Pathology of the Exocrine Pancreas and Extrahepatic Biliary Tract

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Learning Objectives

EXOCRINE PANCREAS

Acute Pancreatitis

- Definition
- Epidemiology
- Etiopathogenesis (with Emphasis on Alcohol and Gallstones)
- Gross and Microscopic Morphology
- Clinicopathologic Degrees of Severity (Interstitial, Necrotizing, Hemorrhagic),
- Clinical Manifestations
- Diagnostic Markers, (Prognosis, Treatment)
Learning Objectives

EXOCRINE PANCREAS

Chronic Pancreatitis

- Definition
- Morphology
- Etiopathogenesis
- Correlation between Pathology and Radiologic Appearance
- Clinical Manifestations and Complications
Learning Objectives

EXOCRINE PANCREAS

Pancreatic Adenocarcinoma

- Molecular/Morphological Progression from In-Situ to Invasive Cancer
- Epidemiology
- Morphology
- Spread
- Clinical Manifestations and Prognosis
Learning Objectives

BILIARY TRACT

Cholelithiasis
- Definition
- Epidemiology
- Classification of Gallstones into Types (Cholesterol and Pigment Stones)
- Differential Morphology and Pathogenesis of Cholesterol and Pigment Stones
- Risk Factors
- Clinical Manifestations
Learning Objectives

BILIARY TRACT

Complications of Cholelithiasis
- Acute Cholecystitis
- Acute Cholangitis
- Empyema
- Perforation
- Fistulas
- Gallstone Ileus
- Acute Pancreatitis
- Gallbladder Carcinoma

Acute Cholecystitis
- Clinical Manifestations and Complications
Learning Objectives

BILIARY TRACT

Chronic Cholecystitis
- Definition
- Main Pathological and Clinical Features

Acute Cholangitis
- Definition
- Causes and Typical Clinical Manifestations (Charcot Triad)

Carcinoma of the Gallbladder
- Etiopathogenesis
- Mode of Spread and Prognosis
Reading

ROBBINS AND COTTRAN 9TH ED.
PP. 856-857, 875-880, 883-894
THIS HANDOUT.
Exocrine Pancreas
Normal Pancreas

- Digestive Enzymes are Synthesized as Inactive Proenzymes
- Proenzymes are Activated by Trypsin
- Trypsin is Active by Duodenal Enteropeptides (Enterokinase)
- In other words – Intrapancreatic Activation is Minimal
- Acinar and Ductal Cells Secrete SPINK1 (Serine Protease Inhibitor Kazal Type 1)
Acute Pancreatitis

**Definition:** Inflammation due to *autodigestion* by inappropriately activated digestive enzymes

**Incidence:** 20/100,000 per year

- Most associated with **alcohol** or **gallstones**: 80%
- Several other etiologies

**M:F ratio**

- 6:1 in cases associated with alcohol abuse
- 1:3 in cases associated with biliary disease
Acute Pancreatitis:
Other Causes

**Obstructive:** Tumors, choledochocoele, parasites (Ascaris lumbricoides and Clonorchis sinensis)

**Metabolic:** Hyperlipoproteinemia, hypercalcemia

**Drugs:** > 80 drugs (diuretics, statins, HAART, valproic acid, oral contraceptives, ACE inhibitors)

**Mechanical:** Trauma, surgery, endoscopic procedures with dye injection (ERCP)

**Vascular:** Shock, embolism, vasculitis

**Infections:** Mumps, coxsackievirus, mycoplasma
Acute Pancreatitis: Genetics

**Genetics:** Mutations of

- **PRSS1** gene encoding *cationic trypsinogen*: Trypsin becomes resistant to inactivation by cleavage and will activate other proenzymes. *Autosomal dominant*

- **SPINK1** encoding *trypsin inhibitor*: Loss of trypsin inhibition, with inappropriate activation of trypsin. *Autosomal recessive*
Acute Pancreatitis: Pathologic Changes

