ETIOPATHOGENENSIS OF CHOLELITHIASIS WITH CHOLEDOCHOLITHIASIS

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2ND YEAR PG
DEPT OF PATHOLOGY
CHOLELITHIASIS

- ETIOLOGY
- TYPES
- PATHOGENESIS
- MORPHOLOGICAL FEATURES
- COMPLICATIONS
CHOLELITHIASIS:
1. Very common throughout the world.
2. Affect 10 to 20% of adult population in developed countries.
3. Majority of the gall stones are silent (>80%).

TYPES:
- Cholesterol stones (>50% cholesterol monohydrate)
- Pigment stones (bilirubin, calcium salts)
ETIOLOGY

**CHOLESTEROL GALL STONES**
- Demography: northern Europeans, North and South Americans.
- Advancing age
- Female sex hormones  Female gender
- Oral contraceptives
- Pregnancy
- Obesity and metabolic syndrome
- Rapid weight reduction
- Gallbladder stasis
- Inborn disorders of bile acid metabolism
- Hyperlipidemia syndromes
Extravascular or Intravascular hemolysis

Blood

Hepatic sinusoid

Unconjugated bilirubin + albumin → Urobinogen

Hepatocyte

Unconjugated bilirubin
transported with ligandin or Z protein
conjugated to glucuronic acid

Conjugated bilirubin

Kidney

Urobinogen excreted in urine

Portal vein

10% • Conjugated bilirubin → bacterial proteases

90% • Urobinogen → Feces

Small intestine
ETIOLOGY: 

PIGMENT GALL STONES

- Demography: Asians more than Westerners, rural more than urban
- Chronic hemolytic syndromes.
- Biliary infection. (Escherichia coli, klebsiella)
- Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency
**CHOLEDOCHOLITHIASIS**

- Presence of a gallstone in the common bile duct.
- 15% who have gall stones develop stones in CBD.

**TYPES**

1. **Primary stones**: Form primarily in the bile ducts (brown pigment stones). Result from stasis and subsequent infection.
2. **Secondary stones**: Form in the gall bladder but migrate to the bile ducts. (most common)
3. **Recurrent stones**: Develop in the ducts >3yr after surgery
Types of stones

- Pure cholesterol stones
- Pigment stones
- Pure pigment stones
- Mixed stones (80%) most common
- Combined stones
<table>
<thead>
<tr>
<th>TYPE OF STONE</th>
<th>INCIDENCE</th>
<th>COMPOSITION</th>
<th>COLOUR/SHAPE</th>
<th>NATURE</th>
<th>NUMBER/SIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIGMENT STONES</td>
<td>5%</td>
<td>CALCIUM BILIRUBINATE</td>
<td>DARK BROWN, CRUMBLES AT PRESSURE</td>
<td>VARIABLE</td>
<td></td>
</tr>
<tr>
<td>PURE PIGMENT STONES</td>
<td>5%</td>
<td>BILE PIGMENT, CA.BILIRUBINATE</td>
<td>BLACK, SHINY, IRREGULAR</td>
<td>DIFFICULT TO CRUSH</td>
<td>MANY (3-5 CMS) IN DIAMETER</td>
</tr>
<tr>
<td>PURE CHOLESTEROL STONES</td>
<td>RARE</td>
<td>PALE, OVAL. C/S: RADITION ARRANGED WITH PIGMENTED NUCLEUS</td>
<td>PALE</td>
<td>SMOOTH SURFACE, CUTS WITH DIFFICULTY</td>
<td>SINGLE (2-5 CM) IN DIAMETER</td>
</tr>
<tr>
<td>MIXED STONES</td>
<td>80%</td>
<td>CHOLESTEROL, BILE PIGMENTS</td>
<td>GREENISH BLACK, SMOOTH SURFACE</td>
<td>VARIABLE</td>
<td></td>
</tr>
<tr>
<td>COMBINED STONES</td>
<td>10%</td>
<td>STONE OF ONE TYPE SURROUNDED BY A SHELL OF ANOTHER TYPE</td>
<td>CHOLESTEROL STONE MAY BE SURROUNDED BY A MIXED STONE</td>
<td>VARIABLE</td>
<td>SINGLE (BARREL STONE)</td>
</tr>
</tbody>
</table>
**Figure 21.40**  ◆ Pure gallstones of various types.

**Figure 21.42**  ◆ Mixed and combined gallstones.
PATHOGENESIS OF CHOLESTEROL STONES
Cholesterol is rendered soluble in bile by aggregation with bile salts and lecithins.

