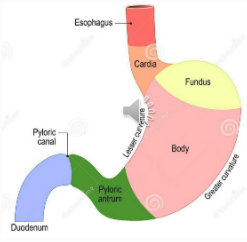
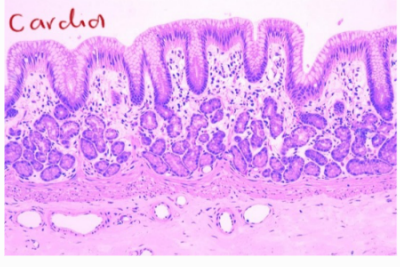
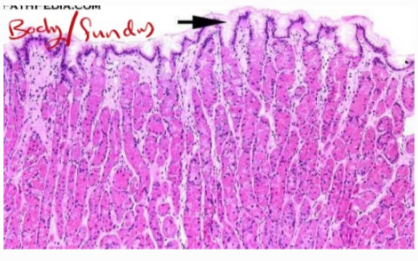
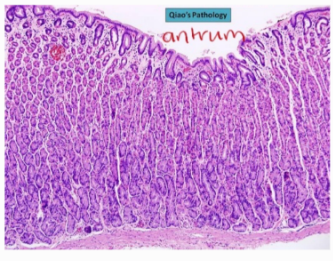
GI | Gastric pathology | ملخص شامل للمحاضرتين الثالثة والرابعة
Done by: Ola Alahdab



- **Layers of the stomach (4):**
Mucosa / Submucosa / Muscularis externa / Adventitia (serosa).
- **Parts of the stomach:**
Proximally: esophagus (through GEJ).
Distally: duodenum (through pyloric sphincter).
The lesser curvature is the line between GEJ and GDJ from the right side, the greater curvature is from the left side.
- Histological sections of stomach (H&E stain):
1. Cardial mucosa:
- The surface epithelium is **highly mucinous;** contains **mucin**. These are called foveolar cells.
- Thickness of cardial mucosa is **less** than thickness of mucosa in body and fundus.
2. Body & fundus mucosa:
- Parietal cells (HCL producing cells): **eosinophilic granular cytoplasm.**
- chief cells: **bluish cytoplasm**.
3. Antrum mucosa:
- There are many antral glands and G cells (gastrin producing cells).





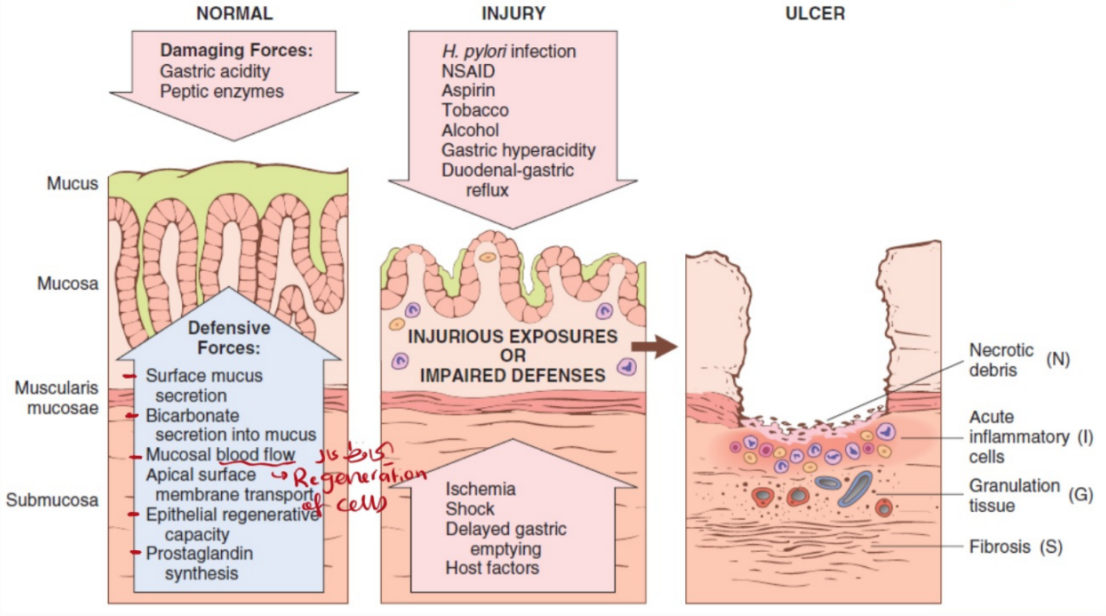


Gastric diseases can be:
1- Inflammatory.
2- Neoplastic.

