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Case Report

Coexisting early gastric adenocarcinomas of pyloric gland-type and intestinal-type with different genetic mutations in the setting of autoimmune gastritis

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Abstract: We report a 58-year-old female with no significant symptoms who was found to have two distinct gastric lesions during routine endoscopy: a 15 mm lesion in the fundus, diagnosed as gastric adenocarcinoma of pyloric gland mucosa-type (GA-PGM), and a 30 mm cauliflower-like mass in the gastric body, identified as well-differentiated tubular adenocarcinoma with gastrointestinal mixed type (GA-TAC), accompanied by multifocal neuroendocrine cell hyperplasia in the background of autoimmune gastritis (AIG). Molecular analysis revealed distinct genetic alterations between the two tumors despite arising within the same gastric background: GA-PGM harbored a KRAS p.Q61H mutation and MDM2 amplification, whereas GA-TAC showed a KRAS p.G12D mutation along with STK11 and additional alterations. This case reports the unusual coexistence of GA-PGM and GA-TAC in the setting of AIG, with the two lesions presenting distinct clinicopathologic and molecular characteristics. Our findings support the hypothesis that these two tumor subtypes originate from distinct metaplastic cell lineages through independent tumorigenic pathways, and add to the limited clinical evidence for the rare entity, GA-PGM.

Keywords: Gastric adenocarcinoma, pyloric gland mucosa-type, autoimmune gastritis

Introduction

Gastric fundic gland-type adenocarcinoma was first described by Tsukamoto et al. in 2007, with distinct clinicopathologic features [1]. It was subsequently proposed as a gastric cancer subtype in 2010 [2] and incorporated into the WHO classification in 2019 [3]. In recent years, the recognition of fundic gland mucosa-type gastric cancer has increased. However, other gastric phenotypes, including pyloric gland adenocarcinoma and gastric adenocarcinoma of pyloric gland mucosa type (GA-PGM), remain poorly characterized and rarely reported.

Here, we report a case of early GA-PGM and gastric adenocarcinoma with gastrointestinal mixed-type tubular adenocarcinoma (GA-TAC) arising in the background of autoimmune gastritis, accompanied by multiple intestinal adenomas.

Case presentation

A 58-year-old woman was admitted six days after a gastric mass was detected during a routine health examination. She was asymptomatic.

Family history was unavailable because both parents were deceased; no known history of hereditary diseases, malignancies, or psychiatric disorders was reported. The patient had no significant past medical history, including hypertension, diabetes mellitus, coronary artery disease, or other major organ diseases. She denied prior infectious diseases (e.g., hepatitis or tuberculosis), as well as any history of major surgery, trauma, or blood transfusion. No known drug or food allergies were reported.

Written informed consent for publication was obtained from the patient at the time of consultation and was approved by the Ethics

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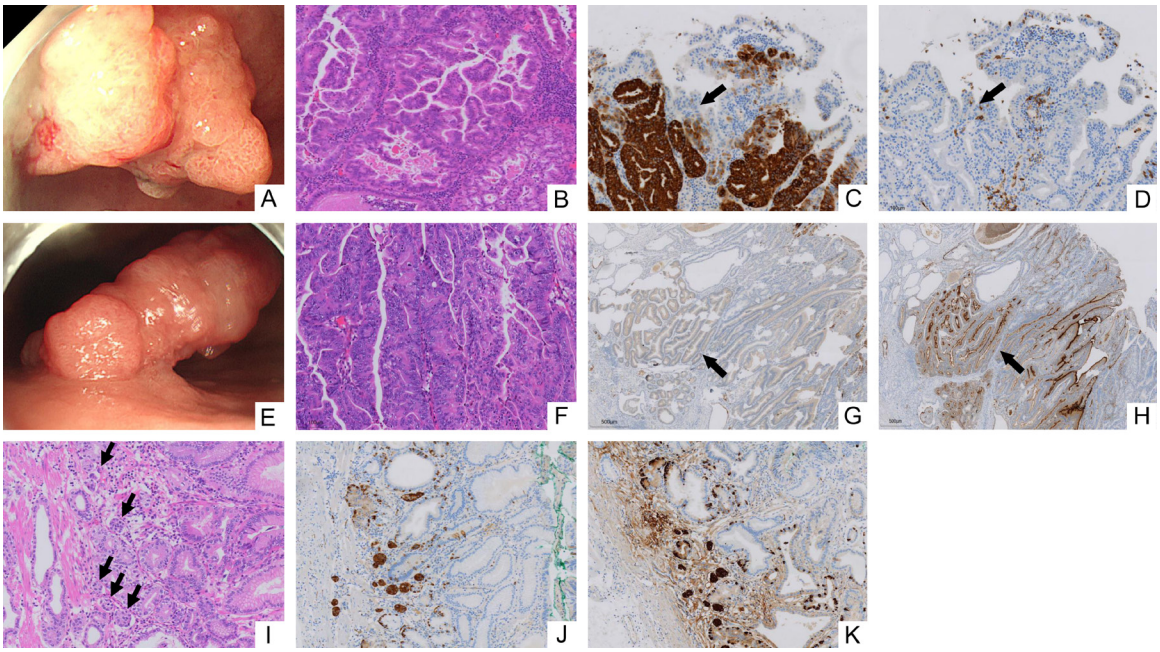

