Pyloric gland adenoma with low-grade intraepithelial neoplasia
A case report and literature review
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Abstract
Rationale: Pyloric gland adenoma (PGA) is often associated with pyloric gland metaplasia. It has high malignant potential but a low clinical diagnosis rate. Therefore, we reported a case of PGA and reviewed the literature to summarize the clinicopathological features of pyloric adenoma.

Patient concerns: A 62-year-old female underwent gastroscopy due to intermittent acid regurgitation and heartburn, which revealed a 4 × 6 mm flat, elevated lesion in the greater curvature of the upper gastric body, with depression in the central region and blood scab attachment.

Diagnosis and intervention: Biopsy revealed gastric adenoma with low-grade intraepithelial neoplasia. The patient was treated with ESD, and pathology showed gastric pyloric gland adenoma with low-grade dysplasia. The cells were positive for MUC6 and MUC5AC immunohistochemically.

Outcomes: The patient received proton pump inhibitors and gastric mucosal protective agents for one month after ESD. She occasionally presented acid regurgitation and heartburn, with no abdominal pain, abdominal distension, melena, or hematochezia. Follow-up gastroscopy will be reexamined 1 year later.

Lessons: PGA has nonspecific performance under endoscopy, and its diagnosis mainly depends on pathology. Clinicians need to increase their ability to recognize such lesions and treat them in time to improve the prognosis.

Abbreviations: AIG = autoimmune gastritis, ATPase = H+/K+ ATPase, DL = demarcation line, HP = Helicobacter pylori, IMSP = irregular microvascular pattern, MUC2 = Mucin apoprotein 2, MUC5AC = Mucin apoprotein 5AC, MUC6 = Mucin apoprotein 6, Pep I = Pepsinogen 1, PGA = pyloric gland adenoma, SMT = submucosal tumor.

Keywords: case report, endoscopic morphology, pathological features, pyloric gland adenoma

1. Introduction
Pyloric gland adenoma is a type of gastric adenoma.[1] It has attracted increasing attention in recent years, and its incidence is low, accounting for 2–2.7% of gastric adenomas. Pyloric gland adenoma is a precancerous lesion that can evolve into adenocarcinoma through low-grade intraepithelial neoplasia to high-grade intraepithelial neoplasia, with a reported carcinogenesis rate of 12–47%.[2–4] However, PGA has no specific symptoms, and anemia related to autoimmune gastritis (AIG) is more common.[5]

Therefore, it is necessary for clinicians to be aware of this entity. We report a case of pyloric gland adenoma found by routine gastroscopy and summarize the endoscopic and pathological features of PGA through a literature review.

2. Case report
A 62-year-old woman suffered intermittent acid regurgitation and heartburn for 3 years. She occasionally had dull pain in the upper abdomen but no nausea, vomiting, melena or weight loss. She took omeprazole irregularly to reduce the symptoms. She had a history of chronic superficial gastritis and Helicobacter pylori infection, which was eradicated successfully 2 years ago. Her father died of pancreatic cancer and had no family history of gastric or colon cancer. There were no abnormalities during physical examination.

Gastroscopy revealed a type IIa lesion in the greater curvature of the upper gastric body, 4 × 6 mm in size, colorless change, that exhibited depression in its center and blood scab attachment. Close observation and FICE mode image enhancement showed that the demarcation line was positive and the surface pattern was
slightly disordered (Fig. 1). The pathology of the biopsy showed
gastric adenoma with low-grade intraepithelial neoplasia.
Immunohistochemical staining revealed MUC6 (+), MUC5ac
(+), MUC2 (-), CD10 (-), Syn (+), CgA (+), p53 (mutant), Ki67
(+), Pep-I (-), and ATPase (-) (Fig. 2).

The patient was treated with endoscopic submucosal dissection
(ESD). The pathological results showed that resected mucosal
tissue was \( 4 \times 6 \) mm in size, and there was a superficial
protuberant lesion (Type 0–IIa) on the surface of approximately
0.6 × 0.4 cm. The histological diagnosis was gastric adenoma of
the pyloric type (with low-grade dysplasia), the lesion was limited
to the mucosal layer, and the horizontal and vertical margins
were negative. Immunohistochemistry staining showed MUC6
(partial +), MUC5AC (partial +), MUC2 (-), CD10 (-), Syn (-),
p53 (wild type), Ki-67 (less than 5%), Pepsinogen-I (-),
Pepsinogen-II (partial +), and ATPase (-).

