

Pathology of Hepatobiliary System

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Morphologic Patterns of Hepatic Injury

- Degeneration
- Intracellular accumulation
- Necrosis and apoptosis
- Inflammation
- Fibrosis

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Degeneration and Intracellular Accumulation

- **Ballooning degeneration:**
 - Swollen oedematous hepatocytes with irregularly clumped cytoplasm and large clear space
 - Result from toxic damage and immunologic insult
- **Foamy degeneration:**
 - Diffuse foamy swollen hepatocytes.
 - Due to retained biliary material.

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- **Steatosis:**
 - Accumulation of fat droplets within hepatocytes
 - Occurs in alcoholic liver disease and pregnancy.
- **Haemochromatosis and Wilson's disease:**
 - Accumulation of iron and copper in hepatocytes, respectively.

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Necrosis and Apoptosis

- **Ischaemic coagulation necrosis:**
 - Hepatocytes are poorly stained and "mummified" and often have lysed nuclei.
- **Councilman bodies:**
 - Isolated hepatocytes become round to form shrunken, pyknotic nuclei and intensely eosinophilic fragmented nuclei in the process of apoptosis.

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- **Lytic necrosis:**
 - Hepatocytes become swollen osmotically and ruptured.
- **Centrilobular necrosis:**
 - Necrosis of hepatocytes immediately around the terminal hepatic veins.
 - Occurs in case of ischaemic injury and a number of drugs and toxic reactions.

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- **Mid-zonal and peri-portal necrosis:**
 - Rarely occur in eclampsia.
- **Focal necrosis:**
 - Limited to scattered cells within hepatic lobules.
- **Bridging necrosis:**
 - Necrosis of contiguous hepatocytes spanning adjacent lobules in portal-to-portal, portal to central, central-to-central fashion occurs in severe inflammation.

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- **Sub-massive necrosis:**
 - Necrosis of entire lobule.
- **Massive necrosis:**
 - Necrosis of entire liver.
- **Macroscopic abscess:**
 - Occur in disseminated candidal or bacterial infections.

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Inflammation

Influx of acute or chronic inflammatory cells into the liver is termed hepatitis. Inflammatory cells may be limited to the sites of entry (portal tracts) or spill over into the parenchyma.

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Regeneration

Regeneration is signified by thickening of the hepatocyte cords and some disorganization of the parenchymal structures.

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Fibrosis

- Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver.
- In initial stage fibrosis develop around portal tracts or the central veins or within the spaces of Disse.
- With continuing fibrosis, liver is subdivided into nodules of regenerating hepatocytes surrounded by scar tissue, termed **cirrhosis**.

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Cirrhosis of Liver

Cirrhosis is a condition in which liver is subdivided into nodules of regenerating hepatocytes surrounded by scar tissue.

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Three features of cirrhosis:

- Bridging fibrous septa in the form of delicate bands or broad scars replacing multiple adjacent lobules.
- Disruption of architecture of the entire liver.
- Parenchymal nodules created by regeneration of encircled hepatocytes.

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• Other features:

- The parenchymal injury and consequent fibrosis are diffuse.
- Nodularity is requisite for diagnosis of cirrhosis.
- The fibrosis is irreversible.
- Vascular architecture is reorganised by the parenchymal damage and scarring.

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Classification of Cirrhosis of Liver

- Aetiological Classification:
 - Alcoholic liver diseases (60-70%)
 - Viral hepatitis (10%)
 - Biliary disease (5-10%)
 - Primary Haemochromatosis (5%)
 - Wilson's diseases (rare)
 - Alpha1-anti-trypsin deficiency (rare)
 - Cryptogenic cirrhosis (10-15%)

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• Morphologic classification:

- Macronodular cirrhosis
- Micronodular cirrhosis
- Mixed type cirrhosis

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• Infrequent types of cirrhosis:

- Cirrhosis in infant and children with galactosaemia and tyrosinosis
- Cirrhosis in liver destruction by diffuse infiltrating cancer.
- Drug-induced cirrhosis
- Cirrhosis in syphilis

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• **Macronodular cirrhosis:** Nodule 3 mm or more.

