Chronic Biliary Disease

Royal College of Pathologists -
Liver Biopsy interpretation
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Overview

- Clinical presentations
- Cases which illustrate:
  - Common disorders
  - Rare disorders
  - Non-biliary disorders presenting with cholestatic liver tests
- Summary

Clinical Presentations

- History
  - Pain
  - Jaundice
  - Abnormal liver biochemistry
  - Weight loss
  - Associated symptoms

Clinical Presentations

- Examination
  - Tenderness
  - Hepatomegaly
  - Distended gallbladder
  - Cachexia

Clinical Presentations

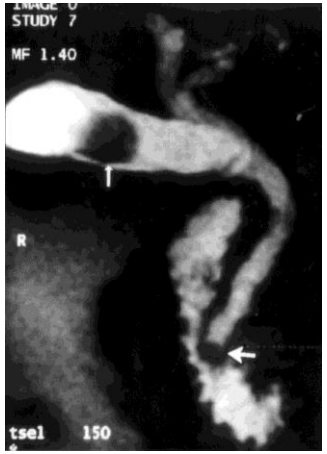
- Investigations
  - Blood tests
  - Imaging
  - Histopathology

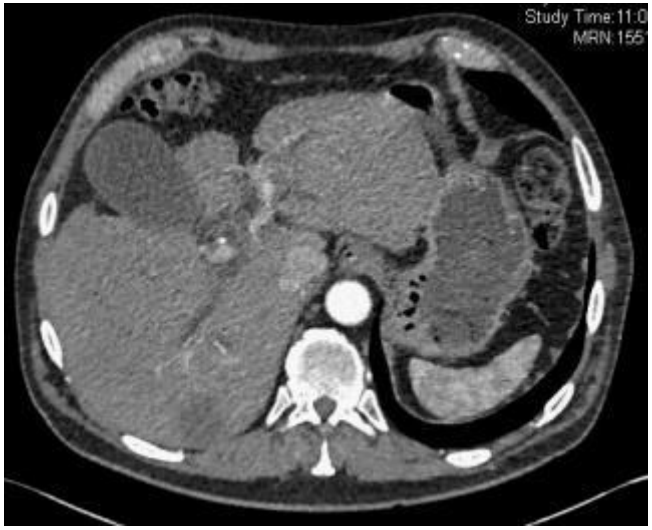
Clinical Presentations

- Blood tests
  - General (LFT, UE, FBC, INR)
  - Liver “screen”
    - Liver AutoAbs and Igs
      - PBC: AMA (PDH), IgM
      - PSC: pANCA
  - Specialised
    - PBC: gp120, sp100, anti-centromere

Clinical Presentations

- Imaging
  - Ultrasound scan
  - MRCP (ERCP)
  - Cross sectional





Clinical Presentations

- Histopathology
  - Cytology
  - Lesional tissue
  - Medical liver biopsy

Clinical Presentations

- Common disorders
  - Stones
  - Cancer
  - Inflammatory disorders
- Rare disorders
- Non-biliary disorders
  - Infiltration
  - Venous outflow issues

Chronic Biliary Disease

- Histological features – biliary interface, ductular reaction, ductopenia, CAP, CK7

CASES

Case 1: Pruritis

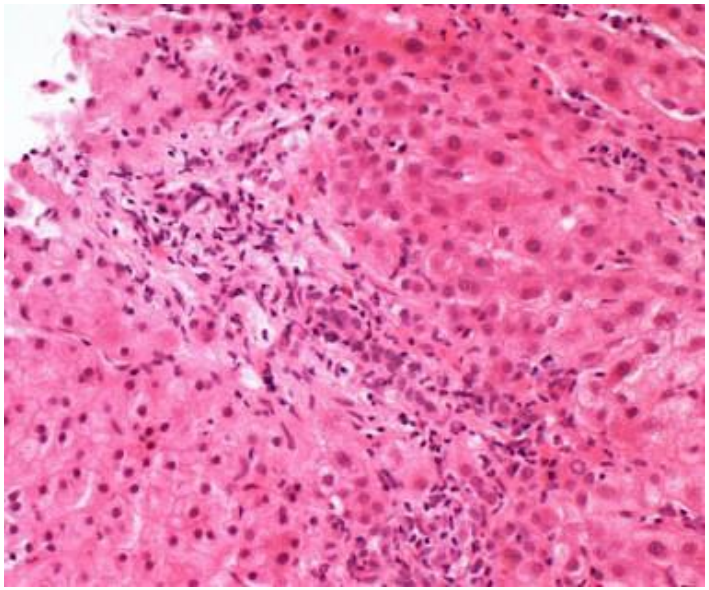
72 yr female

- LFTs - ALP 670 u/l, GGT 3775 u/l, ALT 120 u/l
- ANA weakly positive
- Negative for AMA, SMA, LKM, ds DNA
- USS normal
- Liver biopsy performed

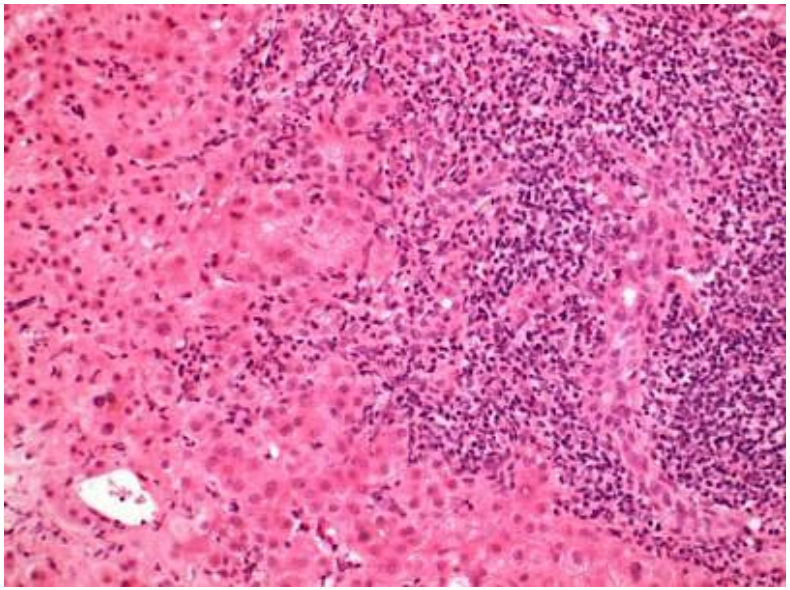
Histology

reticulin

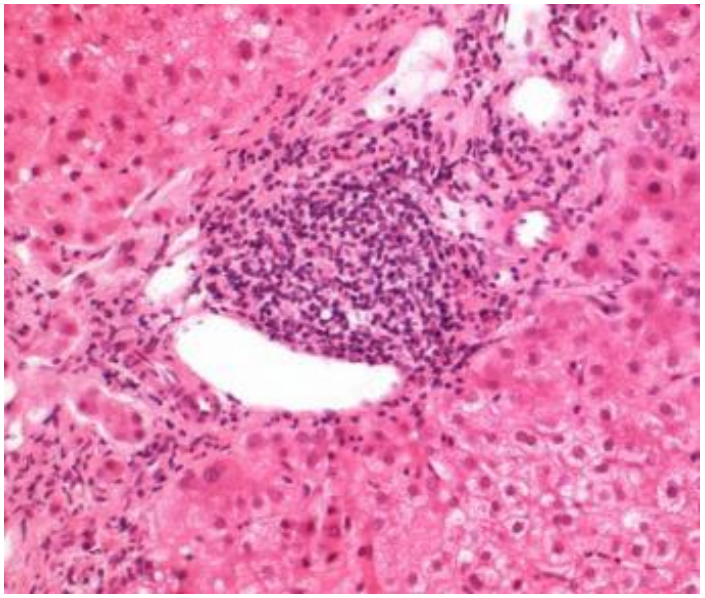
Case 1 Portal changes



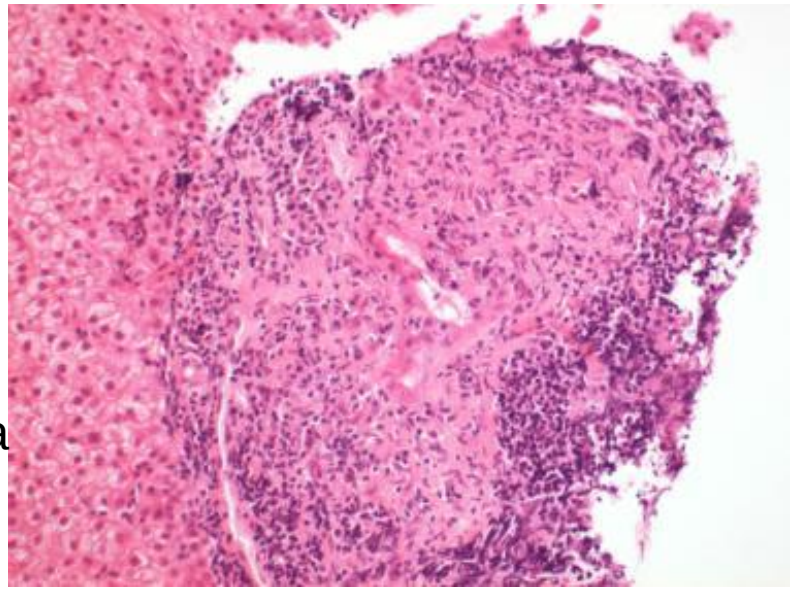
Biliary interface



Interface hepatitis

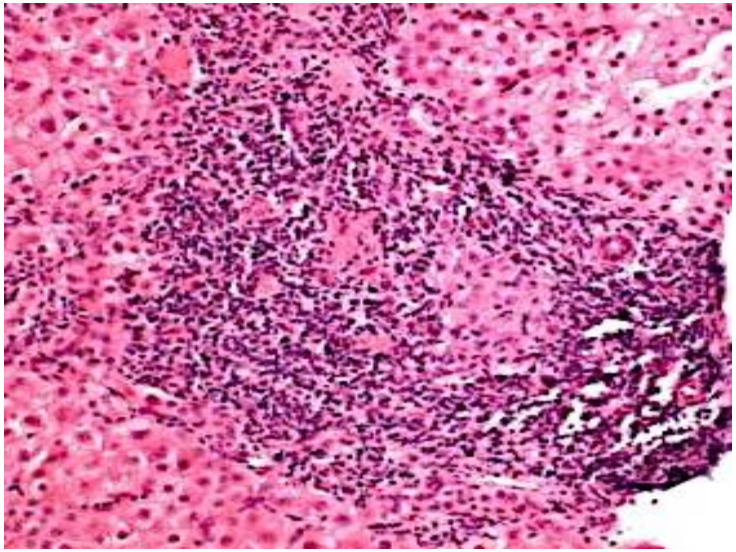


Ductopenia

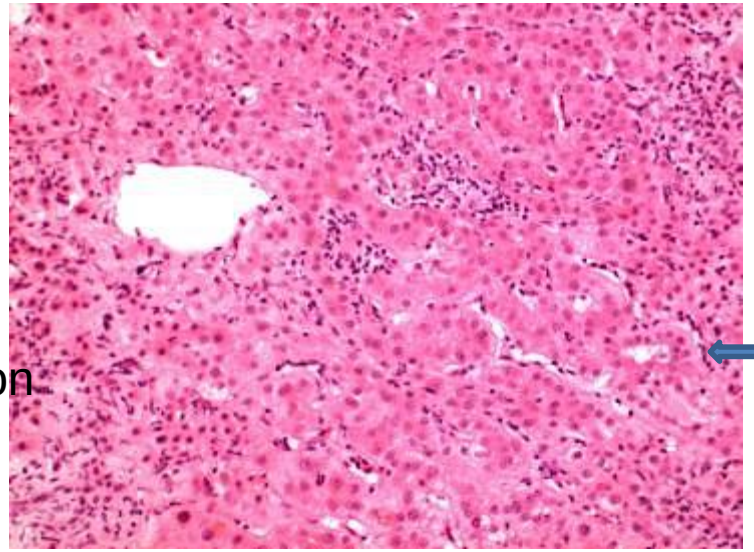


Periductal granuloma

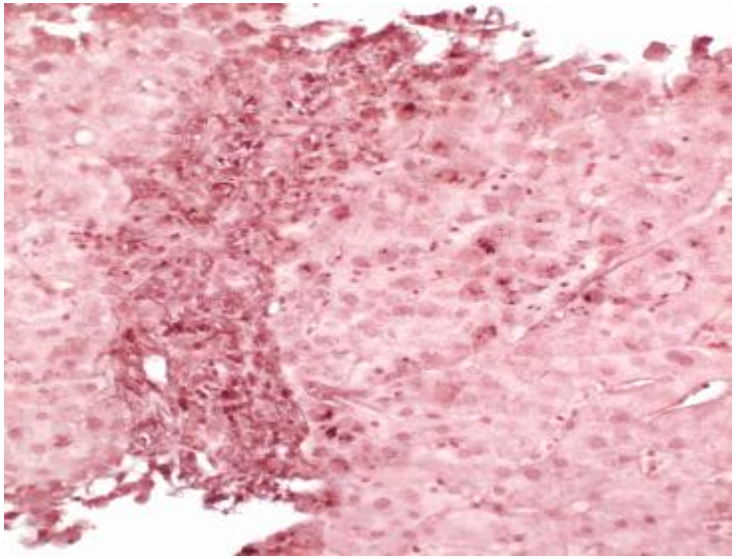
Case 1



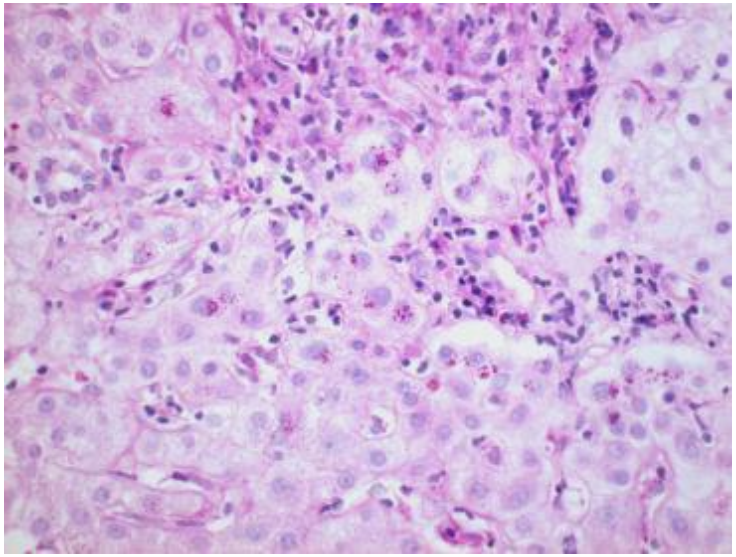
Poorly formed granuloma



Inflammation & rosette



Copper associated protein



orcein

PAS-D

Case 1 Features

- Portal granulomatous inflammation with duct destruction
- Ductopenia
- Minimal periportal copper associated protein
- Mild fibrosis

