PATHOLOGY OF THE STOMACH

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Special thanks to Mike Cohen, M.D. and Pier Luigi Di Patre, MD, PhD
READING


AND

THIS Presentation
LEARNING OBJECTIVES

• Etiology, pathogenesis, morphology and clinical manifestations of different types of acute gastritis, including non-erosive, erosive and hemorrhagic.

• Stress ulcers: in what context they develop.

• Etiology, pathogenesis and manifestations of three types of chronic gastritis: H. Pylori, autoimmune and others (radiation, bile reflux, indwelling tubes, systemic diseases).

• Brief overview of H. pylori and epidemiology of H. Pylori infection.

• H. pylori associated diseases: chronic gastritis, peptic ulcer, gastric adenocarcinoma, gastric lymphoma.

• Diagnosis of H. pylori infection: Urea test, serology, biopsy.
MORE LEARNING OBJECTIVES

• Peptic ulcer disease: Definition, epidemiology, gross and microscopic morphology, clinical manifestations and complications, etiopathogenesis.

• Ménétrier disease.

• Zollinger-Ellison syndrome (gastrinoma).

• Gastric adenocarcinoma: Morphological types (intestinal versus diffuse), epidemiology, molecular pathogenesis, staging and treatment.

• Gastric lymphoma, with emphasis on MALToma.

• Gastrointestinal stromal tumor (GIST): Morphology, pathogenesis, clinical features, treatment with tyrosine kinase inhibitors
GASTRIC INFLAMMATORY CONDITIONS
GASTRIC INFLAMMATORY CONDITION TYPES

Active or acute gastritis
- Neutrophils

Chronic (inactive) gastritis
- Plasma cells
- Lymphocytes

Chronic active gastritis

Gastropathy
- Non-inflammatory “inflammatory” conditions?
MUCOSAL DEFENSE

Mucin layer
“Unstirred” layer of fluid
- Neutral pH

Layer of gastric epithelial cells
- Rapid turnover

Acid/base
- Acid excreted into the stomach
- Bicarbonate absorbed into blood vessels

Vessels release substances into to lamina propria
- Bicarbonate
- Oxygen
- Nutrients

Vessels absorb acid
Prostaglandins
MUCOSAL DEFENSE MECHANISMS

**Protective:**  Mucus, bicarbonate, regeneration, blood flow, prostaglandins

**Damaging:**  H. pylori, medications, alcohol, tobacco, ischemia, delayed emptying
Active/Acute Gastritis

Active inflammation versus gastropathy

Active gastritis classically means that acute inflammatory cells (neutrophils) are present.
- Uncommon without an chronic inflammatory component (chronic/active).

Gastropathy typically is associated with new inflammatory cells
- Edema
- Scant acute inflammatory cells
- Vascular congestion
- Erosions
- Hemorrhage
- Fibrin
- Reactive epithelial changes
“ACTIVE/ACUTE GASTRITIS”: CAUSES

Most frequent causes:
- Helicobacter pylori
- Drugs (NSAIDs), alcohol

Others:
- Ingestion of corrosive substances
- Uremia
- Radiation
- Chemotherapy
- Gastric tubes
- Bile reflux
- Major stress: trauma, shock, burns
DISRUPTION OF PROTECTIVE MECHANISMS

H. pylori - urease secreting with loss of bicarbonate
NSAIDs – COX dependent prostaglandin synthesis (COX-1 versus COX-2)
Age – reduced mucin and bicarbonate
Altitude – reduced oxygen
Harsh chemicals, alcohol, chemotherapy – direct mucosa injury
STRESS ULCERS (STRESS-RELATED MUCOSAL DISEASE)

- Shock, burn, head trauma, sepsis
  - Bleeding or perforation
- Curling ulcers - severe burns: Due to loss of plasma
- Cushing ulcers - closed head injury and increased intracranial pressure
  - Activation of vagal nuclei acid secretion
- Role of PPI or H₂ blockers
- RX underlying condition

From Cushing's original article describing 3 patients who died of perforated ulcer after neurosurgery. Focal hemorrhages and 3 large perforations.

