King Saud University
College of Medicine
Second year – GIT block

Pathology and Pathogenesis of Cholecystitis

Lecture 13

4 3 0 Pathology Team

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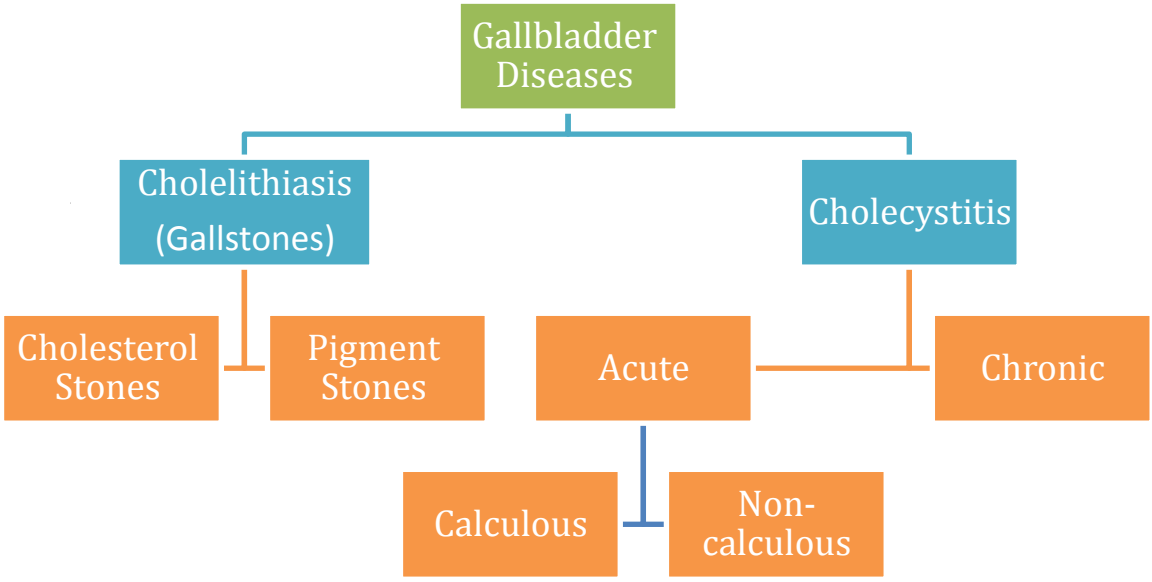


1. Cholelithiasis (Gallstones):

Majority of gallstones (>80%) are "silent," and most individuals remain free of biliary pain or stone complications for decades.

Types:

1. Cholesterol stones(more common): about 80% of the cases, containing more than 50% of crystalline cholesterol monohydrate.
2. pigment stones: the remainder are composed predominantly of bilirubin calcium salts

Prevalence and Risk Factors:

Cholesterol Stones	***Pigment Stones***
Demography: Northern Europe, North and South America, Native Americans, Mexican Americans	Demography: Asian more than Western, rural more than urban
Advancing age	Chronic hemolytic syndromes
Female sex hormones	Biliary infection
Female gender	Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency
Oral contraceptives	
Pregnancy	
Obesity	
Rapid weight reduction	
Gallbladder stasis	
Inborn disorders of bile acid metabolism	
Hyperlipidemia syndromes	

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 four simultaneous defects:

1. Supersaturation of bile with cholesterol is the result of hepatocellular hypersecretion of cholesterol.
2. Cholesterol nucleation (formation of crystals) in bile is accelerated.
3. Gallbladder hypomotility develops. It promotes nucleation typically arround a calcium salt crystal nidus (the point of origin).
4. Mucus hypersecretion in the gallbladder to trap the crystals, enhancing their aggregation into stones.

Prolonged fasting, pregnancy, rapid weight loss, total parenteral nutrition, and spinal cord injury also promote stone formation.

Pathogenesis of Pigment Stones:

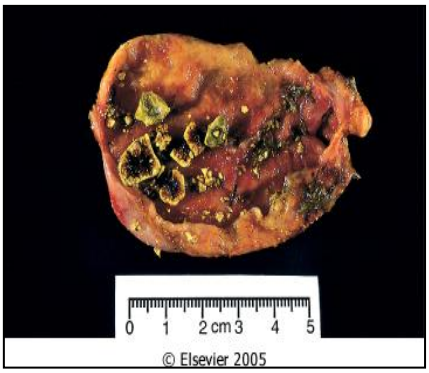
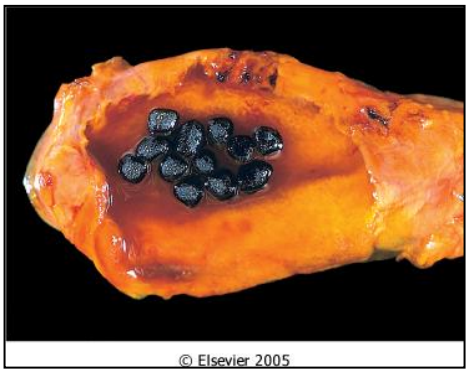
Pathogenesis of pigment stones is based on the presence in the biliary tract of unconjugated bilirubin (which is poorly soluble in water) and precipitation of calcium bilirubin salts.

Thus, infection of the biliary tract, such as: bacterial infections; **E.coli infection** *(the most common one)* or parasitic infections; **Ascaris lumbricoides** or by the liver fluke Opisthorchis sinensis (parasitic in the liver and biliary tract), increases the likelihood of pigment stone formation.

Chronic hemolytic conditions also promote formation of unconjugated bilirubin in the biliary tree.

