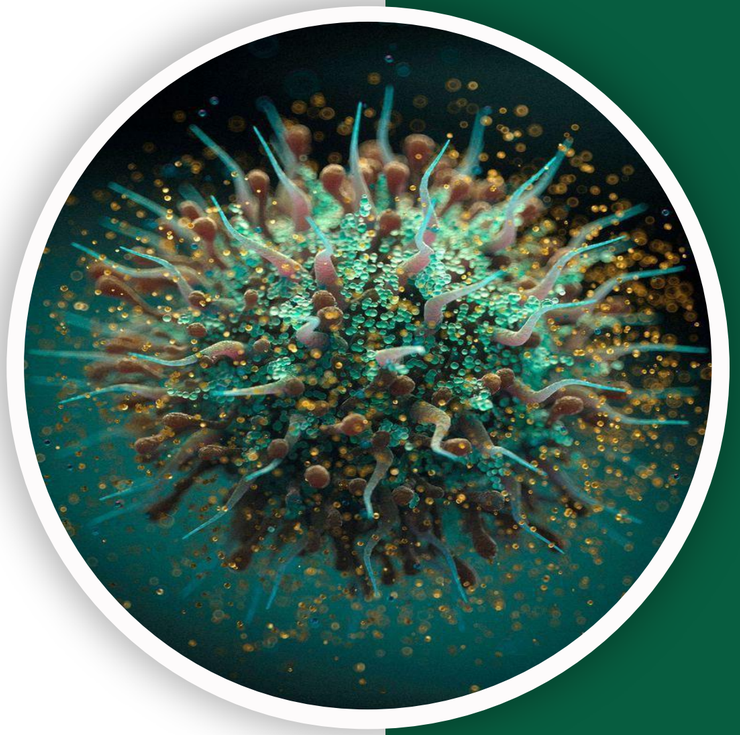
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

GIS Pathology | MID 4

Gastric Diseases Pt.2



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Abdallah Hindash

Click for quiz on the previous lec

- Here is a mind_map for gastric diseases 1+2

(اللهم إنّا نسألك فَهم النّبيّين ، و حِفظ المرسلين ، و الملائكة المقربين ، اللهم اجعل ألسنتنا عامرة بذكرك و قلوبنا بخشيتك و أسرارنا بطاعتك)

Pathology of the stomach-2

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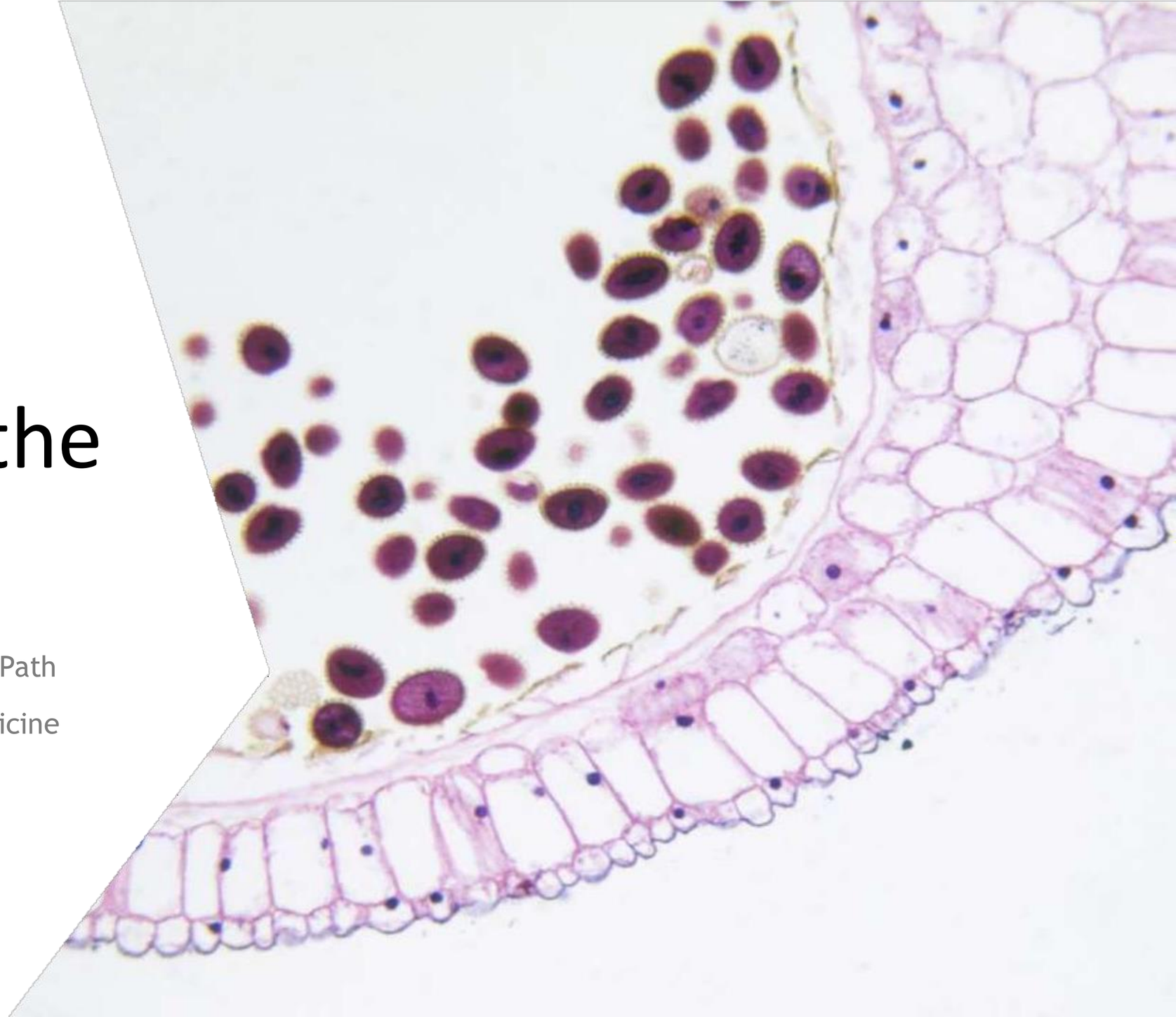


❑ Peptic Ulcer Disease

- Peptic ulcer is ulcer in any site that is exposed to acid and pepsin
- gastric ulcer is a sub type of peptic ulcers so **not every peptic ulcer is gastric one**
- These ulcers can develop as a complication of chronic gastritis, especially when caused by H. pylori infection.
- For example peptic ulcer may be **duodenal , lower esophageal ulcers** (in patients with gastroesophageal reflux disease) , or **ulcers in the mikkel's diverticulum** in the terminal ilium (harbor ectopic gastric mucosa producing gastrin and pepsin).

- Main factors: H. pylori infection or NSAID use (there is a geographical variation)

- **Pathogenesis :**

- Imbalance between mucosal defenses and damaging forces like H.pylori & NSAIDS.
- USA, most cases are NSAID induced (as H. Pylori infection is falling there is eradication and increased use of low-dose aspirin in aged population).
- Any portion of the GIT exposed to acidic gastric juices
- Most common site in gastric: antrum the first site to be affected by this bacteria, first part of duodenum.
- Esophagus in (GERD) or ectopic gastric mucosa (Meckel diverticulum)

❑ Pathogenesis of PUD:

- > 70% of cases are associated with H. pylori infection worldwide.
- Only 5 -10% of H. pylori–infected persons (host factors, bacterial strains).

➢ Not all patients with chronic gastritis must have an ulcer, it depends on factors like: host factors , defense factors & other cofactors (mentioned below)

- Gastric acid is fundamental in pathogenesis. No acid No ulcer
- Cofactors: smoking, chronic NSAIDs, high-dose corticosteroids, alcoholic cirrhosis, COPD (chronic obstructive pulmonary disease), CRF (chronic renal failure), hyperparathyroidism.

➢ They are considered risks that alter the Defense mechanisms of stomach

- **Hyperacidity is caused by:**

a) H. pylori.

b) Parietal cell hyperplasia releasing more acid

c) Excessive secretory response (vagal)

d) Hypergastrinemia as in Zollinger-Ellison syndrome (gastrinomas)

➢ Zollinger–Ellison syndrome is characterized by hypergastrinemia due to a tumor (gastrinoma), resulting in excessive gastric acid secretion .

