

Autoimmune hepatitis – diagnosis in collaboration between clinicians and pathologists

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The morphological diagnosis of inflammatory liver diseases represents one of the most difficult tasks confronting pathologists

- relatively low frequency of liver biopsies
- lack of practice and experience in individual pathologists
- frequent isomorphism of the inflammatory response forms and reactivity to highly heterogeneous stimuli or damage

pathologists rely entirely on
a knowledge of clinical parameters
for liver biopsy tissue diagnostics

The clinician has a “double debt to pay”

in terms

- of obtaining and supplying adequate liver biopsy tissues
- by providing comprehensive information on the clinical and laboratory findings

Of course the clinician has to consider the potential complications of such an invasive measure.

Conclusion:

The better the information
provided by the clinician to the
pathologist -
the better the morphological
diagnosis will be

Requirements for quality of a liver biopsy cylinder

- Length of a biopsy cylinder should be at least 15-30 mm
- Thickness of the cylinders should be 1.2-2 mm
- Cylinder should contain at least 6-8 portal fields

Strong correlation between

- number of portal tracts
and
- the validity of the
morphological diagnosis

As a rule, biopsy cylinders longer than 30 mm do not increase the information content

Laboratory requirements for morphological diagnostics at an Institute of Pathology

- Fixation of liver tissue immediately after extraction of biopsy material (by clinician)
- Fixation with 2.5 - 4% neutral buffered formaldehyde (provided by the pathologist)
- Realization of at least 8 - 10 sectional cuttings
- Standardized staining techniques to assess the liver tissue compartments
- Special methods
 - Immunohistochemistry
 - molecular pathology
 - electron microscopy

International Autoimmune Hepatitis Group Report*: review of criteria for diagnosis of autoimmune hepatitis

- Revised descriptive criteria for diagnosis of autoimmune hepatitis
- Revised scoring system for diagnosis of autoimmune hepatitis

*Alvarez et al 1999

Revised criteria for diagnosis of autoimmune hepatitis (Alvarez et al 1999)

Features	Definite	Probable
1 Features	Definite	Probable
l Liver histology	Interface hepatitis (as defined in text) of moderate or severe activity with or without lobular hepatitis or central-portal bridging necrosis, but <i>without</i> biliary lesions or well-defined granulomas or other prominent changes suggestive of a different aetiology.	Same as for "definite".
§ Serum biochemistry	Any abnormality in serum aminotransferases, especially (but not exclusively) if the serum alkaline phosphatase is not markedly elevated. Normal serum concentrations of α_1 -anti-trypsin, copper and ceruloplasmin.	Same as for "definite" but patients with abnormal serum concentrations of copper or ceruloplasmin may be included, <i>provided that Wilson's disease has been excluded by appropriate investigations.</i>
§ Serum immunoglobulins	Total serum globulin <i>or</i> γ -globulin <i>or</i> IgG concentrations greater than 1.5 times the upper normal limit.	Any elevation of serum globulin <i>or</i> γ -globulin <i>or</i> IgG concentrations above the upper normal limit.
§ Serum autoantibodies	Seropositivity for ANA, SMA or anti-LKM-1 antibodies at titres greater than 1:80. Lower titres (particularly of anti-LKM-1) may be significant in children. Seronegativity for AMA.	Same as for "definite" but at titres of 1:40 or greater. Patients who are seronegative for these antibodies but who are seropositive for other antibodies specified in the text may be included.
γ Viral markers	Seronegativity for markers of current infection with hepatitis A, B and C viruses.	Same as for "definite".
(Other aetiological factors	Average alcohol consumption less than 25 g/day. No history of recent use of known hepatotoxic drugs.	Alcohol consumption less than 50 g/day and no recent use of known hepatotoxic drugs. Patients who have consumed larger amounts of alcohol or who have recently taken potentially hepatotoxic drugs may be included, <i>if there is clear evidence of continuing liver damage after abstinence from alcohol or withdrawal of the drug.</i>

Alcohol content of 1 bottle of beer

$$330 \text{ ml} \cdot \frac{4,8}{100} \cdot 0,8 = 12,7 \text{ g Alcohol}$$

Alcohol content of 1 glass of wine

$$100 \text{ ml} \cdot \frac{11}{100} \cdot 0.8 = 8,8 \text{ g Alcohol}$$

Revised scoring system for diagnosis of autoimmune hepatitis I (Alvarez 1999)

Revised scoring system for diagnosis of autoimmune hepatitis		
Parameters/Features	Score	Notes*
Female sex	+ 2	
ALP:AST (or ALT) ratio:		
<1.5	+ 2	1
1.5–3.0	0	
> 3.0	–2	
Serum globulins or IgG above normal		
>2.0	+3	
1.5–2.0	+2	
1.0–1.5	+1	
<1.0	0	
ANA, SMA or LKM-1		
>1:80	+3	2
1:80	+2	
1:40	+1	
<1:40	0	
AMA positive	–4	
Hepatitis viral markers:		
Positive	–3	3
Negative	+3	
Drug history:		
Positive	–4	4
Negative	+1	
Average alcohol intake		
<25 g/day	+2	
>60 g/day	–2	

Revised scoring system for diagnosis of autoimmune hepatitis II (Alvarez 1999)

Liver histology:		
Interface hepatitis	+3	
Predominantly lymphoplasmacytic infiltrate	+1	
Rosetting of liver cells	+1	
None of the above	-5	
Biliary changes	-3	5
Other changes	-3	6
Other autoimmune disease(s)	+2	7
Optional additional parameters:		8
Seropositivity for other <i>defined</i> autoantibodies	+2	9
HLA DR3 or DR4	+1	10
Response to therapy:		
Complete	+2	11
Relapse	+3	
<hr/>		
Interpretation of aggregate scores:		
Pre-treatment:		
Definite AIH	>15	
Probable AIH	10-15	
Post-treatment:		
Definite AIH	>17	12
Probable AIH	12-17	

Simplified Criteria for the Diagnosis of Autoimmune Hepatitis

(Hennes et al 2008)

Variable	Cutoff	Points
ANA or SMA	$\geq 1:40$	1
ANA or SMA	$\geq 1:80$	
or LKM	$\geq 1:40$	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥ 6 : probable AIH
		≥ 7 : definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

Clinical parameters and symptoms accompanying autoimmune liver damage I

- The female gender predominates
- Occurrence in all age classes
- Occurrence of two peaks in adolescence and in the 4th - 6th decade
- Prototype: young patients with endocrine disorders
- Insidious onset
- General prodromal symptoms in the form of fatigue, anorexia, tiredness, pallor
- Alternating jaundice
- Abdominal pain
- diarrhoea
- Weight loss

Clinical parameters and symptoms accompany autoimmune liver damage II

- Arthralgia
- Non-specific skin changes
- Mild hepatomegaly and splenomegaly
- Highly variable symptoms in individual patients
- Simultaneous occurrence of other autoimmune diseases in the same patient or in first-degree relatives
- Determination of serum levels and changes
 - IgG level
 - biochemistry and antibodies – e.g. pANCA , cANCA, ASGPR and others

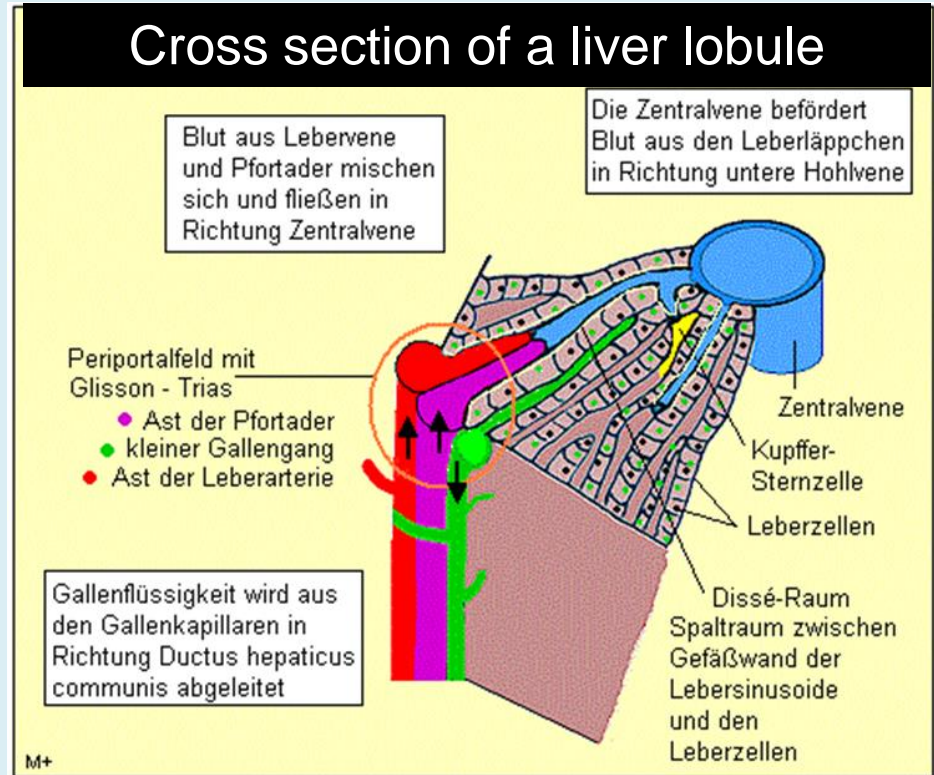
Despite all the advances in diagnostics of autoimmune liver disease, the statement made in 1999 still holds today:

"There are nowadays no specific symptoms, signs, specific liver tests or serum abnormalities, that are of sufficient evidence to be considered part of the diagnostic criteria"

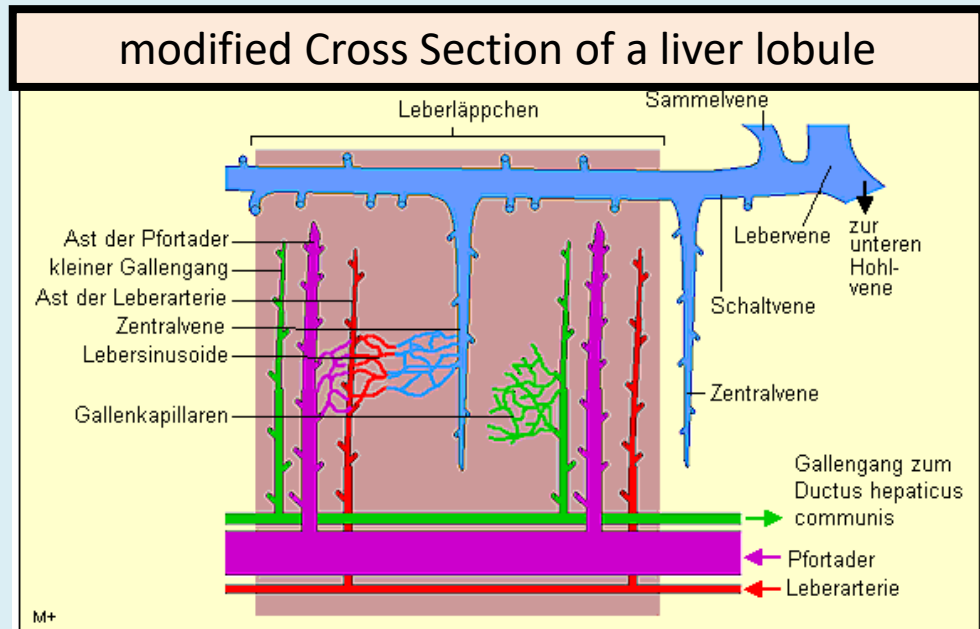
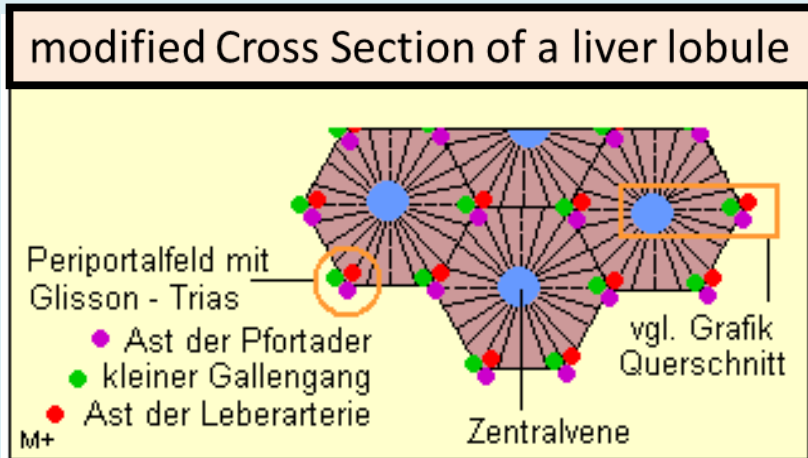
(Alvarez F. 1999)

Normal Histomorphology of the Liver I

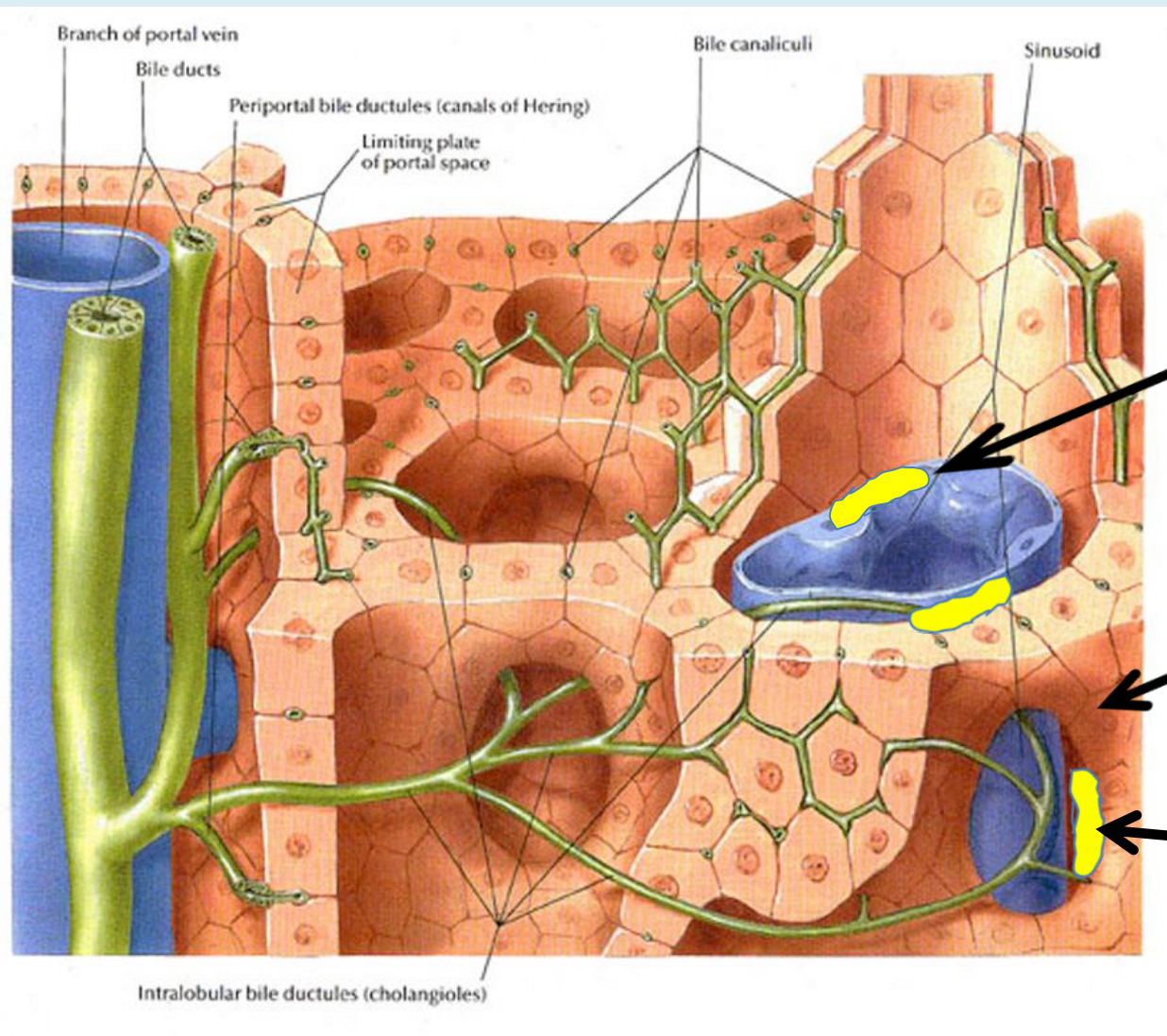
- Portal/peroportale Unit
Periportal/portal unit tract (Glisson tract) with small branches of the portal vein, liver artery, bile ducts + connective tissue
- Sinusoidale Unit
Lobule unit with sinusoids, Kupffer cells (macrophages), sinusoidal endothelial cells and hepatocytes
- Vena centralis



Normal Histomorphology of the Liver II



modified after: MedizInfo
www.medizinfo.de/leber/anatomie/leberfeinbau.shtml



intrasinusoidal
Kupffer cells =
liver macrophages

Dissé-Region

Hepatic stellate cells
perivascular in
Dissé-Region

Classification of Autoimmune Hepatitis

Autoimmune hepatitis is a chronic progressive inflammation of the liver, which if left untreated will ultimately result in progressive destruction of the organ

- Type 1 autoimmune hepatitis
- Type 2 autoimmune hepatitis

Classification of autoimmune hepatitis

Typ		ANA	SMA	Anti-SLA/LP	Anti-LKM1/LC1
1	ANA	+	(+)		
	SMA		+		
	Anti-SLA		(+)	+	
2	Anti-LKM1/LC1				+

Characteristics of Autoimmune Hepatitis Type 1 and Type 2*

Type	Type 1 AIH	Type 2 AIH
Characteristic antibodies	ANA SMA Anti-actin antibodies SLA/LP (tRAP)	LKM
	pANNA and others	
Incidence	worldwide	worldwide rare in North America
Age	all	Childhood / young adults
Gender	female 75%	female 95%
Association with other autoimmune diseases	common	common
Clinical severity	broad range	commonly severe
Histology	very variable	generally advanced
Relaps after drug withdrawal	variable	common
* modified after Krawitt (2006)		

Frequency of Autoimmune Hepatitis

- No sufficient data about frequency and distribution of autoimmune hepatitis
- 17 cases of illness / 1.000.000 people (Wirth, 2010)
- 0.1-1.2 cases of illness /100.000 people in Western Europe
- 0.08-0.015 cases of illness /100.000 people in Japan (Sukerek, 2010)

Concomitant autoimmune diseases of autoimmune hepatitis

- Primary sclerosing cholangitis (PSC)
- Primary biliary cirrhosis (PBC)
- Overlap syndrome of AIH / PBC and AIH / PSC
- Rheumatoid arthritis
- Glomerulonephritis
- Haemolytic anaemias
- Thyroid diseases (e.g. Hashimoto's thyroiditis)
- Diabetes mellitus
- Vitiligo and other skin manifestations
- Coeliac disease
- Chronic inflammatory bowel diseases

Concomitant non-autoimmune diseases of autoimmune hepatitis

- Alcohol damage
- Medical drug-induced damage
- Combined alcohol and drug damage
- Viral hepatitis
- Non-toxic alcoholic steatohepatitis (NASH)
- Metabolic disorders

