جامعة الملك سعود
King Saud University
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MED437
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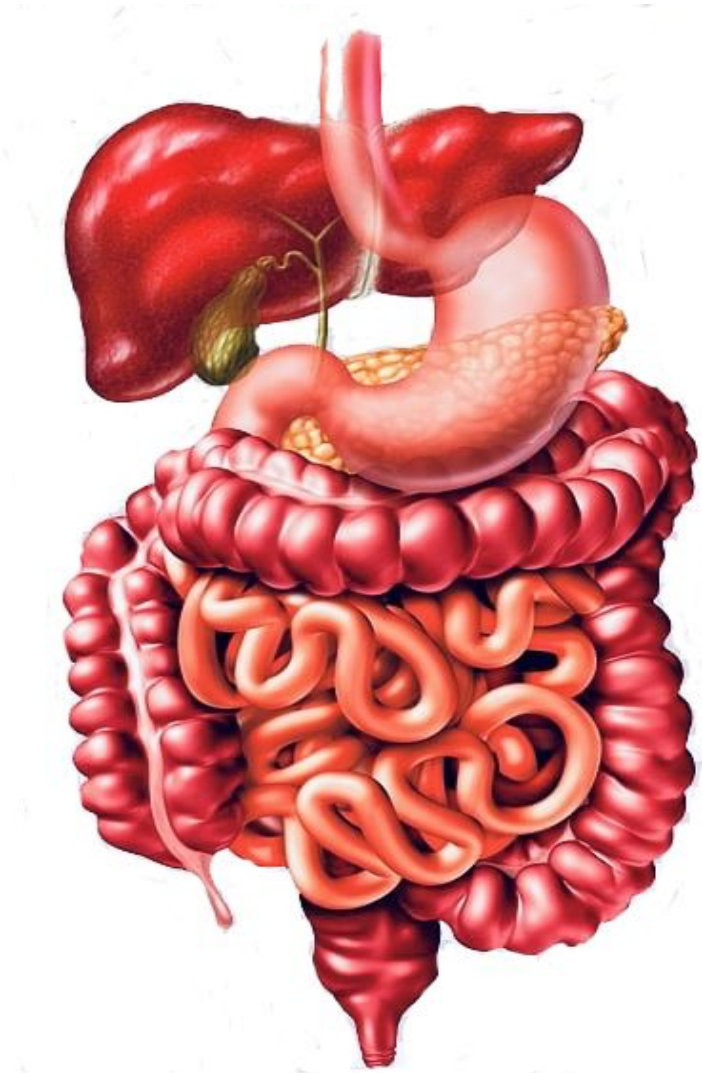
PATHOLOGY
TEAM 437



Acute & Chronic pancreatitis

هذه المحاضرة هي تكريم لكل من يعمل ولا يكرّم،لكل من يعمل بالخفاء،لكل ايادي تدفعنا من ظهورنا لا نرى وجوه اصحابها

Objectives:

- Describe the definition, epidemiology, pathogenesis, morphology, and clinical findings of acute and chronic pancreatitis