❑ Zollinger-Ellison syndrome

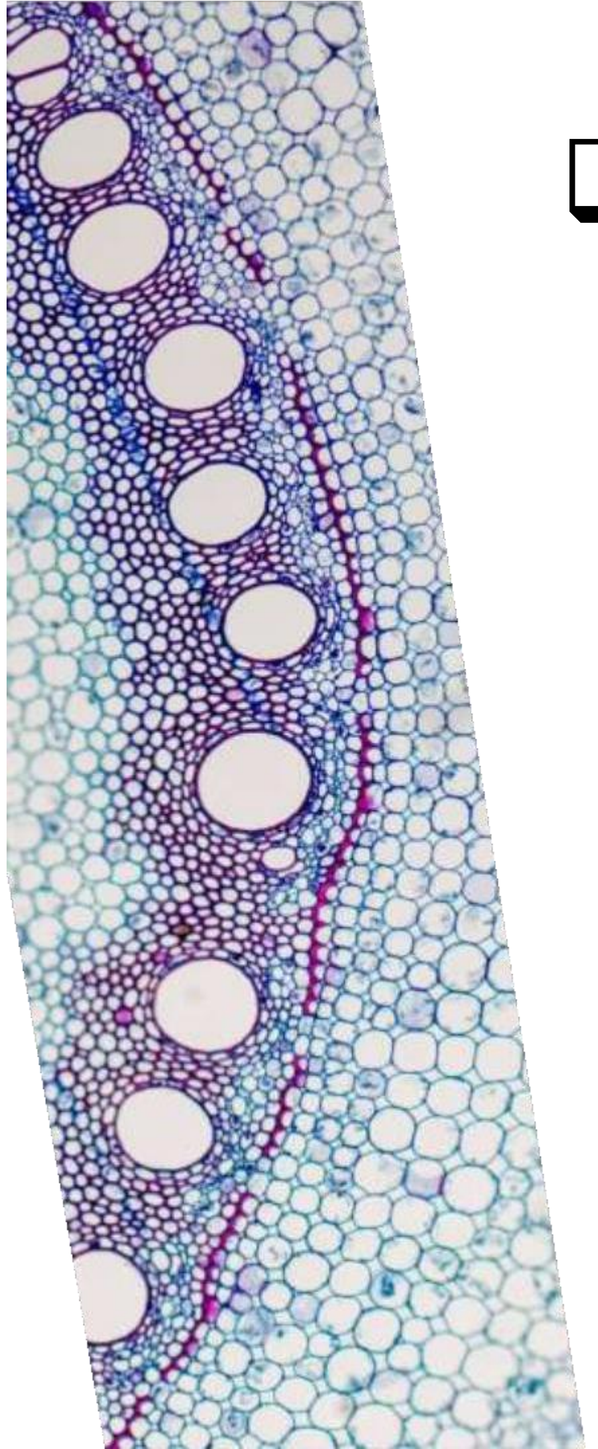
- Multiple peptic ulcerations

➢ **Distribution:**

- Stomach , duodenum, even jejunum **Because of the high acidity in gastric secretions.**
- **A tumor** Caused by uncontrolled release of gastrin by a tumor (gastrinoma) and the resulting massive acid production.

  (Hypergastrinemia: increased gastrin concentration In blood)

➢ **Hypergastrinemia > hyperacidity > peptic ulcers**

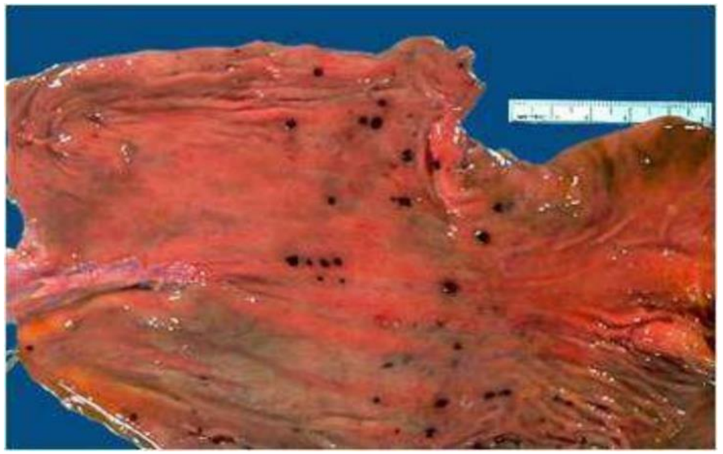


❑ MORPHOLOGY (Of peptic ulcers)

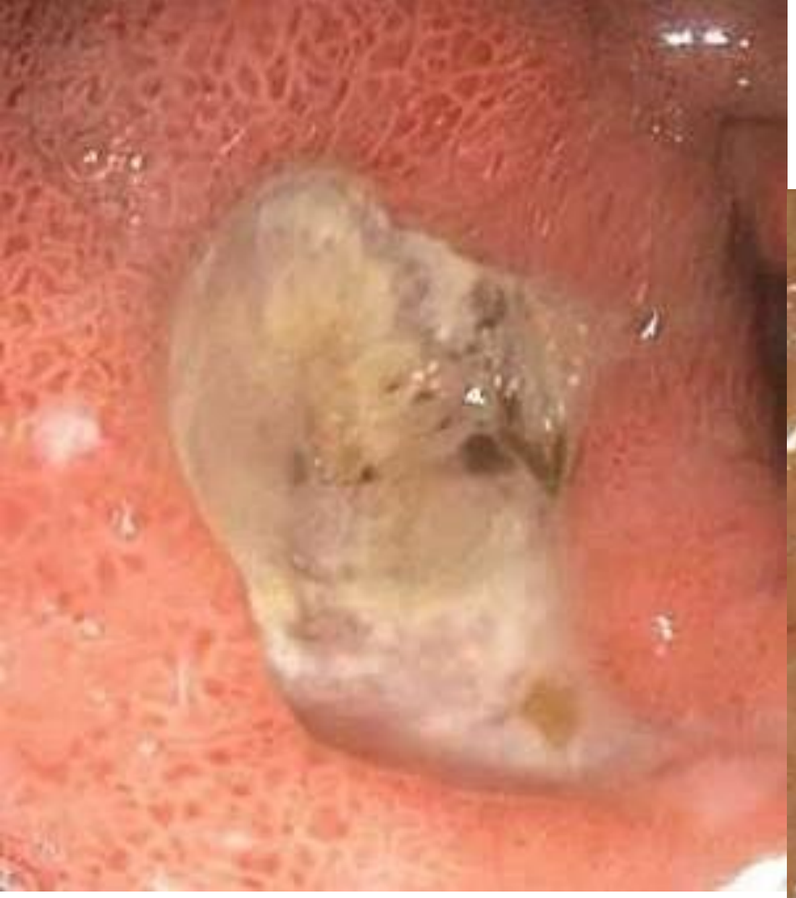
- 4:1, proximal duodenum : stomach. Anterior duodenal wall or antrum.
- >80% solitary. (Single)
- Round to oval, sharply punched-out
- Base of ulcers is smooth and clean
- Granulation tissue.
- Hemorrhage & Perforation are emergency complications.
- Most of the time, the surrounding mucosa shows chronic gastritis.

See next page!

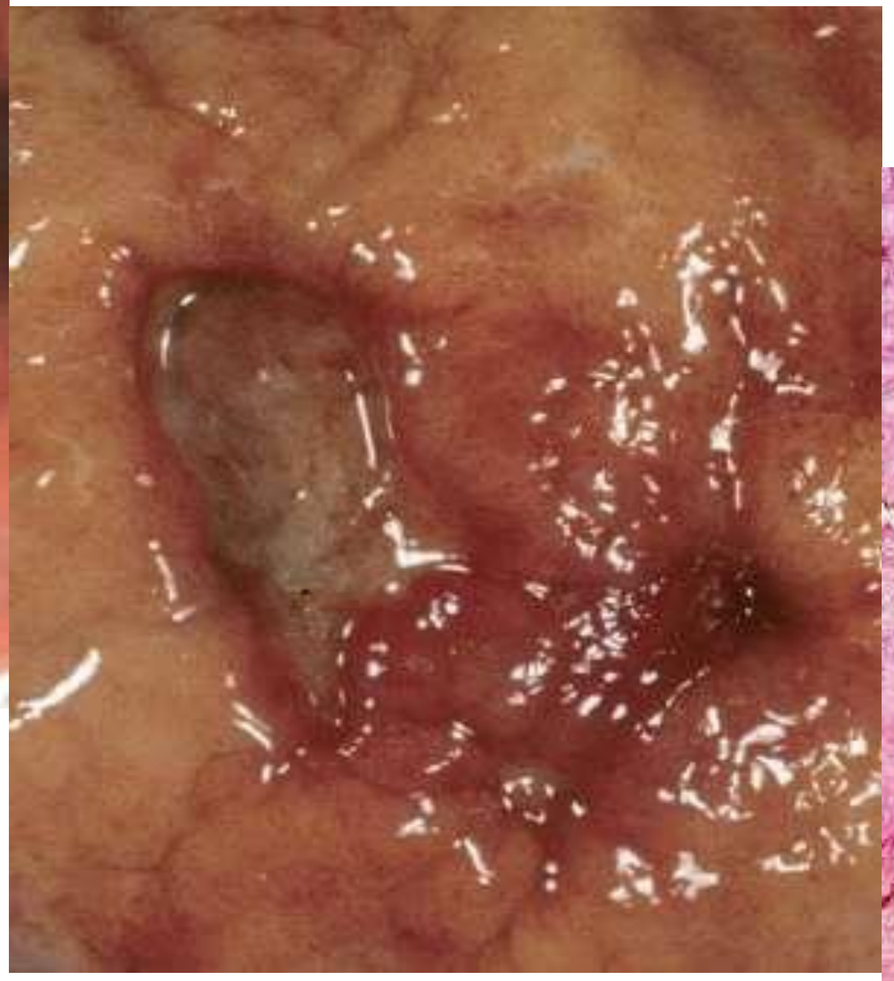
➢ The difference between peptic ulcer and stress ulcer is that:

Peptic ulcers	Stress ulcers From Gastric lec1
• single ulcer • usually in the antrum, punched out • well demarcated larger • background usually whitish or pinkish (due to attempt to healing by granulation) • hyperemia and redness in the surrounding stomach (due to the presence of concomitant chronic gastritis.) See next page for ulcer morphology pictures	• Multiple small ulcers • Happen anywhere in the stomach Ulcer base is brown to black Background is clear – normal mucosa– 

➢ Duodenal ulcers are more common than gastric ulcers;Because stomach is adapted to Hyperacidity .

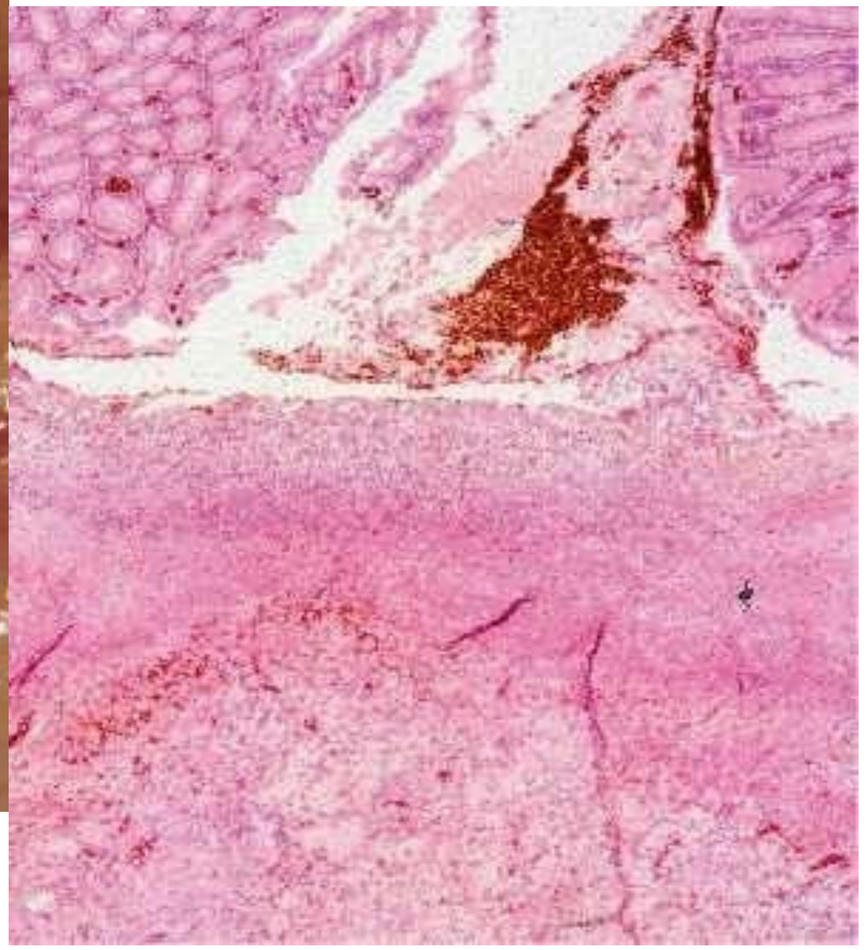


Large in size
The base is white in color(granulation tissue is trying to heal the ulcer)



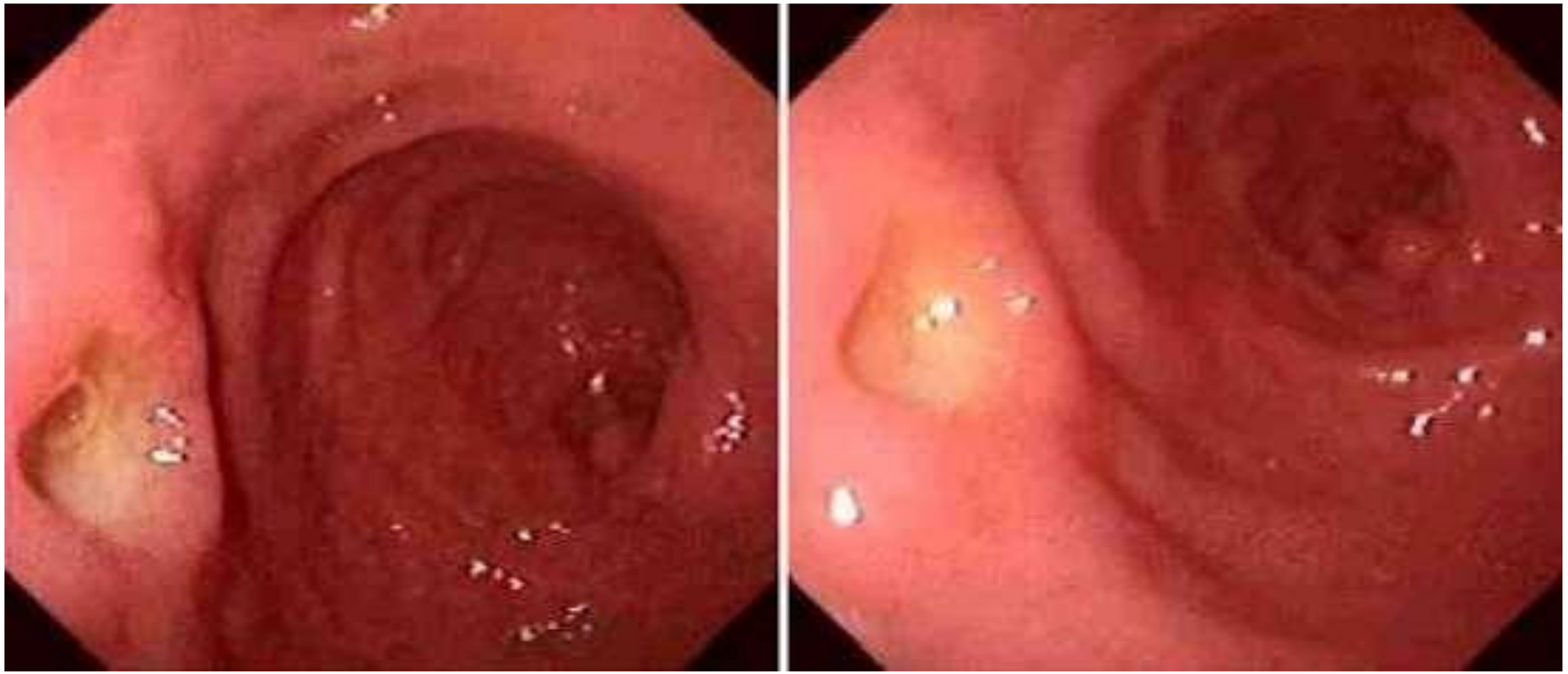
Borders are sharply demarcated with Deep , punched out edges

Microscopically, an ulcer is characterized by loss of the mucosal epithelium, exposure of the underlying tissue, and may be associated with inflammation and bleeding.



Robbins Basic Pathology 10th edition

Duodenal ulcer



As we discussed, it's a single ulcer , very well demarcated lesion & the base of the ulcer is white in color .

Why is the base of the ulcer white in color?

The white color of the ulcer base is due to granulation tissue and fibrosis (scarring), reflecting the healing process in chronic ulcers. Unlike chronic ulcers, acute stress ulcers usually heal without scarring and show complete re-epithelialization.

❑ Clinical Features

- Differs according to severity of the changes
- Epigastric burning or aching pain
- The typical scenario in patients with ulcers is that pain occurs during fasting or when the stomach is empty, and it is relieved after eating. However, this pattern is not present in all patients.
- Complication: Iron deficiency anemia, frank hemorrhage severe upper Gi bleeding , or perforation.

Due to chronic bleeding from the ulcer

- In a patient with iron deficiency anemia, ask about hematemesis and melena (a change in stool color to black) to assess for possible gastrointestinal bleeding.

➢ **Characteristics:**

a) Pain 1 to 3 hours after meals at daytime

b) Worse at night, relieved by alkali or food Nausea, vomiting, bloating, bletching.