Figure 1. Endoscopic and microscopic findings of gastric lesions. A-D. Gastric adenocarcinoma of pyloric gland mucosa-type (GA-PGM). A. Endoscopic appearance of lesions in the gastric fundus. B. Pyloric gland hyperplasia with complex architectural structure and round nuclei (H&E stain, original magnification ×20). C. Strong positive expression of MUC6 in the pyloric gland mucosa (immunohistochemical staining, original magnification ×20). D. Negative expression of CD10 in the lesion (immunohistochemical stain, original magnification ×20). E-H. Gastric adenocarcinoma with gastrointestinal mixed-type tubular adenocarcinoma (GA-TAC). E. Endoscopic appearance of lesions in the gastric body. F. Foveolar gland hyperplasia characterized by complex structure and round nuclei (H&E stain, original magnification ×10). G. Negative expression of MUC6 in the lesion (immunohistochemical stain, original magnification ×4). H. Partial positive expression of CD10 at the edge of glandular lumens (immunohistochemical staining, original magnification ×4). I. Multiple irregular nests of neuroendocrine cells with uniform cell size were observed in the basal layer of the gastric mucosa (H&E stain, original magnification ×10). J. Synaptophysin immunohistochemistry indicates proliferative neuroendocrine cells (immunohistochemical stain, original magnification ×10). K. Chromogranin A (CgA) immunohistochemistry confirms neuroendocrine cell proliferation (immunohistochemical stain, original magnification ×10).

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Gastroscopy revealed a mass measuring approximately 15 mm in diameter at the gastric fundus. The fundic gland mucosa was partially absent and replaced by pyloric gland-type mucosa, characterized by oval crypt openings and marginal crypt epithelium. A clear demarcation line (DL+) was observed, along with an irregular microvascular pattern (IMVP+) and an irregular microsurface pattern (IMSP+) (**Figure 1A**).

In the gastric body, a cauliflower-like mass measuring approximately 30 mm in diameter was identified. The fundic gland mucosa was completely absent and replaced by irregular pyloric gland-type mucosa with marked intestinal metaplasia. Endoscopic features included a distinct demarcation line (DL+), irregular circular microvessels (VEC+, IMVP+), and an absent microsurface pattern (IMSP+) (**Figure 1E**). Colonoscopy revealed multiple polyps.

Histologic examination of the fundic lesion demonstrated atypical hyperplasia of the gastric foveolar epithelium, with enlarged, irregular nuclei and a crowded architecture. Beneath this, pyloric gland-like hyperplasia with cytologic and structural atypia was observed. The glands exhibited complex architectures, including tubular, cribriform, and papillary patterns. Tumor cells showed enlarged nuclei with irregular contours and pale (glassy) cytoplasm. Chief and parietal cells were absent, and the lesion was confined to the mucosa (**Figure 1B**, **1F**).

Table 1. Molecular pathologic changes of GA-PGM and GA-TAC

Somatic mutation	GA-PGM	GA-TAC
Class I	KRAS p.Q61H	KRAS p.G12D
Class II	APC p.R1450*; MDM2 Amp	APC p.S1545*; KMT2C p.E2798Gfs*11
		STK11 p.W308C
Class III	PDGFRA p.S716R	PDGFRA p.S716R; ARAF p.R428*
		B2M p.D79N; ERBB3 p.L326R
MSI	MSS	MSS
MMR	pMMR	pMMR

Class I: Pathogenic variants (P). Class II: Likely pathogenic variants (LP). Class III: Variants of uncertain significance (VUS). MSI: Microsatellite Instability. MMR: Mismatch Repair. GA-PGM: Gastric adenocarcinoma of pyloric gland mucosa type. GA-TAC: gastric adenocarcinoma with tubular adenocarcinoma and gastrointestinal mixed type. * indicates a stop codon.

