# Pathology sheet

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Gastric Polyps and Tumors

**Polyps** may develop as a result of:

Epithelial or stromal cell hyperplasia, Inflammation,

Ectopia,

Neoplasia.

Polyp: any elevated area in the mucosa, and does not indicate the specific cause of this lesion.

Epithelial and stromal cell hyperplasia is a benign condition.

- **Inflammatory and Hyperplastic Polyps:**
  - Up to 75% of all gastric polyps are inflammatory or hyperplastic polyps.
  - Usually develop in association with chronic gastritis/inflammation, which initiates the injury that leads to reactive hyperplasia and polyp growth.
  - Most common in individuals between 50 and 60 years of age.
  - Because the risk of dysplasia correlates with size, polyps larger than **1.5 cm** should be resected and examined histologically.
  - The majority of inflammatory or hyperplastic polyps are smaller than 1 cm in diameter and are frequently multiple.
  - Among individuals with H. pylori gastritis, polyps may regress after bacterial eradication.

Inflammatory = hyperplastic
Inflammatory polyp increases the risk of dysplasia.
The dysplasia can be premalignant in the GI.
Bigger size polyp ➔ increase the chance of malignant transformation.
The polyp of the stomach is different from the polyp of the large and small intestine, the malignancy transformation chance is more in the stomach polyps.

All the polyps should be resected and examined histologically. Usually the polyps are small and don’t exceed the 1.0cm. If we treat the H.pylori infection before the polyp reaches the premalignant stage (dysplasia), the polyp may regress with the treatment, but when the dysplasia is reached it is irreversible (must be resected).

It is most seen in the antral type mucosa.

- **Fundic Gland Polyps:**
  - occur in the gastric body and fundus
  - may be single or multiple.
  - may be asymptomatic or associated with nausea, vomiting, or epigastric pain.
  - occur sporadically and in individuals with familial adenomatous polyposis (FAP).
  - Occur in patients on proton pump inhibitor (PPI) therapy. These drugs inhibit acid production, which leads to increased gastrin secretion and, in turn, oxyntic gland growth.
  - **Dysplasia** and even cancer may occur in FAP-associated fundic gland polyps, but sporadic fundic gland polyps carry no cancer risk.

The fundic gland polyp differ from the inflammatory polyp that it is found in the fundus and body of the stomach.

The main risk factors of the fundic gland polyps are, the FAP, and PPI.

If the patient was taking proton pump inhibitors and got a fundic gland polyp, stoping the treatment or resecting the polyp will be enough.

FAP increases the malignancy transformation chance in multiple organs, so when the patient has FAP and got a fundic gland polyp, the chance of malignancy transformation will increase, not like the PPI patients.
• **Gastric Adenoma:**

- Their frequency increases progressively with age (50 and 60 years of age).
  - males are affected three times more often than females.
  - gastric adenomas are **premalignant** neoplastic lesions. The risk of transformation to invasive cancer is much higher in gastric adenomas than intestinal adenoma.

- the incidence of adenomas is increased in individuals with **FAP**.

- Similar to other forms of gastric dysplasia, adenomas almost always occur on a background of **chronic gastritis** with atrophy and intestinal metaplasia.

- The risk of adenocarcinoma in gastric adenomas is related to the size of the lesion and is particularly increased in lesions greater than **2 cm** in diameter.

- Gastric adenomas are usually solitary lesions less than 2 cm in diameter, most commonly located in the antrum.

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**Adenoma is a type of polyps that is premalignant (dysplastic).**

**The most important thing in the lab report is the size of the polyp.**
The gastric adenoma can happen with or without the FAP syndrome. Commonly happen in patients with chronic gastritis.

Chronic gastritis (especially H. pylori) ➔ gastric atrophy ➔ intestinal metaplasia ➔ dysplasia (if it was flat we call it dysplasia, but if it was in the polyp shape we call it adenoma).

The polyps in the glands are somehow different in shape (dilated glands, and corkscrew appearance, dilated parietal lining and crypts).

The corkscrew appearance is duo to the chronic gastritis.

When the dysplasia is in the GI (adenoma), we will have cigar shaped cells, condensed chromatin (hyperchromasia), pleomorphism (cells different in size and shape), loss of polarity (disorganized cells), increased mitotic activity (including abnormal mitotic figures).

### Gastric Adenocarcinoma

- Adenocarcinoma is the most common malignancy of the stomach, comprising more than 90% of all gastric cancers.
- gastric adenocarcinoma is often separated morphologically into 2 types:
  - **intestinal type**, which tends to form bulky masses
  - **Diffuse type**, which infiltrates the wall diffusely, thickens it, and is typically composed of **signet ring cells**.
- **Intestinal-type gastric cancer**:
  - Predominates in high-risk areas
  - develops from precursor lesions, including flat dysplasia and adenomas.
The mean age of presentation is 55 years, and the male-to-female ratio is 2 : 1.

- **diffuse gastric cancer:**
  - the incidence is relatively uniform across countries,
  - there are no identified precursor lesions,
  - the disease occurs at similar frequencies in males and females.