- Current therapies are aimed at H.pylori eradication & stop NSAIDS if it's the cause (If NSAID therapy must be continued, a proton pump inhibitor should be given for gastrointestinal protection)
- Surgery reserved for complications (such as frank hemorrhage & perforation)

❑ GASTRIC POLYPS AND TUMORS (neoplastic conditions)

- Not necessarily neoplastic ,may be reactive or inflammation

- Gastric Polyps: (descriptive term): finger-like projection above the level of mucosa

a) Inflammatory and Hyperplastic Polyps They don't have the risk of malignant transformation.

b) Gastric Adenoma which are premalignant .

- Gastric Adenocarcinoma

  intestinal and diffuse types

- Lymphoma

  MALToma (the most common)

- Neuroendocrine (Carcinoid) Tumor
- Gastrointestinal Stromal Tumor We won't talk about them

❑ Gastric polyps

- They are totally benign.
- Polyps: masses projecting above the level of adjacent mucosa

- **Inflammatory and Hyperplastic Polyps** (reactive in the background of chronic gastritis)

1. 75% of all polyps of the stomach.
2. Arise in a background of chronic gastritis Regress after H.pylori eradication.

❑ Gastric Adenoma

- It is premalignant and may progress to gastric adenocarcinoma
- Counterpart of colonic adenoma, the same view
- Colonic adenoma is the most common , but Gastric adenoma is more severe than colonic

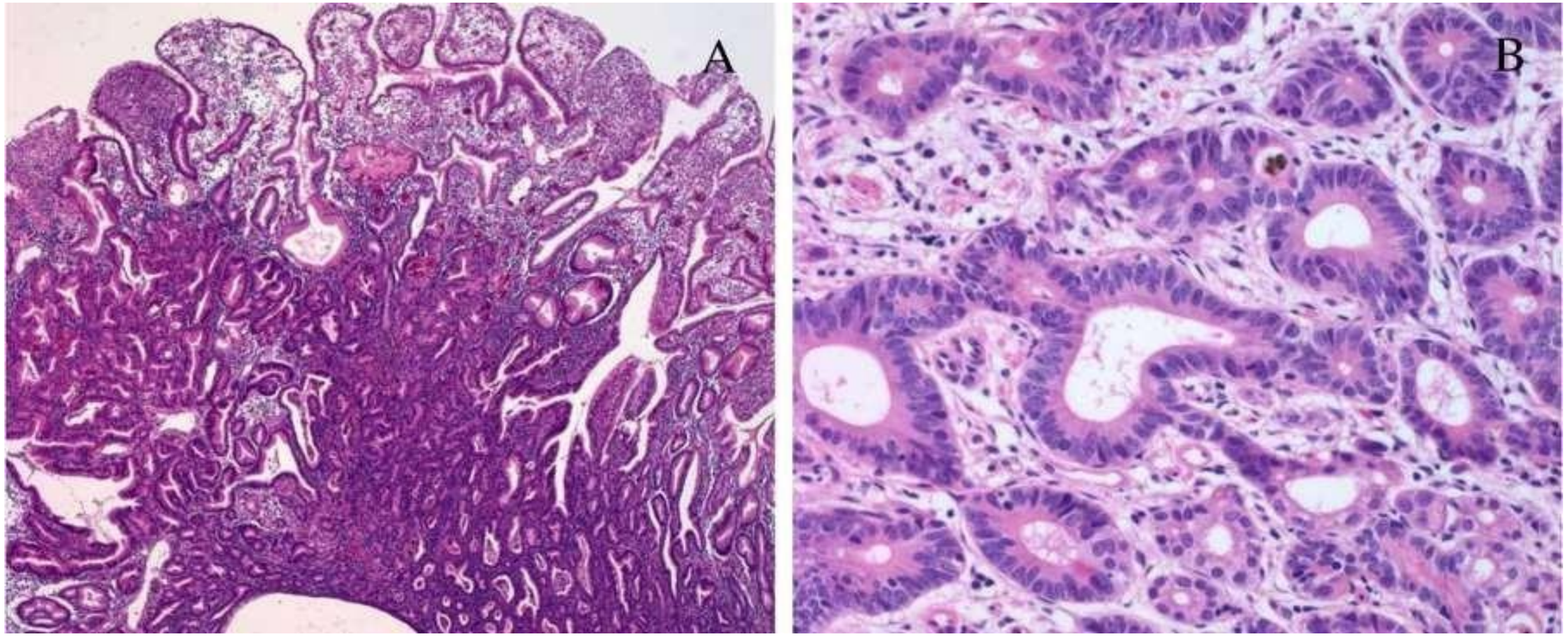
- 10% of all polyps of the stomach.
- Increase with age.
- M: F = 3:1 (more among males)

- Background: chronic gastritis, atrophy and intestinal metaplasia.
- A gastric adenoma is defined histologically by the presence of **Dysplasia, low- or high-grade** (due to the severity of dysplasia under the microscope)
- Risk of adenocarcinoma related to the size (greatest if > 2cm) , The larger the polyp, the higher the risk of adenocarcinoma.
- **Risk of carcinoma higher than colonic adenoma.**
- 30% have concurrent CA.

❑ Gastric adenoma

Under the microscope: **Dysplasia**

Dysplasia = abnormal cells (Agly cells)



- The features of abnormal cells according to the picture are:
- Hyperchromatic nuclei
- High N:C ratio
- Stratification of nuclei
- Enlargement of nuclei

❑ Gastric Adenocarcinoma

(most common type of gastric tumors)

- 90% of all gastric cancers.

the problem is that the symptoms are not specific

- Early symptoms mimic gastritis >>> late diagnosis.
- Marked geographic variation (Japan, Costa Rica, Chile). (most common)
- Screening >> early detection. Not all patient can afford this Screening; there is no national screening program in Jordan .
- Background of mucosal atrophy and intestinal metaplasia.
- PUD does not increase risk, except after surgery

Tumors can present as ulcer sometimes, but this ulcer is malignant from the start not transformed.

- **In USArates dropped > 85%, BUT increased rate of cardia cancer due to GERD & obesity.**
  Depending on type of food and nitrite in food may have association .
  main types: intestinal and diffuse.

Peptic ulcer disease itself does not increase the risk

Tumors may present as ulcers sometimes, but these ulcers are malignant from the beginning no transformation

of nonmalignant ulcer into malignant .

❑Pathogenesis

Stomach cancers are 2 types (Intestinal – Diffuse), which are different under microscopes, genetic mutations, and pathogenesis

- Genetic alterations, the main cause is H.Pylori infections associated chronic gastritis , lesser extent EBV (10%).)

H.Pylori infection → DNA damage → somatic mutations → accumulation of those mutations → cancer over time

Genes that are mutated will differ according to :-

1) The type whether it's:
   - Intestinal type. - Diffuse type.
2) Whether it's familial (inherited) or sporadic

Note :

- Sporadic = patients who had new mutations without any family history, they occur by accumulation of new (de novo) mutations.
- Familial = Patients who inherited genetic mutations from their family.

- Most cases are sporadic.

mostly they're sporadic, Familial cancers constitute only 10% of cases, in these inherited cases sometimes the familial tendency of a specific family makes them more prone to mutations when they're exposed to carcinogens.

Pathogenesis

As said before, we have 2 types (Diffuse and Intestinal), each one of them has familial cases and sporadic cases.

Lauren Classification of gastric adenocarcinoma:-

- Familial diffuse type: germline mutations in *CDH1* (E-cadherin).

In diffuse type the gene that is involved is called E-Catherine gene(which is called the glue of the cells), so it sticks cells together, if it is mutated it leads to decohesion of cells (one of the main characteristic features of gastric diffuse cancers) E-cadherin on this type is lost in a germline mutation, born with it.

- Sporadic diffuse type: somatic CDH1 mutation in 50%.

At this type of diffuse adenocarcinoma, the mutation occurs later but in the same gene (E-cadherin gene)

Patients living in high-risk areas with *H.Pylori* to be more predominant there, can experience intestinal types more than the diffuse types !!!

- Familial intestinal type cancer: FAP, APC gene mutation.

familial intestinal types come with FAP (Familial adenomatous polyposis) , the APC gene is mutated in both FAP syndromes and familial intestinal cancer

- Sporadic intestinal-type cancer : B-catenin mutation

Sporadic cases: P53 mutation + HER2 amplification.

In sporadic cases with concurrent TP53 mutation and HER2 amplification, patients may benefit from anti-HER2 targeted therapy as in cases of breasr cancer, analogous to HER-2 positive breast cancer medications is great therapy.

MORPHOLOGY

Lauren classification (based on morphology and genetic factors): separates gastric cancers into:-

Intestinal type:

Bulky. => bulk tumors or ulcers projecting to the lumen of stomach

Exophytic mass or ulcer.

