Hepatobiliary pathology

LEC 3

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Inherited metabolic disorder

Hemochromatosis is caused by excessive absoprtion of iron, which is primarily deposited in parenchymal organs such as the liver and pancreas, as well as in the heart, joints, and endocrine organs. It results most commonly from an inherited disorder, hereditary hemochromatosis. When iron accumulation occurs as a consequence of parenteral administration of iron, usually in the form of transfusions, it is called acquired hemochromatosis.

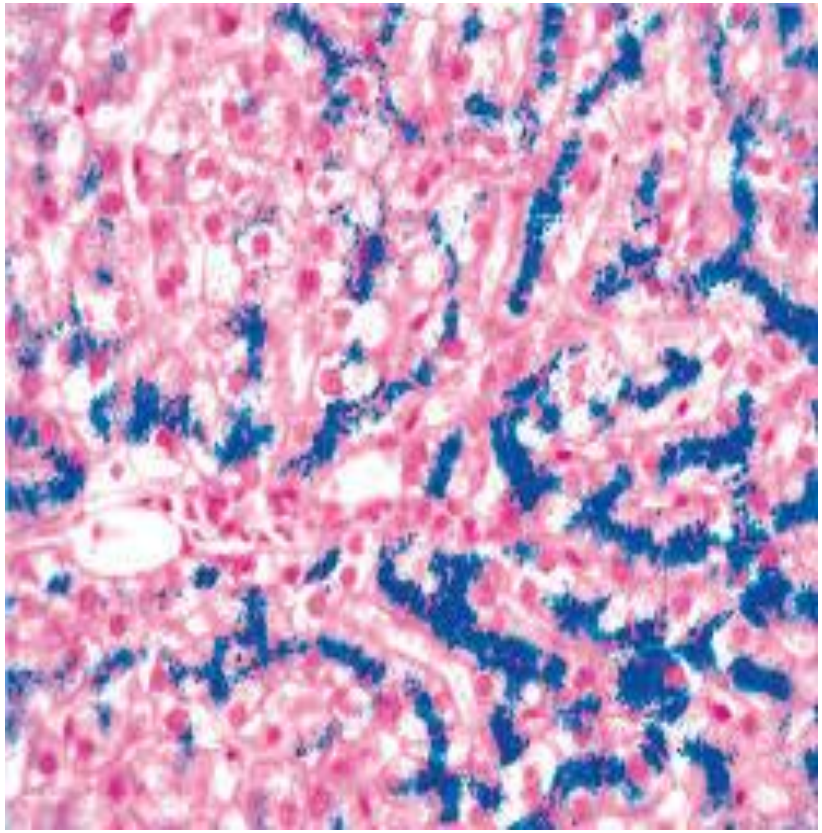
Hemochromatosis

Primary (Hereditary)

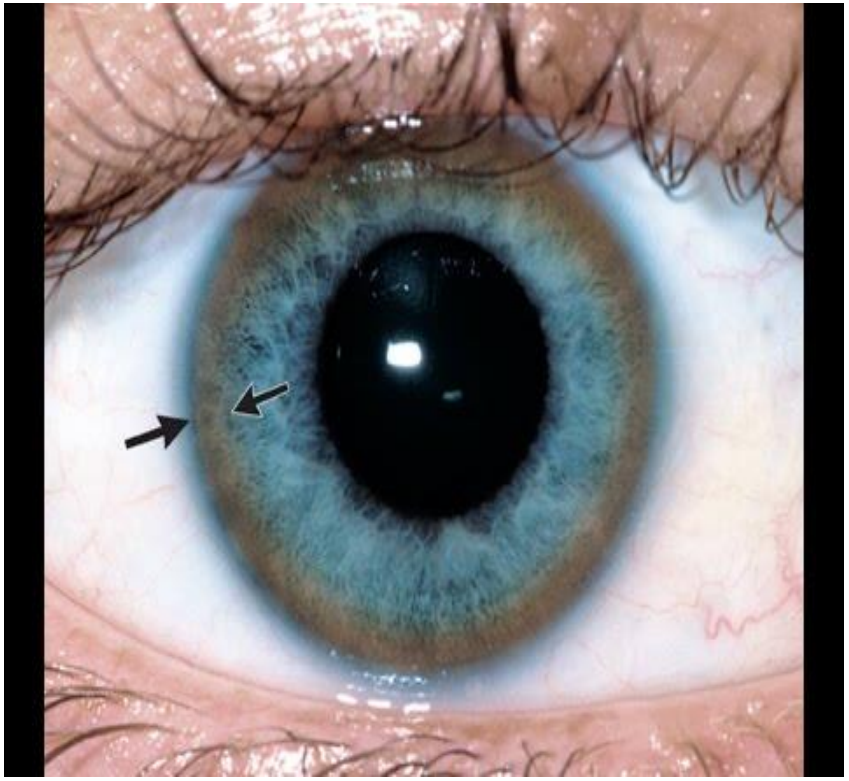
Secondary (Hemosiderosis)

skin pigmentation (bronzing of the skin)

Iron accumulates as hemosiderin in hepatocyte. Iron detection by using (Prussian blue stain)



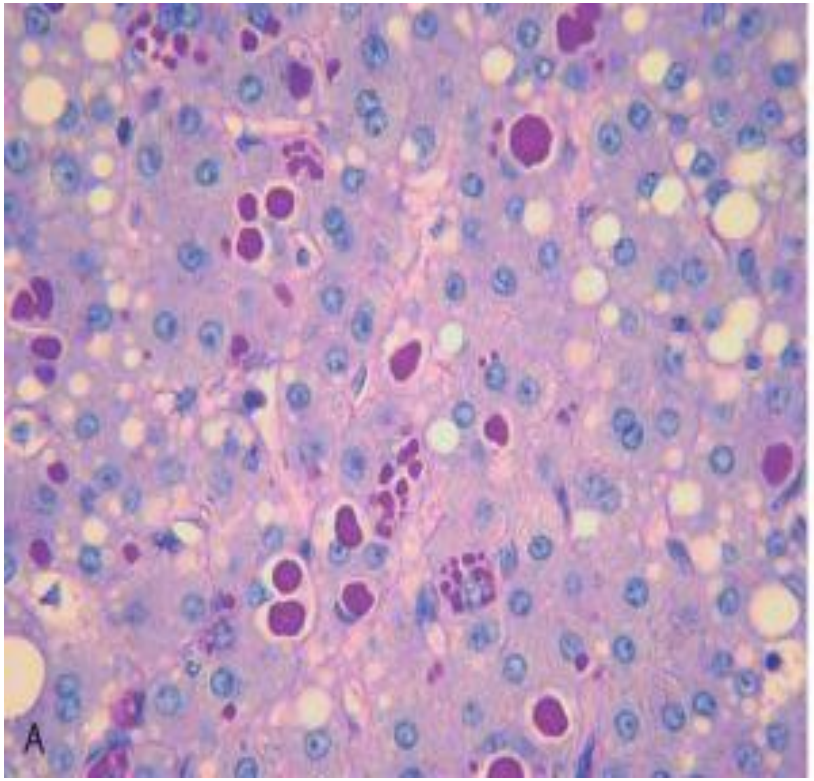
Kayser Fleischer ring (copper deposition in Descemet membrane of the eye)in case of **Wilson disease**: Genetic disorder of copper metabolism resulting in accumulation of toxic levels of copper in various organs (liver, brain and eye) **Cause:** AR disorder with ATP7B mutation.



