J Clin Exp Hematopathol
Vol. 51, No. 2, Nov. 2011

Case Study

Enteropathy-Associated T-Cell Lymphoma Type II Complicated by Autoimmune Hemolytic Anemia

Aiko Kato,[1)] Yoko Takiuchi,[1)] Kazunari Aoki,[1)] Yuichiro Ono,[1)] Hiroshi Arima,[1)] Seiji Nagano,[1)] Sumie Tabata,[1)] Soshi Yanagita,[1)] Akiko Matsushita,[1)] Hayato Maruoka,[1)] Masaya Wada,[2)] Yukihiro Imai,[3)] Takayuki Ishikawa,[1)] and Takayuki Takahashi[1)]

A 74-year-old man was admitted to hospital because of persistent fever, diarrhea, and abdominal pain. CT scanning showed extensive wall thickening of the colon. He was transferred to our hospital because he further developed ascites and paraaortic lymph node swelling. On presentation, he was extremely emaciated with superficial lymph node swelling, ascitic signs, and leg edema. Histological image of a biopsied mesenteric lymph node demonstrated diffuse infiltration of large abnormal T cells. Surface antigen analysis of abnormal cells in the ascites revealed positivity for CD3, CD8, CD56, and weak positivity for CD103. Polymerase chain reaction analysis showed monoclonal rearrangement of the *T cell receptor* (*TCR*) gene. The subtype of TCR was $\alpha\beta$. A diagnosis of enteropathy-associated T cell lymphoma (EATL) type II was made. The lymphoma involved the bone marrow. The patient also had severe hemolytic anemia with a positive Coomb's test result. An additional diagnosis for autoimmune hemolytic anemia (AIHA) was made, which was resistant to methylprednisolone therapy. We first treated him with only vincristine in addition to the steroid to avoid acute tumor lysis syndrome ; however, he died of septic shock that occurred soon after vincristine administration. To the best of our knowledge, this may be the first reported case of EATL complicated by AIHA. 〔*J Clin Exp Hematopathol 51(2) : 119-123, 2011*〕

Keywords: enteropathy-associated T cell lymphoma, autoimmune hemolytic anemia, intestinal intraepithelial T lymphocytes

INTRODUCTION

Enteropathy-associated T cell lymphoma (EATL) is an uncommon intestinal tumor arising from T lymphocytes that reside in intraepithelial space,[1] comprising less than 1% of non-Hodgkin's lymphoma cases.[2] The intestinal intraepithelial T lymphocytes supposed to be a normal counterpart of EATL have dendritic morphology and express surface CD3 and CD8 but not CD4 antigens. The subtype of T cell receptor (TCR) expressed on intestinal intraepithelial T lymphocytes is mostly $\gamma\delta$.[3] The main function of these T cells is to repair damaged intestinal epithelial cells. EATL proliferates along the intestinal lumen or serous membrane without tumor formation. Because of this growth fashion, patients with EATL often develop ileus or intestinal perforation.[2,3] In relation to the growth site of the tumor, EATL patients frequently complain of appetite loss or abdominal pain.

EATL has two subtypes. One is designated as classical EATL, which is often associated with celiac disease. Tumor cells of classical EATL are morphologically heterogeneous and positive for CD3 and CD7, but negative for CD4, CD8, or CD56. The other type is EATL type II, which comprises 10 to 20% of EATL cases. This type of EATL is mainly composed of medium-sized cells, which are positive for CD3, CD7, CD8, and CD56. Type II EATL develops sporadically and is independent of celiac disease.

In general, T cell lymphoma, except for angioimmunoblastic T cell lymphoma (AITL), which often causes autoimmune diseases,[4] is less frequently associated with autoimmune disease/phenomena than B cell lymphoma ;[5] however, Saskia *et al*. reported that T cell lymphoma is more frequently complicated by connective and vascular diseases (sarcoidosis, Wegener's granulomatosis, systemic lupus erythematosus, and periarteritis nodosa) than B cell lymphoma and other malignancies ;[6] therefore, the exact incidence of autoimmune disease/phenomena in T and B cell lymphomas is still controversial and remains to be determined.

Received : March 22, 2011
Revised : July 8, 2011
Accepted : August 2, 2011
[1)]Departments of Hematology and Clinical Immunology, [2)]Gastroenterology, and [3)]Clinical Pathology, Kobe City Medical Center General Hospital, Kobe, Japan
Address correspondence and reprint requests to : Aiko Kato, M.D., Department of Hematology and Clinical Immunology, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-Minamimachi, Chuo-ku, Kobe 650-0047, Japan
E-mail : aikokato@kcho.jp

Few reports are available regarding EATL associated with autoimmune disease except for celiac disease in classical EATL. We encountered a patient with type II EATL complicated by refractory autoimmune hemolytic anemia (AIHA). To our knowledge, this is the first report of the association of EATL and AIHA.

