GI

Pathology

LEC no. 2

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Additional and external information will be in this color (light blue).

Remember:
Chronic gastritis is caused by

1) **H.pylori (most common)**
2) **Autoimmune (around 10% of cases)**

Autoimmune Gastritis

Cause: antibodies directed towards self-antigens.
Those self-antigens are mostly parietal cells (cells of the body and cardia of the stomach) and intrinsic factor.

- Antibodies to parietal cells and intrinsic factor in serum.
- Reduced serum pepsinogen I levels
- Antral endocrine cell hyperplasia
- Vitamin B12 deficiency >>> pernicious anemia and neurologic changes
- Impaired gastric acid secretion (*achlorhydria)*

Or hypochlorhydria (due to the damage of parietal cells)

- Marked *hypergastrinemia*

increased gastrin levels

- Spares the antrum.

in terms of inflammation, it is only found in the body of the stomach.
But we can see some hyperplasia in the antrum.

-Intrinsic factor is found in the stomach and is important in the Absorption of vitamin B12.

-If we do a serology serum test in cases of autoimmune gastritis, we will find only anti-parietal and anti-intrinsic factor antibodies, with no anti-H.pylori antibodies.

- Reduced serum pepsinogen levels can also be seen due to the damage of chief cells (by the inflammation present and not the antibodies).

-A biopsy taken from the body of the stomach will show reduced numbers or even absence of parietal cells.

-less parietal cells = atrophy in the stomach wall = less acid production.

-Reduced acid production will cause the endocrine cells (G cells) in the antrum (which normally secrete HCL (acid)) to proliferate and secrete more gastrin (so hypergasrtinemia but will still have decreased acyl production) in an attempt to compensate for the decrease in acid production leading to antral endocrine cell hyperplasia.

-This hyperplasia can sometimes develop into a tumor => neuroendocrine tumor.

Pathogenesis

Immune-mediated loss of parietal cells >>> reductions in acid and intrinsic factor secretion.

Acid reduction >>> Hyperplasia of antral G cells >>> hypergastrinemia

G cells = antral endocrine cells

Deficient intrinsic factor >> deficient ileal VB12 absorption >> pernicious anemia.

MORPHOLOGY

In endoscopy, you can see erythema (due to inflammation).
Note that the inflammation is in the body not the antrum.

Oxyntic = acid producing = parietal cells

- Damage of the oxyntic (acid-producing) mucosa.
- Diffuse atrophy, thinning of wall, loss of gastric folds
- Lymphocytes, plasma cells, macrophages, less likely neutrophils.
- **Intestinal metaplasia >>> dysplasia >> carcinoma.**
- **G- cell hyperplasia >>> carcinoids.**

In advanced stages (when there's obvious loss in parietal cells) .

-Intestinal metaplasia can be the end result of any chronic gastric disease.
-Biopsy will show goblet cells (so metaplasia) (precursor of adenocarcinoma).

Clinical features

- 60 years, slight female predominance.
- Often associated with other autoimmune diseases
- Dyspepsia.
- Anemia (VB12 or iron)

-Autoimmune diseases tend to cluster together, for ex: a patient will have hashimoto thyroiditis, diabetes type 1, etc..
-Dyspepsia: a clinical term. It means epigastric pain, nausea and vomiting.
-Dyspepsia alone is not a diagnostic feature since H.pylori also has this manifestation. So, serology tests must be done.
-Iron deficiency is found when we have ulcers and bleeding.

Very important summary!!

Table 15.2 Characteristics of *Helicobacter pylori*–Associated and Autoimmune G

Feature	*H. pylori*–Associated	Autoimmune
Location	Antrum	Body
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to markedly increased	Markedly increased
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
Serology	Antibodies to *H. pylori*	Antibodies to parietal cells (H^+,K^+-ATPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, lymphoma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas	Autoimmune disease; thyroiditis, diabetes mellitus, Graves disease

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Complication of chronic gastritis **Regardless of the cause**

- Peptic ulcer.
- Mucosal atrophy.
- Intestinal Metaplasia **a precursor of dysplasia and carcinoma**
- Dysplasia.

Pathology of the stomach- 2

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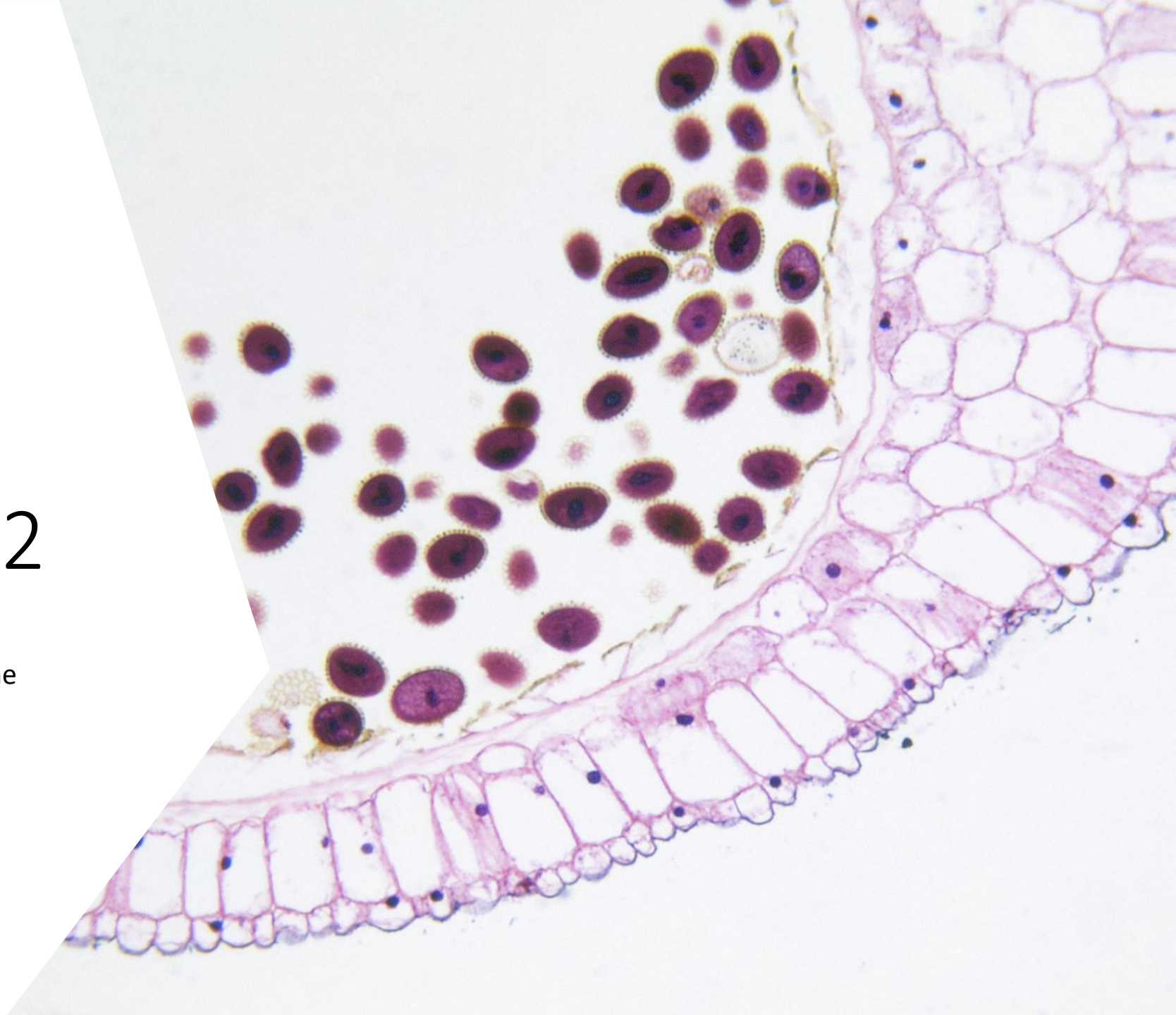


Peptic Ulcer Disease

peptic is a broad word, it refers to any portion of the GI tract that is exposed to acidic juices.
So peptic = any site exposed to acid and pepsin

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

Pathogenesis of PUD:

Not everyone who has gastritis will develop ulcers. For ex: only 5-10% of H.pylori patients develop ulcers.

