A case of celiac disease with type I enteropathy-associated T-cell lymphoma in a Japanese male patient

Hiroto Hiraga, Hirotake Sakuraba, Nahoko Tanaka, Rina Watanabe, Yui Akemoto, Shinji Ota, Hidezumi Kikuchi, Manabu Sawaya, Noriko Hiraga, Daisuke Chinda, Norihiro Hanabata, Tatsuya Mikami, Tadashi Shimoyama, Takenori Takahata, Manabu Tanaka, Noriko Hiraga, Daisuke Chinda, Norihiro Hanabata

A 45-year-old Japanese male patient who was diagnosed with celiac disease (CeD) developed type I enteropathy-associated T-cell lymphoma (EATL). In 2013, the patient was admitted to our hospital with worsening of diarrhea and weight loss. Pathological examination of biopsy specimens from the duodenum and ileum led to a diagnosis of suspected EATL. A previous total colonoscopy (TCS) indicated villous atrophy in the terminal ileum. The patient was changed to a gluten-free diet, and the nutritional status gradually improved. In September 2014, he experienced acute right lower abdominal pain. He underwent urgent surgery, and a perforation was identified in the ileum. A diagnosis of type I EATL was made following histopathological examination. After eight courses of CHOP therapy, the patient entered complete remission. TCS and esophagogastroduodenoscopy with magnifying narrow-band imaging performed in 2015 identified villous regrowth in the distal ileum and duodenum. Capsule endoscopy also found villous regrowth in the entire small intestine. To our knowledge, this is the first case of type I EATL following CeD with villous atrophy before EATL occurrence in a Japanese HLA-DQ2 carrier. The possibility of type I EATL occurring after CeD should be recognized, although CeD is quite rare in Japan.

1. Introduction

Celiac disease (CeD) is an autoimmune malabsorption disorder triggered by the ingestion of gluten-containing grains [1]. CeD is a risk factor for several malignant diseases, including type I enteropathy-associated T-cell lymphoma (EATL) [2]. Human leukocyte antigen (HLA)-DQ2 (DQA1*05/DQB1*02) is expressed in >90% of patients with CeD, and the expression of HLA-DQ2 or HLA-DQ8 (DQA1*0301/DQB1*0302) molecules is necessary for the development of CeD [3]. The gliadin peptides, together with HLA-DQ2 or DQ8, are located on the antigen-presenting cells in the lamina propria and are recognized by CD4-positive cells. These cells produce inflammatory cytokines, such as IFN-γ that mediate inflammatory cell infiltration and atrophy of the mucosal epithelium and lamina propria [4].

Studies from the United States and Europe have reported that the prevalence of CeD is approximately 1% in the general population [5]. However, CeD is rare in the Japanese people and few studies evaluated the incidence of this disease in Japan [6]. In addition, none of the previous reports have included carriers of HLA-DQ2 or DQ8 or patients who developed villous atrophy in the small intestine before EATL occurrence in the Japanese populations. Data in Japan is scarce regarding the significance of capsule endoscopy (CE) and magnifying narrow-band imaging (NBI) in the management of EATL in patients with CeD, although there are a couple of publications on these in the Western countries [7–10].

Herein, we report the case of a 45-year-old Japanese male patient, an HLA-DQ2 carrier, who developed type I EATL following CeD. We also discuss the significance of CE and magnifying NBI in the management of this disease.

2. Case report

A 45-year-old Japanese male patient was admitted to our hospital with worsening diarrhea and weight loss in 2013. In 1981, he was diagnosed with...
ulcerative colitis at 13 years of age. He entered remission following treatment with salazosulfapyridine (SASP) and prednisolone (PSL). Remission was maintained with 6-mercaptopurine (6-MP) 50 mg daily from 2012.

At the beginning of 2013, the patient complained of a slight fever and general malaise. Furthermore, he experienced watery diarrhea (>10 times per day) and weight loss. Total colonoscopy (TCS) exhibited villous atrophy and irregular-shaped ulcers in the terminal ileum without any other colonic lesions (Figure 1(A,B)). CE also showed villous atrophy of the entire small intestinal mucosa, as well as multiple erosions and ulcers in the ileum (Figure 2(A)). Esophagogastroduodenoscopy (EGD) revealed diffuse loss of villi in the duodenum and nodule-aggregated appearance of the duodenal bulb (Figure 3(A)). Magnifying NBI showed a loss of villous architecture with a pit-like structure similar to gastric metaplasia (Figure 3(B)) and multiple notch-like deformations in a circular manner in the descending portion of the duodenum (Figure 3(E,F)). 6-MP was discontinued because pathological examination of the biopsy specimens from the duodenum and