- Diagnosis – AMA negative Primary Biliary Cholangitis

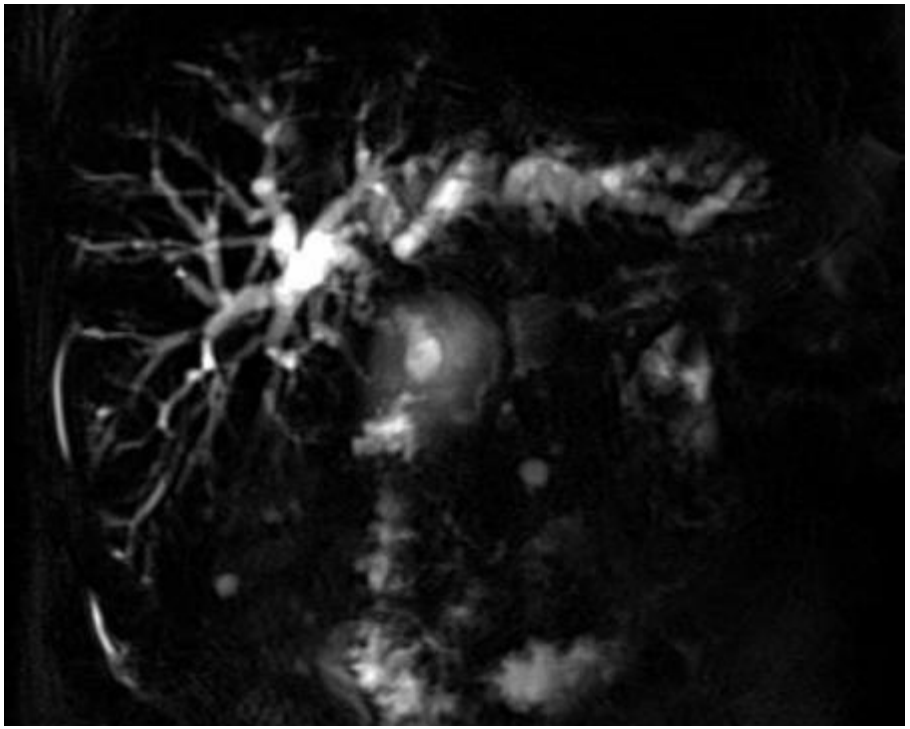
Case 1: Pruritis

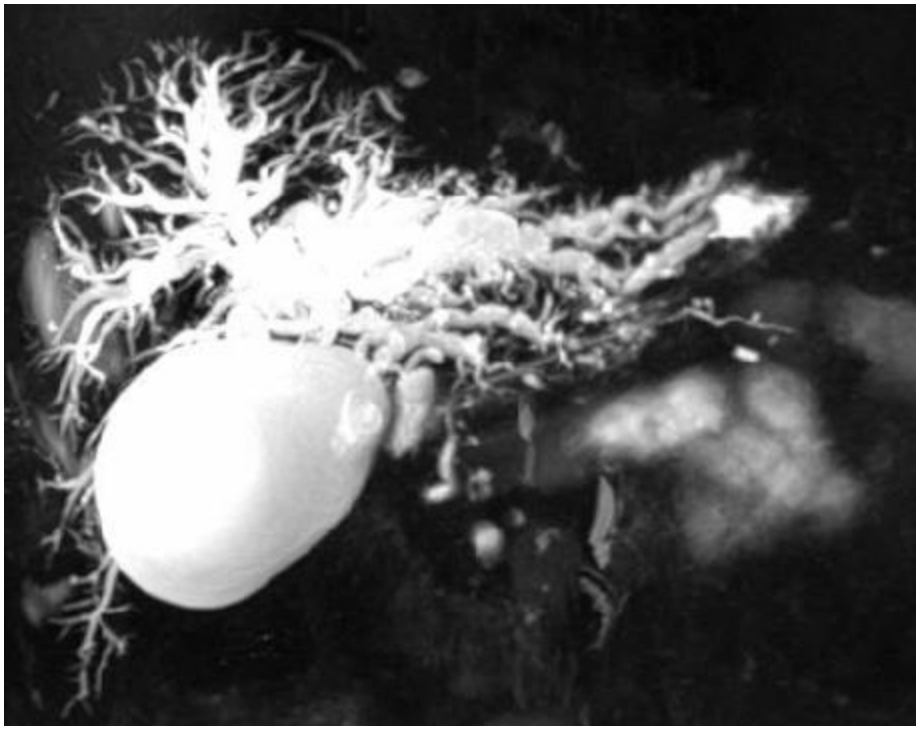
- Anti-centromere pos (portal hypertensive variant)
- Response to ursodeoxycholic acid
- Latest biochemistry:
  - ALP 92 U/L
  - ALT 13 U/L
  - Bili 15 umol/L

Case 2: Liver Transplant Assessment

- 70 y o man
- Ulcerative colitis, but otherwise fit
- Presents with jaundice
- MRI

Case 2: Liver Transplant Assessment



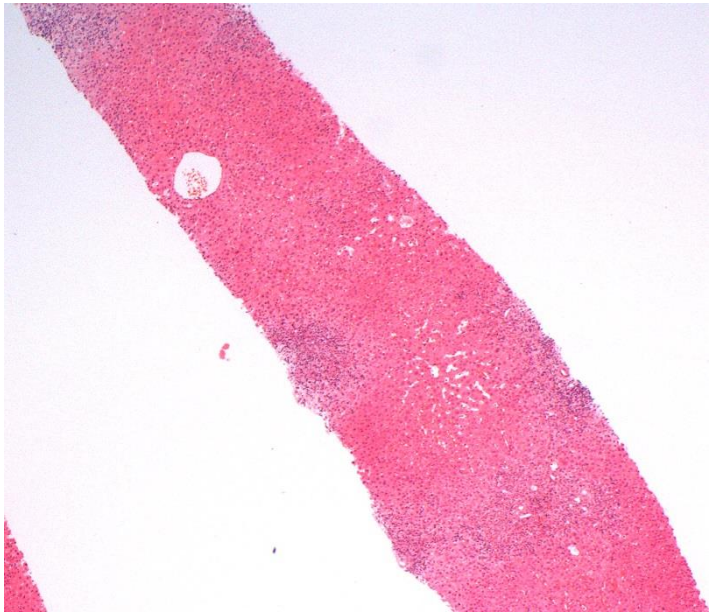


Case 2: Liver Transplant Assessment

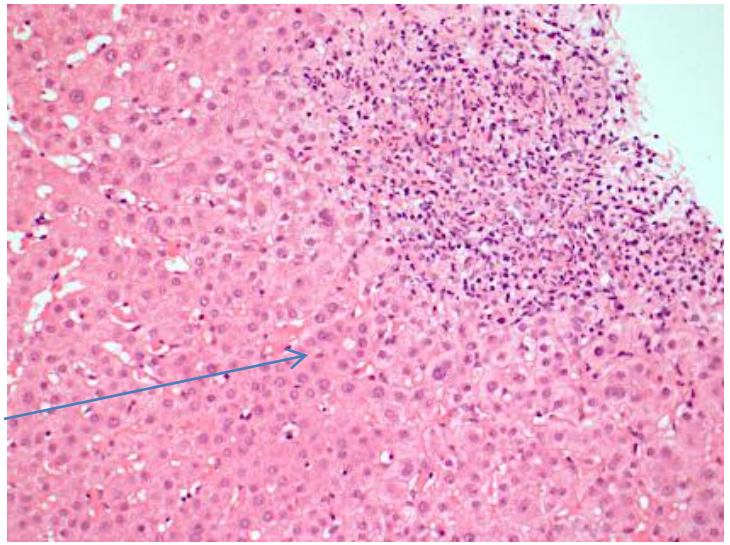
- Elected to undertake liver biopsy to stage liver disease - ? Liver transplantation or surgical reconstruction

