

A rare case of *Helicobacter pylori*-uninfected foveolar-type gastric cancer with submucosal invasion and lymph node metastasis

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Abstract

Gastric cancer without *Helicobacter pylori* infection accounts for less than 1% of all gastric cancers, and is generally considered to be less invasive. This report describes a rare case of *H. pylori*-uninfected gastric cancer with deep submucosal invasion and lymph node metastasis. Endoscopic submucosal dissection was performed, and pathological examination revealed tubular adenocarcinoma with deep submucosal invasion. We diagnosed foveolar-type gastric adenocarcinoma. While many cases of foveolar-type gastric adenocarcinoma, especially of the white elevated type, are reported as early stage gastric cancer, this case is very rare because it showed submucosal invasion and lymph node metastasis.

Keywords

Helicobacter pylori-uninfected, gastric adenocarcinoma, foveolar-type, submucosal invasion, lymph node metastasis

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Introduction

Gastric cancers (GCs) without *Helicobacter pylori* infection account for less than 1% of all GCs. This type of cancer is known to include signet ring cell carcinoma, fundic gland-type GC, and foveolar-type carcinoma.¹ Some reports have demonstrated the occurrence of GC in patients without *H. pylori* infection, described as *H. pylori*-uninfected GC. The prevalence of *H. pylori*-uninfected GC is low, and the clinicopathological features have not been fully documented yet.² The incidence of GC from *H. pylori*-uninfected background stomach is relatively increasing due to the decrease in *H. pylori* infection rate. Although *H. pylori*-uninfected GC is generally considered to be less invasive,³ we report here a case of *H. pylori*-uninfected GC with deep submucosal invasion and lymph node metastasis.

Case presentation

A 68-year-old man was referred to our hospital after a biopsy revealed well-differentiated tubular adenocarcinoma (tub1) in a flat-elevated lesion of the cardia during upper gastrointestinal endoscopy performed as part of a medical checkup (An endoscopic examination is performed once a year as a voluntary GC screening for those over 60 years old where he

lives.). He had type 2 diabetes mellitus but was not taking any medication. He had no history of *H. pylori* eradication or treatment with a proton pump inhibitor. His family history included breast cancer in his mother and renal cancer in a brother. On initial physical examination, his height was 175 cm and weight was 72.8 kg. Vital signs included a body temperature of 36.4°C, blood pressure of 130/82 mmHg, heart rate of 98 beats/min (sinus rhythm), and respiratory rate of 17 breaths/min. There was no conjunctival anemia or ocular conjunctival icterus. Heart sounds were normal with no murmurs and respiratory sounds were clear. The abdomen was flat and soft with no tenderness. An *H. pylori* stool antigen test, urea breath test (UBT), and serum immunoglobulin G (IgG) antigen test were all negative. Esophagogastroduodenoscopy (EGD) performed at our hospital showed a regular arrangement of collecting venules

