GIS.

Sheet no.4

Pathology

Done by: Sham Alsalim.

Correction: // // .

Doctor: Manar Hajeer.

Previously we were studying about the little devil H.pylori (common cause for chronic gastritis), in this lec. we still have some points to mention, then we'll start a new topic, here **BLUE** is for the doctor..

Diagnosis of H.pylori chronic gastritis:

-First, the patient presents with the symptoms discussed before, then we use the **non- invasive** methods to investigate, then we use the **invasive** investigations.

- **Non-invasive:**
  - Serologic test (blood test): anti-H. pylori antibodies (IgA, IgG).

-The problem with this test is that it doesn't mean that the patient is having an active disease, previous infection can also cause the presence of antibodies.

  - Stool test for H. pylori
  - Urea breath test

- **Invasive:**
  - Upper Endoscopy to visualize the stomach of the patient.
  - Gastric biopsy is the best way to detect chronic gastritis or any inflammatory reaction and for visualizing H. pylori in the mucus layer.
  - Bacterial culture (using the biopsy).
  - PCR test for bacterial DNA (using the biopsy).

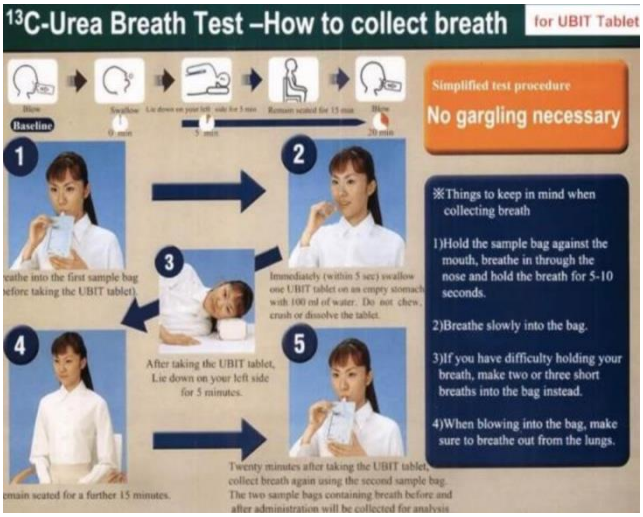
Treatment:

-Eradication therapy for H. pylori which is formed by at least **2 antibiotics** and **proton pump inhibitors** to decrease the acidity. (drug combinations)

-The treatment may need a long period of time for the patient to get rid of the organism.

-If the treatment was not completed, recurrence may take place, this recurrence may be because the bacteria was not completely eradicated with the first treatment or the individual may have been re-infected.

Urease test:



We use this test to detect the presence of the products of bacterial urease enzyme in the breath. How?

-the suspected patient is asked to drink a solution that contains the urea material which contains **radiolabeled carbon.**

-the patient is then left for twenty minutes, then the radiolabeled carbon is detected in the **breath** of the patient.

As we know the **urease enzyme** of the bacteria is the responsible for **splitting** the urea into **ammonia** and **carbon dioxide**.

From this point we've finished talking about the little demon with huge problems H.pylori! Let's start our new lec…

Autoimmune (atrophic) Gastritis:

-Immune-mediated disease directed against the **parietal cells** present in the body and the fundus, damage to these cells leads to **loss of acid and intrinsic factor production** and inactivation of the intrinsic factor directly.

oCharacteristics associated with the disease:

› ABs against parietal cells and intrinsic factor which can be detected in the serum as a clinical feature of the disease.

-Intrinsic factor binds to vitamin B12 and aids in its absorption in the distal ilium.

› Reduced serum pepsinogen I levels, which is produced in the body and the fundus of the stomach, because of damage to these areas.

› As a response to the loss of acid production in the stomach, we will have a reflex G-cell hyperplasia in the antrum (**antral endocrine cell hyperplasia**).

-G cells produce gastrin which is produced as a response to the decrease in acid production (due to parietal cell damage**).**

› Decreased intrinsic factor → Vitamin B12 deficiency → pernicious anemia and neurologic changes associated with autoimmune gastritis.

› Impaired gastric acid secretion (**achlorhydria**).

