Diseases of stomach 2
Gastric Polyps and Tumors
• **Polyps** may develop as a result of:
  
  Epithelial or stromal cell hyperplasia,
  Inflammation,
  Ectopia,
  Neoplasia.
• **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.
• **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.
• **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.
Figure 17-16 Gastric polyps. A, Hyperplastic polyp containing corkscrew-shaped foveolar glands. B, Hyperplastic polyp with ulceration (arrow). C, Fundic gland polyp composed of cystically dilated glands lined by parietal, chief, and foveolar cells. D, Gastric adenoma recognized by the presence of epithelial dysplasia.
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.
• 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.
• Epidemiology:
  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.
• MORPHOLOGY:

Most gastric adenocarcinomas involve the gastric **antrum**; the lesser curvature is involved more often than the greater curvature.
Figure 17-17 Gastric adenocarcinoma. A, Intestinal-type adenocarcinoma consisting of an elevated mass with heaped-up borders and central ulceration. Compare to the peptic ulcer in Figure 17-14A. B, Linitis plastica. The gastric wall is markedly thickened and rugal folds are partially lost.
Figure 17-18 Gastric adenocarcinoma. A, Intestinal-type adenocarcinoma composed of columnar, gland-forming cells infiltrating through desmoplastic stroma. B, Signet-ring cells can be recognized by their large cytoplasmic mucin vacuoles and peripherally displaced, crescent-shaped nuclei.
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%.
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-\( \kappa \)B, a transcription factor that promotes B-cell growth and survival.

NF-\( \kappa \)B 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.
Figure 17-19 Lymphoma. A, Gastric MALT lymphoma replacing much of the gastric epithelium. Inset shows lymphoepithelial lesions with neoplastic lymphocytes surrounding and infiltrating gastric glands. B, Disseminated lymphoma within the small intestine with numerous small serosal nodules. C, Large B-cell lymphoma infiltrating the small intestinal wall and producing diffuse thickening.
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.