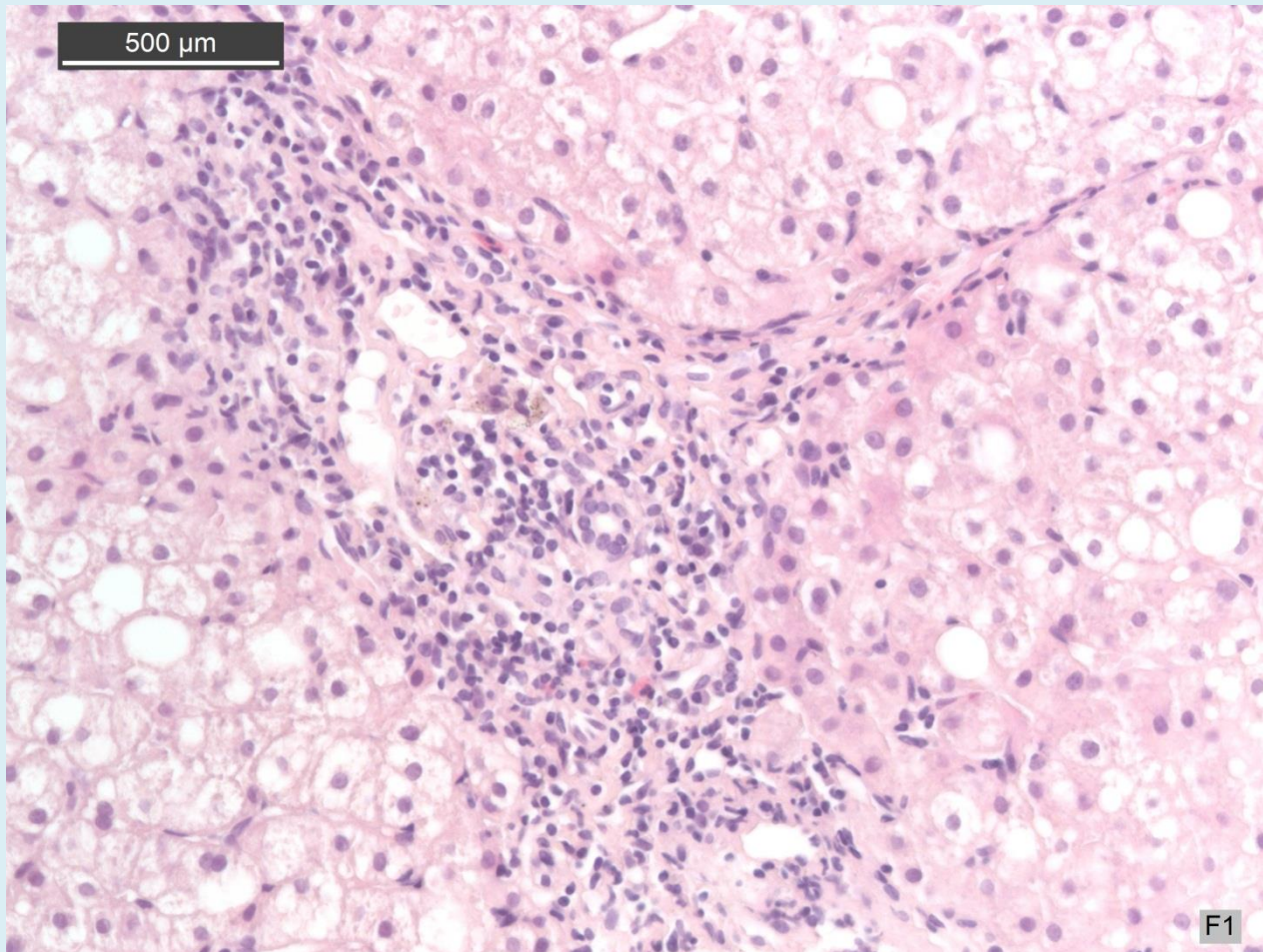
Morphology of autoimmune hepatitis

- **Very variable pattern of liver damage**
- Periportal inflammation
- Interface hepatitis
- Rosetting due to single cell necrosis
- Hydropic swelling of periportal hepatocytes
- Lobular single-cell necrosis
- Kupffer cell hyperplasia
- Necrotic and collapse fields
- Fibroses - porto-portal and portal in chronic disease

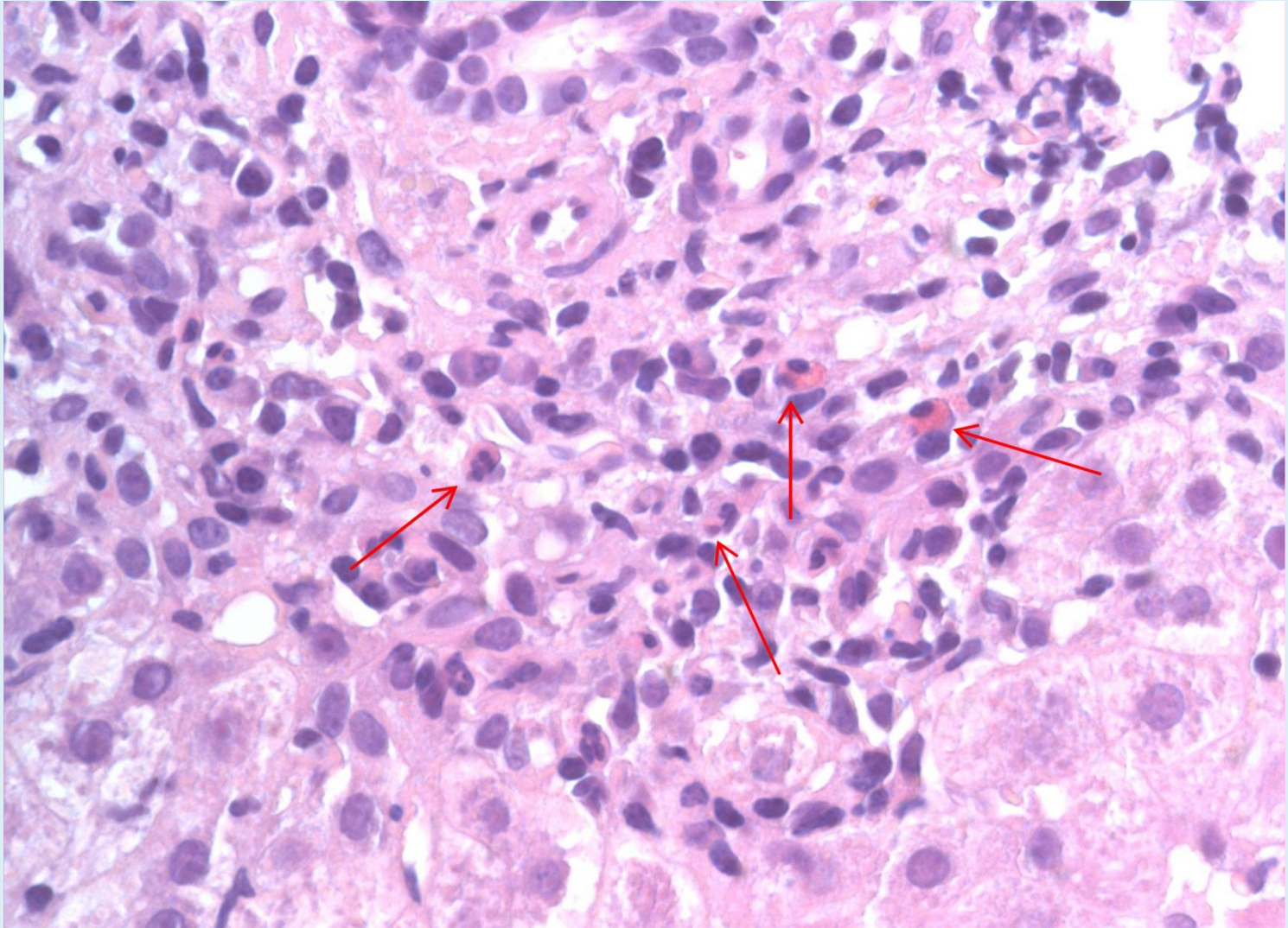
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Inflammatory infiltration of the portal tracts

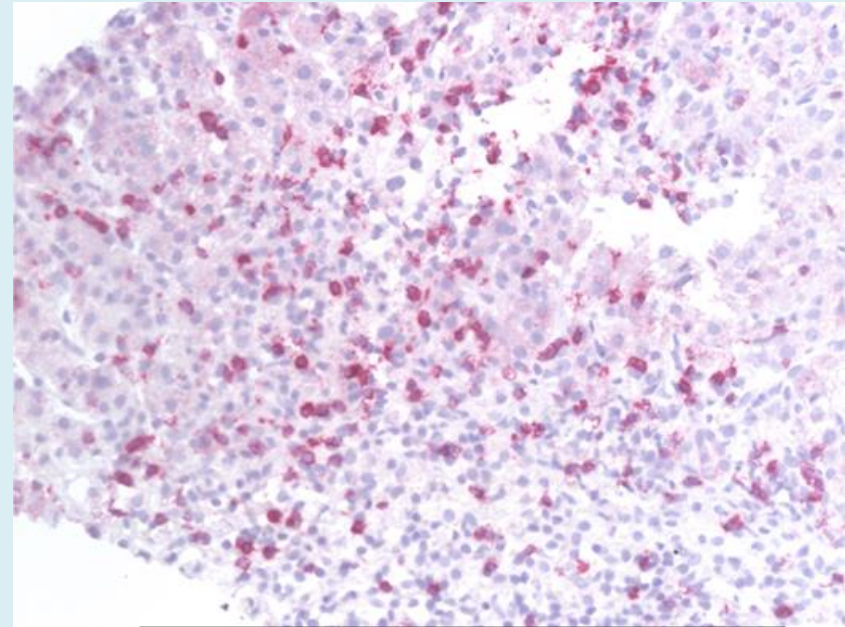
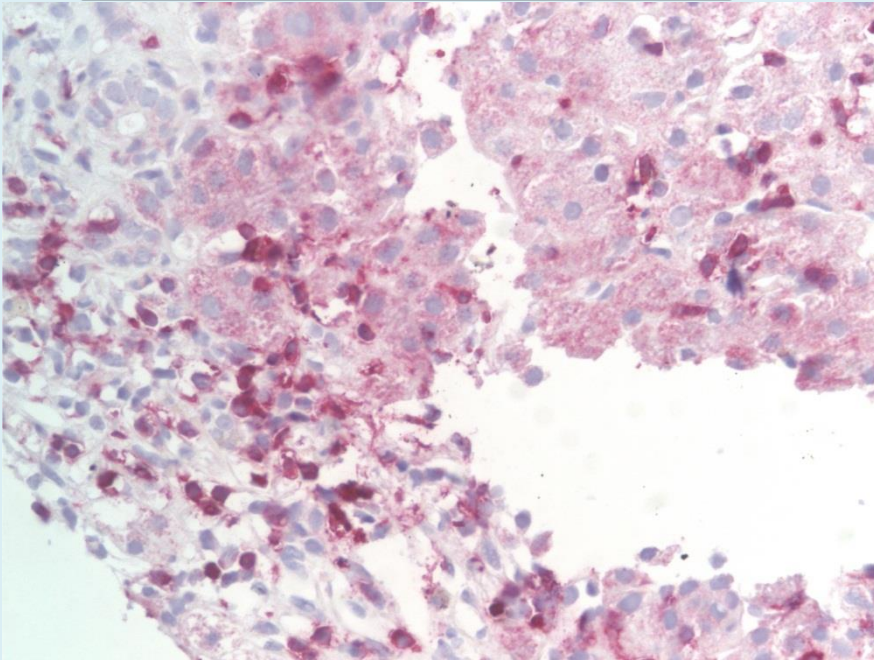


Infiltration of the portal tract by lymphocytes, plasma cells, eosinophilic granulocytes (arrows), histiocytes



Predominant T-lymphocytes

CD3-positive lymphocytes

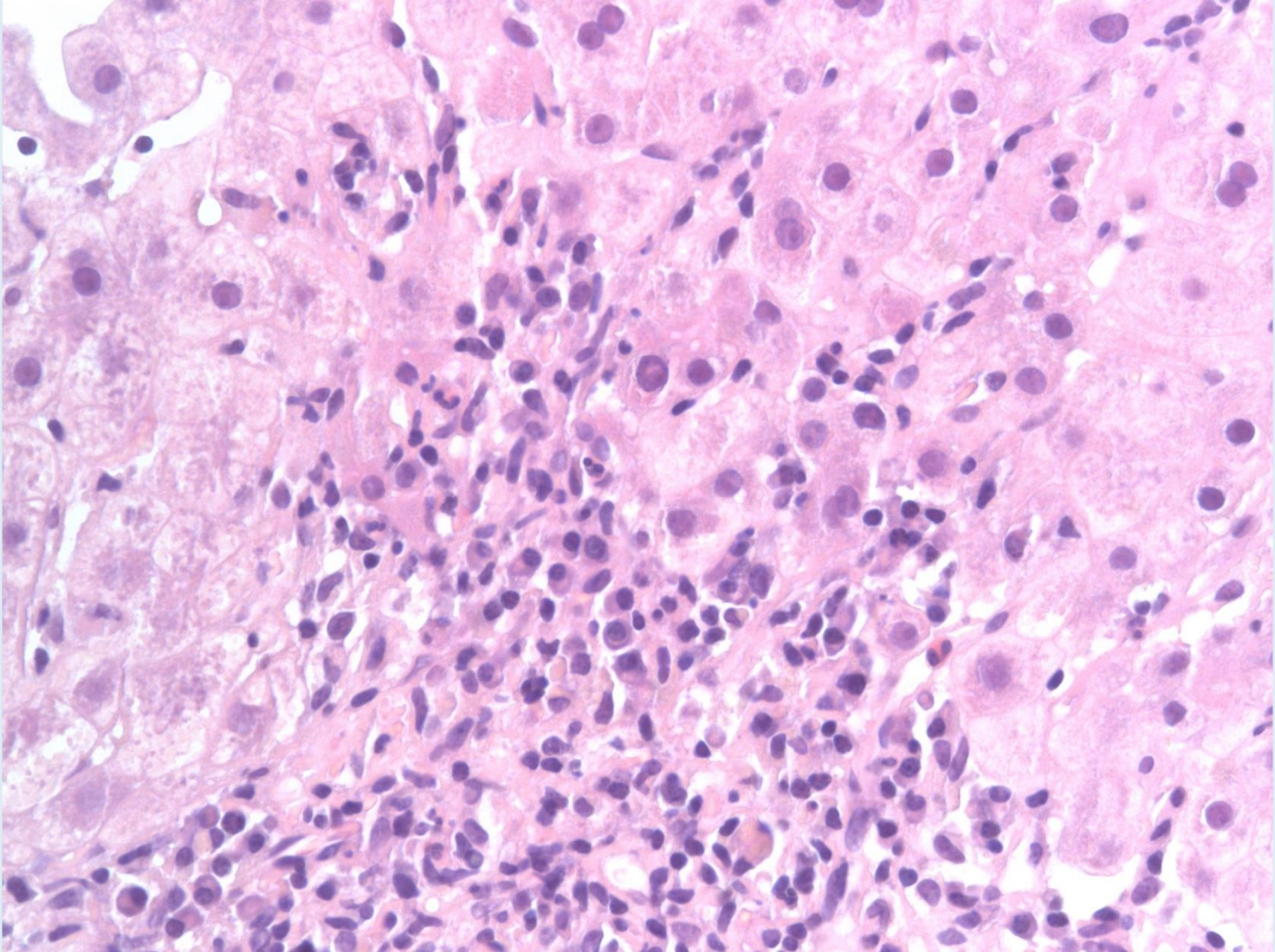


CD8-positive lymphocytes

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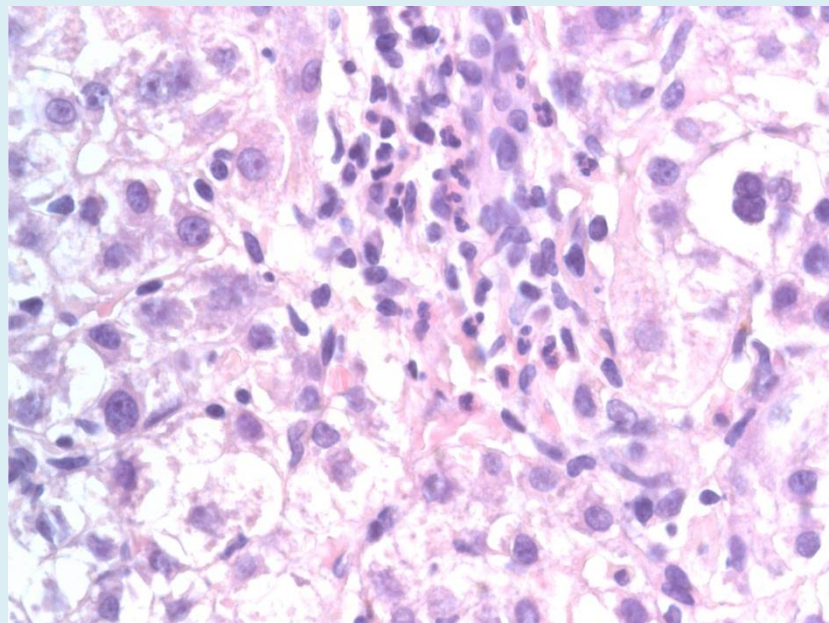
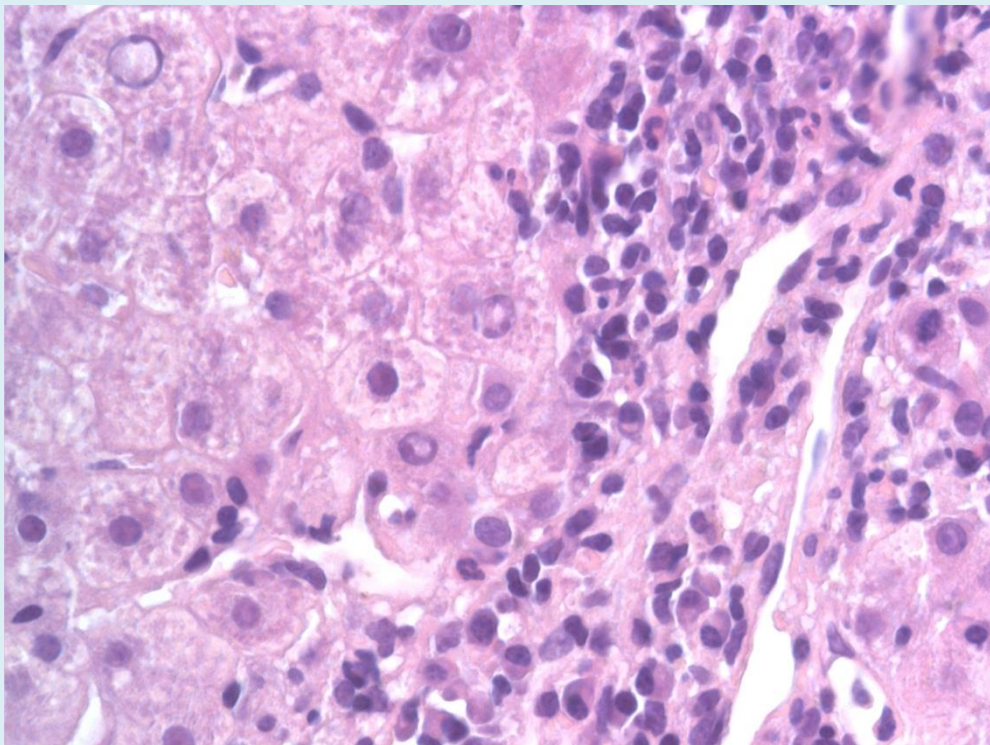
Interface hepatitis and rosetting



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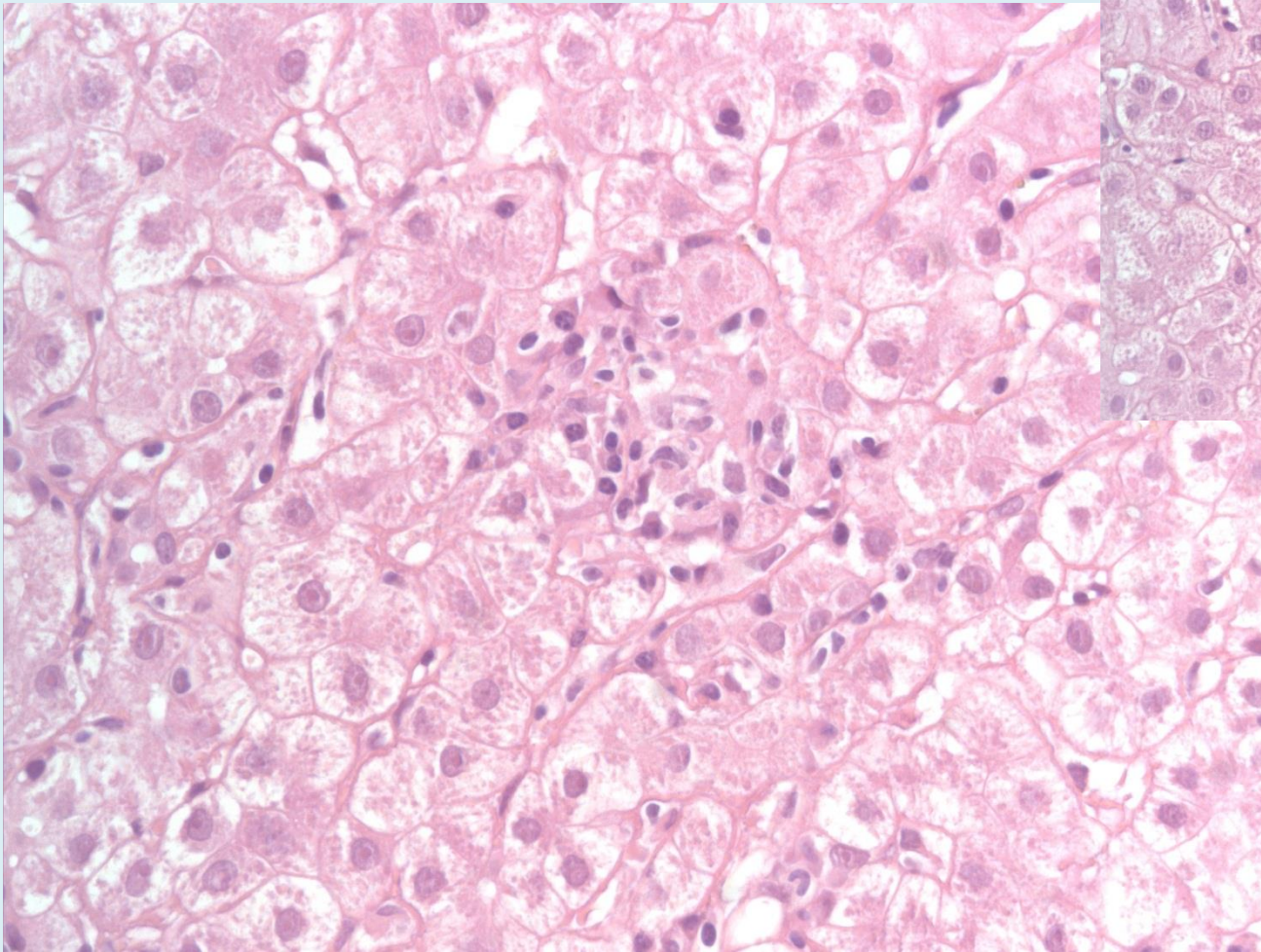
Hydropic swelling of periportally located hepatocytes



