CD56 Positive Intestinal T-Cell Lymphoma: Treatment with High Dose Chemotherapy and Autologous Peripheral Blood Stem Cell Transplantation

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Abstract

A 63-year-old man presented with a perforation of the small intestine. A diagnosis of intestinal T-cell lymphoma (ITCL) was made from CD (cluster differentiation) 3 positivity and a rearrangement of T-cell receptor genes. The tumor also expressed CD56, which suggests it belongs to a rare subtype derived from activated cytotoxic intraepithelial T lymphocytes. Although the prognosis of ITCL has been considered to be very poor irrespective of CD56 positivity, complete remission was achieved in this case by high dose chemotherapy followed by autologous peripheral blood stem cell transplantation (auto-PBSCT) even after relapse. Auto-PBSCT in the earlier stage of the disease might improve the prognosis.

(Key words: natural killer cell-like, perforation of jejunum, jejunostomy, autologous peripheral blood stem cell transplantation)

Introduction

Intestinal T-cell lymphoma (ITCL) accounts for approximately 5% of all primary gastrointestinal lymphomas and is often associated with a preceding history of enteropathy or celiac disease (1, 2). Presentation as an acute emergency with perforation, obstruction, or hemorrhage is common. Immunophenotypically, ITCL expresses T-cell antigens such as CD (cluster differentiation) 3 and CD7 in conjunction with CD103, an antigen largely restricted to intraepithelial T-lymphocytes (IELs) of the intestine (2). Their immunophenotype suggests that they originate from IELs. A small group of ITCL has been reported to express the natural killer (NK) cell marker CD56 (3). Although they belong to the entity of ITCL, they demonstrate some characteristic histological and clinical features constituting a distinct subtype (3). Here we encountered a case of CD56 positive ITCL which showed the typical clinical symptoms previously reported.

Generally the prognosis of ITCL is very poor regardless of the presence or absence of CD56 antigen. A review by Chott et al indicates that about seventy-three percent of patients with ITCLs died within 6 months, and the overall median survival was 3 months (3). But the poor prognosis seems to arise not from lack of chemosensitivity but rather due to poor performance status and complications such as perforation of the jejunum (4). In fact, successful treatment by high dose chemotherapy has been reported in a few cases (4, 5). The present case initially showed a good response to chemotherapy, and even after relapse, complete remission was achieved with high dose chemotherapy supported with auto-PBSCT, which was sustained for eight months. The role of high dose chemotherapy and auto-PBSCT to ITCL is discussed.

Case Report

A 63-year-old Japanese man was admitted to Miyagi Cancer Center because of an abdominal mass. There was no past history of diarrhea or weight loss to suggest celiac disease. Jejunography (Fig. 1) revealed multiple jejunal ulcers. An abdominal bulky mass (19 cm in diameter) involving the jejunum was found on computed tomographic (CT) examination (Fig. 2). There were no abnormal findings in an upper gastrointestinal endoscopy, barium enema, or total colonoscopy. One week after first presentation he complained of tarry stool and shortness of breath. Serum hemoglobin level rapidly reduced from 9.0 g/dl to 5.3 g/dl in a one-week interval, which required red blood cell transfusions. An emergency operation was performed. Intraoperative findings revealed a thick wall of the jejunum at 5cm distal to Treiz ligament and a jejunal perforation as well as diffuse peritonitis. There was also a large mesenteric lymph node which was adhered to the jejunum, mesentery, supe-
Figure 1. Jejunography revealed multiple jejunal ulcers. Jejunography revealed multiple jejunal ulcers.

Figure 2. Computed tomography revealed an abdominal bulky tumor 19 cm in diameter involving the jejunum.

Internal Medicine Vol. 41, No. 9 (September 2002) 735
Figure 3. Histological findings of the tumor of the jejunum. A: Small sized malignant lymphocytes with round nuclei and clear cytoplasms proliferated in the mucosa of jejunum (HE stain, x400). B: The infiltration of the glandular epithelium by neoplastic lymphocytes formed so-called lymphoepithelial lesions (HE stain, x200). Immunohistochemically, the tumor cells were positive for CD3 (C) (x400) and CD56 (D) (x200).

