GIT pathology Lect.2

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In developed countries, peptic ulcers occur in up to 10% of the general population. Chronic infection of the gastric mucosa by the bacterium H. pylori is the most common infection worldwide. Gastric cancer is still a significant cause of death, despite its decreasing incidence.
GASTRITIS this is by definition, "inflammation of the gastric mucosa". It is a microscopic diagnosis. The inflammation may be acute, with neutrophilic infiltration, or chronic, with lymphocytes and/or plasma cells.

Acute gastritis is usually transient in nature. The inflammation may be accompanied by hemorrhage into the mucosa (acute hemorrhagic gastritis) and, sometimes by sloughing (erosions) of the superficial mucosa (acute erosive gastritis). The latter is a severe form of the disease & an important cause of acute gastrointestinal bleeding.
Although a large number of cases have no obvious cause (idiopathic), acute gastritis is frequently associated with:

1. Heavy use of nonsteroidal anti-inflammatory drugs (NSAIDs) particularly aspirin, cancer chemotherapeutic drugs, or radiation
2. Excessive consumption of alcohol, heavy smoking, and ingestion of strong acids or alkali as in suicidal attempts
3. Uremia
4. Severe stress (e.g., trauma, burns, surgery)
5. Mechanical trauma (e.g., nasogastric intubation)
6. Distal gastrectomy (reflux of duodenal contents).
Chronic Gastritis is defined as "chronic inflammation of the gastric mucosa that eventuates in mucosal atrophy and intestinal metaplasia". The epithelial changes may progress to dysplasia, which constitute a soil for the development of carcinoma.

Pathogenesis

The major etiologic associations of chronic gastritis are:

1. Chronic infection by H. pylori
2. Autoimmune damage
3. Excessive alcohol consumption & heavy cigarette smoking
4. Post-antrectomy (due to reflux of bile-containing duodenal secretions)
5. Outlet obstruction, uremia, and other rare causes
Helicobacter pylori Infection and Chronic Gastritis

Infection by H. pylori is the most important etiologic cause of chronic gastritis. Effective treatment with antibiotics has revolutionized the management of chronic gastritis and peptic ulcer disease. Those with H. pylori-associated chronic gastritis are at increased risk for the development of

1. Peptic ulcer disease
2. Gastric carcinoma
3. Gastric lymphoma
H. pylori are curvilinear, gram-negative rods. They have adapted to survive within gastric mucus, which is lethal to most bacteria. The specialized features that allow these bacteria to flourish include:

1. **Motility** (via flagella), allowing them to swim through the viscous mucus

2. **Urease production**, which releases ammonia and CO2 from endogenous urea, thereby buffering the harmful gastric acid in the immediate vicinity of the bacteria

3. **Expression of adhesion molecules**, which enhances binding of the bacteria to adjacent foveolar cells
The bacteria appear to cause gastritis by stimulating production of pro-inflammatory cytokines as well as by directly damaging epithelial cells by the liberation of toxins & degrading enzymes e.g. vacuolating toxin (VacA), urease, proteases and phospholipases. After exposure to H. pylori, gastritis occurs in two patterns:

1. Antral-predominant gastritis with high acid production and elevated risk for duodenal ulcer
2. Pan gastritis with low acid secretion and higher risk for adenocarcinoma
A number of diagnostic tests have been developed for the detection of H. pylori.

1. **Noninvasive tests** including
   a. Serologic test for antibodies
   b. Stool culture for bacterial detection
   c. Urea breath test: based on the generation of ammonia by bacterial urease.

2. **Invasive tests** (through gastroscopy): detection of H. pylori in gastric biopsy tissue samples including
   a. visualization of the bacteria in histologic sections with special stains.
   b. bacterial culture of the biopsy
   c. bacterial DNA detection by the polymerase chain reaction
Autoimmune gastritis

About 10% of chronic gastritis are autoimmune in nature. It results from the presence of autoantibodies to components of parietal cells, including the acid-producing enzyme H+/K+-ATPase, gastrin receptor, and intrinsic factor. Gland destruction and mucosal atrophy lead to loss of acid production (hypo- or achlorhydria). In the most severe cases, production of intrinsic factor is also impaired, leading to pernicious anemia. Affected patients have a significant risk for developing gastric carcinoma and endocrine tumors (carcinoid tumor).
Pathological features of chronic gastritis

- **Autoimmune gastritis** is characterized by diffuse mucosal damage of the body-fundic mucosa, with sparing of antral region (Corpus-predominant gastritis).

- **Environmental gastritis** i.e. due to environmental etiologies (including H. pylori infection) tends to affect antral mucosa (antral gastritis) or both antral and body-fundic mucosa (pangastritis).

