

# Gastric Pyloric Gland Adenoma

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• Pyloric gland adenomas are rare neoplasms of the gastrointestinal tract. Gastric pyloric gland adenomas have been shown to arise in chronically damaged mucosa. The neoplastic glands have gastric pyloric gland differentiation and have a tightly packed organization with occasional cystic dilatation. The individual cells are cuboidal to columnar, with eosinophilic to amphophilic cytoplasm and either no apical mucin cap or a poorly formed apical mucin cap. The nuclei are round to oval, with occasional prominent nucleoli. Immunohistochemically, the neoplastic cells label with markers of gastric pyloric gland differentiation, including MUC6 and MUC5AC. There is limited information regarding the natural history of pyloric gland adenomas, but clinical series have described adenocarcinomas in association with gastric pyloric gland adenomas. The ideal clinical management is adequate sampling of the lesion to investigate for high-grade dysplasia and/or invasive cancer and recommendation to clinical colleagues to investigate the background mucosa for the etiology of chronic gastritis as well as potential additional neoplastic lesions. This review will focus on gastric pyloric gland adenomas.

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Pyloric gland adenomas (PGAs) are rare neoplasms of the gastrointestinal tract that exhibit gastric pyloric gland differentiation. They are most frequently identified in the stomach. Extragastric sites of PGAs include the gallbladder, duodenum, bile duct, and esophagus<sup>1–4</sup>; in the pancreas, similar lesions are termed intraductal papillary mucinous neoplasms of the gastric type, pyloric gland variant, and intraductal papillary mucinous neoplasm with pyloric gland features.<sup>5,6</sup> Pyloric gland adenomas should be recognized as neoplasms with risk for transformation into invasive adenocarcinoma. This review will focus on gastric pyloric gland adenomas.

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## CLINICAL AND ENDOSCOPIC FEATURES

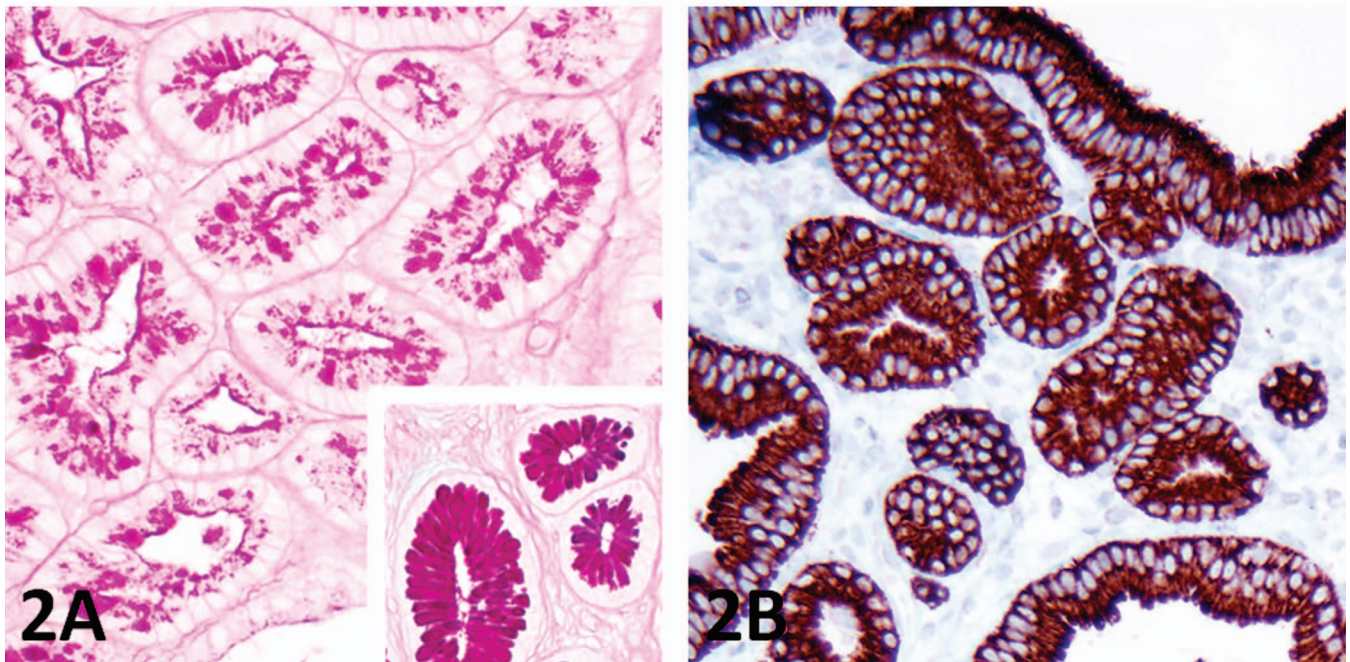
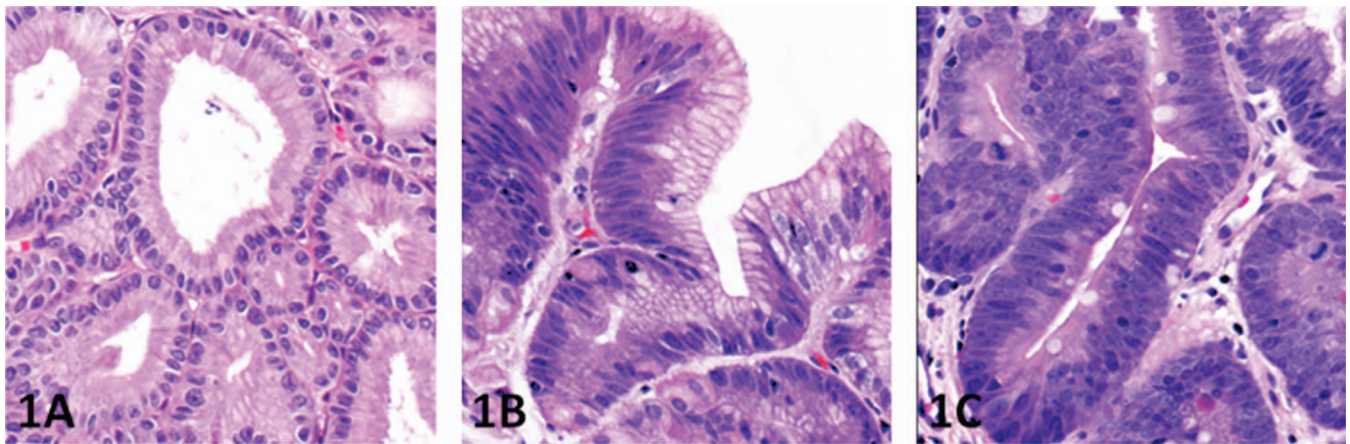
Pyloric gland adenoma of the stomach occurs more commonly in older female patients.<sup>4</sup> In one of the largest series on gastric PGAs, sex distribution was two-thirds female, with an average age of 75 years.<sup>4</sup> In the stomach, the gastric body is the most common location, followed by the gastric transition zone, antrum, and cardia. Patients with PGA present with a range of signs and symptoms that may be related to the polyp or the underlying disease. Anemia has been frequently reported. The anemia may be attributable to decreased iron absorption secondary to hypochlorhydria or achlorhydria, blood loss, or vitamin B<sub>12</sub> deficiency in the setting of autoimmune metaplastic atrophic gastritis.<sup>7,8</sup>

