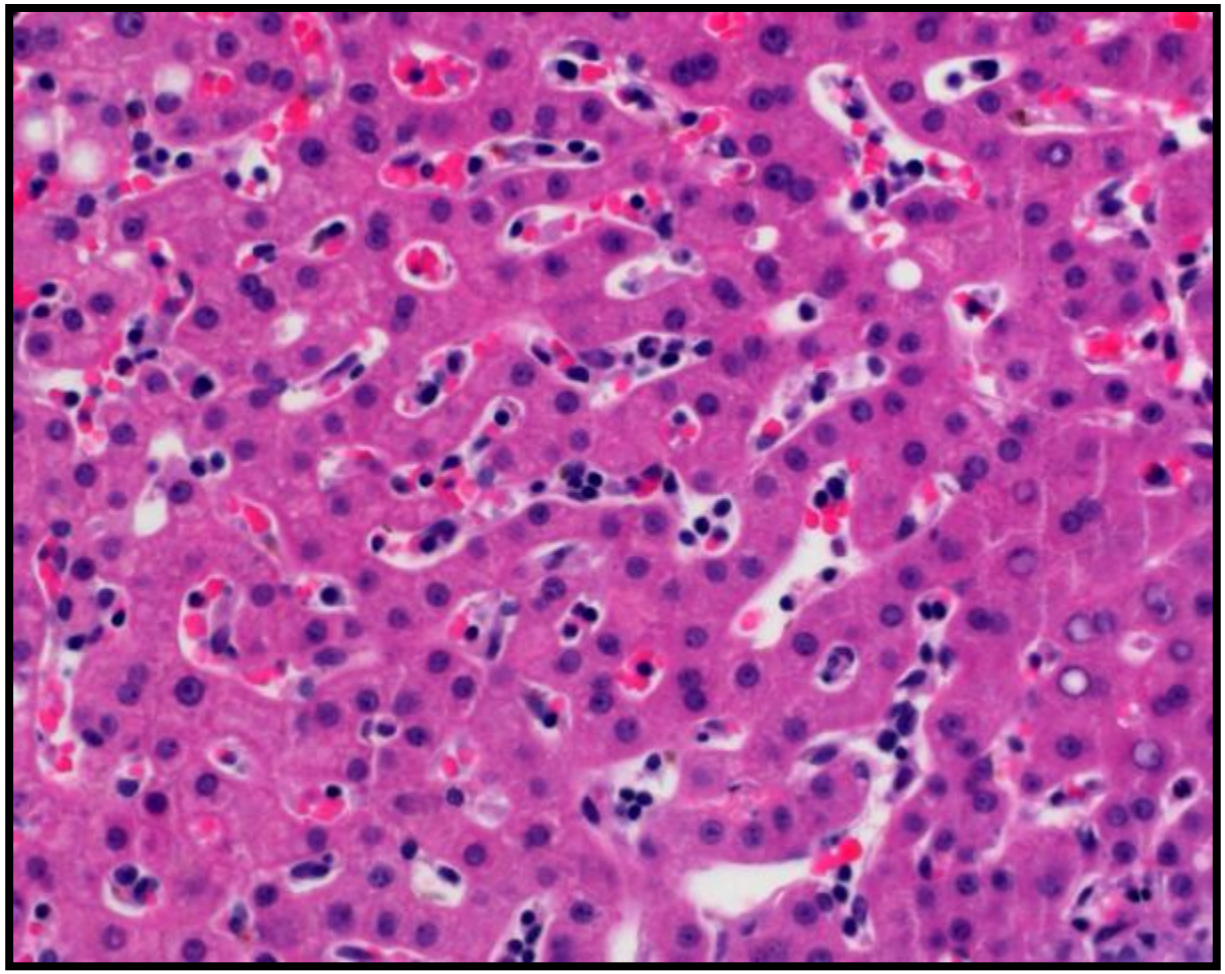
Washington C



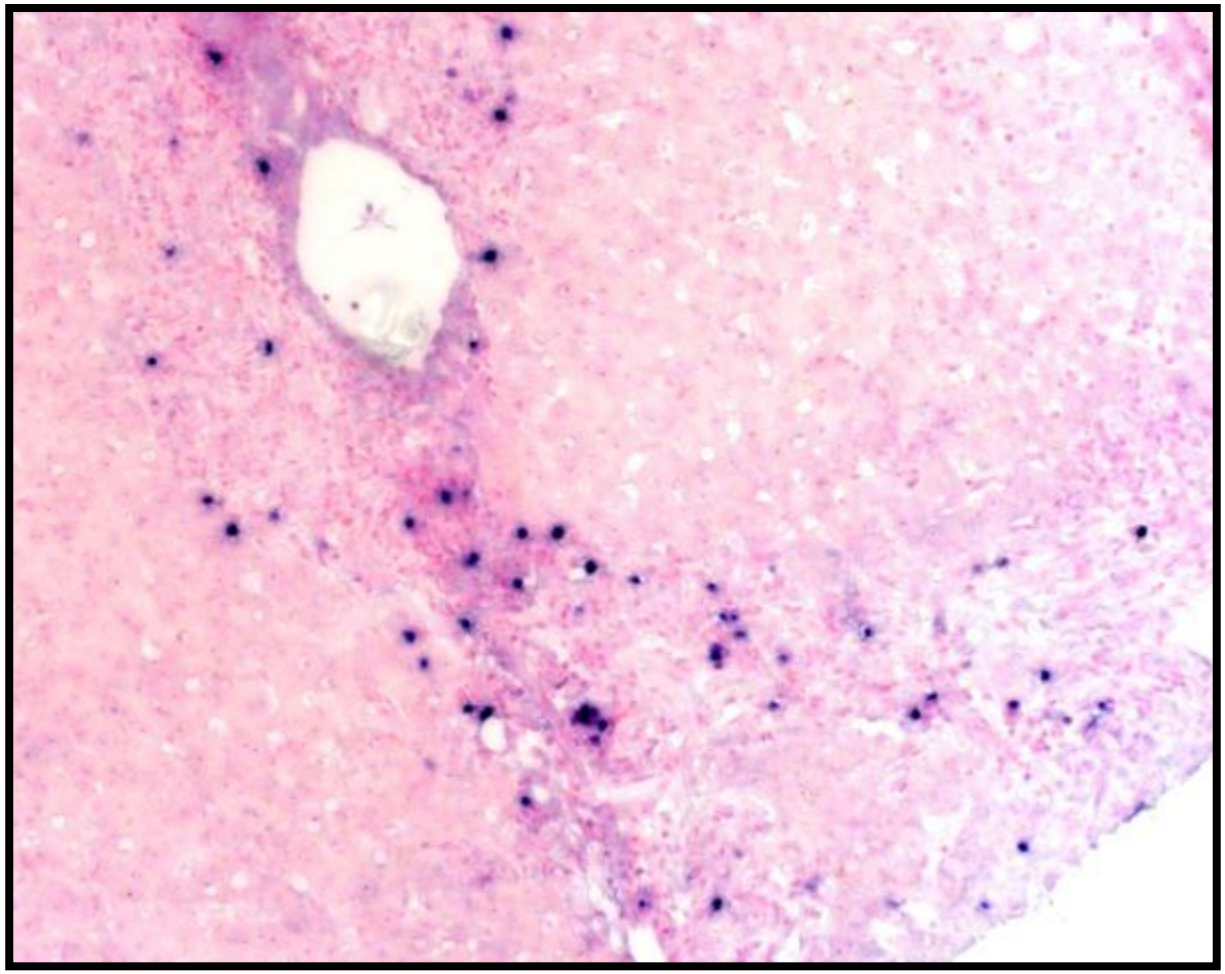

HMB45
SMA

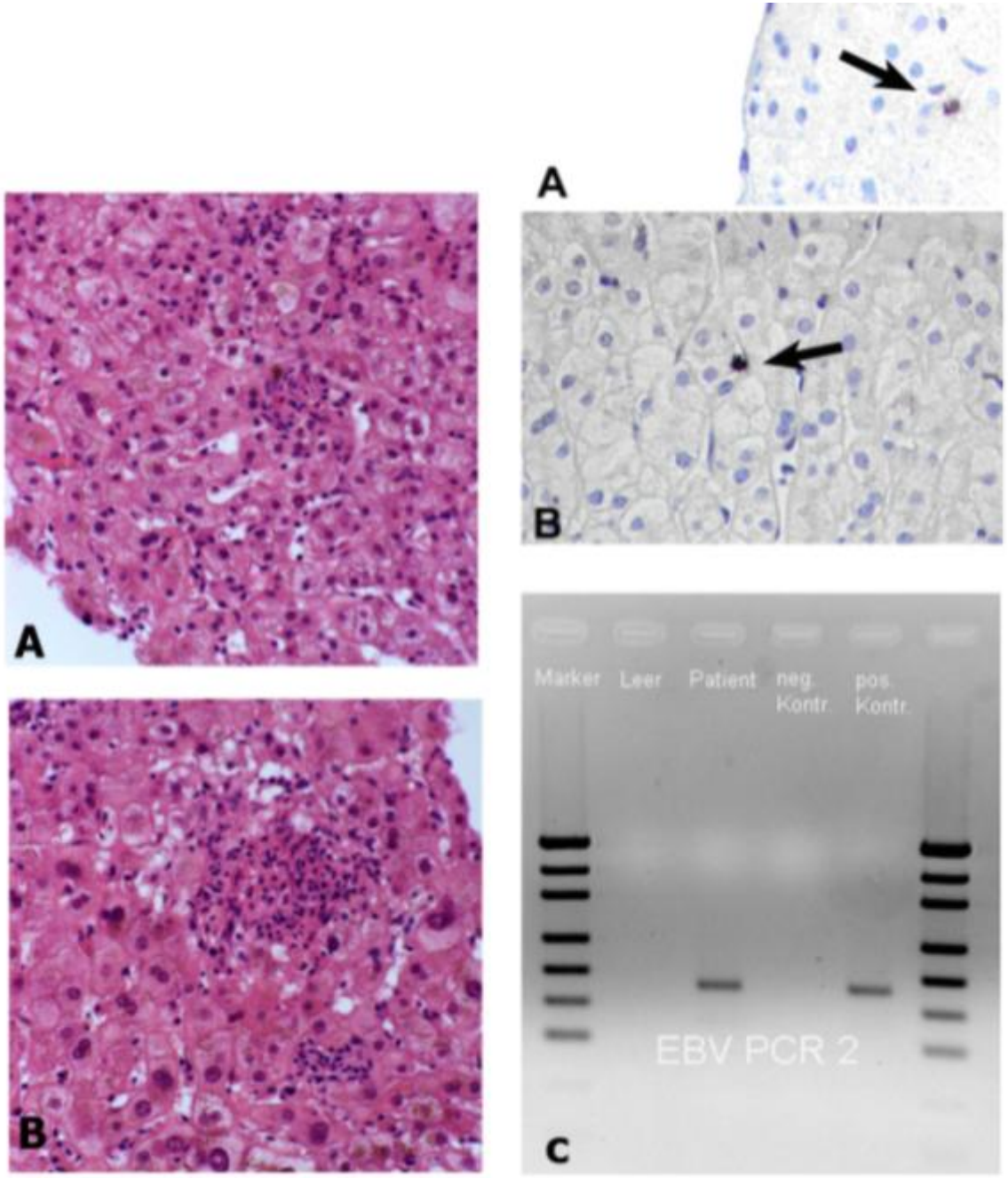



