Gastric neoplasms continue to be a challenge for the surgeon and pathologist. When gastric neoplasms are compared with colonic neoplasms (a more common and well-studied type of malignancy), there are several features of gastric tumors that may account for the difficulties encountered regarding pathology. First, gastric tumors encompass a wide spectrum of pathology when compared to colonic tumors. Some tumors, such as gastrointestinal (GI) stromal tumors and endocrine cell hyperplasia, have an uncertain biologic behavior. Second, gastric tumors share similar nosology with colonic tumors (eg, hyperplastic polyps and adenomatous polyps), but these carry somewhat different clinical implications and pathologic features. Third, gastric cancers are less prevalent than colonic cancers. Therefore, the adenoma-carcinoma sequence and other possible precancerous lesions in the stomach are not as well studied as those in the colon. Finally, molecular pathology has recently elucidated the histogenesis and genetic defects of some interesting gastric tumors, such as GI stromal tumors and juvenile polyps. This chapter focuses on these unique features and on recent developments regarding gastric tumors. A classification of gastric tumors, based mostly on their histologic origins, is shown in Table 11–1.

**GASTRIC POLYPS**

**Adenoma and Dysplasia**

There are no generally accepted definitions of dysplasia and adenoma of the stomach. Dysplasia is best defined as an unequivocal neoplastic epithelial alteration. Adenomas consist of nodules of dysplastic epithelium. However, not all dysplastic epithelia form circumscribed nodules. Dysplasia may be found in flat epithelium. In other words, two types of dysplasias are recognized: adenomatous and nonadenomatous dysplasia. The two types have identical histopathologies.

Adenomas are uncommon in the stomach, in contrast to colonic adenomas, which are more frequent. Gastric adenomas occur almost exclusively in the
antrum. Adenomas are frequently seen in two clinical settings: one setting is in patients with familial adenomatous polyposis, or Gardner's syndrome;\(^3\) the other is associated with chronic atrophic gastritis.

In contrast to adenomas in the colon, most adenomas in the stomach are sessile or grow into flat mucosa; pure pedunculated adenoma is uncommon. Gastric adenoma has a tubular, villous, or mixed tubulovillous appearance in histology. Tubular adenomas tend to be sessile whereas villous and tubulovillous adenomas are more likely to be pedunculated (Figure 11–1, A). Two major microscopic variants are found in adenomas.\(^4\) The intestinal type (the more common type) is composed of dysplastic epithelium arising in the intestinal metaplastic epithelium. Cytologically, these cells have large, elongated, and hyperchromatic nuclei arranged in pseudostratification (see Figure 11–1, B). Goblet cells, Paneth’s cells, and endocrine cells can be seen occasionally. The gastric type (the less common type) is composed of dysplastic epithelium similar to the foveolar epithelium containing PAS(+) (period acid-Schiff-positive) apical neutral mucin. This type of dysplasia usually consists of round and basal nuclei, in contrast to the elongated and pseudostratified nuclei of the intestinal type of dysplasia.

The adenoma-carcinoma sequence in the stomach is not as well defined as that in the colon since the majority of gastric carcinomas do not arise from pre-existing adenomas. It is unlikely that these adenomas have been destroyed by the bulk of a gastric carcinoma because adenomas are also uncommon in early gastric carcinoma,\(^5\) which should have a better preservation of the precursor lesion. The incidence of synchronous carcinomas associated with gastric adenomas varies from report to report\(^6\) and depends on the size and duration of the adenoma. Most carcinoma-associated gastric adenomas are > 2 cm in diameter. It may take 10 to 15 years for a gastric adenoma to transform into carcinoma. Although limited data on its proper treatment have been published, it is reasonable that gastric adenoma should be completely excised by endoscopic or surgical resection.

**Hyperplastic Polyps**

The definition of hyperplastic polyps varies.\(^1,8\) All definitions recognize the basic abnormality, namely, hyperplasia or expansion of the pit compartment. Thus, any mucosal polyp composed of too many pits or made up of elongated pits satisfies the definition of a hyperplastic polyp. Hyperplastic polyps are the most common polyps of the stomach, constituting 50 to 90 percent of all gastric polyps. About two-thirds of hyperplastic polyps occur in the antrum.

---

![Figure 11–1. (A) Endoscopic view of villous adenoma of the stomach. The histologic features are similar to those of villous adenoma of the colon. (B) The epithelial cells contain enlarged, elongated, and hyperchromatic nuclei arranged in a pseudostratified pattern.](image-url)
They tend to develop in association with atrophic gastritis and probably represent regenerative hyperplasia of the foveolar epithelium. *Helicobacter pylori* infection was found to be associated with hyperplastic polyp formation in a recent report.9

The gross appearance of hyperplastic polyps depends on their size, which ranges from 0.5 to 2.5 cm in diameter. The smaller polyps tend to be sessile whereas the larger ones may be pedunculated and lobulated (Figure 11–2, A). The basic histologic abnormalities involve the pits, which are elongated, branched, and distorted. The lengthening exaggerates the surface contours, producing coarse or irregular villi. The distortion takes several forms. Some of the elongated pits have a serrated or corkscrew configuration, others are cystic, and still others branch (see Figure 11–2, B). Superimposed on the pit changes are inflammatory changes. The malignant potential of hyperplastic polyps is low (0.4%); malignancy occurs mostly in polyps > 2 cm in diameter.10 However, it is debatable whether hyperplastic polyps may simply share the same etiologic factors as gastric carcinomas or a precursor of the latter.