Adeno carcinoma is a glandular type cancer.
The intestinal adenocarcinoma is in the mass or ulcer shape.
The malignant ulcer is defined by the irregular margin or the heaped up margin.

In the intestinal adenocarcinoma, the adenocarcinoma mimics the small and large intestines (intestinal metaplasia ⇒ goblet cells ⇒ transform to malignant).

The intestinal type adenocarcinoma arises from the precursor lesions which are, gastric adenoma or, any type of dysplasia.

The high risk areas for the gastric adenocarcinoma are mainly Japan, Chili, and Costa Rica.

The risk factors (associated with chronic gastritis) of the intestinal type are, mucosal atrophy, and intestinal metaplasia because they lead to dysplasia.

The gastric type adenocarcinoma has the same distribution all over the world.

Linitis plastica is caused by the diffused type adenocarcinoma.

When you hear linitis plastica you think of malignant lesions.

In the linitis plastica the whole stomach wall will be like leather, no prominent mass (whole wall is involved).

The diffused type was named because the cells are discohesive (do not mimic the intestines)
The signet ring appearance is due to the mucin and the peripheral nucleus.

In the diffused type we don’t have a precursor lesion, it rises alone.

- Gastric cancer is more common in lower socioeconomic groups and in individuals with multifocal mucosal atrophy and intestinal metaplasia. Intestinal-type
- Gastric dysplasia and adenomas are recognizable precursor lesions associated with gastric adenocarcinoma. Intestinal-type
- The cause of the overall reduction in gastric cancer (intestinal type) is most closely linked to:
  - decreases in H. pylori prevalence.
  - decreased consumption of dietary carcinogens, such as N-nitroso compounds and benzo[a] pyrene, because of the reduced use of salt and smoking for food preservation and the widespread availability of food refrigeration.
  - the remarkable decrease in gastric cancer incidence applies only to the intestinal type, which is most closely associated with atrophic gastritis and intestinal metaplasia.
- The incidence of diffuse type gastric cancer, which was previously low, is now similar to intestinal type gastric cancer. The intestinal and the diffuse types have the same incidence.
Gastric cancer incidence varies markedly with geography. In Japan, Chile, Costa Rica, and Eastern Europe, the incidence is up to 20-fold higher than in North America, northern Europe, Africa, and Southeast Asia.

- **Pathogenesis:**

  While the majority of gastric cancers are not hereditary, the mutations identified in familial gastric cancer have provided important insights into mechanisms of carcinogenesis in sporadic cases.

  - Familial gastric cancer is strongly associated with germline loss-of-function mutations in the tumor suppressor gene **CDH1**, which encodes the cell adhesion protein **E-cadherin**.
  - Loss-of-function mutations in CDH1 are also present in about 50% of sporadic diffuse gastric tumors, Thus, the loss of E-cadherin is a key step in the development of diffuse gastric cancer.

  - Sporadic **intestinal-type** gastric cancers are strongly associated with mutations that result in increased signaling via the **Wnt pathway**. These include loss-of-function mutations in the adenomatous polyposis coli (**APC**) tumor suppressor gene and gain-of-function mutations in the gene encoding **β-catenin**.
  - **FAP patients**, who carry germline APC mutations, have an increased risk of intestinal-type gastric cancer.

  - Genetic variants of proinflammatory and immune response genes (that encode IL-1β, TNF, IL-10, IL-8, and Toll-like receptor 4 (**TLR4**)), are associated with elevated risk of gastric cancer when accompanied by **H. pylori** infection.

Any tumor is associated with either loss of function mutation in tumor suppressor gene or, activating mutation in oncogene.
In gastric carcinoma there are two types of tumor suppressor genes which are, CDH1, and APC (these two are mainly involved in gastric carcinoma).

E-cadherin functions in cells adhesion, so when there is a loss of function mutation in the CDH1 there will be loss of synthesis of E-cadherin $\Rightarrow$ loss of adhesion between cells, and that’s why we find cells discohesive in diffused type adenocarcinoma.

APC is found in chromosome number 5.

- **MORPHOLOGY:**

Most gastric adenocarcinomas involve the gastric antrum; the lesser curvature is involved more often than the greater curvature.

![Image of gastric carcinoma](image-url)
Clinical Features:

Early symptoms of both types of gastric adenocarcinoma resemble those of chronic gastritis and peptic ulcer disease, including dyspepsia, dysphagia, and nausea.

As a result, these tumors are often discovered at advanced stages, when symptoms such as **weight loss, anorexia, early satiety** (primarily in diffuse cancers), **anemia**, and **hemorrhage** trigger further diagnostic evaluation.
• Metastases are often detected at time of diagnosis. Sites most commonly involved include:
  - left-sided supraclavicular sentinel lymph node (Virchow node)
  - periumbilical lymph nodes (Sister Mary Joseph nodule)
  - the left axillary lymph node (Irish node),
  - the ovary (Krukenberg tumor),

• The depth of invasion and the extent of nodal and distant metastases at the time of diagnosis remain the most powerful prognostic indicators in gastric cancer.

