

PATHOLOGY AND PATHOGENESIS OF CHOLECYSTITIS

Pathology and pathogenesis of cholecystitis

Objectives:

- Recognize the predisposing factors of gall stones and cholecystitis.
- Describe the different types of cholecystitis.
- Understand the pathogenesis of acute and chronic cholecystitis

Disorders of the Gallbladder
CHOLELITHIASIS (GALLSTONES)

Disorders of the Gallbladder

CHOLELITHIASIS (GALLSTONES)

- Majority of gallstones (>80%) are "silent," and most individuals remain free of biliary pain or stone complications for decades.
- There are two main types of gallstones:
 - 1. *Cholesterol Stones:***
 - about 80% are cholesterol stones
 - containing more than 50% of crystalline cholesterol monohydrate
 - 2. *Pigment Stones***
 - *composed predominantly of bilirubin calcium salts*

Prevalence and Risk Factors of gallstones

- ***Age and gender:***

- The prevalence of gallstones increases throughout life.
- The prevalence in women of all ages is about twice as high as in men.

- ***Ethnic and geographic:***

- Cholesterol gallstone prevalence approaches 50% to 75% in certain Native American populations (Pima, Hopi, and Navajo), seems to be related to biliary cholesterol hypersecretion.

- ***Heredity:***

- A positive family history imparts increased risk, associated with impaired bile salt synthesis and secretion.

- ***Environment:***

- Estrogens increase hepatic cholesterol uptake and synthesis, leading to excess biliary secretion of cholesterol. (oral contraceptive use and with pregnancy).
- Obesity, rapid weight loss, and treatment with the hypocholesterolemic agent are strongly associated with increased biliary cholesterol secretion

- ***Acquired disorders:***

- Any condition in which gallbladder motility is reduced predisposes to gallstones, such as pregnancy, rapid weight loss, and spinal cord injury.

Prevalence and Risk Factors of gallstones

Cholesterol Stones

- Demography: Northern Europe, North and South America, 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

Pathogenesis of Cholesterol Stones

- Cholesterol is rendered soluble in bile by aggregation with water-soluble bile salts and water-insoluble lecithins, both of which act as detergents.
- *When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals.*
- *Cholesterol gallstone formation involves three simultaneous defects:*

Pathogenesis of Cholesterol Stones

- 1) ***Supersaturation of bile with cholesterol:*** the result of hepatocellular hypersecretion of cholesterol.
- 2) ***Gallbladder hypomotility.*** It promotes nucleation typically around a calcium salt crystal nidus.
- 3) ***Mucus hypersecretion in the gallbladder:*** This traps the crystals, permitting their aggregation into stones.