-Opposite to H. pylori gastritis.

› Typically AI gastritis Spares the antrum.

-Unlike H.pylori gastritis.

› Marked hypergastrinemia.

o Pathogenesis:

› (**immune mediated**) Lymphocyte (**T-cell**) mediated loss of parietal cells with the production of auto-ABs against parietal cells → reduction in acid and secretion.

› Acid **reduction** leads to reflex hypergastrinemia, which is mediated by hyperplasia of antral G cells.

› Reduction in intrinsic factor due to cells and auto-ABs directed against it.

› Deficient intrinsic factor→ deficient ileal VB12 absorption →megaloblastic anemia which has many neurological manifestations.

-Minority of patients develop this anemia, but it's a very important point to differentiate between autoimmune gastritis and helicobacter pylori gastritis.

› Some chief cells damage in the body of the stomach→ reduced pepsinogen production.

-Progression leads to loss of parietal cells in the mucosa, thinning and atrophy of the mucosa, and loss of the folds at these sites.

o **Morphology**

-No H. pylori would be present in specimens (If present, it's NOT the cause).

-Preferred biopsy site is the body.

› Damage of the oxyntic (**acid-producing**) mucosa→ parietal cell loss in the body/fundus.

› With time there'll be Diffuse atrophy, thinning of the wall and loss of rugal folds due to loss of acid producing cells and their damage.

› Lymphocytes, plasma cells, macrophages, and **less** likely neutrophils.

› In long standing cases: Intestinal metaplasia (**due to achlorhydria**) →dysplasia→ adenocarcinoma.

-Risk is present in both types of chronic gastritis.

› Neuroendocrine (**G-cell**) cell hyperplasia as a reflex to reduced acid production, may transform into neuroendocrine tumors. (**in H. pylori gastritis the risk is increased for MALT lymphoma**).

o **Clinical features:**

› Patients are in their 60s (**higher age than H. pylori gastritis patients**), slight female predominance.

› Often associated with other autoimmune diseases like Hashimoto . thyroiditis, type 1 DM, or Graves disease of the thyroid – autoimmune diseases usually tend to cluster together, so when we find AI gastritis we should look for others.

Very important table summarizing all the differences between H. pylori associated gastritis and auto immune gastritis:

*الدكتورة ما ركزت عليه، بس كتير مفيد ...

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

▪ Location, of H. pylori associated gastritis is usually the **antrum**, in **severe cases** can transform into **pangastritis** and cover the entire stomach.

▪ In H. pylori associated gastritis, chronic inflammatory cells and less neutrophils.

▪ In Auto-immune gastritis mainly chronic inflammatory cells. Focus on **lymphocytes**- they're pawns of pathogenesis.

▪ **Decrease** in acid can accompany severe cases of H. pylori **pangastritis** and it's only a slight decrease (**remember originally in H. pylori associated gastritis there's an INCREASE in acid**) not total achlorhydria unlike autoimmune gastritis.

▪ In H. pylori associated gastritis, **gastrin** would only be markedly **increased** in severe cases, in early cases the levels would remain normal.

▪ Sequelae (**secondary results**):

▪In Helicobacter pylori associated gastritis it's **MALT lymphoma**.

▪In autoimmune gastritis it's **Carcinoid tumors** (**neuroendocrine tumors**).

-In this section we'll continue the second part of gastric pathology and we will talk about peptic ulcer disease as well as gastric tumors including gastric polyps and gastric malignancies.

1.Peptic Ulcer Disease:

-Ulcer قرحة it is the loss of mucosa and submucosa.
-Peptic is due to exposure to acid and pepsin coming from the gastric juice.
› Most common location are gastric antrum and first part of duodenum. (**because as you know the first part of duodenum receives the gastric acidic juices from the stomach**).
-Again any area that is exposed to acid and pepsin can develop peptic ulcer disease so it's NOT restricted to the stomach .
› The most common cause of Peptic Ulcer disease in the stomach is H.pylori infection and NSAIDs use .
-Peptic ulcerations that occur in these situations is due to imbalance between protective factors and damaging forces.
-In the beginning it will lead to chronic gastritis, then as a complication it will develop peptic ulcer disease.
› In USA, using NSAIDs is becoming the most common cause of gastric ulcers, as H.pylori Infection is falling and an increased use of low dose aspirin in aged population is taking place.
-As we know aspirin is used as anti-platelet in elderly patient to prevent cardiovascular event.

