GIT Module, Pathology
GALLBLADDER DISORDERS

Dr. Wajd Althakfi, MD

Consultant Histopathology

King Saud University -
Faculty of Medicine

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Objectives

- Introduction
- Recognize the predisposing factors of gall stones (Cholelithiasis) and cholecystitis
- Describe the different types of cholecystitis
- Understand the pathogenesis of acute and chronic cholecystitis
- Understand the gallbladder carcinoma

GALLSTONES (CHOLETHITHIASIS)

Introduction

- Affects 10-20% of adults in Western countries in Northern Hemisphere, 20-40% in Latin American countries & only 3-4% in Asian countries
- Majority of gallstones (>80%) are "silent," and most individuals remain free of biliary pain or stone complications for decades

- **Types:**
  - Cholesterol Stones: Contain crystalline cholesterol monohydrate (80%)
  - Pigment Stones: Made of bilirubin calcium salts

Prevalence and Risk Factors

- **Age and gender:**
  - Prevalence increases throughout life especially above age of 40
  - 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

Prevalence and Risk Factors

- **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

Cholesterol Stones

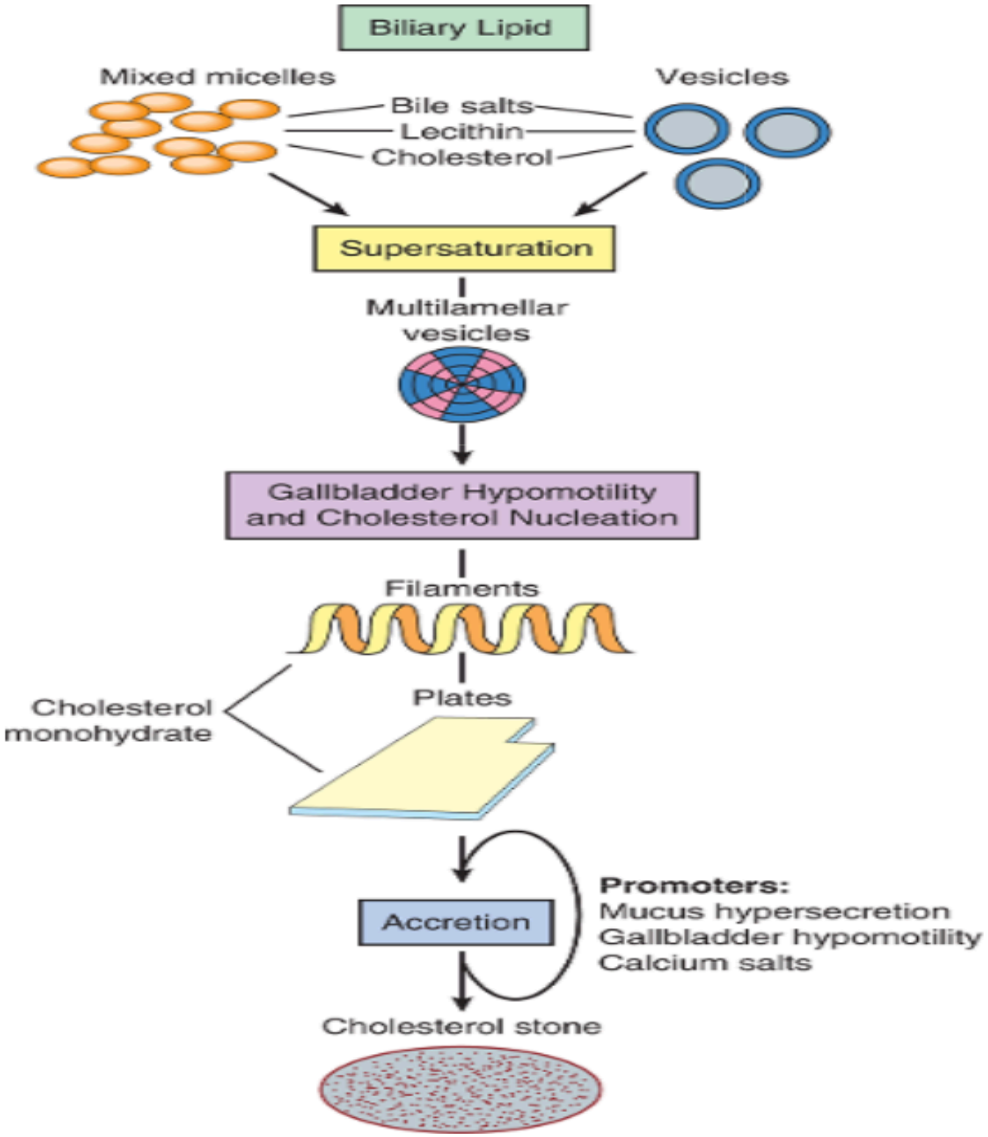
- Demography: Northern Europe, North and South America, Native Americans, Mexican Americans
- Advancing age
- Female sex hormones:
  - Female gender
  - Oral contraceptives
  - Pregnancy
- Obesity and insulin resistance
- Rapid weight reduction
- Gallbladder stasis
- Inborn disorders of bile acid metabolism
- 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

