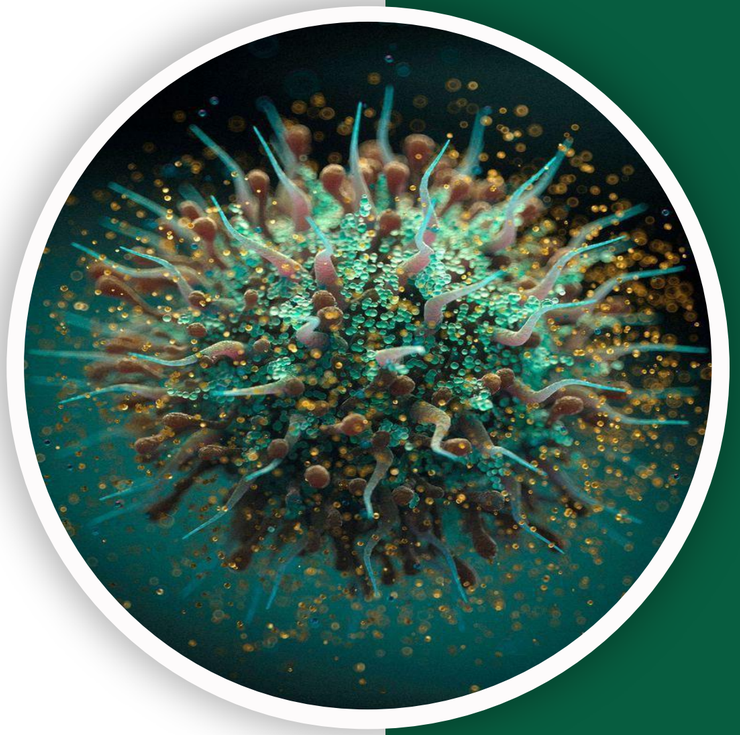
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

GIS Pathology | MID 2

Esophageal diseases 2



Written by : DST

Reviewed by : Bushra Masalha

Abdallah Hindash

Diseases of the Esophagus 2

Manar Hajeer, MD, FRCPath

University of Jordan, School of medicine

Diseases that affect the esophagus

- **1. Obstruction: mechanical or functional.** (Discussed in the previous lecture)
- **2. Vascular diseases: varices.** (Discussed in the previous lecture)
- **3. Inflammation: esophagitis.**
- **4. Tumors.**

Reflux Esophagitis
Gastroesophageal reflux disease, GERD

- Reflux of gastric contents into the lower part of the esophagus
- Most frequent cause of esophagitis
- Most common complaint by patients visiting the outpatient clinics.
- The stratified squamous epithelium of the esophagus is sensitive to the acids that are carried in the gastric juice, which reach the lower part of the esophagus in a recurrent reflex of these contents.
- Protective forces: mucin and bicarbonate from submucosal glands, high LES tone (Lower esophageal Sphincter).
- The submucosal glands of the proximal and distal esophagus contribute to mucosal protection by secreting mucin and bicarbonate. More importantly, constant LES tone prevents the reflux of acidic gastric contents, which are under positive pressure.

Pathogenesis:

- **Decreased lower esophageal sphincter tone**

  (alcohol, tobacco, hiatal hernia, CNS depressants)

  A hiatal hernia occurs when part of the stomach herniates through the diaphragm and enters the thoracic cavity, leading to a decrease in LES tone and increased reflux of contents into the lower esophagus.

  Congenital hiatal hernias are recognized in infants and children, but many are acquired in the later life hiatal hernia is asymptomatic in more than 90% of adult cases. Thus, symptoms which are similar to GERD, are often associated with other cases of lower esophageal sphincter incompetence.

- **Increase abdominal pressure** -(Increase intracranial pressure)

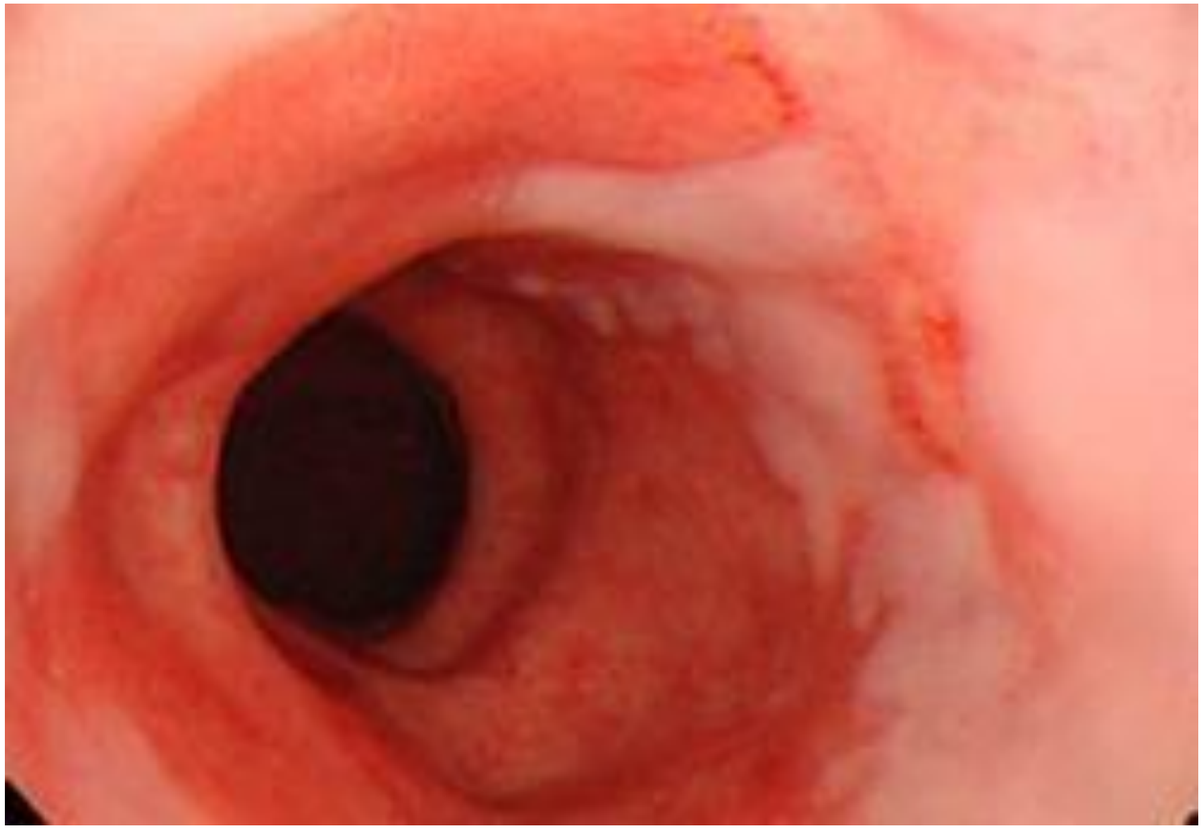
  (obesity, pregnancy, delayed gastric emptying, and increased gastric volume)