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

The major cause, no acid = no ulcers

- Cofactors: smoking, chronic NSAIDs, high-dose corticosteroids, alcoholic cirrhosis, COPD, CRF, hyperparathyroidism.
- **Hyperacidity is caused by**:
- H. pylori.
- Parietal cell hyperplasia.
- Excessive secretory response (vagal)
- Hypergastrinemia as in Zollinger-Ellison syndrome

-Corticosteroids inhibit PGs synthesis (important for the integrity of gastric walls).
-COPD and cirrhosis patients use corticosteroids => further predisposition.

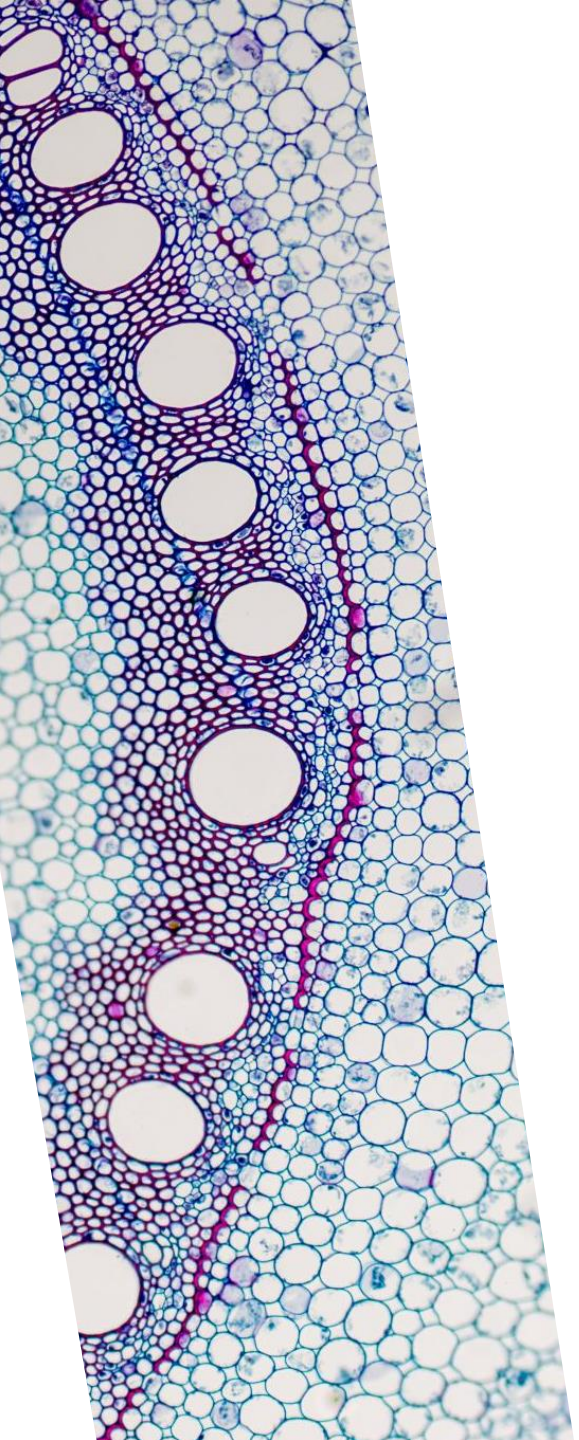
CRF = chronic renal failure.
CRF and hyperparathyroidism cause hypercalcemia, hypercalcemia then causes hypergastrinemia (increased gastrin) resulting in increased acidity.

Zollinger-Ellison syndrome(tumor producing gastrin)

- Multiple peptic ulcerations
- Stomach , duodenum, even jejunum
- Caused by uncontrolled release of gastrin by a tumor (gastrinoma) and the resulting massive acid production.

- **So severe hypergastrinemia and therefore severe or hyper acidity with a huge number of ulcers.**

-not confinded to the stomach.



MORPHOLOGY

The stomach has more protective factors against acidity.

- 4:1, proximal duodenum : stomach.
- Anterior duodenal wall or antrum.
- **>80% solitary (only one large well demarcated ulcer)** .
- Round to oval, sharply punched-out
- **Base of ulcers is smooth and clean**
- Granulation tissue.
- Hemorrhage & Perforation are complications.

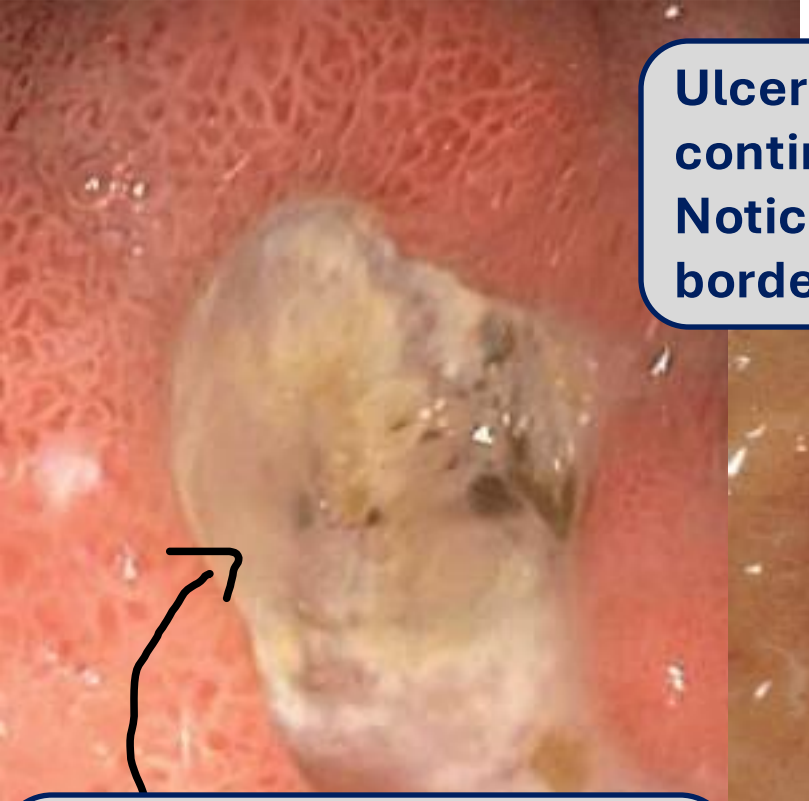
Note that proximal duodenum is affected more than the stomach.

Due to the presence of granulation tissu

Hemorrhage = presents with upper GIT bleeding.
Perforation = presents with rupture to the abdomen and peritonitis (inflammation of the peritoneum).

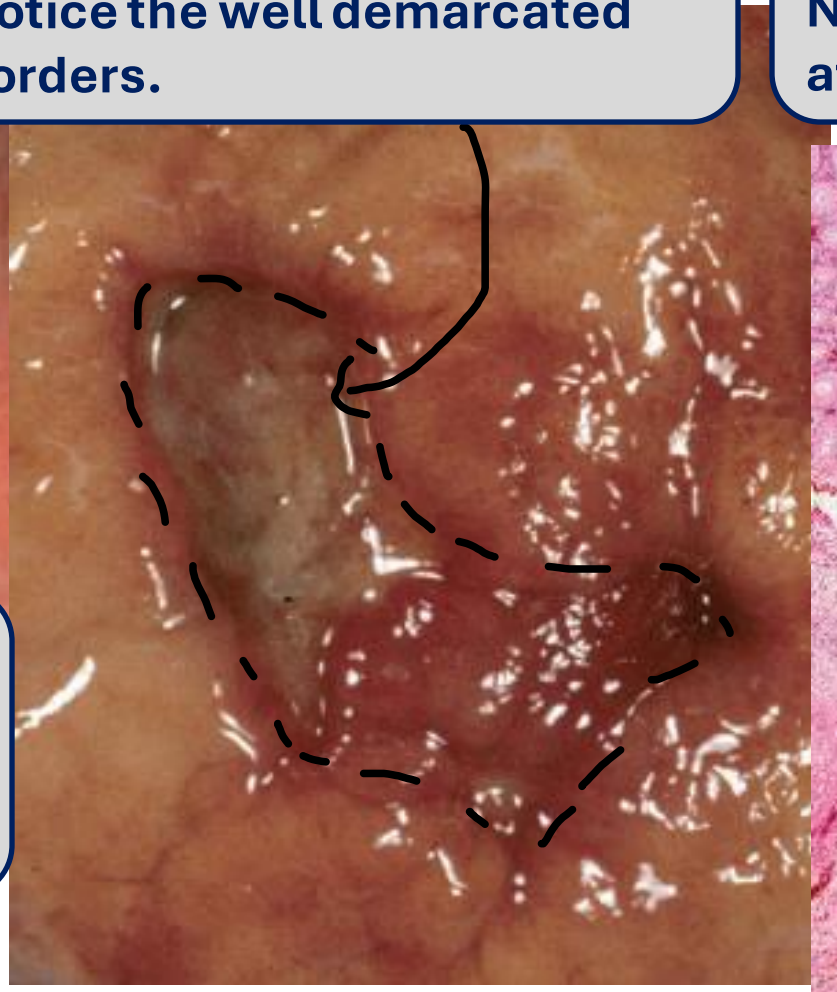
-You need to know what makes them different from stress induced ulcers.

