Chronic Hepatitis

- Symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease for **more than 6 months.**
- With histologically documented inflammation and necrosis.
- Fluctuating levels of serum aminotransferases.
- May or may not progress to cirrhosis.

The Carrier State

- A "carrier" is an individual without manifest symptoms who harbors and can transmit an organism.
- In **HBV, HDV, HCV (0.2–0.6%).**
- Symptoms *free*
- Persistently normal ALT & AST.
- Absence of significant inflammation and necrosis on liver biopsy.

Fulminant Hepatitis

- In very small proportion of patients with acute hepatitis A, B, D, or E.
- Acute liver failure, resulting from submassive or massive hepatic necrosis.

Morphological features of hepatitis

- The main morphologic features of Hepatitis and associated cellular responses:

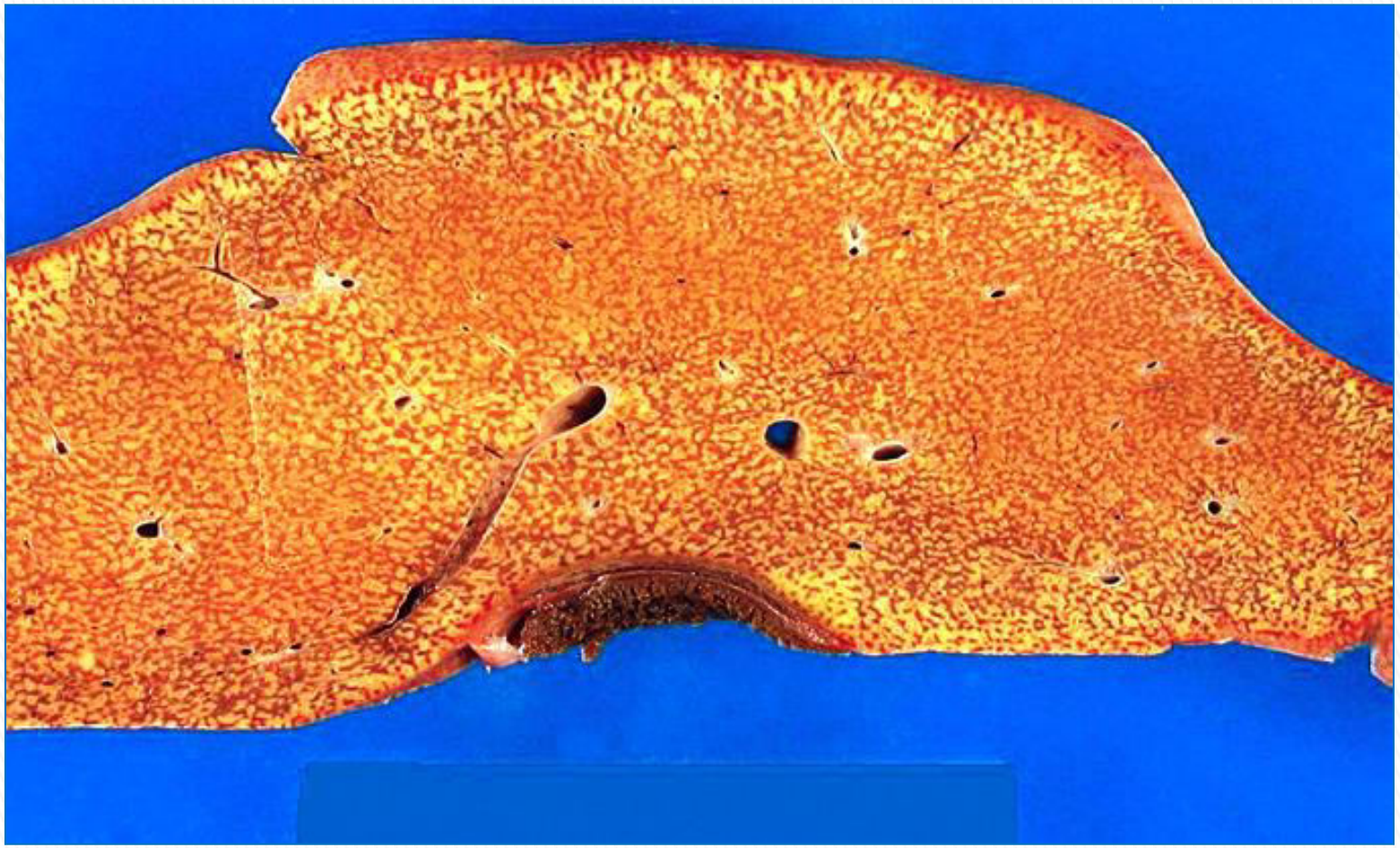
- *Features of acute hepatitis*
- *Features of chronic hepatitis*
- *Specific features of the cause*

Acute hepatitis

Gross appearance:

- *Mild acute hepatitis:*
  - Normal or slightly mottled liver.
- *Massive hepatic necrosis:*
  - The liver may shrink to 500 to 700 g and become covered by a wrinkled capsule.
- **The entire liver or only patchy areas affected**
- **Cut section:** Necrotic areas have a muddy-red appearance with blotchy bile staining.

Acute fulminant hepatitis



Massive necrosis, cut section of liver.
The liver is small (700 g), bile-stained, soft, and congested.

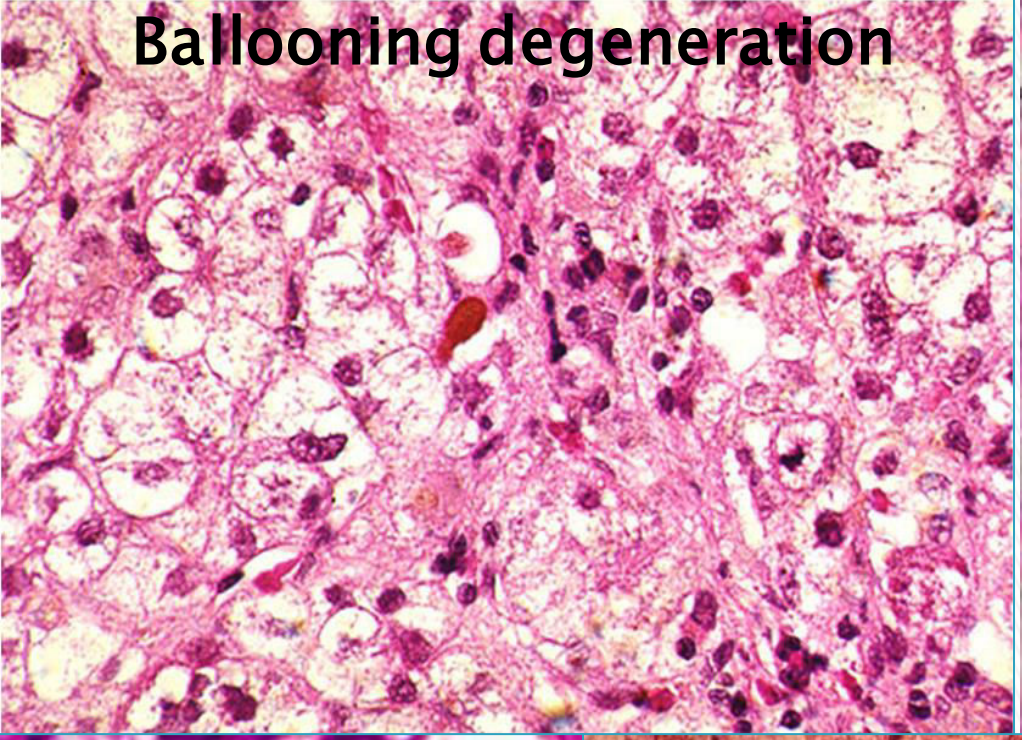
Acute hepatitis

Microscopic features:

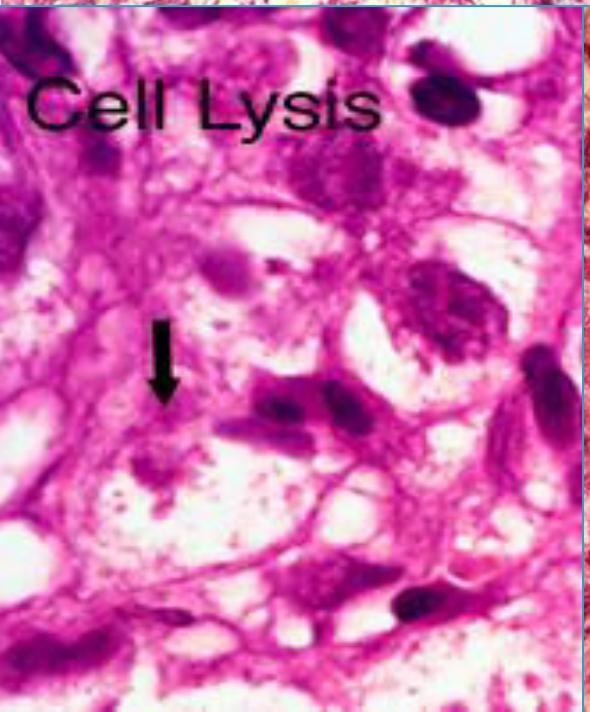
- *Hepatocyte injury*:*
  - Swelling (ballooning or featherydegeneration)
  - Cholestasis: Within hepatocytes or canalicular bile plugs
- *Hepatocyte death*:*
  - **Type:**
    - Necrosis: Cytolysis (rupture – cell drop-out) or coagulative
    - Apoptosis (shrinkage– acidophil or Councilman bodies).
  - **Distripution:**
    - Spotty necrosis (isolated cells)
    - Confluent necrosis (clusters) → Bridging necrosis (portal-portal, central-central, portal-central) → Rarely, fulminant hepatitis with sub/massive necrosis
- *Regenerative changes**:* Hepatocyte proliferation
- *Lobular disarray:* Loss of normal architecture

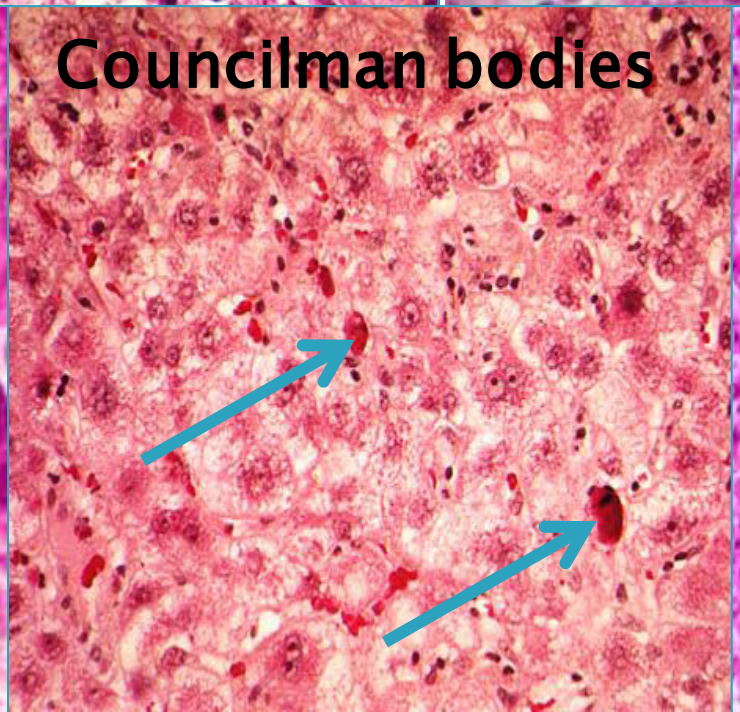
Acute hepatitis

- *Sinusoidal cell reactive changes:*
  - Accumulation of phagocytosed cellular debris (Lipochrome) in activated Kupffer cells
  - Influx of mononuclear cells into sinusoids
- *Portal tracts Inflammation*:* (V. minimal)
  - Predominantly mononuclear
  - Interface hepatitis (uncommon).
- *Ductular reaction*: Formation of new biliary ductules (in severe hepatitis)