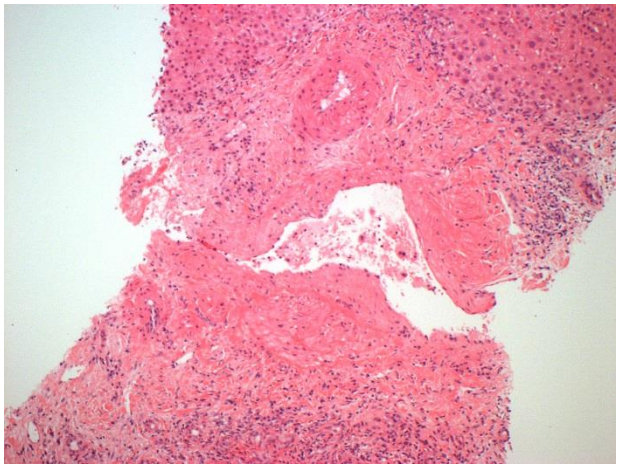
Case 2

Portal inflammation



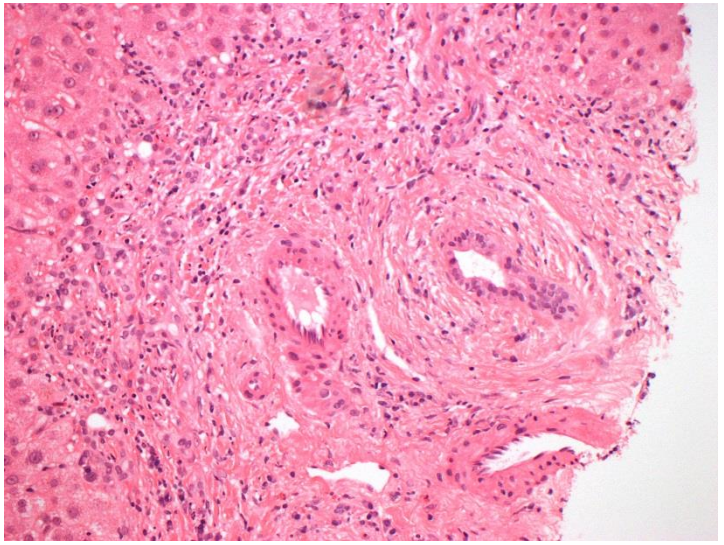
Biliary edge & rosette



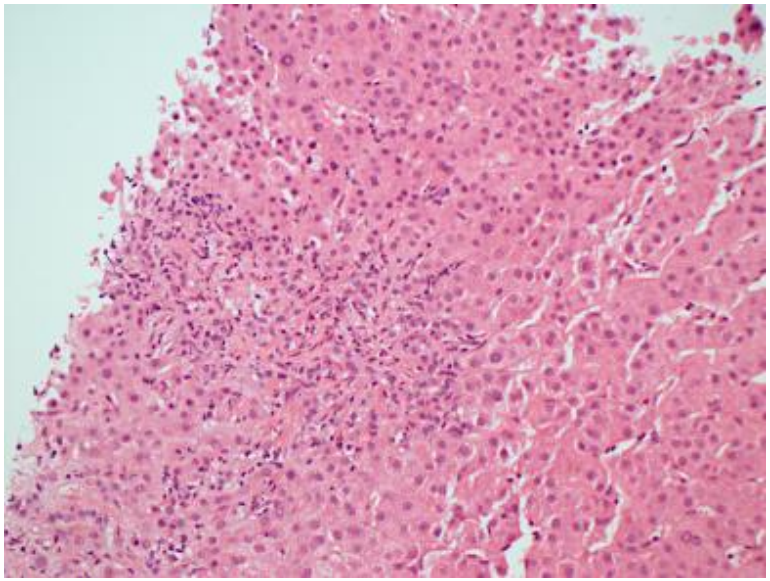


? ductopenia

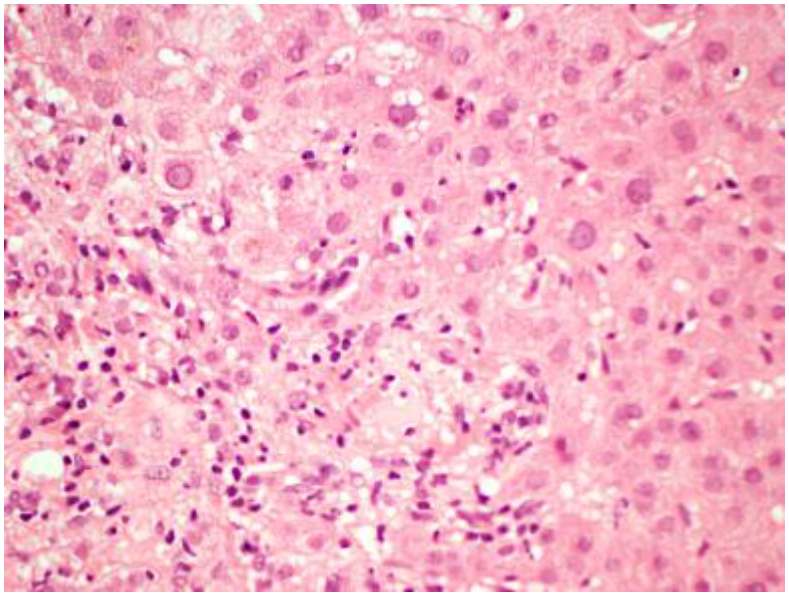
Degenerate duct



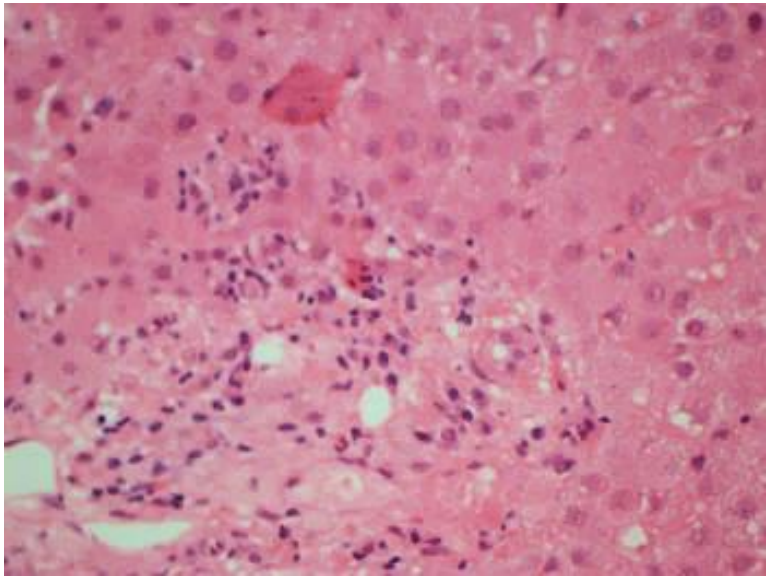
Case 2



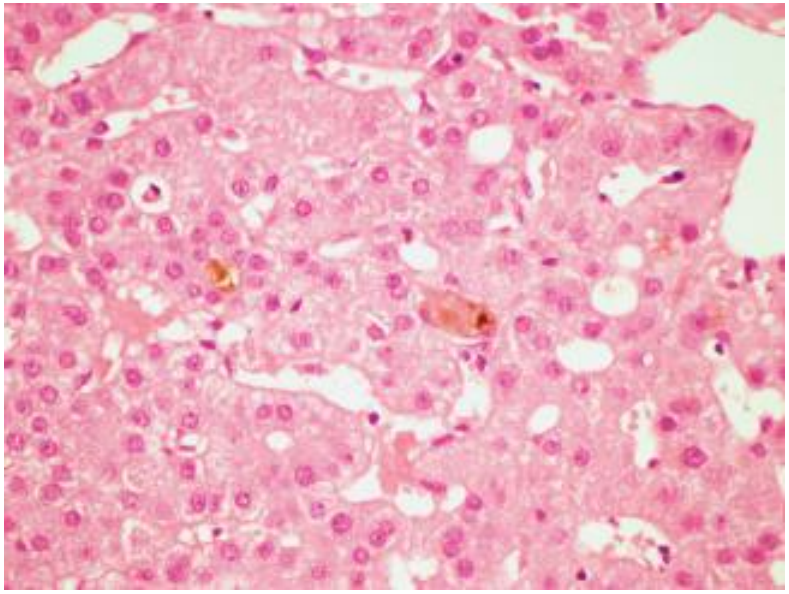
Ductular reaction



Biliary interface

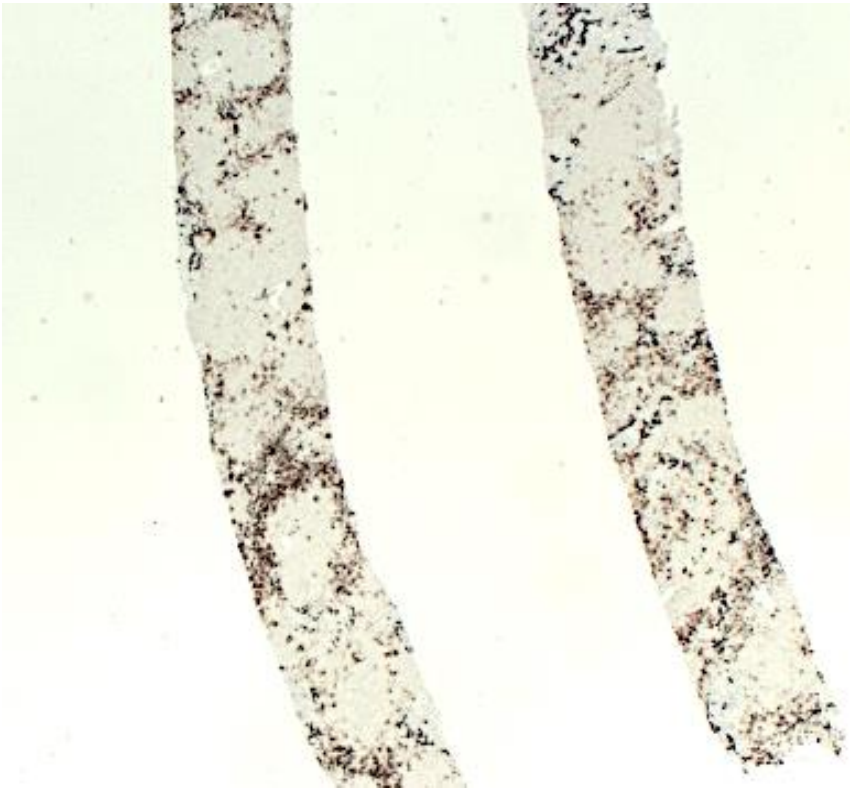


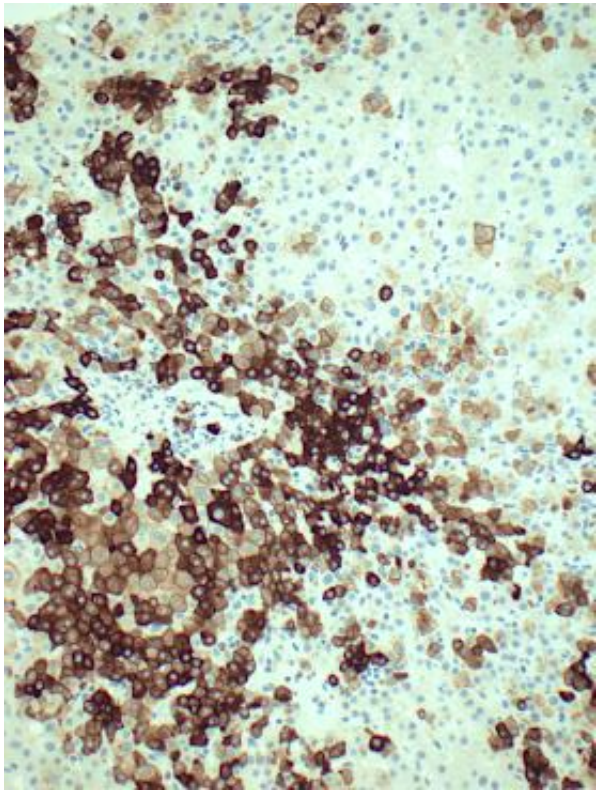
Small ducts present



Cholestasis

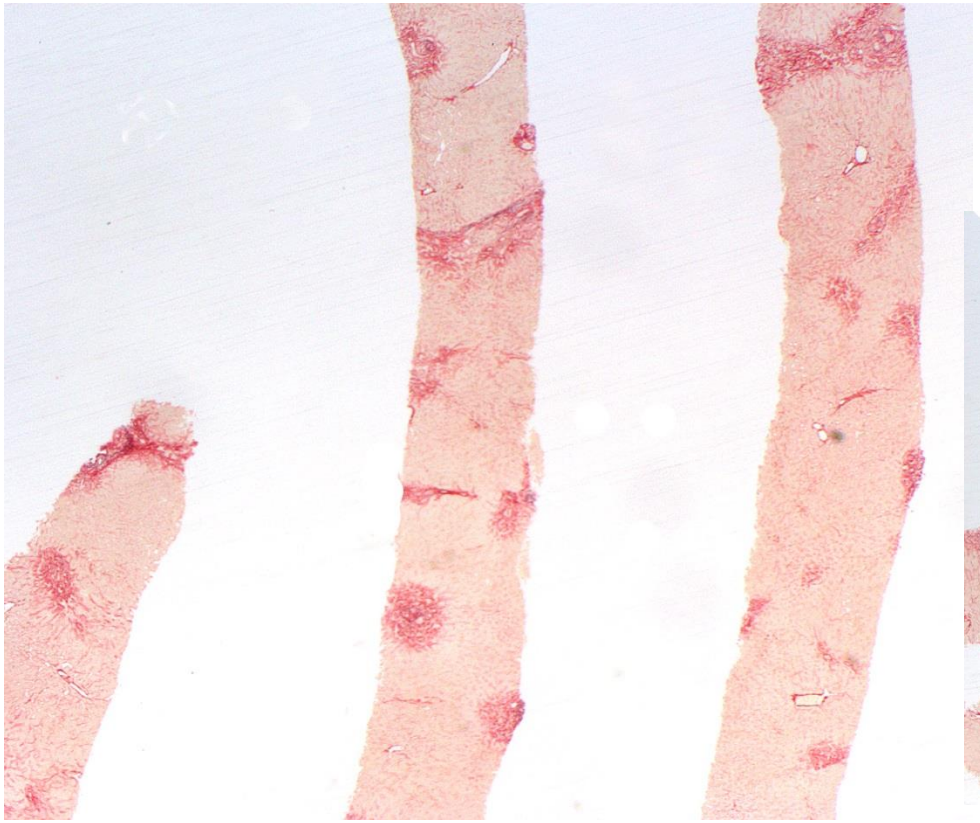
Case 2 - CK 7

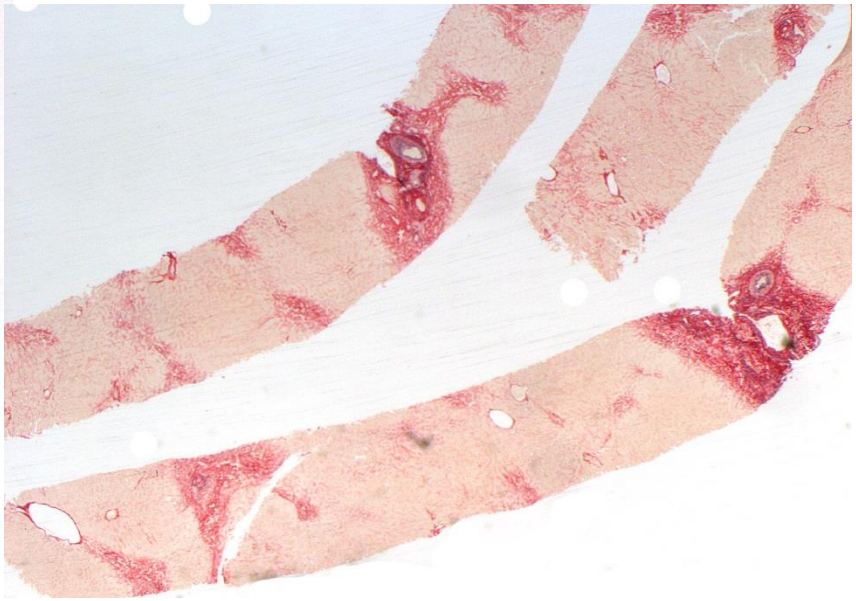




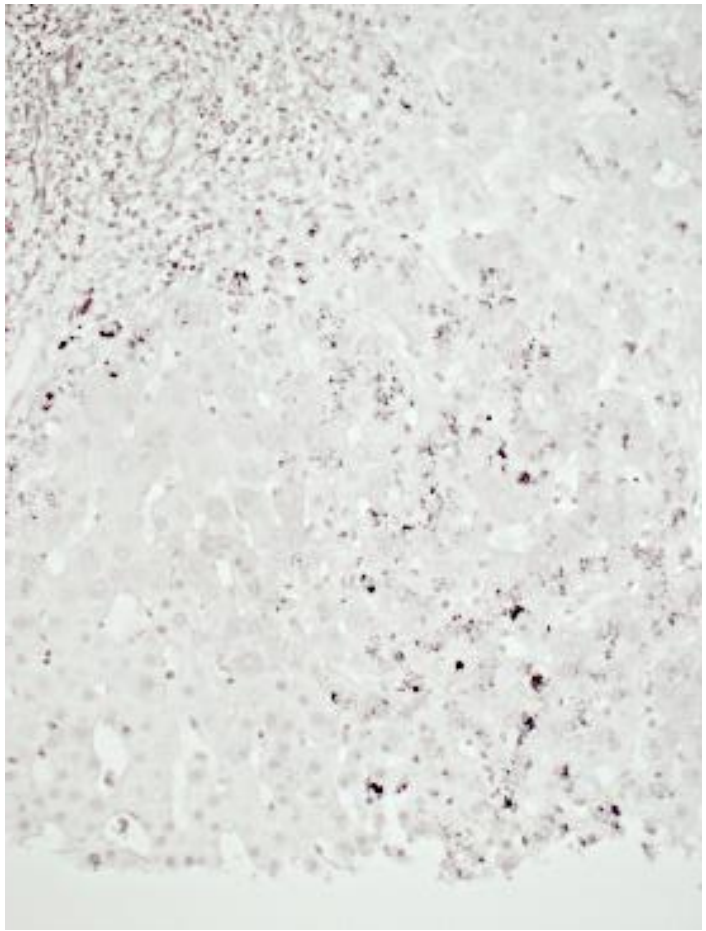
Small portal area with degenerate duct

Case 2 - fibrosis



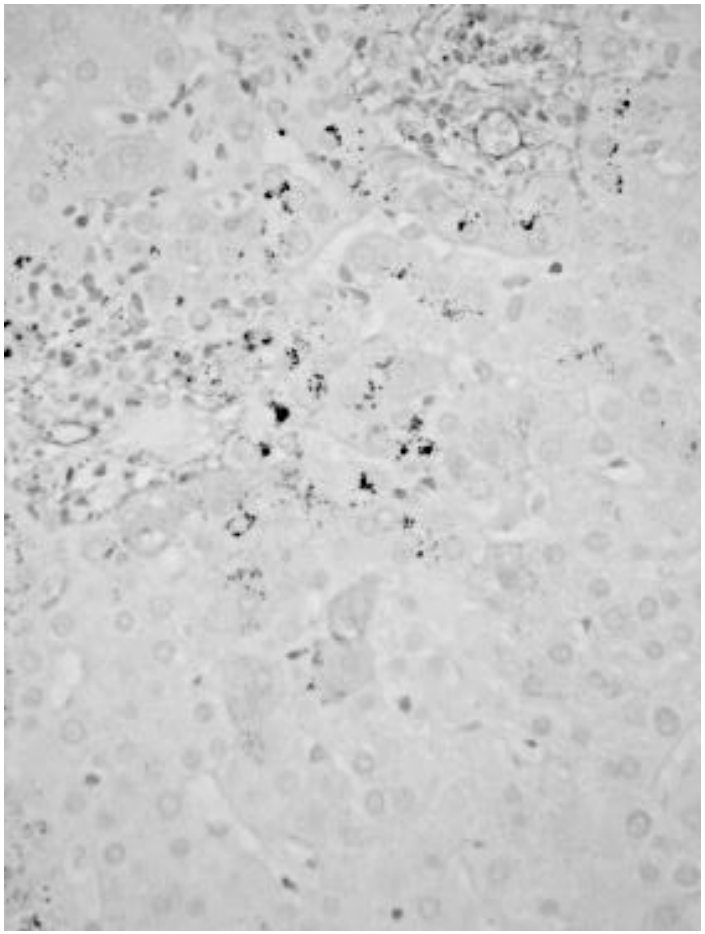


Case 2 Cholate stasis CAP



Large portal tract

Orcein



Small portal tract

Case 2

- Mild portal fibrosis
- Focal ductular reaction with biliary interface
- Degenerate ducts with inflammation
- Extensive hepto-biliary metaplasia/ intermediate phenotype on CK7.
- Cholate stasis & focal cholestasis

- Diagnsosis- suggests Primary Sclerosing Cholangitis affecting mainly large ducts

Case 2: Liver Transplant Assessment

- Due to overall severity of PSC, elected put forward for liver transplantation

9 months later

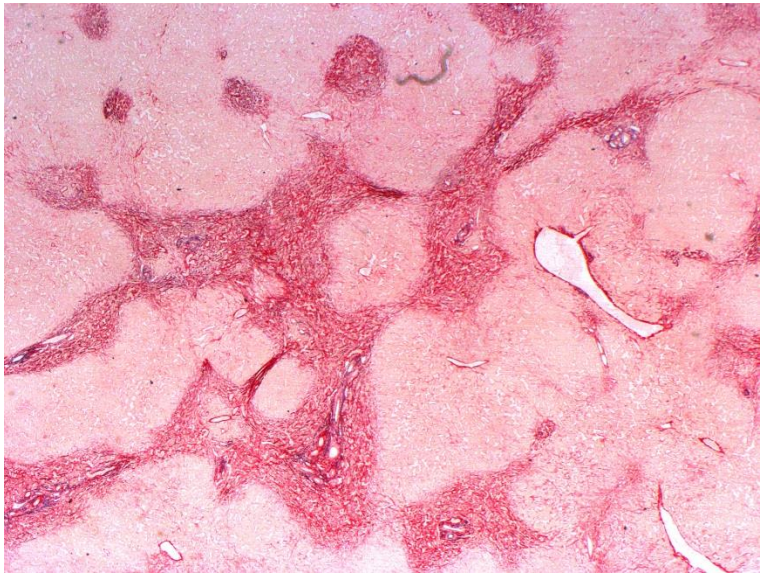
Liver 2780g

– finely nodular, < 3mm

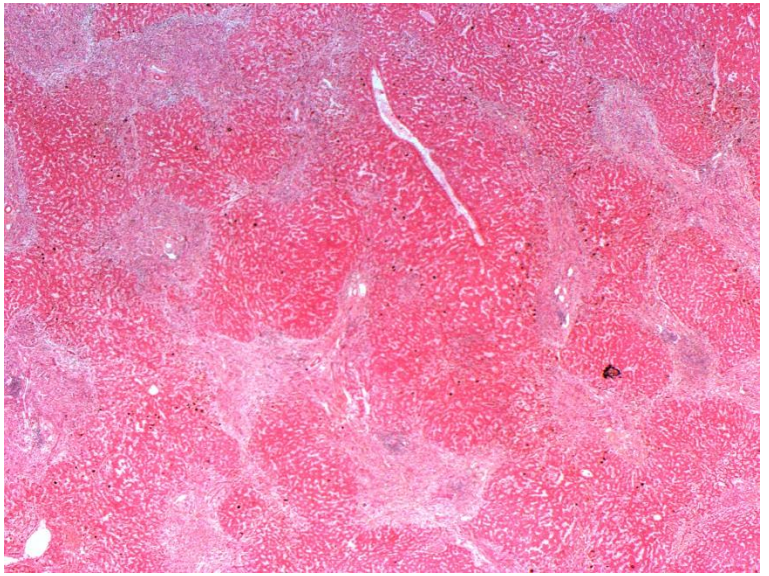
- atrophic left lobe,

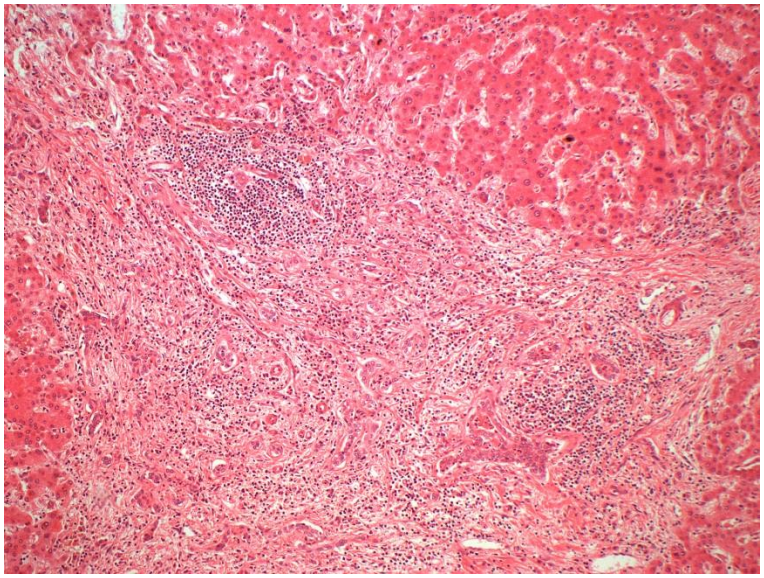
- heavily bile stained, - bile ducts visible and slightly dilated.