In addition to the above-mentioned ordinary hyperplastic polyps, three other variants of hyperplastic polyps are worthy of special mention. The first is focal foveolar hyperplasia,11 which consists of small multiple sessile lesions that are frequently observed endoscopically and which may represent the early and miniature form of hyperplastic polyps. The second variant is inflammatory polyps at the gastroesophageal junction; these polyps are commonly associated with reflux esophagitis.12 The third variant is hyperplastic polyps on the gastric side of gastroenteric anastomoses.13 Hyperplastic polyps occur in approximately 10 percent of gastric remnants, especially after a Billroth II gastrojejunal anastomosis, usually 10 to 15 years after surgery.14 Grossly, they are pedunculated polyps with lobulated and villiform surfaces (Figure 11–3). Histologically, some hyperplastic pits form cystic spaces and extend into the submucosa, a feature that has been

![Figure 11–2. Hyperplastic polyp of the stomach. A, Endoscopic view of a pre-pyloric hyperplastic polyp that shows a lobulated surface. B, The hyperplasia involves the foveolar surface pit epithelium but not the deep mucous glands. Some of the elongated pits have a branched and corkscrewlike appearance.](image-url)
intestine. Dysplasia and carcinoma have been reported in the stomach but are more common in the small and large intestine. The genetic defect of PJS has recently been identified as LBK1/STK11 on chromosome segment 19p13.3, which encodes a serine/threonine kinase.

**Juvenile Polyps**

Juvenile polyps are hamartomatous polyps that can occur in sporadic or familial form. Sporadic juvenile polyps tend to be single and are common in the colon. However, the familial form is usually multiple and also involves other locations of the GI tract, including the stomach and small intestine. Juvenile polyposis is inherited as an autosomal dominant trait and is heterogeneous in genetic mutation. Recent studies have linked juvenile polyposis to mutations in the PTEN gene located on chromosome band 10q23 or in the SMAD4/DPC4 gene located on chromosome band 18q21. SMAD4 is a key cytoplasmic protein in the signal transduction of transforming growth factor-β. Gastric juvenile polyps are characterized by cystically dilated glands surrounded by edematous and inflamed granulation-like stroma. Surface ulceration is common in these polyps. Patients with juvenile polyposis have an increased risk for colorectal cancer, gastric cancer, and pancreatic cancer.

**Fundic Gland Polyps**

Fundic gland polyps are small sessile lesions that occur in the fundus of the stomach. Fundic gland polyps can be found in three different clinical settings: (1) in patients with familial adenomatous polyposis (FAP), (2) in patients without FAP, and (3) in association with the use of omeprazole. There is evidence that both sporadic and FAP-associated fundic gland polyps overexpress transforming growth factor-α (TGF-α) and its receptor. There is also evidence that long-term treatment with omeprazole (a proton pump inhibitor) may be followed by the development of fundic gland polyps.

Fundic gland polyps are small dome-shaped nodules with smooth surfaces (Figure 11–4, A). Usually, they are multiple, especially if they are associated with FAP. Regardless of the clinical setting, fundic
gland polyps have a normal or shortened pit com-
artment that leads into an altered glandular com-
partment that contains cystic glands lined by parietal
and chief cells (see Figure 11–4, B). Fundic gland
polyps that are associated with omeprazole treat-
ment are characterized by parietal cell hypertrophy
with tonguelike projection into the cystically dilated
lumens.25 There is no increased risk of malignant
change in fundic gland polyps in general although
dysplasia has been reported in rare FAP-associated
fundic gland polyps.

Ectopic Pancreas (Pancreatic Heterotopia)
In pancreatic heterotopia, submucosal tumors, 1 to
2 cm in diameter, are found on the greater curvature of
the antrum, forming a dome-shaped mass that pro-
trudes into the lumen.26 Central depression and
umbilication are useful signs on endoscopic exami-
nation (Figure 11–5); however, they occur in only
less than half of the cases. Because patients are usu-
ally asymptomatic, most of these tumors are inci-
dental findings during surgery or autopsy. Any com-
plications that occur in the pancreas, such as
pancreatitis and pancreatic carcinoma, can also
occur in the ectopic pancreas.

