Peripheral T-cell Lymphoma Following Diffuse Large B-cell Lymphoma Associated with Celiac Disease

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Abstract

Celiac disease is a risk factor for lymphoma. Previously, we reported a case of diffuse large B-cell lymphoma (DLBCL) associated with celiac disease in a Japanese patient. Without any signs of DLBCL recurrence, he suddenly developed gastrointestinal symptoms and subcutaneous masses after resuming a gluten-containing diet. Peripheral T-cell lymphoma (PTCL) was diagnosed. Although a complete response was seen for 8 months, he was later admitted again with pleural and pericardial effusion due to PTCL. Expression of cytotoxic molecules, CCR4 and CXCR4 were all confirmed in PTCL cells, and the patient died soon afterwards. Clinically speaking, even though no gastrointestinal symptoms were seen, a gluten-free diet should have been strongly recommended for this patient.

Key words: celiac disease, celiac disease-associated lymphoma, peripheral T-cell lymphoma

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Introduction

Celiac disease is an autoimmune malabsorptive disorder triggered by the ingestion of gluten-containing grains (1, 2). Studies in the United States and Europe have shown the prevalence of this disease to be 1 percent among the general population (3). Among the Japanese, however, celiac disease is believed to be quite rare, and studies concerning the frequency of this disease are scarce (4).

Celiac disease has been shown to be a risk factor for several malignant diseases, including non-Hodgkin’s lymphoma (NHL) (5). Once patients are diagnosed with celiac disease, serious complications are prevented by placing patients on a gluten-free diet (GFD). Previously, we reported a Japanese case of diffuse large B-cell lymphoma (DLBCL) associated with celiac disease (4). There had been no signs of DLBCL recurrence for 31 months after combined chemotherapy including rituximab, but soon after resuming a gluten-containing diet, he developed gastrointestinal symptoms and subcutaneous masses. Peripheral T-cell lymphoma, unspecified (PTCL-U) was diagnosed from a skin biopsy specimen. To our knowledge, there have been no such reports to date of patients who developed PTCL-U in a state of a complete response (CR) of DLBCL associated with celiac disease.

Case Report

A 68-year-old Japanese man was admitted to our hospital with worsening diarrhea, systemic edema, and subcutaneous masses. Three years before admission, he had been treated for DLBCL associated with celiac disease, which was confirmed by a duodenal biopsy. After 6 courses of cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisolone, and rituximab (R-CHOP), a CR was seen for 31 months, as described in our previous report (4). In spite of our strong recommendation of a GFD, the patient’s consumption of gluten-containing foods and drink induced watery diarrhea with weight loss of 10 kilograms over 4 months. However, there were no signs of DLBCL recurrence. Four months later, he complained of systemic edema and an occipital subcutaneous mass. Fever or night sweat was not observed.

Upon physical examination, the patient’s height was 148 centimeters and his weight was 34 kilograms. The liver and spleen were not enlarged. Solid subcutaneous masses with
erythema were palpable on the occiput, right lower jaw, and left hip, but no lymphadenopathy was found. There was peripheral edema without evidence of deep venous thrombosis. The patient’s laboratory data were as follows; total protein, 6.5 g/dl; serum albumin, 2.7 g/dl; lactate dehydrogenase, 179 U/l (normal range, 114-220 U/l); immunoglobulin A (IgA), 1,169 mg/dl; white blood cell count, 3,280/μl; hematocrit, 38.7%; mean corpuscular volume, 86 fL; and serum anti-tissue transglutaminase IgA antibodies (TTG-IgA), 38.2 U/ml (<10). Serum anti-HTLV-1 antibody was undetected. Another GFD resulted in improvement of the diarrhea and edema. Biopsy samples of the occipital subcutaneous mass showed the proliferation of atypical large lymphocytes with pleomorphic, irregular nuclei with prominent nucleoli (Fig. 1A). These lymphocytes were positive for CD3 (Fig. 1B), CD4, and TCRbeta, and negative for CD20 and CD30. EBV was undetected in EBER in situ hybridization analysis. Peripheral T-cell lymphoma, unspecified (PTCL-U) was diagnosed, and lymphoma cells were found in the peripheral blood (13% of white blood cells). His clinical stage was considered as IV A. After 4 courses of CHOP therapy, a CR persisted for 8 months. However, he was admitted again because of shortness of breath due to pleural and pericardial effusion.