Revised By
Hadeel Awartani
Abdullah AlOmar

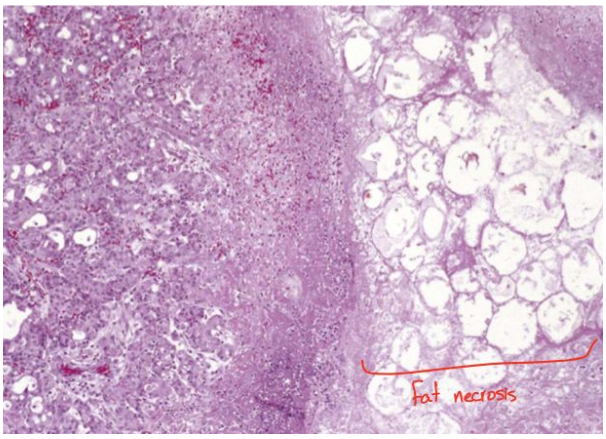
Pancreatitis

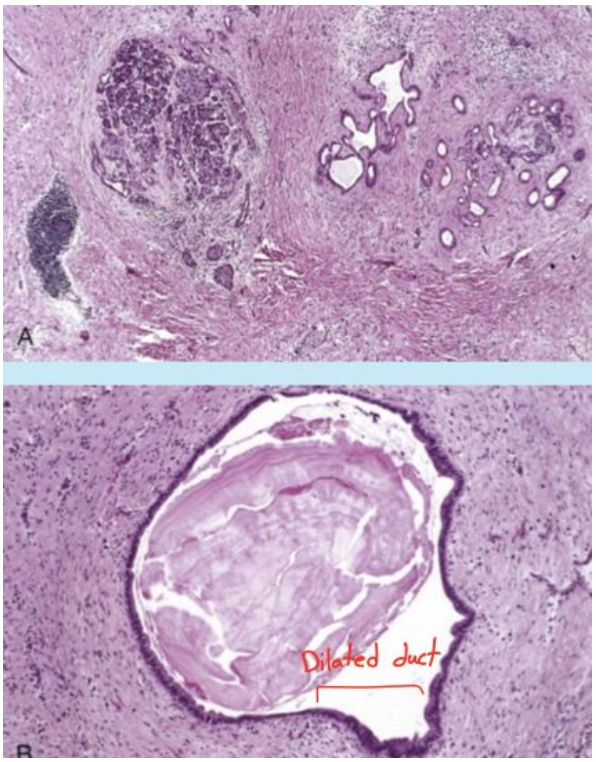
overview
https://youtu.be/ux45pMrtsy0

Pancreatitis: a group of disorders characterized by inflammation of the pancreas, divided into acute and chronic forms.

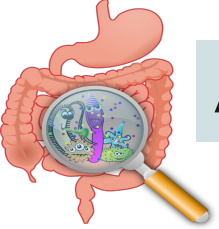
Acute pancreatitis: glands can return to normal if underlying cause of the pancreatitis is removed. Can resolve completely by regeneration of acini

Chronic pancreatitis: irreversible destruction of exocrine pancreatic parenchyma. permanent, main features : fibrosis, ducts dilation and dystrophic calcification *





*Bridge to Histology: طيب حنا خذنا في الهستولوجي ان
The pancreases formed of two main parts (Stroma) , (Paranchyma)it's a mixed gland
Paranchyma حنا كلامنا عن ال
Two glands:
Exocrine: acini & duct produce DIGESTIVE Enz
Endocine:islets of langerhans produce hermons
المهم والمتأثر هي الأكسو لانها هي تنتج الأنزيمات الهاضمة

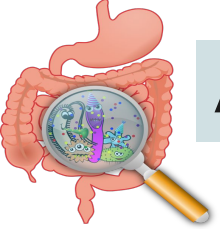


Acute Pancreatitis

osmosis overview

فيه ملخص له بسلايد ٧

Definition	Is a **necro-inflammatory** disease that is characterized by infiltration of the pancreas by **inflammatory cells** and **destruction of the pancreatic exocrine** cells. **Reversible condition.**
Epidemiology	The **incidence** in **Western countries** is 10 to 20 per 100,000 people. 80% of cases in Western countries are associated with one of two conditions: 1- **biliary tract** disease (stones) 2- **alcoholism**. **Gallstones** are present in 35% to 60%. **The male-to-female ratio** is **1 : 3** in the group with biliary tract disease and **6 : 1** in those with alcoholism Alcoholism more in males, Stones more in females
Etiologic Factors : 10% to 20% of cases of acute pancreatitis are idiopathic pancreatitis	
Metabolic	**1-** Alcoholism **2-** Hyperlipoproteinemia(increase lipid in serum) **3-** Hypercalcemia **4-** Drugs (e.g., azathioprine)
Genetic hereditary pancreatitis	Mutations in: • the cationic trypsinogen(PRSS1) autosomal dominant • trypsin inhibitor (SPINK1) genes premature activation of trypsinogen into trypsin or proteins that regulate calcium metabolism
Mechanical	**1-** Gallstones obstruction leads to accumulation of pancreatic enzymes **2-** Trauma sharp trauma mainly most in children « seat belt » **3-** Parasites: e.g. Ascaris lumbricoides and Clonorchis sinensis **4-** Iatrogenic injury: **I.** Operative injury **II.** Endoscopic procedures with dye injection
Vascular decreased blood supply	**1-**Shock **2-**Atheroembolism **3-** Vasculitis **(Polyarteritis nodosa)**
Infectious	**Mumps**, Coxsackievirus, Mycoplasma pneumoniae



Acute Pancreatitis

Pathogenesis: Autodigestion of the pancreatic substance by **inappropriately activated pancreatic enzymes**.