![Figure 1. Total colonoscopic (TCS) findings of the terminal ileum. (A, B) TCS performed in 2013 revealed villous atrophy and irregular-shaped ulcers. (C, D) TCS performed in 2015 identified villous regrowth in the distal ileum. (E) TCS performed in 1991 showed villous atrophy in the endoscopic and (F) pathological findings.](image-url)
ileum resulted in a diagnosis of suspected EATL. Further, a considerable number of apoptotic cells were observed in the epithelium. Biopsy samples obtained via TCS and bone marrow aspiration did not exhibit reconstitution of the TCR \( \zeta \)-chain. The patient decided to receive follow-up without chemotherapy. A previous TCS performed in 1991 indicated villous atrophy in the terminal ileum (Figure 1(E)) and raised intraepithelial lymphocytes were seen in the biopsy specimens (Figure 1(F)). CeD was suspected based on the presence of villous atrophy noted more than 20 years ago, the presence of HLA-DQ2, a high titer (25 U/mL, normal range <4 U/mL) of anti-tissue transglutaminase (tTG) antibody (IgA), and episodes of worsening diarrhea at the time of staying out overnight during hospitalization. In June 2013, the patient was shifted to a gluten-free diet. Subsequently, the bowel movement frequency reduced to 2–3 times per day, and the nutritional status of the patient gradually improved (serum albumin level was 2.5 g/dL before treatment and increased to 2.7 g/dL after treatment), but not enough to live a normal daily life. In August 2013, the patient was discharged after implantation of a central venous port, and he continued receiving outpatient treatment with SASP and a high-calorie infusion at home.

In September 2014, the patient experienced acute right lower abdominal pain and visited our hospital. In addition to peritoneal signs, contrast computed tomography showed thickening of the wall of the ascending colon associated with free air. On the same day, right hemicolectomy and partial resection of the ileum were performed after a perforation was identified in the ileum (at approximately 40 cm proximal to the ileocecal valve) (Figure 4(A,B)). Histopathological examination of the surgical specimens showed atypical monomorphic tumor cells along with a minimal invasion into the ductal epithelium. The tumor cells were negative for CD56 (Figure 4(C)). On the basis of these results, we diagnosed the case as type I EATL. The patient was admitted to the oncology department of our hospital on October 2014 and was administered the first course of 80% dose CHOP therapy (CPA, 1000 mg; ADR, 65 mg; VCR, 1.8 mg; and PSL, 100 mg). He completed a total of four courses of CHOP therapy and was discharged on January 2015. Subsequently, a total of 8 courses of outpatient CHOP therapy were completed, and the patient received post-treatment maintenance monotherapy with PSL. TCS performed in May 2015 identified villous regrowth in the distal ileum (Figure 1(C,D)). EGD with magnifying NBI also showed significant regrowth of the villous architecture in the duodenum (Figure 3(C,D,G,H)). CE found villous regrowth in the entire small intestine despite residual scalloping (Figure 2(B)). The patient had maintained remission for 5 years before he died due to recurrence in June 2018.
3. Discussion

The basic requirements for a definitive diagnosis of CeD are (1) clinical symptoms, including chronic diarrhea, abdominal pain, abdominal discomfort, and weight loss; (2) serological test, including anti-endomysial (EMA) IgA antibody and anti-tTG IgA antibody; (3) histological findings of the small intestinal mucosa; and (4) improvement in the symptoms and signs in the patient after shifting to a gluten-restricted diet. The gold standard for definitive diagnosis is the specific histological findings of the mucosa of the small intestine, particularly the

Figure 3. (A–D) Esophag gastroduodenoscopic (EGD) findings of the duodenal bulb. (A, B) EGD performed in 2013 revealed diffuse loss of villi and nodule-aggregated formation. Magnifying narrow-band imaging (NBI) showed loss of villous architecture with a pit-like structure similar to that of gastric metaplasia. (C, D) EGD with magnifying NBI performed in 2015 demonstrated significant regrowth of the villous architecture. (E–H) EGD findings of the descending portion of the duodenum. (E, F) EGD performed in 2013 revealed diffuse loss of villi and multiple notch-like deformations in a circular manner. (G, H) EGD performed in 2015 showed significant regrowth of the villous architecture.
duodenum. Histological assessment should include lymphocytic infiltration of the mucosal epithelium, mucosal atrophy, villous loss, or increased apoptosis in the epithelial cells. The results are used in the Marsh classification of CeD from types I to IV [11]. Furthermore, subjective recognition of raised intraepithelial lymphocytes in the terminal ileum biopsy could alert the clinician for the possibility of CeD [12].