G I A N T  F O L D  D I S E A S E S
(HYPERPLASTIC GASTROPATHIES)
Normal gastric folds are prominent in the fundus and
are flat in the antrum. Several factors affect the size
of these folds, including age and the degree of gastric
distention. Giant folds are usually defined as large
folds that persist even in the distended stomach. The
precise definition depends on the methods of study.
By radiologic or endoscopic measurement the gen-
eral cut-off size is 1 cm in height or width.27 Giant
fold diseases are heterogeneous in their pathogenesis.
Some giant folds are accompanied by clinical symptoms whereas others are not. Giant folds may be caused by neoplastic or non-neoplastic processes; they may also occur as a variant of normal folds. The most common clinical conditions associated with gastric giant folds are Ménétrier’s disease, Zollinger-Ellison syndrome, and diffuse neoplastic infiltrates.

### Ménétrier’s Disease

Ménétrier’s disease is a syndrome that includes gastric giant folds, protein loss, and decreased gastric acid production. Giant folds occur in the body and fundus, and the antrum appears normal (Figure 11–6, A). The etiology is unknown although there is evidence of excessive production of TGF-α in these patients. A Ménétrier disease–like condition has been observed in transgenic mice that overexpressed TGF-α. Transforming growth factor-α is expressed in the normal surface epithelium and parietal cells of the gastric body mucosa but is absent in normal pit epithelium. It also appears in the hyperplastic pit epithelium in patients with Ménétrier’s disease. Ménétrier’s disease usually develops in adults at a mean age of 55 to 60 years. A self-limited Ménétrier disease–like condition in children is probably postinfectious, occurring especially after Cytomegalovirus infection.

The typical histologic findings are florid pit hyperplasia accompanied by atrophy or loss of deep glands. The pits are unusually elongated and have a corkscrewlike appearance (see Figure 11–6, B). Surface edema is not uncommon, but inflammation is not a significant component. Histologic assessment was formerly limited by the difficulty of performing a full-thickness biopsy of the hyperplastic gastric mucosa.

The course of Ménétrier’s disease is unpredictable. In adults, fully developed disease is usually progressive; however, the disease is generally benign and self-limited in children. Resection is indicated when hypoproteinemia leads to uncontrollable edema. A few patients may respond to H2 (histamine) receptor blockers. A few cases of Ménétrier’s disease are complicated by adenocarcinoma, but it is uncertain whether this is a precursor lesion for gastric cancer.

### Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome is characterized by multiple intractable peptic ulcers, which are usually duodenal, resulting from hypergastrinemia from a gastrin-producing tumor. The tumors are most common in the pancreas but can also be seen in the duodenum. Pancreatic gastrinoma is a component of type I mul-
tiple endocrine neoplasia syndrome (MEN-I).\(^\text{32}\) Grossly, the fundic mucosal folds are enlarged and grow into a cobblestone pattern. Histologic features are characterized by hyperplasia and hypertrophy of parietal cells in the fundic mucosa, caused by the trophic effect of gastrin (Figure 11–7). Enterochromaffin-like endocrine cells of the body are also hyperplastic because of the stimulation of gastrin. In contrast to Ménétrier’s disease, the pit compartment is generally normal in this syndrome. Hypertrophic hypersecretory gastropathy\(^\text{33}\) is a normogastrinemic variant of giant fold disease that resembles Zollinger-Ellison syndrome. Patients with this syndrome have large folds that tend to have a particularly nodular appearance. Although they have hypersecretion of gastric acid and frequent peptic ulcers, they do not have pancreatic tumors or hypergastrinemia.

**Diffuse Neoplastic Infiltrates**

One of the classic gross findings in gastric lymphoma patients is that of fold enlargement. These large folds are usually coarse and irregular. Adenocarcinomas, especially the diffuse signet-ring cell type, can also produce giant folds.

**MALIGNANT EPITHELIAL TUMORS: GASTRIC CARCINOMA**

Gastric carcinoma is the second most common cancer in the world. Its incidence varies from country to country. In the United States, there has been a steady decline in the incidence of gastric cancer; the present rate is approximately 10 cases per 100,000. Nevertheless, it was estimated that approximately 21,500 new cases would be diagnosed in 2000.\(^\text{34}\) There has also been a worldwide decline in the incidence of gastric cancer since 1930.\(^\text{35}\) However, the poor prognosis for advanced gastric carcinomas (a 5-year survival of 16.3% in the United States) makes early diagnosis an important objective.