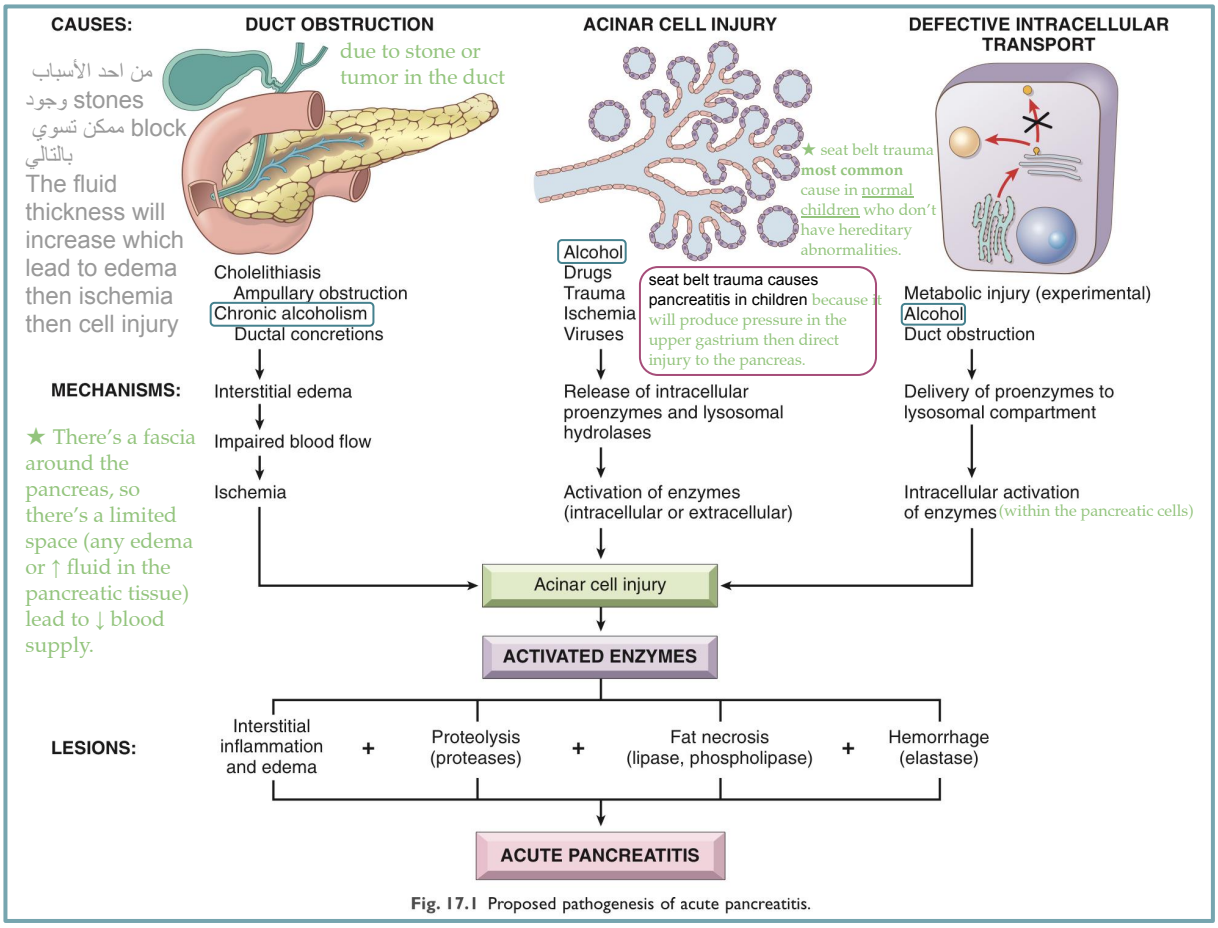


Fig. 17.1 Proposed pathogenesis of acute pancreatitis.

Mechanisms protect the pancreas from enzymatic self- digestion:

Most digestive enzymes are synthesized as <u>inactive</u> proenzymes (zymogens), which are packaged within secretory granules.

Most proenzymes are <u>activated by trypsin</u>, which itself is activated by duodenal enteropeptidase (enterokinase) in the small bowel.

Bridge to physiology:
Trypsin is activated either by Enteropeptidase or another trypsin

Acinar and ductal cells secrete trypsin inhibitors, including serine protease inhibitor Kazal type l (SPINK1), which further limit intrapancreatic trypsin activity. If there's deficiency or mutation in the gene this will lead to hereditary pancreatitis.

Alcohol effects on pancreas:

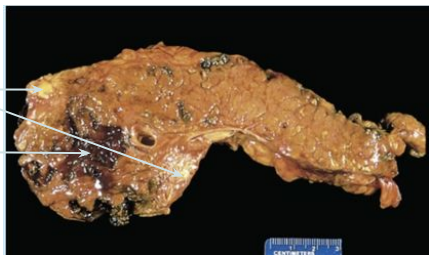
- increases pancreatic exocrine secretion and contraction of the sphincter of Oddi so there will be obstruction.
- Direct toxic effects on acinar cells with induction of oxidative stress in acinar cells.
- Stimulate release of cytokines from acinar cells. These cytokines will induce the neutrophils and inflammatory cells to come to the area so there will be acute pancreatitis.

Acute Pancreatitis

Gross Morphology

Fat necrosis in the peripancreatic fat

Hemorrhage in the head of the pancreas



There is edema in the pancreas.