The endoscopic or gross appearance of PGA is of a polypoid, dome-shaped, or fungating mass.<sup>3,9,10</sup> Gastric PGAs have been documented as relatively large at the time of diagnosis, with an average size of 1.6 cm in one series.<sup>4</sup> In addition to an association with autoimmune metaplastic atrophic gastritis,<sup>7,8</sup> PGAs have also been observed in the setting of *Helicobacter pylori* gastritis and chemical gastritis.<sup>4</sup> Only a small percentage of patients with gastric PGAs have been reported with a nondamaged background gastric mucosa.<sup>4</sup> Extragastric PGAs have also been associated with pyloric gland metaplasia in the setting of chronic mucosal injury.<sup>3,5,11</sup>

## PATHOLOGIC FEATURES AND IMMUNOPHENOTYPE

Pyloric gland adenomas have a histologic appearance that is similar to nonneoplastic gastric pyloric glands. They are composed of tightly packed tubular glands lined with cuboidal or columnar cells (Figure 1, A).<sup>1,4,7</sup> The cells lack well-formed apical mucin caps, which is a useful feature to differentiate PGAs from gastric foveolar-type adenoma (Figure 1, B).<sup>7</sup> In contrast, intestinal-type adenomas are composed of pseudostratified cells, with occasional goblet cells and no apical mucin cap (Figure 1, C). The cytoplasm of the cells in pyloric gland adenoma is eosinophilic to amphophilic. Nuclei are round to oval and contain occasional prominent nucleoli (Figure 1, A). Interestingly, squamous morules have been associated with gastric and gallbladder PGAs but have not been observed in pancreatic lesions.<sup>1,5,11,12</sup>

Special stains and immunohistochemistry may be useful for the identification of PGAs. In comparison with gastric foveolar-type adenomas, PGAs do not have a well-formed mucin cap; the presence of the neutral gastric mucin cap can be examined by a periodic acid–Schiff/Alcian blue stain. Periodic acid–Schiff/Alcian blue demonstrates a bright red, uniform staining of the mucin in epithelial cells of gastric



