B-cell lymphoma showing typical features of angioimmunoblastic T-cell lymphoma

Masaki Mori*1,2, Yusuke Furukawa*1,3, Masaaki Takatoku*1, Tadashi Nagai*1, Kazuo Muroi*1,2, Keiya Ozawa*1,2

Abstract

We present a 52-year-old man who was diagnosed with B cell-derived angioimmunoblastic lymphoma. He was admitted with systemic, including mediastinal and para-aortic, lymphadenopathy, fever and skin itching. Histologically, his lymph nodes showed total obliteration of the normal architecture by a polymorphic infiltrate of large-sized lymphocytes with proliferation of arborizing small blood vessels. In addition, hematological examinations showed biclonal hypergammaglobulinemia, leukocytosis with lymphoblasts and bone marrow involvement of these cells. He was clinicopathologically diagnosed with angioimmunoblastic T-cell lymphoma, but cell surface marker analysis and immunoglobulin heavy chain clonal rearrangement demonstrated that lymphoblasts were derived from B lymphocytes. These findings were suggestive of a B cell origin of the lymphoma cells, therefore, we ultimately diagnosed the disease as a B-cell lymphoma showing typical features of angioimmunoblastic T-cell lymphoma. He has not followed the progressive disease, thus we consider that it will be treated as CD20-positive indolent B-cell lymphoma.

(Key words: angioimmunoblastic T-cell lymphoma; B cell lymphoma; Epstein-Barr virus)

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is clinically characterized by generalized lymphadenopathy, hepatosplenomegaly, fever, loss of body weight, and a variety of immunological abnormalities, such as Coombs-positive hemolytic anemia and polyclonal hypergammaglobulinemia. Morphologically, the destruction of the lymph node architecture by polymorphic cellular infiltrates, including small lymphocytes, plasma cells, and immunoblasts are seen. Because of several typical features, these cases were differed from other oncogenic lymphomas and are proposed as an entity of original disease or syndrome, called "angio-immunoblastic lymphoadenopathy with dysproteinemia (AILD)" or "immunoblastic lymphadenopathy (IBL)". Shimoyama et al first indicated that proliferative neoplastic immunoblasts in clinically and morphologically IBL-like diseases were found to have T-cell markers, proposing "IBL-like T-cell lymphoma" as a distinct non-Hodgkin’s lymphoma of the T-cell system. After that, in the majority of cases histopathologically diagnosed AILD or IBL, atypical cells were proven to be derived from T cells, therefore, these diseases were identified as the same group of peripheral T-cell lymphoma. In the World...
cently, JL Smith et al revealed that functional T cell receptor (TCR) and/or immunoglobulin heavy chain (IgH) oligoclonalities were detected in 6 of 20 (30%) AILD/IBL cases. If the evidence of clonal rearrangements of TCR genes is essential to diagnose AITL, not all cancers that show typical features of AILD/IBL may be T-cell lymphomas. In this paper, we report a patient with AILD/IBL derived from B-cell origin, identified as B-cell lymphoma showing typical features of angioimmunoblastic T-cell lymphoma.

### Case Report

A 52-year-old Japanese man was admitted with generalized lymphadenopathy, low-grade fever and skin itch in March 2002. He had undergone resection of a pancreas tumor due to chronic pancreatitis and partial duodenectomy. He noticed his own bilateral inguinal lymphadenopathy in October 2000, and underwent biopsy of the right inguinal lymph node as an outpatient.Histopathological examination showed obliteration of the normal lymph node architecture by an infiltration of polymorphic cells with a proliferation of arborizing small blood vessels and the disease was diagnosed as AITL. At the same time, he showed generalized lymphadenopathy and the involvement of lymphoblasts in his bone marrow, but not in his peripheral blood. Because he was doing extremely well and had no other complaints, he was fol-