Wilson disease

•**PAS positive** eosinophilic cytoplasmic globules within the hepatocytes in case of **α1-Antitrypsin Deficiency.**

It is an AR disorder characterized by production of defective α1-antitrypsin which accumulates in the hepatocytes. (PiMM the normal most common form,PiZZ markedly reduced level).**clinical:**lung (emphysema) and liver affected



α1-Antitrypsin Deficiency

Tumors of the liver.

Either benign or malignancy.
Malignant tumors are either primary (carcinoma of liver) or secondary (metastatic cancers to the liver).
Most common hepatic neoplasms ***are metaststic carcinomas*** *&* *the* ***sites of primary tumors are usually (colon, lung & breast).***

benign tumors include:

a. cavernous hemangioma (commonest benign tumor of liver).
b. liver cell adenoma.
c. focal nodular hyperplasia.

Liver cell adenoma.

In young childbearing age female who used oral contraceptive pills & it regresses on discontinuation of hormonal use.

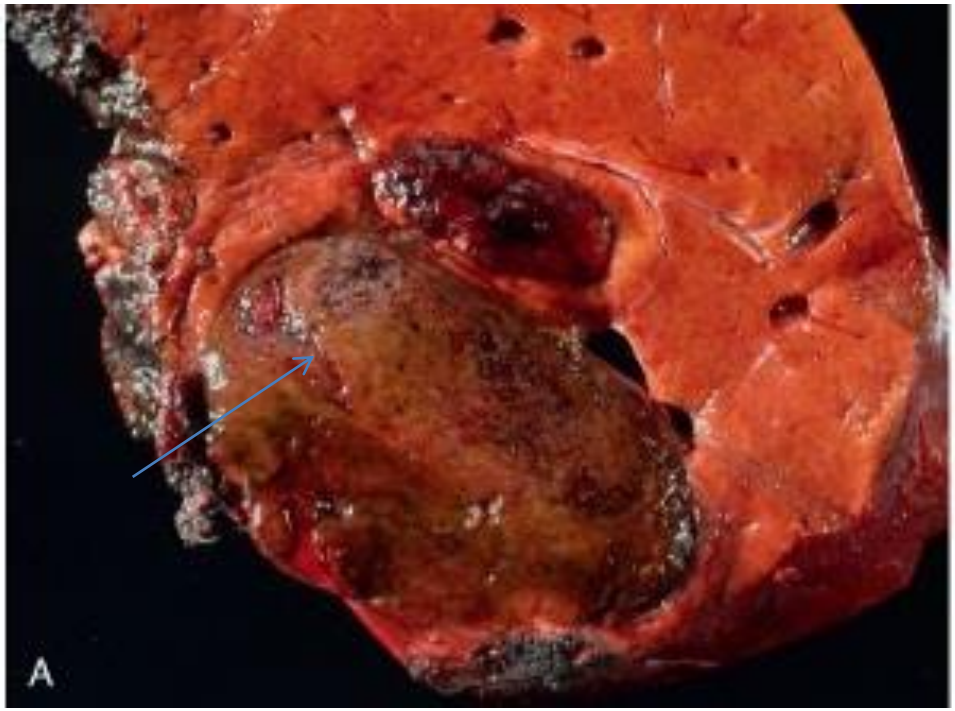
Gross. *Pale tan – yellow or bile stained, well demarcated nodules*, *often beneath the capsule of liver. May reach up to 30cm in diameter.*

Mic.

composed of sheets or cords of cells that may resemble normal hepatocytes or have some variation in cells & nuclear size, portal tracts are absent instead prominent arterial vessels & veins are distributed throughout the tumor.

these adenomas are significant because of 2 reasons*:*

1. *Misdiagnosed as hepatocellular carcinoma.*
2. *Subcapsular adenoma is at risk of rupture particularly during pregnancy (life threatening intra abdominal hemorrhage).*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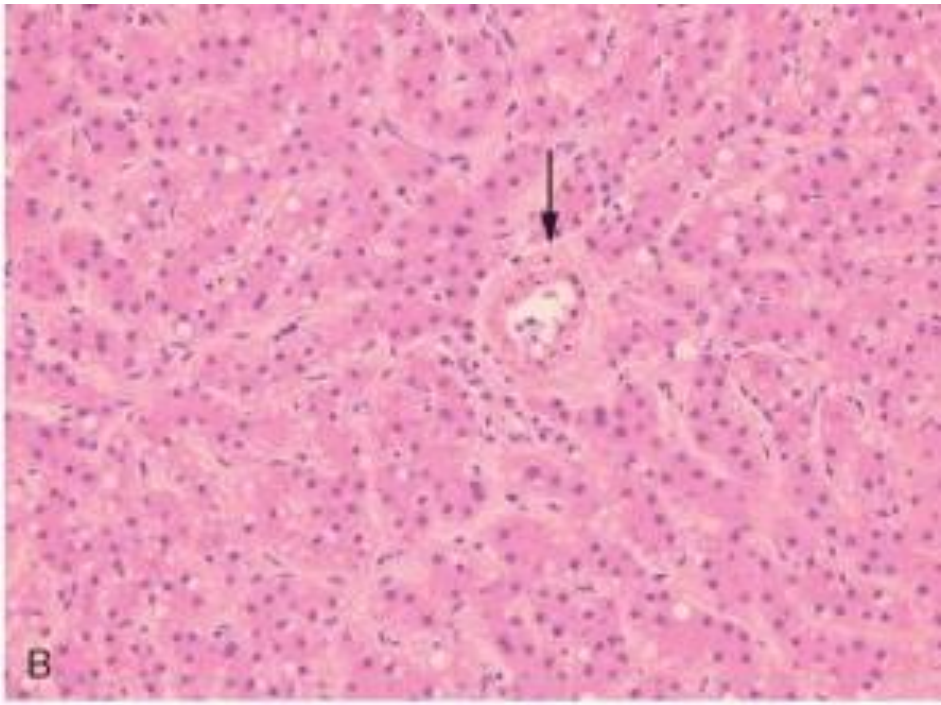
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Hepatocellular Carcinoma(HCC):

Sex: *Male> female* (***this is in high incidence areas related to greater prevalence of HBV infection, alcoholism & chronic liver diseases among the male).***

Race: *Black > white.*

Age: In high incidence areas…….. arise in third to fifth decades of life

Low incidence areas it is often arise in the 6th to 7th decades of life.

Etiology:

1. ***Hepatotropic viruses. HBV, HCV.***
2. ***Cirrhosis.*** About 60% to 80% of HCC associated with cirrhosis.
3. ***Liver cell dysplasia*** . Small cell dysplasia more associated with HCC than large cell dysplasia.
4. ***Thorium dioxide exposure.*** (thorotrast a radiographic contrast). Develop HCC within 20 years of exposure.
5. ***Androgen- anabolic steroid.*** In male patient with long term used of androgen treatment (like in treatment of carcinoma of prostatic carcinoma).