**Figure 1.** A, Pyloric gland adenoma is composed of tightly packed tubular glands lined with columnar cells with amphophilic cytoplasm. The cells do not have apical mucin caps. The nuclei are round, with occasional prominent nucleoli. B, Gastric foveolar-type adenoma: the cells are pseudostratified, with well-formed apical mucin caps. There is nuclear crowding, with prominent nucleoli. C, Intestinal-type adenoma: the cells are pseudostratified, with occasional goblet cells and no apical mucin cap. There is nuclear crowding, with prominent nucleoli (hematoxylin-eosin, original magnification  $\times 200$ ).

**Figure 2.** A, Periodic acid-Schiff/Alcian blue stain demonstrates the absence of an apical mucin cap; there is patchy periodic acid-Schiff staining in the cytoplasm. In comparison, the inset shows nonneoplastic pyloric glands that have well-formed mucin caps and strong staining of gastric neutral mucin. B, MUC6 immunohistochemistry strongly labels the cytoplasm of pyloric gland adenoma (CLH5, Vector) (original magnification  $\times 200$  [A and inset] and  $\times 200$  [B]).

foveolar-type adenomas. In comparison, periodic acid-Schiff/Alcian blue shows only granular cytoplasmic staining of the epithelial cells of PGAs; no mucin cap is identified (Figure 2, A). Pyloric gland adenomas have gastric differentiation that can be confirmed by the presence of gastric-type mucins. Pyloric gland adenomas label by immunohistochemistry specific for gastric mucin apoprotein 6 (MUC6) and MUC5AC (Figure 2, B). In several series, PGAs of different anatomic locations were positive for both MUC5AC and MUC6. MUC6 expression is more specific for PGAs, because both foveolar-type adenomas and PGAs express MUC5AC. Gastric PGAs may have focal intestinal differentiation with nuclear labeling by CDX2 and/or intestinal mucin staining by MUC2 immunohistochemistry.<sup>13</sup>

## MOLECULAR PATHOGENESIS

Expression of p53 has been evaluated in gastric PGAs and has demonstrated less frequent nuclear expression (22.3%) compared with intestinal-type adenomas (85.7%).<sup>14</sup> In this single study of gastric PGAs, the few cases with nuclear p53 expression had features of high-grade dysplasia.<sup>14</sup> Another study demonstrated more frequent nuclear p53 expression in gastric PGAs associated with adenocarcinoma (82.1%) compared with those without associated adenocarcinoma (59.3%).<sup>15</sup> The expression of nuclear p53 may correlate with higher-risk PGAs.

A single Japanese study has examined mismatch repair (MMR) protein expression in PGAs.<sup>16</sup> Gastric PGAs had infrequent loss of MMR proteins by immunohistochemistry,



with only 1 of 23 cases (4.3%) demonstrating loss of both MLH1 and PMS2. In comparison, the same study examined foveolar-type adenomas, intestinal-type adenomas, and gastric adenocarcinomas for MMR protein loss. Similar to PGAs, the intestinal-type adenomas and adenocarcinomas had MMR protein loss in 2.9% and 7% of cases, respectively. In contrast, foveolar-type adenomas had frequent loss of MMR proteins (12 of 23 cases; 52%); 9 cases had loss of MLH1 and PMS2 expression, and 3 cases had loss of MSH2 and MSH6 expression. In isolation, these results might suggest that PGAs are similar to intestinal-type adenomas with regard to retained MMR protein expression (implying microsatellite stability) and tumorigenesis. However, there have been conflicting results from studies that have compared foveolar-type and intestinal-type adenomas for microsatellite instability.<sup>17-19</sup> Two studies showed that gastric foveolar-type adenomas had frequent microsatellite instability, whereas intestinal-type gastric adenomas were microsatellite stable.<sup>18,19</sup> In contrast, a third study of intestinal-type and foveolar-type adenomas found microsatellite instability in 30% of intestinal-type adenomas, but no instability in any foveolar-type adenomas (n = 7).<sup>17</sup> The two studies showing frequent microsatellite instability in foveolar-type adenomas were from Japanese patients. The third study, demonstrating no microsatellite instability in foveolar-type adenomas, was from the United States. Based on these limited and contrasting associations, future studies of PGAs will need to compare histologic subtype and microsatellite instability in both Western and Japanese patients.

