GI
PATHOLOGY

#3

WRITER: Sana Al-Sokhon
CORRECTOR: Rawan Aqaileh
DOCTOR: Manar Hajeer

CHRONIC GASTRITIS

Remember the acute gastritis: has repaid onset, short period of time
While the chronic gastritis: has gradual onset ,long period of time

- *Causes:* **2 main causes**:

- ***Helicobacter pylori associated gastritis: most common.*** **It is responsible of 75% of cases**
- ***Autoimmune atrophic gastritis: less than 10% of cases.***

- **Less common**
- Chronic NSAID
- Radiation injury
- Chronic bile reflux.

Clinical features

The presenting symptoms will not differentiate if it is caused by H.pylori or autoimmune ,because they share the same symptoms :

- Nausea and upper-abdominal discomfort
- Vomiting
- Hematemesis uncommon. **(vomiting of blood)**

- Less severe **than the acute gastritis** but more prolonged symptoms.

Helicobacter pylori Gastritis

H.Pylori like to colonize in the antrum of the stomach, and they associated with increasing acid production ,so that they cause duodenal ulcers ,because the duodenum start to receive much more acidic juice from the stomach (hyperchlorhydria).

- Discovery of the association of H.pylori *w*ith peptic ulcer disease was a revolution.
- Spiral or curved, G-ve, bacilli.
- Underlying cause for almost all duodenal ulcers.
- Majority of gastric ulcers or chronic gastritis.
- Acute infection is subclinical.**(usually,asymptomatic acute infection then it will convert into chronic form)**
- ***Antral gastritis with increased acid production >> peptic ulcer***
- **Pangastritis if severe with hypochlorhydria.** **(In severe cases H.pylori will not stay in antrum rather than will go everywhere in the stomach ,and cause pangastritis).**
- **Intestinal metaplasia and increased risk of gastric cancer.**

It is treated by Triple therapy

-H.Pylori infection decreased in developed countries.

Associated features with H.Pylori infection :

- Poverty, household crowding, limited education, poor sanitation
- Infection is typically acquired in childhood, persists to adult-life.

The infection acquired in childhood and persists until the suitable conditions facilitate chronic gastritis .

- **Pathogenesis:** (H.pylori have virulence mechanisms to stay alive in the acidic environment of the stomach)
- H.pylori adapted to live in the mucus layer, non-invasive**(they don't enter the cells),** by
- **Flagella**: allow motility.
- ***Urease****: split urea to ammonia,* protect bacteria from acidic pH.(By covering itself with basic environment)
- ***Adhesins****:* bacterial adherence to foveolar cells
- ***Toxins****: CagA,* for ulcer or cancer development

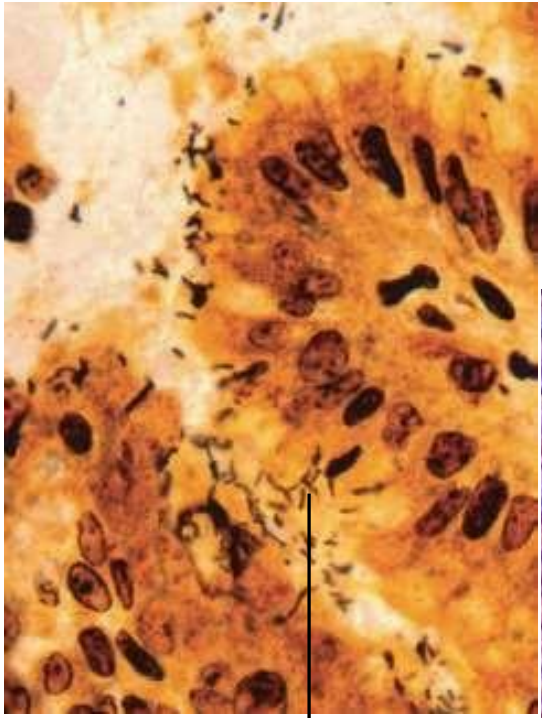
MORPHOLOGY

1-Macroscopic :when the doctor saw redness in the stomach during the endoscopy

2-Microscopic :

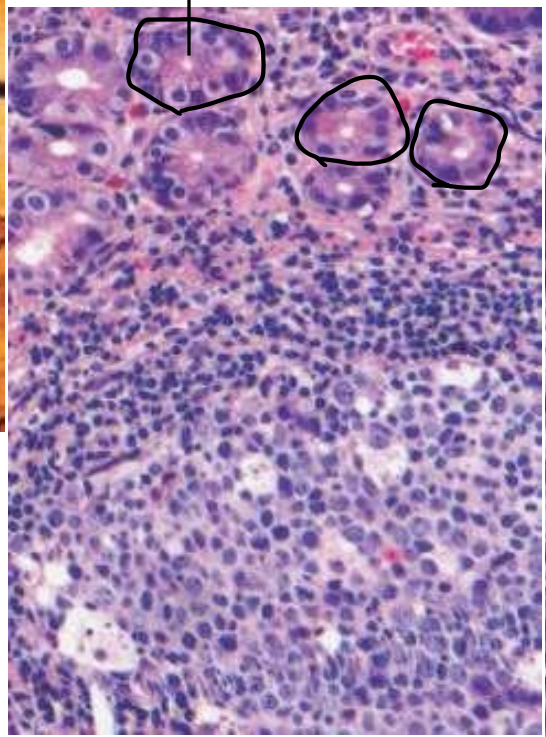
- Gastric biopsy: H. pylori in mucus layer, antrum.
- Neutrophils, Plasma cells, lymphocytes & macrophages. **(chronic inflammatory cells)**
- **Lymphoid aggregates>>> increased risk of MALT lymphoma.**
- **Intestinal metaplasia (goblet cells)>>> dysplasia >> increased risk of adenocarcinoma** **(so that periodic surveillance should take place to make sure this metaplasia regress back to normal with treatment)**

-MALT lymphoma :mucosa associated lymphoid tissue ,low grade lymphoma commonly in the stomach

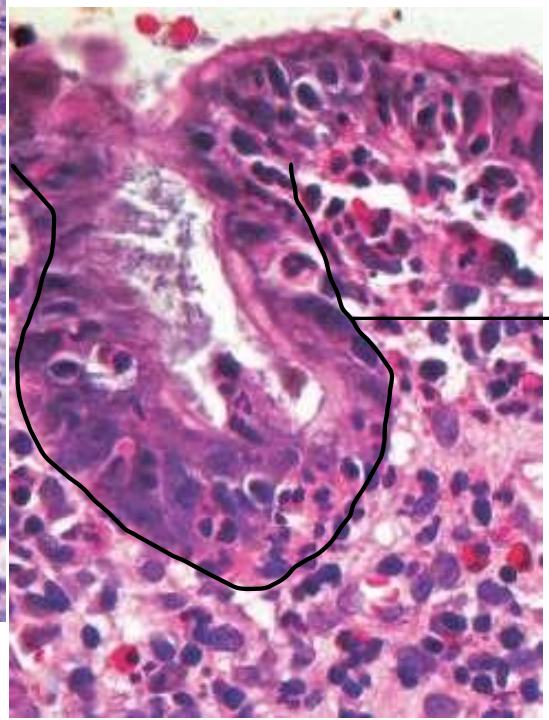


They used antibodies to visualize bacteria (sometimes we can use H&E stain)