➢ Pathogenesis:

› More than 70% of PUD cases are associated with H.pylori infection (**In our region at least**)
-Do all patient with H.pylori infection develop PUD?
✓No, only 5-10% of H.pylori infected individuals develop ulcers, and many of them complain only from chronic gastritis.
› Gastric acid is fundamental in pathogenesis.
-If there is no acid there is no ulcer.
› However there are some cofactors in addition to H.pylori infection that can ease peptic ulceration (**not main causes**) :
-Smoking ,chronic NSAIDs use (if coupled with H.pylori the risk is doubled**) , high dose corticosteroids (**patient that use these should take PPIs**) ,alcoholic cirrhosis , COPD (chronic obstructive pulmonary disease) , CRF (**chronic renal failure**) and hyperparathyroidism(hypercalcimia**
› Hyperacidity is caused by :
-H.pylori, and this hyperacidity can affect gastric mucosa as well as duodenal mucosa .
-Parietal cell hyperplasia.

-Excessive secretory response (vagal).
-Hypergastrinemia as in (Zollinger-Ellison syndrome).

Zollinger-Ellison syndrome:

-Characterized by multiple peptic ulcerations, can develop in stomach , duodenum and even jejunum.

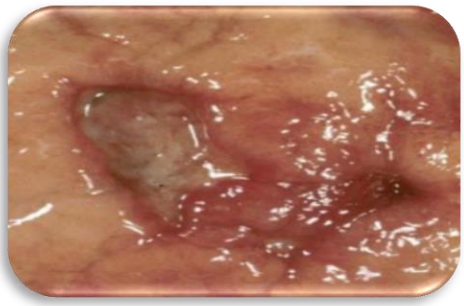
-If there is a massive acid secretion.

› Caused by uncontrolled release of gastrin by tumor (**gastrinoma**) and the resulting massive acid production.

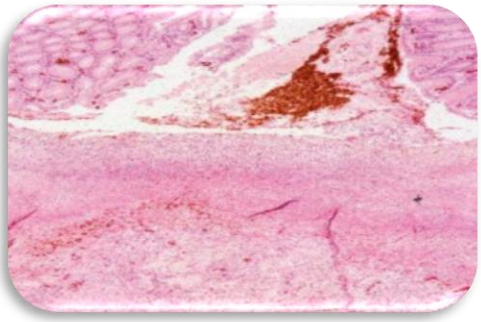
➢ **Morphology:**

› Proximal duodenum is more affected than stomach (4:1).
› Anterior duodenal wall is most affected site of proximal duodenum .
› Peptic ulcer disease is more than 80% of cases is solitary (single ulcer), **EXCEPT** in cases like Zollinger-Ellison syndrome where you can see **multiple ulcerations**.
› Round to oval in shape and sharply punched-out defects.
› Base of ulcer is smooth and clean.
› Formed by granulation tissue (tissue that is formed in attempt to heal the ulcer "you find newly formed blood vessels).

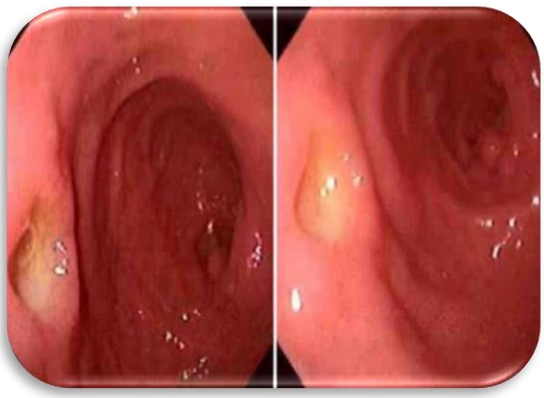
-Hemorrhage & Perforation are possible complications we must be afraid of.



