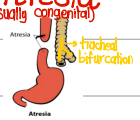
Pathology Summary
By Rahaf Naser

esophageal diseases part 1&2

- Mechanical obstruction
  - Atresia
  - Fistulas
  - Duplications
  - Agenesis
  - Stenosis
- Functional obstruction
  - Achalasia
- Vascular diseases
  - Varices
- Inflammation: esophagitis
  - Esophageal Lacerations
  - Mucosal injury (chemical)
  - Infection
  - Reflex esophagitis
  - Eosinophilic Esophagitis
- Tumors
  - Adenocarcinoma
  - Squamous cell carcinoma

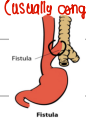
Mechanical obstruction
(congenital or acquired)

Atresia
(usually congenital)



- Thin, noncanalized cord replaces a segment of esophagus.
- * Most common location: at or near the tracheal bifurcation
- Shorty after birth: regurgitation during feeding
  - ± can be with or without fistula
  - → complications if with fistula:
    1) Aspiration
    2) Suffocation
    3) Pneumonia
    4) Sever fluid & electrolyte imbalances

Fistula
(usually congenital)

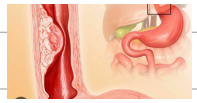


- Upper or lower esophageal pouches to a bronchus or trachea

Duplications
(usually congenital)

Agenesis
(usually congenital) (very rare)
→ The esophagus isn't developed at all

Stenosis

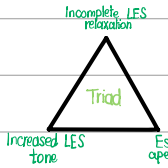


- Acquired >> congenital
  - → It's fibrous thickening of the submucosa & Atrophy of the muscularis propria
  - → due to inflammation & Scarring upon previous injury
- * Causes & → chronic GERD, → Irradiation, → Ingestion of caustic agent, → Systemic sclerosis
- * Clinical presentation:
  - → Progressive dysphagia :-
    Difficulty eating solids that progresses to problems with liquids.

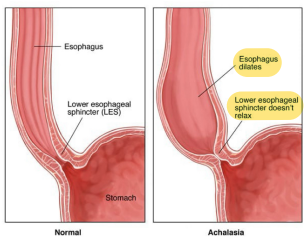
- Needs prompt surgical correction to rejoin the parts of esophagus.

Functional obstruction

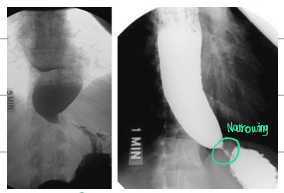
Achalasia



* in this type there is no interfering with the passage of food but there is an abnormality in innervation



* Clinical presentations
  - → Difficulty in swallowing
  - → Regurgitation
  - → Sometimes chest pain
* Diagnoses:



Through Barium swallow, we ask the patient to drink Barium, then xray is taken.
As u can see, LES appears like a string, it's semi closed.

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

Secondary achalasia
- → loss of neural innervation due to damage in:
  - Esophagus
  - Vagus nerve
  - Dorsal motor nucleus of vagus
- → Chagas disease (Trypanosoma cruzi infection) → destruction of the myenteric plexus → failure of LES relaxation → esophageal dilatation

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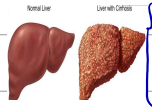
Vascular diseases

Esophageal varices

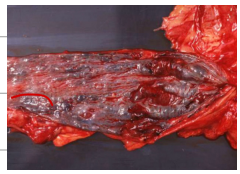


- Causes
  - Cirrhosis and the MC cause of Cirrhosis is Alcoholic liver disease
  - Hepatic schistosomiasis, 2nd MC world wide
- Clinical features
  - often asymptomatic
  - Rupture leads to massive hematemesis & death
  - 50% of patients die from the first bleed despite interventions
  - Death due to: hemorrhage, hepatic coma & hypovolemic shock
  - Rebleeding in 60%

Tortuous dilated veins within the submucosa of the distal esophagus & proximal stomach, diagnosed by endoscopy or angiography.

* in normal conditions: Blood from GIT → Portal vein → liver (detoxification) → by hepatic vein → inferior vena cava (systemic circulation)
  - X in the disease

! diseases that impede portal blood flow will lead to portal hypertension → esophageal varices

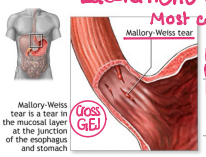


→ distal esophagus is the site of porto-systemic anastomosis

Portal hypertension → collateral (lead to development of) channels in distal esophagus → Shunt of blood from portal to systemic circulation so we'll have dilated collaterals in distal esophagus = varice

Esophagitis

Esophageal Lacerations (not inflammation)



Mallory-Weiss tear is a tear in the mucosal layer at the junction of the esophagus and stomach

Most common

linear laceration & longitudinally oriented & superficial

* Causes → Severe retching → forceful prolonged vomiting

* present with hematemesis

Vomiting → Stretching → tear

heal quickly & no surgical intervention

Chemical esophagitis (mucosal injury)

- Damage to esophageal mucosa by irritants

Clinical symptoms:

- Ulceration & acute infl.
- Only self limited pain
- Odynophagia (علوه مؤلم)
- Hemorrhage, Stricture or Perforation in Sever cases.

eg:
- Alcohol
- Corrosive acids or alkalis
- Excessively hot fluids
- Heavy smoking
- Medicinal pills (doxycycline, bisphosphonates)
- Iatrogenic (chemoTx, radioTx, GvHD)

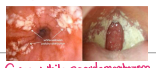
Graft versus host disease

Infectious esophagitis (very rare)

Viral (HSV, CMV) ← | ↓ Bacterial 10% | → Fungal (Candida >> mycormycosis & aspergillosis)

- mostly in debilitated or immunosuppressed

Candidiasis



- Gray-white pseudomembranes
- Adherent
- Composed of matted fungal hyphae & inflammatory cells.

CMV

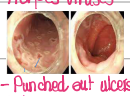
Shallower ulceration

Biopsy:

* Nuclear & cytoplasmic inclusions in capillary endothelium & stromal cells

we call them (Megalo cells) cuz they are very large (upon infection with CMV)

Herpes viruses

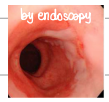


- Punched out ulcers

Histopathology:

* Nuclear viral inclusions
* Degenerating epithelial cells ulcer edge
* Multinucleated epithelial cells

Reflux esophagitis, GERD



- Reflux of gastric contents into the lower esophagus

* Most frequent cause of esophagitis
* MC complaint by GERD patients → squamous epithelium in esophagus is sensitive to acids

● Protective forces → mucin (by submucosal glands) → Bicarbonate → high LES tone

Causes:

1) decreased LES tone (alcohol, tobacco, CNS depressants, hital hernia)
2) Increase abdominal pressure (obesity, Pregnancy, delayed gastric emptying & increased gastric volume)
3) Idiopathic

* Morphology

Macroscopy: Depends on severity
→ In less severe cases (unremarkable)
→ In moderately severe cases (simple hyperemia)
→ In severe cases (ulceration can occure)

Microscopic:
* Eosinophils infiltration (early)
* then neutrophils (more sever)
* Basal zone hyperplasia
* Elongation of lamina propria papillae

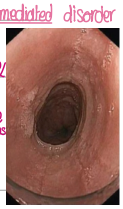
* MC > 40 years
* May occure in infants & children
* Heart burn, dysphagia
* Regurgitation of sour-tasting gastric contents
* Rarely: sever chest pain (mistaken for heart disease)

Tx: PPIs

Eosinophilic Esophagitis

* Chronic immune mediated disorder

Symptoms:
→ food impaction & dysphagia in adults
→ feeding intolerance or GERD-like symptoms in children



Morphology

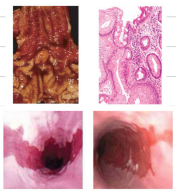
Macro → Rings in the Upper & Mid esophagus

Micro → * ↑ eosinophils within epithelium (Larger than reflux)
* far from GEJ
* Most patients → atopic (atopic dermatitis, allergic rhinitis, asthma) / modest Peripheral eosinophilia

● Tx:
→ Dietary restriction (cow milk & Soy products)
→ Topical or systemic corticosteroids
→ Refractory to PPIs = resistant

(these patients will come to the outpatient clinic suffering from recurrent vomiting, at this point we have to differentiate whether it's a case of GERD or eosinophilic esophagitis).