- **Idiopathic!!**

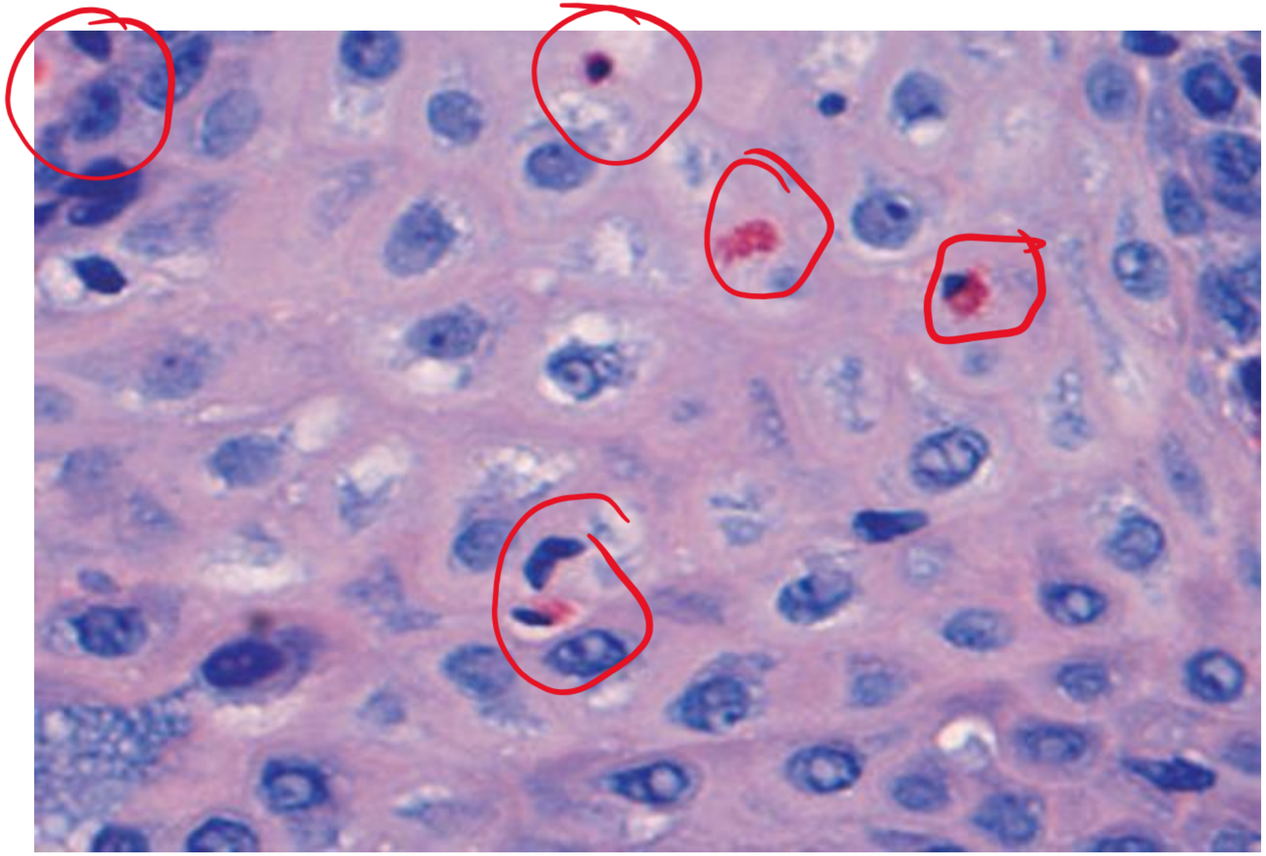
MORPHOLOGY:

- **Macroscopy (endoscopy)**
  - Depends on severity (in mild GERD, the mucosal histology is often Unremarkable, **with no changes, or could have** Simple erythema **and redness due to the inflammation**).
- **Microscopic:**
  - Eosinophils infiltration **of the squamous epithelium (Earliest Manifestation)**
  - **Followed by** neutrophil **infiltration** later (**in** more severe **cases**).
  - Basal zone hyperplasia **of the basal squamous epithelial cells.**
  - **Basal zone hyperplasia** is the **thickening of the basal cell layer** of the epithelium. It occurs when the basal layer (normally confined to a small portion of the epithelium) expands to occupy more than **15–20% of the total epithelial thickness**.
  - Elongation of lamina propria papillae. This happens due to **chronic injury and regeneration**, where these papillae reach the upper 2/3 of the epithelium or even the surface to increase the blood supply and support for the regeneration of the epithelium.
  - **If two of these findings are observed on microscopic examination of biopsies taken from the esophagus, the diagnosis of reflux esophagitis can be strongly supported, along with clinical symptoms and endoscopic findings.**

This image shows erythema of the lower esophagus in a patient with reflux esophagitis.



The cells with granular eosinophilic cytoplasm are identified as **eosinophils**, which are commonly seen in reflux esophagitis as scattered interepithelial eosinophils.



Clinical Features:

- Most common over 40 years.
- May occur in infants and children
- Heartburn (Burning sensation in the epigastric area).
- Dysphagia (difficulty in swallowing).
- Regurgitation of sour-tasting gastric contents, which may reach the mouth in severe cases.
- Rarely: severe chest pain, mistaken for heart disease (acute myocardial infarction, MI), particularly when patients present to the emergency room.

- Tx: proton pump inhibitors to decrease the acid secretion.

Complications:

- Esophageal ulceration, causing peptic ulcerations.
- Hematemesis, which is the vomiting of blood.
- Melena occurs when blood from upper gastrointestinal bleeding passes through the stomach, where it is altered by stomach acid, resulting in black, tarry stools.
- Strictures and stenosis can develop in patients with recurrent and long-standing reflux esophagitis, as the healing of chronic inflammation may involve fibrosis, leading to narrowing the lumen of esophagus.
- Barrett's esophagus, which is a condition characterized by intestinal metaplasia of the esophagus, which is considered a precursor to esophageal adenocarcinoma.

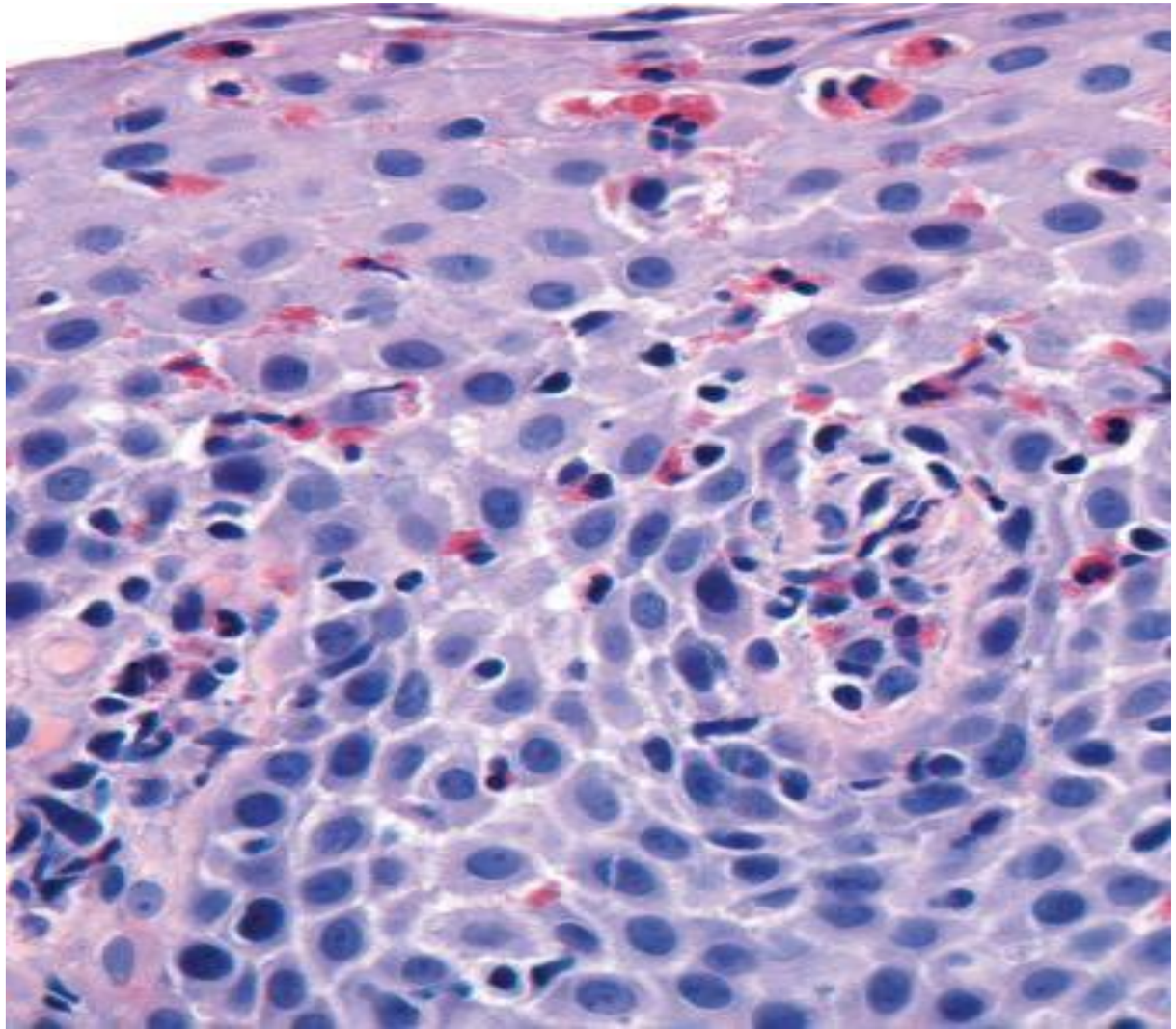
Eosinophilic Esophagitis

- **Characterized by extensive eosinophilic infiltration of the squamous epithelium.**
- Chronic immune mediated disorder
- **Symptoms (variable):**
  - Food impaction and dysphagia in adults
  - Feeding, food allergies, or GERD-like symptoms in children.
  - Patients typically present to outpatient clinics as irritable children with recurrent vomiting. Differentiating between GERD and eosinophilic esophagitis is crucial for proper diagnosis and management.
- **Morphology:**
  - In the classical cases(esosinophilic esophagitis), we might see rings in the upper and mid esophagus, while in reflexes esophagitis affect the lower part of esophagus.
  - Numerous eosinophils in the epithelium(see much more than in reflex esophagitis). The cardinal histologic feature is epithelial infiltration by a large number of eosinophils, particularly in the superficial layers and at sites distant from the gastroesophageal junction.
- **Far from the GEJ.**