1) Stress induced ulcers: multiple, suddenly appearing, small ulcers with black or brown blood-stained base, found anywhere in the stomach, no gastritis in the adjacent mucosa and no scarring, and heal spontaneously when you trat the underlying condition
2) Chronic ulcers: more common in duodenum, mostly solitary (only one ulcer), large, well demarcated (punched out) borders, clean (white or pink) base of ulcers.

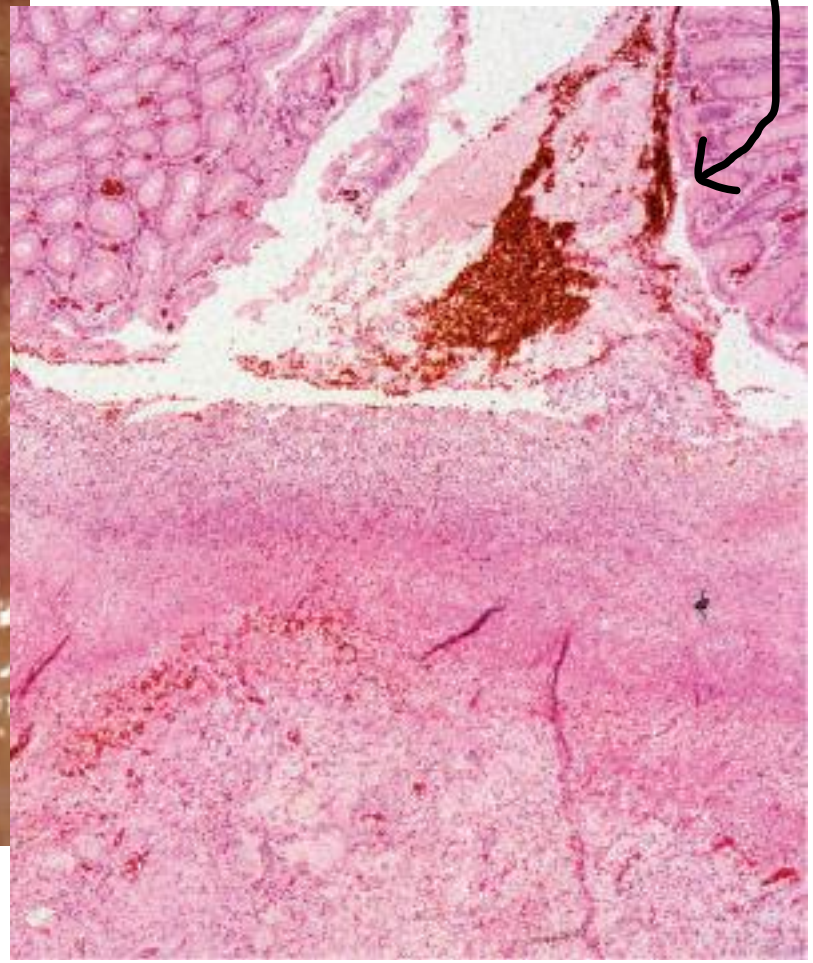


Notice the white base of the ulcer, this white color represents a granulation tissue.

Ulcer means a break in the continuity of the mucosa.
Notice the well demarcated borders.



Microscopically, you can see that it is rich in blood supply.
New blood vessels formation in an attempt to heal the ulcer.



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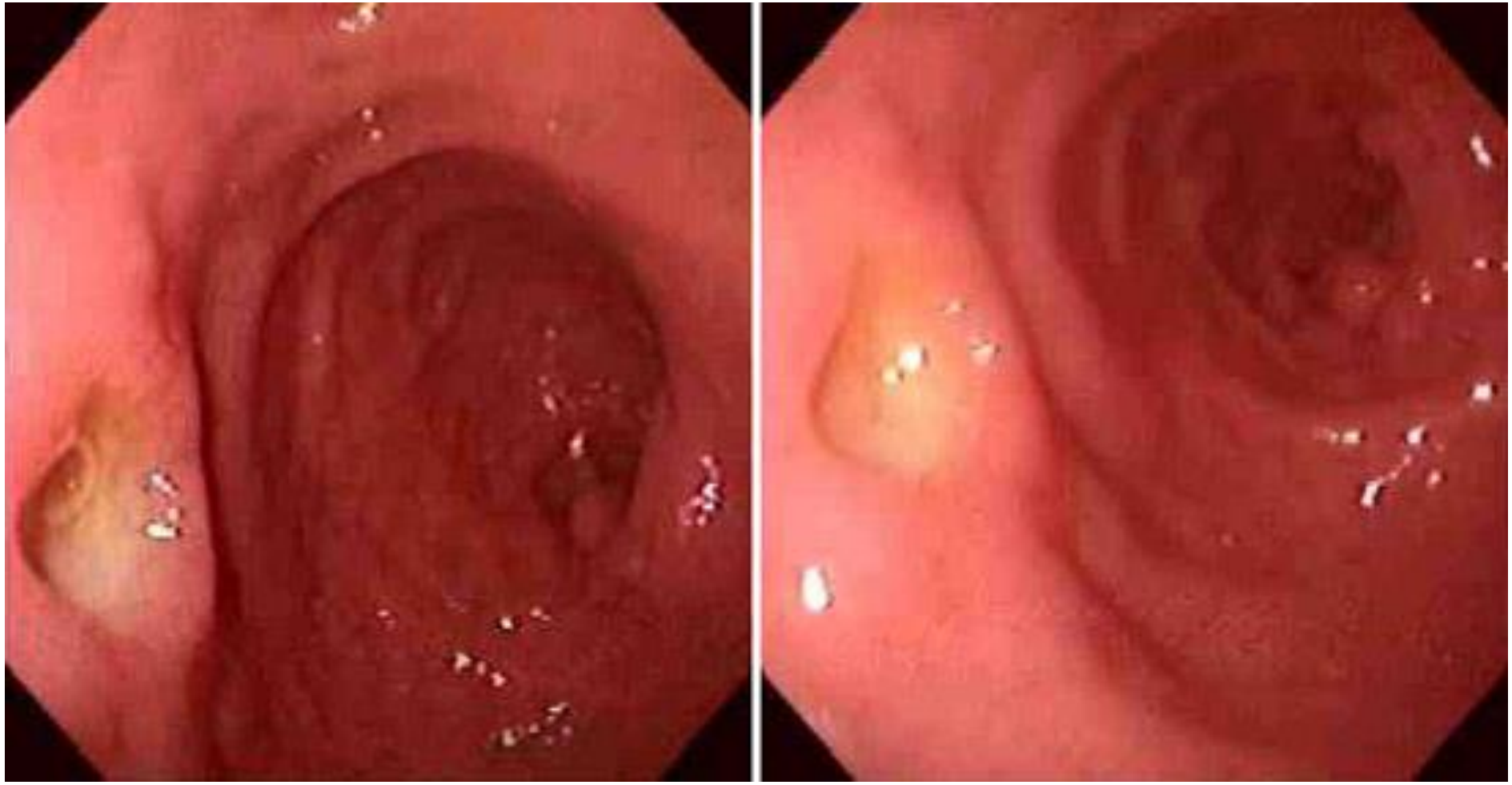
Duodenal ulcer

an ulcer in the anterior wall of the duodenum (notice that it's large).



Clinical Features

iron deficiency is caused by continuous long-term bleeding.

- Epigastric burning or aching pain
- Complication: Iron deficiency anemia, frank hemorrhage, or perforation.
- Pain 1 to 3 hours after meals at daytime
- Worse at night, relieved by alkali or food
- Nausea, vomiting, bloating, bletching.

the pain is described as empty stomach pain.