The four contributing factors for cholelithiasis

1. Supersaturation
2. Gallbladder hypomotility
3. Crystal nucleation
4. Accretion within the gallbladder mucous layer



Pathogenesis

- Bile formation is the only significant pathway for elimination of excess cholesterol from the body; either as free cholesterol or as bile salts
- Cholesterol is water insoluble; so it binds to bile salts & lecithins in the bile
- For stones to be formed:
    1. Cholesterol concentration exceeds solubilizing capacity of bile → bile is supersaturated with cholesterol → it is rendered insoluble → solid cholesterol monohydrate crystals are formed
    2. Gallbladder hypomotility "stasis" → allows time for nucleation and aggregation of cholesterol crystals
    3. Mucus hypersecretion → trap crystals and enhance their aggregation

Pathogenesis

***Cholesterol gallstone formation involves three simultaneous defects*:**

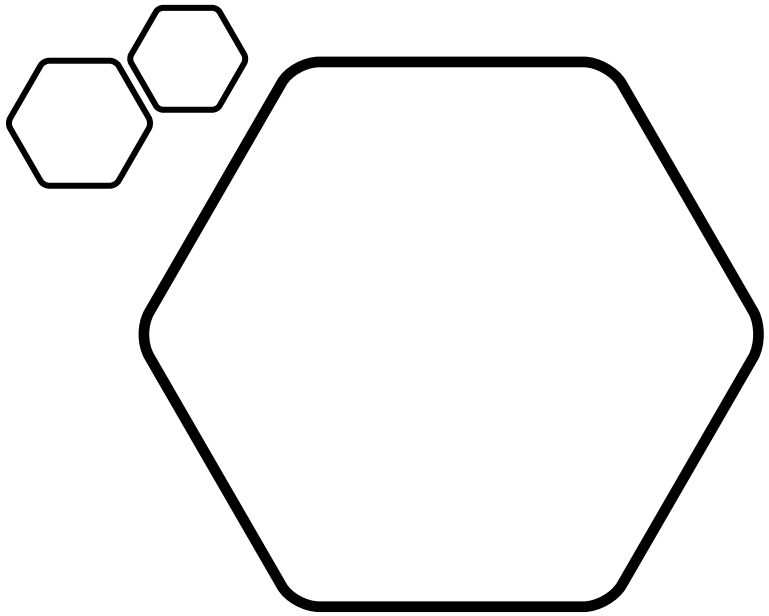
1) **Supersaturation of bile with cholesterol:** the result of hepatocellular hypersecretion of cholesterol
2) **Gallbladder hypomotility:**It promotes nucleation typically around a calcium salt crystal nidus
3) **Mucus hypersecretion in the gallbladder:** This traps the crystals, permitting their aggregation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

Pathogenesis

- High concentration of unconjugated bilirubin in bile precipitates and forms stones “Ex. Chronic hemolytic anemias & biliary tract infections”