Those big cells present gastric glands



Other small cells present lymphocytes and plasma cells

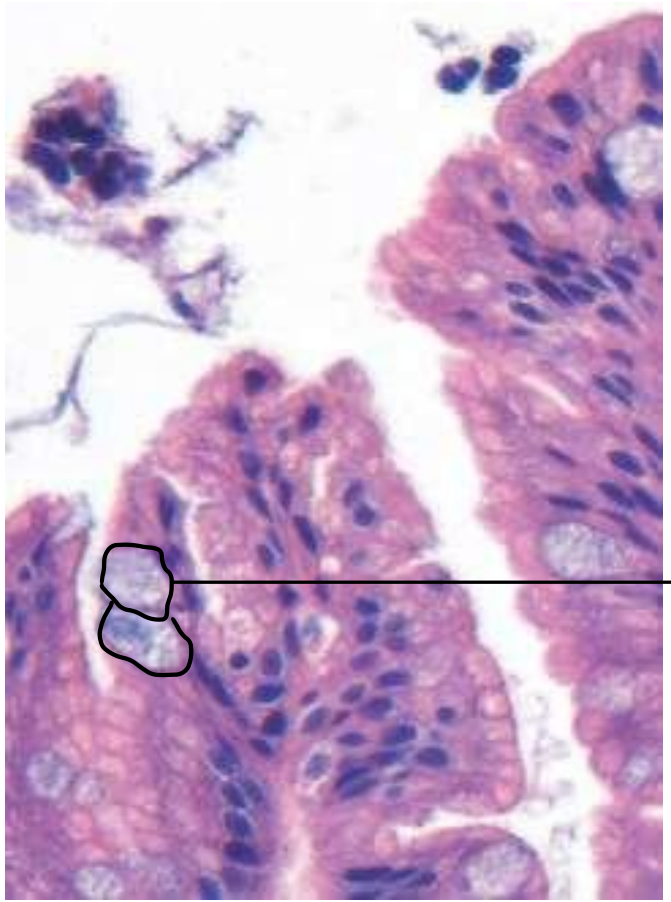


This is a surface of epithelium.

The cells present lymphocytes and plasma cells (and we may find H.pylori)

Robbins Basic Pathology 10th edition

Intestinal metaplasia



The histological clue for the intestinal metaplasia are goblet cells (we mustn't see them in the stomach because they are intestinal type cells)

Robbins Basic Pathology 10th edition

Diagnosis and treatment

If the patient comes with these Symptoms :epigastric pain ,nausea , vomiting , we suspect that he has chronic gastritis
To ensure the diagnosis we start with non-invasive methods to invasive methods :

Non-invasive methods:

- Serologic test: anti-H .pylori antibodies. **(if we have antibodies against H.pylori in the blood sample ,we must emphasis that the sample doesn't represent previous infection)**
- Stool test for H.pylori. **(to find H.pylori or its antigen).**
- Urea breath test.

Urea breath test doesn't preferred by patients , nowadays doctors use rapid urease test during endoscopy to detect the Prescence of urease enzyme by exhalation of a radio labeled carbon.

Invasive methods:

- Gastric antral biopsy (rapid urease test during endoscopy)
- Bacterial culture.
- PCR test for bacterial DNA.

For treatment they use Triple therapy (2 antibiotics with PPI) for 2 weeks ,but the PPI may continue for a month to eradicate H.pylori and to inhibit infection recurrence :

- Treatment: combinations of antibiotics and PPI (triple therapy).

Autoimmune Gastritis (10% of cases)

The chronic gastritis that is caused by H.pylori or autoimmune cause ,they represent the same symptoms with different pathogenesis :

- Antibodies to parietal cells and intrinsic factor in serum.
- Reduced serum pepsinogen I levels (no acid no pepsinogen).
- Antral endocrine cell hyperplasia

Firstly the parietal cells produce HCL ,if we have antibodies that destruct these cells that will lead to achlorhydria (no acid production)
To compensate this situation the body will increase G-cells proliferation-G cells hyperplasia- (these cells produce gastrin which is a peptide hormone that stimulates secretion of gastric acid (HCl)from the parietal cells of the stomach)and that will lead to hypergastrinemia .
يعني ال Gcells بيزيدوا على الفاضي لانه parietal cells خربانين

Also in this disease there are antibodies against intrinsic factor (which is important for vitamin B12 absorption):

- Vitamin B12 deficiency >>> pernicious anemia and neurologic changes (pernicious anemia ,it is a type of megaloblastic anemia)
- Impaired gastric acid secretion (*achlorhydria)*
- Spares the antrum.**(because this disorder affects the parietal cells).**
- Marked *hypergastrinemia*

-The chronic gastritis caused by H.pylori characterized by hyperacidity.
-While the autoimmune chronic gastritis characterized by hypoacidity.

Pathogenesis

-It is an inflammation so we will see lymphocytes , plasma cells, macrophages in the gastric biopsy.

- Immune-mediated loss of parietal cells >>> reductions in acid and intrinsic factor secretion.
- Acid reduction leads to hypergastrinemia
- Hyperplasia of antral G cells
- Deficient intrinsic factor >> deficient ileal VB12 absorption >> megaloblastic anemia.
- Some chief cell damage >> reduced pepsinogen

MORPHOLOGY

- Damage of the oxyntic (acid-producing) mucosa.
- Diffuse atrophy, thinning of wall, loss of rugal folds
- Lymphocytes, plasma cells, macrophages, less likely neutrophils.
- Intestinal metaplasiac >>> dysplasia >> carcinoma.
- Neuroendocrine cell hyperplasia >>> tumors.

Atrophy and thinning of the wall because there is loss of the parietal cells.

Clinical features

- 60 years, slight female predominance.
- Often associated with other autoimmune diseases **(like :diabetes type1 ,Hashimoto's thyroiditis).**

Guess the disease: 

Doctor takes a biopsy from the body of the stomach and told you that he can not see the parietal cells with atrophy in the stomach wall and G-cells hyperplasia ,also he said that the patient suffers from anemia and vitamin B12 deficiency ?

Answer: the patient has autoimmune chronic gastritis (the atrophy of the stomach wall cased by the destruction of the parietal cells).

Summary:

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

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

-H.Pylori gastritis increase the risk of gastric adenocarcinoma and lymphoma(MALToma)

-Autoimmune gastritis increase the risk of carcinoid (neuroendocrine tumor)and adenocarcinoma

Robbins Basic Pathology 10th edition

- Pathology of the stomach-part 2

Manar Hajeer, md, FRCPath

University of Jordan, School of medicine

Peptic Ulcer Disease

-H.Pylori associated with developing countries .

- Most often is associated with H. *pylori* infection or NSAID use
- **Imbalance between mucosal defenses and damaging forces.**

- In USA, NSAID is becoming the most common cause of gastric ulcers: as H.*pylori* infection is falling and increased use of low-dose aspirin**(NSAID drug)** in aged population.
- Any portion of the GIT exposed to acidic gastric juices
- **Most common in gastric antrum, first part of duodenum**.
- Esophagus**(lower part)** in (GERD) or ectopic gastric mucosa (Meckel diverticulum)

-Meckel diverticulum :it is a part of intestinal mucosa

Any portion of the GI tract exposed to acidic juices and get an ulcer the ulcer is called a peptic ulcer.

