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【 CASE REPORT 】

Epstein-Barr Virus-positive Intestinal Diffuse Large B-cell Lymphoma in a Japanese Patient with Celiac Disease: First Reported Case and a Literature Review

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Abstract:

A 60-year-old Japanese woman was diagnosed with celiac disease (CeD) and treated with a gluten-free diet. For five years, she had a good clinical course. However, she complained of inappetence and nausea. Colonoscopy revealed ulcerative tumors in the terminal ileum. A histological examination of biopsy specimens from the ulcerative tumor showed diffuse infiltration of large atypical lymphocytes. Immunohistologically, the atypical lymphoid cells were positive for cluster of differentiation (CD)10 and CD20. Many Epstein-Barr virus-encoded small RNA (EBER)-positive atypical lymphocytes were detected by *in situ* hybridization. This represents the first reported case of Epstein-Barr virus-positive intestinal diffuse large B-cell lymphoma complicated with CeD.

Key words: celiac disease, diffuse large B-cell lymphoma, Epstein-Barr virus

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Introduction

Celiac disease (CeD) is an autoimmune disorder that occurs in genetically susceptible individuals because of an immune-mediated inflammatory reaction to dietary gluten. CeD is one of the most frequent genetic diseases in Europeans and North Americans (1). Among Japanese populations, CeD is believed to be quite rare (2), but there is a strong association between CeD and lymphoma, particularly the rare enteropathy-associated T-cell lymphoma (EATL), which accounts for approximately 30% of CeD-lymphoma cases. Some studies have suggested that other types of lymphomas, including unspecified peripheral T-cell lymphoma, diffuse large B-cell lymphoma (DLBCL) and mucosa-associated lymphoma tissue (MALT) lymphoma, may be complicated with CeD (3-5). However, case reports of DLBCL complicated with CeD are very few (2, 6-9), and Epstein-Barr virus-positive (EBV+) DLBCL has never been reported. Recently, a case of EBV+ cluster of differentiation (CD)20+ mixed lymphoproliferative process with T-cell predominance complicated with CeD was reported (10).

We herein report the first case of EBV+ intestinal DLBCL complicated with CeD.

Case Report

A 60-year-old Japanese woman was admitted to our hospital with worsening diarrhea, inappetence and weight loss. Her body weight had decreased by 20 kg in 1 year (body mass index, 17.58). There was no family history of CeD or other autoimmune disease.

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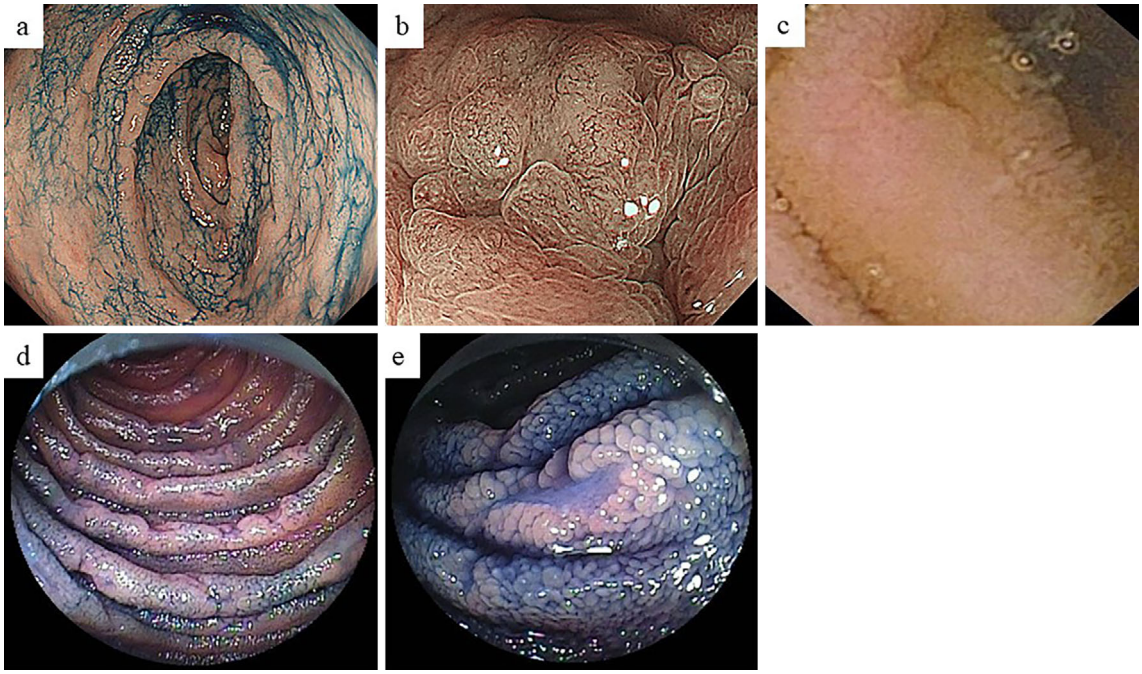

