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【 CASE REPORT 】

Celiac Disease Diagnosed after Gastrectomy for Gastric Cancer

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Abstract:
Celiac disease is a systemic autoimmune disorder leading to manifestations of malabsorption syndrome. A 47-year-old Japanese man developed severe diarrhea after surgery for gastric cancer. The diarrhea persisted for seven months, leading to a state of malabsorption. Celiac disease was suspected based on small bowel capsule endoscopy findings. The duodenal findings observed during gastric cancer surgery were reassessed, and Marsh-Oberhuber classification type 3c celiac disease was diagnosed. The anti-tissue glutaminase antibody test results were positive. The patient was started on a gluten-free diet, following which the diarrhea resolved, and the nutritional status improved. Adjuvant therapy after gastric cancer surgery was initiated.

Key words: celiac disease, gastric cancer, post-gastrectomy, small bowel capsule endoscopy, diarrhea

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Introduction

The prevalence of celiac disease (CD) has increased dramatically in the last 50 years, but many patients remain undiagnosed (1). In countries like Japan with a low prevalence, the antibody test is not covered by the national medical insurance program, and it is extremely rare in clinical practice, presenting a diagnostic challenge. Furthermore, there are different types of CD: symptomatic CD with gastrointestinal symptoms and the latent or asymptomatic type. It is also known as the "Celiac Iceberg" because of its high hidden prevalence.

CD is a systemic autoimmune disease leading to diverse non-gastrointestinal symptoms in addition to manifestations of malabsorption syndrome. However, some cases are asymptomatic, and the disease onset is observed across a wide range of age groups, from weaned children to adults. Several challenges related to the diagnosis and treatment of this disease remain, despite serological and large-scale epidemiological studies in Western countries with a high prevalence of CD (2-5). CD and gastric cancer are both specific to certain geographic regions and ethnic populations worldwide, and the comorbid occurrence of these two diseases is extremely rare (2, 6-9). CD is triggered by both genetic and environmental causes, so the number of patients with this disease is expected to increase. Thus, it is imperative to consider the CD diagnosis even in regions where the prevalence of this disease has conventionally been regarded as low.

We herein report our experience managing a patient with CD in a low-prevalence region where CD was diagnosed after surgery for gastric cancer.

Case Report

The patient was a 47-year-old Japanese man who visited our department for a detailed evaluation of diarrhea. His medical history was significant for atopic dermatitis that had been treated with topical corticosteroids and oral administration of Rupatadine fumarate. He also had a history of intolerance of certain food items, such as bread and noodles, during childhood. He had experienced occasional diarrhea that had been attributed to irritable bowel syndrome. His family history was unremarkable. Seven months earlier, he

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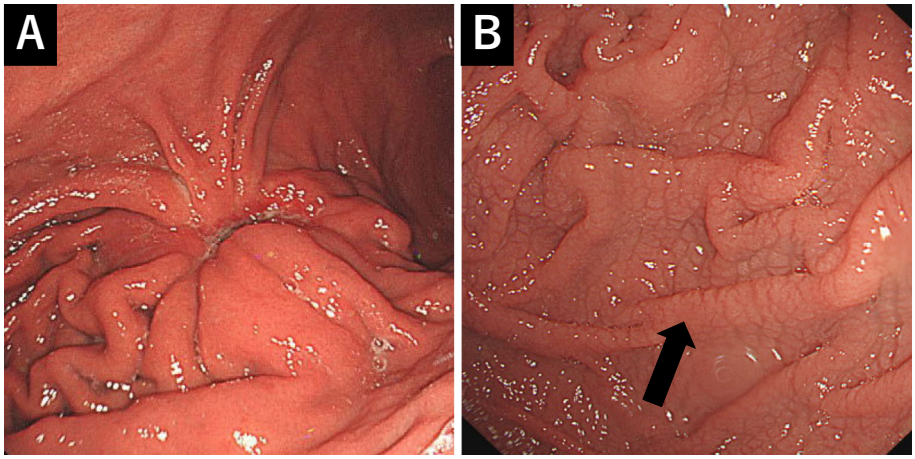

