22 November 2018
BD-IAP UK-LPG Liver Update

PBC/AIH variant/"overlap" syndrome vs PBC with hepatitic features ?

in a UDCA non-responder

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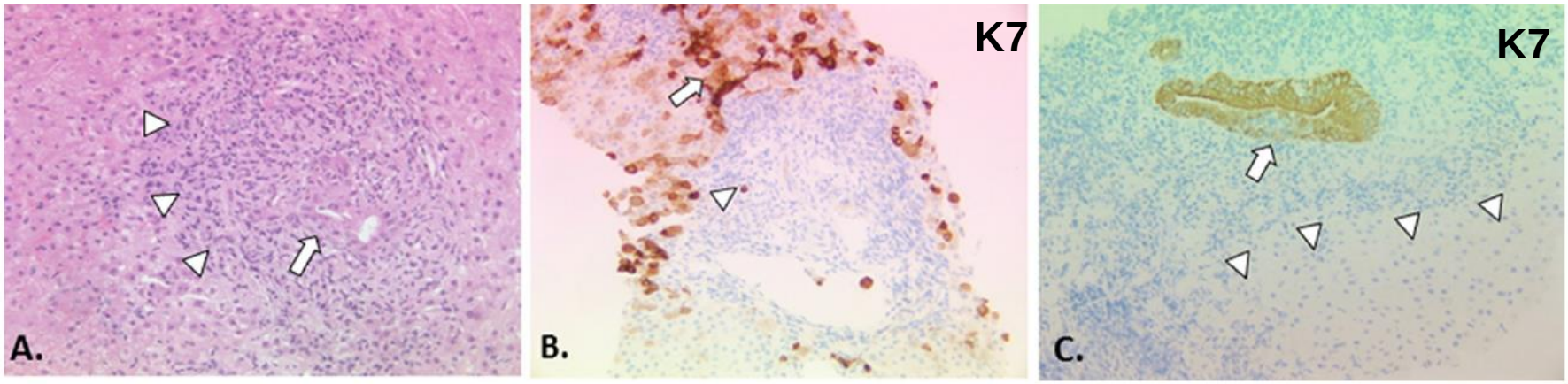
Primary biliary cholangitis (PBC)

- **autoimmune liver disease**
- immunogenetic and environmental factors for disease initiation
- UK prevalence 35/100,000
  annual incidence 2-3/100,000
- Most prevalent in women >50
- immune mediated biliary epithelial cell injury
  cholestasis
  progressive fibrosis

} end-stage biliary **cirrhosis**



Hirschfield et al Gut 2018

Primary biliary cholangitis (PBC)

Diagnosis

- cholestatic liver tests
- antimitochondrial antibodies-M2 (95% patients, >1/40)
- PBC-specific ANA: anti-gp210, anti-sp100

Treatment

Initiation

Ursodeoxycholic acid (UDCA)

2nd line therapy

Obeticholic acid (OCA) indications: - intolerance to UDCA
- high risk disease (UDCA failure)

Predictors of poor prognosis

male gender

younger age at onset (<45)

advanced disease at presentation

Hirschfield et al Gut 2018

Gut 2018;**0**:1–27

The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines

Gideon M Hirschfield,[1,2,3] Jessica K Dyson,[4,5,6] Graeme J M Alexander,[7,8] Michael H Chapman,[9] Jane Collier,[10] Stefan Hübscher,[3,11] Imran Patanwala,[12,13] Stephen P Pereira,[7,8,9] Collette Thain,[14] Douglas Thorburn,[7,8] Dina Tiniakos,[5] Martine Walmsley,[15] George Webster,[9] David E J Jones[4,5,6]

Role of liver biopsy

- Not used for diagnosis or monitoring disease progression unless in clinical trials

  (strong recommendation, high quality of evidence)

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Role of liver biopsy

- Not used for diagnosis or monitoring disease progression unless in clinical trials

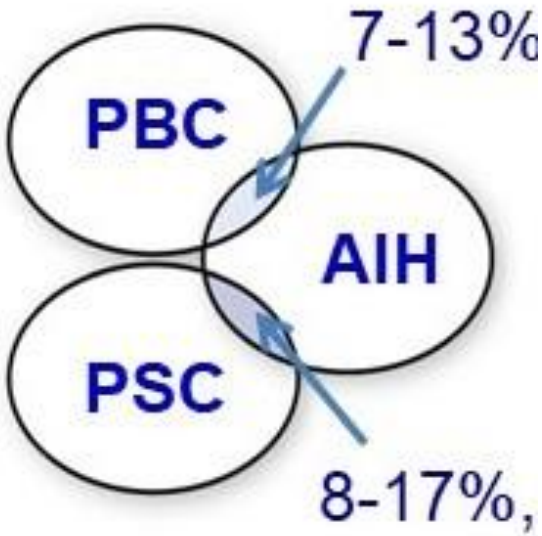
  (strong recommendation, high quality of evidence)

- Liver biopsy recommended for diagnosis and treatment guidance in suspected variant/"overlap" with autoimmune hepatitis

  Expert clinico-pathological review necessary

  (strong recommendation, moderate quality of evidence)

Identification of variant/"overlap" syndromes



49% in children

International Autoimmune Hepatitis Group Position Statement

Patients with autoimmune liver diseases should be **classified according to the predominant feature(s) of their disease**

Boberg, J Hepatol 2011

Challenging differential diagnosis in PBC

- "classical" PBC
- PBC with hepatitic features not needing additional immunosuppressive treatment
- PBC/AIH variant syndrome requiring immunosuppression
- PBC and other concurrent liver disease
  - Non-alcoholic steatohepatitis
  - Drug-induced liver injury
  - Viral hepatitis

Liver biopsy the most important diagnostic tool for the diagnosis of a variant syndrome

EASL 2015 & BSG 2018 guidelines

Paris criteria for the diagnosis of variant syndrome

Simultaneous or consecutive presence ≥ 2 out of 3 biochemical, serological and histological criteria of both PBC and AIH

PBC component criteria

- ALP ≥ 2x upper limit of normal (ULN) or GGT levels ≥5x ULN
- AMA +
- liver biopsy showing florid bile duct lesions

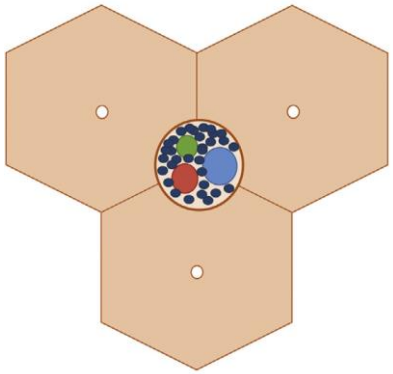
AIH component criteria

- ALT ≥ 5x ULN
- IgG levels ≥ 2x ULN or anti-SMA +
- moderate or severe periportal/periseptal interface hepatitis or lobular acidophilic bodies