- Current therapies are aimed at H.pylori eradication.
- Surgery reserved for complications.

Because H.pylori is responsible for 90% of cases.

complications like hemorrhage and perforation.

GASTRIC POLYPS AND TUMORS

- Gastric Polyps:
- Inflammatory and Hyperplastic Polyps(**benign**)
- Gastric Adenoma

Adenoma = hyperplastic polyp with dysplasia

- Gastric Adenocarcinoma
- intestinal and diffuse types

- Lymphoma **caused by H.pylori**
- MALToma.

- Neuroendocrine (Carcinoid) Tumor
- Gastrointestinal Stromal Tumor

These two will not be discussed

Polyp: any outgrowth projecting above the surface of the mucosa.
-Polyps can be classified into:

1) **Inflammatory and hyperblastic polyps: benign, a result of chronic gastritis, regress after treatment. They represent the majority of cases.**
2) **Gastric adenoma: represent a small portion cases, but they have the risk of malignant transformation.**

Gastric polyps

- Polyps: masses projecting above the level of adjacent mucosa

- **Inflammatory and Hyperplastic Polyps**
- 75% of all polyps.
- Arise in a background of chronic gastritis
- Regress after H.pylori eradication.

Gastric Adenoma

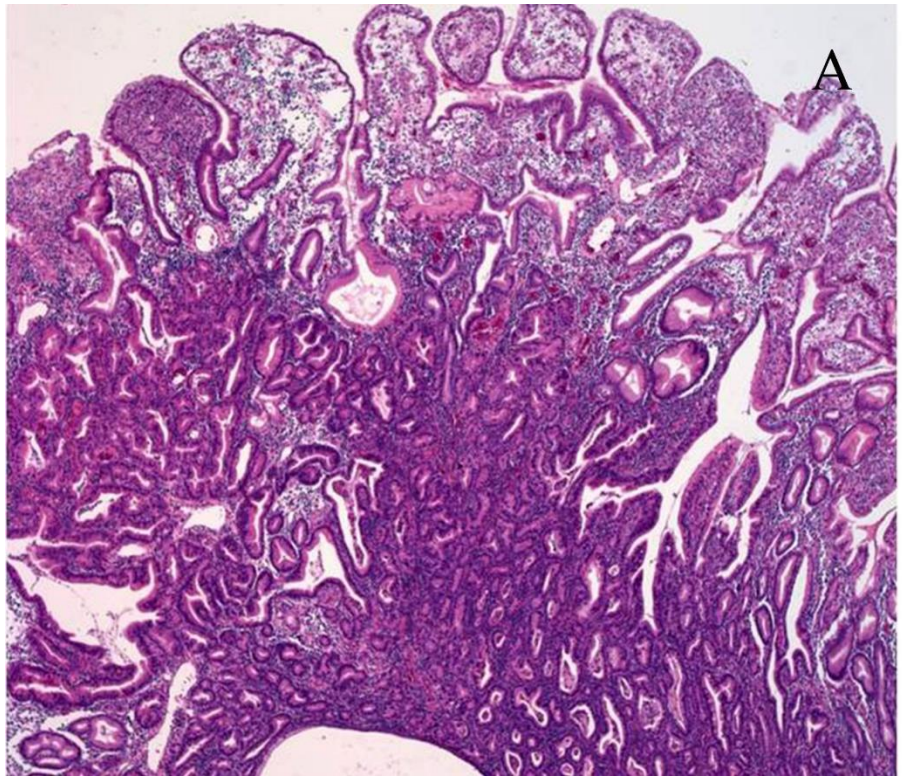
- 10% of all polyps.
- Increase with age.
- M: F = 3:1
- Background: chronic gastritis, atrophy and intestinal metaplasia.
- **Dysplasia, low- or high-grade.**
- Risk of adenocarcinoma related to the size (greatest if > 2cm).
- **Risk of carcinoma higher than colonic adenoma.**
- 30% have concurrent CA.

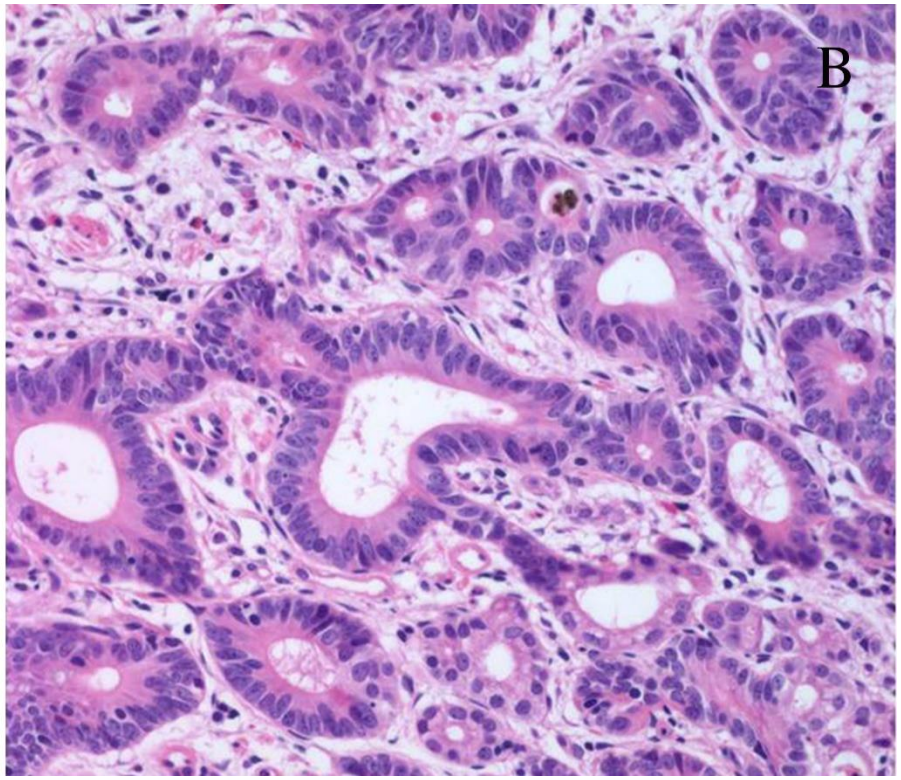
And polyps could be small or large.

Colonic adenomas are very common in older individuals.

Gastric adenoma

A polypoid growth harboring dysplasia.





Gastric Adenocarcinoma

Other cancers are lymphomas, neurodendocrine tumors, etc..

- 90% of all gastric cancers. A tumor of epithelial origin
- Early symptoms mimic gastritis >>> late diagnosis.
- Marked geographic variation (Japan, Costa Rica, Chile).
- Screening >> early detection.
- Background of mucosal atrophy and intestinal metaplasia. Only in the intestinal type.
- PUD does not increase risk, except after surgery

PUD= peptic ucler disease

- **In [illegible] increased rate of cardia cancer due to GERD & obesity.**
- **Two main types: intestinal and diffuse.**

Rates dropped because the incidence of H.pylori dropped.

-It has symptoms close to gastritis which can lead to misdiagnosis or late diagnosis.
-There is geographic variations, areas like Japan, costa Rica, Chile and Eastren Europe are in a higher risk.
-The most common Adenocarcinoma in high-risk countries is the intestinal type that comes from chronic gastritis.
-The diffused type Adenocarcinoma has no geographic variations.
-Screening is only cost-effective in high-risk countries.
-peptic ulcers do not increase the risk. It only does so after surgery because most of the times there will be bile reflux after surgery, and bile is carcinogenic to the stomach.

Pathogenesis

Just like any cancer, it results from the accumulation of many mutations
APC: Adenomatous polyposis coli.

- Genetic alterations (H.Pylori associated chronic gastritis , lesser extent EBV (10%).
- Most cases are sporadic. **H.pylori is the predominant cause**

- Familial diffuse type: germline mutations in *CDH1* (E-cadherin).
- Sporadic diffuse type: somatic CDH1 mutation in 50%.
- Familial intestinal type cancer: FAP, APC gene mutation.
- Sporadic intestinal-type Ca: B catenin mutation

- Sporadic cases: P53 mutation + HER2 amplification.

Sporadic cases of both types.
20% of cases present with HER2 amplification.
This can be used in therapy (targeted therapy).