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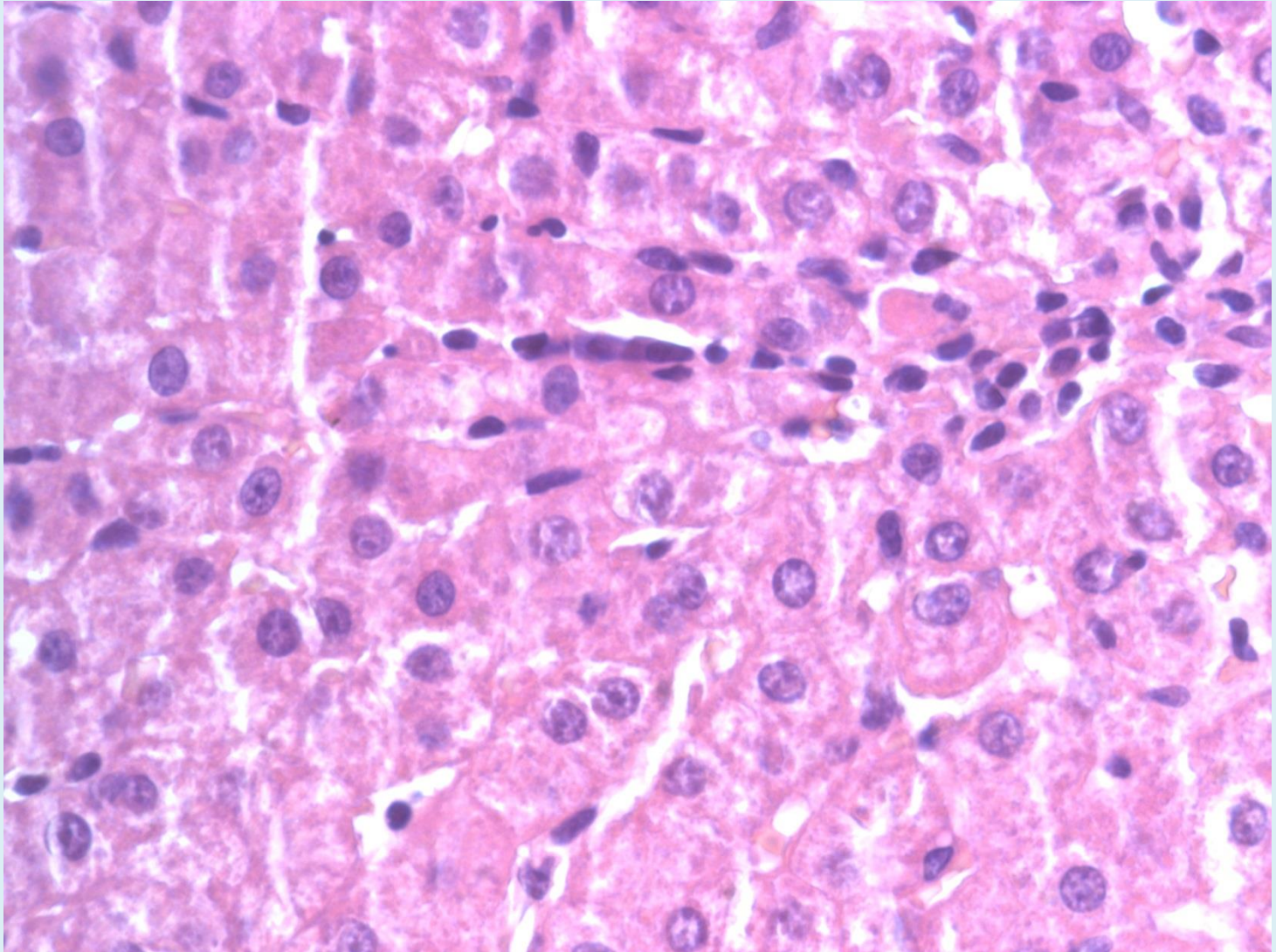
Lobular single cell necrosis



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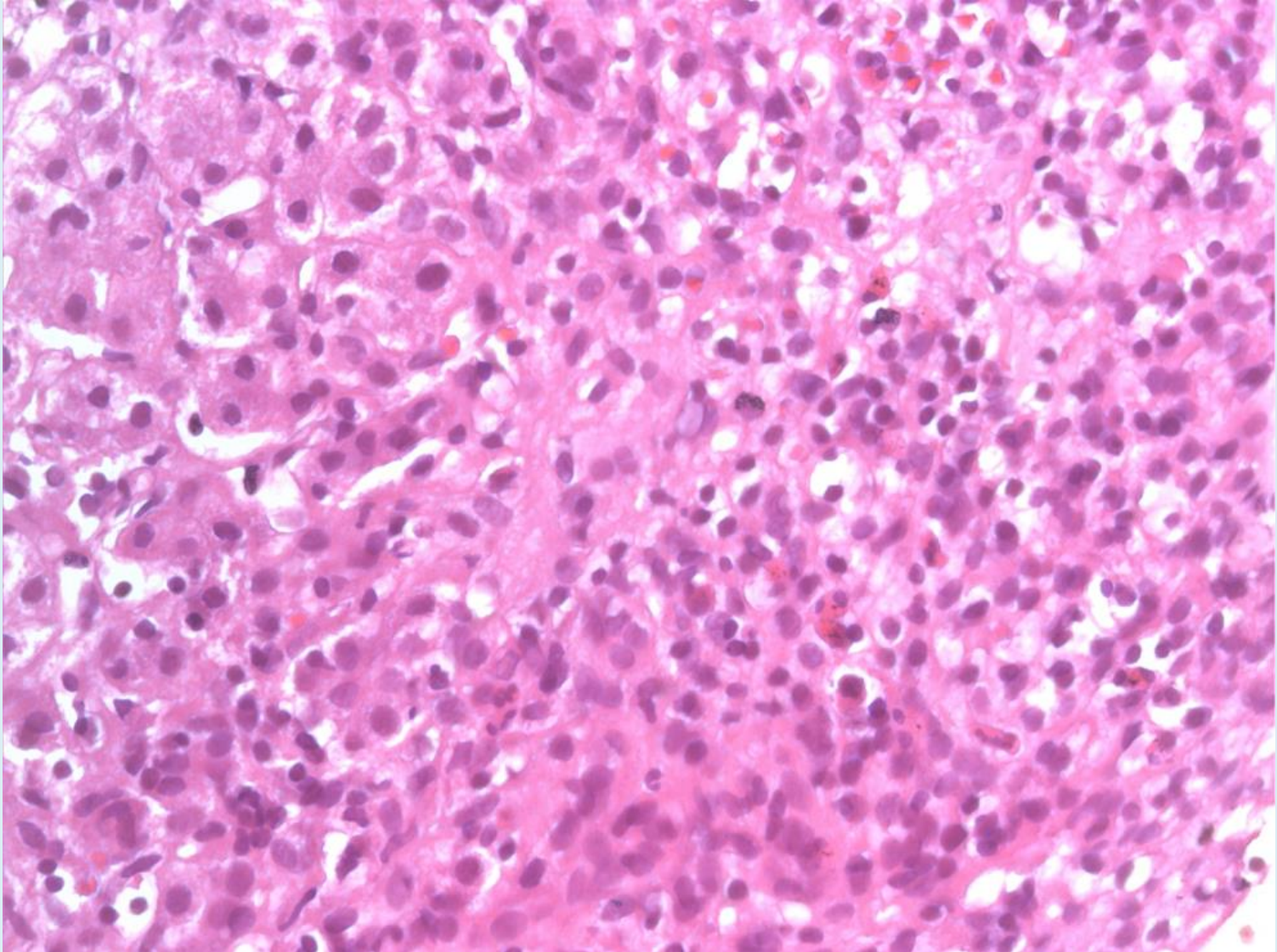
Kupffer cell hyperplasia



Morphology of autoimmune hepatitis

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- **Collapse fields**
- Necrotic fields
- Fibroses - porto-portal and portal in chronic disease

Collapse fields

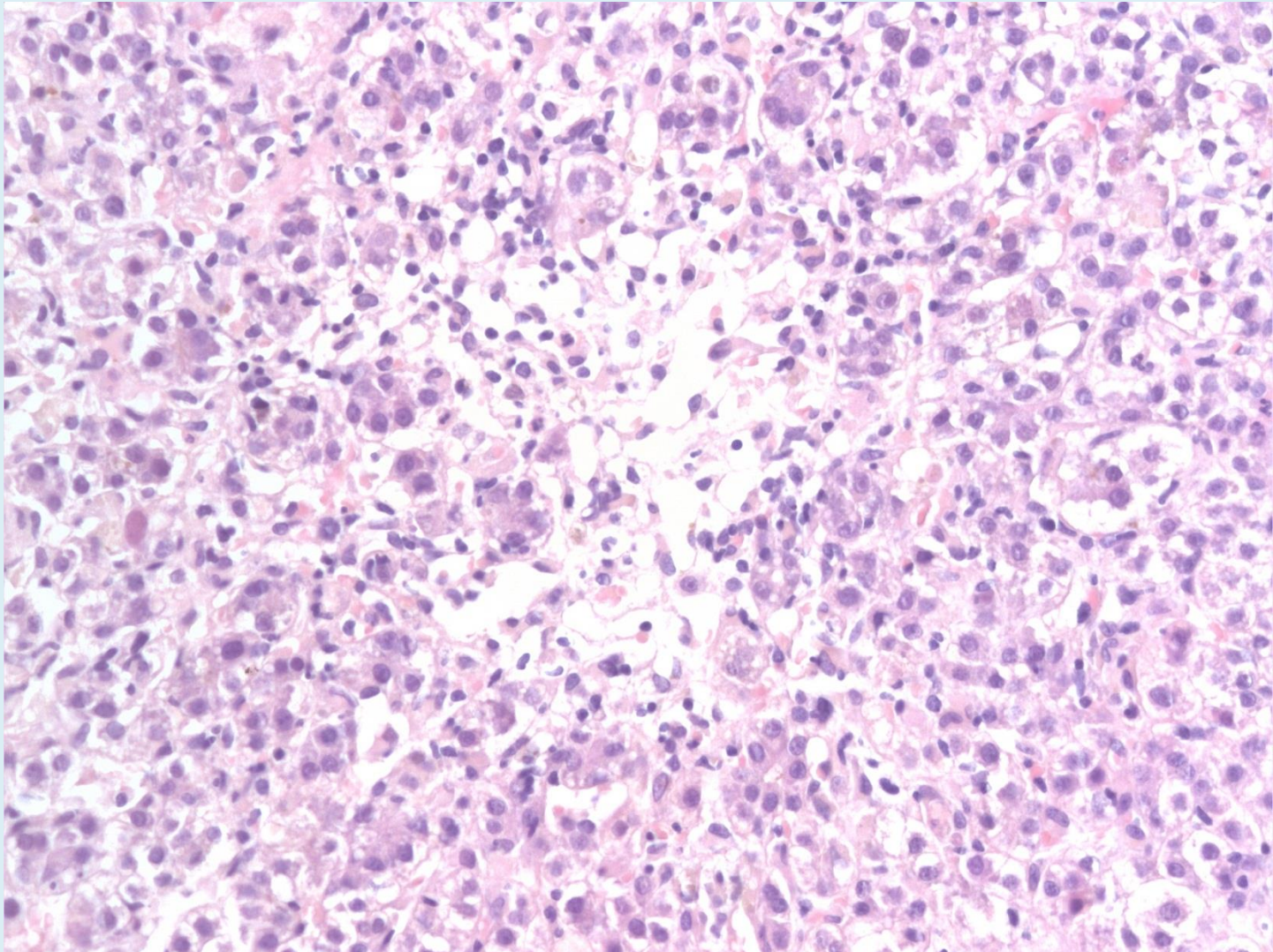


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Necrotic fields

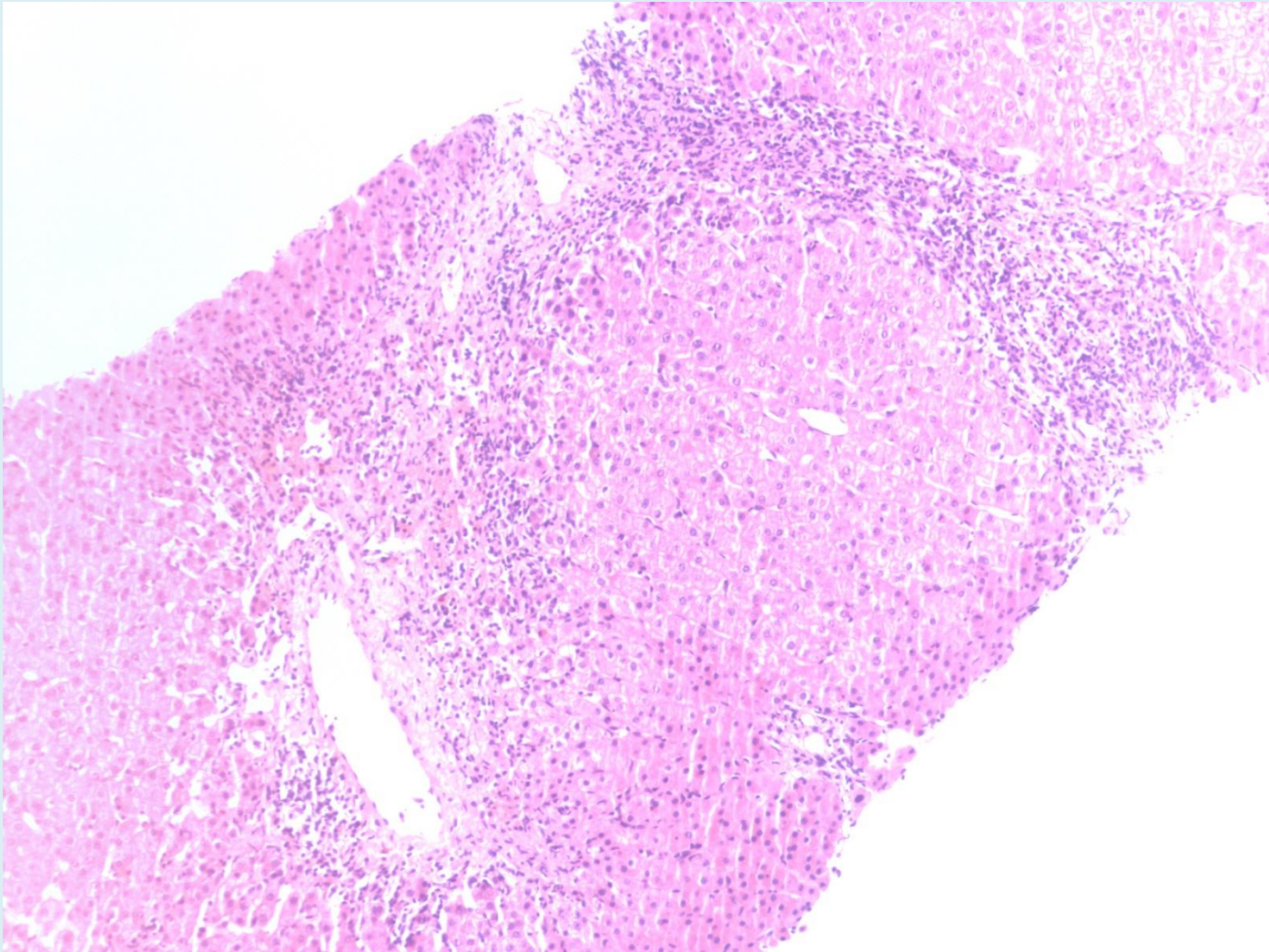
bridge-binding porto-portal and porto-central



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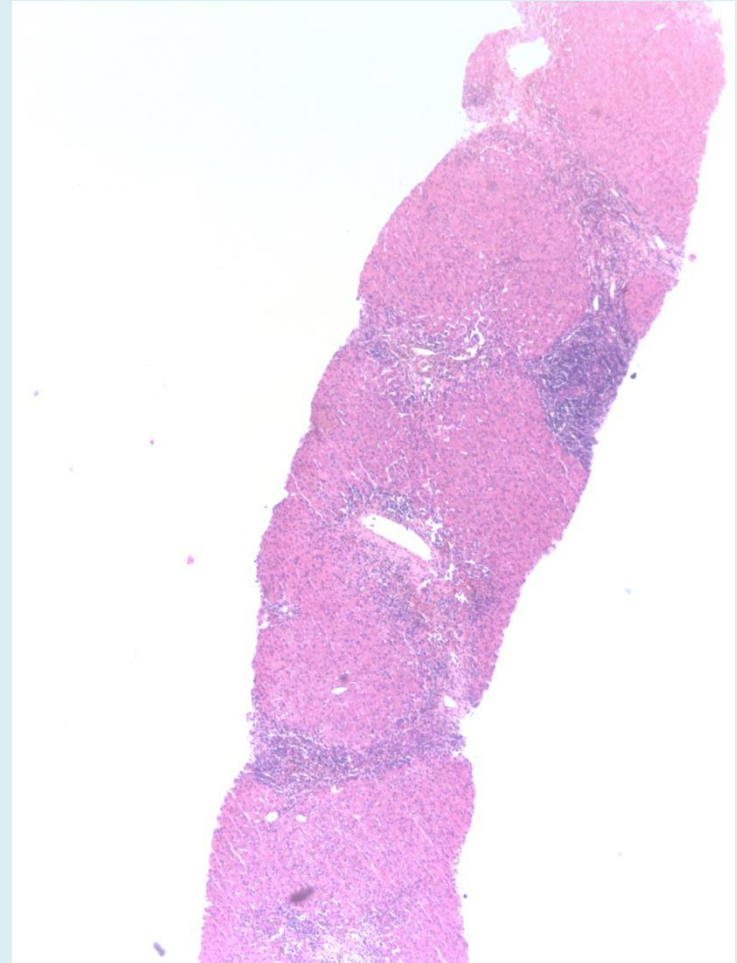
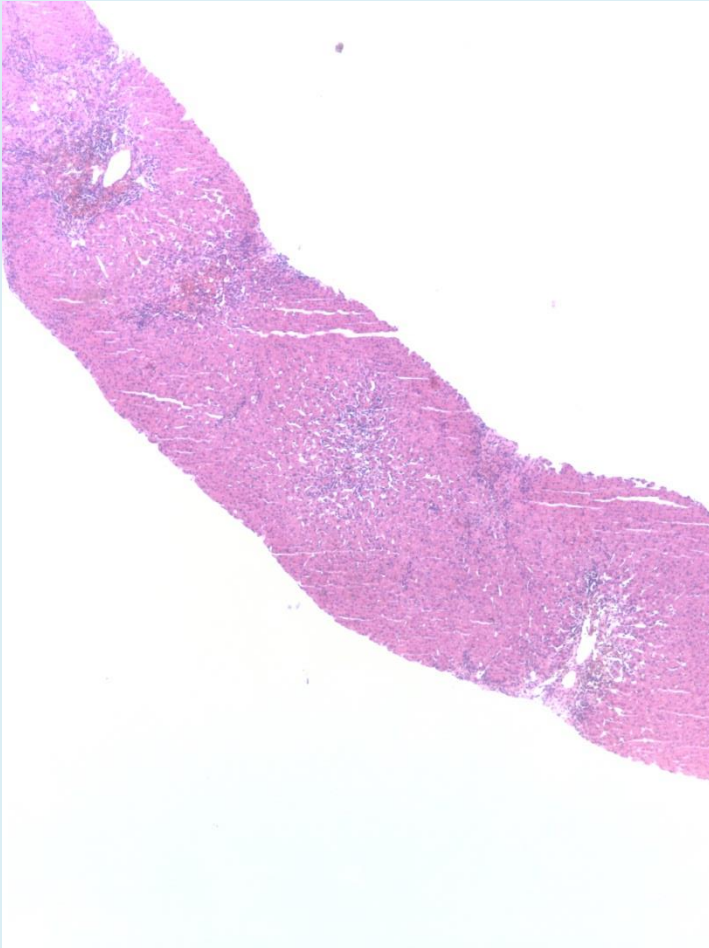
Fibrosis portal and porto-portal transition to chronicity



