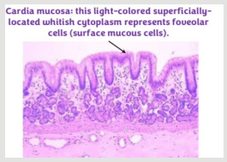
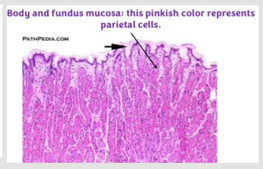
Stomach 1

Parts of stomach

- **Cardia** — mucin secreting foveolar cells
- **Fundus** / **Body** — parietal cells producing (HCL) chief cells producing (pepsin).
- **Antrum (pylorus)** — neuroendocrine G cells (gastrin)





ACUTE GASTRITIS & GASTROPATHY

Acute gastritis: Mucosal injury, neutrophils present.
Gastropathy: regenerative, rare or no inflamm

Causes
- NSAIDs
-alcohol
- bile
-stress-induced

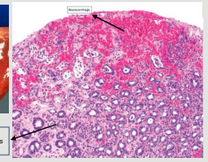
Clinical features:
- Asymptomatic.
- Epigastric pain
- nausea
- vomiting.
- Severe: erosions, ulcers, hematemesis(vomiting of blood)
- melena(presence of blood in feces)

Pathogenesis:- Imbalance between protective and damaging forces

- **Normal State**
  Damaging Forces: Gastric acid + pepsin enzymes.
  Defensive Forces: Mucus layer, bicarbonate, blood flow, rapid cell repair, prostaglandins.
- **Injury Phase**
  Causes:
  Infection: H. pylori (disrupts mucus barrier).
  Drugs: NSAIDs/aspirin (block protective prostaglandins).
  Lifestyle: Alcohol, smoking, stress (reduce defenses).
  Other: Acid hypersecretion, bile reflux.
- **Ulcer Formation**

Main causes of the imbalance :
- NSAIDs (COX1 and COX2 inhibitors)
- Uremic patients (ammonia inhibit bicarbonate transport)
- H pylori (urease produces ammonia)
- Aging (reduced mucin and bicarbonate secretion)
- Hypoxia (high altitudes)
- Harsh chemicals, (acids or bases) (direct epithelial injury)
- Alcohol, NSAIDs, radiation therapy (direct mucosal damage)
-Chemotherapy (inhibit DNA synthesis and cellular renewal)

Morphology :
- Hyperemia (redness).
- Edema and slight vascular congestion
- Neutrophils, lymphocytes plasma cells=> are not prominent.
- Neutrophils : Active inflammation (gastritis) .
- Intact surface epithelium if mild.
- Acute erosive hemorrhagic gastritis (Advanced)



Stress-Related Mucosal Disease

=> **Stress ulcers:** critically **ill** patients with **shock, sepsis**, or severe **trauma**.
=> **Curling ulcers:** proximal duodenum , severe **burns or trauma.**
=> **Cushing ulcers:** stomach, duodenum, or esophagus due to **CNS injury as stroke**, high risk of **perforation**.

Causes
Severe physiologic stress:
- Trauma
- Extensive burns
- Intracranial disease
- Major surgery
- Serious medical disease
- Critically ill patients

Clinical features:
- Nausea, vomiting,
- Melena
- Coffee -ground hematemesis
- Perforation complication.

- Prophylaxis with proton pump inhibitors
- Outcome depends on severity of underlying cause.

Pathogenesis:-

- **Stress related injury:**
  Mostly due to **Local ischemia** caused by:-
  - Systemic hypotension.
  - Decreased blood flow (Splanchnic vasoconstriction)
  - Systemic acidosis (lower intracellular PH).
  - COX2 expression is protective.
- **CNS injury and Cushing ulcers:**
  Direct vagal stimulation, acid hypersecretion.

Morphology :
- Spectrum (Shallow to deep).
- Acute ulcers are rounded and typically < 1 cm.
- Ulcer base brown to black.
- Multiple, anywhere in stomach
- Normal adjacent mucosa
- No scarring; because it's acute not chronic
- Healing with complete epithelialization occurs days or weeks after removal of injurious factors

Gastric diseases

- **Inflammatory**
  - Acute gastritis.
  - Chronic gastritis.
  - Acute gastric ulcer.
  - Chronic peptic ulcer
- **Neoplastic**
  - Benign
  - Malignant

CHRONIC GASTRITIS

Causes
- Helicobacter pylori associated gastritis: most common.
- Autoimmune atrophic gastritis: less than 10% of cases.
Less common
- Chronic NSAID
- Radiation injury
- Chronic bile reflux.

Clinical features:
- Nausea, vomiting and upper-abdominal discomfort
- Hematemesis uncommon.
➡️ Less severe but more prolonged symptoms.

Complications of chronic gastritis
- Peptic ulcer.
- Mucosal atrophy.
- Intestinal Metaplasia
- Dysplasia.

Feature	*H. pylori*–Associated	Autoimmune
Location	Antrum	Body
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to markedly increased	Markedly increased
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
Serology	Antibodies to *H. pylori*	Antibodies to parietal cells (H^+,K^+-ATPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, lymphoma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas	Autoimmune disease; thyroiditis, diabetes mellitus, Graves disease

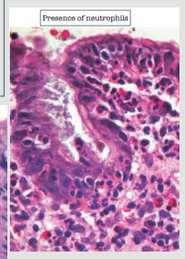
Helicobacter pylori Gastritis

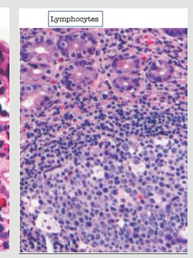
Spiral or curved, G-ve, bacilli.
> In almost **all duodenal ulcers** and **majority of gastric ulcers** or chronic gastritis.
> Epidemiology:
_ Poverty, poor sanitation. Acquired in childhood, persists to adult-life.
_ Acute infection is subclinical.

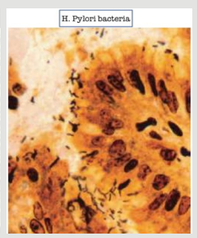
Pathogenesis:
> Non-invasive, adapted to live in the mucus layer due to:
- Flagella: allow motility.
- Urease: split urea to ammonia, protect bacteria from acidic pH.
- Adhesins: bacterial adherence to **foveolar cells**
- Toxins: (CagA) mucosal damage.

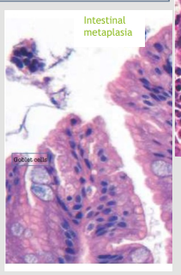
Starts as **Antral gastritis** => stimulate G cells => increased acid production => peptic ulcer =>
If severe: spread to **body** with **atrophy** (damage Parietal cells). => Intestinal **metaplasia** => increased risk of **gastric cancer**.

MORPHOLOGY
~~ Gastric antral biopsy: H. pylori in mucus layer.
~~Regenerative changes (hyperplastic polyps)
~~ Neutrophils, Plasma cells, lymphocytes & macrophages.
~~ **Lymphoid aggregates** >>> increased risk of MALT lymphoma.
~~ Intestinal **metaplasia** (goblet cells)>>> dysplasia >> increased risk of **adenocarcinoma**









Diagnosis and treatment
- Serologic test: anti-H .pylori antibodies.
- Stool test for H.pylori. - Urea breath test.
- Gastric antral biopsy (rapid urease test during endoscopy).
- Bacterial culture.
- PCR test for bacterial DNA.
=> **Treatment**: combinations of 2 antibiotics and PPI (triple therapy).

Autoimmune atrophic Gastritis

=> Antibodies to parietal cells and intrinsic factor in serum.
- Reduced serum pepsinogen I levels
- Antral endocrine cell hyperplasia
- Vitamin B12 deficiency >>> pernicious anemia and neurologic changes
- Impaired gastric acid secretion (Hypo acidity) (**achlorhydria**)
- Marked hypergastrinemia
- Spares the antrum.

Pathogenesis:
loss of parietal cells => reductions in acid and intrinsic factor secretion.
Acid reduction => Hyperplasia of antral G cells => hypergastrinemia (⬆️gastrin)
Deficient intrinsic factor => deficient ileal Vitamin B12 absorption >> pernicious anemia.

MORPHOLOGY
~~ Damage of the oxyntic (acid-producing) mucosa.
~~ Diffuse atrophy, thinning of wall, loss of gastric folds
~~ Lymphocytes, plasma cells, macrophages, less likely neutrophils.
~~ Intestinal metaplasia >>> dysplasia >> carcinoma.
~~ G- cell hyperplasia >>> **carcinoids**.

Clinical features:
_ 60 years, slight female predominance.
_ Often associated with other autoimmune diseases
_ Dyspepsia. عسر هضم
_ Anemia (VB12 or iron)

Note:-
prostaglandins E2 and I2:
Stimulate nearly all the **defense mechanisms** including
1. Mucus and bicarbonate secretion,
2. mucosal blood flow
3. Epithelial restitution.