Hypoxemia and hypotension were improved with thoracentesis and pericardiocentesis. Atypical lymphoid cells seen in effusions (Fig. 2A) were positive for CD3 and CD4, and revealed rearrangement of the T-cell receptor beta gene in southern blot analysis. G-banding analysis of the cells showed complex abnormalities; 47, -Y, add (X) (p22), +add (3) (q12), add (3) (q27) ×2, del (6) (q?), add (8) (q24), add (9) (p13), -13, der (13) t (1 : 13) (q11 : p11), add15 (q15), add (17) (p11), -18, +21, add (21) (p11) ×2, add (22) (q11), +mar1, +mar2 [18/20]. A recurrence of PTCL-U was diagnosed, and he died of lymphoma 2 months later. At autopsy, lymphoma cells were found infiltrating the epicardium, me- centeric and para-aortic lymph nodes, but no lesion in the gastrointestinal tract was noted.

Positivity for cytotoxic molecules and chemokine receptors are known prognostic factors for PTCL-U. As such, we analyzed the expression of TIA-1 (Coulter Immunology, Haleah, FL), granzyme B (Monosan, Uden, the Netherlands), perforin (Novocastra, Newcastle, UK), and CCR4 (BD Biosciences, Mountain View, CA) in occipital subcutaneous mass sections by immunohistochemistry, and found positive staining for all these molecules in lymphoma cells (Fig. 1C, D).

In addition, the phenotype of lymphocytes was determined using anti-CD4-fluorescein isothiocyanate (FITC) (BD Biosciences) and expression levels of chemokine receptors on CD4+ cells were measured using anti-CXCR1-phycoerythrin (PE), anti-CXCR2-PE, anti-CXCR3-PE, anti-
Figure 2. The proliferating PTCL cells in the pleural effusion. (A) The cells are atypical large lymphocytes with pleomorphic, irregular nuclei and basophilic cytoplasm (Wright Giemsa stain, ×400). (B) Surface expression of a panel of chemokine receptors were measured with flow cytometry. CCR4 and CXCR4 were detected on the PTCL cells, but no other chemokine receptors examined were found.

Celiacdisease may beariskfactor for severalmalignantdiseases, including NHL (5, 15). Among the neoplasm associated with celiac disease, ETCL is well known and has been classified as an independent category by the World Health Organization (16). Recent studies on celiac-disease-associated lymphomas have shown that T-cell lymphomas with celiac disease include ETCL, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, subcutaneous panniculitis-like T cell lymphoma, mycosis fungoides, and PTCL-U (17, 18). In a multicenter, case-control study in Italy, no PTCL-U cases were diagnosed among 6 patients with celiac disease out of 653 patients with NHL (15), but 10 out of 56 (18%) cases of malignant lymphoma were PTCL-U in a Swedish population-based cohort of patients with celiac disease (19). Although PTCL-U was associated with celiac disease in this patient, his intestinal mucosa were intact at autopsy and suggested otherwise. However, a Swedish cohort study revealed a significantly increased risk of PTCL-U in lymphomas of non-intestinal origin in addition to intestinal lymphomas (19). These findings indicate that celiac disease might indeed be a risk factor for PTCL-U without intestinal lesions, and that measurement of the serum TTG-IgA levels is recommended for patients with T-cell lymphomas.

Chemokine receptor expression pattern is reported to be a prognostic factor in T (20) and NK-cell (21) malignancies. The prognosis of CCR4-positive PTCL-U is significantly poorer compared with CCR4-negative cases (22), probably since CCR4 plays a crucial role in the migration of lymphocytes to skin (23) and pleural space (24). Accordingly, the lymphoma cells in the occipital subcutaneous mass and the pleural effusion of this patient were positive for CCR4 in immunohistochemistry and flow cytometry, possibly accounting for his rapid deterioration. Positivity for cytotoxic molecules, such as TIA-1, granzyme B, and perforin, all of which were detected in the lymphoma cells of this patient, is also associated with prognosis of lymphoid malignancies (25). However, the exact relationship between cytotoxic
molecules and PTCL-U with celiac disease is not fully understood.

In conclusion, this patient’s clinical history leads to the hypothesis that a gluten-containing diet induced PTCL-U during CR stage in DLBCL. In a Finnish study, no increased rate of NHL or death was seen in patients who adhered to a GFD (26). As such, even if no gastrointestinal symptoms were seen, a GFD should have been strongly recommended in this patient. Further investigation is required to clarify whether a GFD does in fact prevent lymphomatogenesis in the Japanese population.

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References


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