Duodenal Epithelial Polyp
A Clinicopathologic Review

Katrina Collins, MD; Saverio Ligato, MD

Context.—Duodenal epithelial polyps are reported in 1.5% to 3% of individuals referred for upper endoscopy. Most duodenal epithelial polyps are asymptomatic and nonneoplastic; however, a small subset is neoplastic and may progress to adenocarcinoma. Recent advances in immunohistochemical and molecular techniques have helped further characterize these polyps, shedding light on their origin, classification, and risk of progression to adenocarcinoma.

Objective.—To provide a comprehensive clinicopathologic review of nonneoplastic and neoplastic duodenal epithelial polyps, with particular emphasis on recent developments in classification schemes and risk stratification based upon immunohistochemical and molecular profiles.

Data Sources.—This review is based on peer-reviewed literature and the authors’ experiences.

Conclusions.—In this review we provide an update on the clinicopathologic, immunohistochemical, and molecular features of duodenal epithelial polyps and discuss the surveillance recommendations and treatment options available. Particular attention should be placed on recognizing duodenal adenomas with intestinal, gastric, and serrated phenotype, as they have an increased risk of malignant transformation if not completely excised.

Duodenal epithelial polyps have been reported in approximately 1.5% to 3.0% of individuals referred for upper endoscopy. Recent advances in endoscopic techniques have increased the detection rate of these polyps and have allowed removal of lesions up to 2 cm in diameter.1 Duodenal epithelial polyps can occur as sporadic polyps, usually identified incidentally during upper endoscopy performed for other reasons, or in the setting of familial polyposis, in which they are typically multiple in number and often carpet the entire duodenal surface. They may present as sessile or pedunculated polyps, nodules, excrescences, or subtle abnormalities of the mucosa and can be located either in the duodenal bulb, ampullary/periampullary region, or distal duodenum. Most are benign and associated with peptic injury, duodenitis, or inflammatory lesions; however, a small subset is neoplastic with the potential for progression to adenocarcinoma. Histologically, duodenal polyps are largely divided into nonneoplastic epithelial polyps and neoplastic epithelial polyps (Table 1). In this article, we review the salient clinicopathologic features and treatment options of duodenal epithelial polyps, and provide an update on their classification and risk stratification based on morphologic, immunophenotypic, and molecular features, and correlation with clinical outcome.

NONNEOPLASTIC DUODENAL EPITHELIAL POLYPS

Nonneoplastic duodenal epithelial polyps include Brunner gland hyperplastic nodule/polyps (also known as Brunner gland hyperplasia), Brunner gland hamartomas, Brunner gland cysts, ectopic gastric mucosa, pancreatic heterotopia, hyperplastic polyps, inflammatory polyps, and hamartomatous polyps.

Brunner Gland Hyperplastic Nodules/Polyps and Brunner Gland Hamartomas

The distinction between Brunner gland hyperplastic nodules/polyps and Brunner gland hamartomas is arbitrary and has been traditionally based mainly on size. Brunner gland hyperplastic polyps are usually small (0.5 cm–1.5 cm), asymptomatic, and discovered incidentally during upper endoscopy performed for other reasons. Brunner gland hamartomas are larger (>2 cm), and when symptomatic, present as gastrointestinal (GI) hemorrhage or intestinal obstruction, often requiring endoscopic or surgical resection.6–9

In the past, the terms Brunner gland hyperplasia, Brunner gland hamartoma, and Brunner gland adenoma have been used interchangeably causing some confusion in the pathologic classification of these lesions.5,6,9 In fact, prior reports of several large Brunner gland proliferative lesions without definitive evidence of cytologic atypia that were reported as Brunner gland adenomas,5,6 in retrospect, represent examples of Brunner gland hyperplastic polyps or Brunner gland hamartomas.2 Brunner gland hyperplastic nodules/polyps and Brunner gland hamartomas are now
shows a minor mesenchymal component composed of Brunner gland hyperplastic nodules/polyps, but also histology of Brunner gland hamartomas is similar to that of peptic injury secondary to peptic duodenitis. The bulb but can extend through the muscularis mucosa into the lamina propria (Figure 1, A and B). They can be associated with surface villous shortening, gastric foveolar metaplasia, or peptic injury secondary to peptic duodenitis. The surface epithelium overlying the Brunner glands often originate from Brunner glands, but rather from the ducts or the surface epithelium overlying the Brunner glands, we acknowledge some recent studies, both in human and animal models, that have described a new class of duodenal adenoma and carcinoma demonstrating dysplastic Brunner glands.9 In fact, in reviewing the limited literature on Brunner gland adenocarcinoma and dysplasia (adenoma), these authors concluded that the dysplastic or neoplastic glandular epithelium in these polyps does not originate from Brunner glands, but rather from the ducts or the surface epithelium overlying the Brunner glands often involved by gastric foveolar metaplasia. Hence, they concluded that the term Brunner gland adenoma is misleading and should be discouraged; instead the term Brunner gland hyperplasia should be used.9 Although in this review, when we refer to these dysplastic lesions we will use the term duodenal pyloric gland adenoma rather than Brunner gland adenoma, we acknowledge some recent studies, both in human and animal models, that have described a new class of duodenal adenoma and carcinoma demonstrating dysplastic Brunner glands associated with gastric metaplasia.11

Neoplastic

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Adenoma, intestinal type</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Tubular</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Tubulovillous</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Adenoma, gastric type</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Pyloric gland adenoma</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Foveolar adenoma</td>
<td>Very rare</td>
</tr>
<tr>
<td>Serrated adenoma with TSA-like features</td>
<td>Rare</td>
</tr>
<tr>
<td>Neuroendocrine tumors</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Gangliocytic paraganglioma</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Abbreviation: TSA, traditional serrated adenoma.

believed to represent a morphologic continuum of benign hyperplastic/proliferative lesions of Brunner glands.8 As such, the term Brunner gland hyperplasia/hamartoma has been proposed for describing these nonneoplastic lesions.9

Clinical and Endoscopic Findings.—Brunner gland hyperplastic/hamartomatous polyps are benign and are preferentially located in the duodenal bulb, but may also extend into the second or third part of the duodenum. Endoscopically, they may be multiple and present as sessile or pedunculated submucosal nodules and show no sex or racial predilection.

