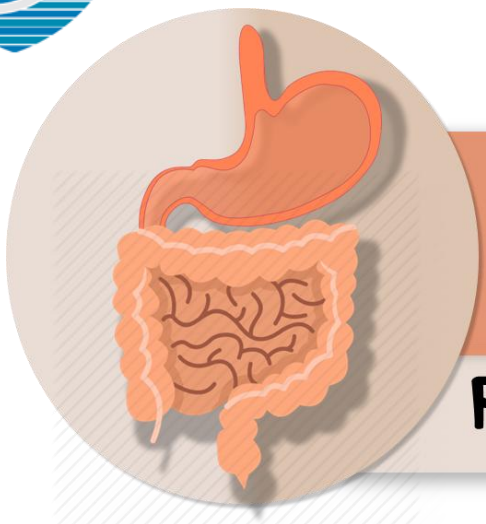

GI system

Pathology

◉ Sheet ○ Slide

Number:	6
Done by:	Mustafa Khader
Corrected by:	-
Doctor:	Maha Shomaf

This lecture tackles the diseases of the Gallbladder and is the last lecture in Gastrointestinal pathology. Just a heads up this lecture is very difficult.

Keep in mind that the treatment of most gallbladder diseases is by surgical means and the most prevalent of its diseases are gallbladder stones.

Cholelithiasis (Gallbladder Stones):

There are two types of stones:

1. **Cholesterol Stones:** is the more prevalent type, accounting for about 80% of the stones in the Gallbladder. This type is formed of ***Crystelline Cholestrol Monohydrate*.**
2. **Pigment Stones:** the less prevalent type as it only accounts for 20% of Gallbladder stones. This type, on the other hand, is formed of ***Bilirubin Calcium Salts***.

Cholesterol stones are important due to their **risk factors** such as:

1. **Geographical Area**: Stones are more commonly found in Western countries due to the high cholesterol in their diets.
2. **Age**: Incidence of stones and age show a positive correlation, meaning that the higher a person's age the more likely he/she will develop stones. This is proven by the fact that the incidence of stones is 25-30% in those greater than 80 years of age and is only 5-6% in those who are less than 40 years of age.
3. **Female Sex Hormones**: Stones can be highly affected and perpetuated by female sex hormones, therefore the classical patient of such stones is usually an elderly female, or a female on oral contraceptive pills.
4. **Obesity:** Due to the high concentration of excreted fatty materials, which will overload the fatty acid excretion pathways through the bile resulting in the formation of such stones.
5. **Hypomotility of Gallbladder:** Conditions related to hypomotility of the Gallbladder induces the stasis of bile, which predisposes to stone formation. Such conditions are:
    a. **Rapid Weight Reduction**
    b. **Pregnancy** (Due to the effect of Progesterone)
    c. **Spinal Cord Injury**

6. **Enzyme Deficiencies:** The formation of bile is a highly enzyme-dependant process, therefore any condition that affects any enzyme in the pathway will also predispose the person to stones. Keep in mind, this is a very rare condition and the other risk factors are far more common.
7. **Hyperlipidaemia Syndromes:** Any conditions that causes an increase in the concentration of free fatty acids in the blood will increase the risk of formation of gallbladder stones. Therefore, a hyperlipidaemic status is always associated with an increased risk of stone formation.

Note: The most important risk factors are age and gender (elderly and female), as 80% of the cases have no other known risk factor.

Now let's move on to the **risk factors** of ***Pigment stones***:

1. **Geographic Area:** Unlike cholesterol stones, which as we discussed previously have an increased prevalence in western countries. **Pigment stones** are more predominant **in Eastern countries such as China** than they are in the West.
2. **Chronic Haemolytic Anaemias:** Any disorder that causes haemolysis of RBCs will increase the concentration of bilirubin in the blood (hyperbilirubinemia). At first the liver will be able to conjugate and excrete this bilirubin. However, at a certain point the liver's capacity will not be able to deal with such a high concentration of bilirubin. This in turn leads to an increase in the concentration of unconjugated bilirubin in the blood (unconjugated hyperbilirubinemia) which predisposes to the formation of pigment stones.
3. **Biliary Infections:** Any bacterial infection in the biliary system increases the risk of stone precipitation.
4. **Gi disorders:** Can be associated with decreased excretion of bilirubin which in turn increases the risk of pigmented stone formation.