6. ***Progestational agent.*** Several cases of HCC & also liver cell adenoma are associated with using of contraceptive pills.
7. ***Aflatoxin.*** This is a product of Aspergillus flavus. Proved to be an etiological factor in development of HCC.
8. ***Schistosomiasis.*** No well evidence to be a cause of HCC.
9. ***Alcohol abuse.***

Symptoms: *abdominal pain, ascites, hepatomegaly, obstructive jaundice; also systemic manifestations.*

Laboratory: *elevated serum AFP (70% sensitive).*

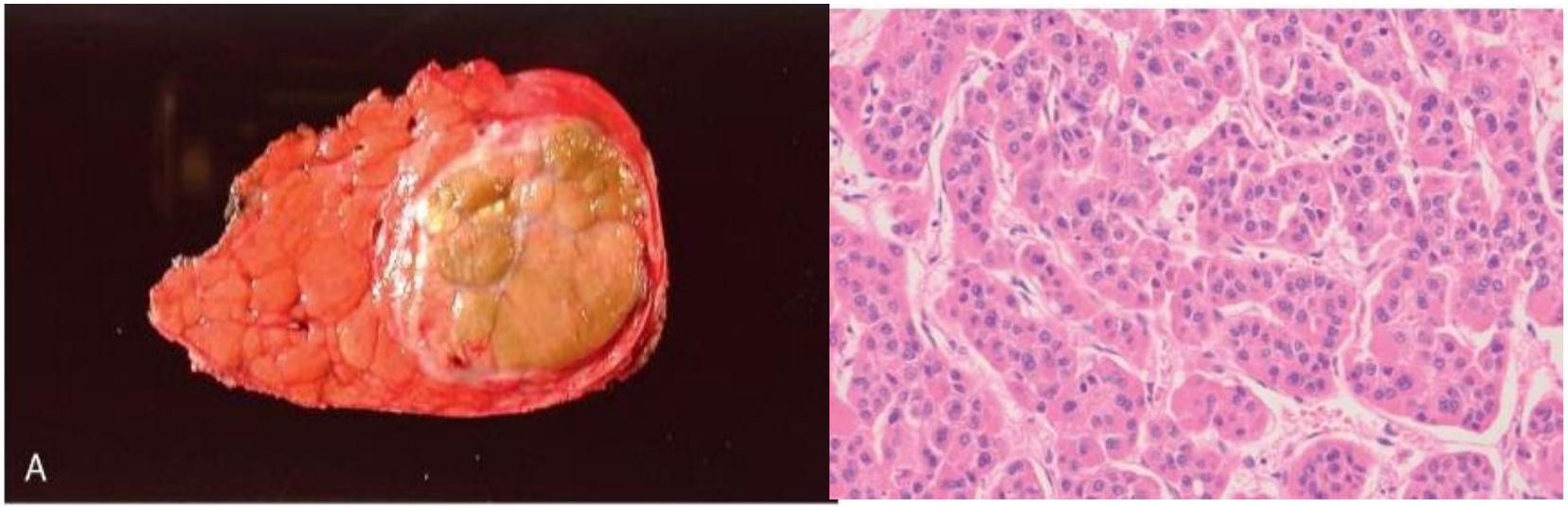
Screening: recommended to *use ultrasound and serum AFP in patients with chronic liver disease; leads to diagnosis of tumors 2 cm or less*, but may not reduce death.

Morphology:

Gross. ***unifocal*** *(massive single tumor).*

multifocal *(wide distributed nodules).*

diffuse *infiltrative cancer (sometime involve the entire liver).*


A

Invasion of vascular channels (very common).

Extend throughout the liver , Obstructed the portal vein, obstructed inferior vena cava & extend to right side of the heart.

Mic.

HCC ranges from ***well differentiated carcinoma*** *that reproduces hepatocytes arranged in cords or small nests.* ***To poorly differentiated lesion*** *which often made up of large multinucleated anaplastic tumor cells.*

Scant stroma in most cases of HCC (so the tumor is usually soft).

1. ***Fibrolamellar HCC.*** *This is not associated with cirrhosis or other risk factors & have better prognosis.*

2. ***Scirrhous carcinoma****. This is hard tumor due to its contents of fibrous tissue.*

Gallbladder Pathology

Cholelithiasis: Also called ***gallstones.***
Affects 10% of adults in developed countries.
80% of gallstones are silent & <1% of children have gallstones.

Risk Factors for Gallstones

Cholesterol Stones

Demography: Northern Europeans, North and South Americans, Native Americans, Mexican Americans

Advancing age

Female sex hormones Female gender

Oral contraceptives

Pregnancy

Obesity and insulin resistance Rapid weight reduction

Gallbladder stasis

Inborn disorders of bile acid metabolism Dyslipidemia syndromes

Pigment Stones

Demography:Asian more than Western, rural more than urban

Chronic hemolysis (e.g., sickle cell anemia, hereditary spherocytosis)

Biliary infection

Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency

MORPHOLOGY

Cholesterol stones

arise exclusively in the gallbladder and consist of 50% to 100% cholesterol. Pure cholesterol stones are pale yellow; increasing proportions of calcium carbonate, phosphates, and bilirubin impart gray-white to black discoloration وThey are ovoid and firm; they can occur singly, but most often there are several, with faceted surfaces resulting from their apposition. Most cholesterol stones are radiolucent, although as many as 20% may contain sufficient calcium carbonate to be radiopaque.

Cholesterol stones

Pigment stones

may arise anywhere in the biliary tree and are classified into black and brown stones. In general, black pigment stones are found in sterile gallbladder bile, while brown stones are found in infected intrahepatic or extrahepatic ducts

Pigment gall stones in patient with hemolysis

Pathogenesis of gallstones:

Three conditions must be met to permit the formation of cholesterol gallstones.

1. Bile must be supersaturated with cholesterol.

2. Nucleation must be kinetically favorable.

3. Cholesterol crystals must be remaining in the gallbladder long enough to aggregate into stones.

Complications of gallstones

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1. 1-2% have acute or chronic cholecystitis
2. Choledocholithiasis (stones in the common bile duct).
3. Cholangitis (inflammation of biliary tree).
4. Empyema (impaction of stone at the neck of gallbladder).
5. Gallstone ileus (a large stone may erode directly into the adjacent loop of small bowel, generating intestinal obstruction).
6. Acute pancreatitis.
7. Biliary fistulae.

Cholecystitis

- Def: Inflammation of the gallbladder
- Can be divided into
  - Acute cholecystitis
  - Chronic cholecystitis
  - Acute superimposed on chronic

Acute: **fever, leukocytosis, RUQ pain**

Chronic: **Subclinical or pain**

Ultrasound can detect stones well

Go hand in hand with stones in gallbladder or ducts

Cholecystitis predisposes to cholelithiasis, and VICE VERSA!

If surgery is required, most is laparoscopic

Cholecystitis:

Acute, Chronic, & acute superimposed on Chronic.