Fat necrosis results from enzymatic destruction of fat cells. The released fatty acids combine with calcium to form insoluble salts that precipitate in situ (appear as foci of yellow-white, chalky material). Calcium that binds to fat came from blood so there will be hypocalcemia in the serum.

Histopathologic Morphology

The morphology of acute pancreatitis ranges from **inflammation and edema** to severe **extensive necrosis** and hemorrhage.

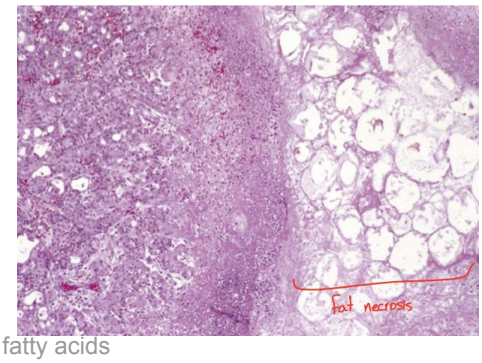
The basic alterations are:

1- An **acute inflammatory reaction** with **edema**

2- **Necrosis of** peripancreatic **fat by lipolytic enzymes**

3- **Proteolytic** destruction of **pancreatic parenchyma.**

4- As as a result of tissue destruction there will be Destruction of blood vessels with subsequent **interstitial hemorrhage.**



Bridge to biochemistry:
Lipase enzyme digest fats resulting 2-monoacylglycerols and fatty acids

Clinical Features

This is one of the acute emergency condition

- Fever, nausea, and vomiting
- Severe, boring **(knife-like) midepigastric pain** (the cardinal manifestation of acute pancreatitis) with radiation into the back because it's a retroperitoneal organ
- Hypovolemic shock in severe cases
- **Tetany:** calcium is used up in binding to fatty acid.

Acute Pancreatitis

Laboratory Findings

- Marked **elevation** of serum **amylase** levels during the first 24 hours, followed within 72 to 96 hours by a rising serum lipase level. Non-specific as it is secreted from the pancreas and salivary glands
- Serum **lipase**: more specific because it's only secreted from the pancreas and lasts longer than amylase in acute pancreatitis; excellent screen for acute pancreatitis.
- Release of lipases and phospholipases produce chalky areas of fat necrosis, with precipitation of calcium that lowers serum calcium (the **worse** the inflammation, the **lower** serum calcium level which predict a **worse** prognosis).

Management

The key to the management is **"resting"** the pancreas by total restriction of food and fluids and by **supportive therapy** (intravenous fluids to replace the fluid supply he/she needs and nasogastric suction from the stomach and intestine). They don't need antibiotics.

Prognosis

- —Most patients recover fully
- About 5% die from:

1- Shock (during the first week of illness).
2- Acute respiratory distress syndrome. Usually fatal.
3- Acute renal failure.

Complications

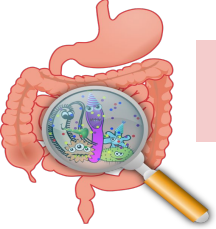
1- **Pancreatic necrosis** (Systemic signs occur earlier than usual with higher fever than usual; sinus tachycardia and greater degree of neutrophilic leukocytosis and peripancreatic infections.
2- **Pancreatic abscess** (sterile) It means there's no bacteria.
3- **Pancreatic pseudocyst** (due to liquefied necrosis area becomes surrounded by granulation tissue, forming a cystic mass with no epithelial lining)
4- Others:

a. hyperglycaemia ↑ glucose (destruction of β-islet cells)
b. hypocalcaemia and 2ry tetany due to Ca binding to FA
c. peritonitis If it's severe, lipases and hydrolysis enzymes will be released in the peritoneum leading to chemical pancreatitis.

Sumup of Acute pancreatitis:
Acute pancreatitis:
اهم شئ نعرفه انه reversible
happy ending.(: في حل للبنكرياتايتس
طيب خلنا نعرف شوي عنه
هي تتأثر لأنها تنتج الأنزيمات الهاضمة لكن بخلل ممكن تنعكس الآية ويبدأ البنكرياس بهضم نفسه Exocrine gland
إيش الأسباب ؟
الأسباب كثيرة ممكن alcohol, gallstones, trauma, (PRSSA1, SPINK1) gene mutations
هذولي اهم الأسباب وللأسف احياناً يكون السبب مجهول بس بنسب ضئيلة
طيب هل معقول ان الجسم أصلاً يخلي أمر يحصل بسهولة ولا عنده دفاعات؟
الجسم بيدافع عن نفسه كيف
أولاً
هذول الأنزيمات الهاضمة مارح تكون ٢٤ ساعة تشتغل وتهضم لا بس لما يحتاجها الجسم فتكون بحالة خمول (zymogens)
ثانياً:
لنفرض ان الجسم يحتاج انه يبدأ هضم الحين أيضاً مب اي شي يحفز هذول الأنزيمات انها تبدأ هضم لاااا
يجي ال trypsin
اللي هو بنفسه يحتاج تحفيز أما من
enteropeptidase or other activated trypsin
بعد ما يتحفز هو يروح يحفزهم عشان يبدون شغل
ثالثاً:
العمل لا يخلو من الخطأ، فرضاً زادت كمية نفس الخلايا
تنتج أنزيم مثبط (ductal and acinar) اللي هو (trypsin inhibitor)
يمنع التربسن انه يحفز المزيد من الأنزيمات فتوقف العملية هنا وتنحل هذي المشكلة البسيطة