Etiology and Pathogenesis.—Although the exact etiology is still poorly understood, associations with duodenal injury secondary to gastric acid hypersecretion, Helicobacter pylori infection, end-stage renal disease, and uremia have been reported.2,10

Histopathology and Immunohistochemistry.—Brunner gland hyperplastic nodules/polyps are characterized by a lobular proliferation of hyperplastic glands, histologically indistinguishable from normal Brunner glands. They are predominantly located in the submucosa of the duodenal bulb but can extend through the muscularis mucosa into the lamina propria (Figure 1, A and B). They can be associated with surface villous shortening, gastric foveolar metaplasia, or peptic injury secondary to peptic duodenitis. The histology of Brunner gland hamartomas is similar to that of Brunner gland hyperplastic nodules/polyps, but also shows a minor mesenchymal component composed of adipose tissue and/or smooth muscle intermixed with multilobulated hyperplastic and sometimes cystically dilated Brunner glands (Figure 1, C and D). Immunohistochemically, both lesions are positive for MUC6 protein (a pyloric gland mucin marker), are negative for MUC5AC (a foveolar mucin marker), and demonstrate a very low proliferative activity index by Ki-67/MIB-1.3,4,8 However, in our experience these 3 markers are not usually necessary for the diagnosis of these 2 lesions.

Clinical Significance and Treatment.—As previously mentioned, owing to their larger size, Brunner gland hamartomas may cause GI hemorrhage or intestinal obstruction requiring endoscopic and sometimes surgical resection.

“Brunner Gland Adenoma”

The concept of Brunner gland adenoma is very controversial and still a matter of ongoing debate.11 Some authors believe that Brunner gland adenoma is a distinct preneoplastic lesion with gastric phenotype, nuclear atypia, and immunohistochemical profile identical to the pyloric gland adenoma of the stomach.12 Others, however, contend that there are no well-documented cases of either true glandular dysplasia or carcinoma arising from the proliferation of the Brunner glands.9 In fact, in reviewing the limited literature on Brunner gland adenocarcinoma and dysplasia (adenoma), these authors concluded that the dysplastic or neoplastic glandular epithelium in these polyps does not originate from Brunner glands, but rather from the ducts or the surface epithelium overlying the Brunner glands often involved by gastric foveolar metaplasia. Hence, they concluded that the term Brunner gland adenoma is misleading and should be discouraged; instead the term Brunner gland hyperplasia should be used.9 Although in this review, when we refer to these dysplastic lesions we will use the term duodenal pyloric gland adenoma rather than Brunner gland adenoma, we acknowledge some recent studies, both in human and animal models, that have described a new class of duodenal adenoma and carcinoma demonstrating dysplastic Brunner glands associated with gastric metaplasia.11

Brunner Gland Cysts

Brunner gland cysts are very rare polypoid or nodular lesions of the duodenum characterized by a submucosal cystic dilation of the Brunner gland ducts. In the past, they have also been referred to as Brunner gland cystadenoma, mucocele of the Brunner glands, and most recently, Brunner gland duct cysts.14 The largest case series reported to date consists of 25 cases with a mean age of 66.2 years and approximately equal sex distribution.15 Endoscopically they present as single or multiple polypoid/nodular lesions, often detected incidentally in the first or second part of the duodenum. They vary in size between 3 mm and 18 mm, and owing to their cystic nature, during the biopsy procedure they may rupture and become flattened.16 Histologically, they show unremarkable surface duodenal mucosa with a unilocular or multinodular cystic dilatation of the Brunner gland ducts immediately underneath the muscularis mucosae. The cysts are lined by an undulating surface epithelium with clear cytoplasm and basally located nuclei usually without cytologic atypia (Figure 2). However, in some cases, a variable papillary architecture involving at least part of the cyst may be identified. Historically, they were believed to represent benign retention cysts without

Table 1. Histologic Classification of Duodenal Epithelial Polyps

<table>
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<tr>
<th>Category</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Nonneoplastic</td>
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<td>Brunner gland hyperplastic nodule/polyp</td>
<td>Frequent</td>
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<tr>
<td>Brunner gland hamartoma</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Brunner gland cyst</td>
<td>Very rare</td>
</tr>
<tr>
<td>Ectopic gastric mucosa</td>
<td></td>
</tr>
<tr>
<td>Gastric foveolar metaplasia</td>
<td>Frequent</td>
</tr>
<tr>
<td>Gastric heterotopia</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Pancreatic heterotopia</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Hyperplastic polyp</td>
<td>Very rare</td>
</tr>
<tr>
<td>Inflammatory polyp</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Hamartomatous polyps</td>
<td></td>
</tr>
<tr>
<td>Peutz-jeghers polyp</td>
<td>Rare</td>
</tr>
<tr>
<td>Juvenile polyp</td>
<td>Rare</td>
</tr>
<tr>
<td>Cowden syndrome polyp</td>
<td>Rare</td>
</tr>
<tr>
<td>Cronkhite-Canada syndrome</td>
<td>Very rare</td>
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</tbody>
</table>

Abbreviation: TSA, traditional serrated adenoma.

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atyria, developing secondary to local obstruction of the draining duct of the Brunner gland. However, some recent studies have suggested that at least some of them may represent an early neoplastic process reminiscent of branch-duct type intraductal papillary mucinous neoplasms. In fact, the epithelial lining may demonstrate either a pure foveolar (MUC5AC+) or mixed foveolar/intestinal (MUC5AC and CDX2+) phenotype, and some of the cells (especially in the papillary component) may demonstrate cytologic atypia consistent with a low-grade dysplasia as supported by expression of S100P (an immunomarker consistently expressed in low-grade pancreatic intraepithelial neoplasia, but not in reactive lesions). However, further studies are needed to confirm this hypothesis.

**Ectopic Gastric Mucosa**

**Clinical and Endoscopic Features.**—Ectopic gastric mucosa is a common finding in duodenal biopsies, generally identified in the duodenal bulb. It consists either of gastric foveolar metaplastic cells without oxyntic glands, known as gastric foveolar metaplasia, or may be associated with oxyntic glands and referred to as gastric heterotopia. The endoscopic appearance is that of 1 or multiple small (<1.5 cm) patches, nodule(s), or, less commonly, pedunculated lesions (Figure 3, A).

**Etiology and Pathogenesis.**—Gastric foveolar metaplasia of the duodenum is generally considered as a reactive/reparative process usually secondary to acid-peptic injury, duodenal ulcer, H pylori infection, or chronic inflammation. Gastric heterotopia is indistinguishable from normal oxyntic gland mucosa of the stomach and traditionally has been considered congenital and benign in nature.