Barrett Esophagus



* Complication of chronic GERD
● Intestinal metaplasia within the esophageal squamous mucosa.
→ 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)

Metaplasia: Squamous epithelium to columnar epithelium + presence of goblet
↓
Dysplasia
↓
Adenocarcinoma

Morphology → Macro: Red tongue extending upward from the GEJ.
→ Micro: Gastric or intestinal metaplasia presence of goblet cells ± Dysplasia (low or high grade) Intramucosal carcinoma & invasion into the lamina propria

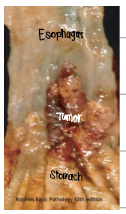
→ Managment of Barrett's: Periodic surveillance endoscopy with biopsy to screen for dysplasia.
- High grade dysplasia & intramucosal carcinoma needs interventions

Complications

Esophageal ulceration | Hematemesis | Melena (black stool) | Strictures (Stenosis) | Barrett esophagus: Most feared Complication

Esophageal tumors

Adenocarcinoma



(on the rise, half of cases in developed countries)

→ Background of Barrett esophagus & long standing GERD.

↓ Risk factors → dysplasia associated Barrett
→ Smoking
↓ Obesity
RadioTx

● Geographic & racial variation (developed countries)

* Male : female (7:1)

Pathogenesis:
* from Barrett >> dysplasia >> adenocarcinoma
* Acquisition of genetic and epigenetic changes
* Chromosomal abnormalities and TP53 mutation

● Morphology → Macro: Distal third. Early: flat or raised patches. Later: exophytic infiltrative masses
→ Micro: forms glands & mucin

● Clinical features: 1) Pain or difficulty Swallowing 2) Progressive weight loss 3) Chest pain 4) Vomiting

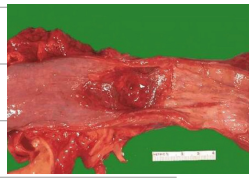
● 5 year survival rate → in advanced Stage: < 25%
→ in early stage: 80%

Squamous cell carcinoma (SCC)

(MC worldwide)

(iron deficiency anemia, dysphagia, webs)
Plummer-Vinson Syndrome ← | Risk factors → Alcohol, Tobacco use, Poverty, Caustic injury, Achalasia

Frequent consumption of very hot beverages
Previous radiation Tx



● Underdeveloped countries

* Male : female (4:1)

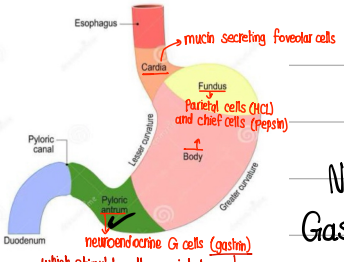
Pathogenesis:
* In western → alcohol & tobacco use
* Other areas → Polycyclic hydrocarbons, nitrosamines, fungus-contaminated foods
* HPV infection implemented in high risk regions

● Morphology → Macro: Middle third 50% (but still can occur at any part)
Polypoid, ulcerated or infiltrative
wall thickening, lumen narrowing
Invade surrounding structures (bronchi, mediastinum, pericardium, aorta)
→ Micro: Pre-invasive: squamous dysplasia & carcinoma in situ
well to moderately differentiated invasive CSS:
Intramural tumor nodules
lymph node metastasis → Upper 1/3 → cervical LNs
Middle 1/3 → mediastinal paratracheal & tracheobronchial LNs
Lower 1/3 → gastric and celiac LNs

● 5 year survival rate → 10% (usually they present late with advanced disease)

● Clinical features: 1) Dysphagia 2) odynophagia 3) obstruction 4) weight loss and debilitation 5) Impaired nutrition & tumor associated cachexia (sever weight loss) 6) Hemorrhage and sepsis if ulcerated 7) Aspiration via a tracheoesophageal fistula

Sections of human the stomach



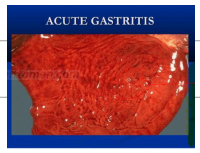
mucin secreting foveolar cells

Parietal cells (HCl) and chief cells (pepsin)

neuroendocrine G cells (gastrin) which stimulates the parietal cells to produce acid.

Gastric pathology part 1&2

- Neoplastic
  - Gastric polyps & tumors
    - Gastric polyps
      - Inflammatory and hyperplastic polyps
      - Gastric adenoma
    - Gastric Adenocarcinoma
      - intestinal type
      - diffuse type
    - Lymphoma
      - diffuse large B cell lymphoma
      - MALToma
    - Neuroendocrine (carcinoid) tumor
    - Gastrointestinal Stromal tumor
- Inflammatory
  - Acute gastritis & Gastropathy
  - Chronic gastritis & Autoimmune gastritis
  - Acute gastric ulcer
  - Chronic Peptic ulcer



Acute gastritis & Gastropathy

mucosal injury, neutrophils present (with inflammation)

regeneration and damage but no inflammation at all

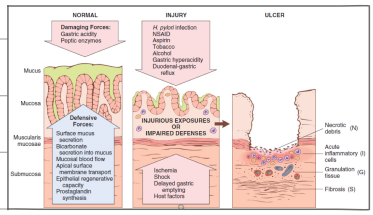
- Imbalance between protective and damaging forces

* Clinical features
  - Asymptomatic
  - epigastric Pain
  - nausea
  - vomiting

→ Sever: erosions, ulcers, hematemesis, melena

Causes:

1) NSAIDs (Cox 1&2 inhibitors) — most common cause ↑acid ↓mucin
2) Uremic patients (ammonia inhibit bicarbonate transport so acidity ↑)
3) H pylori (urease producing ammonia)
4) Old age (reduced mucin & bicarbonate secretion)
5) Harsh chemicals (acids or bases) → direct epithelil injury
6) Hypoxia (high altitudes)
7) Chemotherapy (inhibit DNA synthesis & cellular renewal)
8) Alchol, NSAIDs, radiation therapy → direct mucosal damage



* About prostaglandins E2 and I2

They stimulate nearly all of the the defense mechanisms including

- mucus & bicarbonate secretion
- Mucosal blood flow
- Epithelial restitution

Risk for development of NSAID-induced gastric injury is gratest with non selective inhibitors, but selective cox 2 inhibition can also result in gastropathy or gastritis.
→ cox-2 expression is Protective