The patient recovered well and was followed up for 6 months.
At present, she has no abdominal discomfort. Gastroscopy was
scheduled to be reexamined 12 months after the operation.

3. Discussion
Gastric cancer is a common tumor of the digestive system, and it
has always been a hot topic for researchers. The occurrence of
traditional gastric adenocarcinoma is the result of the stepwise
progression of gastric mucosal inflammation (Helicobacter pylori
infection-atrophy and intestinal metaplasia-dysplasia-gastric
cancer).\(^{[6,7]}\) However, several studies have demonstrated well-
differentiated adenocarcinomas arising in nonintestinalized
gastric mucosa, such as gastric-type well-differentiated adenocarcinomas in hyperplastic polyps of the stomach in 1983.
There has been a question of whether well-differentiated

Figure 1. (A) The lesion was located in the great curvature of the upper segment of the gastric body, as shown by the arrow. (B) Observation showed that the lesion
was type IIa, colorless change, old blood could be seen at the central depression, and the lesion size was \( 4 \times 6 \) mm in size. In FICE mode image (C), the demarcation
line of the lesion was positive, and the surface pattern was dense and slightly disordered.

Figure 2. Pathological images showing PGA with low-grade intraepithelial neoplasia (A) \((100 \times)\); (B) \((200 \times)\), HE staining showed dense tubular glands covered with
monolayer cuboidal to low columnar epithelial cells, mild structural disorder, slightly elongated nuclei, no obvious nucleoli, light staining to eosinophilic cytoplasm,
ground glass shape, and no apical mucinous cap. (C–F) Immunohistochemistry. (C) \((100 \times)\) Ki67 positivity of less than 1%. (D) \((100 \times)\) MUC2 negative. (E) \((100 \times)\)
MUC5AC positive. (F) \((100 \times)\) MUC6 positive.
adenocarcinomas of the stomach are exclusively intestinal type. Along with the development of research, gastric-type well-differentiated adenocarcinoma has been proposed. According to the WHO classification standard published in 2019, gastric adenomas are divided into intestinal type and gastric type according to the direction of differentiation, while gastric type adenomas are further divided into pyloric gland type and foveolar type. In Japan, gastric adenoma refers to pyloric gland adenomas are further divided into pyloric gland type and foveolar type. It can also occur in older women (female: male ratio of 3:1) and often exists in the gallbladder, pancreas, small intestine, rectum and even cervix.

PGA was first reported by Elster in 1976. The incidence of pyloric gland adenoma is relatively low. It occurs more frequently in older women (female: male ratio of 3:1) and often exists in the form of polyps in the stomach (69%). It can also occur in the duodenum, esophagus (Barrett’s esophagus), bile duct, gallbladder, pancreas, small intestine, rectum and even cervix, mostly related to pyloric glandular metaplasia. Histologically, PGA consists of dense tubular glands (occasionally cystic dilatation). The lesions were covered with monolayer cuboidal to low columnar epithelial cells with round nuclei at the base of the cells, no obvious nucleoli, and lightly stained eosinophilic cytoplasm, showing a ground glass shape and no apical mucinous cap. Immunohistochemically, the tumor cells were positive for MUC6 and MUC5AC and negative for intestinal-type markers such as MUC2, CD10 and CDX2. It has been reported that MUC6 and MUC5AC have unique immunohistochemical expression patterns useful for the diagnosis of PGA. MUC6 is diffusely and strongly positive in the whole PGA lesion, while MUC5AC has low or no (lost) expression in the surface epithelium. Ekrem Çakar et al reported a case of PGA with high-grade dysplasia, which suggests that PGA has the potential to become cancerous, which requires the attention of clinicians and pathologists.

PGA has different performance under endoscopy and is difficult to diagnose accurately. Therefore, we reviewed the relevant literature and summarized the endoscopic manifestations, pathological features, and gene and chromosome mutations associated with PGA (Table 1) to improve the understanding of the disease by clinicians and pathologists.