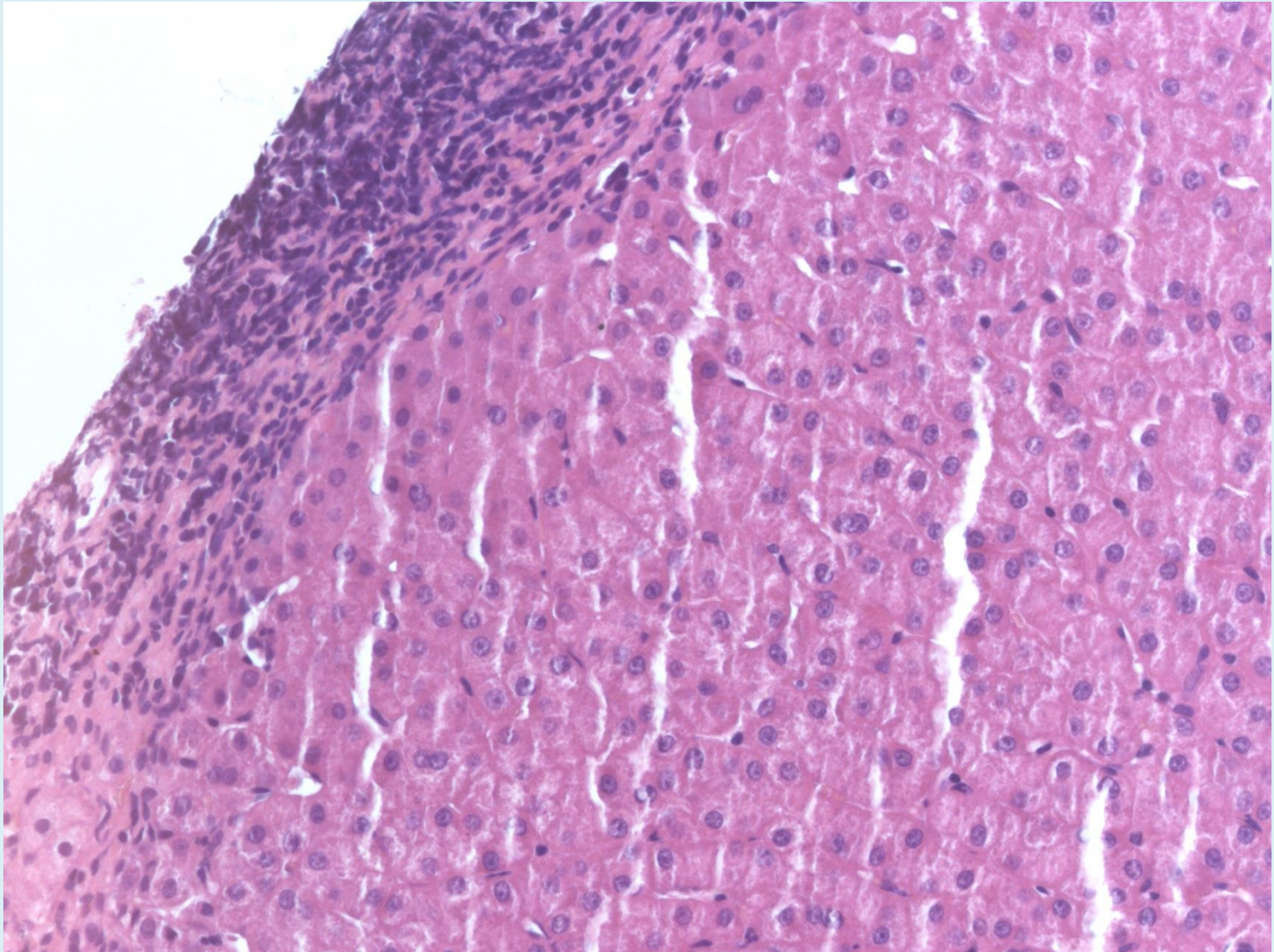
Case A – autoimmune hepatitis

- 24 yrs, female
- GOT 172 U/L
- GPT 368 U/L
- ALP 98 U/L
- total bilirubin 2,5mg/dl
- gamma-GT 120 U/L
- no evidence for viral serum markers