CASE REPORT

On May 11, 2010, a 74-year-old man was admitted to hospital because of diarrhea, abdominal pain, and general fatigue, which had started 2 mon before admission. He had undergone surgery for both hemangioblastoma and meningioma at the age of 62 years. He had not experienced sustained abdominal distress such as diarrhea. Computed tomography (CT) scanning showed extensive wall thickening of the colon. He was transferred to our hospital on May 30 because he further developed ascites and paraaortic lymph node swelling. On presentation, he was extremely emaciated and icteric. Physical examination showed marked leg edema and a few enlarged lymph nodes with a diameter of 1 cm in the neck and armpits. Abdominal tumor was not palpable because of massive ascites, and hepatosplenomegaly was not noted.

Laboratory examination revealed a white blood cell count of 3.8×10^9/L, with a differential count of 1% myelocytes, 1% metamyelocytes, 60% neutrophils, 16% lymphocytes, 21% monocytes, and 0% abnormal cells, hemoglobin concentration of 7.4 g/dL, platelet count of 215×10^9/L, and reticulocyte count of 9.5%. Both total and indirect bilirubin concentrations were elevated to 6.9 mg/dL and 3.2 mg/dL, respectively, while the haptoglobin level was decreased to 10 mg/dL (normally more than 96 mg/dL), indicating hemolysis. Both direct and indirect Coombs' test results were positive ; therefore, a diagnosis of AIHA was made. Bone marrow aspirate showed a nucleated cell count of 6.6×10^4/mL with a differential count of 35.6% erythroblasts, 36.8% granulocytes, 7.2% monocytes, 1.2% lymphocytes, and 13.6% abnormal lymphocytes. Surface antigen analysis of these abnormal lymphocytes will be described later. Neither hemophagocytosis nor increased number of macrophages was observed in the marrow aspirate. In relation to hemolysis, serum concentrations of CH50, C3, and C4 were all decreased to below 10 U/mL (normally 29-48 U/mL), 28 mg/dL (normally 65-135 mg/dL), and 3 mg/dL (normally 13-35 mg/dL), respectively, suggesting that the hemolysis was mediated by complement-activating immunoglobulin (Ig) classes such as IgM or certain subclasses of IgG although we did not determine the Ig class in the present patient. Serum concentration of soluble interleukin-2 receptor was elevated to 2,433 IU/mL (normally 150-505 IU/mL). The serum concentration of albumin was low (2.3 g/dL), while that of C-reactive protein was elevated to 1.9 mg/dL (normally below 0.5 mg/dL).

CT scanning showed extensive wall thickening of the colon and small intestine, and mesenterial lymphadenopathy (Fig. 1). Gallium scintigraphy, however, showed no abnormal accumulation. A biopsy specimen of a mesenterial lymph node, which was obtained by laparoscopy, histologically demonstrated massive infiltration of abnormal lymphocytes (Fig. 2). On immunohistochemistry, these lymphocytes were positive for CD3, CD56, and perforin but negative for

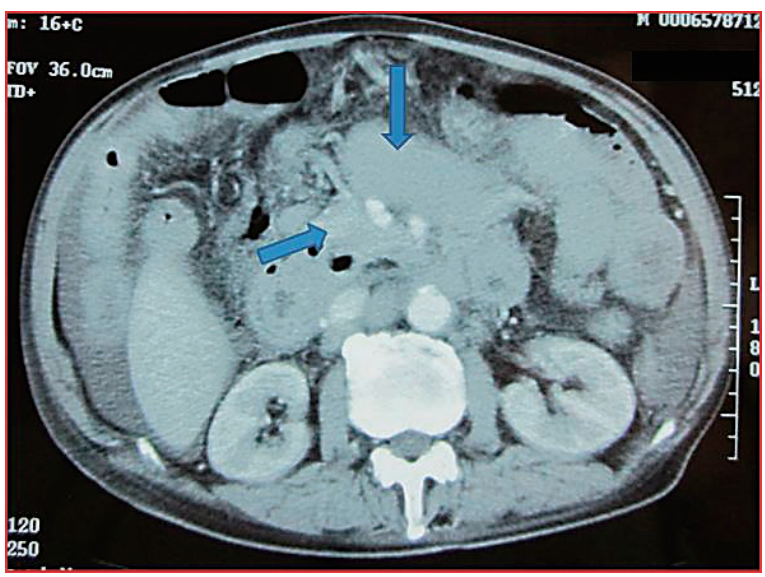


Fig. 1. Contrast computed tomography scanning of the abdomen, which was performed on admission, shows extensive wall thickening of the colon and small intestine (*arrows*), and mesenterial lymphadenopathy.