Ballooning degeneration

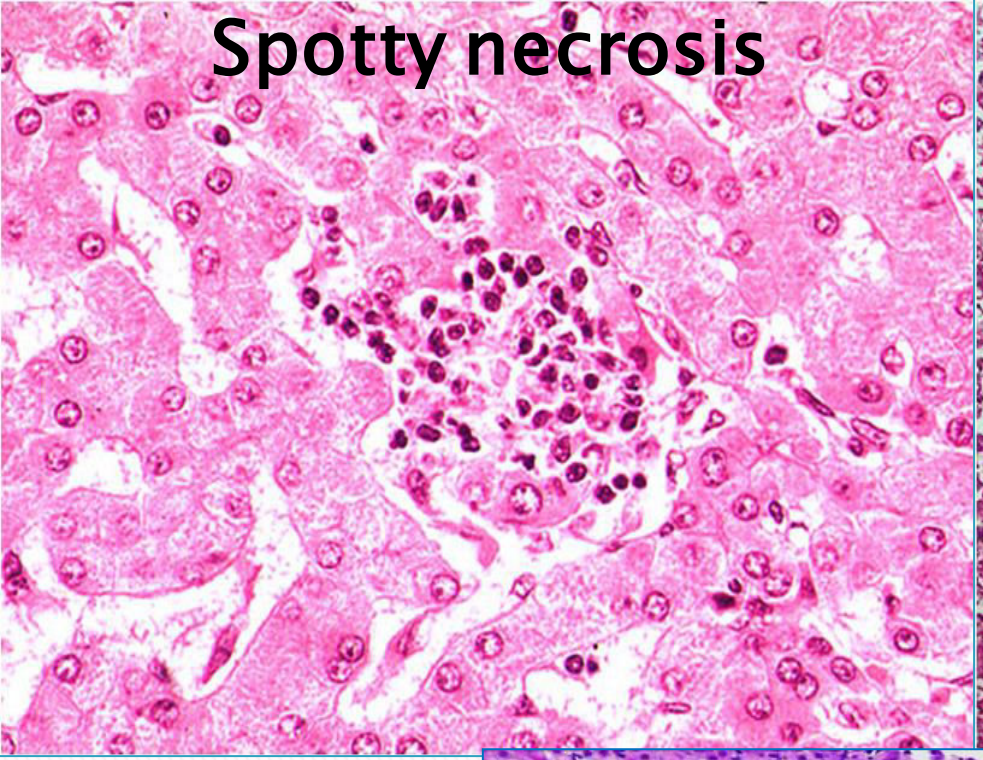

Cholestasis with bile plug


Cell Lysis

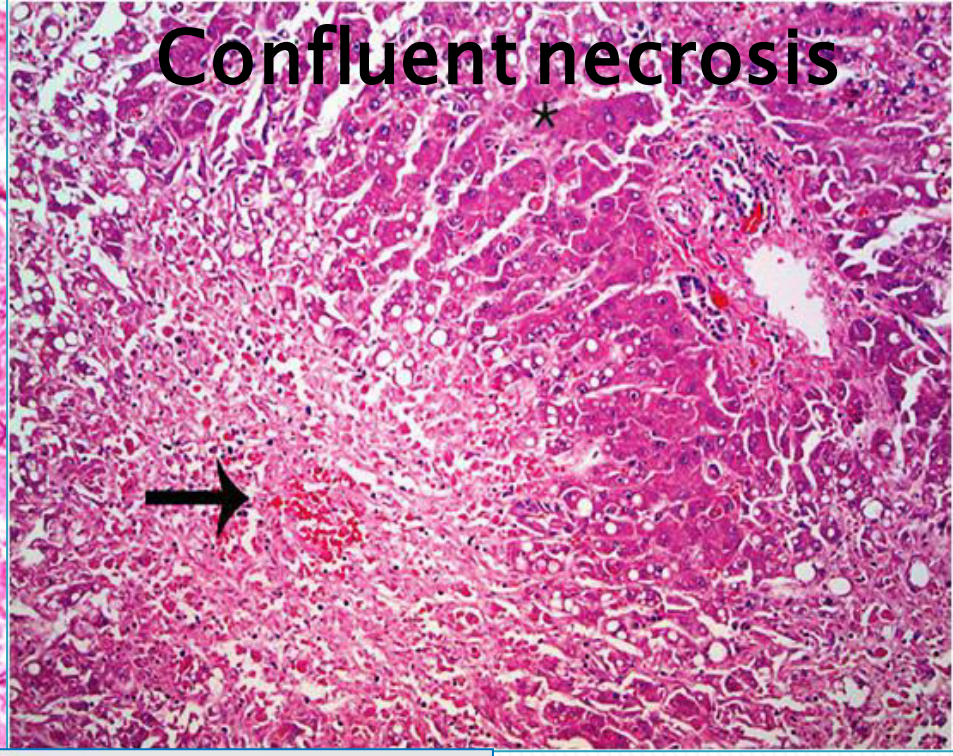

Councilman bodies


Coagulative necrosis

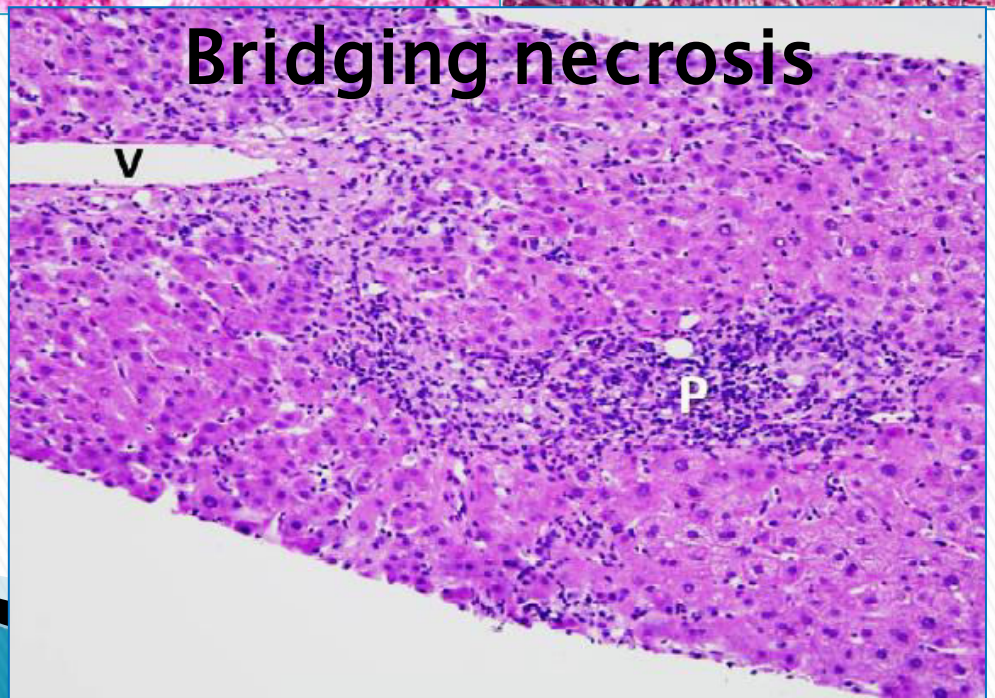
Spotty necrosis

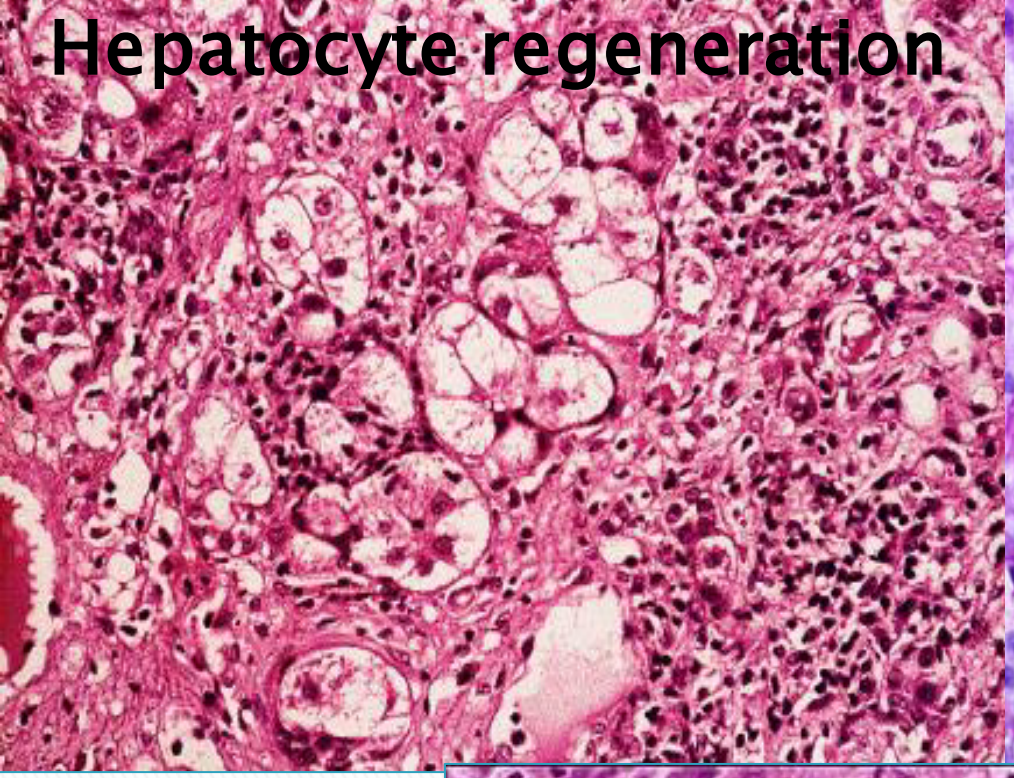


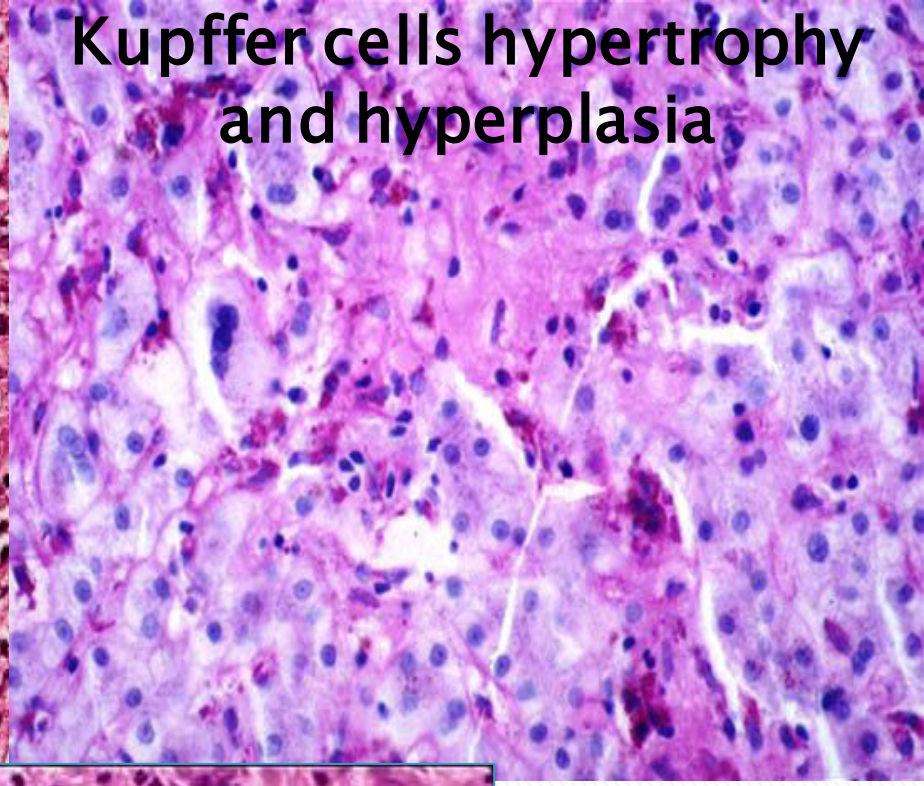
Confluent necrosis

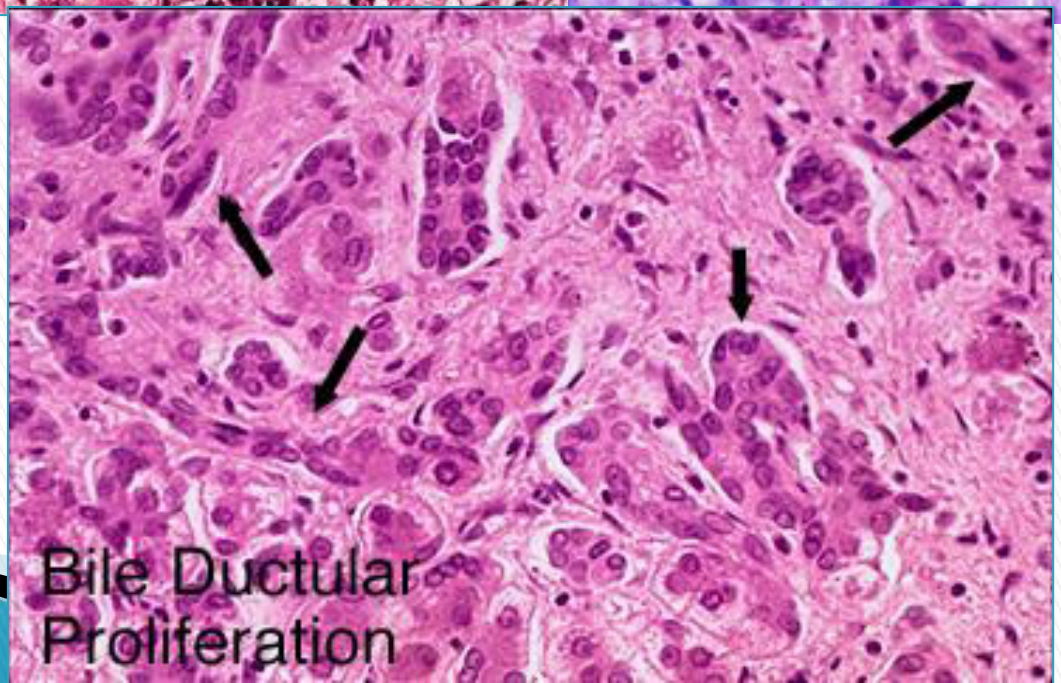


Bridging necrosis




Hepatocyte regeneration


Kupffer cells hypertrophy
and hyperplasia

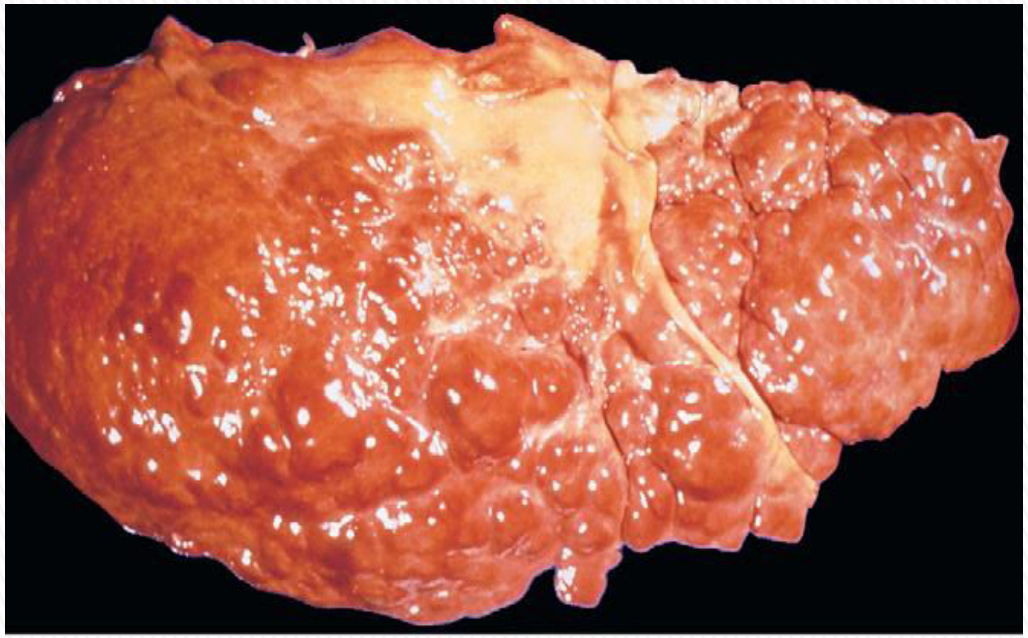

Bile Ductular
Proliferation

Chronic hepatitis

Gross appearance :