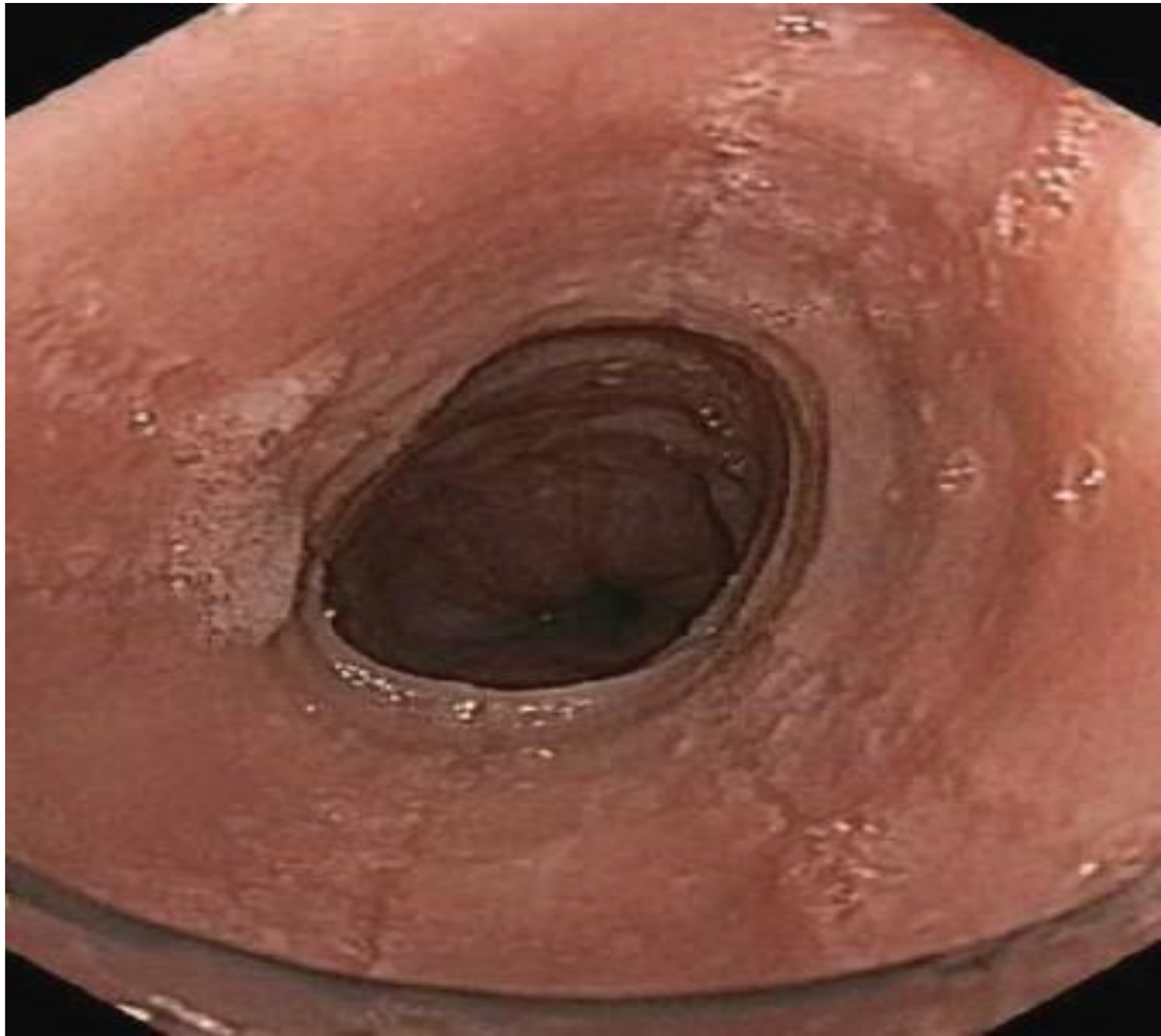
  - These findings can help differentiate between GERD and eosinophilic esophagitis, as they are treated with different approaches.

1
1

Eosinophilic esophagitis characterized by numerous eosinophils infiltrating the squamous epithelium.



The endoscopic appearance reveals esophageal rings, which can cause symptoms such as dysphagia and food impaction in the patient.



1
2

Management:

- Most patients are atopic and typically exhibit other atopic manifestations—such as atopic dermatitis (eczema), allergic rhinitis, or asthma—and may also have modest peripheral eosinophilia, defined as an elevated eosinophil count on peripheral blood examination.
- Refractory to PPIs; patients will not respond, the symptoms will not be alleviated.
- **Treatment:**
  - Dietary restrictions focus on eliminating foods that provoke symptoms, such as cow's milk (particularly in children) and soy products.
  - Topical or systemic corticosteroids.

Extra table for comparison

Feature	Eosinophilic Esophagitis (EoE)	Gastroesophageal Reflux Disease (GERD)
Clinical Presentation	- Dysphagia (especially solids) - Food impaction - History of atopy (asthma, eczema, allergic rhinitis) - Affects young males commonly - Poor response to PPIs alone	- Heartburn (burning sensation) - Regurgitation of sour-tasting gastric contents -Most common over 40 years. May occur in infants and children - Usually improves with PPIs
Endoscopic Findings	- Rings ("trachealization" of esophagus) - Linear furrows - White exudates (eosinophilic microabscesses) - Narrow-caliber esophagus	- May appear normal or show signs of erosive esophagitis - Mucosal erythema or ulcers - Hiatal hernia may be present - Less likely to have rings or furrows
Histologic Findings	- ≥15 eosinophils per high-power field (HPF) - Eosinophilic microabscesses - Superficial layering of eosinophils - Inflammation often patchy	- Usually <15 eosinophils/HPF - Basal zone hyperplasia and elongation of papillae - Mild eosinophilia may be present - More diffuse inflammation pattern