• **Micronodular cirrhosis:** Nodule less than 3 mm.

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Viral Hepatitis

- Unless otherwise specified, the term 'viral hepatitis' is reserved for infection of the liver by a small group of viruses having a particular affinity for the liver such as Hepatitis viruses A, B, C, D and E.
- Other systemic viral infection may involve the liver such as Epstein-Barr virus, cytomegalo virus and yellow fever virus.

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Hepatitis A Virus (HAV)

- Causes infectious hepatitis
- Infectious hepatitis is a benign, self-limited disease.
- Incubation period: 2 to 6 weeks.
- HAV does not cause chronic hepatitis or carrier state, rare causes fulminant hepatitis.
- Fatality rate: 0.1%

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Hepatitis B Virus (HBV)

- Causes 'serum hepatitis'
- HBV can produce:
 - Acute hepatitis
 - Non-progressive chronic hepatitis
 - Progressive chronic hepatitis ending in cirrhosis
 - Fulminant hepatitis with massive liver necrosis.
 - An asymptomatic carrier state with or without progressive diseases.
 - Backdrop for hepatitis D virus (HDV).

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- HBV plays an important role in the development of hepatocellular carcinoma.
- Incubation period: 4 to 26 weeks.
- Serum markers: HBsAg, HBeAg, Anti-HBe, Anti-HBc and Anti-HBs.
- Presence of HBsAg in serum for 6 months or longer after initial detection is known as carrier state.

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- The presence of HBsAg alone does not necessarily indicate replication of complete virions. Patients may be asymptomatic and without liver damage.
- Chronic replication of HBV is characterised by presence of circulating HBsAg, HBeAg, and HBV DNA, usually with anti-HBc, occasionally with anti-HBs.

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Hepatitis C (HCV)

- HCV has high rate of progression to chronic liver disease and eventual cirrhosis.
- Incubation period: 2 to 26 weeks.
- Persistent infection and chronic hepatitis are the hallmark of HCV infection.
- Repeated bout of hepatic damage is the characteristic features of HCV infection.
- Cirrhosis can be present at the time of diagnosis or may develop during a period of 5 to 10 years.

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Hepatitis D Virus (HDV)

- HDV causes infection when it is encapsulated with HBsAg.
- Simultaneous infection with HBV and HDV result in hepatitis ranging from mild to fulminant disease.

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Hepatitis E Virus (HEV)

- Hepatitis is self-limited.
- It is not associated with chronic liver diseases.
- Incubation period: 6 weeks.

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Clinicopathologic Syndromes of Viral Hepatitis

- **Carrier State:** Without clinically apparent diseases or with chronic hepatitis.
- **Asymptomatic infection:** Serologic evidence only.
- **Acute hepatitis:** anicteric or icteric
- **Chronic hepatitis:** without progression to cirrhosis or with progression to cirrhosis.
- **Fulminant hepatitis:** Submassive to massive hepatic necrosis.

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Carrier State:

- The liver biopsy is more or less normal.
- Viable isolated hepatocytes or clusters of cells have ground glass, finely granular eosinophilic cytoplasm, laden with HBsAg. Hepatocytes may have sanded nuclei imparted by abundant HBeAg.

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Acute Viral Hepatitis

- Morphological changes in acute hepatitis are virtually the same regardless of the causative agent and can be mimicked by drug reaction.
- Grossly the liver is slightly enlarged.

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Major histological findings are:

- Ballooning degeneration
- Fatty change
- Apoptosis
- Hyperplasia and hypertrophy of Kupffer cells
- Infiltration of portal tract by a mixture of inflammatory cells.
- Periportal spill over of inflammatory cells.

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Chronic Viral Hepatitis

Chronic hepatitis is defined as symptomatic, biochemical or serological evidence of continuing or relapsing hepatic disease for more than 6 months, with histologically documented inflammation and necrosis.