Discussion

The clinical features of the present case were consistent with typical ITCL (1, 2); initially the disease was restricted to the jejunum and mesenteric lymph nodes forming multiple jejunal ulcers with a perforation, although not preceded by enteropathy. Despite ITCL having the common synonymous terminology of “enteropathy-associated T-cell lymphoma”, many cases do not have a history of enteropathy in Japan (10) and in Western countries (3, 4). In the present case immunohistochemical examination revealed positivity for CD3 and for CD7. Although southern blot analysis of TCRβ chain was not performed because fresh or frozen tissues were not available, PCR examination from paraffin sections revealed the rearrangement of TCRγ chain, which indicated the T-cell clonality. TCRγ gene rearrangement by PCR is useful to determine T-cell lineage when only paraffin sections are available for examination as described previously (3, 6).

Immunohistochemical studies suggested that ITCL is derived from the normal human jejunal IELs (11, 12). IELs include a ~15% fraction of CD56+ cells that could be the origin for CD56+ ITCL (3). Chott et al reported that 21% of ITCL...
were CD56+ (3). Three of eleven Japanese cases of ITCL were reported to be CD56 positive (10). Some overlapping historical and clinical features between CD56+ and CD56− cases indicate that the former and the latter belong to the same clinopathological entity of ITCL. On the other hand CD56+ ITCLs constitute a distinct subtype showing some characteristic features: 1) higher incidence (80%) of CD8 positivity, 2) monomorphic small to medium-sized histology, 3) lack of preceding diagnosis of celiac disease, and 4) higher incidence of intestinal perforation (3). In the present case, both the histological and clinical findings were consistent with that of CD56 positive cases reported by Chott et al except for CD8 positivity. The discrepancy of CD8 positivity does not deny the diagnosis of CD56+ ITCL, as many cases of the ITCL in REAL classification and some cases (3/15) of the CD56+ ITCL by Chott et al are reported to be negative for CD8.

Macon et al reported NK-like T-cell lymphoma, presuming that they might arise from thymic-independent T cells of the hepatic sinusoids and intestinal mucosa, and were distinct from T-LGL leukemia (13). In sixteen cases they mentioned, only one case involved the jejunum and two cases, the duodenum. Seventeen cases of CD56 positive NK-like T-cell lymphoma with primary presentation in the gastrointestinal tract were presented by Chim et al (6). It is not clear whether or not these cases belong to the same category of CD56 positive ITCL mentioned above, as there are many characteristics in common including phenotype (CD3+, CD4−, CD7+, CD8+, CD56+, CD57−), but some differences in the histologic features exist; while the NK-like T-cell lymphoma by Macon and Chim tends to have the large granular lymphocyte morphology, the other tends to have monomorphic small to medium-sized morphology.

Some cases of ITCL are reported to be associated with Epstein-Bar virus (EBV). In 14% of the gastrointestinal T-cell lymphomas from Western Europe and North America, the tumors were found to be EBV positive mainly detected by in situ hybridization for EBV-encoded early nuclear RNAs (EBER) (14). The higher incidence of positivity were found in the cases from Mexico and Asia (14). The role of EBV in NK-like T-cell lymphoma remains to be elucidated. In our case although serological study suggested a prior infection of EBV, no examination was done to detect the direct association of EBV to the tumor including in situ hybridization for EBERs.

ITCL are reported to have a very aggressive clinical course irrespective of CD56 positivity. It is reported that the median survival was three months for both of CD56− and CD56+ cases (3). All seventeen patients with primary NK-like T cell lymphoma of the gastrointestinal tract in the review by Chim et al showed survival of twenty days to five months (6). Most of them did not receive any chemotherapy or did not finish the complete course because of poor performance status or treatment-related complications. In the present case, the preceding partial jejunostomy reduced the risk of jejunal bleedings or perforations, which enabled chemotherapy to be performed safely and resulted in complete remission. From the literature and the present case, it might be postulated that not only the poor sensitivity to the chemotherapy but also the complications are responsible for the poor prognosis.

There are only a few reports of high dose chemotheraphy and auto-PBSCT in the cases of ITCL. Gale et al reported that, of thirty-one ITCL cases they mentioned, only one case that received auto-PBSCT resulted in CR and disease-free survival for sixty-four months (4). Forty cases of peripheral T cell lymphoma which received high dose therapy with stem cell transplantation were reported by Blystad et al (5), although they included only two cases of ITCL and the details of each case were not described. They argued that the poor prognosis of T-cell lymphoma might be overcome by frontline high dose chemotherapy and transplantation. In our case auto-PBSCT was effective even in a state after relapse, although the remission duration was not so long. Using this strategy as an upfront therapy for patients with ITCL may improve their outcomes.

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References