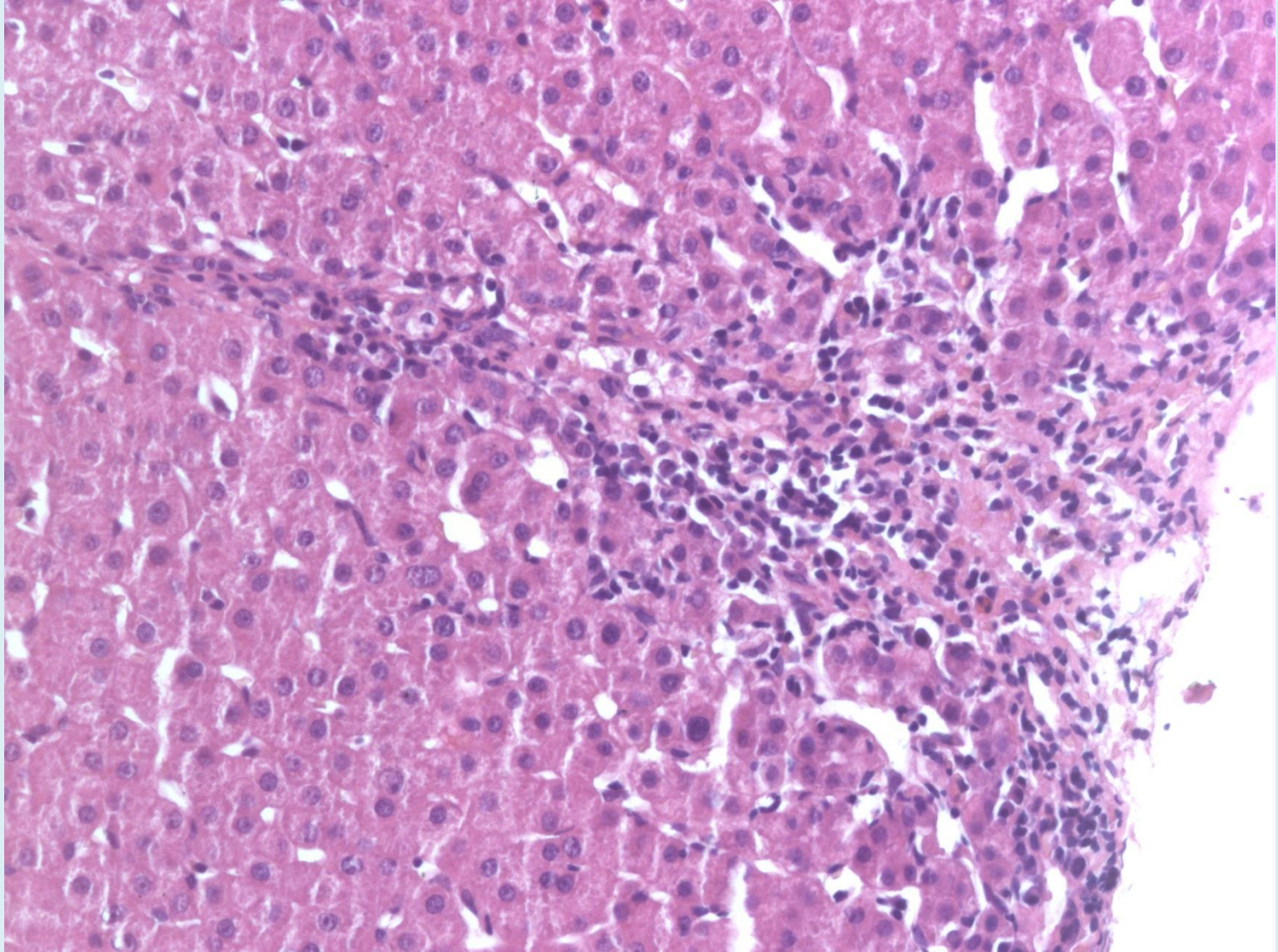
Case A – autoimmune hepatitis



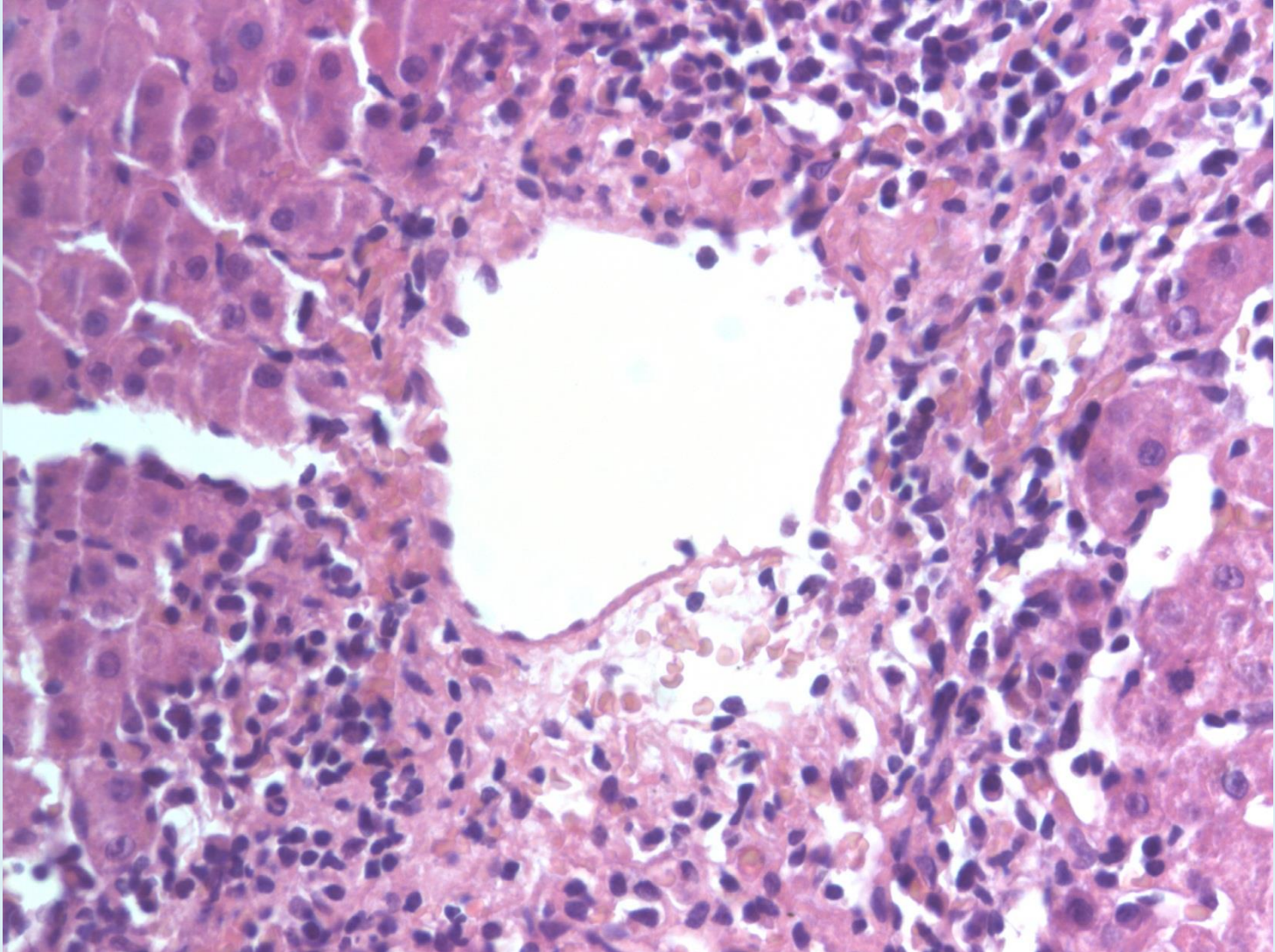
Case A – autoimmune hepatitis



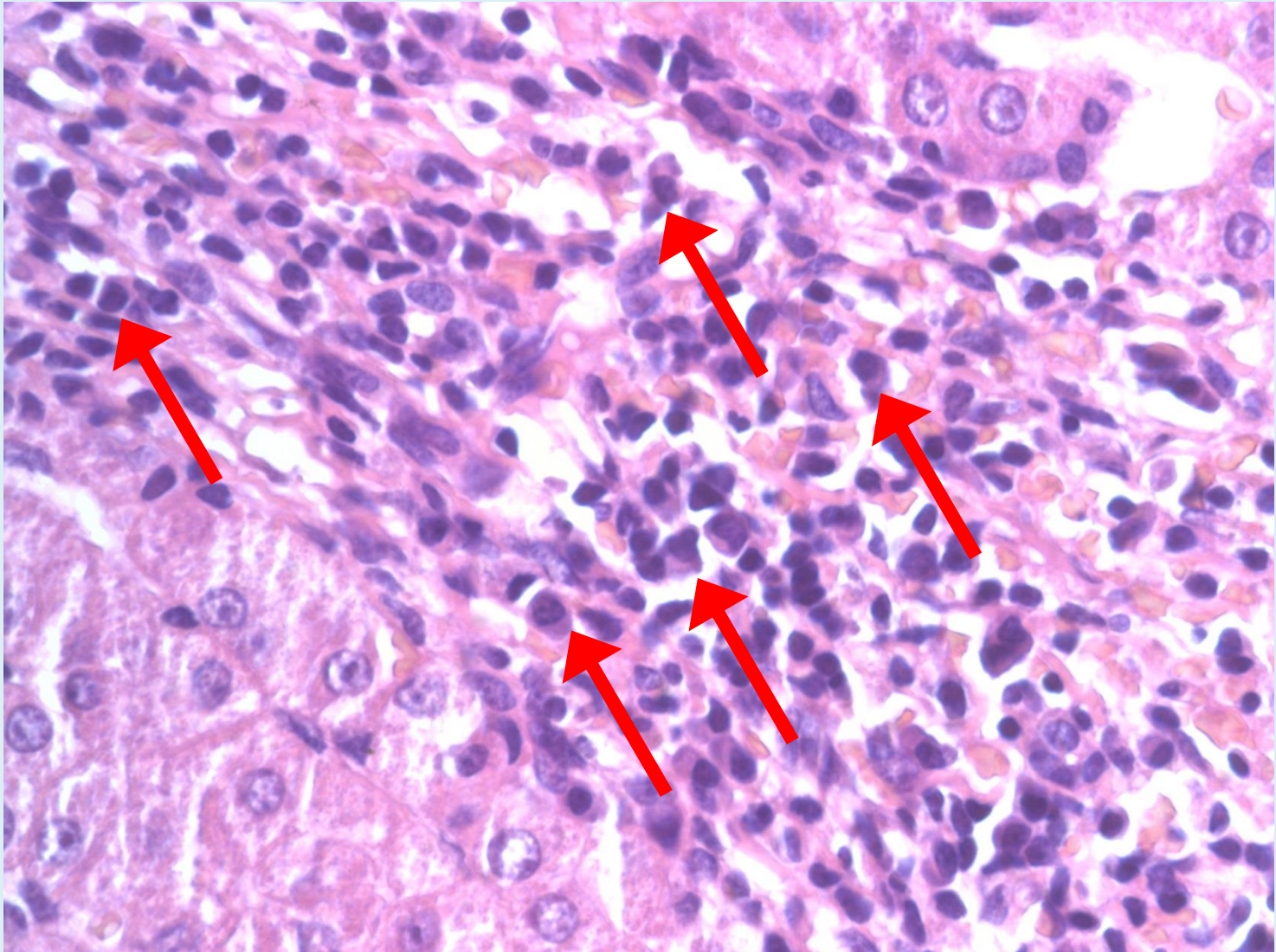
Case A – autoimmune hepatitis



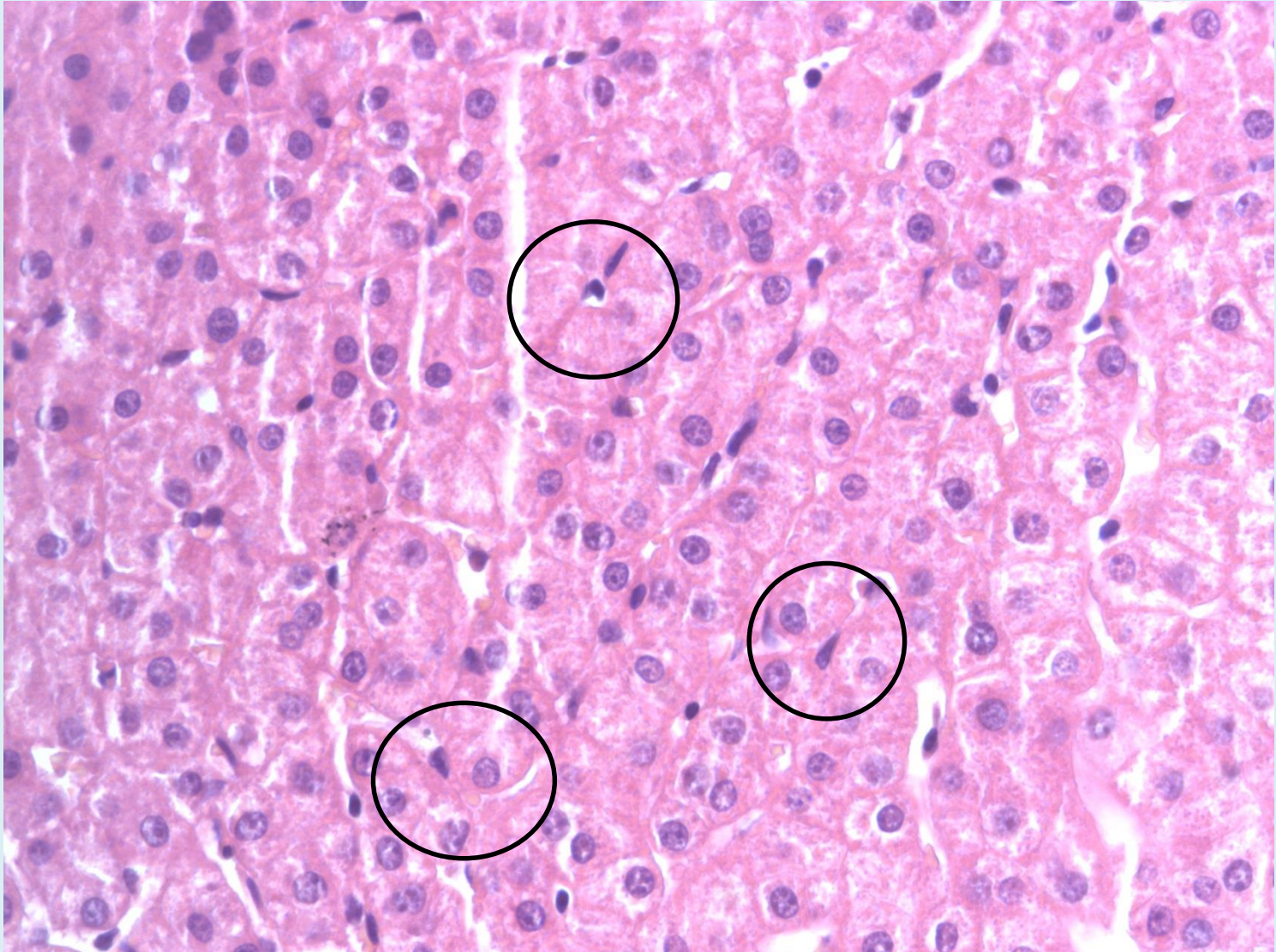
Case A – autoimmune hepatitis



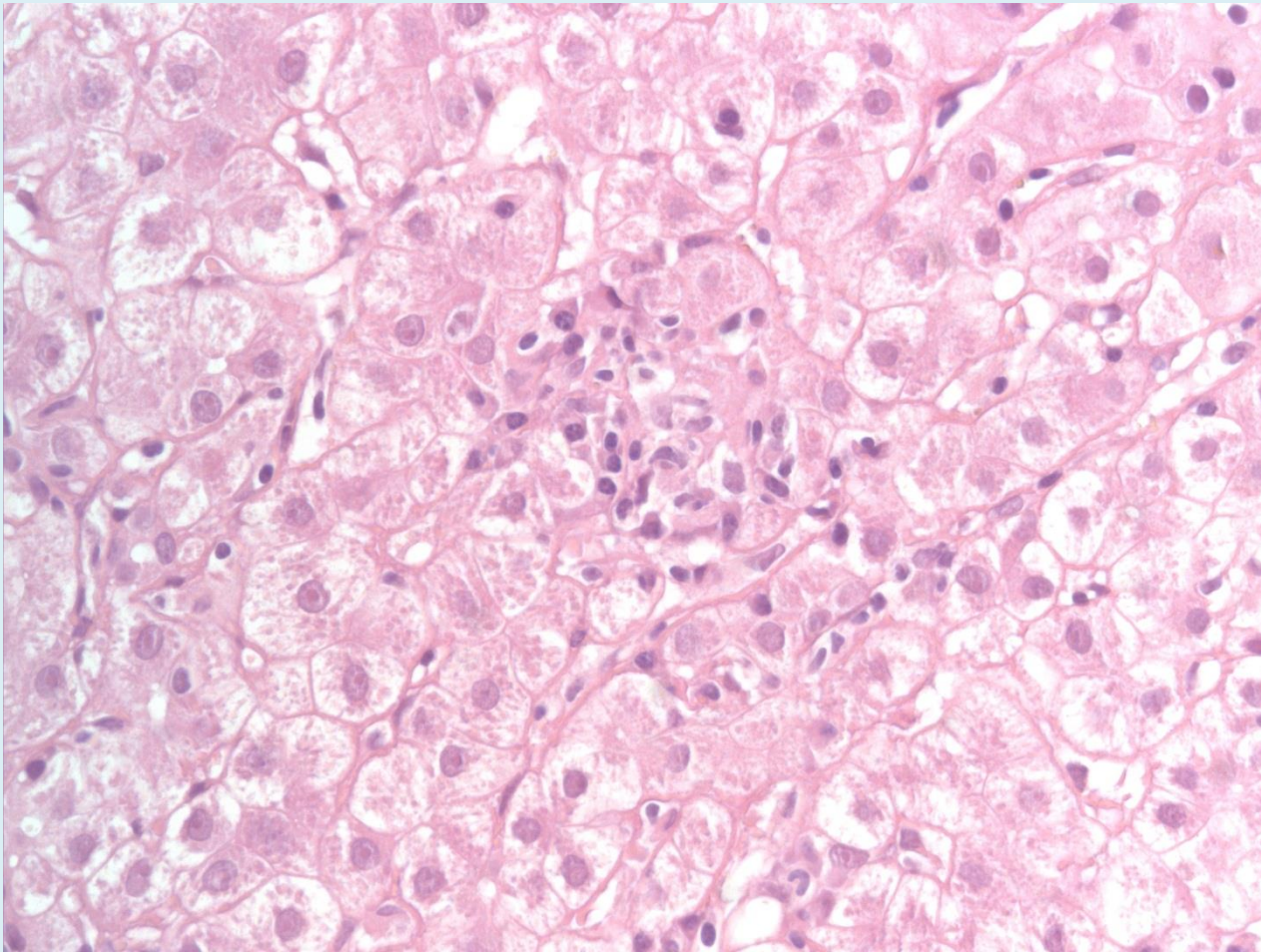
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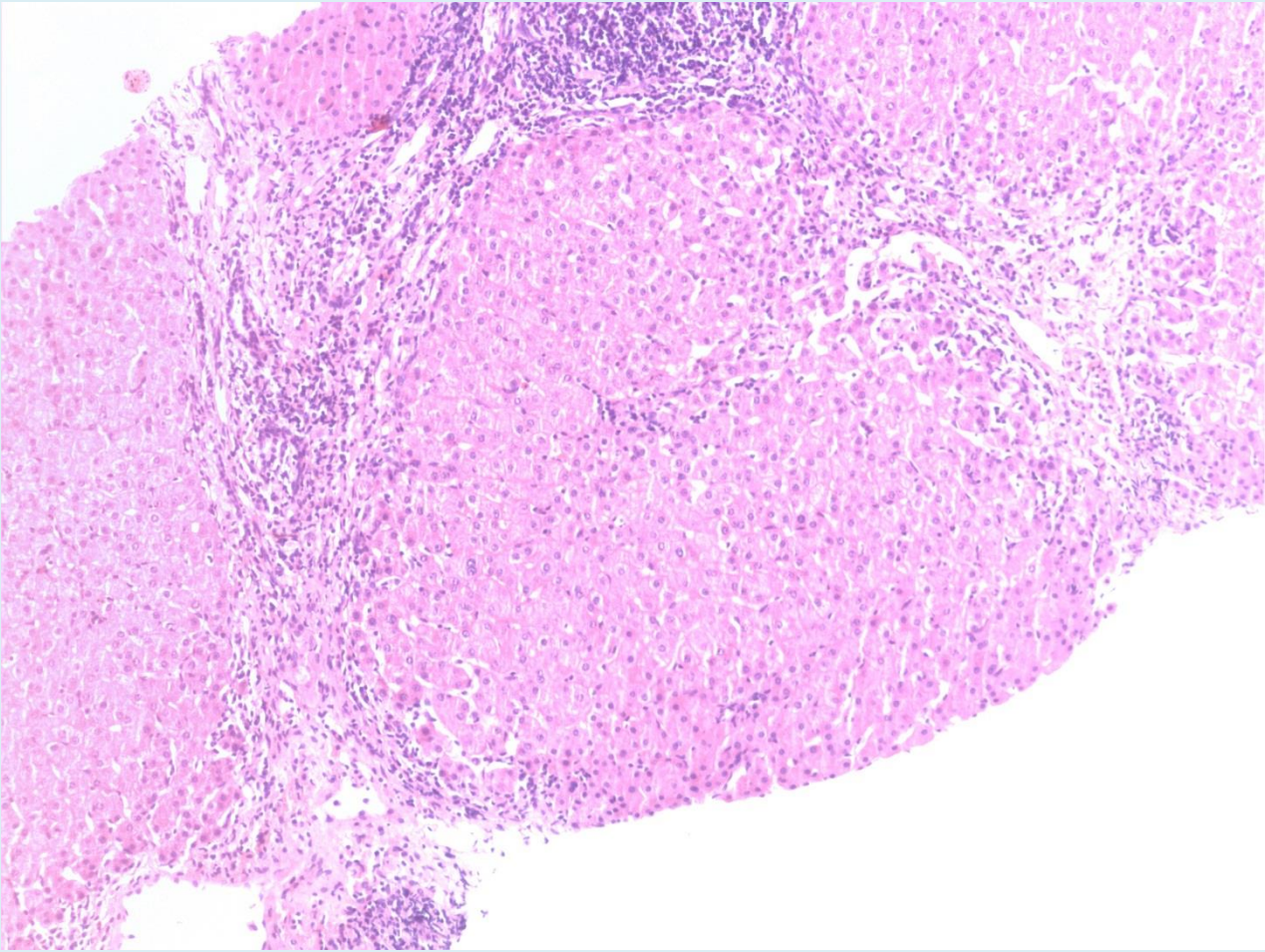
Case A – autoimmune hepatitis



Case A – autoimmune hepatitis



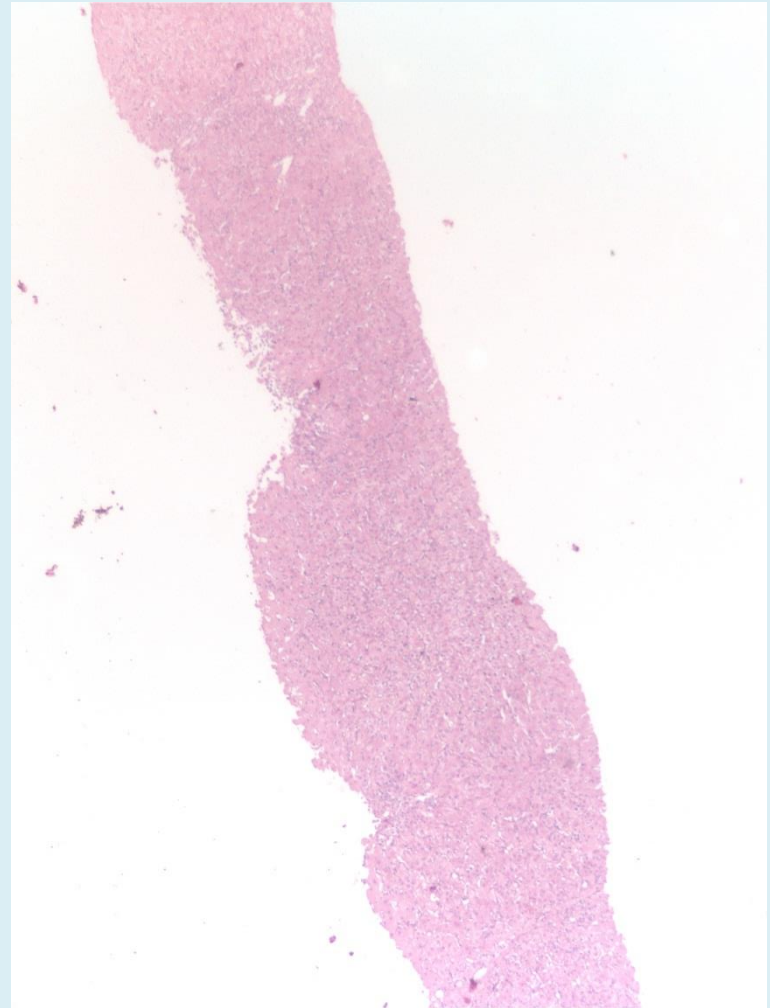
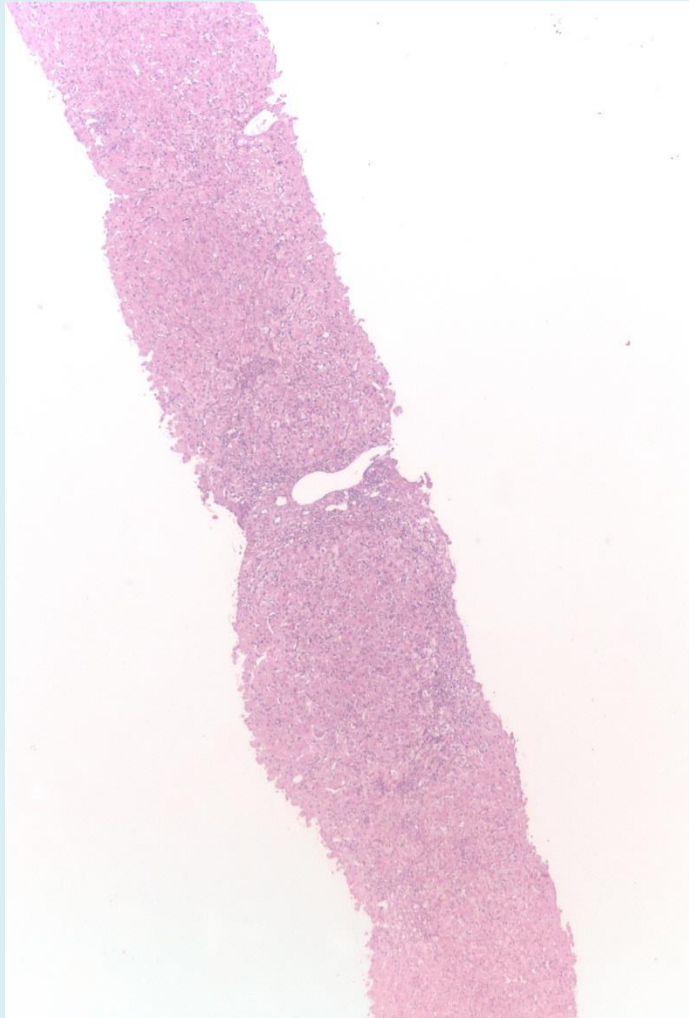
Case A.– autoimmune hepatitis



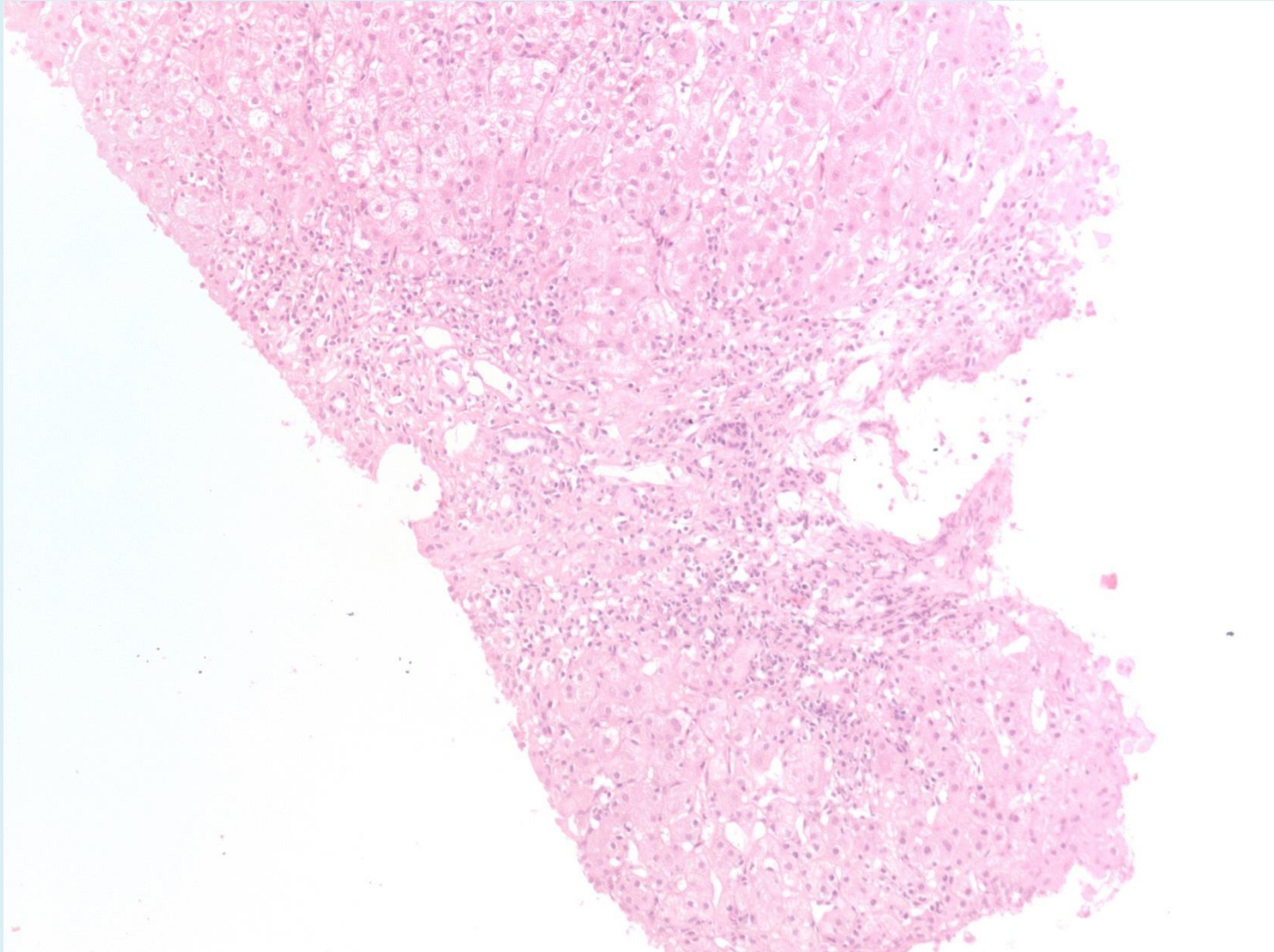
Case B – autoimmune hepatitis

- 48 yrs
- female
- GOT 380 U/L
- GOT 320 U/L
- Gamma GT 180 U/L
- Gamma-globuline 64%
- ALP 180 U/L
- Total bilirubin 1,2 mg%
- ANA positive
- Alcoholism