Explant case 2

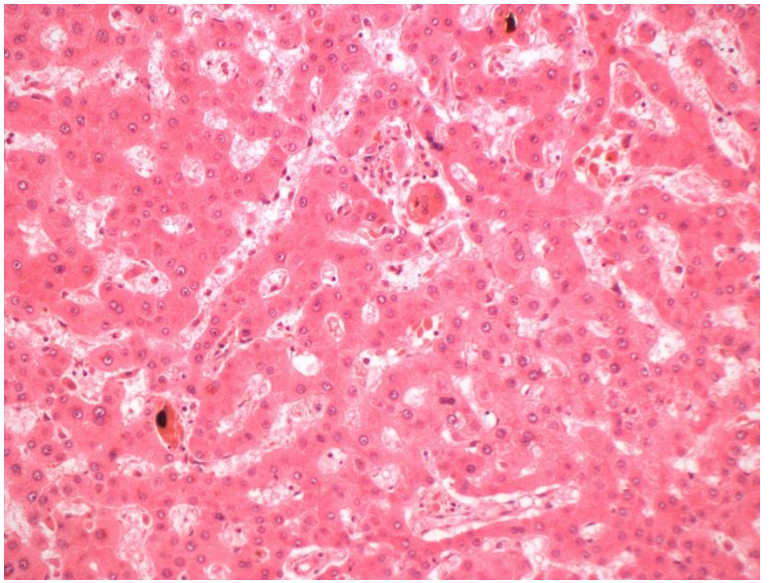


EPSR
Variable fibrosis



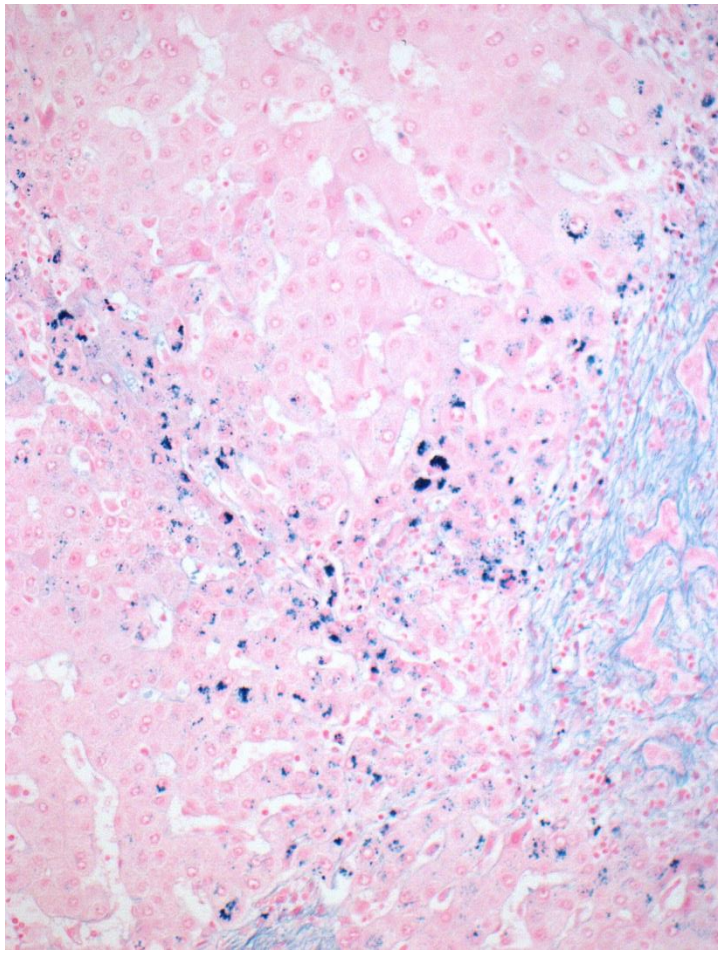


Porto-septal inflammation

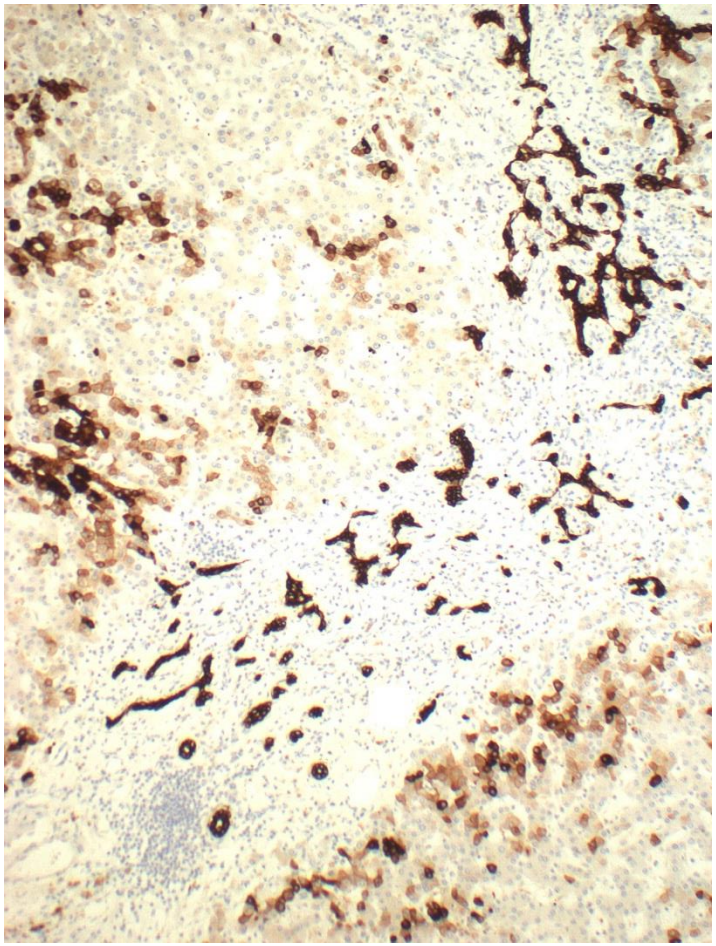


Cholestatasis

Explant Case 2

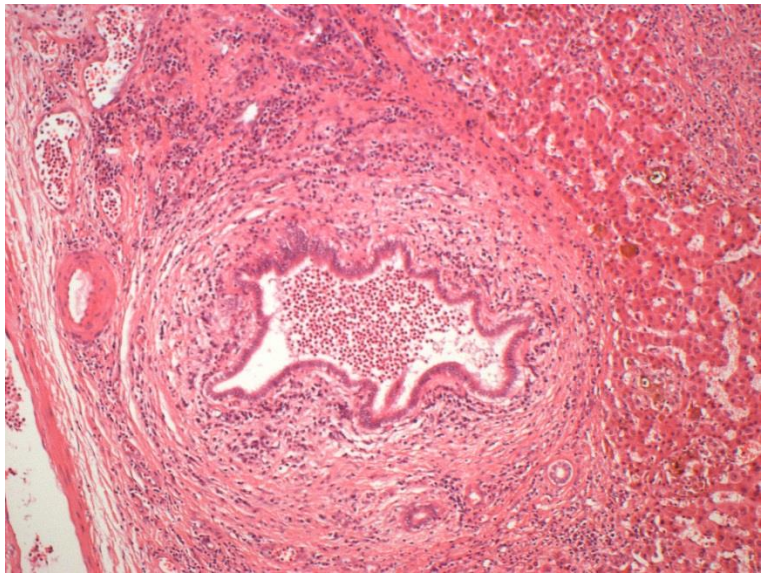


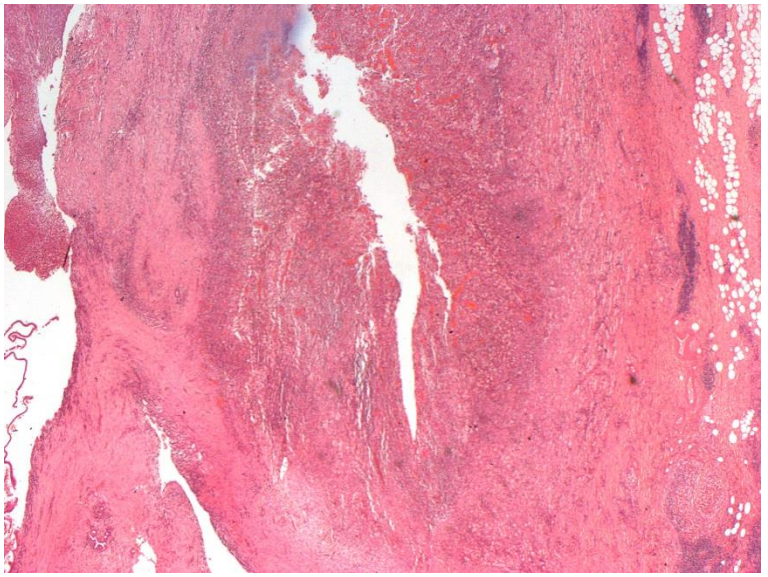
Victoria Blue

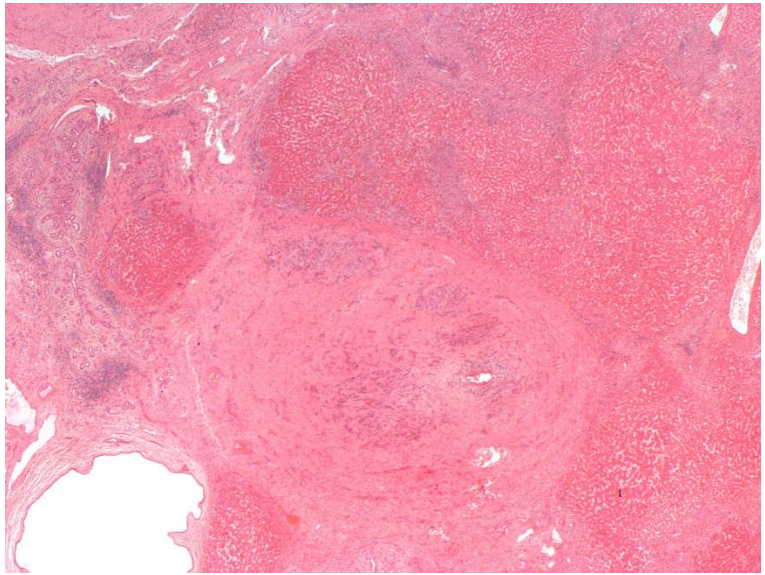


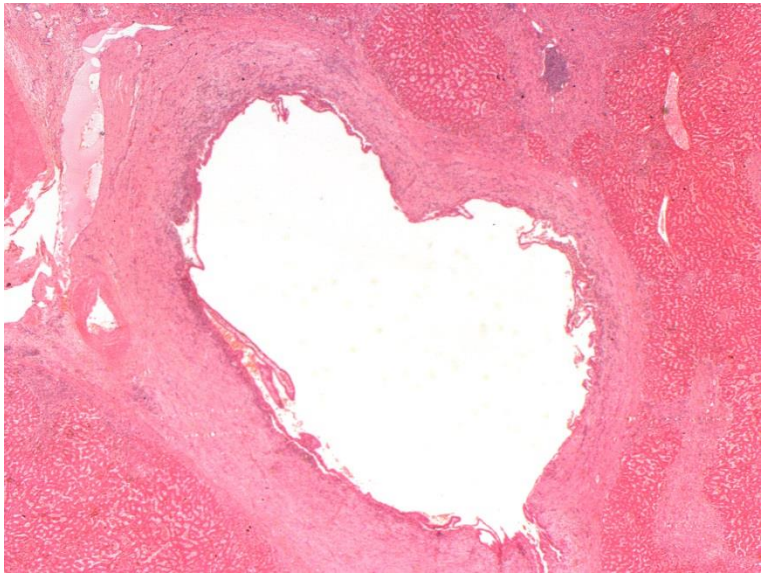
CK 7

Case 2 Explant – Major septal ducts









Staging in Biliary Disease-Japanese system

Nakanuma Histopathology 2006

- Initially assessed and validated in PBC and out performed other histology staging systems *(Kakuda Human Pathol 2013)*
- Successfully evaluated for prognosis in multicentre PSC cases *(deVries Hepatology 2017)*

Japanese system

Histological staging	**0**	**1**	**2**	**3**
Fibrosis (F)	Absent or limited in portal tracts	Periportal fibrosis (incomplete septa)	Bridging fibrosis	Cirrhosis
Bile duct loss (B)	Absent	<1/3 portal tracts	1/3–2/3 portal tracts	>2/3 portal tracts
Chronic cholestasis (C) (orcein +ve) *	**Absent**	**<1/3 periportal areas**	**1/3–2/3 periportal areas**	**>2/3 of periportal areas**

Case 2: Liver Transplant Assessment

- Seen in clinic recently and well
- Unfortunately, surveillance colonoscopy has revealed a rectal cancer on the background of quiescent colitis
- Being worked up for colectomy

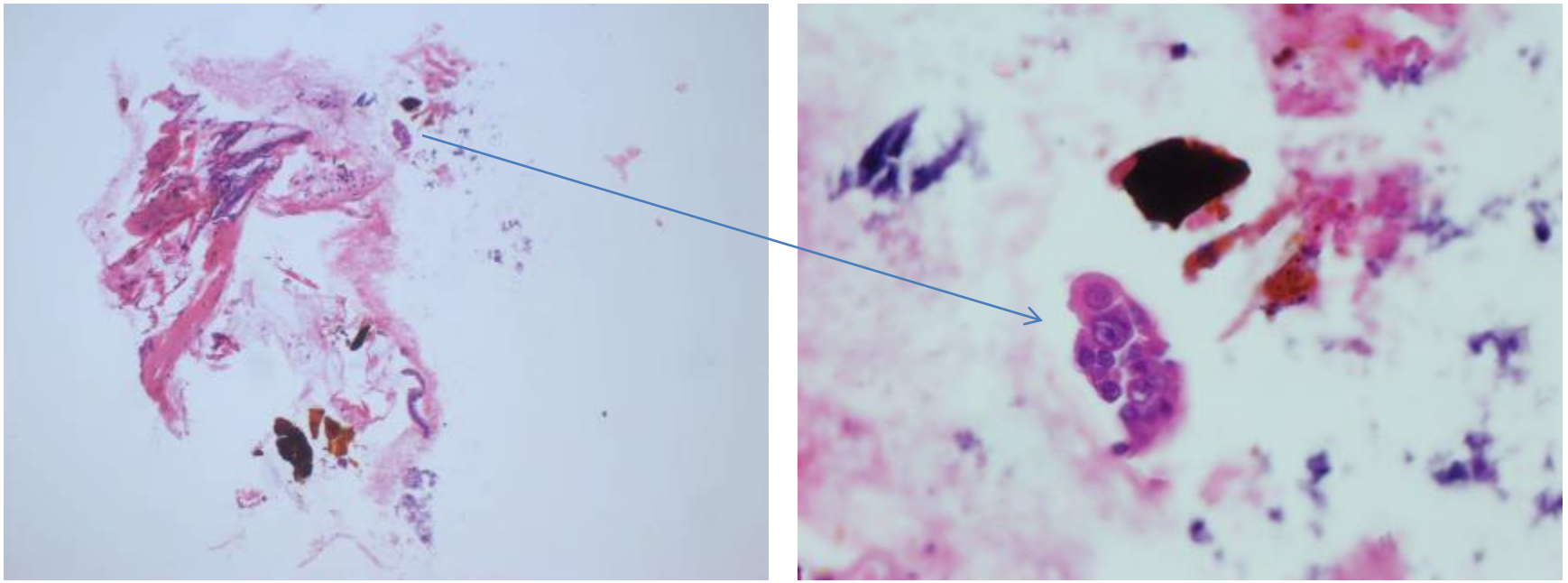
Case 3: Jaundice

- 74 y o lady admitted with jaundice and cholangitis
- Dilated ducts at ultrasound scan
- Cross sectional imaging