Pathogenesis of Pigment Stones

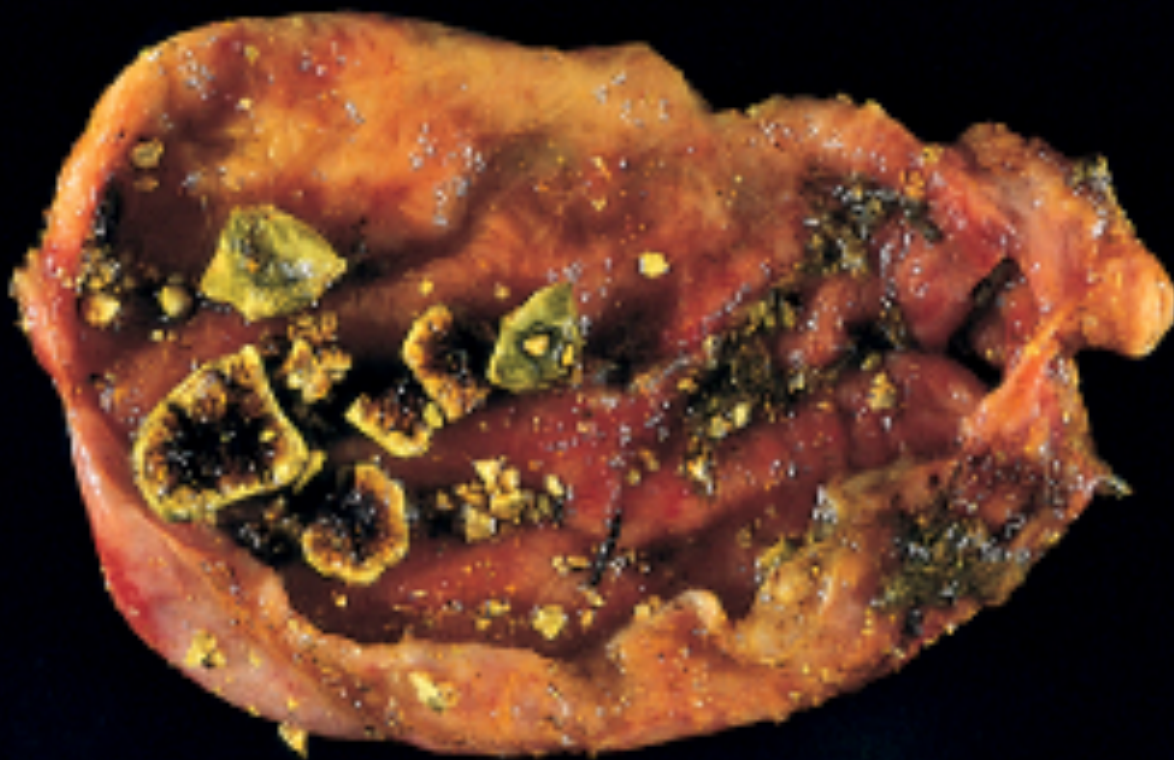
- Pathogenesis of pigment stones is based on the presence in the biliary tract of unconjugated bilirubin (which is poorly soluble in water) and precipitation of calcium bilirubin salts.
- Thus, infection of the biliary tract, as with *Escherichia coli* or *Ascaris lumbricoides* or by the liver fluke *Opisthorchis sinensis*, increases the likelihood of pigment stone formation.
- Chronic hemolytic conditions also promote formation of unconjugated bilirubin in the biliary tree.

Morphology

- **Cholesterol stones** arise exclusively in the gallbladder and are composed of cholesterol ranging from 100% pure (which is rare) down to around 50%.
- pale yellow, round to ovoid to faceted, and have a finely granular, hard external surface.
- **Stones composed largely of cholesterol are radiolucent; only 10% to 20% of cholesterol stones are radio-opaque.**

Morphology

- **Pigment gallstones** are black and brown.
- "Black" pigment stones are found in sterile gallbladder.
- "Brown" pigment stones are found in infected intrahepatic or extrahepatic bile ducts.
- Both are soft and usually multiple.
- Brown stone are greasy.
- Because of calcium carbonates and phosphates, **approximately 50% to 75% of black stones are radio-opaque.**





Cholesterolosis

- An incidental finding, is **cholesterolosis**. Cholesterol hypersecretion by the liver promotes excessive accumulation of cholesterol esters within the lamina propria of the gallbladder. The mucosal surface is studded with minute yellow flecks, producing the "strawberry gallbladder"

Clinical Features of Gallstones

- 70% to 80% of patients remain asymptomatic
- Symptoms:
 - spasmodic or "colicky" right upper quadrant pain, which tends to be excruciating. It is usually due to obstruction of bile ducts by passing stones.

Complications of Gallstones

- Empyema
- Perforation
- Fistula
- Inflammation of the biliary tree (cholangitis)
- Pancreatitis
- Obstructive cholestasis
 - The larger the calculi, the less likely they are to enter the cystic or common ducts to produce obstruction; it is the very small stones, or "gravel," that are the more dangerous.
 - Occasionally, a large stone may erode directly into an adjacent loop of small bowel, generating intestinal obstruction ("gallstone ileus")
- Gallbladder carcinoma
 - The most important risk factor associated with gallbladder carcinoma is gallstones (cholelithiasis), which are present in 95% of cases

CHOLECYSTITIS

CHOLECYSTITIS

- Inflammation of the gallbladder may be acute, chronic, or acute superimposed on chronic. It almost always occurs in association with gallstones.