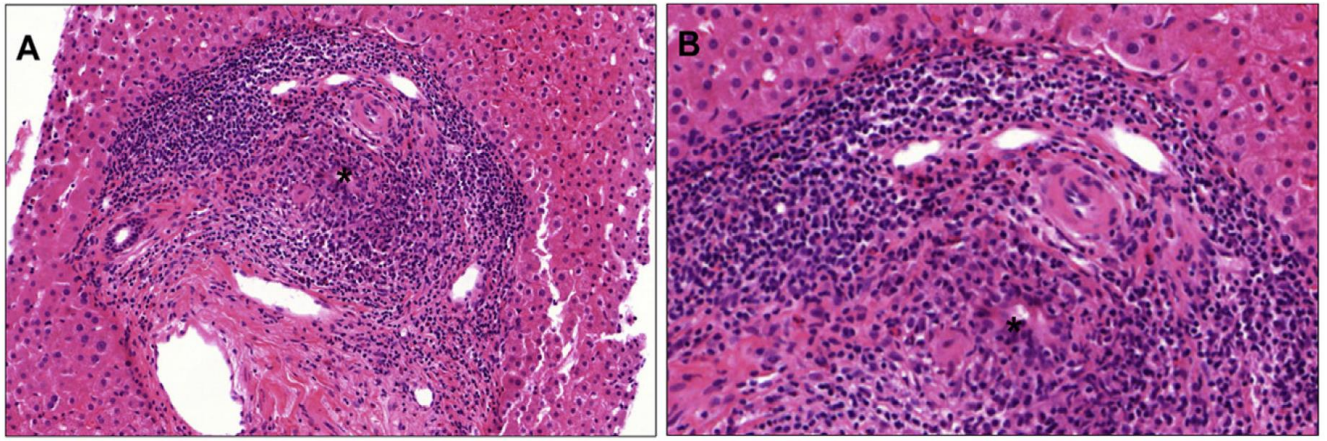
Chazouillères et al, Hepatology 1998

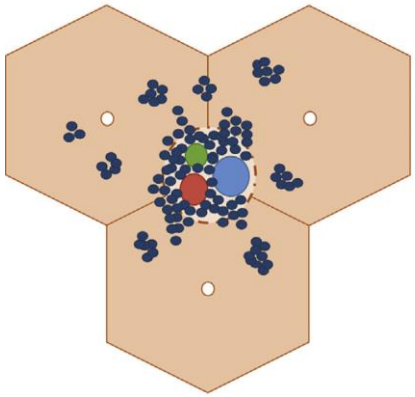
Sensitivity 92%, specificity 97%

Kuiper et al, Clin Gastroenterol Hepatol 2010

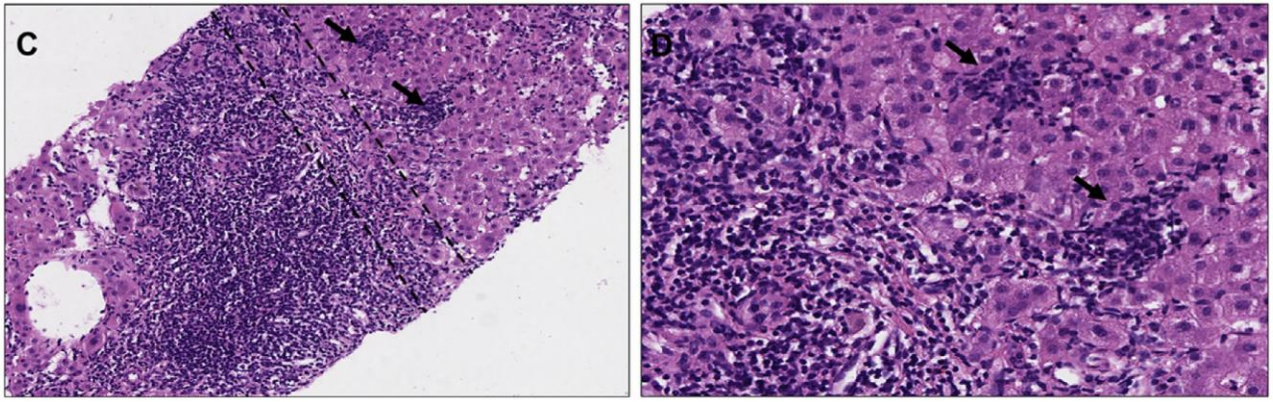


classical PBC





variant PBC/
”overlap” with AIH



Lobular inflammatory activity may be more important for the diagnosis of variant syndromes than interface inflammatory activity

Schulz, Best Pract Res Clin Gastroenterol 2018

Conditions that should alert fort the presence of a PBC variant syndrome

	Indicator for the presence of a variant syndrome
Laboratory findings Autoantibodies	- Markedly elevated transaminases and/or IgG levels - Presence of AIH-specific autoantibodies (in particular anti-SLA/LP)
Histology	- Prominent interface hepatitis and lobular inflammatory activity - mHAI score > 4/18
Course of disease	- Inadequate response to UDCA - Sudden increase of transaminases or deterioration of liver function

Schulz, Best Pract Res Clin Gastroenterol 2018

….and diagnostic uncertainties for PBC/AIH variant syndromes - 2018

	Uncertainties
Laboratory findings Autoantibodies	- Cut-off values - Specificity and diagnostic value of autoantibodies (anti-SLA/LP, anti-SMA, anti-dsDNA) - Relevance of antibody titers - Prognostic relevance of autoantibodies
Histology	- Cut-off values - Interobserver variability
Course of disease	- PBC patients with inadequate response to UDCA: difficult demarcation between a variant syndrome of PBC and a 'classical', difficult-to-treat PBC (an additional immunosuppressive treatment should be considered in the former and a second-line PBC therapy in the latter case)

Schulz, Best Pract Res Clin Gastroenterol 2018

PRACTICE POINTS

- **PBC patients may present with additional features of AIH**

  simultaneously or consecutively (1-11% based on Paris criteria)

- **Variant/"overlap" syndromes of PBC should be suspected** in pts with
  - remarkable elevation of transaminases and/or IgG levels,
  - AIH-specific autoantibodies (particularly anti-SLA/LP) **and**
  - **mHAI score of >4/18 on liver biopsy**

Schulz, Best Pract Res Clin Gastroenterol 2018

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  - remarkable elevation of transaminases and/or IgG levels,
  - AIH-specific autoantibodies (particularly anti-SLA/LP) **and**
  - **mHAI score of >4/18 on liver biopsy**

- **Patients with a suspected variant/"overlap" syndrome of PBC** should receive a **complete diagnostic work-up** including biochemistry, serology and **liver biopsy**

- **Patients with variant syndromes of PBC** should be treated with a **combination of UDCA and immunosuppression** analogous to AIH treatment guidelines

Schulz, Best Pract Res Clin Gastroenterol 2018

Circulation LS – Case 10

Female 50 years

PBC, UDCA non-responder. Elevated ALT, ? AIH overlap.

