Most Significant/Common Diseases (Focus of Lecture)

- Acute Pancreatitis
- Chronic Pancreatitis
- Pseudocysts
- Pancreatic Adenocarcinoma

Additional Topics

- Congenital anomalies
- Cystic Neoplasms
REVIEW
Pancreas Anatomy

Normal Pancreas

Islets
Duct
Ductule
Exocrine Pancreas: Acinar cells secrete digestive enzymes and proenzymes

Small ductules secrete bicarbonate

Larger ducts produce mucin
Endocrine Pancreas: Islets of Langerhans secrete insulin, glucagon, somatostatin, PP, VIP and Serotonin

Function

- Endocrine pancreas secretes insulin which controls the blood sugar; also secretes other hormones – including glucagon
- Exocrine pancreas produces and delivers 2-2.5 liters/day of bicarbonate rich fluid containing digestive enzymes and proenzymes

With such powerful enzymes .... Why doesn’t pancreas digest itself?
SELF-DIGESTION PREVENTED BY:

- Inactive proenzymes are synthesized (exception: amylase and lipase)
- Enzymes are in membrane bound zymogen granules
- Activation of proenzymes requires activation of trypsinogen to trypsin
- *Trypsin inhibitors are present*
- *Trypsin can inactivate itself*
- Resistance of acinar cells

ACUTE PANCREATITIS

- Acute inflammatory process of the pancreas
  - Usually associated with acinar cell injury
  - Usually nonprogressive
- Range from mild self limited disease to a life threatening acute inflammatory process

Acute Pancreatitis

- Characterized by acute onset of abdominal pain resulting from enzymatic necrosis and inflammation of the pancreas
- 10-20 cases per 100,000
- 80% of cases associated with biliary tract disease or alcohol(ism)
  - Male:Female
    - 1:3 biliary tract disease
    - 6:1 alcoholism
Etiologic Factors

- Obstruction of pancreatic ductal system
  - Gallstones
  - Papillary neoplasms
  - Other (choledochocles, divisum, parasites)
- Alcohol
  - Drugs [Azathoprine, estrogens, furosemide, many more]
- Trauma
- Metabolic
  - Hypertriglyceridemia, hyperparathyroidism - hypercalcemia
- Vascular (ischemia)
  - Shock, emboli, vasculitis (PAN)
- Infectious
- Mumps
- Genetic
  - Mutations in cationic trypsinogen and trypsin inhibitor gene

Pathogenesis Summary

- Anatomic changes of acute pancreatitis suggest autodigestion of pancreatic substance by inappropriately activated pancreatic enzymes
Acute pancreatitis

1. Microvascular leakage causing edema
2. Necrosis of the fat by lipolytic enzymes
3. Acute inflammation
4. Proteolytic destruction of pancreatic parenchyma
5. Destruction of blood vessels and subsequent interstitial hemorrhage

Acute necrotizing and hemorrhagic pancreatitis

Acute pancreatitis histology

Parenchymal necrosis
Fat necrosis
Acute Pancreatitis
• Clinicopathologic correlation
  – Abdominal pain
  – Elevated plasma amylase and lipase
  – Diffuse fat necrosis  hypocalcemia
  – Acute respiratory distress syndrome
  – Acute renal failure
  – Disseminated intravascular coagulation
  – Fluid sequestration
• Full blown acute pancreatitis is a medical emergency!

Acute Pancreatitis
• Treatment
  – Supportive
    • Analgesia
    • IV fluids
    • Correction of electrolyte abnormalities
    • Oral intake when pain improves (mild pancreatitis)
  – Address underlying cause

Acute Pancreatitis
• Sequelae
  – 5% death
  – Pancreatic abscess
  – Pancreatic pseudocyst
  – Infected necrotic debris
CHRONIC PANCREATITIS

• Definition
  – Progressive fibroinflammatory process of the pancreas that results in permanent structural damage
    • Repeated bouts of mild to moderate pancreatic inflammation ->
    • Continued loss of pancreatic parenchyma ->
    • Replacement by fibrous tissue ->
    • Irreversible impairment in pancreatic function
      – Exocrine followed by endocrine