ACUTE/ACTIVE GASTRITIS: CLINICAL MANIFESTATIONS

Epigastric discomfort, gnawing/burning pain
Loss of appetite
Nausea, vomiting, bloating
Hematemesis or melena if significant bleeding present

*H. pylori*: Often asymptomatic
NORMAL STOMACH

Endoscopy

Histology
“ACUTE/ACTIVE GASTRITIS”: NON-EROISIVE, EROISIVE, HEMORRHAGIC

Mild acute gastritis
Mild erythema and scattered tiny erosions
Intraepithelial neutrophils

Moderate acute erosive gastritis:
Multiple erosions (red spots)

Severe acute hemorrhagic gastritis


**Reactive Gastropathy** – scant inflammation, hyperplastic epithelium, vascular ectasia

**Erosive Gastropathy** – loss of surface epithelium, fibrin deposition along the surface
CHRONIC AND CHRONIC ACTIVE GASTRTIS
CHRONIC (INACTIVE) GASTRITIS

Helicobacter pylori

Autoimmune gastritis

Other causes: Radiation, chronic bile reflux, indwelling tubes, systemic diseases, idiopathic
HELICOBACTER PYLORI

Gram-negative, spiral shaped, flagellate, microaerophilic bacterium
Predominately in gastric antrum
Lives within the mucus layer
Transmission: oral-oral, fecal-oral
Survives in the acidic gastric
• urease
• adhesins
• flagella
Proteases and phospholipases break down mucus
Variable virulence, host defense and inflammatory factors

\[
\text{C}=\text{O(NH}_2\text{)2} + \text{H}^+ + 2\text{H}_2\text{O} \overset{\text{urease}}{\rightarrow} \text{HCO}_3^- + 2 \text{NH}_4^+
\]

Barry J. Marshall
H. PYLORI: EPIDEMIOLOGY

Prevalence of H. pylori infection correlates with poverty, household crowding, lack of education, i.e. low socio-economic status.

Prevalence increases with age: 50% over age 60, 20% below age 40.

In poor countries, infection is acquired in childhood.
H. PYLORI: ASSOCIATED DISEASES

Most infected individuals are asymptomatic (80%)

Diseases associated with H. pylori infection:
- Chronic (active) gastritis
- Peptic ulcer
- Atrophic gastritis
- Gastric adenocarcinoma
- Gastric lymphoma

Acquire duodenal ulcer at a rate of 1% per annum

Nearly all patients with duodenal ulcer have H. pylori

Green square: uninfected people
Circle: total number of infected people
**H. PYLORI: CHRONIC (ACTIVE) GASTRITIS**

**Endoscopy:**
- Erythema
- Nodular appearance of mucosa
- Thickening of rugae

**Pathology:**
- Intraepithelial neutrophils
- Interstitial plasma cells and fewer lymphocytes
- H. Pylori on the surface (H&E and special stains)
- Patchy distribution
- Not commonly seen on intestinal metaplastic or duodenal mucosa
CHRONIC (ACTIVE) GASTRITS
**H. PYLORI: DIAGNOSIS**

Breath urea test

Circulating antibodies (serology)

Esophagogastroduodenoscopy and biopsy

Stool antigen
H. PYLORI: HISTOLOGICAL IDENTIFICATION

IMMUNOHISTOCHEMISTRY

SILVER

GIEMSA

MCMULLEN

From: J Clin Pathol, 2000, 53: 756
H. PYLORI: TREATMENT

Combinations of antibiotics and proton pump inhibitors

Relapses and re-infection can occur

Vaccine – therapeutic and prophylactic (developmental stage)
AUTOIMMUNE GASTRITIS — 1