Stomach 2

Peptic Ulcer Disease

- Main factors: H. pylori infection or NSAID use
- **Imbalance between mucosal defenses and damaging forces.**
- Any portion of the GIT exposed to acidic gastric juices
- Most common in gastric antrum, first part of duodenum.
- Esophagus in (GERD) or ectopic gastric mucosa (Meckel diverticulum)

Pathogenesis of PUD:

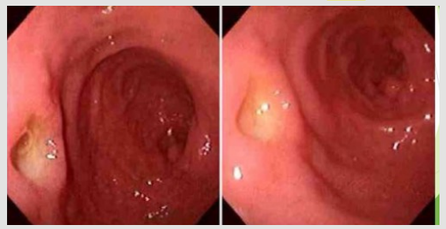
> 70% of cases are associated with H. pylori infection worldwide.
Only 5 -10% of H. pylori–infected persons (host factors, bacterial strains).
Gastric acid is fundamental in pathogenesis.
Cofactors: smoking, chronic NSAIDs, high-dose corticosteroids, alcoholic cirrhosis, COPD, CRF, hyperparathyroidism.
Hyperacidity is caused by:
- H. pylori.
- Parietal cell hyperplasia.
- Excessive secretory response (vagal)
- Hypergastrinemia as in Zollinger-Ellison syndrome

Zollinger-Ellison syndrome
Multiple peptic ulcerations
> Stomach , duodenum, even jejunum
> Caused by uncontrolled release of gastrin by a tumor (gastrinoma) and the resulting massive acid production.

MORPHOLOGY

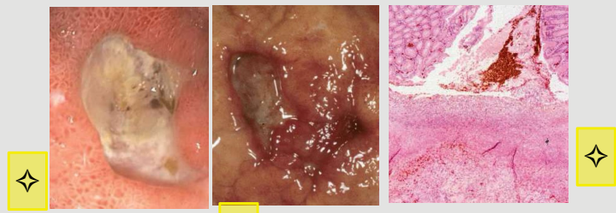
4:1, proximal duodenum : stomach.
~ Anterior duodenal wall or **antrum**.
~ >80% solitary.(isolated alone)
~ Round to oval, sharply punched-out
~ Base of ulcers is smooth and clean
~ **Granulation tissue.**
~ Hemorrhage & Perforation are complications.

Duodenal ulcer



Clinical Features

- Epigastric burning or aching pain
- Complication: Iron deficiency anemia, **frank hemorrhage**, or perforation.
- Pain 1 to 3 hours after meals at daytime
- Worse at night, relieved by alkali or food
- Nausea, vomiting, bloating, bletching.
- Current therapies are aimed at H.pylori eradication.
- Surgery reserved for complications.



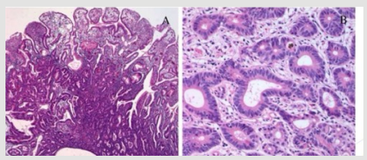
GASTRIC POLYPS AND TUMORS

Gastric polyps

Polyps: masses projecting above the level of adjacent mucosa
- 75% of all polyps.
- Arise in a background of chronic gastritis
- Regress after H.pylori eradication.

- Inflammatory polyps
- Hyperplastic Polyps

Gastric Adenoma: (Second type of polyps)
- 10% of all polyps.
- Increase with age.
- M: F = 3:1
- Background: chronic gastritis, atrophy and intestinal metaplasia.
- **Dysplasia=> low- or high-grade.**
- Risk of adenocarcinoma related to the size (greatest if > 2cm).
- Risk of carcinoma higher than colonic adenoma.
- 30% have concurrent colonic adenoma.



Dysplasia

Gastric adenocarcinoma

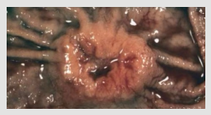
In mucosa

- 90% of all gastric cancers.
- Early symptoms mimic gastritis => late diagnosis.
- Marked geographic variation (Japan, Costa Rica, Chile).
- Screening >> early detection.
- Background of mucosal atrophy and intestinal metaplasia.
- PUD does not increase risk, except after surgery
- In USA rates dropped > 85%, BUT increased rate of cardia cancer due to GERD & obesity.

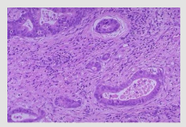
Pathogenesis
~ Genetic alterations (H.Pylori associated chronic gastritis , lesser extent EBV (10%).
~ Most cases are sporadic.

Lauren classification: separates gastric cancers into

Intestinal — -Bulky. - Exophytic mass or ulcer. - Form glands.
- Familial intestinal type cancer: FAP, APC gene mutation.
- Sporadic intestinal-type:- B catenin mutation



Sporadic cases: P53 mutation + HER2 amplification

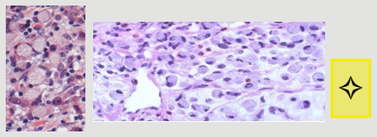


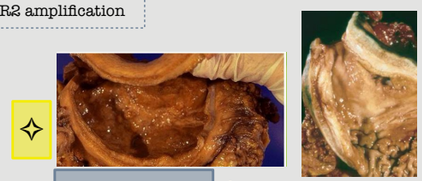
Clinical Features

~ High-risk areas
~ Develops from precursor (adenoma, dysplasia associated w/ intestinal metaplasia)
~ Mean age 55 yrs.
~ M:F 2:1

Diffuse — -Infiltrative growth pattern - Discohesive cells (signet ring cells) - Desmoplastic reaction (stiffens wall, flat ruge, linitis plastica).
- Sporadic diffuse type: somatic CDH1 mutation in 50%.
- Familial diffuse type: germline mutations in CDH1 (E-cadherin).

Signet ring cells: large mucin vacuoles that expand the cytoplasm and push the nucleus to the periphery





Linitis plastica

Clinical Features

~ Incidence uniform across countries.
~ No precursor lesion.
~ M:F 1:1
~ Younger age.

Most powerful prognostic factors: depth of invasion & extent of nodal and distant metastasis at the time of diagnosis

Lymphoma

- Stomach is the most common site of extranodal lymphoma.
- 5% of all gastric malignancies.

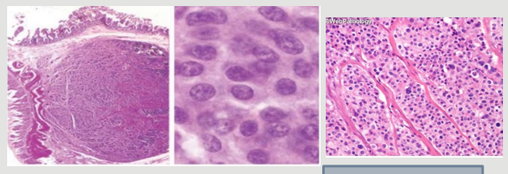
Most common type : extranodal marginal zone B-cell lymphomas (MALToma)=> (indolent)

Second most common lymphoma: diffuse large B cell lymphoma (aggressive)

Neuroendocrine (Carcinoid) Tumor

In submucosa

- Tumors arising from neuroendocrine-differentiated gastrointestinal epithelia (e.g., G cells).
- > 40% occur in the small intestine.
- Associated with endocrine cell hyperplasia, chronic atrophic gastritis, and Zollinger- Ellison syndrome
- Slower growing than carcinomas.



Nest pattern
Salt and pepper nuclei

carcinoid syndrome
> Due to vasoactive substances
> Seen in 10% of cases.
> strongly associated with metastatic disease.
> manifest as Cutaneous flushing, sweating, bronchospasm, colicky abdominal pain, diarrhea, and right- sided cardiac valvular fibrosis

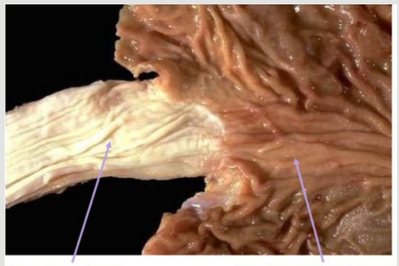
Gastrointestinal Stromal Tumor

Not_edited

esophagus-1

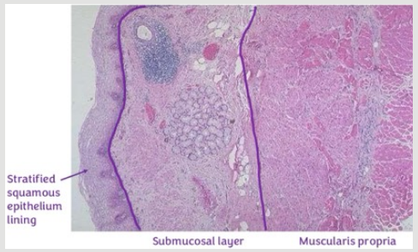
Anatomy and histology

Muscular tube extending from the epiglottis to the Gastroesophageal junction.
Lined by non-keratinized stratified squamous epithelium



Normal esophageal mucosa which has Tan to Pale Pink color.

In contrast with the **normal** gastric mucosa which has a light brown color.



Diseases that affect the esophagus

Obstruction

- Mechanical; congenital or acquired
  Ex. Atresia, Fistulas,duplications, agenesis(esophagus not developed at all) and stenosis
- Functional like achalasia

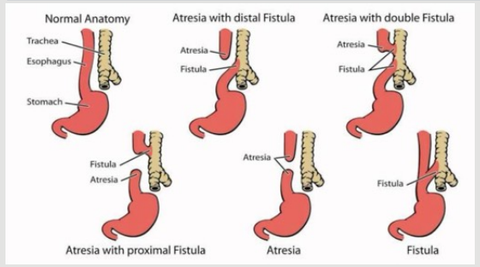
Atresia

Mechanical obstruction

~ In a segment of esophagus => Thin, non-canalized cord
~ Most common location: at or near the tracheal bifurcation.
~ +- fistula (upper or lower esophageal pouches to a bronchus or trachea).
~ Shortly after birth: regurgitation during feeding

• Needs prompt surgical correction (rejoin).
in order for the baby to be able to eat and swallow.

• Complications if with fistula:
• Aspiration
• Suffocation
• Pneumonia
• Severe fluid and electrolyte imbalances.



Atresia = انقطاع كامل.
Stenosis = تضيّق موضعي.

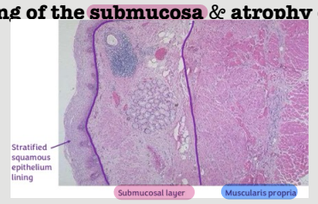
Esophageal stenosis

Mechanical obstruction

~ Acquired >>>Congenital.
~ Characterized by: Fibrous **thickening of the submucosa** & **atrophy of the muscularis propria**.
~ Due to inflammation and scarring

Causes:
• Chronic GERD.
• Systemic sclerosis.
• Irradiation
• Ingestion of caustic agents

Clinical presentation:-
• Progressive dysphagia.
• Difficulty eating solids that progresses to problems with liquids.