You can see the punched-out, very delineated edges of ulcers and the white, clean and oval background.



You can see the intact mucosa on the periphery of the ulcer. At the center the epithelium is lost and new blood vessels



Duodenal ulcer(under endoscopy): There is a well circumscribed ulcer in the wall of duodenum.

➢ Clinical features:

›The most common symptom is epigastric burning or aching pain.
› This pain typically comes after 1 to 3 hours after meals at daytime.
› The pain is worse at night and relieved by alkali or drinking some milk or food .
› The patient may also complain from nausea, vomiting, bloating and belching/تجشؤ
› Iron deficiency anemia caused by chronic blood loss from ulcers, some patients come to you with symptoms of anemia (**pallor, dizziness, loss of appetite**).

-Iron deficiency anemia is a long-term complication of PUD.

› Sometimes the patient may represent complication of **frank hemorrhage**:

-So in these cases the patient will complain from hematemesis (vomiting of blood**) and melena (**dark sticky feces**).**

› Another complication is perforation (**the patient comes with severe abdominal pain, peritonitis, rigid abdomen and this need immediate surgical correction**).

➢ Treatment:

› Current therapies are aimed at H.pylori eradication.
› Surgery is reserved for complications like **perforation** or **hemorrhage**.

2.Gastric Polyps and Tumors :

- Gastric Polyps ,are subdivided into:

-Inflammatory and Hyperplastic Polyps. -Gastric Adenoma.

- Gastric Adenocarcinoma ,and they subdivided into :

-Intestinal type. -Diffuse type.

- Lymphoma

-The most common lymphoma that arise from the stomach is MALToma (Mucosa associated lymphoid tissue lymphoma**).**

- Neuroendocrine (**Carcinoid**) Tumors.
- Gastrointestinal Stromal Tumor.

A) Gastric polyps:

-Polyps: masses projecting above the level of adjacent mucosa, **ANYTHING** can cause gastric polyps like:

› Epithelial or stromal cell hyperplasia, inflammation, ectopia "ex : ectopic pancreatic mucosa in the stomach" or neoplasia.
› So it is descriptive term, not specific to neoplasms.

-When we say gastric polyp we will reserve this term to two conditions :

1) Inflammatory and Hyperplastic polyps:

✓ They constitute about 75% of all polyps.

✓ Usually arise in background of chronic gastritis.

✓ Regress spontaneously after H.pylori eradication.

✓ Risk of dysplasia if the size of polyp > 1.5 cm (**very large**).

-But remember most of the time these polyps are very small and there is no risk to have neoplasia or dysplasia, so no need to worry about yourself if you are diagnosed with hyperplastic polyp.

-It is a reactive condition, not considered a neoplastic condition, completely benign.

2) Gastric Adenoma:

-It is considered **precancerous**, not like hyperplastic gastric polyps, these are **neoplastic**.

✓ They only constitute of 10% of all polyps (**not very common like colonic adenomas**).

✓ Increase with age, and Males are affected more than Females (**3:1**) .

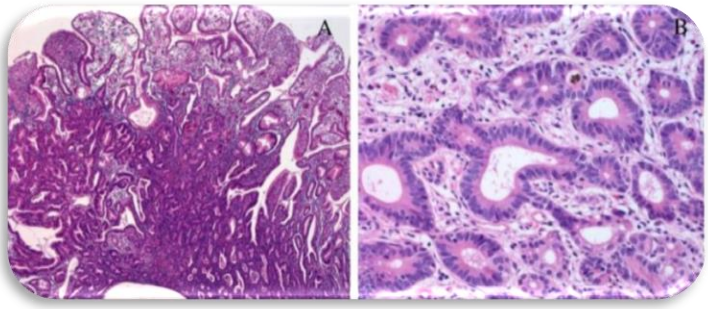
✓ Usually there is a background of chronic gastritis, atrophy and intestinal metaplasia.

✓ Dysplasia is present in **ALL** cases (**not present in hyperplastic polyps**) and it can be low or high grade.

-Of course, patients with high grade dysplasia are at higher risk to develop adenocarcinoma.