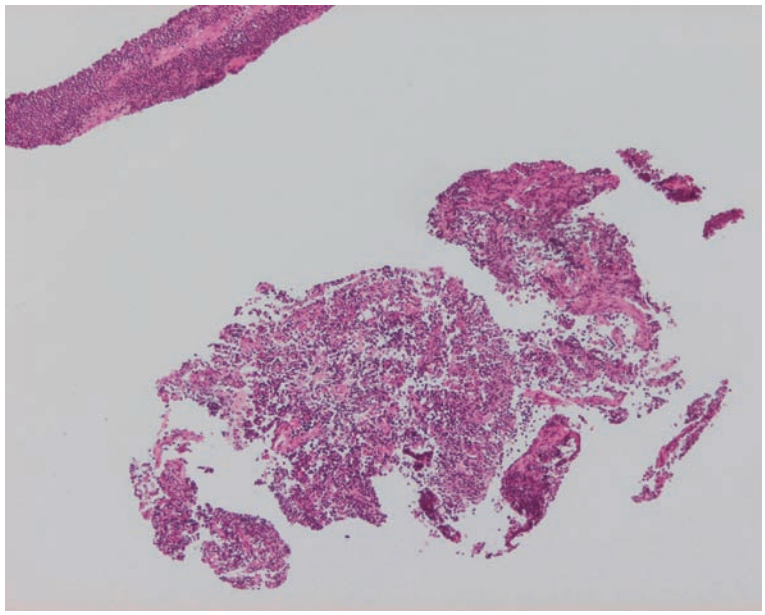


Fig. 2. Histologic image and immunohistochemistry of a biopsied mesenterial lymph node. (***2A***) Only infiltration of medium to large lymphocytes is seen (H-E staining, × 100). (***2B***) These cells have a nucleus with a fine chromatin network and prominent nucleoli. Many cells are seen in the karyorrhexis (H-E staining, × 400).

CD4 and CD8 (Fig. 3). Polymerase chain reaction analysis showed monoclonal rearrangement of the TCR-γ gene. In the ascites, many abnormal lymphocytes with azure granules in the cytoplasm were seen (Fig. 4A). Bone marrow-infiltrating abnormal lymphocytes with similar azure granules are also shown in Fig. 4B. On flow cytometric analysis, these neoplastic cells in the ascites were positive for CD3, CD7, CD8, CD56, and CD103 (weak: 18% of tumor cells). Interestingly, 52.8% of these cells in the ascites were positive for CD4 in addition to the antigen expression described as above, while abnormal lymphocytes in the bone marrow were negative for CD4 and CD103 although the expression of other antigens was similar to that of tumor cells in the ascites. The subtype of TCR expressed on abnormal lymphocytes was $\alpha\beta$ either in the ascites or in the bone marrow. Karyotypic analysis of the bone marrow cells revealed no chromosomal abnormality. We made a final diagnosis of AIHA-associated EATL type II.

The patient was treated with intravenous methylprednisolone (mPSL) (60 mg/day) to improve AIHA from day 3 after admission ; however, the hemolysis was refractory to mPSL so red blood cell transfusion was required. As chemotherapy for EATL, we started with 0.8 mg of vincristine alone to prevent acute tumor lysis syndrome on day 5 ; however, the size of abdominal tumors, which became palpable after volume reduction of ascites, was unchanged. Instead, a few abnormal lymphocytes appeared in the peripheral blood. His general status and laboratory findings, including anemia and liver function, worsened and he died of septic shock on day 13. An autopsy was not performed.