Achalasia

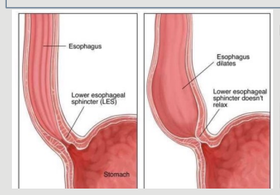
Functional obstruction

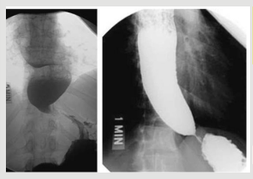
Primary achalasia
Degeneration of distal esophageal inhibitory neurons.
Idiopathic / Most common

Secondary achalasia → • **Chagas disease**, Trypanosoma cruzi infection>>destruction of the myenteric plexus>> failure of LES relaxation>> esophageal dilatation.
Loss of neural innervation due to damage in:
• Esophagus. • Vagus nerve (Which innervates the esophagus) • Dorsal motor nucleus of vagus

Clinical presentation
• Difficulty in swallowing
• Regurgitation
• Sometimes chest pain. Due to aspiration

Triad:
• Incomplete lower esophageal sphincter relaxation
• Increased lower esophageal sphincter tone
—> no complete relaxation —> the sphincter will be semi-closed.
• Esophagealaperistalsis.
= No peristaltic movement.
• Primary >>>secondary.





Barium swallow test:

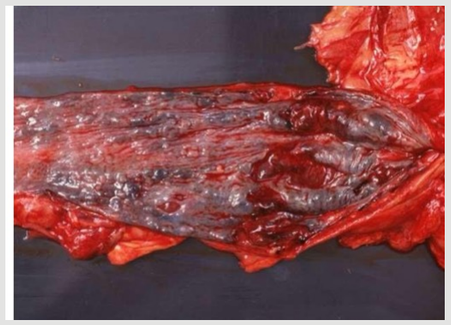
Vascular diseases: varices.

• Tortuous dilated veins within the submucosa of the distal esophagus and proximal stomach.
• Diagnosis by endoscopy or angiography

Pathogenesis:
Usually due to **portal hypertension**
• Portal circulation: blood from GIT>>portal vein>>liver (detoxification)>>(via hepatic vein) inferior vena cava.
• Diseases that impede portal blood flow >> portal hypertension >>esophageal varices.
• Distal esophagus : site of Porto-systemic anastomosis.
• Portal hypertension>>collateral channels in distal esophagus>>shunt of blood from portal to systemic circulation>>dilated collaterals in distal esophagus>>varices

Causes of portal hypertension
- Cirrhosis is most common Alcoholic liver disease.
- Hepatic schistosomiasis 2 most common worldwide.

Clinical Features
Often asymptomatic.
Rupture leads to massive hematemesis and death.
20% of patients die from the first bleed despite interventions.
Death due to hemorrhage, hepatic come, and hypovolemic shock.
Rebleeding in 60%.



Inflammation: esophagitis.

Caused by:
- Esophageal Lacerations. } In this lecture
- Mucosal Injury } In this lecture
- Infections } In this lecture
- Reflux Esophagitis } In next lecture
- Eosinophilic Esophagitis } In next lecture

Esophageal Lacerations
Mallory Weiss tears are most common=> Due to severe retching or forceful **prolonged vomiting => Present with hematemesis** => Gastric contents in vomitus => stretching => tear

Linear lacerations => longitudinally oriented => Cross the GEJ. => Superficial
Only on mucosa => Heal quickly , no surgical intervention

Chemical Esophagitis

Damage to esophageal mucosa by irritants
- Alcohol
- Corrosive acids or alkalis
- Excessively hot fluids
- Heavy smoking
- Medicinal pills (doxycycline and bisphosphonates)
- Iatragenic (chemotx, radiotx , GVHD)

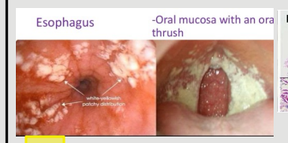
Clinical symptoms & morphology
- Ulceration and acute inflammation.
- Only self-limited pain, odynophagia (pain with swallowing).
- Hemorrhage, stricture, or perforation in severe cases

Infectious Esophagitis

Mostly in debilitated or immunosuppressed.
Caused by

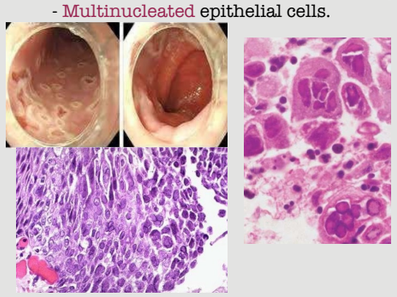
Bacterial: 10%.

Fungal (candida >>> mucormycosis & aspergillosis)
• **Adherent**
• Gray-white **pseudo membranes**
• Composed of matted fungal hyphae and inflammatory cells

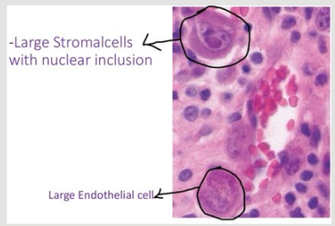


Viral (HSV, CMV)

Herpes viruses
Punched-out ulcers Can be seen by endoscopy
Histopathologic:
- **Nuclear viral inclusions**
- Degenerating epithelial cells ulcer edge
- Multinucleated epithelial cells.



CMV viruses
Shallower ulcerations.
Biopsy: **nuclear and cytoplasmic inclusions** in capillary endothelium and stromal cells.(Mega cells)



Tumors

esophagus-2

Diseases that affect the esophagus

- **Obstruction: mechanical or functional**
- **Vascular diseases: varices.**
- **Inflammation: esophagitis.**
- **Tumors**

Reflux Esophagitis

Gastroesophageal reflux disease, GERD

- Reflux of gastric contents into the lower part of the esophagus
- Most frequent cause of esophagitis
- Most common complaint by patients visiting the outpatient clinics.
- The stratified squamous epithelium of the esophagus is sensitive to the acids.
- Protective forces: **mucin and **bicarbonate from submucosal glands, **high LES tone

Pathogenesis:

- Decreased lower esophageal sphincter tone => caused by (alcohol, tobacco, hiatal hernia, CNS depressants)
- Increase abdominal pressure => caused by (obesity, pregnancy, delayed gastric emptying, and increased gastric volume)
- Idiopathic!!

MORPHOLOGY:

=> Macroscopy (endoscopy)

- Depends on severity (in mild GERD, the mucosal histology is often Unremarkable, **with no changes, or could have Simple erythema** and redness due to the inflammation).

=> Microscopic:

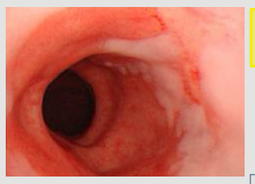
- **Eosinophils infiltration** of the squamous epithelium (Earliest Manifestation)
- Followed by **neutrophil infiltration** later (in more severe cases).
- Basal zone **hyperplasia of the basal squamous epithelial cells**.
- **Elongation of** lamina propria **papillae**. This happens due to chronic injury and regeneration.

Clinical Features:

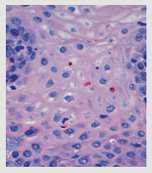
- Most common over 40 years.
- May occur in infants and children
- Heartburn (Burning sensation in the epigastric area).
- Dysphagia (difficulty in swallowing).
- Regurgitation of sour-tasting gastric contents, which may reach the mouth in severe cases.
- Rarely: severe chest pain, mistaken for heart disease (acute myocardial infarction, MI), particularly when patients present to the emergency room.
- Tx: proton pump inhibitors to decrease the acid secretion.

Complications:

- Esophageal ulceration, causing peptic ulcerations.
- Hematemesis. • Melena. • Strictures • Barrett's esophagus



erythema of the lower esophagus



cells with granular eosinophilic cytoplasm are identified as eosinophils

Eosinophilic Esophagitis

- Chronic immune mediated disorder

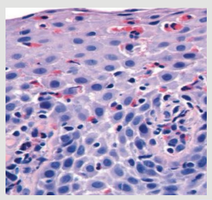
Symptoms:

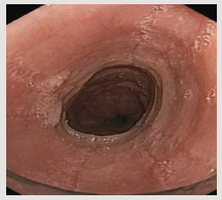
- Food impaction and dysphagia in adults
- Feeding, food allergies, or GERD-like symptoms in children.

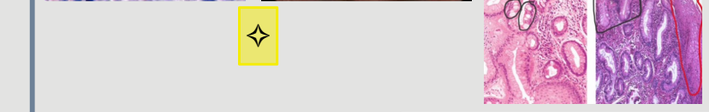
- **Morphology**:
- we might see rings in the upper and mid esophagus.
- Numerous eosinophils in the epithelium.
- Far from the GEJ.

Management:

- Most patients are atopic—such as atopic dermatitis (eczema), allergic rhinitis, or asthma and modest peripheral eosinophilia.
- Refractory to PPIs; patients will not respond.
- **Treatment**:
- Dietary restrictions ,such as cow's milk (particularly in children) and soy products.
- Topical or systemic corticosteroids.







Barrett Esophagus- precancerous condition.