ALT 255, ALP 615, bilirubin 53, IgG 15.5

Clinically, cirrhosis

Fibroscan 15.6 kPa
Impaired synthetic function

AUTOANTIBODIES	
Anti-AMA-M2 Ab	+
Anti-AMA M2 3E(BPO) Ab	+
Anti gp210 Ab	+
ANA screen	-
Anti-SMA	-
Anti-LKM	-

LS10 according to Paris criteria for diagnosis of variant syndrome

Simultaneous or consecutive presence ≥ 2 out of 3 biochemical, serological and histological criteria of both PBC and AIH

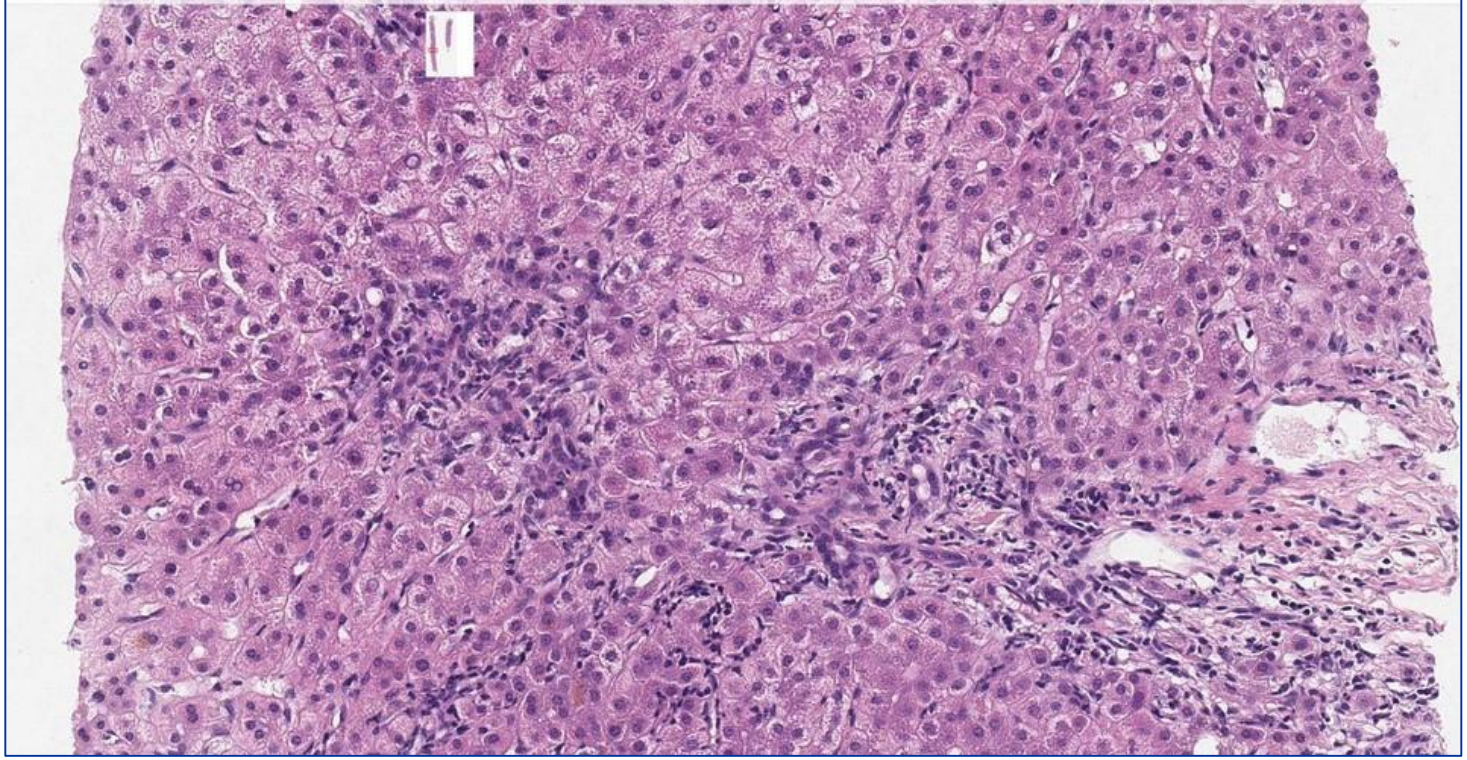
PBC component criteria

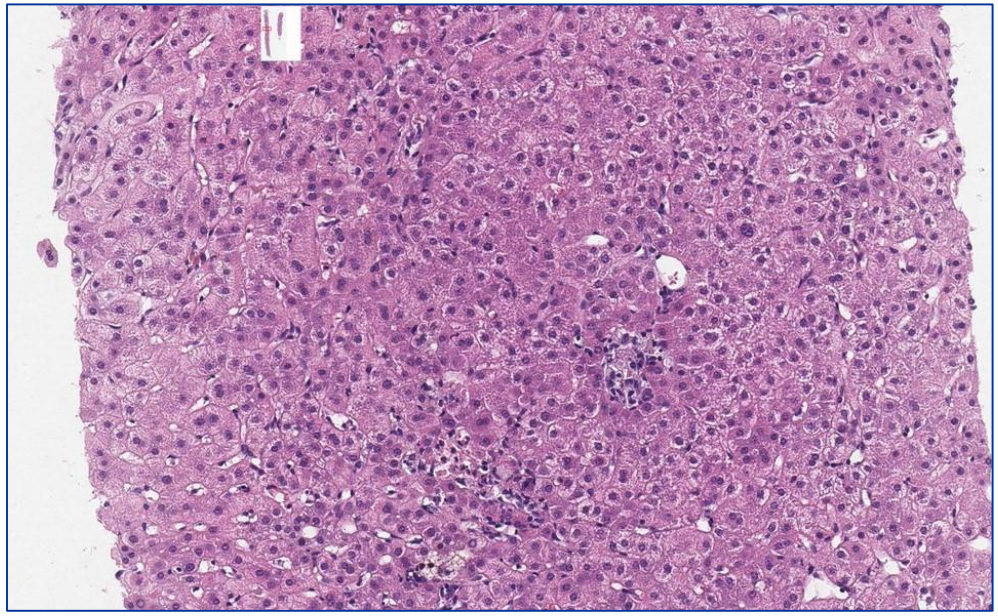
- ALP 615 (≥ 2x 130 ULN) or GGT levels ≥5x ULN
- AMA +
- liver biopsy in keeping with PBC