Carcinoma arising in the gastric cardia appears to have different etiologic factors and a different biologic behavior from distal noncardia carcinoma.\(^\text{36}\) First, the incidence of cardia carcinoma has recently increased in many countries whereas the incidence of noncardia gastric carcinoma has decreased. Second, cardia carcinoma is associated more with reflux esophagitis whereas noncardia carcinoma is associated more with *Helicobacter pylori* infection. However, there are several controversies regarding the issue of cardia carcinoma. First, there is no consensus on the anatomic definition of the cardia. Second, there are no distinct morphologic features that separate cardia carcinoma from Barrett’s carcinoma; some cardia cancers can grow upward into the distal esophagus whereas Barrett’s carcinomas can sometimes extend below the junction, to involve the cardia. Third the recently described entities of cardia intestinal metaplasia and carditis (inflammation of the gastric cardia) raise the issue of their etiology and possible role in cardia carcinoma. Understanding of the pathogenesis of cardia carcinoma must await more clinicopathologic studies in the future.
The precancerous lesions of gastric cancer are not as well defined as those of colon cancers, in which an adenoma-carcinoma sequence has been widely accepted. Several predisposing conditions are associated with increased risk of cancer, including *H. pylori* infection, atrophic gastritis, subtotal gastrectomy, immunodeficiency syndrome, and Ménétrier’s disease. Correa recognized a stepwise progression from normal epithelium to chronic gastritis, followed by intestinal metaplasia, dysplasia, and carcinoma.\(^{37}\) Intestinal metaplasia has been associated with gastric carcinoma of the intestinal type in epidemiologic, prospective, and morphologic studies.\(^{38}\) However, the overall incidence of cancer developing in patients with intestinal metaplasia is so low that routine biopsy is not justified for the screening of gastric cancer.

It is noteworthy that *H. pylori* has been declared as a group I carcinogen by the World Health Organization.\(^{39}\) The strongest evidence of an association between *H. pylori* and gastric carcinoma comes from a series of prospective studies in which banked sera from blood donors were used.\(^{40}\) Several reports indicated a significantly increased risk of gastric cancer in donors with positive serum antibodies for *H. pylori*, compared to age- and gender-matched controls with negative antibody titers.\(^{41}\) Both intestinal and diffuse types of cancer have been linked to *H. pylori* infection. However, only noncardia cancers are associated with *H. pylori*.

### Early Gastric Carcinoma

Based on the depth of invasion, gastric carcinoma can be divided into early gastric cancer and advanced gastric cancer. Early gastric carcinoma (EGC) is defined as a gastric carcinoma with invasion confined to the mucosa and submucosa, regardless of the presence or absence of lymph node metastases.\(^{42}\) The concept of EGC is different from that of carcinoma in situ or gastric dysplasia, in which cancer cells have not penetrated the basement membrane and have no metastatic potential. Some patients with EGC may already have lymph node metastases. However, the overall “cure” rate by surgery for these patients is higher than for patients with advanced gastric carcinoma. In Japan, the 5-year survival of patients with EGC after resection is approximately 95 percent, compared to only 5 to 15 percent for all other gastric carcinomas.\(^{43}\)

Early gastric carcinoma was first recognized in Japan, where the incidence of gastric carcinoma is high. In 1962, the Society for Gastrointestinal Endoscopy of Japan recognized three major gross morphologic types of EGC: protruded (type I), superficial (type II), and excavated (type III).\(^{44}\) The superficial type is further divided into elevated (IIa), flat (IIb), and depressed (IIc) subtypes. This classification may help the endoscopist to identify subtle mucosal alterations. However, the correlation of gross findings with histology and prognosis is poor. The histologic types of EGC vary among different reports. In general, differentiated carcinomas (tubular or papillary) are more common in type I (protruded) EGC. Undifferentiated carcinomas (signet-ring cell, mucinous, and poorly differentiated) are found more often in the depressed groups (IIc and IIc+III) (Figure 11–8).

### Advanced Gastric Carcinoma

There are several classification systems\(^{45–47}\) for advanced gastric carcinoma, based on the gross morphology or histopathology (Table 11–2). The classifications based on gross morphology are less useful because of their low predictive value for patients’ prognoses. The simplest and most widely used system is Lauren’s classification,\(^{45}\) which divides gastric carcinoma into two types: intestinal and diffuse (Table 11–3). The intestinal type is presumed to arise from intestinalized gastric mucosa and closely resembles ordinary colon cancer. Grossly, the tumors are usually nodular, polypoid, or fungating (Figure 11–9, A). Histologically, they are characterized by various extents of glandular formation and by frequent association with intestinal metaplasia (see Figure 11–9, B). The liver is the most common site of metastases. In contrast, the diffuse type is grossly ill defined and may have the appearance of a plaque or linitis plastica (which has the gross appearance of a leather bottle) (Figure 11–10, A). The histology is remarkable for isolated and poorly differentiated carcinoma or signet-ring cells (see Figure 11–10, B). Metastases are commonly found in the serosa or lymph nodes.
Borrmann’s classification is widely used for describing the gross appearance of gastric carcinoma:48 type I is a polypoid and fungating tumor, type II is a polypoid tumor with a central ulceration, type III is an ulcerated tumor with infiltrative margins, and type IV is the linitis plastica variety.