Figure 1. Endoscopic findings of the duodenum and jejunum in the patient. a: Indigo carmine spray enhancement of the duodenal second portion showing the mosaic-patterned mucosa and decreased folds. b: Magnifying endoscopic view with narrow-band imaging of the duodenal second portion showing flat, featureless mucosa and broad villi with villous atrophy. c: Capsule endoscopy showing edematous mucosa with erosion in the jejunum. d, e: Double-balloon endoscopy (indigo carmine spray enhancement) showing edematous mucosa with erosion in the jejunum.

At the time of admission, her laboratory data were as follows: total protein, 5.9 g/dL; serum albumin, 2.2 g/dL; erythrocyte sedimentation rate (60 minutes), 47 mm (normal range, 3-15 mm); white blood count, 16,700/μL; hemoglobin 10.3 g/dL (normal range, 11.3-15.2 g/dL), hematocrit, 32.4% (normal range, 35.1-44.4%); anti-tissue transglutaminase IgA antibodies (TTG-IgA) 9 U/mL (<4); anti-gliadin IgA antibodies (AGA-IgA) 74 units (<20); EBV-IgG 320 dil (<10); EBV-IgM <10 dil and EBV nuclear antigen 40 dil (<10).

Esophagogastroduodenoscopy (EGD) revealed mosaic-patterned mucosa and decreased folds in the second portion of the duodenum (Fig. 1a). Magnifying endoscopy with narrow-band imaging (ME-NBI) revealed flat, featureless mucosa and broad villi (Fig. 1b). Capsule endoscopy and trans-oral double-balloon endoscopy demonstrated edematous mucosa with erosion in the jejunum (Fig. 1c-e). Colonoscopy revealed aphthoid lesions in the colon.

A histological examination of a targeted biopsy specimen from the duodenal flat, featureless mucosa and broad villi showed severe inflammatory cell infiltration and atrophy of villi with modified Marsh classification type 3b (Fig. 2). Therefore, she was diagnosed with CeD and treated with a gluten-free diet.

No susceptible human leukocyte antigen (HLA) type was detected; the HLA type was found to be HLA DQ9. Her clinical symptoms improved gradually after starting the gluten-free diet. EGD and ME-NBI performed 13 months later revealed improvement in the mosaic-patterned mucosa and atrophy of villi (Fig. 3a, b). A histological examination of a biopsy specimen from the duodenal mucosa showed improvement in the severe inflammatory cell infiltration (Fig. 3c). For five years, she had a good clinical course.

However, she was admitted to our hospital with inappetence and nausea. Colonoscopy revealed ulcerative tumors in the terminal ileum (Fig. 4a). A histological examination of a biopsy specimen from the ulcerative tumor showed diffuse infiltrate of large, atypical lymphocytes with round nuclei (Fig. 4b). Immunohistologically, the atypical lymphoid cells were positive for CD10, CD20 (Fig. 4c), BCL6, CMYC (50%) and MIB1 (80%) but negative for CD3, CD4, CD8, CD56, CD30 and MUM1. Many EBV-encoded small RNA (EBER)-positive atypical lymphocytes were detected by *in situ* hybridization (Fig. 4d). ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET) showed the uptake of FDG in the terminal ileum (Fig. 5a). Bone marrow specimens showed no evidence of bone marrow invasion. She was diagnosed with EBV+ DLBCL complicated with CeD. Her clinical stage was considered to be stage I.

She was treated with four courses of combined chemotherapy including cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab (R-CHOP). After chemotherapy, FDG-PET did not show any active disease elsewhere, nor any uptake of FDG in the terminal ileum (Fig. 5b). She continued to be treated with the gluten-free diet and remains alive.