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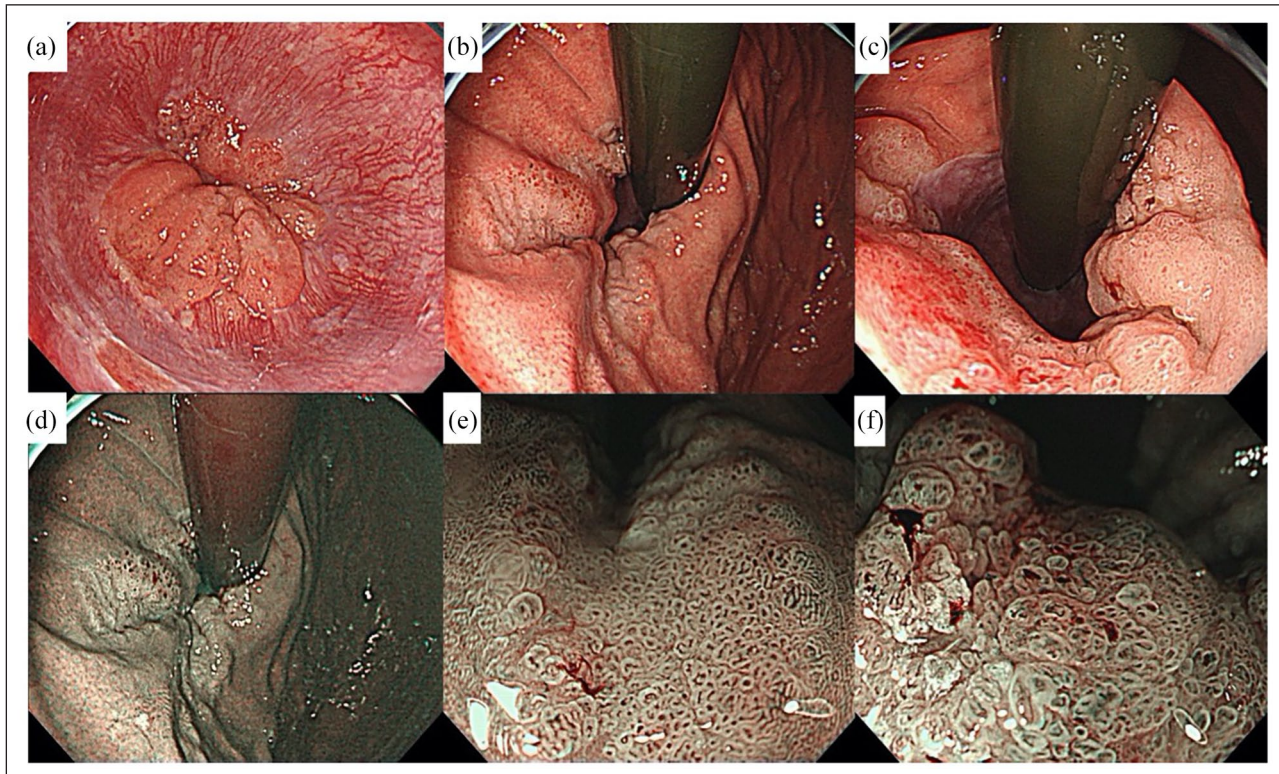


Figure 1. Gastrointestinal endoscopic examination findings. (a, b, c) Endoscopy revealed a gastric body without atrophy of the background mucosa. The lesion was seen as a whitish, flattened, elevated lesion with depressions extending from the esophagogastric junction to the lesser curvature of the upper body, white light endoscopy. (d, e, f) Magnifying endoscopy with narrow-band imaging revealed a papillary or villous-like fine mucosal pattern with intra-structural irregular vessels in all lesions of unequal size and an enlarged white zone.

(RAC) throughout the gastric body without atrophy of the background mucosa. The lesion was seen as a whitish, flattened, elevated lesion with depressions from the esophagogastric junction (EGJ) to the lesser curvature of the upper body. The lesion was approximately three-quarters the circumference of the cardia (Figure 1(a)–(c)). There was no area suspicious of hard texture in the lesion, and the depth was expected to be intramucosal (Categories 4.2, 4.3, and 4.4 of the revised Vienna classification).⁴ There was no Barrett's mucosa at the EGJ. Magnifying endoscopy with narrow-band imaging (NBI) showed granular and papillary mucosal patterns of unequal size and an enlarged white zone (Figure 1(d)–(f)). The microvascular structure showed dilated and tortuous atypical vessels, which were more distinct on the anal side (Figure 1(e)). The demarcation line was identifiable around the entire circumference, and the lesion measured approximately 50 mm in size. Contrast-enhanced computed tomography (CT) did not show wall thickening or masses in the cardia. There was no significant lymph node enlargement or findings suggestive of metastasis. Based on the above, the lesion was suspected to have a diameter of 50 mm and a depth of invasion of T1a(M). Endoscopic submucosal dissection (ESD) was performed, and the tumor was resected en bloc. The lesion was a type 0–IIa + IIc tumor that measured 75 mm × 60 mm (Figure 2). Pathological