1. Acute inflammation: **Edema** and neutrophilic infiltration

2. Activation of lipases and phospholipases: **Fat necrosis** in peripancreatic and omental adipose tissue

3. Activation of proteases: **Pancreatic necrosis**

4. Activation of elastase: digestion of vessel walls leading to interstitial **hemorrhage**
Acute Pancreatitis: Types

**Increasing degrees of severity**

1. **Acute interstitial pancreatitis:** Edema, fat necrosis in peripancreatic fat
2. **Acute necrotizing pancreatitis:** Parenchymal necrosis, areas of hemorrhage, fat necrosis in peripancreatic fat as well as in omentum, mesentery and subcutaneous fat
3. **Acute hemorrhagic pancreatitis:** Extensive parenchymal necrosis and hemorrhage, with near-total destruction of pancreas
Acute Pancreatitis:
Gross Changes

Fairly early acute pancreatitis with focal fat necrosis and hemorrhage
duke.edu

Advanced acute pancreatitis with fat necrosis and hemorrhage
radiopaedia.org
Acute Pancreatitis:

Gross Changes

Moderately advanced acute pancreatitis: Numerous yellow-white foci of fat necrosis

Severe acute pancreatitis: Large areas of hemorrhage in the pancreas
Normal Pancreas

[Image of a histological section of the pancreas highlighting islet cells and acinar cells]

https://pancreas.org/pancreas/normal-pancreas/
Acute Pancreatitis:
Microscopic Changes

Histopathologic hallmarks of acute pancreatitis:
Parenchymal necrosis (left) and fat necrosis (right)
Acute Pancreatitis: Microscopic Changes

Peripancreatic fat necrosis and hemorrhage
Acute Pancreatitis: Microscopic Changes
Acute Pancreatitis: Microscopic Changes

Extensive hemorrhagic necrosis leading to patient death
Acute Hemorrhagic Pancreatitis
Microscopic Changes

Pathology Outlines
Acute Pancreatitis: Clinical

**Acute abdomen**
- Severe, constant epigastric pain radiating to the back
- Nausea and vomiting

**Systemic manifestations:**
- Fever
- Shock
- Diffuse alveolar damage – ARDS
- Disseminated intravascular coagulation (DIC)
- Acute tubular necrosis (ATN) and acute renal failure
Acute Pancreatitis: Diagnosis, Treatment, Prognosis

Diagnosis:
- Blood levels of lipase (most specific marker) and amylase
- Other blood studies: Hyperglycemia, hypocalcemia, leukocytosis, mild elevation of liver enzymes
- Urinalysis for glycosuria
- Imaging studies: Ultrasound, CT, MRI

Treatment: Pancreatic rest by NPO, intravenous fluids, analgesics

Mortality: 5%, due to shock, DIC, ARDS, renal failure

Sequelae: Pancreatic pseudocyst, which may become infected, leading to abscess
Pancreas Edema

Pancreatic Hemorrhagic Necrosis
Pancreatic Pseudocyst

Sonogram showing **pseudocyst** (CYST). GB, gallbladder; MPV, portal vein. Behind the large pseudocyst is the calcified head of the pancreas. A dilated common bile duct (asterisk) is noted.

CT scan showing **pseudocyst**. Note the large, lobulated fluid collection (arrows) surrounding the tail of the pancreas (arrowheads). Note also the dense, thin rim in the periphery representing the fibrous capsule of the pseudocyst.
Chronic Pancreatitis

Chronic condition leading to loss of pancreatic parenchyma and **irreversible functional damage**

Causes overlap with those of acute pancreatitis:

- Alcohol - most
- Obstruction of pancreatic duct by tumors, pseudocysts, pancreas divisum, etc.
- Hereditary pancreatitis due to mutations of PRSS1 and SPINK1
- Cystic fibrosis
- Autoimmune – IgG4 related disease
- *Idiopathic*: About 40%, probably most caused by unrecognized genetic alterations
Chronic Pancreatitis: PATHOGENESIS

Due to **recurrent bouts of acute pancreatitis**, loss of pancreatic parenchyma and scarring

**Obstruction** of ducts by inspissated pancreatic excretion: prevalent in alcohol-induced cases

Production of **cytokines** that promote deposition of collagen and fibrosis: TGF-β and PDGF
Chronic Pancreatitis: Pathologic Changes

Scarring of the parenchyma, calculi and an extrapancreatic pseudocyst. nature.com
Chronic Pancreatitis: Pathologic Changes