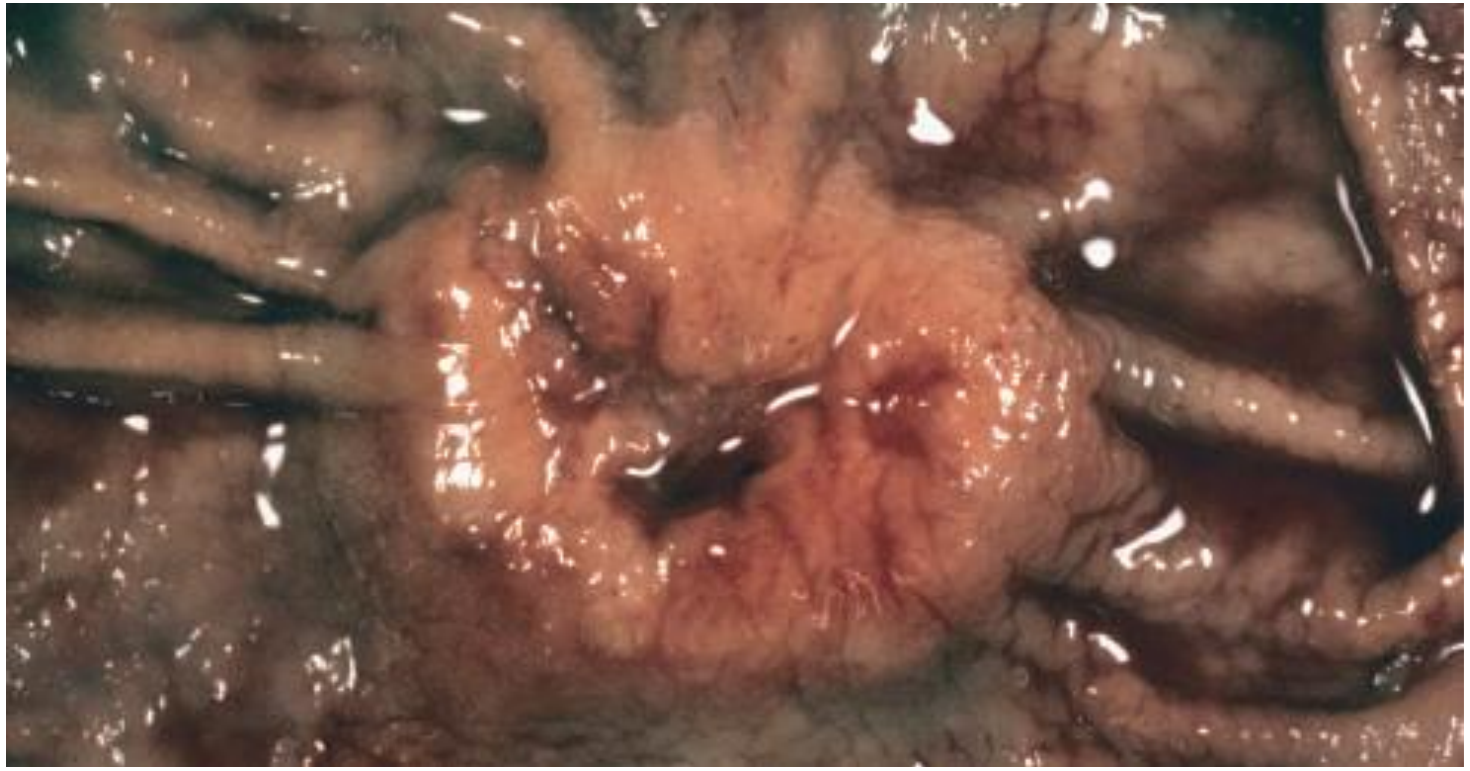
The diffused type is always associated with E-cadherin mutation (CDH1).
It is responsible for the adhesion between cells. So, no cadherin Will result in seperation of cells. (that's why it's called diffused type).

MORPHOLOGY

- Lauren classification: separates gastric cancers into
- **Intestinal type:**
- Bulky.
- Exophytic mass or ulcer.
- Form glands.

- **Diffuse type:** **No mass can be seen in endoscopy, Hard to diagnose.**
- Infiltrative growth pattern
- Discohesive cells (signet ring cells)
- Desmoplastic reaction (stiffens wall, flat ruge, linitis plastic).

-It is called intestinal because it is similar to the intestinal type cancer, like colonic cancer Under the microscope.
Intestinal type is mostly a result of a precursor lesion (metaplasia => dysplasia => carcinoma).
-Diffused type has no precursor (easy to miss in diagnosis).

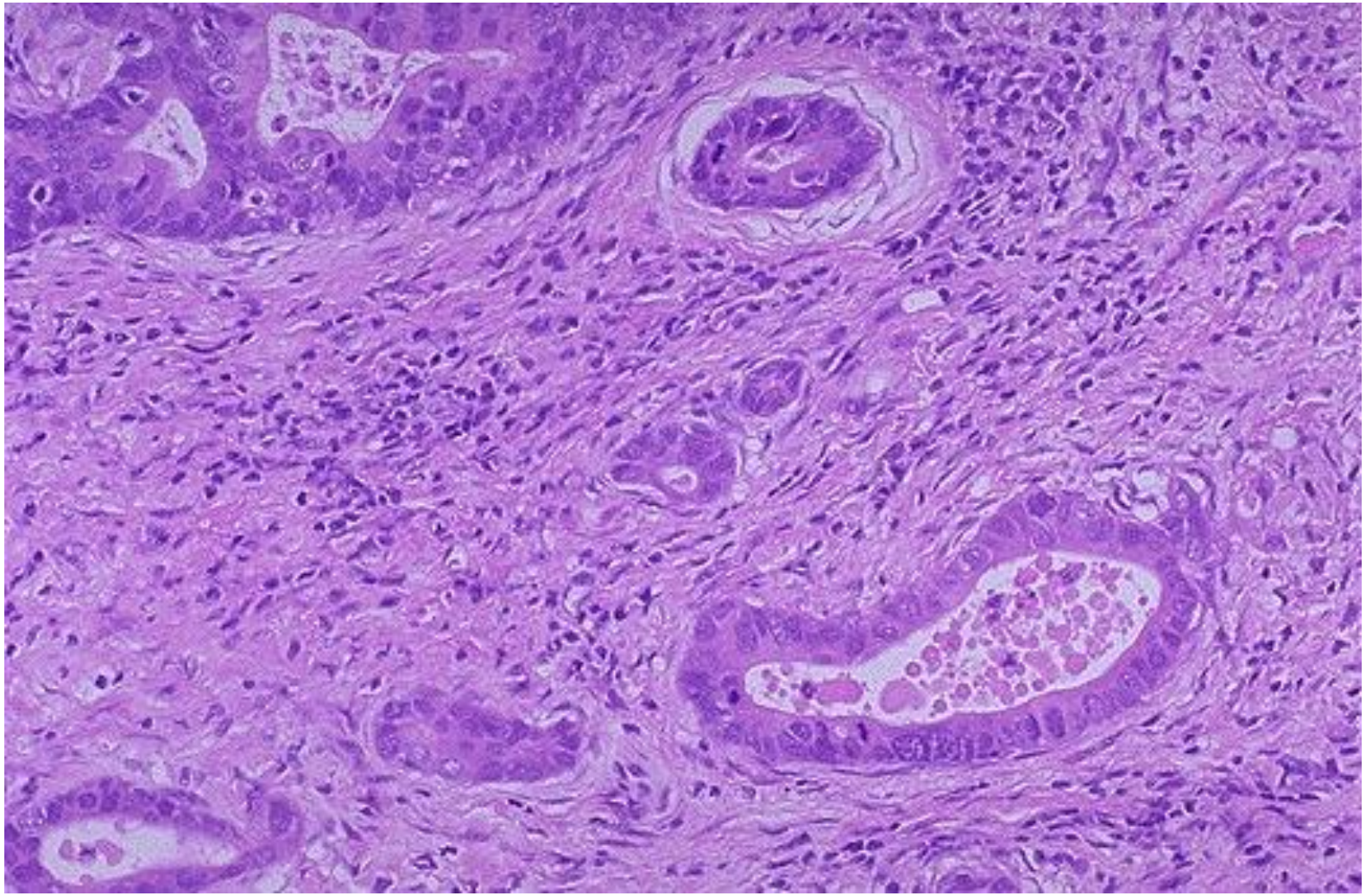


Intestinal type

You can see the mass

Intestinal type

You can see the glands microscopically
Therefore, it is the intestinal type.