Pathogenesis:

1. **Cholesterol Stones:** The main process of excretion of cholesterol is through the bile. Cholesterol as we all know is a fatty material, therefore, water insoluble. To overcome this obstacle our bodies aggregate the cholesterol with bile salts and Lecithins, forming a complex of all three molecules together. This causes cholesterol to become water soluble and thus allowing for its excretion. However, the solubility of cholesterol is dependant on the overall concentration of each of the three molecules in the complex. Therefore, if there is any disturbance of the concentrations the solubility of cholesterol will be affected, rendering a problem with its excretion. For the formation of stones to occur we need some prerequisites such as:
    a. **Supersaturation of bile with cholesterol:** This will cause the molecules forming the complex to become unable to cope with the high concentration of cholesterol, thus maintaining its insolubility, leading to its precipitation and stone formation.
    b. **Precipitation of organic and inorganic salts:** Salts such as Calcium can precipitate forming the nucleus to which the cholesterol precipitates around.
    c. **Gallbladder Stasis:** Immobility of the gallbladder will enhance the precipitation.
    d. **Hypersecretion of Mucus:** The mucus causes other substances from the bile to "stick" to each other forming another nucleus for the cholesterol to precipitate onto.
2. **Pigment stones:** Since these stones are formed of unconjugated bilirubin with Calcium salts, then the pathogenesis is simple. All we need is a condition that causes the increase of unconjugated bilirubin. Conditions that cause such an increase are:
    a. **Infection by E. Coli:** An infection with E. Coli causes the release of the microbial enzyme, B-glucuronidase. This enzyme affects the bilirubin glucuronidases causing an increase of unconjugated bilirubin.
    b. **Haemolytic Anemias:** as described previously.

Morphology:

1. **Cholesterol Stones:**
    a. Found exclusively in the gall bladder
    b. Consists of 50-100% cholesterol
    c. Usually yellow in color due to the high concentration of cholesterol
    d. Faceted surfaces due to one stone rubbing on another
    e. Radiolucent in radiological imaging if they are pure cholesterol. Thus, a normal radiograph is not enough to exclude cholesterol from your differential diagnosis.
    f. Radiopaque if they contain at least 20% calcium crystals
    g. Usually multiple
2. **Pigment stones:**
    a. Can be found anywhere in the biliary tree and not only in the gallbladder and therefore can cause obstruction.
    b. Usually black or brown in color
    c. Usually radiopaque

Clinical Features:

1. Patients with stones may remain for years without any specific symptoms.
2. Patients with stones in the gallbladder will complain of symptoms following a heavy fatty meal such as abdominal discomfort (a non-specific symptom).
3. In the case that the stone gets lodged into the bile duct the patient will have obstructive jaundice and severe pain (constant or colicky) due to stretching of the common bile duct from the stone. The patient will show up with all the symptoms of jaundice such as pruritis, decreased bilirubin in faeces (clay appearance) and increased bilirubin in urine. Also, this may predispose to a superimposed infection in the common bile duct ascending from the GI Tract which may lead to empyema (gallbladder abscess). This is a very serious issue as the stone may irritate the mucosal lining of the common bile duct leading to its perforation causing bacterial or chemical peritonitis.
4. Fistula formation may occur with adjacent organs such as small bowel and stomach.

5. Pancreatitis may occur by the stone traveling all the way down to the Ampulla of Vater leading to the obstruction of the pancreatic duct. This obstruction causes backflow of pancreatic secretions to the pancreas and leads to life threatening inflammation of the pancreas.
6. If the stone is big enough it may pass into the duodenum and cause intestinal obstruction and irritation to the intestinal mucosa.

