GIT Pathology

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The stomach

Histology:

The normal gastric wall has the same layers as does the rest of the gut:

A-The mucosa: is composed of 2 major compartment:

1-the foveolar: surface epithelium and gastric pits (invagination from the surface), is columnar mucinous epithelium.

2- glandular component: which are either;

* Mucous secreting in the antrum, cardia and pylorus

* Glands composed of **chief cells** that secrete pepsin, and **parietal** cells that secrete acid (HCl) and intrinsic factor (IF) in the fundus and body

B- The submucosa

C- The muscular layer

D- The serosa

Gastritis

It is defined as inflammation of the gastric mucosa.

1- Acute gastritis with **neutrophilic** infiltration.
2- Chronic gastritis with **lymphocytic** infiltration.

Acute gastritis:

Is acute inflammation of the gastric mucosa.

Etiology:

- Heavy use of (non-steroidal anti-inflammatory drugs NSAID)
- Excessive alcohol intake
- Heavy smoking
- Uremia
- Severe stress (burn, trauma, surgery)
- Systemic infection (e.g. salmonellosis).
- Treatment with chemotherapeutic drugs.

Clinical features:

Epigastric pain, nausea and vomiting, sometimes hematemesis

Grossly: Congested, edematous surface.

Microscopically:

1- Neutrophils among the surface epithelial cells.
2- Erosion (loss of superficial epithelial cells) resulting in a defective mucosa.
3- Sometimes hemorrhage → acute hemorrhagic gastritis.

Chronic gastritis:

Defined as presence of mucosal inflammatory changes leading to:

- Mucosal **atrophy**
- H-pylori are found nestled within the mucus layer overlying the mucosal epithelium.
- Epithelial **metaplasia** (replacement of the gastric epithelium with columnar &goblet cells of the intestinal variety).
- Sometimes **dysplasia** which makes the background for carcinoma.
- H-pylori induced proliferation of lymphoid tissue within gastric mucosa is a precursor of gastric lymphoma.

- There is **No Erosion (**to differentiated from gastric ulceration)

Etiological factors:

1- Chronic inflammatory processes (helicobacter pylori H.P) which makes the most important factor and present in about 50% of cases.
2- Immunological (autoimmune) in association with pernicious anemia which makes about 10% of cases.
3- Toxic e.g. alcohol &cigarette smoking.
4- Post-surgical e.g. reflux of biliary duodenal secretion
5- Motor and mechanical causes including: obstruction, bezoars.
6- Radiation
7- Granulomatous conditions
8- Miscellaneous e.g. amyloidosis.

Helicobacter pylori Gastritis (Type B)

*It is the most common cause of chronic gastritis.
* It can arise at any age.
* It involves the **antrum** of the stomach
* It is highly associated with 1. Peptic ulcer disease 2. Gastric carcinoma 3. Gastric lymphoma

H. pylori bacteria

- Are curvilinear, gram-negative rods, adapted to live in the gastric mucus, which is lethal to most bacteria. **Its virulence is linked to the following factors:**

1. *Flagella*, which allow the bacteria to be motile in viscous mucus
2. Bacterial **protease** and **phospholipase** break down the glycoprotein –lipid complex in the gastric mucoid, thus weakening the first line of mucosal defence.
3. *Urease,* which generates ammonia from endogenous urea and thereby elevates local gastric pH and enhances bacterial survival
4. *Adhesins* that enhance bacterial adherence to surface foveolar cells
5. *Toxins,* such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin gene A (VacA) which are responsible for the inflammatory response.

- Infection is typically acquired in childhood and persists for life without treatment, transmission is primarily by the fecal-oral route.

Microscopically:

1. Organisms (Spiral-shaped H. pylori) are abundant within surface mucus, easily demonstrated with immunostains or histochemical stains.
2. The mucosa is infiltrated by chronic inflammatory cells (lymphocyte and plasma cells), and neutrophils in case of active inflammation.
* Lymphoid aggregates, some with germinal centers, are frequently present.
3. Mucosal atrophy and intestinal metaplasia are **sequelae** that can be the first step toward development of gastric adenocarcinoma.

Autoimmune Atrophic Gastritis (Type A)

*It accounts for less than 10% of cases of chronic gastritis
* Occur in late adult life.
* The **body and fundus** mucosa is mostly affected. typically spares the antrum
* There is a production of antibodies against the **parietal** cells which causes:

- Defective gastric acid secretion (hypo- or achlorhydria)
- Decrease in intrinsic factor secretion.

