Hemochromatosis

- **Excessive accumalation of body iron (liver & pancreas)**
- **1ry or 2ry (genetic or acquired)**
- **Genetic hemochromatosis (4 variants)**
- **The most common form is aut.recessive disease of adult onset caused by mutation in the HFE gene on chr.6**

Causes of acquired hemosidrosis :

1-multiple transfusions

2-ineffective erythropoiesis (β-thalassemia)

3-increased iron intake (Bantu sidrosis)

4-chronic liver disease

Clinical Features:

1- Micronodular cirrhosis (all patients)
2- D.M (75-80%)
3- Skin prigmentation 75-80%)
4- Cardiomegaly (arrhythmias, cardiomyopathy)
5- Joints disease
6- Testicular atrophy

- **Symptoms appear 5th – 6th decades**
  not before age 40
- **M:F ratio 5 - 7: 1**
- **earlier clinical presentation in males partly because physiologic iron loss (menstruation, pregnancy) retards iron accumulation in women.**

Pathogenesis

-1ry defect in intestinal absorption of dietary iron.

-Total body iron 2-6gm in adults 0.5gm in liver mostly in hepatocytes

- In disease >50gm of iron accumulated → 1/3 in liver

- There is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5-1 gm/yr.

- **HFE gene regulates the level of hepcidin hormone synthesized in liver**
- **Hepicidin normally inhibits iron absorption.**
- **When hepcidin levels are reduced there is increased iron absorption.**
- **HFE gene deletion causes→ ↓Hepcidin levels→ iron overload**

-Two mutations can occur in HFE gene:

1-Mutation at 845 nucleotide → tyrosine substitution for cystine at AA 282

(C282 Y)

2-aspartate substitution for histidine at AA 63 (H63D)

10% of pts. have other gene mutations

-Carrier rate for C282Y is 1/70

-Homozygosity is 1/200

- 80% of pts. are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation

-10% of pts. are either homozygous for H63D mutation or compound heterozygous for C282Y/H63D mutation

- **Excessive Fe deposition → toxicity of the tissues :**
    1. **Lipid peroxidation**
    2. **Stimulation of collagen formation**
    3. **DNA damage**

Morphological changes:

- No inflammation

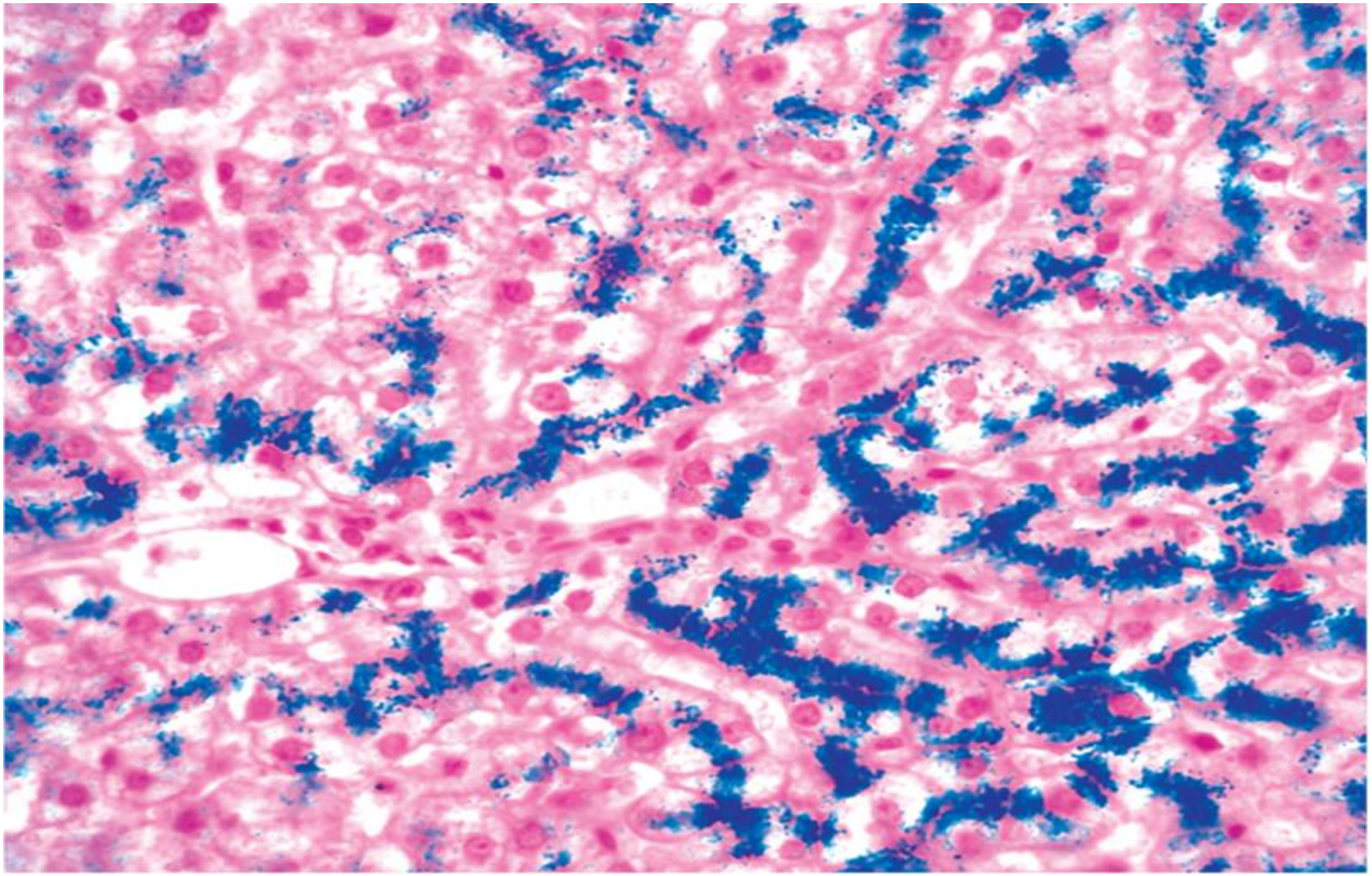
1-Deposition of hemosiderin in diffferent organs