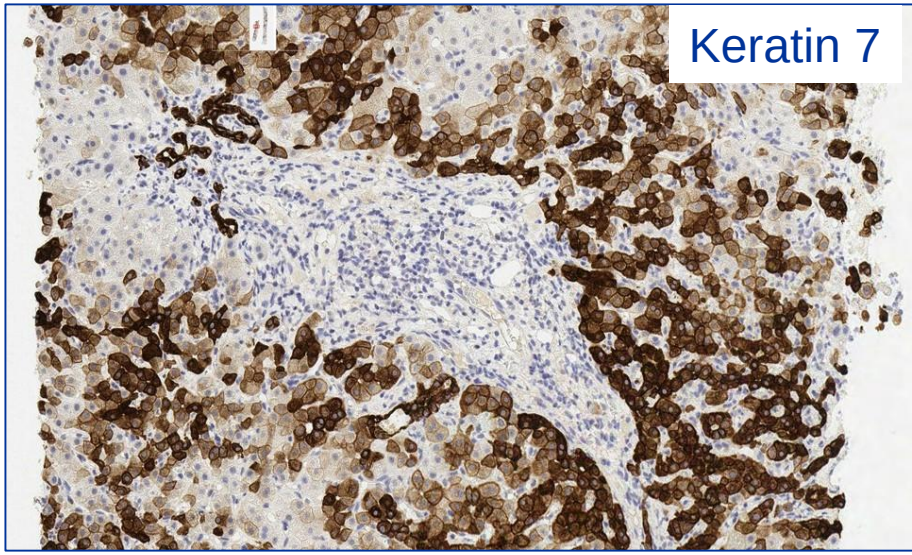
AIH component criteria

- ALT 255 (≥ 5x 40 ULN)
- IgG 15.5-18.5 (< 2x 16.0 ULN) or anti-SMA + NO
- moderate or severe periportal/periseptal interface hepatitis or lobular acidophilic bodies ???

LS10







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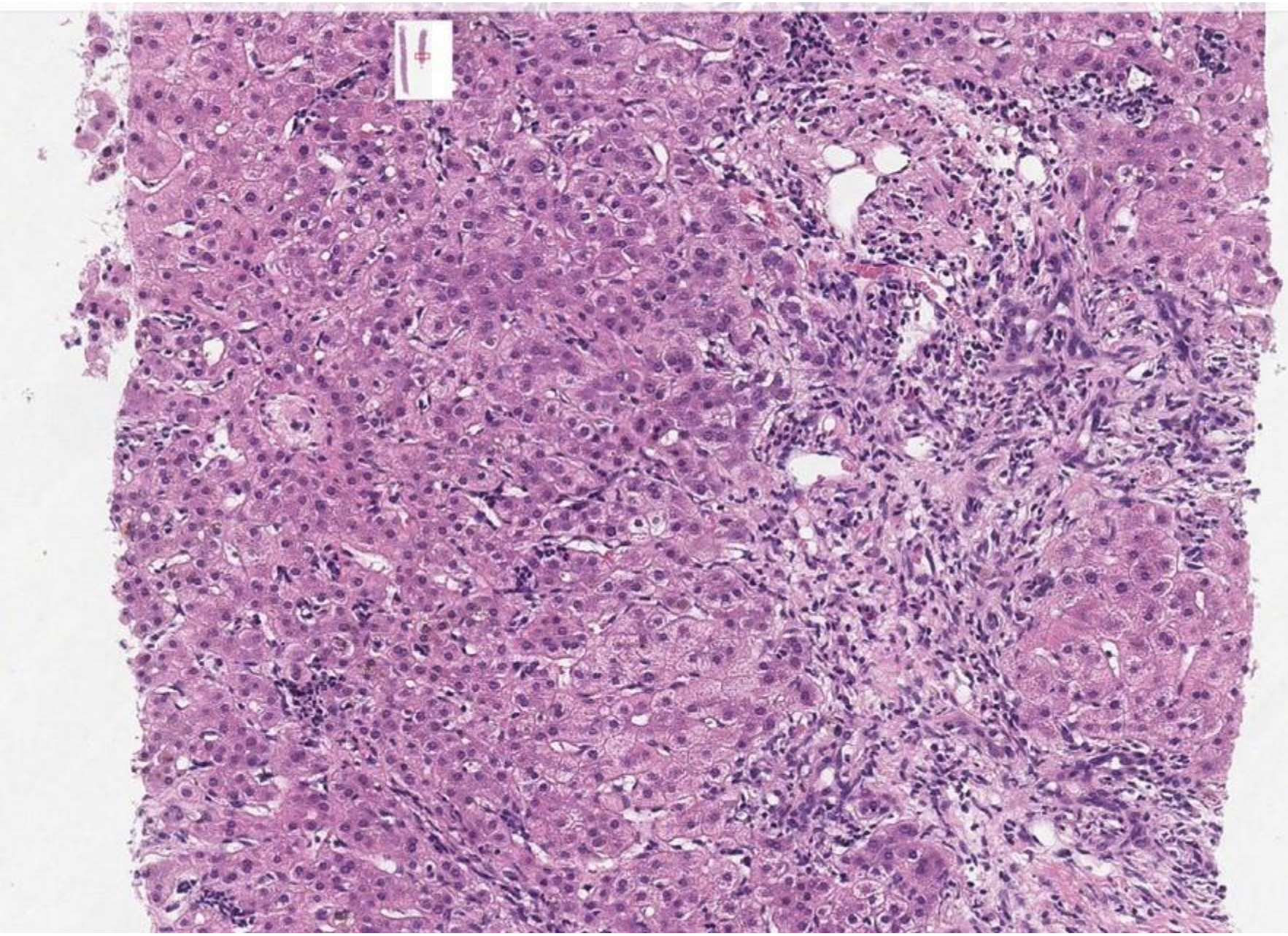