So peptic ulcers mainly occur in the stomach but may occur in the first part of the duodenum or the lower part of the esophagus.

Pathogenesis

-The main cause of chronic gastritis and chronic ulcers is H.pylori ,and we have to treat it .

- **More than 70% of PUD cases are associated with H. *pylori* infection**
- Only 5 -10% of H. *pylori*–infected individuals develop ulcers. **(especially in long standing and untreated cases).**
- **Gastric acid is fundamental in pathogenesis.** **(no acid – no ulcer)**
- **Cofactors: smoking, chronic NSAIDs, high-dose corticosteroids, alcoholic cirrhosis, COPD, CRF, hyperparathyroidism**.

  CRF : chronic renal failure.

- **Hyperacidity is caused by**:
- H. pylori.
- Parietal cell hyperplasia.
- Excessive secretory response (vagal)
- Hypergastrinemia as in *Zollinger-Ellison syndrome* ***(tumor)***

Produce gastrin.

Zollinger-Ellison syndrome

-This tumor cause hyperacidity ,sometimes found in pancreas .
And hyperacidity causes ulcers.

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

MORPHOLOGY

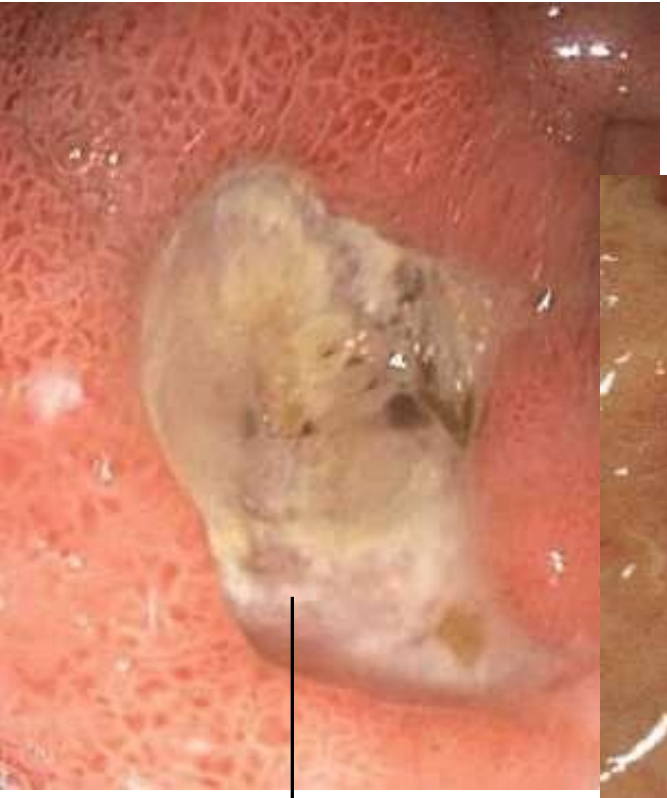
Remember :

Acute ulcers :multiple ,dark colored (filled with blood), comes from healthy background stomach , distributed everywhere .while,

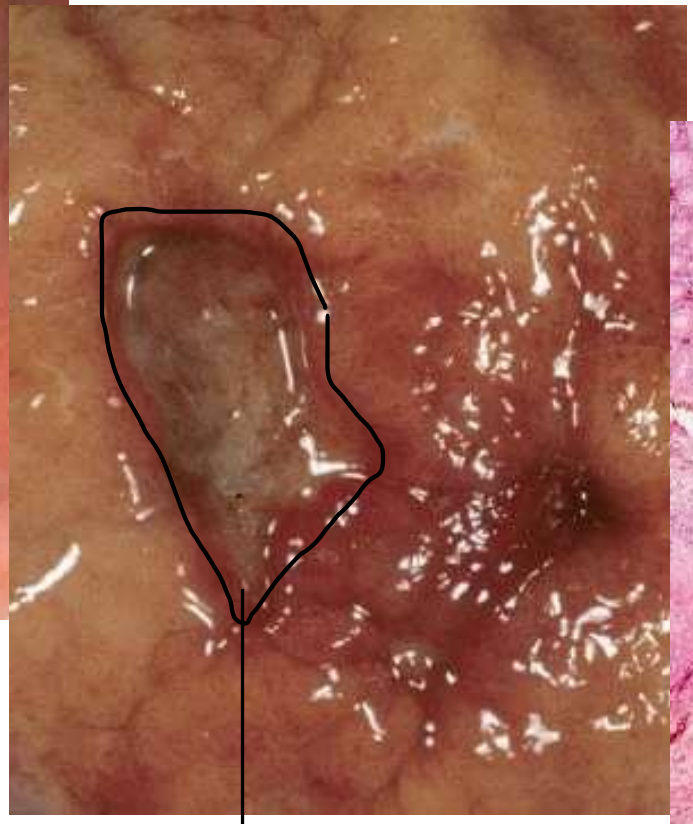
Chronic ulcers: single ulcers ,the base is clean (because of attempts of healing , unless bleeding takes place), the stomach with chronic gastritis (comes from unhealthy background)

- 4:1, proximal duodenum : stomach. **(because the stomach adapt with acidic environment)**
- Anterior duodenal wall
- **>80% solitary**.
- Round to oval, sharply punched-out defect
- Base of ulcers is smooth and clean
- Granulation tissue.
- Hemorrhage & Perforation are complications.

  If the patient comes with deep ulcer (perforation) ,he will have catastrophic peritonitis .

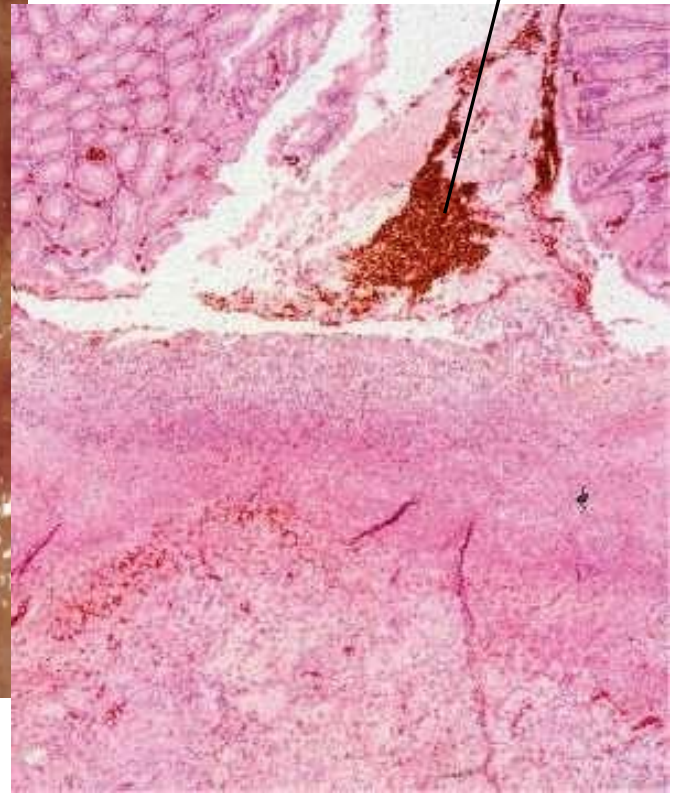


Its base is white ,with clean base .



Prominent edges with clean base.