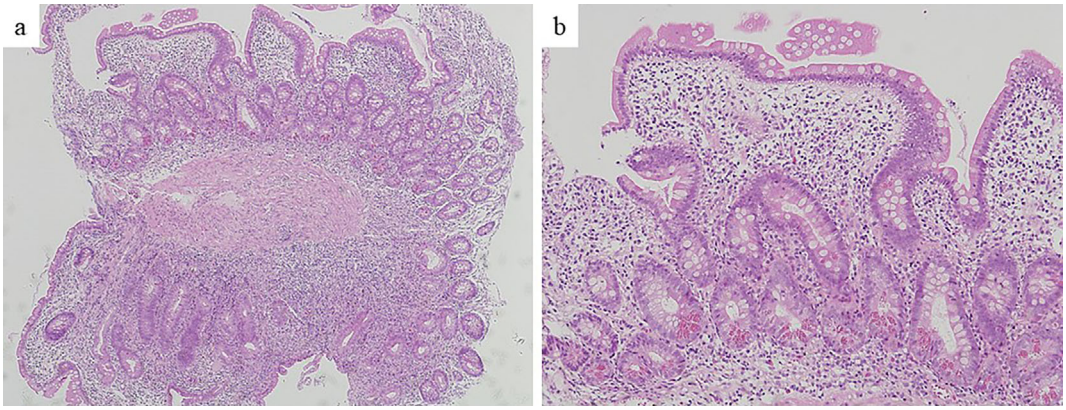

Figure 2. **Histological findings of the duodenum in the patient. Atrophy of villi and severe inflammatory cell infiltration are seen in the duodenum. a: Hematoxylin and Eosin (H&E) staining, ×10 magnification, b: H&E staining, ×20 magnification.**

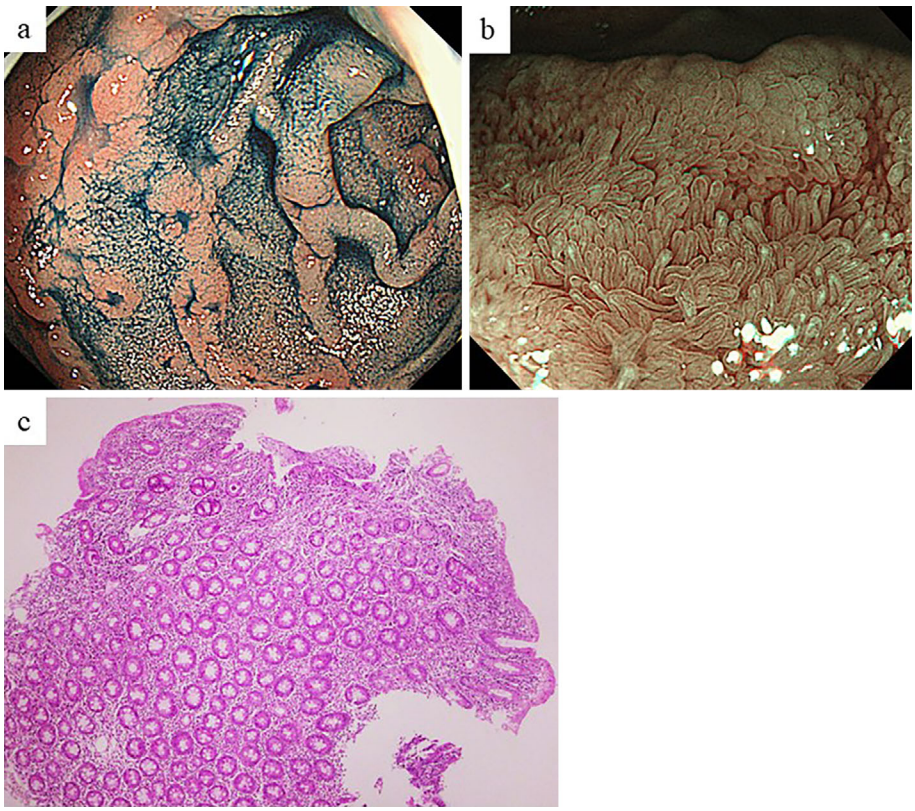

Figure 3. **Endoscopic and histological findings of the duodenum in the patient after a gluten-free diet. a: Indigo carmine spray enhancement showing improvement in the mosaic-patterned mucosa. b: Magnifying endoscopic view with narrow-band imaging of the duodenal second portion showing improvement of the atrophy of the villi. c: Histological findings of the duodenum showing improved severe inflammatory cell infiltration. Hematoxylin and Eosin staining, ×10 magnification.**

Discussion

CeD is an immune-mediated chronic gastrointestinal disease triggered by gluten-containing grains (1). The gold standard for the definitive diagnosis of CeD is specific histological findings in the mucosa of the small intestine, particularly the duodenum. Patchy villous atrophy in the duodenum can be identified easily with ME-NBI as areas of stunted or flattened villi. The usefulness of ME and ME-NBI with targeted biopsies for the diagnosis of CeD has been previously reported (11). In the present case, ME-NBI with targeted biopsies in the duodenum was performed, and histological findings characteristic of CeD were confirmed.