Basel B



Basel B: EBV hepatitis

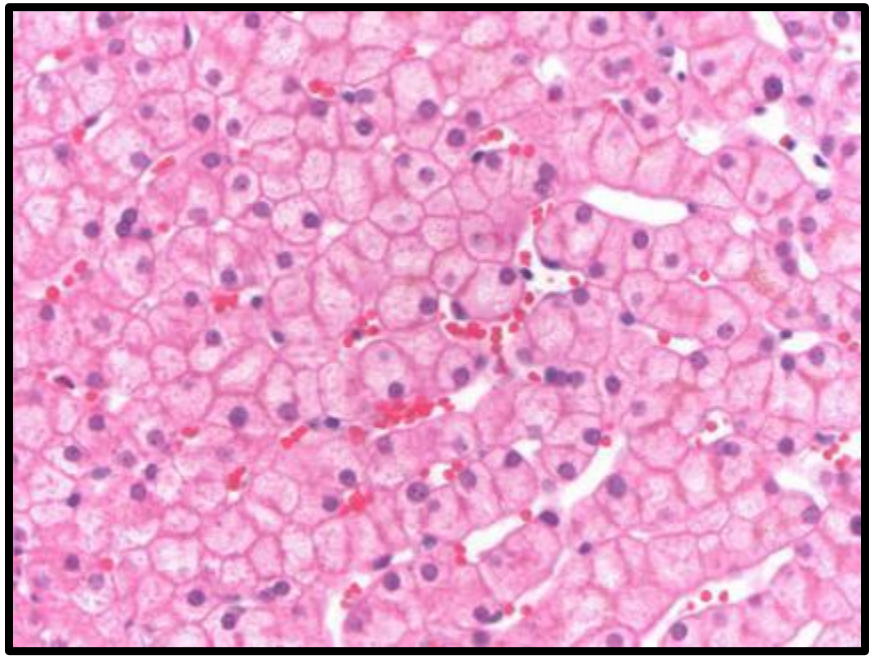




Drebber et al. J Hepatology 2006