- Normal → Focal scarring → Cirrhosis

Cirrhosis

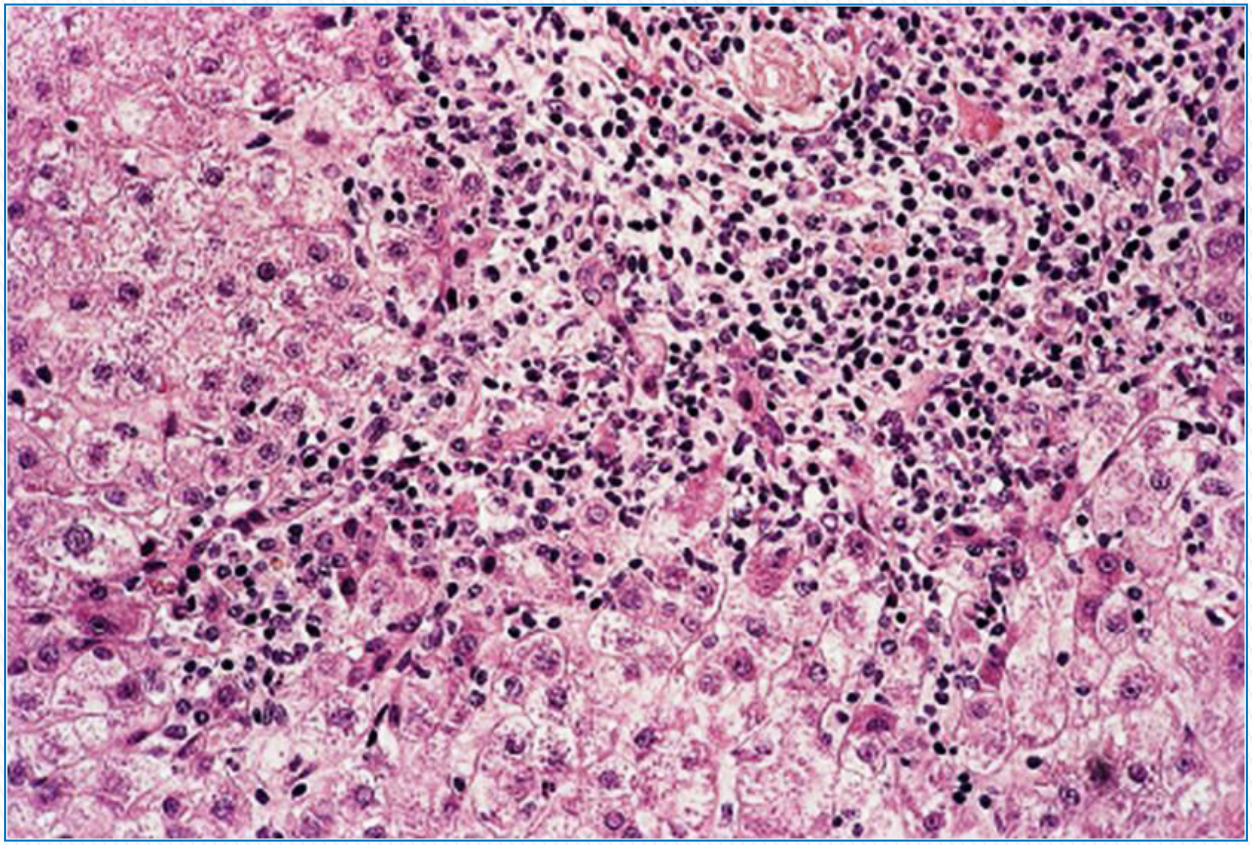


Chronic hepatitis

Microscopic features:

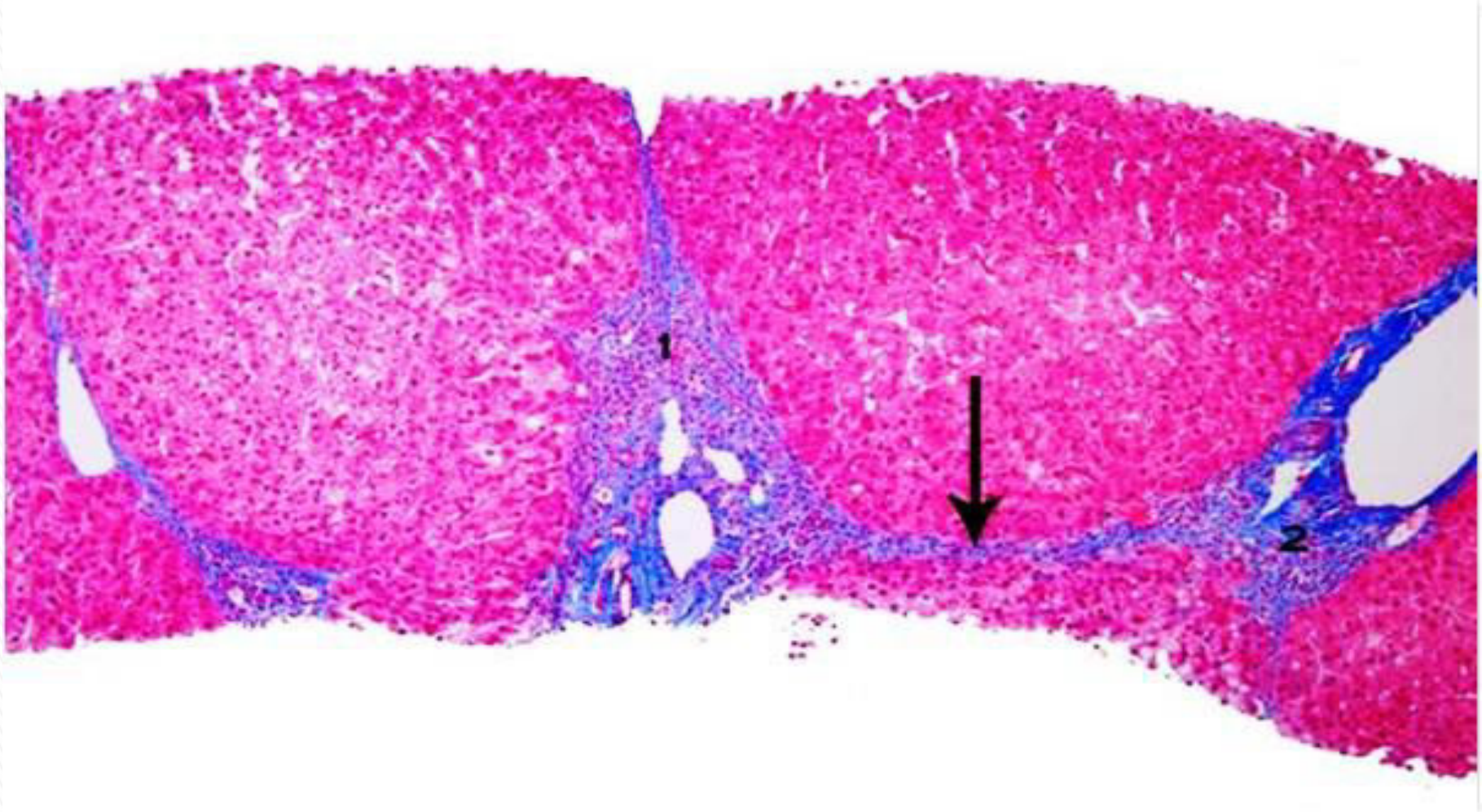
- ***Changes shared with acute hepatitis (less prominent):***
  - Hepatocyte injury, death, bridging necrosis, regeneration, sinusoidal cell reactive changes.
- ***Portal tracts Inflammation:***
  - More prominent (aggregates)
  - Interface hepatitis (***common***)
- ***Fibrosis (the hallmark):***
  - Portal → Periportal → Bridging fibrosis → Cirrhosis

Interface hepatitis
(Piecemeal necrosis)



The spillage of inflammatory infiltrate beyond the portal tracts, associated with death of hepatocytes in the limiting plate mainly by **apoptosis**

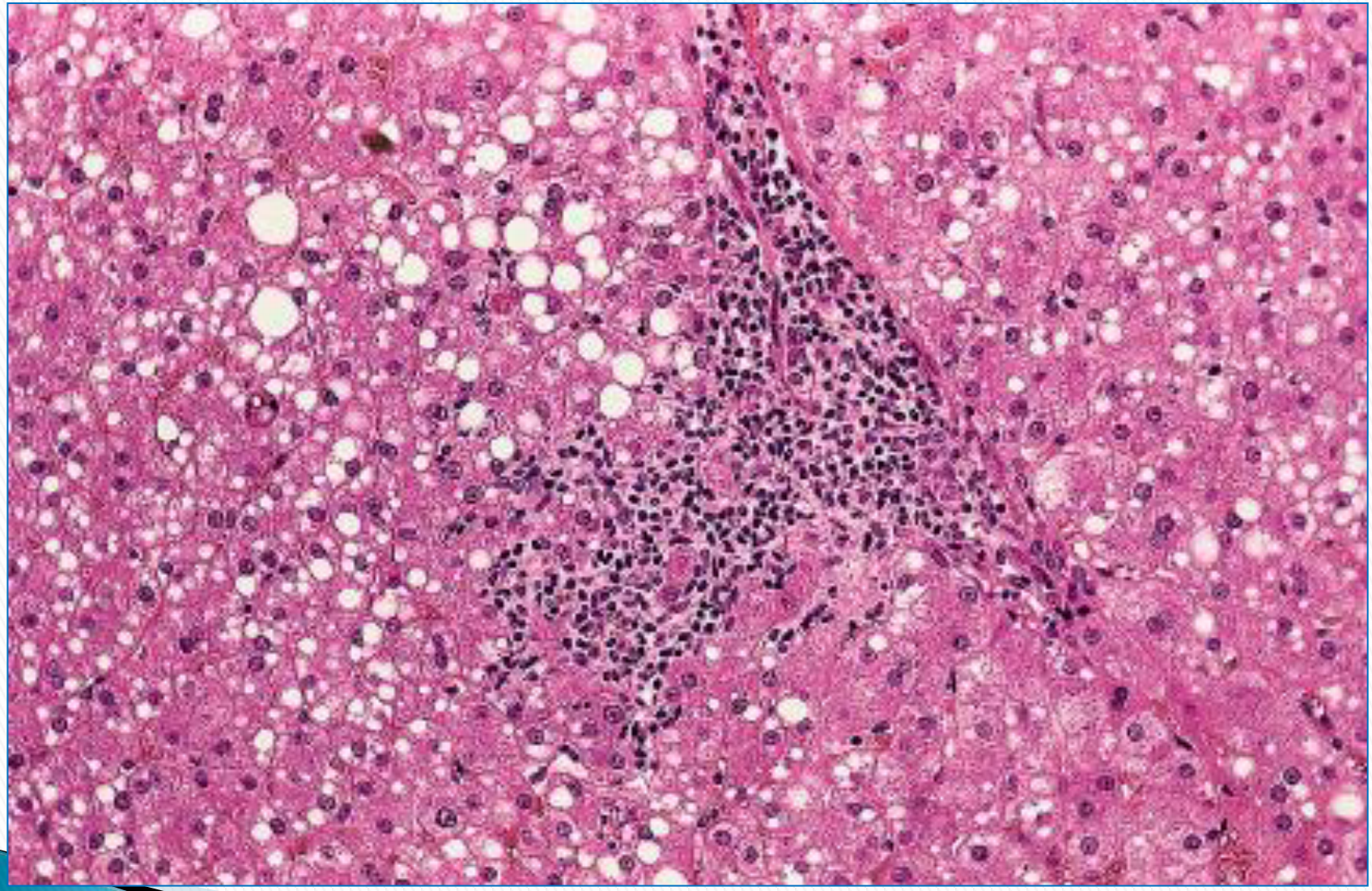
Bridging fibrosis



Specific features

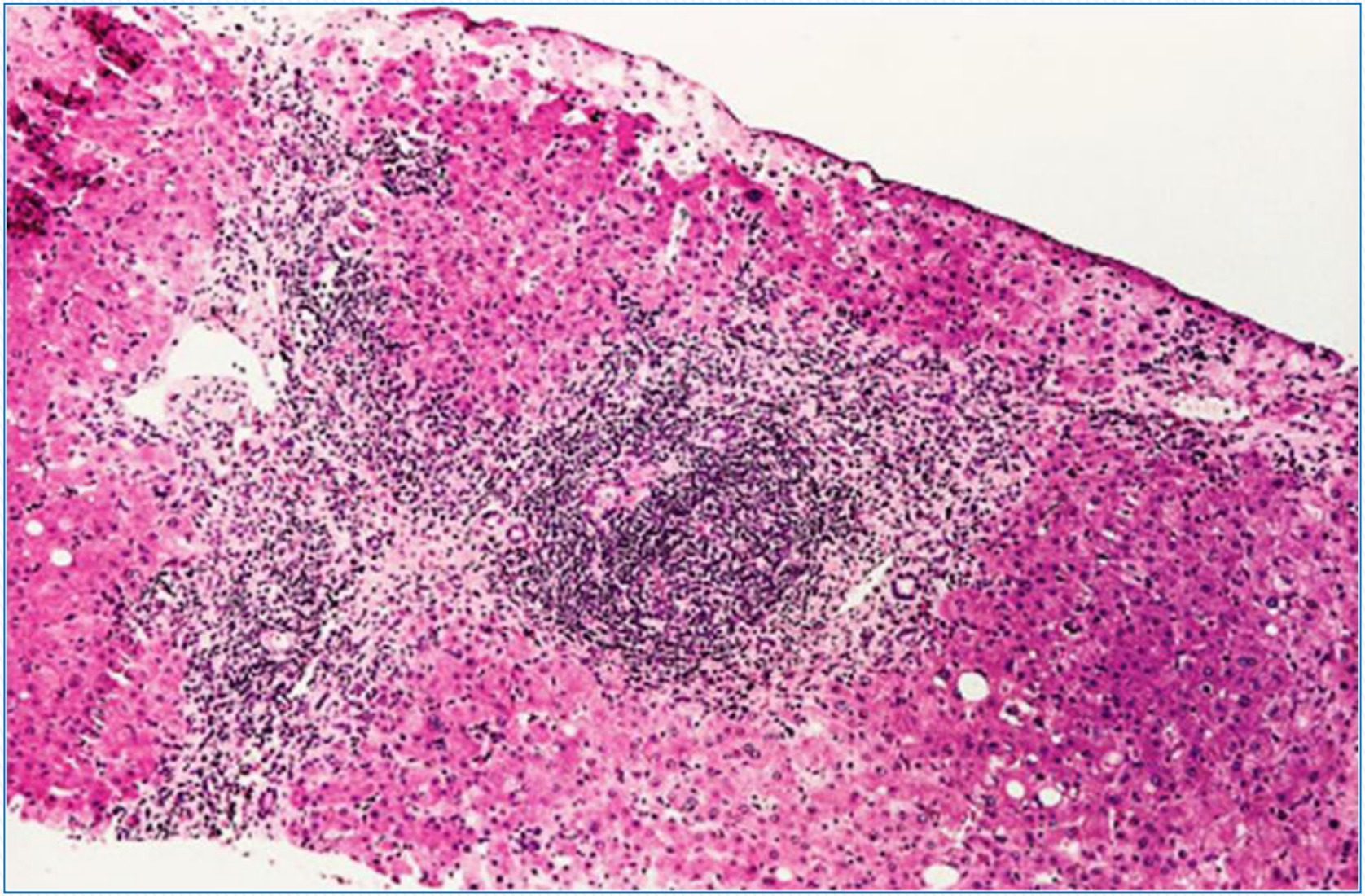
- HCV:
  - **Steatosis:** Fatty change (common)
  - **Lymphoid aggregates** in the portal tracts
  - **Bile duct lesion:** Inflammatory infiltrate of bile duct epithelium ± bile duct damage