examination revealed tubular adenocarcinoma in the submucosal layer, with a maximum depth of more than 3500 μm (Figure 3(a) and (b)), mild lymphatic invasion (Figure 3(c) and (d)), and venous invasion. The horizontal resection margin was negative, and the vertical margin was positive. Histopathologically, the lesion was located in the stomach 11 mm from the squamous epithelium and extended into the esophagus. Atypical epithelial cells with round, enlarged, and well-defined nuclei proliferated in the form of differentiated glandular ducts, irregular glandular ducts, fused glandular ducts, and papillae, forming the tumor (Figure 3(b)). In the advanced part of the tumor, the infiltrating layer was composed mainly of small differentiated glandular ducts, some of which were disrupted, and leakage of mucus was observed. Immunohistological examination revealed that the tumor was positive for MUC5AC, MUC6, and proton pump (proton pump/H⁺/K⁺-ATPase alpha subunit), but negative for MUC2, CD10, CDX2, and pepsinogen (Figure 4). The diagnosis was foveolar-type adenocarcinoma. The final pathological diagnosis was a type 0–IIa + IIc, 75 mm × 60 mm, tub1 > 2 > pap, pT1b (SM2) (>3500 μm), pUL0-, Ly1, V1, and pHM0. pVM1, which was noncurative (endoscopic curative grade C2 (eCura C2) tumor).⁵ This was an indication for additional surgical resection. There was no suspicion of Barrett's mucosa.

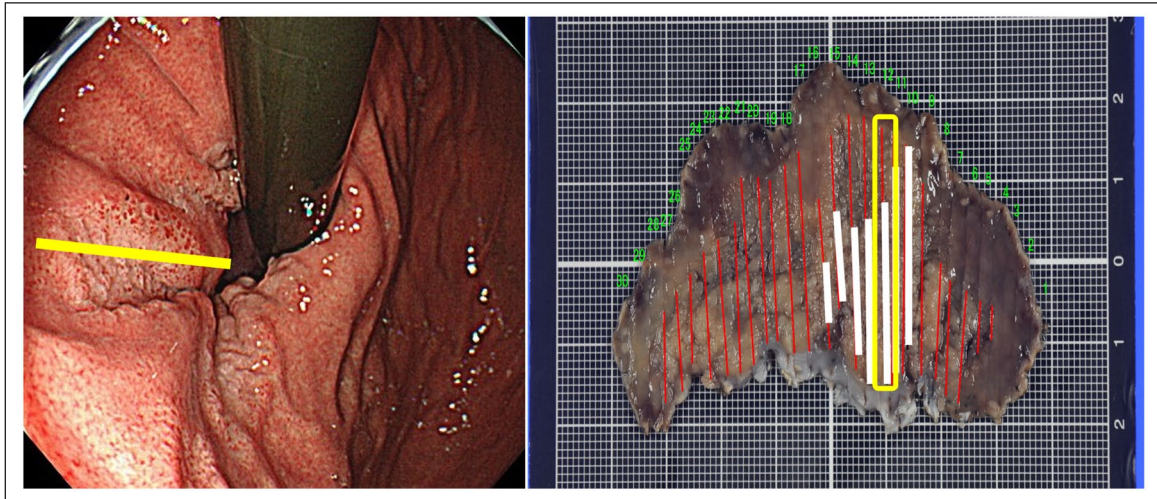


Figure 2. Stomach tissue specimen from endoscopic submucosal dissection. The location and extent of the tumor (red line) and submucosal invasion (white lone) in the resected specimen are shown. The area shown in yellow was cut up by pathology. Histopathological examination shows that the deepest part reaches more than 3500 μm below the lower edge of the muscle plate.

