

[CASE REPORT]

A Rare Case of Hypertrophic Gastropathy with Adenocarcinoma Arising from a Gastric-type Adenoma

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Abstract:

A 60-year-old man was referred for the investigation of giant gastric folds, life-threatening anemia and hypoproteinemia. A combination of multiple endoscopic procedures derived a clinical diagnosis of protein-losing gastropathy with two gastric adenomas. After two months of alimentary therapy, the patient received total gastrectomy and fully recovered. The final pathological diagnosis was hypertrophic gastropathy of unknown origin with concomitant adenocarcinoma arising from a gastric type adenoma.

Key words: hypertrophic gastropathy, protein-losing gastropathy, gastric type adenoma

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Introduction

Hypertrophic gastropathy is a rare condition characterized by giant gastric folds. Similar findings are observed in Menetrier's disease and hypertrophic hypersecretory gastropathy, and only a full-thickness histological examination of the gastric wall can derive a proper diagnosis.

We herein report a case of hypertrophic gastropathy with life-threatening anemia and hypoproteinemia successfully diagnosed by a combination of endoscopic diagnostic procedures.

Case Report

A 60-year-old man was admitted to a previous hospital because of anorexia, fatigue and weight loss of 5 kg that had developed 2 months earlier. He had a history of gastritis and gastric polyp and had undergone *Helicobacter pylori* (*H. pylori*) eradication 5 years ago. Final screening endoscopy was performed 2 years ago with no abnormal findings. He had no other underlying disease and was not on any medications. He did not drink alcohol but smoked 20

cigarettes per day. His mother had died from colon cancer at 40 years of age. On admission, his body mass index was 19.8, his Eastern Cooperative Oncology Group performance status was 3, and he was weak and generally thin with pitting edema observed in both legs. A large right inguinal hernia was also observed. His serum hemoglobin level was 3.6 g/dL, and albumin was 1.1 g/dL. No proteinuria was observed.

An esophagogastroduodenoscopy (EGD) revealed giant folds of the gastric body. Although Borrmann type IV advanced gastric cancer was suspected, a histologic examination of multiple biopsies from the folds revealed no malignancy. He received 6 packs of red blood cell and 2 units of albumin infusion and then was referred to our hospital for further treatment. In addition to anemia and hypoproteinemia, a serological analysis revealed slight elevation of fibrinogen, C-reactive protein and gastrin as well as deficiency of iron, ferritin and vitamin B₁₂. Tumor markers were all negative. Rheumatoid factor and anti-parietal cell antibody were weakly positive, and an anti-cytomegalovirus antibody analysis suggested prior infection (Table). A second EGD revealed remarkable hypertrophy of the gastric wall from the fundus to the antrum (Fig. 1a and b) along with gi-

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Table. Laboratory Data on Admission.

Peripheral Blood		Biochemistry		Serology	
WBC	7,450 / μ L	TP	4.9 g/dL	CEA	2.6 ng/mL
RBC	352 / μ L	Alb	1.8 g/dL	AFP	8.7 ng/mL
Hb	10.5 g/dL	AST	18 U/L	CA19.9	7 U/mL
Ht	33 %	ALT	20 U/L	CA125	9 U/mL
Plt	19.1 / μ L	LDH	187 U/L	Anti- <i>H. pylori</i> IgG	<3 U/mL
MCV	93.8 fL	ALP	364 U/L	CMV IgG	positive
MCH	29.8 pg	γ -GTP	33 U/L	CMV IgM	negative
MCHC	31.8 %	AMY	102 U/L	Fe	13 μ g/dL
Coagulation system		BUN	106 mg/dL	ferritin	10.1 ng/mL
PT	10.7 s	Cre	0.44 mg/dL	Gastrin	460 pg/mL
APTT	28.1 s	Na	136 mEq/L	Anti-parietal cell antibody	10
Fibrinogen	433 mg/dL	K	4.2 mEq/L	Anti-CCP	<0.6 U/mL
		Cl	105 mEq/L	ANA	<40
		Ca	7.3 mg/dL	RF	21 IU/mL
		CRP	0.71 mg/dL	Complement titer	46.2 CH50/mL
				IgG	895 mg/dL
				IgG4	36 mg/dL
				Vitamin B ₁₂	119 pg/mL
				folate	5.8 ng/mL