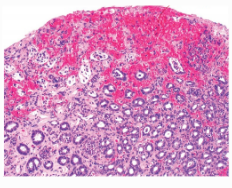
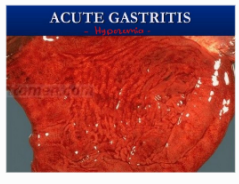
1- Inflammatory conditions of the stomach:
A) **Acute** conditions:
Acute gastritis. | Acute gastric ulcers.
B) **Chronic** conditions:
Chronic gastritis. | Chronic peptic ulcers.
- **Peptic**: Any area that is exposed to acid and pepsin coming from gastric juice.

● Acute gastritis & Gastropathy:
Both are similar conditions, the difference is in morphology:
- Acute gastritis: **Mucosal injury, neutrophils present**.
- Gastropathy: **regenerative changes in mucosa due to damage, NO inflammation**.
- **Causes of both**:
NSAIDs, alcohol, reflux of bile from duodenum to stomach, & stress-induced (physiological stress like in surgical procedures & critically ill patients).

- **Clinical features**:
Asymptomatic or epigastric abdominal pain with nausea and vomiting.
- **Pathogenesis**:
Imbalance between the natural forces of stomach. (The pic summarizes everything)



- Prostaglandins offer protection by **increase mucus, bicarbonate, & blood flow** to mucosa.
- Damaging forces: توضيح لبعض النقاط
1) NSAIDs → inhibit COX → decrease PGs.
2) Uremic (renal failure) & H. pylori infected patients.
H. pylori produces **urease** that splits urea into ammonia that interferes with the transport of bicarbonate to the mucous layer.
3) Old age | Hypoxia | Harsh chemicals | Alcohol | and radiation therapy.
4) Chemotherapy, by interference with DNA synthesis & mitotic capacity, decrease cell proliferation or causing direct damage.

- **Morphologic features of acute gastritis**:
- Non-specific & minor.
- **Macroscopically**: **hyperemia** (mainly).
- **Microscopically**: Hyperemia, erythema, congestion of vessels and edema in the lamina propria, Intact surface epithelium, lymphocytes, plasma cells, & neutrophils (not a prerequisite to diagnose acute gastritis, they are a sign of active inflammation & can be seen in acute or chronic gastritis).
- neutrophils can be used to differentiate between **gastropathy (negative/ not present)** and **acute gastritis (positive)**.
- **In the Advanced cases**: Erosions and hemorrhage (acute erosive hemorrhagic gastritis).

○ Stress-Related Mucosal Disease:

● Acute Gastric Ulcers:

◇The best way to deal with it is **prophylaxis** with PPIs.◇
- **Caused by:** severe physiologic stress:
Trauma | Extensive burns | increased intracranial pressure | Major surgery | severe medical disease | Critically ill patients, patients with MI | traffic road accidents

- Types of Acute Gastric Ulcers:

1) Stress ulcers:

- In critically ill patients with shock, severe hypertension, sepsis, or severe trauma.
- Causes:

1) Local ischemia (mainly), because of Systemic hypotension/heart failure/Splanchnic vasoconstriction (reduced blood flow to GIT).

2) Systemic acidosis → lower PH → acidosis in cells → damage.

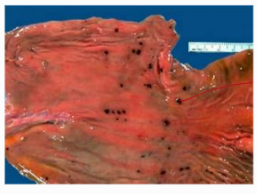
COX2 is protective against stress ulcers.

2) Curling ulcers: in proximal duodenum, due to severe burns or trauma.

3) Cushing ulcers: in stomach, duodenum, or esophagus.

Associated with increased intracranial pressure, high risk of perforation can rupture the peritoneum and cause **peritonitis**.

- Causes: direct vagal nerve stimulation (like in cases of increased intracranial pressure), causes acid hypersecretion.
- Diagnoses: endoscopy & clinical manifestations, NOT BIOPSIES.