Case study: Brisbane B

- 22 year old male
- Athlete; competitive swimmer
- Raised ALT > 100 persistent
- All serology negative
- Clinically well; no signs of CLD



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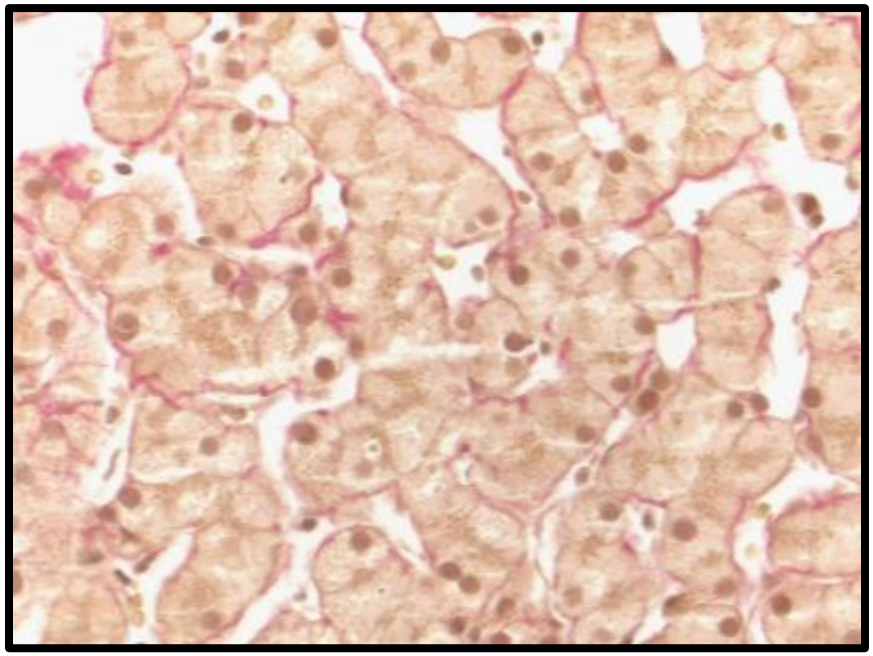