- These are composed predominantly of insoluble calcium bilirubinate salts

Morphology

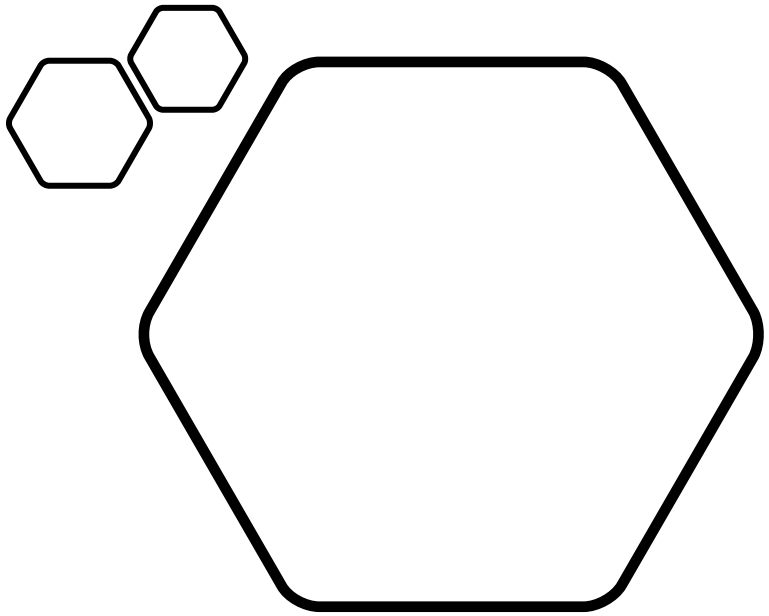


- Arise exclusively in the gallbladder a
- Composed mainly of of cholesterol (50-100%)

- Pure cholesterol stone:
  - ✓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 - Cholesterol gallstones

Morphology



- Pigment gallstones:
  - ✓Black and brown
  - ✓Black stones found in sterile gallbladder
  - ✓Brown stones 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

Morphology - Pigment gallstones

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

- 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: empyema, perforation, fistula, cholangitis, pancreatitis, gallstone ileus “intestinal obstruction”, gallbladder carcinoma

CHOLECYSTITIS

Acute Cholecystitis

CHOLECYSTITIS

- Inflammation of the gallbladder
- Acute, chronic, or acute superimposed on chronic
- It almost always occurs in association with gallstones
- Two types:
  1. Acute calculous cholecystitis
  2. Acute acalculous cholecystitis

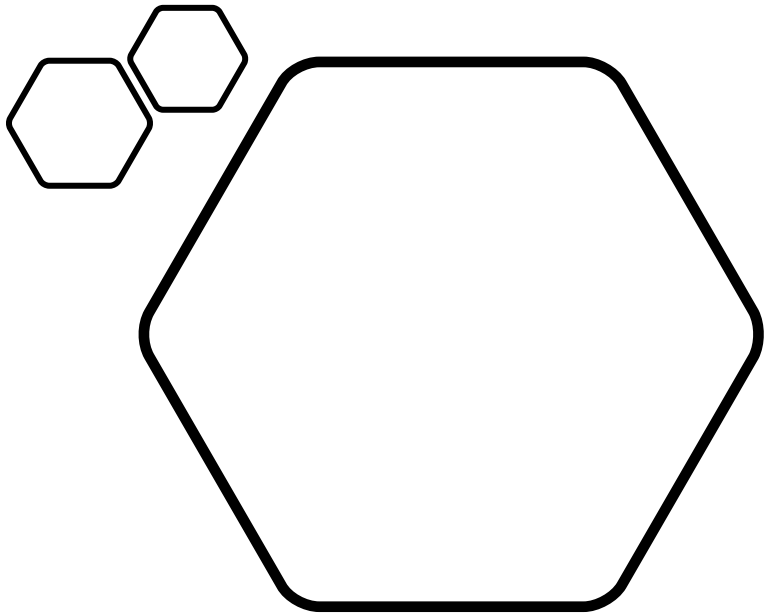
1. Acute Calculous Cholecystitis

- Acute inflammation of GB that contains stones
- Is precipitated in 90% by obstruction of cystic duct or gallbladder neck
- Is most common major complication of gallstones & most common reason for emergency cholecystectomy

Acute Cholecystitis - Pathogenesis

- Obstruction of bile outflow ➔ chemical irritation & inflammation of GB wall
- Mechanisms:
  - Phospholipases derived from mucosa ➔ hydrolyze biliary lecithin to lysolecithin which is toxic to mucosa
  - Disruption of normally protective glycoprotein mucous layer ➔ exposes
  - mucosal epithelium to detergent action of bile salts
  - Prostaglandins released within distended GB wall ➔ enhance mucosal & mural inflammation
  - Distention & ↑ intraluminal pressure ➔ compromise blood flow to mucosa

