Cholecystitis
  acute
  chronic
Gallbladder tumors
  Adenomyoma (benign)
  Adenocarcinoma

Pancreatitis
  acute
  chronic

Pancreatic tumors

Intro to Gallbladder & Pancreas Pathology

Helen Remotti M.D.

Gallstones (Cholelithiasis)

- 10 - 20% Adults
- 35% Autopsy: Over 65
- Over 20 Million
- 600,000 Cholecystectomies
- #2 reason for abdominal operations

Cholesterol/mixed stones

Choledocholithiasis (Stones in the common bile duct)

- Pain: Epigastric, RUQ-stones may be passed
- Obstructive Jaundice-may be intermittent
- Ascending Cholangitis - Infection: to liver
- 20%: No pain; 25% no jaundice

Acute cholecystitis = ischemic injury

Chronic Cholecystitis

- Associated with calculi in 95% of cases.
- Multiples episodes of inflammation cause GB thickening with chronic inflammation/ fibrosis and muscular hypertrophy.
- Rokitansky - Aschoff Sinuses (mucosa herniates through the muscularis mucosae)
- With longstanding inflammation GB becomes fibrotic and calcified “porcelain GB”
Chronic Cholecystitis

- Fibrosis
- Chronic Inflammation
- Rokitansky - Aschoff Sinuses
- Hypertrophy: Muscularis

Chronic cholecystitis

Cholesterolosis

Focal accumulation of cholesterol-laden macrophages in lamina propria of gallbladder (incidental finding).

Rokitansky-Aschoff sinuses

Adenomyoma of Gall Bladder
Carcinoma: Gall Bladder

Uncommon: 5,000 cases / year
Fewer than 1% resected G.B.
Sx: same as with stones
5 yr. survival: Less than 5%
(survival relates to stage)

90%: Stones
Long Hx: symptomatic stones
Stones: predispose to CA., but uncommon complication
Case 1

56 year old woman presents to ER in shock, following rapid onset of severe upper abdominal pain, developing over the previous day.

Hx: heavy alcohol use.

LABs: Elevated serum amylase and elevated peritoneal fluid lipase

Acute Pancreatitis

Patient developed rapid onset of respiratory failure necessitating intubation and mechanical ventilation.

Over 48 hours, she was increasingly unstable, with evolution to multi-organ failure, and she expired 82 hours after admission.

An autopsy was performed.

Elastase destruction of blood vessels – with hemorrhage
**Acute Pancreatitis**

- Edema, congestion
- Advanced hemorrhagic pancreatitis, fat necrosis
- Necrotic abscess, gangrene

**Chronic Pancreatitis**

Continuing inflammation with irreversible changes in architecture, structure and function.

Fibrosis of parenchyma with distortion of duct architecture, loss of exocrine secretory function.

Changes may be focal or widespread.

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**Pathophysiology of acute pancreatitis**

<table>
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<th>Stage</th>
<th>Description</th>
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| Stage 1 | Pancreatic injury  
   Edema, inflammation, fat necrosis, variable necrosis of pancreatic secretory cells |
| Stage 2 | Local (peripancreatic) effects  
   Retroperitoneal edema, extensive fat necrosis, tissue with "third-spacing" of fluid and electrolytes |
| Stage 3 | Systemic complications  
   Hypotension/shock, metabolic disturbances, organ failure, sepsis |

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**Acute Pancreatitis**

US: 45% of cases have gallstones and choledocholithiasis;  
35% associated with heavy alcohol ingestion

Pathology: Enzyme release is triggered with digestion of pancreas, necrosis of fat and lobules, hemorrhage from damaged blood vessels.

Variable severity: may lead to liquefactive necrosis, hemorrhage.  
Mild cases – may have local complications: abscess, pseudocyst.
Chronic pancreatitis

Complications of Chronic Pancreatitis
Chronic abdominal pain, severe and unremitting, radiating to back
Malabsorption due to reduced enzyme secretion. (After 90% of pancreas is fibrotic, reduced lipase and trypsin secretion lead to steatorrhea).
Pancreatic diabetes associated with decreased islets.
Pancreatic pseudocysts with extension or rupture in adjacent organs.

Case 2
67 year old woman with recent onset painless jaundice.
History of 15lb weight loss over last 3 months.
She smoked 1 pack per day x 35 years.
Physical exam: palpable GB
ERCP was performed with Endoscopic Ultrasound (EUS) evidence of a large mass in the head of the pancreas.
An endoscopic FNA was performed.