HCV



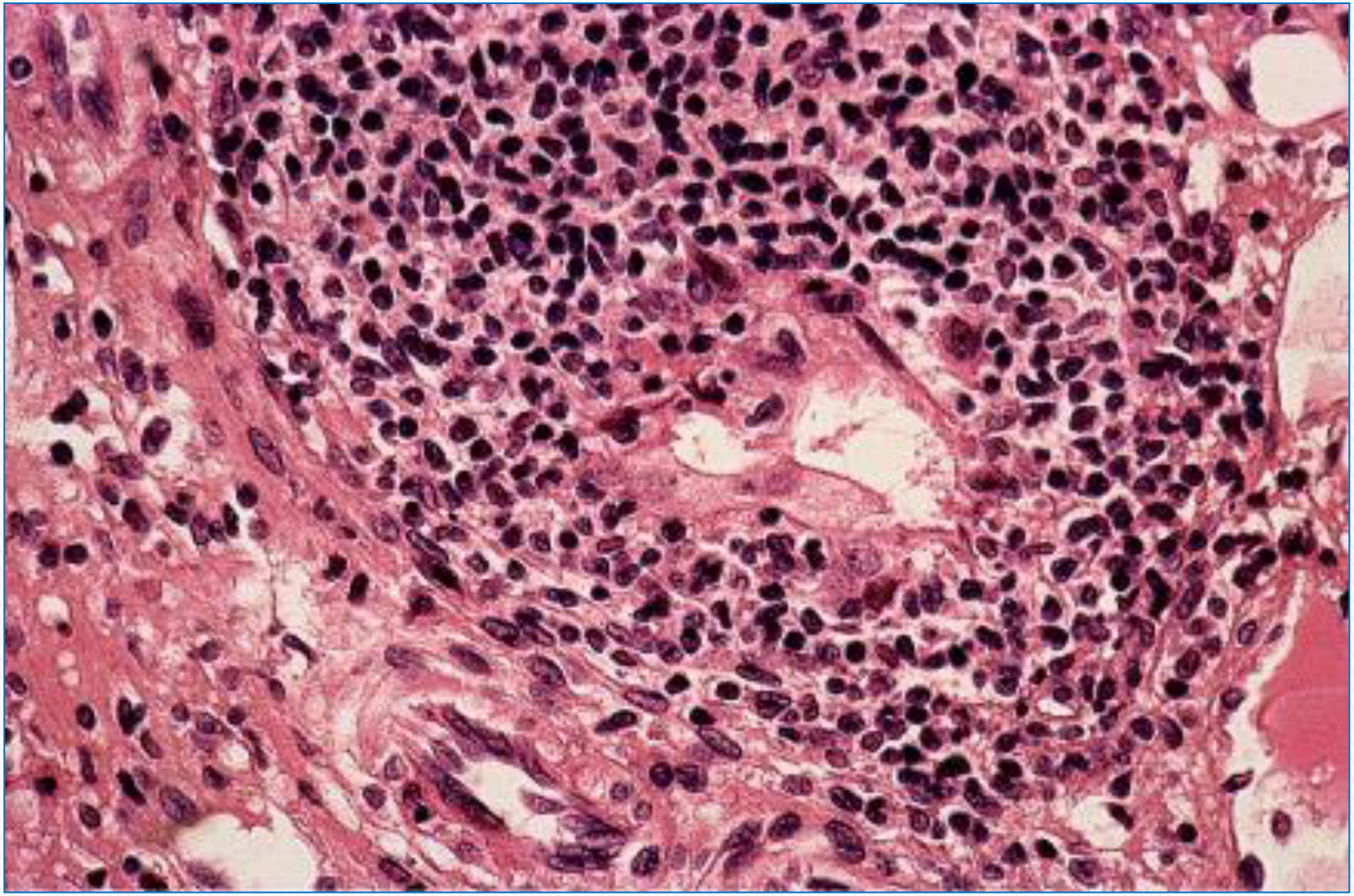
Steatosis, portal inflammation & interface hepatitis

HCV



Scattered macrovesicular steatosis & lymphoid aggregate in portal tract

HCV



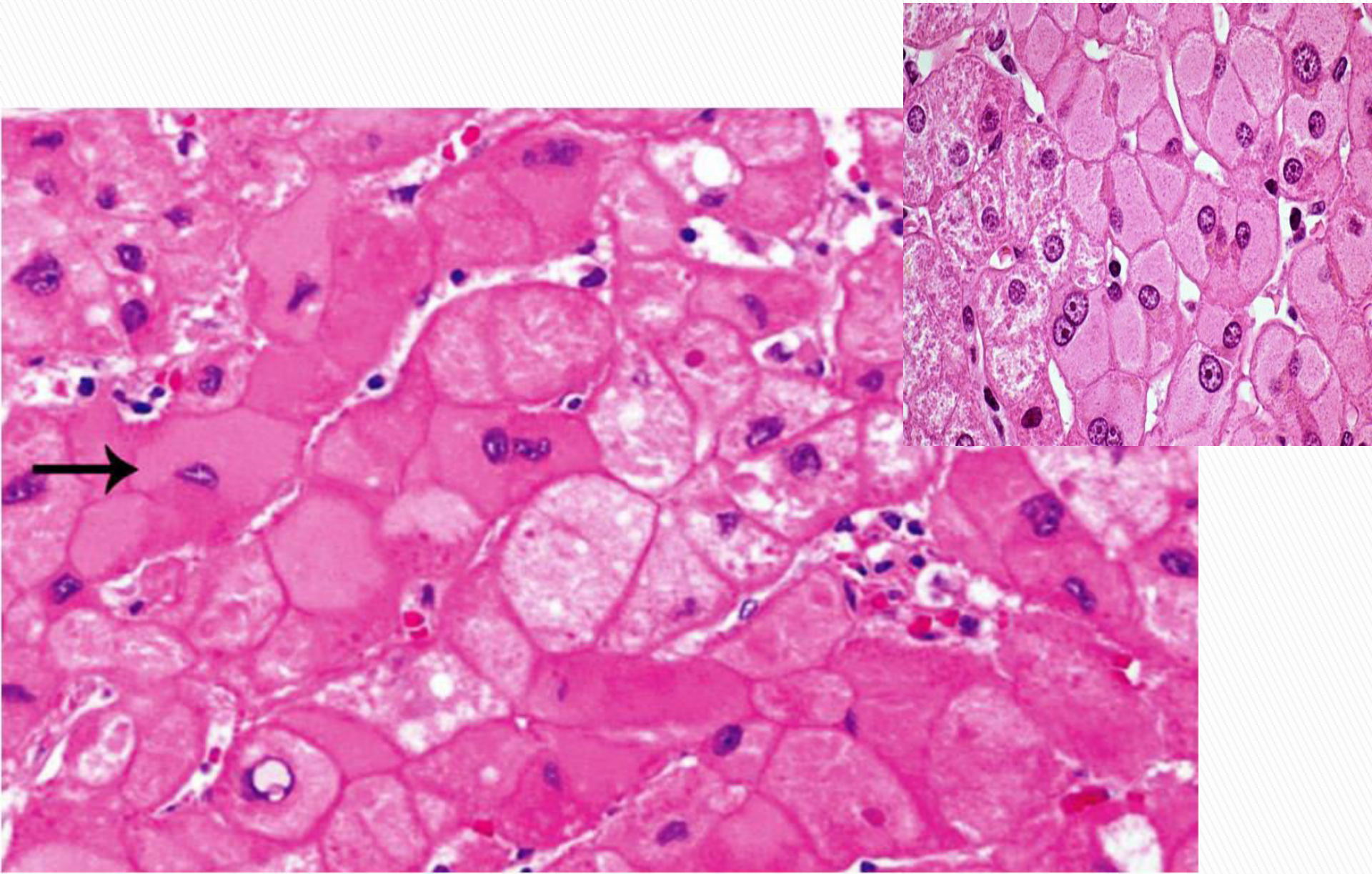
Irregular & damaged bile duct

Specific features

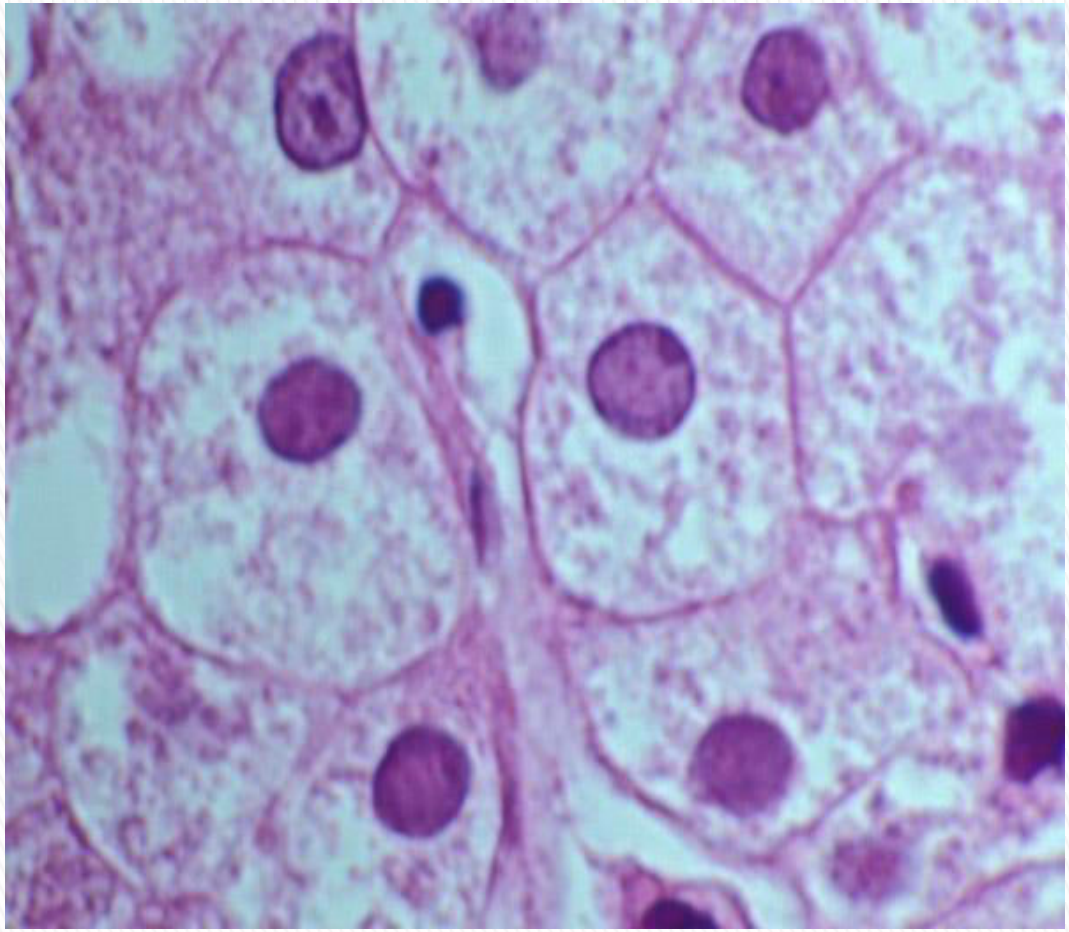
- **HBV:**
- **"Ground-glass"** hepatocytes:
  - A finely granular, pale eosinophilic cytoplasm*.
  - Due to the presence of HBsAg in the SER.