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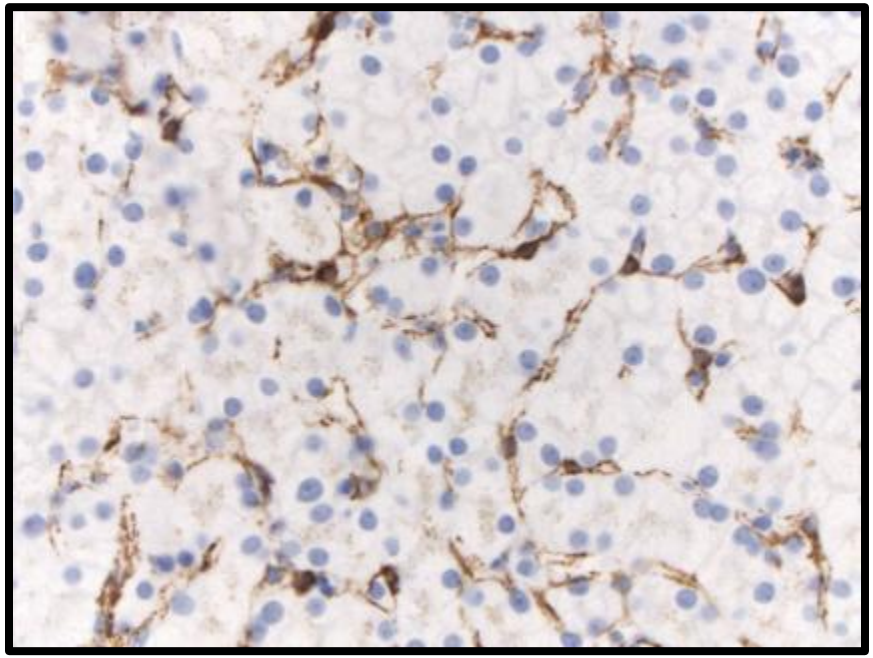
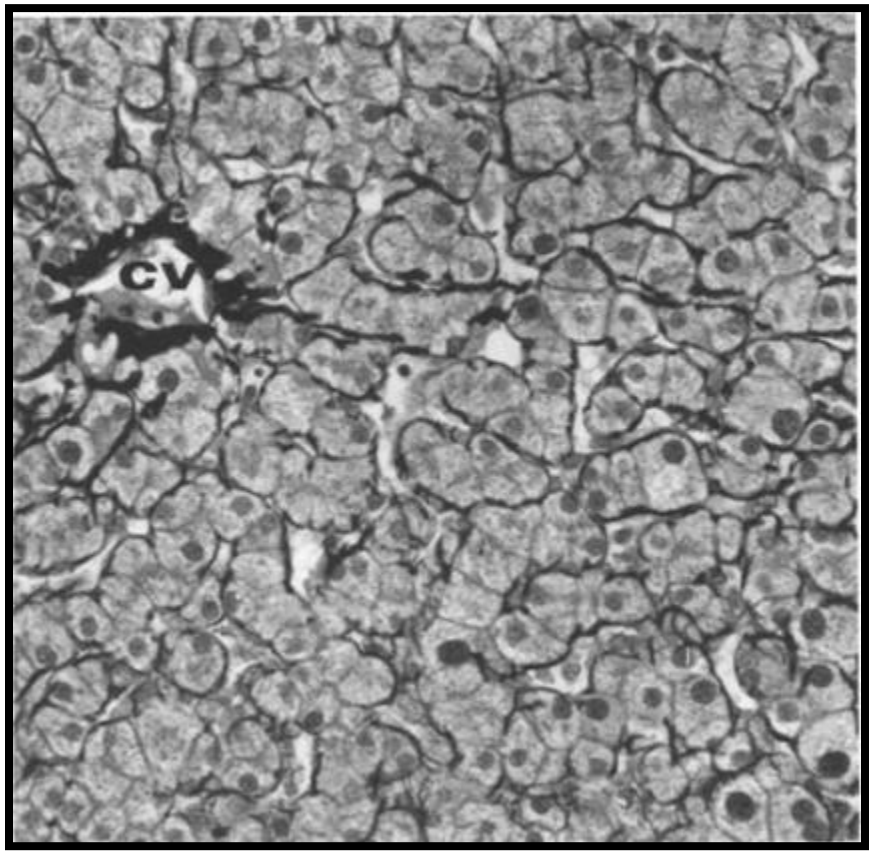


Diffuse sinusoidal “micro”fibrosis

- ITP (Lafon Virchows Arch A 1987)
  - platelet destruction and KC activation?
- Myelofibrosis (Degott Liver 1985; 5:276 -- Bordeaux)
  - PDGF elaboration? (had NRH)
- Post transplant: paediatric
- Diabetic patients – subsinusoidal collagen (I, II IV), stellate cell activation and BM (Latry Hum Pathol 1985; 18:775)



Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
- Storage disorders
- Vascular
- Neoplastic
- Miscellaneous

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
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- Atypical mycobacteria
- Malaria (pigment)
- Schistosomiasis (pigment)
- Leishmaniasis
- Others

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
- Storage disorders
- Vascular
- Neoplastic
- Miscellaneous
- Amyloid
- Light chain disease
- Diffuse sinusoidal fibrosis

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
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- Miscellaneous

- CESD
- Cystinosis
- GM1 gangliosidosis type III
- Fabry disease
- Metachromatic leukodystrophy
- Niemann-Pick disease
- Hypervitaminosis A

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
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- Sinusoidal obstruction syndrome and NRH
- Peliosis hepatis
- Microvascular flow abnormalities: sickle cell anaemia etc

Simple classification of sinusoidal lesions

- Infective
- Space of Disse obliteration
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- Vascular
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- Miscellaneous

- Angiosarcoma
- Epithelioid haemangioendothelioma
- ? Angiomyolipoma
- Sarcomas
- Non-Langerhans histiocytosis
- Lymphoproliferative disease: Tγδ lymphoma; EBV driven

Gnomes in 2011: good news from the football field