Form glands.

(Intestinal type glands) Usually preceded by intestinal metaplasia

Intestinal metaplasia → intestinal type adenocarcinoma

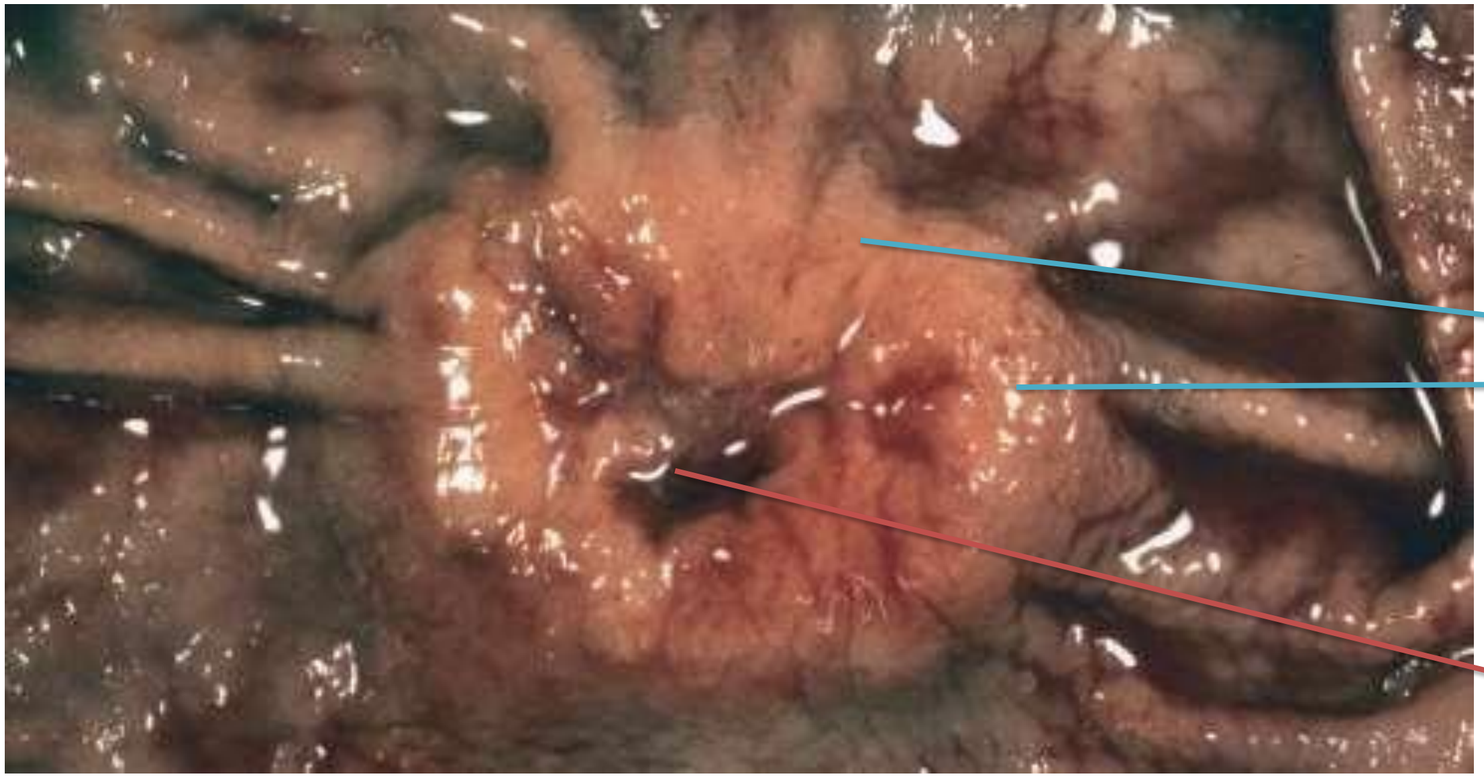
Diffuse type:

Infiltrative growth pattern

Discohesive cells (signet ring cells) due to a mutation in E-Cadherin gene

Desmoplastic reaction (AKA fibrotic response, which leads to thickening of the stomach wall with stiffness) (stiffens wall, flat ruge, linitis plastica).

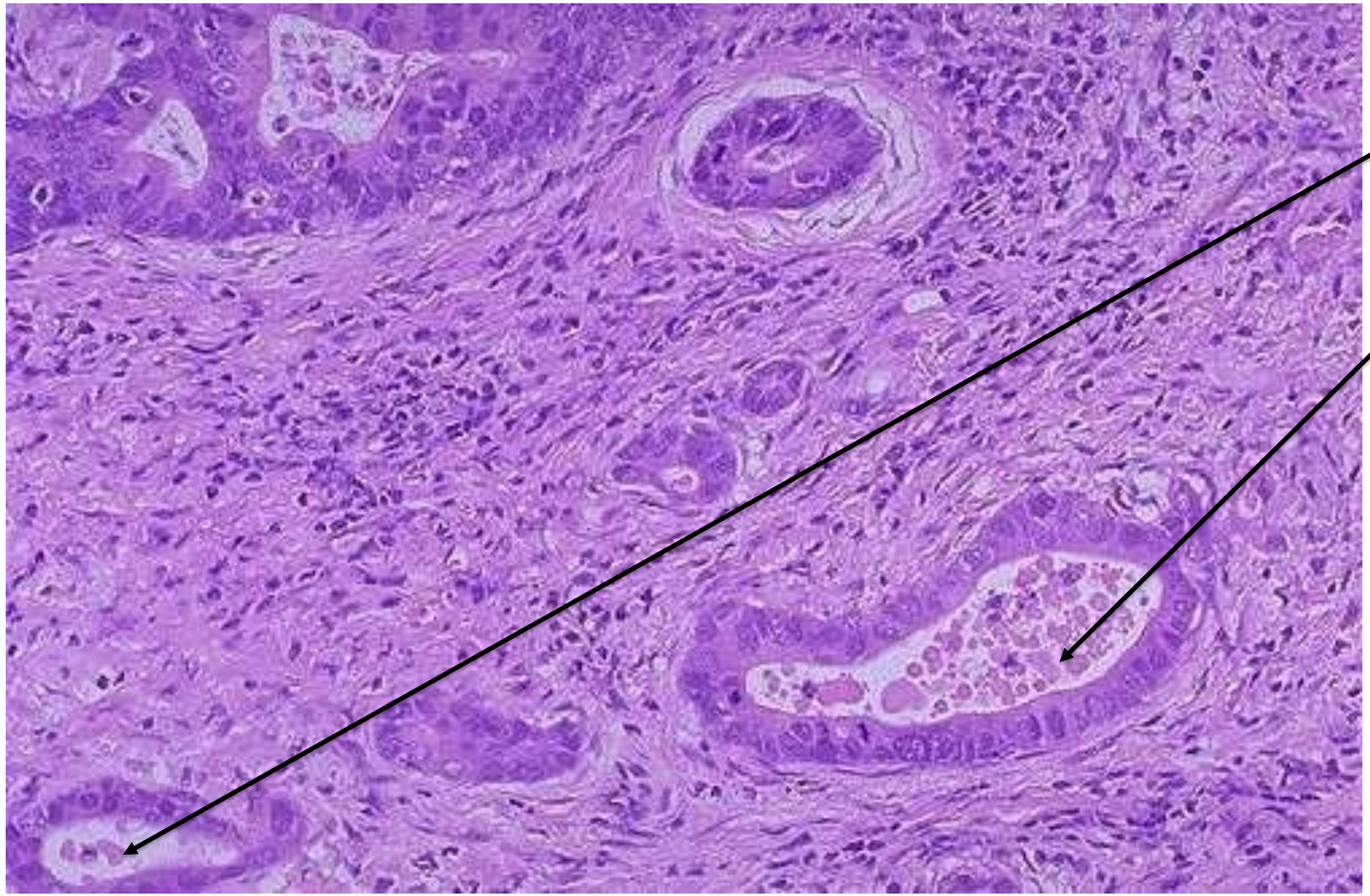
Diffuse type is tricky, It doesn't form a mass, the mucosa is normal, but they cause the thickening of stomach wall seen in imaging procedures (like CT scan), can't be seen during endoscopy



