Systemic pathology

**PATHOLOGY OF THE GIT**

## THE ORAL CAVITY & OROPHARYNX

Many pathological processes can affect the constituents of the oral cavity.

1. **PROLIFERATIVE LESION**;Irritation fibroma , ossifying fibroma, pyogenic granuloma , peripheral giant cell `
2. granuloma
3. **INFLAMMATERY ULCERATION**; traumatic ,aphthous, herpetic
4. **INFECTIONS ;**Herpes simplex infections, oral candidiasis (thrush) ,deep Fungal Infections .

## THE TUMOR AND PREMALIGNANT LESIONS

***Leukoplakia*** is a white patch that cannot be scraped off and cannot be attributed clinically or microscopically to any other disease i.e. if a white lesion in the oral cavity can be given a specific diagnosis it is not a leukoplakia. As such, white

patches caused by entities such as candidiasis are not leukoplakias. *All*

*leukoplakias must be considered precancerous (have the potential to progress to squamous cell carcinoma) until proved otherwise through histologic evaluation.*

***Erythroplakias*** are red velvety patches that are much less common, yet much more serious than leukoplakias. The incidence of dysplasia and thus the risk of complicating squamous cell carcinoma is much more frequent in erythroplakia

compared to leukoplakias. Both leukoplakia and erythroplakia are usually found between ages of 40 and 70 years, and are much more common in males than females. The use of tobacco (cigarettes, pipes, cigars, and chewing tobacco) is

the most common incriminated factor.

#### Squamous cell carcinoma

The vast majority (95%) of cancers of the head and neck are squamous cell carcinomas; these arise most commonly in the oral cavity.

## ESOPHAGUS

The main functions of the esophagus are to:

1. Conduct food and fluids from the pharynx to the stomach
2. Prevent reflux of gastric contents into the esophagus.

These functions require motor activity coordinated with swallowing.

## CONGENITAL ANOMALIES

Several congenital anomalies affect the esophagus including:

1. the presence of ***ectopic*** gastric mucosa & pancreatic tissues within the esophageal wall.
2. ***congenital cysts*** *&****congenital herniation*** of the esophageal wall into the thorax.
3. The ***atresia****,* a segment of the esophagus is represented by only a noncanalized cord, with the upper pouch connected to the bronchus or the trachea and a lower pouch leading to the stomach.
4. ***Mucosal webs*** are shelf-like, eccentric protrusions of the mucosa into the esophageal lumen. These are most common in the upper esophagus. The triad of upper esophageal web, iron-deficiency anemia, and glossitis is referred to as ***Plum mer-Vinson syndrome***.
5. ***Esophageal rings*** unlike webs are concentric plates of tissue protruding into the lumen of the distal esophagus.

Episodic dysphagia is the main symptom

1. ***Stenosis*** consists of fibrous thickening of the esophageal wall. Although it may be congenital, it is more frequently the result of severe esophageal injury with inflammatory scarring, as from gastroesophageal reflux disease (GERD), radiation, scleroderma and caustic injury. Stenosis usually manifests as

progressive dysphagia , at first to solid food but eventually to fluid as well.

# Esophagitis

This term refers to inflammation of the esophageal mucosa. It may be caused by a variety of physical, chemical, or biologic agents.

***Reflux Esophagitis (Gastroesophageal Reflux Disease or GERD)*** is the most important cause of esophagitis and signifies esophagitis associated with reflux of gastric contents into the lower esophagus. The action of gastric juices is vital to

the development of esophageal mucosal injury.

#### Gross (endoscopic) features

These depend on the causative agent and on the duration and severity of the exposure.

Mild esophagitis may appear grossly as simple hyperemia. In contrast, the mucosa in severe esophagitis shows confluent erosions or total ulceration into the submucosa.

#### Microscopic features

Three histologic features are characteristic:

1. Inflammatory cells including eosinophils within the squamous mucosa.
2. Basal cells hyperplasia
3. Extension of lamina propria papillae into the upper third of the mucosa.

The clinical manifestations consist of dysphagia, heartburn, regurgitation of a sour fluid into the mouth, hematemesis, or melena. Rarely, there are episodes of severe chest pain that may be mistaken for a "heart attack."

## TUMORS

### Benign Tumors

*Leiomyomas*are the most common benign tumors of the esophagus.

### Malignant Tumors

Carcinomas of the esophagus (5% of all cancers of the GIT) have, generally, a poor prognosis because they are often discovered too late. Worldwide,

squamous cell carcinomas constitute 90% of esophageal cancers, followed by adenocarcinoma.

Other tumors are rare.

## STOMACH

In developed countries, peptic ulcers occur in up to 10% of the general population. Chronic infection of the gastric mucosa by the bacterium Helicobacter 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.

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

### 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)

#### 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 evidecnced 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.

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.

1. Several bacterial products cause epithelial cell injury.
2. 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.
3. 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.

1. Chronic use of NSAIDs: this suppresses mucosal prostaglandin synthesis; aspirin also is a direct irritant.
2. Cigarette smoking: this impairs mucosal blood flow and healing of the ulcer.
3. Corticosteroids: these in high doses and with repeated use encourage ulcer formation.
4. 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

1. Patients with the following diseases are *more prone to develop duodenal ulcer*

exposes

* 1. alcoholic cirrhosis
  2. chronic obstructive pulmonary disease
  3. chronic renal failure
  4. hyperparathyroidism.