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, PT: prothrombin time, APTT: activated partial thromboplastin time, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ -GTP: γ -glutanyl transpeptidase, AMY: amylase, BUN: blood urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chlorine, Ca: calcium, CRP: C-reactive protein, CEA: carcinoembryonic antigen, AFP: alpha fetoprotein, CA19-9: carbohydrate antigen 19-9, CA125: carbohydrate antigen 125, CMV: cytomegalovirus, Fe: ferrum, Anti-CCP: anti-cyclic citrullinated peptide, ANA: anti-nuclear antibody, RF: rheumatoid factor

ant folds in the greater curvature from the gastric angle to upper body. The mucosa was edematous and covered with dense mucus. Distensibility of the gastric wall was maintained, and no gastric residue was observed. Narrow-band imaging with magnifying endoscopy (NBIME) revealed that the marginal crypt epithelium was enlarged, showing variable size and shape. These findings were observed throughout the entire stomach but were more severe in the upper body (Fig. 1c and d) than in the antrum (Fig. 1e and f).

A biopsy from the antrum and body revealed no malignancy. At the greater curvature of the gastric antrum, two non-pedunculated polypoid lesions [70 mm (Fig. 2a) and 10 mm in diameter] were observed. Both polypoid lesions were lobulated and resembled each other. NBIME revealed two patterns in the large lesion: an enlarged marginal crypt epithelium (Fig. 2b) and small, irregular surface structure (Fig. 2c). In the small lesion, only a small, irregular surface structure was observed. A biopsy of both lesions showed gastric-type adenoma.

In the duodenum, four polypoid lesions were detected and endoscopically diagnosed as adenomas. Colonoscopy revealed multiple polyps suggestive of adenomas along with reddish hypertrophic mucosa in the rectum. Endosonography of the stomach revealed remarkable thickness of the first and second layers of the gastric wall throughout the whole stomach. Abdominal ultrasonography revealed splenomegaly and portal venous gas. Computed tomography revealed remark-

able thickening and edematous changes of the whole gastric wall. A large tumor was observed in the antrum without enlarged lymph nodes. Protein-losing scintigraphy using ^{99m}Tc-human serum albumin revealed the accumulation of radioactivity along the greater curvature of the stomach. Radioactive albumin was collected from the gastric juice. Echocardiogram revealed a reduced cardiac ejection fraction of 32%. A clinical diagnosis of protein-losing gastropathy with multiple gastric adenomas was made. For a further histological confirmation, diagnostic endoscopic mucosal resection (EMR) was performed four times - one procedure each for the small gastric polypoid lesion, the enlarged mucosa of the gastric upper body and antrum, and an adenomatous polyp in the duodenal bulb. The pathologic results were adenoma for the gastric polypoid lesion, hypertrophic mucosa for the enlarged gastric mucosa, and duodenal adenoma.

Alimentary therapy with a high-protein and elemental diet along with the administration of iron, tranexamic acid and proton-pump inhibitors were started. After 2 months, his hemoglobin level increased to 13.8 g/dL, his serum albumin level was 3.1 g/dL, and his cardiac ejection fraction improved to 39%. At present, total gastrectomy with a right inguinal hernia repair surgery and mucosectomy of multiple duodenal adenomas have been performed. The postoperative course was uneventful, and he was discharged on POD 8. One month after surgery, his hemoglobin level was 14.9 g/dL, the albumin level increased to 3.5 g/dL without alimen-