Acute cholecystitis:

1-Acute calculous cholecystitis:

90% of cases

caused by gallstone obstruction of the neck or the cystic duct

2- Acute acalculus cholecystitis Which occurs in the absence of gallstones

Pathogenesis of acute calculus cholecystitis:

three important mechanisms are involved in development of acute calculus cholecystitis.

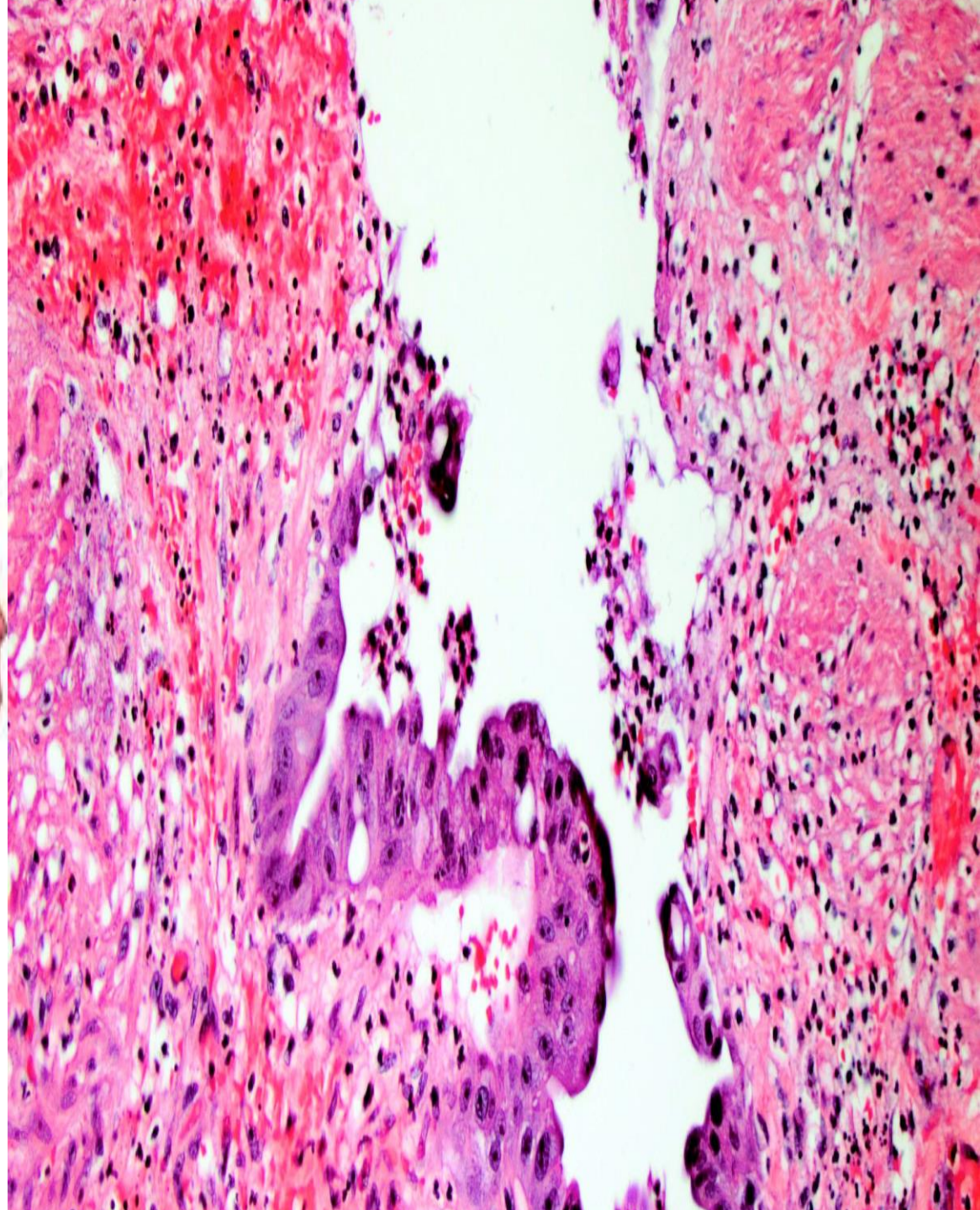
1-Chronic obstruction of bile flow by stones…distention & increased in the intraluminal pressure that compromise the blood flow.

2-Chemical irritation & inflammation of gallbladder wall

as the normal protective glycoprotein mucosal layer is disrupted exposing the mucosal epithelium to direct detergent action of the bile salts.

3-Release of hydrolytic enzymes from the mucosa (phospholipase) which hydrolyzed the biliary lecithin into lysolecithine, which is toxic to the mucosa.


Normal gallbladder
Inflamed gallbladder
Gallstone
Swollen mucosa



Gross:

enlarged, distended gallbladder; congested vessels .

Serosal and mucosal exudates,

thickened wall with edema and hemorrhage; ulcers with blood clot, pus and bile.

In 90% of cases, stones are present; obstruct the neck of gallbladder or the cystic duct.

When the lumen of gallbladder is filled with frank pus. This condition is called empyema of gallbladder.

In more severe cases the gallbladder is transformed into a green- black necrotic organ, termed gangeranous cholecyetitis.

Microscopically:

- Initially :edema,
- Vascular congestion, hemorrhage,
- later mucosal and mural necrosis with **neutrophils**; variable reactive epithelial changes resembling Dysplasia.

Complications of acute cholecystitis

1-**mucocele** of the gallbladder

2-Empyema: local abscess formation of the gallbladder.

3-Secondary bacterial infection of the biliary tree (**Ascending bacterial cholangitis**).

4-Gallbladder **perforation or ruptures: escape of the contents into the peritoneal cavity leads to localized or generalized peritonitis.**

5-Biliary – enteric fistula. due to ulceration of the gallbladder by a large cholesterol stone through the duodenum or the colon.

6- Pancreatitis.

7- Obstructive choleycystitis, small gall stones more dangerous because enter the cystic duct or common bile duct lead to obstruction & **secondary biliary cirrhosis**.

8- increase the risk of carcinoma of the gallbladder.

Acute **Acalculus** cholecystitis. **no gallstones**.

Represent 10% of cases.

Causes.

(1) The postoperative state after major nonbiliary surgery.

(2) Severe trauma (e.g. car accident……etc).

(3) Severe burns.

(4) Sepsis.

There are multiple events are thought to contribute to acalculus cholecystitis. Like dehydration, gallbladder stasis, shock & bacterial contamination.

Chronic cholecystitis:

Results from repeated attacks of acute cholecystitis, usually insidious, accompanied by dyspeptic symptoms or biliary colic.

Gallstones are almost always present.

95% of cases are associated with gallstones.

- Bacteria present in 11-30%, similar organisms as in acute cholecystitis (Escherichia coli & enterococci).
- 75% of cases are in female within the fourth decade of life

Morphology :

Gross:

Variable(may be normal size, contracted or enlarged)

thickening of gallbladder wall, variable adhesions.

Ulceration of mucosa is may be due to pressure by stones.