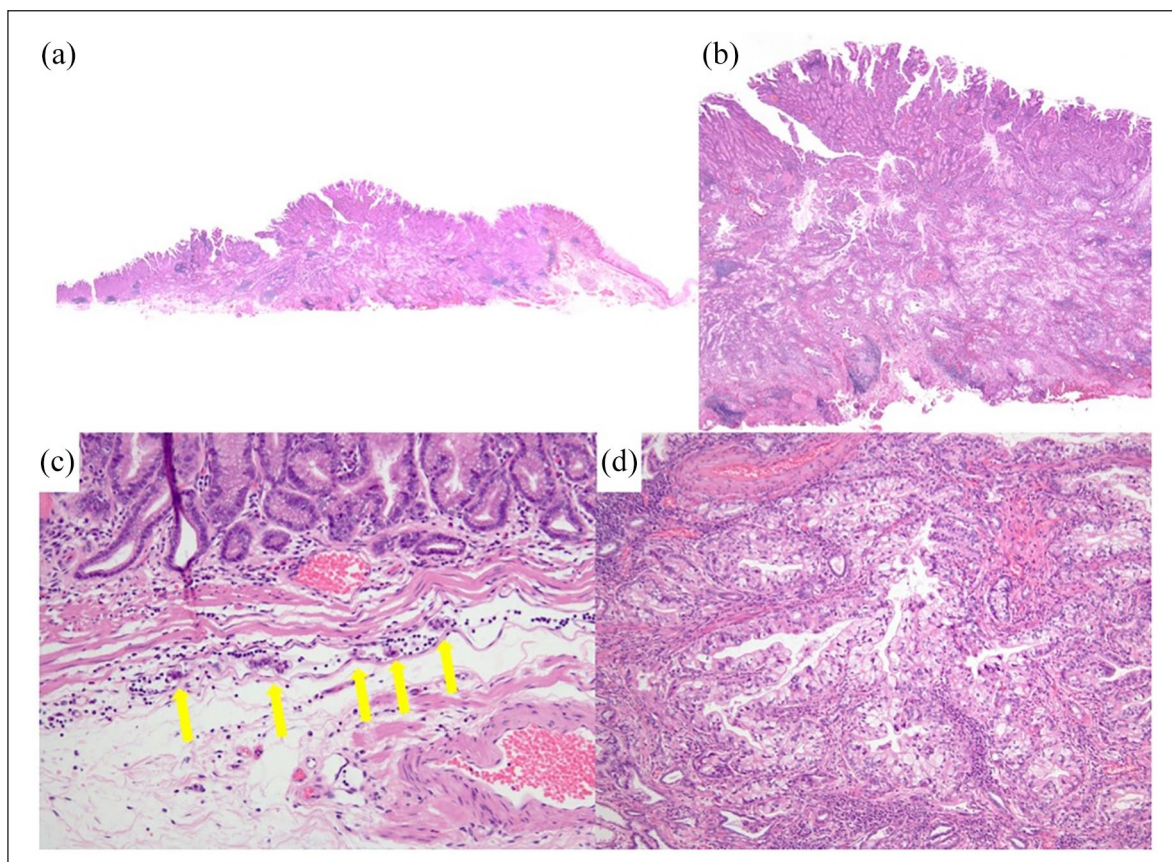


Figure 3. Representative histological images of a hematoxylin–eosin-stained, paraffin-embedded surgical specimen. (a) The tumor grew mainly in the stomach and extended into the esophagus. (b) The center of the cancer is growing in all layers, is exposed at the vertical margin, and has undergone thermal degeneration. Original magnification 20 \times . (c) Image of a moderately differentiated ductal adenocarcinoma with proliferation of fused atypical gland ducts and pale cytoplasm. Original magnification 40 \times . (d) Cancer cells with faint cytoplasm are floating in the lymphatic vessels, indicating endolymphatic tumor emboli. Original magnification 20 \times .