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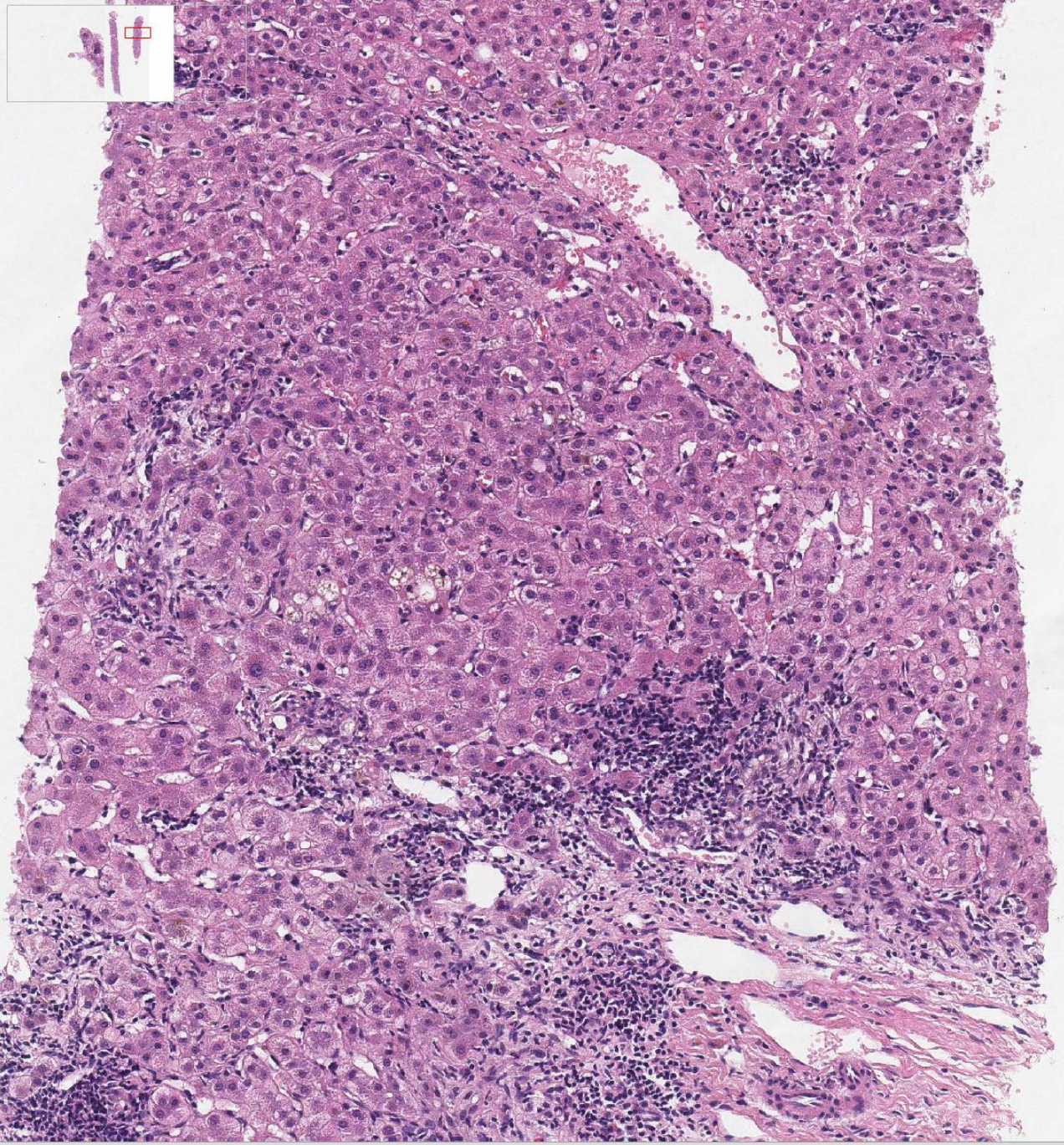

