GIS 4

PATHOLOGY

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Hello everybody, in this sheet we will continue the second part of gastric pathology and we will talk about peptic ulcer disease as well as gastric tumors including gastric polyps and gastric malignancies.

1) Peptic Ulcer Disease:

- Ulcer means (قرحة) and it is the loss of mucosa and submucosa
- Peptic: due to exposure to acid and pepsin coming from the gastric juice

Note: Any area that is exposed to acid and pepsin can develop peptic ulcer disease so it's not restricted to the stomach .

Ex: Esophagus in (GERD), Meckel diverticulum (seen in the ileum and it can contain ectopic gastric mucosa)

- ✓ **Most common location are gastric antrum and first part of duodenum** (because as you know the first part of duodenum receives the gastric acidic juices from the stomach)
- ✓ **The most common cause of Peptic Ulcer disease in the stomach is H.pylori infection and NSAIDs use** .

Peptic ulcerations that occur in these situations is due to imbalance between mucosal defenses and damaging forces. In the beginning it will lead to chronic gastritis, then as a complication it will develop peptic ulcer disease.

- ✓ **In USA, using NSAIDs is becoming the most common cause of gastric ulcers, as H.pylori Infection is falling and an increased use of low dose aspirin in aged population is taking place.** As we know aspirin is used as anti-platelet in elderly patient to prevent cardiovascular event.

Pathogenesis:

- ✓ **More than 70% of PUD cases** are associated with **H.pylori infection** (In our region at least)
- ❖ Do all patient with H.pylori infection develop PUD?
  No, only 5-10% of H.pylori infected individuals develop ulcers, and many of them complain only from chronic gastritis.
- ✓ **Gastric acid is fundamental in pathogenesis**. If there is no acid there is no ulcer
- ✓ **However there are some cofactors in addition to H.pylori infection that can ease peptic ulceration (not main causes) :**
  Smoking , chronic NSAIDs use (if coupled with H.pylori the risk is doubled) , high dose corticosteroids (patient that use these should take PPIs) , alcoholic

cirrhosis , COPD (chronic obstructive pulmonary disease) , CRF (chronic renal failure) and hyperparathyroidism

- ✓ **Hyperacidity is caused by :**
- H.pylori, and this hyperacidity can affect gastric mucosa as well as duodenal mucosa .
- Parietal cell hyperplasia.
- Excessive secretory response (vagal).
- Hypergastrinemia as in (Zollinger-Ellison syndrome).

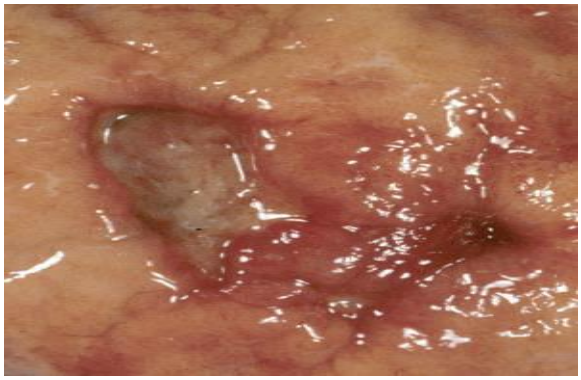
Zollinger-Ellison syndrome:

- ✓ **Characterized by multiple peptic ulcerations.**
- ✓ Can develop in **stomach , duodenum and even jejunum** "if there is excessive acid secretion"
- ✓ Caused by **uncontrolled release of gastrin by tumor (gastrinoma) and the resulting massive acid production**.

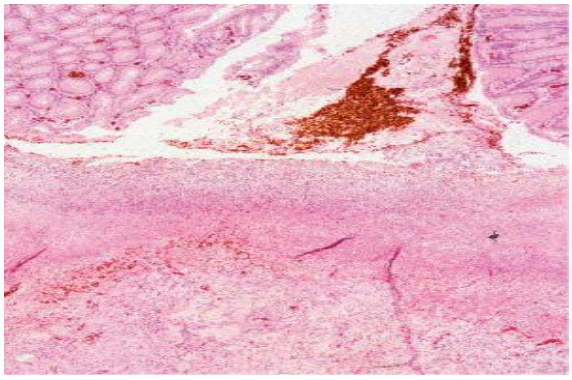
Remember: gastrin is a hormone that stimulates parietal cells to produce acid .