Intestinal type

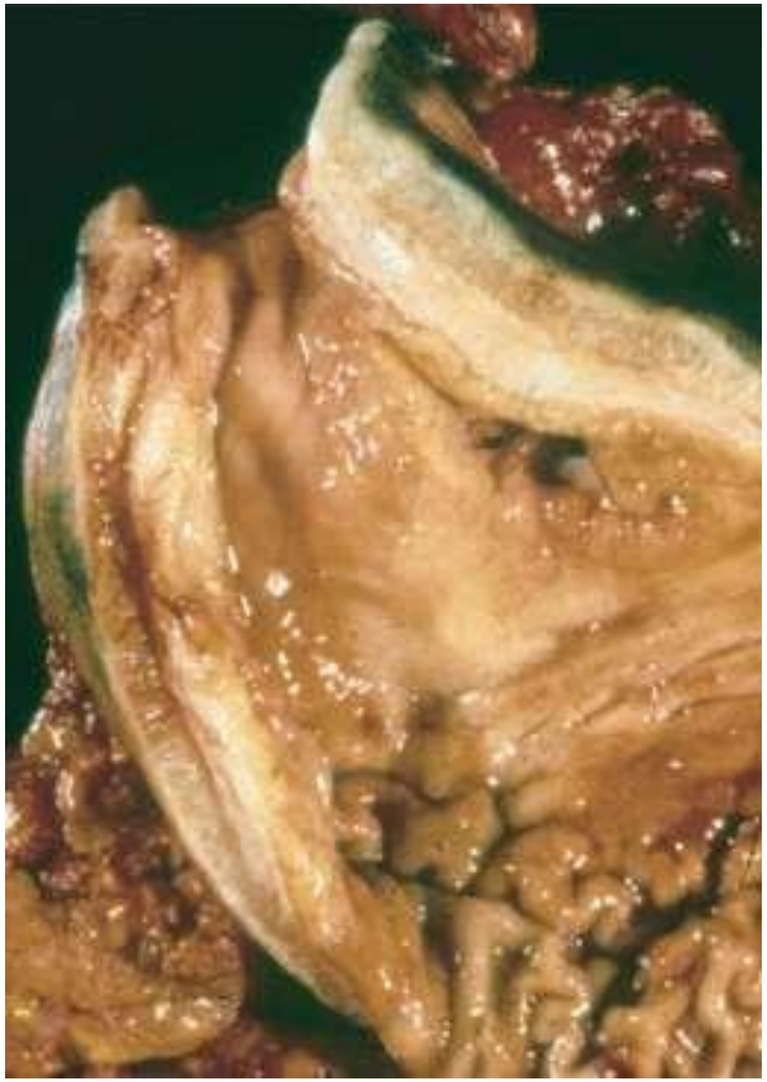
There is a Tumor, with an ulcer in the center of it

Intestinal type



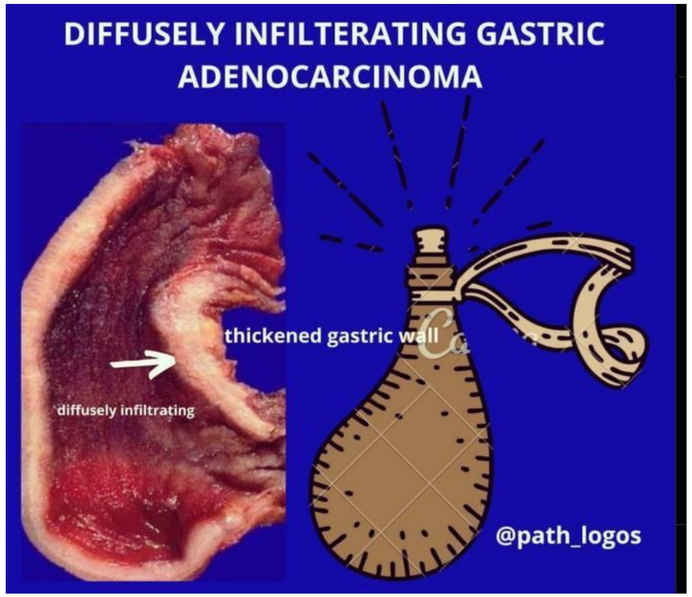
Under the microscope they tend to form glands

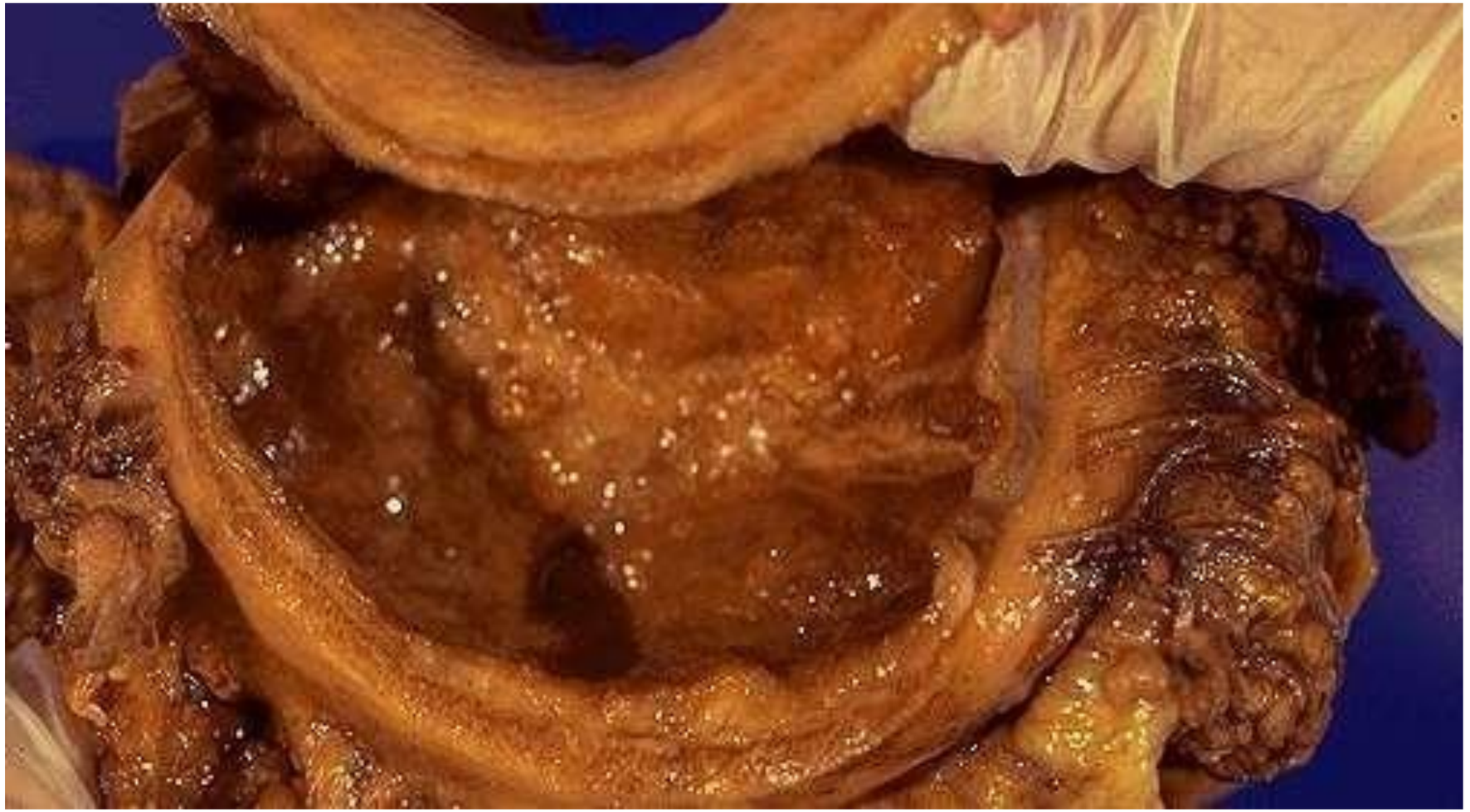
Linitis plastica



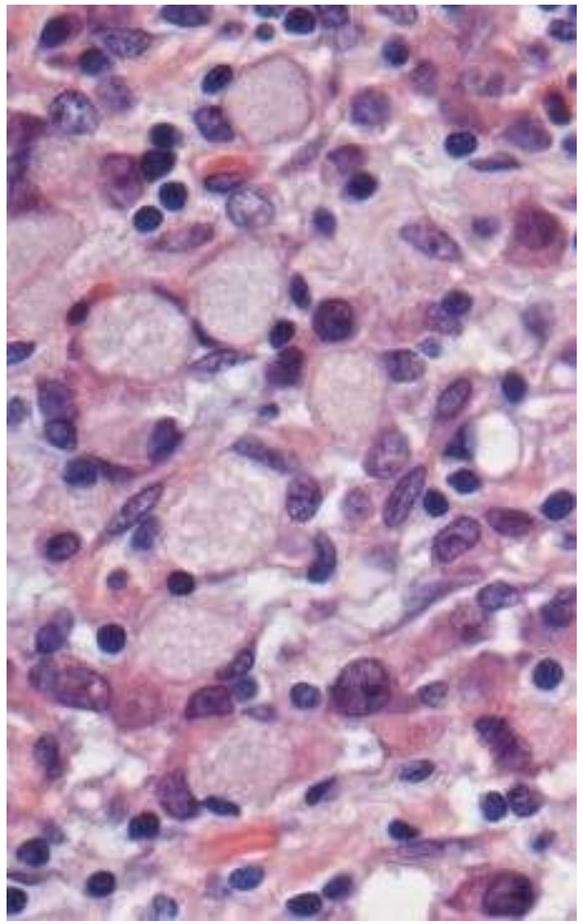
In this type, there is no tumor in the stomach, but there's a thickening of the stomach wall

Another pic.