Figure 1. **(A) Esophagogastroduodenoscopy before surgery showed advanced gastric cancer. (B) A review of the esophagogastroduodenoscopic findings when gastric cancer had first been found revealed mosaic-patterned mucosa in the second part of the duodenum (arrow).**

Table. **Laboratory Data before Gastrectomy, before GFD Therapy, and Four Months after Starting GFD Therapy.**

Parameter	Before gastrectomy	Before GFD therapy	4 months after GFD	Normal range
White blood cells (/μL)	4,090	1,200	4,500	3,300-8,600
Hemoglobin (g/dL)	15.2	10.2	13.2	13.7-16.8
Platelets ($\times 10^4$/μL)	25.9	26	31.6	15.8-34.8
AST(U/L)	31	40	33	13-30
ALT (U/L)	30	40	40	10-42
ALP (U/L)	193	273	334	106-322
BUN (mg/dL)	9.2	3.7	13.2	8.0-20
Creatinine (mg/dL)	0.63	0.54	0.73	0.65-1.07
CRP (mg/dL)	0.02	0.1	0.15	0.2>
Total cholesterol (mg/dL)	205	123	236	142-219
Triglyceride (mg/dL)	49	99	128	40-149
Blood sugar (mg/dL)	95	105	120	73-109
Total serum protein (g/dL)	7.5	5.3	7.8	6.6-8.1
Albumin (g/dL)	4.2	2	4.3	4.1-5.1
Sodium (mmol/L)	138	141	140	138-145
Potassium (mmol/L)	4.7	3.3	5	3.6-4.8
Chloride (mmol/L)	101	106	99	101-108
Calcium (mg/dL)	-	7.7	9.9	8.8-10.1
Copper (μg/dL)	-	12	147	80-130
Phosphorus (mg/dL)	-	3	4.2	2.7-4.6
Magnesium (mg/dL)	-	2.1	2.5	1.7-2.3

GFD: gluten-free diet, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, CRP: c-reactive protein

had been diagnosed with advanced gastric cancer at a local hospital, and distal gastrectomy with Billroth-1 reconstruction had been performed (Fig. 1A). He developed severe diarrhea (over 10 times/day) postoperatively. He also tested positive for *Helicobacter pylori* IgG antibodies. The gastric cancer was classified as stage IIIA according to the International Union Against Cancer TNM classification and required adjuvant chemotherapy, which was deferred due to refractory diarrhea that was resistant to drug therapy (10). Subsequently, he developed a malabsorption syndrome. He was then referred to our hospital.

On an examination, the patient's height and weight were 181 cm and 61 kg, respectively. He was noted to have lost 10 kg since the gastric cancer surgery. Abdominal fullness and edema in both lower limbs were observed. Regarding non-digestive symptoms, he had no joint pain, failure to thrive, or depression. Blood investigations revealed the following results: hemoglobin, 10.2 g/dL (normal range: 13.7-16.8 g/dL); albumin, 2.0 g/dL (normal range: 4.1-5.1 g/dL); potassium, 3.3 mmol/L (normal range: 3.6-4.8 mmol/L); and cholesterol, 123 mg/dL (normal range: 142-219 mg/dL) (Table). The specific IgE antibody titer test for food allergies