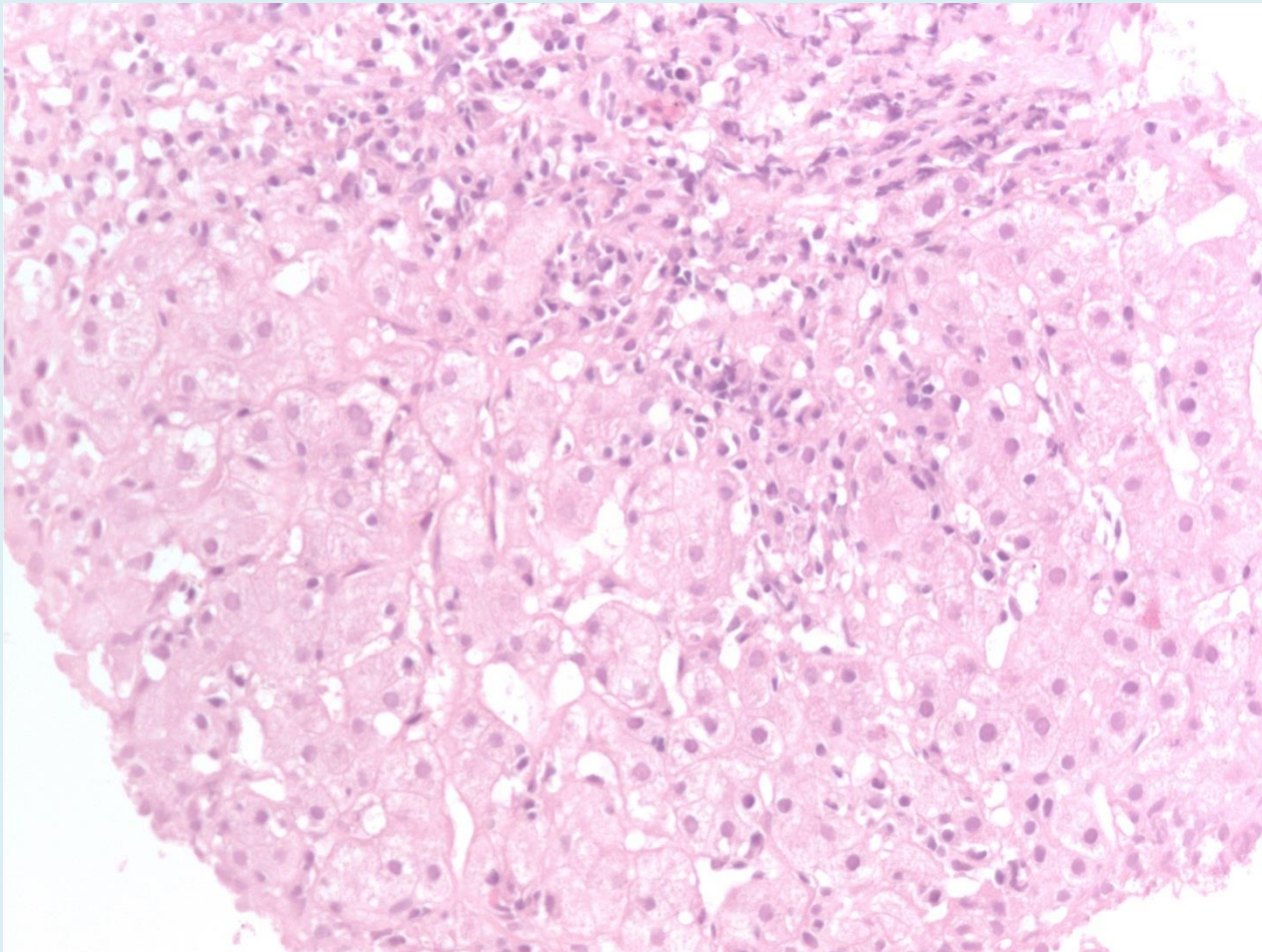
Case B – autoimmune hepatitis



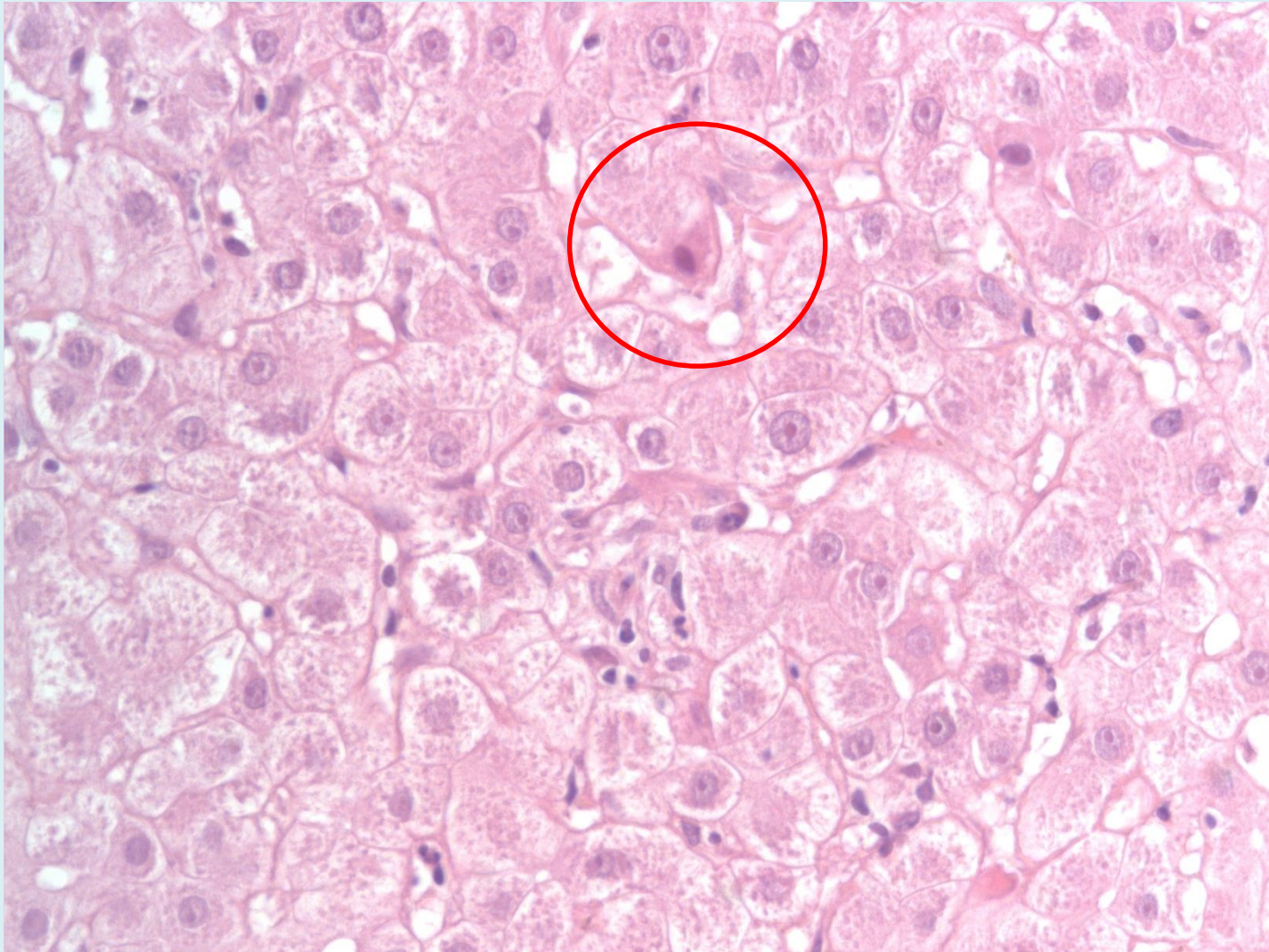
Case B – autoimmune hepatitis



Case B – autoimmune hepatitis



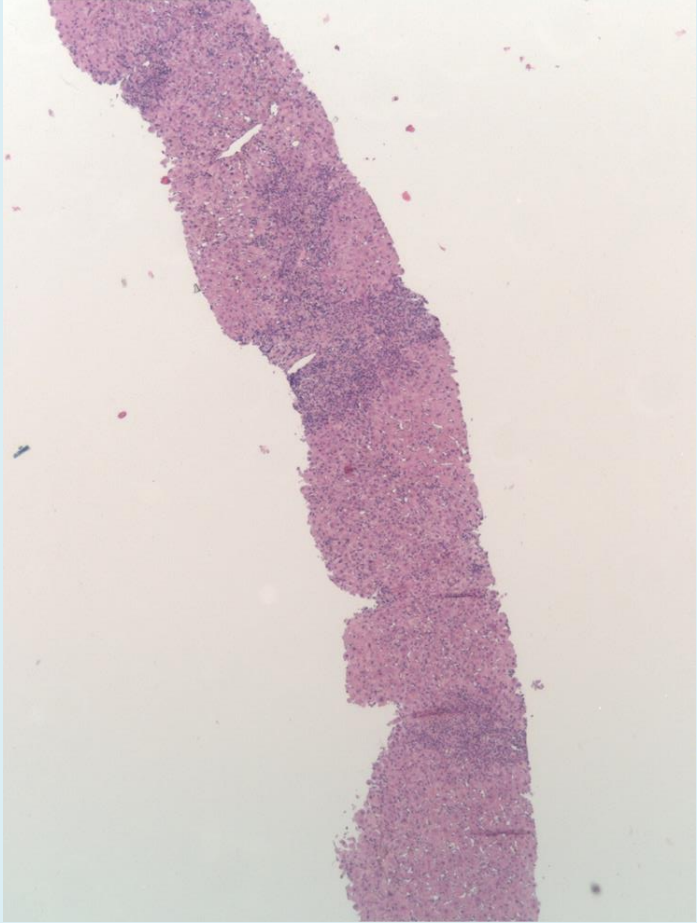
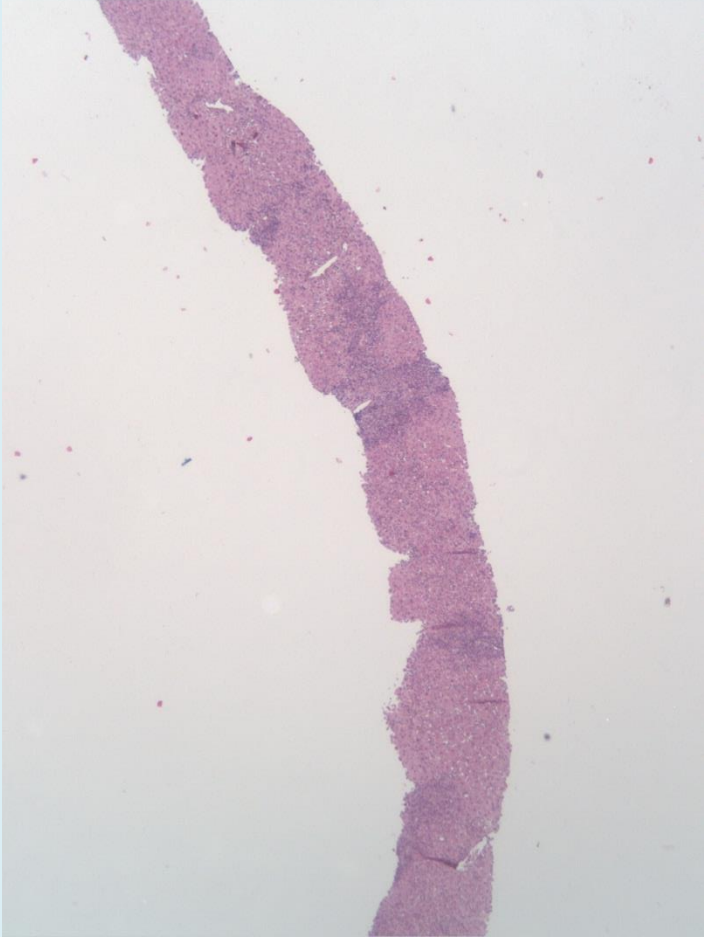
Case B. – autoimmune hepatitis



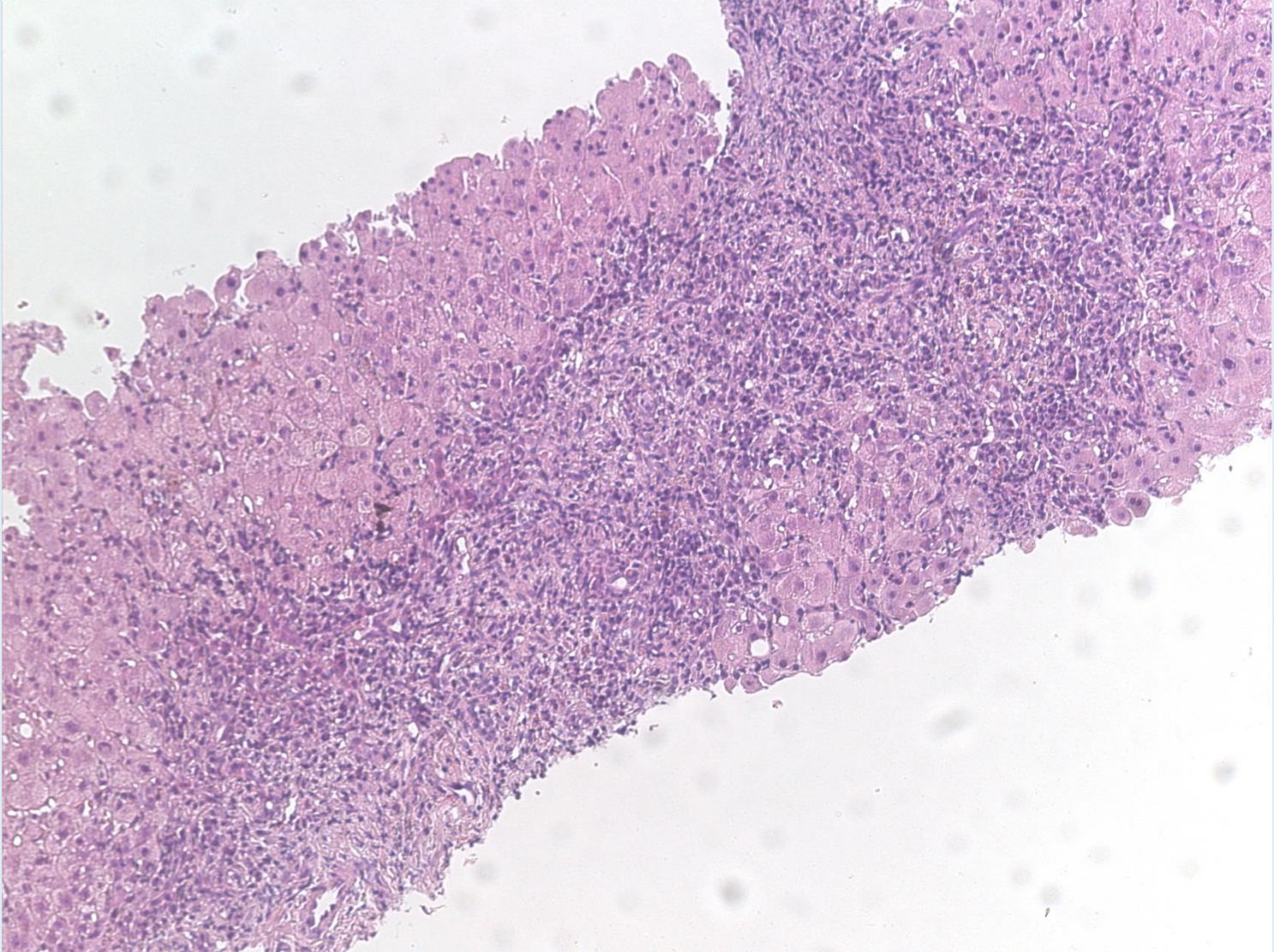
Case F – autoimmune hepatitis

- 63 yrs
- Female
- SMA elevated
- ANA negative
- Gamma-Globulin 33,1%
- GOT 360 U/L
- GPT 510 U/L
- Gamma-GT 180 U/L
- ALP 260 U/L