Chronic Pancreatitis

• Predisposing factors
  – LONG TERM ALCOHOL ABUSE
  – Long standing obstruction
    • Biliary tract disease/calculi
    • Pancreas divisum
    • Neoplasms, pseudocysts
  – Tropical pancreatitis – Africa and Asia
  – Hereditary pancreatitis
  – Cystic fibrosis transmembrane conductance regulator gene mutation
  – Idiopathic (up to 40%)

Chronic Pancreatitis

Proposed pathogenetic mechanisms

• Hypersecretion of protein; insufficient ductal bicarbonate
  – Proteinacious plugs form within ducts, obstruct ducts
    • Nucleus for calcification, stone formation
    • Duct injury, scar ->Further obstruction

• Direct toxic effect

• Antioxidant imbalance
  – Generation of free radicals in “stressed” acinar cells ->
    injury

  – Profibrinogenic cytokines
Chronic Pancreatitis

- Pathology
  - Fibrosis
  - Reduced number and size of acini (exocrine pancreas)
  - Obstruction and dilatation of pancreatic ducts
    - Protein plugs
  - Late stage loss of Islets of Langerhans (endocrine pancreas)
  - Pseudocyst formation
  - Calcified concretions

Chronic pancreatitis

Normal

Ductal dilatation
calcifications

Chronic pancreatitis

Extensive fibrosis
Rare acinar tissue
Residual islets

Dilated duct
Inspissated concretions
Chronic Pancreatitis

- Clinico-pathologic correlation
  - Recurrent attacks of abdominal pain
    - Radiation of pain to back
    - Triggers - ETOH, overeating, opiates
  - Recurrent attacks of jaundice or vague indigestion
  - Exocrine pancreatic insufficiency
    - Steatorrhea
  - Diabetes mellitus
  - Pancreatic calcifications on imaging

Extensive Pancreatic Calcifications
PANCREATIC PSEUDOCYSTS

- Localized collections of pancreatic secretions in pancreatic interstitium as a result of damaged ducts
  - Acute or Chronic Pancreatitis or Trauma
- Lacks a true epithelial lining
- Abdominal mass, abdominal pain
  - May become infected/hemorrhage

Pancreatic pseudocyst

A 42-year old obese woman presents with a 1 day history of severe abdominal pain which radiates to her back. She has no known medical problems. She does not smoke cigarettes. She drinks one glass of wine ~twice per month. There is no history of drug abuse. She takes ranitidine as needed for heartburn. Her BP is 90/45, respirations 32/min, pulse 104/min. Physical exam shows marked epigastric tenderness to palpation. Laboratory studies reveal elevated serum amylase (850 U/L) and lipase (675 U/L) and hypocalcemia. Which of the following is most likely associated with the pathogenesis of this patient’s condition?

A. Alcohol abuse
B. Carcinoid tumor
C. Cholelithiasis
D. Hypoparathyroidism
E. Hypercholesterolemia
**Pancreatic Carcinoma**

AKA Infiltrating ductal adenocarcinoma of the pancreas

- 4th most frequent cause of cancer death in US
- Pathogenetic factors
  - Pancreatic intraepithelial neoplasia (PanIN)
    - Precursor lesions
  - Smoking
  - Familial clustering has been reported
  - Chronic pancreatitis
  - Diabetes mellitus

**Molecular Carcinogenesis**

PanIN = Pancreatic Intraepithelial Neoplasia

**Pancreatic Carcinoma**

- Pathology
  - Location
    - Head of Pancreas (60%)
    - Body (15%)
    - Tail (5%)
    - Diffuse (20%)
  - Gritty gray-white solid firm masses
Pancreatic Carcinoma

- Histology
  - Adenocarcinoma
    - Poorly formed infiltrating glands
    - Majority of ductal origin
  - Dense stromal fibrosis “desmoplastic response”

- Local invasion
  - Adjacent nerves
  - Spleen, adrenals, transverse colon, stomach, vertebral column
    - Regional lymph nodes involved
      - Peripancreatic, gastric, mesenteric, omental, portahepatic
  - Distant metastases
    - Liver, lungs, bones

Perineural invasion
Pancreatic Carcinoma

• Clinico-pathologic correlation
  — Remain clinically silent until tumor impinges on other structures
  — Obstructive jaundice
  — Pain is usually first symptom
  — Weight loss, anorexia, malaise, weakness signs of advanced disease