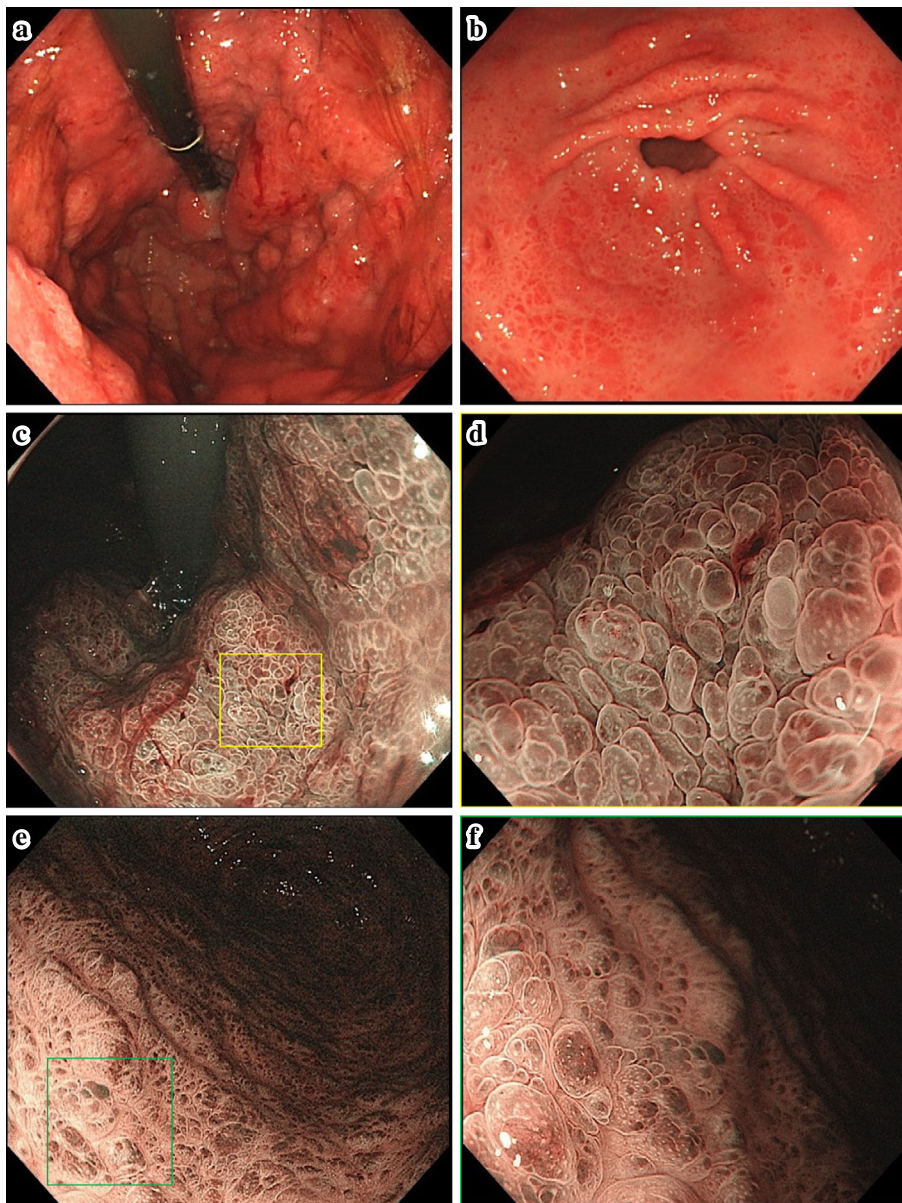


Figure 1. a) A retroflex view of the stomach shows edematous and hypertrophic mucosa with reddened giant folds covered with thick mucus. b) Mucosa of the gastric antrum shows reddened hypertrophic mucosa with granular changes. c) Narrow-band imaging (NBI) of the mucosa of the cardia shows hypertrophic mucosa. d) Magnification with NBI of the mucosa in the yellow square of (c) shows enlarged marginal crypt epithelium of variable size and shape. e) NBI of mucosa of the antrum shows granular changes with multiple brownish areas. f) Magnification with NBI of the mucosa in the green square of (e) shows enlarged marginal crypt epithelia of variable size and shape, findings similar to those in the gastric body.

tary therapy, the cardiac ejection fraction improved to 49%, and portal vein gas disappeared. Capsule endoscopy was performed with no apparent tumor in the small bowel. A second colonoscopy was performed to treat the multiple polyps. The reddish hypertrophic mucosa in the rectum has disappeared. A total of eight polyps were endoscopically resected, with one being a submucosal invasive carcinoma with vessel invasion, three being high-grade adenomas, and four being low-grade adenomas. Three months after gastrectomy, additional laparoscopic sigmoidectomy with D2 lymph node dissection was performed, showing no local re-

sidual tumor but one regional lymph node metastasis (pT1N1aM0, Stage IIIA). The postoperative course was uneventful, and he was discharged on postoperative day 6. The clinical course is summarized in Fig. 3.