-The risk of adenocarcinoma is also related not only to degree of dysplasia, but also to the size of polyp (greatest if the polyp size > 2 cm **).**

✓ When we diagnose gastric adenoma in a biopsy, there is a risk that 30% of the patients have concurrent gastric adenocarcinoma .



Morphology (under microscope):
-We must see dysplasia, and in this picture, it is low grade.
-Masses have polypoid appearance .

B) Gastric Adenocarcinoma:

› Comprises 90% of all gastric cancers (**others: lymphomas, GI stromal tumors.. etc**)

› Two main types : intestinal and diffuse

-The most important thing about gastric adenocarcinoma is that the symptoms are NOT specific and they mimic those of gastritis and PUD, that's why in some cases of epigastric adenocarcinoma are diagnosed at late stage (bad prognosis**).**

› The most important thing to do is screening and early detection in high risk patients.
› The rates vary markedly according to geography, more common in Japan, Costa Rica and Chile.
› Occurs in the background of mucosal atrophy and intestinal metaplasia. Metaplasia→ dysplasia→ adenocarcinoma, the common scenario for mucosal carcinomas in different locations.
› PUD does not increase the risk, it's the gastritis, atrophy and the presence of intestinal hyperplasia that increases it, except after surgery, **why ?! because some PUD patients are at increased risk of bile reflux from the small intestine to the stomach (irritant).**
› In USA, the rates dropped for more than 85% but there is increase rate of cardia cancer due to GERD & obesity.

➢ Pathogenesis:

-Always about genetic alterations due to H.pylori infection associated chronic gastritis (**most common**) , to lesser extent EBV (**10%**) .
› Most cases are sporadic.
-In any cancer we can have familial cases(less common**) and sporadic cases.**
› In **diffuse type(**diffusely infiltrating the wall of the stomach**)** gastric adenocarcinoma:
• Familial cases : mutations in CDH1 (**E-cadherin**) "the cells lose adhesion due to loss of E-cadherin"
• Sporadic cases: CDH1 mutation in 50% .
› In the **intestinal type(**similar to colonic cancer**)** of gastric adenocarcinoma:
• Familial cases: APC gene mutation associated with Familial adenomatous polyposis syndrome is also associated with increased risk of colonic polyps .
• Sporadic cases: B-catenin mutation.
-P53 mutation is involved in sporadic cancer of both types .

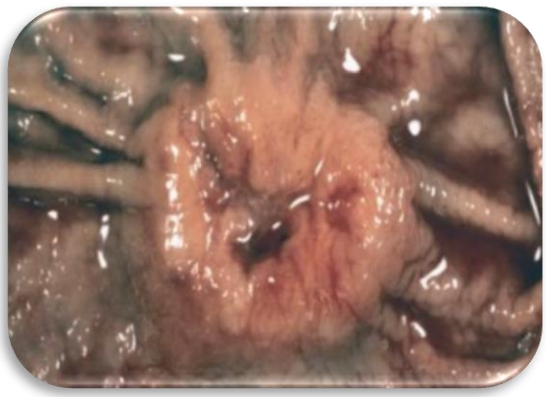
➢ Morphology:

-Lauren classification: classifies gastric cancers into intestinal and diffuse types.

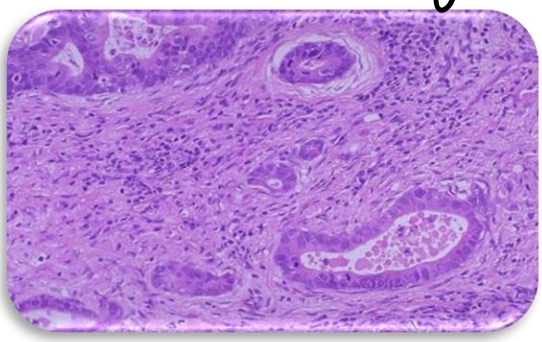
❖ Intestinal type:

-Bulky.
-Exophytic mass or ulcer(endoscopically).
-Form glands (microscopically).

#An endoscopy taken from a patient with a gastric mass.
-You can see ulcer but, it's somehow fungating and delineated from the surrounding normal gastric mucosa.