  — Tumor markers: Elevated CA19-9 and CEA in some cases

Pancreatic Carcinoma

• Head of pancreas
  — “Obstructive jaundice”
    • Tumor obstructs ampullary region/common bile duct
    • Obstruction prevents conjugated bile from entering duodenum, bile pressure increases in the biliary tract, and conjugated bile enters the vascular space
    • Distention of biliary tree

Pancreatic Carcinoma

• Body and Tail of Pancreas
  — Does not impinge on biliary tract
  — “Silent” for a long time
  — Large, locally invasive, disseminated at time of diagnosis
Pancreatic Carcinoma

Trousseau Sign
- Migratory thrombophlebitis
  - Spontaneously appearing and disappearing venous thromboses
- 10% of patients
- Attributed to elaboration of platelet-aggregating factors and procoagulants from tumor

Pancreatic Carcinoma

- Symptomatic course of disease
  brief/progressive
- Less than 20% of tumors are resectable at time of diagnosis
- < 5% 5 year survival

Pancreatic ca with a stent
Pancreatic Cystic Neoplasms

- Serous Cystadenoma
- Mucinous Cystic Neoplasms
- Intraductal Papillary Mucinous Neoplasms

<table>
<thead>
<tr>
<th>Pancreatic Cystic Neoplasms</th>
<th>Behavior</th>
<th>Gross morphology</th>
<th>Histopathology</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous Cystadenoma</td>
<td>Benign</td>
<td>Small cysts</td>
<td>Small cysts lined by cuboidal cells which are glycogen-rich</td>
<td>Female to male 2:1, Age 70s, Nonspecific symptoms</td>
</tr>
<tr>
<td>Mucinous Cystic neoplasms</td>
<td>Malignant</td>
<td>Cysts filled with thick mucin</td>
<td>Cysts lined by columnar epithelium</td>
<td>Majority women, Painless, slow growing masses</td>
</tr>
<tr>
<td>Intraductal Papillary Mucinous Neoplasms (IPMN)</td>
<td>Benign to malignant</td>
<td>Arise in main pancreatic duct or major branch</td>
<td>Lined by columnar epithelium</td>
<td>Men &gt; women, Head of pancreas</td>
</tr>
</tbody>
</table>

Whipple Procedure
Serous Cystadenoma

- Benign cyst composed of cuboidal glycogen rich cells

Pancreatic Mucinous Cystadenoma

Pancreatic Mucinous Cystadenocarcinoma

Dysplasia with invasion through basement membrane into stroma = Cystadenocarcinoma
IPMN
Main pancreatic duct distended by tumor
Extending into smaller ducts
Mucinous epithelial cells
Invasion = malignant adenocarcinoma

Congenital Anomalies
- Agenesis
  - Absence of pancreas
- Annular pancreas
  - Ring of pancreatic tissue encircles duodenum
- Pancreas Divisum
- Ectopic pancreas

Pancreas Divisum
- Failure of fetal duct system to fuse
- 3-10% population
- Increased pancreatic pressure ➔
- Possible Chronic pancreatitis
Ectopic Pancreas

- Displaced pancreatic tissue
  - 2% of autopsies
  - Stomach and duodenum, jejunum, Meckel diverticulum, ileum
    - Submucosa
  - Few millimeters to centimeters
  - Glands (ducts and acinar tissue) and islets of Langerhans
  - Asymptomatic or pain, mucosal bleeding
  - 2% of islet cell neoplasms

A 51-year-old man has a history of chronic alcohol abuse. He has had multiple bouts of epigastric abdominal pain in the past year. For the past month, he has had more frequent and worsening abdominal pain. Physical examination reveals right upper and left upper quadrant pain. An abdominal plain film radiograph reveals no free air, but there is extensive peritoneal fluid collection along with dilated loops of small bowel. An abdominal CT scan reveals an 8 cm cystic mass in the tail of the pancreas. Which of the following is the most likely diagnosis?

A. Pancreatic adenocarcinoma
B. Pancreatic pseudocyst
C. Acute pancreatitis
D. Pancreatic mucinous cystadenoma