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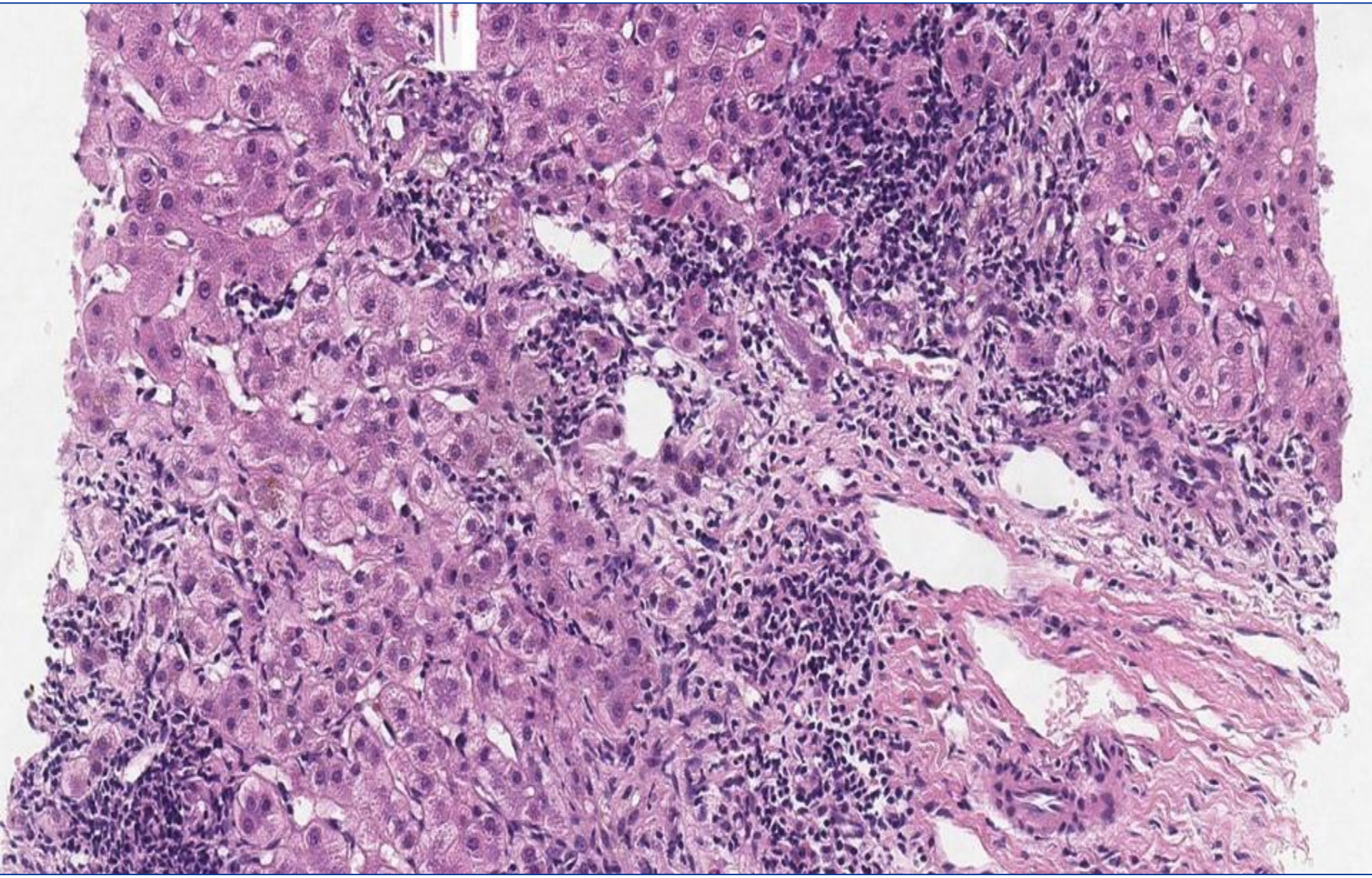
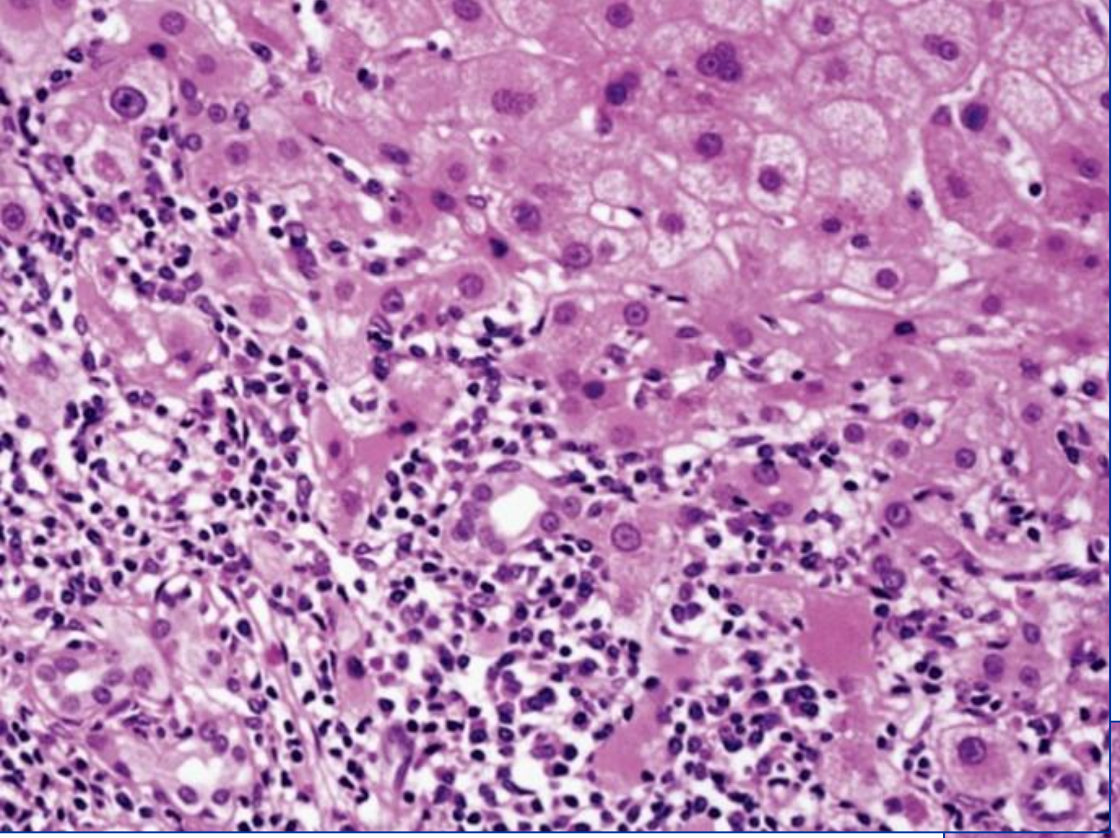
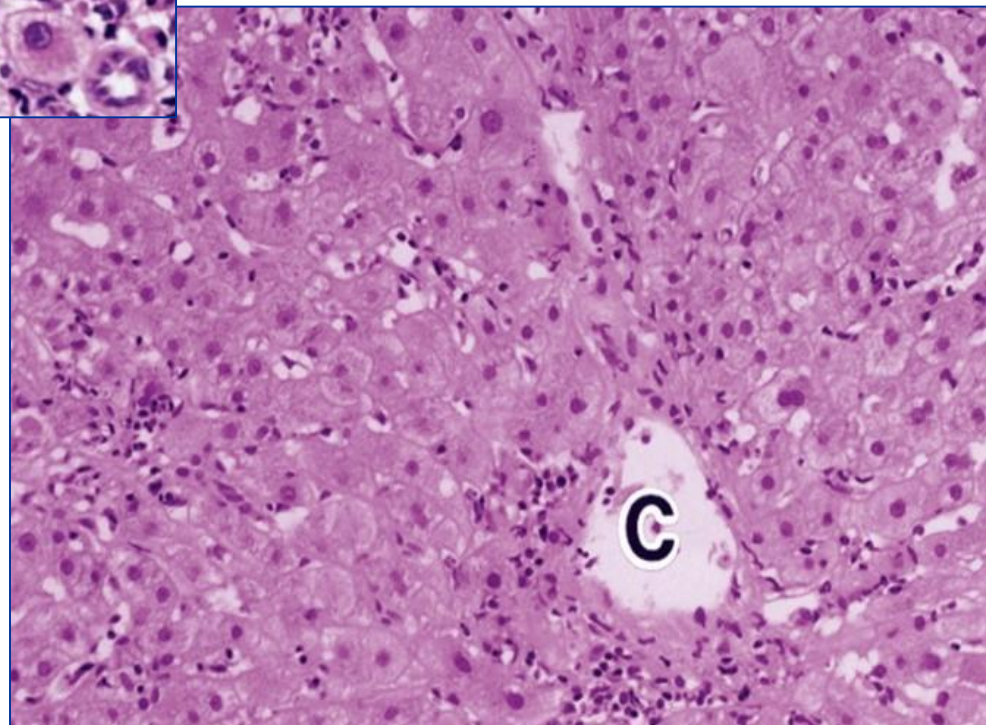
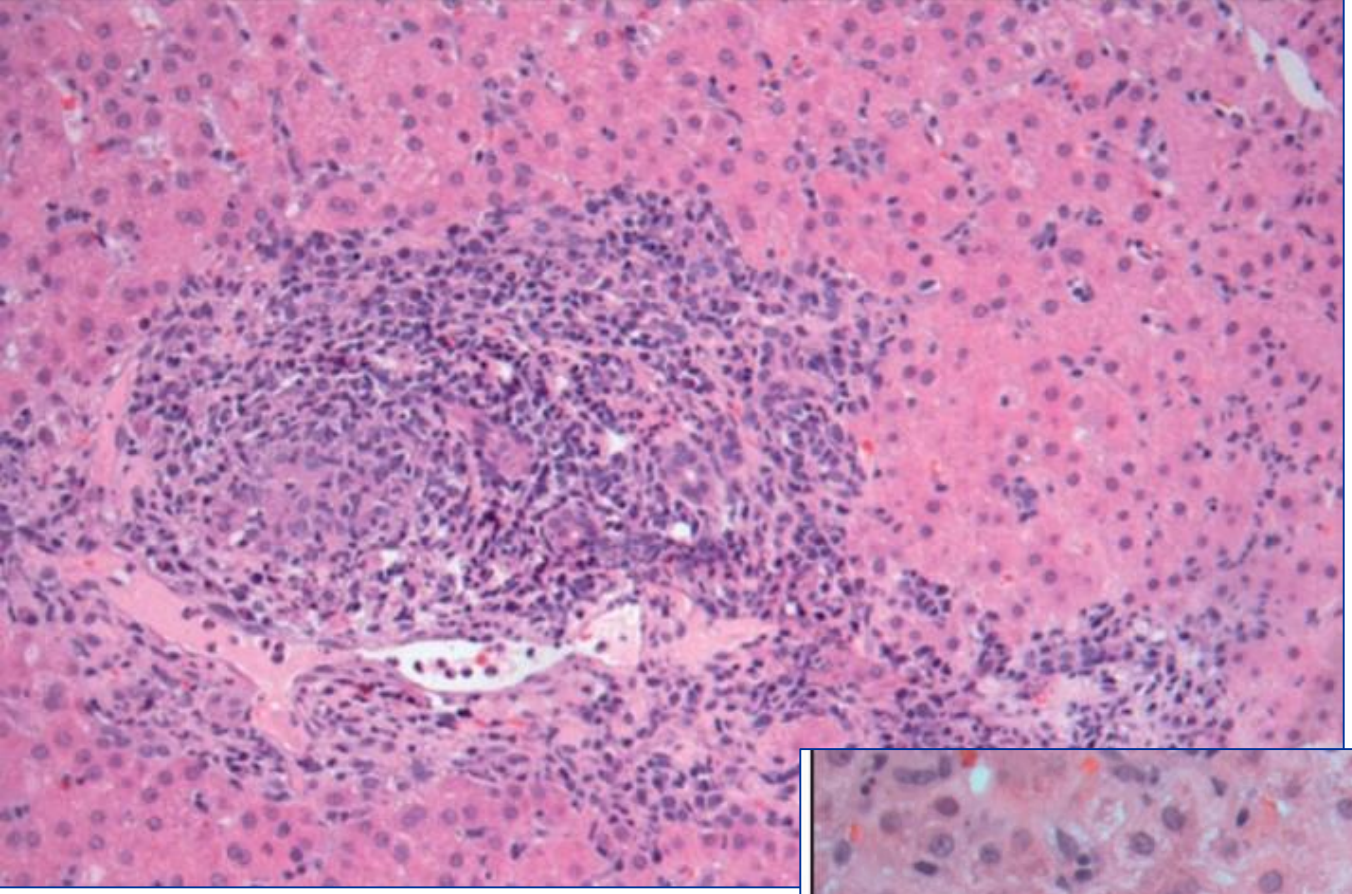