Gastric carcinoma usually emerges as a localized tumor and spreads to the adjacent structures by one of three modes: lymphatic invasion, hematogenous dissemination, and peritoneal extension. The most common mode is lymphatic metastasis to lymph nodes along the greater and lesser curvature of the stomach. Occasionally, supraclavicular nodes (Virchow’s nodes) may be involved, via the thoracic duct. The liver is the most common site of hematogenous spread. The lungs and the central nervous system are not commonly involved by gastric cancer. Peritoneal spread can involve many locations in the abdominal cavity; however, the ovaries (Krukenberg’s tumor) and the rectal shelf (Blumer’s tumor) are typically involved by peritoneal spread. Other sites of peritoneal extension include the pancreas, the transverse colon, and the undersurface of the diaphragm.

Pathologic Staging and Prognostic Factors for Gastric Carcinoma

The tumor-node-metastasis (TNM) system has become the principal method of staging gastric cancer. The extent of disease is determined by the following three components: (1) the primary tumor (T), which represents the depth of invasion through the gastric wall; (2) the regional lymph nodes (N), which include the lymph nodes along the lesser and greater curvature as well as the pancreatic and splenic areas; and (3) distant metastasis (M), which refers to spread to the liver, peritoneal surfaces, and nonregional lymph nodes, including the retropancreatic,

Table 11–2. CLASSIFICATION OF GASTRIC ADENOCARCINOMA

<table>
<thead>
<tr>
<th>Based on Gross Morphology</th>
<th>Based on Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ming</td>
<td>Lauren</td>
</tr>
<tr>
<td>Expanding</td>
<td>Intestinal</td>
</tr>
<tr>
<td>Infiltrating</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Stout</td>
<td>WHO</td>
</tr>
<tr>
<td>Fungating</td>
<td>Papillary</td>
</tr>
<tr>
<td>Ulcerating</td>
<td>Tubular</td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>Mucinous</td>
</tr>
<tr>
<td>Diffusely infiltrating</td>
<td>Signet-ring</td>
</tr>
</tbody>
</table>

WHO = World Health Organization.

Table 11–3. COMPARISON OF INTESTINAL AND DIFFUSE TYPES OF GASTRIC CARCINOMA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intestinal Type</th>
<th>Diffuse Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross appearance</td>
<td>Elevated, fungating</td>
<td>Depressed, infiltrating</td>
</tr>
<tr>
<td>Histology</td>
<td>Glandular</td>
<td>Isolated</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Liver</td>
<td>Lymph nodes, serosa</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>Almost 100%</td>
<td>Less common</td>
</tr>
<tr>
<td>Sex predominance</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>~ 20%</td>
<td>Young</td>
</tr>
<tr>
<td>5-year survival</td>
<td>Slightly above age</td>
<td>Unknown, genetic?</td>
</tr>
<tr>
<td>Etiology</td>
<td>Diet, environment, Helicobacter pylori</td>
<td>(associated with blood group A)</td>
</tr>
</tbody>
</table>
para-aortic, portal, retroperitoneal, and mesenteric nodes. In 1997, the American Joint Committee on Cancer (AJCC) published its fifth revised staging criteria for gastric carcinoma ⁴⁹ (Tables 11–4 and 11–5). The major change in this current version is the reclassification of regional lymph node metastases (N) according to the number of positive nodes rather than the distance from the tumor edge to the lymph nodes, as proposed in a prior version.

The most useful prognostic factors are the depth of invasion and the spread to regional lymph nodes. The location and Borrmann’s gross morphologic types are two other important prognostic factors. Distal gastric carcinoma has a more favorable prognosis than proximal cancer. Borrmann types I and II have a better prognosis than Borrmann types III and IV, independent of the status of lymph node metastases. Both histologic type and grade have an impact on the prognosis. The intestinal type of gastric cancer classified by Lauren has a better prognosis than the diffuse type. Low-grade adenocarcinoma also has a better prognosis than high-grade cancer. The overall prognosis for gastric cancer is poor; the 5-year survival rate is less than 20 percent, even after “curative” surgery.

Various molecular markers, including oncogenes and tumor-suppressor genes, have been used to predict prognosis. For instance, amplification of the HER-2/neu gene seems to be a prognostic factor of metastatic potential.⁵⁰ However, the application of such molecular markers in clinical practice awaits further study.

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**Figure 11–9.** Advanced gastric carcinoma of the intestinal type. A, Resection specimen shows a protruding mass in the antrum, corresponding to Borrmann’s type I adenocarcinoma. B, Histologic study of the same case shows gland-forming adenocarcinoma and adjacent intestinal metaplasia.

**Figure 11–10.** Advanced gastric carcinoma of the diffuse type. A, Resection specimen shows marked thickening of the wall, having the contour of a leather bottle (the so-called linitus plastica of Borrmann’s type IV adenocarcinoma). B, Histologic study of the same case shows diffuse infiltration of isolated signet-ring cells, without any glandular formation.
ENDOCRINE TUMORS

Various types of endocrine cells are present throughout the entire GI tract. In the stomach, the two key endocrine cell types are gastrin-producing G cells and histamine-producing enterochromaffin-like (ECL) cells. G cells are located at the junction of the gastric pits and pyloric glands in the antrum whereas ECL cells are found between the parietal and chief cells in the fundus. In the normal stomach, gastrin is secreted by G cells in response to negative feedback by hydrochloric acid. Gastrin, in turn, drives the ECL cells to produce histamine, which is the main activator of acid secretion by parietal cells51 (Figure 11–11).

