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# The liver in systemic inflammatory disorders

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# Wide range of diseases

- 'General' inflammatory disorders
- Connective tissue disorders
- Inflammatory bowel disease
- Fatty liver disease
- Granulomatous disease
- Amyloidosis
- IgG4-related systemic sclerosing disease
- Effects of treatment for systemic disease

# When to biopsy

- Liver biopsy may not be performed in systemic conditions known commonly secondarily to affect the liver
- The liver may be affected by a second disease process
- Liver biopsy may provide evidence for a systemic disease process

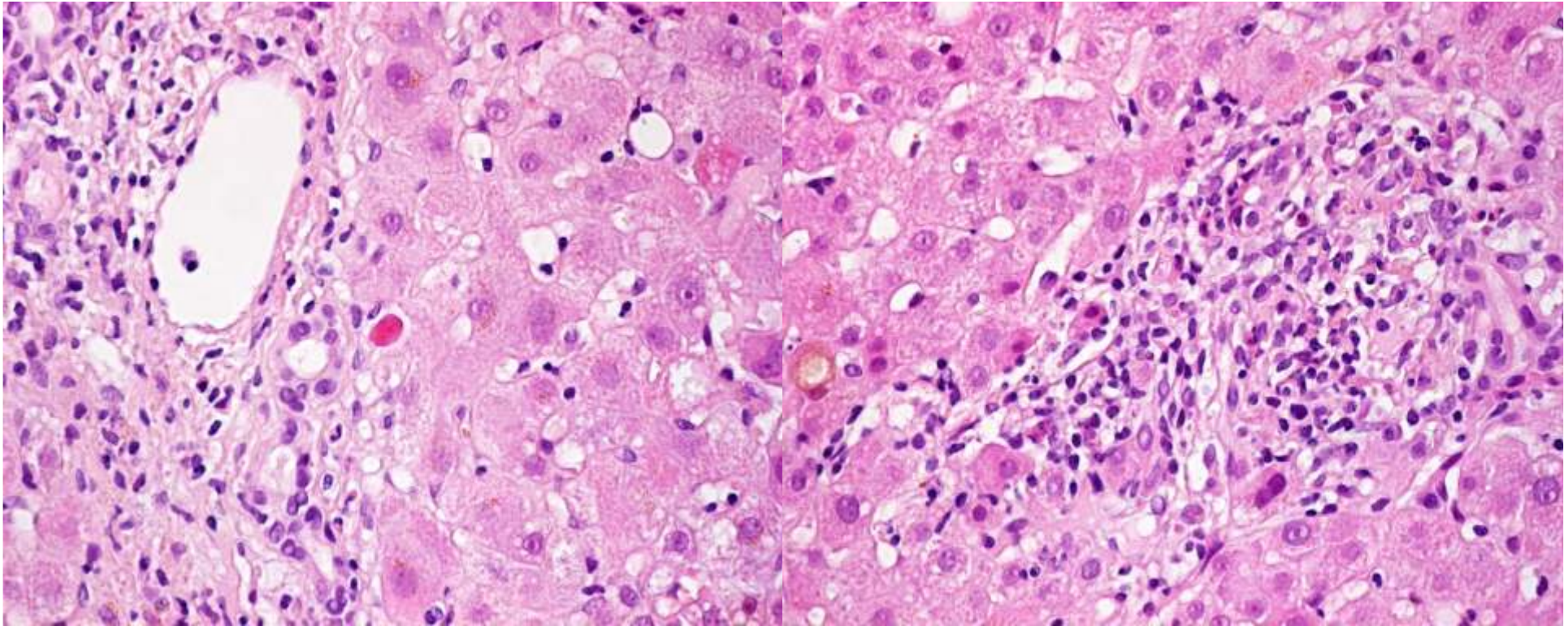
# Inflammatory disorders

- Systemic viral infections are common cause
- Biopsy performed if LFTs are significantly abnormal or do not normalise quickly enough
- Biopsy may be performed in unwell patients while serology is being requested
- Liver usually shows non-specific changes
  - Ceroid-laden macrophages in parenchyma and portal tracts

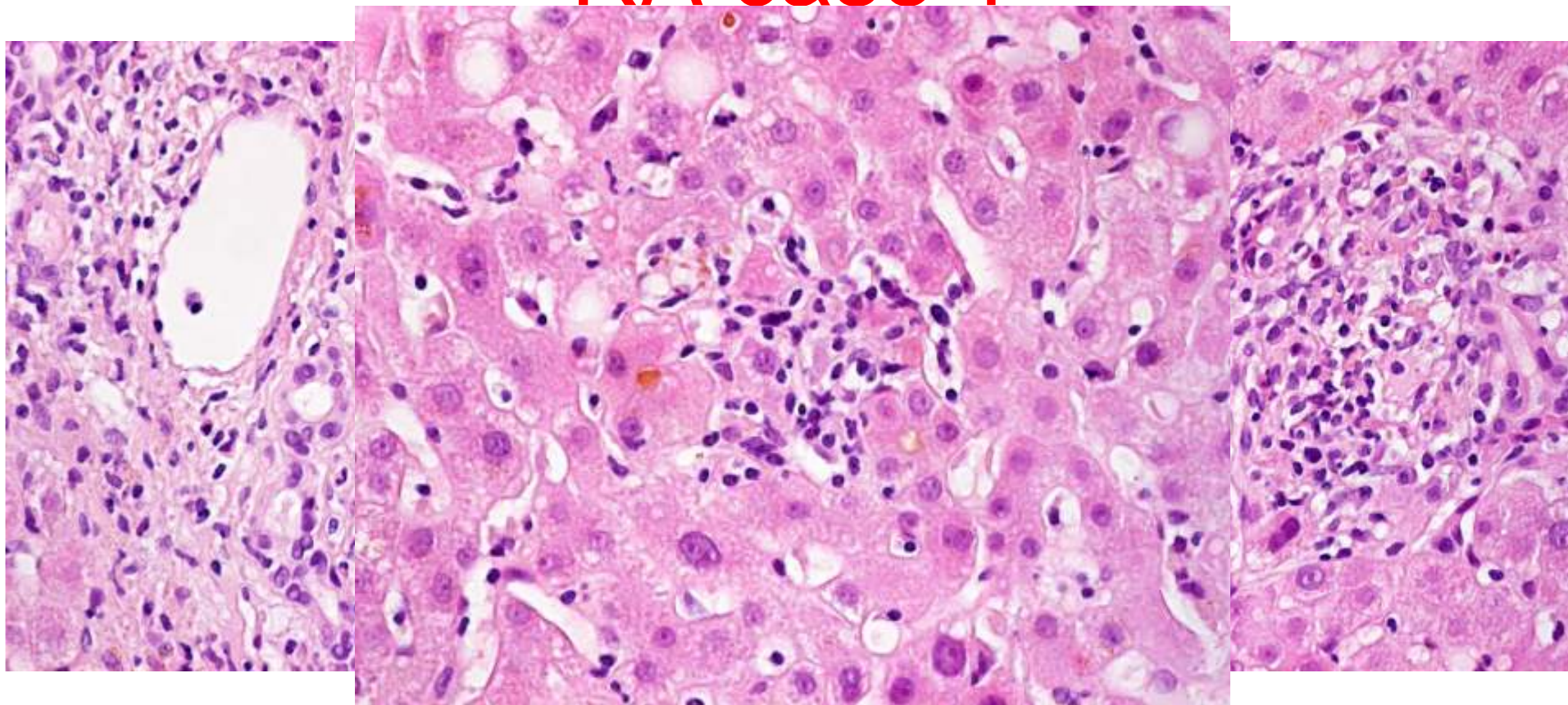
# Connective tissue disorders

- Rheumatoid arthritis
  - *Abnormal LFTs common (18-50%)*
  - Steatosis
  - Portal fibrosis
  - Vasculitis
  - Nodular regenerative hyperplasia
  - *Autoimmune hepatitis*