Morphology

- Hyperemia (redness)
- Eclema and slight Vascular congestion in lamina propria
- Intact Surface epithelium (If mild)
- Neutrophils, lymphocytes, and plasma cells are not prominent
- Advanced: Erosions & hemorrhage, acute erosive hemorrhagic gastritis
- Nuetrophils: Active inflammation (in gastritis) but not seen in gastropathy

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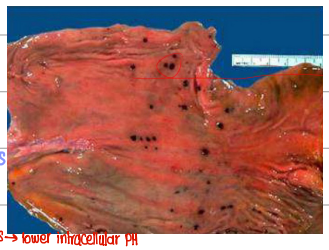
Stress-Related Mucosal Disease acute gastric ulcers

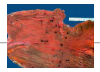
causes

- Severe physiologic Stress
- Trauma
- Extensive burns
- Intracranial disease
- Major Surgery
- Serious medical disease
- Critically ill patients

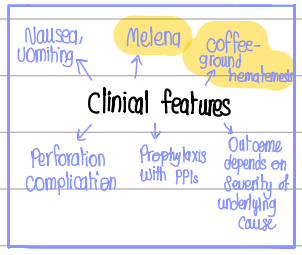


* Stress ulcers: Critically ill patients with shock, sepsis, or severe trauma.
  - mostly due to local ischemia caused by systemic hypotention, splanchnic vaso constriction (stress induced) and systemic acidosis → lower intracellular pH
- Curling ulcers: proximal duodenum, Severe burns or trauma.
- Cushing ulcers: Stomach, duodenum, or esophagus, intracranial disease, CNS injury as stroke, high risk of perforation.
  - due to direct vagal stimulation, acid hypersecretion (↑ acid production) and leads to ulcer.

● Morphology



→ Acute ulcers are rounded and typically less than 1 cm in diameter
→ Shallow to deep
→ Ulcer base brown to black
→ Anywhere in stomach
→ Usually, multiple
→ Normal adjacent mucosa (no inflammation or gastritis in between)
→ No Scarring (because it's acute)
→ Heal with complete epithelialization occurs days or weeks after removal of injurious factor



Chronic gastritis

Causes
- Radiation injury
- H.pylori (MC)
- autoimmune atrophic gastritis — less than 10% of cases
- chronic NSAID
- Chronic bile reflux from duodenum to stomach

Clinical features
- Nausea and upper-abdominal discomfort
- Vomiting
- Hematemesis uncommon
- less sever but more prolonged symptoms

Diagnosis and treatment
- Serologic test: anti-H.pylori antibodies
- Stool test for H.pylori
- Urea breath test
- Gastric antral biopsy (Gold standard) (rapid urease test during endoscopy)
- Bacterial culture
- PCR test for bacterial DNA

Helicobacter pylori gastritis (75% of cases)

Spiral or curved G-ve bacilli

Underlying cause for almost all duodenal ulcers & majority of gastric ulcers or chronic gastritis

- ⟩= Antral gastritis with increased acid production → peptic ulcer
- ⟩= If it's sever with hypochlorhydria it causes → Pangastritis
- ⟩= Intestinal metaplasia and increased risk of gastric cancer

Starts as antral gastritis → Stimulate G cells → increased acid production → Peptic ulcer

If sever → spread to body with atrophy (damage parietal cells)

& the most important complication is Intestinal metaplasia and increased risk of gastric cancer

- → H.pylori adapted to live in the mucus layer, non invasive
- → It has flagella → fer motality
- → It secretes ureas enzyme which splits urea to ammonia, to protect the bacteria from acidic pH
- → Bacterial adherence to foveolar cells
- → Toxins: Cag A for ulcer er Cancer development

Morphology
- Regenerative changes (hyperplastic polyps)
- Gastric biopsy: H.pylori in mucus layer, antrum
- Neutrophils, plasma cells, lymphocytes & macrophages
- Lymphoid aggregates → increased risk of MALT lymphoma
- Intestinal metaplasia (goblet cells) → in stomach where they shouldn't be because it's an intestinal type of cell
  - dysplasia → increased risk of adenocarcinoma

● Tx: combination of antibiotics & PPI (triple therapy)

Autoimmune Gastritis (less than 10% of chronic gastritis cases)

Immune-mediated loss of parietal cells ∴ ↓ acid & IF

Pathogenesis → Hyperplasia of antral G cells → acid reduction → leads to hypergastrinemia

- Deficient IF → Deficient ileal Vit B12 absorption → megaloblastic anemia
- Some Chief cell damaged ∴ pepsinogen ↓

* antibodies to parietal cells & intrinsic factor (IF) in serum
* Reduced serum pepsinogen I levels
* Antral endocrine cell hyperplasia
* Spares the antrum
* Vit B12 deficiency → pernicious anemia and neurologic changes
* Impaired gastric acid secretion (achlorhydria)
* Marked hypergastrinemia
~→ 60 years, slight female predominance
~→ often associated with other autoimmune disease
=< Dyspepsia (clinical description to the upper abdominal discomfort, nausea and vomiting)

Damage of the oxyntic (acid producing) mucosa

Morphology →
- Diffuse atrophy, thinning of wall, loss of rugal folds
- Lymphocytes, Plasma cells, macrophages, less likely neutrophils
- Intestinal metaplasia → dysplasia → Carcinoma
- Neuroendocrine cell hyperplasia → tumors

Table 15.2 Characteristics of Helicobacter pylori–Associated and Autoimmune Gastritis

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

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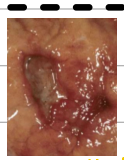
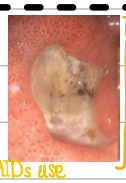
* in USA, NSAID is becoming the most common cause of gastric ulcers as H.pylori infection in falling & increased use of low-dose aspirin in aged population



peptic ulcer disease

Imbalance between mucosal defenses and damaging forces



- Round to oval, Sharply Punched-Out defect
- Base of ulcers is smooth, clean and white
- Granulation tissue
- Hemorrhage & perforation are complications
- Background has gastritis so it's red in appearance

Most often associated with H.pylori or NSAIDs use

Can happen at any portion of the GIT exposed to acidic gastric juices
- most common in gastric antrum, first part of duodenum
- and can be in esophagus in (GERD) or ectopic gastric mucosa (Meckel diverticulum)

Hyperacidity is caused by:

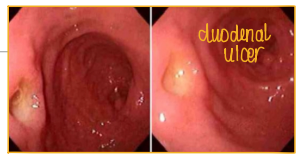
1) H.pylori
2) Parietal cell hyperplasia
3) Excessive Secretory response (vagal)
4) Hypergastrinemia as in Zollinger-Ellison Syndrom
   - ↳ It's a syndrom caused by uncontrolled release of gastrin by a tumor (gastrinoma) and the resulting massive acid production
   - ↳ It affects Stomach, duodenum, even jejunm
   - ↳ Multiple peptic ulceration

Clinical features
- → epigastric burning or aching pain.
- → Pain 1 to 3 hs after meals at day-time, ulcer pain typically on empty stomach
- → worse at night, relieved by alkali or food.
- → Nausea, vomiting, bloating, bletching
- → Complications: Iron deficiency anemia, frank hemorrhage, or perforation, bleeding, hematemesis, melena.
- → Current therapies are aimed at H.pylori eradication,
- →Surgery reserved for complications

- more than 70% of PUD cases are associated with H.pylori infection
- Only 5-10% of H.pylori-infected individuals develop ulcers
- Gastric acid is fundamental in pathogenesis
- Cofactors: smoking, chronic NSAIDs (Steroids), high-dose corticosteroids, alcoholic cirrhosis, COPD, Chronic renal failure, hyperparathyroidism. (more calcium → more gastrin → more acidity)
- 4:1 (Proximal duodenum : Stomach)

*All duodenum ulcers is caused by H.pylori but almost gastric ulcers caused by it.