**Histopathology.**—In duodenal gastric foveolar metaplasia the epithelium consists of gastric foveolar-type columnar cells containing neutral mucin replacing both absorptive cells and goblet cells of the villi (Figure 3, B). Duodenal gastric heterotopia consists of oxyntic gastric mucosa with
both parietal and chief cells and overlying surface gastric foveolar metaplastic epithelium (Figure 3, C). The adjacent duodenal mucosa may be normal or associated with varying degrees of inflammation.2

Clinical Significance and Treatment.—Although in most cases gastric foveolar metaplasia and gastric heterotopia represent benign lesions, some studies have raised the possibility that a subset of them may be neoplastic and represent a precursor of adenomas and gastric-type adenocarcinomas.18,19 In fact, in a recent study Matsubara et al20 identified mutations in GNAS and/or KRAS in 55% of cases with duodenal gastric foveolar metaplasia and 28% of cases with gastric heterotopia. These lesions are usually small and asymptomatic; however, when very large they may cause obstruction or intussusception requiring endoscopic or rarely, surgical excision.

Pancreatic Heterotopia

Clinical and Endoscopic Features.—Pancreatic heterotopia is a developmental abnormality in which normal pancreatic tissue is found in an abnormal location without accompanying anatomic and/or vascular connection to orthotopic pancreas.21 Pancreatic heterotopia can be observed in any GI tract organ. It is most common in the duodenum but can also be found in the jejunum, liver, biliary tract, and omentum.22 The endoscopic appearance of pancreatic heterotopia is that of a small nondescriptive nodule covered by normal duodenal mucosa, often with central umbilication corresponding to the opening of the main duct. Such lesions when large may become symptomatic, most commonly presenting with abdominal pain, obstruction, intussusception, stricture, or bleeding.

Etiology and Pathogenesis.—Although the pathogenesis is unknown, the most likely hypothesis is that it originates from embryonic migration of pancreatic buds into the duodenal wall.

Histopathology.—Pancreatic heterotopia consists of normal-appearing pancreatic tissue, and the Von Hippel classification recognizes 3 types: type I, the most common, consists of all 3 pancreatic elements (complete pancreatic heterotopia) (Figure 3, D); type II contains acini and ducts; and type III is composed only of ducts and rare acinar cells.23 Gaspar Fuentes et al24 classify ectopic pancreas into 4 types: type I composed of all pancreatic elements (complete heterotopia); type II composed of ducts only (canalicular heterotopia), which when surrounded by smooth muscle is also referred to as adenomyoma25; type III with only acini (exocrine heterotopia); and type IV with only clusters of neuroendocrine cells (endocrine heterotopia).

Clinical Significance and Treatment.—Pancreatic heterotopia can undergo pathologic changes similar to those observed in the pancreas such as pancreatitis, pseudocyst, abscess formation, and rarely, dysplasia and malignancy.22 Endoscopic or surgical resection is the treatment of choice when they become large and symptomatic or show evidence of dysplastic features.

Hyperplastic Polyps

Clinical and Endoscopic Features.—Hyperplastic polyps of duodenum are very rare and a total of 16 cases have so far been reported.26–30 The largest series consists of 9 cases including 3 male and 6 female patients with a mean age of 52.2 years (range, 21–72 years).27 Typically, they are asymptomatic and discovered incidentally and most commonly located in the second part of the duodenum. The endoscopic appearance may reveal a sessile or pedunculated polyp with or without surface ulceration ranging in size between 5 mm and 27 mm. Rarely they may cause symptoms such as anemia or GI bleeding.

Etiology and Pathogenesis.—Their pathogenesis has not been clarified yet; however, most patients with hyperplastic polyps are associated with H pylori infection or other form of gastroduodenal disease. No evidence of association with serrated polyps or other chronic inflammatory diseases has been identified.27

Histopathology, Immunohistochemistry, and Molecular Characteristics.—Most duodenal hyperplastic polyps reported so far in the literature (14 of 16 cases; 87.5%) have the histologic appearance of a microvesicular hyperplastic polyp of the large bowel, characterized by hyperplastic, columnar microvesicular mucinous epithelium with luminal and crypt serration lacking cytologic atypia (Figure 4, A).27 However, in a few case reports,28,30 a gastric phenotype with polyoid hyperplasia of the surface has been described, raising the possibility that at least some of these lesions may represent examples of inflammatory duodenal polyps with gastric foveolar metaplasia rather than hyperplastic polyps.

Similar to the colorectal hyperplastic polyps, MUC6 is expressed only at the crypt bases and MUC2AC on the superficial hyperplastic epithelium. MUC2 is identified only if goblet cells are present and CDX2 usually shows negativity. The latter is particularly helpful in differentiating hyperplastic duodenal polyps, usually CDX2+, from duodenal serrated adenomas with traditional serrated adenoma (TSA)-like features, which are usually CDX2+ and have a more aggressive behavior. The proliferative activity index by Ki-67/MIB-1 is low and no p53 overexpression is identified. In one study,27 BRAP59 mutations were described in 2 of 6 cases (33%) and KRAS mutations in another 2 cases (33%).27 These findings support the hypothesis that these duodenal
polyps may be similar to the microvesicular hyperplastic polyps of large bowel, which also harbor \textit{BRAFV600E} or \textit{KRAS} mutations in 70% and in 10% to 15% of cases, respectively.\textsuperscript{31}

**Clinical Significance and Treatment.**—Although duodenal hyperplastic polyps are rare, benign, and usually asymptomatic, Rosty et al\textsuperscript{27} have raised the possibility that some of them, especially those harboring \textit{KRAS} mutation, may represent a precursor lesion of the duodenal serrated adenoma with TSA-like features. In fact, it has been shown that both hyperplastic polyps and duodenal serrated adenomas with TSA-like features harbor \textit{KRAS} mutations more frequently (33% and 38% of cases, respectively) than hyperplastic polyps of the colon (15%). However, this hypothesis needs further validation and until then the risk of recurrence and progression of hyperplastic polyps of duodenum should be considered as uncertain and treated with complete endoscopic resection.\textsuperscript{27}

**Inflammatory Polyps**

**Clinical and Endoscopic Features.**—Nonneoplastic inflammatory polyps are inflammatory proliferations of the duodenal mucosa (inflammatory pseudopolyps) usually associated with Crohn disease, ulcerative colitis, or other inflammatory processes such as peptic duodenitis, or rarely with primary immunodeficiency.\textsuperscript{32} They are usually small and asymptomatic; however, when large, they may result in heme-positive stools, GI bleeding, or recurrent abdominal pain due to intermittent obstruction. The most common inflammatory polyps of duodenum are the pseudopolyps found associated with Crohn disease.