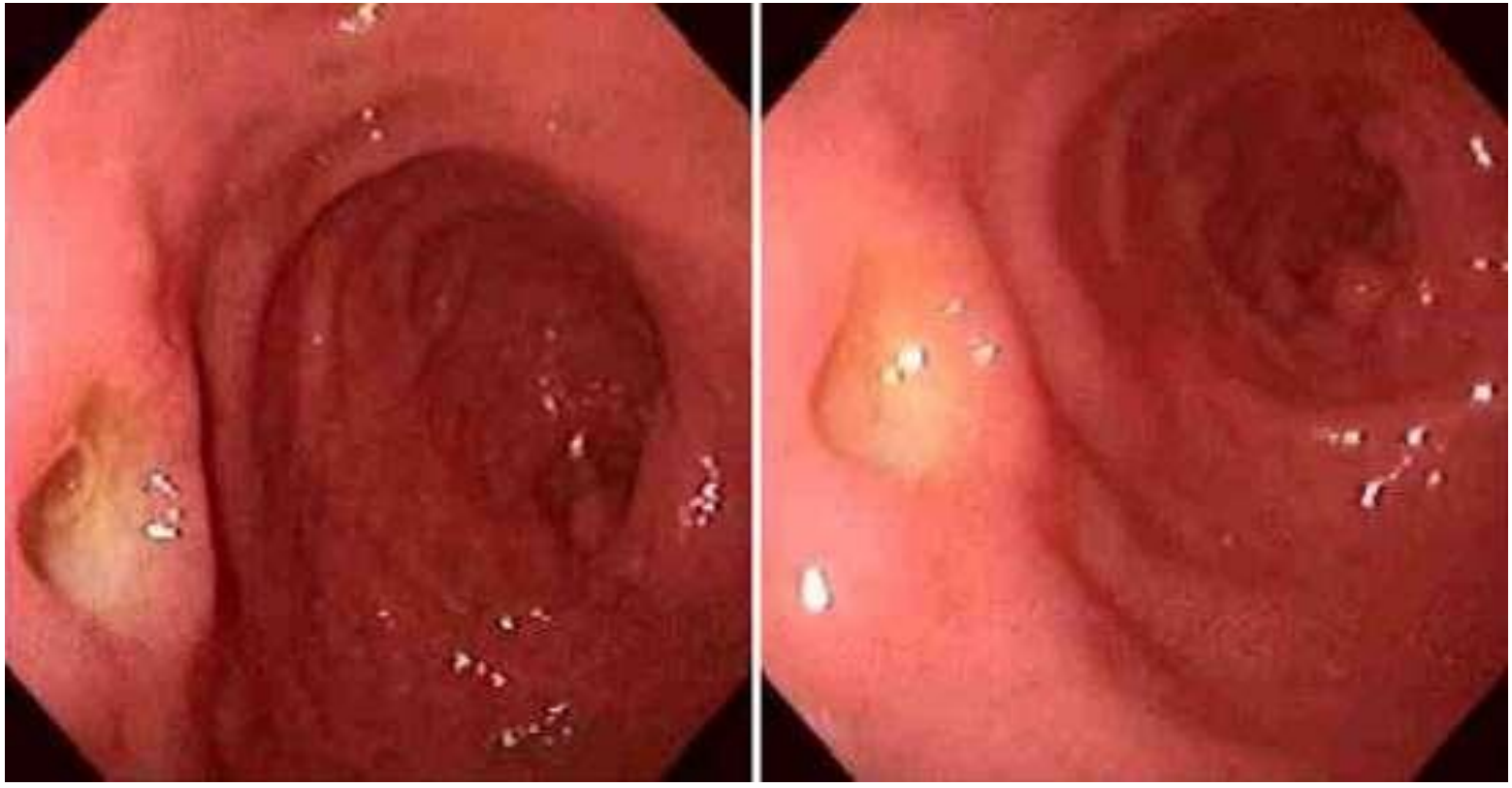
Ulcer: it is a loss of the mucosa with exposure of the submucosa (due to this bleeding can takes place). You can see the intact mucosa on the periphery of the ulcer.



Robbins Basic Pathology 10th edition

Duodenal ulcer

The anterior wall of duodenum is exposed commonly .



Clinical Features

The clinical features of chronic ulcers mimesis those for chronic gastritis ,but here they are more severe and related to food (the pain relieved by eating food or drinking milk for example).

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

-If the ulcer comes with bleeding it may cause hematemesis (if the bleeding continues and becomes chronic bleeding it will lead to anemia).

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

GASTRIC POLYPS AND TUMORS

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

- Gastric Adenocarcinoma **(gastric malignancies/cancers):**
- intestinal and diffuse types

- Lymphoma
- MALToma.

- Neuroendocrine (Carcinoid) Tumor
- Gastrointestinal Stromal Tumor **(gist tumor)**

Gastric polyps

- Polyps: masses projecting above the level of adjacent mucosa
- Epithelial or stromal cell hyperplasia, inflammation, ectopia, or neoplasia.

- **Inflammatory and Hyperplastic Polyps** They are not neoplastic (they don't carry a risk for subsequent cancer development).
- 75% of all polyps.
- Arise in a background of chronic gastritis (if we take a biopsy from its adjacent ,we will notice the chronic gastritis).
- Regress after H.pylori eradication.

-sometimes polyps removed completely by endoscopy for diagnosis.

Gastric Adenoma

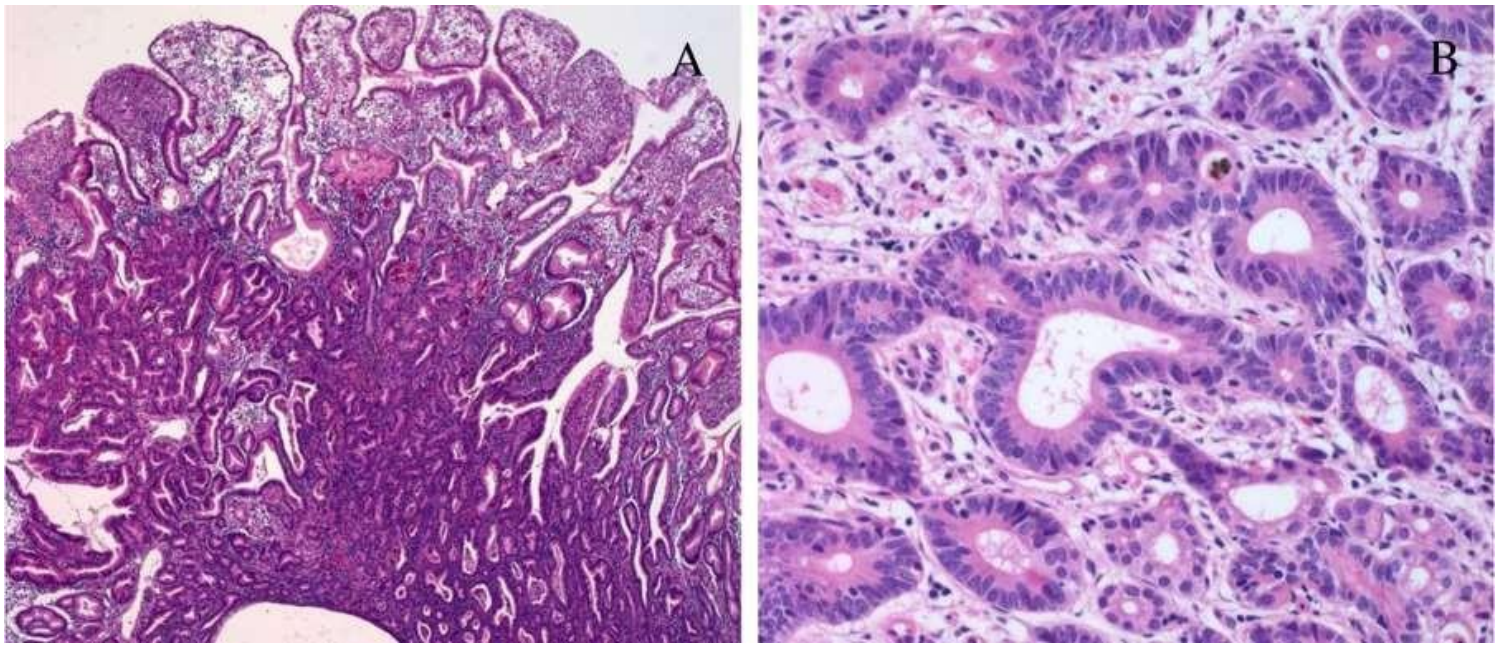
-Gastric adenoma ,it is a precursor for gastric adenocarcinoma ,and it must have dysplasia .