Endocrine Cell Hyperplasia

In most cases, gastric endocrine cell hyperplasia is secondary to hypochlorhydria, with a small portion due to MEN-I syndrome.52 Type A chronic atrophic gastritis (CAG) is the main cause of hypochlorhydria. Acid-suppressing drugs such as H₂ blockers or proton pump inhibitors can also induce endocrine cell hyperplasia in rodents and humans (although carcinoid tumor was reported only in rodents).

Two types of endocrine hyperplasia are associated with hypochlorhydria: G-cell hyperplasia of the antrum and ECL hyperplasia in the fundus.53 Hypochlorhydria lifts the negative-feedback mechanism of hydrochloric acid and then induces G-cell hyperplasia. In turn, G cells cause ECL-cell hyperplasia, via hypergastrinemia.

Carcinoid Tumor

Gastric carcinoid tumor accounts for about 3 percent of all GI carcinoids. It has gained additional atten-

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**Table 11-4. STAGING OF GASTRIC CARCINOMA: TUMOR-NODE-METASTASIS GROUPING***

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor (T)</th>
<th>Node (N)</th>
<th>Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (intraepithelial tumor without invasion of the lamina propria)</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria or submucosa</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades muscularis propria or submucosa</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades adjacent structures</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

**Table 11-5. STAGING OF GASTRIC CARCINOMA: STAGE GROUPING***

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Classifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0 M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1 N1 M0</td>
</tr>
<tr>
<td>II</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T2 N1 M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3 N1 M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4 N0 M0</td>
</tr>
</tbody>
</table>

TNM = tumor-node-metastasis.

*American Joint Committee on Cancer criteria, 1997.

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Figure 11–11. Schematic diagram of the control of gastric acid by G cells and enterochromaffin-like (ECL) cells in the normal stomach. Gastrin released by normal G cells in the antrum stimulates fundic ECL cells to release histamine, which stimulates the secretion of hydrochloric acid (HCl) by parietal cells. The intragastric acidity exerts a feedback inhibition on the gastrin release by G cells.
tion recently because of reports on experimentally induced rodent gastric carcinoid with long-term usage of gastric acid inhibitors such as omeprazole. Gastric carcinoid is heterogeneous and consists of three clinical subtypes, as discussed below.

**Carcinoid Associated with Type A Chronic Atrophic Gastritis with or without Pernicious Anemia**

Type A chronic gastritis, presumably autoimmune in etiology, is caused by antibodies to parietal cells and intrinsic factor in a patient’s serum. The disease involves only the fundic mucosa, leading to glandular atrophy, achlorhydria, and eventually pernicious anemia in a majority of patients. The antral mucosa is intact; the antral G cells, without the negative feedback of hydrochloric acid, undergo hyperplasia, which results in the autonomous secretion of gastrin. Hypergastrinemia, in turn, causes ECL-cell hyperplasia and subsequent transformation into carcinoid tumor. The pathogenetic pathway is summarized in Figure 11–12. This is the most common variant, and it often has a benign course. Histologically, the lesions are usually small, multiple, and confined to the gastric mucosa (Figure 11–13, A). The fundic mucosa is atrophic, but the antrum is characterized by G-cell hyperplasia (see Figure 11–13, B) clinically associated with hypergastrinemia. Lymph node or distant metastasis is uncommon. According to Rindi and colleagues, this is a relatively benign tumor, and conservative therapies such as endoscopic removal or gastric resection (including the gastrin-producing mucosa) seem appropriate. Tumor regression has been reported after antrectomy, which removes the bulk of G cells.

**Carcinoid Associated with Zollinger-Ellison Syndrome**

Carcinoids associated with Zollinger-Ellison syndrome (ZES) account for 8.6 percent of all gastric carcinoids and occur almost exclusively in patients with MEN-I syndrome. Unlike CAG-associated carcinoids, hypergastrinemia in ZES is associated with gastrinoma in the pancreas rather than G-cell hyperplasia in the antrum. Furthermore, the fundic mucosa is hypertrophic because of the trophic effect of gastrin. The pathogenetic pathway is summarized in Figure 11–14. Surgery should aim at the localization and excision of gastrinoma. The mere excision of gastrin-producing gastric mucosa does not halt the progression of carcinoid tumor.

**Carcinoid Tumor of Sporadic Form**

Carcinoid tumors of sporadic form are gastrin independent and are not associated with hypergastrinemia. The fundic mucosa appears normal. Sporadic carcinoids account for about a quarter of all gastric carcinoids and have a worse prognosis than carcinoids associated with CAG or ZES. Patients usually have larger tumors and are in more advanced stage of disease. Therapy should be more aggressive in light of the malignant potential of this tumor. In addition to surgery, combined chemotherapy and radiation may be required for neuroendocrine carcinoma.