**Atrophy** of the exocrine parenchyma with extensive fibrosis and calcium deposits

Residual ducts and islets of Langerhans

**Dilated ducts** filled with proteinaceous concretions

In late stages, islets also disappear
Chronic Pancreatitis: Pathologic Changes

Relatively early stage

Late stage
Chronic Pancreatitis: 
Pathologic Changes

Severe fibrosis with loss of acinar cells. Note residual islets (arrow head) of Langerhans and ducts (arrow).
Chronic Pancreatitis

**CT Scan:** Contrast-enhanced CT scan of the abdomen showing an atrophic pancreas with multiple calcifications (*arrows*). Note the markedly dilated pancreatic duct seen in this section through the body and tail (*open arrows*).
Chronic Pancreatitis: Pancreatic pseudocyst

Localized collection of necrotic and hemorrhagic material walled off by fibrous tissue

Usually arise after an episode of acute pancreatitis or trauma

No epithelial lining (unlike cystic neoplasms)

Can become infected, compress adjacent structures or perforate
Chronic Pancreatitis: Clinical manifestations

**Abdominal pain:** Recurrent or persistent, gets worse with eating and alcohol consumption

**Malabsorption:** Insidious development of pancreatic insufficiency and *weight loss, steatorrhea*

**Jaundice:** From compression of common bile duct

**Diabetes mellitus:** in late stages

**Pseudocyst:** Must be differentiated from cystic neoplasm
Pancreatic Neoplasms
Exocrine Pancreas

Cystic neoplasms
- Serous cystic neoplasms
- Mucinous cystic neoplasms
- Intraductal papillary mucinous neoplasms (IPMNs)
- Solid-pseudopapillary mucinous neoplasms

Pancreatic carcinoma (infiltrating ductal carcinoma)

Acinar cell carcinoma

Pancreatoblastoma
Pancreatic Adenocarcinoma

**Fourth** most frequent cause of cancer-related death in USA

Majority occur at 60-80 years of age

**Risk factors:**
- **Smoking** doubles the risk
- Fat-rich diet
- Chronic pancreatitis
- Gene mutations: Peutz-Jeghers syndrome, hereditary chronic pancreatitis, p-16 mutations, BRCA$_2$

**Carcinogenesis:** As in many other epithelial cancers, pancreatic adenocarcinoma is believed to progress from normal epithelium to precursor lesions (Pancreatic Intraepithelial Neoplasia – PanIN) to invasive carcinoma
Pancreatic Adenocarcinoma: Pancreatic Intraepithelial Neoplasia (PanIN)

PanIN: The epithelium of this pancreatic duct is hyperplastic and atypical: High nucleo-cytoplasmic ratio and crowding of epithelial cells
Pancreatic Adenocarcinoma:
Molecular Pathogenesis

NORMAL  PanIN-1A  PanIN-1B  PanIN-2  PanIN-3  INVASIVE CARCINOMA

Telomere shortening  Inactivation of p16  Inactivation of p53
Mutations of K-RAS  SMAD4  BRCA2

Pancreatic Adenocarcinoma: Pathology
Pancreatic Adenocarcinoma: Pathology

Poorly defined, firm, gray-white tumor in the head of pancreas.

Desmoplastic reaction (formation of fibrous tissue) is characteristic of this cancer.

Disorganized glandular structures surrounded by fibrotic stroma. Nerve infiltration is characteristic.
Pancreatic Adenocarcinoma: Pathology

2minutemedicine.com
Pancreatic Adenocarcinoma: Pathology
Pancreatic Adenocarcinoma:
Progression

Invasion of surrounding structures, lymphatic and hematogenous metastases occurs EARLY

Diagnosis made at late stages

Cancer of the head: obstruction of common bile duct and jaundice
  o Courvoisier law: Jaundice due to neoplasia causes dilatation of gallbladder, while jaundice due to stones does not distend the gallbladder since the gallbladder is usually fibrotic.