Liver
Pancreas
Myocardium
Pituitary
Adrenal
Thyroid & parathyroid
Joints
Skin

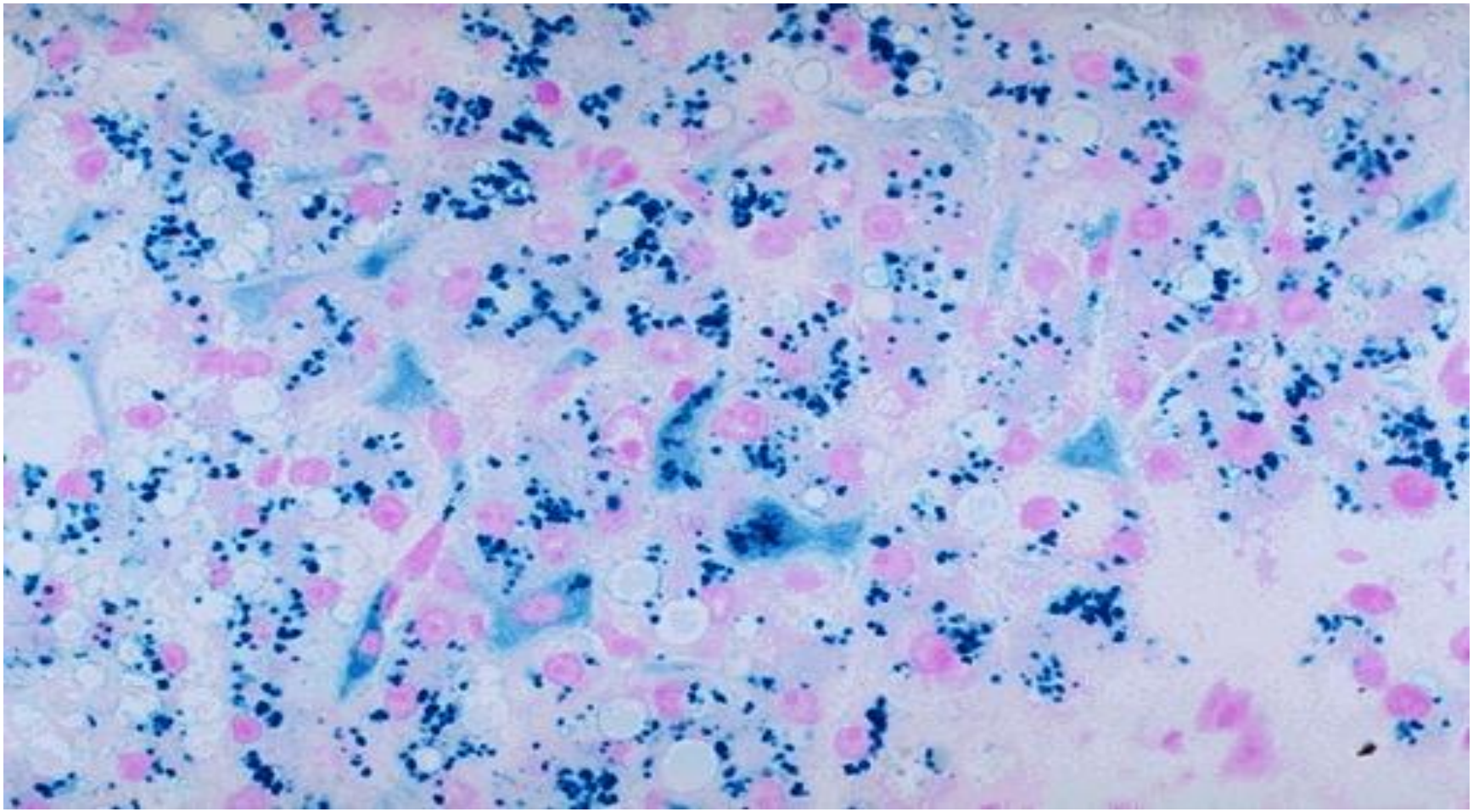
2-Cirrhosis

3-Pancreatic fibrosis

Hemosiderosis



Hemosiderosis



4-Synovitis

5-Polyarthritis(pseudogout)

6-Pigmentation of liver

7-Fibrosis of pancreas & myocardium

8-Atrophy of testes

- **Death may result from:**
- 1-cirrhosis
- 2-hepatocellular carcinoma
- 3-cardiac disease.
- The risk of hepatocellular carcinoma development in patients with hemochromatosis is 200-fold higher than in normal populations

Wilson Disease

-aut. Recessive disorder of Cu metabolism

-mutation in ATP7B gene on chr. 13 which encodes an ATPase metal ion transporter in Golgi region

-> 80 mutations

-Gene freq. 1:200

-Incidence is 1:30000

Pathogenesis

Main source of Cu is from diet

↓

Absorption of ingested Cu (2-5 mg/d)

↓

Complex with albumin

↓

Hepatocellular uptake

↓

Incorporation with α-2-globulin to form Ceruloplasmin

↓

Sec. into plasma

(90 – 95% of plasma Cu)

↓

Hepatic uptake of ceruloplasmin

↓

Lysosomal degradation

↓

Secretion of free Cu into bile

- **In Wilson disease absorbed Cu. Fails to enter the circulation in the form of ceruloplamin & the biliary excertion of Cu. is ↓**
- **Defective function of ATP-7B →failure of Cu. excretion into bile & inhibits sec. of ceruloplasmin into the plasma →Cu. accumulation in liver**

-↑Cu. Accumulation in the liver reults in:-

1-Production of free radicals

2-binding to sulfhydryl groups of cellular proteins

3-displacement of other metals in hepatic metalloenzymes

-By the age of 5yrs. Cu. Spills over to circulation causing hemolysis & involvement of other organs as brain & cornea also kidneys, bones joints & parathyroid glands

-Urinary exc. Of cu. ↑

Morphology

Liver

1-Fatty change

2-Acute hepatitis

3-chronic hepatitis

4-cirrhosis

5-massive hepatic necrosis

(rhodanine stain or orcein stain)

Brain:

Toxic injury to basal ganglia esp. the putamen causing atrophy & cavitation

Eye:

kayser- Fleischer rings

green – brown depositis of Cu. in descemet membrane in the limbus of the cornea

(hepatolenticular degeneration)

- **Clinically**

-Presentation > 6 yrs of age

-Most common presentation is acute on top of chronic hepatitis

-Neuropsychiatric presentation can occur

behavioral changes

Frank psychosis

Parkinson disease- like syndrome

- **DX**

1- ↓ in serum ceruloplasmin level

2- ↑ in urinary exc. Of Cu.

3- ↑ hepatic content of copper

> 250 mg/gm dry wt.