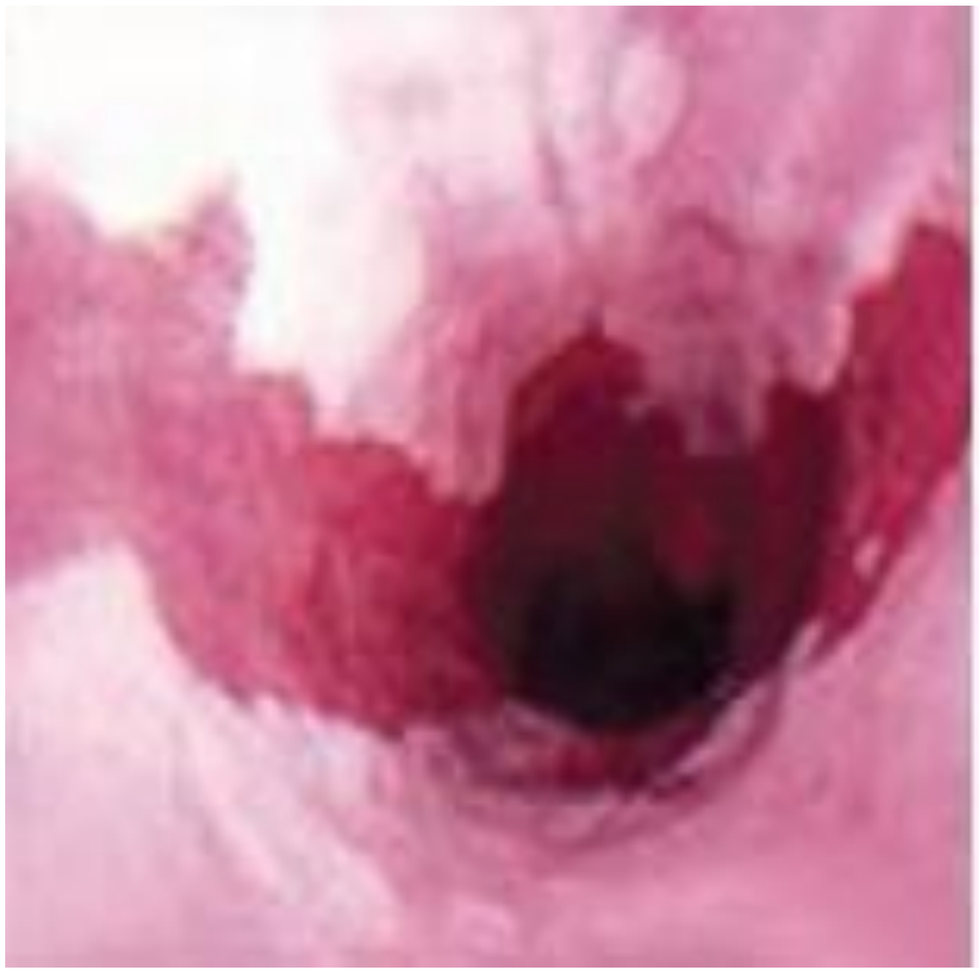
5-Barrett Esophagus

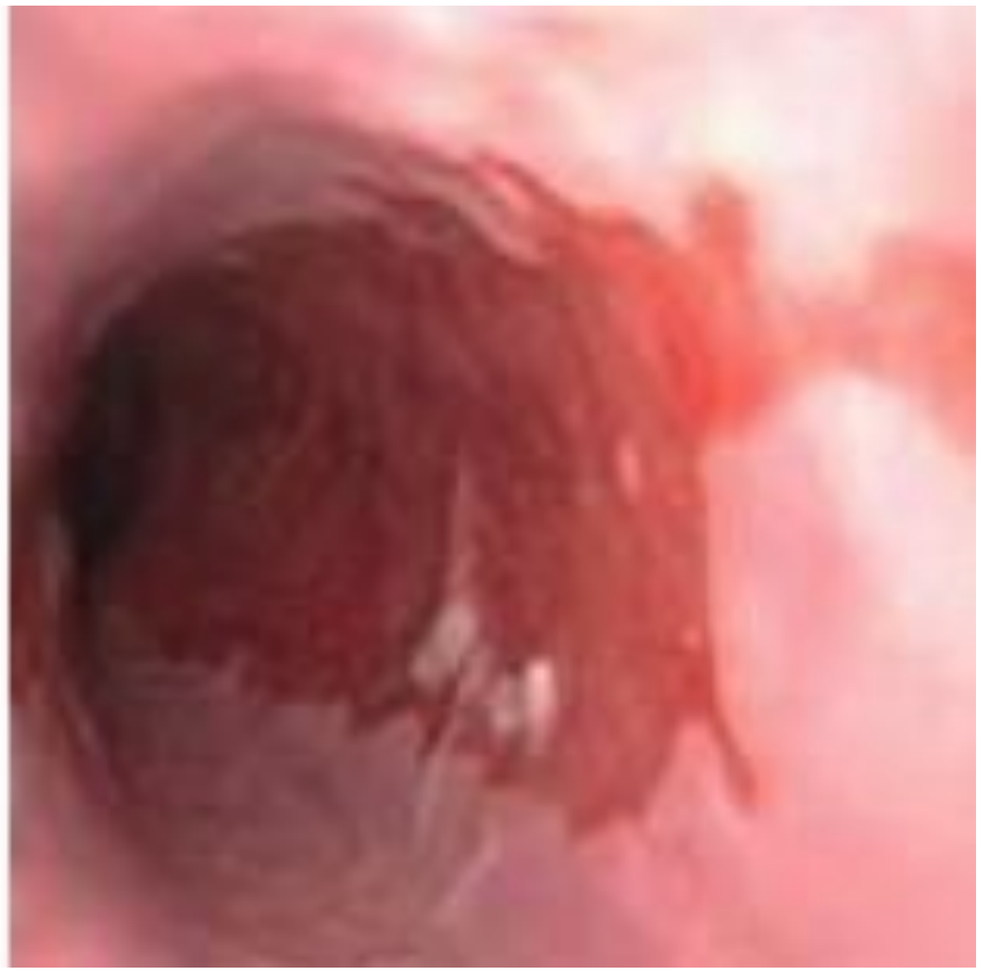
- Complications of chronic GERD
- Intestinal metaplasia occurs when the normal squamous epithelium of the esophagus is replaced by **intestinal-type epithelium**, including **the presence of goblet cells**, which are typically absent in the esophagus. This change is a hallmark of **Barrett's esophagus**.
- 10% of individuals with symptomatic, **long-standing** GERD
- **Affects the** Males >>females, 40-60 yrs
- **It's important to establish the diagnosis of Barrett's esophagus because it's a direct** precursor of esophageal adenocarcinoma
- **The annual risk of developing dysplasia in patients with intestinal metaplasia (Barrett's esophagus) is approximately** 0.2-1% /year. **Dysplasia may be classified as low- or high-grade and is recognized as the immediate precursor of adenocarcinoma**.

MORPHOLOGY

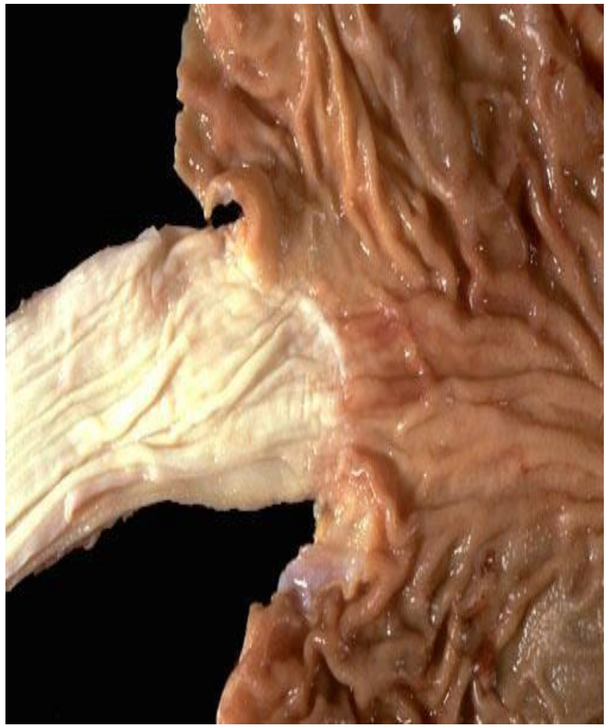
- Endoscopy:
  - Red tongues extending upward from the GEJ.
- Histology:
  - **Intestinal metaplasia (defined by** Presence of goblet cells)
    - **Barrett's esophagus** can only be diagnosed in the presence of **intestinal metaplasia**. Therefore, **biopsy** is essential not only for establishing the diagnosis but also for monitoring the regression of metaplasia or the potential development of **dysplasia**.
  - +-Dysplasia: low-grade or high-grade
  - Intramucosal carcinoma (early carcinoma): invasion into the lamina propria.

Red tongues extending upward from the gastroesophageal junction are characteristic of **Barrett's esophagus**. **Biopsy** samples from these areas typically reveal the presence of **intestinal metaplasia** with **goblet cells**.