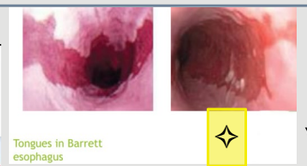
- Complication of chronic GERD
- Intestinal metaplasia.
- 10% of individuals with symptomatic GERD
- Males>> females, 40-60 yrs
- Direct precursor of esophageal adenocarcinoma
- 0.2-1% /year develop dysplasia (precursor of adenocarcinoma)

MORPHOLOGY

- Endoscopy:
- Red tongues extending upward from the GEJ.
- Histology:
- Intestinal metaplasia (defined by Presence of goblet cells)
- +-Dysplasia: low-grade or high-grade
- Intramucosal carcinoma (early carcinoma): invasion into the lamina propria.

Management of Barrett

Periodic surveillance endoscopy with biopsy to screen for the development of dysplasia.
If High-grade dysplasia & intramucosal carcinomas developed, this patient needs interventions.



Adenocarcinoma

- Background of Barrett esophagus and long-standing GERD.
- Risk is greater if: documented dysplasia is present, smoking, obesity, radio Tx.
- Male : female (7:1) very high in males
- There is geographic and racial variation in adenocarcinoma incidence in developed countries

Pathogenesis:

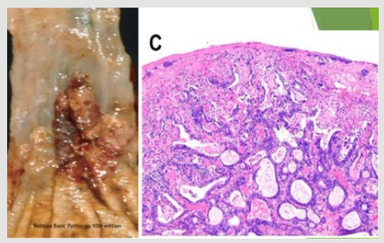
- From Barrett —> dysplasia —> adenocarcinoma.
- By Acquisition of genetic and epigenetic changes.
- with Chromosomal abnormalities and TP53 mutation.

MORPHOLOGY of Adenocarcinoma:

- They occur in the distal third of the esophagus,most affected by (GERD) and reflux esophagitis.
- Early morphologic changes of the lesion: flat or raised patches
- Later: exophytic infiltrative masses
- Microscopically, these tumors are adenocarcinomas, characterized by the formation of **glandular structures** and the **production of mucin**.

Clinical Features:

- Dysphagia (difficulty swallowing) and odynophagia (painful swallowing)
- Progressive weight loss. • Chest pain. • Vomiting.
- Advanced stage at diagnosis: 5-year survival <25%.
- Early stage: 5-year survival 80%



Squamous Cell Carcinoma

- Male : female (4:1)
- More common in rural, low resource, and under-developed countries.
- Not associated with reflux esophagitis!!
- Risk factors:
- Alcohol • Tobacco use • Poverty
- Caustic injury, including exposure to acidic or alkaline substances.
- Achalasia. • Plummer-Vinson syndrome (iron deficiency Anemia, dysphagia, and esophageal webs). • Frequent consumption of very hot beverages. • Previous radiation Tx.

Pathogenesis:

- In western: alcohol and tobacco use.
- Other areas: nutritional deficiency, exposure to polycyclic hydrocarbons, nitrosamines, fungus-contaminated foods.
- HPV infection has been implicated in squamous cell carcinoma in high-risk regions

MORPHOLOGY:

- arises in the **middle third of the esophagus**, accounting for approximately 50% of cases. In contrast, **adenocarcinoma typically involves the distal (lower) third of the esophagus.**
- Polypoid, ulcerated, or infiltrative wall thickening and luminal narrowing.
- Invade surrounding structures (bronchi, mediastinum, pericardium, aorta).

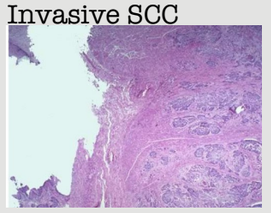
Microscopy:

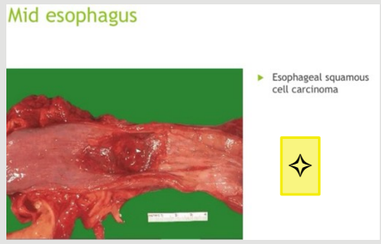
- Pre-invasive: the precursor lesion is **squamous dysplasia** & **carcinoma in situ**.
- Well to moderately differentiated **invasive SCC**.
- Intramural **tumor nodules** away from the main tumor , due to lymphatic drainage
- Lymph node metastases according to the site of the tumor:
- Upper 1/3: cervical LNs
- Middle 1/3: mediastinal, paratracheal, and tracheobronchial LNs.
- Lower 1/3: gastric and celiac LNs

Clinical Features:

- Dysphagia. • Odynophagia. • Obstruction
- Weight loss and debilitation
- Impaired nutrition & tumor associated cachexia
- hemorrhage and sepsis accompany tumor ulceration.
- it presents with symptoms caused by aspiration of food via a tracheoesophageal or tracheobronchial fistula
- Dismal Prognosis: 5-year survival rate ~10%

Invasive SCC





Intestinal pathology, part 1

Diseases of the intestines

- **Intestinal obstruction**
- **Vascular disorders**
- **Malabsorptive diseases and infections**
- **Inflammatory intestinal diseases.**
- **Polyps and neoplastic diseases**

Intestinal obstruction → Acute / Chronic

Clinical picture of intestinal obstruction.
- Abdominal pain
- Distention
- Vomiting
- Constipation.

Mechanical obstruction:

Intussusception

=> Segment of the intestine constricted by peristalsis, telescopes into the immediately distal segment.
=> Once trapped, invaginated segment is propelled by peristalsis, and pulls mesentery with it.
=> Most common cause of intestinal obstruction in children younger than 2 years of age.
=> Untreated progresses to obstruction and infarction.

Causes

_ Idiopathic in most cases.
Other causes:
_Peyer patches hyperplasia (rotavirus vaccine, viral infections). _ Meckles diverticulum (ileum)
_ Old children & adults: Intraluminal mass or tumors

Clinical features:

- Abdominal swelling. - Vomiting
- Pain. - Passing stools mixed with blood and mucus (**currant jelly stool**)

Management

- Contrast **enemas** (diagnostic and therapeutic) in uncomplicated idiopathic cases.
- **Surgery** if complicated by infarction or if masses are the leading point.

Meckel's diverticulum
- The most common congenital anomaly of the GI tract
- Incomplete obliteration of omphalomesenteric duct
- True diverticulum.
=> Remember (rule of 2):
... About 2% of people have them;
... Located 2 feet from the ileocecal valve.
... 2 inches in length.
... 2 types of heterotopic mucosa (gastric or pancreatic).
نسيج طبيعي لكنه بمكان غير طبيعي
... Most common cause of lower GI bleeding before age of 2.

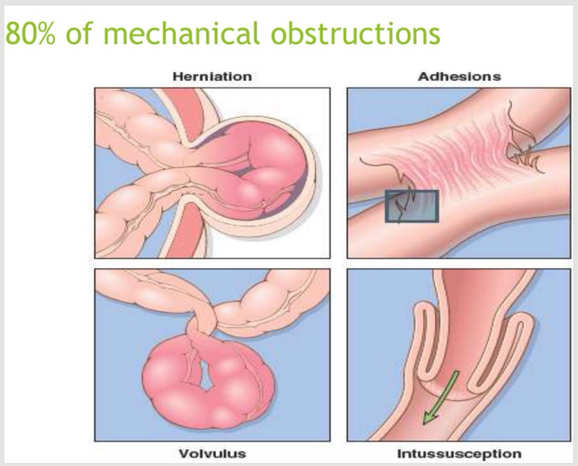
Clinical presentation

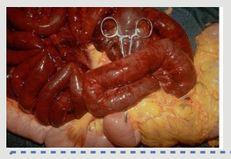
- Can be asymptomatic and discovered incidentally.
- Ulceration, lower GI bleeding or perforation from ectopic gastric mucosa.
- Bowel obstruction due to the intussusception, volvulus or adhesive band.
- Can be confused with acute appendicitis.

- Hernias
- Volvulus

Could lead to infarction of bowel

- Adhesions
- Tumors
- Diverticulitis
- Infarction





Bowel infarction

Non-mechanical obstruction

Hirschsprung Disease

- Congenital defect in **colonic innervations**
- Congenital aganglionic megacolon
- More common in males/ More severe in females
- Risk increase in siblings.

Typical presentation:

=> Neonatal failure to pass meconium
=> Later: Obstructive constipation.

Pathogenesis

~ During embryogenesis: disrupted migration of neural crest cells from cecum to rectum.
~ Aganglionosis: Distal intestinal segment lacks both: Meissner submucosal
plexus and the Auerbach (myenteric) plexus.
~ Failure of coordinated peristaltic contractions.
~ RET Mutations: in familial cases and 15% of sporadic.(RET=receptor tyrosine kinase)
- Other genes and environmental factors play role.
=> More in Down syndrome.

Morphology

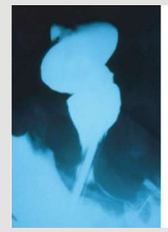
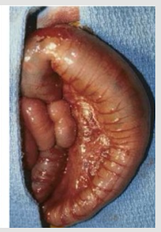
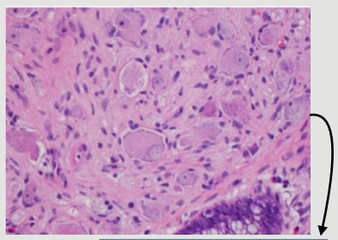
- Rectum always involved, Most cases in rectosigmoid
- Extent is variable.
- Aganglionic region normal or contracted
- Proximal normal segment progressively dilated.
- BIOPSY to confirm absence of ganglion cells.
- **Diagnostic** workup: barium enema, biopsy.