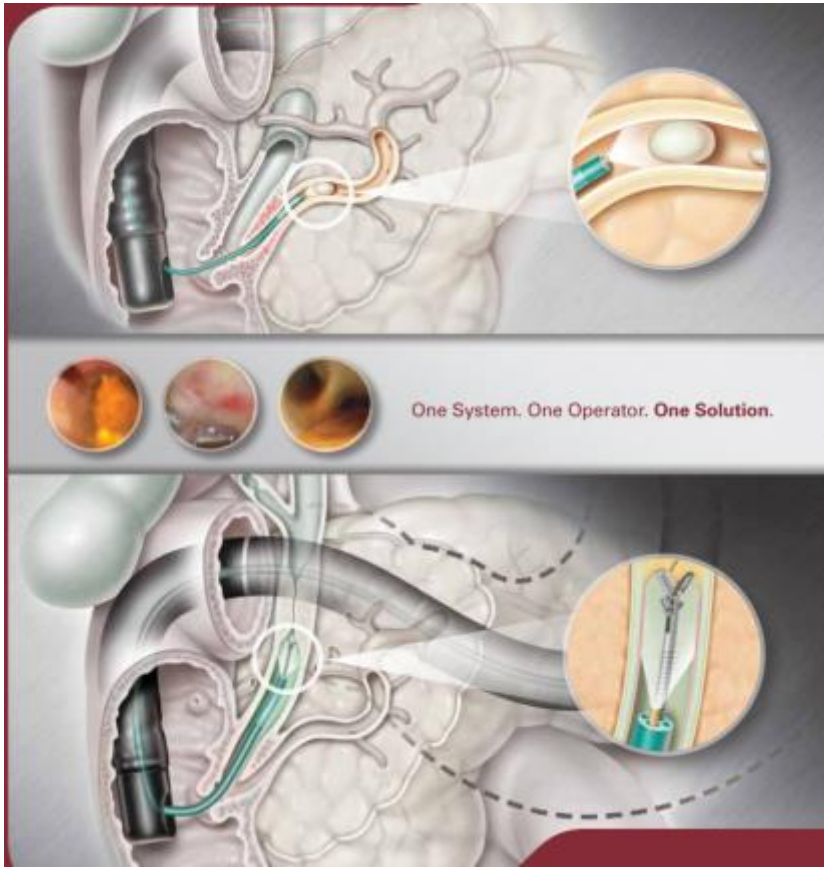
Case 3: Jaundice

Case 3: Jaundice

Biliary brush



Case 3: Jaundice



Case 3: Jaundice

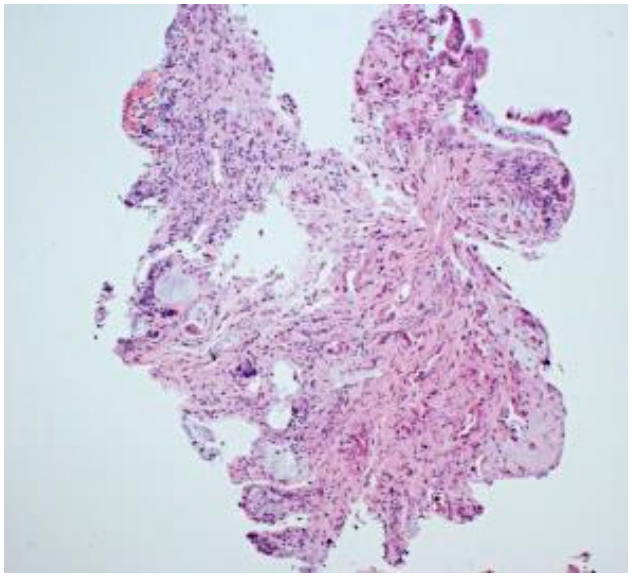
SpyGlass and SpyBite

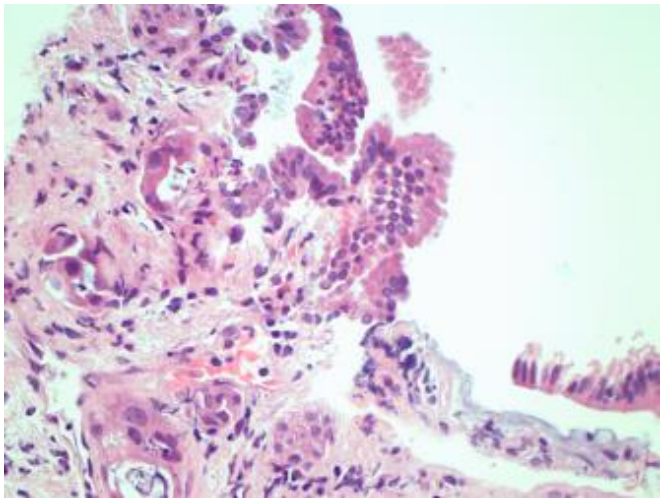
Case 3: Jaundice

SpyGlass and SpyBite

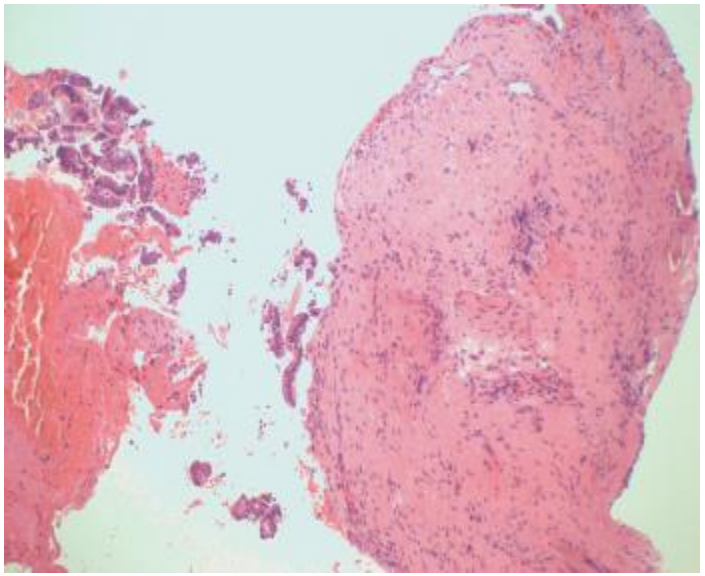


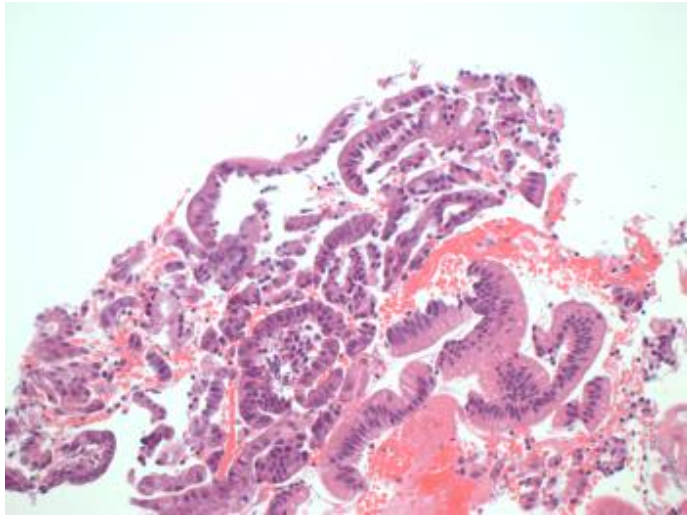
Spybite Bx





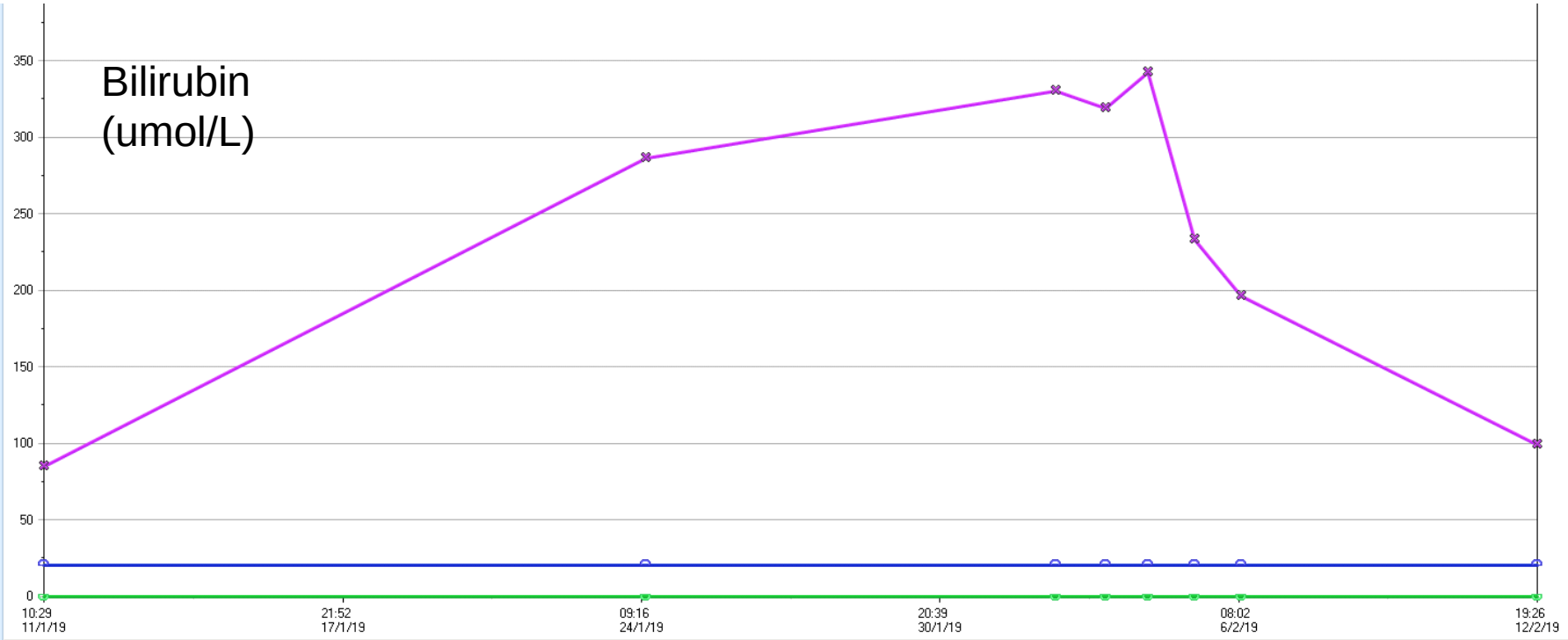
Endobiliary Bx





Jaundice

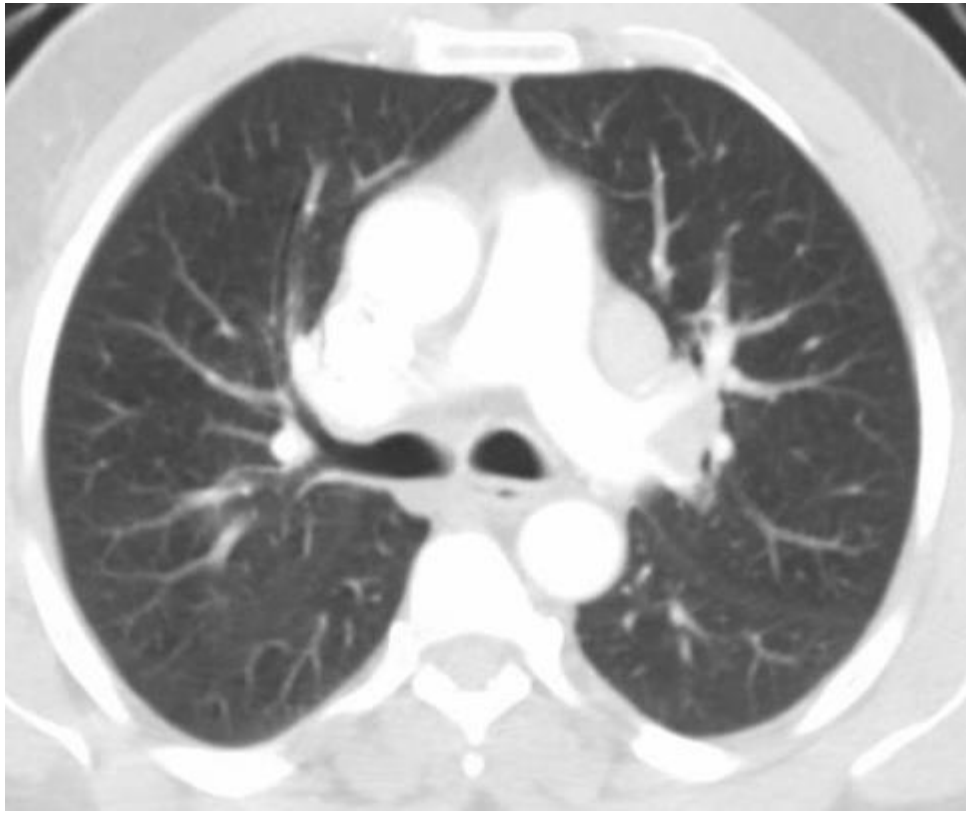
- Currently cholangiocarcinoma is being staged to determine operability