**Hyperplasia-Dysplasia-Neoplasia Sequence of Gastric Carcinoids**

The histogenesis of carcinoid tumors in most organs has not been established. Gastric carcinoids are the only carcinoid tumors with a well-documented
hyperplasia-dysplasia-neoplasia sequence based on experimental and clinical observations. It was postulated that the lack of feedback inhibition by gastric acid (hypochlorhydria) is the common cause of G-cell hyperplasia resulting from various conditions, including atrophic gastritis with or without pernicious anemia, vagotomy, chronic administration of H₂ antagonists, or proton pump inhibitors. Hypergastrinemia secondary to G-cell hyperplasia causes ECL-cell hyperplasia in turn. Detailed histologic examination by Solcia and colleagues⁵⁸ has documented the progression of ECL-cell hyperplasia to dysplasia and finally to microcarcinoid and invasive carcinoid.

**MESENCHYMAL TUMORS**

Gastrointestinal mesenchymal tumor is a broad term to cover tumors of heterogeneous cell lineage, including smooth-muscle, neural, adipose, vascular, or lymphatic origin; the remaining histologically uncommitted tumors are collectively named gastrointestinal stromal tumors (GISTs).⁵⁹,⁶⁰ However, it has been found recently that these “traditional” GISTs show

Figure 11–13. Gastric carcinoid associated with type A chronic atrophic gastritis. A, The fundic mucosa shows multiple nodules of carcinoid tumor arising from the base of the mucosa. Diffuse intestinal metaplasia and atrophy of deep fundic glands indicate a late stage of type A chronic atrophic gastritis. B, The antral mucosa shows G-cell hyperplasia secondary to hypochlorhydria, demonstrated by immunostaining for gastrin (red color).
Pathology of Gastric Neoplasms

Figure 11–14. Schematic diagram of gastric carcinoid associated with Zollinger-Ellison syndrome (ZES). Gastrin-producing tumors in the pancreas cause hyperplasia of enterochromaffin-like (ECL) cells. Long-term hyperplasia of ECL cells is subject to the risk of malignant transformation into carcinoid tumor. The treatment of ZES should aim at the removal of the gastrinoma or a total gastrectomy. Antrectomy alone will not eliminate the risk of carcinoid tumor in the fundus. (HCl = hydrochloric acid.)

Two histologic patterns: spindle cell (70%) and epitheloid cell (30%) (see Figure 11–15, B).

The histologic features that correlate best with development of recurrence and metastasis include mitotic activity, tumor size, and the presence of tumor necrosis. Gastrointestinal stromal tumors with the following histologic features are considered malignant: (1) mitotic counts higher than 5 mitoses/10 high-power fields; (2) size larger than 5 cm; and (3) large areas of necrosis, hemorrhage, hypercellularity, or atypia.59

Immunohistochemically, GISTs are typically positive for vimentin, CD34, and CD117/c-kit protein. A hematopoietic progenitor cell antigen, CD34 can occur in a wide variety of mesenchymal tumors of fibroblastic, lipomatous, and endothelial origin; CD117 is a more specific marker for a diagnosis of GIST61 (see Figure 11–15, C). Patients with a mutation of the c-kit gene have more frequent recurrences and a higher mortality than those without the mutation.63

Leiomyoma

Leiomyomas are benign smooth-muscle tumors that are most commonly seen in the cardia. Grossly, the tumor is well circumscribed, with muscular proliferations demonstrating a whorled and elastic cross section.

Gastrointestinal Stromal Tumor

Although GISTs can occur throughout the entire GI tract, the stomach is the most common site, accounting for 60 to 70 percent of all cases. These tumors occur predominantly in persons over 40 years of age, with an equal sex incidence. Benign GISTs outnumber malignant ones by a margin of 10:1. Although GISTs are rare in individuals under the age of 40 years, malignant GISTs occur more often in this age group.

Grossly, benign GISTs are usually sharply demarcated nodules 2 to 5 cm in diameter (Figure 11–15, A). Malignant GISTs are usually more than 10 cm in maximal diameter and often show mucosal ulceration and areas of necrosis and hemorrhage. Malignant GISTs often show spread of multiple tumor nodules into the surrounding omental or mesenteric soft tissue. However, GISTs do not disseminate to the regional lymph nodes. Microscopically, GISTs show

mutation of the c-kit proto-oncogene (CD117) and loss of DNA on chromosome arm 14q.61 Because CD117 is positive only for mast cells and interstitial cells of Cajal (ICCs) in the GI tract, it was postulated that GISTs originate from ICCs and should be renamed interstitial cells of Cajal tumors.62

Lipoma and Neurofibroma/
Neurofibromatosis

Lipomas are rare benign tumors that occur in the gastric submucosa. Small lipomas are usually asymptomatic; however, some lipomas larger than 3 cm in diameter can cause ulceration, epigastric pain, bleeding, and gastric outlet obstruction. Grossly, lipomas are round well-defined submucosal nodules with a typical yellowish cross section. Histologically, the tumor consists of mature adipose tissue with no significant inflammation unless the mucosa is ulcerated.