α-1-Antitrypsin Defeciency

- **Aut. Recessive disorder**
- **freq. 1:7000 in N. american white population**
- **α-1-antiryrpsin is a protease inhibtor as elastase, cathepsinG , proteinase 3 which are released from neutrophils at the site of inflammation.**

-The gene pi. Is located on chr. 14.

-At least 75 forms of gene mutation are present

-The most common genotype is pi.MM present in 90% of individuals.

- **PiZZ genotype→↓level of α-1-ntitrypsin in blood (only 10% of normal) are at high risk of developing clinical disease**

Pathogenesis

-The mutant polypeptide (PiZ) is abnormally folded & polymerizes causing its retention in the ER of hepatocytes.

-Athoyugh all individual with Pizz genotype accumulate α-1-AT-Z protein only 10% of them develop clinical liver disease .

-This is due to lag in ER protein degradation pathway.

-The accumulated α-1-AT-Z is not toxic but the autophagocytic response stimulated within the hepatocytes appear to be the cause of liver injury by autophagocytosis of the mitochondria.

-8-10% of patients develop significant liver damage.

Morphology

- **Intracytoplasmic globular inclusions in hepatocytes which are acidophilic in H&E sections.**
- **The inclusions are PAS+ve & diastase resistant.**
- **Neonatal hepatitis cholestasis & fibrosis**

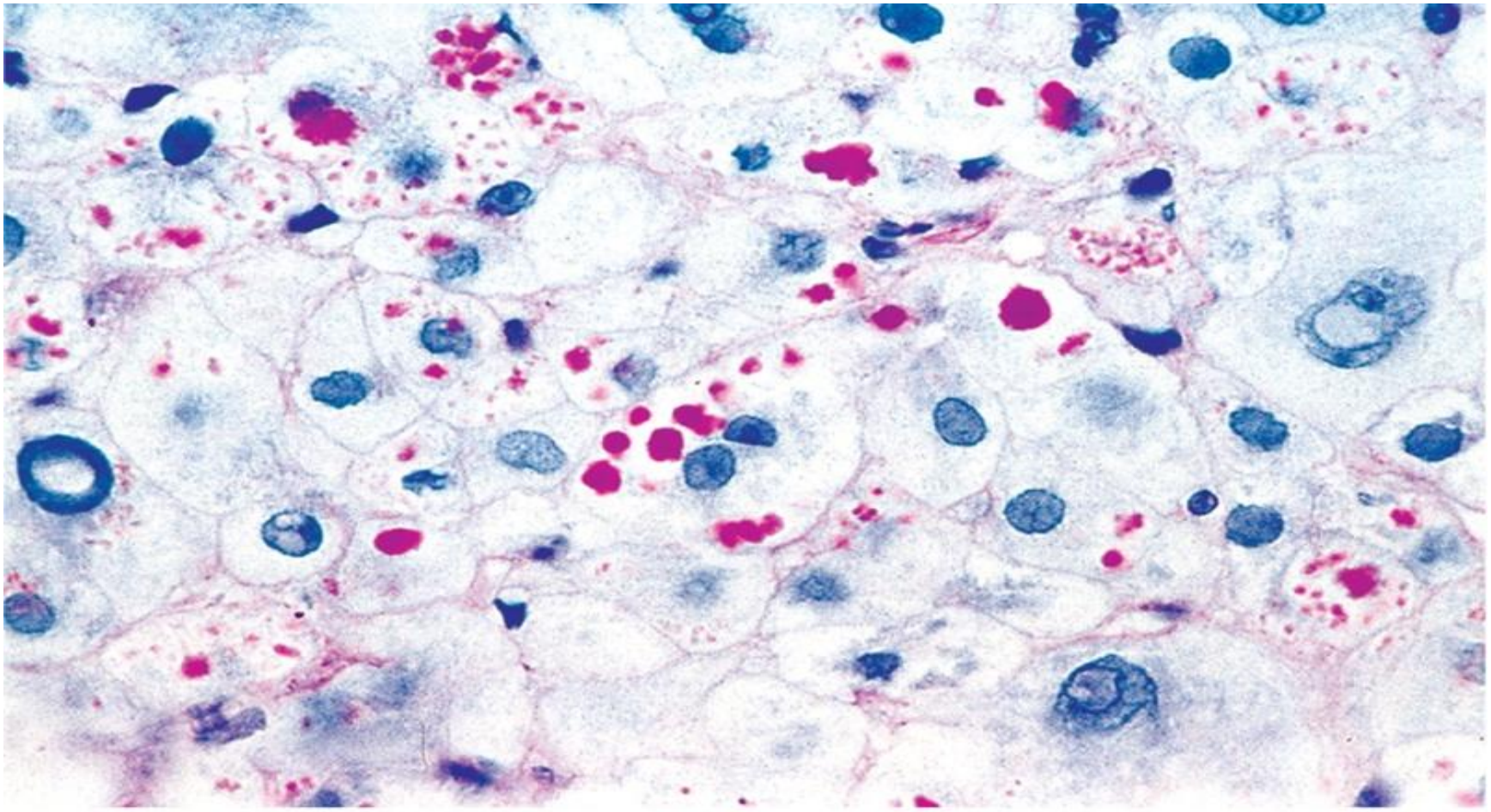
- **Chronic hepatitis**
- **Cirrhosis**
- **Fatty change**
- **Mallory bodies**

Clinical features

- **Neonatal hepatitis with cholestatic jaundice appears in 10 – 20% of newborns with the disease .**
- **Attacks of hepatitis in adolescence**
- **Chronic hepatitis & cirrhosis**
- **HCC in 2- 3 % of Pizz adults**

α-1-Antitrypsin Defeciency

Intracytoplasmic globular inclusions in hepatocytes (PAS stain)



Reye's Syndrome

-Fatty change in liver & encephalopathy.

-< 4 yr.

-3 – 5 d after viral illness.

-↑liver & abn. LFT.

-Vomiting lethargy.

-25% may go into coma.

- Death occurs from progressive neurologic deterioration or liver failure.
- Survivors of more serious illness may be left with permanent neurologic impairments.

Pathogenesis

- **The pathogenesis of Reye syndrome involves a generalized loss of mitochondrial function.**
- **Reye syndrome is now recognized as the prototype of a wide variety of conditions known as *"mitochondrial hepatopathies."***
- **Reye syndrome has been associated with aspirin administration during viral illnesses, but there is no evidence that salicylates play a causal role in this disorder.**

Morphology

- The key pathologic finding in the **liver** is microvesicular steatosis.
- Electron microscopy of hepatocellular mitochondria reveals pleomorphic enlargement and electron lucency of the matrices with disruption of cristae and loss of dense bodies.
- In the **brain,** cerebral edema is usually present.