*Both pics are typical for intestinal type.



#You can see the malignant glands infiltrating the wall of the stomach.
-Adenocarcinoma tend to form glands and mucin.

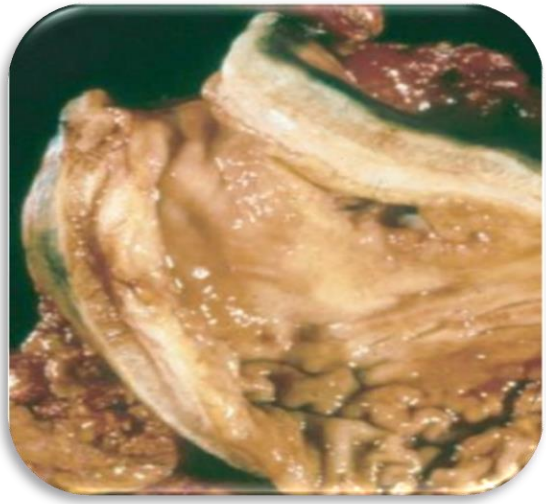
❖ Diffuse gastric cancers :

-Non mass forming tumors (endoscopically), because these tumors are usually Infiltrative, this will lead to thickening of gastric mucosa and **NOT** the formation of gastric mass, sometimes this will be **deceiving** because the endoscopy is **normal** but **under microscopic** examination there is **tumor**.

-Under microscopic examination the tumor cells are usually **discohesive** (E-cadherin gene mutation) and form signet ring cell كانه خاتم

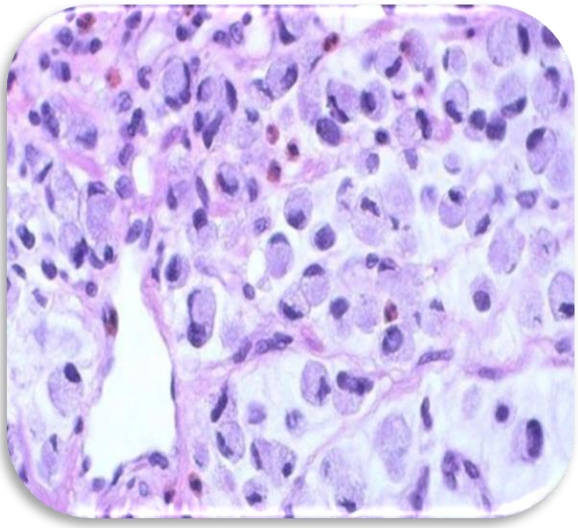
✓ That's why the other name for diffuse type of gastric cancer is **signet ring carcinoma** of the stomach .

-These tumors usually result in **strong desmoplastic** reaction that will lead to thickening of the wall of the stomach and what we call **linitis plastica** (the wall of stomach becomes very thick and rigid).



#You don't see any mass here but main change is thickening of gastric wall.
-This is typical appearance for stomach that is affected with diffuse type.

#You can see those infiltrating signet ring cells with large droplets of mucus and the nucleus is pushed to the side of the cell.
-Remember that the most important genetic abnormality in this type is: E-cadherin mutations that's why the cells here lose adhesion and they appear as discohesive single cells.



➢ **Clinical features :**

❖ Intestinal type gastric cancer :

- Predominant in high risk areas (**like Japan , Costa Rica and Chile .. etc**)
- Usually develops from precursors(**adenoma,dysplasia**)
- Affected age groups: (**mean age 55 years**) .
- Males are more affected than Females (**2:1**)

❖ Diffuse type gastric cancer :

- Incidence is uniform across all countries.
- Usually no precursor lesion (**genetic abnormality only**)
- Younger groups are affected.
- Males and Females are affected **equally**.

› The patient presents with a very bad tumor .
› The symptoms are not specific for cancer (**they can be seen in chronic gastritis and PUD**).
› Weight loss and cachexia are alarming.
-The drop in gastric cancer incidence applies only to intestinal type (perhaps due to early detection and treatment of H.pylori**), whereas the diffuse type is increasing nowadays.**
› Incidences of intestinal and diffuse types are now similar in some regions.
› Most powerful prognostic factors :

1.Depth of invasion.