Complications

* Enterocolitis * Fluid and electrolyte disturbances
* Perforation * Peritonitis

Treatment:

- Surgical resection of aganglionic segment and anastomosis of normal segments.

Ganglionic cells with dominant nucleolus

- Neurological disorders.
- Drugs

Intestinal pathology, part 1 Cont.

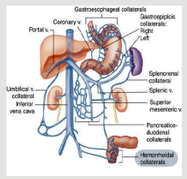
Diseases of the intestines

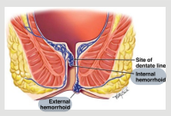
Intestinal obstruction | **Vascular disorders** | **Malabsorptive diseases and infections** | **Inflammatory intestinal diseases.** | **Polyps and neoplastic diseases**

VASCULAR DISORDERS OF BOWEL

Angiodysplasia

=> Malformed submucosal and mucosal blood vessels.
- Most often in cecum and right colon.
- 6th decade of life.
- Less than 1% of adult population.
- 20% of cases of lower GI bleeding.
- Blood is bright red in color.





Hemorrhoids

=> Dilated anal and perianal collateral vessels that connect the portal and caval venous systems.

Predisposing factors:

. Constipation and straining. .Venous stasis of pregnancy . Portal hypertension.

. External (below anorectal line, inferior hemorrhoidal plexus) and internal (above anorectal line, superior hemorrhoidal plexus).

Morphology:

=> Thin-walled, dilated, submucosal vessels beneath anal or rectal mucosa.

Symptoms:

=> Bleeding (bright red), pain due to thrombosis and inflammation

Treatment:

=> Sclerotherapy (injects a chemical to shrink hemorrhoid) , rubber band ligation(band cuts off blood supply to hemorrhoid), infrared coagulation(Heat treatment to shrink hemorrhoid) . Hemorrhoidectomy(Surgery)

Ischemic Bowel Disease

DIARRHEAL DISEASE

Diarrhea: increase in stool mass, frequency or fluidity.
- **Dysentery**: painful , bloody, small volume diarrhea

Infectious Enterocolitis/Ischemia/ Inflammatory bowel diseases.....can cause diarrhea

malabsorptive | Secretory | osmotic | exudative

=> Chronic.
=> Defective absorption of fats, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes, minerals and water
=> Hallmark is : **steatorrhea**. (excessive fat, bulky, frothy, yellow, greasy stool)

Mechanisms of malabsorption

(2 digestion,2 transport)
- Intraluminal digestion.
- Terminal digestion.
- Transepithelial transport.
- Lymphatic transport.

Manifestations:
- Weight loss, anorexia,
- Flatus, abdominal distention,
- Borborygmi (intestinal noise), Muscle wasting
- Anemia and mucositis (iron, pyridoxine (VB6), folate, or vitamin B12 deficiency)
- Bleeding (vitamin K deficiency)
- Osteopenia and tetany (calcium, magnesium, or vitamin D deficiency)
- Neuropathy (vitamin A or B12 deficiency)
- Skin and endocrine disorders.

Pancreatic insuffciency. | **Crohn disease** | **Celiac disease** | **Cystic Fibrosis** | **Lactase (Disaccharidase) Deficiency** | **Abetalipoproteinemia**

Celiac disease

- Gluten sensitive enteropathy. - Immune mediated enteropathy
- Wheat, rye or barley. - Genetically predisposition HLA-DQ2 or HLA-DQ8.
- Treatment: gluten free diet.
- Association with: type 1 diabetes, thyroiditis, and Sjogren syndrome

Pathogenesis

Gluten >>> gliadin >>deamidated by TTG(tissue trans glutamines)>> react with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells >>> CD4+ T cells activation >>> cytokines >>> tissue damage>> B cell activation >> antibodies

Serology:
~ Anti- tissue transglutaminase antibodies
~ Anti-gliadin antibodies.
~ Anti -endomysial antibodies

MORPHOLOGY
- Second portion of the duodenum or proximal jejunum.
- Triad: intraepithelial lymphocytosis (CD8+ T cells), crypt hyperplasia, and villous atrophy.
- Lamina propria: lymphocytes, plasma cells, eosinophils.....
- IEL & villous atrophy are not pathognomonic, seen in viral enteritis.

Clinical Features

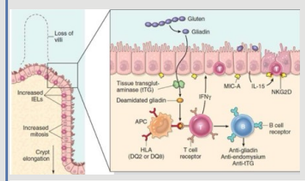
Children 6-24 months :
Classical: Irritability, abdominal distention, anorexia, diarrhea, failure to thrive, weight loss, or muscle wasting
Non-classical: abdominal pain, nausea, vomiting, bloating, or constipation. Blistering skin lesion, dermatitis herpetiformis, in 10% of Pnts.

Adults (30-60 years)
Anemia: iron deficiency/ B12 and folate deficiency: less common./ Diarrhea , bloating, and fatigue.
Missed diagnosis: Silent celiac (positive serology and biopsy but asymptomatic).
Increased risk of **enteropathy associated T cell lymphoma** & Small intestinal **adenocarcinoma**.

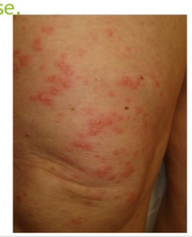
Diagnosis: Clinical, histologic and serologic correlation.

Non invasive serologic tests:
Most sensitive: —Anti tissue transglutaminase antibody, IgA. — Anti deamidated gliadin antibodies, IgA & IgG
Most specific, but less sensitive :- Antiendomysial antibody.

Invasive tests: small bowel biopsy.



Dermatitis herpetiformis with celiac disease.



Cystic Fibrosis

Mutations in cystic fibrosis transmembrane conductance regulator (**CFTR**)
... Defects in ion transport across intestinal and pancreatic epithelium.
... Thick viscous secretions.
... Mucus plugs in pancreatic ducts >>> pancreatic insufficiency (80% of patients)
... Meconium ileus in neonates.
... Defect in **intraluminal digestion.**

Lactase (Disaccharidase) Deficiency

- Osmotic diarrhea
- Lactose remains in the gut lumen.
- Lactase found at apical brush border membrane
- Normal biopsy findings.

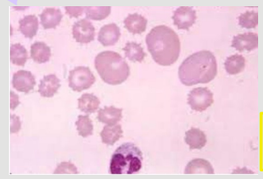
Congenital : AR, genetic mutation, rare, explosive diarrhea, watery, frothy stools & abdominal distention, after milk ingestion

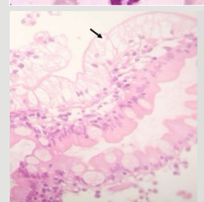
Acquired : very common, downregulation of gene, after weaning. Affects 2/3 of worlds population (50% of USA population).

Transient: caused by injury after infectious or inflammatory insults (reversible)

Abetalipoproteinemia

- Autosomal recessive, rare.
- Inability of enterocytes to secrete triglyceride-rich chylomicrons.
- Lack of absorption (Transepithelial transport defect of lipoproteins, FAs and fat-soluble vitamins).
- Infants' with failure to thrive, diarrhea, and steatorrhea
-Vitamin K deficiency, skeletal CNS and retinal abnormalities
- Spur cells in peripheral blood.
- Monoglycerides and triglycerides accumulate in epithelial cells.





Micrograph showing enterocytes with a clear cytoplasm (due to lipid accumulation) characteristic of abetalipoproteinemia.

Intestinal pathology, part 2

Diseases of the intestines

- Intestinal obstruction
- Vascular disorders
- Malabsorptive diseases and infections
- Inflammatory intestinal diseases.
- Polyps and neoplastic diseases

INFLAMMATORY INTESTINAL DISEASE

Pathogenesis:
Combined effect of:
Altered host interaction with intestinal microbiota. + Intestinal Epithelial dysfunction + Aberrant mucosal immune responses.

Epidemiology
. Adolescence & young adults. . 2nd peak in fifth decade.
. Geographic variation. . Proposed explanation => Hygiene hypothesis: childhood exposure to environmental microbes prevents excessive immune system reactions. No firm evidence

Causes:-
- Genetic predisposition
- Immune response to intestinal microbes.
- Inappropriate mucosal damage.

Sigmoid Diverticulitis

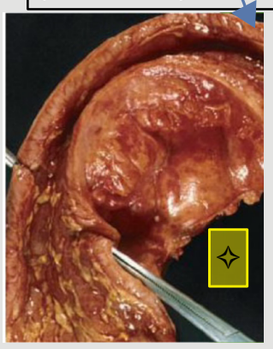
- Acquired Pseudodiverticula
- Rare <30 years, common >60years.
- Multiple (diverticulosis)

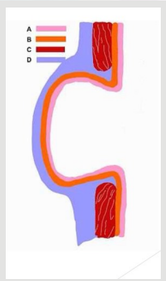
Pathogenesis:
... Elevated intraluminal pressure.
... Unique location (discontinuous muscle layer at points of nerve and vessels entry).
... Longitudinal muscle layer is discontinuous in colon (taeniae coli)
... Area of weakness: outward herniation of mucosa and submucosa .
... Most common in sigmoid (narrowest part)
... Exaggerated peristaltic contractions.
... causes:- Low fiber diet, constipation, sedentary lifestyle, obesity, and smoking.