Morphology:

- ✓ **Proximal duodenum is more affected than stomach (4:1)**
- ✓ **Anterior duodenal wall is most affected site of proximal duodenum .**
- ✓ **Peptic ulcer disease is more than 80% of cases is solitary** (single ulcer), except in cases like Zollinger-Ellison syndrome where you can see multiple ulcerations.
- ✓ **Round to oval in shape and sharply punched-out defects**.
- ✓ **Base of ulcer is smooth and clean.**
- ✓ **Formed by granulation tissue** (tissue that is formed in attempt to heal the ulcer "you find newly formed blood vessels").
- ✓ **Hemorrhage & Perforation are possible complications**.

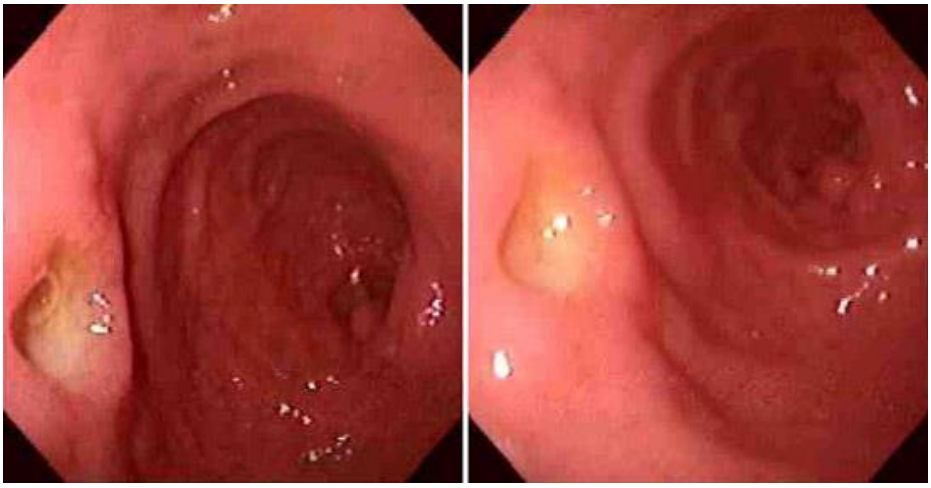


→ You can see the punched-out, very delineated edges of ulcers and the white, clean and oval background.



→You can see the intact mucosa on the periphery of the ulcer. At the center the epithelium is lost and new blood vessels inflammatory cells, and hemorrhage can be seen.

Duodenal ulcer (under endoscopy) :



→There is a well circumscribed ulcer in the wall of duodenum.

Clinical features:

- **The most common symptom is epigastric burning or aching pain.**
- **This pain typically comes after 1 to 3 hours after meals at daytime.**
- **The pain is worse at night and relieved by alkali or drinking some milk or food .**
- **The patient may also complain from nausea, vomiting, bloating and belching (تجشؤ)**
- **Iron deficiency anemia caused by chronic blood loss from ulcers**. Some patients come to you with symptoms of anemia (pallor, dizziness, loss of appetite).
  - Iron deficiency anemia is a long-term complication of PUD.
- **However, sometimes the patient may represent complication of frank hemorrhage**. So in these cases the patient will complain from hematemesis (vomiting of blood) and melena .
- **Another complication is perforation** (the patient comes with severe abdominal pain, peritonitis, rigid abdomen and this need immediate surgical correction).

Treatment:

- **Current therapies are aimed at H.pylori eradication**
- **Surgery is reserved for complications like perforation or hemorrhage**

2) Gastric Polyps and Tumors :

- Gastric Polyps , are subdivided into :
  - Inflammatory and Hyperplastic Polyps.
  - Gastric Adenoma.
- Gastric Adenocarcinoma , and they subdivided into :
  - Intestinal type

- diffuse type
- Lymphoma
  - **The most common lymphoma that arise from the stomach is MALToma** (Mucosa associated lymphoid tissue lymphoma)
- Neuroendocrine (Carcinoid) Tumors
- Gastrointestinal Stromal Tumor

A) Gastric polyps:

- **Polyps: masses projecting above the level of adjacent mucosa**
  - Anything can cause gastric polyps like: **Epithelial or stromal cell hyperplasia, inflammation, ectopia** "ex : ectopic pancreatic mucosa in the stomach" **or neoplasia**.
  - So it is descriptive term, not specific to neoplasms.
  - When we say gastric polyp , we will reserve this term to two conditions :

1) Inflammatory and Hyperplastic polyps:

- ✓ **They constitute about 75% of all polyps.**
- ✓ **Usually arise in background of chronic gastritis.**
- ✓ **Regress spontaneously after H.pylori eradication.**
- ✓ **Risk of dysplasia if the size of polyp > 1.5 cm.**
- But remember most of the time these polyps are very small and there is no risk to have neoplasia or dysplasia, so no need to worry about yourself if you are diagnosed with hyperplastic polyp.