Second most frequent form of chronic gastritis

Autoimmune process targeting parietal cells and intrinsic factor:
  - **Autoantibodies** to parietal cells and IF present early
  - Injury mediated by **CD4+ lymphocytes**, not autoantibodies

**Chronic inflammation** of mucosa (picture) with mucosal **atrophy** in body/fundus
  - Antrum and cardia unaffected, in contrast to H. pylori gastritis
AUTOIMMUNE GASTRITIS

Pathophysiology: **Hypochlorydria**
- Compensatory hyperplasia of G-cells in the antrum
- Carcinoids often develop

**Vitamin B12 deficiency:**
- **Pernicious anemia** (megaloblastic)
- Neurologic disease
- Atrophic glossitis

**Intestinal metaplasia** in atrophic mucosa, leading to risk of adenocarcinoma

Disease develops over decades
Diagnosis made around 60

Intestinal metaplasia: Note goblet cells

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Mucosal Arophy and Intestinal Metaplasia

Long standing gastritis
- Autoimmune gastritis
- Helicobacter pylori

Loss of parietal cell mass

Intestinal metaplasia (goblet cells)

Increased risk of adenocarcinoma
- Possibly due to bacterial overgrowth
- Carcinogenic nitrosamines
Mucosal Arophy and Intestinal Metaplasia

Unremarkable gastric fundic mucosa

Early intestinal metaplasia

Severe atrophic gastritis
CHRONIC GASTRITIS: OTHER TYPES

**Eosinophilic gastritis**
- Allergic reaction (cow’s milk, soy protein)
- Immune disorders

**Lymphocytic gastritis**
- Associated with celiac sprue

**Granulomatous gastritis**
- Infection
- Sarcoidosis
- Crohn disease
- Idiopathic
Mucosal Arophy and Intestinal Metaplasia

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PEPTIC ULCER DISEASE
PEPTIC ULCER DISEASE (PUD)

Lifetime risk of developing PUD is 10% for men, 4% for women
Estimated number of people with active PUD: 4 million
Duodenal:Gastric PUD is 4:1
H. pylori associated with 65% gastric and near 100% duodenal disease

From The Helicobacter Foundation
**PEPTIC ULCER**

- **Gross features:**
  - Solitary, well-circumscribed mucosal defect
  - Flat margins and smooth base
  - Depth up to muscularis propria
- **Histology:** 4 layers
  - 1) Superficial fibrinous exudate,
    - 2) acute and chronic inflammation,
    - 3) granulation tissue,
    - 4) fibrosis
- **Healing leads to** scar
Malignant transformation of peptic ulcers is rare

Gastric cancer often presents as an ulcerated mass

“Malignant ulcers” have heaped-up margins and irregular base

Gastric ulcers should always be biopsied to rule out cancer
PEPTIC ULCER VERSUS ULCERATED CANCER

Above – **Peptic ulcer.** Note adjacent benign mucosa and base with exudate, granulation tissue and benign gastric wall

Right – **Ulcerated gastric cancer.** Note minimal exudate, no granulation tissue and base of malignant glands
PEPTIC ULCER: LOCATION

- **Gastric ulcers** along lesser curvature at junction between body and antrum
- **Duodenal ulcers** located in the duodenal bulb within a few cm from pylorus on anterior surface
PEPTIC ULCER: CAUSES

In total (duodenal + gastric ulcers) 70% of patients with PUD have H. pylori
- Fewer than 20% of people with H. pylori develop PUD

Other etiologic factors:

**NSAIDS and corticosteroids:** Inhibit prostaglandin synthesis

**Smoking:** Reduces mucosal blood flow

**Psychological stress:** Increases acid production

**Genetic predisposition**

**Cirrhosis, COPD, chronic renal failure, hyperparathyroidism:** Unclear mechanisms
Epigastric gnawing, burning **pain** related to mealtimes

**Onset of pain** in relation to meals depends on location, duodenal versus gastric:
- **DU**: 30 min to 3 hour after meal, relieved by antacids or food
- **GU**: immediately before or during meal, precipitated by food