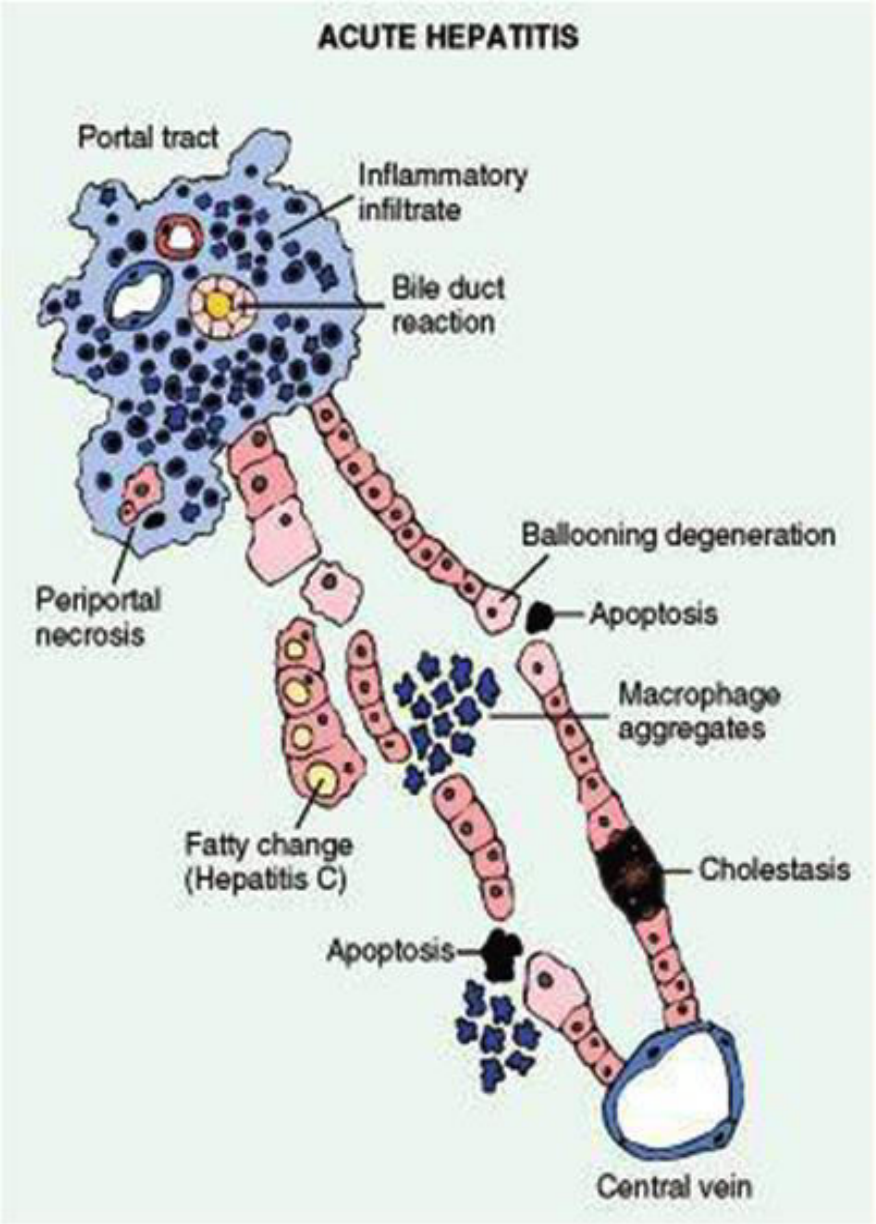
- **"Sanded" nuclei:**
  - Finely granular pale eosinophilic central part of the nucleus
- Due to abundant intranuclear HBcAg.

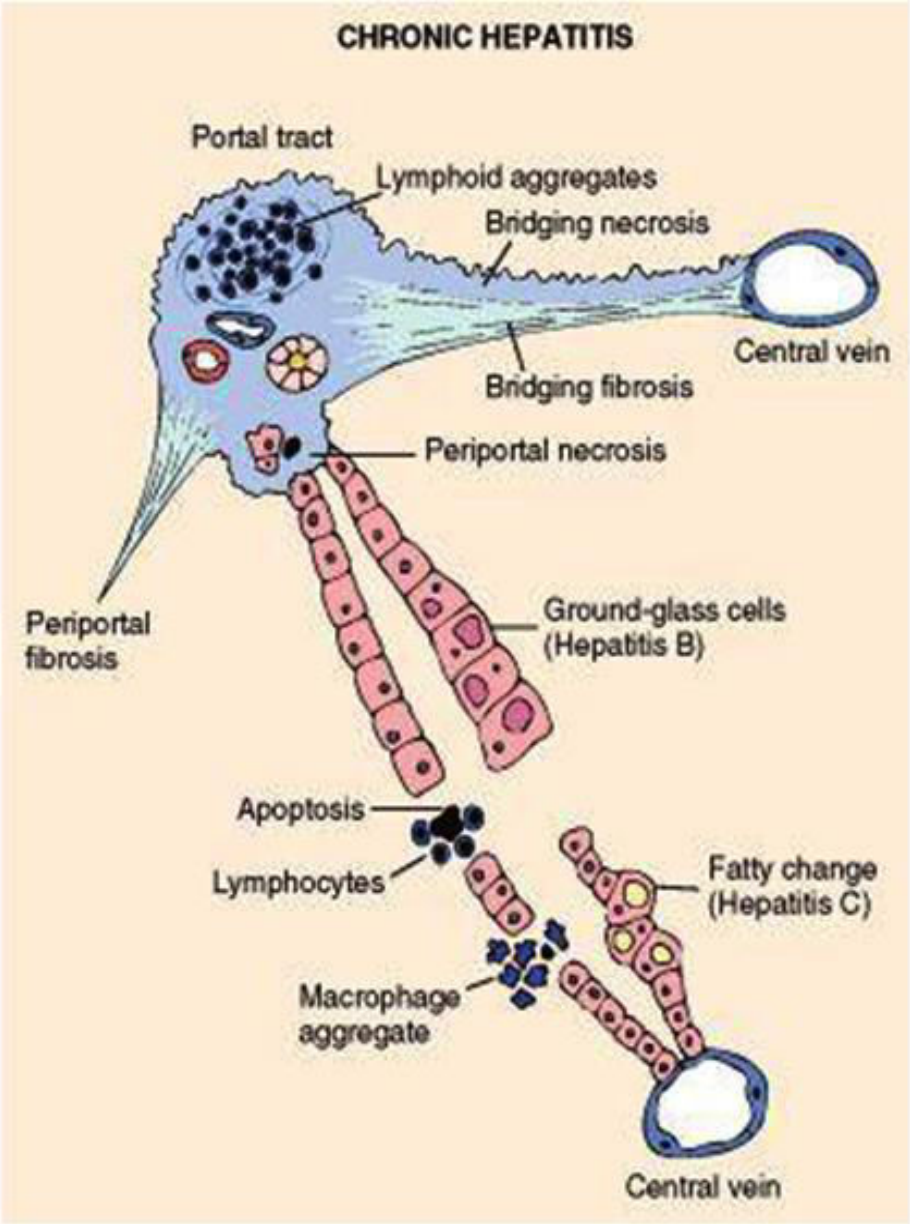
Ground-glass appearance



Sanded nuclei







Fibrosis is shown only for chronic hepatitis

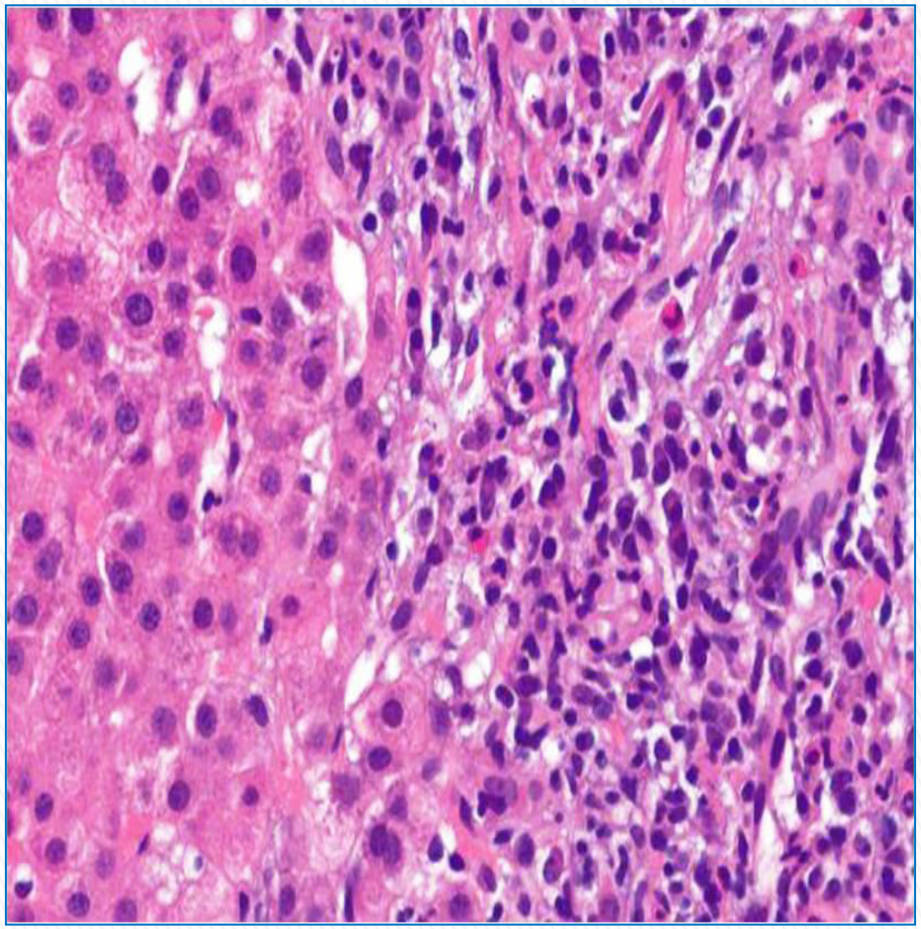
Autoimmune hepatitis

- **Clinical presentation:**
- Mainly as a syndrome of chronic hepatitis (rarely; acute or fulminant hepatitis).
- ***Female*** predominance (70%).
- Absence of serologic markers of *a viral infection*
- Elevated serum *IgG* (>2.5 g/dL)
- Elevated titers of *autoantibodies* (in 80%):
  - ***Antinuclear antibodies, anti-smooth muscle antibodies, liver/kidney microsomal antibody, and/or anti-soluble liver/pancreas antigen.***
- Other autoimmune diseases is seen in 60%*.

Autoimmune hepatitis

The histologic features:
Indistinguishable from chronic viral hepatitis;

- Usually severe hepatitis + necrosis
- Prominent hepatitic rosettes
- Early fibrosis
- Plasma cells in the infiltrate



Interface hepatitis with prominent plasma cells

Prognosis & treatment

- Indolent → Severe course.
- Dramatic response to immunosuppression.
  - Full remission is *unusual*
- The overall risk of cirrhosis is 5%

Diseases of the intrahepatic biliary tract

- **Primary biliary cirrhosis (PBC)**
  - Destruction of intrahepatic bile ducts

- **Primary sclerosing cholangitis (PSC)**
  - Involves extrahepatic and large intrahepatic bile ducts

Primary Biliary Cirrhosis

- A chronic progressive *cholestatic liver disease*
- **Characterized by:**
  - Nonsuppurative destruction of small and medium-sized intrahepatic bile ducts.
  - Portal inflammation and scarring.
  - Cirrhosis late in the course.

Primary biliary cirrhosis

- Middle-aged **women**, 40 – 50 y.
- > 90% have high titers of antimitochondrial antibodies (AMA) directed to specific domains of mitochondrial acid dehydrogenase enzymes
- **Associated extrahepatic conditions**:
- Sjögren syndrome, scleroderma, thyroiditis, Rheumatoid arthritis, Raynaud phenomenon, membranous glomerulonephritis, celiac disease…

Clinical picture of PBC

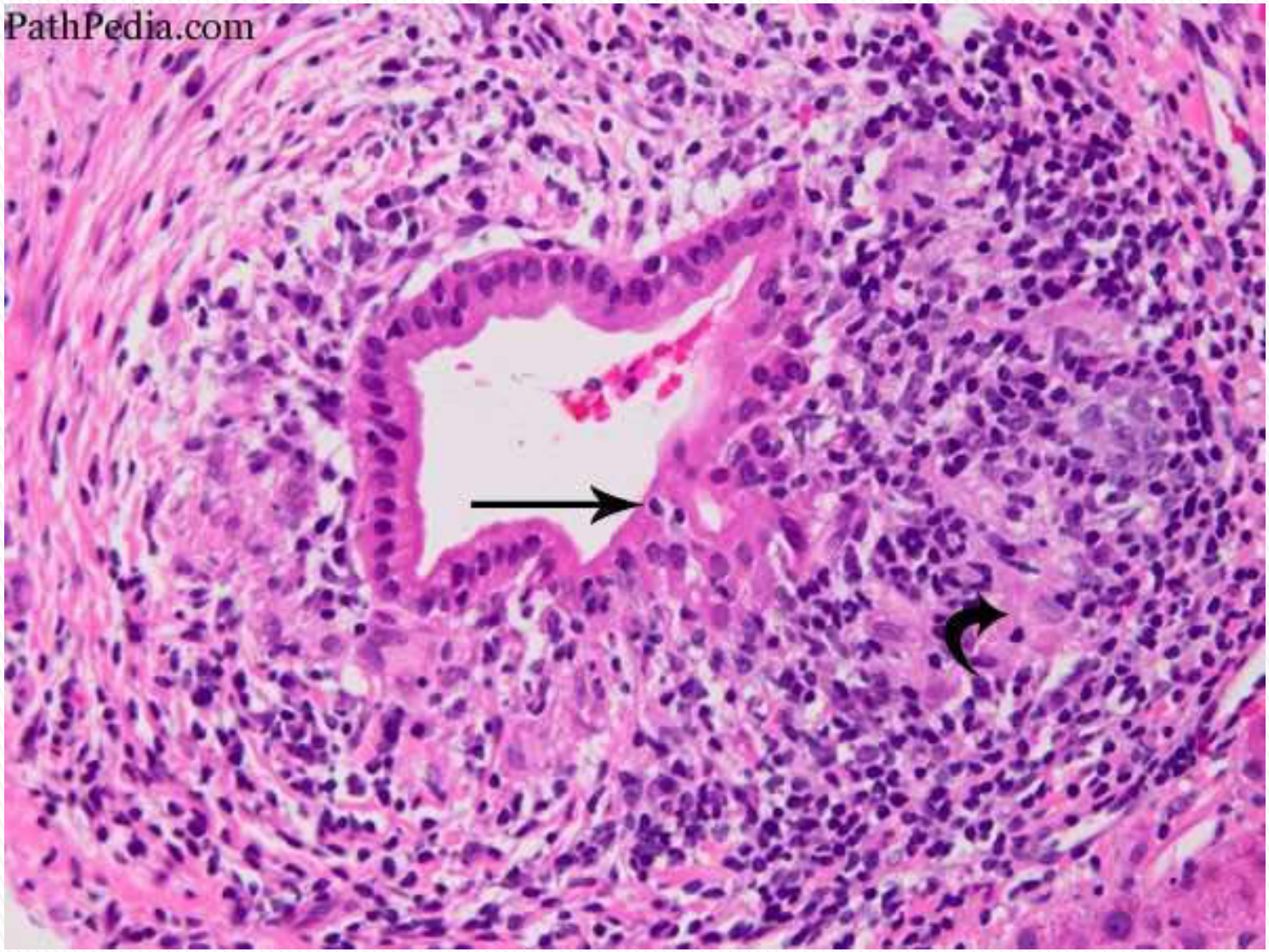
- *Insidious* onset, usually presenting as **pruritus.**
- Jaundice develops late.
- Hepatic failure over two or more decades.