- An ulcer in the stomach always requires a biopsy. (you don't directly try to treat as if it was an H.pylori infection as it might be a malignant ulcer from the start.
- Mainly anterior duodenal wall
- > 80% solitary



Gastric polyps & tumors = neoplasia

- Gastric polyps
  - Inflammatory and hyperplastic Polyps 75%
  - Gastric adenoma
- Gastric Adenocarcinoma
  - intestinal type
  - diffuse type
- Lymphoma
  - diffuse large B cell lymphoma
  - MALToma
- Neuroendocrine (Carcinoid) tumor
  - tumor come from G cell
- Gastrointestinal Stromal tumor

Gastric polyps

Inflammatory and hyperplastic polyps

Arise in a background of chronic gastritis
& regress after H. pylori eradication

* Completely benign, no risk to transform to malignancy

Gastric adenoma

* benign but carries risk of malignancy (precursor for cancer)

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

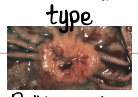
Gastric adenocarcinoma

90% of all gastric cancers
Early symptoms mimic gastritis >>> late diagnose for the cancer

Screening >>> early detection
→ Background of mucosal atrophy and intestinal metaplasia
→ PUD doesn't increase risk, except after surgery.
→ In USA rates dropped >85%, but increased rate of cardia cancer due to GERD & obesity

Lauren classification

Intestinal type



* Bulky, exophytic mass or ulcer
* Forms glands and mucin
* develeops from precursor (adenoma, dysplasia associated with intestinal metaplasia, H.pylori gastritis, and adenomas)
* Mean age 55 yrs
* M:F (2:1)

→ The drop in gastric cancer incidence applies only to the intestinal type

→ Intestinal type is similar to colonic cancer

→ High risk areas:
(Japan, Costa Rica, Chile)

Pathogenesis:
-Genetic alterations due to H. pylori associated chronic gastritis , lesser extentEBV (10%).
-Most cases are sporadic.
-Familial diffuse type cases:Germline mutations in CDH1 (E-cadherin).
-Sporadic diffuse type: Somatic CDH1 mutation in 50%.
-Familial intestinal type cancer: FAP, APC gene mutation
-Sporadic intestinal-type : B catenin mutation
-P53 mutation & HER2 amplification in some sporadic cases in both types

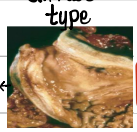
↳ It's tyrosine. Kinase, it's expressed in enlargement and proliferation in tumors especially in breast cancer

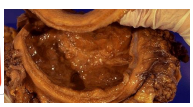
→ Incidences of Intestinal and diffuse types are now similar in some regions except high risk regions.

- More powerful prognostic factors: depth of invasion (T stage) & lymph nodes (N stage) and distant metastasis (M stage) at the time of diagnose (TNM Stage)
- → The stage is the most common powerful prognostic factor
- Most cases Dx at advanced stage
- 5 year survival 90% to 20% for early and advanced tumors, respectively.
- Tx: Surgery, chemotherapy, targeted Tx (anti HER2) (immunotherapy)

diffuse type

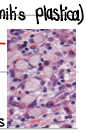
Linitis plastica





→ Infiltrative growth pattern (infiltrates the wall of the stomach and no mass in lumen of stomach, so the stomach appears empty)

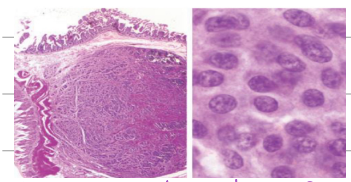
→ Desmoplastic reaction (thick wall, linitis plastica)
→ Discohesive cells (signet ring cells)
Large mucin vacuols that expand the cytoplasm and push the nucleus to the periphery



→ Incidence uniform across countries
→ No precurser lesion or mass
→ M:F (1:1)
→ younger age
→ Symptoms overlap with chronic gastritis, in addition to weight loss.
→ It tends to metastasize more

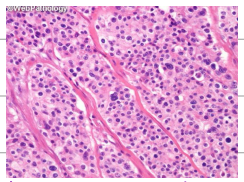
Neuroendocrine (Carcinoid) tumor

→ Tumors arising from neuroendocrine-differentiated gastrointestinal epithelia (eg: G cells)
→ > 40% occure in the small intestine
→ associated with endocrine cell hyperplasia, chronic atrophic gastritis and Zollinger-Ellison syndrome
→ Slower growing than carcinoma (it has good prognosis than carcinoma)



Intramural or submucosal masses (Small polypoid lesions)

Tumor cells arranged as nest



Islands, trabeculae, Strands, glands, or sheets of uniform cells with Scant, Pink granulation Cytoplasm and Salt and Pepper Chromatin

---

Lymphoma

diffuse Large B cell lymphoma ← Lymphoma → MALToma

→ Stomach is the most common site of extranodal lymphoma
→ 5% of all gastric malignancies
→ Most Common type: indolent extranodal marginal zone B-cell lymphomas (MALToma), which is caused by H.pyleri & if we treat H.pylori, it will regress
→ Second most common lymphoma: diffuse large B cell lymphoma (an agressive tumor and difficult to treatment)

Strongly associated with metastatic disease and carcinoid tumor

Due to vasoactive substances ← **Carcinoid syndrome** → Seen in 10% of cases that have liver metastasis

Isn't seen in all cases just in patients with liver metastasis

Cutaneous flushing, sweating, bronchospasms, colicky abdominal (due to vasoactive substances that will increase peristaltic contraction) pain, diarrhea, and right-sided cardiac valvular fibrosis

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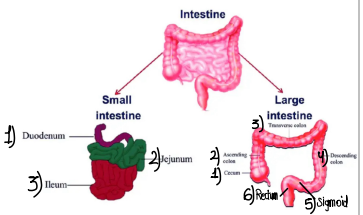
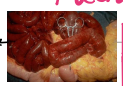
Intestinal pathology (all parts)



- **Intestinal obstruction**
  - mechanical
    - Intussusception
    - Hernias
    - Adhesions
    - Volvulus
    - Tumors
    - Diverticulitis
    - Infraction
  - non-mechanical
    - Hirschsprung disease
    - Neurological disorders
    - Drugs... etc
- **Vascular disorders**
  - Ischemic Bowel disease
  - Hemorrhoids
- **Malabsorptive** → celiac disease
  - cystic fibrosis ← diseases and infections
  - lactase deficiency
  - Diarrheal disease & malabsorptive diarrhea
  - Abetalipoproteinemia
- **Inflammatory bowel disease**
  - Sigmoid diverticulitis
  - Chronic inflammatory bowel disease (CIBD)
    - Crohn disease
    - Ulcerative colitis
- (Colonic) Polyps and neoplastic diseases