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• Classification:

- **Chronic persistent hepatitis:** Inflammation is confined to portal tracts.
- **Chronic active hepatitis:** Portal tract inflammation spills over into parenchyma and surrounds regions of necrotic hepatocytes.
- **Chronic lobular hepatitis:** Persistent inflammation is confined to the lobule.

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Association of hepatitis virus with chronic hepatitis

- **HAV:** Extremely rare
- **HBV:** Develops in more than 90% of neonates and 5% of infected adults, of which one-fourth progress to cirrhosis.
- **HCV:** Develops in more than 50% of infected patients, of whom half progress to cirrhosis.
- **HDV:** Rare
- **HEV:** Does not produce chronic hepatitis

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Chronic hepatitis with HBV and apparently with HCV contributes significantly to the development of primary hepatocellular carcinoma.

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Morphology in chronic viral hepatitis

- **In mildest form:**
 - An inflammatory infiltrate is limited to portal tracts, consisting of lymphocytes, macrophages, occasional plasma cells, neutrophils or eosinophils. Liver architecture is preserved.
- **In progressive disease:**
 - Piece meal necrosis or bridging necrosis may occur.

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Autoimmune Hepatitis

It is a chronic hepatitis of unknown aetiology, which has clinical and histological features virtually indistinguishable from chronic viral hepatitis.

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Fulminant Hepatitis

- When hepatic insufficiency progress from onset of symptoms to hepatic encephalopathy within two to three weeks it is termed as fulminant hepatitis.
- Histologically necrosis may wipe out entire lobules or destroy central and midzonal regions sparing periportal region of lobules.

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Alcoholic Liver Disease

Chronic alcohol consumption has a variety of adverse effects, of these three are important:

- Hepatic steatosis
- Alcoholic hepatitis
- Cirrhosis

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Haemochromatosis

Haemochromatosis is characterised by the excessive accumulation of body iron, most of which is deposited in the parenchymal organ, such as the liver and pancreas.

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Types:

- Hereditary haemochromatosis or primary haemochromatosis
- Secondary haemochromatosis

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• Fully developed cases exhibits:

- Micronodular cirrhosis
- Diabetes mellitus
- Skin pigmentation

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• Morphology:

- Deposition of haemosiderin in the liver, pancreas, myocardium, pituitary gland and thyroid gland.
- Cirrhosis
- Pancreatic fibrosis

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Wilson's Disease

Wilson's disease is an autosomal disorder marked by the accumulation of copper in many tissues and organs, principally the liver, brain and eye.

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• Mechanism:

- During metabolism in liver copper is incorporated into α 2-globulin to form ceruloplasmin and secreted into plasma.
- The gene for Wilson's disease is on chromosome 13 and encodes a transmembrane copper transporting ATPase located on the hepatocytes canalicular membrane.
- Majority of the patients are compound heterozygous containing different mutations of the Wilson's disease gene on each.
- Defective bile excretion leads to copper accumulation causes toxic liver injury.

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• Hepatic Changes are:

- Fatty changes
- Acute hepatitis
- Chronic hepatitis
- Massive hepatic necrosis

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Nodular Hyperplasia

- Solitary or multiple, well demarcated but poorly encapsulated hyperplastic hepatocellular nodule may develop in the non-cirrhotic liver.
- Nodule ranges up to many centimetres in diameter.

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• Two types:

- Focal nodular hyperplasia and nodular regenerative hyperplasia
- Nodular regenerative hyperplasia may affect the entire liver with round spherical nodule in the absence of fibrosis.

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Adenoma

- Arise from hepatocytes or bile duct epithelial cells.
- Liver cell adenomas are pale, yellow-tan and usually bile stained nodules.
- Histologically composed of normal hepatocytes or have some variation in cell and nuclear size.

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- Bile duct adenomas are firm, pale and usually single discrete nodule.
- They are almost never bile stained.
- They are composed of uniformly sized epithelium lined channels or ducts separated by a scant to abundant connective tissue stroma and sharply demarcated from the surrounding liver.