- **LAB tests:**
- ⇑ Serum alkaline phosphatase.
- ⇑ cholesterol levels.
- Hyperbilirubinemia (late).
- ⇑ titre of AMA in 95% of cases

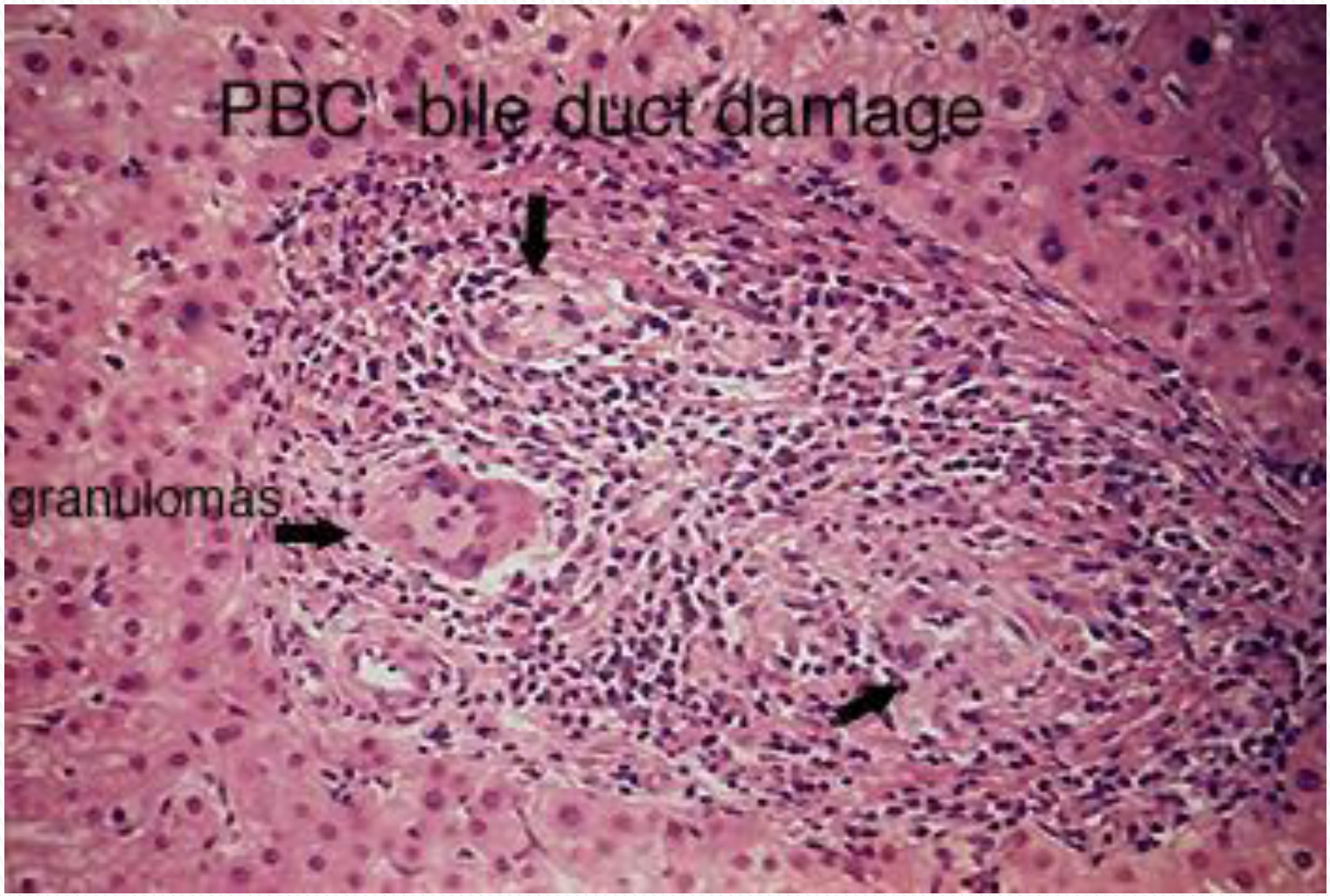
Morphology of PBC

- **Early lesions:**
  - Dense mononuclear inflammatory cell infiltrate in the portal tract + **Granulomatous** inflammation.
  - **Florid duct lesion:** intraepithelial infiltration of lymphocytes and granuloma with destruction of *intralobular* ducts.
  - **Ductular reaction**: bile ductular proliferation.

PBC

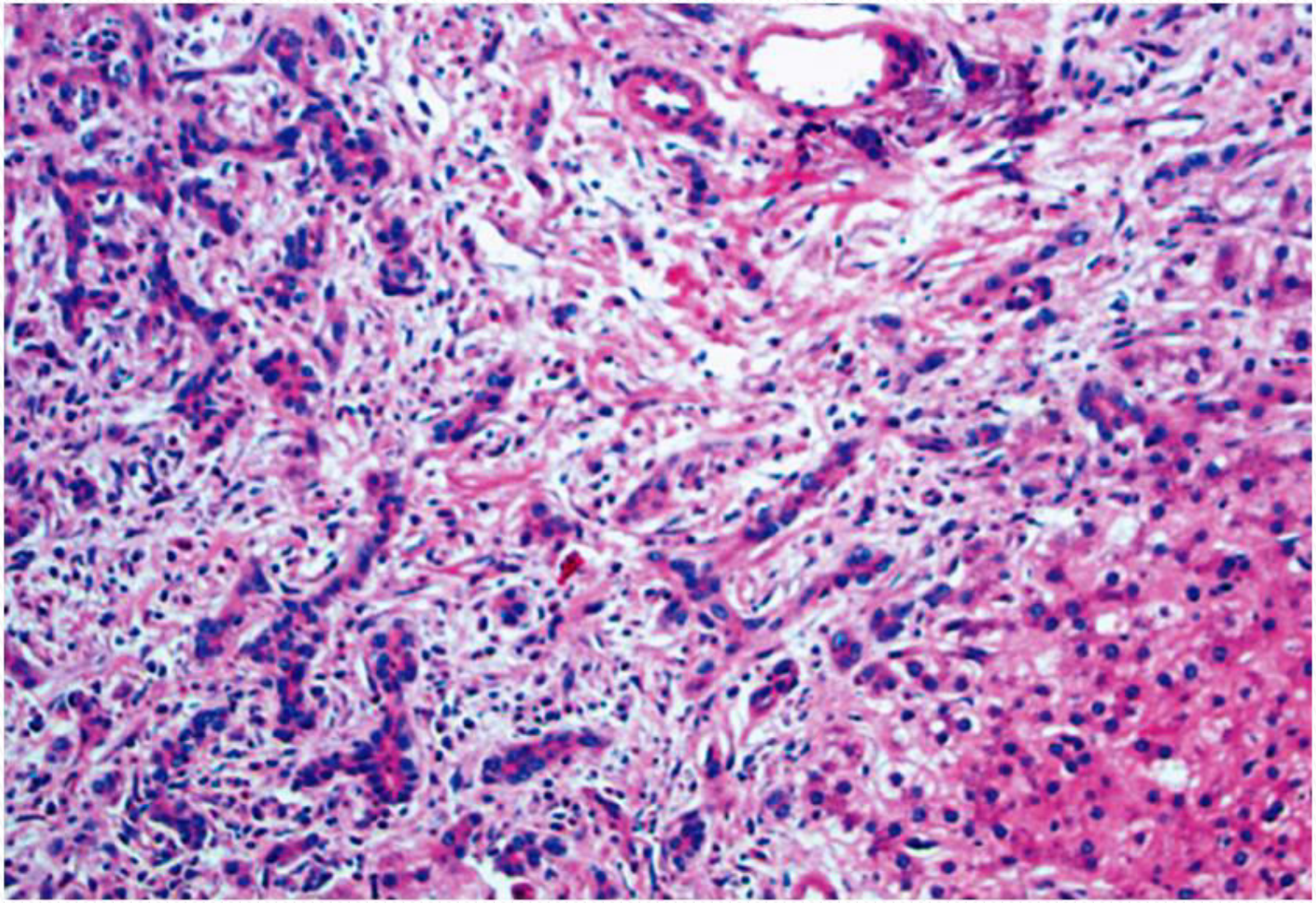


Primary biliary cirrhosis



A portal tract is markedly expanded by an infiltrate of lymphocytes, plasma cells & granulomatous reaction (florid duct lesion)

Primary biliary cirrhosis



Ductular proliferation in a fibrotic septum

Morphology of PBC

- Inflammation and necrosis of the periportal hepatic parenchyma → Portal tract scarring & bridging fibrosis → Biliary cirrhosis
- Generalized cholestasis
- Interlobular bile ducts are absent in the end stage of primary biliary cirrhosis.

Primary Sclerosing Cholangitis

- A chronic cholestatic disorder
- **Characterized by:**
  - Progressive *fibrosis* and destruction of extrahepatic and large intrahepatic bile ducts.

Primary sclerosing cholangitis

- Common in association with IBD (esp. UC) → UC present in 70% of patients with PSC, while PSC present in 4% of patients with UC
- **P-ANCA** is present in 80% of cases.
- Age: 3rd to 5th decades.
- **M**:F is 2:1.

Clinical picture of PSC

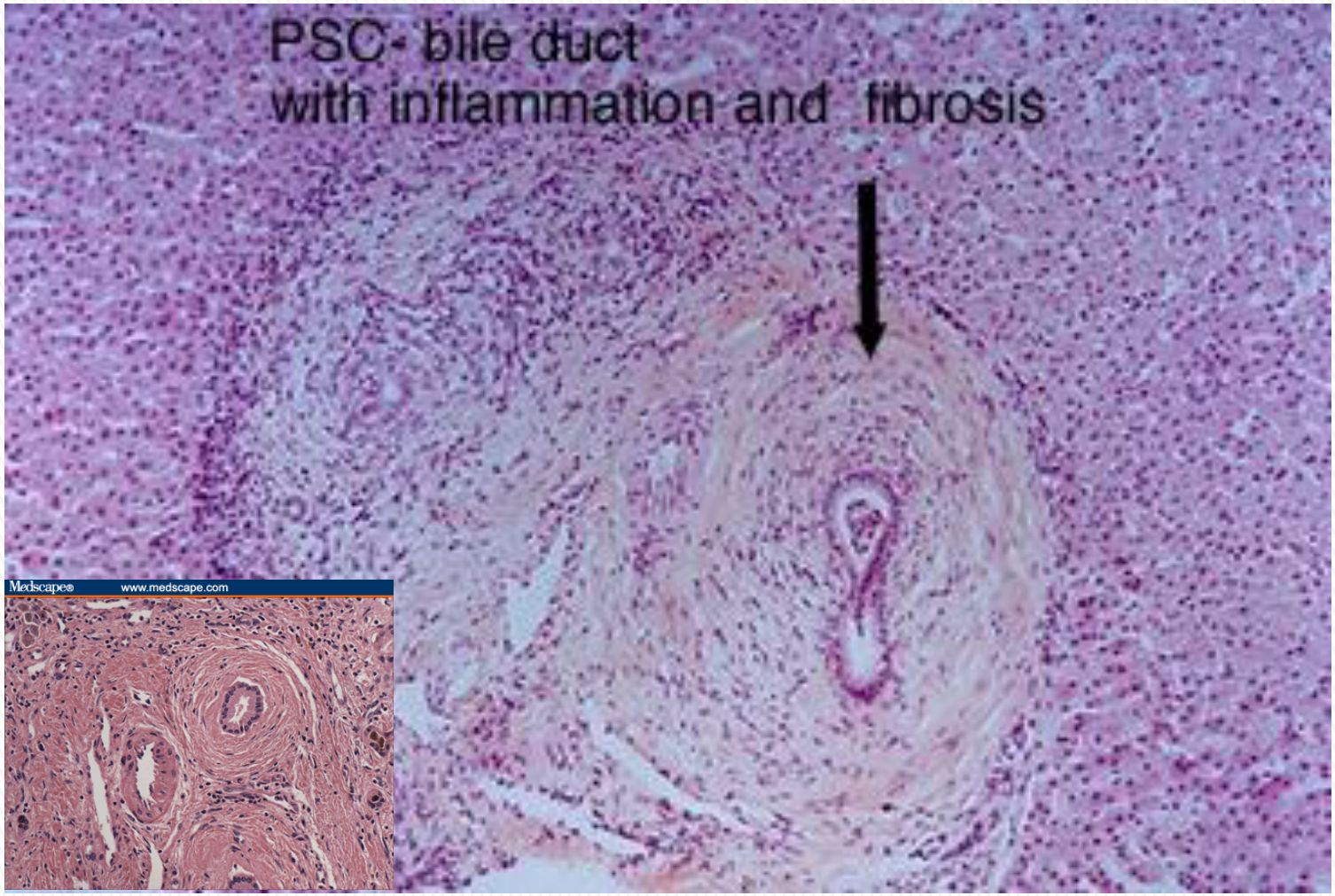
- Insidious onset*.
- Progressive fatigue, pruritus, and jaundice
- Chronic liver disease late in the course
- PSC has a protracted course over years

- **Cholangiocarcinoma** may develop in 10–15% of individuals (median time of 5 years from diagnosis).