Intestinal obstruction

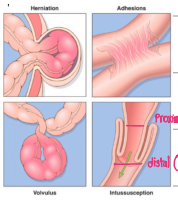
Mechanical



Bowel infraction ←

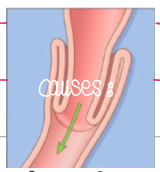
- Intussusception
- Hernias
- Adhesions
- Volvulus
- Tumors
- Diverticulitis
- Infraction

} 80% of cases



*Intussusception

- Segment of the intestine constricted by a wave of peristalsis, telescopes into the immediately distal segment
- Once trapped, invaginated segment is propelled by peristalsis, and pulls mesentery with it (so should be treated as soon as possible)
- Untreated progresses to infraction
- → The most common cause of intestinal obstruction in children < 2 yr



Meckles diverticulum (ileum) ← causes: → Idiopathic in most cases (< 2 years old)

Old children & adults: Intraluminal mass or tumors ← causes: → Peyer patches hyperplasia (lymphoid hyperplasia) (rotavirus vaccine, viral infection)

Pain ← Clinical features → Vomiting

Abdominal Swelling

Currant jelly stool (passing stool mixed with blood and mucus)

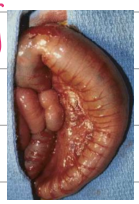
Management

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

⅔ Abdominal pain
Distention
Vomiting
Constipation
Acute or chronic intestinal dilation ← (any)

Non-mechanical (functional)

- Hirschsprung disease
- Neurological disorders
- Drugs... etc



Morphology

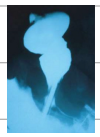
- Rectum always involved
- Extent is variable
- Most cases in rectosigmoid
- Aganglionic region normal or contracted
- Proximal normal segment progressively dilated

*Hirschsprung disease

more common in males but more severe in females & Risk increase in siblings.

- congenital defect in colonic innervations
- Congenital aganglionic megacolon

⇝ Neonatal failure to pass meconium
⇝ Later: obstructive constipation



*Diagnostic workup: barium enema, microscopic, Biopsy (gold standard)

Pathogenesis:
-During embryogenesis;
-Disrupted migration of neural crest cells from cecum to rectum.
-Lack of Meissner submucosal plexus and the Auerbach myenteric plexus.
-Failure of coordinated peristaltic contractions.
-Mutations in RET: in familial cases and 15% of sporadic
-Other genes and environmental factors play role.

- More in down syndrome

→ Rectum always involved. Most cases in rectosigmoid (in sever cases it may affect the entire colon)
→ Extent is variable
→ Aganglionic region is normal or contracted

Meckel's diverticulum (one of the causes)

- The most common congenital anomaly of GIT
→ Incomplete obliteration of omphalomesentric duct
→ True diverticulum (all pouching contains mucosa, Submucosa, muscularis & serosa)
* can be asymptomatic and discovered incidentally
* can be confused with acute appendicitis

=(Ulceration, lower GI bleeding or perforation from ectopic gastric mucosa

=(Bowel obstruction due to the intussusception, volvulus or adhesive band

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)
* Most common cause of lower GI bleeding before age of 2

Complications:

1) Enterocolitis 2) Fluid & electrolyte disturbances 3) perforation 4) Peritonitis

Tx°

Surgical resection of aganglionic segment and anastomosis of normal segment

Vascular disorders

Hemorrhoids

→ Dilated anal & perianal collateral vessels that connect the portal and caval venous systems.

=C Bleeding (fresh blood) - pain - thrombosis - inflammation

* Predisposing factors:
  - → constipation & Straining
  - → venous stasis of pregnancy
  - → Portal hypertension (recall that it cause: - Esophageal varices - hemorrhoids)

→ External (below anorectal line) (↗ inferior hemorrhoidal plexus) and internal (above anorectal line) (↗ Superior hemorrhoidal plexus) hemorrhoids

→ Thin-walled, dilated, Submucosal vessels beneath anal or rectal mucosa

*Tx: Sclerotherap, rubber band ligation, infrared coagulation, Hemorrhoidectomy

Angiodysplasia

↓

Malformed Submucosal and mucosal blood vessels.

* Location: Most often in cecum and right colon
  - → 6th decade of life
  - → less than 1% of adult population
  - → 20% of cases of lower GI bleeding (in elders in sixth decade of life) is caused by Angiodysplasia.

*Blood is bright red in color (recall the upper GI bleeding causes darker brown/black stools (melena))

Ischemic bowel Disease

↓

It's a disease that affects older groups (people who already have atherosclerosis and ischemic heart disease)

---

* Diarrheal disease (in general) — Secretory, Osmotic, malabsorptive (will be discussed), exudative

Diarrhe → increase in stool mass, fregency or fluidity.

Dysentery → painful, bloody, small volume diarrhea.

⇝ can be found in many diseases like:

Pancreatic insufficiency - celiac disease - Crohn disease - cystic fibrosis - Lactase deficiency - Abetalipoproteinemia - Infectious Enterocolitis - Inflammatory bowel disease - Infectious Enterocolitis - Ischemia - Inflammatory bowel diseases.

Malabsorptive disorders

Malabsorptive diarrhea (chronic!)

→ defective absorption of fat and water

AKED ← Soluble vitamins, proteins, carbohydrates, electrolytes, minerals and water

* defect in one of the following
  - Intraluminal digestion
  - Terminal digestion
  - Transepithelial transport
  - lymphatic transport

Hallmark is: steatorrhea (excessive fat, bulky, frothy, yellow/greasy stool)

Manifestations:

- weightloss, anorexia
- Flatus, abdominal distention
- Borborygmi, Muscle wasting
- Anemia and mucositis (iron, Pyridoxine (VB6), folate, or vit B12 deficiency)
- Bleeding (vitK deficiency)
- Osteopenia and tetany (Ca, mg, or vit D deficiency)
- Neuropathy (vit A or B12 deficiency)
- Skin & endocrine disorders

Cystic fibrosis

→ A defects in ion transport across intestinal & pancreatic epithelium due to mutation in Cystic fibrosis transmembrane conductance regulator (CFTR)

→ So we will have thick viscous Secretions

mucus plugs in Pancreatic ducts → pancreatic insufficiency (in 80% of patients)

So pancreatic enzymes will go back to the pancreas causing digestion of pancreatic cells & deficiency of digestive enzyme in the intestine causing problems in digestion and absorption

→ To resolve this, pancreatic enzymes are given as oral tablets to aid in digestion

* Meconium ileus in neonates
* Defect in intraluminal digestion

Celiac disease

→ Immune mediated enteropathy

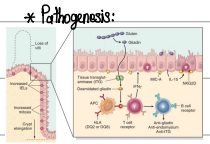
→ Gluten sensitive enteropathy

→ Wheat, rye or barley !!

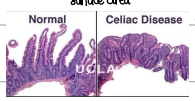
*Tx: gluten free diet

- Genetically Predisposition → HLA-DQ2, HLA-DQ8
- It has association with: type 1 diabetes, thyroiditis, Sjogren syndrome

* Pathogenesis:



Gluten >> gliadin >> react with HLA-DQ2 or HLA-DQ8 on antigen Presenting cells >> CD4 T cells activation >> cytokines >> tissue damage (mainly enterocytes damage.) → loss of villus architecture which is important in increasing surface area



Lactase deficiency

- Lactase found at typical brush border membrane so when there is no Lactase, Lactose will remain in the gut lumen.
- Osmotic diarrhea.