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Hepatoblastoma

- Malignant tumour usually of young childhood.
- Exhibits two anatomic type:
 - epithelial type
 - mixed epithelial and mesenchymal type.

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- Epithelial type composed of small polygonal fetal cells, even smaller embryonal cells forming acini, tubular or papillary structures.
- Mixed type contains foci of mesenchymal differentiation, may contains primitive mesenchyme, osteoid, cartilage or striated muscle.

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Primary Carcinoma of Liver

- Hepatocellular Carcinoma (HCC) or Hepatoma (90%)
- Cholangiocarcinoma
- HCC is strongly associated with HBV infection.
- HCC is also associated with chronic infection with HCV and alcohol consumption.
- Cholangiocarcinomas are associated with previous exposure to Thorotrast and billiary invasion by liver fluke *Opisthorchis sinensis*.

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Pathogenesis

- Repeated cycle of cell death and regeneration in HBV and HCV infection accumulate mutation and eventually transform some hepatocytes.
- In HBV associated liver cancer, the viral DNA is integrated into host genome leading to transformation.
- HBV DNA integration induces genome instability.

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- Aflatoxin, produced by food spoilage moulds, are most potent environmental factors implicating in hepatocellular carcinogenesis. Aflatoxins are activated in hepatocytes, their products interlude into DNA to form mutagenic adduct with guanosine. It may cause G to T transversion at 249 codon of P53 tumour suppressor gene.

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- It appears that HBV infection, Aflatoxin exposure and genetic variation act synergistically in some world regions to increase risk for HCC.
- It would appear that stimulation of hepatocellular division in the midst of ongoing necrosis and inflammation theme common to HCC cases not associated with HBV infection such as alcoholic cirrhosis, HCV infection and primary Haemochromatosis.

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Morphology

- HCC may be unifocal, multifocal or diffusely infiltrative
- HCC are usually paler than the surrounding liver substances. Some times it takes a green hue when composed of well-differentiated hepatocytes of secretory bile. Cholangiocarcinomas are rarely bile staining.

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- HCC composed well-differentiated to highly anaplastic undifferentiated cells.
- Cholangiocarcinoma composed of anaplastic cuboidal to low columnar cells.

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Metastatic Tumours

- Metastatic involvement of the liver is far more common than primary neoplasm
- Common organs are breast, lungs and colon.

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Cholelithiasis (Gall Stone)

- Affect 10 to 20% of adult populations in developed countries.
- Majorities of gall stones are asymptomatic
- Gall stones are mainly two types:
 - Cholesterol stone (~80%)
 - Pigment stone (~20%)
 - Mixed

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- Risk factors of cholelithiasis:
 - Cholesterol stone:
 - Demography: Northern Europe, North and South Africa, native Americans, Mexican Americans.
 - Advance age
 - Female sex hormone
 - Female gender
 - Oral contraceptive
 - Pregnancy
 - Obesity
 - Rapid weight reduction
 - Gall bladder stasis
 - Inborn disease of bile acid metabolism
 - Hyperlipidaemia syndrome

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– Pigment stone:

- Demography: Asian more than Western; Rural more than urban.
- Chronic haemolytic syndrome
- Biliary infection

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• Pathogenesis:

- **Cholesterol stone:** When cholesterol becomes supersaturated, it cannot remain dispersed and nucleate into solid cholesterol monohydrate crystals.
- **Pigment stone:** Calcium salt of un-conjugated bilirubin is participated in the formation of pigment stones. Biliary tract infection induces de-conjugation of excreted bilirubin glucuronides to formation of pigment stone.

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Morphology

• **Pure Cholesterol Stone:**

- Pale yellow, round to ovoid, finely granular, hard external surface.
- Transection reveals a glistening radiating crystalline palisade.
- Single or multiple
- Surface of multiple stone may be faceted.
- Usually Radioluscent; 10-20% are radio-opaque.

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• **Pigment stone:**

– **Black pigment stone:**

- Found in sterile gall bladder bile.
- Composed of unconjugated bilirubin, calcium carbonate, calcium phosphate and mucin.
- Usually speculated and moulded.