When cholesterol concentration exceeds the solubilising capacity of bile, cholesterol can no longer remain dispersed; it nucleates into solid cholesterol monohydrate crystals.

A. Supersaturation of bile with cholesterol
B. Hypomotility of the gall bladder.
C. Accelerated cholesterol crystal nucleation
D. Hypersecretion of mucus in the gall bladder
I. NORMAL MIXED MICELLES
Cholesterol + Lecithin + Bile acids

II. LITHOGENIC BILE
- ↑ HMG-CoAR
- ↓ 7α-OHase
- ↓ MDR3

III. SUPERSATURATION OF BILE
- ↓ Bile acid pool
- ↑ Cholic acid → Deoxycholic acid
- Hypersecretion of cholesterol (Etiologic factors)

IV. CHOLESTEROL NUCLEATION
- Pro-nucleating factors (Mucin, non-mucin glycoproteins)
- Anti-nucleating factors (Apolipoproteins A1 and AII)

V. GALLBLADDER HYPOMOTILITY
Cholecystokinin

VI. BILIARY SLUDGE

VII. GALLSTONE
Cholesterol (CH) and phospholipids (PL) are secreted into the bile as unilamellar vesicles. Simple micelles are aggregates of bile acids.

Being natural detergents, bile acids dissolve parts of the vesicles and incorporate CH and PL into the thermodynamically stable mixed vesicles.

More CH is carried as vesicles when its absolute or relative concentration is high. As they fuse into multilamellar vesicles, each other and form crystals.

CH supersaturation is required but not enough for the formation of gallstones. These result from an imbalance of pronucleating factors such as mucous glycoproteins and antinucleating substances.
PATHOGENESIS OF BROWN PIGMENT GALL STONES
Billirubin and biliary lipids contained in vesicles and micelles are degraded by bacterial enzymes to free acids and unconjugated bilirubin (UCB).

Biliary lipids combine with calcium and precipitate as calcium salts. Bacterial and epithelial mucin, other glycoproteins, and UCB are other components of brown stones.
PATHOGENESIS OF BLACK PIGMENT GALL STONE
Unconjugated bilirubin (UCB) is maintained in solution by micelles and vesicles.

An absolute or relative increase of UCB may result in the formation of calcium bilirubinate salts.

In addition to organic calcium salts, calcium carbonate and phosphate precipitates when the concentration of free calcium exceeds and binding capacity of micelles and other binders.
COMPLICATIONS

- Acute and chronic cholecystitis
- Jaundice
- Acute cholangitis
- Acute pancreatitis
- Gallstone ileus
- Empyema and mucocele
- Biliary fistula
- Perforation
- Gall bladder cancer
ACUTE CHOLECYSTITIS

- Episode of acute biliary pain accompanied by fever and right hypochondrial tenderness and guarding with persistence of symptoms beyond 24hrs.

- Associated with gall stones (90%).

- Classified into **CALCULOUS, ACALCULOUS, EMPHYSEMATOUS**.
Occlusion of the neck of gall bladder or cystic duct by stone

Increased intraluminal pressure

Dilatation of the gall bladder and edema of bladder wall
Acute Calculous Cholecystitis: Pathogenesis

BILIARY TRACT

OBSTRUCTION → Hydrolysis of luminal lecithins by mucosal phospholipases → Production of toxic lysolecithins

Exposure of epithelium to direct detergent action of bile salts

Disruption of glycoprotein mucus layer

(+) GB distention & inc. intraluminal pressure

Compromised mucosal blood flow

(+) GB dysmotility

INFLAMMATION
stones

obstruction to bile outflow

Distended gall bladder

Compromise mucosal blood flow

Increase intraluminal pressure

Prostaglandin released

Mucosal and mural inflammation

deinflammation of gall bladder wall due to phospholipases from the mucosa hydrolyzes biliary lecithin to lysolecithin (toxic to the mucosa)

disrupt normal protective glycoprotein layer

exposed the mucosal epithelium to the direct detergent action of bile salts Superimposed bacterial infection
Pathogenesis - Acute acalculous cholecystitis

- **Shock:** Whether due to sepsis, heart failure, haemorrhage, fluid loss from burns, etc…
- **Use of vasopressors**
- **Decreased splanchnic blood flow**
- **Dehydration, or intravascular volume depletion**
- **Prolonged starvation**
  - The ICU diet
  - Absence of normal cholecystokinin-induced gall bladder contraction
- **Gall bladder wall ischaemia**
- **Increased bile viscosity**
  - **Bile stasis**
  - **Distended gall bladder**
- **Thickened gall bladder wall with gangrenous areas**
  - **Highly concentrated bile salts**
ACUTE CHOLECYSTIS - GROSS
Acute cholecystitis - microscopy
Neutrophilic infiltration

Dilated congested blood vessels
Acute emphysematous cholecystitis

- Uncommon variant of acute cholecystitis characterised by production of gas by the infecting bacterial organism.