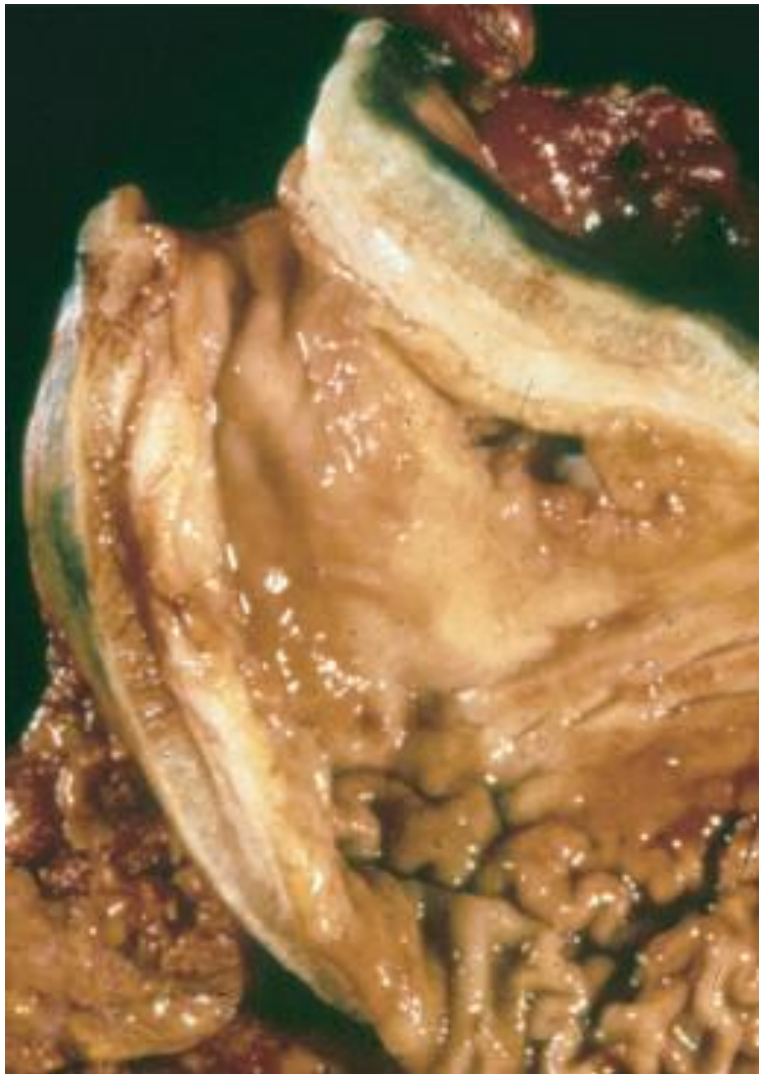


Linitis plastica

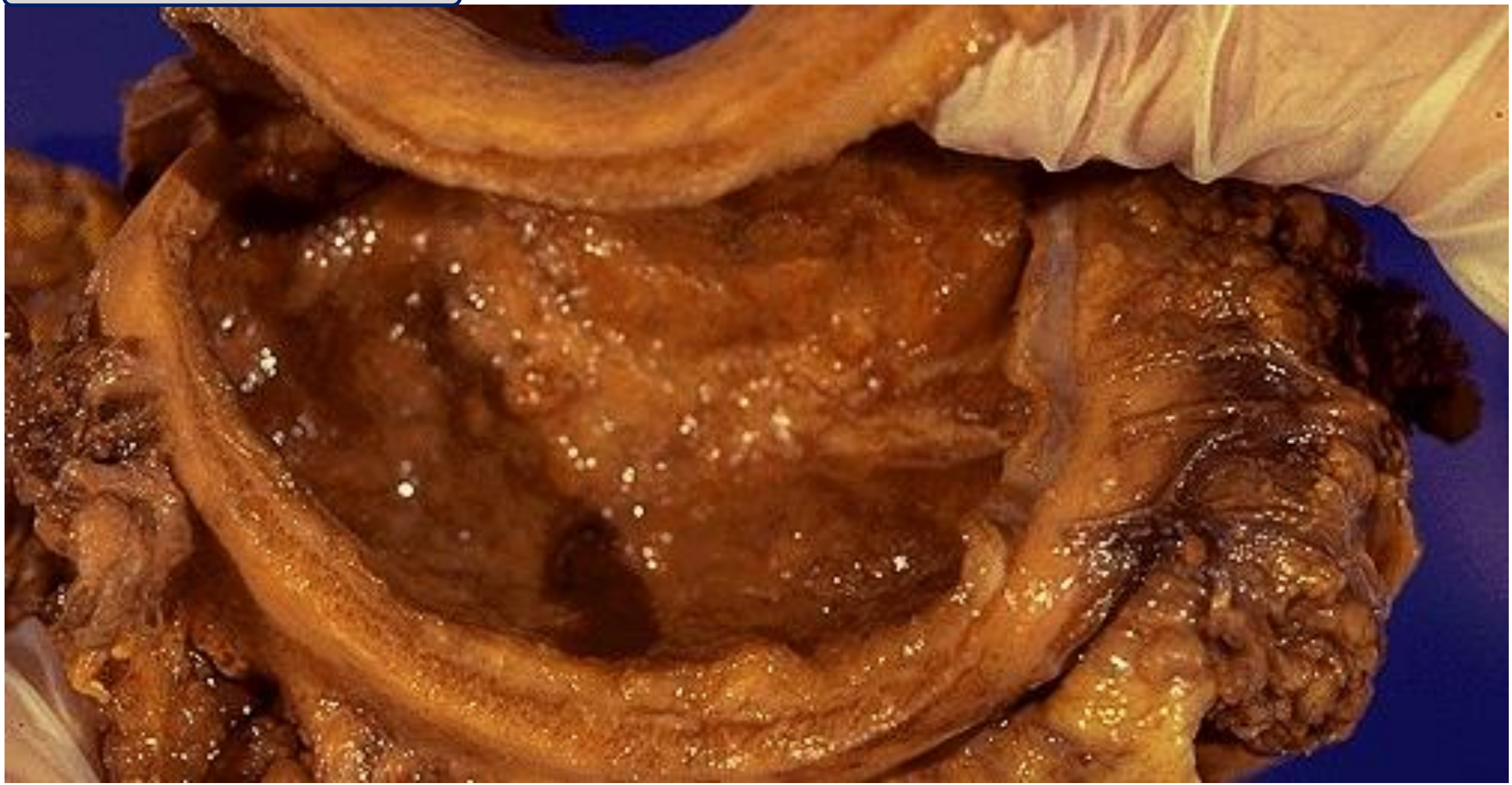
Diffuse growth pattern, you can see the thickening of the intestinal wall.

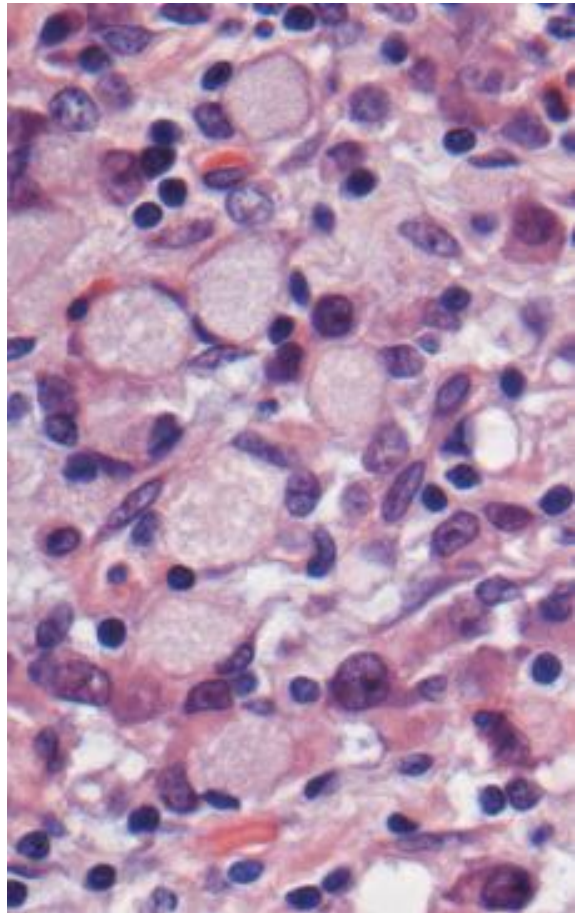
No masses can be seen.