- Morphology:

› usually **Multiple** (unlike chronic peptic ulcers which are solitory)
› Acute ulcers are **rounded**, variable in size but typically **less than 1 cm in diameter.**
› Shallow to deep.
› **Normal surrounding mucosa.**
› Ulcers' bases are brown to **black**, due to the effect of gastric juices on blood.
› Occur anywhere in stomach.
› **No scarring** (a characteristic of these ulcers, unlike chronic peptic ulcers)
› Complete healing occurs days or weeks after removal of injurious factors.

- Clinical features:
- Nausea, vomiting with **dark blood bits** (due to **acidic juice**) (Coffee-ground hematemesis)
› Melena (black stool caused by upper GI bleeding).
› Some cases: high degree of hemorrhage (need blood transfusions)
→ Perforation complication.

● CHRONIC GASTRITIS:

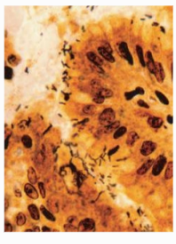
- Causes:
- **Helicobacter pylori** (mostly).
› **Autoimmune atrophic gastritis**: less than 10% of cases.
- Less common causes: Chronic NSAID use | Radiation injury | Chronic bile reflux.
- **Clinical features:** Nausea, Vomiting.

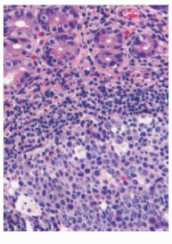
The most common cause of chronic gastritis is H. pylori.

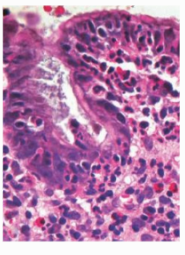
1- H. pylori:

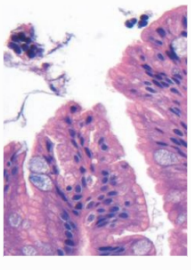
- Demonstrated with **H&E stain** or other specialized stains like **giemsa**.
- Present **in almost all duodenal ulcers** (present in stomach of patients with duodenal ulcers)

- **Acute** infection is **subclinical**.
- Usually acquired **in childhood**.
- Live in the **antrum** of stomach and causes **antral gastritis** which leads to stimulation of antral **G-cells** → increased **gastrin** hormone production → activation of **parietal cells** → increased **acid** production → **peptic ulcer.**
- In severe cases the inflammation can spread all over the stomach affecting the body and the fundus causing **pangastritis** and **damage to the parietal cells,** (this means that in severe cases the bacteria can cause **hypo-secretion** of acid).
- In severe cases: **Intestinal metaplasia** in stomach and increased risk of **gastric cancer** (In most cases gastric cancer is associated with a background of chronic gastritis and intestinal metaplasia). The intestinal metaplasia is then transformed into **dysplasia** and then **adenocarcinoma**.
- In duodenal ulcer/duodenitis, the bacteria would still in stomach, the hyper acidity is what causes the problem.
- **Pathogenesis**:
› H. pylori lives in the mucus layer, and it's usually **non-invasive**.
- It has mechanisms to protect itself from the acidic environment, like:
■ Flagella. ■ Urease. ■ Adhesins: adherence to **foveolar cells** of the stomach.
■ Toxins: mainly **cytotoxin associated gene A** → encodes **(CagA)** that aids in ulcer or cancer development by damaging epithelial cells.
- **Morphology:**
- By **endoscopy** & **biopsy, antrum** is the best site to obtain a biopsy.
- Macroscopically: **hyperemia** (most important)
- Microscopically: inflammatory response in mucosa, predominated by:
• **Neutrophils** in the lamina propria or attacking glands of antrum and causing small abscesses (in active disease).
• **Plasma cells, lymphocytes & macrophages**, in lamina propria.
• **Intestinal metaplasia (intestinal epithelium with goblet cells)**, can progress to dysplasia → adenocarcinoma (in long standing disease).
→ We can't find the bacteria in areas of intestinal metaplasia in cases of complication of chronic gastritis.
• **Lymphoid aggregates (lymphoid follicles with reactive germinal centers)** this increases risk of mucosa-associated lymphoid tissue **MALT lymphoma** (in more severe cases).