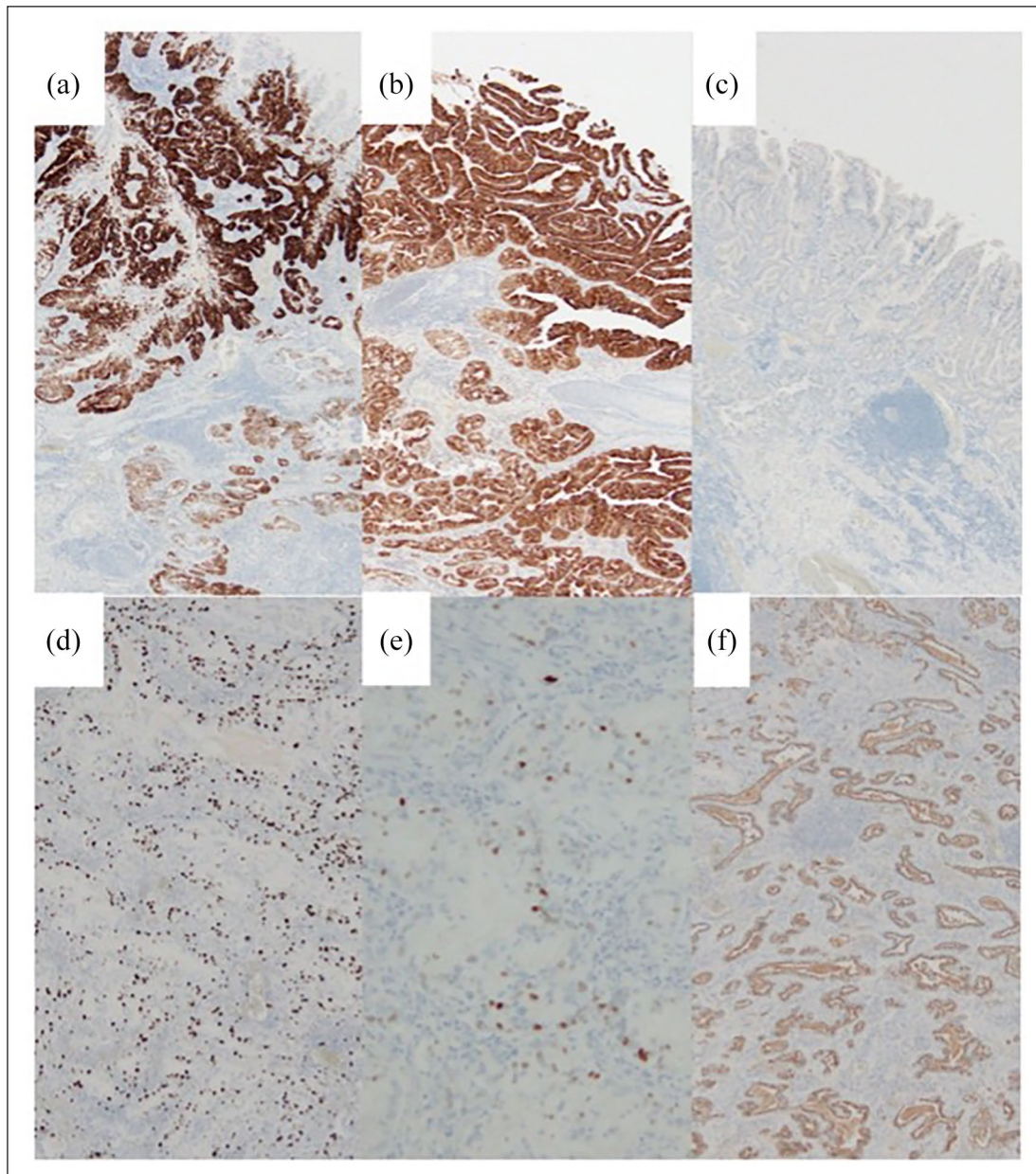


Figure 4. DAB-stained immunohistochemistry for MUC6, MUC5AC, pepsinogen-I, ki-67, p53, proton pump (proton pump/H+/K+-ATPase alpha subunit) in the same gastric cancer. Tumor showed focal positive staining for MUC6 (a) and MUC5AC (b), proton pump (f), and negative staining for pepsinogen-I (c). Ki-67 (d) and p53 (e) were both weakly positive, but the positivity rate was low. Original magnification 20 \times .

We decided to perform additional resection. The patient underwent proximal fundectomy and double tract reconstruction in the Department of Gastroenterological Surgery. The oral and anal sides of the gastrectomy specimen were submitted for rapid intraoperative examination, and both were confirmed to be negative.

Postoperative pathological examination revealed adenocarcinoma with lymph node metastasis (Figure 5) but no residual lesion in the ESD scar. Chemotherapy with S-1 was started postoperatively. There has been no recurrence over a year and half since surgery.