Cancer of body and tail: Remains silent for longer time

Invasion: Retroperitoneum, spleen, transverse colon, adrenals, spine, stomach

Metastases: Regional lymph nodes, liver and lungs
Pancreatic Adenocarcinoma: Clinical Manifestations

- Pain
- Obstructive jaundice
- Weight loss, anorexia, malaise
- **Trousseau sign:** Migratory thrombophlebitis due to secretion of procoagulants factors by the tumor in 10% of cases
- When diagnosed, 80% are inoperable
- Overall 5-year survival: <5%

Armand Trousseau (1801-1867)
Extrahepatic Biliary System
Cholelithiasis

In the US, >20 million people have gallstones, including 20% of women and 8% of men >40

- 40% of women > 65 have gallstones

**Cholesterol stones:** 80% of gallstones (90% in the West), composed of >50% of cholesterol monohydrate

**Pigment stones:** 20% of gallstones, composed predominantly of bilirubin and calcium salts and < 20% of cholesterol
Gallstones

Cholesterol stones:
Light yellow to brown, rather large

- Cholesterol mixed with variable amounts of calcium carbonate, phosphates, bilirubin
- 10-20% radio-opaque (due to calcium carbonate)

PIGMENT STONES:
BLACK OR BROWN, SMALL

- Black stones: Unconjugated bilirubin plus calcium salts, found in sterile bile, radiopaque
- Brown stones: Unconjugated bilirubin plus calcium soaps, found in infected bile, radiolucent
Cholesterol Stones: Pathogenesis

**Supersaturation:** Cholesterol concentration in excess of solvent capacity
- Increased cholesterol synthesis
- Decreased bile acid synthesis
- Decreased phospholipid secretion

**Nucleation:** Formation of cholesterol “nuclei,” tiny aggregates of cholesterol crystals
- Pro-nucleating factors: mucoproteins, immunoglobulins
- Anti-nucleating factors: apolipoproteins, lecithin

**Hypomotility** of gallbladder

**Accretion** within the mucous layer
Pigment Stones: Pathogenesis

**Black stones:** Occur in patients with chronic hemolytic conditions e.g. sickle cell anemia, thalassemia, megaloblastic anemia, etc.

- Other predisposing conditions: Cirrhosis, ileal disease or resection, cystic fibrosis

**Brown stones:** Result from deconjugation of bilirubin by $\beta$-glucuronidase produced by bacteria or parasites

- Associated with chronic gallbladder infection or infestation (liver flukes important in Eastern Asia)
### Gallstones: Risk Factors

<table>
<thead>
<tr>
<th>CHOLESTEROL STONES</th>
<th>PIGMENT STONES</th>
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<tbody>
<tr>
<td>Western countries, America</td>
<td>Asians more than Westerners</td>
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<tr>
<td>Age</td>
<td>Biliary infections (brown stones)</td>
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<tr>
<td>Females, oral contraceptives, pregnancy</td>
<td>Chronic hemolysis (black stones)</td>
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<tr>
<td>Obesity and rapid weight loss</td>
<td>Various GI disorders (black stones)</td>
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<td>Hyperlipidemia</td>
<td>– i.e. ileal resection or bypass, Crohn’s disease, cystic fibrosis</td>
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<tr>
<td>Inborn errors of bile acid metabolism</td>
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Cholelithiasis: Clinical Manifestations

Most are asymptomatic

Cumulative risk to become symptomatic is low:
- Rate of 1-4%/year

Biliary pain when a stone, usually small, becomes impacted in the cystic or common bile duct

RUQ or epigastric pain, constant, radiates to the right shoulder

Ultrasound of the biliary tract: Distended gallbladder containing a single large stone (arrow) which casts an acoustic shadow.
Cholelithiasis: Complications

1. **Acute cholecystitis**: Most frequent complication requiring surgery
2. **Acute cholangitis**: Infection of biliary tract, due to stones in the common bile duct
3. **Empyema**: Purulent infection of gallbladder, which becomes filled with pus
4. **Perforation**: Causes acute bilious peritonitis
5. **Fistulas**: Duodenum, colon, jejunum, stomach, abdominal wall, renal pelvis
6. **Gallstone ileus**: Bowel obstruction by a large stone that erodes directly into a bowel loop
7. **Acute pancreatitis**
8. **Gallbladder carcinoma**
Acute Cholecystitis