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

  Unlucky patients, when the doctor removes gastric adenoma at the same time it will develop cancer (gastric adenocarcinoma).

Gastric adenoma

It is a mass with dysplasia, dysplasia means :
1-the nuclei are enlarged
2-hyperchromatic (dark blue and stratification)
3-they look ugly with high grade of dysplasia .



Gastric Adenocarcinoma

the patient has thought that he has chronic gastritis and treated by Pylori eradication without endoscopy or biopsy for years especially if he did serum antibodies test or stool antigen analysis ,so they present late with advanced stage of diagnosis .

- 90% of all gastric cancers.
- Early symptoms mimic gastritis >>> late diagnosis.
- Rates vary markedly with geography (Japan, Costa Rica, Chile).
- Screening >> early detection.
- **Background of *mucosal atrophy and intestinal metaplasia*** *(precancerous)*
- ***PUD does not increase risk, except after surgery***
- ***In USA rates dropped > 85%, BUT increased rate of cardia cancer due to GERD & obesity.***

  In USA the intestinal type dropped due to H.pylori eradication , because intestinal type associated with H.pylori infection.
- ***Two main types: intestinal and diffuse.***

1- intestinal type is associated with intestinal metaplasia .
2- diffused type is not associated with intestinal metaplasia.

Pathogenesis

1-Familial and inherited intestinal type :

- Genetic alterations due to H.pylori associated chronic gastritis , lesser extent EBV (10%) **(long term infection of H.pylori it will build up certain mutations in the stomach especially if there is intestinal metaplasia).**
  - FAP**(familial adenomatous polyposis syndrome that increase of colonic polyps as well):** APC gene mutation, intestinal type cancer.

2-sporadic intestinal type:

- Most cases are sporadic.**(result from somatic mutations ,acquired later in life)**
- Sporadic intestinal-type Ca: B catenin mutation

- 1–Familial diffuse type cases: mutations in *CDH1* (E-cadherin). **E-cadherin connects the cells together so the mutation in this gene leads to less adhesion between cells(it is the most characterized feature for the familial diffuse type).**
- 2–Sporadic diffuse type Ca: CDH1 mutation in 50%.

- P53 mutation in sporadic cancer of both types.

(sporadic intestinal and sporadic diffuse types)

-Previously, the intestinal type was more common but due to H.pylori eradication the intestinal and diffused types become comparable nowadays.

MORPHOLOGY

We have gastric cancer types because they differ in morphology:

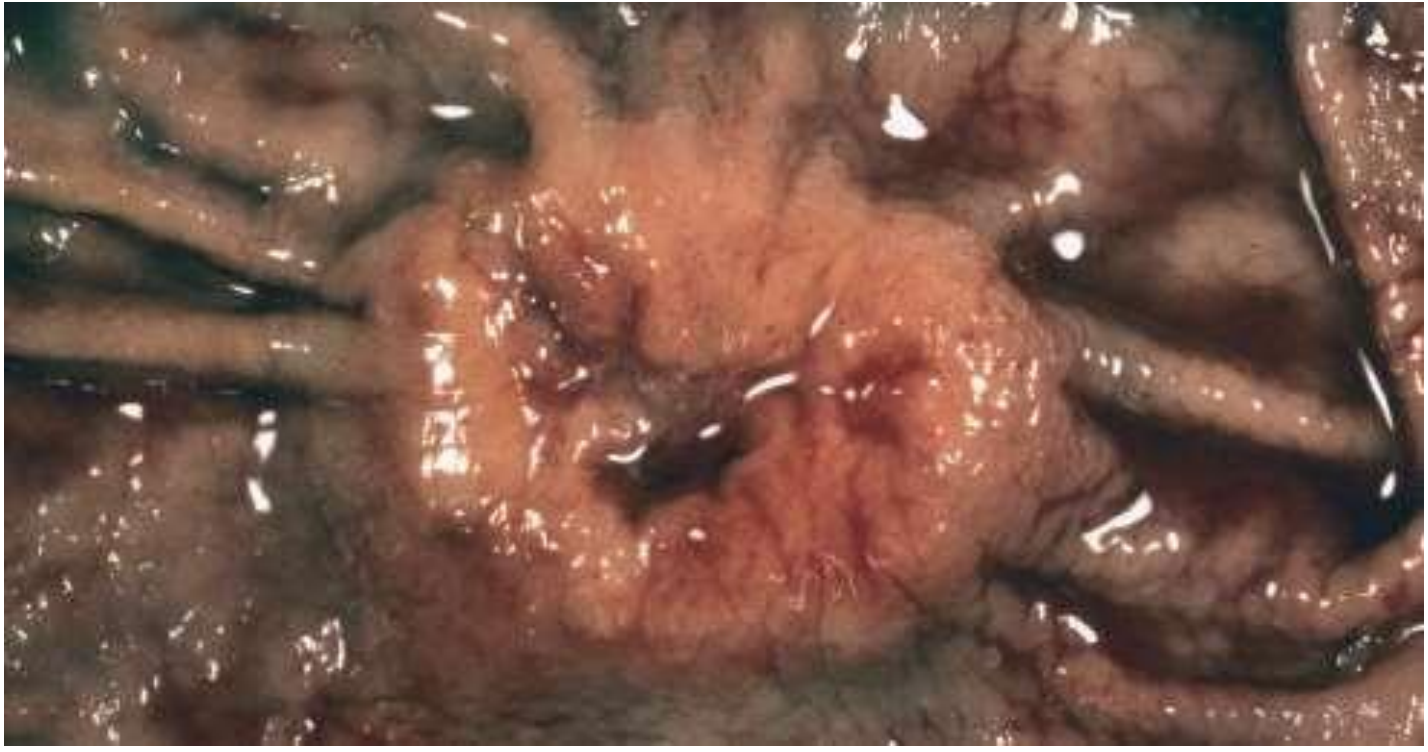
- Lauren classification: separates gastric cancers into intestinal and diffuse types.
- **Intestinal type morphology:(it has underlying intestinal metaplasia resemble the colonic cancer).**
- 1–Bulky.**(mass that projects to the lumen of the stomach ,it doesn't make obstruction unless it is large tumor or find in the cardia ,so obstruct gastroesophageal junction or find in the pylorus then obstruct gastroduodenal junction).**
- 2– Exophytic mass or ulcer.
- 3–Form glands.