Budd – Chiari Syndrome

Hepatic Vein Thrombosis

-Thrombotic occlusion results from the thrombosis of two or more major hepatic veins.

-characteristics:

-Hepatomegaly

-Wt.gain

-Ascitis

-Abd. Pain

Causes:

1-PCV

2-Pregnancy

3-Postpartum

4-Oral contraceptive

5-PNH

7-Mechanical obstruction

8-Tumors as HCC

9-Idiopathic in 30% of the cases

-

Morphology

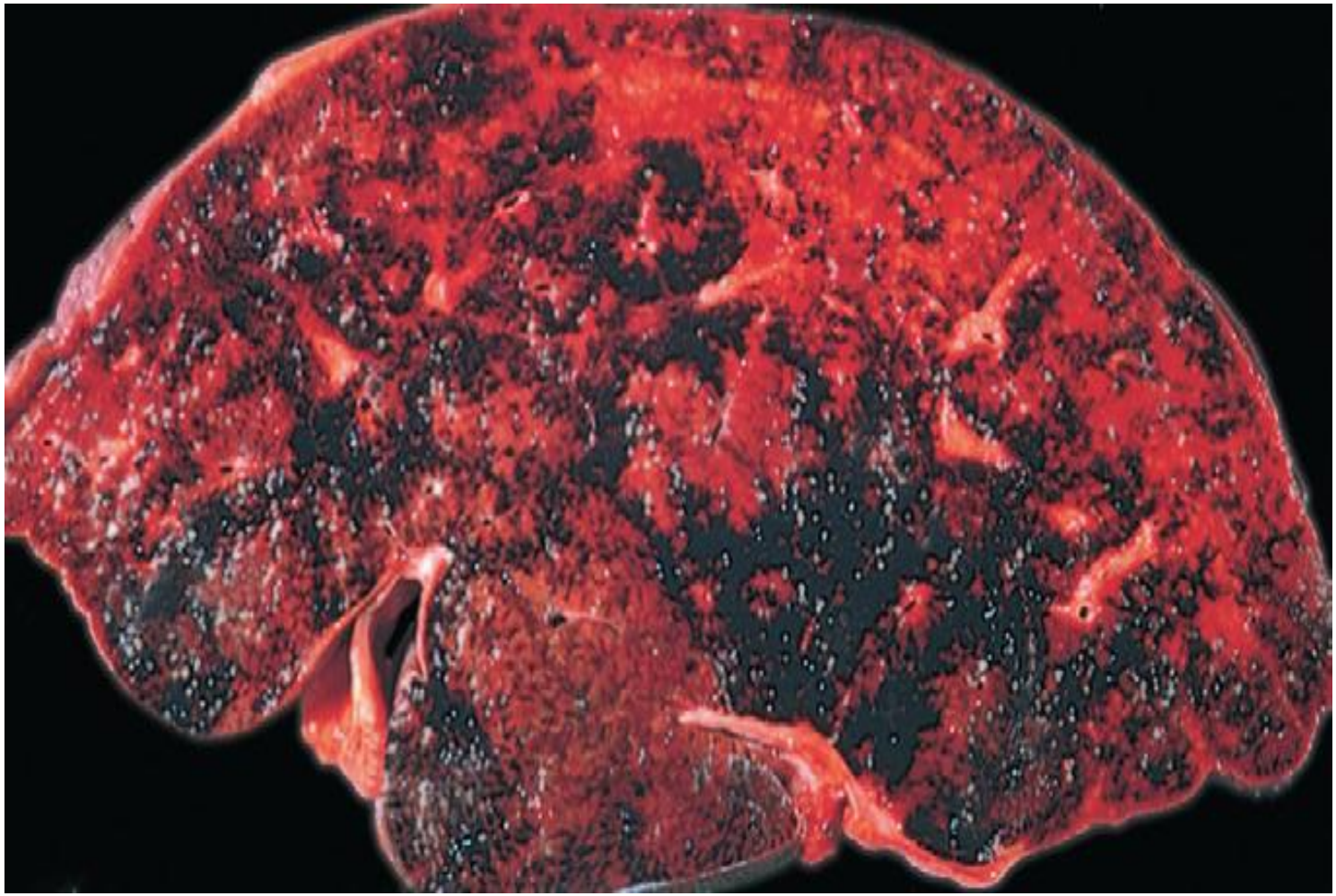
-Swollen liver with tense capsule

-centrilobular congestion & necrosis

-Fibrosis

-Thrombi

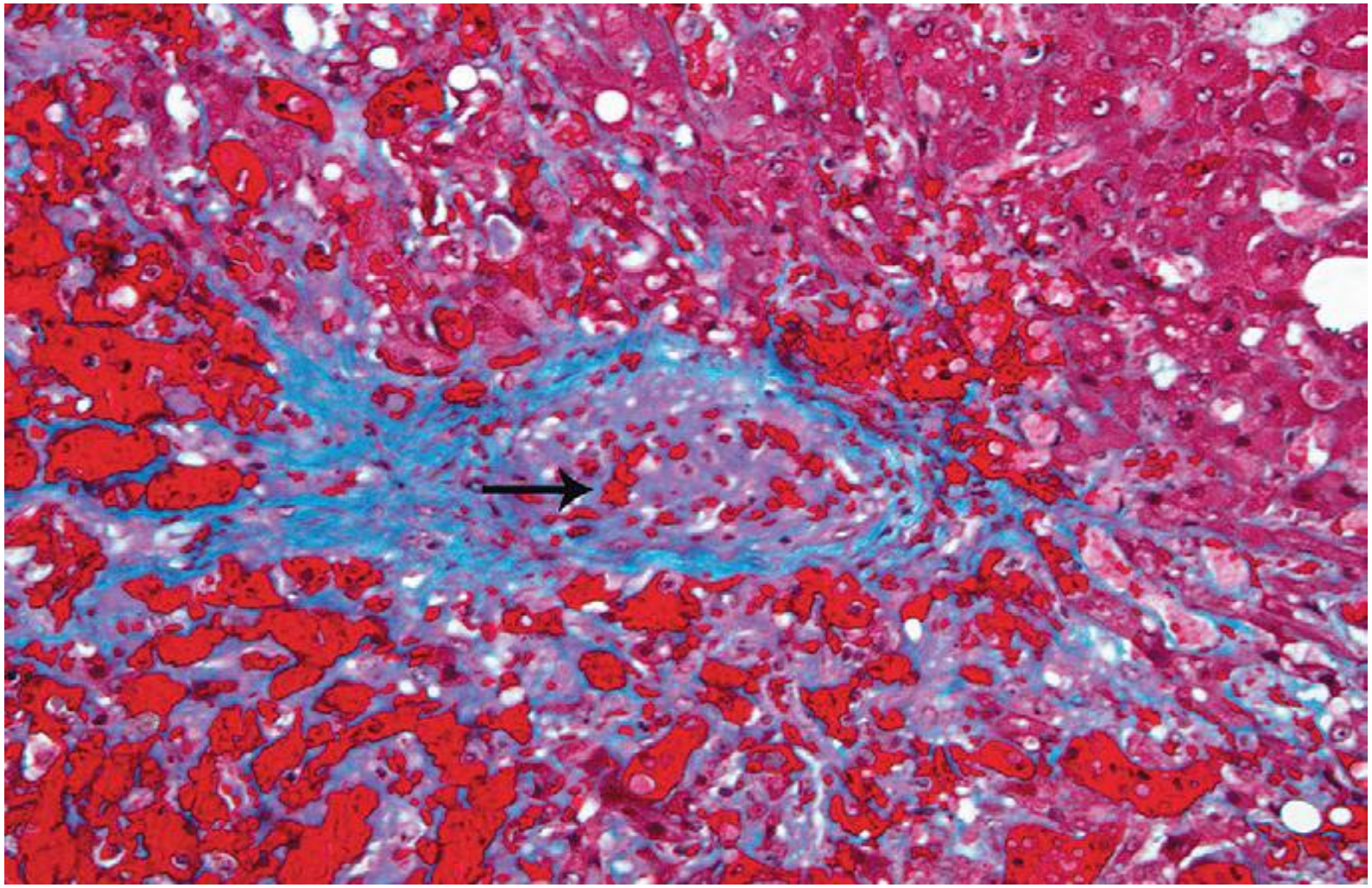
Budd-Chiari syndrome



Sinusoidal Obstruction Syndrome (Veno-occlusive disease)

- **Originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloids.**
- **Obstruction syndrome is caused by toxic injury to sinusoidal endothelium.**
- **Damaged endothelial cells slough off and create emboli that block blood flow.**

Sinusoidal obstruction syndrome
A central vein is occluded by cells and newly formed collagen (arrow).
There is also fibrosis in the sinusoidal spaces(MT stain).



- **Endothelial damage is accompanied by passage of red blood cell into the space of Disse, proliferation of stellate cells, and fibrosis of terminal branches of the hepatic vein**
- **This occurs in the first 20-30 days after bone marrow transplantation**

. Which is caused by:

1-Drugs as cyclophosphamide

2-Total body radiation

.Incidence

-20% in recepients of allogeneic marrow transplant

-**Clinical presentation**

Mild – severe

Death if does not resolve in 3 months

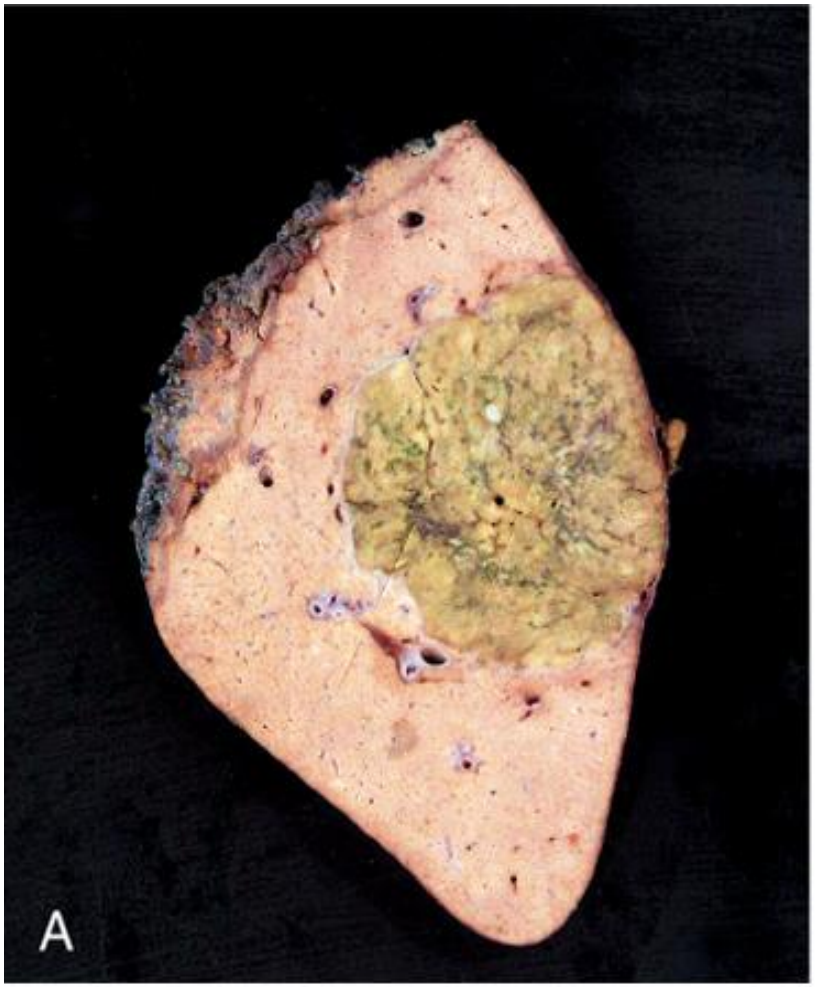
Liver tumors

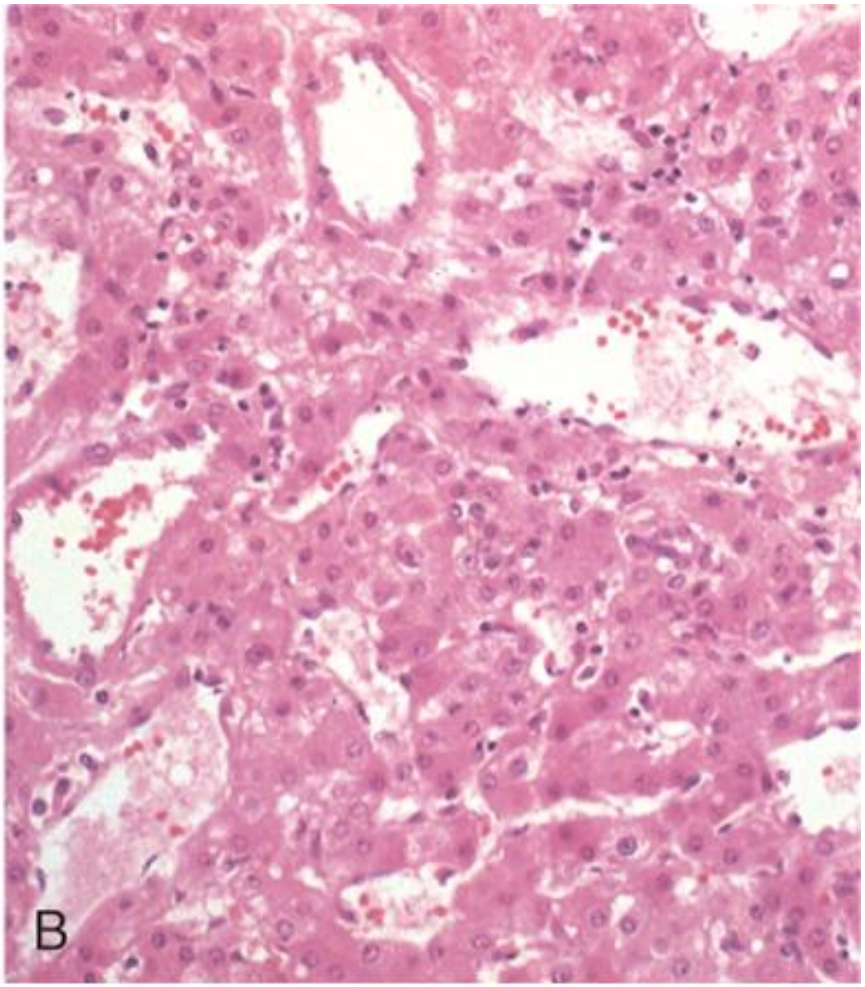
- **Most common benign tumor is cavernous hemagioma**
- **Usually <2cm**
- **Subcapsular**

Liver cell adenoma

- **Young female**
- **Childbearing age who have used oral contraceptive steroids.**
- **It may regress on discontinuance of hormone use.**

Hepatic adenoma





- Liver cell adenomas are significant for three reasons:
- (1) when they present as an intrahepatic mass, they may be mistaken for the more ominous hepatocellular carcinoma
- (2) subcapsular adenomas are at risk for rupture, particularly during pregnancy (under estrogenic stimulation), causing life-threatening intra-abdominal hemorrhage
- (3) although adenomas are not considered precursors of hepatocellular carcinoma, adenomas carrying β-catenin mutations carry a risk of developing into cancers.

Liver Nodules

Focal noudular hyperplasia

- **Well demarcated hyperplastic hepatocytes with central scar.**
- **Non-cirrhotic liver.**
- **Not neoplasm but nodular regeneration.**
- **Local vascular injury.**
- **Females of reproductive age.**
- **No risk of malignancy.**
- **20% of cases have cavernous hemagnioma.**

Macroregenerative Nodules

- Cirrhotic liver
- Larger than cirrhotic nodules
- No atypical features
- Reticulin is intact
- No malignant potential

Dysplastic nodules

- Larger than 1 mm
- Cirrhotic liver
- Atypical features, pleomorphism and crowding
- High proliferative activity
- High or low dysplasia
- Precancerous (monoclonal, +ve gene mutations
- Types:

1. Small – cell dysplastic nodules
2. Large – cell dysplastic nodules

Hepatocellular carcinoma

- **5.4% of all cancers**
- **Incidence:**
  <5/100000 population in N&S America
  N& central Europe
  Australia
  15/100000 population in Mediterranean
  36/100000 population in Korea, Taiwan
  mozambique, china

- **Blacks > white**
- **M:F ratio**
  3:1 in low incidence areas. >60yr
  8:1 in high incidence areas. 20-40yr

Predisposing Factors

1. **Hepatitis carrier state**
   vertical transmission increases the risk 200X
   cirrhosis may be absent
   young age group (20-40yr)
2. **>85% of cases of HCC occur in countries with high rates of chronic HBV infection**

3-Cirrhosis

In western countries cirrhosis is present in 85-90% of cases

>60yr

HCV & alcoholism

4. Aflatoxins

5. Hereditary tyrosinemia (in 40% of cases)

6. Hereditary hemochromatosis

Pathogenesis

1. Repeated cycles of cell death & regeneration
   HBC, HCV, gene mutations, genomic instability
2. Viral integration
   HBV DNA intergration which leads to clonal expansion of hepatocytes
3. HBV DNA intergration which leads to genomic instability not limited to integration site.

4. HBV
   X-protein which leads to transactivation of viral & cellular promoters,activation of oncogenes and Inhibition of apoptosis
5. Aflatoxins (fungus Aspirgillus flavus) mutation of p53
6. Cirrhosis
   HCV
   Alcohol
   Hemochromatosis
   Tyrosinemia (40% of pts. Develop HCC despite adequate dietary control)