Gross Morphology



- Enlarged and tense, and bright red to green-black
- Serosa is frequently covered by fibrin or fibrinopurulent exudate.
- The lumen is filled with a cloudy or pure pus, “empyema”
- The wall is thickened, edematous, and hyperemic
- Transformed into a green-black necrotic “gangrenous cholecystitis”
- No histological differences between acute acalculous and calculous cholecystitis, except for the absence of macroscopic stones in the former

Gross Morphology

Clinical Features

- Severe, usually constant right upper abdominal pain, radiating to right shoulder
- Lasts > 6 hrs
- Fever, nausea, leukocytosis & prostration are classic
- RUQ tenderness & rigidity
- Conjugated hyperbilirubinemia “ if CBD is obstructed
- Mild attacks usually subside spontaneously within 1-10 days
- Recurrence is common
- ~ 25% are ill enough → emergency surgery

2. Acute Acalculous Cholecystitis

- No stones found in 5-12% of GBs removed for acute cholecystitis
- Most occur in seriously ill patients
- Occur in the following circumstances:
  - ✓ Following major surgery
  - ✓ Severe trauma
  - ✓ Severe burns
  - ✓ Multisystem organ failure
  - ✓ Sepsis
  - ✓ the postpartum state

✓Other contributing factors: dehydration, GB stasis & sludging, vascular compromise, and bacterial contamination

CHOLECYSTITIS

Chronic Cholecystitis

2. Chronic Cholecystitis

- Usually no history of previous acute attacks
- It is associated with cholelithiasis in over 90% of cases
- Obstruction of GB outflow by stones is **NOT** a requisite
- Due to supersaturation of bile
- Microorganisms can be cultured from bile in the only 1/3 o cases; *E. coli and enterococci*