- **Diffuse gastric cancers morphology:(the doctor during endoscopy will not see anything because the tumor tend to grow within the wall that will lead to thickening in the wall of stomach without causing mass).**
- 1–Infiltrative growth pattern**(within the wall of stomach).**
- 2–Discohesive cells (signet ring cells)
- 3–Desmoplastic reaction (thick wall, linitis plastic).

-When taking a biopsy we will not see glands or intestinal epithelium ,it looks like single non-adherent cells to each other in the mucosa .

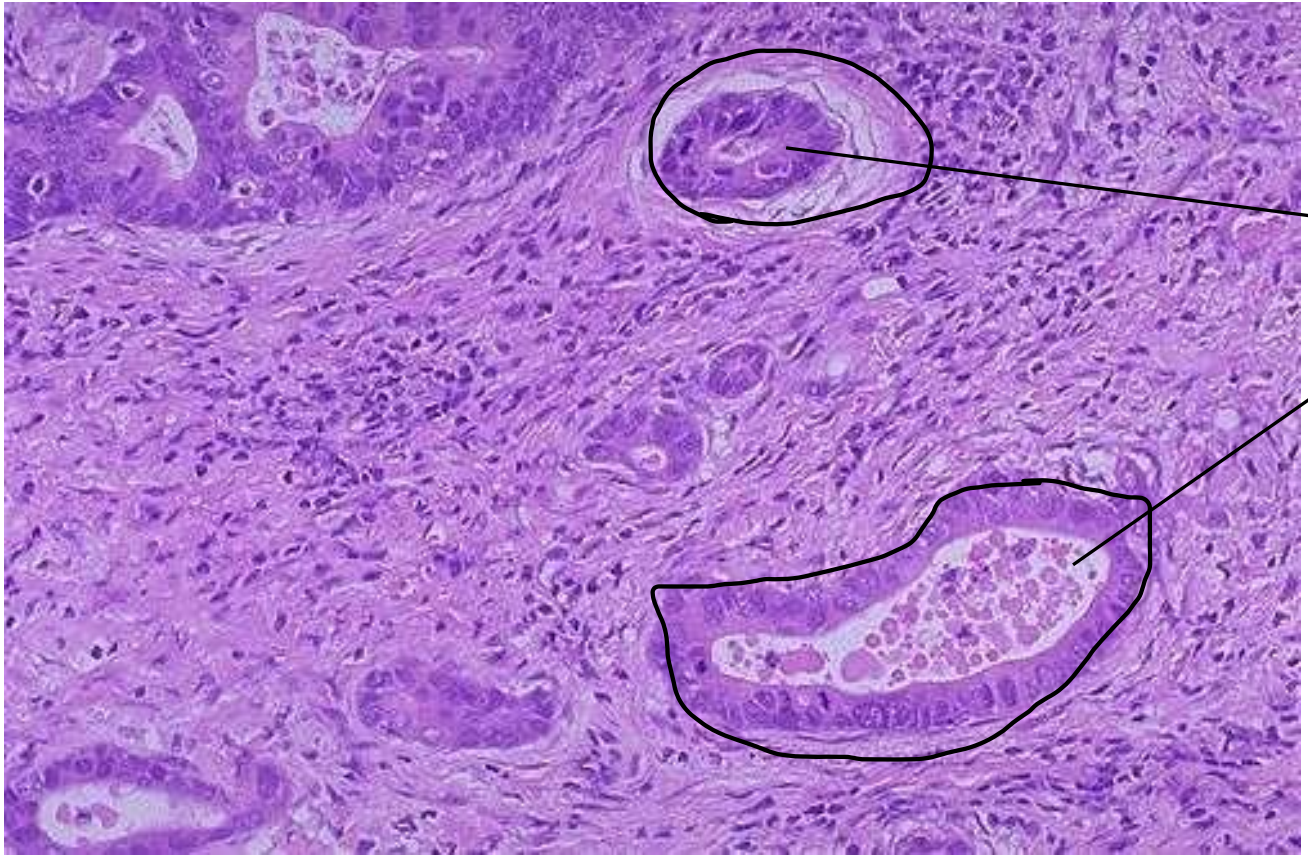
Intestinal type

There is a mass so it is intestinal type :



Intestinal type

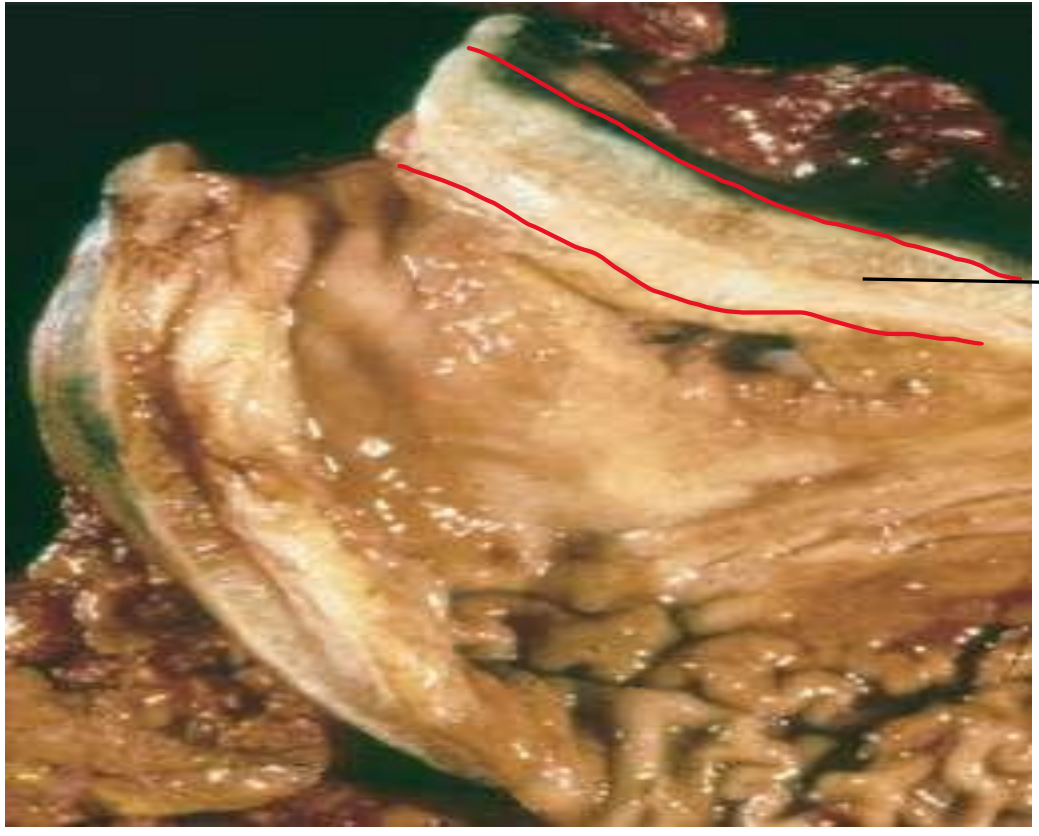
-Under the microscope intestinal type appears ugly dysplastic glands ,infiltrative within the wall of stomach .