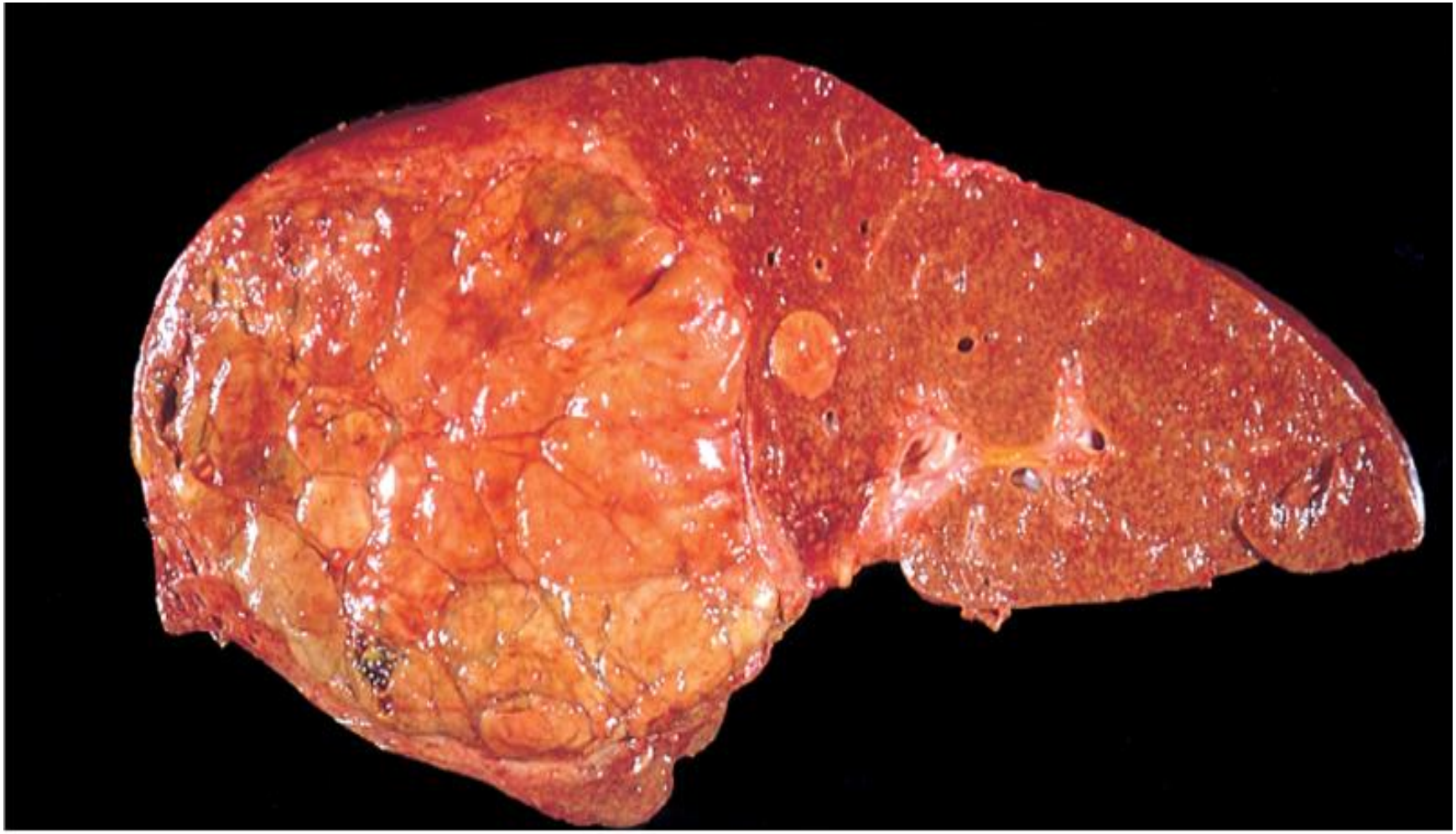
Morphology

1. Hepatocellular carcinoma (HCC)
2. Cholangiocarcinoma (CC)
3. Mixed

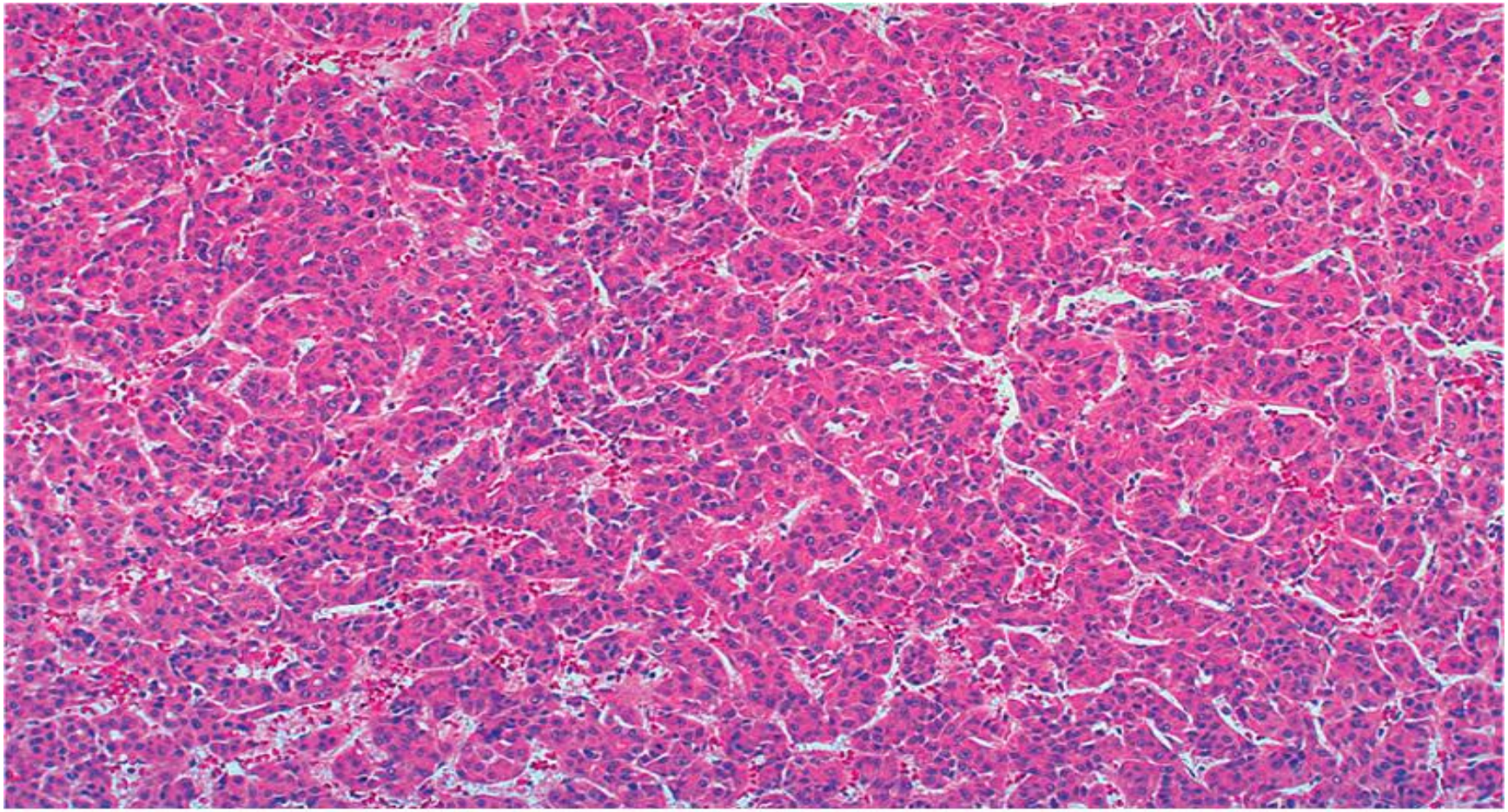
- Unifocal
- Multfiocal
- Diffusely infiltrative

Hepatocellular carcinoma, unifocal, massive type. A large neoplasm with extensive areas of necrosis has replaced most of the right hepatic lobe in this noncirrhotic liver. A satellite

tumor nodule is directly adjacent.