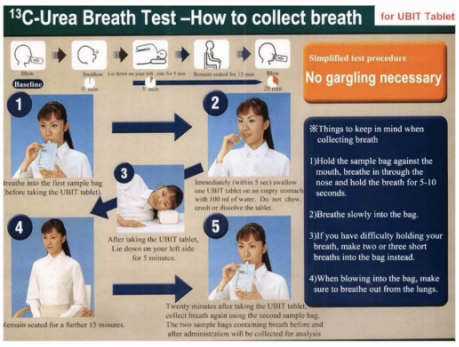

Warthin-starry silver stain, multiple H.pylori with black discoloration.


Lymphoid follicle with reactive germinal center, between the gastric glands in LP, indicates chronic gastritis.


many neutrophils = active state of the chronic disease.


intestinal metaplasia with goblet cells (complication of chronic gastritis associated with *H. pylori*

*All pics are from the antrum.



- Diagnosis of H. pylori chronic gastritis:
- Non-invasive:
• Serologic test (blood test): anti-H. pylori antibodies (IgA, IgG).
• Stool test for H. pylori.
• Urea breath test.
- Invasive:
• Upper Endoscopy.
• Gastric biopsy, (the best way to detect chronic gastritis & to detect H. pylori in mucus).
• Bacterial culture (using the biopsy).
• PCR test for bacterial DNA (using the biopsy).
- Treatment: at least 2 antibiotics and PPIs.

2- Autoimmune (atrophic) Gastritis: (atrophic due to mucosal atrophy that happens)

- Immune-mediated disease causes damage to **against parietal cells** in the body & fundus, leading to **loss of acid (HCL) and intrinsic factor production inhibition.**
- Characteristics of disease:
1. **Abs against parietal cells and intrinsic factor,** detected in the serum.
- **Immune/T-cell-mediated loss of parietal cells** (+ production of auto-ABs against parietal cells), causes reduction in acid secretion.
- **Cells and auto-ABs** directed against intrinsic factor, causes its reduction.
- The Intrinsic factor binds to vitamin B12 and aids in its absorption in the distal ilium.
- Decreased intrinsic factor=**Vitamin B12 deficiency**=**pernicious anemia/megaloblastic anemia** and neurologic changes.
- This anemia is very important to differentiate between autoimmune gastritis and H. pylori gastritis.

NO intrinsic factor = NO B12 absorption.

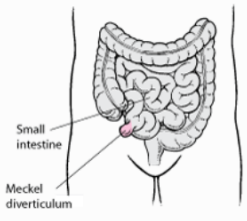
2. Reduced serum pepsinogen I levels, which is produced in body and fundus, because of some chief cells damage.
3. Antral endocrine cell hyperplasia (reflex G-cell hyperplasia in antrum), as a response to the loss of acid production in stomach.
- G cells produce **gastrin** as a response to the **decrease** in acid production (due to parietal cell damage).
- Impaired gastric acid (HCL) secretion **(achlorhydria).** (opposite to H. pylori gastritis)
- AI gastritis spares the antrum unlike H.pylori gastritis.
- Marked **hypergastrinemia,** mediated by antral G cells hyperplasia, due to acid reduction.
- Progression leads to **loss of parietal cells in the mucosa**, **damage of the oxyntic (acid-producing) mucosa**, **thinning and atrophy of mucosa**, & **loss of the rugal folds at these sites**.
- In long standing cases: **Intestinal metaplasia** (due to **achlorhydria**) → dysplasia → adenocarcinoma. (Risk is present in both types of chronic gastritis).
- Neuroendocrine cell **(G-cell) hyperplasia** due to reduced acid production, may transform into **neuroendocrine tumors**. (in H. pylori gastritis the risk is for MALT lymphoma).
- Morphology:
- Preferred biopsy site is **body or fundus** NOT antrum.
- No H. pylori present in specimens (If present, it's NOT the cause!).