*normal biopsy findings

- we have 2 types

Congenital	Acquired
- AR (rare)	- follow viral or bacterial enteritis, down regulation of gene after childhood
- genetic mutation	
- explosive diarrhea	
- Watery frothy stool	
- abdominal distention after milk ingestion	

Abetalipoproteinemia

↓

- AR (rare)
- Infants with failure to thrive, diarrhea and steatorrhea
- Lack of absorption of fat & fat soluble vitamins
- Inability to synthesize triglyceride rich lipoproteins
- Transepithelial transport defect of TG and FAs
- Monoglycerides & triglycerides accumulate in epithelial cells.

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

↓ celiac disease (continuation) ↓

⇝ * Serology → Anti-tissue transglutaminase antibodies
→ Anti-gliadin antibodies
→ Anti-endomysial antibodies

↓ celiac disease (continuation) ↓

⇝ Clinical features:

- Children 6-24 months:

* classical or non classical symptoms
  - classical: Irritability, abdominal distention, anorexia, diarrhea, failure to thrive, weight loss, muscle wasting.
  - non classical: abdominal pain, nausea, vomiting, bloating or constipation.

* Blistering skin lesion, dermatitis herpetiformis in 10% of Pts

- Adults (30-60 years)

* Anemia, iron deficiency
* B12 & folate deficiency (less common)
* Diarrhea, bloating, and fatigue
* Missed diagnosis: Silent celiac or latent celiac
* Increased risk of enteropathy associated T cell lymphoma & small intestinal adenocarcinoma.

⇝ Morphology: → 2nd portion of the duodenum or proximal jejunum

→ Intraepithelial lymphocytosis ($CD8^+$ T cells)

→ Triad: villous atrophy, Crypt hyperplasia

→ lamina propria: lymphocytes, plasma cells, eosinophils...

→ IEL & villous atrophy are not pathognomic, Seen in viral enteritis

●Diagnosis: Clinical, histologic & serologic correlation

↓celiac disease (continuation)↓

Diagnosis:

- 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

Inflammatory bowel disease

1. Chronic inflammatory bowel disease (CIBD)
   - Crohn disease
   - Ulcerative colitis
2. Sigmoid diverticulitis

1. Inflammatory bowel disease

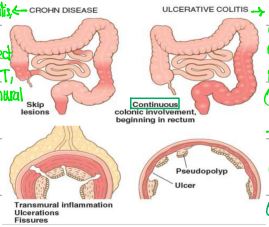
(For both diseases)
- Chronic
- Genetic predisposition
- Inappropriate mucosal damage

Crohn disease

- Morphology
  - Macro
    - Regional enteritis
    - Any area of GIT.
    - Most common sites: terminal ileum, ileocecal valve, and cecum
    - Small intestine alone 40%
    - Small intestine & colon 30%
    - Colon only 30%
    - Skip lesions
    - Strictures common → Small bowel Stricture
    - 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 Myopathy)
    - Creeping fat
  - Micro
    - Neutrophils in active disease
    - Crypt abscesses
    - Ulceration
    - Distortion of mucosal architecture (repeated cycle)
    - Paneth cell metaplasia in left colon
    - Mucosal atrophy
    - (Hallmark): noncaseating granulomas only in 35% of cases

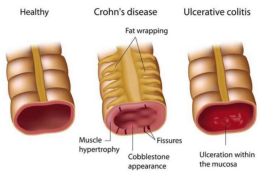
regional enteritis ← CROHN DISEASE: frequent ileal involvement; affect any area in GIT; frequently transmural

ULCERATIVE COLITIS → limited to colon and rectum; extends only into mucosa & submucosa (in continuous pattern)



- Small intestine is normal except in (backwash ileitis) Small intestines are involved. (always involves the rectum)

- Epidemiology:
  - → Adolescence & young adults
  - → 2nd peak in 5th decade.
  - → Geographic variation
  - → Hygiene hypothesis: Childhood exposure to environmental microbes prevents excessive immune system reactions. (Firm evidence is lacking!!)



- Clinical features:
  1) Intermittent attacks of mild diarrhea, fever & abdominal pain.
  2) acute right lower-quadrant pain and fever (20%)
  3) Bloody diarrhea and abdominal pain (colonic disease)
  4) Asymptomatic intervals (weeks to months)

  Triggers: physical or emotional Stress, Specific dietary items, NSAID use, and cigarette smoking.

- Complications:
  1) Colonics: Iron-deficiency anemia
  2) Small bowel: Hypoproteinemia & hypoalbuminemia, malabsorption of nutrients, vit B12 and bile salts.
  3) Fistulas, Peritoneal abscesses, Strictures.
  4) Risk of colonic and small intestinal adenocarcinoma.

- Pathogenesis:

  Combined effect of:
  - → Altered host interaction with intestinal microbiota
  - → Intestinal epithelial dysfunction
  - → Aberrant mucosal immune response

- Extra intestinal manifestations:
  - Uveitis (inflammation in iris)
  - Migratory polyarthritis
  - Sacroiliitis
  - Ankylosing Spondylitis
  - Erythema nodosum

  - Primary Sclerosing Cholangitis (more with UC)
  - Clubbing of the fingertips

Ulcerative Colitis

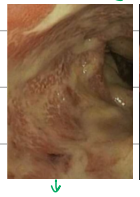
- Pan Colitis
- occasionally, focal appendiceal or cecal infl.
- Limited disease: Ulcerative proctitis or Ulcerative Proctosigmoiditis

- Morphology
  - Macro
    - Broad-based ulcers
    - Pseudopolyps

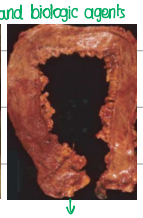
    - Mucosal atrophy in long standing
    - Mural thickening absent
    - Serosal surface normal
    - No strictures
    - Toxic megacolon (damage of NP, disturbed neuromuscular function)

  - Micro
    - Inflammatory infiltrates
    - Crypt abscesses
    - Crypt distortion
    - Epithelial metaplasia
    - Submucosal fibrosis
    - Inflammation limited to mucosa and submucosa
    - No skip lesions
    - NO granulomas (Crohn ✓)

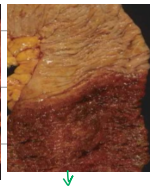
- Clinical features:
  1) Relapsing remitting disorder
  2) Attacks of bloody mucoid diarrhea + lower abdominal cramps
  3) Temporarily relieved by defecation
  4) Attacks last for days, weeks, or months.
  5) Asymptomatic intervals
  6) Infectious enteritis may trigger disease onset, or cessation of smoking
  7) colectomy cures intestinal disease only.
  8) anti-inflammatory and biologic agents



↓ Mucopurulent material & ulcers

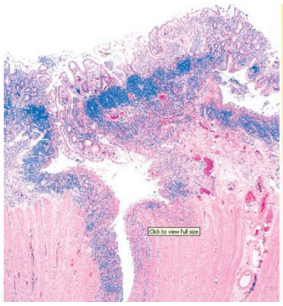


↓ Pancolitis



↓ Abrupt transition between normal & disease segment

fissure



Crohn disease of the colon showing a deep fissure extending into the muscle wall, a second, shallow ulcer (upper right), and relative preservation of the intervening mucosa. Abundant lymphocyte aggregates are present, evident as dense blue patches of cells at the interface between mucosa and submucosa