The histologic analysis of the gastric specimen

Macroscopically, the folds of the greater curvature, anterior and posterior walls of the gastric body were remarkably rugal with surface granular changes, and the mucosa of the antrum showed fine granular changes (Fig. 4a).

Microscopically, the mucosa of the pyloric gland was

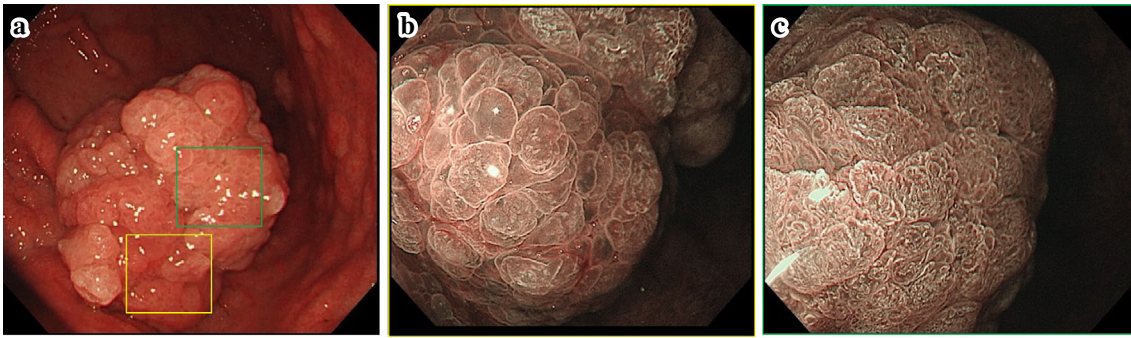


Figure 2. a) A large 70-mm-sized semi-pedunculated tumor was observed in the anterior wall of the antrum. Observation by magnification with NBI revealed two different structures: an enlarged marginal crypt epithelium (b, yellow area) and small, irregular surface structure (c, green area) within the tumor.

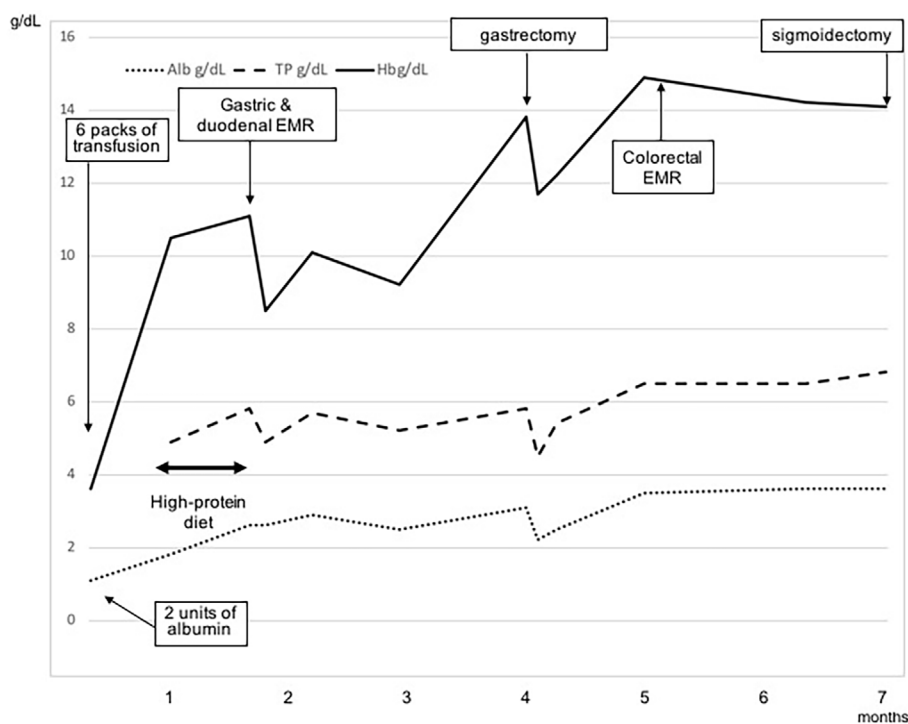


Figure 3. Clinical course of the patient with changes in the serum albumin, total protein and hemoglobin levels.