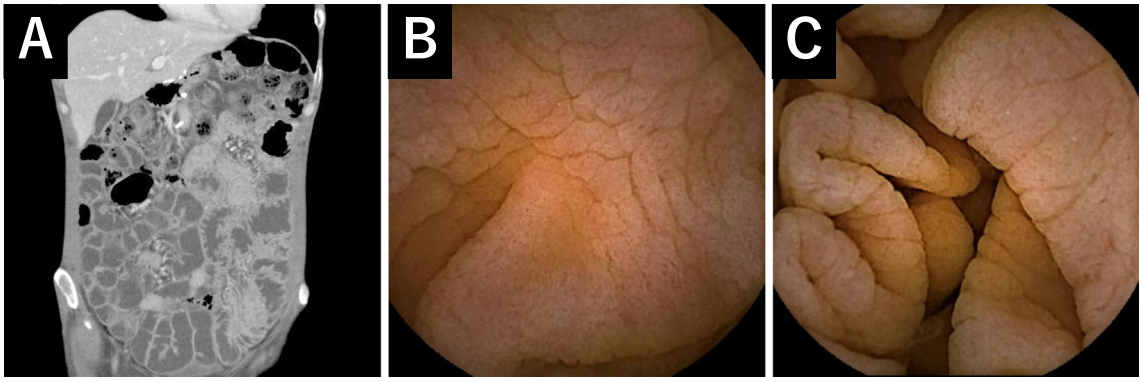

Figure 2. **(A) Computed tomography results were suggestive of enteritis. (B, C) Capsule endoscopy of the small intestine revealed marked villus atrophy in the small intestine, especially in the jejunum, a scalloped appearance, and the disappearance of the Kerckring valves. (B) shows the jejunum, an image which shows the position at 3% of the entire small intestine and (C) one which shows the position at 24%.**

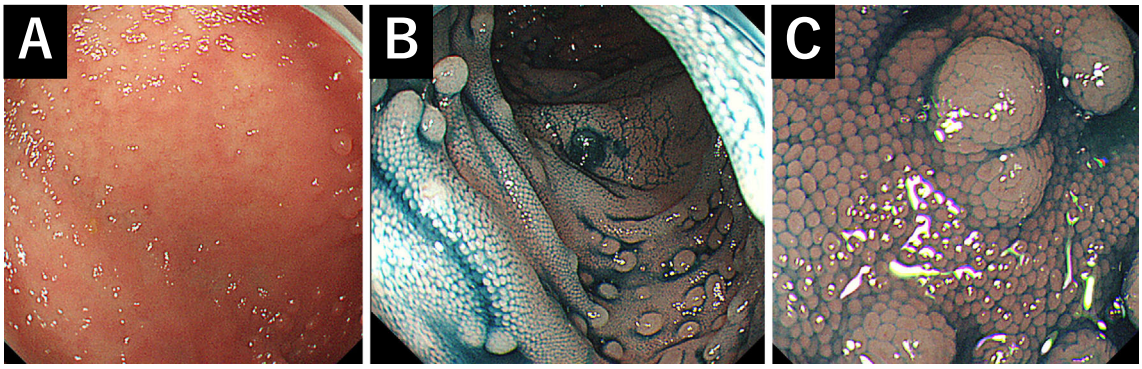

Figure 3. **The terminal ileum observed by colonoscopy (performed seven months after gastrectomy) before starting the gluten-free diet. (A) Mildly atrophied villi and lymphoid follicles were found at the terminal ileum on colonoscopy, but unlike the jejunum, the atrophy was not severe. (B) Indigo-staining endoscopic picture. (C) Image-enhanced endoscopy.**

was applied to 12 food types, including gluten and barley, but all were negative except for peanuts and almonds. Antinuclear antibody, proteinase-3 (PR3)-antineutrophil cytoplasmic antibody (ANCA), and myeloperoxidase (MPO)-ANCA were all negative, and the thyroid hormone level was within the normal range. He was observed to have anemia, an electrolyte imbalance, and a poor nutritional status.

Computed tomography suggested enteritis, and capsule endoscopy of the small intestine revealed marked villus atrophy in the small intestine, especially in the jejunum, scalloping appearance, and disappearance of the Kerckring chick wall (Fig. 2). Colonoscopy at our hospital (seven months after gastrectomy) showed villi slightly smaller than normal at the terminal ileum, but the findings were not as marked as those observed in the jejunum (Fig. 3). CD was suspected based on the above findings, and the patient was tested for the following: 1) tissue transglutaminase IgA [anti-tissue glutaminase antibody IgA (tTG)] was positive (a high titer, exceeding 100-fold, U/mL, positive ≥4; QUANTA Lite® h-tTG IgA; INOVA Diagnostics, San Diego, USA), and 2) human leucocyte antigens (HLAs) DQ2 and DQ8 were detected (DQB1 02:02 and 03:02 alleles detected by polymerase chain reaction sequence-based typing). A review of the esophagogastroduodenoscopic findings from when the gastric cancer had first been detected revealed mosaic-patterned mucosa in the second part of the duodenum (Fig. 1B). The duodenal mucosa from the surgical material obtained by gastrectomy showed a flattened villous structure of the mucosa, erosion and disappearance of the surface epithelium, and marked infiltration of lymphocytes into the mucosal stroma; thus, Marsh-Oberhuber classification type 3c CD was diagnosed (Fig. 4A) (11).