The complications of CeD are malignant tumors including type I EATL which is a tumor that originates from the T-lymphocytes in the ductal epithelium and usually develops as a mass comprising polymorphic large-size tumor cells. Type I EATL often has an inflammatory background in association with CeD, with villous atrophy or ductal hyperplasia in the small intestine. Generally, most cases of EATL appear to have a poor prognosis because of malabsorption, high recurrence rate, and intestinal perforation. Type I EATL appears to be frequently found in Northern Europe, a common area of CeD, while type II EATL is more commonly observed in Asia [13]. This, to our knowledge, is the first case of a Japanese HLA-DQ2 carrier with type I EATL following CeD.

The efficacy of CE and NBI has been proven by endoscopic evaluation of numerous diseases, including CeD [14,15]. This case indicated the usefulness of CE and magnifying NBI of the duodenum in the management of EATL pre- and post-treatment. In pre-treated EATL, CE shows total villous atrophy, multiple erosions, and ulcers of the small intestine, whereas magnifying NBI of the duodenum reveals loss of villous architecture with a pit-like structure similar to that in gastric metaplasia. Moreover, significant villous regrowth after treatment suggests therapeutic effectiveness. The biopsy obtained from the terminal ileum 20 years ago was useful for the definitive diagnosis of CeD.

In conclusion, the possibility of a type I EATL following CeD in an HLA-DQ2 carrier should be recognized, although CeD is rare in Japan. CE and

Figure 4. Histopathological examination of the surgical specimens. (A) Macroscopic findings and (B) low-magnification view of the perforated site in the ileum (approximately 40 cm proximal to the ileocecal valve). (C) Low-magnification view and phenotypic characteristics of enteropathy-associated T-cell lymphoma (EATL).
magnifying NBI of the duodenum, including biopsy, are very important for the diagnosis and therapeutic evaluation of EATL.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**References**

[1] Kagnoff MF. Overview and pathogenesis of celiac disease. Gastroenterology. 2005;128(4 Suppl 1): S10–S18.

[2] Catassi C, Bearzi I, Holmes GK. Association of celiac disease and intestinal lymphomas and other cancers. Gastroenterology. 2005;128(4 Suppl 1): S79–S86.

[3] Green PH, Jabri B. Coeliac disease. Lancet. 2003; 362(9381):383–391.

[4] Nilsen EM, Jahnsen FL, Lundin KE, et al. Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease. Gastroenterology. 1998;115(3): 551–563.

[5] Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med. 2002;346(3):180–188.

[6] Fukunaga M, Ishimura N, Fukuyama C, et al. Celiac disease in non-clinical populations of Japan. J Gastroenterol. 2018;53(2):208–214.

[7] De Luca L, Ricciardiello L, Rocchi MBL, et al. Narrow band imaging with magnification endoscopy for Celiac disease: results from a prospective, single-center study. Diagn Ther Endosc. 2013; 2013;S80526.

[8] Tabibian JH, Perrault JF, Murray JA, et al. Narrow band imaging evaluation of duodenal villi in patients with and without celiac disease: a prospective study. World J Gastrointest Endosc. 2019; 11(2):145–154.

[9] Akin E, Ersoy O. Capsule endoscopy in celiac disease. Gastroenterol Res Pract. 2012;2012:676073.

[10] Zammit SC, Sanders DS, Cross SS, et al. Capsule endoscopy in the management of refractory coeliac disease. J Gastrointestin Liver Dis. 2019;28:15–22.

[11] Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology. 1992;102(1):330–354.

[12] Hopper AD, Hurlstone DP, Leeds JS, et al. The occurrence of terminal ileal histological abnormalities in patients with coeliac disease. Dig Liver Dis. 2006;38(11):815–819.

[13] Takeshita M, Nakamura S, Kikuma K, et al. Pathological and immunohistological findings and genetic abberations of intestinal enteropathy-associated T cell lymphoma in Japan. Histopathology. 2011;58(3):395–407.

[14] Banerjee R, Reddy DN. High-resolution narrow-band imaging can identify patchy atrophy in celiac disease: targeted biopsy can increase diagnostic yield. Gastrointest Endosc. 2009;69(4):984–985.

[15] Kurien M, Evans KE, Aziz I, et al. Capsule endoscopy in adult celiac disease: a potential role in equivocal cases of celiac disease? Gastrointest Endosc. 2013;77(2):227–232.