-How deep the tumor goes in the gastric wall?
-Is it just limited to mucosa or does it infiltrate submucosa, muscularis propia or even reach the serosa? (**very important prognostic factor**).
-More depth = poorer prognosis.

2.Presence of lymph node metastasis

3.Presence of distant metastasis at the time of diagnosis.

› Most cases are diagnosed at advanced stage, and that's because the symptoms are usually **NON** specific and the patient comes too late .
› 5 years survival are variable according to the time of diagnosis, from 90% to 20% for early and advanced tumors, respectively .

➢ **Treatment :**

›Surgery +/- chemotherapy and targeted therapy (**using Anti-HER2 "also used to treat breast cancer"**).
-The lymph node and distant metastasis depend on the stage of the disease, high stage means poor prognosis.

C) Lymphoma:

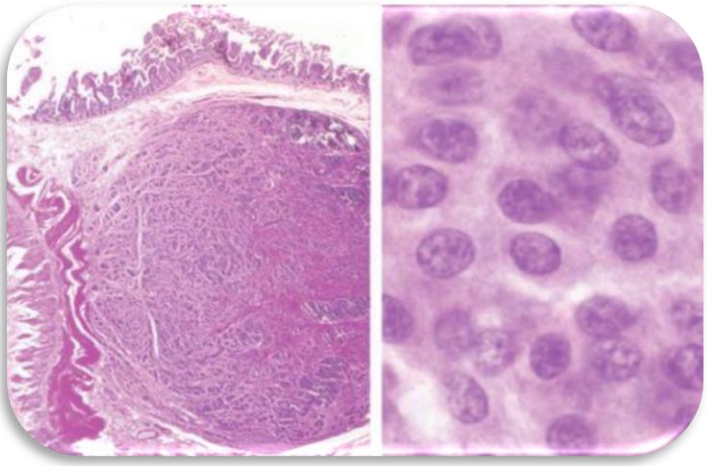
-Lymphoma is most found in lymph nodes. However, they can be found somewhere else (**extranodal**).

› The stomach is the most common site for extranodal lymphoma Lymphoma: tumor of lymphoid cells (**B-lymphocyte and T-lymphocyte**).
› Gastric lymphoma only constitute 5% of all gastric malignancies.
› Most common type of lymphoma in the stomach is: **MALToma** which is an indolent (**low grade**) extranodal marginal zone B-cell lymphomas.
› Second most common type of lymphoma in the stomach is: **diffuse large B cells lymphoma**.

D) Neuroendocrine (Carcinoid) Tumor :

› They arise from neuroendocrine cells that are present in gastric mucosa (**ex: G cells "responsible for production of Gastrin hormone"**).
› More than 40% occur in the small intestine.
› Usually they are associated with endocrine cell hyperplasia, chronic atrophy gastritis and Zollinger-Ellison syndrome .
› Slower growing than carcinomas, thus the name (**carcinoids**).

- **Morphology :**



#Intact mucosa on the surface with a nodule of tumor in the submucosa.
-This is a typical location for neuroendocrine tumors.
-They present as polyps but when you remove the polyp and send it to the pathologist, it is NOT a gastric polyp NOR adenoma, this polypoid growth is due to a submucosal nodule of tumor composed of neuroendocrine cells.
-Most important microscopic appearance for neuroendocrine cells is their nuclei showing salt and pepper chromatin appearance.
-Islands, trabeculae, strands, glands, or sheets of uniform cells with scant, pink granular cytoplasm and salt and pepper chromatin.

Carcinoid syndrome:

› Carcinoid tumors can be associated with carcinoid syndrome, but this is only seen in 10% of cases.
› Strongly associated with metastatic disease (**If there is no metastasis, no carcinoid syndrome**).
› This is usually due to production of vasoactive substances by neuroendocrine cells.

➢ Clinical features:

›Cutaneous flushing (**the patients face is very red**).
› Excessive sweating.
› Bronchospasm.
› Colicky abdominal pain.
› Diarrhea.
› Right-sided cardiac valvular fibrosis.

صنع بكل حب والله