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• **Brown Pigment Stone:**

- Found in infected intrahepatic or extrahepatic ducts.
- Contains pure calcium salt of unconjugated bilirubin, mucin, cholesterol and calcium salt of palmitate and stearate.
- Are laminated and soft.

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50-75% pigment stones are radio-opaque.

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Cholecystitis

- **Types:**
 - **Acute Cholecystitis**
 - Acute calculus cholecystitis
 - Acute acalculus cholecystitis
 - **Chronic Cholecystitis**

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Acute Calculus Cholecystitis

- Is an acute inflammation of gall bladder precipitated 90% of them by obstruction of the neck or cystic duct.
- Results from chemical irritation and inflammation of the obstructed gall bladder. Mucosal phospholipases hydrolyses luminal lecithin to lysolecithin. Mucous layer is disrupted. Exposed mucosal epithelium is come in contact with detergent action of bile salts. Gall bladder immotility develops; resulting distension and increase intraluminal pressure reduces the blood flow of mucosa.

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- The gall bladder is usually enlarged and tense. The surface shows green-black discolouration. Serosa may cover by fibrin or suppurative coagulated exudate. The gall bladder may fill with pure pus (empyema). The wall is thickened and oedematous. The wall may be necrosed (gangrenous cholecystitis).

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- Histological findings are oedema, leucocytic infiltration, vascular congestion, frank abscess formation or gangrenous necrosis.

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Acute Acalculus Cholecystitis

- Results from direct ischaemic compromise as cystic artery is an end artery.
- Predisposing factors:
 - Post-operative state
 - Severe trauma
 - Severe burn
 - Multisystem organ failure
 - Sepsis
 - Prolonged intravenous hypralimentation
- Postpartum state

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- **Contributory factors:**
 - Dehydration and multiple blood transfusions.
 - Gall bladder stasis
 - Accumulation of billiary slugs and viscous bile
 - Inflammation and oedema of wall
 - Bacterial contamination and generation of lysolecithin

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- Morphology:
 - There is no specific difference between acute calculus and acalculus cholecystitis.

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Chronic Cholecystitis

- Chronic cholecystitis may be a sequel to repeated bouts of mild-to-moderate acute cholecystitis
- About 90% are associated with cholelithiasis
- E. coli and Enterococci can be cultured from bile in about one-third of cases.

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- Gall bladder may be contracted, normal or enlarged in size.
- Serosa is usually smooth and glistening or dull by subserosal fibrosis.
- On sectioning, the wall is thickened, opaque, grey-white and less flexible than normal.

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- The lumen contains fairly clear, green-yellow, mucoid bile and usually stones.
- The mucosa may normal, thin or atrophied.
- In mildest case, only scattered lymphocytes, plasma cells and macrophages are found in mucosa and subserosal fibrous tissue.

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- In more severe cases, there is marked subepithelial and subserosal fibrosis accompanied by mononuclear cells infiltration.
- Inflammatory proliferation of the mucosa and fusion of the mucosal folds may give rise to buried crypts of epithelium within the gall bladder wall. Out pouching of the mucosal epithelium through the wall may be present which is known as Rokitansky-Aschoff sinus.

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- Rare features:
 - Porcelain gall bladder – extensive dystrophic calcification within gall bladder wall.
 - Xanthomatous cholecystitis – Shrunken, nodular necrosis and haemorrhage.
 - Hydrops gall bladder – Atrophic, chronically obstructed gall bladder containing only clear secretion.

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Carcinoma of the Gall Bladder

- 60-90% are associated with cholelithiasis
- Exhibit two patterns: Infiltrating and fungating
- Most common sites: Fundus and necks.
- Most common histologic type: Adenocarcinoma
- About 5% are squamous cell carcinoma.
- Minority are carcinoid and mesenchymal tumours.

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Diseases of extrahepatic bile ducts

- Biliary atresia
- Choledocolithiasis
- Ascending cholangitis
- Choledocal cyst
- Carcinoma of extrahepatic duct

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