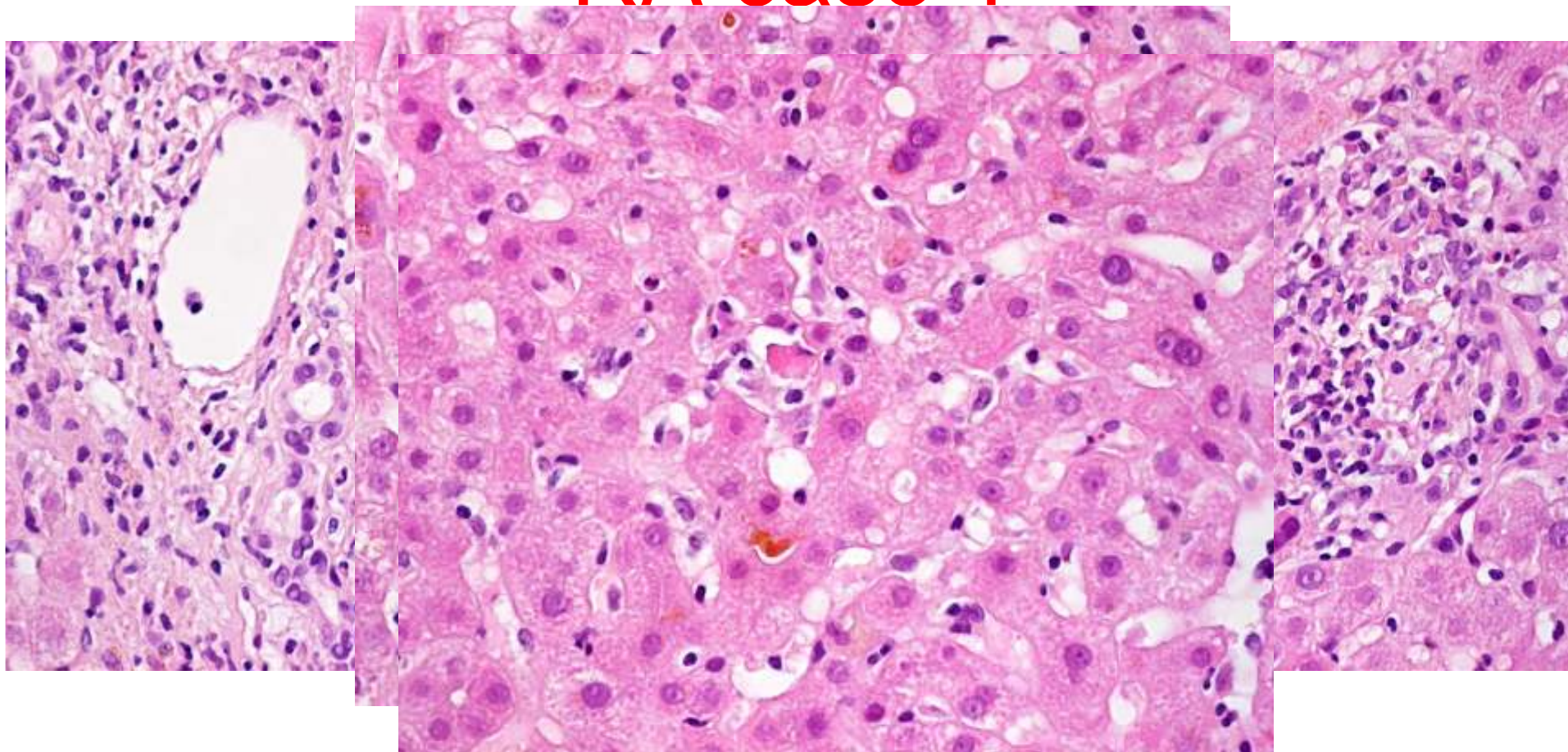
# RA case 1



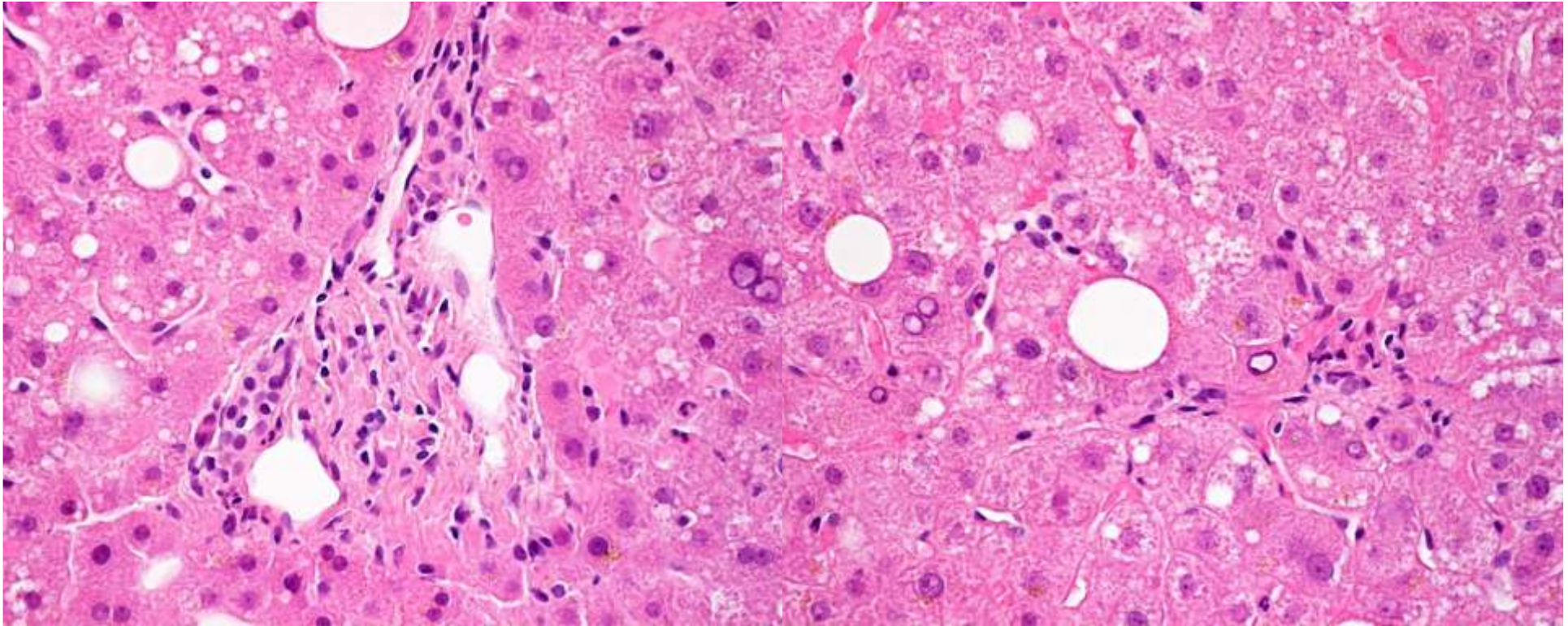
# RA case 1



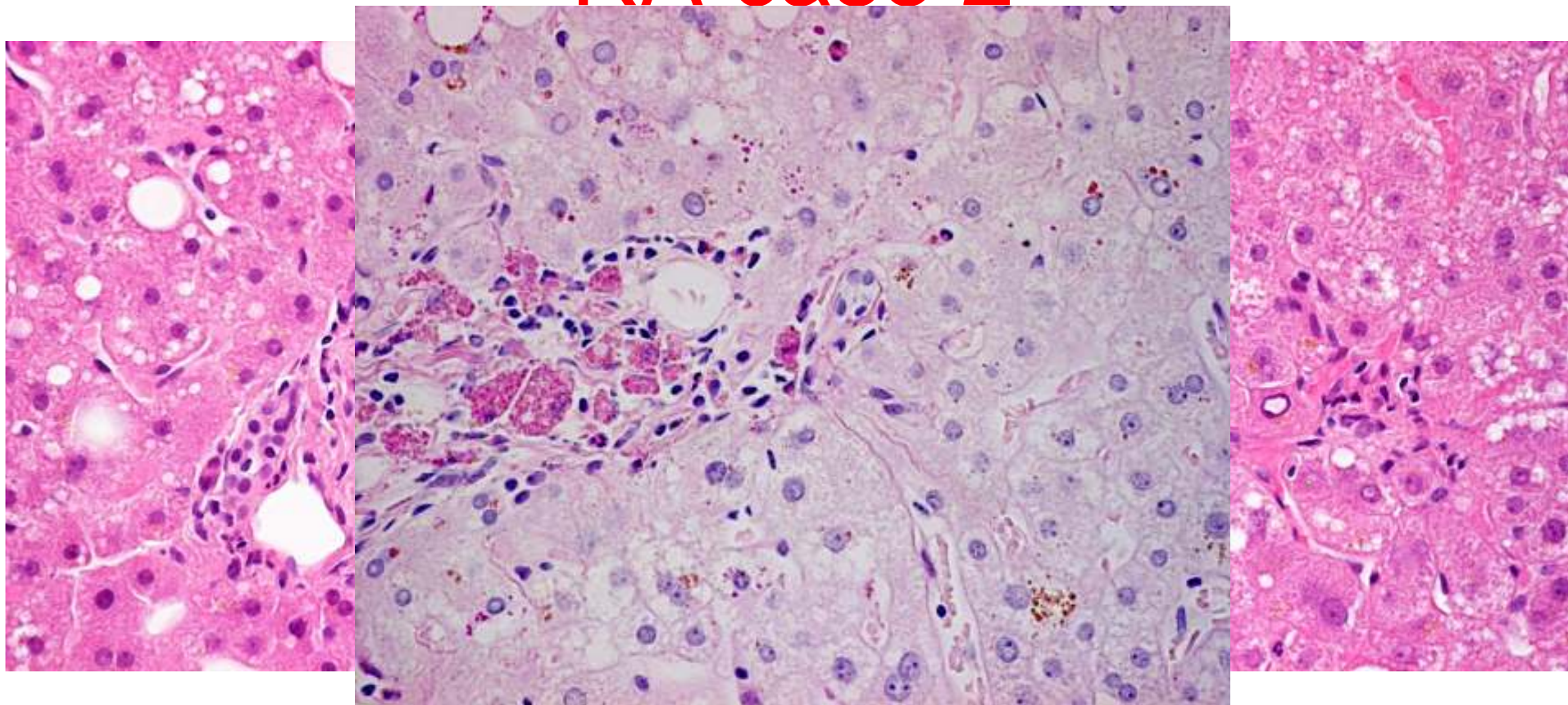
# RA case 1



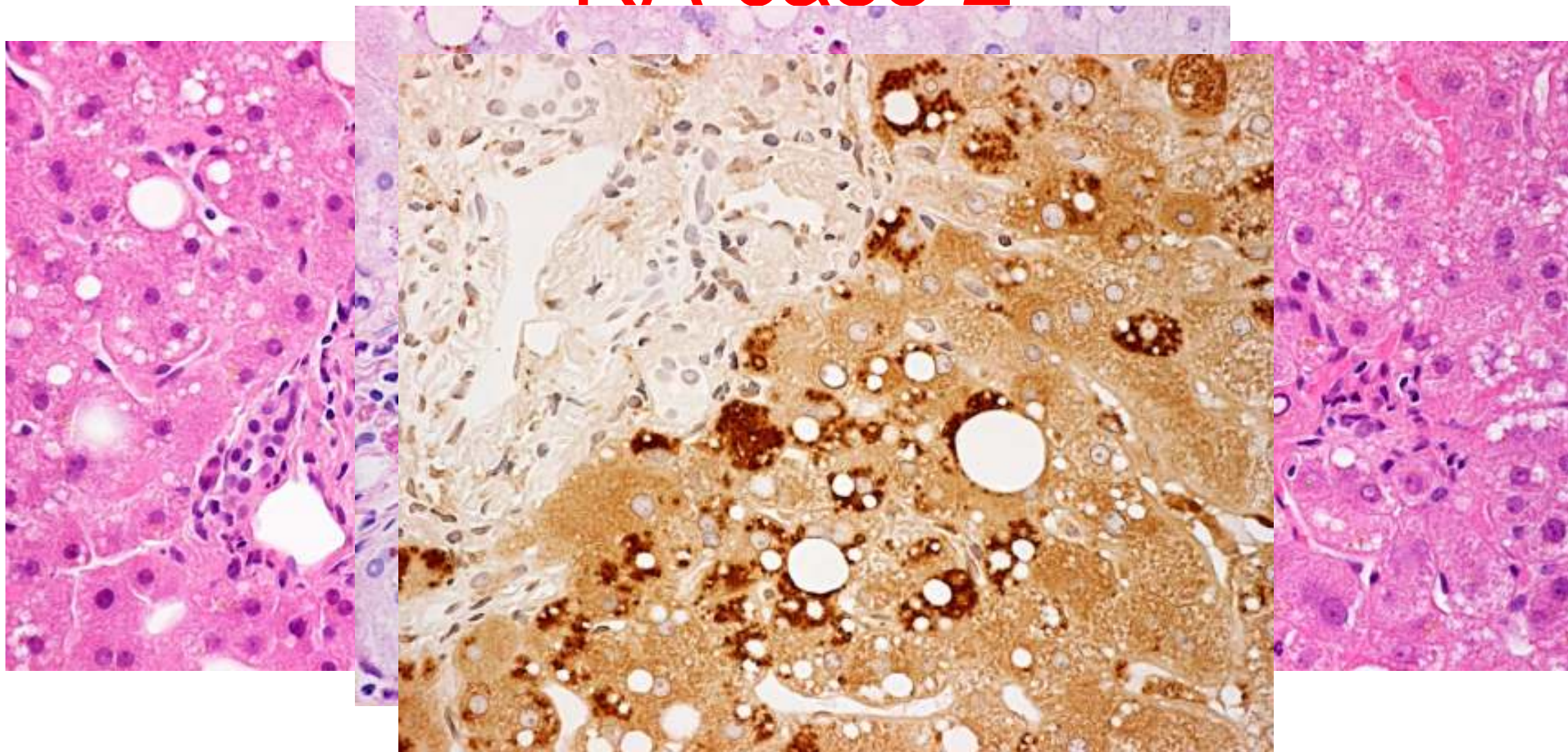
# RA case 2



# RA case 2



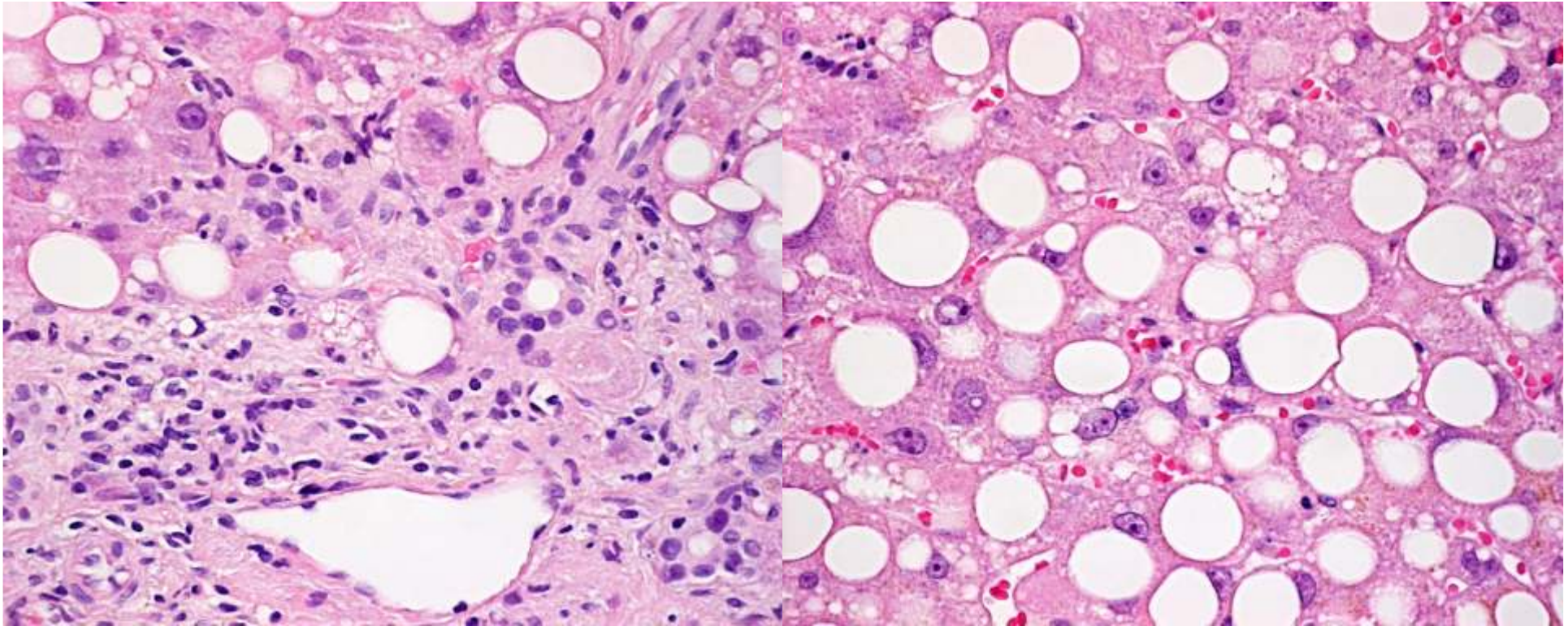
# RA case 2



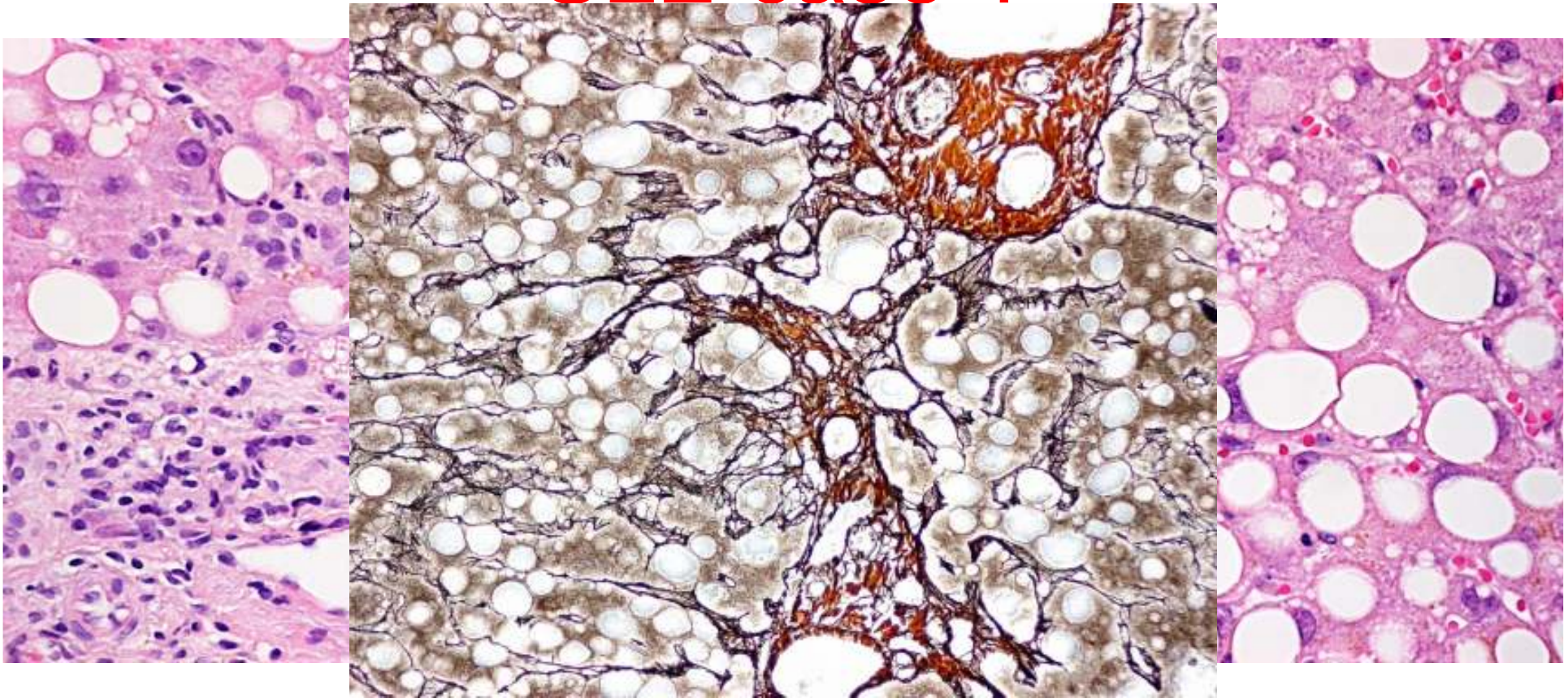
# Connective tissue disorders

- Systemic lupus erythematosus
  - *Subclinical liver involvement common (25-50%)*
  - Steatosis
  - Portal inflammation, granulomas
  - Nodular regenerative hyperplasia
  - Veno-occlusive disease
  - Budd-Chiari syndrome
  - HELLP syndrome (haemolytic anaemia, elevated liver enzymes, low platelets)
  - *Autoimmune hepatitis*