Based on the above, the patient was diagnosed with: (1) Gastric fundus: GA-PGM, pType-Ips, 15 mm, pTisN0M0, UL0, Ly0, V1, pHM0, pVM0; (2) Gastric body: GA-TAC, gastrointestinal mixed type, pType-Ips, 30 mm, pTisN0M0, UL0, Ly0, V1, pHM0, pVM0.

Histologic examination of the colorectal lesions revealed multiple polyps, including tubular adenomas and hyperplastic polyps; the largest lesion was a traditional serrated adenoma. Detailed histologic findings are available in the Figure S1.

Immunohistochemical analysis revealed the following findings. Regarding mucin phenotype and proliferation index, the GA-PGM lesions demonstrated strong immunoreactivity for MUC6 and absent CD10 expression, indicating pyloric gland lineage (**Figure 1C**, **1D**). The Ki-67 labeling index was low (<5%) in the pyloric gland adenocarcinoma component, whereas a higher proliferative index was observed in the surface foveolar epithelium. In contrast, the GA-TAC lesions exhibited negative MUC6 staining and positive CD10 staining, consistent with a mixed gastric-intestinal phenotype (**Figure 1G**, **1H**). The Ki-67 index was focally elevated. H&E staining and immunohistochemical analysis also revealed neuroendocrine cell hyperplasia in the background (**Figure 1I-K**).

Molecular testing revealed distinct molecular alterations in GA-PGM and GA-TAC (**Table 1**). GA-PGM harbored a KRAS p.Q61H mutation, along with APC p.R1450*, MDM2 amplification, and PDGFRA p.S716R. The tumor was microsatellite stable (MSS), with no detectable mismatch repair (MMR) gene alterations. GA-TAC harbored a KRAS p.G12D mutation and additional alterations, including KMT2C p.E2798Gfs11, APC p.S1545, and STK11 p.W308C. Further mutations included B2M p.D79N, ARAF p.R428, ERBB3 p.L326R, and PDGFRA p.S716R. This tumor was also microsatellite-stable (MSS), with no detectable MMR gene alterations (**Table 1**).

The patient underwent endoscopic submucosal dissection (ESD) without additional adjuvant therapy. At 18-month follow-up, no recurrence or other abnormalities were detected.

Discussion

Compared to fundic gland-type tumors, pyloric gland neoplasms are considerably less common and remain under-investigated. Pyloric gland adenoma (PGA), first described in 1990, occurs predominantly in older women and is frequently associated with autoimmune gastritis (AIG) [4, 5]. Histologically, these tumors show strong MUC6 expression in the glandular component, with MUC5AC expression in the surface epithelium [4].

A multicenter clinicopathologic study of 67 cases classified PGA into three immunophenotypic subtypes: (1) Mixed type, with variable expression of MUC6 and MUC5AC in deeper glands; (2) Pure pyloric type, with diffuse MUC6 expression and superficial MUC5AC expression; and (3) Predominant foveolar type, with diffuse MUC5AC expression and minimal (<10%) MUC6 expression in deeper glands, raising differential diagnostic consideration with foveolar-type adenoma [6].

PGA is most frequently reported in the setting of AIG, although overall reports remain limited.

Pyloric gland adenocarcinoma is even rarer. A recent case described by Hirata et al. (2024) demonstrated submucosal invasion by pyloric gland-type adenocarcinoma without an associated foveolar component [7].

In theory, analogous to fundic gland mucosa-type adenocarcinoma, gastric adenocarcinoma of pyloric gland mucosa type (GA-PGM) may exist; however, no prior reports have clearly documented this entity. The present case is therefore notable, demonstrating malignant transformation of both pyloric gland and foveolar epithelium, supporting a diagnosis of GA-PGM. Moreover, synchronous occurrence of GA-TAC with a gastric-intestinal mixed phenotype has not, to our knowledge, been previously reported. The presence of background neuroendocrine cell hyperplasia further supports underlying AIG.