Curvoissier’s Law – enlarged palpable GB

Patient’s FNA
Dx: Adenocarcinoma

Normal pancreas ductal epithelium
Pancreatic Ductal Adenocarcinoma: Clinical

- Represents the most common pancreatic neoplasm
- 2nd most common GIT cancer
- 4th leading cause of cancer death
- M > F; > 50 years at initial presentation usually
- Symptoms:
  - Abdominal pain, weight loss, jaundice, pancreatic insufficiency, malabsorption; Migratory thrombophlebitis – “Trouseau’s sign”
- Site:
  - head (60-70%) > body (10-15%) > tail (5-10%)
- Contributing factors:
  - smoking, carcinogens, genetics

Pancreatic Ductal Adenocarcinoma: Pathology

- Macroscopic:
  - Usually a solitary mass
  - poor demarcation
  - firm to gritty consistency
  - depends upon location, but bile stasis specifically for the head of pancreas neoplasms

Chronic Pancreatitis:

Pancreatic Ductal Adenocarcinoma: FNA
Normal  AdenoCA

Invasion into peripancreatic soft tissue

Benign – lobular  Malignant- haphazard

Pancreatic adenocarcinoma – Lymph node metastases

Invasive growth with associated desmoplasia

Pancreatic adenocarcinoma – perineural invasion
**Pancreatic Ductal Adenocarcinoma: Pathology**

- Microscopic:
  - loss of lobular architecture
  - architectural and cytomorphologic features indicative of malignancy:
    - loss of cell differentiation, hyperchromatic nuclei, increased N:C, prominent nucleoli, mitotic activity
  - intraductal carcinoma
  - invasive growth associated with desmoplasia
  - neurotropism, extratumoral vascular invasion
  - extension into peripancreatic soft tissue
  - secondary pancreatitis due to obstruction

**Definition of Tumor (T)**

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis In situ carcinoma
- T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
- T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
- T3 Tumor extends directly into any of the following: duodenum, bile duct, peripancreatic tissues
- T4 Tumor extends directly into any of the following: stomach, spleen, colon, adjacent large vessels

**Critical area to evaluate - uncinate margin**

Margin most likely To be positive is the Uncinate margin - Retropertitoneal/mesenteric Margin along the right Lateral border of the SMA And should be inked.

**Pancreatic Cancer Prognosis**

- 2 yr survival – 28%
- 5 yr survival – 3-12%

- Mean survival in untreated patients 3 mo.
- Mean survival after radical resection 10-20 mo

- (Less than 20% of patients are surgical candidates).

**Pancreas Cancer Genetics**

5-10% of cases are familial, some with defined genetic syndromes

Hereditary Pancreatitis: germline mutations in trypsinogen gene on 7q35 with 40% lifetime risk of developing pancreatic cancer.

Pancreatic cancers described in BRCA2 mutations in familial breast cancer kindreds.

Associated with germline p16 mutations, and HNPCC.

Role of oncogenes: KRAS-90%, p16-95%, p53-75%
In-situ progression to Cancer

Pan IN (Pancreatic Intraepithelial Neoplasia)
PanIN-3 – cribriform, papillary, micropapillary (rarely flat)
(marked loss of polarity, nuclear crowding, enlarged nuclei,
pseudostratification, and hyperchromasia, abnormal mitoses)

Pan IN (Pancreatic Intraepithelial Neoplasia)
PanIN-1A-flat epithelium; basal nuclei, abundant supranuclear cytoplasm
PanIN-1B – papillary, micropapillary architecture; cytology same as 1A.

Pan IN (Pancreatic Intraepithelial Neoplasia)
PanIN-2- flat or papillary, micropapillary; some nuclear abnormalities
(some loss of polarity, nuclear crowding, enlarged nuclei,
pseudostratification, and hyperchromasia – but less than PanIN-3)

Pancreatic Cystic Lesions
- *Mucinous cystic neoplasm* (benign, borderline or malignant)
- *Intraductal papillary mucinous neoplasm* (benign, borderline or malignant)
- *Serous cystadenoma* (benign)
- *Pseudocyst* (benign – NOT a NEOPLASM)

PANCREATIC CYSTIC LESIONS

MCN
Mucinous cystic Neoplasm
NOT connected with pancreatic ducts!

Mucinous cystadenocarcinoma

Mucinous cystadenoma

Mucinous Cystic Neoplasms

MCNs

Mainly Females (mean age 45)
Abdominal Pain or Mass

Sample extensively to rule out invasive component

Classification:  Mucinous cystadenoma (minimal atypia)
   Borderline MCNs (moderate atypia, papillary architecture)
   MCN with CIS (high grade cytology, cribriform architecture)
   Invasive CA (destructive stromal invasion, usual ductal CA)

Gross:  large (mean 10cm); Body/Tail; Multilocular, unilocular rare
No communication with pancreatic duct.