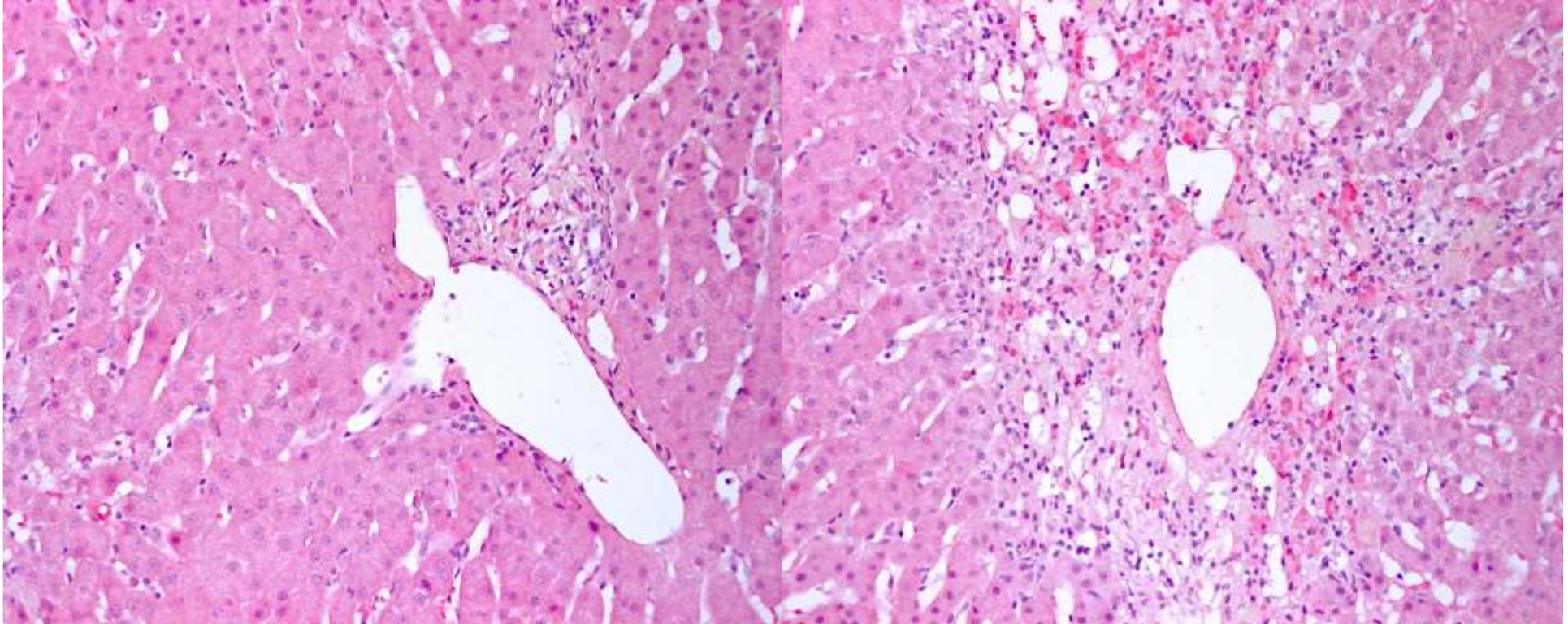
# SLE case 1



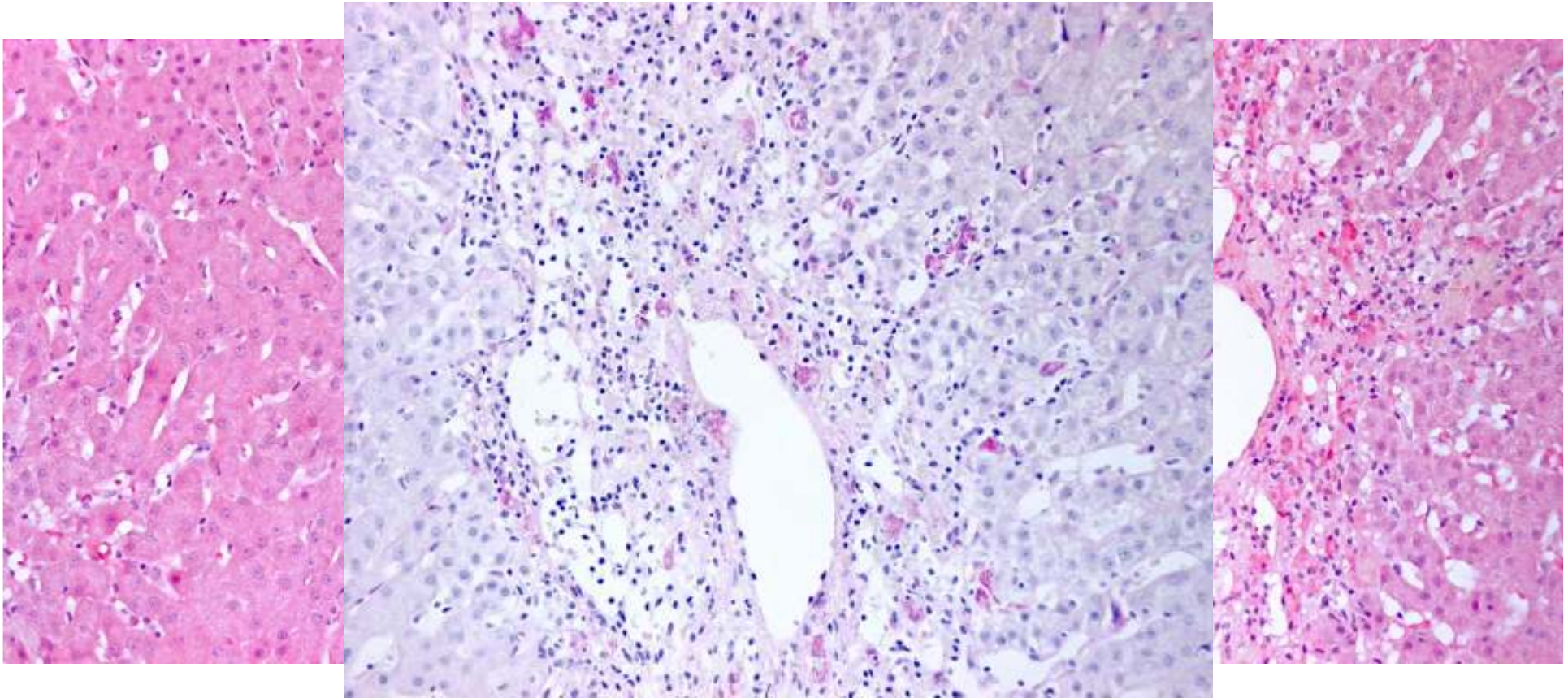
# SLE case 1



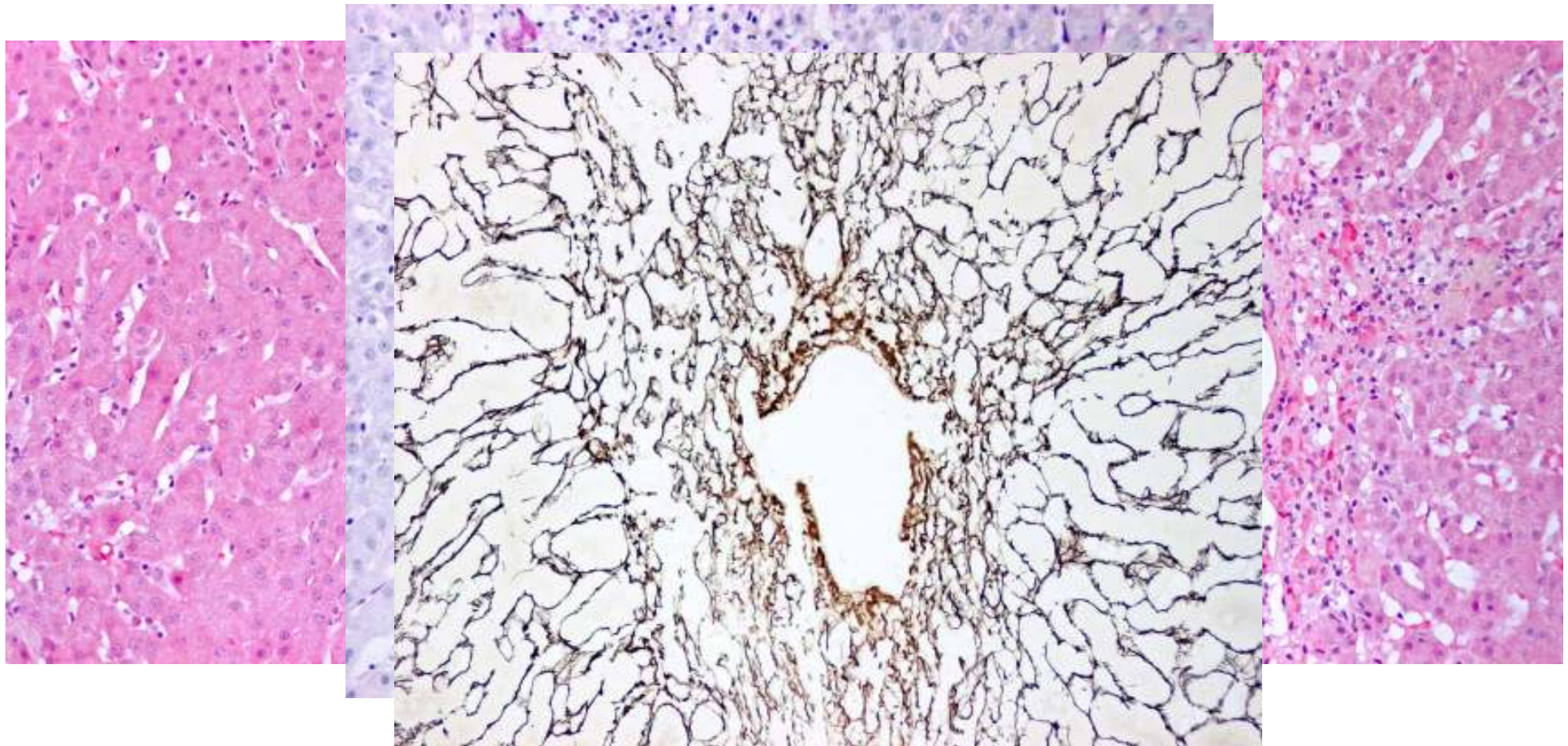
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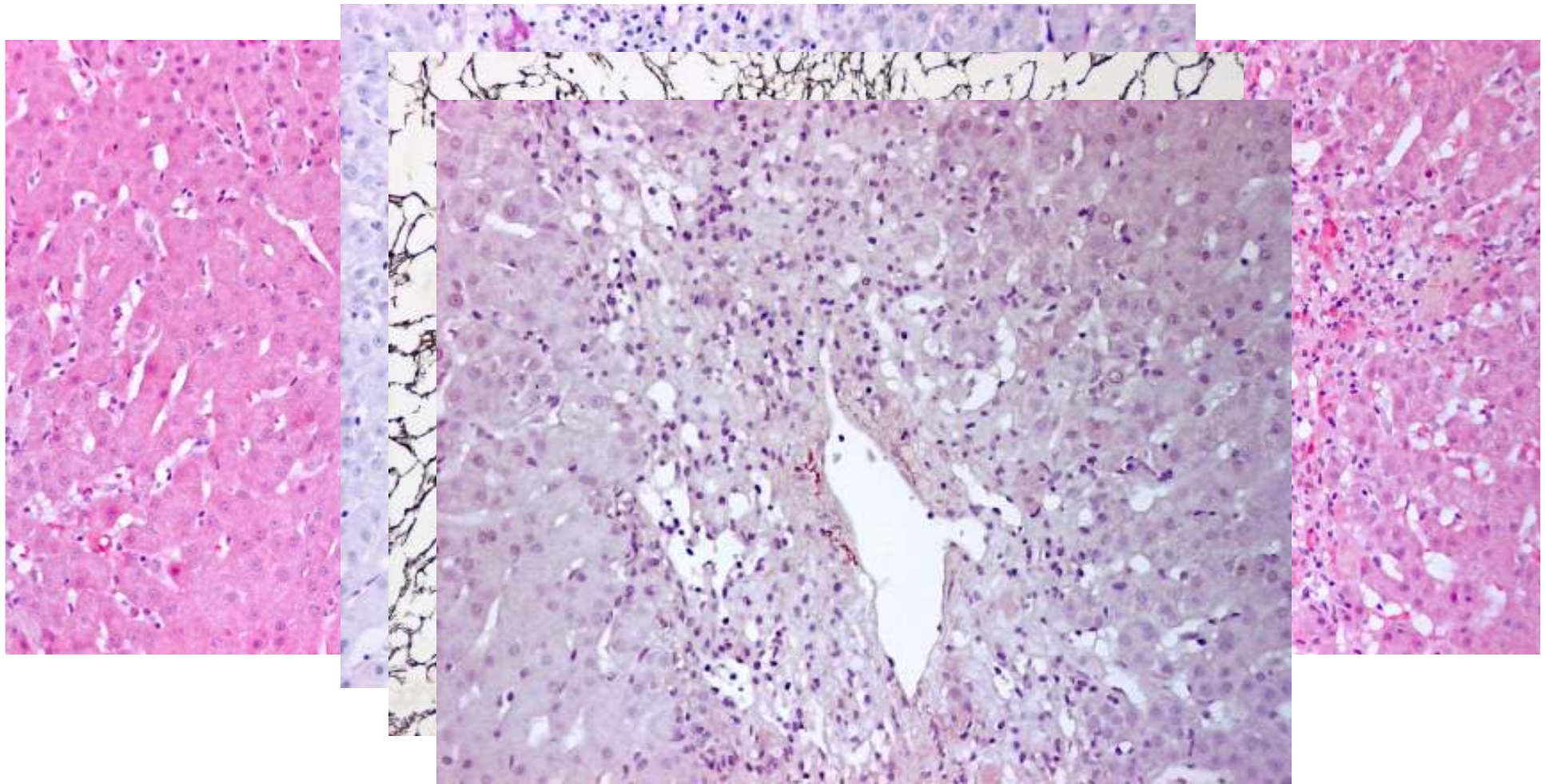
# SLE case 2



# SLE case 2

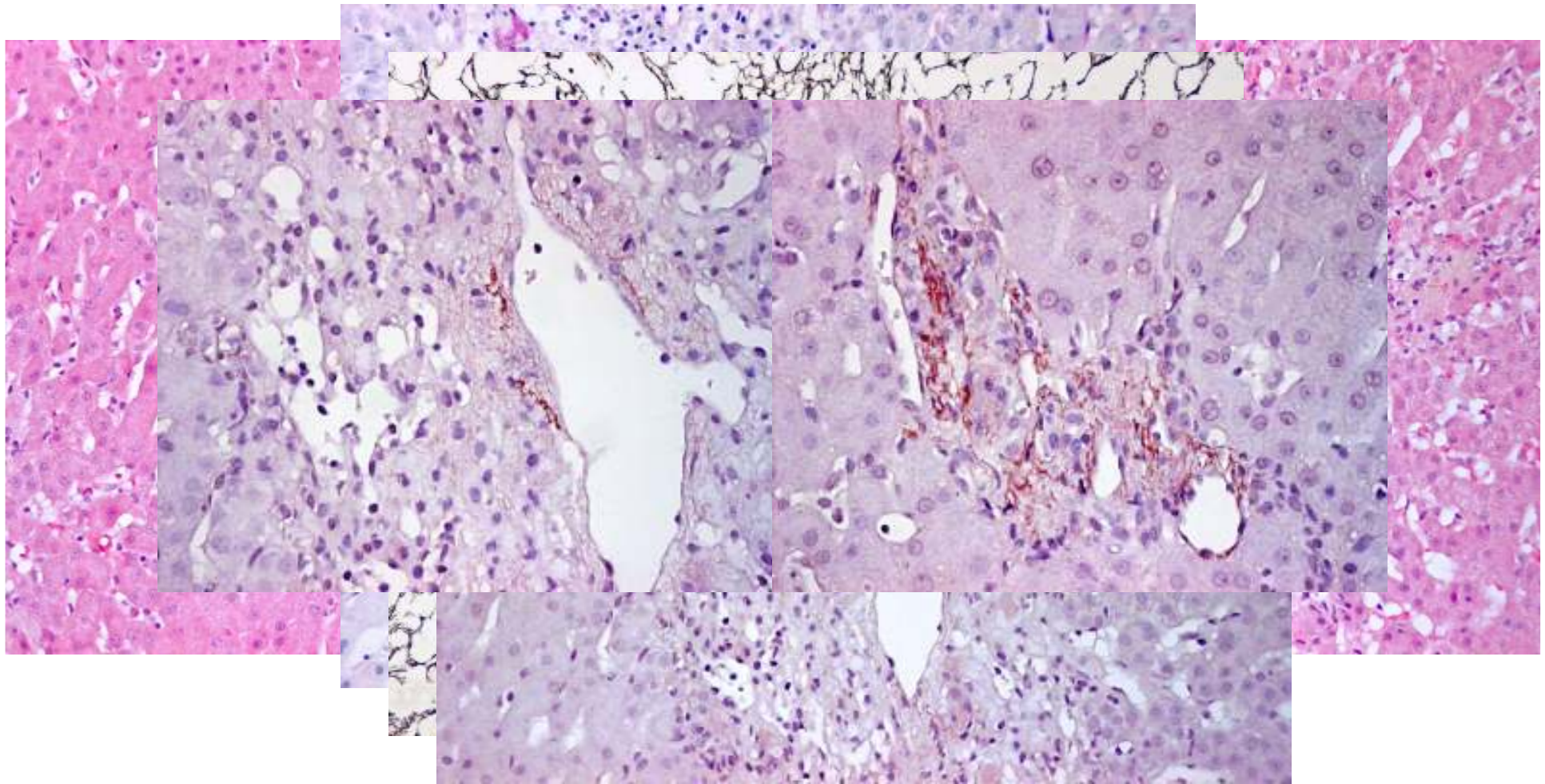


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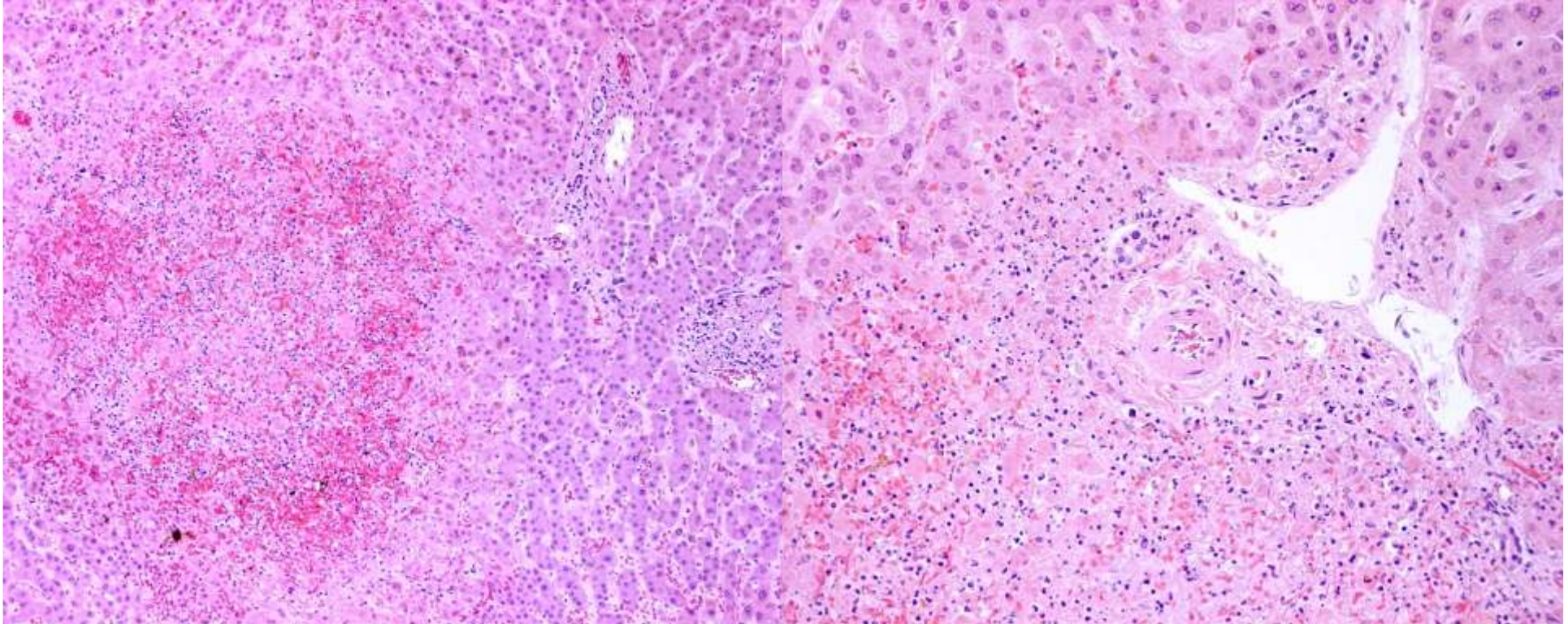