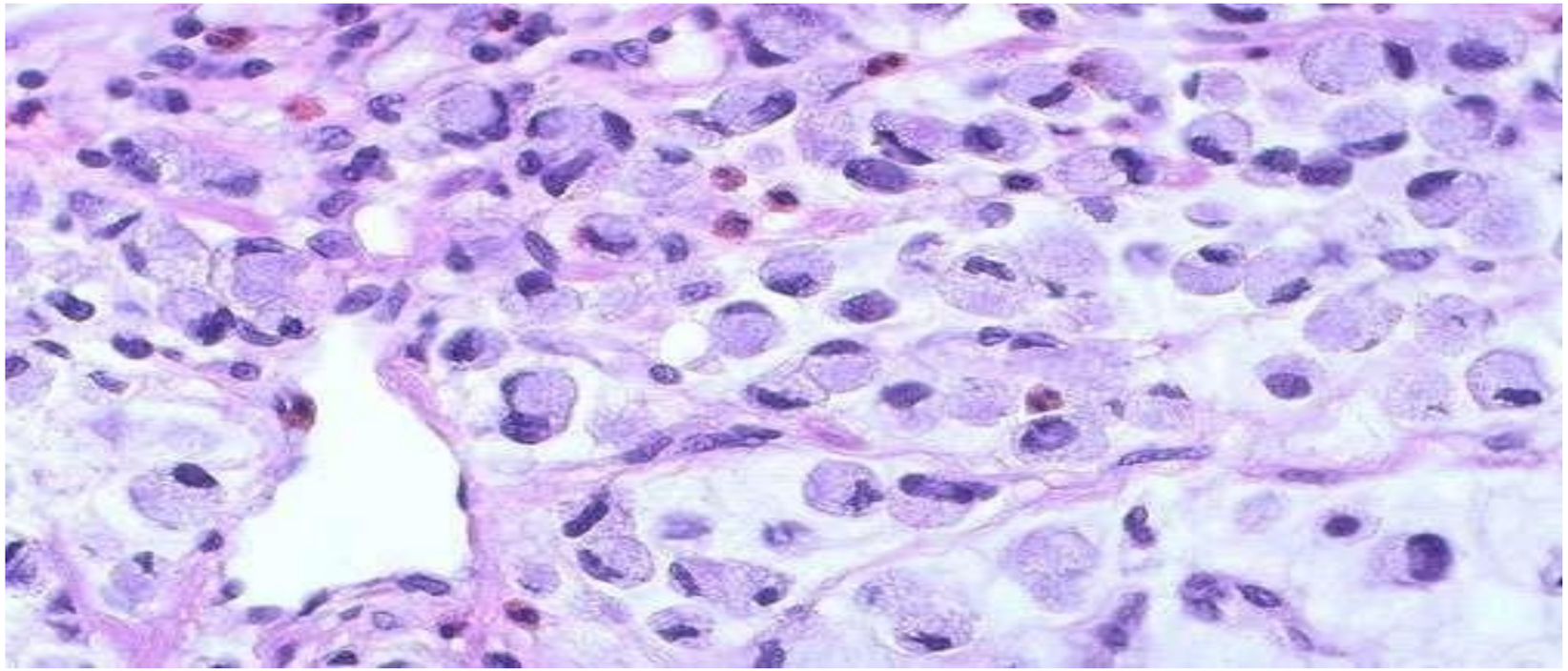
Longitudinal opening of the stomach appears the thickening of the wall



Signet ring cells: large mucin vacuoles that expand the cytoplasm and push the nucleus to the periphery,

Under the microscope , cells are discohesive, sometimes they form a signet ring cell morphology. The nucleus is displaced to one side, and a droplet of mucous replacing the cytoplasm

شكله زي الخاتم



Diffuse type, signet ring cells

Clinical Features

- Intestinal-type gastric cancer
- High-risk areas
- Develops from precursor (adenoma , dysplasia associated w/ intestinal metaplasia → Develops into intestinal type)

Mean age 55 yrs. Old age group

- Males :Females 2:1

Diffuse type gastric cancer:

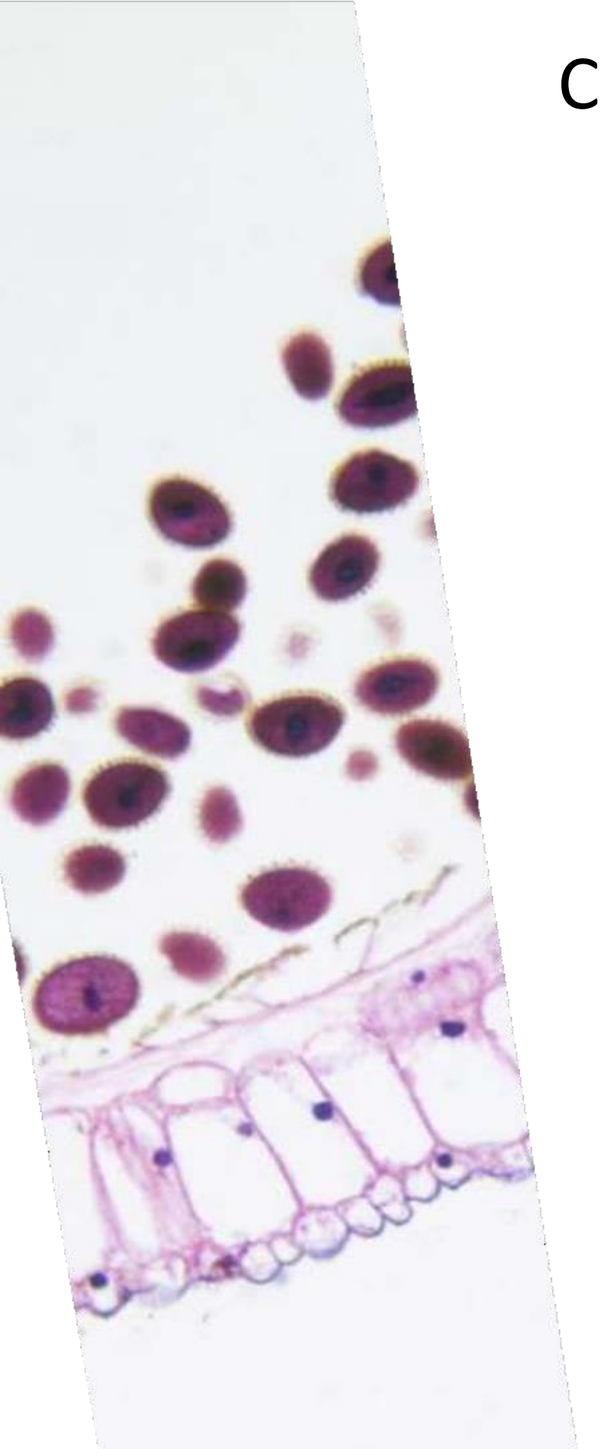
Incidence uniform across countries.

No precursor lesion. It develops from only a gene mutation in E-cadherin gene

Males:Females 1:1

Younger age.

Ex. A young patient in thirties with gastric cancer most probably it's a diffuse type, a very bad tumour with a bad deterioration



Clinical features:

The drop in gastric cancer incidence applies only to the intestinal type.
Because diffuse types aren't affected by any prevention or screening programs

Incidences of intestinal and diffuse types are now similar in some regions.
Most powerful prognostic factors: depth of invasion & extent of nodal and distant metastasis at the time of diagnosis
The prognosis (how the tumor will behave in the future or the outcome) depends on the stage => size of the tumor, depth of invasion, lymph node mets and distant mets.

So stage is the most important prognostic factor.

Most cases discovered at advanced stage. Why? Because symptoms aren't specific similar to chronic gastritis, it could be ignored by the patient for years till developing into an advanced stage.