طيب لنفرض الآن أن جاكم مريض يعاني من
severe abdominal pain , fever, nausea , vomiting
و يوم تعرفون عن المريض اكثر يتضح انه alcoholic
ليش قلت abdominal pain
وما قلت mid epigastric pain
لان الدكتورة قالت ممكن نجيبه بهذي الصيغة مع أعراض
وتحددون + يوم يجيكم مريض مارح يقولكم المنطقة بالضبط بس يقول بطني
طيب الحين أول شي تتركون القهوة اللي بيدكم وتقومون للشغل 😂 + ما تقدرون ما تفكرون ب بنكرياتاتيس بس يبيلكم تسوون فحوصات عشان تتأكدون،
وش شفتم بالبنكرياس؟ Fat necrosis , hemorrhage
للتوضيح fat necrosis due to destruction of fat cells that released fatty acid combine with calcium
كالسيوم؟ أي كالسيوم لأن طبيعي يتأثر ولو رجعتوا لل
factors فيه Mutation of proteins that regulate calcium
لا تقولولي سحبتو عليها🌚 ما يصحش يا جماعة
طيب وش شفتم بالهستولوجي ؟
acute inflammatory reaction with edema, fat necrosis, destruction of pancreatic Parenchyma and blood vessels destruction

سويتوله laboratory test؟
Marked elevation of amylase enzyme + lipase enzyme why lipase? Fat necrosis
يتلاقون الامايليز مرتفع بس لأول ٢٤ ساعة ف ماهو محدد انه اكيوت بنكرياتايتس
ال lipase لانه يجلس فترة يطول ف هو indicator of acute pancreatitis
بيكون فيه كالسيوم زي ما عرفنا قبل ليش كلما كانت كمية الكالسيوم أقل كانت الحالة أسوا
كيف تتعامل معاه؟ acute pancreatitis عرفتم الحين ان المريض عنده
اهم شئ انك تقول للمريض يرتاح ويترك المسبب الرئيس لو كحول يتركها
يكثرموية gallstone
supporting therapy

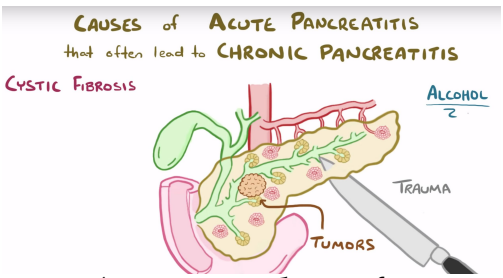


Chronic pancreatitis

osmosis overview

Chronic Pancreatitis	Chronic pancreatitis is defined as **prolonged inflammation** of the pancreas with **irreversible** destruction of exocrine parenchyma, and, in the late stages, associated with pancreatic insufficiency, steatorrhea, diabetes due to destruction of islet- beta cells, pancreatic calcification, and fibrosis.
Epidemiology	• The prevalence of chronic pancreatitis ranges between 0.04% and 5% • Occurs in men more often than women • Most affected patients are middle-aged males

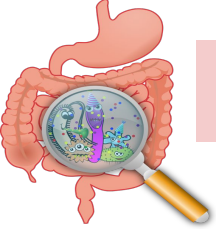
Chronic pancreatitis: Causes



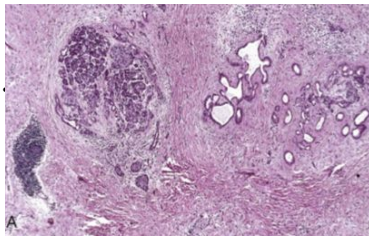
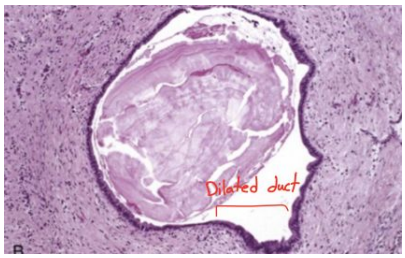
➔ Majority idiopathic

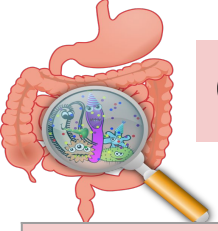
➔ Known causes:

1. ***Alcohol*** *abuse is the most common known cause* (protein plugs form in ducts and become calculi in the pancreatic duct)
2. **Cystic fibrosis** causes a thick secretion because there is no water within the secretion is the *most common cause in children.* Germline mutations in CFTR gene (cystic fibrosis transmembrane conductance regulator)
3. Biliary tract disease: calculi or malformation
4. Malnutrition is the most common cause in developing countries
5. Autoimmune disorder
6. Long-standing obstruction of the pancreatic duct by calculi or neoplasm.