Sometimes you can see loss of folds (flat) due to the diffused growth => Linitis plastica.



Thickened stiff gastric wall

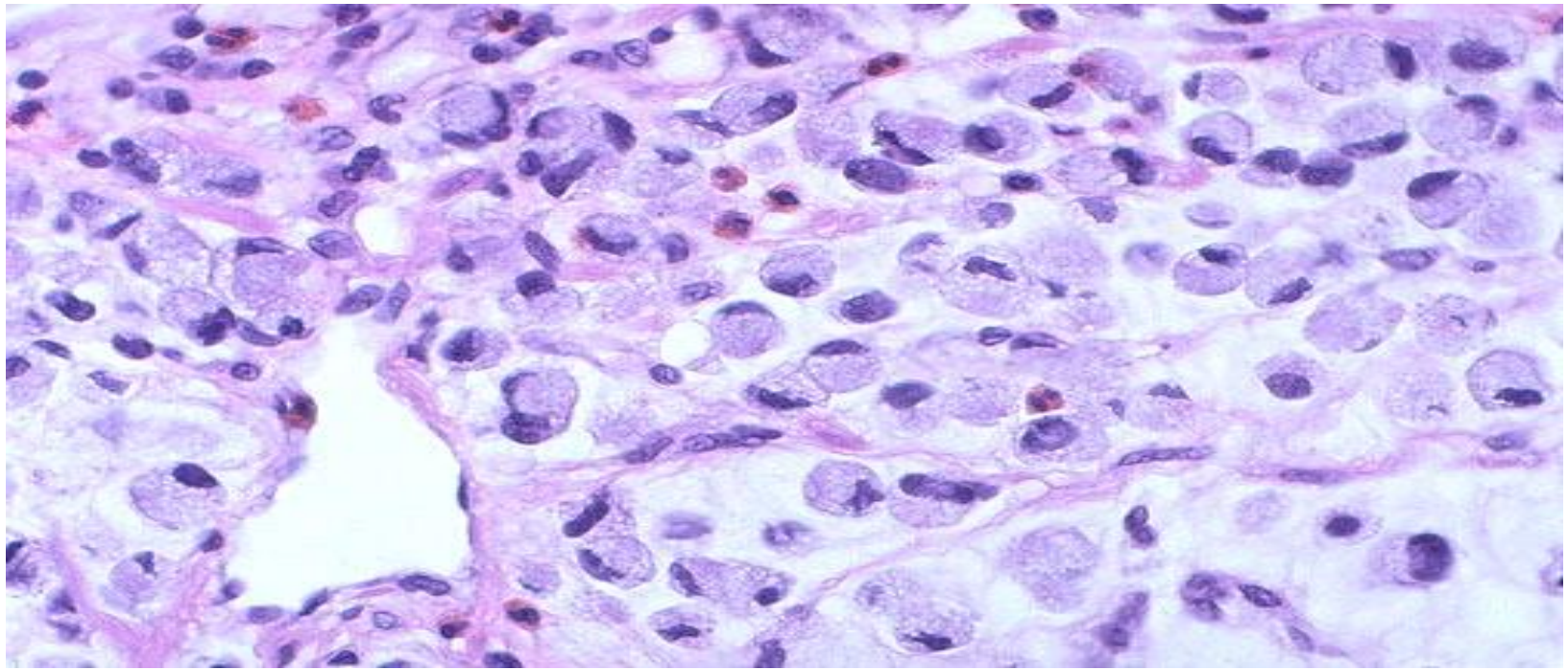




Found in the diffused type

Signet ring cells:

large mucin vacuoles that expand the cytoplasm and push the nucleus to the periphery,



No glands

Diffuse type, signet ring cells

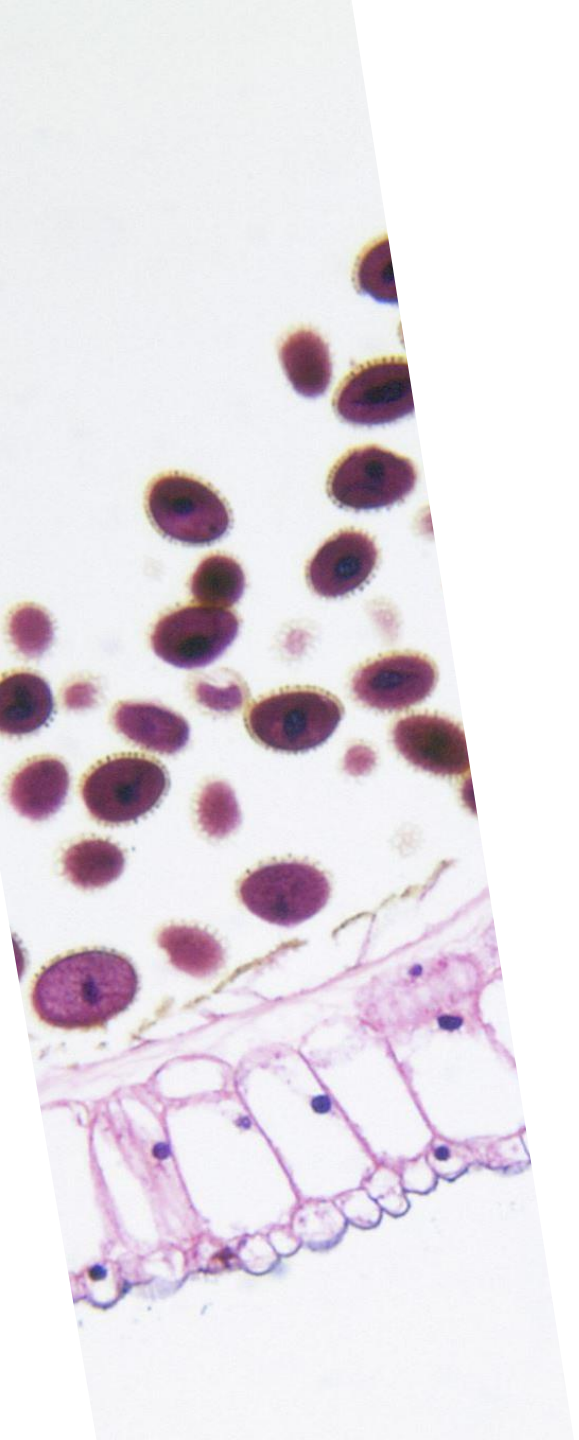
Clinical Features

- **Intestinal-type gastric cancer**
- High-risk areas
- Develops from precursor (adenoma, dysplasia associated w/ intestinal metaplasia)
- Mean age 55 yrs.
- M:F 2:1

- **Diffuse type gastric cancer:**
- Incidence uniform across countries.
- No precursor lesion.
- M:F 1:1
- Younger age.

no mass formation

more common in younger individuals.
So, if you see a 30 years old patient with gastric cancer, it is mostly the diffused type.
It is a bad tumour => can infiltrate walls and metastasis.



Clinical features:

Clinical features similar to chronic gastritis.

- The drop in gastric cancer incidence applies only to the intestinal type.
- 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**

Most powerful prognostic factor is the cancer stage.

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

Grade vs Stage

Stage: it is decided by the depth of tumour invasion, lymph node metastases and distant metastases

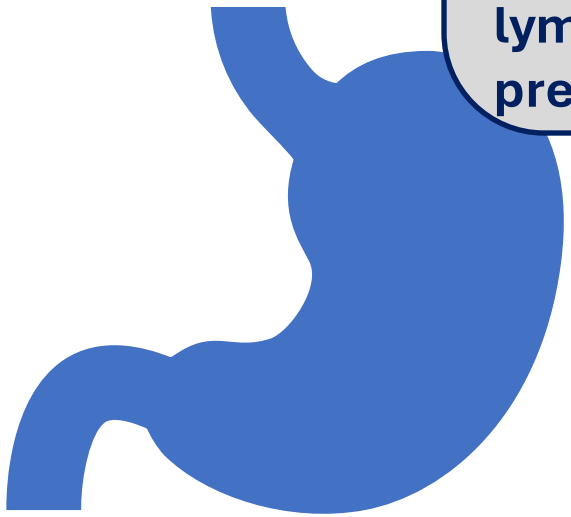
Stage 1 or 2 => early stage

Stage 3 or 4 => advanced stage

Lymphoma

- **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)
- Second most common lymphoma: diffuse large B cell lymphoma (aggressive)

Marginal zone lymphoma is an indolent lymphoma (slowly growing).
Diffuse type lymphoma is an aggressive and bad lymphoma.