Stomach PGA was mostly found in the fundus and body (64%), followed by the cardia (8%) and antrum (7%) of the stomach; the intermediate zone is the least common (5%).

### Table 1

The endoscopic and pathologic characteristics of pyloric gland adenoma reported in the literature and the case report.

| Author/year | Cases | Age/Sex | Site | Endoscopic morphology | Size | Status of the unaffected gastric mucosa | Magnifying endoscope/EUS | Immunoreactivity | Carcinogenesis |
|-------------|-------|---------|------|-----------------------|------|--------------------------------------|---------------------------|----------------|--------------|
| Vett et al\[15\]/2003 | 90 | 73/F | Corpus 58 | Antrum | 7–25.2 mm | HP+ 16 | – | – | 30% |
| Golger et al\[16\]/2008 | 1 | 79/F | Antrum | Polyp | 20 mm | HP- | IMVP-asteroid-shaped mucosal pits | MUC6+ | – |
| Chen et al\[17\]/2009 | 41 | 73/F | Body of stomach 9 | Intestinal metaplasia 6 | AIG 4 | – | – | MUC6+ | – |
| Çakar et al\[18\]/2013 | 1 | 60/M | Proximal gastric corpus | Polyp with a lobulated surface | 20 mm | – | – | MUC6+ | – |
| Salem SB et al\[19\]/2014 | 1 | 74/M | Fundus | Polypoid lesion | 20 mm | – | DL+ | MUC6+ | – |
| Nakajo et al\[20\]/2018 | 1 | 80/F | Greater curvature of the middle gastric body | Flat elevated lesion | 20 mm | HP eradication | IMVP+ including closed-loop vessels with repeated irregular anastomoses | MUC6+ | – |
| Choi et al\[21\]/2018 | 67 | 66/F | Body/fundus 45 | Polypoid lesion or mass 62 mucosal irregularity 2 | – | AIG 15 | – | MUC6+ | 16.4% |
| Pei et al\[22\]/2019 | 1 | 75/M | Cardia 2 | Flat, elevated lesion | 20 mm | – | – | MUC6+ | – |
| Min et al\[23\]/2020 | 1 | 69/M | Posterior wall of the upper part of the gastric body | SMT-like elevated lesion, with an opening on the surface of the tumor | 10 mm | HP-nonatrophic gastritis | – | MUC6+ | – |
| Present case | 1 | 62/F | Greater curvature of upper gastric body | Flat, elevated lesion | 6 mm | HP-nonatrophic gastritis | – | MUC6+ | – |

AIG = autoimmune gastritis, DL = demarcation line, EUS = endoscopic ultrasound, HP = Helicobacter pylori, IMVP = irregular microsurface pattern, IMVP = irregular microvascular pattern, SMT = submucosal tumor.
There have also been a few cases in the remnant stomach. Under white-light model gastroscopy, most PGA lesions appear as polyoid and nodular protuberances or as uneven mucosa, flat eminences, ulcer-like lesions or submucosal tumor (SMT)-like lesions. The average lesion size is 1.0–2.5 cm. Some cases suggest that there are openings on the surface of the protuberant lesions, which should be distinguished from ectopic pancreas, neuroendocrine tumors (NETs), SMT-like adenocarcinoma and proliferative polyps. Immunohistochemistry is helpful for differential diagnosis and for judging the source of lesions of nonmucosal origin. The relationship between PGA and background mucosa is still controversial. Viet M et al investigated 90 lesions of PGA and showed that autoimmune gastritis (AIG) was found in 34% of cases, of which the infection rate of HP was 30%. Only 3.8% of cases had a normal gastric mucosa. However, the results of another study were quite the opposite: 22.4% of PGA patients had AIG, and 35.8% had normal gastric mucosa. Studies by Zong-Ming Chen et al showed that 60% of PGA showed an intestinal metaplasia background, and 40% of lesions were associated with AIG. Thus, further study is needed to clarify the relationship between PGA and background mucosa. At present, there is a lack of data about the manifestations of PGA under magnifying endoscopy and endoscopic ultrasound. According to the literature reports, the surface pattern of the lesion is star-shaped or elongated in magnified NBI mode. Demarcation lines, surface microvascularity (loop-like vessels) and surface microstructure pattern changes, and even structural loss, will be observed when accompanied by intraepithelial neoplasia or even carcinogenesis. The lesions were located in the superficial layer of the mucosa; even in the submucosa, there were isoechoic patterns, and some areas showed nonechoic patterns under endoscopic ultrasonography.