- Lymphocytes, plasma cells, macrophages, and **less likely neutrophils**.
(H. pylori associated gastritis → chronic inflammatory cells & neutrophils).
(AI gastritis → mainly chronic inflammatory cells).
- **Clinical features**:
- Patients are in their 60s (higher age than H. pylori gastritis patients).
- Slight **female** predominance.
- Often associated with other autoimmune diseases like **Hashimoto thyroiditis, type 1 DM**, or **Graves disease of the thyroid**.
- autoimmune diseases usually tend to cluster together, so when we find AI gastritis we should look for others.

Table 15.2 Characteristics of *Helicobacter pylori*–Associated and Autoimmune Gastritis

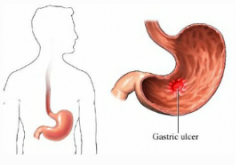
Feature	*H. pylori*–Associated	Autoimmune
Location	Antrum	Body
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to markedly increased	Markedly increased
Other lesions	Hyperplastic/inflammatory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

● Chronic peptic Ulcer:



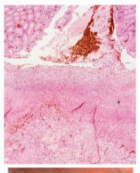
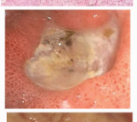
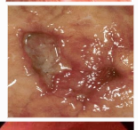
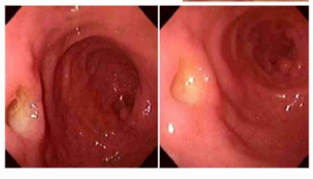
- **Peptic**: Any area that is exposed to acid and pepsin coming from gastric juice.
- **Ulcer**: loss of mucosa and submucosa.
Ex: Esophagus in (GERD), Meckel diverticulum (in ileum, can contain ectopic gastric mucosa).
- Starts as chronic gastritis, then develop to peptic ulcer.
- **Site**: **antrum and first part of duodenum** (because it receives gastric acidic juices from stomach). Anterior duodenal wall of proximal duodenum is **more affected** than stomach(4:1)
- **Pathogenesis**: **H. pylori (mostly) and NSAIDs** (like aspirin).
*only 5-10% of H. pylori cases develop ulcers, unless there is **cofactors** that increase risk: Smoking, chronic NSAIDs use, high dose corticosteroids, **alcoholic cirrhosis** , COPD (chronic obstructive pulmonary disease), CRF (chronic renal failure), and hyperparathyroidism.
- **NO ACID = NO ULCER**, **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 in stomach, duodenum, and jejunum.
- **Caused by: uncontrolled gastrin release by tumor** (**gastrinoma**) and the resulting massive acid production. (↳ composed of G-cells)
- **Complications**: hemorrhage & perforation.
Uncontrolled gastrin ➡️ excessive acid secretion ➡️ Zollinger-Ellison syndrome.

- **Morphology**:
- solitary (single ulcer) in 80% of cases, except in cases like Zollinger-Ellison syndrome. **(RECALL: stress ulcers are multiple not solitory).**
- **Round-oval** in shape and sharply **punched-out**.
- Base of ulcer is smooth, clean, & formed by **granulation tissue** (forms during healing process, has a **whitish/pinkish** color)
- intact mucosa on the periphery, lost epithelium in the center, new blood vessels, inflammatory cells, hemorrhage.
- **well circumscribed ulcer** in the wall of duodenum.

- **Clinical features:**
• **Epigastric burning or aching pain**. (mostly)
• Pain comes after 1 to 3 hours after meals at daytime. لما المعدة تكون فاضية
• Worse at night, relieved by alkali or drinking milk or food .
• Nausea, vomiting, bloating and belching تجشؤ.
- **Complications**:
• **Iron deficiency anemia** (caused by chronic blood loss from ulcers), symptoms: pallor, dizziness, loss of appetite. It is a long-term complication.
• **Frank hemorrhage** (frank=severe), thue **hematemesis** (blood vomiting) and **melena**.
• **perforation** (cause severe abdominal pain, peritonitis, rigid abdomen).
- **Treatment**:
- H.pylori eradication & Surgery in case of complications.

2- Gastric Polyps and Tumors: (neoplastic conditions)

A) Gastric Polyps:
1. Inflammatory and Hyperplastic Polyps. 2. Gastric Adenoma.
B) Gastric Adenocarcinomas: intestinal or diffuse.
C) Lymphoma: MALToma (mostly).
D) Neuroendocrine (Carcinoid) Tumors.
E) Gastrointestinal Stromal Tumor.