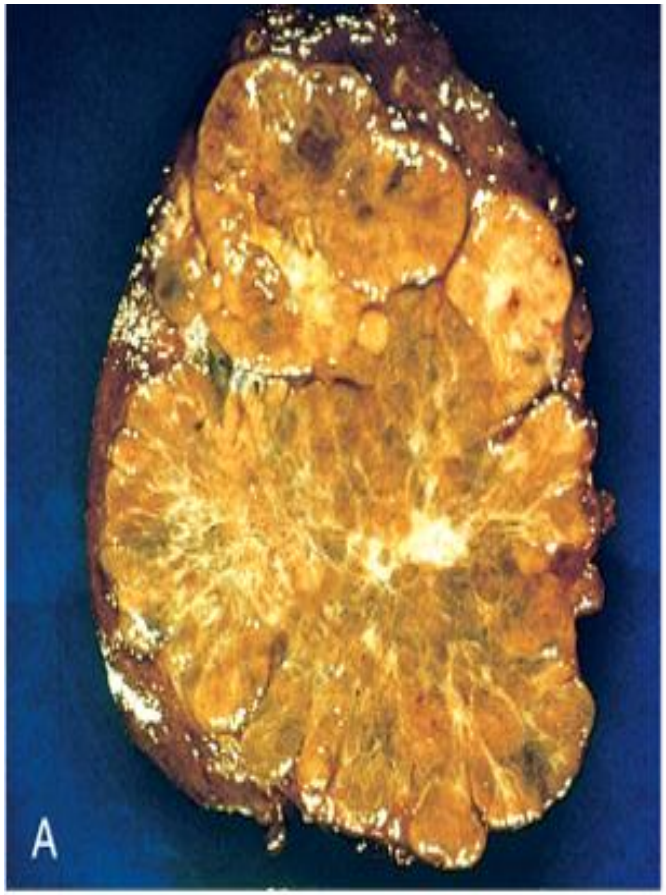
Hepatocellular carcinoma

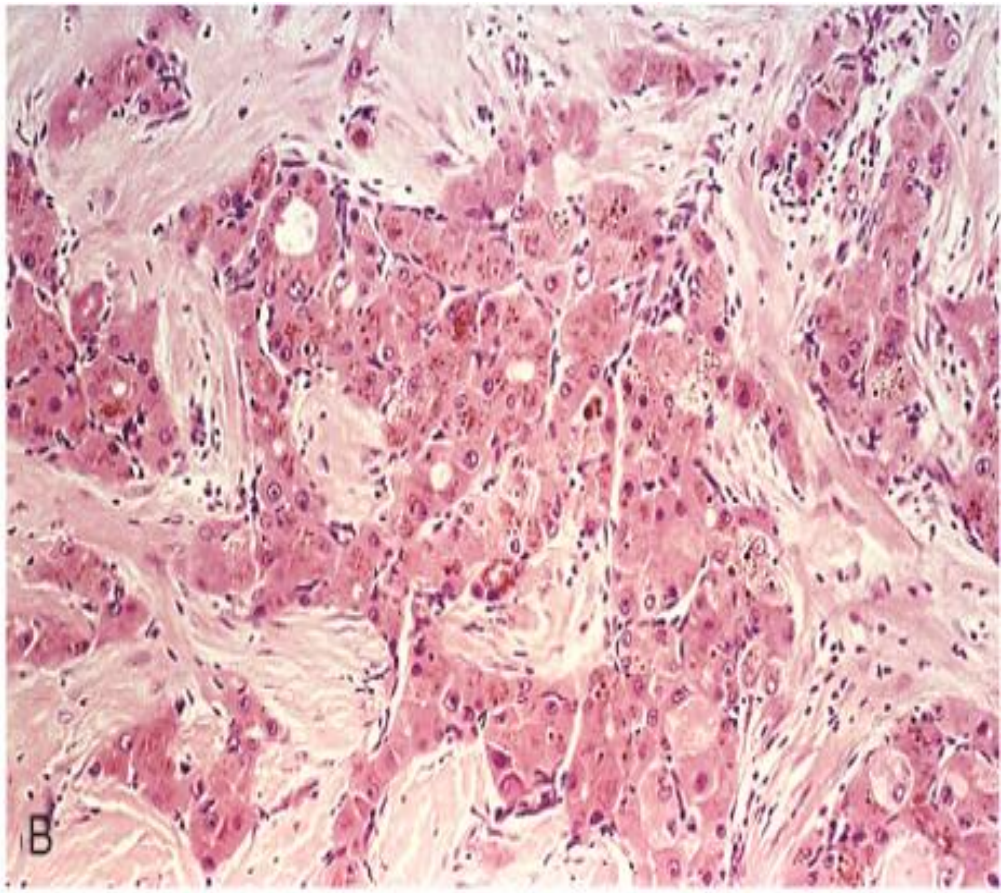


- Vascular invasion is common in all types.
- Well ---- Anaplastic

- **Fibrolamellar carcinoma**
  20-40 yr. M=F
  No relation to HBV or cirrhosis
  better prognosis
  single hard scirrhous tumor
- Cholangiocarcinoma are desmoplastic

Fibrolamellar carcinoma .





metastasis

Vascular – lungs, bones, adrenals, brain, in 50% of cholagiocarcinoma

- C/P
  abd. Pain, malaise, wt. loss
  increase α-feto protein in 60 – 75% of pts.

- α-feto protein increases also with:
  1-yolk sac tumor
- 2- cirrhosis,
- 3-massive liver necrosis,
- 4-chronic hepatitis,
- 5-normal pregnancy,
- 6-fetal distress or death
- 7- fetal neural tube defect.

Prognosis

- Death within 7 -10 months
- **Causes:**

1-Cachexia

2-GI bleeding

3-Liver failure

4-Tumor rupture and hemorrhage

THE END