Morphology of PSC

- **Fibrosing cholangitis of bile ducts**:
  - The characteristic feature of **PSC**
  - Affected portal tracts show concentric periductal **onion-skin fibrosis** & lymphocytic infiltrate.
- Progressive atrophy of the bile duct epithelium leads to obliteration of the lumen*
- In between, bile ducts are ectatic & inflamed.
- Cholestasis & biliary cirrhosis.

Primary sclerosing cholangitis



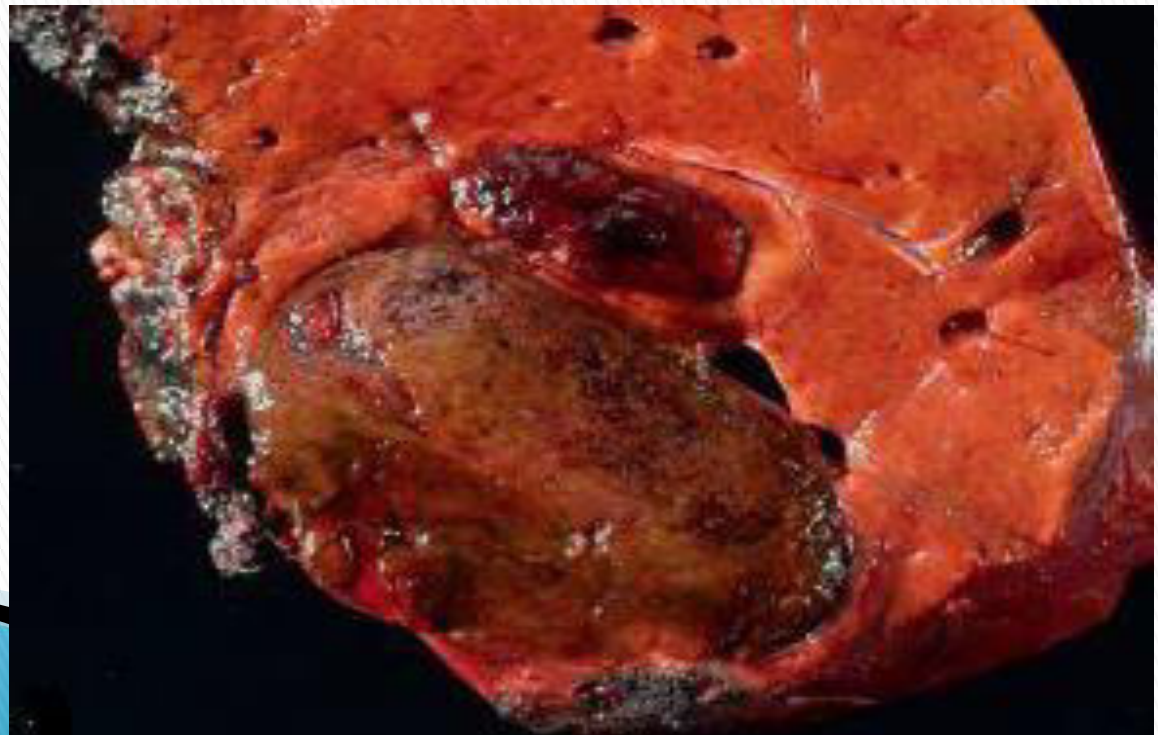
A bile duct undergoing degeneration is entrapped in a dense, "onion-skin" concentric scar

Main Features of Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

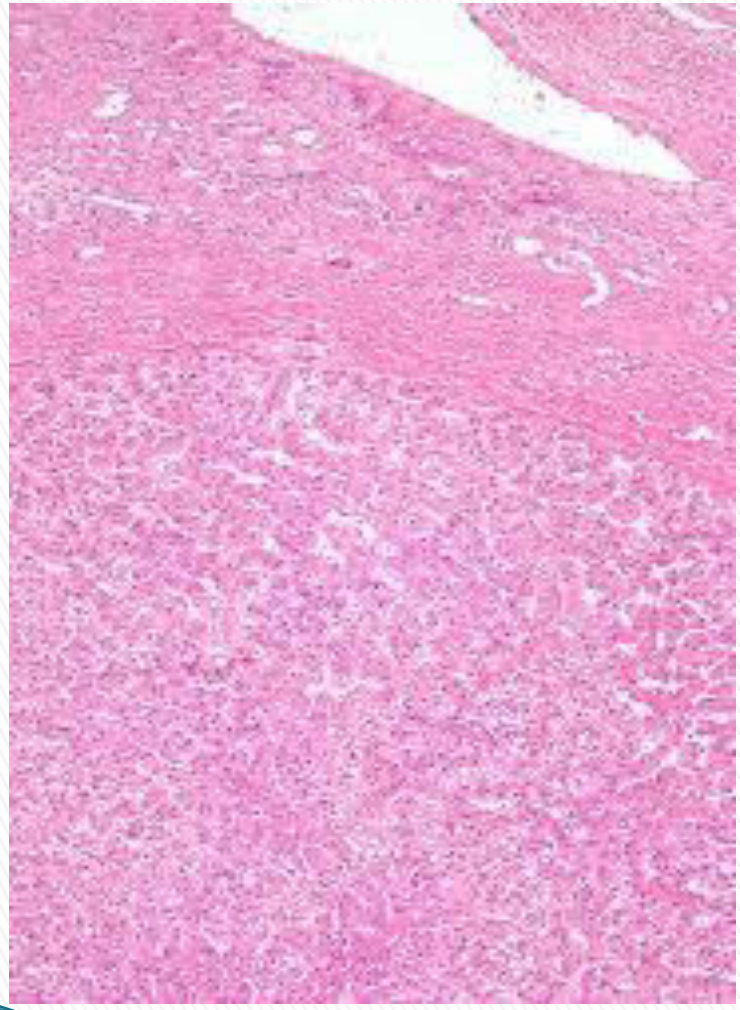
Parameter	Primary Biliary Cirrhosis	Primary Sclerosing Cholangitis
Age	Median age 50 years (30-70)	Median age 30 years
Gender	90% female	70% male
Clinical course	Progressive	Unpredictable but progressive
Associated conditions	Sjögren syndrome (70%)	Inflammatory bowel disease (70%)
	Scleroderma (5%)	Pancreatitis (≤25%)
	Thyroid disease (20%)	Idiopathic fibrosing diseases (retroperitoneal fibrosis)
Serology	95% AMA positive	0% to 5% AMA positive (low titer)
	20% ANA positive	6% ANA positive
	60% ANCA positive	82% ANCA positive
Radiology	Normal	Strictures and beading of large bile ducts; pruning of smaller ducts
Duct lesion	Florid duct lesion; loss of small ducts	Concentric periductal fibrosis; loss of small ducts

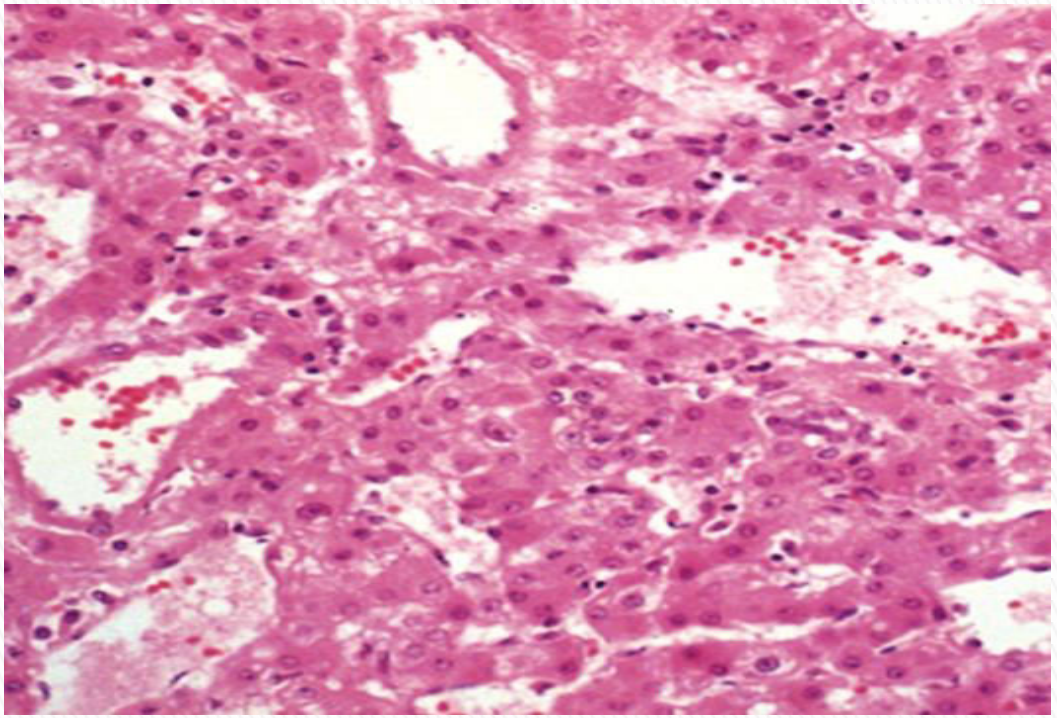
Hepatic Adenoma

- Usually occurs in **women** of childbearing age who have used **OCPs** (may *regress* on discontinuance use).
- **Subcapsular,** yellow or bile stained nodule.



Liver cell adenoma





Cords of normal hepatocytes, prominent vascular supply, ***with no portal tracts.***

Why is liver cell adenoma significant?

- May be mistaken for **HCC**.
- Risk for rupture (esp. in pregnancy) → massive intra-abdominal hemorrhage
- Adenomas carrying *β-catenin mutations* carry a risk of developing into cancers.

Hepatocellular carcinoma (HCC)

- **Epidemiology:**
- *Asian and African countries (> 85% of HCC):*
  - Chronic HBV infection.
  - Aflatoxin increases the risk.
  - In 50% of cases, HCC occur without cirrhosis.
  - **M**:F → 8:1, 20 – 40 years.
- *Western countries:*
  - Incidence increases rapidly →due to HCV & chronic alcoholism.
  - In 90% of cases tumors develop in persons with cirrhosis
  - **M**:F → 3:1, rarely before 60 years.

Pathogenesis

- **Major etiologic associations:**
  - Infection with HBV or HCV
  - Chronic alcoholism
  - Aflatoxin (derived from *Aspergillus flavus)* → *cause mutation in p53*
  - Hemochromatosis
  - Tyrosinemia

- **Cirrhosis & HCC:**
  - An important contributor but not a requisite.
  - HCC in HCV occurs almost exclusively in the setting of cirrhosis

Pathogenesis

- **Precancerous lesions**
  - *Small-cell* and *high-grade* dysplastic *nodules* in cirrhotic livers
    - Distinguishing from early HCC is difficult.
    - An important criterion is nodule vascularization visualized by imaging.
- **Cell of origin in HCC:**
  - The tumors may arise from both mature hepatocytes and progenitor cells (oval cells)

Morphology of HCC

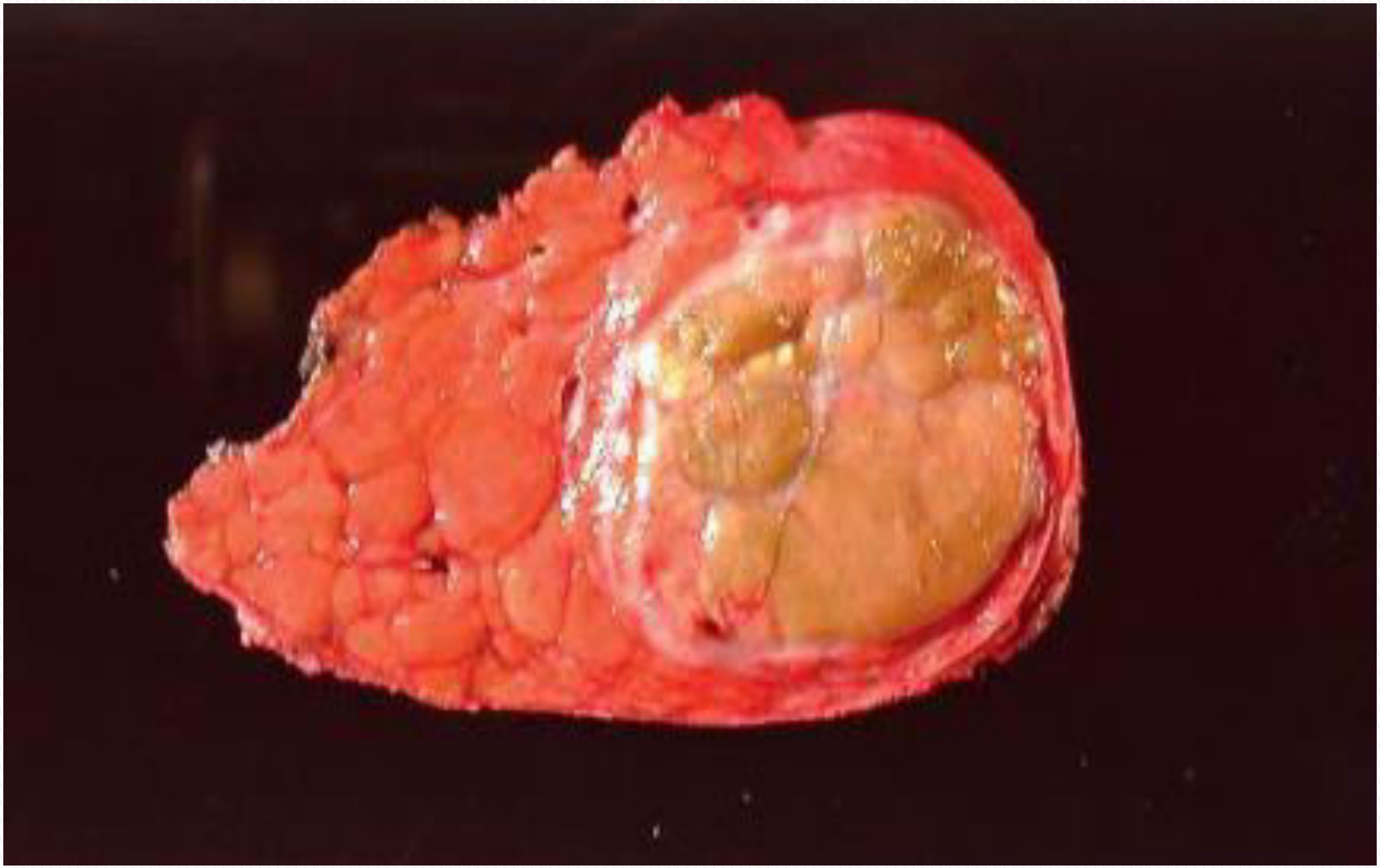
- **Gross appearance:**
  - *Unifocal* (usually massive).
  - *Multifocal* (variable sized nodules).
  - *Diffusely infiltrative.*