**Histopathology.**—These lesions are characterized either by polypoid proliferations of elongated glands, resembling hyperplastic polyps of stomach, or polypoid growths of granulation tissue with acute and chronic inflammation of the lamina propria, and ulceration of the surface epithelium (Figure 4, B). These lesions may also show granulomas when associated with Crohn disease.

**Treatment.**—Snare polypectomy for small lesions, endoscopic mucosal resection, or submucosal endoscopic dissection for larger lesions is the treatment of choice.

**Hamartomatous Polyps**

Hamartomatous polyps of the duodenum represent a heterogeneous group of inflammatory polypoid lesions...
often occurring in the setting of familial polyposis syndromes or very rarely as isolated sporadic polyps.

Clinical and Endoscopic Features.—Syndromic hamartomatous polyps may involve the entire GI tract; however, the duodenum is usually much less commonly involved. Endoscopically, they may present as small polyps or nodules or as large lesions that may produce symptoms of intestinal obstruction or intussusception.

Histopathology.—Microscopically, they are usually characterized by a variable mixture of epithelial and stromal elements featuring epithelial hyperplasia, cystic dilation of glands, stromal overgrowth, edema, acute and chronic inflammation, surface erosion, and Brunner gland hyperplasia. The correct identification and classification of these lesions is critical to the management of these patients because of their association with the development of GI malignancies as well as other extraintestinal lesions.

Specific Hamartomatous Duodenal Polyps

Peutz-Jeghers Polyps.—Peutz-Jeghers polyposis is an autosomal dominant syndrome characterized by multiple benign GI hamartomatous polyps, mucocutaneous pigmentation, and tumors of ovary or testis resulting from mutations in the serine-threonine kinase (STK11) tumor suppressor gene located on chromosome band 19p13.3 in approximately 50% of the families with Peutz-Jeghers polyposis. Additional genes are yet to be identified. They can be located throughout the GI tract and especially in the jejunum and duodenum, where they are identified in 78% of cases.

Endoscopically, they may appear sessile or pedunculated with a smooth multilobulated appearance varying in size from a few millimeters up to several centimeters. Histologically, they are characterized by branching bands of smooth muscle surrounded by glandular epithelium and normal lamina propria (Figure 4, C). Sometimes, they may have foci

Figure 4. A, Hyperplastic polyp. At low power, elongated fronds of surface epithelium with a sawtooth appearance and crypts composed of small crowded mucinous glands. At high power (inset), the hyperplastic epithelium shows microvesicular mucinous cells and rare goblet cells with apical mucin vacuoles. No cytologic atypia is seen. B, Inflammatory polyp. At low power, a central polypoid epithelial proliferation surrounded by ulcerated duodenal mucosa (pseudopolyp). C, Peutz-Jeghers polyp. Lower power: the polyp is characterized by an arborizing network of smooth muscle bundles surrounded by benign glandular epithelium and normal lamina propria. D, Juvenile polyp. Polypoid mucosa with areas of surface epithelial erosion showing cystically dilated glands embedded in an expanded lamina propria with areas of dense stroma and vascular congestion (hematoxylin-eosin, original magnifications ×10 [A through D] and ×20 [A inset]).
of adenomatous mucosa and very rarely progress to adenocarcinoma. Polypectomy is recommended in order to achieve an accurate diagnosis and because these polyps have a risk of malignant transformation.

Juvenile Polyps.—These polyps may be sporadic or associated with juvenile polyposis syndrome (JPS), which is an autosomal dominant syndrome with high penetrance linked to abnormalities in the signaling of transforming growth factor-β (TGF-β) via genetic abnormality of SMAD4 or BMPRIAI genes in about 50% to 60% of patients with JPS. Endoscopically, they typically appear as smooth, pedunculated, or sessile mucosal lesions that may be associated with surface ulceration. The histology consists of cystically dilated glands mixed with a markedly edematous/inflamed stroma, erosions of surface epithelium, and underlying granulation tissue (Figure 4, D). Juvenile polyposis syndrome is associated with increased risk of cancer (~10%), particularly in colon and stomach; however, the rarity of these lesions in the duodenum precludes an adequate assessment of their neoplastic risk in this location.

Polyps in Cowden Syndrome.—This syndrome, also known as PTEN (phosphatase and tensin homolog) hamartoma tumor syndrome, is a rare autosomal dominant disorder that has been linked to germline mutations in the PTEN gene located on chromosome band 10q23.3. It is characterized by multiple hamartomas and hyperplastic lesions of the skin, mucous membranes, brain, thyroid, and entire GI tract. In the GI tract, these hamartomatous polyps may occur in the duodenum more commonly than previously believed (36.5%). Endoscopically, they appear as small (2–5 mm) lesions with a color similar to the surrounding duodenal mucosa. Histologically, they may present as multiple hamartomatous polyps of differing types featuring juvenile-type polyps, ganglioneuromas, lipomas, and adenomas. If a PTEN mutation is identified, the risk of adenocarcinoma of breast, thyroid, and endometrium appears increased; however, an excess risk of GI cancer has not been well established.

Polyps in Cronkhite-Canada Syndrome.—Cronkhite-Canada syndrome is a rare acquired nonfamilial form of diffuse GI polyposis that typically affects adults in their fifth and sixth decade of life. These polyps are usually identified in the stomach but may also involve the duodenum. In isolation, they may be indistinguishable from juvenile or hyperplastic polyps, and are usually diagnosed in the presence of dramatic GI symptomatology characterized by weight loss, diarrhea, and nutritional deficiencies. Owing to the accompanying findings of hypoalbuminemia, hypocalcemia, anemia, severe electrolyte deficiencies, and severe malabsorption, these patients have a poor prognosis with a mortality rate of 60%. Histologically, these polyps appear similar to juvenile polyps, but in contrast with the classical juvenile polyps, the intervening mucosa, both in the stomach and duodenum, is also abnormal featuring severe edema, congestion, and inflammation.

NEOPLASTIC DUODENAL EPITHELIAL POLYPS

At present, duodenal adenomatous polyps are classified according to the mucin phenotype into intestinal (89.1%) and gastric type (10.9%). The intestinal-type polyps are morphologically subdivided into tubular and tubulovillous adenomas and the gastric-type into pyloric gland adenomas and foveolar adenomas. The most recently described neoplastic duodenal polyp is the serrated adenoma with TSA-like features resembling the TSA of the large bowel. This polyp represents a new distinct category of duodenal dysplastic polyp characterized by a significant risk for progression to adenocarcinoma.