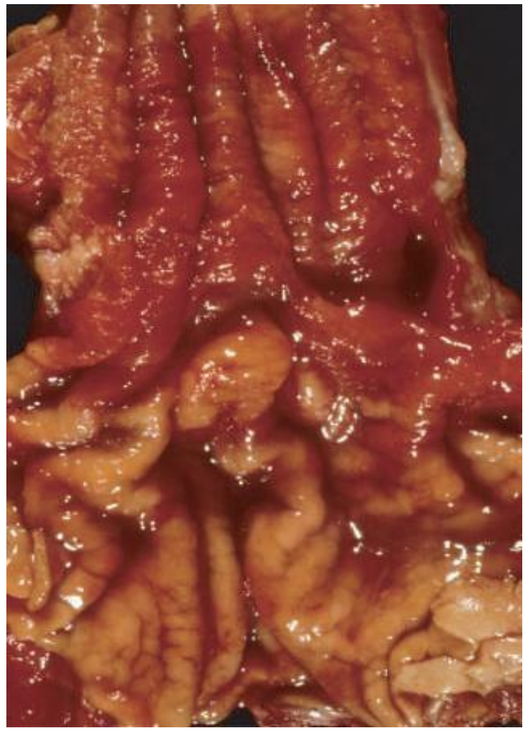


Normal esophagus with a tan/light pink color

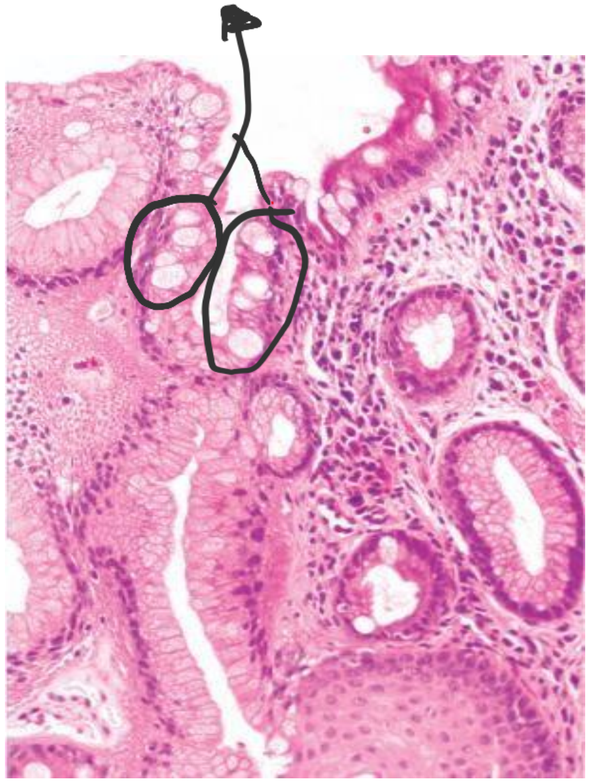


Red and erythematous esophagus which represents the Barrett's esophagus.

Note the small islands of paler squamous mucosa within the Barrett mucosa.



This biopsy from the esophagus reveals **goblet cells**, a hallmark of **intestinal metaplasia.**

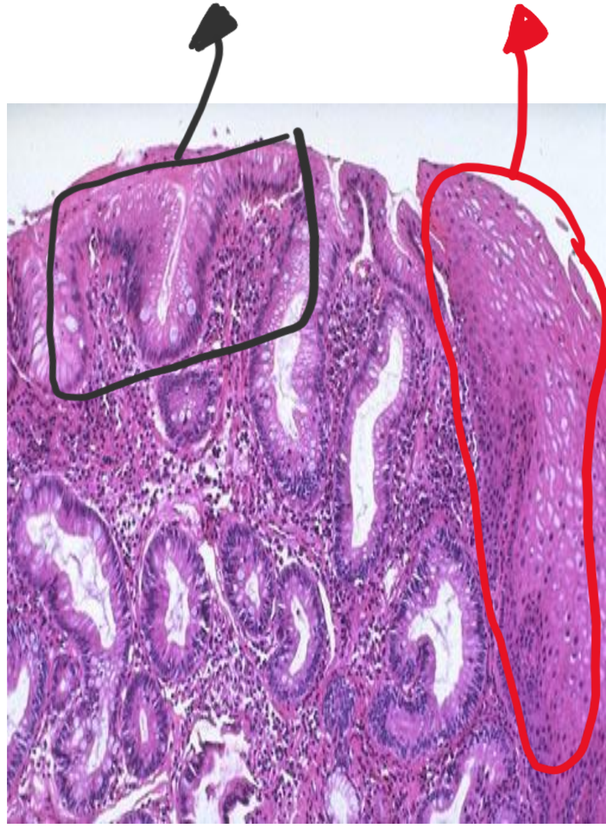


The red Arrow :

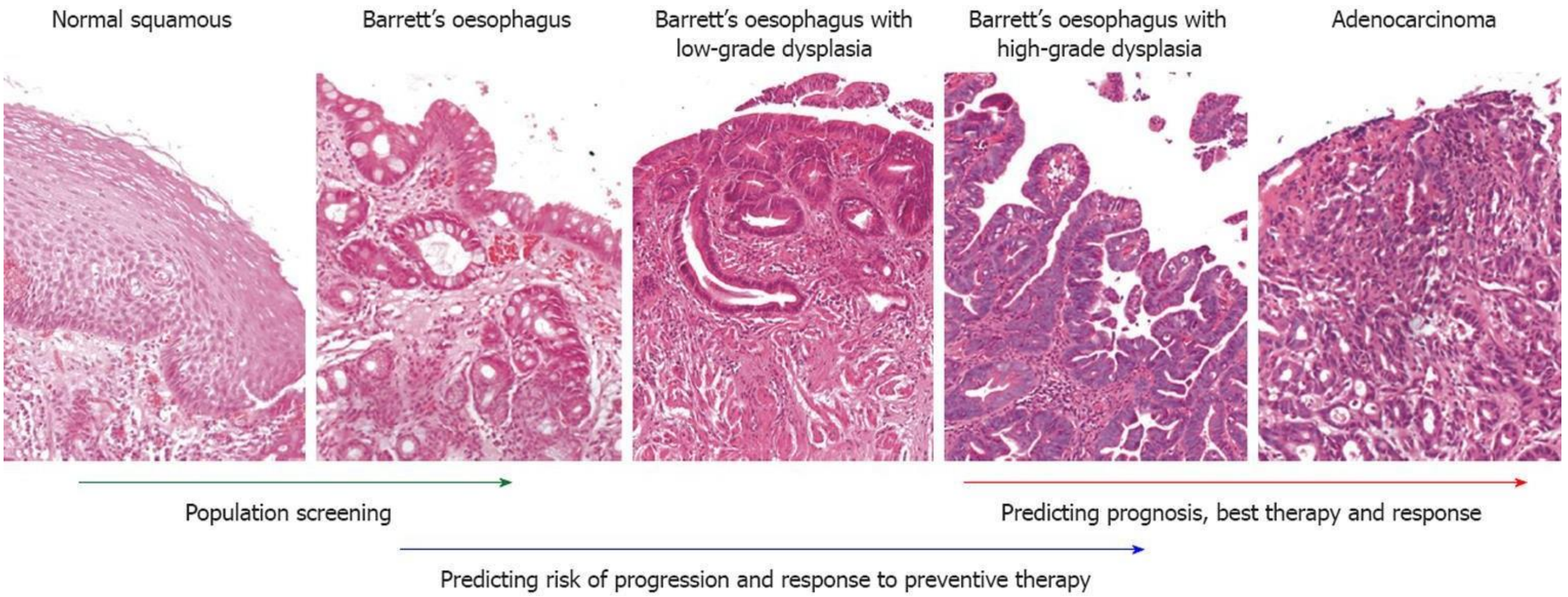
Represents the **normal** squamous epithelium in the esophagus.

The black Arrow :

is indicative of **intestinal metaplasia**, where **goblet cells**, filled with bluish mucin, can be observed on **H&E staining**.



This image shows:
the progression from normal squamous epithelium to **Barrett's esophagus**, followed by the development of **low-grade dysplasia**, then **high-grade dysplasia**, and ultimately to **invasive adenocarcinoma**



Management of Barrett

Patients undergo periodic surveillance endoscopy combined with biopsy, and we do this to screen and protect the patient from the dangerous stages by spotting the pre-cancerous cells before they turn into cancer.

Periodic surveillance endoscopy with biopsy to screen **for the development** of dysplasia.