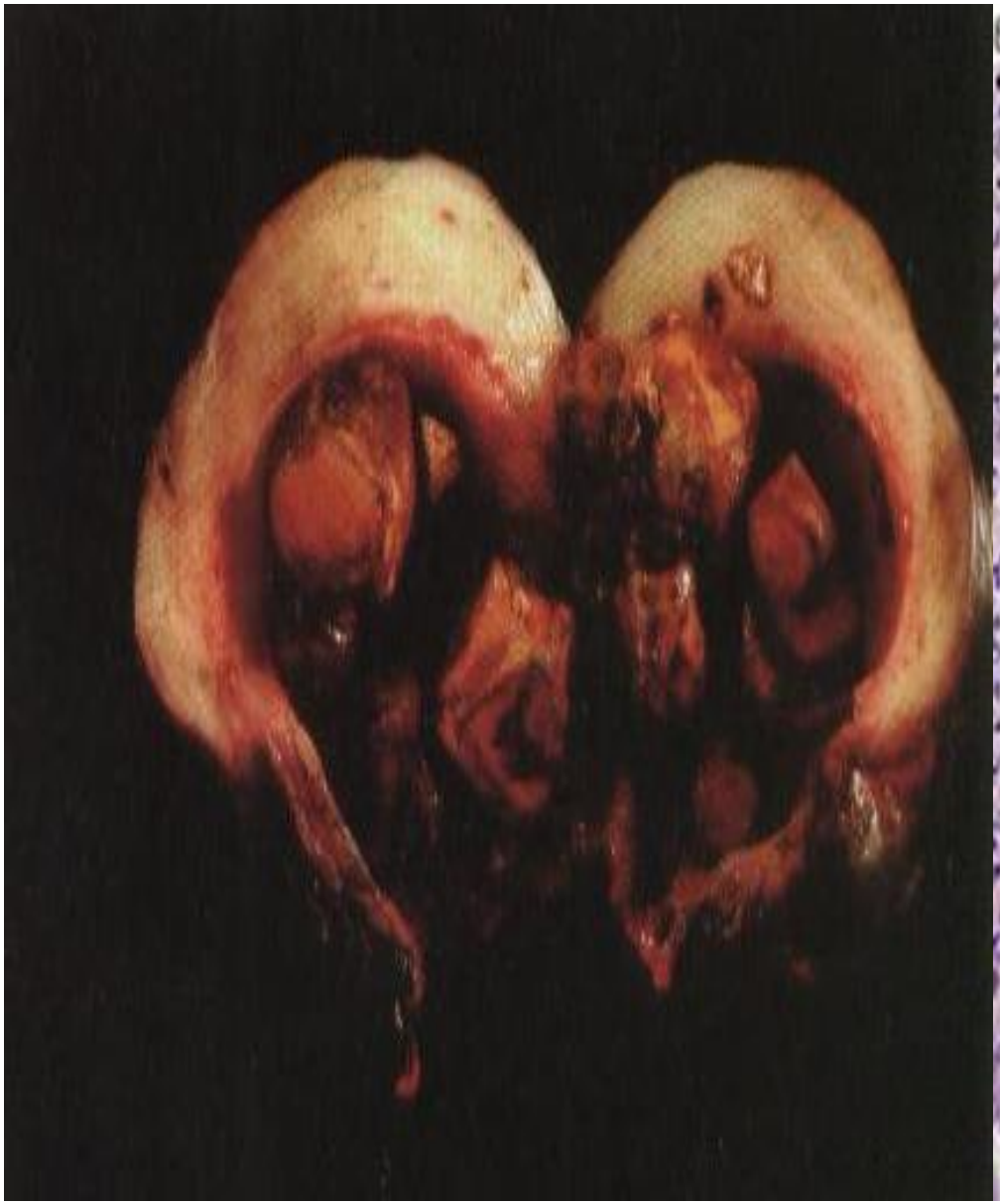
Mic.

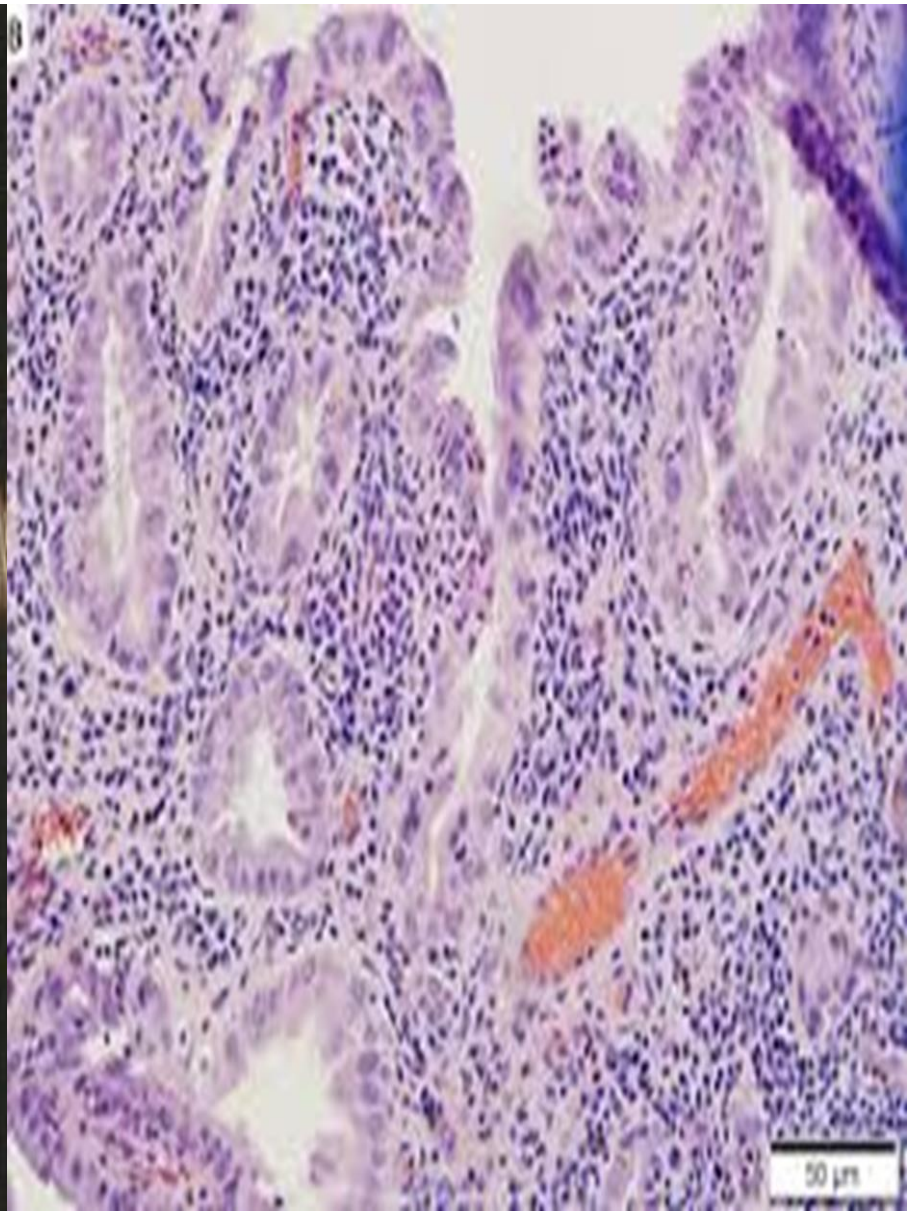
Mucosa shows variable degrees of mononuclear inflammatory cells infiltration & fibrosis.