The histopathological findings of the duodenal specimens obtained by esophagogastroduodenoscopy and of the terminal ileum obtained by colonoscopy (performed at our hospital 7 months after gastrectomy) showed marked lymphocyte infiltration, and CD3 immunostaining was also confirmed to be strongly positive. These findings strongly suggested CD (Fig. 4B-D) (12). One week after commencing a gluten-free diet (GFD), the diarrhea resolved. One month later, his nutritional status (including albumin levels) showed improvement. Adjuvant therapy was initiated after gastric cancer sur-

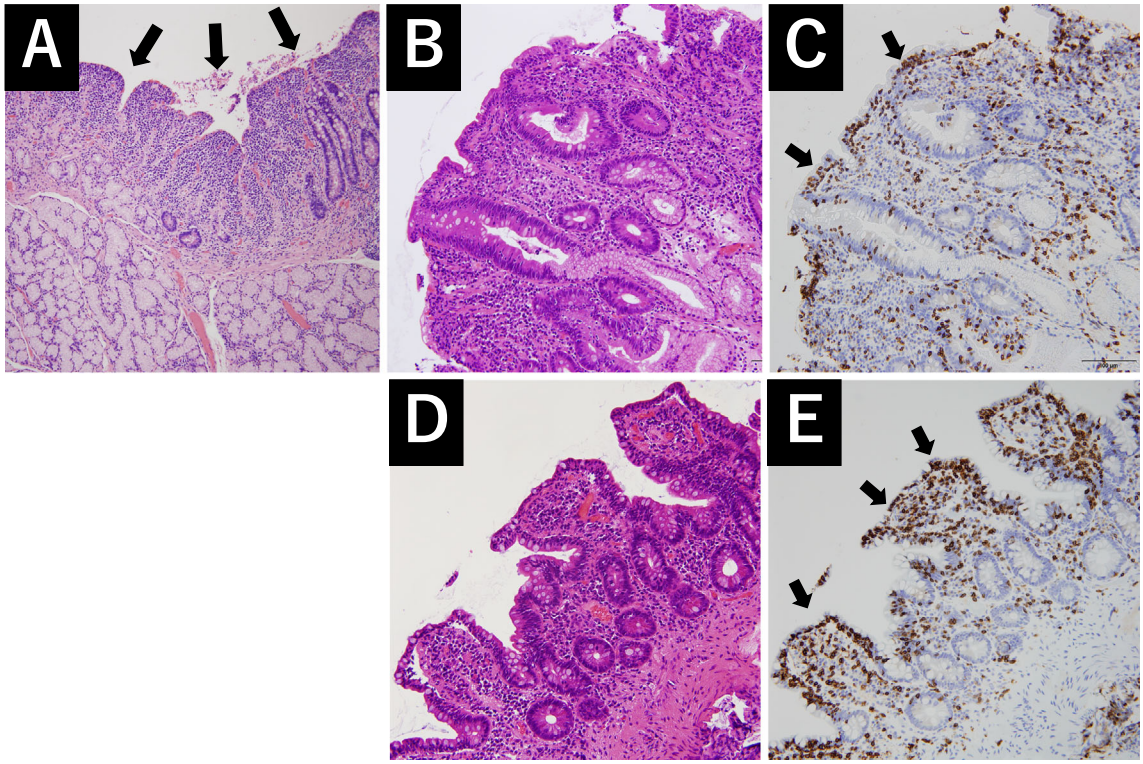

Figure 4. **(A) Hematoxylin and Eosin (H&E) staining, ×10: The duodenal mucosa from the surgical material obtained by gastrectomy showed a flattened villous structure of the mucosa, erosion and disappearance of the surface epithelium, and marked infiltration of lymphocytes into the mucosal stroma (arrow). (B) H&E staining, ×20: The duodenal mucosa on esophagogastroduodenoscopy before starting the GFD also showed a flattened villous structure of the mucosa and marked infiltration of lymphocytes into the mucosal stroma. (C) CD3, ×20: The duodenal mucosa on esophagogastroduodenoscopy before starting the GFD also showed intraepithelial lymphocytes (IELs), and the arrow indicates CD3-positive T lymphocytes infiltrating the epithelium (arrow). (D) H&E staining, ×20: The terminal ileum mucosa obtained by colonoscopy showed mild changes in villous structure and lymphocyte infiltration. (E) CD3, ×20: The terminal ileum mucosa obtained by colonoscopy was densely populated with CD3-positive T lymphocytes only on the surface of the epithelium (arrow).**

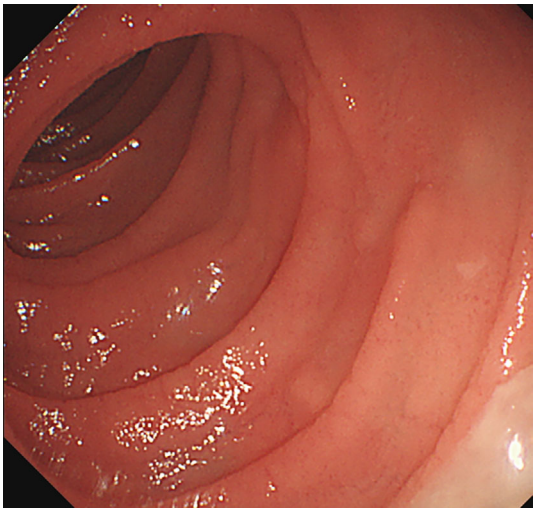

Figure 5. **Esophagogastroduodenoscopy performed nine months after starting a GFD showed improvement in the mucosa of the horizontal portion of the duodenum. GFD: Gluten-free diet**

gery, but after 10 courses of FOLFOX (leucoverin, 5-fluorouracil and oxaliplatin), the gastric cancer had become progressive. Therefore, a second course of chemotherapy is now under consideration. Nine months after the diagnosis of CD, while still on the GFD, there has been no recurrence of the diarrhea, and esophagogastroduodenoscopy has shown improvement in the mucosa of the horizontal portion of the duodenum (Fig. 5).