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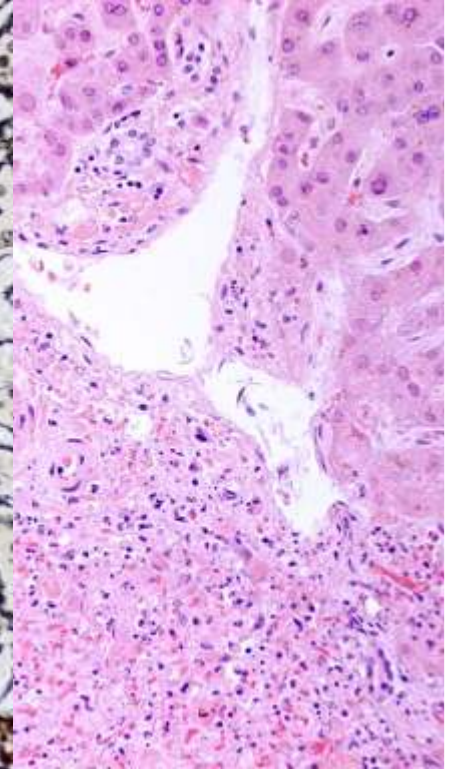
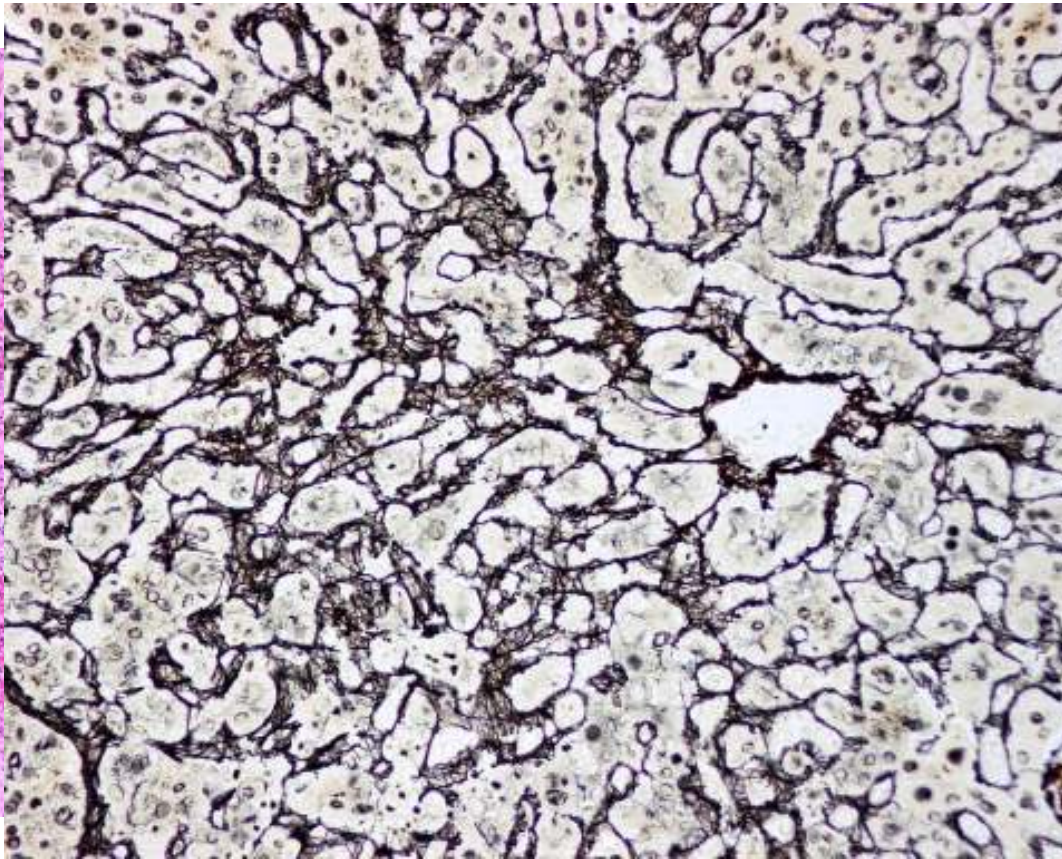
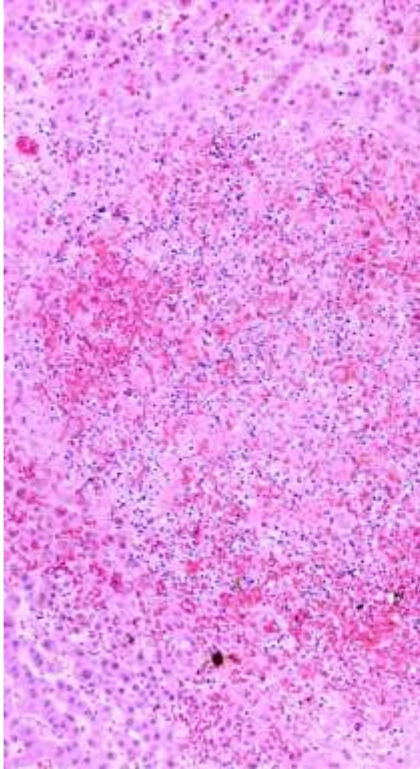
# SLE case 2



# SLE case 3



# SLE case 3



# Liver involvement in SLE

- Mayo Clinic 2008
- 40 SLE patients with abnormal LFTs
  - 8 NAFLD (5)
  - 8 Viral (3)
  - 6 Autoimmune hepatitis (4)
  - 4 Drug-induced (1)
  - 3 PBC (3)
  - 11 Miscellaneous (4)
- 44 month median follow-up
- 93% had no 'serious' liver disease

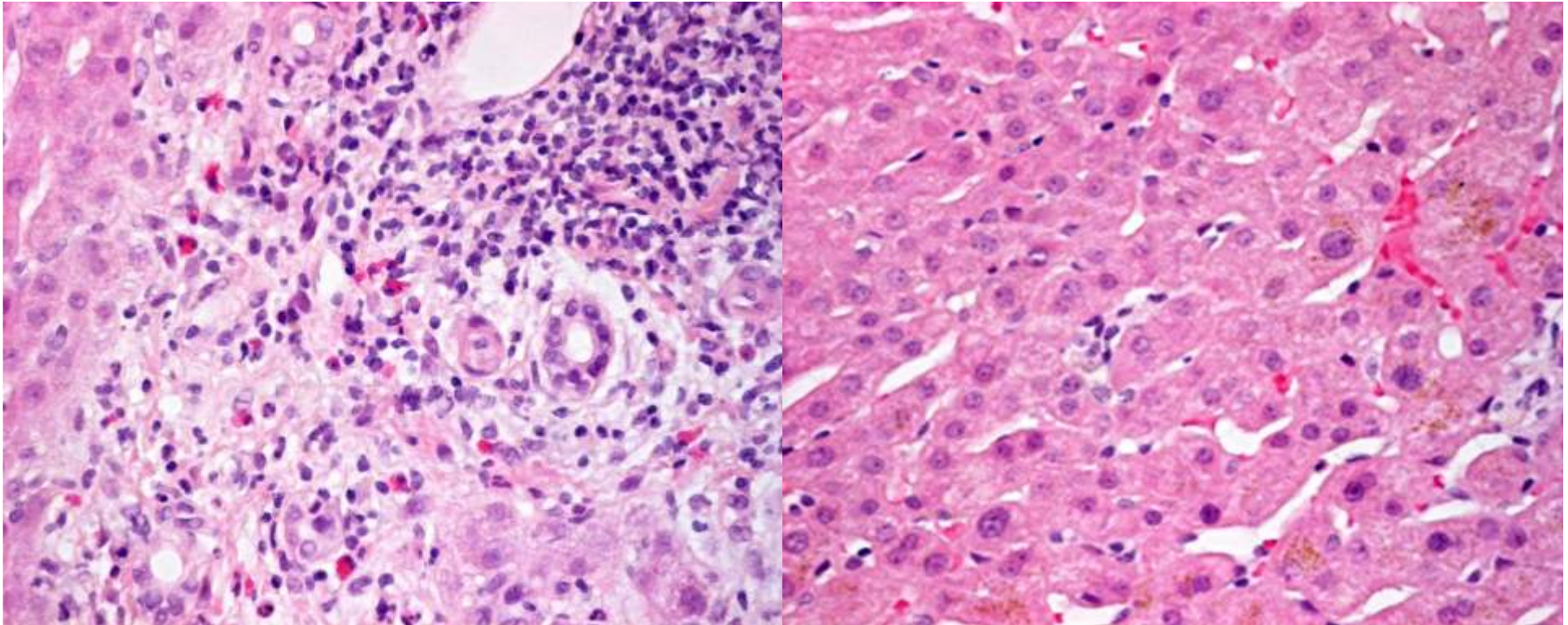
# Connective tissue disorders

- Sjögren's syndrome
  - May occur in association with primary biliary cirrhosis
  - Increased AMA titre in 7-10%
  - Liver biopsies may show early PBC changes
- Scleroderma/CREST syndrome
  - Associated with primary biliary cirrhosis
  - Increased AMA titre in up to 25%

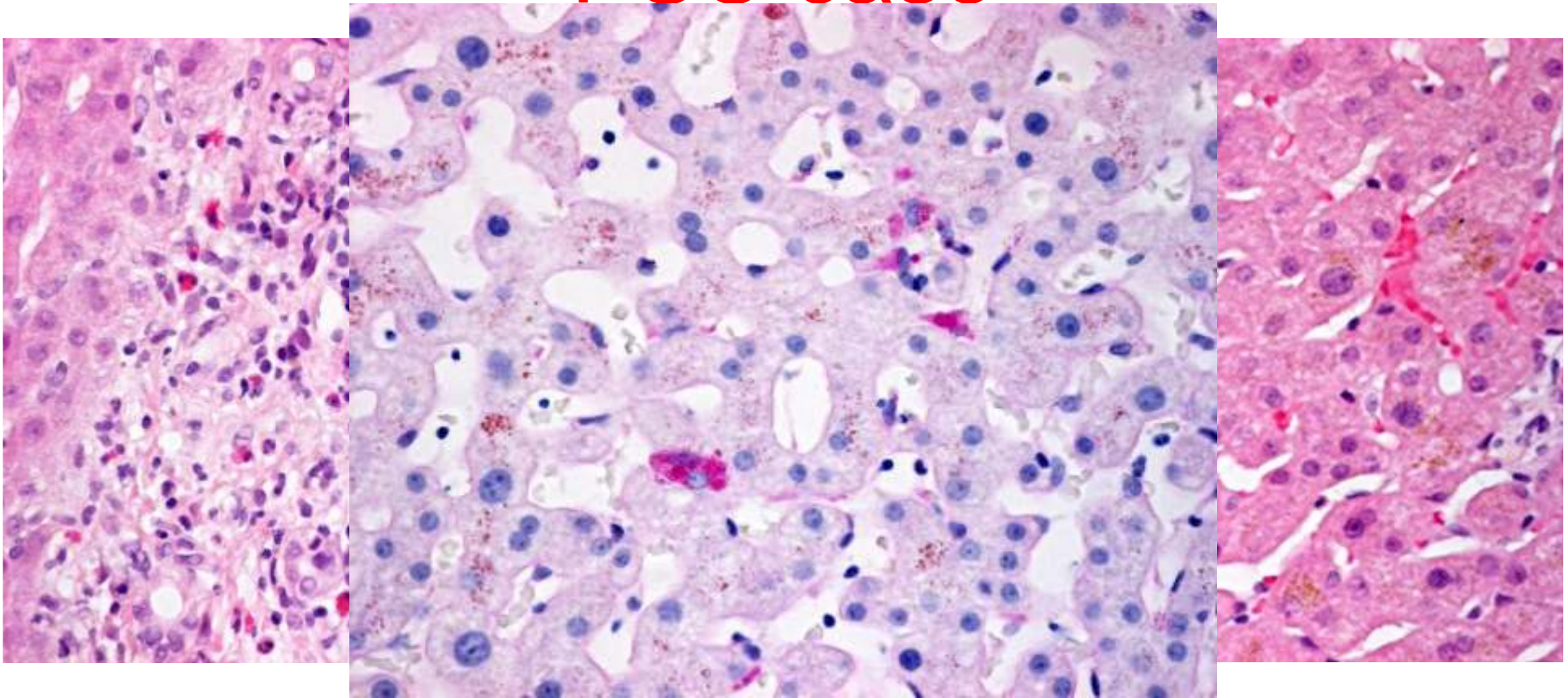
# Inflammatory bowel disease

- Sclerosing cholangitis
- Most common in association with UC
- Liver biopsy appearances varied
- Classical chronic biliary changes
  - Additional stains may be useful
    - Orcein, rhodanine, cytokeratin (CK) 7
- Specific features may be lacking
- MRCP or ERCP often useful