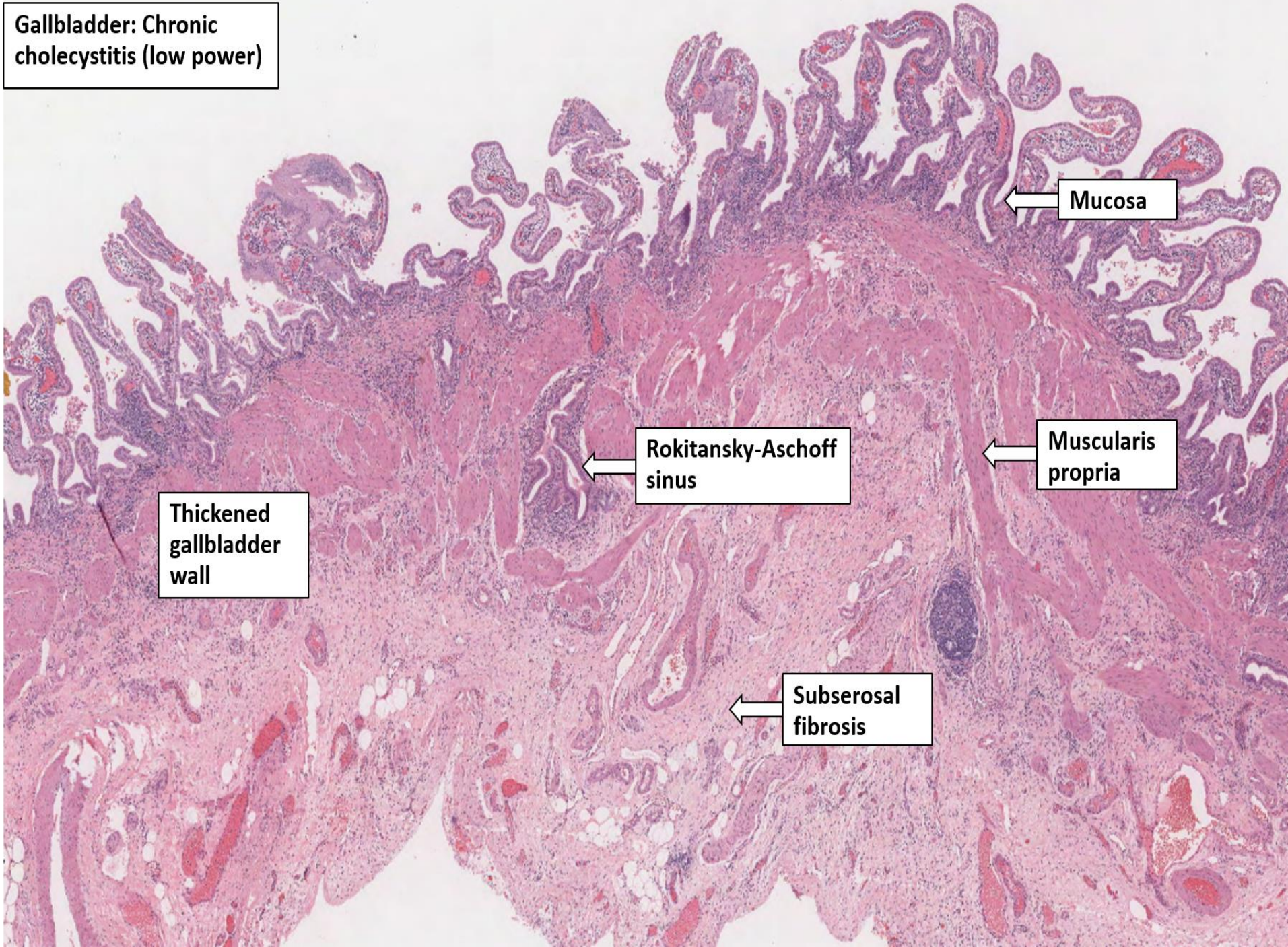
Surface epithelium may be relatively normal, atrophic, or shows hyperplastic or metaplastic changes.

The gallbladder wall may show fibrosis, smooth muscle hypertrophy.

Chronic cholecystitis






Gallbladder: Chronic cholecystitis (low power)
Mucosa
Rokitansky-Aschoff sinus
Muscularis propria
Thickened gallbladder wall
Subserosal fibrosis

Complications of chronic cholecystitis :

1. Acute cholecystitis.
2. Choledocholithiasis.
3. Acute pancreatitis.
4. Gallstone ileus.
5. Biliary fistulas.

Tumors of the gall bladder

Benign tumors: very rare as fibroma, lipoma & papilloma.

Malignant: Uncommon, Mainly **adenocarcinoma**

- female : male 3-4:1.
- seventh decade of life.
- Gallstones are present in 60% to 90% of cases.

Gall stone is an important factor in its causation

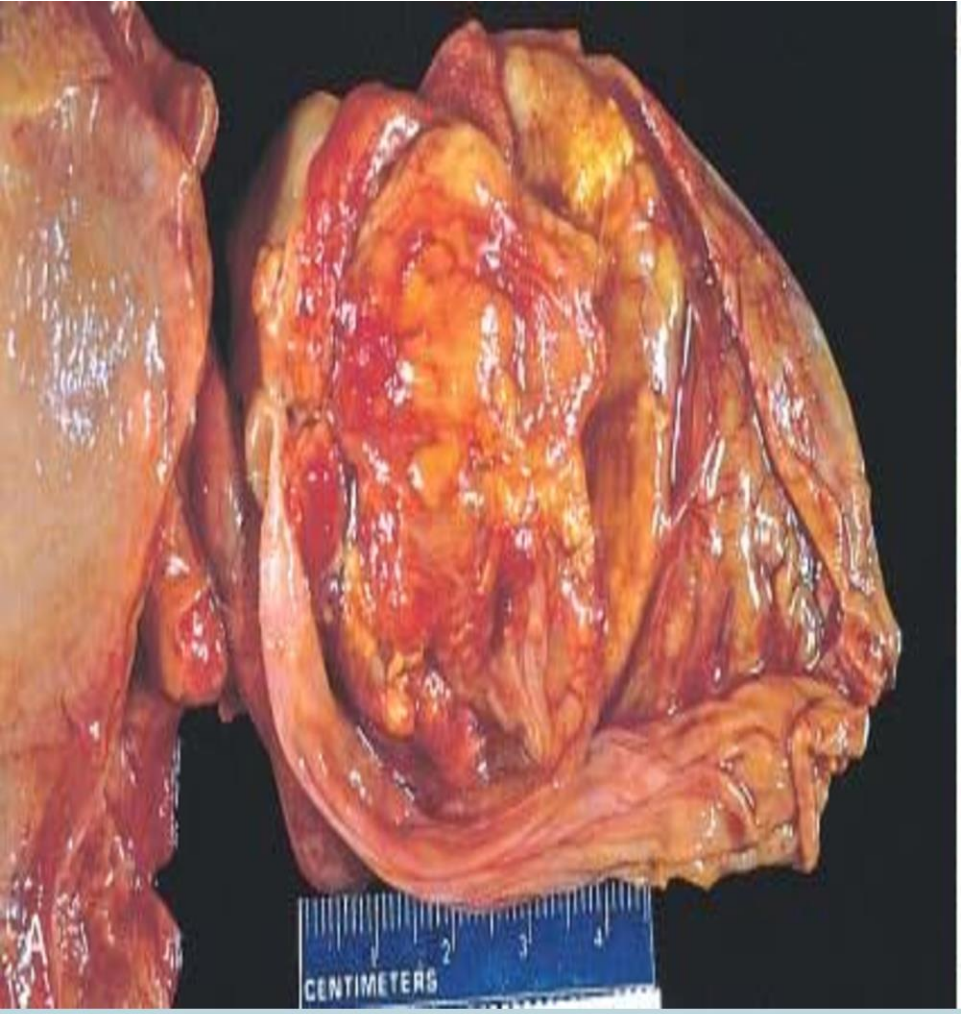
Usually slowly growing & infiltrating type,