- Impaired Vit B12 absorption and later on pernicious anemia as a result of the above cause.
- Often associated with marked hypergastrinemia (The absence of acid production stimulates gastrin release, resulting in hypergastrinemia and hyperplasia of antral gastrin-producing G cells.

*It can be associated with other autoimmune diseases e.g. diabetes, thyroiditis.
*There is high risk of developing **gastric carcinoma.**
Clinical picture: Asymptomatic., Or with epigastric pain. Or pernicious anemia.
Microscopically:

1. The mucosa is infiltrated by lymphocytes & plasma cells, often in association with lymphoid aggregates and follicles.
2. Glandular atrophy.
3. Intestinal metaplasia, recognizable as the presence of goblet cells admixed with gastric foveolar epithelium

Acute gastric ulcer:

It means the development of: focal, acutely developing mucosal **defects**.
Causes:

1- Non-steroidal anti-inflammatory drugs (NSAID).
2- May appear after severe physiological stress, whatever its nature;

So it is called (STRESS ulcer) e.g.
-After severe burn (CURLING ulcer)
-After head or CNS injury (CUSHING ulcer)
- After severe trauma e.g (sepsis and major surgery)
Pathogenesis:
The development of acute mucosal defects in the above causes results from different settings:
1-In case of patient taking NSAID there will be a decrease in PG secretion which has an important protective effect on the mucosa.
2- Direct stimulation to the vagal nuclei (in head traumas) by increased intracranial pressure may cause hypersecretion of gastric acid.
3-In severe trauma &burns, systemic acidosis which lowers the mucosal cell PH which are already hypoxic by impaired mucosal blood flow.
Morphologically:
Multiple, small, round-oval, superficial-deep, and may lead to perforation.
Clinical features:
Either asymptomatic or bleeding.

Chronic peptic ulcer:

An *ulcer*: is a defect in the mucosa causing a discontinuity of the surface **epithelium** which may extend into the **muscularis mucosae** into the **submucosa**, or **deeper.**
Peptic ulcer: is an ulcer occurring in the areas of the GIT that are exposed to the acid –pepsin secretion as in:

- duodenum } **98%** of cases
- stomach
- lower esophagus
- margin of gastroenterostomy
- Meckel diverticulum that have an ectopic gastric mucosa

Pathogenesis:
Peptic ulcer appears to be produced by an **imbalance** between the gastroduodenal mucosal defense mechanisms and the damaging forces.

Defense forces:

1- Surface mucous layer secreted by the epithelial cells.
2- Bicarbonate secretion into the mucous.
3- Mucosal blood flow
4- Apical surface of the mucosal cells protects against back diffusion of H ion.
5- Epithelial regenerative capacity
6- Elaboration of prostaglandins from adequate blood flow

Aggressive forces:

1- Gastric acidity (HCL) secretion.
2- Peptic enzymes.
3- Other induced cause:
- H. pylori infection.
- Aspirin
- NSAIDs
- Cigarette
- Alcohol

-**H. pylori** infection is the most important cause &present in 70% of GU.
*For ***D.U, H. pylori*** present in 70-90%
- **Genetic** susceptibility play role also that is 20-40% of D.U have a +ve family history.

Morphologically:
1. Site: G.U usually located at the lesser curvature
D.U at the first 2.5 cm of the duodenum
2. Size: 2-4 cm, sometimes larger
3. Number: usually solitary, sometimes two
4. Shape: round- oval, the margin of the crater is Punched out, perpendicular unlike ulcerated cancers, there is No significant elevation or beading of the edges.
5. Floor: clean
6. Base: firm
7. Edge: overhanging
8. Depth: may vary.

- Ulcer-related scarring may involve the entire thickness of the gastric wall; puckering of the surrounding mucosa creates mucosal folds that radiate from the crater in spoke-like fashion. This is different from malignant ulcers where there is flattening of the mucosal folds (because of malignant infiltration) in the immediately surrounding of the ulcerative.

Microscopically:
Four zones could be identified;

- Base &margin have a thin layer of necrotic fibrinoid debris
- Beneath is a layer of neutrophilic inflammatory cell infiltration
- In the deeper layers there is a granulation tissue formation.
- The granulation tissue rests on a fibrous tissues scarring.

