Enteropathy-type T-cell Lymphoma Showing Repeated Small Bowel Rupture and Refractoriness to Chemotherapy: a Case Report

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The majority of gastrointestinal lymphomas arise in the stomach, whereas lymphomas occurring in the intestine are relatively rare and a limited fraction of them show the T-cell phenotype with clinical manifestations similar to de novo celiac disease. Enteropathy-type T-cell lymphoma is extremely rare in Japan, presumably owing to the very low incidence of celiac disease among the Japanese population. Here, we report a 66-year-old Japanese male who was diagnosed as having enteropathy-type T-cell lymphoma preceded by diarrhea and intermittent bloody stool for over 1 year. He was admitted to our hospital as an emergency case because of panperitonitis due to intestinal perforation. After immediate partial small-bowel resection, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy was started. However, the disease was highly refractory and was exacerbated with leukemic transformation. Subsequent salvage chemotherapy could not be completed because of the formation of spontaneous jejuno-abdominal fistula, followed by fatal septic shock. Particular attention should be paid to the peculiar clinical manifestations of enteropathy-type T-cell lymphoma such as malnutrition, frequent intestinal perforation and refractoriness to chemotherapy.

Key words: enteropathy-type T-cell lymphoma – intestinal perforation – jejuno-abdominal fistula – panperitonitis

INTRODUCTION

The majority of gastrointestinal lymphomas arise in the stomach and many of them are categorized as diffuse large cell lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma of B-cell origin (1,2). On the other hand, lymphomas occurring in the intestine are relatively rare and a limited fraction of them show the T-cell phenotype with clinical manifestations similar to de novo celiac disease. This uncommon subtype of peripheral T-cell lymphoma is now one of the recognized clinicopathological entities of primary gastrointestinal lymphoma and classified as a specific subtype with the term ‘intestinal T-cell lymphoma’ by the Revised European–American Lymphoma Classification (3) and ‘enteropathy-type T-cell lymphoma’ by the World Health Organization Classification (4,5).

Enteropathy-type T-cell lymphoma does not always occur with ‘enteropathy’, and shows a variety of clinical courses (6). Several previous studies in Western countries described relations between the features of a celiac disease unresponsive to gluten withdrawal from the diet, chronic infiltration of T-lymphocytes in the intestinal epithelium and clonal evolution of T-cell lymphoma (7,8). The results of immunophenotypic analyses on neoplastic cells and association with Epstein–Barr virus (EBV) infection have been reported, but the normal counterpart of this malignant cell has not been elucidated (9–11). This disease entity appears to have heterogeneity and its clinical behavior remains largely unclear.

This paper documents the remarkable clinical course of a Japanese patient with enteropathy-type T-cell lymphoma preceded by celiac disease-like intestinal presentations. The disease was highly refractory to chemotherapy regimens and the patient suffered from repeated small-bowel rupture and panperitonitis.

CASE REPORT

A 66-year-old Japanese male suddenly complained of severe abdominal pain and was admitted to our hospital as an emergency case in July 2001. He had developed intermittent watery diarrhea and bloody stool in October 1999. Malnutrition with hypoalbuminemia, body weight loss and peripheral edema...
were progressive and he had undergone endoscopic examinations at several hospitals. However, repeated biopsies of the gastrointestinal tract showed only inflammatory ulcers without any diagnostic malignant morphological features and a definitive diagnosis was not obtained.

At his admission, since chest radiography revealed the existence of free air under the diaphragm (Fig. 1), he was judged to be suffering from panperitonitis due to perforation of the intestine. Computed tomography imaging showed a marked wall thickness of the small intestine and tumor formation at the terminal ileum with mesenteric lymphadenopathy. A partial small-bowel resection was performed immediately. Specimens from the resected tumor showed macroscopic multiple patchy segmented lesions in the small intestine (Fig. 2) and diffuse infiltration of monomorphic medium-sized lymphoma cells throughout the affected intestinal wall (Fig. 3A and B). The lymphoma cells also showed intraepithelial spread at the mucosal periphery of the masses.

The resected tumor was studied using paraffin-section immunohistochemistry with the avidin–biotin complex method and primary antibodies to the antigens CD3, CD4, CD5, CD8, CD10, CD20 and CD56. In addition, it was studied for granzyme-B and T-cell intracellular antigen-1 (TIA-1). Immunophenotypic analysis was also performed with flow cytometry (EPICS XL-MCL, Beckman Coulter, Miami, FL), using a panel of monoclonal antibodies. The lymphoma cells were CD2+CD3+CD4+CD5+CD8+CD10+CD19+CD20+CD30+CD33+CD34+CD56+ and were positive for cytoplasmic staining for cytotoxic granule-associated molecules including TIA-1 and granzyme B (GrB) (Fig. 3C and D). Surface CD3 and cytoplasmic CD3 were both positive. Based on the histopathological and immunophenotypic findings, a diagnosis of enteropathy-type T-cell lymphoma was made. EBV-encoded small RNA type-1 (EBER-1) was not detected with in situ hybridization. Serum antibody to human T-cell leukemia virus type I or serum antibody to human immunodeficiency virus was negative. His bone marrow was not infiltrated with lymphoma cells at diagnosis. Serum LDH was elevated (711 IU/l; normal range, 234–484 IU/l) and performance status and nutritional health were poor.