Acute Cholecystitis: *Two types*

Acute calculous cholecystitis & Acute acalculous cholecystitis

- **Acute calculous cholecystitis** is an acute inflammation of the gallbladder, precipitated 90% of the time by obstruction of the neck or cystic duct.

It is the primary complication of gallstones and the most common reason for emergency cholecystectomy.

- **Acute acalculous cholecystitis** occurs in the absence of gallstones, generally in severely ill patient.
 - Most cases occur in the following circumstances:
 - (1) the postoperative state after major, nonbiliary surgery
 - (2) severe trauma (motor vehicle accidents, war injuries)
 - (3) severe burns
 - (4) multisystem organ failure
 - (5) sepsis
 - (6) prolonged intravenous hyperalimentation
 - (7) the postpartum state.

Acute Cholecystitis: Pathogenesis

- Acute calculous cholecystitis results from chemical irritation and inflammation of the obstructed gallbladder. *These events occur in the absence of bacterial infection; only later in the course may bacterial contamination develop.*

Acute Cholecystitis:

Morphology

- In **acute cholecystitis**, the gallbladder is usually enlarged and tense, and bright red to green-black. The serosal covering is frequently layered by fibrin and, in severe cases, by exudate.
- There are no morphologic differences between acute acalculous and calculous cholecystitis, except for the absence of macroscopic stones in the former. In the latter instance, an obstructing stone is usually present in the neck of the gallbladder or the cystic duct.

Acute Cholecystitis:

Morphology

- The gallbladder lumen is filled with a cloudy or turbid bile that may contain fibrin and frank pus, as well as hemorrhage. When the contained exudate is virtually pure pus, the condition is referred to as **empyema of the gallbladder**.
- In mild cases, the gallbladder wall is thickened, edematous, and hyperemic.
- In more severe cases, it is transformed into a green-black necrotic organ, termed **gangrenous cholecystitis**, with small-to-large perforations.



Acute Cholecystitis:

Clinical Features

- Progressive right upper quadrant or epigastric pain, frequently associated with mild fever, anorexia, tachycardia, sweating, and nausea and vomiting. The upper abdomen is tender. Most patients are free of jaundice
- when the cystic duct is obstructed in acute calculous cholecystitis, patient present with remarkable sudden severe upper abdominal pain radiating to right shoulder. This constitute an acute surgical emergency
- it may present with mild symptoms that resolve without medical intervention.

Acute Cholecystitis: Clinical Features

- Clinical symptoms of acute acalculous cholecystitis tend to be more insidious, since symptoms are obscured by the underlying conditions precipitating the attacks. A higher proportion of patients have no symptoms referable to the gallbladder. The incidence of gangrene and perforation is much higher than in calculous cholecystitis.