thick at 2-2.5 mm and showed foveolar hyperplasia (Fig. 4b). Immunohistochemical studies revealed chief cell and parietal cell differentiation (Fig. 4c) and no hyperplasia of gastrin-producing cells in the antrum. The mucosa of the gastric body was thick, namely 3-4 mm thicker than the normal fundic gland mucosa, which showed heterogeneous hypertrophy of the fundic glands, with several normal-appearing mucosa, secondary atrophy of fundic glands, and the appearance of cystic glands (Fig. 4d). In the submucosa, heterotopic gastric glands with fibrosis were observed. Immunohistochemically, the ratio of foveolar to propria glands was almost normal (1:4), and chief cells and parietal cells showed normal distributions (Fig. 4e). Therefore, the background stomach was diagnosed as hypertrophic gastropathy of unknown origin.

A large semi-pedunculated tumor 96×72 mm in size was observed. Macroscopically, the surface had a villous appearance (Fig. 4a). The cut surface showed heterogeneous cystic changes, and the center was rather grayish. Microscopically, the tumor showed hyperplasia of the foveolar epithelium, pyloric glands with heterogeneous cystic glands, and a localized dark-stained area with high cellularity (Fig. 4f). This area showed the proliferation of irregular glands with columnar cells of varying sizes and round, enlarged nuclei. The histological diagnosis was differentiated adenocarcinoma with cytological low-grade atypia (Fig. 4g). Immunohistochemically, MUC5AC and MUC6 were negative (Fig. 4h). Other areas of the pedunculated tumor were diagnosed as gastric type adenoma [intraepithelial neoplasia of gastric phenotype (1)] which showed a proliferation of