Most commonly due to stones blocking the cystic duct

Inflammation caused by:
- Ischemia of wall secondary to distention
- Breakdown of lecithin to lysolecithin by mucosal phospholipases
- Secondary bacterial infection: E. coli, Klebsiella, Streptococcus, Clostridium

Gallbladder is enlarged, tense, with blotchy serosal surface covered with fibrin. The lumen contains stones and cloudy or frankly purulent exudate.
Acute Cholecystitis: Clinical Manifestations

Two thirds of patients had previous attacks

Biliary pain that persists longer than 5 hours

Anorexia, nausea, vomiting, tachycardia

Low-grade fever

Mild leukocytosis (10,000-15,000s)

Signs of local peritoneal irritation: Rebound tenderness

Enlarged gallbladder, tense on palpation

Murphy sign: Pain on subcostal palpation during deep inspiration

No jaundice, unless the stone blocks the common bile duct
Acute Cholecystitis:
Complication

Empyema
Acute Cholecystitis: Complications

Gangrenous cholecystitis

Perforation
Gallbladder
Normal histology
Acute Cholecystitis
Acute Acalculous Cholecystitis

Ischemia
- Cystic artery is an end artery
- Edema of the wall
- Hypomotility

Biliary sludge – cystic duct obstruction

Risk factors
- Sepsis with hypotension
- Immunosuppression
- Diabetes mellitus
- Major trauma and burns
- Infections
Acute Acalculus Cholecystitis

Symptoms often insidious
Symptoms obscured by predisposing condition
Maintain high risk of suspicion
Delay in diagnosis can lead to gangrenous changes and perforation
Chronic Cholecystitis

Associated with cholelithiasis in 90% of cases

Due to recurrent bouts of acute cholecystitis or manifesting without preceding attacks

Unclear pathogenesis: Bile supersaturation common cause of both chronic cholecystitis and stone formation and chronic low grade inflammation

In 1/3 of cases bacteria are present

Asymptomatic or manifests with biliary pain, acute cholecystitis or complications

Thick fibrotic walls in chronic cholecystitis
Chronic cholecystitis

Mucosal and subserosal chronic inflammation

Thickened muscular layer

Outpouching of mucosa through the muscular layer (Rokitansky-Aschoff sinuses)
Chronic Cholecystitis: Complication

Porcelain Gallbladder
Chronic Cholecystitis: Complication

Porcelain Gallbladder

@GIPathologyURMC
Acute Cholangitis

Gallstones in the common bile duct (choledocholithiasis) usually come from the gallbladder, leading to **acute cholangitis**

Bacteria present in 75% of cases (ascending infection)

*Treatment:* Antibiotics, ERCP with sphincterotomy

Endoscopic retrograde cholangiogram (ERC) showing choledocholithiasis. The biliary tract is dilated and contains multiple radiolucent calculi.
Acute Cholangitis

Charcot’s triad
- Fever
- Jaundice
- RUQ pain (usually with rigors)

Reynold’s pentad
- Fever
- Jaundice
- RUQ pain (usually with rigors)
- Altered mental status
- Hypotension
Carcinoma of the Gallbladder

Incidence: 2/100,000

Usually diagnosed at late stages: 5-year survival is 5%

**Cholelithiasis** is the most important risk factor

Other predisposing condition: Infectious agents
Carcinoma of the Gallbladder

Early
Intermediate
Late
Tumour-specific

Age (years)

~30–40
Normal gallbladder
Gallstones and chronic inflammation

~45
Dysplasia

~55
Carcinoma in situ

~60
Invasive carcinoma

TP53 mutations
mDNA mutations
COX2 overexpression
Methylation of TSG promoters

Loss of heterozygosity at 3p and 8p

Mutations in FHIT and CDKN2A
Loss of heterozygosity at 9q, 18q and 22q

KRAS mutations

Nature Reviews, Cancer 2004, 4: 695
Carcinoma of the Gallbladder

Gallbladder carcinoma invading the liver and regional lymph nodes

Most cases are adenocarcinomas

Clinical presentation similar to that of cholelithiasis. Clinical detection is usually too late for curative treatment.
Gallbladder
Unknown
Pancreatitis

Hi Pancweas!

I maked these!

you like dem?
QUESTIONS?