Chronic pancreatitis

Chronic pancreatitis is characterised by:	1- Parenchymal fibrosis. 2- Reduced number and size of acini with relative sparing of the islets of langerhans 3- Variable dilation of pancreatic ducts 4- Calcium deposition
Gross morphology	• Gland is hard pancreas normally is a soft gland • Sometimes with extremely dilated ducts and visible calcification
Microscopic morphology	1- **Extensive fibrosis** and atrophy has left only residual islets and ducts. 2- Chronic inflammatory cells 3- few acinar  1- **Dilated ducts.** 2- Inspissated **eosinophilic** ductal concretions in case of alcoholic chronic pancreatitis. كنها رجال عنده لحية 
Clinical features	1- Silent. 2- Severe pain radiating into the back(attacks may be precipitated by alcohol abuse, overeating or the use of opiates). 3- Malabsorption (indicates >90% exocrine function destroyed. 4- Type 1 diabetes mellitus (70% of cases).

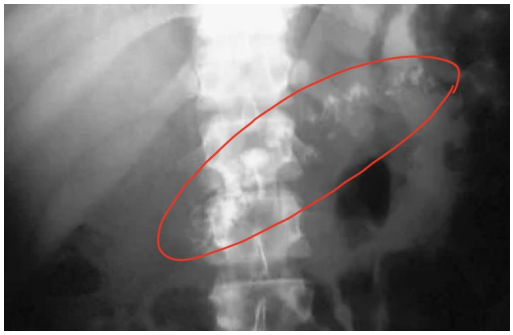


Chronic pancreatitis

Diagnosis

- Requires a high degree of suspicion.
- Gallstone-induced obstruction may be evident as jaundice or elevation in serum levels of alkaline phosphatase.
- Serum amylase is variable and less reliable than in acute disease.
- Lipase in chronic pancreatitis is not useful.
- Calcification within the pancreas by computed tomography (ct scan) and ultrasonography.(the most useful)

Plain abdominal radiography shows coarse **dystrophic calcification** in the distribution of the pancreas.



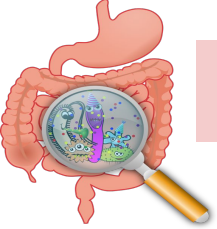
Prognosis

- Not an immediately life-threatening condition.
- The long term outlook for individuals with chronic pancreatitis is poor, with a 20 to 25 year motility rate of 50%.
- Pancreatic exocrine insufficiency, chronic malabsorption,and diabetes mellitus can all lead to significant morbidity and contribute to mortality.
- In other patients severe chronic pain is a dominant problem.
- Pancreatic pseudocysts in about 10% of patients.
- Patients with hereditary pancreatitis, have a 40% lifetime time risk of developing pancreatic cancer.

(Whether this increased cancer risk extends to other forms of chronic pancreatitis is unclear)

Treat-ment

1- Abstain from alcohol.
2- Simple analgesics or NSAIDs.
3- Fat soluble Vitamins.



Chronic pancreatitis

Pathogenesis:

- Most often **follows repeated episodes of acute pancreatitis**
- Chronic **alcohol** ingestion results in the secretion of protein-rich pancreatic fluid, which leads to the deposition of inspissated protein plugs and obstruction of small pancreatic ducts

Chronic pancreatic injury (whatever its cause) → leads to → local production of inflammatory mediators → promote fibrosis and acinar cell loss

EXAMPLE

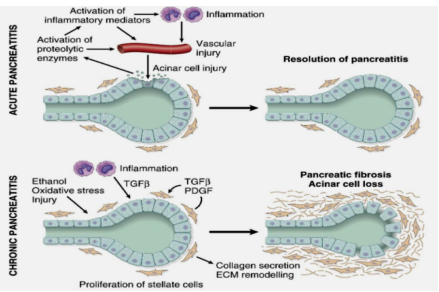
- transforming growth factor β (**TGF-β**
- platelet-derived growth factor (**PDGF**

- **TGF-β** and **PDGF** result in

proliferation of myofibroblasts → secretion of collagen → remodeling of the extracellular matrix (ECM)