Comparison between benign and malignant ulcer:

Feature	Benign ulcer	Malignant ulcer
Margins	Punched out	Heaped up
Floor	Clean	Necrotic debris
Surrounding mucosa	Spoke wheel pattern	Ironed out

Clinical features:

- **Epigastric pain:**
- The pain tends to occur 1 to 3 hours after meals during the day, is worse at night, and is relieved by alkali or food.
- Nausea, vomiting, bloating, and belching may be present.
- **Might present with complications.**

Complications:

1- **Healing and scarring:** which lead to contracture, caused by contraction of the fibrous scar-→ *pyloric obstruction especially if the ulcer is located in the prepyloric area→ vomiting, dehydration and hyperkalemic alkalosis.
* hour-glass deformity, if the ulcer is higher up in the stomach.

2- **Bleeding: occur in 1\3 of patients** &lead to:
   - Hematemesis (coffee ground appearance due to blood hemolysis by acid) and melena
   - iron deficiency anemia due to *chronic* loss of small amounts of blood

3- **Perforation:** leading to escape of the gut content into the peritoneal cavity→ peritonitis presented with *acute* abdominal pain & is the major cause of death.

4- **Penetration:** of the ulcer into the adjacent structures e.g small intestine.

5- **Malignant transformation:** occur in less than 1% of G.U

N.B: D.U ***never*** show a malignant transformation

Tumors of the stomach

- **Benign:**
- Polyps (hyperplastic or adenomatous), Leiomyomas and Lipomas.
- **Malignant:**
- Adenocarcinoma and Lymphoma
- **Others:**
- Gastro -Intestinal "Stromal" Tumor (GIST) and Carcinoid (neuroendocrine)

Benign tumors:

Gastric polyps

In the alimentary tract, the term **polyp** is applied to any nodule or mass that projects above the level of the surrounding mucosa. They are uncommon and classified as non-neoplastic or neoplastic.

- ***Hyperplastic polyps*** (the most frequent; 90%) are small, sessile and multiple in about 25% of cases. There is hyperplasia of the surface epithelium and cystically dilated glandular tissue.
- ***Adenomatous polyp (adenoma)*** (10% of polypoid lesions): They contain

proliferative dysplastic epithelium and hence have malignant potential. They are usually single, and may grow up to 4 cm in size before detection. Up to 40% of gastric adenomas contain a focus of carcinoma; there may also be an adjacent carcinoma that is why histologic examination of all gastric polyps is obligatory.

- Other specific types of gastric polyps are relatively uncommon and include fundic gland polyps, hamartomatous Peutz-Jeghers polyps, juvenile polyps, and inflammatory fibroid polyp

Malignant tumor

Carcinoma is the most important and the most common (90%) of malignant tumors of the stomach. Next in order of frequency are lymphomas (5%); the rest of the tumors are even rarer e.g. carcinoids, and gastrointestinal stromal tumors (GISTs) and leiomyosarcoma.

Gastric adenocarcinoma:

- It is the most common malignancy of the stomach, comprising more than 90% of all gastric cancers.
- Gastric cancer incidence varies markedly with geography. it is particularly high in countries such as Japan.
- It is more common in lower socioeconomic groups.
- There are mainly two subtypes of carcinoma: intestinal and diffuse. These sub-types appear to have different pathogenetic mechanisms of evolution.

Etiology &pathogenesis:

In intestinal type adenocarcinoma:

1- Environmental factors

1- Diet

* Nitrites and nitrates used for preservation of food
* Smoked food &pickled vegetables
*Increased salt intake.
* Lack of fresh fruit and vegetables (antioxidants present may inhibit nitrosation)
* Cigarette smoking.
* Low socioeconomic status

2- Host factors:

A. Chronic gastritis with intestinal metaplasia whether caused by *Helicobacter pylori Infection* or *Autoimmune gastritis*.
B. Adenomatous polyps
C. Genetic: Family history of gastric carcinoma.

In diffuse type carcinoma (signet ring)

- Risk factors undefined except rare inherited **mutation of E cadherin**
- Infection with H pylori and chronic gastritis often absent

Question ???

What is the relation between chronic atrophic gastritis and gastric carcinoma??

Answer:

1- In chronic gastritis the chronic inflammatory process may lead to metaplasia, then dysplasia followed by tumor formation or anaplasia.