CeD has been associated with many different subtypes of lymphoma (12). Over an average 9.4 years of follow-up in

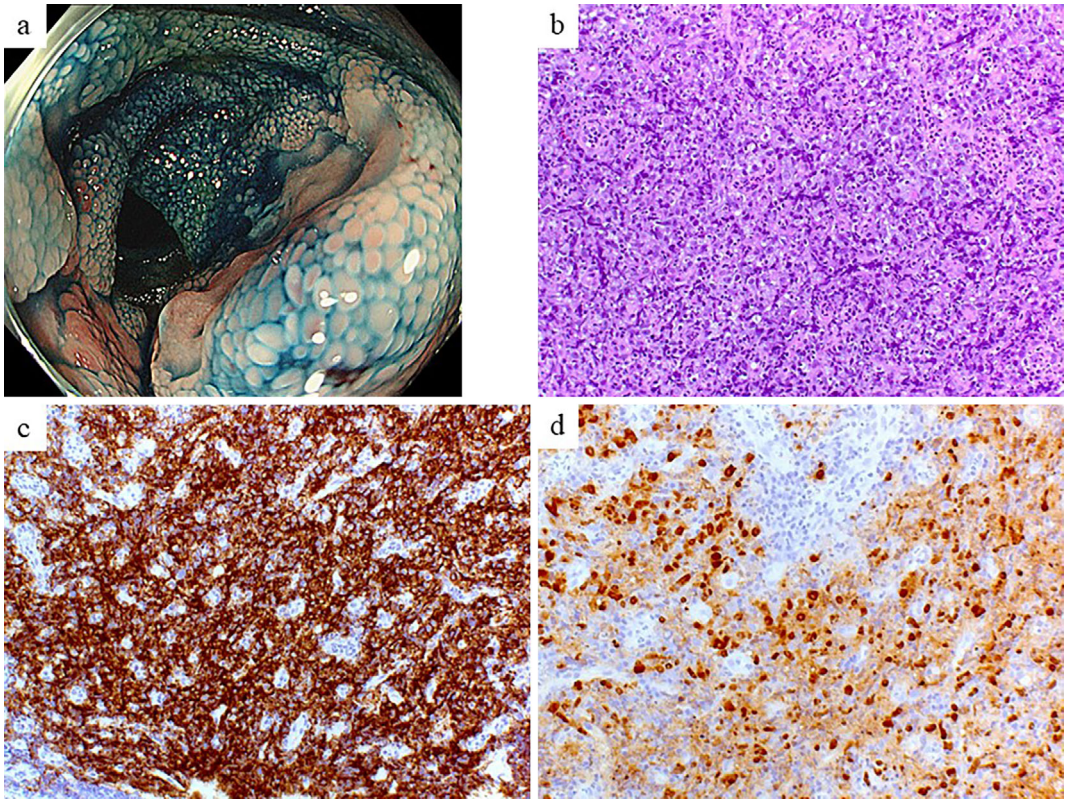

Figure 4. **Endoscopic and histological findings of the terminal ileum. a: Indigo carmine spray enhancement showing an ulcerative tumor in the terminal ileum. b: Histological findings showing diffuse infiltration of large, atypical lymphocytes with round nuclei. Hematoxylin and Eosin staining, ×40 magnification. The tumor cells were positive for (c) CD20 (×40 magnification) and (d) Epstein-Barr virus-encoded small RNA (×40 magnification).**

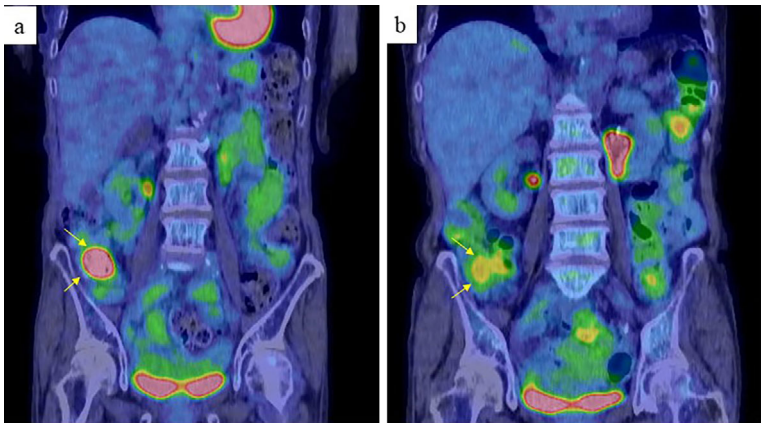

Figure 5. **^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET). a: FDG-PET showing the uptake of FDG in the terminal ileum (yellow arrows). b: FDG-PET showing no uptake after chemotherapy (yellow arrows).**