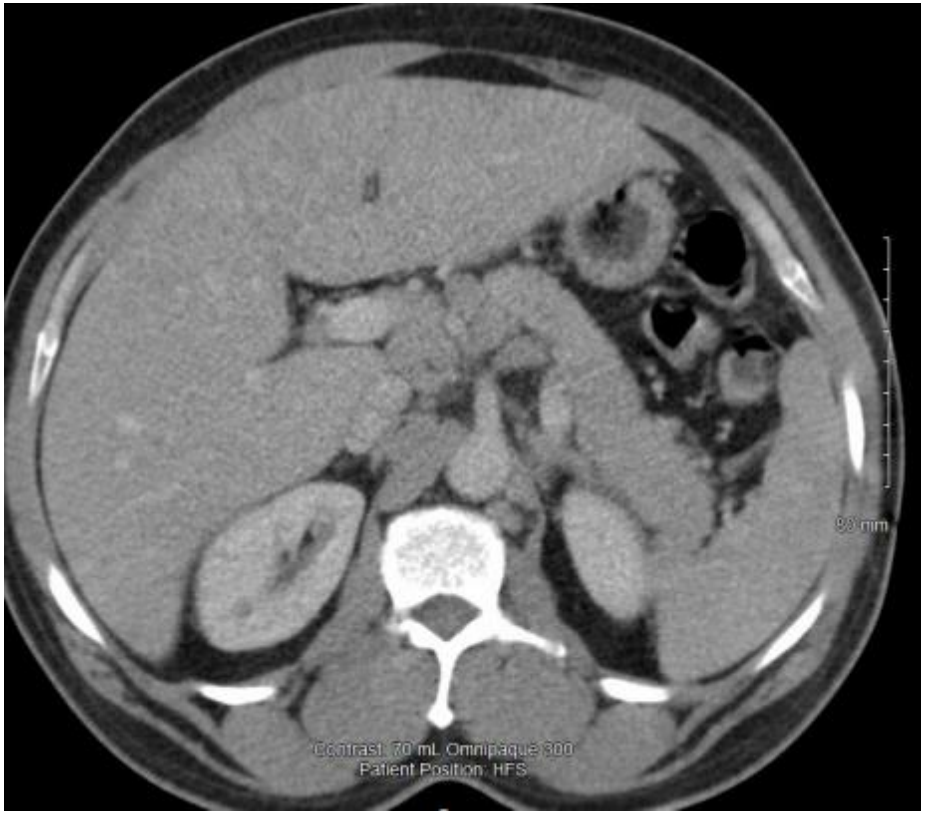


Case 4: Cholestatic Liver Tests

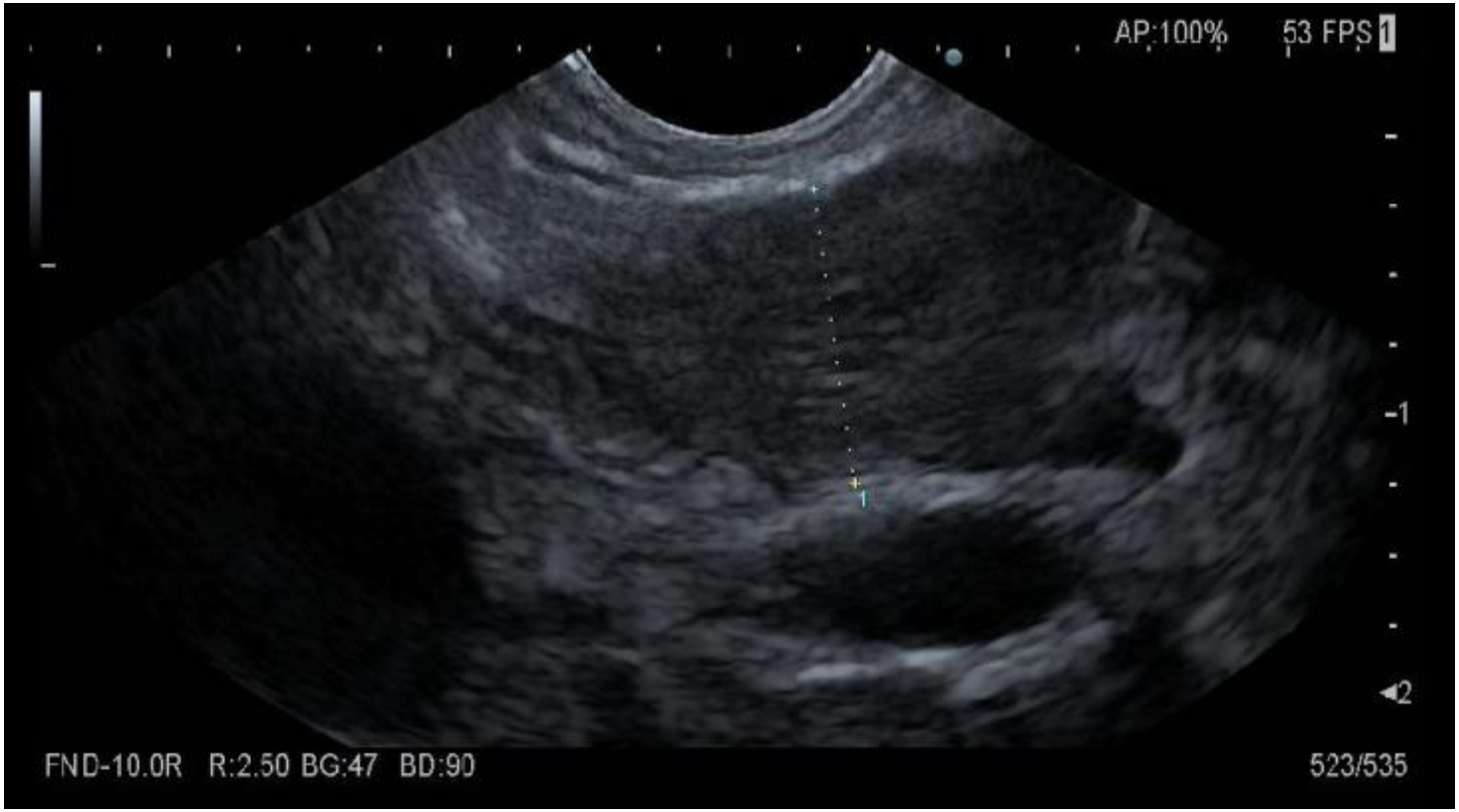
- 49 y o black African man originally from Zimbabwe
- Background HIV well established on HAART
- Cholestatic liver tests followed by skin lesions

Case 4: Cholestatic Liver Tests



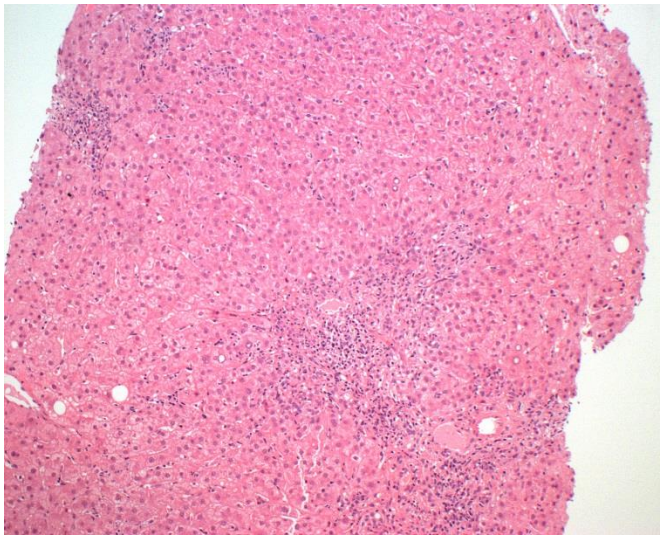


Case 4: Cholestatic Liver Tests

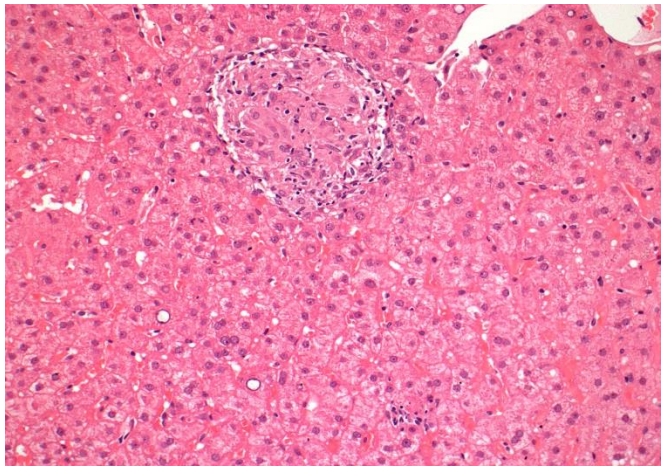


Case 4: Cholestatic Liver Tests

EPSR spiculated portal tracts

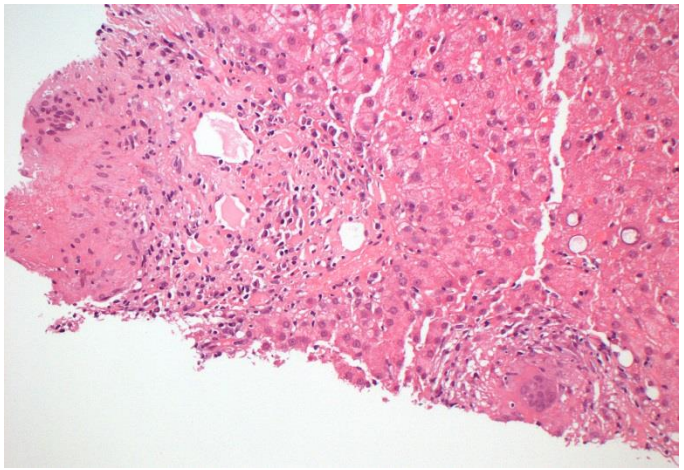


Portal & lobular inflammation



perivenular

Granulomata



portal

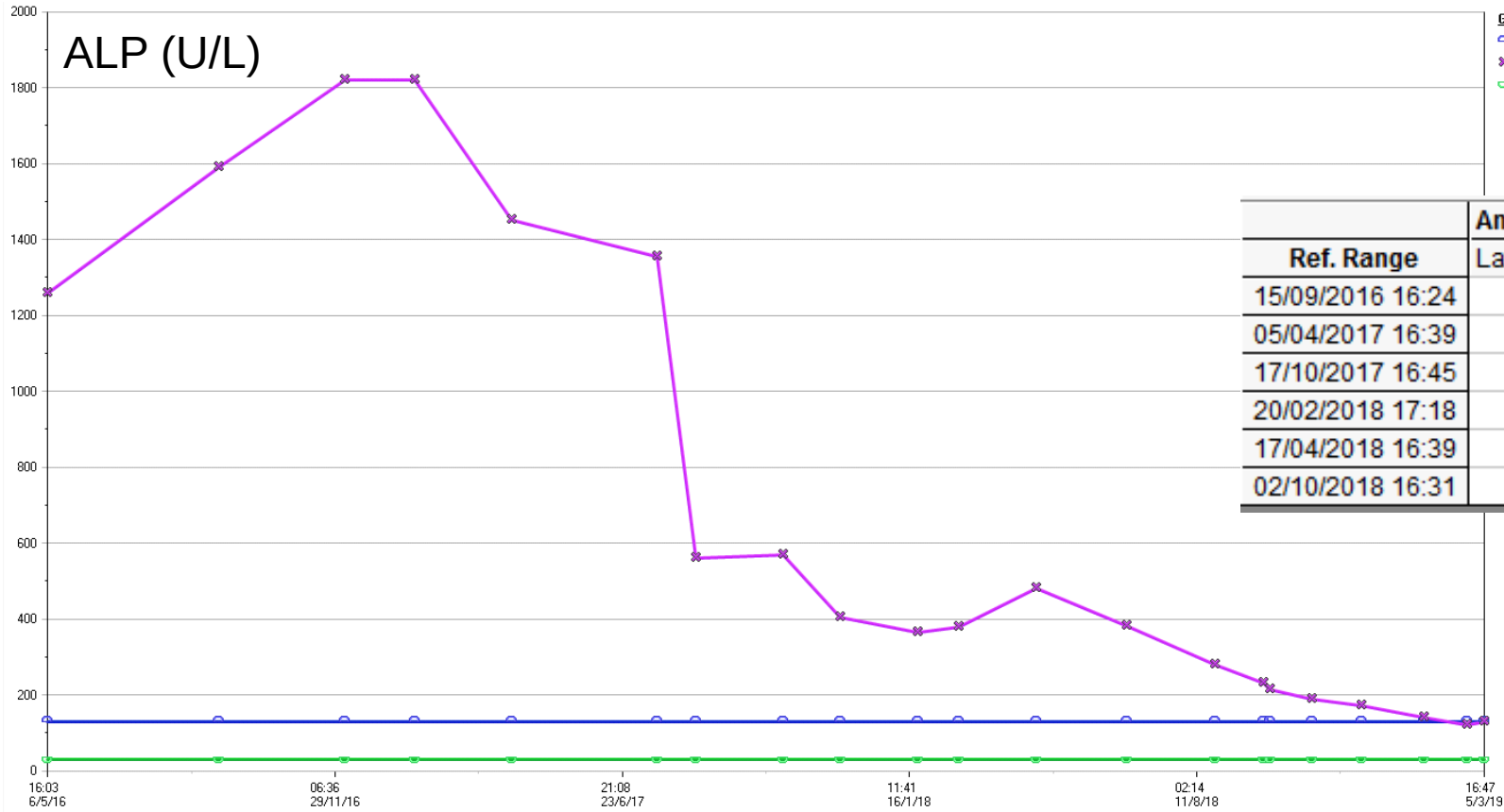
Case 4: Cholestatic Liver Tests

- Granulomatous infiltrate, portal and lobular – non-necrotising, some epithelioid
- Ductular reaction and biliary interface
- Trace of copper associated protein
- Portal fibrosis, occasionally hyalinised granuloma
- Regenerative hepatocytes, small necro-inflammtory foci and Kupffer cell hyperplasia

- Diagnosis – suggestive of Sarcoidosis

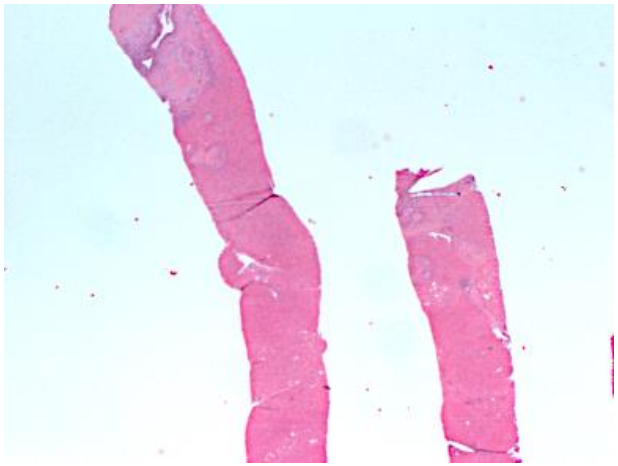
Case 4: Cholestatic Liver Tests

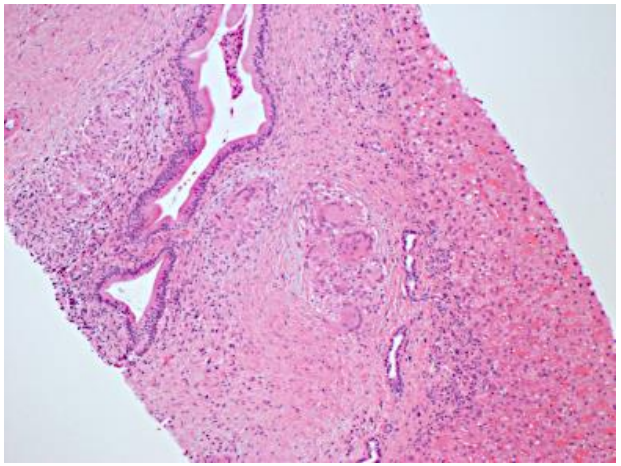
- Started on steroids and MMF



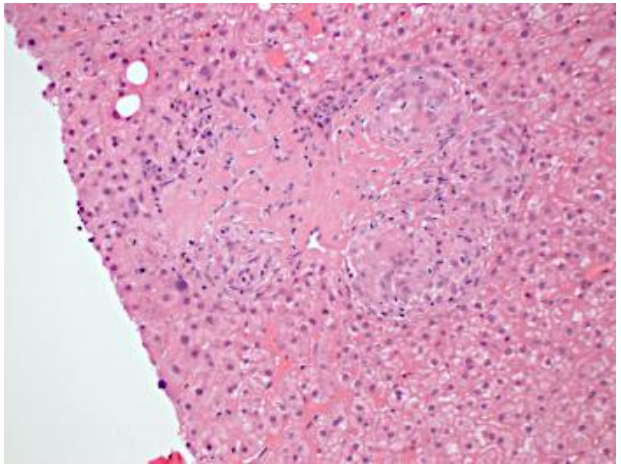
	Angiotensin C E
Ref. Range	Latest Ref Range: 0-52 U/l
15/09/2016 16:24	191 ▲
05/04/2017 16:39	>120 ▲
17/10/2017 16:45	<120 ▲
20/02/2018 17:18	>120 ▲
17/04/2018 16:39	>120 ▲
02/10/2018 16:31	185 ▲

Case 4 follow up Bx





Periductal granuloma



Hyalinising periportal granuloma

EPSR

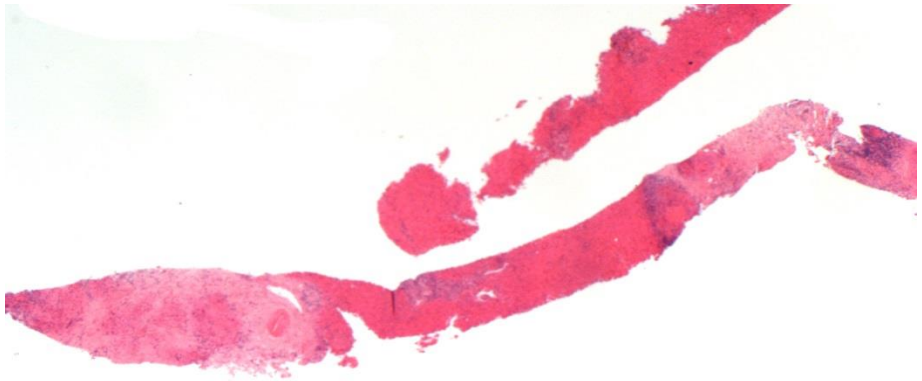
Follow up Biopsy

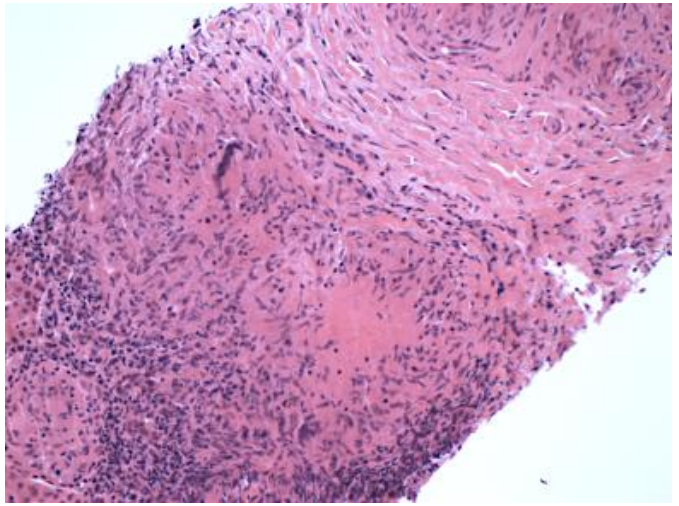
- Follow up biopsy showed some decrease in inflammation, especially lobular; no progression in bridging fibrosis although portal fibrosis remains