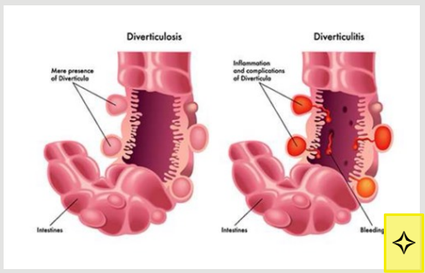
Clinical Features
Mostly asymptomatic / Intermittent lower abdominal pain /Constipation or diarrhea.

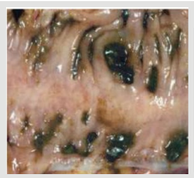
Tx
High fiber diet. / Antibiotics in diverticulitis. / Surgery

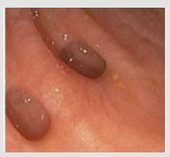
MORPHOLOGY
=> Flask-like outpouchings —— Between taeniae coli.
=> Thin wall (atrophic mucosa, compressed submucosa)
=> Attenuated or absent muscularis propria.
=> Obstruction leads to diverticulitis.
=> Risk of perforation.
=> Recurrent diverticulitis leads to fibrosis (strictures).







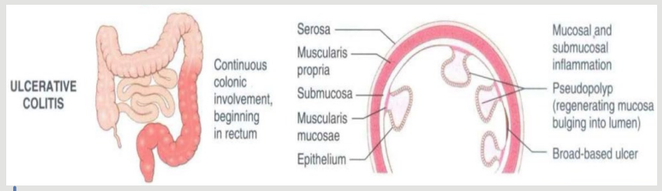




-Always involves the rectum
- Extends proximally in continuous pattern.
- Pancolitis.
- No skip lesions
- Occasionally focal appendiceal or cecal inflammation.
-Limited diseases: Ulcerative proctitis or ulcerative proctosigmoiditis
- Small intestine is normal (except mild **backwash ileitis**)

Chronic Inflammatory bowel diseases (CIBD)

Ulcerative colitis: limited to the colon and rectum, extends only into mucosa and submucosa.

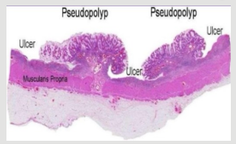


Morphology

Macroscopic
- Broad-based ulcers.
- Pseudo polyps (regenerating mucosa)
- Mucosal atrophy in long standing
- Mural thickening absent
- Serosal surface normal
- No strictures
- Toxic megacolon (damage of MP, disturbed neuromuscular function)

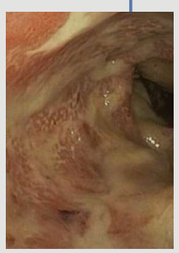

Toxic megacolon

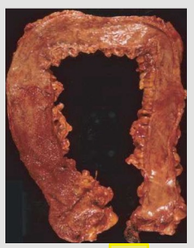
Microscopic
- Inflammatory infiltrates
- Crypt abscesses
- Crypt architecture distortion
- Epithelial metaplasia
- Submucosal fibrosis
- Inflammation limited to mucosa and submucosa.
- **No skip lesions**. - No granulomas.

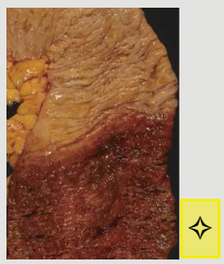


Clinical Features

~ Relapsing remitting disorder
~ Attacks of bloody mucoid diarrhea +lower abdominal cramps
~ Temporarily relieved by defecation
~ Attacks last for days, weeks, or months.
~ Asymptomatic intervals.
~ Infectious enteritis may trigger disease onset, or cessation of smoking.
~ Colectomy cures intestinal disease only
~ Anti-inflammatory and biologic agents.


Mucopurulent material and ulcers.

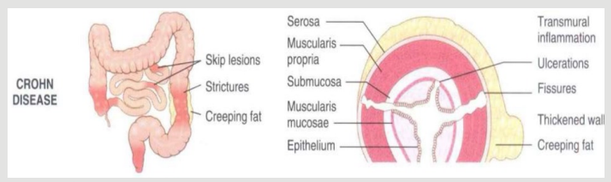

Pancolitis


Abrupt transition b/w normal and disease segment.

Colitis-Associated Neoplasia
=> Long standing UC and CD.
=> Begins as dysplasia >>>> carcinoma.
=> Colonoscopy surveillance programs.

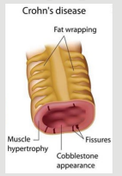
Risk depends on
- Duration of disease: increase after 8-10 years .
- Extent of involvement: more with pancolitis.
- Inflammation: frequency & severity of active disease with neutrophils.

Crohn disease: regional enteritis, frequent ileal involvement, affect any area in GIT, frequently transmural.



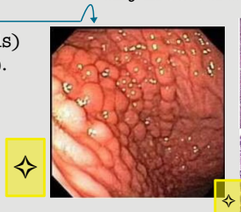
Morphology

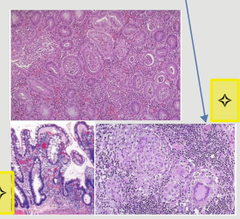
Macroscopic
- Regional enteritis. -Any area of GIT.
- Most common sites: terminal ileum, ileocecal valve, and cecum. Small intestine alone 40% / Small intestine and colon 30% / Colon only 30%
There are **Skip lesions** && Strictures
- Earliest lesion: aphthous ulcer
- Elongated, **serpentine** ulcers.
- Edema , loss of bowel folds.
- Cobblestone appearance
- Toxic megacolon (before fibrosis)
- Fissures (fistulas, perforations).
- Thick bowel wall (transmural inflammation, edema, fibrosis, hypertrophic MP) >>strictures.
- Creeping fat



Creeping fat

Microscopic
- Neutrophils in active disease.
- Crypt abscesses.
- Ulceration.
- Distortion of mucosal architecture (repeated cycles)
- Paneth cell metaplasia in left colon
- Mucosal atrophy.
- **Noncaseating granulomas** (hallmark) only in 35% of cases. Anywhere!!





Clinical Features

~ Intermittent attacks of mild diarrhea, fever, and abdominal pain.
~ Acute right lower-quadrant pain and fever (20%)
~ Bloody diarrhea and abdominal pain (colonic disease)
~ Asymptomatic intervals (weeks to months)
~ Triggers: physical or emotional stress, specific dietary items, NSAID use, and cigarette smoking.

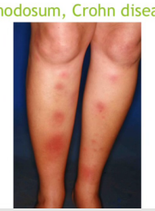
Complications

~ Colonic: Iron-deficiency anemia.
~ Small bowel: Hypoproteinemia and hypoalbuminemia, **malabsorption** of nutrients, vitamin B12 and bile salts
~ Fistulas, peritoneal abscesses, strictures
~ Risk of colonic and small intestinal adenocarcinoma

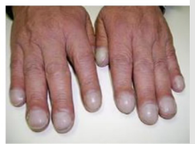
Extra intestinal manifestations

~ Uveitis. ~ Migratory polyarthritis.
~ Sacroiliitis. ~Ankylosing spondylitis
~ Erythema nodosum. ~ Clubbing of the fingertips
~ Primary sclerosing cholangitis (more with UC)

Erythema nodosum, Crohn disease



Clubbing



Intestinal pathology, part 3

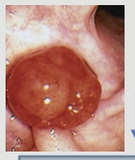
Diseases of the intestines

- **Intestinal obstruction**
- **Vascular disorders**
- **Malabsorptive diseases and infections**
- **Inflammatory intestinal diseases.**
- **Polyps and neoplastic diseases**

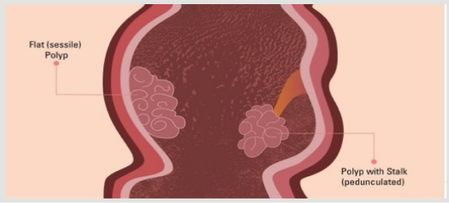
common site for polyps=> Colon

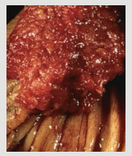
COLONIC POLYPS AND NEOPLASTIC DISEASE

According to their architecture



Sessile polyp: no stalk





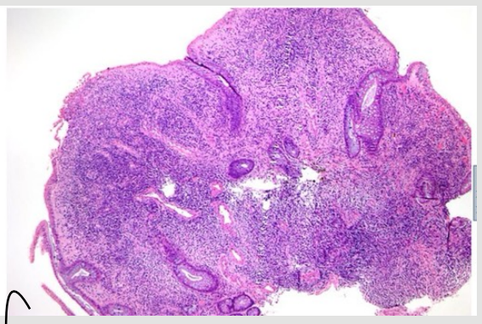
Pedunculated polyp: stalk.

According to Malignancy Potential

- Non neoplastic polyps
- Neoplastic polyps Adenoma

Inflammatory Polyps

- Solitary rectal ulcer syndrome.
- Impaired relaxation of anorectal sphincter .
- Recurrent abrasion and ulceration of the overlying rectal mucosa.
- Chronic cycles of injury and healing give a polypoid mass of inflamed and reactive mucosal tissue.
- Rectal bleeding, mucus discharge and polyp.