**Dyspeptic symptoms**: Bloating, nausea, vomiting

**Weight**: Loss in gastric ulcers. **Gain** in duodenal ulcers

Hematemesis, melena: **Anemia**
PEPTIC ULCER: COMPLICATIONS

• **Perforation:** Acute, life-threatening

• **Bleeding:**
  – From small vessels: Chronic bleeding, iron-deficiency anemia
  – From large vessels: Melena, hematemesis, shock

• **Gastric outlet obstruction:** Ulcers in distal stomach and duodenal bulb may cause reversible obstruction by edema or fixed stenosis by scarring

• **Penetration** into adjacent organs, liver and pancreas
OTHER GASTRIC CONDITIONS
MÉNÉTRIER DISEASE
(HYPERPLASTIC HYPERSECRETORY GASTROPATHY)

Due to hyperproduction of $\text{TGF-}\alpha$

Hyperplasia of foveolar epithelium in body/fundus

**Thickening of rugae**, with cerebriform appearance

Excessive protein secretion leading to **protein-losing enteropathy**

Weight loss, diarrhea, edema

Increased risk of **adenocarcinoma**

Supportive treatment
ZOLLINGER-ELLISON SYNDROME

- Caused by a gastrinoma, gastrin-secreting neuroendocrine tumor
- Usually in the pancreas or small intestine
- Leads to hyperplasia of parietal cells and hyperchlohydria
- Multiple gastric and duodenal ulcers, chronic diarrhea
- Two thirds of gastrinomas are malignant but slow-growing
- 25% associated with MEN I

Gastrinoma: Uniform epithelial cells with round nuclei and finely dispersed chromatin ("salt-and-pepper")
TUMOR NEOPLASMS
NEOPLASTIC PATHOLOGY OF STOMACH

- Polyps
- Adenocarcinoma
- Lymphoma
- Gastrointestinal stromal tumor (GIST)
GASTRIC POLYPS: 3 TYPES

A. Hyperplastic/inflammatory: Most common, chronic gastritis, unlikely malignant transformation

B. Fundic type: Found in FAP and PPI treatment; no malignant potential

C. Adenomatous: Neoplastic type, with dysplasia (low, high), malignant potential related to degree of dysplasia and size
GASTRIC ADENOCARCINOMA

90% of gastric malignant tumors

Initial symptoms: Non-specific dyspepsia

Advanced stage: Weight loss, anemia

Incidence varies widely throughout the world

Screening is cost-effective in high-incidence countries

Incidence in Western countries dropped in 20th century

Migrants acquire the risk of country to where they move

ADENOCARCINOMA: 2 TYPES

**Intestinal type**
- Ulcerated mass

**Diffuse type**
- Leather bottle

**Histological features**
- Gland formation
- Signet-ring cells
Intestinal type (90%)

Bulky, ulcerated tumors

Glandular structures

Associated with known risk factors: H. pylori, atrophic gastritis, intestinal metaplasia/dysplasia, adenomatous polyps

Predominates in high-risk areas

Diffuse type (10%)

Diffusely infiltrative, with desmoplastic reaction: *Linitis plastica*

Non-cohesive signet-ring cells

Not associated with H. pylori or other risk factors

Uniform incidence across countries
GASTRIC CARCINOMA: HISTOLOGY

Intestinal Type

Diffuse Type
ADENOCARCINOMA: EPIDEMIOLOGY

Epidemiology supports strong role of environmental factors

H. pylori found in 2/3 of cases

Other risk factors: Smoking and alcohol, atrophic (autoimmune) gastritis, low socioeconomic status

Dietary carcinogens: N-nitroso compounds, benzopyrene

Protective factors: Vegetables, citrus fruits containing Vitamin C and E, beta-carotene
Intestinal and diffuse types follow different pathogenetic pathways