- Bile cultures are positive for clostridial organisms most common clostridium welchii.

- Contributing factor: Vascular occlusion of cystic artery by atherosclerosis or small vessel disease.
Chronic cholecystitis - Gross
MICROSCOPY – CHRONIC CHOLECYSTITIS

Case 22: Chronic cholecystitis

Rokitansky-Aschoff sinuses
VARIANTS
Form of chronic acalculous cholecystitis characterized by a diffuse, plasma cell-rich inflammatory infiltrate mostly confined to lamina propria (not extending to deeper layers).

Associated with autoimmune disorders such as ulcerative colitis, primary sclerosing cholangitis, and autoimmune pancreatitis, IgG4-related autoimmune disorders that afflict the pancreatobiliary tract, and accordingly was termed sclerosing cholecystitis.

Occur secondary to obstructive processes in extrahepatic bile ducts.
Numerous prominent lymphoid follicles are present in the lamina propria throughout the gallbladder are referred to as follicular cholecystitis.

Such cases constitute less than 0.1% of cholecystectomies.

Typhoid fever, Gram-negative infections (98) and sclerosing cholangitis.

Follicular cholecystitis may or may not be associated with gallstones.
Marked infiltrate composed predominantly or almost exclusively of eosinophils.

It often involves the muscular layer but may be transmural or restricted to the mucosa.

The cystic duct may also contain eosinophils.

Peripheral eosinophilia syndromes, including allergic conditions such as asthma, and atopic diseases as well as the so-called hypereosinophilic syndrome.
Characterized by a prominent proliferation of foamy macrophages often associated with cholelithiasis.

Occur due to ulceration of the gallbladder mucosa and/or rupture of Rokitansky-Aschoff sinuses with extravasation of bile.

Lymphocytes, plasma cells, and Touton-like or foreign-body-type giant cells (often with cholesterol crystals) are usually admixed with the foamy macrophages.

XANTHOGRANULOMATOUS CHOLECYSTITIS
CHOLESTEROSIS

Increased hepatic synthesis of cholesterol and triglycerides

- Gross: lipid deposits appear as yellow flecks against a dark green background.
- When extensive form cholesterol polyps.
**MICROSCOPY**

- Accumulation of foamy macrophages in the expanded lamina propria.
PORCELAIN GALLBLADDER

- Calcification of gall bladder
- Complication of chronic cholecystitis
- Gross: wall and surfaces of the gall bladder are hard, pearly white.
CHOLANGITIS

- Inflammatory diseases of bile ducts are collectively called cholangitis.

- TYPES: simple obstructive, recurrent cholangitis syndrome, primary sclerosing cholangitis.
ACUTE PANCREATITIS
Perforation

Non-inflamed gallbladder with or without stones

Very severe inflammation with necrotic patches

Perforation in 48 hours or less
HYDROPS OR MUCOCELE: Distension of gall bladder by a clear watery or mucoid material.
- May contain over 1500 ml of fluid.

EMPYEMA: Acute cholecystitis in presence of bacteria containing bile progress to suppurative infection.
- Gall bladder is filled with purulent material.
Gallbladder Mucocele (Hydrops)

Empyema and Mucocele of the gallbladder

Empyema and Mucocele

- Acute cholecystitis
- Empyema
- Mucocele
BILIARY FISTULA

- Biliary fistula is a type of fistula in which bile leaks from the bile ducts into surrounding areas.

- Gall stone associated necrosis and inflammation of gall bladder and bile ducts.
References

- ANDERSONS PATHOLOGY VOL 2; TENTH EDITION; PG NO 1601 -1607
- BOYDS TEXTBOOK OF PATHOLOGY TENTH EDITION; VOL 2; PG NO 1053 -1062
- ROBBINS AND COTRAN PATHOLOGIC BASIS OF DISEASE; 9TH EDITION; VOL 2; PG NO 860 - 873.
- STERNBERG'S DIAGNOSTIC SURGICAL PATHOLOGY VOL 1; 5TH EDITION PG NO 1165 - 1178
THANK YOU