Same causative agent as intestinal type adenocarcinoma which is H.pylori.
Treatment of H.pylori can decrease the risk of lymphoma or regress the lymphoma if already present.

It is called extranodal because most lymphomas happen in the lymph nodes.
So, we must specify that this one is extranodal.

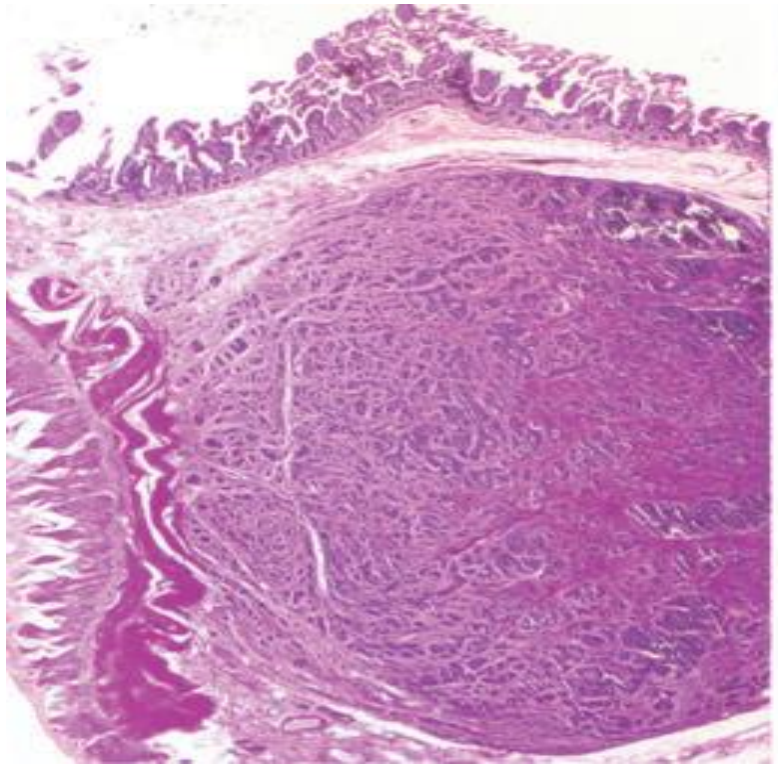
Neuroendocrine (Carcinoid) Tumor

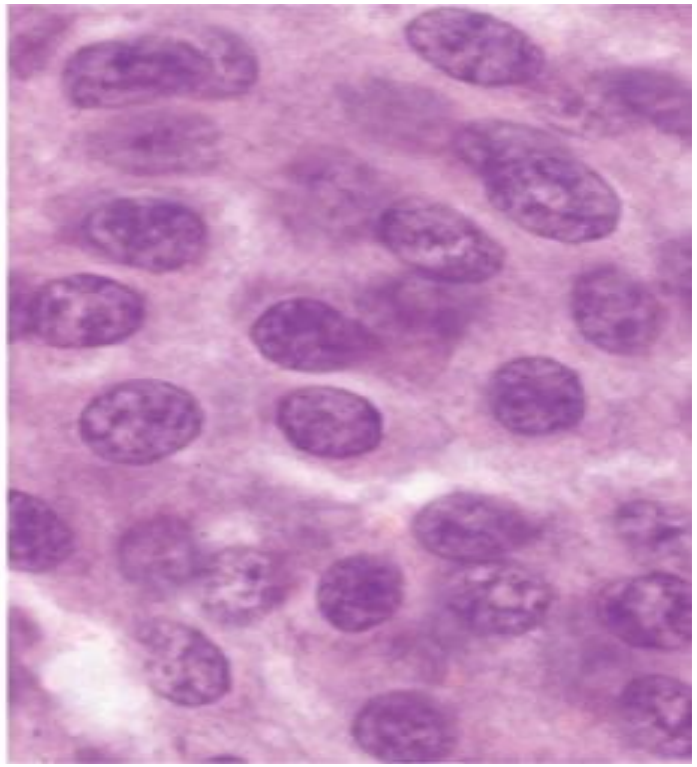
G cells are found in the antrum, proliferation of G cells can give us this tumour.

- Tumors arising from neuroendocrine-differentiated gastrointestinal epithelia (e.g., G cells).
- **> 40% occur in the small intestine**.
- Associated with endocrine cell hyperplasia, chronic atrophic gastritis, and Zollinger- Ellison syndrome
- **Slower growing than carcinomas**.

Others may arise anywhere along the GIT or even at other sites like the respiratory tract.

-Neuroendocrine cells are cells that secrete hormones.
-Carcinoid is a small carcinoma.

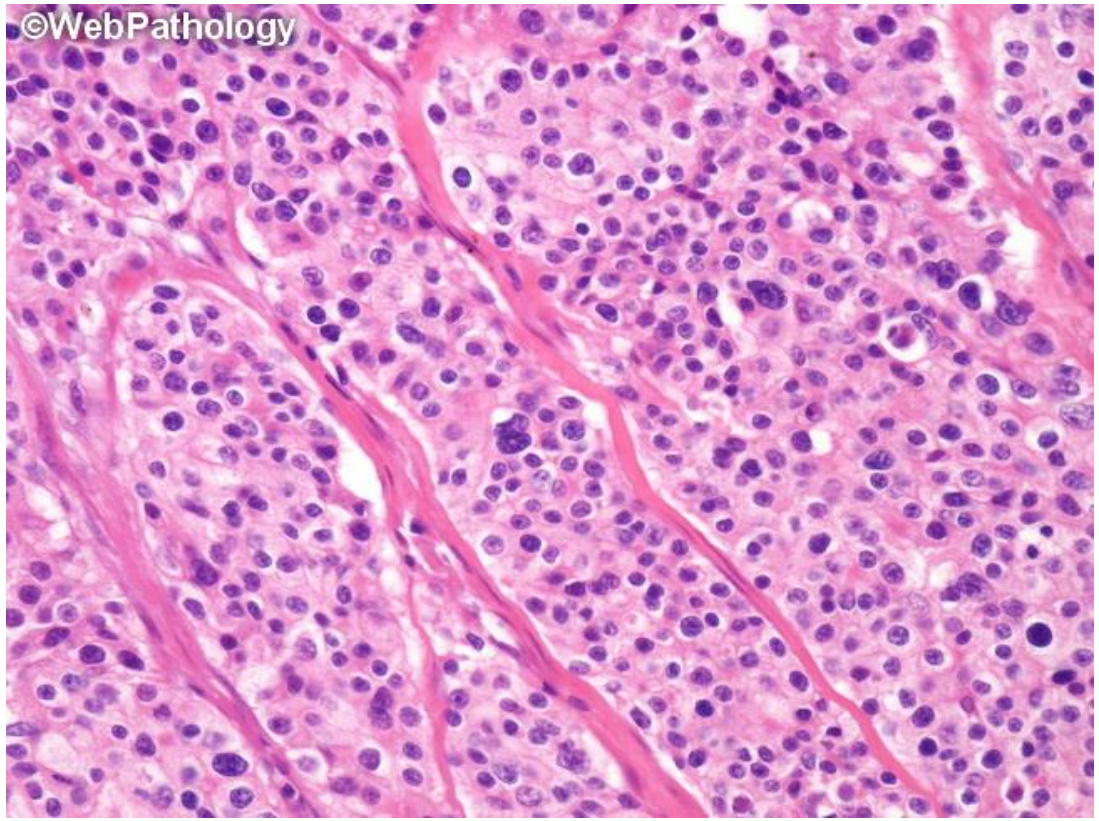




Intramural or submucosal masses (small polypoid lesions)

-Neuroendocrine tumour can present with a polyp that can be seen with endoscopy.
-Slowly growing, which means it is mostly an incidental finding.
-Under the microscope they show typical nuclear feature called salt and piper chromatin (not fine chromatin).

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



Those tumours can also form islands and show nesting (each group of cells are clustered together and separated from the other groups).

carcinoid syndrome

-Not common.
-Related to the release of vasoactive neuroendocrinal substances.

Due to vasoactive substances

Seen in 10% of cases.

strongly associated with metastatic disease.

Especially hepatic metastases

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

Bronchospasm will result in a difficulty in breathing.

GOOD LUCK!!!:)