Gross (endoscopic) features

- The mucosa of the affected regions is usually hyperemic and has coarser rugae than normal.

- With long-standing disease, the mucosa may become thinned and flattened because of atrophy.
Microscopic features:
Irrespective of cause or location, the microscopic changes are similar:

- The mucosa is infiltrated by lymphocytes & plasma cells.
- Frequently the lymphocytes are disposed into aggregates i.e. follicles, some with germinal centers.
- Neutrophils may or may not be present.
Several additional histologic features are characteristic; these include

- **Intestinal metaplasia**: the mucosa may become partially replaced by metaplastic columnar cells and goblet cells of intestinal morphology; these may display flat or villous arrangement. If the columnar cells are absorptive (with ciliated border) the metaplasia is termed complete, otherwise it is incomplete.

- **Atrophy** as evidenced by marked loss of the mucosal glands. Parietal cells, in particular, may be absent in the autoimmune form.
**Dysplasia**: with long-standing chronic gastritis, the epithelium develops dysplastic changes. Dysplastic alterations may become so severe as to constitute in situ carcinoma. The development of dysplasia is thought to be a precursor lesion of gastric cancer. It occurs in both autoimmune and H. pylori-associated chronic gastritis.

In those individuals infected by H. pylori, the organism lies in the superficial mucus layer on the surface and within the gastric pits. They do not invade the mucosa. These bacteria are most easily demonstrated with silver or Giemsa (special) stains.
PEPTIC ULCER DISEASE
An ulcer is defined as "a breach in the mucosa of the alimentary tract that extends into the submucosa or deeper." Although they may occur anywhere in the alimentary tract, they are most common in the duodenum and stomach. Ulcers have to be distinguished from erosions. The latter is limited to the mucosa and does not extend into the submucosa.
Peptic Ulcers are chronic, most often solitary lesions and usually small. They occur in any portion of the GIT exposed to the aggressive action of acid-peptic juices. They are located, in descending order of frequency in:

1. Duodenum (first portion)
2. Stomach, (usually antral, along the lesser curve)
3. Gastro-esophageal junction (complicating GERD or Barrett esophagus)
4. Margins of a gastro-jejunostomy
5. Multiple in the duodenum, stomach, and/or jejunum
6. Within or adjacent to a Meckel diverticulum (containing ectopic gastric mucosa)

The male-to-female ratio for duodenal ulcers is 3:1, and for gastric ulcers 2:1. Women are most often affected at or after menopause.
Pathogenesis of peptic ulcers

Peptic ulcers are produced by an imbalance between gastro-duodenal mucosal defenses and the damaging forces, particularly of gastric acid and pepsin.

Hyperacidity is not necessary; only a minority of patients with duodenal ulcers has hyperacidity, and it is even less common in those with gastric ulcers.

H. pylori infection is a major factor in the pathogenesis of peptic ulcer. It is present in virtually all patients with duodenal ulcers and in about 70% of those with gastric ulcers; that is why peptic ulcer disease is now considered infectious in nature. Antibiotic treatment of the infection promotes healing of ulcers and prevents their recurrence.
The possible mechanisms by which this tiny organism impairs mucosal defenses include:

1. *H. pylori* induce intense inflammatory and immune responses. As a result there is increased production of pro-inflammatory cytokines, most notably, IL-8, by the mucosal epithelial cells. This recruits and activates neutrophils with their damaging properties.

2. Several bacterial products cause epithelial cell injury; this is mostly caused by a vacuolating toxin called VacA. *H. pylori* also secrete urease, proteases and phospholipases, which also cause direct epithelial damage.

3. *H. pylori* enhance gastric acid secretion and impair duodenal bicarbonate production, thus reducing luminal pH in the duodenum with its damaging effects on the duodenal mucosa.

4. Thrombotic occlusion of surface capillaries is provoked by a bacterial platelet-activating factor. Thus, an additional ischemic element may contribute to the mucosal damage.
Most persons (80-90%) infected with H. pylori do not develop peptic ulcers. Perhaps there are unknown interactions between H. pylori and the mucosa that occur only in some individuals.

Other factors may act alone or in concert with H. pylori to encourage peptic ulceration:

1. Gastric hyperacidity: this when present, may be strongly ulcerogenic. The classic example is Zollinger-Ellison syndrome, in which there are multiple peptic ulcerations in the stomach, duodenum, and even jejunum. This is due to excess gastrin secretion by a gastrinoma and, hence, excess gastric acid production.