Chronic cholecystitis

Chronic cholecystitis

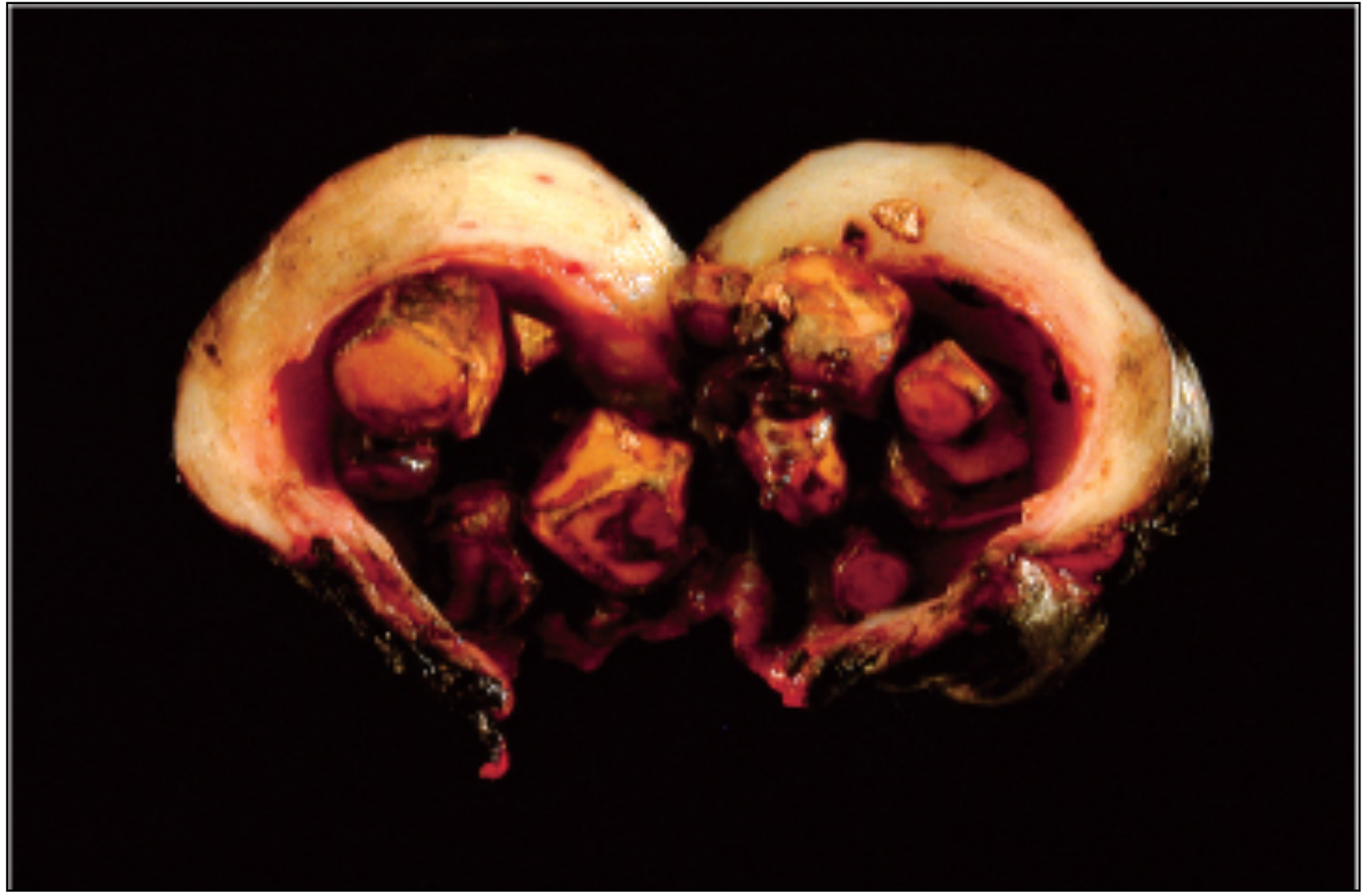
- Chronic cholecystitis may be a sequel to repeated bouts of mild to severe acute cholecystitis, but in many instances, it develops in the apparent absence of antecedent attacks.
- It is associated with cholelithiasis in over 90% of cases.

Chronic cholecystitis

- The symptoms of calculous chronic cholecystitis are similar to those of the acute form and range from biliary colic to indolent right upper quadrant pain and epigastric distress.
- Patients often have intolerance to fatty food, belching and postprandial epigastric distress, sometimes include nausea and vomiting.

