Pathology of the Exocrine Pancreas - Handout

Acute Pancreatitis

- What is Acute Pancreatitis?

  It is an **acute** inflammatory process of the pancreas that is associated with acinar cell injury.

  With respect to severity it can range from mild self-limited disease to a life threatening acute inflammatory process.

  ~20% of patients with acute pancreatitis have a severe course; up to 30% of patients with severe acute pancreatitis die.

- What are the 2 most common causes of acute pancreatitis?

  ALCOHOL (alcoholism with regular heavy alcohol use)

  GALLSTONES

- Describe the pathogenesis of acute pancreatitis.

  Ultimately the inappropriate activation of enzymes inside the pancreas leads to autodigestion.

  There is inappropriate activation of trypsinogen to trypsin (the key enzyme in the activation of pancreatic zymogens) and a lack of prompt elimination of active trypsin inside the pancreas. Activation of digestive enzymes causes pancreatic injury and results in an inflammatory response that is out of proportion to the response of other organs with a similar insult.

  The acute inflammatory response itself causes substantial tissue damage and may failure or death.

- Describe how alcohol or biliary tract disease spark the pathogenesis of acute pancreatitis.

  Alcohol may act as a toxin that directly injures acinar cells releasing activated enzymes which autodigest the pancreas. Alcohol may also lead to defective intracellular transport of proenzymes to the lysosomal compartment which lead to intracellular activation of enzymes and acinar cell injury.

  Biliary obstruction, such as by gallstones, can lead to reflux of bile into the pancreatic ducts. This increased back-pressure leads to acinar cell injury.

  See Robbins Figure 16-2
• What are some other causes of acute pancreatitis, besides alcohol and gallstones?

The list is long:

Drugs – 100 or more drugs have been thought to cause acute pancreatitis. Azathioprine and estrogens are 2 of the most commonly implicated.

Direct trauma to the pancreas

Vascular – Hypotension, emboli, vasculitis – all leading to ischemic injury to the pancreas

Hypertriglyceridemia

Marked hypercalcemia (particularly in the face of hyperthyroidism) – calcium is thought to activate trypsin in the pancreas

Infections – such as mumps

Hereditary/Genetic causes - Mutations in cationic trypsinogen and trypsin inhibitor gene

Idiopathic – of unknown causes

• Describe the pathologic findings seen in 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

• What is hemorrhagic pancreatitis?

This is the most severe form of acute pancreatitis – extensive parenchymal necrosis is accompanied by diffuse hemorrhage within the gland.

• What are the typical clinical manifestations of acute pancreatitis?

Sudden onset of severe abdominal pain which may radiate to the back
Nausea and vomiting
Fever, sweating, tachypnea, and tachycardia

• Which enzymes appear in high concentration in the blood during acute pancreatitis?

Amylase: It is a sensitive marker of acute pancreatitis. However, hyperamylasemia is not specific for acute pancreatitis, and it may be of extrapancreatic origin.

Lipase: Is more specific than amylase.
Why can hypocalcemia develop during acute pancreatitis?

Fat necrosis leads to local formation of calcium soaps, and this process consumes calcium from the blood, typically leading to hypocalcemia 2 to 4 days after the onset of acute pancreatitis.

What is the approach to treatment of acute pancreatitis?

Supportive (ie support complications of acute renal failure, ARDS, DIC)
Analgesia
IV fluids (patients may have extensive fluid sequestration)
Correction of electrolyte abnormalities
Oral intake when pain improves in mild pancreatitis
Antibiotics with evidence of infection of necrotic debris or abscess formation
Address underlying cause

Chronic Pancreatitis

What is chronic pancreatitis?

A progressive fibroinflammatory process of the pancreas that results in permanent structural damage and loss of exocrine followed by endocrine function. Chronic pancreatitis may become a debilitating disease characterized by chronic pain, malabsorption, diabetes mellitus.

What are causes of chronic pancreatitis?

Chronic pancreatitis may be the outcome of recurrent attacks of acute pancreatitis. The most common cause is chronic alcohol abuse

Other predisposing factors:
Long standing biliary obstruction: Calculi, Pancreas divisum, Neoplasms, Pseudocysts
Tropical pancreatitis – Africa and Asia
Hereditary pancreatitis
Cystic fibrosis transmembrane conductance regulator gene mutation
Idiopathic (up to 40%)

What are the proposed pathogenetic mechanisms of chronic pancreatitis?

Mechanisms may include:

-Hypersecretion of protein with insufficient ductal bicarbonate leading to proteinacious plug formation within ducts. This obstruct ducts and serves as a nidus for calcification and stone formation. Duct injury leads to scar formation and further obstruction
-Direct toxic effects on the acinar pancreas with microinjury and fibrosis.
-Antioxidant imbalance in the setting of “stressed” acinar cells which generate free radicals leading to cellular injury.
- Profibrinogenic cytokines play a key role in the development of fibrosis.

- What are the morphologic changes seen in chronic pancreatitis?
  
  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 (can be seen on radiographic images)

- What are the clinical manifestations of chronic pancreatitis?
  
  Persistent upper abdominal pain radiating to the back, often precipitated by alcohol
  (These symptoms are related to the involvement of nerves by fibrosis.)
  Malabsorption due to pancreatic insufficiency—steatorrhea and vitamins A, D, E, and K
  deficiency
  Diabetes mellitus due to pancreatic endocrine insufficiency

**Pancreatic Pseudocyst**

- What is a pancreatic pseudocyst?
  