DISCUSSION

Regarding the immunophenotypic features of lymphoma cells in the present patient, tumor cells in the ascites were positive for CD3, CD7, CD8, CD56, and CD103 (weakly), but negative for CD4. Although this phenotypic pattern is compatible with that of EATL type II and lymphoma involvement of the colon and small intestine was strongly suggested by CT imaging, another diagnosis of "intestinal T cell lymphoma" should be taken into consideration because we did not carry out histopathological analysis of involved intestines. In addition, to the best of our knowledge, the association of intestinal T cell lymphoma and AIHA has not been reported previously. There were some differences in the phenotypic pattern of lymphoma cells between invasion sites. Lymphoma cells in the bone marrow were negative for CD103, which is an adhesive molecule expressed on intestinal intraepithelial T lymphocytes, and is necessary for T lymphocytes when they reside in intestinal epithelium. In the present patient, CD103-negative lymphoma cells might have selectively infiltrated the bone marrow and accumulated there. Furthermore, some lymphoma cells in the ascites were simultaneously positive for CD4 and CD8. Regarding the cellular

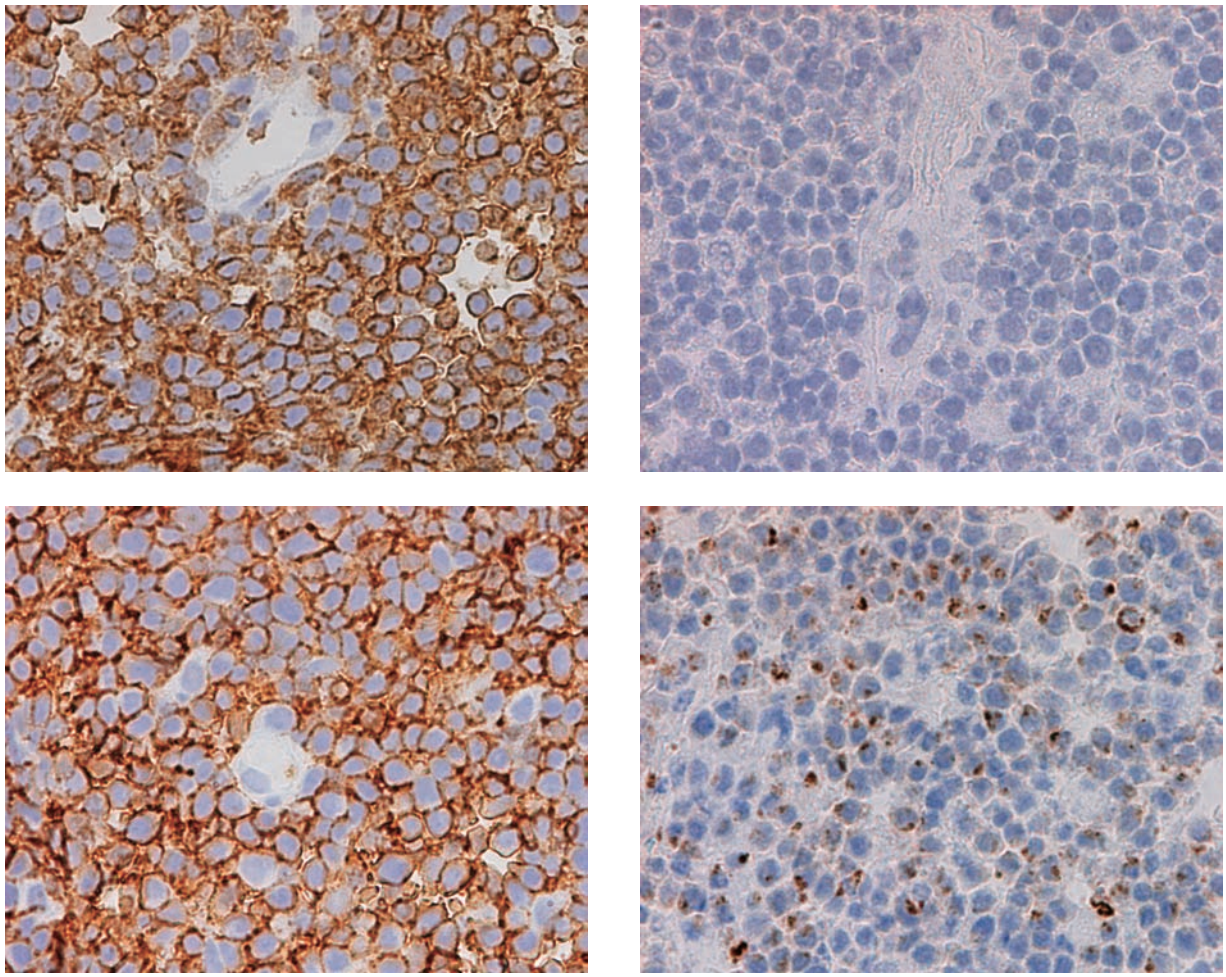


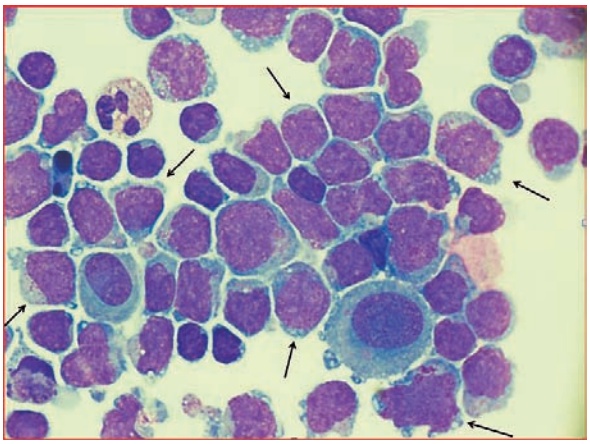
Fig. 3. Immunohistochemistry of the biopsied mesenterial lymph node. (***3A***) These cells are positive for CD3 (× 400). (***3B***) These cells are negative for CD4 (× 400). (***3C***) These cells are positive for CD56 (× 400). (***3D***) These cells are positive for perforin (× 400).

origin of EATL in T cell ontogenesis, this finding is interesting and may indicate that EATL cells originated from double-positive T cells.

Sallah *et al*. reported that 3% of all non-Hodgkin lymphomas are complicated by AIHA irrespective of their clinical stage. They also reported that T cell lymphomas are more often accompanied by AIHA than B cell lymphomas.[7] In particular, it is well known that AITL is frequently associated with AIHA.[8] Nevertheless, to the best of our knowledge, this is the first reported case of EATL complicated by AIHA.