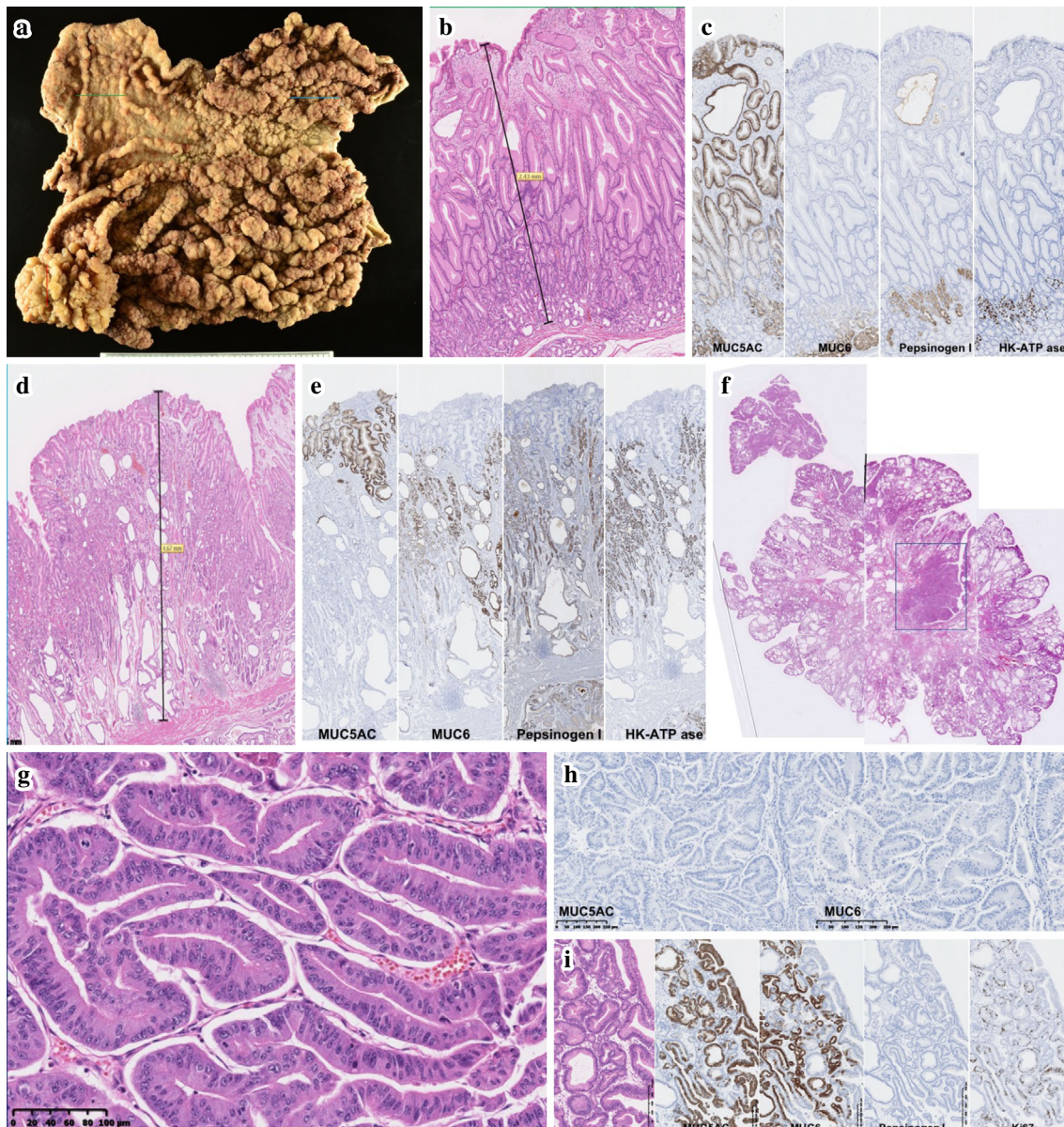


Figure 4. a) Macroscopic view of the stomach. The folds of the greater curvature and anterior and posterior walls of the gastric body were remarkably rugal with surface granular changes, and the mucosa of the antrum showed fine granular changes. b) Section of the green line in (a). Microscopically, the mucosa of the pyloric gland was thick at 2-2.5 mm and showed foveolar hyperplasia. c) Immunohistochemical studies of (b) revealed chief cell and parietal cell differentiation. d) Section of the blue line in (a). The mucosa of the gastric body was thick at 3-4 mm more than the normal fundic gland mucosa. Heterogeneous hypertrophy of fundic glands, with several normal appearing mucosa, secondary atrophy of fundic glands, appearance of cystic glands were observed. e) Immunohistochemical studies of (d) revealed that the ratio of foveolar to propria glands was almost normal (1:4), and chief cells and parietal cells showed normal distributions. f) Section of the large semi-pedunculated tumor 96×72 mm in size [red line in (a)]. Microscopically, the tumor showed hyperplasia of the foveolar epithelium, a pyloric gland with heterogeneous cystic glands, and a localized dark-stained area with high cellularity. g) The inset box in (f) shows proliferation of irregular glands with columnar cells of varying sizes and round, enlarged nuclei. The histological diagnosis was differentiated adenocarcinoma with cytological low-grade atypia. h) Immunohistochemically, the cancer area was negative for MUC5AC and MUC6. i) The majority of the pedunculated tumor demonstrated gastric type adenoma which showed a proliferation of irregular sized glands with either spindle or round-shaped nuclei. Immunohistochemical studies revealed that these glands were positive for MUC5AC and MUC6 and negative for pepsinogen I, and Ki-67-positive proliferative cells showed an uneven distribution.

irregular-sized glands with either spindle or round-shaped nuclei (Fig. 4i) Immunohistochemical studies revealed that these glands were positive for MUC5AC and MUC6 and negative for pepsinogen I, and Ki-67-positive proliferative cells showed an uneven distribution (Fig. 4i). There was no submucosal invasion of the adenocarcinoma. The final diagnosis was well-differentiated adenocarcinoma pT1aN0M0, Stage IA (2) arising from gastric-type adenoma with a background of hypertrophic gastropathy.

Discussion

The differential diagnoses of giant folds of the stomach include hypertrophic gastritis, Menetrier's disease, juvenile polyposis, Cronkite-Canada syndrome and diffuse cystic malformation. Similar secondary changes may be observed in diffuse infiltrative cancer, malignant lymphoma, sarcoidosis, amyloidosis, Zollinger-Ellison syndrome, multiple gastric ulcers or acute gastritis. In the present case, the pathologic examination of the whole stomach did not reveal any findings that might have been responsible for secondary changes. Juvenile polyposis, Cronkite-Canada syndrome or diffuse cystic malformation were all unlikely based on the results of pathology.