Case 5: Jaundice

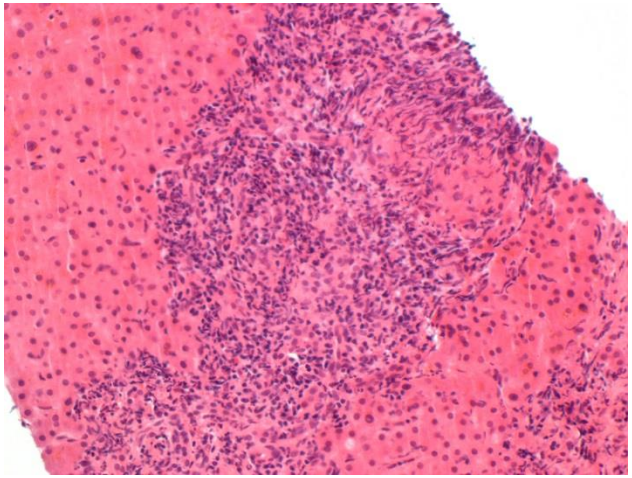
- 44 y o black African female
- Well controlled HIV on HAART
- Jaundice
- CT shows hilar LNs

Case 5

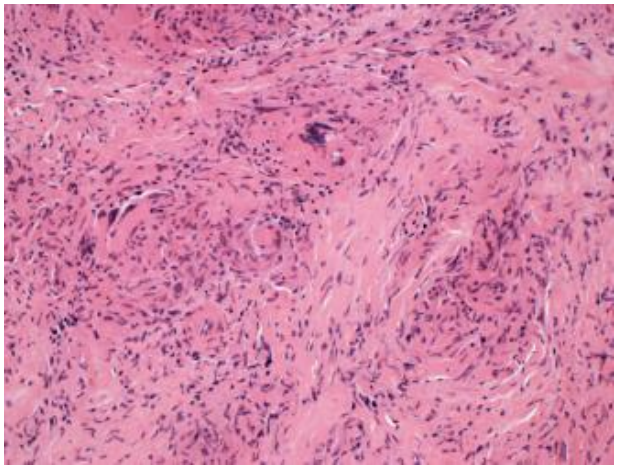




Necrotic granuloma



Portal inflammation ? granuloma



Fibrosis and giant cells

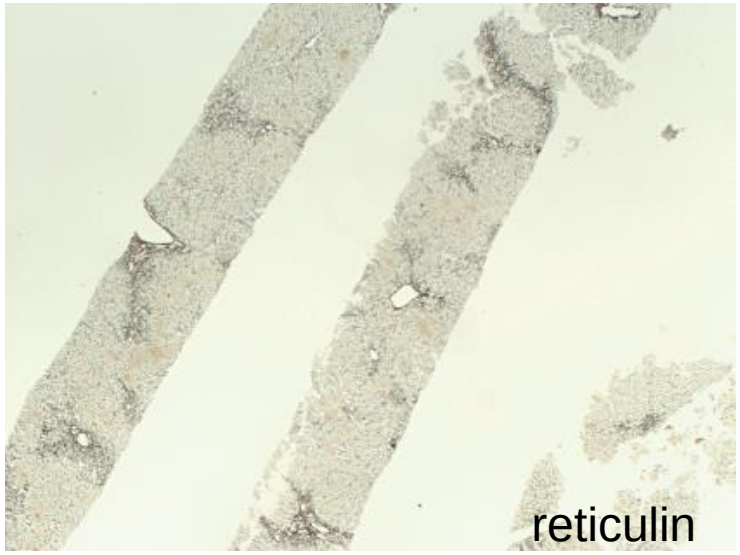
Non-Biliary Causes of Elevated ALP

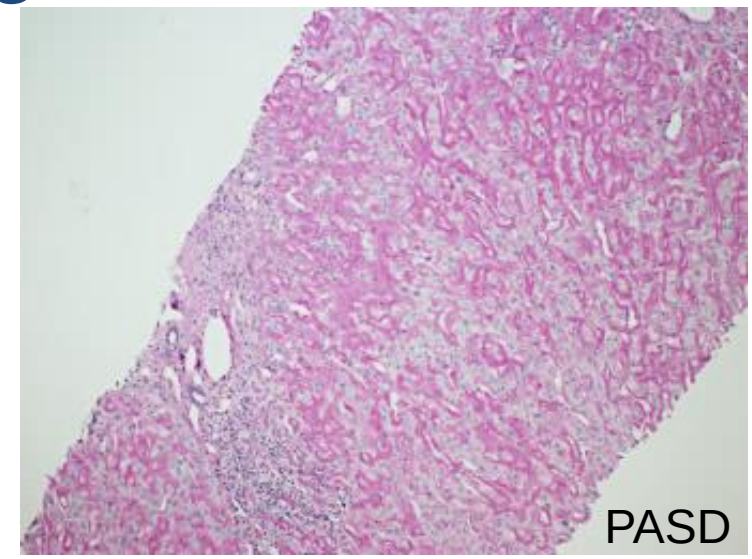
- Venous outflow problems
  - Heart failure
  - Thrombosis
  - Post transplant hepatic vein issues
- Infiltrative diseases

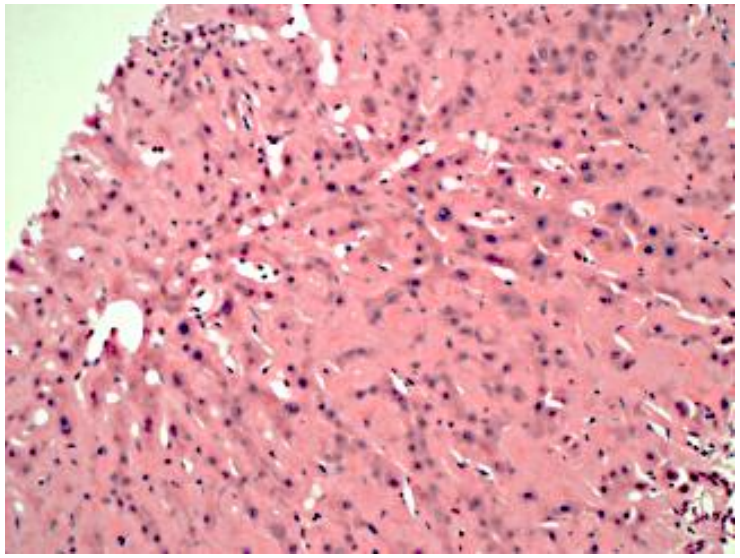
Case 6: Abdominal Pain and Weight Loss

- Tender hepatomegaly
- Cholestatic liver tests
- Imaging non-contributory
- Liver bx

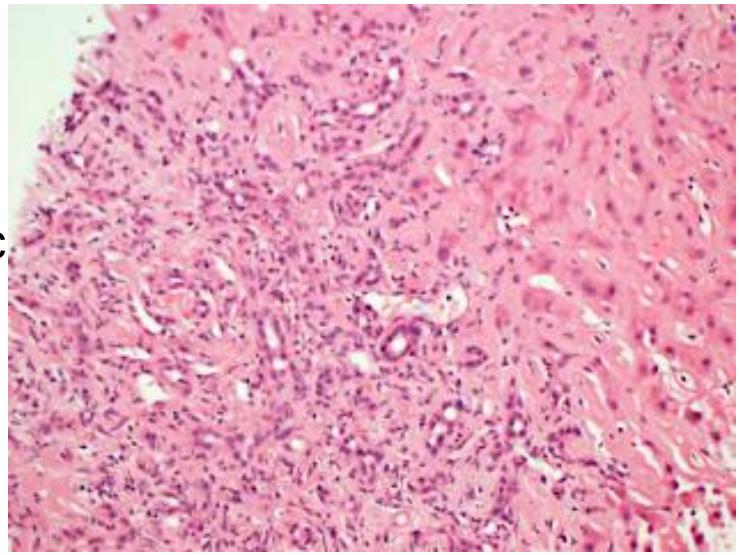
Case 6







Dense acellular eosinophilic peri - sinusoidal deposition



Also red with congo red & slight birefringence

Case 6: AL Amyloidosis

- Lymphoplasmacytic (LPL) lymphoma
- Stable with bendamustine chemotherapy

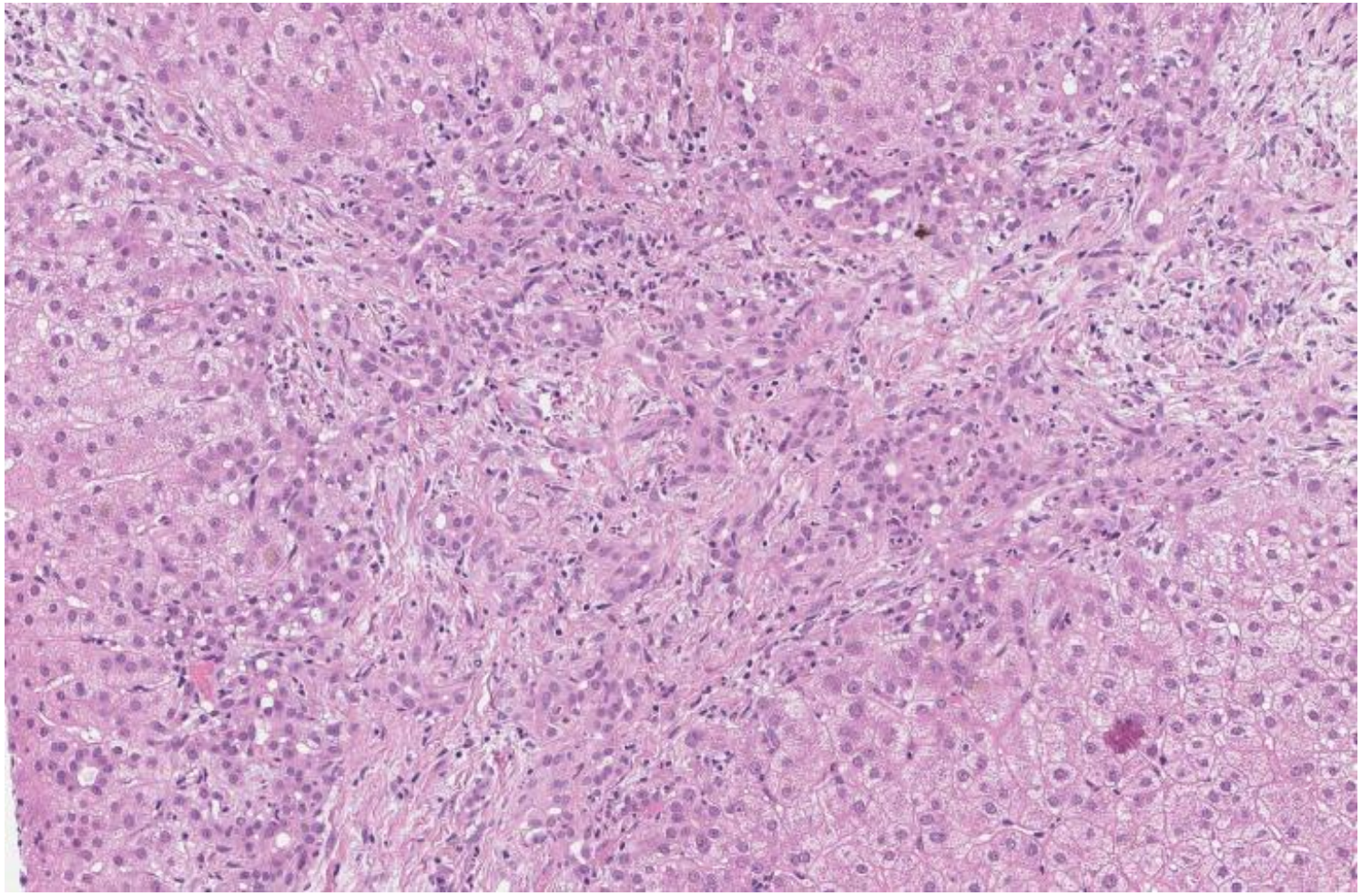
Summary

- The histological hallmarks of biliary disease have been highlighted through a series of cases
- Histological features include biliary interface, ductular reaction, ductopenia, CAP, CK7
- Examples appear at the end of the presentation

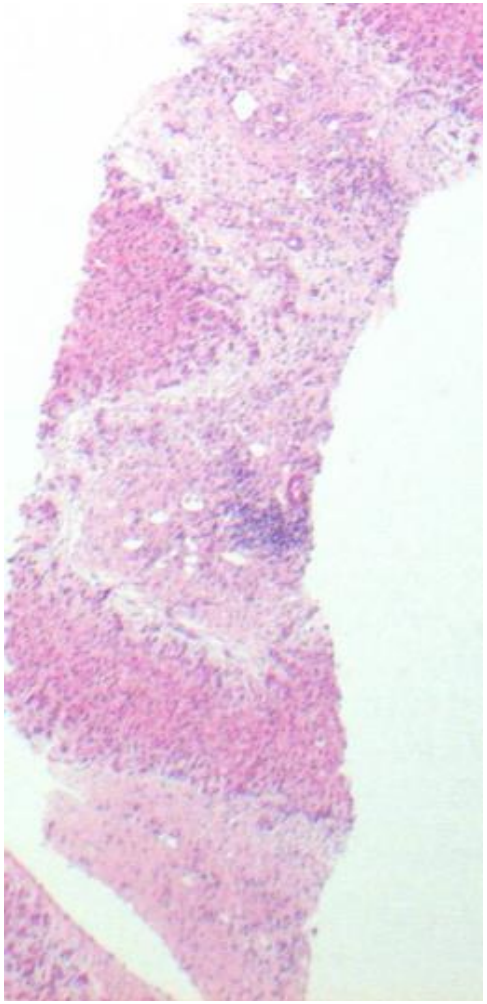
Conclusions

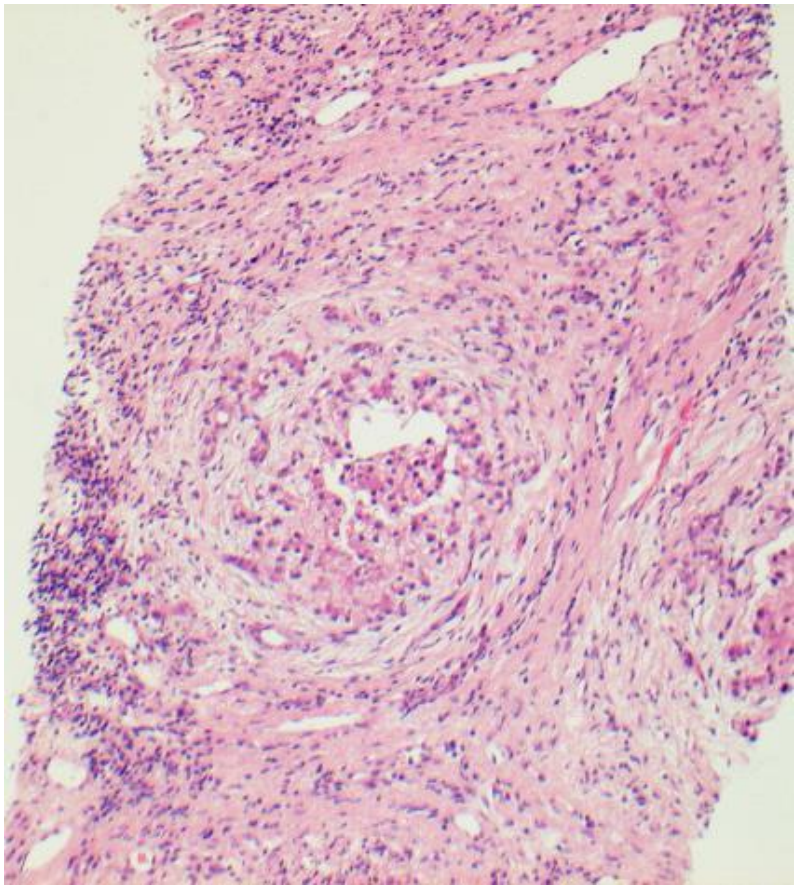
- Role of tissue diagnosis in biliary disease is evolving
- With PBC, more atypical variants are being identified
- For all biliary disease, histological staging may be problematic due to level of ducts affected and heterogeneity of disease/sampling variation
- Sampling techniques for biliary tract neoplasia are improving
- As always in liver disease, accurate histology reporting is dependent on clinicoradiological correlation