● A) Gastric Polyps: **Polyps**: projections above mucosa level.

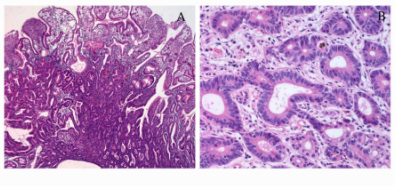
causes: hyperplasia, inflammation, neoplasia, ectopia (eg: pancreatic mucosa in stomach).

1. Inflammatory and Hyperplastic Polyps: (75% of all polyps)

- Reactive condition, **not a neoplasia**.
- Arise from **chronic gastritis** (mostly).
- No risk of malignancy (except if polyp size >1.5 cm ➡️ **Dysplasia**), (10% of all polyps).
- Regress spontaneously after H. pylori eradication.

2) Gastric Adenoma: (adenoma=must have dysplasia)

- Pre-cancerous condition, **a neoplasm**.
- Arise from **chronic gastritis**, atrophy and intestinal metaplasia.
- Dysplasia is in all cases.



- In high grade dysplasia, or if polyp size >2 cm ➡️ high risk of **adenocarcinoma**.
- Increase risk with age, M>F (3:1).
- **Diagnosis**: biopsy.
- 30% have **concurrent gastric adenocarcinoma**. (Concurrent=at the same time).

● B) Gastric Adenocarcinoma: (90% of all gastric cancers).

- Has 2 types: intestinal and diffuse.
- Arises from **mucosal atrophy** & **intestinal metaplasia**.

> **Intestinal type is associated with intestinal metaplasia**
> **Metaplasia ➡️ dysplasia ➡️ adenocarcinoma**
> (the common scenario for mucosal carcinomas)

- **Early symptoms mimic gastritis and PUD ones** مشكلة هاد المرض. (That's why some cases are diagnosed at late stage (poor prognosis)).
- Secrening & early detection is important.
- **Gastritis**, **atrophy** and the presence of **intestinal hyperplasia** increase the risk.
- **PUD doesn't increase the risk** (except after surgery, because some PUD patients may have bile reflux from small intestine to stomach (irritant)).
- **Pathogenesis**:
- **Genetic alterations due to H.pylori**-associated chronic gastritis (mostly)
- **EBV** (less, 10%) .
- sporadic (mostly). (Sporadic=غير وراثي)

1. Diffuse gastric adenocarcinoma:

- **Familial cases**: mutations in CDH1 ➡️ loss of E-cadherin ➡️ loss of cells adhesion.
- **Sporadic cases**: mutations in CDH1 (50%).

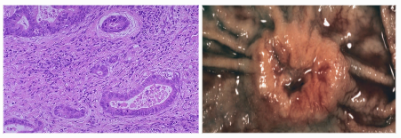
2. intestinal gastric adenocarcinoma:

- **Familial cases**: **APC gene mutation**, associated with **Familial adenomatous polyposis syndrome (FAP)**, (This syndrome increases risk of colonic polyps, also).
- **Sporadic cases**: B-catenin mutation.

> **P53 mutation is involved in sporadic cancer of both types.**

- **Morphology**:
- Lauren classification classifies gastric cancers into intestinal and diffuse.
- **Intestinal type** gastric cancer:

1. Bulky (gastric mass), fungating & delineated from the surrounding normal gastric mucosa.
2. Exophytic (polypoid) mass or ulcer (endoscopically)
3. Form glands (microscopically).

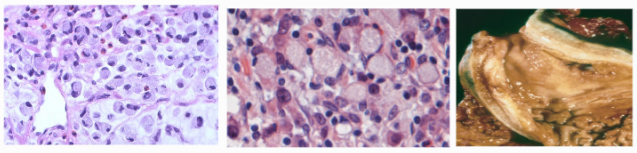


- **Diffuse type** gastric cancer: **(signet ring carcinoma)**

Tumor with **NO MASS** (endoscopically), because these tumors are usually infiltrative. This will lead to **thickening of gastric mucosa and not the formation of gastric mass**.