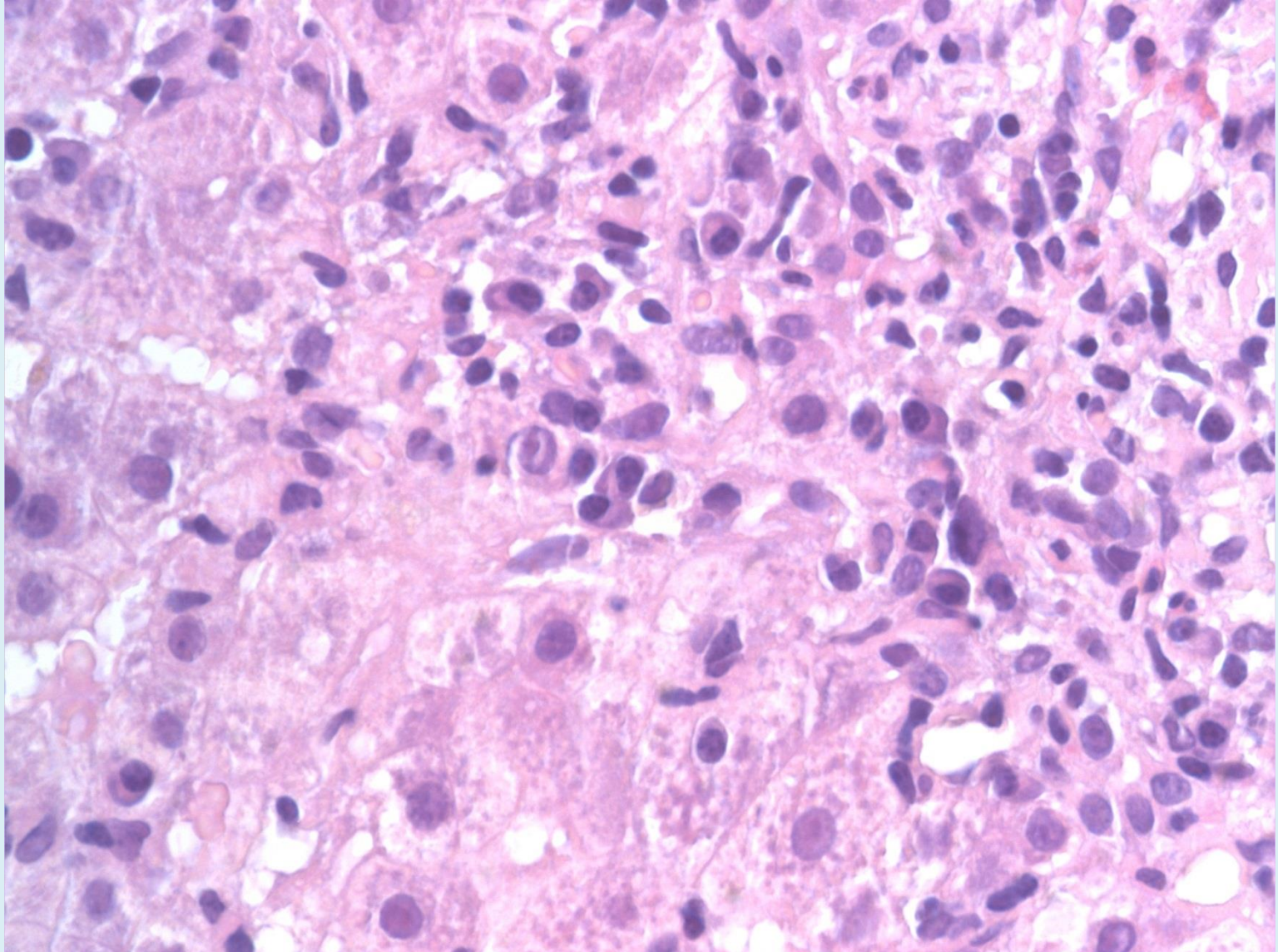
Case F – autoimmune hepatitis



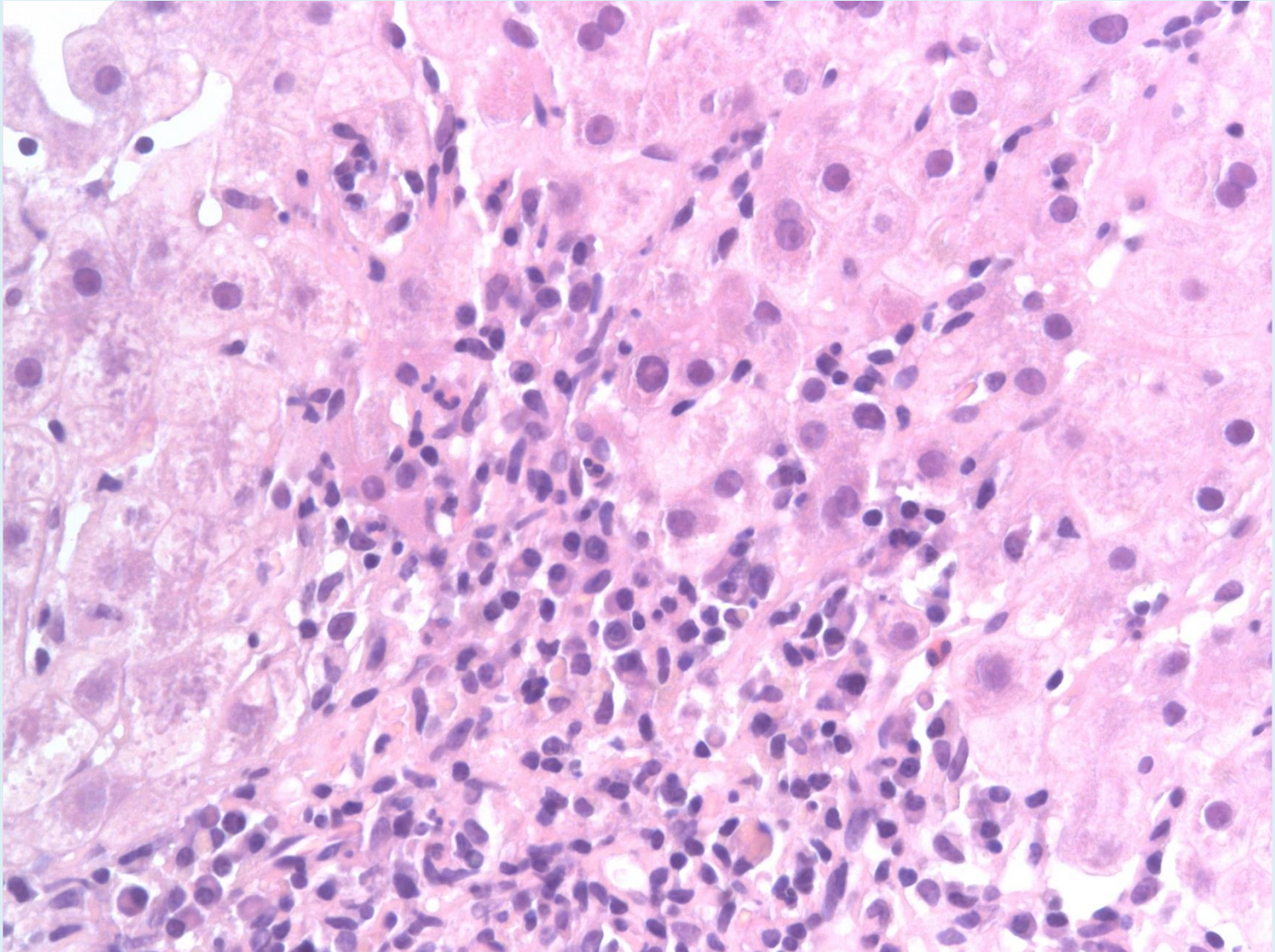
Case F – autoimmune hepatitis



Case F – autoimmune hepatitis



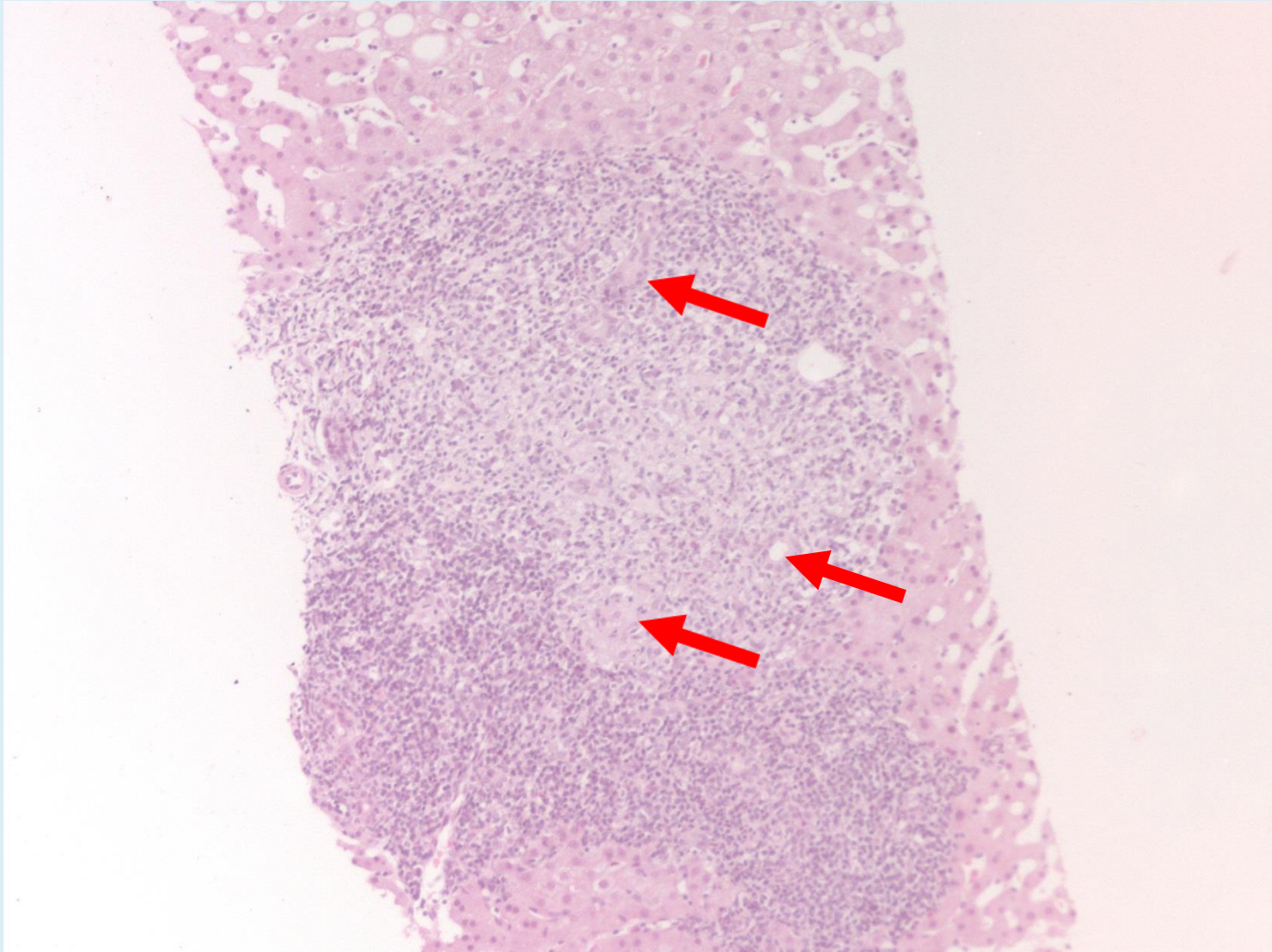
Case F. – autoimmune hepatitis



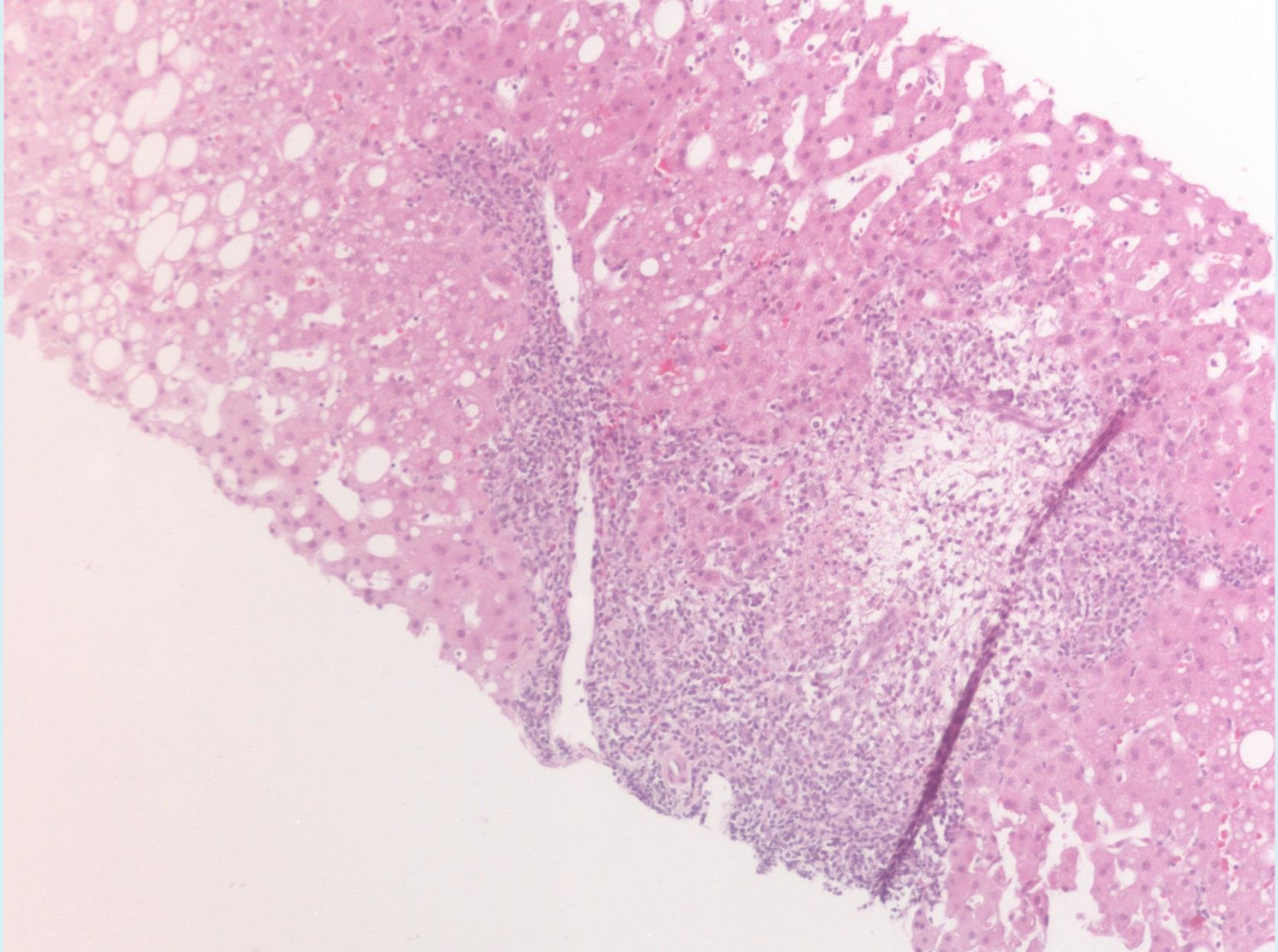
Case D – Overlap-Syndrom AIH/PBC

- 38 yrs
- Male
- Positive for ANA and AMA
- Gamma-globuline elevated
- Gamma-GT 95 U/L
- GOT 220U/L
- GPT 265 U/L
- ALP 275 U/L
- Clinical diagnosis: hepatitis of unknown etiology

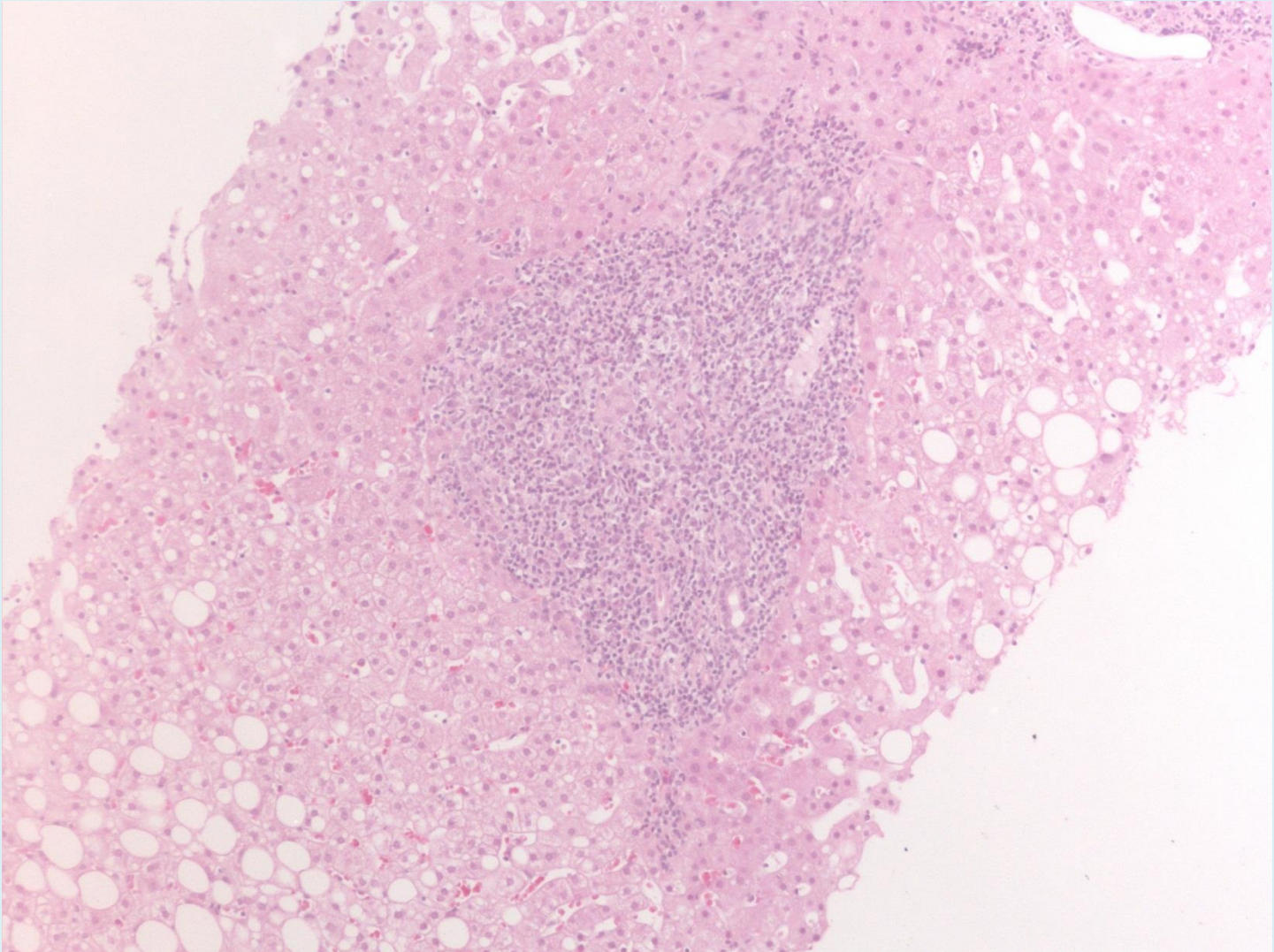
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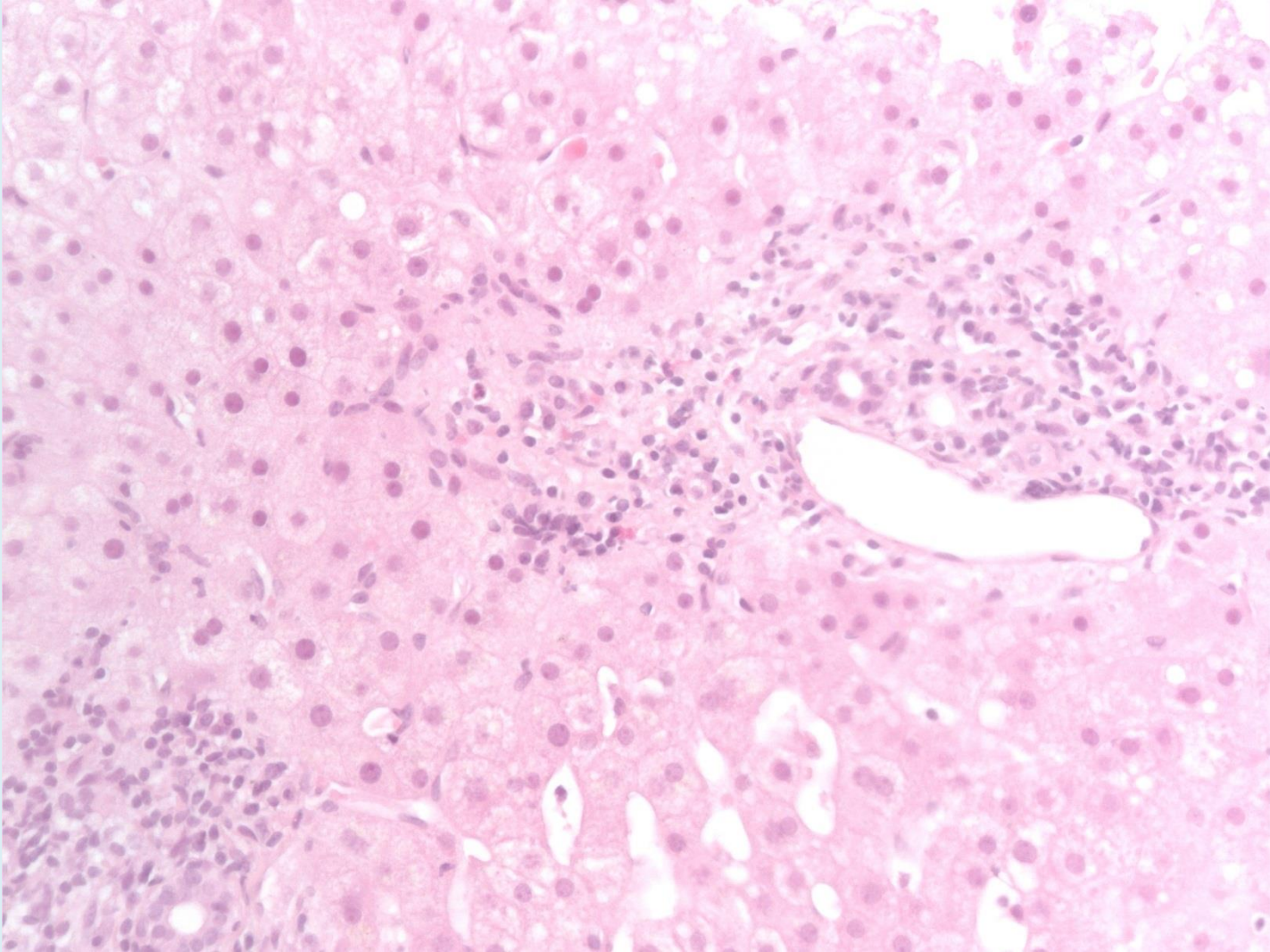
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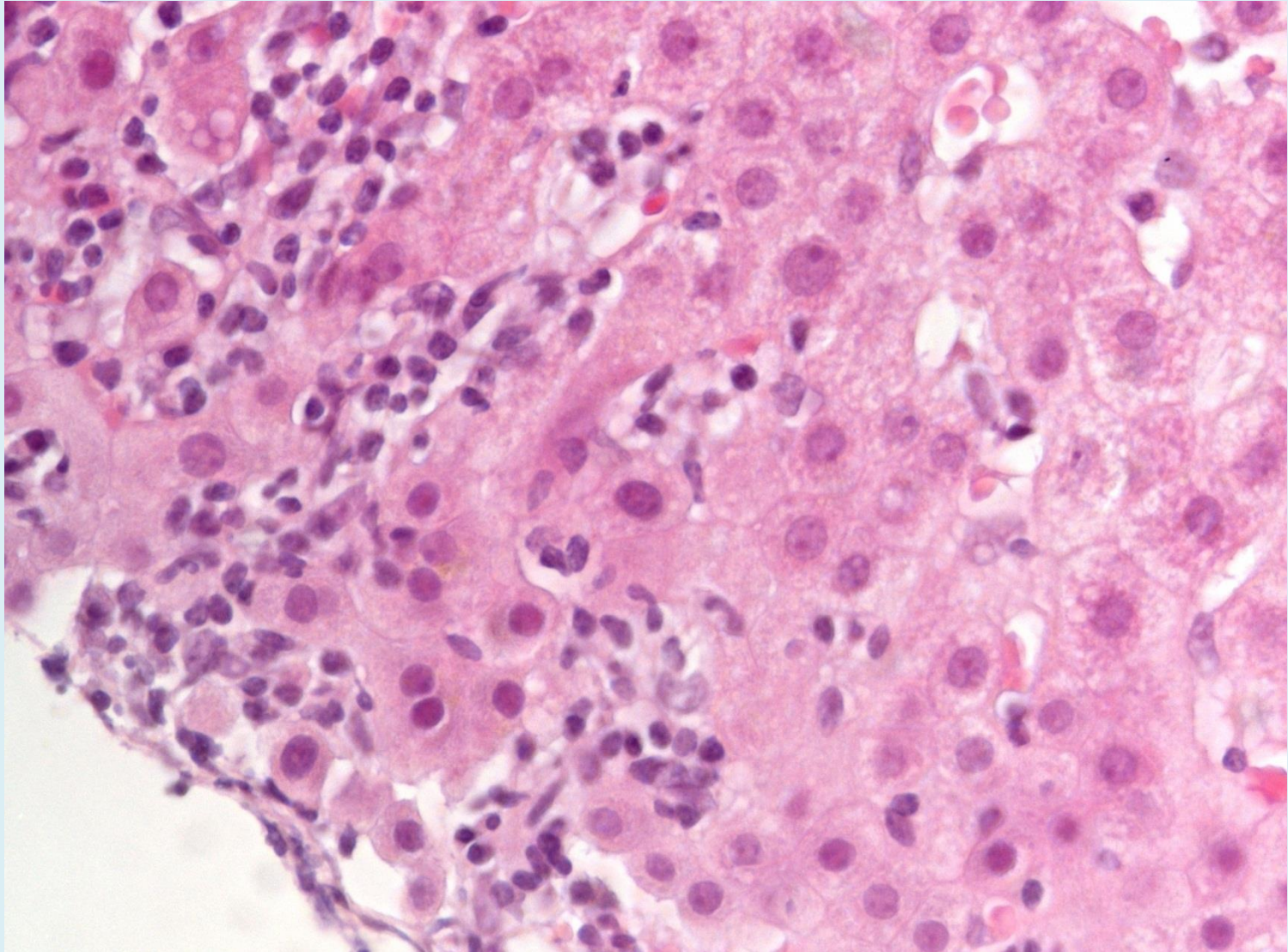
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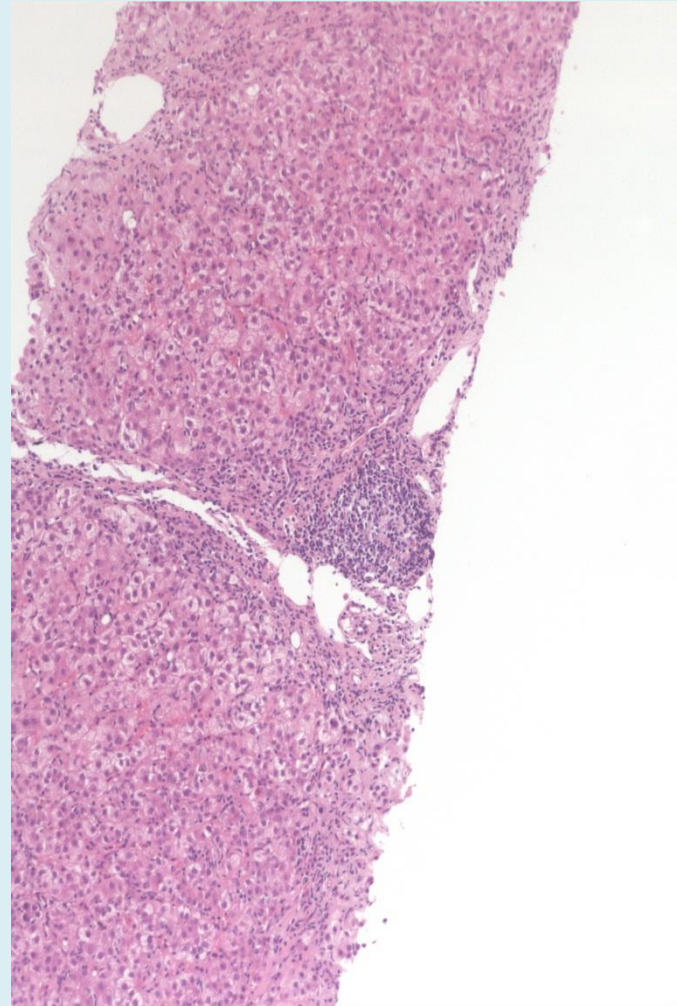
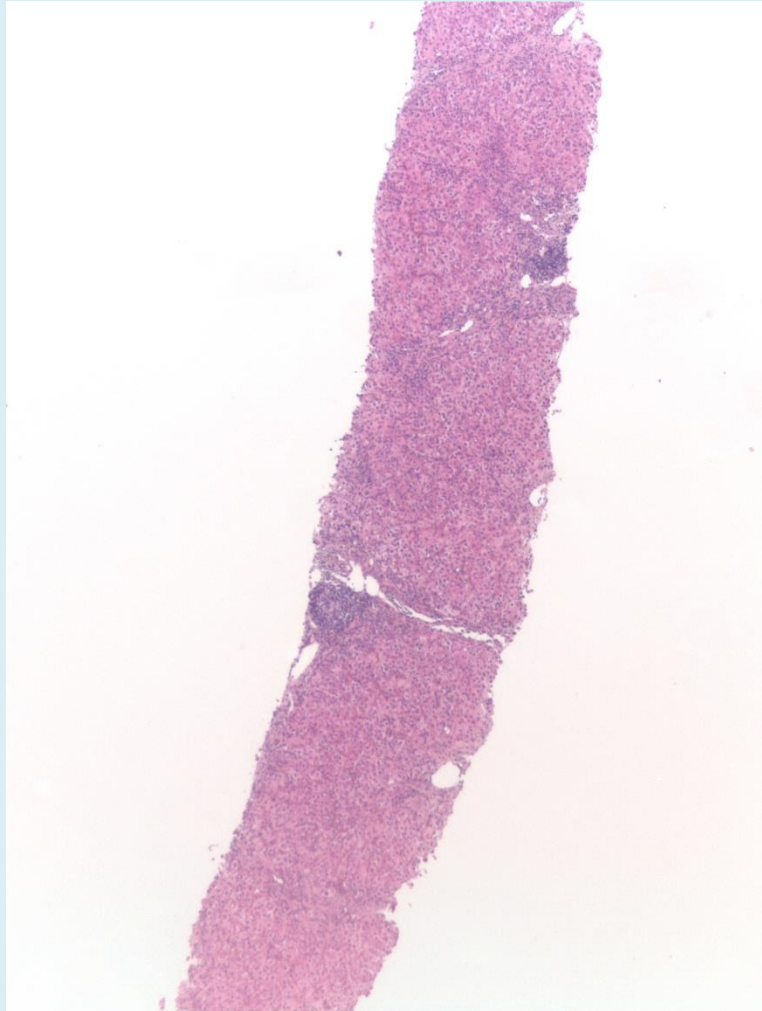
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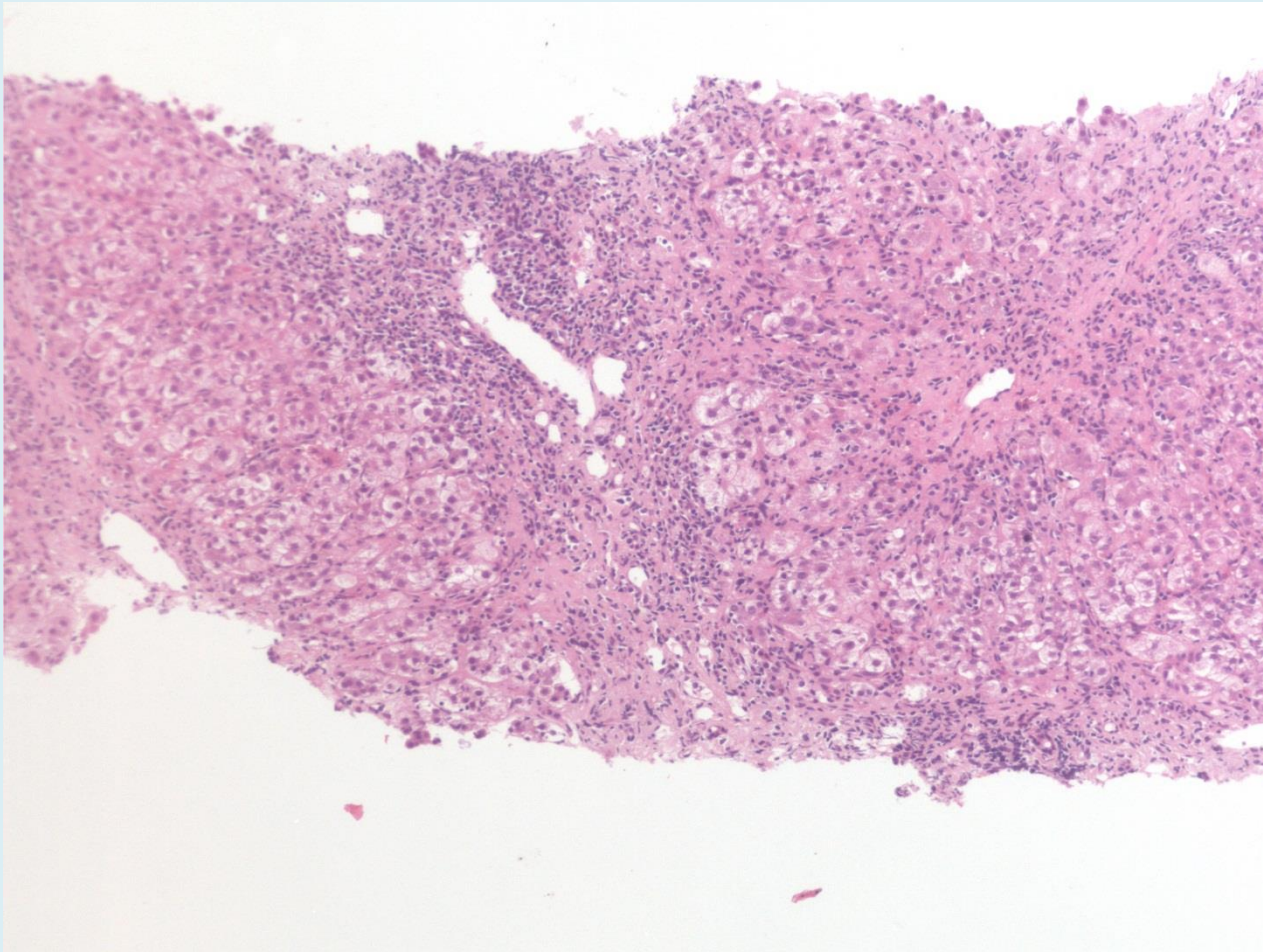
Case C – Overlap-Syndrom AIH/PBC