• With surgical resection, the 5-year survival rate of early gastric cancer can exceed 90%, even if lymph node metastases are present. In contrast, the 5-year survival rate for advanced gastric cancer remains less than 20%.

The early stage of adenocarcinoma doesn’t have specific symptoms and, can be asymptomatic.

The patient may come with the symptoms of chronic gastritis as, epigastric pain, nausea, vomiting, dyspepsia, dysphagia (these symptoms are nonspecific so, we will have a delayed diagnoses).

The general criteria's of gastric cancer are the three A's:

Anemia, anorexia, abdominal pain.

In The gastric tumor mainly, the prognosis is based on the staging of the tumor.

We can do the staging if we know the extent of the tumor, does it exist in mucosa alone, or it reached the submucosa, or reached the serosa.

The more the tumor went deep the more its stage is.
If metastasis to lymph nodes happened it has worse prognosis than when it is absent.

Lymph node metastasis is also used in staging.

When you examine a patient and find palpable and enlarged lymph nodes that are a sign that this patient has a GI cancer.

**Lymphoma**

- Although extranodal lymphomas can arise in virtually any tissue, they do so most commonly in the GI tract, particularly the stomach.
- Nearly 5% of all gastric malignancies are primary lymphomas, the most common of which are indolent extranodal marginal zone B-cell lymphomas. In the gut these tumors are often referred to as lymphomas of mucosa-associated lymphoid tissue (MALT), or MALTomas.
- Pathogenesis:
  - Extranodal marginal zone B-cell lymphomas usually arise at sites of chronic inflammation.
  - They can originate in the GI tract at sites of preexisting MALT, such as the Peyer patches of the small intestine, but more commonly arise within tissues that are normally devoid of organized lymphoid tissue. In the stomach, MALT is induced, typically as a result of chronic gastritis. *H. pylori* infection is the most common inducer in the stomach and, therefore, is found in association with most cases of gastric MALToma.

Remarkably, *H. pylori* eradication results in durable remissions with low rates of recurrence in most MALToma patients.
• Three translocations are associated with gastric MALToma:
  t(11;18)
  t(1;14)
  t(14;18)
Each of the three translocations has the same net effect, the constitutive activation of NF-κB, a transcription factor that promotes B-cell growth and survival.

NF-κB is constitutively active in tumors bearing translocations involving MLT or BCL10, and **H. pylori treatment is ineffective.**
• As with other low-grade lymphomas, MALTomas can transform into more aggressive tumors that are histologically identical to diffuse large B-cell lymphomas.
• This is often associated with additional genetic changes, such as inactivation of the tumor suppressor genes that encode p53 and p16.
Lymphoma is a tumor that arises from lymphocytes. Lymphoma can arise from any place that has lymphocytes, like H.pylori chronic gastritis (if untreated acquired mutations in lymphocytes).

The mutations in the lymphomas are usually as translocations. Many mutations are involved in the gastric lymphomas, but we have mainly three types of mutations, (11, 18), (1,14), (14, 18).

Chromosome 14 has the IgH gene, while chromosome 18 has BCL-10, and chromosome 11 has MLL(MLT) gene, and chromosome 1 has ABL-2(not for memorizing, what you need to know is the translocations).

If one of these mutations happened, even if we treat the H.pylori, this lymphoma will be irreversible.

This lymphoma is called MALTOMA or, MALT lymphoma. MALTOMAS are low grade lymphomas.

If one of the translocations happened and, no treatment was given to the patient, there will be other type of mutations like, the p53 mutation, and this lymphoma transforms from the low grade to the high grade.

The lymphoma is usually as small nodules distributed in the wall.

The lymphoma starts as

• Clinical Features:

The most common presenting symptoms are dyspepsia and epigastric pain.

Hematemesis, melena, and constitutional symptoms such as weight loss can also be present.

Because gastric MALTomas and H. pylori gastritis often coexist and have overlapping clinical symptoms and endoscopic appearances, diagnostic difficulties may arise, particularly in small biopsy specimens.

Other types of gastric tumors:
- **Carcinoid Tumor** (well-differentiated neuroendocrine tumor): arise from diffuse components of the endocrine system and are most common in the GI tract, particularly the small intestine.

- **Gastrointestinal Stromal Tumor (GIST):**

is the most common mesenchymal tumor of the abdomen. Occurs most often in the stomach.

The most important symptom in lymphoma is a patient that diagnosed with H.pylori and he is taking treatment but doesn’t improve.

The carcinoid tumor and the gastrointestinal stromal tumor don’t rise in the stomach alone, they can rise in the small and large bowel as well and, they are malignant lesions, but the carcinoid tumor is defined as low grade lesion.

The carcinoid tumor arises in any place in the body while, GIST rises mainly in the stomach and small intestine.

The GIST is a stromal tumor and depends on mutations in epidermal growth factor.

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