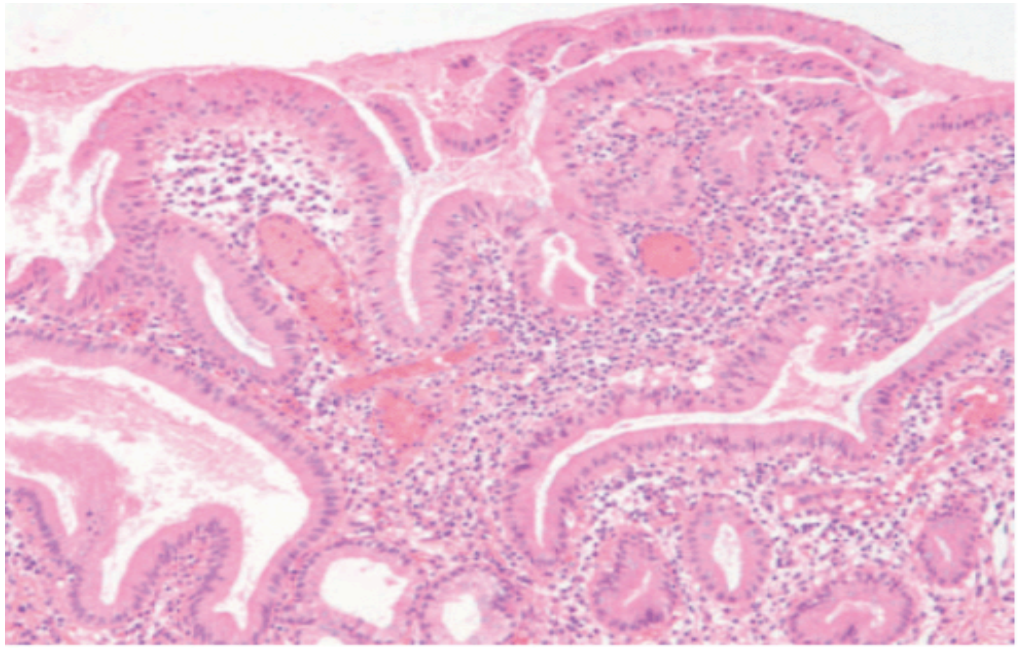
Morphology

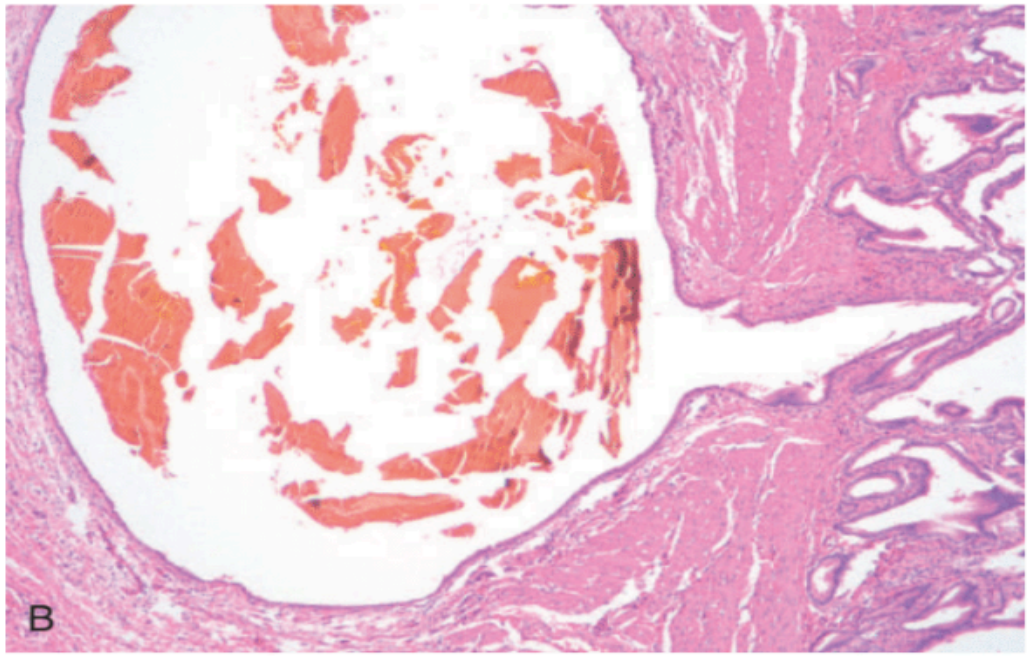
Grossly:

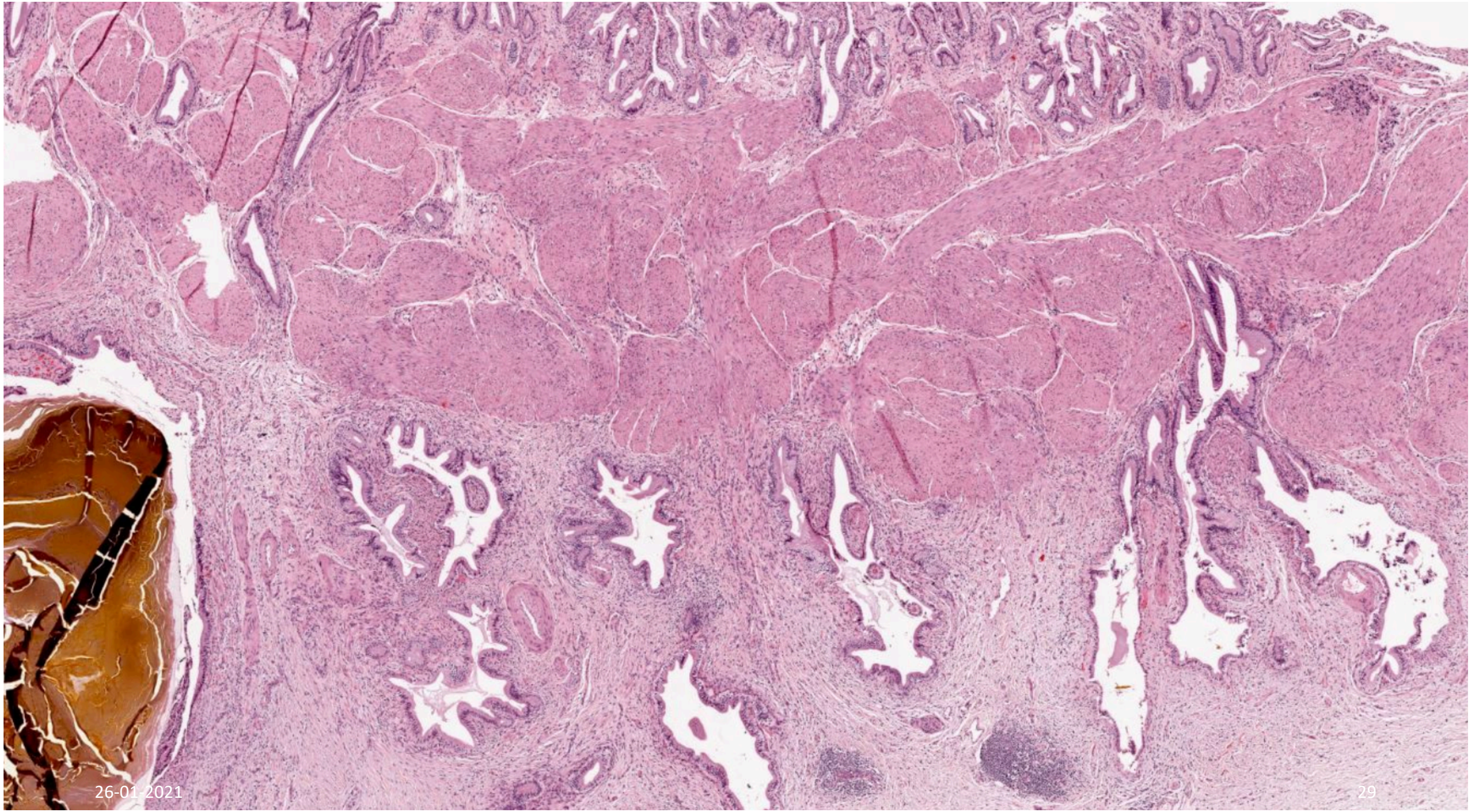
- Variable and sometimes minimal
  - ✓Gallbladder is small, normal in size or enlarged
  - ✓Thickened wall "fibrosis"
  - ✓Almost always contains stones