As Schindler described, three forms of hypertrophic gastritis may be recognized microscopically: a) chronic hypertrophic interstitial gastritis, b) chronic hypertrophic proliferative gastritis and c) chronic hypertrophic glandular gastritis (3). In this case, the diffuse proliferation of glandular elements, parietal cells, chief cells and mucus neck cells was observed, findings that were compatible with chronic hypertrophic glandular gastritis. Although this patient developed severe hypoproteinemia, there were no findings of degenerative changes in the glandular layer and no absence of parietal or chief cells suggestive of Menetrier's disease. The findings of protein loss into the gastric juice and no marked increase in the serum gastrin level did not support the diagnosis of hypertrophic hypersecretory gastropathy reported by Stempien et al. (4). The acidity level was not evaluated before treatment, but this patient did not have peptic ulcer diseases or persistent diarrhea. Therefore, the final diagnosis of this patient was protein-losing hypertrophic gastropathy.

Giant fold formation in the stomach has been reported as a consequence of severe *H. pylori* gastritis. Increased production of interleukin 1 β and hepatocyte growth factor caused by *H. pylori* infection may contribute to fold thickening of the stomach by stimulating epithelial cell proliferation and foveolar hyperplasia (5). Eradication of *H. pylori* in such patients should result in the improvement of gastritis and regression of the giant folds. In this case, however, eradication of *H. pylori* had already been performed five years earlier, and a screening EGD performed two years ago showed no abnormal findings. Screening for other causes, such as collagenous and autoimmune diseases, was negative. Histologically, there was no proliferation of gastrin-producing cells; therefore, our diagnosis was hypertrophic

gastropathy of unknown origin.

The clinical diagnosis of hypertrophic gastropathy should be made by a combination of multiple modalities. Giant folds covered with copious amounts of thick mucus are typical findings on EGD but are not specific for this disease. The distensibility of the gastric wall is good compared to Borrmann type IV gastric cancer. Endosonography is useful for evaluating which layer of the gastric wall is swollen. Simple biopsy specimens are not sufficient, because the assessment of both the mucosal and submucosal architecture is required for a proper histological evaluation. Diagnostic EMR is useful for this purpose. In the present case, the mucosal surface was observed by NBIME, which revealed enlargement of the marginal crypt epithelium with variable size and shape. There were no findings of destroyed mucosal structures or irregular vascular vessels, which are commonly observed in cases of adenocarcinoma. These findings correlated well with those on microscopy, which showed hypertrophy of the foveolar forming multiple concavity and convexity.

The most suitable treatment for hypertrophic gastropathy has not yet been established. Alimentary therapy with a high-protein and elemental diet was somewhat effective in this case. However, full recovery was achieved only after total gastrectomy. Total gastrectomy was selected because the hypertrophic gastric folds were prominent in the fundus, cardia and body of the stomach, and the antrum also showed hypertrophic mucosa with a large polypoid tumor.

Whether or not patients with hypertrophic gastropathy are at an increased risk of cancer is an unsolved question. There have been reports of patients with histologically proven hypertrophic gastropathy with synchronous gastric adenocarcinoma and other tumors of the gastrointestinal tract (6). The exact incidence of adenocarcinoma among hypertrophic gastropathy remains unclear because of the rarity of the disease. Similar findings of hypertrophy of foveolar epithelium and pyloric glands were observed within the tumors, suggesting that these tumors arose from the hypertrophic stomach. Furthermore, gastric-type adenomas have been reported to have a higher incidence of harboring concomitant adenocarcinoma or of developing adenocarcinoma than intestinal-type adenomas (7). Frequent mutations in *GNAS* and *KRAS* have been reported in gastric-type adenomas (8). Although a gene analysis was not performed in the present case, the occurrence of multiple gastric-type adenomas from a non-atrophic mucosal background suggests the possibility of some kind of genetic alteration.

In summary, we encountered a rare case of hypertrophic gastropathy with concomitant adenocarcinoma arising from a gastric-type adenoma. An accurate diagnosis and suitable subsequent treatment are necessary in such rare cases. In this sense, the combination of multiple endoscopic diagnostic modalities, including observation, NBIME, endosonography and diagnostic EMR, played important roles in achieving a favorable outcome.

The authors state that they have no Conflict of Interest (COI).

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