878,161 patients diagnosed with 33 autoimmune diseases (Ads) including CeD, the overall standardized incidence ratio (SIR) for non-Hodgkin lymphoma (NHL) after Ads was 1.6 and for NHL after CeD, it was 4.8 (13). Strict adherence to a gluten-free diet may decrease the risk of lymphomagenesis and development of other cancers complicated with untreated CeD (14, 15). However, the mechanisms underlying extraintestinal lymphomagenesis in CeD are unknown (16). In a retrospective cohort study of 1,285 patients with CeD, 40 patients with lymphoproliferative disorders (LPD), including 33 with NHL, were identified. Of the 33 patients with NHL, 12 suffered from EATL, 5 had non-EATL T-cell lymphoma, 16 had B-cell NHL (6 DLBCL, 5 MALT, 3 mantle cell lymphoma, and 1 each with follicular lymphoma and post-transplant LPD) (4). The six case reports of intestinal DLBCL complicated with CeD, including

Table. Summary of Six Cases of Intestinal DLBCL Complicated with CeD.

Ref	Age	Gender	Duration of CeD (months)	Albumin (g/dL)	Intestinal site	Endoscopic findings	EBER	Stage	Treatment	Prognosis
(2)	65	M	60	1.7	Duodenum	Edema, erosion	NA	IV	R-CHOP	CR
(6)	62	F	10	-	Intestine	Ulcer	NA	-	R-CHOP	CR
(7)	36	M	204	-	Jejunum	-	NA	I	R-CHOP	CR
(8)	56	M	24	normal	Ileum	Ulcer	NA	II	R-CHOP	CR
(9)	54	M	12	1.7	Jejunum	Thickened wall, polyp	NA	I	Surgery	CR
Our patient (2020)	60	F	60	2.2	Ileum	Ulcer	+	I	R-CHOP	CR

DLBCL: diffuse large B-cell lymphoma, CeD: celiac disease, Ref: references, EBER: Epstein-Barr virus-encoded small RNA, NA: not available, R-CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab, CR: complete remission

our case, are summarized in Table (2, 6-9). These included 4 men and 2 women (mean age, 55.5 years old). The average duration of CeD was 61.7 months. The endoscopic type mainly consisted of ulcerative tumor, the treatment was mainly chemotherapy (R-CHOP), and all cases had good prognoses. CeD patients with B-cell lymphomas had a better prognosis than those with T-cell lymphoma (16). Our case was a rare case of intestinal DLBCL in a Japanese patient with CeD, and there was a good prognosis after chemotherapy.

The 2017 World Health Organization classification of malignant lymphoma encompassed these diverse diseases and emphasized that EBV+ DLBCL, not otherwise specified (NOS), often affects both young and elderly immunocompetent patients (17). EBV+ intestinal DLBCL occurred in patients with compromised immune systems, those treated for lymphoma-associated immunodeficiency, and those with iatrogenic immunodeficiency (18). The mechanisms involved in autoimmunity and lymphomagenesis may be secondary inflammation due to autoimmune stimulation, cytokine and chemokine release, and certain infections (e.g., human immunodeficiency virus, hepatitis C, and EBV) and genetic factors predisposing patients to both Ads and lymphomas may also play a substantial role (19). Eight of the 36 EBV+ gastrointestinal DLBCL patients were receiving therapeutic immune suppression for rheumatoid arthritis, Crohn's disease, and malignant lymphoma (20).

To our knowledge, there have been no previous case reports of EBV+ intestinal DLBCL complicated with CeD. Recently, the relationship between CeD-induced immunosuppression, including malnutrition, and EBV-associated LPD was reported (10). Therefore, we examined EBER using *in situ* hybridization to confirm the relationship between Ced and EBV+ intestinal DLBCL in the present case. Compared with EBV-negative (EBV-) intestinal DLBCL, EBV+ cases had a higher rate of CD30 positivity, performance status 2-4, multiple intestinal lesions, and an international prognostic index of high-intermediate/high. Among the intestinal DLBCL patients receiving rituximab-containing chemotherapy, EBV+ intestinal DLBCL patients had a significantly worse overall survival than EBV- intestinal DLBCL patients (18). Therefore, it is necessary to conduct careful follow-up while being alert for the possibility of recurrence of DLBCL in the present case.

In summary, we reported the first case of EBV+ intestinal DLBCL in a Japanese patient with CeD. This case illustrates the need for careful clinical and pathological evaluations of patients with CeD for the possibility of underlying lymphoma.

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

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