Duodenal Adenoma With Intestinal Phenotype

Clinical and Endoscopic Features.—Duodenal adenomas with intestinal phenotype account for approximately 25% of benign neoplasms of the small intestine. They are classified according to their location: ampullary, periampullary, or distal to the ampulla. They are also classified clinically into sporadic duodenal adenomas and adenomas associated with genetic syndromes such as familial adenomatous polyposis (FAP), attenuated FAP, or MUTYH-associated adenomatous polyposis (MAP). Sporadic duodenal adenomas account for approximately 40% of all intestinal-type duodenal adenomas and are usually identified in elderly men (60–80 years of age). Most are asymptomatic, usually arising in the second part of the duodenum, and endoscopically appearing as sessile or flat rather than pedunculated polyps. In a study evaluating the risk of adenocarcinoma in nonampullary sporadic duodenal adenomas, Okada et al concluded that lesions with low-grade dysplasia and smaller than 20 mm have a low risk of progression to adenocarcinoma (4.7%) and some risk of progression to high-grade dysplasia (17%) with adenomas that are larger than 20 mm, or have HGD, have a higher rate of progression to adenocarcinoma (approximately 54.5%). However, most duodenal adenomas with intestinal phenotype are found in individuals with FAP (60%) and in approximately 17% to 25% of individuals with MAP. Endoscopically, they present as multiple sessile polyps with a predilection for the distal duodenum and periampullary region, and owing to their small size may be missed during upper endoscopy. However, with the aid of chromoscopic techniques, the number of detected polyps may increase considerably.

Etiology and Pathogenesis.—Familial adenomatous polyposis is an inherited autosomal dominant syndrome due to a germline mutation in 1 copy of the adenomatous polyposis coli (APC) gene, a tumor suppressor gene located on the long arm of chromosome 5 (5q21–22). This condition is characterized by the formation of hundreds of intestinal-type adenomas in the colon and small bowel with approximately 65% of people with this condition developing duodenal adenomas. The pathogenesis of both sporadic duodenal adenomas and FAP-associated duodenal adenomas is not well elucidated; however, it is believed that it may be analogous to that proposed for colorectal carcinoma in which there is progressive accumulation of abnormalities in the APC pathway. Instead, MAP is an autosomal recessive condition caused by biallelic germline mutations of the MUTYH gene. Carriers of 1 MUTYH gene mutation have a milder clinical presentation and not much is known about the impact on the development of duodenal polyps.

Histopathology, Immunohistochemistry, and Molecular Characteristics.—Sporadic duodenal adenomas, FAP-related adenomas, and MAP-related adenomas are morphologically indistinguishable and are characterized by adenomatous transformation of the small intestinal epithelium, similar to that observed in the colonic adenomas. They are classified as tubular adenoma, composed of small tubular glands lined by eosinophilic absorptive epithelium with pseudostratified hyperchromatic nuclei (Figure 5, A),
and tubulovillous adenoma demonstrating a villous architecture covered by dysplastic epithelium with cytologic features similar to those described in tubular adenomas (Figure 5, B). When they progress to HGD both architectural complexity, characterized by distorted and/or cribriform glands, and cytologic atypia with large hyperchromatic nuclei with prominent nucleoli and loss of nuclear polarity, are observed. Immunophenotypically, they are defined by the expression of CD10 (Figure 5, C), CDX2 (Figure 5, D), and/or MUC2 proteins but not MUC5AC and MUC6. However, in a recent study, 76.9% of duodenal adenomas with intestinal phenotype demonstrated focal gastric phenotype, which is supported by MUC5AC and MUC6 positivity.19 Emerging evidence shows that both sporadic duodenal adenomas and FAP-related adenomas show molecular alterations similar to those observed in colorectal adenoma characterized by frequent genetic alterations, involving the APC and KRAS genes. DNA mismatch repair abnormalities and TP53 mutations are identified only rarely and no BRAF mutations are present.45 Instead, duodenal cancer developing in MAP-related adenomatous polyps demonstrates a specific somatic KRAS mutation variant (c.34 G>T in codon 12), which is found in approximately 64% of cases.

**Clinical Significance and Treatment.**—Individuals with FAP-related duodenal adenomas have a 100- to 300-fold increased lifetime risk for developing duodenal or periampullary carcinoma.7 Spigelman et al16 developed a 4-stage classification (0–IV) system for evaluating the severity of duodenal adenomatosis in individuals with FAP (Table 2), and based on the degree of risk of developing carcinoma, recommendations on the frequency of surveillance and treatment options were issued (Table 3).

This staging system has been validated by other studies17,48 and stratifies the risk of developing duodenal carcinoma from the number, size, histology, and degree of dysplasia of the polyps. Based on this system, approximately

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<th>Table 2. Modified Spigelman Score</th>
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<td>Polyp size, mm</td>
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<tr>
<td>Histology</td>
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<td>Dysplasia</td>
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</tbody>
</table>

Abbreviation: —, not applicable.
Duodenal adenomas with gastric phenotype are subclassified into pyloric gland adenoma and foveolar adenoma.\textsuperscript{19,49} In contrast to the duodenal adenomas with intestinal phenotype, they are preferentially located in the proximal duodenum\textsuperscript{19} and very often have a pedunculated appearance.\textsuperscript{39}

**Clinical and Endoscopic Features.**—Duodenal pyloric gland adenoma is a rare neoplasm demonstrating morphologic, immunohistochemical, and molecular similarities to the pyloric gland adenoma of the stomach. Lesions with similar morphology and immunohistochemical phenotype have also been described in the pancreas, biliary tree, esophagus, and rarely in the rectum; however, their most frequent localization is in the duodenum and in the stomach.\textsuperscript{50–53} They usually occur in older individuals with a mean age of 74 years (range, 52–87 years). Additionally, they may be associated with syndromic polyposis such as FAP\textsuperscript{64} and according to some reports, with Lynch syndrome.\textsuperscript{55} Endoscopically, they may present as submucosal nodules, flat lesions, or more often as protruding polypoid lesions varying in size between 5 mm and 28 mm with a median diameter of 15.3 mm.

**Etiology and Pathogenesis.**—The histogenesis of duodenal pyloric gland adenomas remains unclear. Kushima et al\textsuperscript{53} was the first to suggest that pyloric gland adenoma may originate from Brunner glands. According to these authors, when the duodenal mucosa is damaged, a process of mucosal regeneration ensues in the Brunner glands, giving origin to generative cell zones ("neo-G zones") with proliferation of pluripotent stem cells within Brunner glands and ducts.