Glands with necrosis center

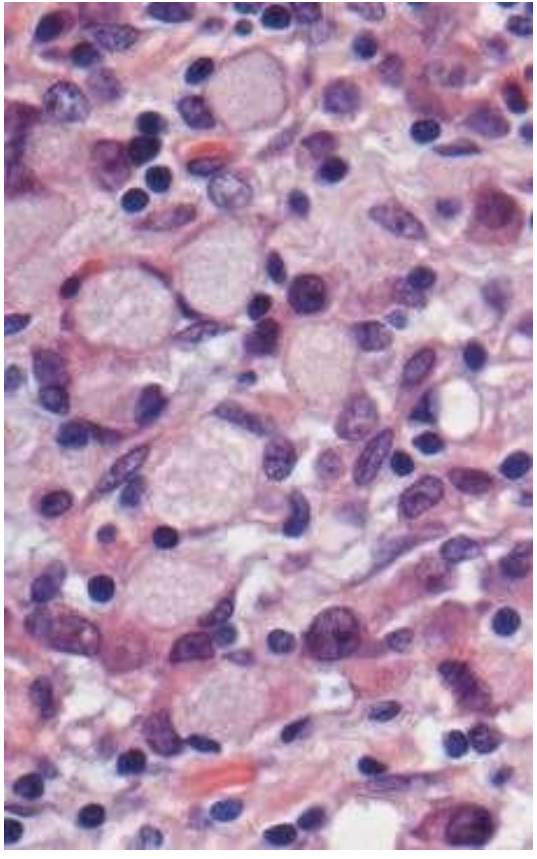
Linitis plastica(diffuse type)

There is no mass, but there is a thickening in the wall of stomach ,we call it linitis plastic (that is result from the fibrosis and desmoplastic reaction).



Thick wall (it is white in color)

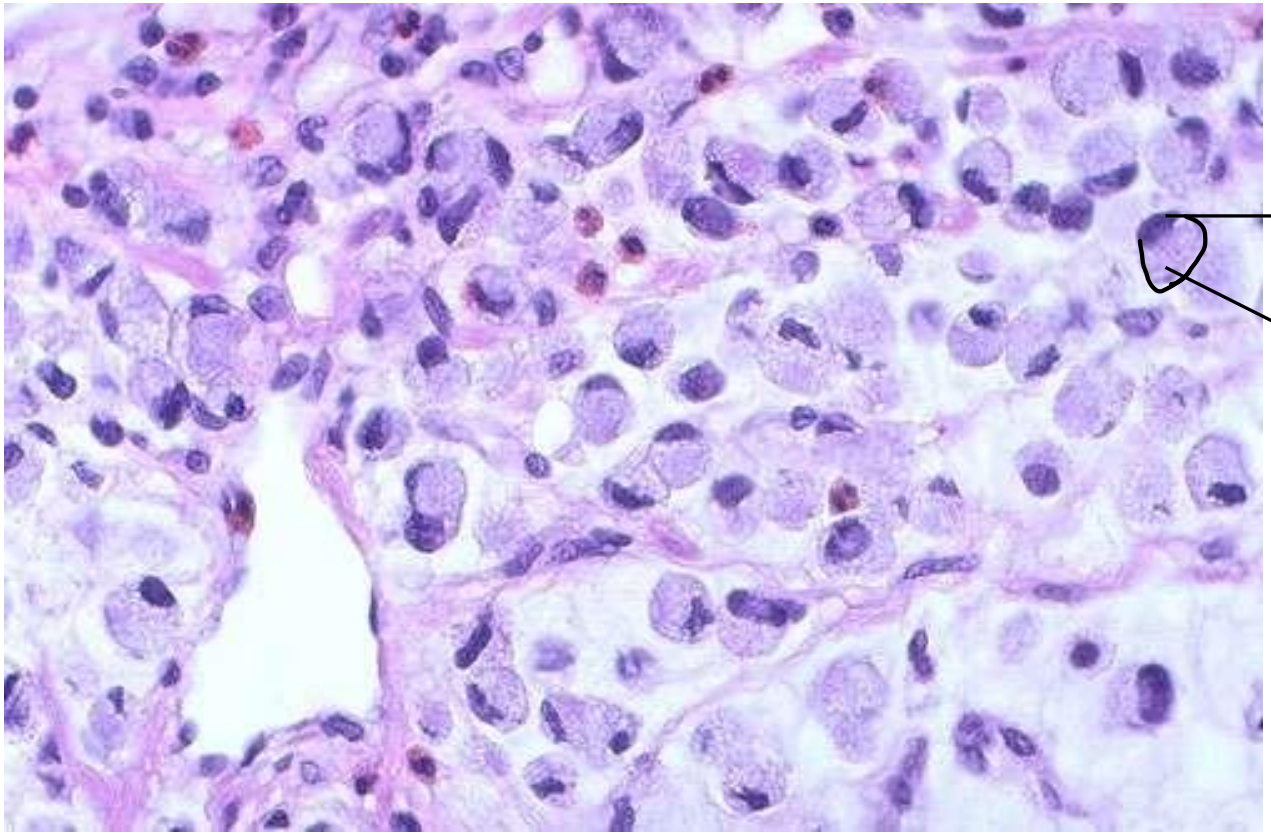
Signet ring cells:
large mucin vacuoles that expand the cytoplasm and push the nucleus to the periphery,



Under the microscope the diffuse type looks like rings (discohesive cells)

Diffuse type, signet ring cells

الخلايا مفرفطين مو ماسكين ببعض



The nucleus (pushed to the periphery)

Cytoplasm containing mucus

Clinical Features

The clinical features present with symptoms similar to chronic gastritis (epigastric pain , nausea , vomiting),however the cancer associated with stomach manifestations mostly weight loss(cachexia).

- **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.**(there is no geographic variations because it is just a mutation without anything that increase it).**
- No precursor lesion.
- M:F 1:1
- Younger age.

-its prognosis very bad.

- Symptoms overlap with chronic gastritis, in addition to weight loss.

- 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(T-stage) & extent of nodal and distant metastasis at the time of diagnosis(stage is the most powerful prognostic feature which means metastasis to lymph nodes or distant sites).**

- **Most cases Dx at advanced stage.**
- 5 year survival 90% to 20% for early and advanced tumors, respectively.
- Tx: surgery, chemotherapy, targeted Tx (anti HER2)

Treatment differ from patient to patient because it depends on age ,stage , and expression of certain markers.

Lymphoma

-Lymphoma normally takes place in lymph nodes, but because the stomach has extra mucosa associated lymph tissue it is in higher risk of extranodal lymphoma .