- Sometimes this will be deceiving because **the endoscopy is normal but microscopically there is tumor**, but **tumor cells are discohesive (E-cadherin loss)** & form **signet ring** cells;

- Signet ring cells: infiltrating cells with large droplets of mucus, the nucleus is pushed to the side زي شكل الخاتم. No E-cadherin, so cells appear as discohesive single cells.
- Strong **desmoplastic reaction** causes thickening & rigiding of stomach wall, which called **linitis plastica**.



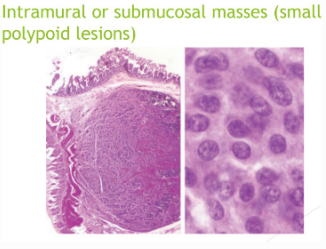
- **Clinical features:**
- **Intestinal type** gastric cancer:
• Usually **develops from precursors** (adenoma, dysplasia).
• Mean age 55 years, M>F (2:1).
- **Diffuse type** gastric cancer:
• Usually **no precursor** lesion (genetic abnormality only).
• Younger groups are affected, M=F.
- The patient presents with a **very bad tumor**.
- The symptoms are not specific for cancer (can be seen in chronic gastritis & PUD).
- **Weight loss & cachexia** are alarming.
- **prognostic factors**: (depends on TNM classification)
1) **Depth of invasion**, **More depth = poorer prognosis.**
2) Presence of **lymph node metastasis**
3) Presence of **distant metastasis.**
- Most cases are diagnosed at advanced stage, because symptoms are usually non specific.
- **Treatment** :
✓ Surgery +/- chemotherapy & targeted therapy using Anti-HER2 (also treat breast cancer).

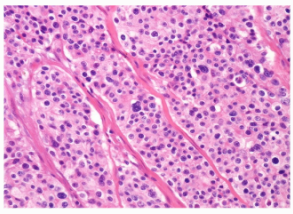
● C) Lymphoma:

- **Lymphoma**: tumor of lymphoid cells (B-lymphocyte and T-lymphocyte).
- Found in lymph nodes (mostly), can be found extranodal.
- **Stomach is the most common site for extranodal lymphoma.**
- Gastric lymphoma only constitute 5% of all gastric malignancies.
- Most common type of lymphoma in stomach is **MALToma** which is an **indolent** extranodal marginal zone B-cell lymphomas. (Indolent = low grade)
(RECALL: MALToma is associated with H. Pylori).
- Second most common type of lymphoma in stomach is **diffuse large B cells lymphoma**.

● D) Neuroendocrine (Carcinoid) Tumor: carcinoid = cancer مصغّر

- Arises from neuroendocrine cells (that are present in gastric mucosa, like G-cells).
- More than 40% occur in the **small intestine**.
- Usually associated with **endocrine cell hyperplasia, chronic atrophy gastritis,** and **Zollinger-Ellison syndrome**.
- Slower growing than carcinomas, thus the name (carcinoids).
- **Morphology** :
→ Intact mucosa on the surface with a nodule of tumor **in submucosa**.
- Present as polyps but when you remove the polyp and send it to the pathologist, **it is not a gastric polyp nor adenoma**, this polypoid growth is due to a **submucosal nodule of tumor composed of neuroendocrine cells**.
Most important microscopic appearance for it is **nuclei showing salt &**





pepper chromatin **appearance,** & Islands, trabeculae, strands, glands, or sheets of uniform cells with scant, pink granular cytoplasm.

- Carcinoid syndrome:

-Carcinoid tumors can be associated with carcinoid syndrome, seen in 10% of cases only.

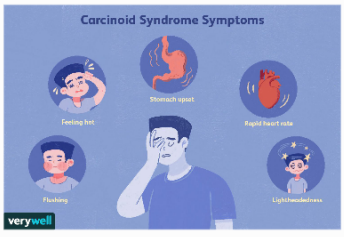
- **Strongly associated with metastatic disease.**

NO metastasis, NO carcinoid syndrome.

- This is usually due to **production of vasoactive substances** by neuroendocrine cells.

- **Clinical features:**

- **Cutaneous flushing** (the patients face is very red), **excessive sweating**, **bronchospasm**, **colicky abdominal pain** مغص, **diarrhea,** and **right-sided cardiac valvular fibrosis**.



extra

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