If High-grade dysplasia & intramucosal carcinomas developed, this patient needs **interventions.**

6-ESOPHAGEAL TUMORS

½ of the cases are due to squamous cell carcinoma (most common worldwide)

Adenocarcinoma (on the rise, ½ of the cases in the developed countries)

Adenocarcinoma:

- Background of Barrett esophagus and long-standing GERD.
- Risk is greater if: documented dysplasia is present, smoking, obesity, radioTx. RadioTX = patient with prior Radiotherapy
- Male : female (7:1) remarkably high in males
- There is geographic and racial variation in adenocarcinoma incidence, with rates being higher in developed countries, partly due to higher obesity prevalence. Obesity increases the risk of gastroesophageal reflux disease (*GERD*), which is strongly associated with the development of *Barrett's esophagus*, a condition that can increase the risk of progressing to *adenocarcinoma.*

Pathogenesis:

- From Barrett>>dysplasia>>adenocarcinoma.
- By Acquisition of genetic and epigenetic changes.
- with Chromosomal abnormalities and TP53 mutation.

This process is a **multistep** one that is influenced by multiple **environmental factors**.

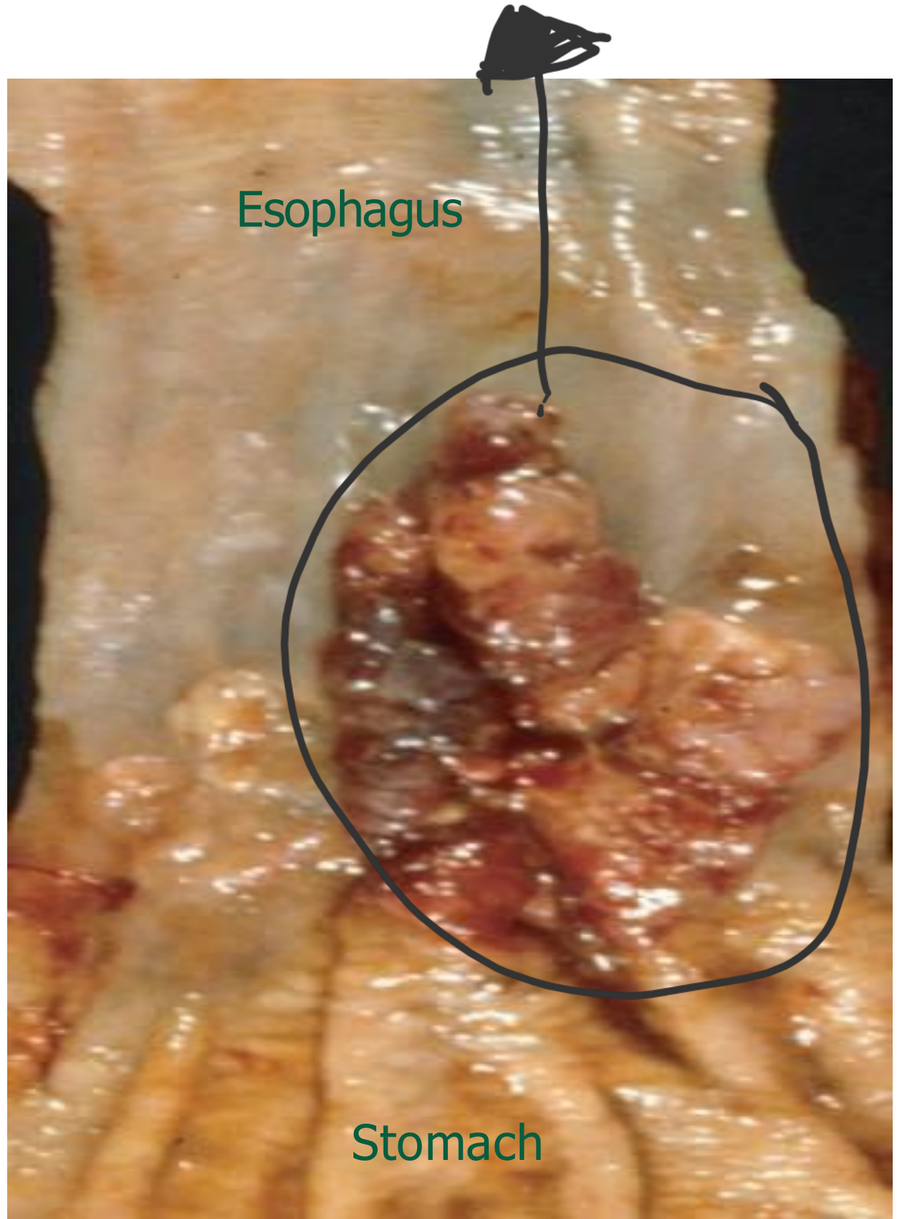
MORPHOLOGY of Adenocarcinoma:

- They occur in the distal third of the esophagus, which is the region most affected by gastroesophageal reflux disease (GERD) and reflux esophagitis.

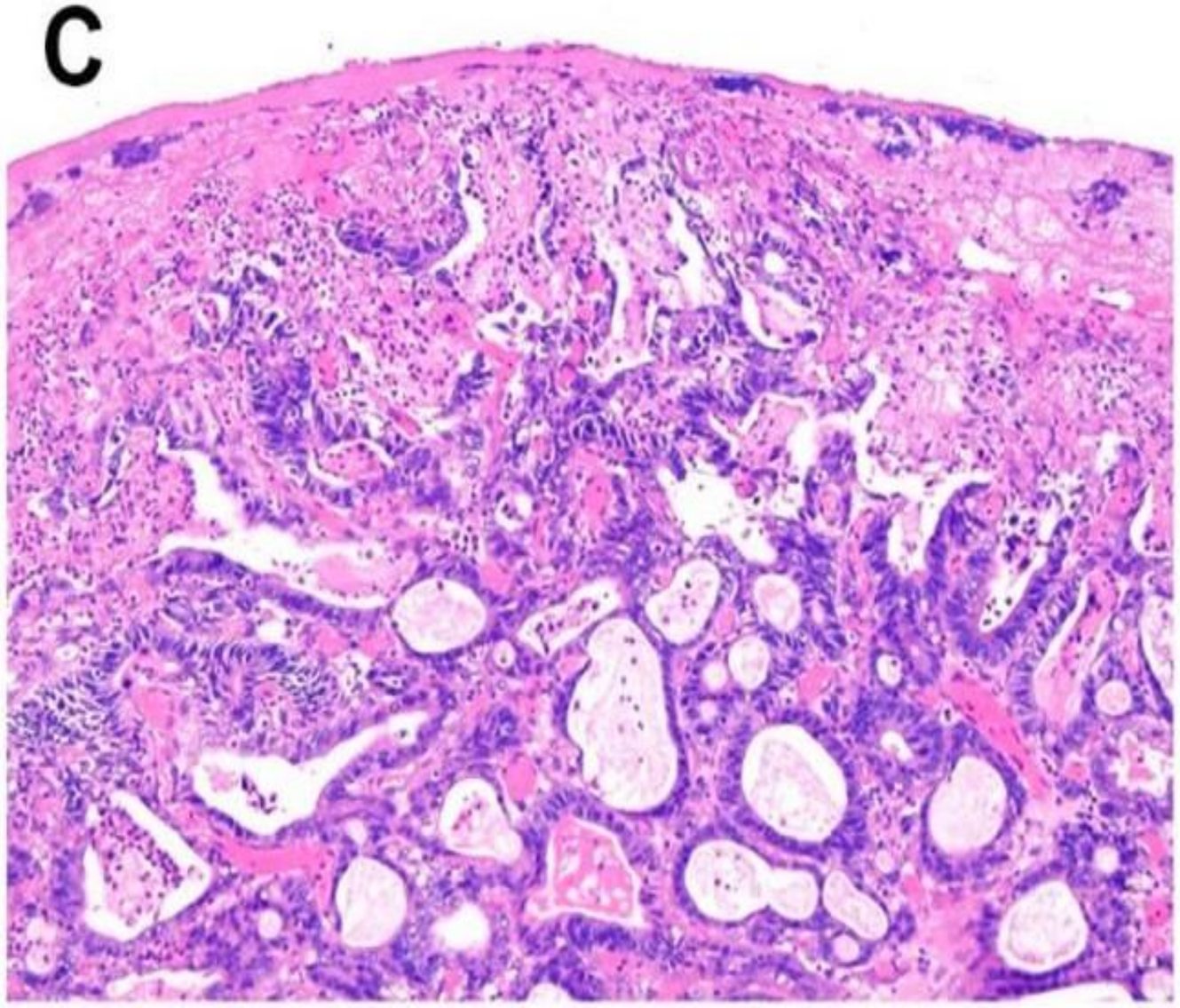
- Early morphologic changes of the lesion may present as: flat or raised patches

- Later: exophytic infiltrative masses
  - Later in its progression, the lesion becomes more exophytic, meaning it protrudes into the esophageal lumen and may cause luminal obstruction. Additionally, it begins to infiltrate the esophageal wall with longitudinal spread, extending both proximally and distally along the esophagus.
- Microscopically, these tumors are adenocarcinomas, characterized by the formation of glandular structures and the production of mucin.