Discussion

Although *H. pylori*-uninfected GC is reported to account for less than 1% of all GCs,¹ its incidence has varied widely from 0.66% to 14% in previous reports.⁶⁻¹¹ The incidence of *H. pylori* infection is decreasing rapidly in younger age groups, and the number of reports of *H. pylori*-uninfected GC is expected to relatively increase in the future. Although a definition of *H. pylori*-uninfected GC has yet to be established, Matsuo et al.¹ defined it as a case in which (1) two or more diagnostic methods (such as serum *H. pylori* antibody

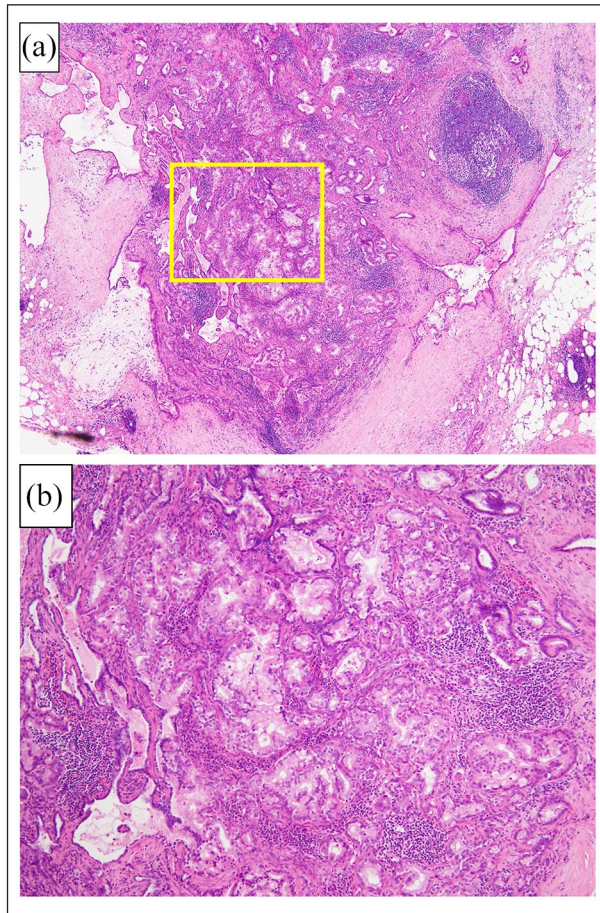


Figure 5. Hematoxylin and eosin staining of paraffin-embedded lymph node specimen after surgery. (a) Representative histologic images are shown. There are no tumor remnants, but there is metastasis in lymph nodes 1, 7, and 9. Original magnification 20 \times . (b) Enlarged image of the area indicated by the yellow square. Original magnification 40 \times .

and stool, urine, and UBTs) are negative, (2) histopathological examination shows no gastritis, and (3) endoscopic examination shows no atrophy (with RAC). Moreover, Ono et al.⁶ suggested that it is important to exclude histological atrophy, gastritis, and endoscopic gastritis, to use multiple methods for diagnosing *H. pylori* infection, and to exclude a history of *H. pylori* eradication. They also suggested that it is important to define the diagnosis by multiple tests, including at least two tests for infection (serum antibody, stool, urine, and UBT) and histological and endoscopic gastritis. Our patient had no history of *H. pylori* eradication, serum antibody, stool antigen, and UBTs were negative, and there was no endoscopic or histological atrophy. Therefore, we excluded *H. pylori* infection.

Yamada et al.² reported the characteristics of 16 cases of GC without *H. pylori* infection, which were classified as undifferentiated-type GCs that were mainly pure signet ring cell carcinoma, fundic gland-type, and foveolar-type. Sato et al.⁷ reported four further cases, including the intestinal type. In recent years, there have been increasing reports of

foveolar-type tumors characterized by small reddish elevated lesions,^{8,9} which Nomura et al.¹⁰ called “raspberry-like” tumors because of their morphology. The location of GC was divided into the upper one-third (U), middle one-third (M), and lower one-third (L) of the stomach. Collectively, these tumors can be classified into five clinicopathological types: (1) ring cell carcinoma, which presents as faded lesions in the M-L region; (2) gastric basal gland-type gastric carcinoma, often recognized as submucosal tumor-like elevation in the U-M region; (3) flat-elevated epithelial gastric carcinoma, recognized as a whitish flat elevation in the U-M region; (4) raspberry-type foveolar adenocarcinoma, recognized as an erythematous polypoid lesion in the U-M region; and (5) intestinal-type GC, which presents as a depressed lesion with marginal elevation in the L region.⁷