2- In chronic gastritis, there is decrease in HCL secretion which promotes the growth of abnormal intragastric bacteria which act on dietary **nitrate** and convert them into **nitrite**

which assist in further conversion of dietary amines into **N- nitrosocompounds** which is an important carcinogen.

Grossly:

* Most of them located at the antrum

1- they are either **exophytic** (fungating) OR

2- **Ulcerative** (excavating) OR

Flat or depressed---diffuse thickening of the wall without obvious mass (lenities plastica and it look like leather bottle.

Microscopically:

The type is adenocarcinoma, classified into two types:

1- Intestinal type:
   - Malignant cells forming neoplastic intestinal glands resembling those of colonic adenocarcinoma.
   - It is the predominant type in high risk areas
   - Occur in old age group (55) years
   - Better prognosis than other type

2- Diffuse type:
   - The tumor is less differentiated
   - The cells accumulate intracellular mucin forming **a signet ring**
   - No glandular formation
   - Occur in a slightly younger age group (48) years
   - worse prognosis
   - Risk factors: undefined except rare inherited mutation of E cadherin
   - Infection with H pylori and chronic gastritis often absent

Spread:

1- Local spread: to adjacent organs: e.g esophagus, duodenum.

2- Lymphatic spread: to regional lymph nodes

For obscure reasons the earliest LN metastasis may sometimes involve a supraclavicular lymph node (**Virchow's node)**

3- Transcoelomic spread: in which the tumor cells shed into the peritoneal cavity and if it gets implanted on both ovaries it will form the interesting ***KRUKENBERG TUMOR***

4- Hematogenous spread: to the liver and lung.

Clinical features:

The most important are:

- Anorexia (loss of appetite)
- Severe weight loss
- Anemia

} with epigastric pain

Prognosis:

Prognostic indicators are;

1.The depth of invasion and

2.The extent of nodal and distant metastasis

- For early gastric ca. which is limited to the mucosa or submucosa, the 5-years survival rate is 90-95%
- For advanced gastric ca. the 5-years survival rate is 15%.

<u>Gastric Lymphomas</u>

- Represent 5% of all gastric malignancies. However, the stomachis the most

common site for extra-nodal lymphoma (20%). Nearly all primary gastric lymphomas are B-cell type and of mucosa-associated lymphoid tissue (MALT lymphomas). The majority of gastric lymphomas (>80%) are associated with chronic gastritis and H. pylori infection.

The role of H. pylori infection as an important etiologic factor for gastric lymphoma is supported by the elimination of about 50% of early gastric lymphomas with antibiotic treatment for H. pylori. Generally, the prognosis of gastric lymphoma is better than carcinoma.

Gastrointestinal Stromal Tumor

The most common mesenchymal tumor of the abdomen, and more than half of these tumors occur in the stomach.

Epidemiology Overall, GISTs are slightly more common in males. The peak incidence of gastric GIST is around 60 years of age, with less than 10% occurring in persons younger than 40 years of age.

GISTs appear to arise from the interstitial cells of Cajal, which express c-KIT, are located in the muscularis propria, and serve as pacemaker cells for gut peristalsis.

Pathogenesis:

Approximately 75% to 80% of all GISTs have mutations of the gene encoding the tyrosine kinase c-KIT.

Another 8% of GISTs have mutations platelet-derived growth factor receptor A (PDGFRA)

Morphology

Gross: solitary, well circumscribed, fleshy, submucosal mass.

Mic: composed of thin, elongated spindle cells or plumper epithelioid cells.

The most useful diagnostic marker is c-KIT, consistent with the relationship between GISTs and interstitial cells of Cajal, which is immunohistochemically detectable in 95% of these tumors.

Clinical Features

Symptoms of GISTs at presentation may be related to mass effects or mucosal ulceration.

Complete surgical resection is the primary treatment for localized gastric GIST.

The prognosis correlates with:

tumor size, mitotic index, and location, with gastric GISTs being somewhat less aggressive than those arising in the small intestine.

Recurrence or metastasis is rare for gastric GISTs less than 5 cm but common for mitotically active tumors larger than 10 cm.

Patients with unresectable, recurrent, or metastatic disease often respond to imatinib, an inhibitor of the tyrosine kinase activity of c-KIT and PDGFRA.

Metastases may form multiple small serosal nodules or fewer large nodules in the liver; spread outside of the abdomen is uncommon.