This is an **exophytic mass at the GEJ.**



Microscopic examination confirms the diagnosis of invasive adenocarcinoma.



Clinical Features:

- **Dysphagia (difficulty swallowing)** and **odynophagia (painful swallowing)** occur due to the **exophytic tumor obstructing the esophageal lumen**.
- Progressive weight loss may result from **tumor-induced cachexia** and **reduced oral intake due to dysphagia.**
- Chest pain
- Vomiting.
- Advanced stage at diagnosis: 5-year survival <25%.
- Early stage: 5-year survival 80%

The time is important, unfortunately if the tumor was discovered lately, the survival rate for 5 years will be less than 25%. However, if the patient is lucky & tumor was discovered early, his survival rate for 5 years will be now 80%.

Squamous Cell Carcinoma:

- Male : female (4:1) **more in males**
- More **common** in rural, low resource**, and under-developed** countries.
- **Risk factors:**
  - **Not associated with reflux esophagitis**
  - Alcohol
  - Tobacco use
  - Poverty
  - Caustic injury, including exposure to **acidic or alkaline substances.**
  - Achalasia.
  - Plummer-Vinson syndrome (iron deficiency Anemia, dysphagia, and esophageal webs)
  - Frequent consumption of very hot beverages
  - Previous radiation Tx.

Note: One or more of these risk factors, especially when combined with **environmental exposures**, may contribute to the development of **esophageal squamous cell carcinoma.**

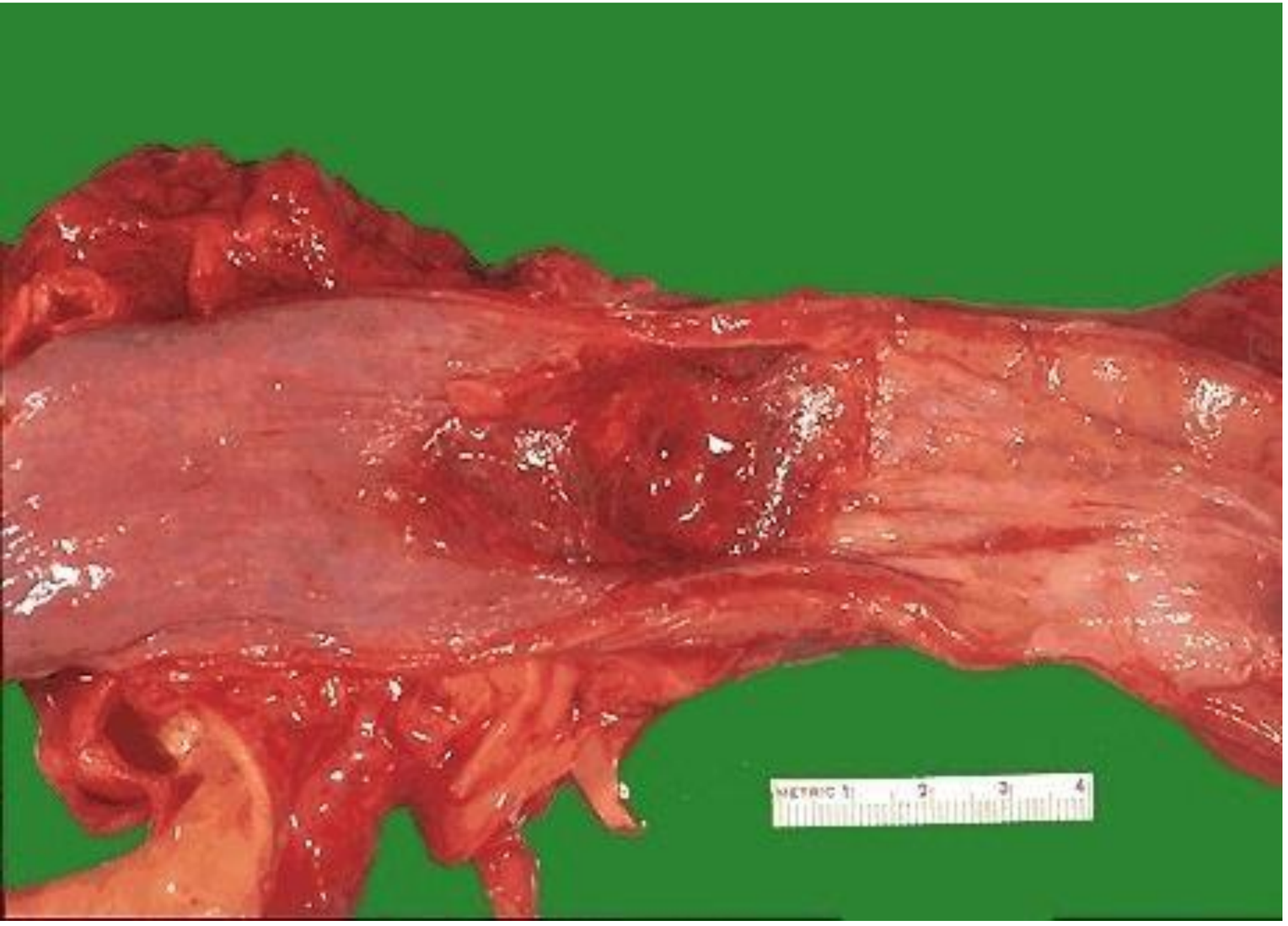
Pathogenesis:

- In western countries: alcohol and tobacco use.
- Other areas: nutritional deficiency, exposure to polycyclic hydrocarbons, nitrosamines, fungus-contaminated foods.
- HPV infection has been implicated in squamous cell carcinoma in high-risk regions, particularly as part of upper aerodigestive tract malignancies.

MORPHOLOGY:

- Squamous cell carcinoma most commonly arises in the middle third of the esophagus, accounting for approximately 50% of cases. In contrast, adenocarcinoma typically involves the distal (lower) third of the esophagus.
- Polypoid, ulcerated, or infiltrative masses which lead to esophageal wall thickening and luminal narrowing, resulting in progressive dysphagia.
- Invade surrounding structures (bronchi, mediastinum, pericardium, aorta).

Mid esophagus:



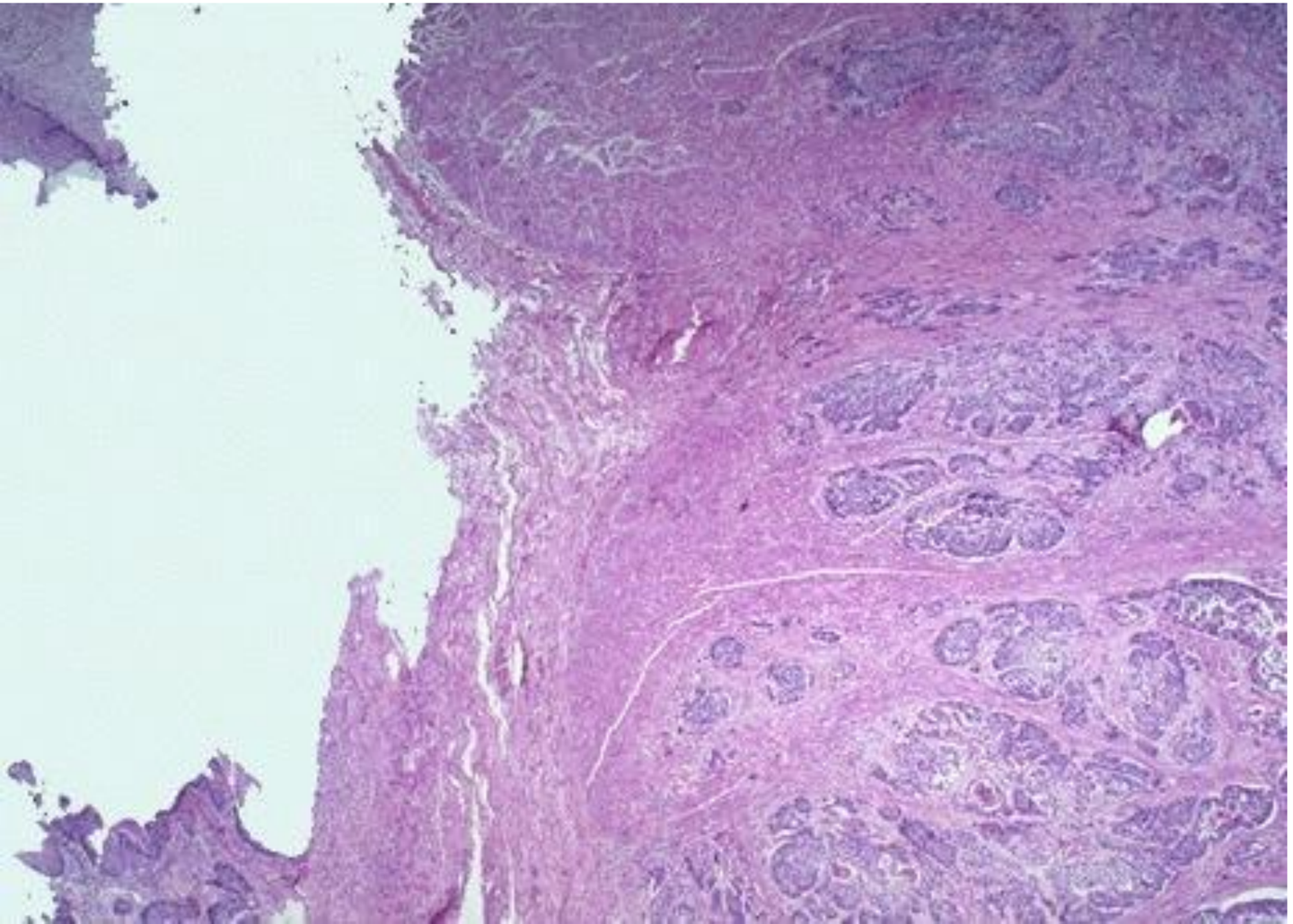
- This is the bulging mass in the mid esophagus !

Microscopy:

- Pre-invasive: the precursor lesion is squamous dysplasia & CIS.
- Invasive: Well to moderately differentiated invasive SCC.
- Intramural tumor nodules away from the main tumor, due to extensive lymphatic drainage. As a result, tumor cells can spread longitudinally along the esophagus, even at the time of initial diagnosis.
- Lymph node metastases according to the site of the tumor:
  - Upper 1/3: cervical LNs
  - Middle 1/3: mediastinal, paratracheal, and tracheobronchial LNs.
  - Lower 1/3: gastric and celiac LNs.

CIS: Carcinoma-in-situ
SCC: Squamous Cell Carcinoma
LNs: Lymph nodes

Invasive SCC



- Composed of cells of squamous origin similar to the normal lining of the esophagus.

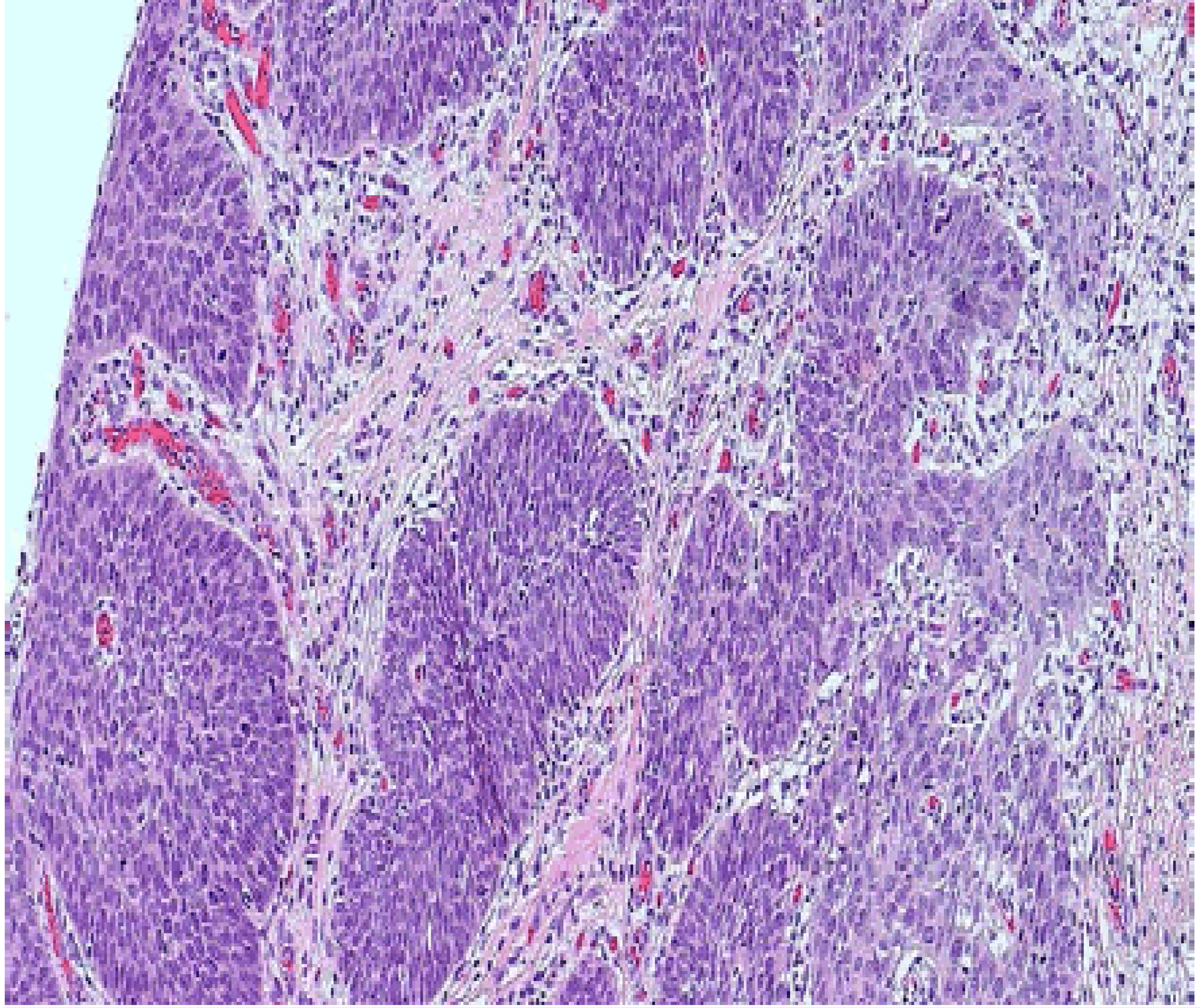


Figure 4: Squamous cell carcinoma of the esophagus with focal invasion into the muscularis mucosa and associated desmoplastic response.

Clinical Features:

- Dysphagia
- Odynophagia
- Obstruction
- Weight loss and debilitation
- Impaired nutrition & tumor associated cachexia
- As with adenocarcinoma, hemorrhage and sepsis may accompany tumor ulceration.
- Occasionally, squamous cell carcinoma of the upper and mid esophagus presents with symptoms caused by aspiration of food via a tracheoesophageal or tracheobronchial fistula
- Dismal Prognosis: 5-year survival rate ~10%, as most patients present with advanced-stage disease.

رسالة من الفريق العلمي:

قال النبي ﷺ:

"من سنّ في الإسلام سنة حسنة فله أجرها وأجر من عمل بها بعده"

السنة الحسنة هي أن يبدأ الإنسان عملاً صالحًا مشروعًا أو يحيي سنة نبوية فيتبعها الناس، فيكون له أجرها وأجر من عمل بها.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			