2. Chronic use of NSAIDs: this suppresses mucosal prostaglandin synthesis; aspirin also is a direct irritant.

3. Cigarette smoking: this impairs mucosal blood flow and healing of the ulcer.

4. Corticosteroids: these in high doses and with repeated use encourage ulcer formation.
5. Rapid gastric emptying: this is present in some patients with duodenal ulcers; this phenomenon exposes the duodenal mucosa to an excessive acid load & hence ulcerations

6. Patients with the following diseases are more prone to develop duodenal ulcer exposes
   a. alcoholic cirrhosis
   b. chronic obstructive pulmonary disease
   c. chronic renal failure
   d. hyperparathyroidism.

Chronic renal failure and hyperparathyroidism are associated with hypercalcemia. The latter stimulates gastrin production and therefore acid secretion.

7. Personality and psychological stress seems to be important contributing factors.
Gross features

The vast majority of peptic ulcers are located in the first portion of the duodenum or in the stomach, in a ratio of about 4:1. Gastric and duodenal ulcers may coexist in up to 20% of the cases. Gastric ulcers are predominantly located along the lesser curvature.

Although over 50% of peptic ulcers have a diameter less than 2 cm but about 10% are greater than 4 cm. Ulcerated carcinomas (which tend to be large) may be less than 4 cm in diameter and may be located anywhere in the stomach. Thus, size and location do not differentiate a benign from a malignant ulcer.

The classic peptic ulcer is a round to oval with sharply demarcated crater. The margins are usually level with the surrounding mucosa or only slightly elevated. Heaping-up of these margins is rare in the benign ulcer but is characteristic of the malignant ones.
Peptic ulcers penetrate the wall to a variable extent. When the entire wall is penetrated, the base of the ulcer may be formed by adherent pancreas, omental fat, or liver.

The base of a peptic ulcer is smooth and clean, owing to peptic digestion of any exudate that may form. Sometimes, thrombosed or patent blood vessels (the source of life threatening hemorrhage) are evident at the base of the ulcer.

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.
Microscopic features:

In active ulcers four zones are recognized

1. The base and walls have a superficial thin layer of necrotic fibrinoid necrosis.

2. Beneath this layer is a zone of predominantly neutrophilic inflammatory infiltrate.

3. Deeper still, there is granulation tissue infiltrated with inflammatory cells. This rests on

4. Fibrous or collagenous scar.

H. pylori-associated chronic gastritis is seen in up to 100% of patients with duodenal ulcers and in 70% with gastric ulcers. With present-day therapies aimed at inhibition of acid secretion (H2 receptor antagonists and parietal cell H+/K+-ATPase pump inhibitors), and eradication of H. pylori infection (with antibiotics), most ulcers heal within a few weeks.
The complications of peptic ulcer disease are

1. Bleeding is the most frequent complication (20%). It may be life-threatening; fatal in 25% of the affected patients. It may be the first warning of an ulcer.

2. Perforation is much less frequent (5% of patients) but much more serious being fatal in 60% of patients.

3. Obstruction (from edema or scarring) occurs in 2%, most often due to pyloric channel ulcers but may occur with duodenal ulcers. Total obstruction with intractable vomiting is rare.

4. Malignant transformation does not occur with duodenal ulcers and is extremely rare with gastric ulcers. When it occurs, it is always possible that a seemingly benign gastric ulcer was, from the outset an ulcerative gastric carcinoma.
Acute Gastric Ulceration

Focal, acutely developing gastric mucosal defects are a well-known complication of

1. Therapy with NSAIDs
2. Severe stress (stress ulcers) as in shock states, extensive burns & severe trauma; they usually occur in proximal duodenum (Curling ulcers)
3. Sepsis
4. Raised intracranial pressure or intracranial surgery; these are seen as gastric, duodenal, and esophageal ulcers & are designated as Cushing ulcers, which carry a high incidence of perforation.
Generally, acute ulcers are multiple lesions predominantly gastric but sometimes also duodenal. They range in depth from mere shedding of the superficial epithelium (erosions) to deeper lesions that involve the entire mucosal thickness and deeper (ulceration). Acute ulcers are not precursors of chronic peptic ulcers.
Gross features:

- Acute ulcers are usually small (less than 1 cm) and circular.
- The ulcer base is frequently stained a dark brown by the acid digestion of blood.
- They differ from chronic peptic ulcers by the following:
  1. They are found anywhere in the stomach, and are often multiple
  2. The margins and base of the ulcers are not indurated
  3. The related mucosal folds (rugae) are normal (chronic peptic ulcer, which show convergence on the ulcer).
Microscopically

- There is focal loss of the mucosa & at least part of the submucosa
- Unlike chronic peptic ulcers, there is no chronic gastritis or scarring.
- Healing with complete re-epithelialization occurs after the causative factor is removed.