Cholecystitis:

Almost always occurs in association with stones. This inflammation can be:

1. **Acute**
2. **Chronic**
3. **Acute on top of chronic**

Acute Cholecystitis: Can be categorized into two forms:

1. **Acute calculous cholecystitis:** meaning that the inflammation is associated with a stone.
    a. **Clinical features:**
        i. Severe pain in the right upper quadrant that may radiate to the shoulder mimicking the symptoms of a myocardial infarction.
        ii. Tenderness in right subcostal region
        iii. Manifestations of inflammation: Fever, malaise, Leukocytosis
        iv. Symptoms may spontaneously subside due to the stone moving, however, recurrence of symptoms is very common.
    b. **Treatment:** The treatment of choice is usually cholecystectomy.
2. **Acute Acalculous Cholecystitis:**
    a. The symptoms are usually concealed since the patient has a more severe overlying condition such as:
        i. Post-op after major non-biliary surgery
        ii. Severe trauma and burn leading to dehydration
        iii. Sepsis

b. Mechanism:
   i. Dehydration
   ii. Gallbladder Stasis
   iii. Vascular Compromise
   iv. Bacterial Contamination

Chronic Cholecystitis:

1. **Clinical symptoms:**
   a. Recurrent attacks of steady or Colicky epigastric or Right Upper Quadrant pain or to be more precise abdominal discomfort after heavy fatty meals.
   b. Nausea & vomiting
   c. Fat intolerance
   d. Almost always associated with GB stones.
2. **Mechanism:**
   a. Obstructions are not a feature
   b. E. coli infection is usually present
   c. Supersaturation of bile leads to stone formation
3. **Morphology:**
   a. Changes are variable to the gallbladder it may be enlarged, contracted, or normal in size depending on the number of stones present.
   b. Not only the mucosa is inflamed but the whole wall is inflamed (transmural)
   c. Mucosal ulcerations
   d. Lymphocytic infiltration
4. **Complications:** similar to the clinical features discussed for gallbladder stones.

Carcinomas of the Gall Bladder:

The typical patient is an elderly female (usually >70 years of age), prognosis is usually very poor (5-year survival rate 1%), and is usually associated with gallbladder stones (60-90% of cases)

Morphology:

1. Infiltrating or exphytic
2. Infiltrating tumors are commonly scirrhous

3. Lateral walls of Fundus and neck (neck causes symptoms earlier) of the gallbladder are the most common sites.
4. Types of carcinomas:
    a. Adenocarcinoma 95%
    b. Adenosquamous or squamous cell carcinoma
    c. Carcinoid (rarely)
    d. Mesenchymal (also rare)
5. Local spread:
    a. Liver
    b. Cystic Duct
    c. Adjacent Lymph nodes
6. Distant spread:
    a. Peritoneum
    b. GI tract
    c. Lung

Clinical Features:

1. Can be found incidentally after cholecystectomy (lucky patients)
2. Features similar to gallbladder stones:
    a. Nausea
    b. Vomiting
    c. Pain
    d. Jaundice

Cholangiocarcinoma:

A malignant adenoma of the biliary system (such as common bile duct), incidence is very rare, and the male to female ratio is equal.

Predisposing factors:

1. Sclerosing cholangitis
2. Congenital fibropolycystic disease of biliary system
3. Thorostat (a radioactive substance used previously in radiology)
4. Chronic infection by liver fluke

Metastasis:

1. Lung
2. Bone
3. Adrenal Glands
4. Brain

Clinical Features: Depends on the site, if the site is in a place where obstruction may occur the symptoms will have early onset, however, if it does not cause obstruction the symptoms have very delayed onset.

Prognosis:

1. 1-2 yrs. Survival rate 13-25%
2. Median survival rate is 6 months

CARCINOMA OF THE EXTRAHEPATIC BILIARY TREE:

1. Uncommon (rare)
2. Manifests with painless jaundice
3. 1/3 of patients have stones

Risk factors:

1. Biliary tree flukes (clonorchis)
2. Primary sclerosing cholangitis
3. Inflammatory bowel disease
4. Choledochal cyst
5. Thorostat

Tumors at the Ampulla of Vater

Morphology:

1. Mostly Adenocarcinoma
2. Rarely Squamos Cell Carcinoma

Klatskin Tumors:

Present at the liver hilum at the junction between the right and left hepatic ducts.

Clinical Features:

1. Jaundice
2. Discoloration of stool
3. Nausea
4. Vomiting
5. Hepatomegaly
6. Enlarged gallbladder
7. Dark urine
8. Increased alkaline phosphatase
9. Increased prothrombin time
10. Increased ALT and AST

Prognosis: Very bad with mean survival time 6-18 months.