**Diffuse type:** CDH1 mutations with loss of E-cadherin function (cell adhesion) key event in diffuse type

**Intestinal type:** Increased risk in FAP, mutations of β-catenin (intracellular signal transducer involved in growth regulation), p53 mutations, polymorphisms of pro-inflammatory genes
**GASTRIC ADENOCARCINOMA: STAGING AND TREATMENT**

**Stage** most important prognostic factor:
- **Depth of invasion** and **nodal/distant mets**

Early stages, limited to mucosa and submucosa: 90% 5-year survival

Early gastric cancer can be treated with **endoscopic mucosal resection**

Advanced stages: 20% 5-year survival

Overall 5-year survival rate: <30%

**Treatment:** Surgery plus combination of radiation and chemotherapy

**Trastuzumab** (Herceptin), a monoclonal antibody that inactivates HER2/neu receptors, approved in 2010 for treatment of gastric adenocarcinoma
GI tract is the most frequent site of extranodal lymphomas

Lymphoma represents 5% of gastric malignant tumors

Majority of lymphomas are derived from Mucosa-Associated Lymphatic Tissue (MALT) and are thus called MALTomas

- It’s an extranodal marginal-cell lymphoma
MALTOMAS: PATHOGENESIS

Arise at sites of **chronic inflammation**, most commonly due to H. pylori

**EARLY STAGE:** Reversible

- Antigen-dependent activation of **NF-κB**, a growth-promoting transcription factor, through increased expression of MLT and BCL-10 genes
- Antibiotic treatment of H. pylori infection results in remission of MALToma

**LATE STAGE:** Irreversible

- Specific translocations lead to **constitutive** activation of **NF-κB**
- MALTomas will not regress with antibiotic treatment
MALTomas: Morphology

MALTomas are B-cell lymphomas

Dense lymphocytic infiltrate expanding the lamina propria

Neoplastic lymphocytes surround and infiltrate glands producing typical lymphoepithelial lesions

Slow-growing, eventually transform into high-grade lymphomas (diffuse large B-cell lymphoma)
GASTRO-INTESTINAL STROMAL TUMOR (GIST)

GIST is the most common non-epithelial tumor of the stomach. Other non-epithelial tumors: leiomyoma, schwannoma. All 3 look similar histologically: Spindle-cell tumors. GIST occurs in the 50s-60s. Children with GIST usually have Carney triad (gastric GIST, paraganglioma, pulmonary chondroma). Don’t make confusion with Carney Syndrome, autosomal dominant, cardiac myxoma, skin hyperpigmentation, endocrine overactivity.
GIST: PATHOGENESIS

GIST originates from \textit{interstitial cells of Cajal}, pacemaker cells in the muscularis propria

Two genes are mutated in GIST

- \textbf{c-KIT} (AKA CD117), a tyrosine kinase receptor for \textit{stem cell factor}, in 90\% of cases

  OR

- \textbf{PDGFRA}: Platelet-derived growth factor receptor \( \alpha \), a tyrosine kinase related to \textbf{c-KIT}, in 8\% of cases
GIST: MORPHOLOGY

- Solitary, well-demarcated tumor covered by intact or ulcerated mucosa
- Can grow to large size
- Histologically, most tumors are composed of spindle-shaped cells arranged in long fascicles
- Markers
  - CD34
  - CD 117 (c-Kit)
  - DOG1
DD: GIST, LEIOMYOMA, SCHWANNOMA

GIST: positive for CD-117

Leiomyoma: Positive for smooth muscle actin

Schwannoma: Positive for S-100
Anemia is the most frequent presenting sign, due to mucosal ulceration and bleeding

Vague abdominal pain, feeling of fullness, vomiting

Late stage: Metastases to the liver and peritoneal cavity

Prognosis: Size, mitoses, location

Treatment: Surgical removal, commonly by laparoscopic surgery

For unresectable and metastatic tumors, treatment with selective **tyrosine kinase inhibitors:**

- Imatinib (Gleevec), sunitinib (Sutent)
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