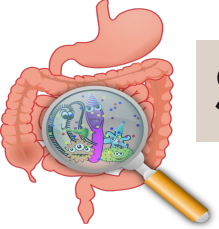
acute: Distraction of the acinar epithelium=>secondary inflammation =>affection of blood vessels =>hemorrhage and edema but the parenchyma itself does not affected => the affected acinar can be regenerated and back to normal

chronic: ethanol/oxidative stress/injury to the epithelium=>inflammation => release TGF beta and PDGF => proliferation of stellate cells around the acinar cell=> collagen secretion and ECM remodulation=>calcification and fibrosis =>pancreatic insufficiency



the difference between acute and chronic pancreatitis

Acute pancreatitis	Chronic pancreatitis
Acinar injury results in release of proteolytic enzymes, leading to activation of the clotting cascade, acute inflammation, vascular injury, and edema. In most patients, complete resolution of the acute injury occurs with restoration of acinar cell mass.	Repeated episodes of acinar cell injury lead to the production of **TGF-β and PDGF**, resulting in proliferation of myofibroblasts, secretion of collagen and irreversible loss of acinar cell mass, fibrosis, and pancreatic insufficiency



Summary

Acute Pancreatitis

— is a form of reversible pancreatic parenchymal injury associated with inflammation. —

Acute pancreatitis may be caused by
1. Excessive alcohol intake
2. Pancreatic duct obstruction (e.g., gallstones)
3. Genetic factors (e.g.,PRSS1,SPINK1)
4. Traumatic injuries
5. Medications
6. Infections (e.g., mumps)
7. Metabolic disorders leading to hypercalcemia
8. Ischemia

— The key feature of all of these causes is that they promote the inappropriate activation of digestive enzymes within the substance of the pancreas —

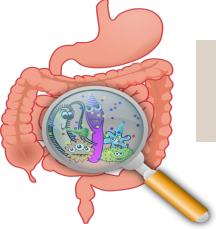
Clinical features include:
acute abdominal pain, systemic inflammatory response syndrome, and elevated serum lipase and amylase levels

Chronic pancreatitis

is characterized by irreversible injury of the pancreas leading to fibrosis, loss of pancreatic parenchyma, loss of exocrine and endocrine function, and high risk of developing pseudocysts —

Chronic pancreatitis may be **idiopathic** or caused by:
1. Repeated bouts of acute pancreatitis
2. Chronic alcohol abuse
3. Germline mutations in genes such as CFTR
4. Malnutrition (most common cause in developing countries)
5. Autoimmune disorder
6. Long-standing obstruction of the pancreatic duct by calculi or neoplasms —

Clinical feature include:
intermittent or persistent abdominal pain, intestinal malabsorption and diabetes



Pathoma

Acute and chronic pancreatitis

EXOCRINE PANCREAS

I. ANNULAR PANCREAS

A. Developmental malformation in which the pancreas forms a ring around the duodenum; risk of duodenal obstruction

II. ACUTE PANCREATITIS

A. Inflammation and hemorrhage of the pancreas

B. Due to autodigestion of pancreatic parenchyma by pancreatic enzymes

1. Premature activation of trypsin leads to activation of other pancreatic enzymes.

C. Results in liquefactive hemorrhagic necrosis of the pancreas and fat necrosis of the peripancreatic

D. Most commonly due to alcohol and gallstones; other causes include trauma, hypercalcemia, hyperlipidemia, drugs, scorpion stings, mumps, and rupture of a posterior duodenal ulcer.

E. Clinical features

1. Epigastric abdominal pain that radiates to the back
2. nausea and vomiting
3. Periumbilical and flank hemorrhage (necrosis spreads into the periumbilical soft tissue and retroperitoneum)
4. Elevated serum lipase and amylase; lipase is more specific for pancreatic damage.
5. Hypocalcemia (calcium is consumed during saponification in fat necrosis)

F. Complications

l. Shock- due to peripancreatic hemorrhage and fluid sequestration

2. Pancreatic pseudocyst-formed by fibrous tissue surrounding liquefactive necrosis and pancreatic enzymes

i. Presents as an abdominal mass with persistently elevated serum amylase

ii. Rupture is associated with release of enzymes into the abdominal cavity and hemorrhage.

3. Pancreatic abscess-often due to E coli; presents with abdominal pain, high fever, and persistently elevated amylase

4. DIC and ARDS

III. CHRONIC PANCREATITIS

A. Fibrosis of pancreatic parenchyma, most often secondary to recurrent acute pancreatitis

1. Most commonly due to alcohol (adults) and cystic fibrosis (children); however, many cases are idiopathic.

B. Clinical features:

I. Epigastric abdominal pain that radiates to the back

2. Pancreatic insufficiency-results in malabsorption with steatorrhea and fat soluble vitamin deficiencies. Amylase and lipase are not useful serologic markers of chronic pancreatitis.