According to the immunohistochemical characteristics, PGA can be divided into three types:

1. mixed type: both MUC6 and MUC5AC are expressed, but MUC6 expression is much greater, and the expression of MUC6 in deep glands is generally between 20% and 90%;
2. pure pyloric type: MUC6 is diffusely expressed, and MUC5AC is expressed only in the superficial fovea epithelium; and
3. foveolar-dominant type: diffuse MUC5AC expression, MUC6 expression in deep glands < 10%. Mixed PGA is more common.

In the early stage of PGA, there may be no change in dysplasia; rather, this stage is mainly characterized by the dense distribution of glands. After the appearance of dysplasia, the nuclear/cytoplasmic ratio is increased. It has been reported that the expression of p53 in PGA is lower than that in intestinal adenoma but increases progressively from high-grade intraepithelial neoplasia to adenocarcinoma in PGA. The high expression of p53 may indicate that PGA has a relatively high carcinogenic potential. A Japanese study showed that the loss rate of mismatch gene repair proteins in PGA was similar to that in intestinal adenomas but much lower than that in foveolar-type adenomas, suggesting that PGA microsatellites are relatively stable. Namrata Setia et al confirmed this through second-generation sequencing. However, the results of another US study were contradictory, and further study according to ethnicity is needed.

Kushima et al successfully confirmed the instability and precancerous nature of PGA for the first time and confirmed the “pyloric adenoma-adenocarcinoma sequence” of PGA by comparative genomic hybridization (CGH) analysis, which showed that PGA shared genetic and phenotypic characteristics with gastric adenocarcinoma. GNAS and KRAS mutations were also found to occur frequently in gastric PGA. Namrata Setia et al showed that the mutation rates of GNAS and KRAS in PGA were 67% and 41%, respectively, and that 2 mutations existed simultaneously in most cases. Histological techniques and CGH analysis showed amplifications of chromosomes 17pq and 20q in PGA and amplification of chromosome 20q in invasive gastric adenomas. Thus, the above studies on the genetic and chromosomal features of PGA confirm its high carcinogenic potential.

It has been reported in the literature that larger lesions, villous tubular structure, AIG and mixed PGA are more likely to become cancerous. Although the local recurrence rate of PGA is less than 10%, it is necessary to follow up according to the postoperative pathological results.

The patient’s lesions were Type 0-IIa, located on the greater curvature of the upper part of the stomach. Pathology showed that the glands and cells were similar to the pyloric glands and were accompanied by low-grade intraepithelial neoplasia. Immunohistochemistry showed that MUC5AC was diffusely expressed, and deep glands expressed MUC6, which meets foveolar-dominant type PGA.

In the process of endoscopy, endoscopists should pay attention to whether there is the possibility of PGA when finding protuberant lesions of the stomach body, which need to be differentiated from fundus glandular gastric cancer, hyperplastic polyps, and submucosal tumors. Detailed observation, biopsy and pathological examination, especially immunohistochemistry, play an important role in its diagnosis. To improve the diagnostic ability of such diseases. First, endoscopists were needed to learn more about PGA, including predilection sites, endoscopic morphological characteristics and high-risk groups. Second, endoscopists should strictly follow the endoscopic examination standard specifications and carefully examine during the operation. Finally, endoscopists and pathologists were needed to maintain good communication. For the disease to be diagnosed, endoscopists should give the pathologist a reminder, and the final diagnosis should be given after mutual consultation.

4. Conclusion

Pyloric gland adenoma is common in elderly women. Under endoscopy, most of the lesions were polyoid-like lesions, which usually occurred in the fundus and body of the stomach. The pyloric gland-like structure was observed pathologically under light microscopy. Immunohistochemistry, MUC6 and MUC5AC were helpful for diagnosis. Because of its malignant potential, clinicians should attend to the possibility of pyloric gland adenoma and pursue timely treatment.

Author contributions

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