Discussion

We encountered a rare case of CD, first recognized after gastrectomy for gastric cancer. The geographic region of this patient's residence (Japan) has a low prevalence of CD. Direct exposure of the small bowel to gluten and gut flora due to alterations caused by gastrectomy probably worsened the diarrhea and led to malabsorption, thus making the CD symptoms more readily discernable. This patient's course suggests that undiagnosed CD can be exacerbated by gastrectomy and that a certain proportion of patients believed to have irritable bowel syndrome may instead have underlying

CD, even in regions with a low prevalence.

CD is diagnosed in adults based on a combination of clinical, serological, and histopathological findings. However, reports of CD are extremely rare in Japan and the tTG test is not covered by the national health insurance program, which may delay the diagnosis of CD in those with persistent postoperative diarrhea (1, 3, 13-16). Due to these factors, it took seven months to confirm the CD diagnosis in our present case. CD was suspected only after observing characteristic findings on small bowel capsule endoscopy performed at our hospital. The surgical specimen was then reassessed, and the tTG test was performed for a definitive diagnosis.

CD presents with diverse non-classical symptoms, and a study from the UK found that a diagnosis of CD can be delayed by up to 13 years (3). Furthermore, patients with irritable bowel syndrome are reportedly four times more likely to be diagnosed with CD, based on histopathology, than healthy individuals. It is difficult to predict CD in asymptomatic patients or based on clinical symptoms alone in patients with non-classical symptoms (17). The incidence of CD is reportedly increasing worldwide, and the incidence in Western nations is approximately 1% (1-3, 14). However, HLA gene type variations and disparities in patterns of gluten consumption result in clear differences in the epidemiology of CD based on geography and ethnicity, and reports of CD in Japan and other parts of East Asia continue to be extremely rare (2, 15, 16).