Feature	Crohn Disease	Ulcerative Colitis
Macroscopic		
Bowel region affected	Ileum ± colon	Colon only
Rectal involvement	Sometimes	Always
Distribution	Skip lesions	Diffuse
Stricture	Yes	Rare
Bowel wall appearance	Thick	Thin
Inflammation	Transmural	Limited to mucosa and submucosa
Pseudopolyps	Moderate	Marked
Ulcers	Deep, knifelike	Superficial, broad-based
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Serositis	Marked	No
Granulomas	Yes (~35%)	No
Fistulas/sinuses	Yes	No

Feature	Crohn Disease	Ulcerative Colitis
Clinical		
Perianal fistula	Yes (in colonic disease)	No
Fat/vitamin malabsorption	Yes	No
Malignant potential	With colonic involvement	Yes
Recurrence after surgery	Common	No
Toxic megacolon	No	Yes

*Colitis associated neoplasia

→ long standing Ulcerative colitis & Crohn disease

→ Begins as dysplasia → Carcinoma

* colonoscopy surveillance programs.

*Risk depends on:

1) duration of disease : increase after 8-10 years

2) Extent of involvement: more with pancolitis

3) Inflammation: frequency & severity of active disease with neutrophils

② Sigmoid diverticulitis

Mostly asymptomatic

Clinical features

Intermittent lower Abdominal pain — Constipation or diarrhea

high fiber diet

Surgery ← Tx: → Antibiotics in diverticulitis

*elevated intraluminal pressure in the Sigmoid colon

*Acquired, can come from low fiber diet & constipation & exaggerated peristaltic contractions

*Pseudodiverticulae

Cuz muscular layer isn't included

(Unique location)

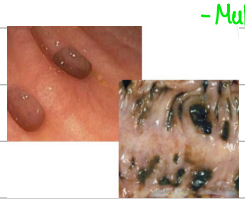
*longitudinal muscle layer is discontinuous in colon (taeniae coli)

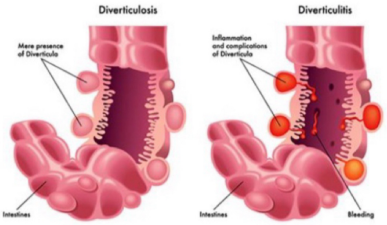
*Outpouchings of colonic mucosa & Submucosa

*most common in sigmoid (narrowest part)

● Morphology:

1) Flask outpouchings
2) Between taeniae coli
3) Thin wall (atrophic mucosa, compressed submucosa)
4) Attenuated or absent muscularis
5) Obstruction leads to diverticulitis
6) Risk of perforation
7) Recurrent diverticulitis leads to strictures (Stenosis) ← Diverticulitis → Constipation



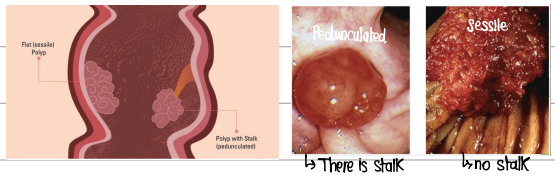


- Aquired pseudodiverticula
- Rare < 30 years
- Common > 60 years
- Multiple (diverticulosis)

Clonic polyps and neoplastic disease

(Colon is the most common site for polyps)

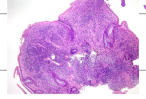
→ we have 2 types of polyps



↳ There is stalk ↳ no stalk

Non neoplastic

Inflammatory polyps



→ Solitary rectal ulcer syndrome

→ caused by impaired relaxation of anorectal sphincter

→ Lead to Recurrent abrasion and ulceration of the overlying rectal mucosa

→ Chronic cycles of injury and healing give a polypoid mass of inflamed & reactive mucosal tissue.

hamartomatous polyps

Sporadic or Syndromatic

→ Disorganized, tumor-like growth composed of mature cell types normally present at that site

2 types

Juvenile polyps (Most common) (*means young age)

- Sporadic & Solitary (Not Recurrent)

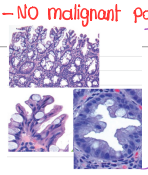
Peutz-Jeghers Syndrome

- Autosomal dominant (rare)
- Mean age (10-15 years)

Hyperplastic polyps

Common

- 6th - 7th decade
- Decreased epithelial turnover and delayed Shedding of surface epithelium
- pileup of goblet cells & epithelial over crowding
- NO malignant potential



- Hyperplastic polyp
- * left colon
- * Rectosigmoid
- * Small < 5mm
- * Multiple
- * Crowding of goblet

Neoplastic

adenoma

* most common and clinically important

* Increase with age

50% of adults > 50 years (western world)

Definition: presence of epithelial dysplasia (low or high)

* Precursor for majority of colorectal adenocarcinoma but most adenomas do not progress to carcinoma

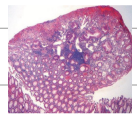
* USA: Screening colonoscopy starts at 45 years & earlier screening with family history

* western diets and lifestyles increase risk

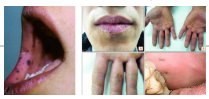
→ The patient usually complains of rectal bleeding, mucous discharge

- Children (< 5 yrs (Mean age 5))
- Rectum
- Syndromic are multiple (Recurrent)
- Autosomal dominant syndrome of juvenile polyposis
- TGF-β signaling pathway germline mutation (SMAD-4)

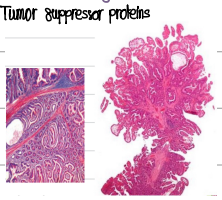
- Increased risk of adenocarcinoma
- Pedunculated = Stalk
- Reddish lesions
- Cystic spaces on cut sections
- Dilated glands filled with mucin & inflammatory debris
- Granulation tissue on surface



- Multiple gastrointestinal hamartomatous polyps
- Most common in Small intestines
- Large, Pedunculated, Lobulated
- Mucocutaneous hyperpigmentation



- Increased risk for several malignancies:
  Colon/pancreas/breast/lung/ovaries/uterus/testes
- LKB1/STK11 gene mutation.
  ↳ Tumor suppressor proteins



→ It's large, arborizing network of connective tissue, smooth muscle, lamina propria.

→ Glands lined by normal-appearing intestinal epithelium.

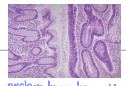
→ Christmas tree pattern

& absorptive cells
* Serrated surface

* Biopsy is important

Colon Adenoma

Hallmarks (epithelial dysplasia)



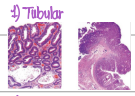
nuclear hyperchromasia, elongation, Stratification, high N/C ratio

* Size: most important correlate with risk for malignancy (40% if > 4 cm)

& High grade dysplasia is the 2nd factor.

→ Architecture:

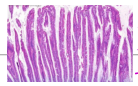
1) Tubular



- Pedunculated
- Small tubular glands

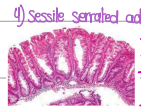
2) Tubulovillous

3) Villous



- long slender villi
- Large & sessile
- More frequent invasive foci

4) 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

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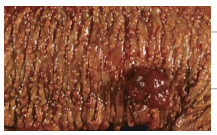
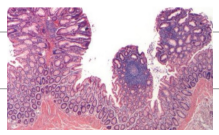
* Familial Syndromes

(genetic basis)

Syndromes associated with colonic polyps and increased rates of colon cancer

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

* 100% of patients develop colorectal carcinoma, if untreated, often before age of 30.