Microscopic:

- Chronic inflammation in the wall with submucosal & subserosal fibrosis
- Prominent Rockitansky-Aschoff sinuses "outpouchings of mucosal epithethelium through GB wall







Clinical Features

- Recurrent attacks of steady epigastric or RUQ pain
- Nausea, vomiting & fatty food intolerance are frequent

Complications

- Bacterial superinfection → cholangitis or sepsis
- Gallbladder perforation → local abscess
- Gallbladder rupture → diffuse peritonitis
- Biliary enteric fistula → entry of air and bacteria into biliary tree & possible gallstone-induced intestinal obstruction “ileus”
- Aggravation of pre-existing medical illness → cardiac, pulmonary, renal, or liver decompensation

Carcinoma of the Gallbladder

Carcinoma of the Gallbladder

- Most common malignant tumor of the extrahepatic biliary tract
- Mainly in 7th decade of life
- Slightly more common in women
- Usually discovered late “unresectable”; mean 5 - year survival rate is 5-12%
- **Risk Factors:**
  - ✓Gallstones (found in 95% of caIses)
  - ✓Infections of the biliary tree
  - ✓Both➔chronic inflammation
  - ✓Primary sclerosing cholangitis

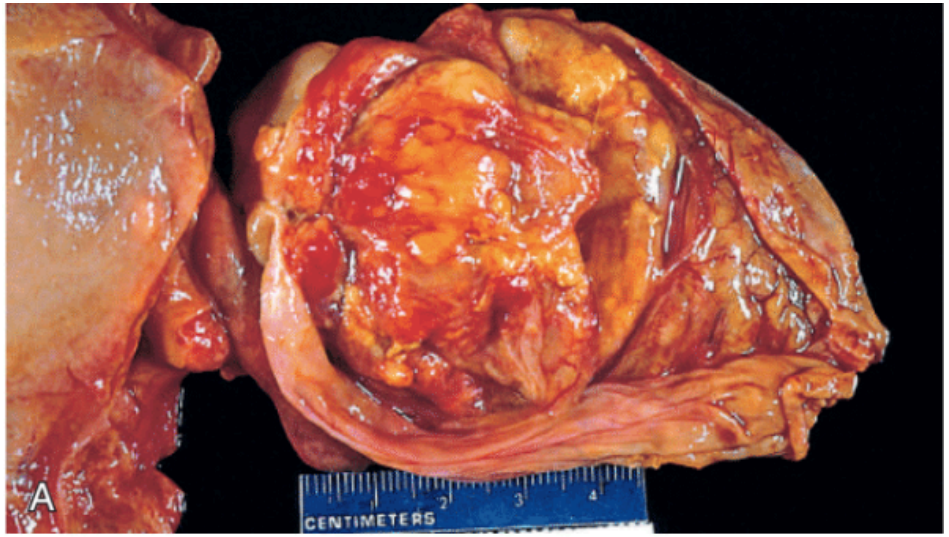
Morphology

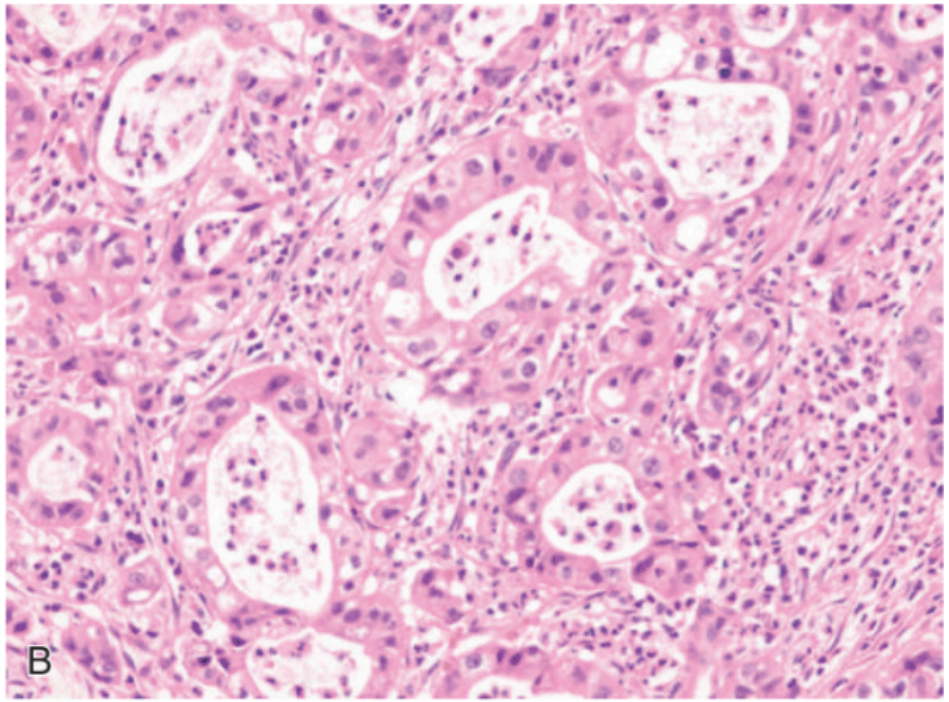
Gross patterns of growth:

1. Exophytic:
   - ✓Irregular, cauliflower-like mass growing into lumen & invading the underlying wall at same time
2. Infiltrating:
   - ✓More common pattern of growth
   - ✓Poorly defined area of diffuse wall thickening & induration

Microscopic:

- ✓Most are adenocarcinomas
- ✓5% SCC or adenosquamous





Clinical Features

- Cancer is usually discovered at time of surgery for stone
- Similar to gallstones: insidious abdominal pain, jaundice, anorexia, nausea & vomiting
- Only 10% are discovered early at a resectable stage, usually presents at advanced stage

Summery

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- Gallbladder diseases include cholelithiasis and acute and chronic cholecystitis, and gall bladder cancer.
- Gallstone formation is a common condition in Western countries. The great majority of the gallstones are cholesterol stones. Pigmented stones containing bilirubin and calcium are most common in Asian countries, due to the higher incidence of chronic hemolytic disorders and liver fluke infestations in these locales.
- Risk factors for the development of cholesterol stones are advancing age, female gender, estrogen use, obesity, and heredity.
- Cholecystitis almost always occurs in association with chole-lithiasis, although in about 10% of cases it occurs in the absence of gallstones.
- Acute calculous cholecystitis is the most common reason for emergency cholecystectomy.
- Gall bladder cancer is almost always associated with gall stones. Because of the advanced stage at diagnosis, it has a very poor prognosis.

THANK YOU

ROBBINS BASIC PATHOLOGY, TENTH EDITION