Gastric cancer is associated with risk factors such as *H. pylori* infection, age, and salt intake. This malignancy has the fifth highest incidence among cancers worldwide. It is rare in Western nations but common in East Asia, including Japan, Eastern Europe, and South America. Like CD, gastric cancer is characterized by clear geographic and ethnic disparities (6). The risks of malignant lymphoma and adenocarcinomas of the esophagus, small and large bowel, the liver, and pancreas are known to be higher in patients with CD, according to a population-based study. CD patients also have an increased risk of developing cancer depending on the age at the diagnosis of CD (7). However, reports of comorbid gastric cancer are extremely rare (3, 7-9). The epidemiological differences between these two diseases are speculated to account for the rarity of the two being diagnosed together. In addition, to our knowledge, there have been no reports of CD diagnosed after gastric cancer surgery, making this the first documented case in the literature.

CD is an autoimmune disease caused by gliadin in gluten. Gliadin, which is enriched in proline and glutamine, is resistant to proteolysis by gastric, pancreatic, and intestinal brush border peptidases. Gliadin is absorbed into the mucosa by the transcellular or paracellular pathway from intestinal mucosal epithelial cells and is then deaminated by the enzyme tissue transglutaminase (3, 5, 18). Therefore, the decreases in gastric acid and pepsin that occur after gastrectomy are considered to have little influence. We speculate that the main cause of CD exacerbation after gastrectomy is the rapid influx of gliadin into the small intestine due to the shortened food retention time and poor miscibility in the postoperative stomach. In a study of CD developing after upper gastrointestinal tract surgery, the symptoms of CD became prominent starting in the early postoperative period, leading to severe diarrhea and weight loss (19).

It is challenging to treat patients, including children, who are undiagnosed and asymptomatic and thereby constitute the "Celiac Iceberg" (1-3). The populations in regions with a low CD prevalence are switching to Western dietary habits. Thus, it is possible that some patients with CD are being misdiagnosed with irritable bowel syndrome. Furthermore, some high-risk patients who are positive for both HLA-DQ2 and DQ8 exist even in regions like Japan, where the overall frequency of HLA-DQ2 is low. This observation warrants the accumulation and analysis of more data from similar cases.

The only accepted treatment is strict, lifelong adherence to a GFD. In some cases, however, a GFD alone is not sufficient. Many recent and currently underway trials have explored nondietary treatments for CD. For example, formulations targeting endopeptidases and tight junction modulators are now being examined in clinical trials. These are expected to serve as adjuvant therapies in combination with a GFD (3, 5, 20).

Small bowel capsule endoscopy is extremely useful for diagnosing CD, with a reported sensitivity of 89% and specificity of 95%. However, it is not indicated for all patients in regions with a high prevalence due to its diagnostic power being reduced in the presence of partial villous atrophy or non-atrophic lesions. This modality is also costly. Its use is only recommended for limited atypical or treatment-resistant cases (1, 21, 22). In countries like Japan with a low CD prevalence, where the serological test for CD is not readily available, the insurance-covered capsule endoscopy test may play an essential role in managing the current need for reliable diagnostic procedures. Therefore, it should be considered before attempting to diagnose suspected cases using other parameters.

Furthermore, we learned from this case that endoscopists must carefully examine other areas of the intestine, even if one large lesion is found. It is also important that endoscopists understand the clinical symptoms before performing an examination, carefully observing the duodenum and performing an appropriate biopsy. Regarding the pathological findings, CD3 immunostaining as shown in this case was useful for the diagnosis, along with characteristic findings, such as those of the Marsh-Oberhuber classification (11, 12).

We herein report our experience managing a patient diagnosed with CD whose diarrheal symptoms became more severe after gastrectomy for gastric cancer. This patient's course suggests that CD can be exacerbated by gastrectomy and that it may be present in certain individuals diagnosed with irritable bowel syndrome, even in geographic regions with a low prevalence. The incidence of CD is rising rapidly

worldwide and may be encountered even in regions where the disease is generally rare. Therefore, CD must be considered in the differential diagnosis of chronic diarrhea.

The patient provided his informed consent for publication.

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

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