Both von Recklinghausen’s neurofibromatosis and type II multiple endocrine neoplasia (MEN-II) can affect the GI tract.64 These lesions include mucosal neuromas and ganglioneuromas (in both syndromes) and plexiform neuromas (in von Recklinghausen’s
disease). However, the stomach is less frequently involved than the small intestine and the colon.

**Granular Cell Tumor and Glomus Tumor**

Granular cell tumors are proliferations of plump spindled or epitheloid cells, which are presumably Schwann cells in origin. The cytoplasm stains positively with periodic acid–Schiff stain (PAS) and S-100 protein. The tumors are located at the submucosa or muscularis propria of the stomach.

Glomus tumor is a rare vascular tumor that is presumed to arise from the normal structure of the glomus body. The tumor commonly occurs in the antrum as a solitary nodule in the muscularis propria. Histologically, the round and uniform tumor cells are surrounded by vascular space and can sometimes be mistaken for carcinoid tumors (Figure 11–16). The tumor cells are immunoreactive for smooth-muscle actin, vimentin, laminin, and type IV collagen. The tumors are mostly benign and solitary although a multiple glomus tumor with intravascular spread has been reported.⁶⁵

**LYMPHOPROLIFERATIVE DISORDERS**

The GI tract is the most common site of primary extranodal non-Hodgkin’s lymphoma, and more than 50 percent of all GI lymphomas arise from the stomach. However, the overall number is small, and gastric lymphomas account for less than 5 percent of all gastric tumors. There is no satisfactory classification of GI lymphomas at present.⁶⁶ Except for a few cases of T-cell lymphoma, the majority of gastric lymphomas are of B-cell origin. Approximately 90 percent of gastric lymphomas are of the diffuse type, and only 10 percent of them are of the follicular type. In a report in 1983, Isaacson and Wright...
found that low-grade gastric lymphomas have histologic features more similar to mucosa-associated lymphoid tissue (MALT) than to nodal lymphoid tissue. The term “MALT lymphoma” was suggested later for this group of lymphomas. Only MALT lymphoma is discussed in this chapter because it accounts for > 90 percent of all gastric lymphomas.

**Mucosa-Associated Lymphoid-Tissue Lymphoma of the Stomach**

Several patterns of gastric lymphoma are noted at endoscopic examination: ulceration, gastritis, polyloid mass, and diffuse growth (Figure 11–17, A). In general, the gross appearance is related to the tumor grade. Low-grade lymphomas are usually superficial with focal ulceration whereas high-grade lymphomas show diffuse infiltration or nodular growth with extensive ulceration. The gastric antrum is the most common site of involvement, followed by the body and the cardia.

Low-grade MALT lymphomas are characterized by lymphoepithelial lesions, subepithelial plasma cells, and reactive lymphoid follicles. A lymphoepithelial lesion refers the intraepithelial migration of atypical lymphocytes (see Figure 11–17, B). These
atypical lymphocytes are of B-cell origin rather than being T cells, which make up a population of normal intraepithelial lymphocytes. Reactive lymphoid follicles are surrounded by neoplastic lymphocytes in the marginal zone.

The etiology of gastric lymphoma is not completely understood. Associations with *H. pylori* infection, immunodeficiency disorders, and autoimmune states such as celiac sprue have been reported. Wotherspoon and colleagues found *H. pylori* infection in 92 percent of patients with gastric lymphoma, compared with an infection rate of 50 percent to 60 percent in the general population.68 Hussell and associates have shown that certain strains of *H. pylori* can stimulate the in vitro proliferation of gastric lymphoma cells.69 This process is T-cell dependent and can respond to antibiotic treatment, of these monoclonal lymphocytes may be antigen dependent and can respond to antibiotic treatment, which eliminates *H. pylori* infection and removes the antigenic stimulation.70 Persistent antigenic stimulation in conjunction with dietary mutagens eventually generates monoclonal lymphoid cells. Initially, some of these monoclonal lymphocytes may be antigen dependent and can respond to antibiotic treatment, which eliminates *H. pylori* infection and removes the antigenic stimulation.71 Unlike the low-grade lymphomas in lymph nodes, MALT lymphomas tend to be localized in the stomach, without involving the bone marrow.

Low-grade MALT lymphoma can transform into a high-grade lymphoma. Microscopically, it is difficult to distinguish between a high-grade lymphoma of the MALT type and the nodal type unless the preceding low-grade disease (such as the presence of lymphoepithelial lesions and reactive follicles) is identified. This raises another issue in distinguishing primary gastric MALT lymphoma from a nodal lymphoma with secondary gastric involvement. The lack of Bcl-2 protein, CD5, and CD10, as well as the positive expression of KB61 in gastric MALT lymphoma, may help in the distinction.72

REFERENCES