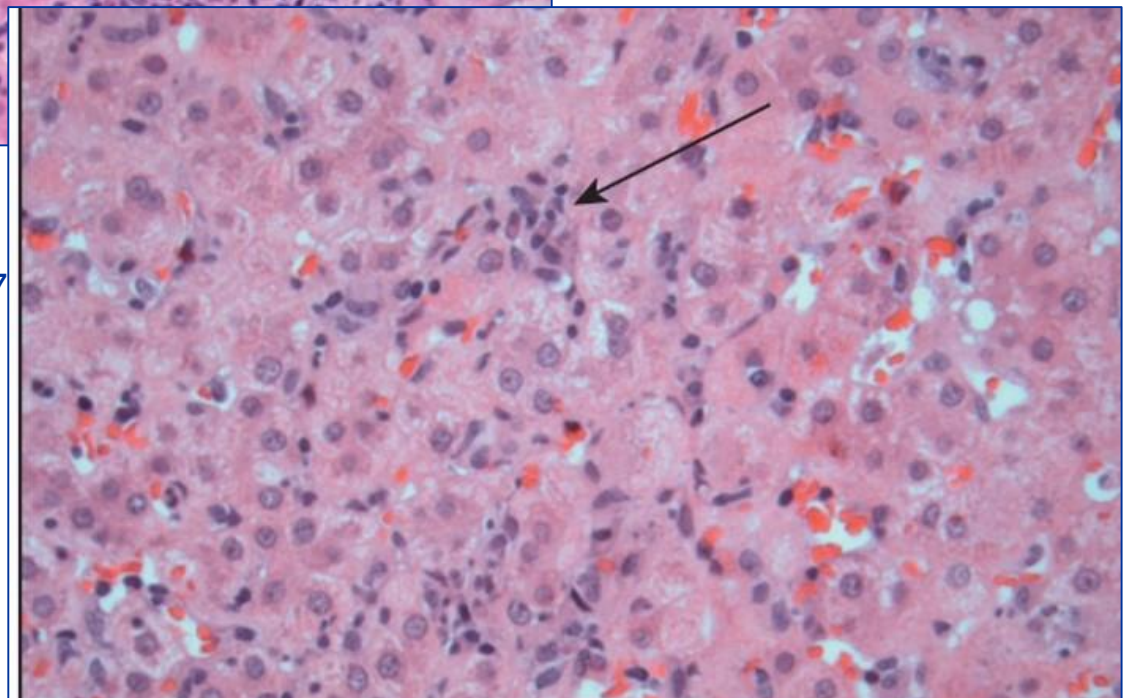


PBC

MacSween's Pathology of the Liver, 2017







PBC/AIH variant

MacSween's Pathology of the Liver, 2017

Circulation LS – Case 10 Follow up

Liver biopsy March 2018 No overlap, ductopenia, cholestasis

Second line therapy: OCA once weekly May 2018 + UDCA

Deteriorating liver function, jaundiced

Liver transplantation October 2018

Native liver histology: no bridging fibrosis or cirrhosis

very marked ductopenia

occasional portal granulomas

Discharged within 9 days, doing well since

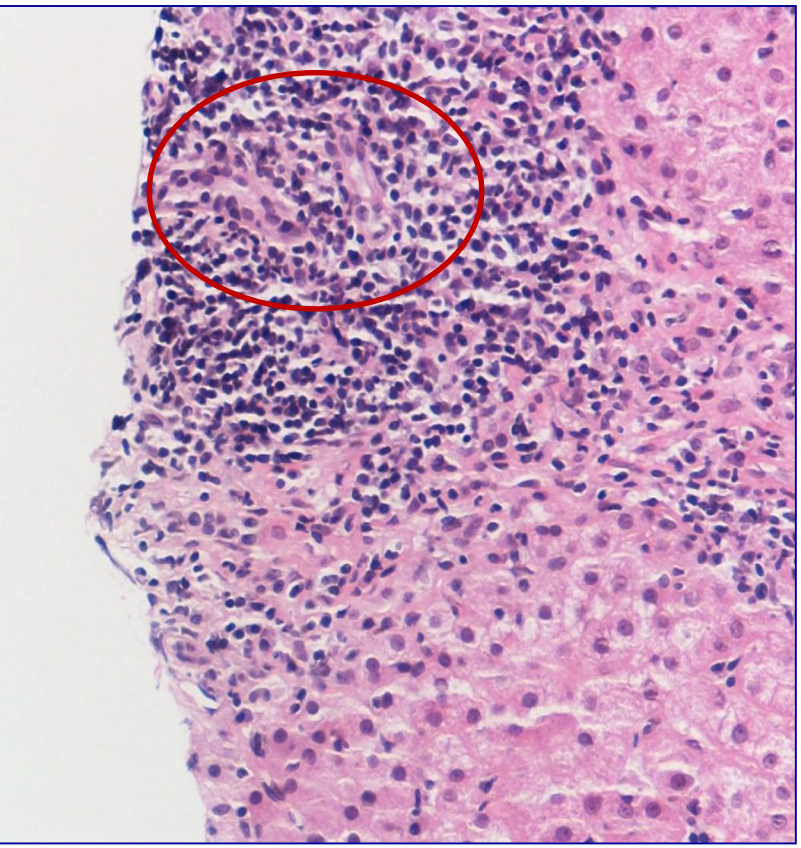
A multi-centre platform for research and stratified medicine in PBC (MRC Funded)