→ Tumors are *yellow-white*, punctuated by bile staining and areas of hemorrhage or necrosis

→ All patterns of HCC have a strong propensity for *invasion of vascular channels*:

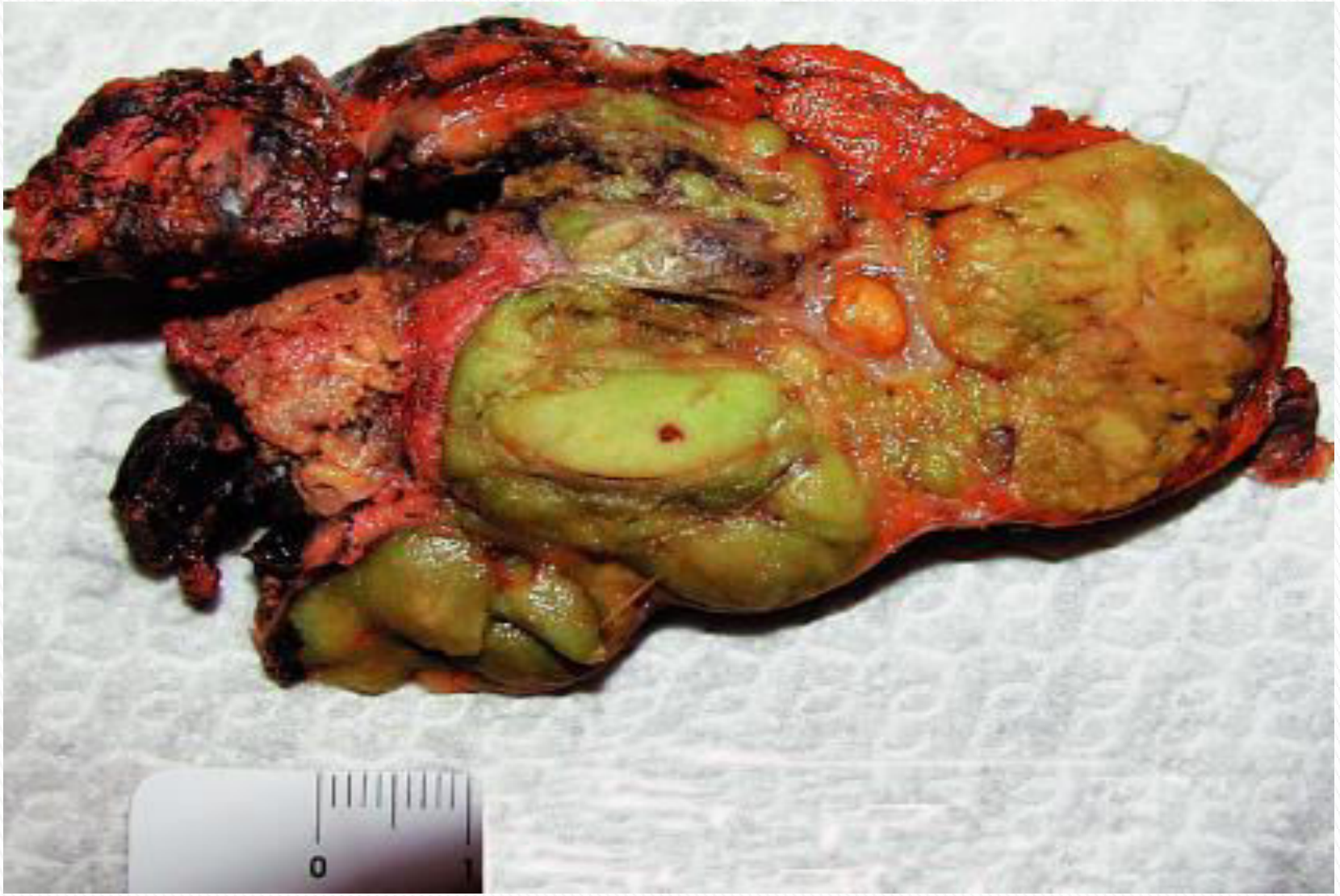
- Extensive intrahepatic metastases
- Occasionally snake-like masses of tumor invade the portal vein or IVC extending into the right side of the heart.

HCC



A unifocal, massive neoplasm replacing most of the right hepatic lobe in a noncirrhotic liver; a satellite tumor nodule is directly adjacent

Bile stained HCC



Multifocal HCC in cirrhotic liver

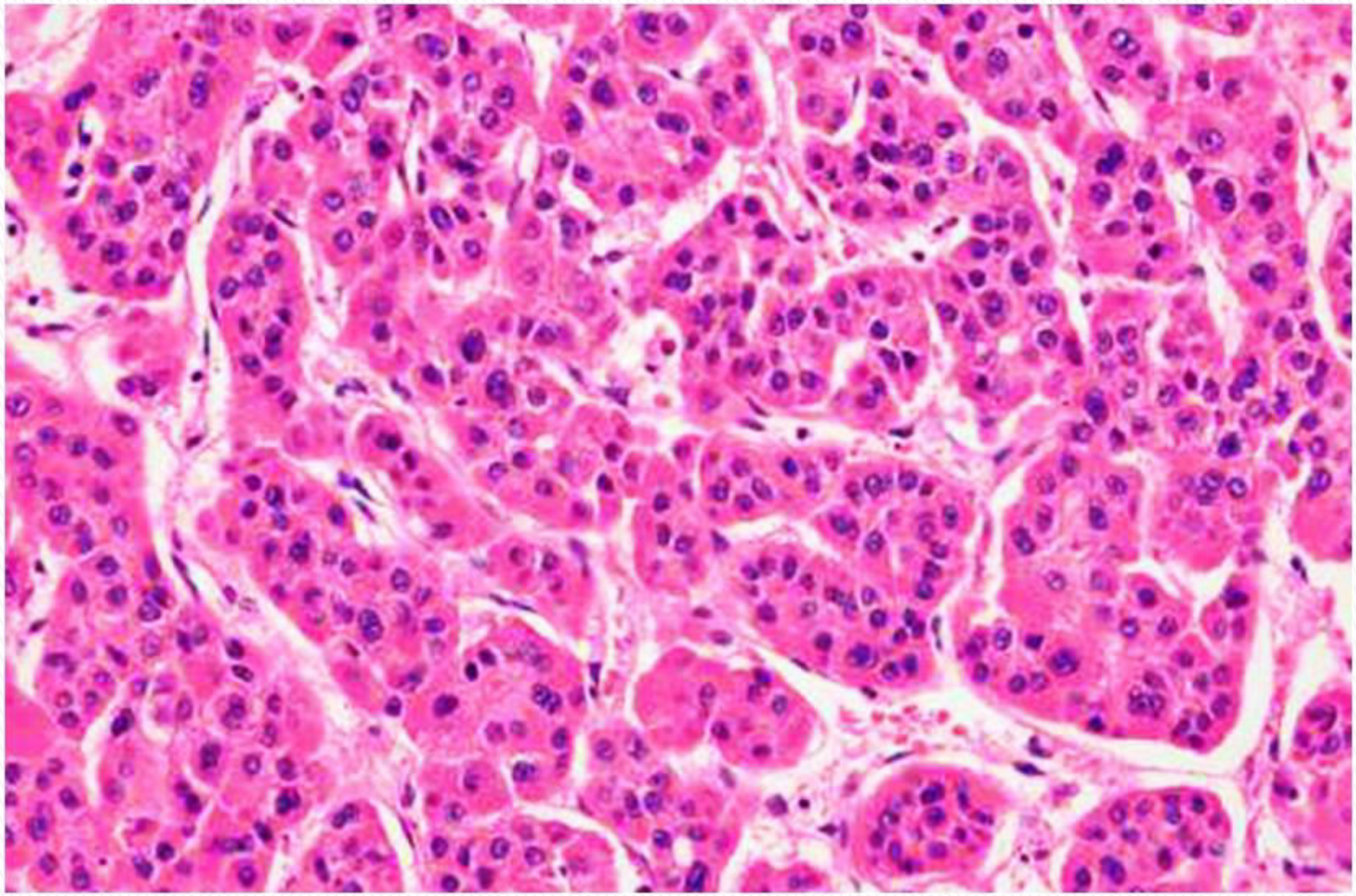
Morphology of HCC

- **Microscopic appearance:**
  - *Well-differentiated* (Hepatocytes arranged in thick cords, trabeculae or glandular patterns).
  - *Moderately differentiated*
  - *Poorly differentiated* (anaplastic or multinucleate tumor giant cells).

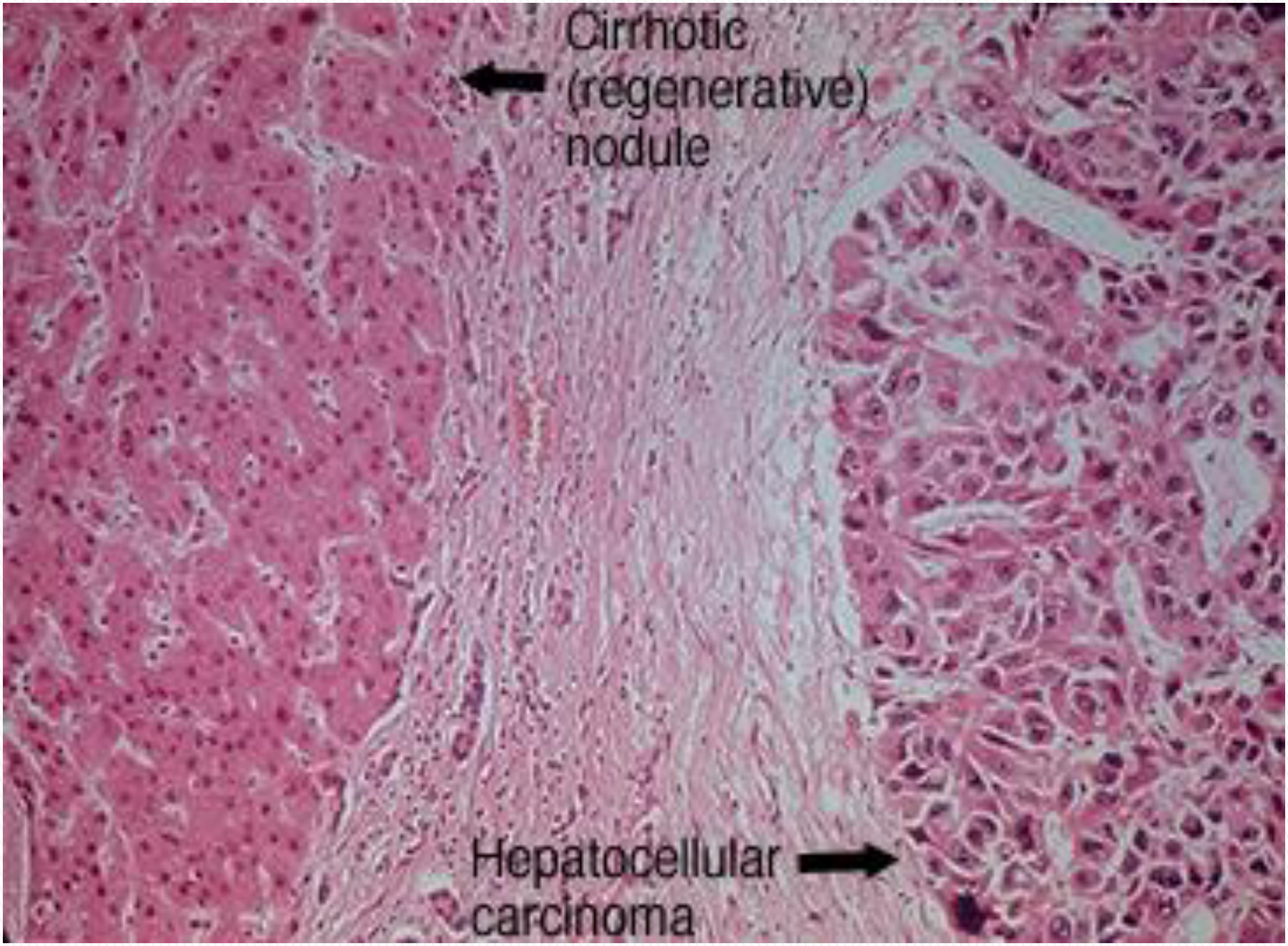
→ ***Other features:***

- Loss of reticulin stain (important sign).
- Bile pigment.
- Acidophilic hyaline inclusions resembling MB.

Well differentiated HCC



Tumor cells are arranged in nests, sometimes with a central lumen


Cirrhotic
(regenerative)
nodule
Hepatocellular
carcinoma

Clinical picture of HCC

- Silent hepatomegaly
- Often encountered in individuals with **cirrhosis**:
  - →Rapid increase in liver size, worsening of ascites, or the appearance of bloody ascites, fever, & pain call attention to HCC
- 50% of patients have very high levels of serum α-fetoprotein *(> 1000 ng/mL).*

Prognosis of HCC

- The overall prognosis of HCC is grim (depends mainly on **stage).**
- The median survival is 7 months.
- Prognosis is better for individuals who have:
  - A single tumor
  - < 2 cm in diameter
  - Good LFT

Prognosis of HCC

- **Causes of death:**

1. Profound cachexia,
2. GI or esophageal variceal bleeding
3. Liver failure
4. Rarely, rupture of the tumor with fatal bleeding.

Treatment of HCC

- The most effective therapies are:
  - Surgical resection of smaller tumors
  - Liver transplantation for patients with small tumors and good liver function.
- Tumor recurrence rate is > 60% at 5 years
- The best hope for preventing HCC in regions endemic for HBV infection is a comprehensive anti-HBV immunization program.