These cells may differentiate toward the surface, forming areas of gastric foveolar metaplasia or downwards giving rise to Brunner gland hyperplasia or Brunner gland hamartoma. According to this hypothesis, metaplastic foveolar epithelium originating from the "neo-G zone" is prone to mutation errors leading to the generation of dysplastic polyps, such as pyloric gland adenoma, and ultimately carcinoma.\textsuperscript{53,56} In support of this hypothesis is the observation that in all the sites of origin pyloric gland adenoma is often, but not always, associated with gastric foveolar metaplasia and/or gastric heterotopia.\textsuperscript{21,54,57,58} Additionally, in a recent molecular study a significant number of cases of gastric foveolar metaplasia (55%) and gastric heterotopia (28%) of the duodenum were found to be associated with GNAS and/or KRAS mutations which, interestingly, represent the same type of mutations usually identified in the duodenal pyloric gland adenoma and adenocarcinoma with gastric phenotype.\textsuperscript{20}

**Histopathology, Immunohistochemistry, and Molecular Characteristics.**—Most duodenal pyloric gland adenomas present as polypoid lesions (Figure 6, A) composed of tightly packed pyloric tubules (Figure 6, B) or cystically dilated glands lined by a monolayer of cuboidal to low columnar cells with basally located nuclei, demonstrating a very subtle atypia and slightly enlarged nucleoli. The cytoplasm is abundant, glassy, and slightly eosinophilic and some of the glands may contain mucinous cells and clear cells. Occasionally, rare goblets cells or Paneth cells may be identified; however, they represent most likely residual native intestinal epithelial cells rather than a component of pyloric gland adenoma.\textsuperscript{50,57} Other times, they may present as submucosal nodules (Figure 6, C) or as flat lesions (Figure 6, D).

When these adenomas progress to low-grade dysplasia, the glands become irregularly shaped, with enlarged and hyperchromatic nuclei, inconspicuous nuclei, and rare mitotic figures (Figure 6, C [inset]). Instead, in HGD, the glands are more complex with some cribriform architecture, enlarged nuclei with loss of polarity, mild membrane irregularity, nuclear pleomorphism, scattered enlarged nucleoli, and increased mitotic activity\textsuperscript{50,53} (Figure 6, D [inset]). The immunoprofile of duodenal pyloric gland adenomas is defined by diffuse expression of pyloric gland mucin MUC6 (Figure 6, E) and selective expression of MUC5AC (Figure 6, F) along the superficial gastric foveolar epithelium and only focally in the underlying glands. This last finding is useful in differentiating a pyloric gland adenoma from Brunner gland lesions, especially in small biopsy specimens. In fact, MUC5AC shows positivity in the superficial and focally in the glandular component of pyloric gland adenomas but negativity in Brunner glands. In addition, CDX2, CD10, and MUC2 (intestinal markers) usually show negativity and this is helpful in differentiating duodenal adenomas with pyloric phenotype from those with intestinal phenotype. An increased proliferative activity index by Ki-67/MB-1 and overexpression for p53 may also be found especially in those polyps with HGD.\textsuperscript{50} Adenocarcinoma arising in these polyps is either of gastric or mixed (gastric and intestinal) phenotype as supported by

<table>
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<th>Spigelman Stage</th>
<th>Total Points</th>
<th>Frequency of Surveillance</th>
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<tr>
<td>0</td>
<td>0</td>
<td>Every 4 y</td>
</tr>
<tr>
<td>I</td>
<td>≤4</td>
<td>Every 2–3 y</td>
</tr>
<tr>
<td>II</td>
<td>5–6</td>
<td>Every 1–3 y</td>
</tr>
<tr>
<td>III</td>
<td>7–8</td>
<td>Every 6–12 y</td>
</tr>
<tr>
<td>IV</td>
<td>9–12</td>
<td>Expert surveillance every 3–6 mo</td>
</tr>
</tbody>
</table>

Surgical evaluation
Complete mucosectomy or Whipple procedure if duodenal papilla is involved
Figure 6. Duodenal pyloric gland adenoma. A, Exophytic pattern of duodenal pyloric gland adenoma. B, In this example, the polyp is composed of vilous tracts of surface epithelium and tightly packed, variably dilated glands lined by cuboidal cells (inset). C, Duodenal pyloric gland adenoma with a submucosal/nodular morphology featuring glands with round contours and enlarged/hyperchromatic nuclei consistent with low-grade dysplasia (inset). D, Flat pyloric gland adenoma with most glands demonstrating round contours focally becoming complex and cribriform with large nuclei, some prominent nucleoli, and loss of nuclear polarity consistent with high-grade dysplasia (inset). E, Most of the glands are positive for MUC6, whereas (F) the surface foveolar epithelium and some of the glands are positive for MUC5AC (hematoxylin-eosin, original magnifications ×10 [A and C], ×20 [B and D], and ×40 [B, C, and D insets]; original magnification ×10 [E and F]).
maintained coexpression of MUC6, MUC5AC, and CDX2 immunostains. The most frequent molecular abnormalities detected in duodenal pyloric gland adenomas include mutations in oncogenes KRAS (70%) and GNAS (50%), and less frequently, CTNNB1 and tumor suppressor genes SMAD4 and TP53. APC mutations are usually absent.

Clinical Significance and Treatment.—Duodenal pyloric gland adenomas are neoplastic lesions with a reported malignant transformation rate between 12% and 30% of cases. In a series of 10 pyloric gland adenomas of duodenum, Chen et al. found low-grade dysplasia in 10.5% of these cases, HGD in 42.1%, and invasive carcinoma in 10.5%. Furthermore, Vieth et al. showed focal transition to adenocarcinoma in 30% of cases. It appears that there is a correlation between size increase of the lesion (>20 mm) and occurrence of HGD and adenocarcinoma. However, regardless of the degree of atypia and mucin phenotype, if these polyps are completely resected, no cases of recurrence or progression have been reported. Instead, in cases where the polyps were not completely excised, progression to adenocarcinoma with gastric phenotype has been documented.

Duodenal foveolar-type adenomas are very rare lesions, representing approximately 2.7% of duodenal adenomas with gastric phenotype and have a median tumor diameter of 9.7 mm (range, 8–20 mm). All of these lesions are polypoid and histologically have a tubulovillous architecture with tall columnar epithelium resembling foveolar gastric epithelium with various degrees of dysplasia (Figure 7). Immunohistochemically, they are composed of MUC5AC-positive (Figure 7 inset) cells, rare MUC6-positive cells, and complete absence of intestinal-type mucin phenotype. Owing to their rare occurrence, little is known about their molecular abnormalities.