5-year survival 90% to <30% for early and advanced tumors, respectively.
Tx: surgery, chemotherapy, targeted Tx (anti HER2)

Lymphoma

The lymphoma mainly occurs in lymph nodes, but it could affect extranodal sites and the most common site is the stomach

- **Stomach is the most common site of extranodal lymphoma.**
- 5% of all gastric malignancies.
- Most common type : extranodal marginal zone B-cell lymphomas (MALToma) (indolent with good prognosis) => caused by H.pylori
- Second most common lymphoma: diffuse large B cell lymphoma (aggressive means it's a high grade tumour)

Neuroendocrine (Carcinoid) Tumor

Carcinoid = mini carcinoma

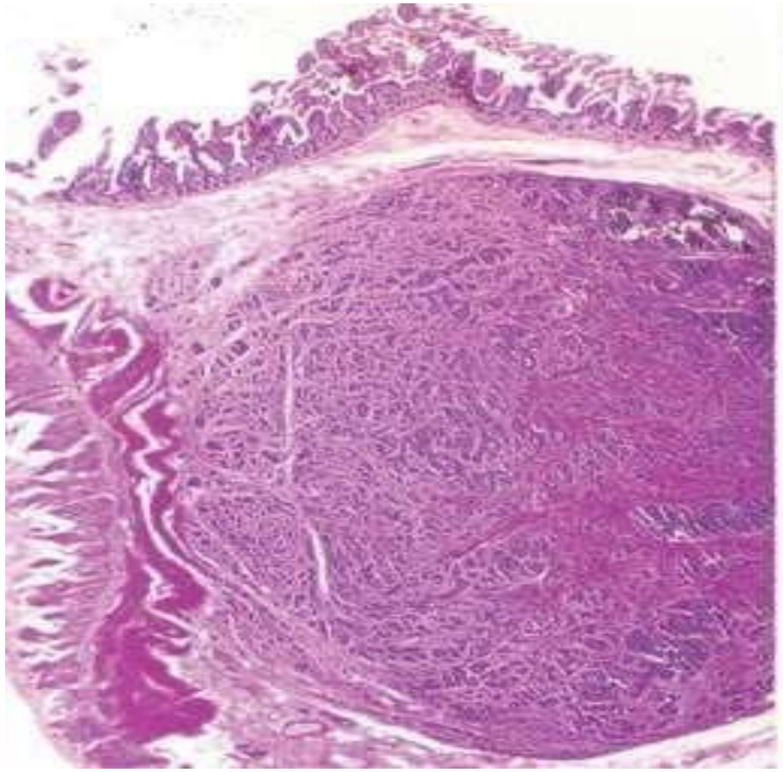
Tumors arising from neuroendocrine-differentiated gastrointestinal epithelia (e.g., G cells).

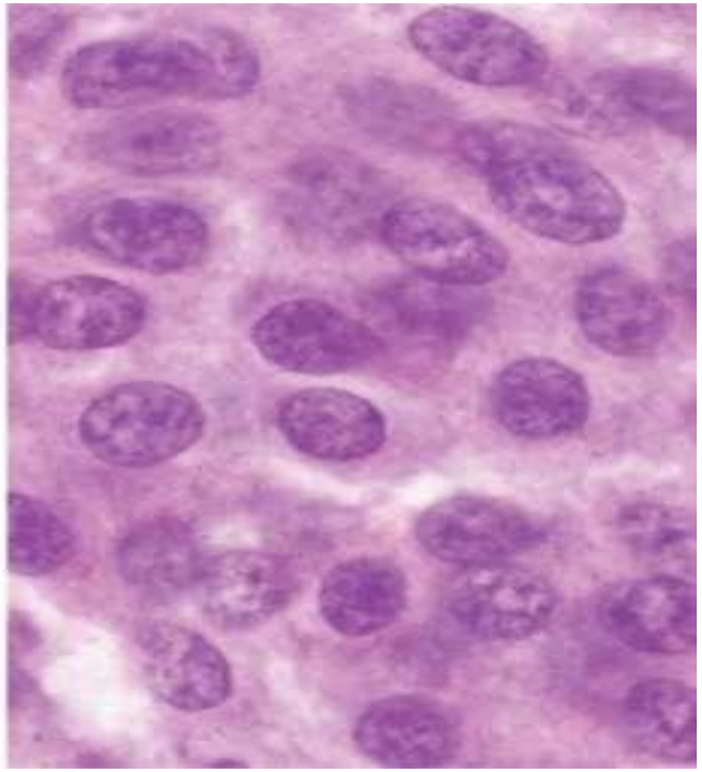
> 40% occur in the small intestine. But it could occur anywhere in GI system

- They occur in stomach on a background of autoimmune gastritis
- Autoimmune gastritis => G-cell hyperplasia => **carcinoids**.

Associated with *endocrine cell hyperplasia*, chronic atrophic *gastritis*, and *Zollinger- Ellison syndrome*

Slower growing than carcinomas. With good prognosis



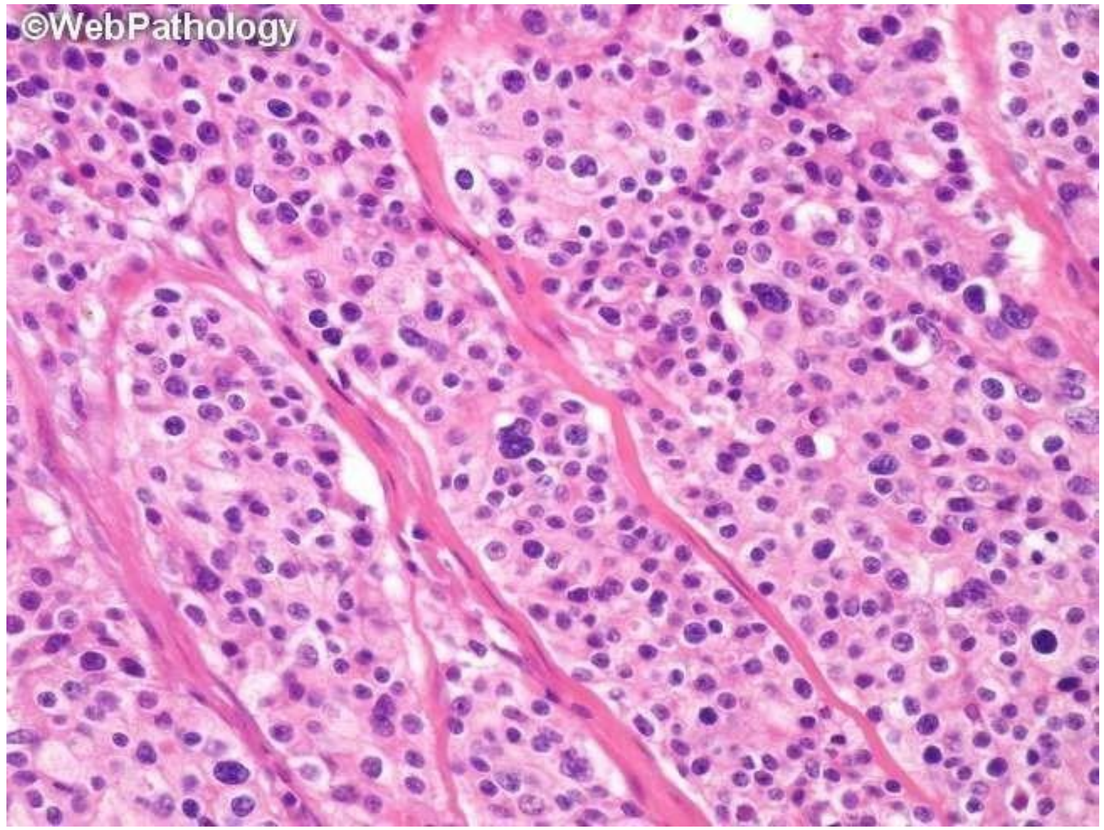


Under microscope they form nodules in the ***Submucosa*** unlike intestinal and diffused adenocarcinoma which were found in mucosa.

The cells characteristically showing salt and pepper appearance
(Salt and pepper nuclei morphology is special for neuroendocrine tumors or carcinomas)

Intramural or submucosal masses (small polypoid lesions)

Islands, trabeculae, strands, glands, or sheets of uniform cells with scant, pink granular cytoplasm and salt and pepper chromatin.



Other features of lymphoma
- **Abundant cytoplasm**
- **found as islands or nests**

When do we think about Neuroendocrine tumor?
1 if nesting pattern is seen under microscope
2 salt and pepper nuclei are seen

carcinoid syndrome

Not all patients with carcinoid tumor should have carcinoid syndrome

Due to vasoactive substances. Those vasoactive amines are produced by Neuroendocrine cells

Seen in 10% of cases.

strongly associated with metastatic disease.
Mostly liver metastasis

Manifesting as =>

Cutaneous flushing, sweating, bronchospasm, colicky abdominal pain, diarrhea, and right-sided cardiac valvular fibrosis

Additional Resources:

رسالة من الفريق العلمي:

External Explanation :

- **YouTube channel called (*ILOVEPATHOLOGY*)**

After Studying :

- **ChatGPT : When you finish studying, try to solve a quiz using it**

اللهمُ وفقني وافتح على قلبي ونوربصيرتي ولا تضيع

لي يا الله تعبًا وسخرلي من حيُث لا أحتسب عونًا

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

Corrections from previous versions:

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