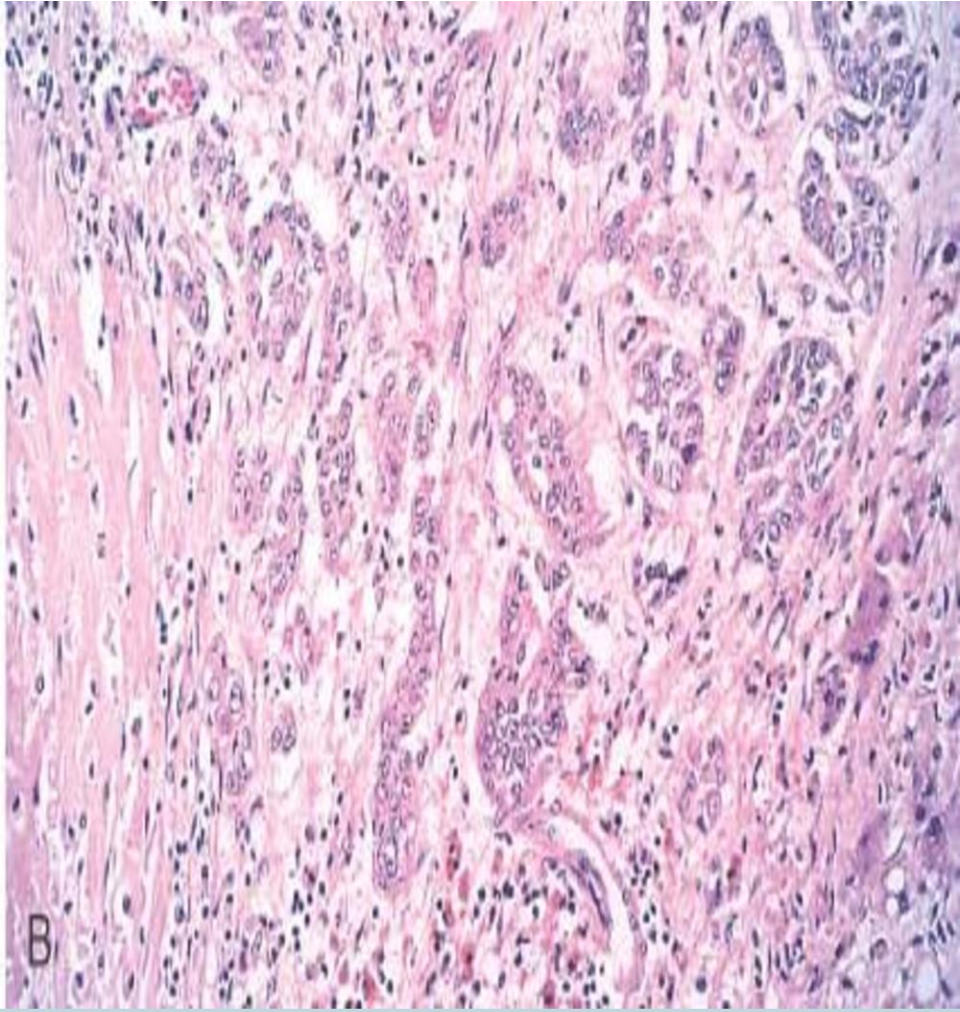
- Direct invasion to the liver or metastasized to the lymph nodes Bile duct carcinoma usually presented with **obstructive jaundice**.

Morphology of gall bladder ca

- **Gross: either**
- (1) Infiltrative (diffuse).
- (2) Exophytic (irregular, cauliflower mass).
- Sometimes contain gallstones
-

- **Micro:** most cases are adencarcinoma. Some are papillary & other are poorly differentiated carcinoma.





Adenocarcinoma of the gallbladder

Cholangitis

It is referred to acute inflammation of the wall of bile ducts, which always caused by bacterial infection of the normally sterile lumen.

Causes:

1. Gallstones.
2. Complications of biliary surgery.
3. Tumors.
4. catherterization of biliary.
5. Acute pancreatitis
6. Benign strictures.
7. Parasitic infections.

Pathogenesis of cholangitis

: two mechanisms are involved.

A.

Obstruction of biliary tree. (stones, tumors, ….etc)

B.

Bacterial infection. (Most likely enter biliary tree through the sphincter of oddi rather than hematogenous route. The bacteria are usually G-ve aerobes such as E.coli, Klebsiella, clostridium, bacteroides).

These two mechanisms are must be occur together.

Symptoms of cholangitis: include fever, abdominal pain, and jaundice

Carcinoma of biliary tree.(cholangiocarcinoma).

It is referred to carcinoma of intrahepatic &extrahepatic ducts.

Those of **intrahepatic bile ducts** are closely resemble to HCC.

While those of **extrahepatics d**ucts are usually cause **painless, progressive deepening jaundice.**

more in elderly male.

Risk factors of chlangiocarcinoma:

1-Primary sclerosing cholangitis.

2-Inflammatory bowel diseases.

3-Gallstones.

Morphology of cholangiocarcinoma

Gross. Is either:

1. **Grey, firm nodules.**
2. **Diffuse infiltrative lesions.**

Mic.