Bleeding from superficial gastric erosions or ulcers sufficient to require transfusion develops in up to 5% of these patients. If the underlying cause is corrected recovery is complete.
TUMORS OF THE STOMACH

These can be classified as benign and malignant lesions.

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.
CANCERS OF THE STOMACH

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), leiomyosarcoma, and schwannoma.
Gastric Carcinoma is a quite common tumor in the world. There are, however, marked geographical variations in its incidence; it is particularly high in countries such as Japan. It is more common in lower socioeconomic groups. There has been a steady decline in both the incidence and the mortality of gastric cancer. There are mainly two subtypes of carcinoma: intestinal and diffuse. These sub-types appear to have different pathogenetic mechanisms of evolution.
Pathogenesis
The major factors thought to affect the genesis of gastric cancer apply more to the intestinal type, as the risk factors for diffuse gastric cancer are not well defined.

1. *Helicobacter pylori* Infection: this generally increases the risk five-fold. The bacterial infection causes chronic gastritis, followed by atrophy, intestinal metaplasia, dysplasia, and carcinoma. Long-standing mucosal inflammation is associated with damage of epithelial cells, which leads to compensatory epithelial cell proliferation, and hence increased risk of genomic mutation. Since most individuals infected with *H. pylori* do not develop cancer, other factors must be involved in carcinogenesis.
2. **Adenomatous polyps**: 40% of adenomas harbor carcinomatous foci; also adjacent carcinoma is found in relation to adenomatous polyps in 30% of the cases.

3. **Environmental factors**: when families migrate from high-risk to low-risk areas (or the reverse), successive generations acquire the level of risk that prevails in the new environments. The diet is suspected to be a primary factor. Consumption of preserved and salted foods; water contamination with nitrates; and lack of fresh fruit and vegetables are common in high-risk areas. The intake of green, leafy vegetables and citrus fruits, which contain antioxidants such as vitamin C, vitamin E and beta-carotene, seems to play a protective role.

4. **Autoimmune gastritis**, like H. pylori infection, increases the risk of gastric cancer.
Gross features

-The most common location of gastric carcinomas is the pyloric antrum (50%). A favored location is the lesser curvature. Although less common, an ulcerative lesion on the greater curvature is more likely to be malignant.

-Depth of invasion is the most important determinant of prognosis. Early gastric carcinoma is defined as "a lesion confined to the mucosa and submucosa." Advanced gastric carcinoma is a neoplasm extending into the muscular wall.

-The three macroscopic growth patterns of gastric carcinoma, which may be evident at both the early and advanced stages, are: 1. Fungating (exophytic) 2. Flat or depressed 3. Ulcerative (excavated).
Fungating tumors are readily identified by radiography and endoscopy in contrast to flat (depressed) malignancy. Ulcerative cancers may closely mimic chronic peptic ulcers. In advanced cases, there are heaped-up, beaded margins and necrotic bases. The neoplastic tissue extends into the surrounding mucosa and wall; this leads to flattening of the mucosa surrounding the ulcer.

Uncommonly, a broad region of the gastric wall or the entire stomach is extensively infiltrated by malignancy, creating a rigid, thickened "leather bottle," termed linitis plastica.
Microscopic features

There are two main microscopic type of gastric carcinoma; intestinal and diffuse.

The intestinal variant is composed of neoplastic glands with mucin in their lumina. The diffuse variant is composed of mucus-containing cells, which do not form glands, but infiltrate the mucosa and wall as scattered individual and small clusters of cells. In this variant, mucin formation expands the malignant cells and pushes the nucleus to the periphery, creating "signet ring" morphology.
Sometimes, there is excessive mucin production that generates large mucin lakes (mucinous carcinoma).

Infiltrative tumors often evoke a strong desmoplastic reaction (fibrosis), in which the scattered cells are embedded; the fibrosis creates local rigidity of the wall.

Whatever the microscopic type, all gastric carcinomas eventually penetrate the wall to involve the serosa and spread to regional and more distant lymph nodes.
Prognosis
This depends primarily on
1. The depth of invasion and
2. The extent of nodal and distant metastasis
The histologic type (intestinal or diffuse) has minimal independent prognostic significance. The five-year survival rate of surgically treated early gastric cancer is 90%; this drops to below 15% for advanced gastric cancer.
Gastric Lymphomas represent 5% of all gastric malignancies. However, the stomach is 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 Tumors (GISTs) these are thought to originate from the interstitial cells of Cajal (normally control gastrointestinal peristalsis). 95% of GISTs stain with antibodies against c-KIT (CD117). The tumor can protrude into the lumen or extrude on the serosal side of the gastric wall. Microscopically, the tumor can exhibit spindle cells, plump "epithelioid" cells, or a mixture of both. Most of the tumors are quite cellular but mitotic activity is variable.