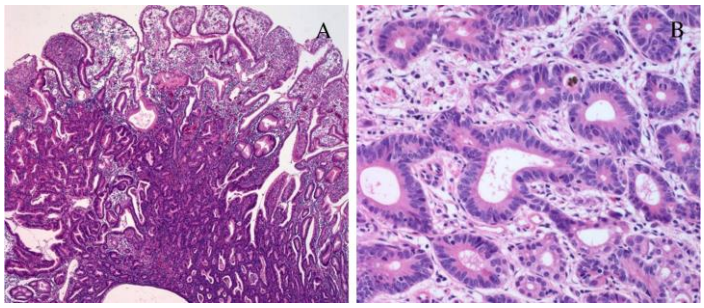
Note: It is a reactive condition, not considered a neoplastic condition.

2) Gastric Adenoma:

- It is considered precancerous , not like hyperplastic gastric polyps , these are neoplastic .
- ✓ **They only constitute of 10% of all polyps** (not very common like colonic adenomas)
- ✓ **Increase with age, and Males are affected more than Females (3:1) .**
- ✓ **Usually there is a background of chronic gastritis, atrophy and intestinal metaplasia**
- ✓ **Dysplasia in all cases** (not present in hyperplastic polyps) and it can be **low or high grade.**
- Of course, patients with **high grade dysplasia are at higher risk to develop adenocarcinoma**. The risk of adenocarcinoma is also related not only to degree of dysplasia, **but also to the size of polyp (greatest if the polyp size > 2 cm).**
- ✓ When we diagnose gastric adenoma in a biopsy, there is a **risk that 30% of the patients have concurrent gastric adenocarcinoma .**

Morphology (under microscope):

→We must see dysplasia, and in this picture, it is low grade. Masses have polypoid appearance .



B) Gastric Adenocarcinoma:

- ✓ **Comprises 90% of all gastric cancers** (others: lymphomas, GI stromal tumors.. etc)
- ✓ **Two main types : intestinal and diffuse**
- **The most important about gastric adenocarcinoma is that the symptoms are not specific and they mimic those of gastritis and PUD**. That's why **some cases of epigastric adenocarcinoma are diagnosed at late stage (poor prognosis).**
- ✓ **The most important thing to do is screening and early detection in high risk patients**
- ✓ **The rates vary markedly according to geography, more common in Japan, Costa Rica and Chile.**
- ✓ **Occurs in the background of mucosal atrophy and intestinal metaplasia.**
- Metaplasia ⟶ dysplasia ⟶ adenocarcinoma, the common scenario for mucosal carcinomas in different locations.
- ✓ **PUD does not increase the risk.** It is the gastritis, atrophy and the presence of intestinal hyperplasia that increases it, **except after surgery**, why ? because some PUD patients are at increased risk of bile reflux from the small intestine to the stomach (irritant) .
- ✓ **In USA, the rates dropped for more than 85% but there is increase rate of cardia cancer due to GERD & obesity**.

Pathogenesis:

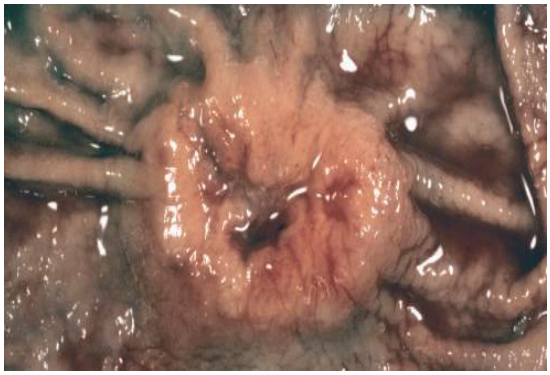
- ✓ Always about **genetic alterations due to H.pylori infection associated chronic gastritis** (most common) , **to lesser extent EBV (10%) .**
- ✓ **Most cases are sporadic.**
- In any cancer we can have familial cases and sporadic cases.
- ✓ **In diffuse type gastric adenocarcinoma :**
  - **Familial cases : mutations in CDH1 (E-cadherin)** **"the cells lose adhesion due to loss of E-cadherin"**
  - **Sporadic cases: CDH1 mutation in 50% .**
- ✓ **In the intestinal type of gastric adenocarcinoma :**
  - **Familial cases: APC gene mutation associated with Familial adenomatous polyposis syndrome (FAP).**
    This syndrome is also associated with increased risk of colonic polyps .
  - **Sporadic cases: B-catenin mutation.**
- ✓ **P53 mutation is involved in sporadic cancer of both types** .