The association between AIG and gastric cancer remains incompletely defined. Available evidence suggests that AIG is relatively uncommon among gastric cancer patients. However, in gastric cancer patients with AIG, the co-occurrence of AIG and *Helicobacter pylori* gastritis is relatively common [8]. Some studies have found that in individuals who are seronegative for *Helicobacter pylori*, AIG may act as an independent driver of gastric carcinogenesis [9]. Recent Mendelian randomization analysis by Zhang et al. demonstrated a causal association between AIG/pernicious anemia and gastric cancer, identifying multiple implicated proteins (e.g., RAMP3, FGF3, TGFB2) and enrichment of cytokine-receptor interaction and PI3K-AKT signaling pathways. These findings support enhanced surveillance in patients with AIG, particularly those with pernicious anemia [10].

Notably, the Ki-67 index in the GA-PGM component was <5%, suggesting relatively indolent biological behavior and a favorable prognosis compared to conventional gastric adenocarcinoma.

Molecular analysis revealed distinct mutational profiles between the two tumors. The fundic lesion harbored KRAS p.Q61H and MDM2 amplification, whereas the gastric body lesion exhibited KRAS p.G12D and STK11 p.W308C mutations. Although both tumors carried KRAS alterations, the differing mutation sites may contribute to divergent biological behavior and therapeutic responses. The presence of MDM2 amplification exclusively in the fundic lesion suggests enhanced suppression of the p53 pathway. Conversely, STK11 mutation, detected only in the gastric body lesion, has been associated with metabolic reprogramming and therapeutic resistance, potentially influencing clinical outcomes.

Both tumors also harbored *APC* mutations at different loci, which may differentially affect Wnt/β-catenin signaling activity. Additionally, the gastric body tumor demonstrated a higher burden of variants of uncertain significance (e.g., *B2M*, *ARAF*, *ERBB3*), suggesting greater genomic complexity. Despite these differences, both lesions were microsatellite stable (MSS) and lacked mismatch repair gene alterations, indicating comparable genomic stability.

The two tumors exhibited significant differences in molecular features, which may represent distinct tumor types with different biologic behaviors. This suggests that atrophy in autoimmune gastritis can include pyloric gland metaplasia and intestinal metaplasia. Pyloric gland tumors (pyloric gland adenomas/adenocarcinomas) originate from pyloric gland metaplasia, while common tubular adenomas/adenocarcinomas originates from intestinal metaplasia. Due to their different pathogenesis, their molecular changes are also different.

Finally, colonoscopy revealed multiple colorectal polyps, including tubular adenomas and a traditional serrated adenoma. Since no evidence of malignancy was identified, we did not conduct further investigations.

In conclusion, we report a rare case of early GA-PGM and GA-TAC with different molecular changes occurring in the background of autoimmune gastritis, which has not been documented in the literature to date.

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Disclosure of conflict of interest

None.

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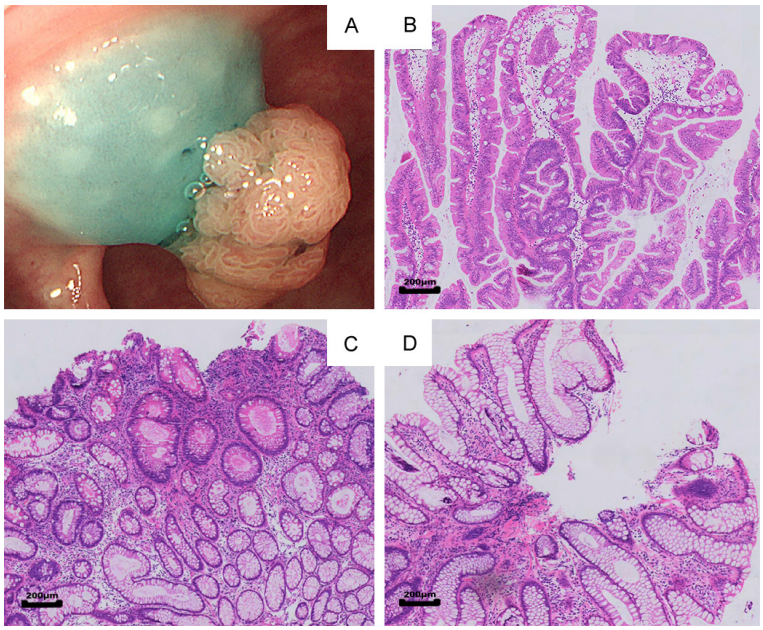

Figure S1. Intestinal lesions (Supplementary Material). A. Findings from endoscopy of traditional serrated adenoma (TSA). B. Microscopic view of TSA (H&E stain, original magnification ×4). C. Tubular adenoma (H&E stain, original magnification ×4). D. Hyperplastic polyp (H&E stain, original magnification ×4).