- UK-PBC Consortium **>170 NHS Trusts across the UK**
- Recruitment to the cohort commenced **1st January 20**08 and is ongoing
- **3 work-strands** - Recruitment, Phenotyping and Disease Stratification
  - Mechanisms of UDCA Non-Response
  - The User Interface
- Main Academic Centres: Newcastle, Birmingham, Cambridge

- **Specific aims related to histology:**

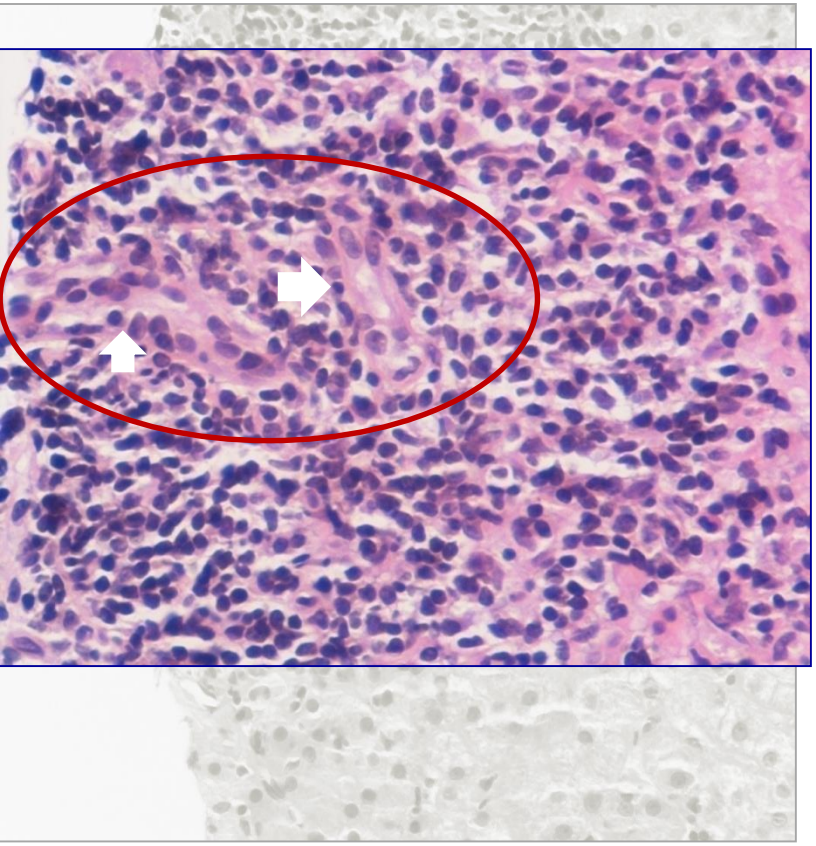
  To establish histological predictive indicators of response to current and future treatments.

Identification of variant/“overlap” syndromes



- 10% AIH: bile duct destruction

Identification of variant/"overlap" syndromes



- 10% AIH: bile duct destruction
- 10-28% AIH: lymphocytic cholangitis

de Boer, Histopathology 2015

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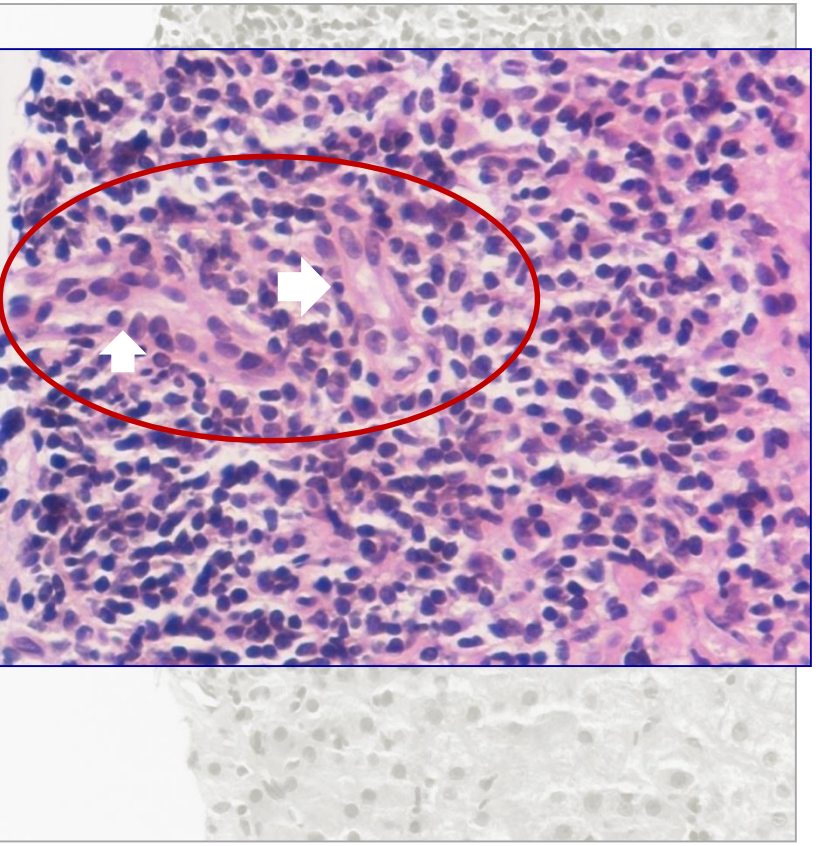

- 10% AIH: bile duct destruction
- 10-28% AIH: lymphocytic cholangitis

de Boer, Histopathology 2015

BUT

- AIH: bile duct injury is focal
- IgM/IgG ratio in the inflammatory infiltrate helps in D.D.

Abe, Med Mol Morphol 2014

Liver histology can **support** the clinical diagnosis of a variant/"overlap" syndrome, **highlight** the predominant disease and thus **guide** treatment

Czaja, Clin Gastroenterol Hepatol 2014