Morphology:

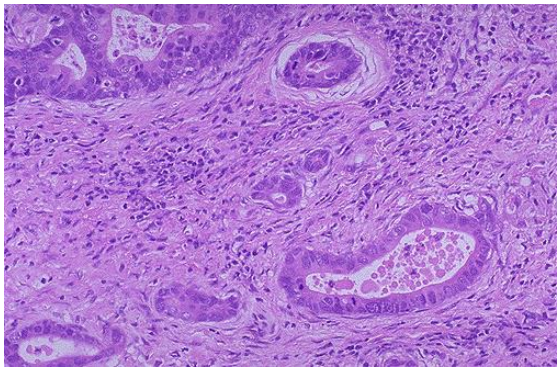
✓ Lauren classification: classifies gastric cancers into intestinal and diffuse types .

✓ **Intestinal type :**

- **Bulky**
- **Exophytic mass or ulcer (endoscopically)**
- **Form glands (microscopically)**



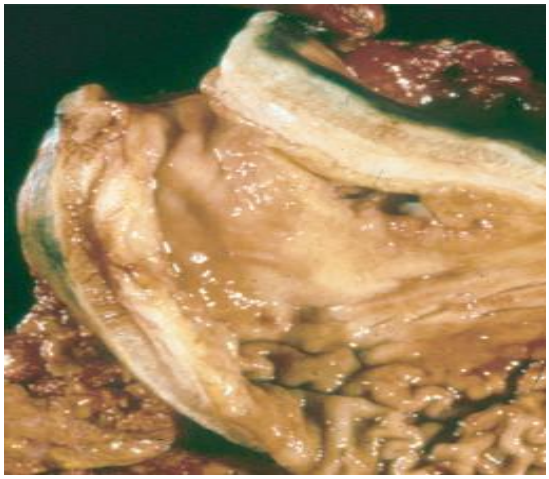
→This picture is taken from endoscopy for a patient with a gastric mass
So, you can see here ulcer but it's somehow fungating and delineated from the surrounding normal gastric mucosa. This is typical for intestinal type.



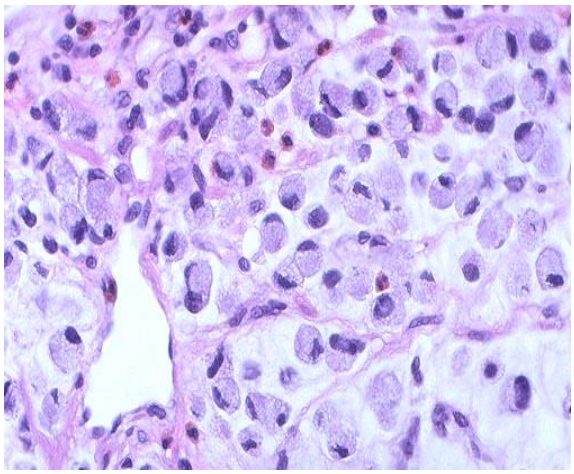
→ In This picture you can also see the malignant glands infiltrating the wall of the stomach. adenocarcinoma tend to form glands and mucin (typical view for intestinal type)

✓ **Diffuse gastric cancers :**

- **Non mass forming tumors (endoscopically), because these tumors are usually infiltrative.** <u>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 under microscopic examination there is tumor.</u>
- **Under microscopic examination the tumor cells are usually discohesive**(E-cadherin gene mutation) **and form signet ring cells (زي شكل الخاتم)**. <u>That's why the other name for diffuse type of gastric cancer is signet ring carcinoma of the stomach .</u>
- **These tumors usually result in strong desmoplastic reaction that will lead to thickening of the wall of the stomach and what we call linitis plastica** (the wall of stomach becomes very thick and rigid)



→You don't see any mass here
but main change is thickening of gastric wall. This is typical appearance for stomach that is affected with diffuse type.