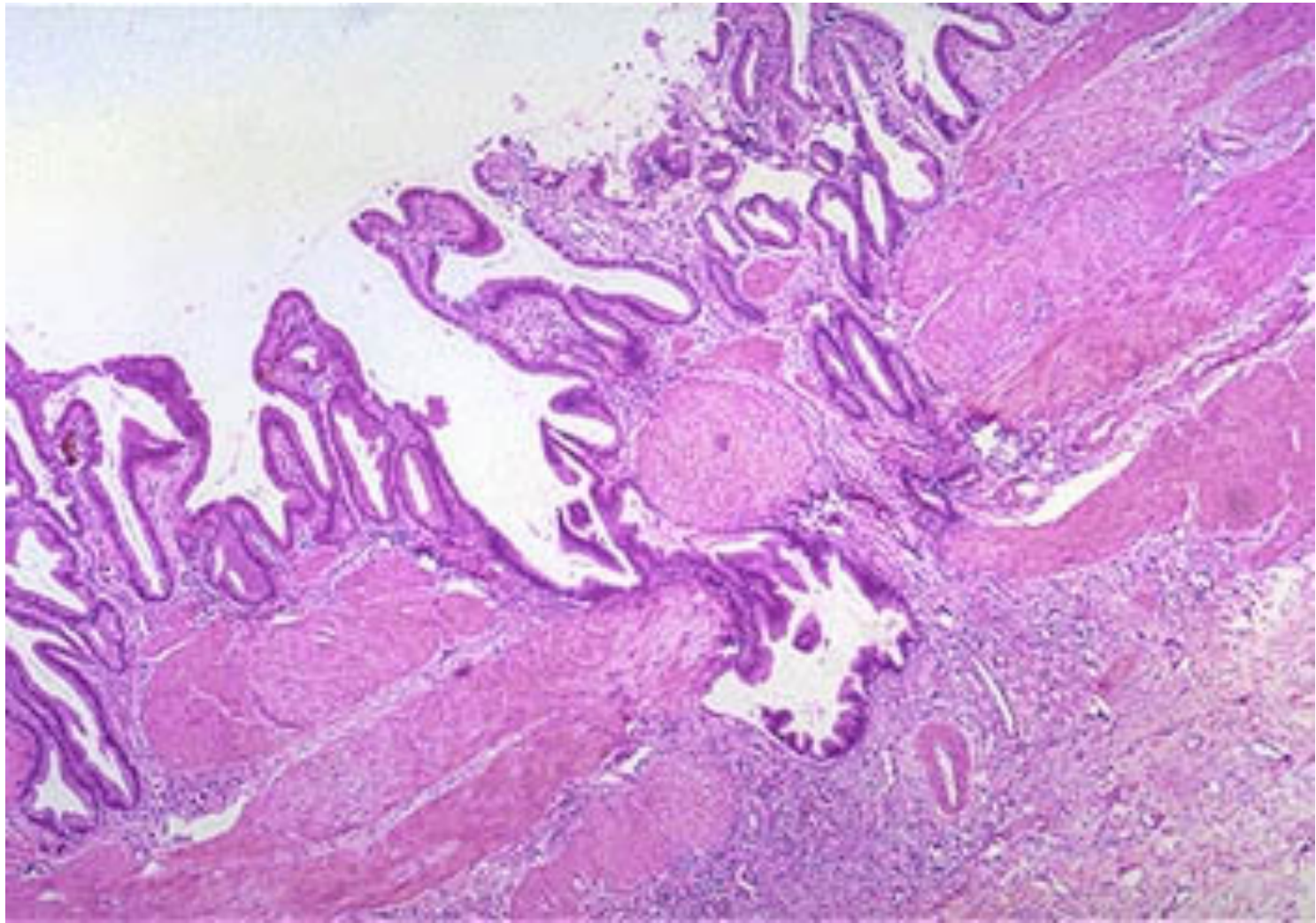
Morphology: Gross

- The morphologic changes in chronic cholecystitis are extremely variable and sometimes minimal. Gall bladder may be contracted (fibrosis), normal in size or enlarged (from obstruction). The wall is variably thickened. Stones are frequent.



Morphology: Histology

- The degree of inflammation is variable. Outpouchings of the mucosal epithelium through the wall (**Rokitansky-Aschoff sinuses**) may be quite prominent.
- **Extensive dystrophic calcification** within the gallbladder wall may yield a **porcelain gallbladder**, occur rarely, notable for a markedly increased incidence of associated cancer.
- **Xanthogranulomatous cholecystitis** is also a rare condition in which the gallbladder is shrunken, nodular, fibrosed and chronically inflamed with abundant lipid filled macrophages.
- **Hydrops of the gallbladder** an atrophic, chronically obstructed gallbladder may contain only clear secretions



Complications: Acute and chronic cholecystitis

- Bacterial superinfection with cholangitis or sepsis
- GB perforation & local abscess formation
- GB rupture with diffuse peritonitis
- Biliary enteric (cholecystenteric) fistula with drainage of bile into adjacent organs, and potentially gallstone-induced intestinal obstruction (ileus)
- Aggravation of pre-existing medical illness, with cardiac, pulmonary, renal, or liver decompensation