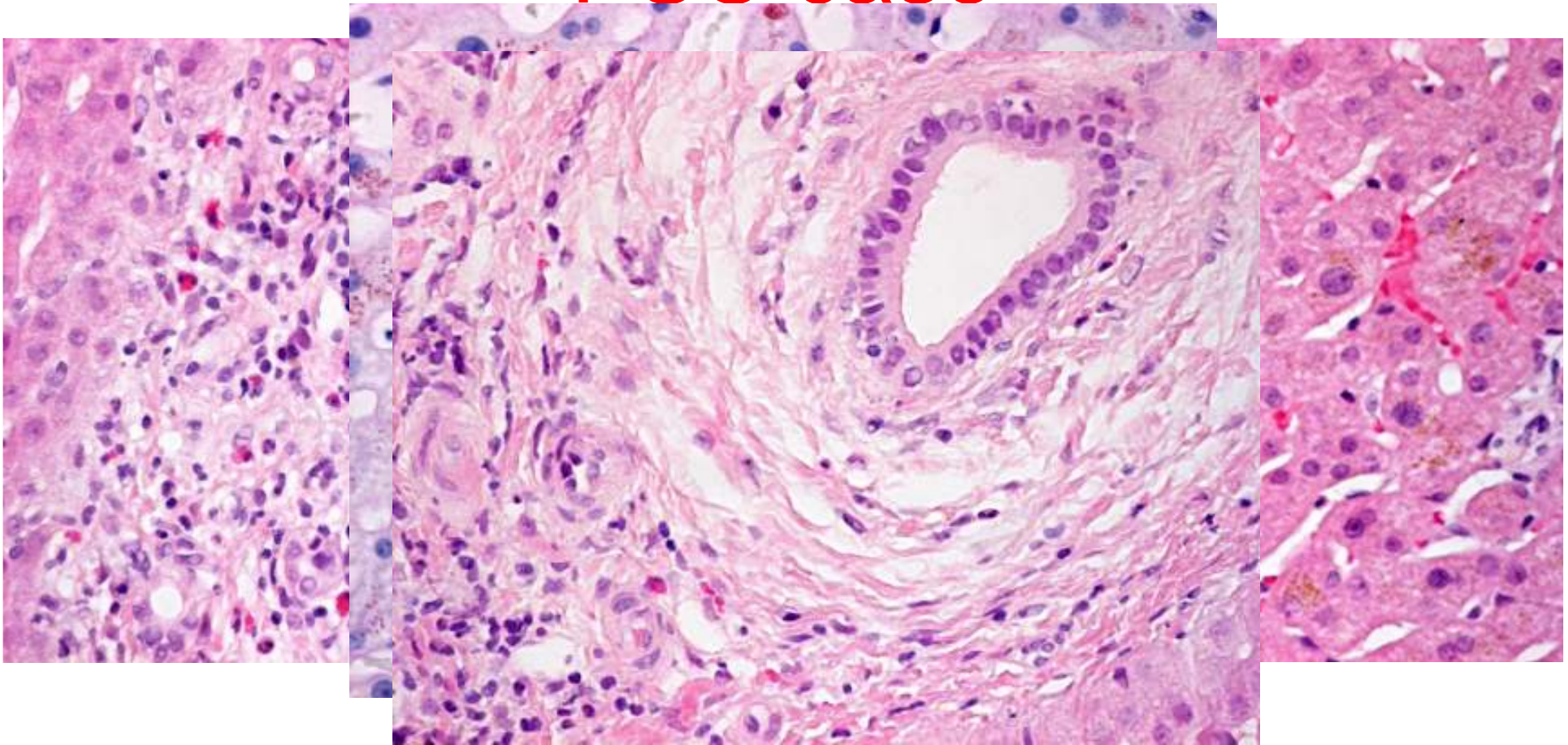
# PSC case



# PSC case

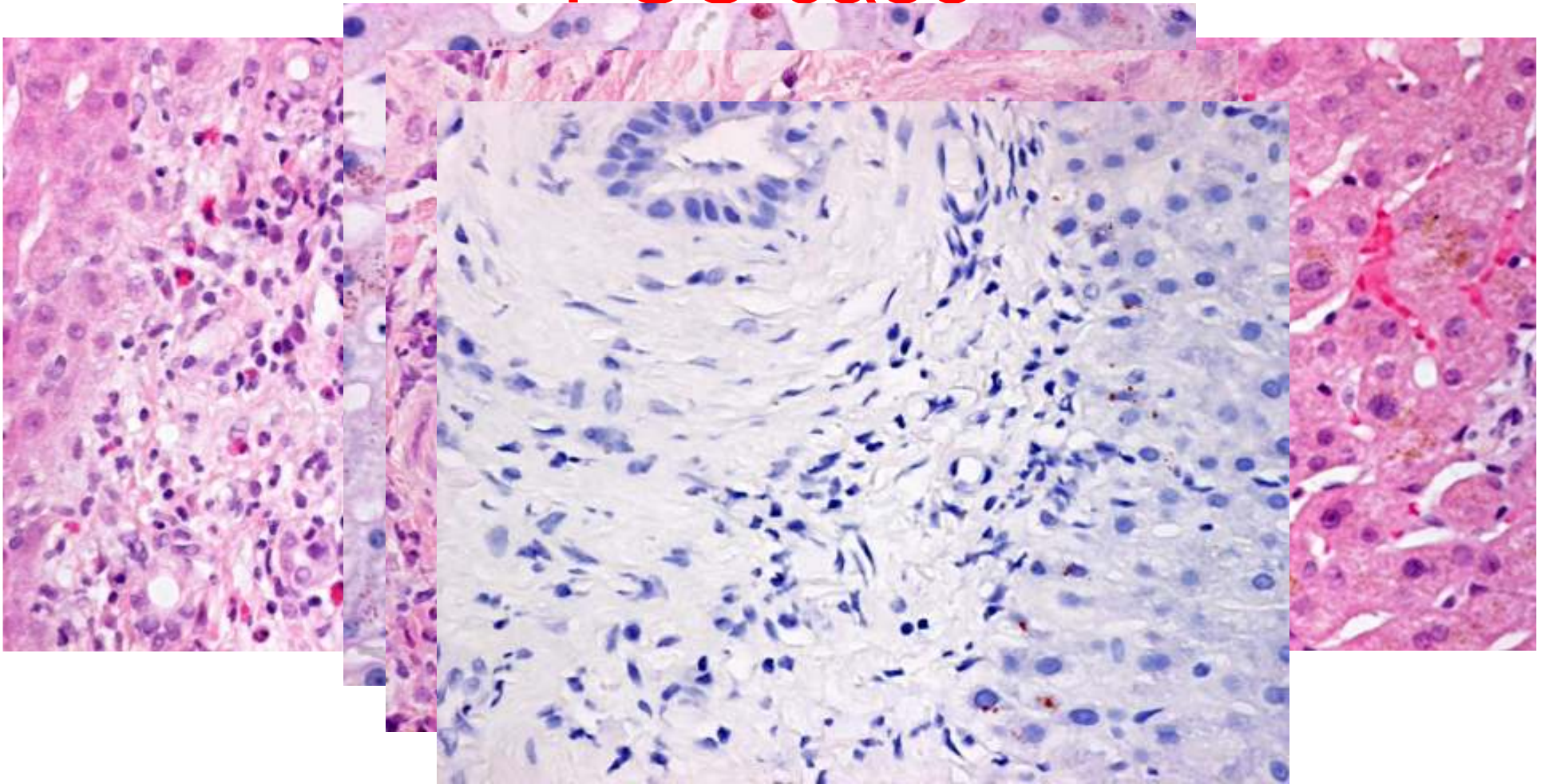


# PSC case



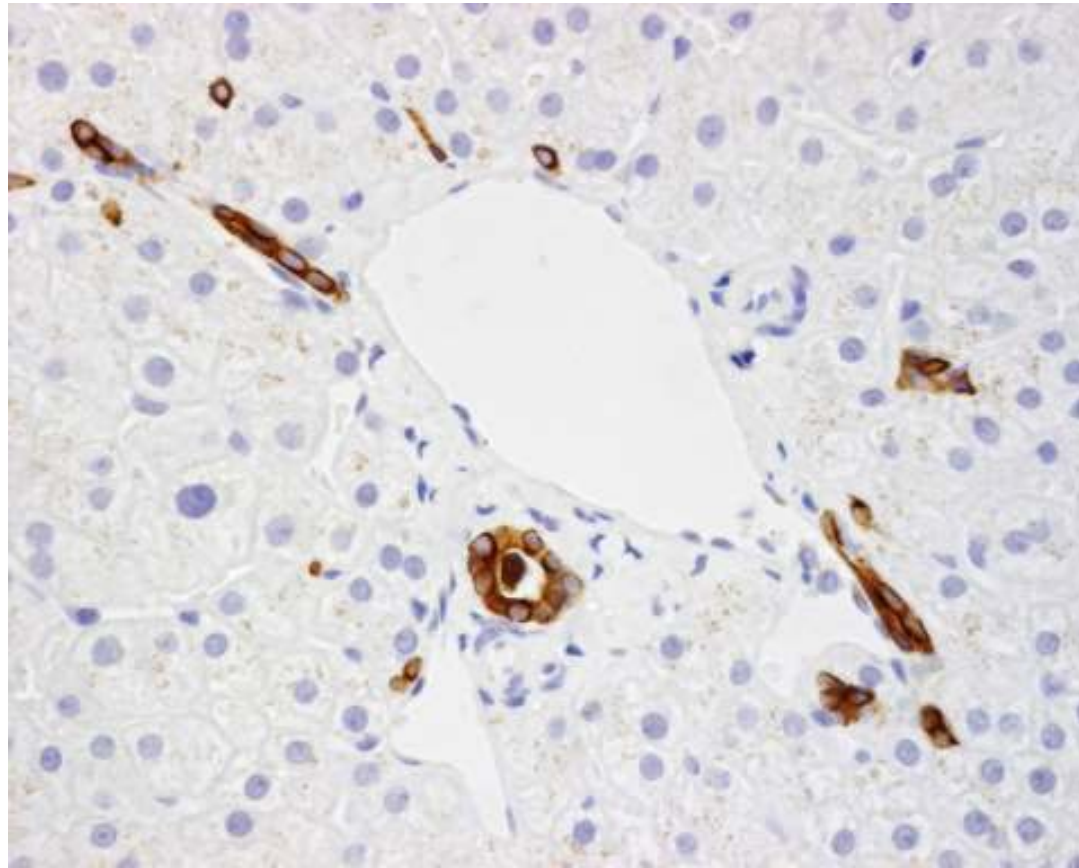
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# PSC case



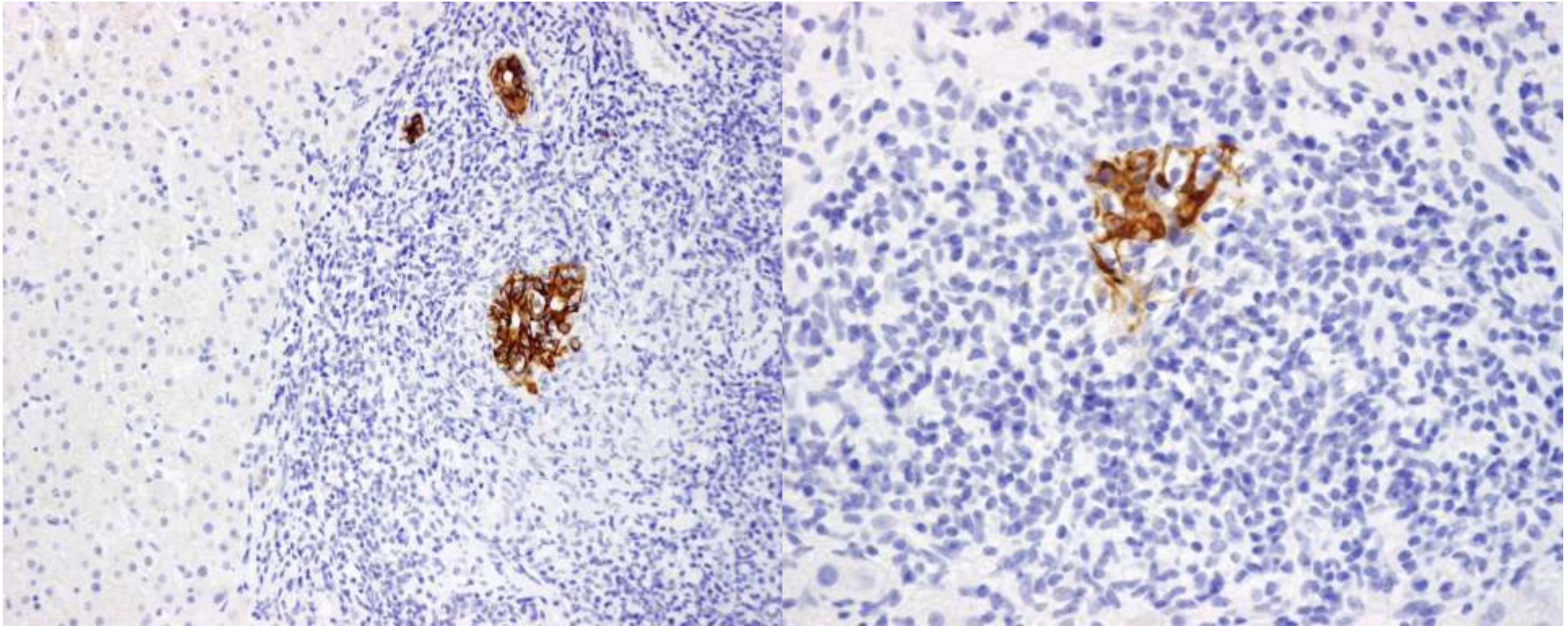
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# CK-7