• Standard therapy: prophylactic colectomy before 20 year of age.

! Risk for extraintestinal manifestations:

variants of FAP

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)

Hereditary nonpolyposis colorectal cancer (HNPCC) (Lynch syndrome)

→ Autosomal dominant

→ Clustering of tumors: colorectum, endometrium, Stomach, ovary, ureters, brain, Small bowel, hepatobiliary tract and skin.

→ Colon cancer at younger age other than sporadic cancers

→ Right colon with excessive mucin production

→ Only few adenomatous precursors (typically sessile serrated adenomas)

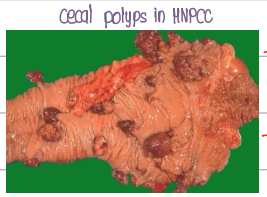
→ Inherited germ line mutation in DNA mismatch repair genes (These genes are important in detection, resection and repair of errors in DNA replication)

→ Accumulation of mutations in microsatellite DNA (Short repeating Sequences)

→ Resulting in microsatellite instability.

→ Majority of cases involve either MSH2 or MLH1

cecal polyps in HNPCC



- Right side of the colon, the Cecum
- Multiple polyps but not to the level of the FAP associated polyps

---

* Sporadic colon cancers

Colonic adenocarcinoma

(Most common malignancy in the gastrointestinal tract) ⟵ lung cancer!! الرئة بعد ثاني سرطان بسبب

→ Small intestine is uncommonly involved by neoplasia.

→ Peak: 60 to 70 years, males > females

→ 20% under 50 years

→ Developed countries lifestyles and diet
(low intake of vegetable fiber and high intake of carbohydrates and fat, obesity, smoking and alcohol).

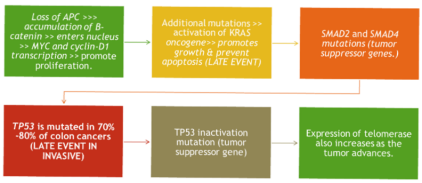
- Aspirin or other NSAIDs have a protective effect cuz COX-2 promotes epithelial proliferation.
  → Prevention: dietary modification, pharmacologic chemoprevention

pathogenesis

1) Heterogeneous molecular events 2) Sporadic >> familial

Two pathways
Step wise accumulation of multiple mutations

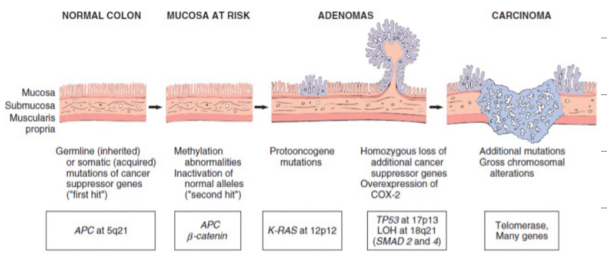
APC / β-catenin pathway (chromosomal instability)
↓
increased WNT signaling
→ classic adenoma carcinoma sequence
→ 80% of sporadic colon tumors
- Loss of APC → accumulation of β-catenin → enters nucleus → promote proliferation ← MYC & Cyclin-D1 transcription



→ Mutation of the APC tumor suppressor gene: early event
→ Additional mutation → activation of KRAS oncogene: late event
→ TP53 is mutated in 70% - 80% of colon cancers: late event in invasive
→ SMAD2 & SMAD4 mutations (tumor suppressor genes)
→ expression of telomerase also increases as the tumor advances.

→ APC is a key negative regulator of β-catenin, 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)

Microsatellite instability pathway due to defects in DNA mismatch repair
→ DNA mismatch repair deficiency
(loss of mismatch repair genes)
→ Mutations accumulate in microsatellite repeats
→ 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-β and BAX genes)
→ BRAF mutations common. However, P53 & KRAS are absent.

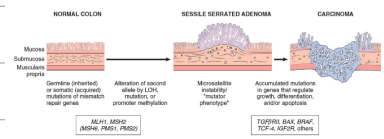


Morphology

Macro
(right) Proximal colon tumors & Polypoid, exophytic masses
(right) Proximal colons rarely cause obstruction
(left) Distal colons annular lesions (napkin ring) constrictions and narrowing

Micro
→ Dysplastic glands with strong desmoplastic response
→ Necrotic debris (dirty necrosis) are typical
→ Some tumors give abundant mucin or forms signet ring cells.

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.



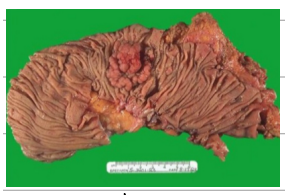
* Poor differentiation and mucinous histology → poor prognosis

* Most important prognostic factors are:

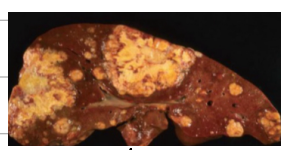
1) Depth of invasion (mucosa, submucosa, MP, serosa)
2) lymph node metastasis (needs Rx and chemo)
3) Distant metastasis (lung and liver) can be resected
4) tumors w/ microsatellite instability (immune checkpoint inhibitor therapy)

- Right sided tumors are highly associated with microsatellite instability.

Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis (70% of FAP)	APC/WNT pathway	*APC*	Autosomal dominant	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	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma



↓
Exophytic adenocarcinoma



↓
liver metastasis

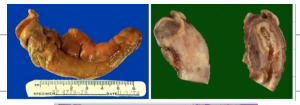
we talked about sigmoid diverticulum, now we'll talk about the normal true diverticulum of the cecum

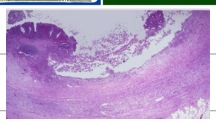
Acute appendicitis

(most common in adolescents and young adults & may occure in any age)

→ Difficult to confirm preoperatively, Surgical emergency.

Dx of acute appendicitis:





→ Mesenteric lymphadenitis
→ Acute salpingitis
→ Ectopic pregnancy
→ Mittelschmerz (pain associated with ovulation)
→ Ovarian cysts torsion
→ Rupture meckel diverticulitis
→ Crohn disease

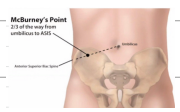
* increased luminal pressure
↓
impaired venous drainage
↓
Ischemic injury & Stasis associated bacterial proliferation
↓
Inflammatory response rich in neutrophils & edema

* obstruction by fecalith in 50-80% of cases (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 formation
- Acute gangrenous appendicitis >> necrosis and ulceration >> rupture

Early acute appendicitis: Periumbilical pain
Later: Pain Localized to the right lower quadrant

Nausea, vomiting, Low grade fever, mildly leukocytosis ← **Clinical features** → A classic physical finding is McBurney's sign (McBurney's Point)



↓
Sign & symptoms are often absent, creating difficulty in Clinical diagnosis

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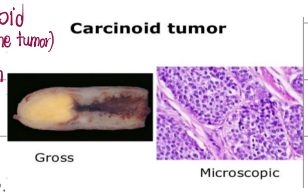
Tumors of the appendix

→ The most common tumor is 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.