Micro:  Columnar mucin cells, intestinal or gastric foveolar type.
   Ovarian stroma (ER+, PR+, inhibin+)
   DD:  IPMN (Head/communicate with duct, no ovarian stroma)
   Pancreatic Pseudocyst (MCN lining can be denuded)

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Clinical spectrum: benign to malignant

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Mucinous epithelium; “ovarian type stroma”
Clinical spectrum: benign to malignant

PANCREATIC CYSTIC LESIONS

MCN
IPMN
Intraductal Papillary Mucinous Neoplasm (IPMN)

Communicates with duct Mucin oozes out of ampullae

Intraductal Papillary Mucinous Neoplasm (IPMN)

- IPMT (first named in 1995)
- Radiologic or grossly visible lesion (>1cm)
- Contiguous or multicentric with cytologic atypia
- Head of pancreas; More common in male >60 y.
- Invasive tumors associated with 30% of IPMNs (often colloid type – more indolent clinical behavior than usual invasive ductal-NOS.)
- Resection often with frozen sections, since most lesions are contiguous.
- Grade (Benign, Borderline, Intraductal CA);
- DD: Mucinous cystic neoplasms, PanIN (resembles small IPMN)

IPMNs (Intraductal Papillary Mucinous Neoplasms)

Associated with the pancreatic duct Clinical spectrum: benign to malignant

PANCREATIC CYSTIC LESIONS

Serous Cystadenoma
IPMN
MCN
Pancreatic serous cystadenoma

- Aka microcystic adenoma, glycogen rich adenoma
- F/M = 7/1; mean age 66y
- Association with von Hippel Lindau syndrome
- Symptoms: none, local pain, obstruction if in head
- Clinical behavior: benign
- Gross: mean 11 cm; multiloculated mass, cysts filled with clear fluid; spongy; often central scar.
- Micro: small cystic spaces lined with cuboidal cells with clear cytoplasm (glycogen rich); round nuclei; some cases papillary.

Pancreatic Pseudocyst

- Not neoplastic - result of acute pancreatitis
- Localized collections of pancreatic secretions that follow pancreatitis, trauma, ductal calculi.
- Symptoms: Painful, Hemorrhage, Infection, Perforation
- Treatment: excise small pseudocysts in body/tail; drain cysts in head.
- Gross: 85% solitary, usually unilocular in/near pancreas; thick irregular wall, ragged inner surface.
- Micro: No epithelial lining, fluid has high amylase
- Cyst arises from drainage of pancreatic secretions from damaged ducts into interstitial tissue; wall consists of fibrous tissue/granulation tissue.

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Pancreatic Endocrine Neoplasms

- 5% of pancreatic neoplasms
- “Islet cell Tumors” – inaccurate; arise from pluripotential ductal cells that differentiate along neuroendocrine lines.
- All have malignant potential except microadenomas (<5mm); No definite criteria to distinguish between benign and malignant (except for mets)
Pancreatic Endocrine Neoplasms

Microscopic

Nests of uniform polygonal cells
Delicate vasculature
Salt and Pepper (stippled) chromatin.
Often (no necrosis, low mitotic activity)
Immunostains do not correlate with secretion.
(Other than chromogranin and synaptophysin; specific stains: glucagon, insulin, PP, VIP, ACTH, somatostatin not really useful.)

Pancreatic Endocrine Neoplasms

Functional - recognizable syndrome; detect hormone in serum.
- Insulinoma (most common); hypoglycemia; 10% malignant
  - 10% assoc with MEN1
- Gastrinoma; duodenal ulcers; 75% malignant
  - 25% assoc with MEN1

Nonfunctional - no syndrome; normal serum hormone levels (except Pancreatic Polypeptide).
- Incidental; Obstructive Sx- head of pancreas; 50 – 90% malignant.

Pancreatic Endocrine Neoplasms

- Usually occur in body/tail
- Hypervascular, circumscribed
- Highlighted with Octreotide Scan (somatostatin receptors)
- Usually slow growing, mets to LNs, liver, bone (recommend resection of mets)
Pancreatic Endocrine Neoplasms

Classification:

Neuroendocrine neoplasm, well differentiated
- Low grade: 0-1 mit/50HPF; no necrosis
- Intermediate grade: >2mit/50 HPF; +/- necrosis

Neuroendocrine carcinoma, high grade
Small cell carcinoma / large cell neuroendocrine
- High grade: >10mit/10 HPF; widespread necrosis