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# CK-7 in PBC



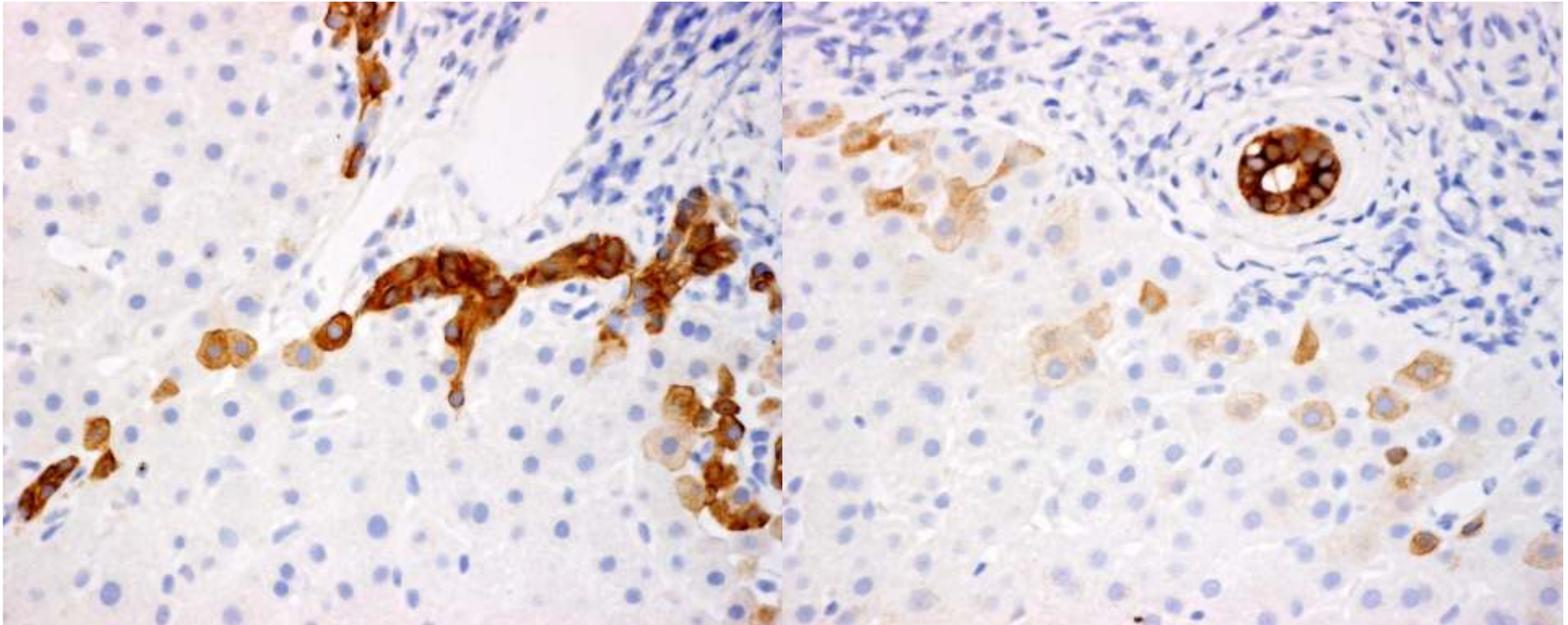
# Hepatic progenitor cells

- Are these true stem cells?
  - Show evidence of multipotent differentiation
  - Appear to increase in number in some liver diseases
  - *Not certain whether they are capable of self-renewal*
  - *Could they be bone marrow derived?*

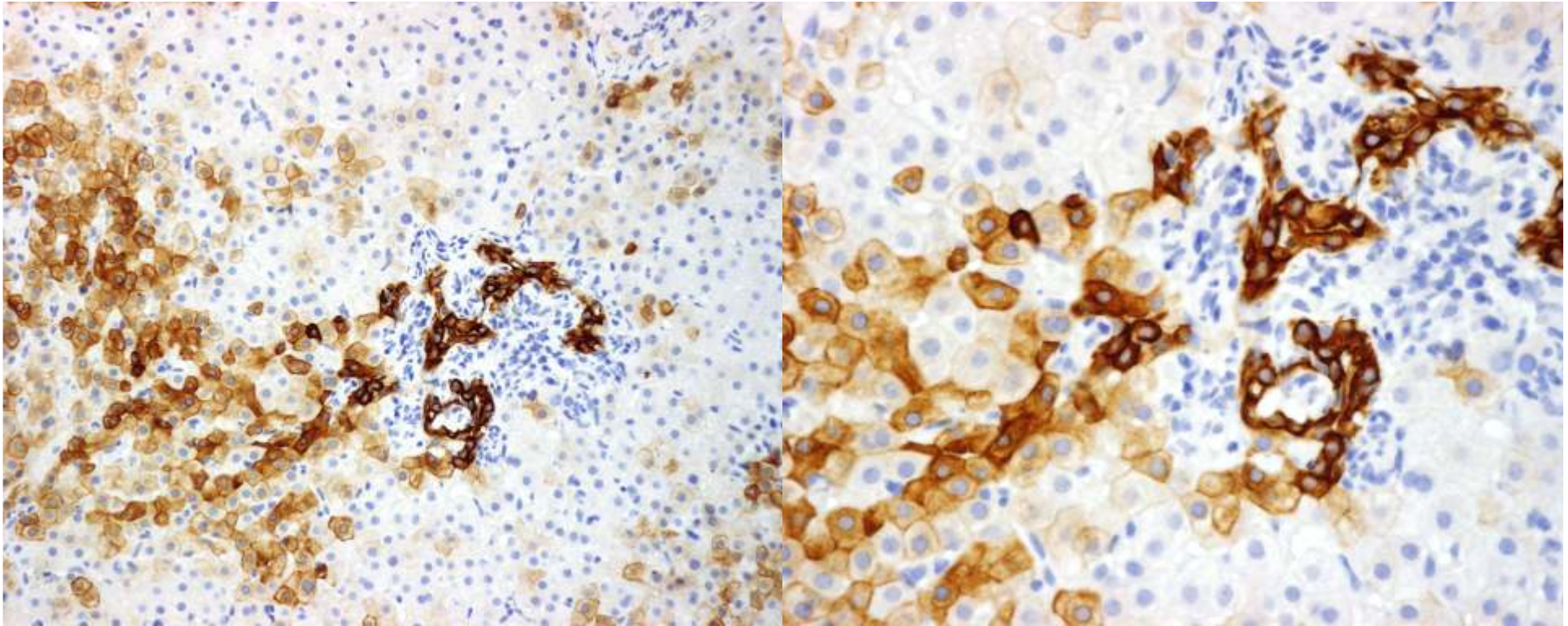
# Hepatocyte CK-7 expression

- Normal hepatocytes do not express CK-7
- Periportal hepatocytes express CK-7 in chronic biliary tract disease
  - CK-19 is not expressed in this situation
- Degree of CK-7 expression related to disease stage in primary biliary cirrhosis

# CK-7 in early PSC



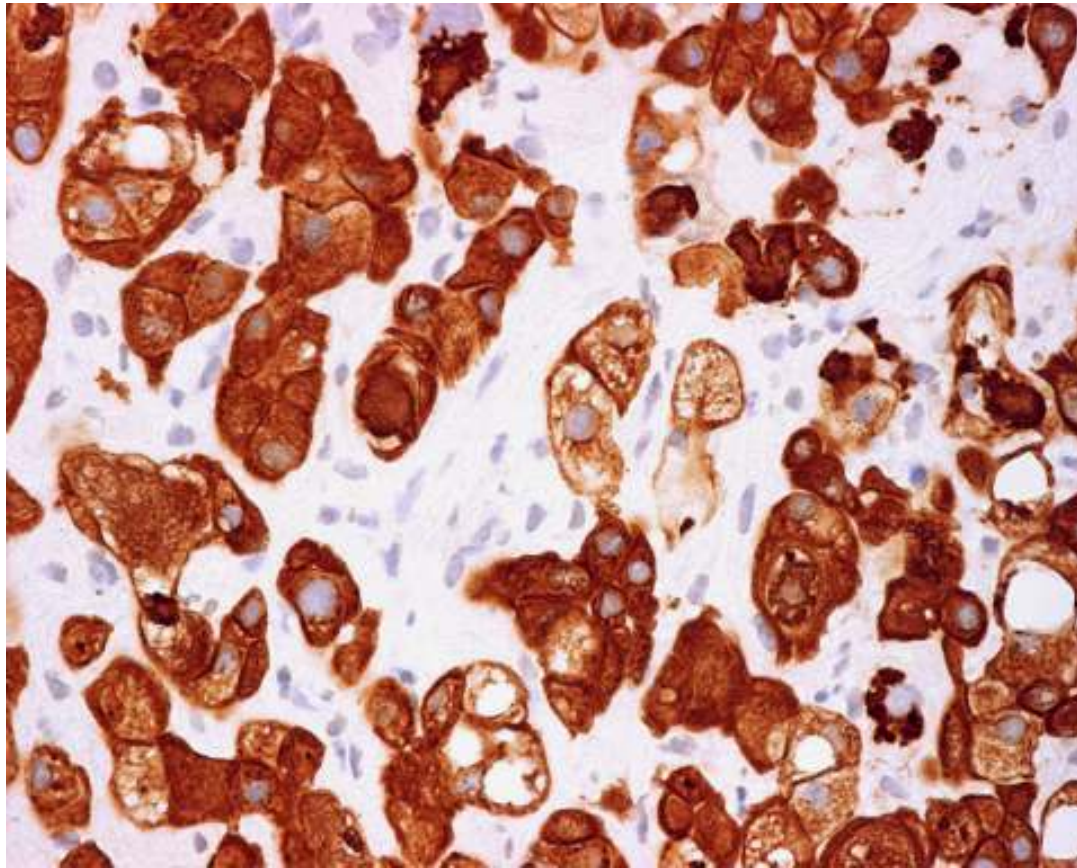
# CK-7 in PBC



# Fatty liver disease

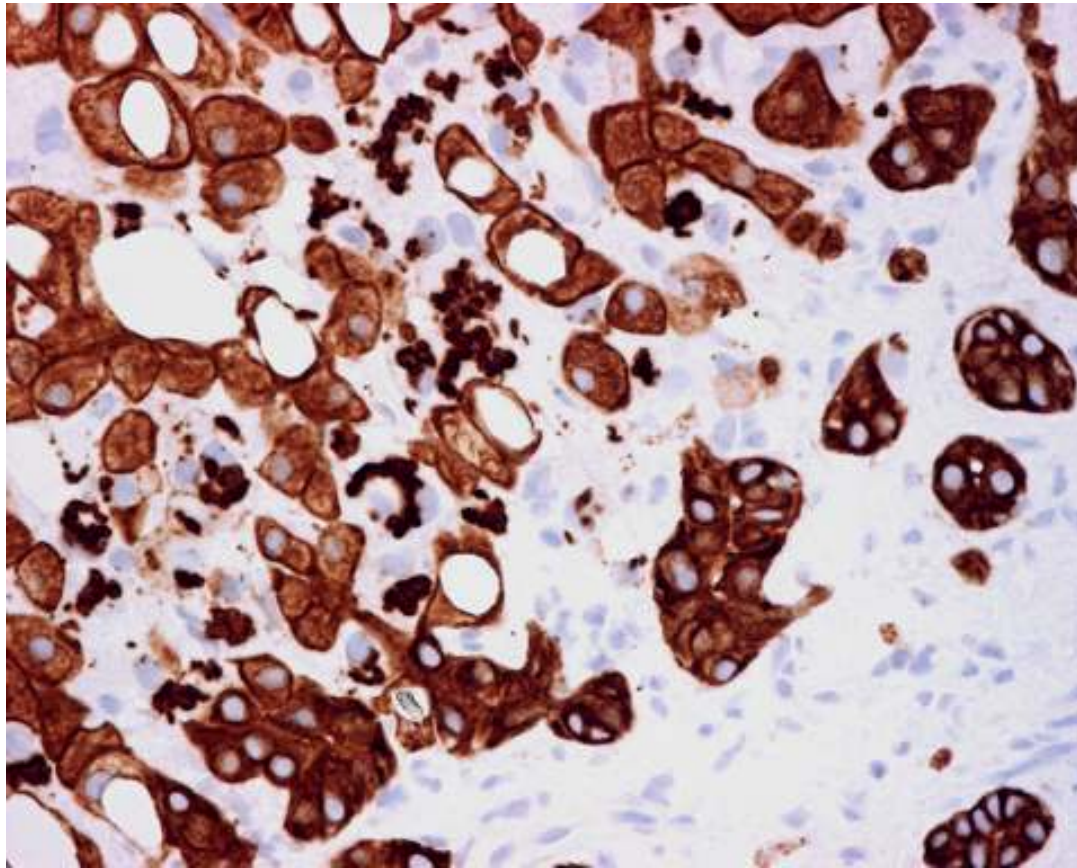
- Metabolic syndrome
- Fatty liver, central obesity, type 2 DM, hypertension, dyslipidaemia
- A form of systemic inflammatory process
  - Increased CRP, pro-inflammatory ILs e.g. IL-6
- Biopsy important to confirm diagnosis, exclude additional conditions and determine disease stage

# CK-8 in steatosis



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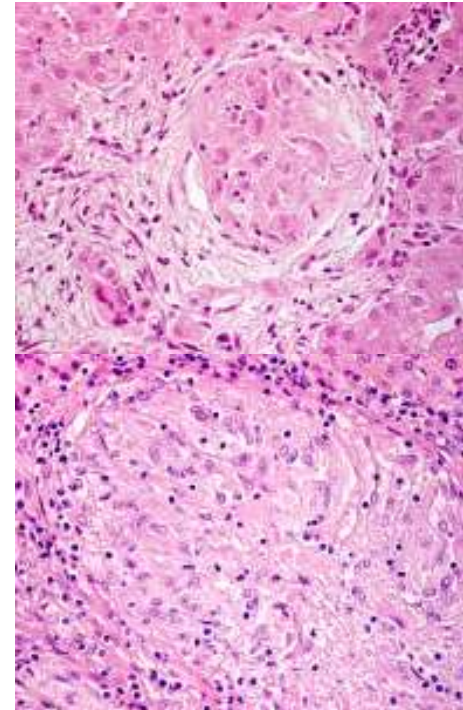
# CK-8 : Mallory-Denk bodies



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# Granulomatous disease

- Huge range of potential causes!
  - Primary liver disease
    - PBC, PSC, autoimmune hepatitis
  - Systemic granulomatous disease
    - Sarcoidosis, Crohn's disease
  - Infections
  - Drugs
    - Many e.g. allopurinol, phenytoin, various antibiotics
  - Malignancy