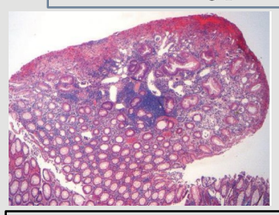


* * Bluish foci correspond to inflammatory cells which could be lymphocytes , plasma cells and neutrophils
* * Glands are scant, few glands are left because of inflammation and destruction due to inflammation => these glands are benign looking

Hamartomatous Polyps

- Sporadic or syndromic.[Under microscope they look the same]
~ Hamartomatous polyposis syndromes.
=> Disorganized, tumor-like growth composed of mature cell types normally present at that site.

- **Juvenile Polyps**

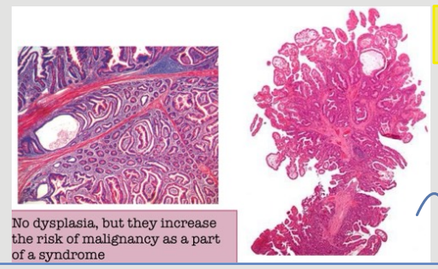


Pedunculated, Reddish lesions, Cystic spaces on cut sections => Dilated glands filled with mucin and inflammatory debris.
Granulation tissue on surface.

  - **Sporadic**
    ... Solitary. <5 years of age
    ... seen in Rectum, with bleeding
  - **Syndromic** (juvenile polyposis).
    ... Dozens. < 5 years
    ... Autosomal dominant.
    ... Transforming growth factor-β (TGF-β) signaling pathway germline mutation (SMAD4).
    ... Increased risk for colonic adenocarcinoma and others.

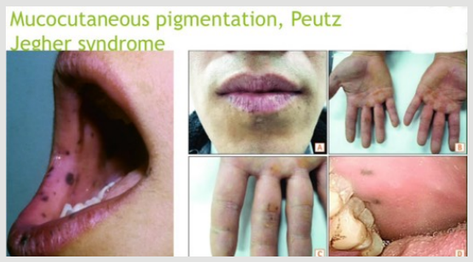
- **Peutz-Jeghers Syndrome**

- Autosomal dominant, rare
- Multiple gastrointestinal hamartomatous polyps
- Mucocutaneous **hyperpigmentation**
- Increased risk for several malignancies: colon, pancreas, breast, lung, ovaries, uterus, and testes,
- LKB1/STK11 germline mutation (tumor suppressor protein).



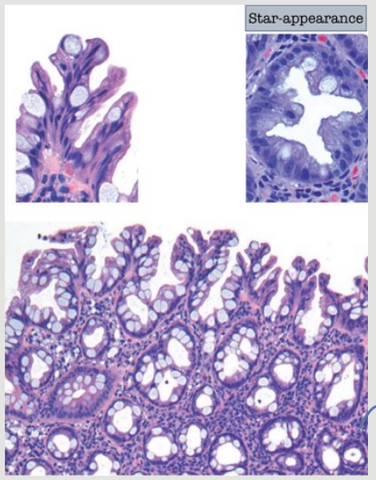
No dysplasia, but they increase the risk of malignancy as a part of a syndrome

- Mostly in small intestine. - Large, pedunculated, lobulated.
- Arborizing network of connective tissue, smooth muscle, lamina propria and glands. - Normal-appearing intestinal epithelium. - Christmas tree pattern.



Hyperplastic Polyps

- Common
- 6-7th decades.
- Decreased epithelial turnover and delayed shedding of surface epithelium >>> pileup of goblet cells & epithelial overcrowding
- No malignant potential
- Biopsy is important.



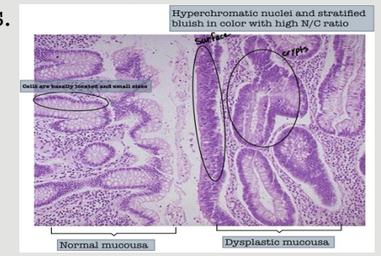
=> Left colon => Recto-sigmoid.
=> Small < 5 mm => Often multiple
=> **Crowding of goblet & absorptive cells.** => Serrated surface.

Neoplastic polyps Adenoma

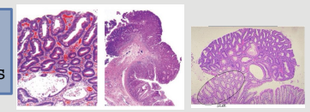
- Most common and clinically important
- 50% of adults > 50 years. (western world)
- **Precursor for majority of colorectal adenocarcinomas**
- USA: screening colonoscopy starts at 45 yrs.
- Earlier screening with family history.
- Western diets and lifestyles increase risk.

Colon adenoma

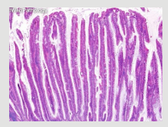
- Hallmark: epithelial dysplasia
- Nuclear hyperchromasia, elongation, stratification, high N/C ratio.
- Size is most important correlate with risk for malignancy. (40% if > 4cm)
- High-grade dysplasia is a second factor
- Architecture: Tubular, villous, tubulovillous.



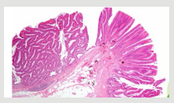
- **Tubular adenoma**:
  -Pedunculated
  -small tubular glands



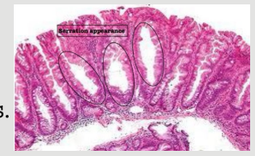
- **Villous adenoma.**
  - Long slender villi.
  - Large and sessile.
  - More frequent invasive foci



- **Tubulovillous adenoma**



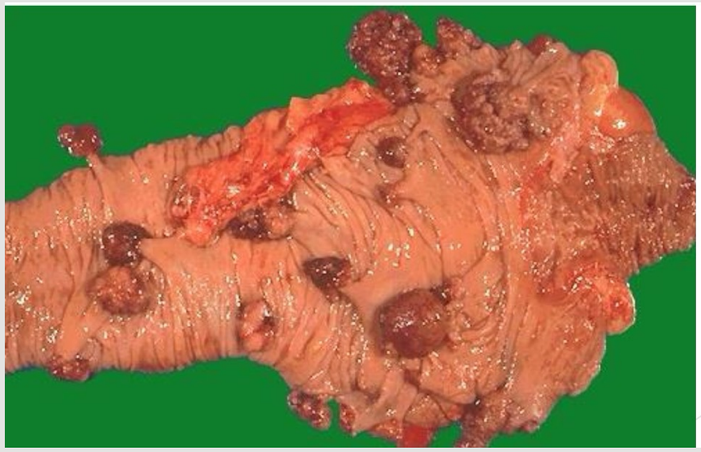
- **Sessile serrated adenoma**



- Overlap with hyperplastic polyps.
- Lack dysplasia
- Malignant potential similar to conventional adenomas.
- Serrated architecture throughout full length of glands.
- Basal crypts dilated.

Hereditary Nonpolyposis Colorectal Cancer: HNPCC, Lynch syndrome

- Autosomal dominant. Inherited germ-line mutations in DNA mismatch repair genes (detection, resection and repair of errors in DNA replication).
- Increased risk of: Colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, and skin cancers.
- Colon cancer at younger age than sporadic cancers
- Right colon, abundant mucin.
- Only few adenomatous precursors (typically **sessile serrated adenomas**).
- Accumulation of mutations at 1000x higher rates in microsatellite DNA (short repeating sequences)
- Resulting in **microsatellite instability.**
- 5 genes identified but Majority of cases involve either MSH2 or MLH1.



Familial Syndromes

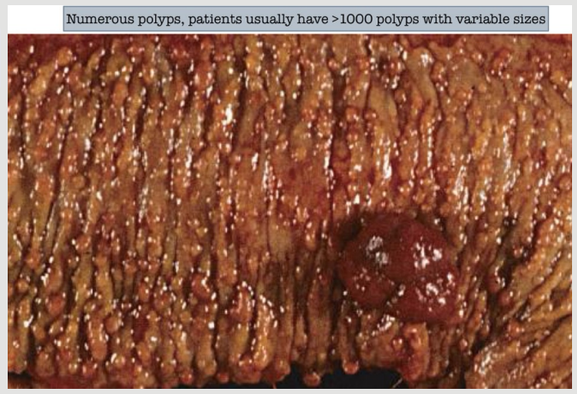
… Syndromes associated with colonic polyps and increased rates of colon cancer
… based on Genetic basis.

Familial adenomatous polyposis FAP

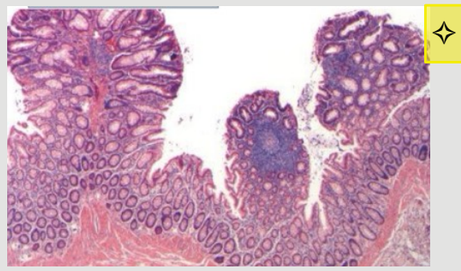
- Autosomal dominant.
- Numerous **colorectal adenomas**: teenage years.
- Mutation in APC gene.
- At least 100 polyps are necessary for a diagnosis of classic FAP.
- Morphologically similar to sporadic adenomas<<Under microscope they look the same, they harbour dysplasia with low ir high grade>>
- 100% of patients develop colorectal carcinoma, IF UNTREATED, often before age of 30.
- Standard therapy: prophylactic colectomy.
- Risk for extraintestinal manifestations

Variants of FAP:
=> Specific APC mutations.

Gardner syndrome: intestinal polyps + osteomas (mandible, skull, and long bones); epidermal cysts; desmoid and thyroid tumors; and dental abnormalities.