1. Personality and psychological stress seems to be important contributing factors.

### Gross features

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,2 to 4cm in diameter.

### 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.

### 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.

1. ***Malignant transformation*** does not occur with duodenal ulcers and is extremely rare with gastric ulcers.

## 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 obligate

## 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.

## IDIOPATHIC INFLAMMATORY BOWEL DISEASE (IBD)

The two disorders known as inflammatory bowel disease (IBD) are Crohn's

disease (CD) and ulcerative colitis (UC). These diseases have distinctly different clinical and pathological features. Both CD and UC are chronic, relapsing inflammatory disorders of obscure origin. CD is an autoimmune disease that may affect any portion of the gastrointestinal tract from mouth to anus, but most often involves the distal small intestine and colon. UC is a chronic inflammatory disease limited to the rectum and colon. Both exhibit extra-intestinal inflammatory manifestations*.*

#### Etiology and Pathogenesis

In the normal GIT, the mucosal immune system is always ready to respond against ingested pathogens but is unresponsive to normal intestinal microflora.

The exact cause (s) leading to the above is still not established, hence the designation idiopathic. It is postulated that IBD result from exaggerated local immune responses to microflora in the gut, in genetically susceptible individuals.

Thus, the pathogenesis of IBD involves

1. Failure of immune regulation
2. Genetic susceptibility
3. Environmental triggers specifically microbial flora.

### Crohn Disease

#### Pathological features

When fully developed, Crohn disease is characterized pathologically by

1. Sharply segmental and typically transmural involvement of the bowel by an inflammatory process with mucosal damage
2. The presence of
   * Small noncaseating granulomas
   * Deep fissures that may eventuate in the formation of fistulae

#### Clinical Features

The disease usually begins with intermittent attacks of diarrhea, fever, and abdominal pain, spaced by asymptomatic periods lasting for weeks to many months. In those with colonic involvement, occult or overt fecal blood loss may lead to anemia.

#### Extraintestinal manifestations of this disease include

1. Arthritis & finger clubbing
2. Red nodules of the skin
3. Primary sclerosing cholangitis.
4. Renal disorders
5. Systemic amyloidosis
6. An increased incidence of cancer of GIT in patients with long standing progressive CD.

## ULCERATIVE COLITIS

In contradistinction to CD, ulcerative colitis is a chronic ulcero-inflammatory disease limited to the colon and affecting only the mucosa and submucosa; it extends in a continuous fashion proximally from the rectum. Well-formed

granulomas are absent. However, like CD, UC is a systemic disorder associated in some patients with arthritis, uveitis, hepatic involvement (primary sclerosing cholangitis), and skin lesions. The onset of disease peaks between ages 20 and 25 years***.***

#### Microscopic features

The basic mucosal alterations in UC are similar to those of colonic CD, with inflammation, chronic mucosal damage, and ulceration.

There is diffuse, predominantly chronic inflammatory infiltrate in the lamina propria.

Neutrophilic infiltration of the epithelial layer may produce crypt abscesses.

The latter are not specific for UC and may be observed in CD or any active inflammatory colitis.

Unlike CD, there are no granulomas.

Destruction of the mucosa leads to broad-based ulcerations that are superficial

i.e. extending at most into the submucosa.

Isolated islands of regenerating mucosa bulge upward to create pseudopolyps. Features of chronic but healed (inactive) disease include submucosal fibrosis;

mucosal architectural distortion and atrophy

### Tumors of the Colon and Rectum

*Non-neoplastic and benign neoplastic lesions of the colo-rectum are collectively known as polyps,* which are common in the older adult population. Epithelial

polyps that arise as the result of proliferation and dysplasia are termed

*adenomatous polyps* (adenomas). They are precursors of carcinoma.

### Hyperplastic Polyps

These are the most common polyps of the colon and rectum. They are small (usually <5 mm in diameter) and appear as smooth protrusions of the mucosa. They are often multiple and consists of well-formed glands and crypts lined by non-neoplastic epithelial cells.

### Adenomas (Adenomatous polyps)

Adenomas are intraepithelial neoplasms that range from small, often pedunculated lesions to large neoplasms that are usually sessile. The prevalence of colonic adenomas increases progressively with age. Males and females are affected equally. .

All adenomas by definition arise as the result of dysplastic epithelial proliferation. The dysplasia ranges from low-grade to high-grade. There is *strong evidence that adenomas are precursors for invasive colorectal adenocarcinomas.*

## COLORECTAL CARCINOMA

Most carcinomas arise from preexisting adenomas. A great majority (98%) of all cancers in the large intestine are adenocarcinomas. The peak incidence for colorectal cancer is 60 to 70 years of age; fewer than 20% of cases occur before

the age of 50 years. .Both genetic and environmental influences contribute to the development of colorectal cancers. When colorectal cancer is found in a young person, preexisting ulcerative colitis or one of the polyposis syndromes must be suspected.

Tumors in the proximal colon tend to grow as polypoid, exophytic masses that extend along one wall of the capacious cecum and ascending colon .

Obstruction is uncommon .

All colon carcinomas are microscopically similar. Almost all are

adenocarcinomas that range from well-differentiated to undifferentiated, frankly anaplastic masses. Many tumors produce mucin, which is secreted into

the gland lumina or into the interstitium of the gut wall. Because these secretions dissect through the gut wall, they facilitate extension of the cancer and worsen

the prognosis. Cancers of the anal zone are predominantly squamous cell in origin.