Ductular reaction & biliary interface

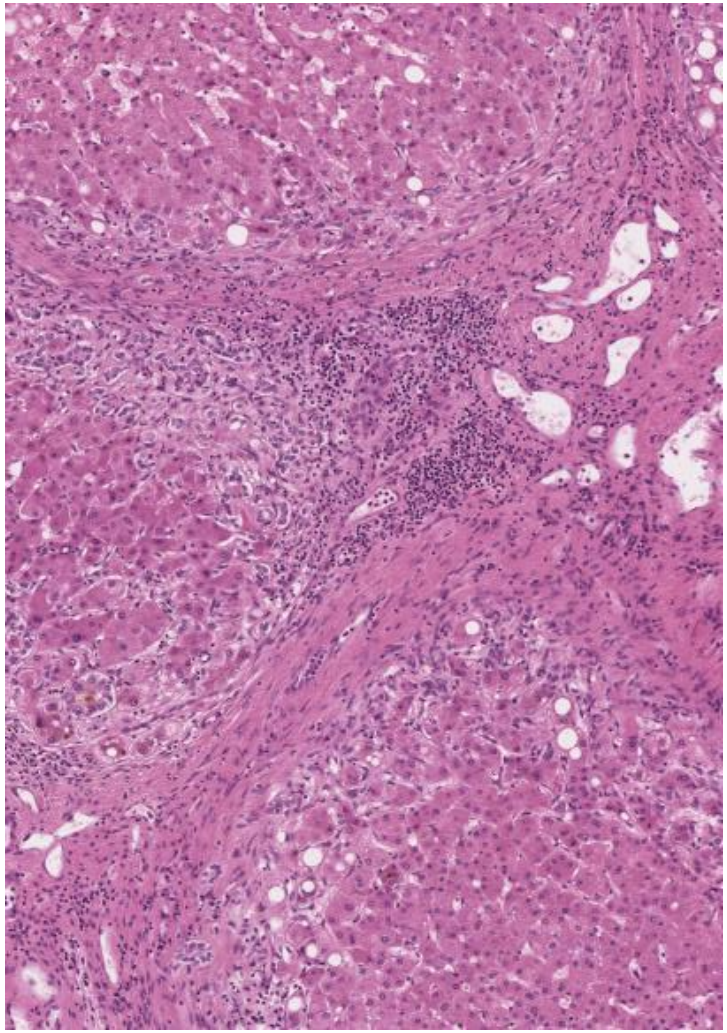


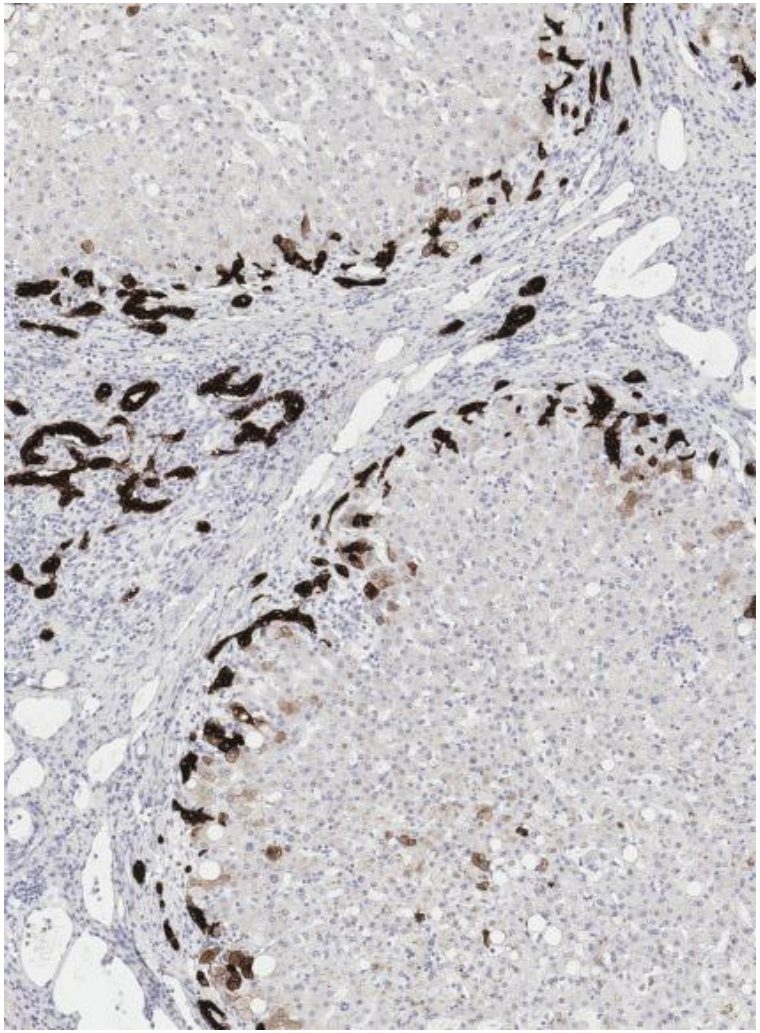
Peripheral haloing due to biliary interface activity



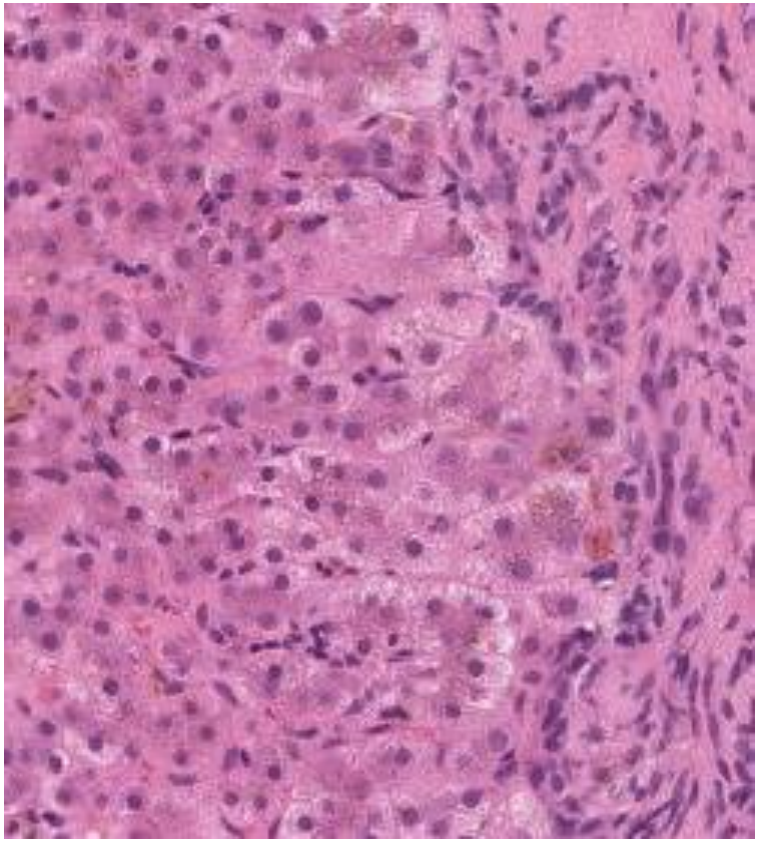


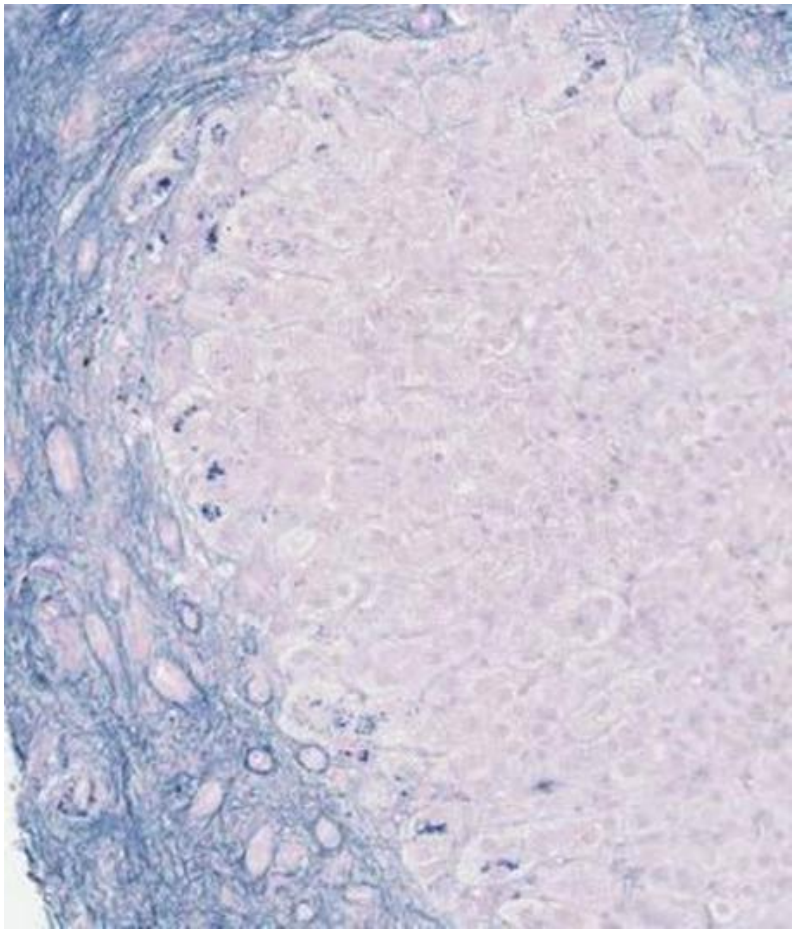
Neoductules highlighted by CK 7





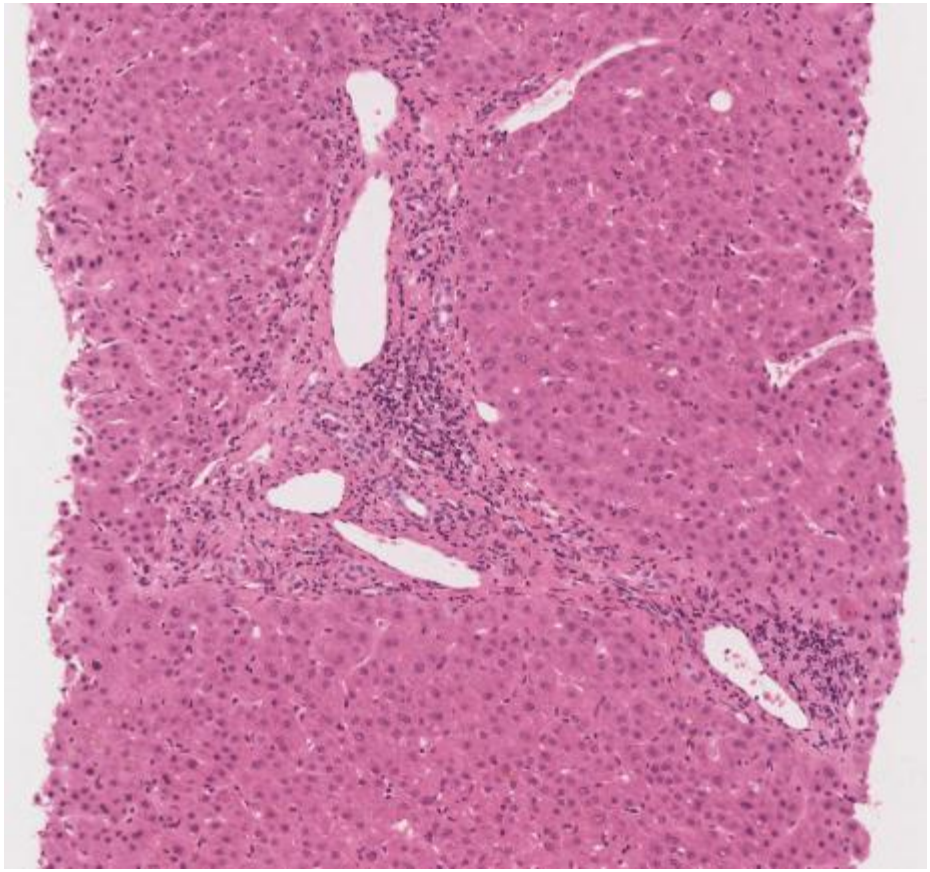
Cholate stasis – copper associated/ binding protein demonstrable

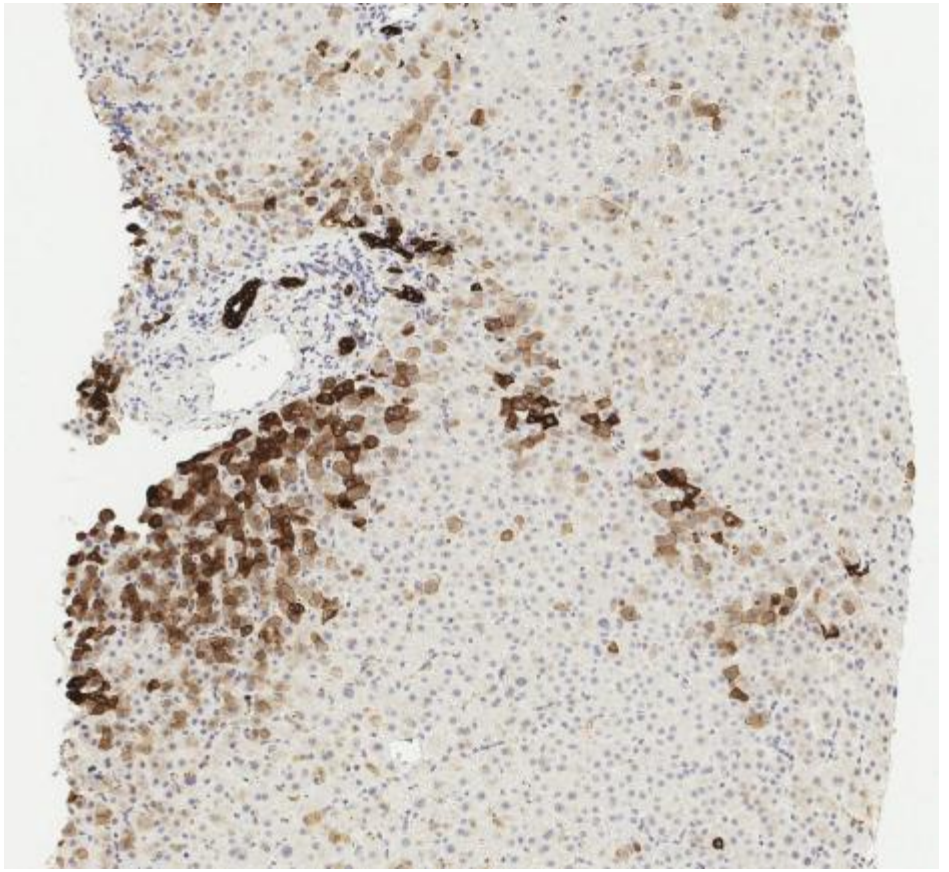




Victoria Blue

CK7 immunohistochemistry, with hepato-biliary metaplasia/ ductal/aberrant phenotype/ intermediate phenotype





Ductopenia with CK 7