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy was started. Watery diarrhea and tumor fever were transiently improved; however, these symptoms deteriorated again before the next cycle of CHOP. Bone marrow suppression and febrile neutropenia were so severe that the dosage of the second cycle of CHOP had to be reduced. Nevertheless, he developed severe neutropenia followed by sepsis due to *Escherichia coli*. The lymphoma was highly refractory to the CHOP chemotherapy and leukemic transformation was recognized. The chemotherapy regimen was switched to EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) (12). This second-line chemotherapy could not be completed because of the formation of spontaneous jejuno-abdominal fistula on day 4. The perforation arose along the suture of the small bowel resection and the fistula rapidly became worse in size and number within a day. The patient died of septic shock associated with the second panperitonitis in September 2001 on day 6 of the EPOCH regimen.

**DISCUSSION**

Intestinal perforation is one of the well-recognized complications of enteropathy-type T-cell lymphoma and can occur...
Enteropathy-type T-cell lymphoma spontaneously without any therapeutic interventions (6,9). However, in previous reports, the precise clinical features concerning gastrointestinal complications were not adequately documented in the 13 cases reported from Japan (9) and repeated small-bowel rupture was not described even in the largest series on 31 cases reported from the UK (6), although a few such cases have been reported (13,14). The rupture usually occurs as an intra-abdominal accident and there has been no report of jejuno-abdominal fistula during chemotherapy so far as we are aware. Our patient suffered from two separate perforations of the small bowel at intervals. The first rupture manifested as peritonitis due to intestinal perforation without any therapeutic intervention at the emergency admission and the second occurred as jejuno-abdominal fistula during salvage chemotherapy. It is likely that the fragility of the affected small intestine is related to the cytotoxic and invasive features of infiltrating T-lymphoma cells.

In enteropathy-type T-cell lymphoma, the infiltrating neoplastic intraepithelial lymphocytes or intramucosal lymphocytes frequently appear cytologically normal and only immunohistochemical or flow cytometric analysis revealed their monoclonality. Chott et al. classified the histological subtypes of enteropathy-type T-cell lymphoma based on morphological findings (11). In the present case, the lymphoma cells showed the immunophenotype CD2+CD3+CD4–CD5+CD8+CD10–CD19–CD20–CD30–CD33–CD34–CD56+ and TIA-1+GrB+, which is compatible with the monomorphic medium-sized cell type according to the classification of Chott et al. EBER-1 was not detected with in situ hybridization in the present case. Several studies suggested that EBV may play an etiological role in the pathogenesis of enteropathy-type T-cell lymphoma, but this is still controversial (9,15,16). The frequency of the association of EBV infection with this T-cell lymphoma may differ depending on the populations studied.

It is noted that enteropathy-type T-cell lymphoma often arises with preceding celiac disease-like symptoms. However, it has been a controversial issue whether enteropathy-type T-cell lymphoma is associated with celiac disease itself. Celiac disease is a gluten-sensitive enteropathy, but a minority of patients with celiac disease-like enteropathy are resistant to

Figure 3. Histopathological findings of the affected small intestine. (A) Intraepithelial infiltration of medium-sized atypical lymphocytes in the mucosa of the resected small intestine (hematoxylin–eosin, original magnification ×400). (B) Diffuse infiltration of lymphoma cells with medium-sized irregular-shaped nuclei (hematoxylin–eosin, original magnification ×400). (C) Lymphoma cells are diffusely positive for CD8 (immunoperoxidase, original magnification ×400). (D) The cytoplasms of most of the lymphoma cells are positive in a dot-like manner for cytotoxic granule-associated molecules, TIA-1 (immunoperoxidase, original magnification ×400).
gluten-free diet, so-called refractory sprue or unclassified sprue. The pathogenesis of celiac disease is now considered the result of a complex interplay of genetic, especially HLA-DQ2 and DQ8 and variable environmental factors (17). In fact, the incidence of celiac disease is approximately one in 300–3000 in Caucasians, but there have been only a few case reports in Japan (18). On the other hand, refractory sprue is apparently a distinct disorder, which comprises at least two different underlying causes. One is autoimmune enteropathy and the other is associated with enteropathy-type T-cell lymphoma (19). It is unclear whether celiac disease could subsequently change to T-cell lymphoma or enteropathy is simply accompanied by neoplastic change (7,8,20). In either case, both celiac disease and enteropathy-type T-cell lymphoma are uncommon among the Japanese population (21–23). Katoh et al. reported the clinicopathological features of 13 Japanese cases of enteropathy-type T-cell lymphoma (9). Only seven of them presented with enteropathy and none had a history of celiac disease. In the present case, preceding diarrhea and intermittent bloody stool had been observed for over 1 year before the diagnosis of enteropathy-type T-cell lymphoma.

There is no standard therapy for enteropathy-type T-cell lymphoma. Many of the reported cases are resistant to various chemotherapy regimens and it was difficult to obtain long-term survival in this disease. Moreover, many patients with this disease have poor nutritional status or general ill-health at diagnosis owing to the long period of diarrhea and malabsorption. This may be related to the excessive toxicity and difficulty of conducting planned chemotherapy. A recent study suggested that a very small fraction of this aggressive T-cell lymphoma can be successfully treated with conventional-dose chemotherapy or high-dose chemotherapy with autologous hematopoietic stem cell rescue (6). If the patient’s general condition permits, high-dose chemotherapy may be one of the therapeutic options for this extremely poor-prognostic disease.

In summary, we have reported a Japanese male patient with enteropathy-type T-cell lymphoma complicated with celiac disease-like intestinal presentations and repeated small-bowel rupture. His lymphoma was highly refractory to chemotherapy regimens. Although enteropathy-type T-cell lymphoma is an extremely rare disease in Japan, particular attention should be paid to its peculiar clinical manifestations.

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References