- **Stomach is the most common site of extranodal lymphoma.**
- 5% of all gastric malignancies.
- Most common type : indolent extranodal marginal zone B-cell lymphomas (MALToma,it is a **low grade lymphoma)**
- Second most common lymphoma: diffuse large B cell lymphoma**(aggressive)**

Neuroendocrine (Carcinoid) Tumor

-It is a small cancer(little)

- Tumors arising from neuroendocrine-differentiated gastrointestinal epithelia (e.g., G cells).
- **> 40% occur in the small intestine.(but they can occur in the stomach)**

-Sometimes they associated with carcinoid syndrome (which is a constellation of symptoms and features that come together)

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

  - **Slower growing than carcinomas.**

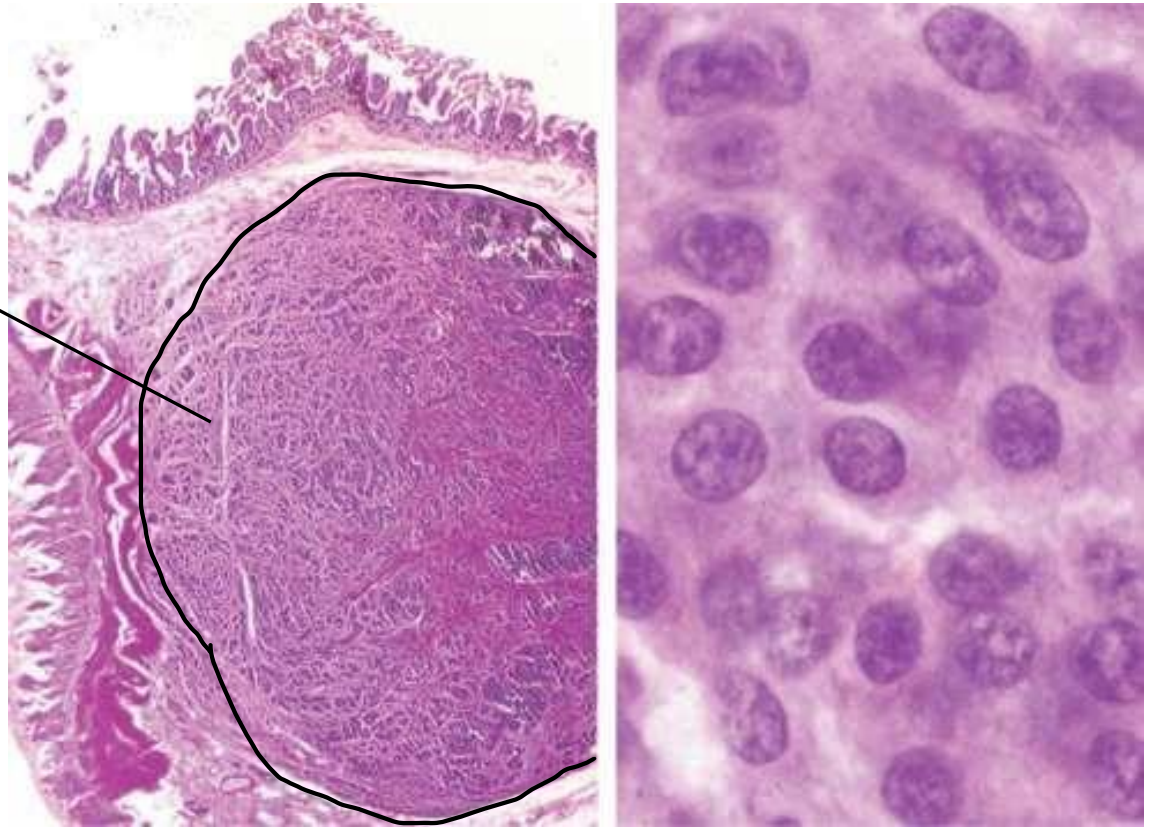
-It has a good prognosis unless it metastasizes .

Intramural or submucosal masses (small polypoid lesions)

-those tumors tend to be located in the submucosa(projecting to the lumen) as a nodules .

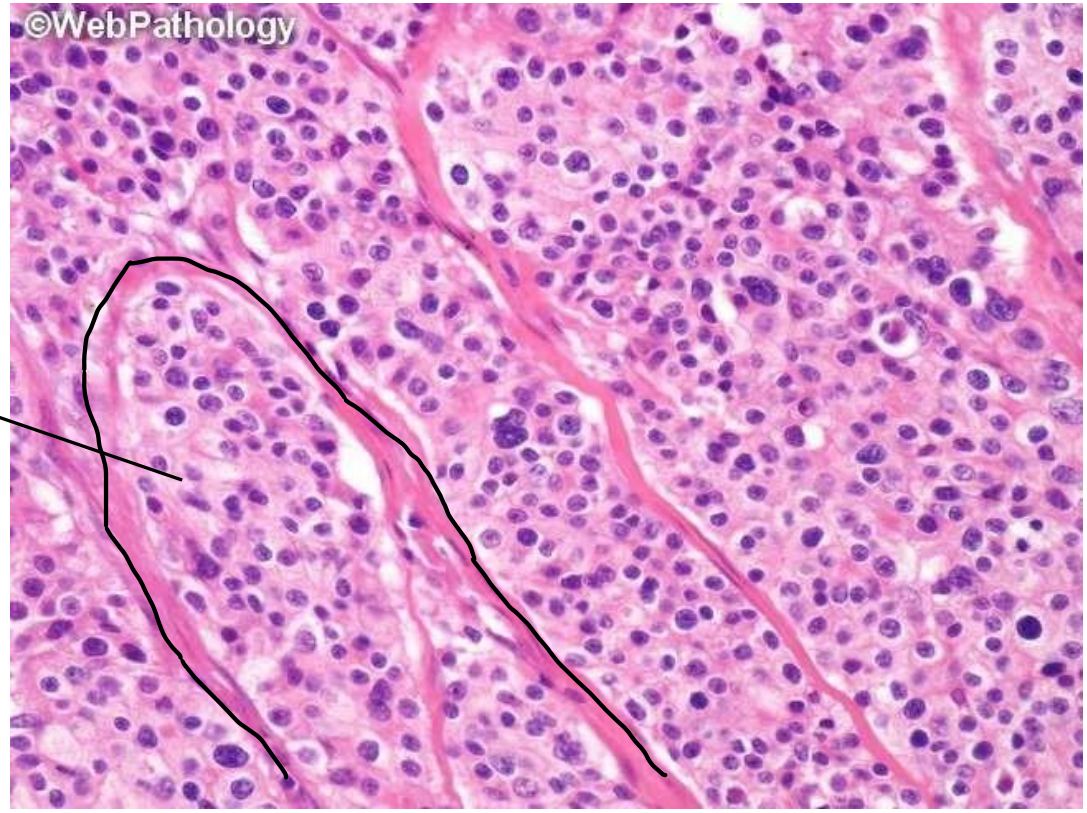
-The cells under the microscope have a nesting pattern .

-The nuclei show a salt and pepper chromatin pattern(not smooth chromatin as usual).



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

Nesting means compartmentalization of cells .



carcinoid syndrome

- Due to vasoactive substances **(vasoactive amines production).**
- Seen in 10% of cases.
- *strongly associated with metastatic disease.**(especially , metastasis to liver)***

-All of these symptoms due to vasoactive amines production:

- **Cutaneous flushing, sweating, bronchospasm, colicky abdominal pain, diarrhea, and right-sided cardiac valvular fibrosis (the bronchospasm due to smooth muscles contraction in the wall of bronchi).**

V2:

- Slide no.38 :
- The carcinoid associated with chronic autoimmune atrophic gastritis (it was mentioned in previous slides) ولكن ليطمئن قلبي
- Slide no.39 :
- It was smooth chromatin ,but
- The nuclei show salt and pepper chromatin pattern (not smooth chromatin as usual)
-