In this case, the lesion was located in the region of the gastric cardia on a background of mucosa without *H. pylori* infection or atrophy and was recognized macroscopically as a flat ridge of the same color with white zone. On magnification, the microstructure of the surface was mildly uneven, and the vascular structure was denser than in the surrounding area with conspicuous dilated and tortuous atypical vessels. Histopathological analysis revealed a complete gastric-type tumor with predominantly foveolar epithelial tissue that was positive for MUC5AC and MUC6 and negative for MUC2, CD10, CDX, proton pump, and pepsinogen. Given that the histological and endoscopic findings were mainly characteristic of foveolar epithelium, we judged the tumor to be a flat-elevated foveolar-type adenocarcinoma.

The tumor needed to be differentiated from Barrett’s adenocarcinoma because its center was located 11 mm from the antral side of the EGJ. Siewert et al. classified adenocarcinoma of the EGJ as a tumor centered within 5 cm above or below the EGJ, and this case was type II (1 cm on the mouth side to 2 cm on the anal side of the EGJ).¹² There was no pathological evidence of Barrett’s mucosa; therefore, the possibility of adenocarcinoma on a background of Barrett’s esophagus was excluded.

Tumors with the characteristics observed in this case are typically classified as foveolar-type adenoma according to the World Health Organization (WHO) classification. This type of tumor is often detected as early stage GC according to previous reports. In this case, however, submucosal invasion and lymph node metastasis were observed.

We performed a PubMed search up to April 2021 using the keywords “foveolar-type,” “*Helicobacter pylori*,” “negative,” “uninfected,” and “gastric adenocarcinoma.” Excluding the raspberry-type tumor, there were 11 cases with endoscopic findings similar to those in our case^{2,7} (Table 1). The mean age was 57.1 years, the male-to-female ratio was 6:5, and the mean tumor length was 47.7 mm. All the tumors were in the U region. As in the present report, all of these reports described a laterally growing, flattened lesion with the same color and a white tone on endoscopy. Both lesions showed a papillary-shaped or villous-shaped fine mucosal pattern with irregular intratumoral vessels on

Table 1. Summary of 11 reported case of gastric adenocarcinoma without *Helicobacter pylori* infection.

	Age	Sex	Location	Size	Morphology	Depth	Histology	Ly	V
Yamada 2018									
1–4	52.3 ± 10.4	M/F, 3/1	U	27.3 ± 11.2	0–IIa	m		0	0
Sato 2020									
5	34	F	U	35	0–IIa	m	tub1	0	0
6	66	F	U	33	0–IIa	m	pap	0	0
7	63	M	U	55	0–IIa	m	tub1	0	0
8	69	F	U	98	0–IIa	m	tub1	0	0
9	51	F	U	28	0–IIa	m	tub1	0	0
10	72	M	U	63	0–IIa	m	tub1	0	0
11	64	M	U	42	0–IIa	m	tub1 > pap	0	0

We performed a PubMed search through to April 2021 using the keywords “foveolar type,” “*Helicobacter pylori*,” “negative,” “uninfected,” and “gastric adenocarcinoma,” and excluded the term “raspberry-type tumor.”

NBI magnification, which is considered a characteristic endoscopic finding. All lesions were confined to the mucosal layer, and no vascular invasion was observed in the early stage of GC. We did not find any reports of submucosal invasion or lymph node metastasis as were present in our case.

Conclusion

We encountered a case of well-differentiated gastric carcinoma that was a white elevated foveolar-type adenocarcinoma arising in the fundic gland region of the *H. pylori*-uninfected stomach. While many cases of foveolar-type adenocarcinoma have been reported as early stage GC, this case is noteworthy because it showed submucosal invasion and lymph node metastasis. The prevalence of GC should dramatically decrease as the *H. pylori* infection rate decreases. There are many variations of *H. pylori*-uninfected GC, and further accumulation of cases and clarification of its characteristics are needed.

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Declaration of conflicting interests

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Ethical approval

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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