Until recently, activating mutations in PGAs have not been characterized in gastric lesions. Recent profiling of activating mutations in *GNAS* and *KRAS* in a large series of adenomas reveals a pattern that distinguishes PGAs from foveolar-type and intestinal-type adenomas (of note, this is the same study that examined the MMR status of these polyps as mentioned above).<sup>16</sup> In this recent study, multiple cases of PGAs (n = 35) were compared with foveolar-type adenomas (n = 23), intestinal-type adenomas (n = 54), and gastric adenocarcinomas (n = 71). In 63% of PGAs, activating mutations of *GNAS* at amino acid residues 201 or 227 were identified. In comparison, this series identified no *GNAS* mutations in foveolar-type adenomas, intestinal-type adenomas, or adenocarcinomas. *KRAS* mutations were identified in 41% of PGAs, compared with 9% of foveolar-type adenomas, 9% of intestinal-type adenomas, and 1% of gastric adenocarcinomas. Interestingly, 37% of the PGAs had dual-activating mutations in both *GNAS* and *KRAS*. No *BRAF* mutations were identified in any of the cases of adenoma or adenocarcinoma. Based on this single series, it appears that PGAs have a distinct mutational profile enriched for mutations in *GNAS*. There have been several recent studies of *GNAS* mutations in non-PGA gastrointestinal polyps. The first was in the setting of McCune-Albright syndrome, a disease defined by activating mutations in *GNAS*.<sup>20</sup> All patients in this series had activating mutations in codon 201 identified in either the blood, normal tissue, and/or polyp. The histologic features described in the polyps were not consistent with PGA. These polyps were described as hyperplastic, with gastric differentiation and arborizing smooth muscle; the authors classified these polyps as Peutz-Jeghers syndrome hamartomatous polyps. A separate investigation of a series of Peutz-Jeghers syndrome polyps revealed no *GNAS* mutations.<sup>21</sup> The role of *GNAS*-activating mutations in gastrointestinal polyps has had limited investigation, but they appear to play a role in PGA. The

presence of *GNAS* and *KRAS* mutations are markers that differentiate the various gastric adenoma subtypes, and they may also be linked to the biology of their progression to adenocarcinoma.

Cytogenomic changes have been studied in PGAs arising in the stomach, esophagus, and cystic duct.<sup>10,22-24</sup> In these cases, comparative genomic hybridization array revealed complex genetic changes of copy number variation across the genome. In one series, comparative genomic hybridization array changes were compared between PGAs and intestinal-type gastric adenomas.<sup>22</sup> Pyloric gland adenomas and intestinal-type adenomas shared chromosomal changes, including gains in 9, 11q, and 20, as well as losses in 5, 6, 10, and 13q. No significant differences were found between the set of PGAs and intestinal-type adenomas examined. Based on these cytogenomic findings, the authors concluded that PGAs and intestinal-type adenomas do not differ at the level of gross DNA copy number variation.<sup>22</sup>

For several decades, the morphologic and immunohistochemical differences between PGAs and other gastric adenomas have been recognized. Data on the mutational profile of these neoplasms are emerging and indicate that PGAs may have distinct genetic alterations compared with other gastric adenomas.

## DIFFERENTIAL DIAGNOSIS, CLINICAL MANAGEMENT, AND PROGNOSIS

Gastric adenomas are broadly classified into gastric type and intestinal type according to 2010 World Health Organization classification.<sup>25</sup> Gastric-type adenomas are subclassified into PGA and foveolar-type adenoma. Intestinal-type adenoma, the most common type of neoplastic polyp in the upper gastrointestinal tract, consists of intestinal-type absorptive cells, with a variable admixture of goblet and/or Paneth cells.<sup>26,27</sup>

The most common diagnostic challenge with PGAs is distinguishing them from foveolar-type adenomas.<sup>7</sup> Foveolar-type adenomas have a well-formed apical mucin cap, label immunohistochemically by MUC5AC, and are negative for MUC6. In contrast, PGAs do not have a well-formed apical mucin cap and have labeling for both MUC5AC and MUC6.

Pyloric gland adenomas remain a rare neoplasm; however, there are clues that this lesion may be underrecognized and underreported. In the largest series from Germany, all gastric polyps were examined during a 10-year period.<sup>4</sup> Pyloric gland adenomas accounted for less than 3% of all gastric polyps in this series (including reactive or inflammatory polyps) and for 9% of neoplastic gastric polyps. Pyloric gland adenomas are clinically significant because they are neoplasms with malignant potential rather than a hyperplasia of metaplastic glands. Gastric PGAs have frequent association with adenocarcinoma, ranging from 12% to 30% of cases in the two largest series.<sup>4,7</sup> Increased recognition of PGAs among pathologists and the further understanding of the molecular mechanisms involved in their neoplastic transformation will improve classification and management.

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