# Sarcoidosis

- Usually asymptomatic
- Portal hypertension
  - Arterio-venous shunts
  - Increased sinusoidal resistance
  - Phlebitis leading to fibrosis/cirrhosis
- Cholestasis
  - May resemble PBC or PSC
- Budd-Chiari syndrome

# Granulomas & infections

- Bacterial
  - TB, MAI, brucellosis, leprosy
- Parasitic
  - Schistosomiasis
- Viral
  - Hepatitis C, CMV
- Fungal
  - e.g. histoplasma, cryptococcus, candida

# Amyloidosis

- Liver involvement seen in both AL and AA amyloidosis
- Liver involved in up to 70% of AL amyloidosis
- May be asymptomatic
- Disturbances of hepatic function indicate advanced disease
  - Other organs often affected e.g. nephrotic syndrome

# IgG4-related systemic sclerosing disease

- Autoimmune pancreatitis
- Multi-system involvement
  - Sclerosing cholangitis
- Diagnostic criteria
  - Characteristic radiological appearances
  - Raised serum IgG4 concentration
  - Increased tissue IgG4-positive plasma cells
- Steroid responsive

# AIP - Radiological features



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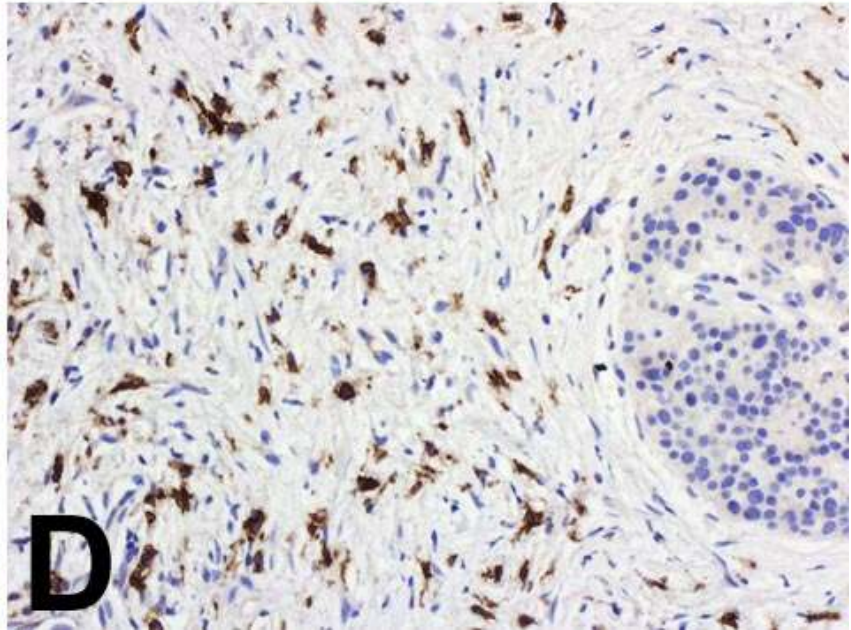
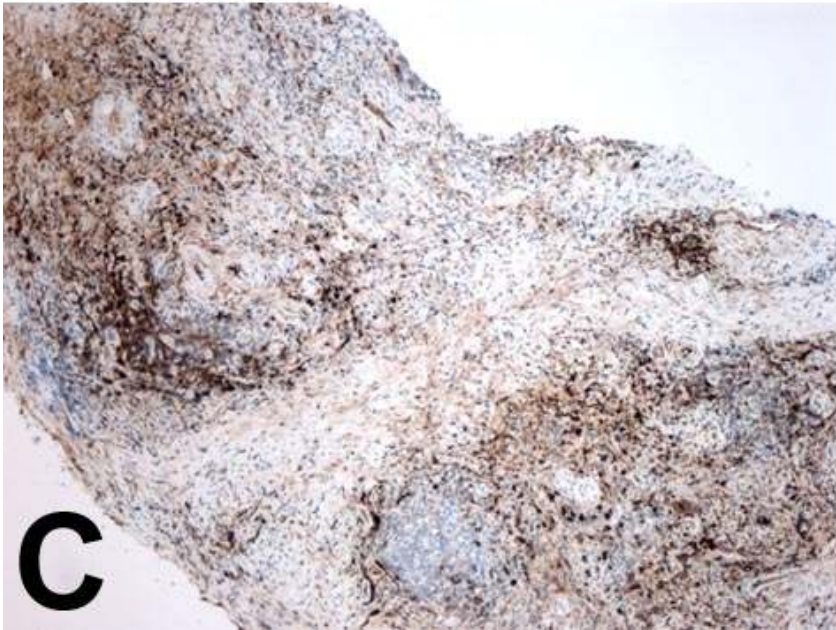
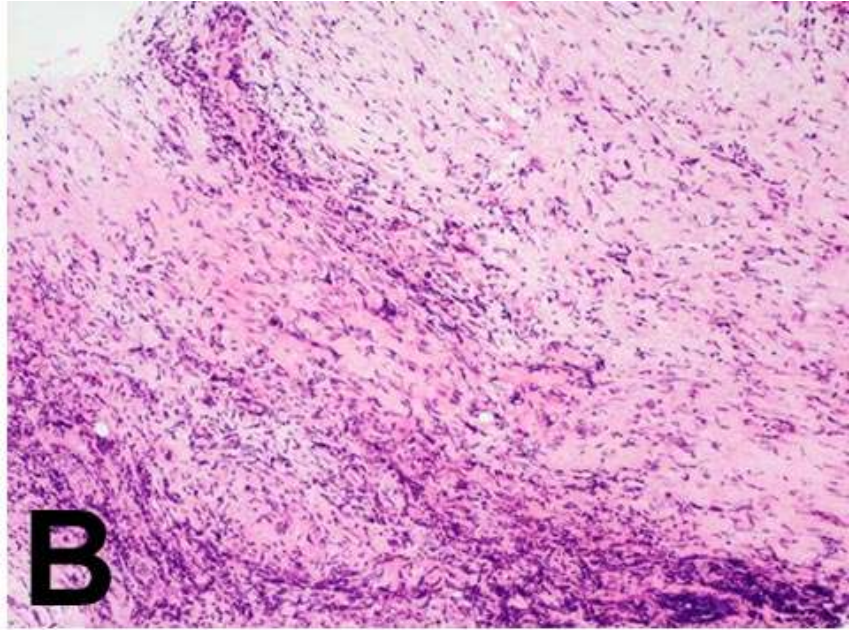
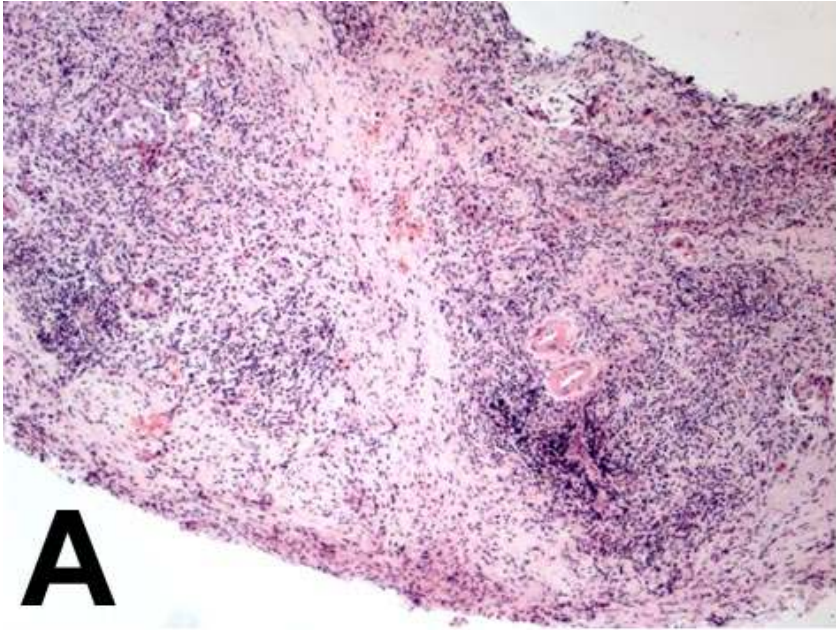


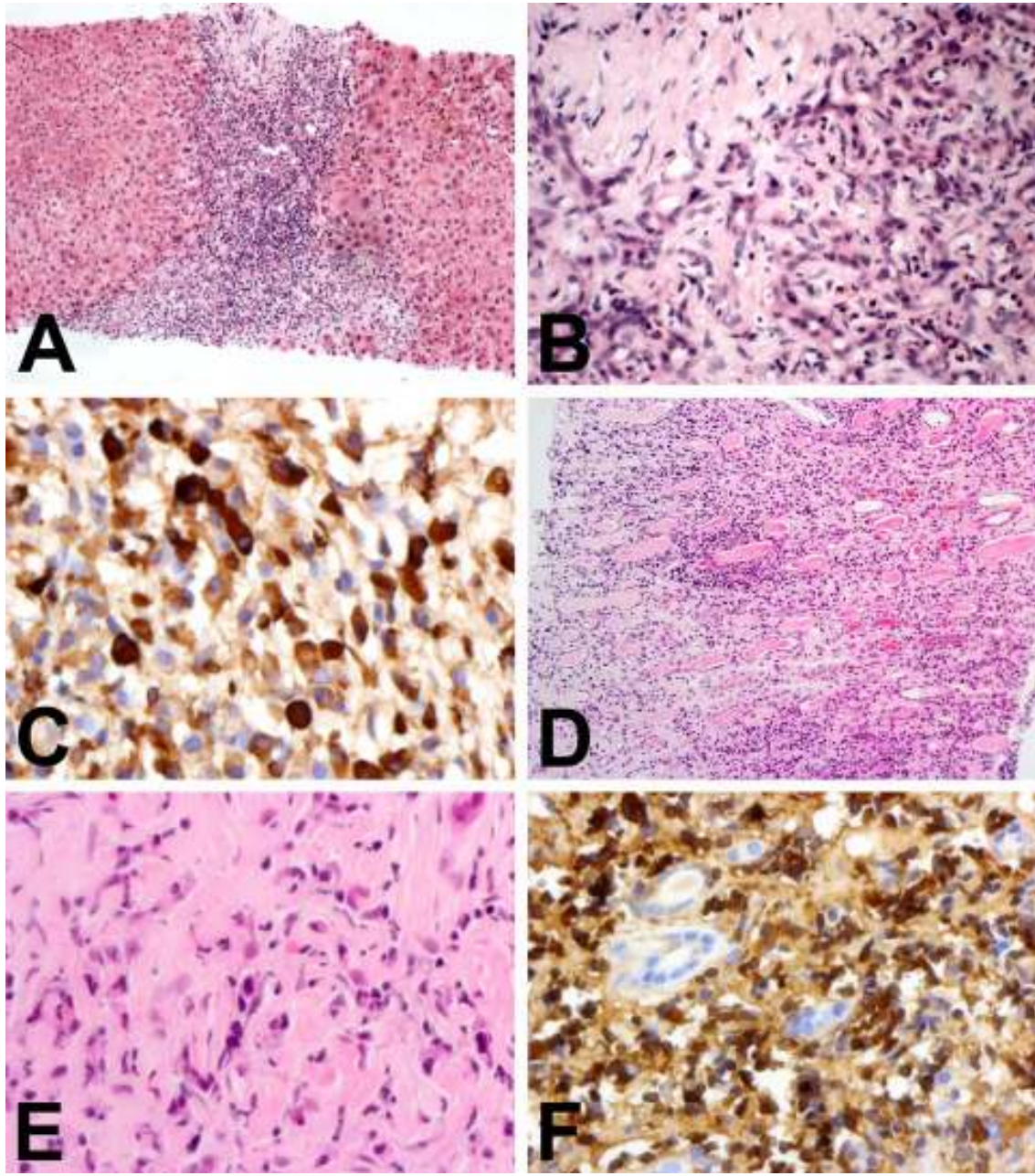
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# AIP - Radiological features



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# Effects of treatment

- Very varied potential causes!
- Treatments can damage liver
  - Especially if a second disease process is present
- Appearances of drug-related changes can simulate other conditions

# Methotrexate and the liver

- Psoriasis, arthritis
- Serum fibrosis markers
- Fatty change
- Portal fibrosis & cirrhosis
- *Liver changes with underlying disease*
  - *Psoriasis*
- Need to involve hepatologist if concerned

# Methotrexate safety

- Paris 2009
- Review of 88 previous studies
  - 13% showed significant LFT changes
  - 3.7% stopped drug permanently due to toxicity
- Data on risk of cirrhosis conflicting
  - Meta-analysis suggested fibrosis in 2.7% after four years treatment

# Treatment in SLE

- South Korea 2008
- 141 SLE patients
  - 46 significantly abnormal LFTs
  - 11 presumed toxic hepatitis
  - 6 herbal medicines
  - 3 anti-TB medication
  - 1 antibiotics
  - 1 valproic acid
- All improved when agents stopped and with steroids

# Summary

- Must interpret liver biopsies in the context of as much relevant clinical information as it is possible to obtain
- Liver changes in systemic inflammatory diseases are varied and may be altered by treatments
- Good links with hepatology team are essential, including regular meetings

# References

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