Turcot syndrome: intestinal adenomas and CNS tumors (medulloblastomas >> glioblastomas)



Intestinal pathology, part 4

Diseases of the intestines

Intestinal obstruction | **Vascular disorders** | **Malabsorptive diseases and infections** | **Inflammatory intestinal diseases.** | **Polyps and neoplastic diseases**

Colonic Adenocarcinoma

~ Most common malignancy of the gastrointestinal tract (2nd cause of cancer related death after lung cancer)
~ Small intestine is uncommonly involved by neoplasia.
~ Peak: 60-70 years, males>females, <20% before 50.
~ Developed countries lifestyles and diet.
~ Risk factors: Low intake of vegetable fiber and high intake of carbohydrates and fat. Obesity, smoking and alcohol.
~ Aspirin or other NSAIDs have a protective effect (Cyclooxygenase-2 (COX-2) expressed in 90% of carcinomas, even adenomas, promotes epithelial proliferation).
~ Prevention: dietary modification, pharmacologic chemoprevention.

Pathogenesis
=> Heterogeneous molecular events (genetic and epigenetic).
=> Sporadic >>>> familial.

Stepwise accumulation of multiple mutations in both pathways

APC/β-catenin pathway >> increased WNT signaling

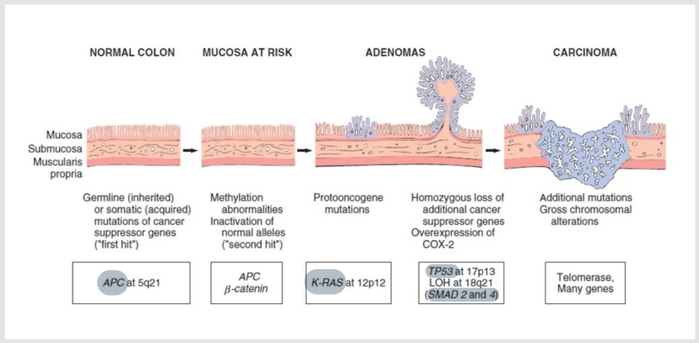
Microsatellite instability pathway due to defects in DNA mismatch repair

Colonic Adenocarcinoma

APC/β-catenin pathway: chromosomal instability

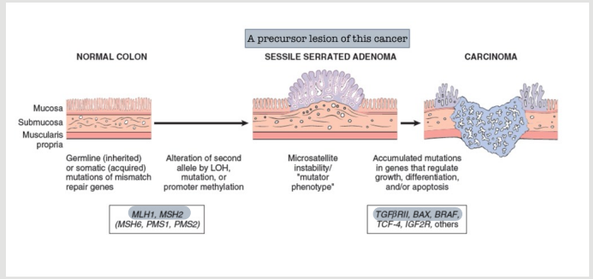
~ Classic adenoma carcinoma sequence.
~ 80% of sporadic colon tumors
~ Mutation of the APC tumor suppressor gene: EARLY EVENT
~ APC is a key negative regulator of β-catenin (promotes degradation), a component of the WNT signaling pathway.
~ Both copies of APC should be inactivated for adenoma to develop (1st and 2nd hits).
~ **Chromosomal instability by deletions** (hallmark)

Loss of APC >>> accumulation of B-catenin >> enters nucleus >> MYC and cyclin-D1 transcription >>promote proliferation >>>Additional mutations >> activation of KRAS oncogene>> promotes growth & prevent apoptosis (LATE EVENT) >>>SMAD2 and SMAD4 mutations (tumor suppressor genes.) TP53 is mutated in 70%-80% of colon cancers (LATE EVENT IN INVASIVE)>>> TP53 inactivation,mutation (tumor suppressor gene)>>> Expression of telomerase also increases as thetumor advances.



The microsatellite instability pathway

~ DNA mismatch repair deficiency (Loss of genes)
~ Mutations accumulate in microsatellite repeats (**mostly** non-coding)
~ Microsatellite instability
~ Silent if microsatellites located in noncoding regions
~ Uncontrolled cell growth if located in coding or promoter regions of genes involved in cell growth and apoptosis (TGF-B and BAX genes)
~ BRAF mutations common. However, P53 and KRAS are absent



Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis (70% of FAP)	APC/WNT pathway	*APC*	Autosomal dominant (First hit=> inherited as germline mutation; Second hit => occurs as somatic mutation)	None	Tubular, villous; typical adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	*MSH2, MLH1*	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (80%)	APC/WNT pathway	*APC*	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%–15%)	DNA mismatch repair (Microsattelite instability)	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

MORPHOLOGY

Macroscopic:
- Proximal colon tumors=> polypoid, exophytic masses
- Proximal colon=> rarely cause obstruction.
- Distal colon=> annular lesions "**napkin ring**" constrictions & narrowing

Microscopic:
- Dysplastic GLANDS with strong desmoplastic response (firm).
- Necrotic debris (dirty necrosis) typical.
- Some tumors give abundant mucin (poor Px) or form signet ring cells.

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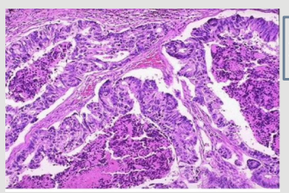
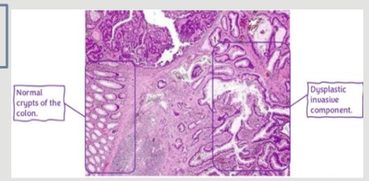
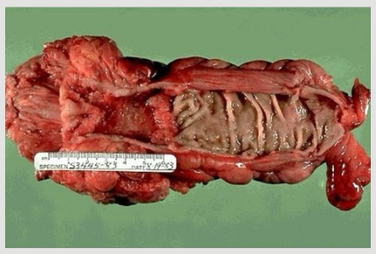


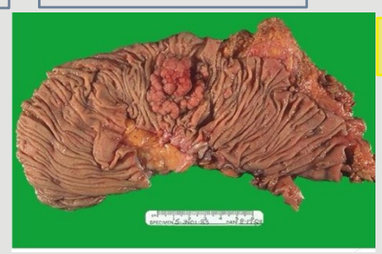
Adenocarcinoma with necrosis



Recto-sigmoid adenocarcinoma, napkin ring



Exophytic adenocarcinoma



Clinical Features

- Endoscopic screening >> cancer prevention
- Early cancer is **asymptomatic** !!!!!!
- Cecal and right-side cancers: Fatigue and weakness (iron deficiency anemia)
- Iron-deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise.
- Left sided carcinomas: occult bleeding, changes in bowel habits, cramping left lower-quadrant discomfort.

Prognosis:

- Poor differentiation and mucinous histology >> poor prognosis
- Most important two prognostic factors are
1. Depth of invasion (mucosa, submucosa, MP, serosa)
2. Lymph node metastasis. (needs Rx and Chemox)
In addition:
=> Distant **metastasis to liver** (most common) and **lung**. (solitary mets can be resected).
=> Tumors with microsatellite instability (immune checkpoint inhibitor therapy)

Appendix diseases

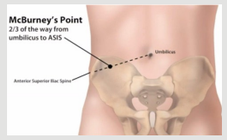
ACUTE APPENDICITIS

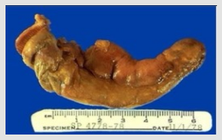
- Most common in adolescents and young adults.
- May occur in any age.
- Difficult to confirm preoperatively, surgical emergency.

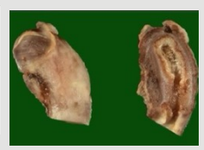
list of possible **conditions that share the same symptoms of appendicitis** :-
~ Mesenteric lymphadenitis,
~ Acute salpingitis,
~ Ectopic pregnancy,
~ Mittelschmerz (pain associated with ovulation),
~ Ovarian cysts torsion
~ Rupture Meckel diverticulitis
~ Crohn disease

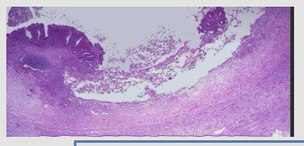
Pathogenesis:
... Increased luminal pressure >> impaired venous drainage >> ischemic injury & stasis associated bacterial proliferation >>> inflammatory response rich in neutrophils & edema.
... Luminal obstruction in 50-80% of cases by fecalith (small mass-like stone of stool), less commonly : gallstone, tumor, worms....
... Diagnosis requires neutrophilic infiltration of the muscularis propria
Acute suppurative appendicitis >> more severe >> focal abscess within wall.
Acute gangrenous appendicitis >> gangrenous necrosis and ulceration>> rupture.

Clinical Features
- Early acute appendicitis: periumbilical pain
- Later: pain localizes to the right lower quadrant,
- Nausea, vomiting, low-grade fever, mildly leukocytosis.
- A classic physical finding is **McBurney's sign** (McBurney's point).
- Signs and symptoms are often absent, creating difficulty in clinical diagnosis



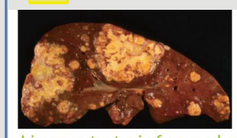






TUMORS OF THE APPENDIX

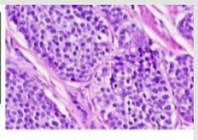
- The most common tumor: **carcinoid** (neuroendocrine tumor)
- Incidentally found during surgery or on examination of a resected appendix
- Distal tip of the appendix
- Nodal metastases & distant spread are **rare.**



Liver metastasis from colon cancer.

Gross

Tend to be on the tip of the appendix with yellow discoloration



Microscopic

The tumor shows a nesting pattern with salt and pepper chromatin, typical of a neuroendocrine tumor.