Angioimmunoblastic T-cell Lymphoma Developed with Lymphocytic Pleural Effusion

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Abstract

Angioimmunoblastic T-cell lymphoma (AILT) is a rare variant of nodal and aggressive lymphoma. It is sometimes difficult to distinguish AILT from reactive lymphoid hyperplasia from the histopathological aspect. We report a case of AILT which developed with bilateral pleural effusion. The effusion consisted predominantly of small lymphoid cells. Analyses of the effusion showed trisomy 3, and rearranged bands of TCR β gene. Flow cytometry showed a very small amount of CD10-positive cells. Although we could not further identify the tumor cells in this case, analysis of pleural effusion cells will increase our understanding of the pathogenesis and the pathophysiology of AILT.

Key words: CD10, CD56, trisomy 3, TCR, EBV

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Introduction

Angioimmunoblastic T-cell lymphoma (AILT) was first described in 1974 by Frizzera et al as a reactive disease, angioimmunoblastic lymphadenopathy with dysproteinemia (1). AILT was recently grouped into nodal mature T-cell lymphoma, shows a relationship to Epstein-Bar virus (EBV) infection, and is sometimes complicated with pleural effusion (2, 3). Although the character of tumor cells in AILT has not been established, a microdissection study on lymph nodes showed that CD4-positive T-cells aberrantly expressing CD10 have monoclonal T-cell receptor bands in polymerase chain reaction, indicating the possible tumor cells (4). Due to the difficulty of obtaining a histological differential diagnosis mostly from reactive lymphoid hyperplasia, it is sometimes necessary to repeat biopsies of lymph nodes to obtain a diagnosis.

In this study, we report a case of AILT which developed with lymphocytic bilateral pleural effusion followed by systemic lymphadenopathy. Clonal proliferation of lymphoma cells was detected in the pleural effusion, although the lymphoma cells could not be identified, cytologically. This report shows the involvement of pleural effusion as a component of the lymphoma, and emphasizes the significance of pleural effusion in future investigations of the pathogenesis and pathophysiology of AILT.

Case Report

An 83-year-old male was admitted to hospital after experiencing malaise and dyspnea for ten days. At admission, bilateral pleural effusion was diagnosed from a chest X-ray and a mild increase in LDH (273 IU/L) and CRP (3.0 mg/dL) were observed. Red and white blood cell counts, and liver and renal function were almost normal until the end of the course. Antibody to human immunodeficiency virus (HIV)-1 was negative in his serum. We could not detect swelling of lymph nodes on physical examination or on computed tomography at admission. The patient developed a fever exceeding 38°C seven days after admission. Pleurocentesis was performed twice in the month following admission because of the rapid increase of the pleural effusion (Fig. 1), and more than one liter of pleural effusion was drained during each pleurocentesis procedure. The pleural effusion was sent for examination after each procedure. The

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protein concentration in the effusion equaled 3.6 g/dl and exceeded 50% of that in the serum, indicating the effusions were exudates. Most of the cells in the effusion were small lymphoid cells, and we could not detect atypical cells from the cytological aspect (Fig. 2).

Neck lymph node swelling became prominent two months after admission, and enlargement of axillary, mediastinal and abdominal para-aortic lymph nodes and splenomegaly were observed on computed tomography. Furthermore, an increase in IgG and soluble IL-2 receptors in the serum (2,022 mg/dl and 12,100 U/ml, respectively) was observed during this period. A lymph node biopsy was performed on the patient’s neck and later diagnosed as AILT, although it was very difficult to make a definitive diagnosis because of the very small number of clear cells in the lymph node. Tortuous neovascularization, a minuscule amount of clear cells and eosinophil infiltration (Fig. 3A), a ‘burned out’ pattern of follicles by immunostaining of follicular dendritic cells with anti-CD21 (Fig. 3B), CD10 expression in CD3-positive cells (Fig. 3C and D), and scattered EBER-positive cells by in situ hybridization were observed in the lymph node.

Pleurocentesis was performed again in an effort to aid the diagnosis. Cells in the pleural effusion were subjected to flow cytometry analysis. Cytogram showed the pure population of lymphoid cells in the pleural effusion. The cells in the lymphoid cell population, 81.4% of the total cells, were selected and divided into two groups according to the intensity of CD45 expression and level of side scatter: 23.6% had high side scatter and CD45dim, while 49.2% had a low side scatter signal and CD45bright. In the high side scatter group, percentages of CD2-, CD3-, CD4-, CD8- and CD56-positive cells were 95.6%, 14.2%, 7.7%, 16.0% and 82.7%, respectively, indicating the presence of CD8-positive T-cells and a large number of natural killer (NK) cells-like CD56-positive cells. CD20-weakly-stained cells represented 2.4% of this group, indicating very small number of B-cells in this group. In the low side scatter lymphoid cell group, there were 99.8% CD2-positive, 85.3% CD4-positive, 14.2% CD8-positive and 0.7% CD20-weakly-stained cells. In this low side scatter group with lower than 0.7% of B-cells, 9.0% (4.4% of total cells in the effusion) were stained positive for CD10, a marker of premature B-cells.