→You can see those infiltrating signet ring cells with large droplets of mucus and the nucleus is pushed to the side of the cell. Remember that the most important genetic abnormality in this type is E-cadherin mutations that's why the cells here lose adhesion and they appear as discohesive single cells

Clinical features :

✓ **Intestinal type gastric cancer :**

- **Predominant in high risk areas (like Japan , Costa Rica and Chile .. etc)**
- **Usually develops from precursors (adenoma, dysplasia)**
- **Affected age groups: (mean age 55 years) .**
- **Males are more affected than Females (2:1)**

✓ **Diffuse type gastric cancer :**

- **Incidence is uniform across all countries.**
- **Usually no precursor lesion (genetic abnormality only)**
- **Younger groups are affected.**
- **Males and Females are affected equally.**

- The patient presents with a very bad tumor .
- The symptoms are not specific for cancer (they can be seen in chronic gastritis and PUD)
- Weight loss and cachexia are alarming.

✓ **The drop in gastric cancer incidence applies only to intestinal type** (perhaps due to early detection and treatment of H.pylori), whereas the diffuse type is increasing nowadays.

- Incidences of intestinal and diffuse types are now similar in some regions.

✓ **Most powerful prognostic factors :**

1) Depth of invasion (How deep the tumor goes in the gastric wall?) Is it just limited to mucosa or does it infiltrate submucosa, muscularis propia or even reach the serosa? (very important prognostic factor). More depth = poorer prognosis.

2) Presence of lymph node metastasis

3) Presence of distant metastasis at the time of diagnosis.

✓ Most cases are diagnosed at advanced stage, and that's because the <u>symptoms are usually non specific and the patient comes too late</u> .

✓ 5 years survival are variable according to the time of diagnosis, from 90% to 20% for early and advanced tumors, respectively .

Treatment :

✓ **Surgery +/- chemotherapy and targeted therapy** (using Anti-HER2 "also used to treat breast cancer").

- The lymph node and distant metastasis depend on the stage of the disease, high stage means poor prognosis.

C) Lymphoma:

✓ **Lymphoma is most found in lymph nodes. However, they can be found somewhere else (extranodal)**

✓ **The stomach is the most common site for extranodal lymphoma**

- **Lymphoma: tumor of lymphoid cells (B-lymphocyte and T-lymphocyte).**

✓ **Gastric lymphoma only constitute 5% of all gastric malignancies.**

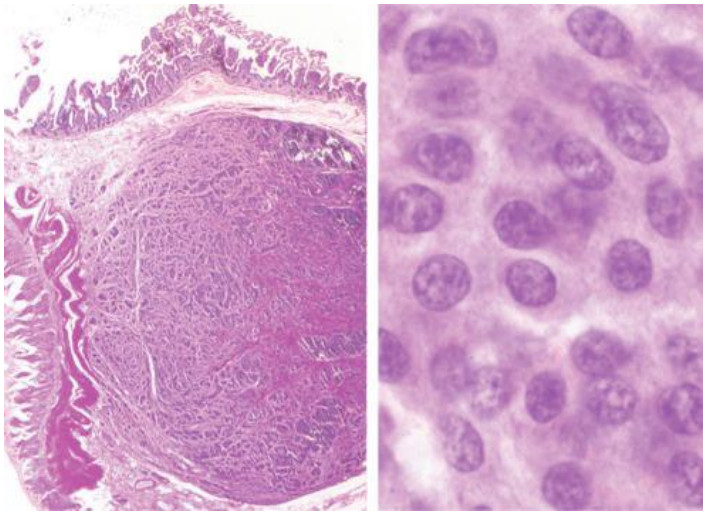
✓ **Most common type of lymphoma in the stomach is: MALToma which is an indolent (low grade) extranodal marginal zone B-cell lymphomas .**

✓ **Second most common type of lymphoma in the stomach is: diffuse large B cells lymphoma**

D) Neuroendocrine (Carcinoid) Tumor :

- ✓ **They arise from neuroendocrine cells that are present in gastric mucosa** (ex: G cells "responsible for production of Gastrin hormone").
- ✓ **More than 40% occur in the small intestine.**
- ✓ **Usually they are 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 the submucosa. This is a typical location for neuroendocrine tumors. They 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 neuroendocrine cells is their nuclei showing salt and pepper chromatin appearance.

Islands, trabeculae, strands, glands, or sheets of uniform cells with scant, pink granular cytoplasm and salt and pepper chromatin. (from the slides).

Carcinoid syndrome:

- ✓ **Carcinoid tumors can be associated with carcinoid syndrome, but this is only seen in 10% of cases.**
- ✓ **Strongly associated with metastatic disease** (If there is 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, diarrhea and right-sided cardiac valvular fibrosis .

Good Luck