3. Dystrophic calcification of pancreatic parenchyma on imaging; contrast studies reveal a 'chain of lakes' pattern due to dilatation of pancreatic ducts.

4. Secondary diabetes mellitus-late complication due to destruction of islets

5. Increased risk for pancreatic carcinoma

Questions

1. Chronic pancreatitis is characterized by long-standing inflammation of the pancreas with .....:
A. At later stages inflammation of the endocrine parenchyma
B. Fibrosis
C. Inflammation of the exocrine parenchyma
D. Destruction of the ducts

2. The most helpful finding to diagnose chronic pancreatitis is:
A. Elevations of serum amylase
B. Calcifications within the pancreas
C. Elevated levels of serum alkaline phosphatase.
D. Persistent or recurrent abdominal and back pain

3. Which of the following medications commonly precipitate chronic pancreatitis?
A. Thiazide diuretics
B. Azathioprine
C. Estrogens
D. Opiates

4. The pancreatic ducts become extremely dilated in case of :
A. Pseudocysts of Pancreas
B. Chronic Pancreatitis
C. Acute Pancreatitis
D. Autoimmune pancreatitis

5. In pancreatitis, inflammation is caused when:
A. Pancreatic enzymes escape into the pancreatic tissue and begin to digest the pancreas itself
B. Gallstones obstruct the cystic duct
C. Massive amounts of fluid accumulate in the peritoneal cavity
D. Regenerative nodules are formed

6- What are the most frequent laboratory findings in patients with acute pancreatitis?
A. Elevation of serum lipase followed by elevation of amylase.
B. Normal amylase level with elevation of lipase level only.
C. Normal lipase level with elevation of amylase level only.
D. Elevation of amylase levels followed by a rising of lipase.

7. Which of the following is NOT a complication of chronic pancreatitis?
A. Pancreatic exocrine insufficiency
B. Malabsorption
C. Acute ischemia
D. Diabetes mellitus

8. The most common etiologies of acute pancreatitis (AP) are
A. Idiopathic and medications.
B. Endoscopic retrograde cholangiopancreatography and gallstone
C. Abdominal trauma and pregnancy.
D. Ethanol and gallstones

Questions

9. The most likely medication to cause AP in a patient taking the following medications is:
A. Potassium chloride
B. Calcium carbonate
C. Hydrochlorothiazide
D. L-thyroxine.

10. A 30-year-old male got into a road accident resulting in abdominal trauma, after examination you notice a 17 cm in diameter isolated collection of necrotic- haemorrhagic material in the pancreas. What do you expect?
A. Pseudocysts of Pancreas
B. Chronic Pancreatitis
C. Acute Pancreatitis
D. Autoimmune pancreatitis

11. Gene mutation associated with acute pancreatitis?
A. PRSS1, SPINK1
B. SFTR
C. HLA- DR
D. p53

12. A 52 year old male present to the accident and emergency complaining of a severe abdominal pain radiating to the back. The patient is known alcoholic . He is found to have increased serum amylase. What is the most likely diagnosis in this case?
A. Chronic pancreatitis.
B. Acute pancreatitis.
C. Perforated colon.
D. Acute appendicitis.

Answers:

1- B	2-B	3- D	4-B	5-A	6-D
7-C	8-D	9-C	10-A	11-A.	12-B

Short questions to test yourself:

1. How is chronic pancreatitis different from acute pancreatitis?
Chronic pancreatitis is defined by **irreversible** destruction of exocrine pancreatic parenchyma while acute pancreatitis is a **reversible** condition.

2. The two most common causes of acute pancreatitis are?
-Biliary tract disease
-Alcoholism.

3.Mention some differential diagnosis of acute pancreatitis?
-Ruptured acute appendicitis.
-Perforated peptic ulcer
-Acute cholecystitis.

كل الشكر والتقدير للجهود العظيمة
من قبل أعضاء فريق علم الأمراض الكرام

قادة فريق علم الأمراض

فايز غياث الدرسوني

شيرين العكيلي

اعضاء فريق علم الأمراض

راكان محمد الغنيم
سلطان ناصر الناصر
عادل عبدالعزيز السحيباني
حسن محمد العريني
تركي عيد الشمري
سلطان بن عبيد
عبدالجبار اليماني
عبدالله المعيذر
منصور العبرة
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مها العَمري
مجد البراك
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قد تتعرض للفشل،
ليس لانك لا تستطيع لكن لتتعلم
درساً لِتُصحح خطأً، لتنهض
مجدداً فأنت تستطيع

Best of luck.

References:
*Slides/Pathoma/Robbins

Any questions/comments and suggestions:
* EMAIL: pathology437@gmail.com
*TWITTER : @pathology437