- **cholangiocarcinoma is arising from bile duct epithelium.**

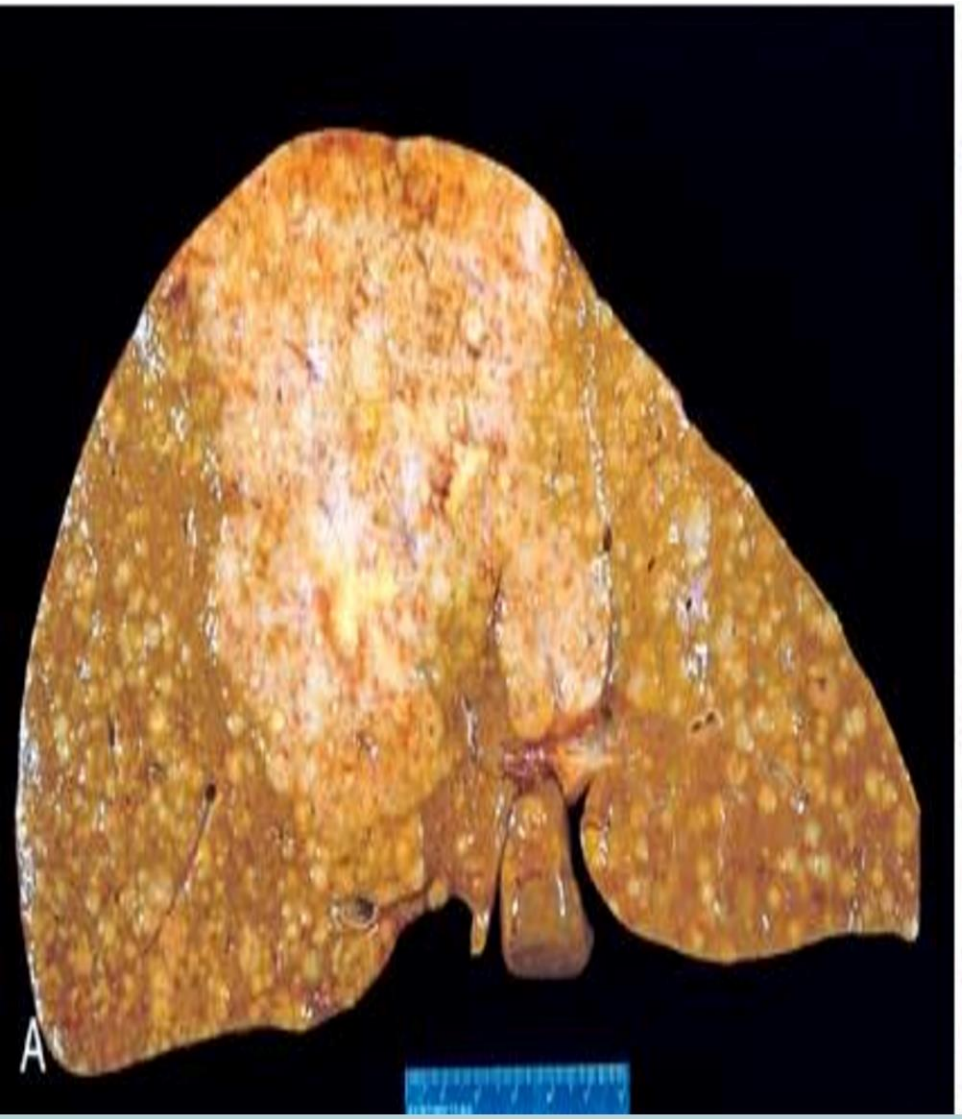
It resemble **adenocarcinoma**, mostly moderately differentiated sclerosing carcinoma.

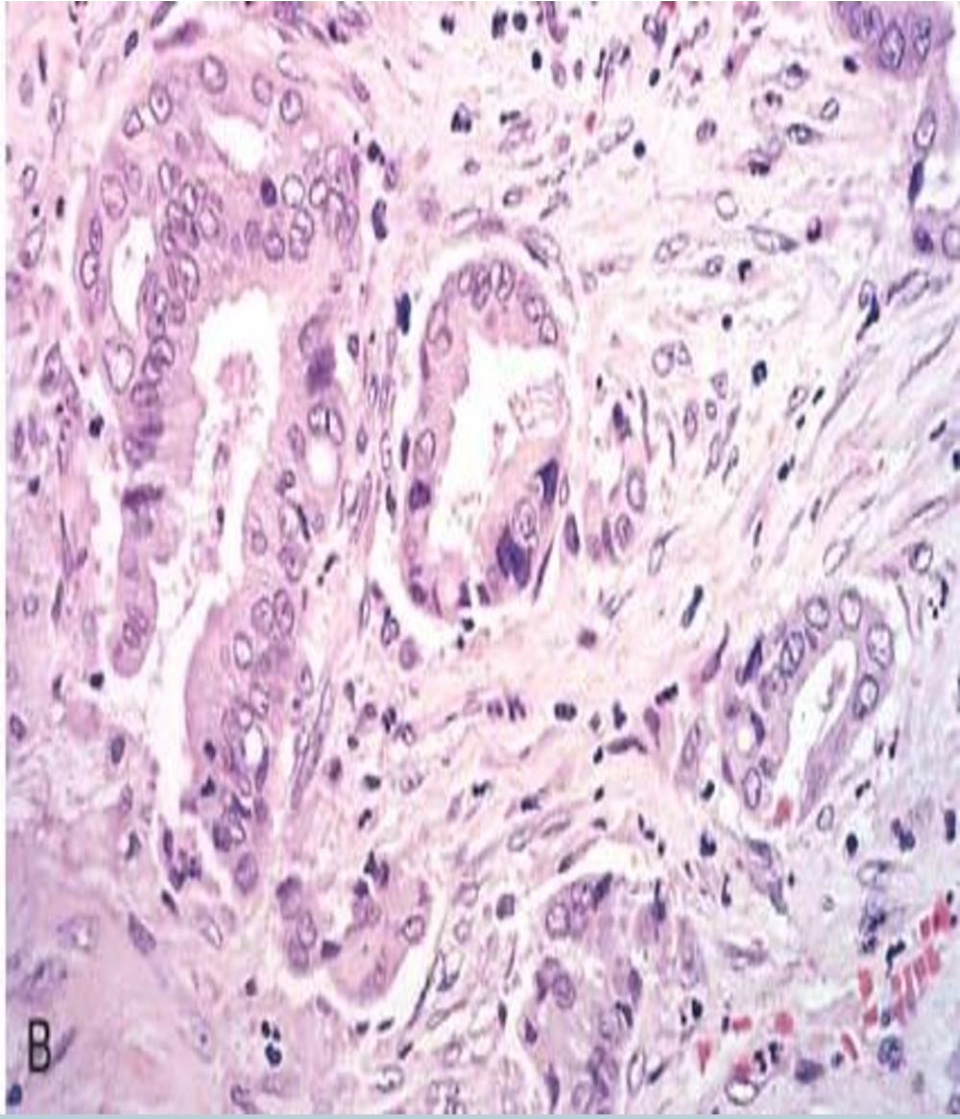
- glandular, or trabecular structures that are lined by anaplastic cuboidal low columnar epithelial cells ; with dense collagenous stroma separate the glandular elements. **(desmoplastic carcinoma).**

Cholangiocarcinoma

Hematogenous metastasis to the lung, bones (mainly vertebrae), adrenals & brain in 50% of the cases., but less frequent with hepatocellular carcinoma.

Also 50% of cholangiocarcinoma spread by lymph node metastasis, mainly peri-hilar, peri-pancreatic & Para-aortic lymph nodes above & below the diaphragm, also less frequently with hepatocellular carcinoma.





CHOLANGIOCARCINOMA