Duodenal Serrated Adenoma With TSA-like Features

“Traditional Serrated Adenoma of Duodenum”

Duodenal serrated adenoma is a very rare type of adenoma morphologically resembling serrated adenomas of colorectum, but reportedly demonstrating different molecular alterations and a more aggressive clinical behavior.

Clinical and Endoscopic Features.—Review of the literature has identified approximately 73 serrated adenomas with TSA-like features involving the upper GI tract (esophagus [1], stomach [35], duodenum [35], pancreas [1], and gallbladder [1]) with almost 53.4% demonstrating HGD or association with adenocarcinoma. Currently, approximately 36 serrated adenomas with TSA-like features have been reported in the duodenum, with the largest series consisting of 13 patients (12 serrated adenomas and 1 serrated adenocarcinoma) with a median age of 71 years and a similar male to female ratio. Although slow growing, these polyps have been associated with an aggressive behavior, with almost 28.6% progressing to adenocarcinoma. Endoscopically, they appear as papillary lesions varying in size from a few millimeters to a few centimeters.

Etiology and Pathogenesis.—The etiology and the causes for their aggressive behavior are unknown; however, some studies have raised the possibility that hyperplastic polyps of the duodenum, especially those with KRAS mutation, may represent a precursor lesion of serrated adenomas with TSA-like features. More recently, Rubio has also proposed an alternative pathway of carcinogenesis in which CpG island methylation phenotype (CIMP-high) would play a pivotal role in the development of these polyps independently of BRAF mutation.

Histopathology, Immunohistochemistry, and Molecular Characteristics.—Histologically, they are similar to TSAs of the colorectum, featuring a prominent serration in more than 50% of the polyp, ectopic crypt foci, and predominance of cells with tall eosinophilic cytoplasm and pencillate/pseudostratified nuclei (Figure 8, A and B). They can demonstrate low- or high-grade dysplasia and may progress to adenocarcinoma with serrated morphology (Figure 8, C and D). Furthermore, several examples with a mixed TSA-like and adenomatous morphology have also been described. Immunohistochemically, they demonstrate an intestinal phenotype with expression of CDX2, abnormal nuclear staining for β-catenin in 23% of cases, and abnormal p53 expression in 31% of cases. MUC2 expression is observed only in serrated adenomas containing goblets cells (58%), and high Ki-67/MIB-1 expression is seen in 62% of cases with HGD. As previously mentioned, expression of CDX2 may be clinically useful in distinguishing benign hyperplastic polyps (CDX2-) from potentially aggressive traditional serrated adenomas (CDX2+). The molecular profile is characterized by KRAS mutation in 38% of cases, CpG island methylation phenotype (CIMP-high) in 50% of cases, and MGMT (O(6)-methylguanine-DNA methyltransferase) in 8% of cases. Interestingly, no BRAFV600E mutation or loss of expression of MLH1 was identified in any case.

This molecular profile differs from that reported in TSAs of the colon, in which BRAF mutation is identified in 67% of cases and KRAS mutation in 22% of cases. These preliminary results suggest that TSAs of duodenum do not develop through the same serrated neoplasia pathway as in the large bowel, in which CIMP-high and BRAF mutation evolve concomitantly, but rather from an alternative TSA pathway of carcinogenesis in which CIMP-high represents an early and common molecular event independently of BRAF mutation. Summarized in Tables 4 and 5 are the main immunohistochemical and molecular features of the above-discussed clinically significant duodenal epithelial polyps.
Figure 8. Duodenal serrated adenoma with traditional serrated adenoma (TSA)–like features. A, Polyp with elongated fronds demonstrating a serrated architecture with sawtooth pattern. B, On intermediate power, ectopic crypt formation (arrow) and low-grade pseudostratified nuclei with eosinophilic cytoplasm resembling a TSA of colon are seen. C, Low-power view of duodenal serrated adenoma with high-grade dysplasia. D, High-power view highlights the prominent pseudostratification and hyperchromasia of nuclei with loss of nuclear polarity (hematoxylin-eosin, original magnifications ×10 [A and C] and ×20 [B and D]).

Figure 9. Duodenal neuroendocrine tumor. A, Submucosal tumor nests composed of tightly packed round cells with a rosette-like architecture (inset). B, High-power view of another duodenal neuroendocrine tumor composed of small to medium-sized glands with eosinophilic and finely granular cytoplasm, nuclei with stippled chromatin, and intraluminal microcalcifications. An immunostain for somatostatin (inset) shows positivity, suggesting the diagnosis of somatostatinoma (hematoxylin-eosin, original magnifications ×10 [A], ×40 [A inset], and ×20 [B]; original magnification ×40 [B inset]).
Abbreviations: TSA, traditional serrated adenoma; +, positive; −, negative.

**Table 4. Immunohistochemical Profile**

<table>
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<tr>
<th></th>
<th>MUC6</th>
<th>MUC5AC</th>
<th>CD10</th>
<th>CDX2</th>
<th>MUC2</th>
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<tr>
<td>Brunner gland hyperplasia/hamartoma</td>
<td>++ (diffuse)</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Adenoma with pyloric gland phenotype</td>
<td>++ (diffuse)</td>
<td>+ (patchy)</td>
<td>−</td>
<td>−</td>
<td>+ (goblet cells)</td>
</tr>
<tr>
<td>Adenoma with foveolar gastric phenotype</td>
<td>+/-</td>
<td>++ (diffuse)</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Adenoma with intestinal phenotype</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+ (goblet cells)</td>
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<tr>
<td>Hyperplastic polyps</td>
<td>++ (crypts)</td>
<td>+ (surface)</td>
<td>−</td>
<td>−</td>
<td>+ (goblet cells)</td>
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<tr>
<td>Serrated adenoma with TSA-like features</td>
<td>++ (crypts)</td>
<td>+ (surface)</td>
<td>+/-</td>
<td>++</td>
<td>+ (goblet cells)</td>
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**Table 5. Molecular Profile**

<table>
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<tr>
<th></th>
<th>BRAF</th>
<th>KRAS</th>
<th>GNAS</th>
<th>MGMT</th>
<th>CIMP-H</th>
<th>APC</th>
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<tr>
<td>Ectopic gastric mucosa</td>
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<td>+/-</td>
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<td>−</td>
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<td>Adenoma with pyloric gastric phenotype</td>
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<td>++</td>
<td>++</td>
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<td>Adenoma with foveolar gastric phenotype</td>
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<td>−</td>
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<td>Adenoma with intestinal phenotype</td>
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<td>++</td>
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<td>Hyperplastic polyps</td>
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<td>+</td>
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<tr>
<td>Serrated adenoma with TSA-like features</td>
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<td>+</td>
<td>Unknown</td>
<td>+</td>
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</tbody>
</table>

Abbreviations: APC, adenomatous polyposis coli; CIMP-H, CpG island methylator phenotype-high; MGMT, O(6)-methylguanine-DNA methyltransferase; TSA, traditional serrated adenoma; +, positive; −, negative.