Cytogenetic abnormality was also examined for pleural effusion cells. Twenty cells in metaphase after 24 to 48 hours of culture were analyzed and the results revealed that three cells exhibited trisomy of the third chromosome, indicating a clonal proliferation of cells. We also performed PCR of EBV, real-time PCR of human herpes virus (HHV)-8, and Southern blotting of TCR β-chain Cβ1 and human T-cell lymphotropic virus (HTLV)-1 on DNA extracted from pleural effusion cells. The results showed the presence of EBV DNA and a clonal band in the TCR β-chain (Fig. 4), but not HHV-8 or HTLV-1.

After the diagnosis, the patient’s treatment included the administration of 30 mg of prednisolone. Because of his age and his general condition, we did not choose to do chemotherapy, such as the combination therapy of cyclophosphamide, doxorubicin, vincristine and prednisolone, which have been reported to have effect on AILT (3). Pleurodesis was performed three times on his left chest. These treatments led to the temporary alleviation of the patient’s symptoms. He died four months after admission because of disseminated intravascular coagulation.

**Discussion**

AILT is a mature T-cell lymphoma representing 2.35% of lymphomas in Japan (5). Its clinical manifestation is represented by skin rash and polyclonal hypergammaglobulinemia, in addition to symptoms typical of lymphomas such as high fever, night sweating, weight loss and generalized lymphadenopathy. The differential diagnosis of AILT includes autoimmune disorder, viral infections, Castleman’s disease, atypical T-zone hyperplasia, peripheral T-cell lymphoma of other types, T-cell/histiocyte-rich large B-cell lymphoma and Hodgkin lymphoma. Diagnosis of AILT is difficult in cases in which cellular atypia is minimal. Furthermore, the use of
Figure 3. Histological findings of neck lymph node. A: Lymph node under high microscopic magnification shows a small number of ‘clear cells’ (arrows). B: Immunostaining of the lymph node with anti-CD21 showing ‘burned out’ formation of follicular dendritic cells. C, D: Immunostaining of the continuous sections of the lymph node. C: CD3 immunostaining. D: CD10 immunostaining. Arrows indicate cells stained with both CD3 and CD10.

Figure 4. Southern blotting of TCR β-chain Cβ1 on pleural effusion DNA. After the digestion with EcoRI, DNA was subjected to Southern blotting. Lane 1: normal control; Lane 2: patient. Arrows on the right indicate the rearranged band of TCR β-chain Cβ1. a lymph node biopsy specimen may be limited. Pleural effusion has already been reported as a complication associated with AILT (3), and may be a frequently occurring complication. In this report, we showed the presence of lymphoma cells in the pleural effusion of an AILT patient and demonstrated that the pleural effusion is more suitable for verifying the existence of lymphoma cells in cases of AILT involving pleural effusion, if the characteristics of the lymphoma cells are clearly identified.

Although the existence of lymphoma cells in the pleural effusion was demonstrated by Southern blotting of the TCR β gene and other examinations, we could not specifically identify the tumor cell population in this case. Attygalle et al reported the presence of CD10-positive T-cells in lymph nodes of AILT, and monoclonal TCR in CD10-positive T-cells in all five of their cases (4). We also observed CD10-positive cells in the low-side-scatter T-cell subset, the group showing less atypia in the effusion and which accounted for only 4.4% of pleural effusion cells. It is possible that the remaining 95.6% of pleural effusion cells are reactive lymphocytes, which make diagnosis difficult. However, it is generally thought that more than 5% of lymphoma cells are needed to detect TCR rearrangement by Southern blotting, which suggests the possibility of lymphoma cells hiding in other subsets. The high side scatter and CD45dim group, in
which a large portion of cells are CD2-, CD7- and CD56-positive and CD3- and CD5-negative which are compatible with NK cells, are generally thought to be the lymphoma cells, although changes in more than three of the surface molecules are uncommon in mature types of lymphoma. The possible existence of other subsets as lymphoma cells cannot be excluded.

It is rare to observe bilateral pleural effusion as a first manifestation of AILT, although the association of pleural effusion and AILT has been already reported (3). Primary effusion lymphoma (PEL) is well known to develop with pleural effusion (6). PEL, a large B-cell lymphoma with no lymphadenopathy, develops mostly in patients with advanced HIV infection, but rarely in elderly patients without HIV infection (7). PEL is related to HHV-8 infection. The present case of confirmed T-cell lymphoma with lymphadenopathy without HIV nor HHV-8 infection, is obviously different from PEL.

Although we could not identify the tumor cell population in the present case, we revealed the existence of lymphoma cells in the lymphocytic pleural effusion of a patient with AILT. In the future, sorting cells from a pleural effusion, which is easier to manipulate than other specimens, into categories such as CD10 positive or negative T-cells, CD56 positive cells and B-cells, and analyzing TCR and/or immunoglobulin rearrangement, EBV infection and other cellular functions, will help to identify tumor cells in cases of AILT involving effusion, and hence clarify the biology of the disease.

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References

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