Morphology:

Type	cholesterol	pigment
Colour	pale yellow	black and brown
Location	gallbladder	"Black" pigment stones are found in sterile gallbladder. "Brown" pigment stones are found in infected intrahepatic or extrahepatic bile ducts.
Composed Of	cholesterol ranging from 100% pure (which is rare) down to around 50%.	unconjugated bilirubin, calcium carbonates and phosphates
Features	- round to ovoid to faceted, - finely granular - hard external surface.	- Both are soft and usually multiple. - Brown stone are greasy.
Radiological Appearance	- Stones composed largely of cholesterol are radiolucent (not shown in x-ray); only 10% to 20% of cholesterol stones are radio-opaque	Approximately 50% to 75% of black stones are radio-opaque (because there's a lot of calcium)

Grossly		

Clinical Features:

70% to 80% of patients remain asymptomatic throughout their lives.

Symptoms: spasmodic or "colicky" right upper quadrant pain, which tends to be excruciating and often will radiate to the right shoulder. It is usually due to obstruction of bile ducts by passing stones.

Complications: include empyema, perforation, fistulae, inflammation of the biliary tree (cholangitis), and obstructive cholestasis or **pancreatitis** with ensuing problems.

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 because they tend to block ducts eg. The pancreatic duct.

- Occasionally, a large stone may erode directly into an adjacent loop of small bowel, generating intestinal obstruction ("gallstone ileus").

What is "gallstone ileus"?

Ileus or gastrointestinal atony is a disruption of the normal propulsive gastrointestinal motor activity duo to obstruction of the intestine by gallstones.

- Direct extension = increased risk for carcinoma of the gallbladder if the gallstone is more than 1 cm

Cholesterolosis:

Definition: cholesterol hypersecretion by the liver.

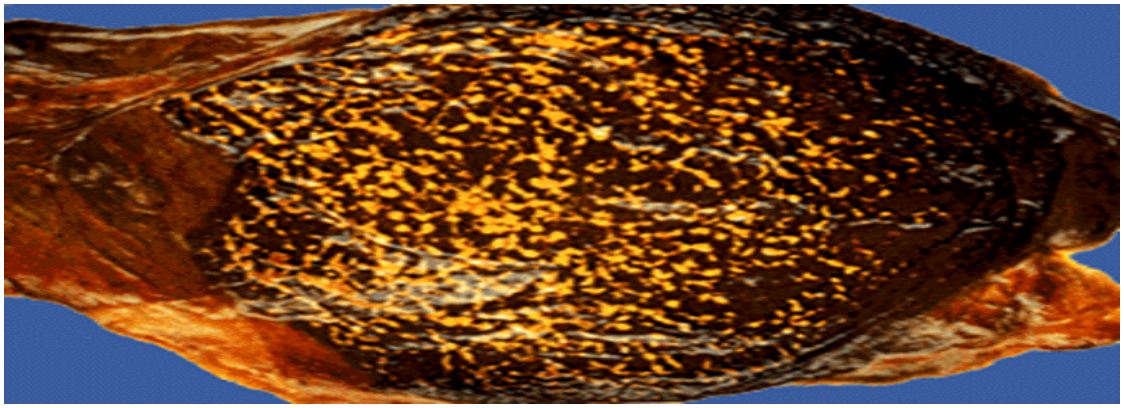
Microscopically:

They're characterised by the presence of foamy cells (containing cholesterol ester) in the lamina propria.

Grossly:

The gallbladder mucosal surface appears green in colour, and within it you will find yellow streaks that correspond with the foamy cells "strawberry gallbladder".

Strawberry Gallbladder



2. Cholecystitis:

Definition: inflammation of the gallbladder that may be acute, chronic, or acute superimposed on chronic.

It almost always occurs in association with gallstones.

Types:

A. Acute Cholecystitis:

Subtypes	Acute Calculous Cholecystitis	Acute Acalculous Cholecystitis
Definition	It is an acute inflammation of the gallbladder, precipitated 90% of the time by obstruction of the neck or cystic duct. N.B: It is the primary complication of gallstones and the most common reason for emergency cholecystectomy.	It occurs in the absence of gallstones, generally in severely ill patient: 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.

Pathogenesis of acute calculous cholecystitis:

It 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.

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 exudates (neutrophils are seen under the microscope).

— 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.

— 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. This is a very serious complication that can cause death → emergency surgery must be performed.

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.

Type	Acute Calculous Cholecystitis	Acute Acalculous Cholecystitis
Features	may appear with remarkable suddenness and constitute an acute surgical emergency or may present with mild symptoms that resolve without medical intervention.	- Tend to be more insidious, since symptoms are obscured by the underlying conditions precipitating the attacks. e.g: burns, sepsis... etc - 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.

B. Chronic cholecystitis:

Chronic cholecystitis may be a sequel to repeated attacks of mild to severe acute cholecystitis, but in many instances, it develops in the apparent absence of antecedent (previous) attacks.

It is associated with cholelithiasis in over 90% of cases.

Symptoms:

- 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, and postprandial (after meals) epigastric distress, sometimes include nausea and vomiting.

Morphology:

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.

- On histology, the degree of inflammation is variable. Outpouchings of the mucosal epithelium through the wall (**Rokitansky-Aschoff sinuses** is used as a diagnostic tool) may be quite prominent.

- Rarely, extensive dystrophic calcification within the gallbladder wall may yield a **porcelain gallbladder**, 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.

- Finally, an atrophic, chronically obstructed gallbladder may contain only clear secretions, a condition known as **hydrops of the gallbladder**.

Complications of acute and chronic cholecystitis:

- Bacterial superinfection with cholangitis or sepsis
- Gallbladder (GB) perforation & local abscess formation.
- GB ruptures 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.