  A localized collection of pancreatic secretions in pancreatic interstitium as a result of damaged ducts.
  Importantly – a pseudocyst LACKS a true epithelial lining. The “Wall” of the pseudo cyst is formed by compressed pancreatic tissue, granulation tissue, chronic inflammation.

- What are causes?
  
  Acute pancreatitis, chronic pancreatitis, trauma.

- Are there complications?
  
  They may cause a mass effect, become infected, rupture.

**Pancreatic Cancer (Ductal Adenocarcinoma)**

- Summarize the epidemiology of pancreatic cancer
  
  The median age at diagnosis is 71 years old; it is rarely diagnosed in patients <40 years old.
  It is a common cancer which is lethal; >90% of patients diagnosed with pancreatic cancer die from the disease.
• What are risk factors associated with pancreatic cancer?
  
  Smoking
  Long standing diabetes mellitus
  Chronic pancreatitis
  Familial clustering has been reported

• What is the precursor lesion and associated molecular pathogenesis?

  There is a very high rate of KRAS mutations in pancreatic adenocarcinoma. The majority are of ductal origin.
  The precursor lesion is pancreatic intraepithelial neoplasia. There is a stepwise progression of pancreatic intraepithelial neoplasia from low grade to high grade. These are associated with accumulating genetic alterations.

• Describe the morphologic features of pancreatic cancer.

  These cancers appear as gray-white gritty, firm masses. With respect to location in the pancreas where they arise in:
  Head of Pancreas (60%)
  Body (15%)
  Tail (5%)
  Diffuse (20%)

  Histologically they are composed of poorly formed glands which incite dense stromal fibrosis (desmoplasia).
  The tumors invade
  Adjacent nerves
  Spleen, adrenals, transverse colon, stomach, vertebral column
  Regional lymph nodes: Peripancreatic, gastric, mesenteric, omental, portahepatic

  Distant metastases to Liver, lungs, bones

• Describe the clinical manifestations of pancreatic cancer.

  Most cancers remain clinically silent until the tumor impinges on other structures
  Pain is usually first symptom
  Obstructive jaundice with tumors arising in the head of the pancreas
  Weight loss, anorexia, malaise, weakness are signs of advanced disease
  Depression

  There is NO effective screening modality.
  Tumor markers CA19-9 and CEA may be elevated and used to monitor response to therapy or disease progression

• What is “Trousseau’s Sign”?
Migratory thrombophlebitis - Spontaneously appearing and disappearing venous thromboses. It is seen in ~10% of patients with pancreatic cancer attributed to elaboration of platelet-aggregating factors and procoagulants from the tumor.

- What is a "Whipple Procedure"?

Surgical resection is the only potentially curative therapy for patients with pancreatic cancer. After thorough assessment only 15-20% of patients are considered to be candidates for surgical resection.

For tumors in the head and neck of the pancreas, a pancreaticoduodenectomy (the Whipple procedure) is performed.

Tumors in the body or tail of the pancreas are removed via a distal pancreatectomy.

**Pancreatic Cystic Neoplasms**

<table>
<thead>
<tr>
<th>Type</th>
<th>Behavior</th>
<th>Gross morphology</th>
<th>Histopathology</th>
<th>Clinical Characteristics</th>
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| **Serous Cystadenoma**      | Benign           | Small cysts, clear, straw colored fluid              | Small cysts lined by **cuboidal** cells which are glycogen-rich | - Female to male 2:1  
- Age 70s  
- Nonspecific symptoms |
| **Mucinous Cystic neoplasms** | Mucinous cystadenoma = benign | Cysts filled with thick mucin  
NOT connected to main pancreatic duct | Cysts lined by **columnar** epithelium  
**Cytologically benign to severely dysplastic**  
(Low grade, moderate, severe dysplasia) | - Majority women  
- Body/tail pancreas  
- Painless slow growing masses |
| **Intraductal papillary mucinous neoplasms** | Benign to malignant | Arise in main pancreatic duct or major branch | Lined by **columnar** epithelium  
Various degrees of dysplasia | - Men > women  
- Head of pancreas |
Congenital Anomalies of the Pancreas

- What is pancreatic agenesis?
  Absence of the pancreas; usually associated with multiple other congenital organ anomalies.

- What is an Annular pancreas?
  The head of the pancreas encircles the duodenum. This may narrow the duodenum and interfere with passage of food.

- Describe pancreas divisum.
  It is a congenital anomaly of the anatomy of the ducts of the pancreas in which a single pancreatic duct is not formed, but rather remains as two distinct dorsal and ventral ducts. Normally, in embryogenesis, the two ducts will fuse together to form one main pancreatic duct.
  
  In pancreas divisum the major drainage of the pancreas is done by the dorsal duct which opens up into the minor papilla.
  
  The majority of patients with pancreas divisum have no symptoms. A small subgroup of patients may develop chronic pancreatitis.

- Where can “ectopic” pancreatic tissue be found? Are there clinical manifestations?
  Ectopic pancreatic tissue refers to displaced pancreatic tissue.
  
  Glands (ducts and acinar tissue) and Islets of Langerhans and be found in the Stomach and duodenum, jejunum, Meckel diverticulum, ileum. There are usually in the submucosa
  
  These ectopic foci of pancreatic tissue may be asymptomatic; they may cause pain, mucosal bleeding; 2% of islet cell neoplasms can arise in ectopic pancreas