- 16 yrs
- Male
- Icterus
- General prodromi
- GOT 680 U/L
- GPT 530 U/L
- Gamma-GT 160U/L
- ALP 310U/L
- Bilirubin elevated
- Positivity for ANA, SMA, AMA, ANCA, IgG elevated
- Negativity for serum viral markers

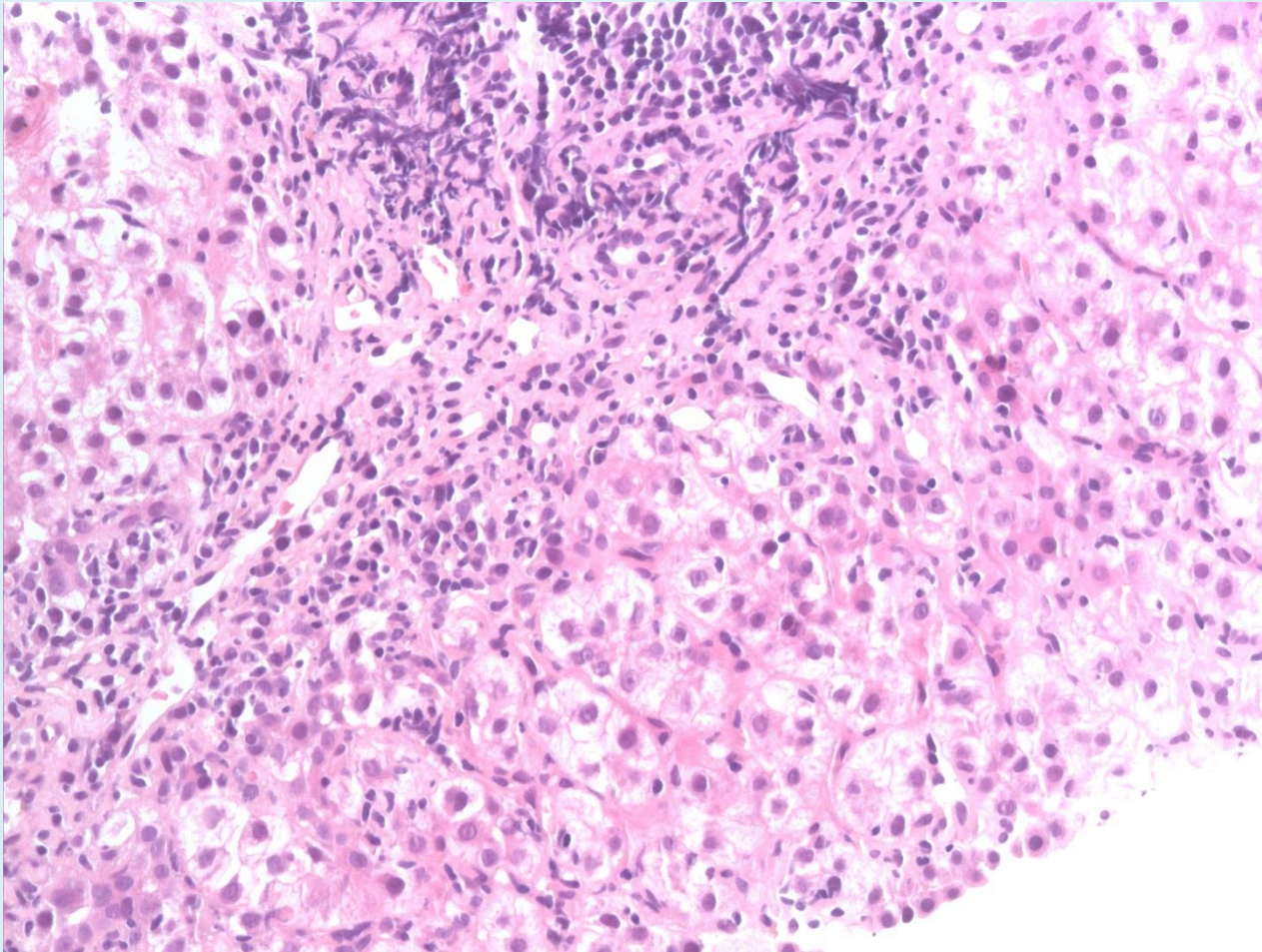
Case C – Overlap-Syndrom AIH/PBC



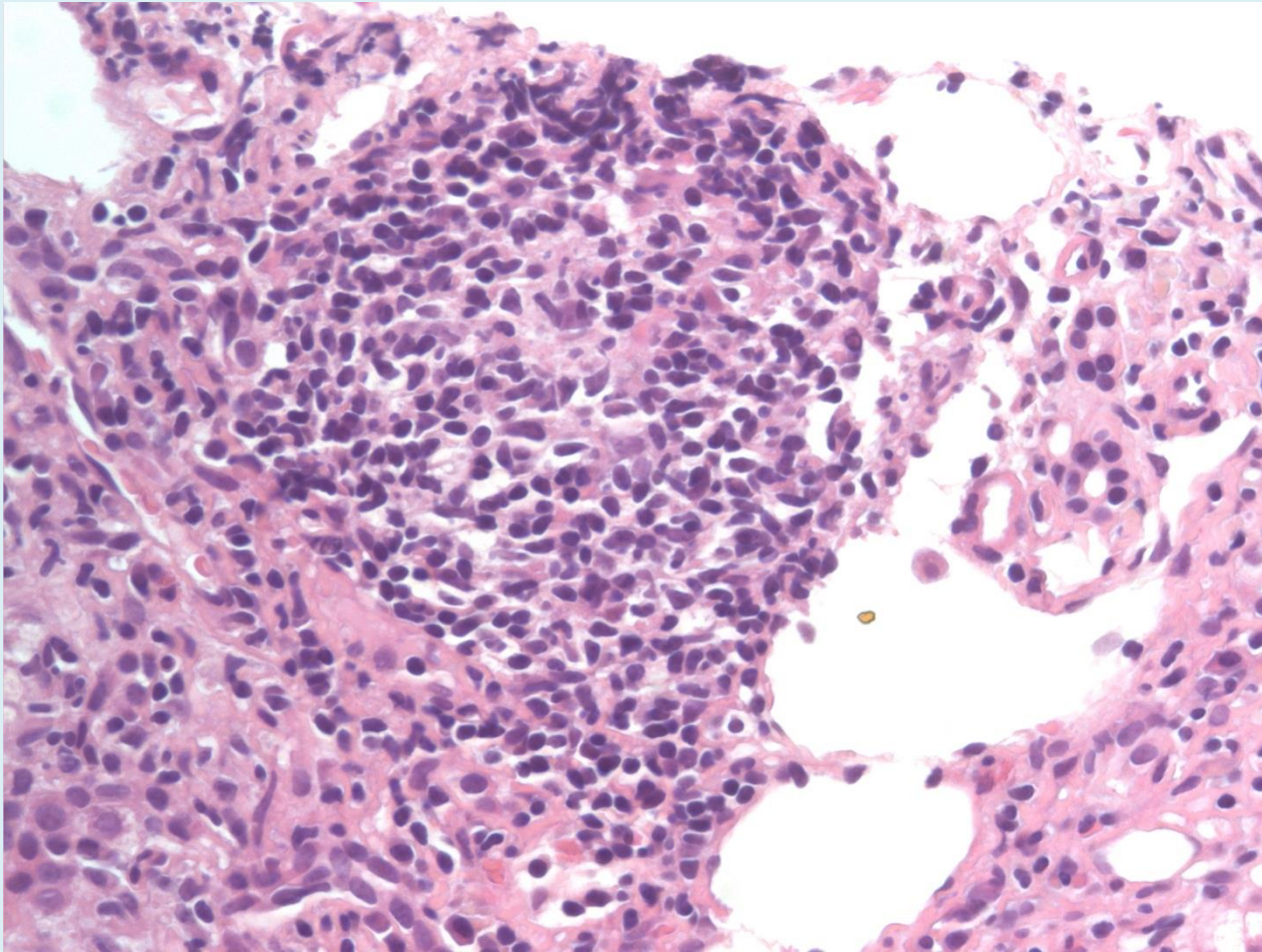
Case C – Overlap-Syndrom AIH/PBC



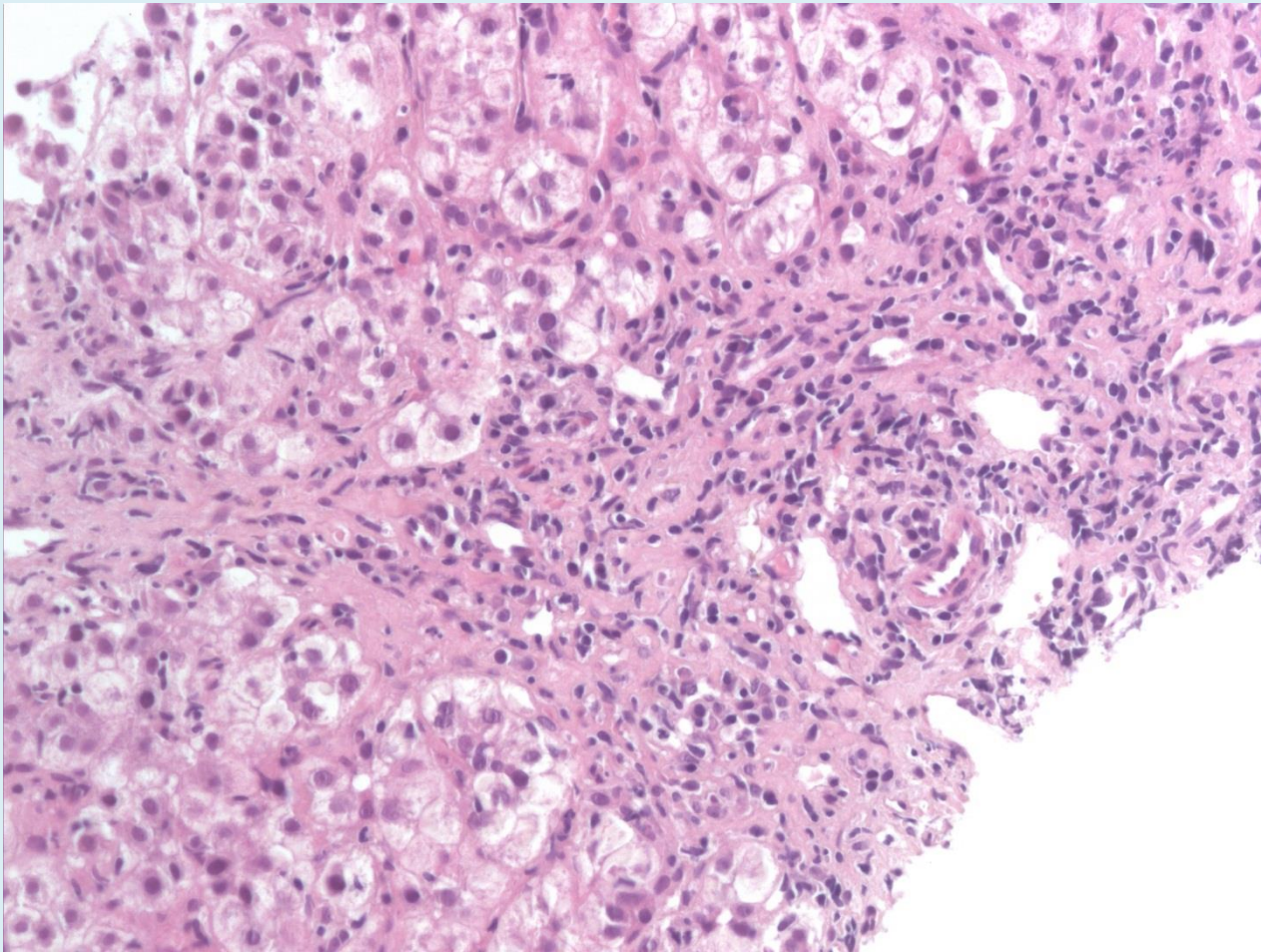
Case C – Overlap-Syndrom AIH/PBC



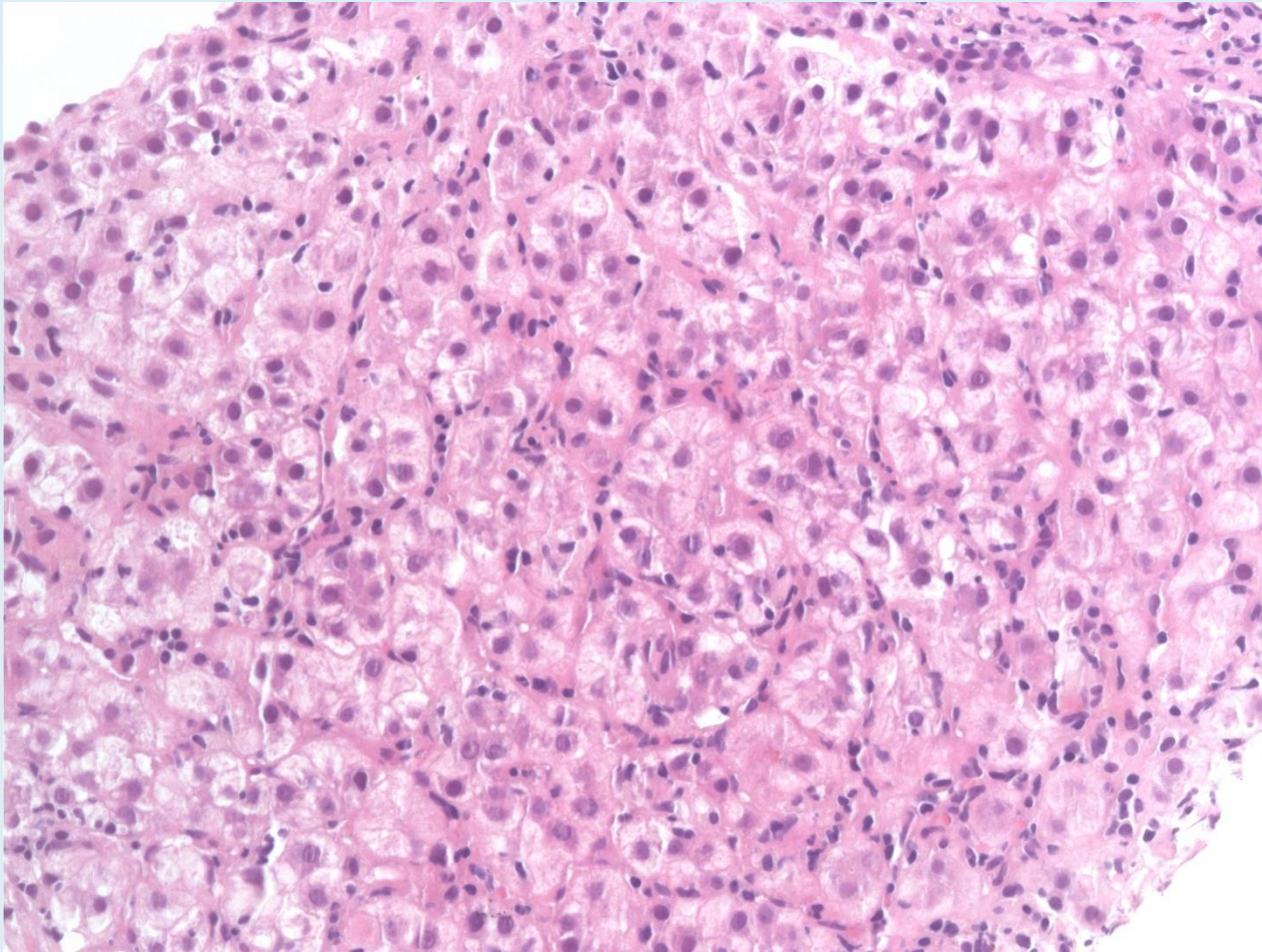
Case C – Overlap-Syndrom AIH/PBC



Case C – Overlap-Syndrom AIH/PBC



Case C. – Overlap-Syndrom AIH/PBC



I thank you for your attention
and
patience with this special issue