**Prognosis and Treatment.**—Because of their rarity, the natural history, prognosis, and appropriate clinical management is unclear. However, the high frequency of HGD suggests that these serrated adenomas may represent aggressive lesions with high malignant potential. Consequently, the recommendation is for a complete removal by either endoscopic or surgical procedures to rule out the possibility of a synchronously growing invasive carcinoma or to prevent cancer progression.

**NEUROENDOCRINE TUMORS**

**Clinical and Endoscopic Features.**—Intestinal neuroendocrine tumors (carcinoids) are most commonly encountered in the ileum,69 with only less than 5% localized in the duodenum and ampulla.70

They present usually as subepithelial polypoid lesions ranging from 1 to 2 cm in diameter. Endoscopically, they appear as a white or yellow polyplike lesion with central dimpling or ulceration.71 They are often clinically “silent” tumors but hormonal expression can be identified by immunohistochemistry. Occasionally, they can be functional and associated with clinical syndromes due to hormone hypersecretion, such as the gastrinoma.72 Based on the World Health Organization 2010 classification scheme, neuroendocrine tumors of duodenum are classified as malignant tumors and graded as low grade (grade 1), intermediate grade (grade 2), neuroendocrine carcinomas (grade 3), and mixed adenoneuroendocrine carcinomas. The grading system of these neoplasms is based on the mitotic rate and Ki-67 labeling index, as described in Table 6.72

Gastrin-producing neuroendocrine tumors (gastrinomas) are the most common neuroendocrine tumors of the duodenum (62%). They may occur sporadically or in association with multiple neuroendocrine neoplasia type 1 (MEN-1) syndrome and are often associated with Zollinger-Ellison syndrome. They may be multicentric, deeply infiltrating and even when small (<1 cm) can demonstrate an aggressive behavior with lymph node metastasis (5%–10% of cases), especially if functional.72

**Histopathology.**—Duodenal gastrinoma exhibits ribbons, insular, or trabecular patterns of growth, and occasional rosetting. The nuclei are usually centrally located and demonstrate a fine stippled “salt and pepper” chromatin (Figure 9, A, and inset). Nucleoli are infrequent and usually only rare mitoses are observed. The cells are immunoreactive for chromogranin A and synaptophysin is positive only in about 50% of cases.

Duodenal somatostatinoma is the second most common (18%) neuroendocrine tumor of the duodenum and is associated with neurofibromatosis type 1 in one-third of cases. In contrast to pancreatic somatostatinoma, the duodenal somatostatinoma is usually nonfunctioning, presents with abdominal pain, nausea, or obstructive jaundice. However, rarely it may be functional and associated with the clinical triad of diabetes mellitus, cholelithiasis, and steatorrhea.73 Histologically, it demonstrates a glandular or tubular architecture with intraluminal psammomatous calcifications and can be mistaken for a metastatic carcinoma. The cells are immunoreactive for chromogranin A, synaptophysin, and somatostatin74 (Figure 9, B, and inset).

Duodenal/ampullary gangliocytic paragangliomas are rare (9%) neoplasms also included as neuroendocrine tumors of the duodenum. In a review of the literature, Okubo et al75 identified 192 cases with an age range from 15 years to 84 years (mean, 52.3 years) and a size range from 5.5 to 100 mm (mean, 25 mm). They may be asymptomatic or present with GI bleeding (45.1%), abdominal pain (42.8%), and anemia (14.5%).75 Endoscopically, they may present as sessile submucosal nodules or as subepithelial pedunculated polyps (Figure 10, A). Histologically, they are triphasic tumors containing a mixture of spindle cells (often positive for S100, chromogranin, and synaptophysin), epithelial cells organized in nests (staining for chromogranin and synaptophysin), and ganglion-type cells, which stain for neuro-
markers such as neurofilament and Hu protein, but also for many neuroendocrine markers\(^7\) (Figure 10, B through E).

Although most duodenal gangliocytic paragangliomas have a good prognosis, if they involve the muscular wall and have a size greater than 2 cm, they can metastasize to regional lymph nodes in 25% to 50% of cases, mainly attributable to the endocrine component of the lesion.\(^7\)

Ampullary neuroendocrine tumors appear to have a more aggressive behavior than nonampullary neuroendocrine tumors; in fact they generally are higher-grade tumors with a clinical presentation often characterized by obstructive jaundice due to compression or obstruction of the ampulla.\(^7\)

**Treatment.**—Neuroendocrine tumors up to 2 cm in size that are limited to the submucosa and without lymph node metastasis can be removed endoscopically. In situations of multifocality or larger duodenal neuroendocrine tumors, surgery will be required.

In conclusion, it is our hope that this review will be a useful resource for the clinician and surgical pathologist in the diagnosis, risk stratification, and treatment of common and relatively uncommon duodenal epithelial polyps encountered in daily practice.

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**Table 6. World Health Organization 2010 Classification of Neuroendocrine Tumors (NETs) in the Gastrointestinal and Pancreatobiliary Tract**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic Count/10 HPFs</th>
<th>Ki-67 Labeling Index, %</th>
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<tbody>
<tr>
<td>NET, grade 1</td>
<td>&lt;2</td>
<td>&lt;3</td>
</tr>
<tr>
<td>NET, grade 2</td>
<td>2–20</td>
<td>3–20</td>
</tr>
<tr>
<td>NEC, grade 3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

Abbreviations: HPF, high-power field; NEC, neuroendocrine carcinoma.

---

**Figure 10.** Duodenal gangliocytic paraganglioma. A, Endoscopic view showing a pedunculated polyp (arrow). B, Low-power microscopic view of submucosa multinodular lesion. C, Higher-power view: the lesion consists of a spindle cell component (left side) with isolated ganglion cells (arrow) and clusters of epithelioid cells (right side). D, Immunostaining for S100 shows positivity in the spindle cells. E, Chromogranin highlights the epithelioid and ganglion cells (arrow) (hematoxylin-eosin, original magnifications \(\times4\) [B] and \(\times10\) [C]; original magnification \(\times4\) [D and E]).