In terms of the mechanism of AIHA development in T cell lymphomas, it has been speculated that cytokines produced by lymphoma cells (interleukin-2, 4, 6, etc.) stimulate autoreactive B cells, which exist even in healthy individuals, to produce antibodies directed to red blood cells.[9] As another possibility regarding hemolysis, cytotoxic activity of lymphoma cells in the present case should be taken into consideration because the lymphoma cells showed the phenotype of cytotoxic T lymphocyte and expressed a cytotoxic protein, perforin. Cytoplasmic azure granules observed in the lymphoma cells may also have reflected the cytotoxic nature of the present lymphoma. Therefore, possible cytotoxic activity of marrow-infiltrating lymphoma cells may have contributed to the resistance of hemolysis to steroid therapy.

It has been shown that non-Hodgkin's lymphomas complicated by AIHA exhibit significantly poor prognosis.[9] Sallah *et al*. stated that earlier control of AIHA using an immunomodulator such as cyclosporine A (CyA) is important.[9] In the present patient, however, it was difficult to employ an immunomodulator because of his poor performance status. Nevertheless, earlier use of an immunomodulator should be taken into consideration in subsequent patients with EATL complicated by AIHA to improve their outcome. Indeed, the efficacy of CyA alone both for AITL and for AIHA was shown in a previous report.[8]



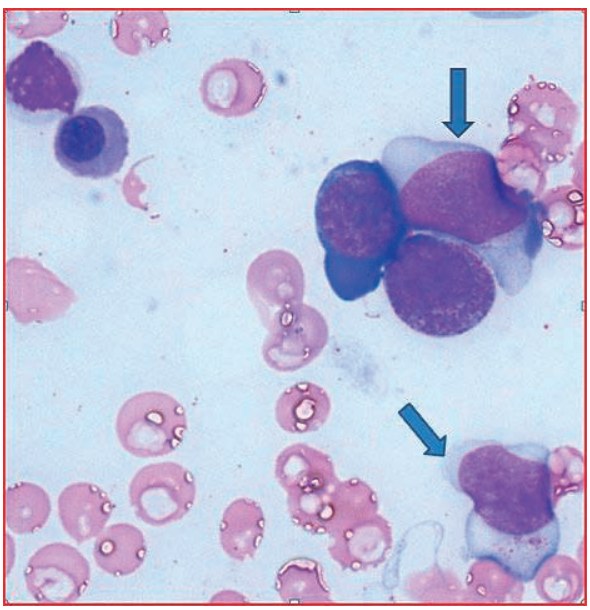


Fig. 4. Smear preparation of cells in the ascites (*4A*) and bone marrow (*4B*). (***4A***) Smear preparation of cells in the ascites. Many medium to large abnormal lymphocytes with cytoplasmic azure granules are seen (*arrows*). (***4B***) Abnormal lymphocytes with cytoplasmic azure granules in the bone marrow (*arrows*). Morphological diversity in the cellular maturation from blastoid to moderately immature features is seen.

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