### Table I  Laboratory findings

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Serological study</th>
<th>Bone marrow (sternum)</th>
<th>Surface markers of peripheral lymphoblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 15.7 × 10⁶/L</td>
<td>CRP 1.2 mg/dL</td>
<td>NCC 0.111 × 10⁷/L</td>
<td>CD2 7.8%</td>
</tr>
<tr>
<td>blast 25.0%</td>
<td>IgG 3.462 mg/dL</td>
<td>MgK 1.7</td>
<td>CD3 23.9%</td>
</tr>
<tr>
<td>seg 29.5%</td>
<td>IgA 162 mg/dL</td>
<td>M/E 69.0%</td>
<td>CD4 7.7%</td>
</tr>
<tr>
<td>lymph 42.5%</td>
<td>IgM 510 mg/dL</td>
<td>blast 69.0%</td>
<td>CD5 13.6%</td>
</tr>
<tr>
<td>mono 1.5%</td>
<td>Ferritin 142.3 ng/mL pro 2.8%</td>
<td>CD6 6.5%</td>
<td></td>
</tr>
<tr>
<td>eosin 1.5%</td>
<td>RA (−) mye 1.4%</td>
<td></td>
<td>CD7 6.5%</td>
</tr>
<tr>
<td>RBC 4230 × 10⁶/L</td>
<td>HBsAg (−)</td>
<td></td>
<td>CD8 2.1%</td>
</tr>
<tr>
<td>Hb 13.0 g/dL</td>
<td>HCV Ab (−)</td>
<td></td>
<td>CD9 0.4%</td>
</tr>
<tr>
<td>Ht 39.6%</td>
<td>Cold agglutination ×2,048 seg 7.6% TCRγ/δ 0.3%</td>
<td>CD10 0.7%</td>
<td></td>
</tr>
<tr>
<td>Pt 169 × 10⁹/L</td>
<td>EBV VCA IgM &lt;10 eos 1.2%</td>
<td>CD11 0.7%</td>
<td></td>
</tr>
<tr>
<td>&lt; Blood chemistry &gt;</td>
<td>EBV VCA IgG ×80 lymph 0.6%</td>
<td>CD19 90.5%</td>
<td></td>
</tr>
<tr>
<td>TP 9.1 g/dL</td>
<td>EBV EBNA &lt;10 mono 0.8%</td>
<td>CD20 93.5%</td>
<td></td>
</tr>
<tr>
<td>Alb 3.1 g/dL</td>
<td>Immunolectrophoresis plasma 0.4%</td>
<td>CD23 88.0%</td>
<td></td>
</tr>
<tr>
<td>T-Bil 0.32 mg/dL</td>
<td>M-protein(+) erythrobl 11.0%</td>
<td>CD25 77.9%</td>
<td></td>
</tr>
<tr>
<td>GOT 35 mU/mL</td>
<td>IgM(k) + IgG(k)type Karyotype 46,XY SmIg(h) 96.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPT 33 mU/mL</td>
<td>&lt; Coagulation study &gt;</td>
<td>SmIg(k) 94.8%</td>
<td></td>
</tr>
<tr>
<td>ALP 144 mU/mL</td>
<td>PT 12.5 sec Alp 6.6%</td>
<td>CD33 8.8%</td>
<td></td>
</tr>
<tr>
<td>γGTP 30 mU/mL</td>
<td>APTT 29.2 sec ALP 6.6%</td>
<td>CD34 0.5%</td>
<td></td>
</tr>
<tr>
<td>LDH 376 mU/mL</td>
<td>Fib 459 mg/dL</td>
<td>CD38 82.9%</td>
<td></td>
</tr>
<tr>
<td>BUN 11 mg/dL</td>
<td>AT-III 85.4%</td>
<td>HLA-DR 90.9%</td>
<td></td>
</tr>
<tr>
<td>Cre 0.61 mg/dL</td>
<td>FDP 6.6 mg/mL</td>
<td>CD11b 92.2%</td>
<td></td>
</tr>
<tr>
<td>UA 4.6 mg/dL</td>
<td></td>
<td>CD11c 15.8%</td>
<td></td>
</tr>
<tr>
<td>Na 137 mEq/L</td>
<td></td>
<td>CD14 69.3%</td>
<td></td>
</tr>
<tr>
<td>K 4.1 mEq/L</td>
<td></td>
<td>CD15 9.0%</td>
<td></td>
</tr>
<tr>
<td>Cl 106 mEq/L</td>
<td></td>
<td>CD56 3.7%</td>
<td></td>
</tr>
</tbody>
</table>

Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues issued in 1999, AITL was classified into mature (peripheral) T-cell neoplasms. On the other hand, recently, JL Smith et al revealed that functional T cell receptor (TCR) and/or immunoglobulin heavy chain (IgH) oligoclonalities were detected in 6 of 20 (30%) AILD/IBL cases. If the evidence of clonal rearrangements of TCR genes is essential to diagnose AITL, not all cancers that show typical features of AILD/IBL may be T-cell lymphomas. In this paper, we report a patient with AILD/IBL derived from B-cell origin, identified as B-cell lymphoma showing typical features of angioimmunoblastic T-cell lymphoma.
followed without treatment for about one year. Four months before admission, peripheral lymphoblasts had appeared, and low-grade fever and skin itch started. On physical examination he had cervical, supraclavicular, axillar and inguinal lymphadenopathy, but was not pale and became febrile. Gallium scintigraphy and computed tomography similarly showed generalized lymphadenopathy, including mediastinal and paraaortic lymphadenopathy, and mild hepatosplenomegaly, but their sizes were unchanged over the past year. The laboratory abnormalities were white cell count $15.7 \times 10^9/L$ including lymphoblasts and bone marrow involvement of lymphoblasts ($Table$ $I$). Serum aspartate aminotransferase was 35 mU/mL (normal values 11-30 mU/mL), alanine aminotransferase 33 mU/mL (normal values 4-30 mU/mL), lactate dehydrogenase 376 mU/mL (normal values 215-410 mU/mL), both IgM-kappa and IgG-kappa type hypergammaglobulinemia, and mild hepatosplenomegaly, but their sizes were unchanged over the past year.

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We next analyzed the origin of peripheral lymphoblasts by flowcytometry. Surprisingly, these cells expressed CD5, CD10 and high kappa/lambda ratio ($Table$ $I$), supporting the monoclonal proliferation of B cells. Still more, IgH clonal rearrangement was identified, but neither TCR J-gamma nor TCR C-beta1 clonal rearrangement were identified in his peripheral lymphoblasts by Southern blotting ($Figure$ $1$). We reanalyzed the former lymph node samples by immunochemical staining, revealing that atypical large cells were positively stained with L-26 but negatively with UCHL-1 ($Figure$ $2$), and negatively with EBV-encoded short RNA species (EBER)-1 in situ hybridization (data not shown). These results suggest that the neoplastic cells were derived from B-cell origin, therefore we diagnosed the disease as B-cell lymphoma showing typical features of angioimmunoblastic T-cell lymphoma. Because it didn’t advance during admission, he was discharged without treatment. After that, we have been regularly observing him, but not progressive. We consider that his disease will be treated as CD20-positive indolent B cell lymphoma.

Figure 1. Southern blotting analysis of patient’s peripheral blood samples. (a) Ig-H JH rearrangement. Restriction enzymes: 1; Bam HI+Hind III, 2;Hind III. (arrows: bands showing IgH clonal rearrangement) (b) TCR J rearrangement. Restriction enzymes: 1; Eco RI, 2; Bam HI, 3; Hind III. (c) TCR C rearrangement. Restriction enzymes: 1; Bam HI, 2; Eco RV, 3; Hind III.
Systemic lymphoproliferative disorders, which are characterized by independent clinical findings including generalized lymphadenopathy, hepatosplenomegaly, fever, skin rash, polyclonal hypergamma-globulinemia, and Coombs-positive hemolytic leukemia, have been recognized and described as AILD, IBL, and other names. In these diseases it has been histologically reported that lymph nodes show total obliteration of the normal architecture by a polymorphic infiltrate of large-sized lymphocytes with a proliferation of arborizing small blood vessels. Historically, many AILD/IBL-like diseases having clinically and histologically typical features were at first considered as a group of nonneoplastic lymphoproliferative disorders with abnormal B-cell hyperimmunity, but phenotypic and genotypic findings that the majority of lymphoid cells are proliferating T cells allowed classification of the disease as an entity of peripheral T-cell lymphoma. Our case was diagnosed as AITL at the first medical examination, too. Recently, it has been reported that the neoplastic cells of AITL can be identified by aberrant expression of CD10 and this examination may established objective criteria for the diagnosis of this disease, but the expression of CD10 was not detected in the peripheral lymphoblasts of our case. C Lome-Maldonado et al reported

Discussion

Systemic lymphoproliferative disorders, which are characterized by independent clinical findings including generalized lymphadenopathy, hepatosplenomegaly, fever, skin rash, polyclonal hypergamma-globulinemia, and Coombs-positive hemolytic leukemia, have been recognized and described as AILD, IBL, and other names. In these diseases it has been histologically reported that lymph nodes show total obliteration of the normal architecture by a polymorphic infiltrate of large-sized lymphocytes with a proliferation of arborizing small blood vessels. Historically, many AILD/IBL-like diseases having clinically and histologically typical features were at first considered as a group of nonneoplastic lymphoproliferative disorders with abnormal B-cell hyperimmunity, but phenotypic and genotypic findings that the majority of lymphoid cells are proliferating T cells allowed classification of the disease as an entity of peripheral T-cell lymphoma. Our case was diagnosed as AITL at the first medical examination, too. Recently, it has been reported that the neoplastic cells of AITL can be identified by aberrant expression of CD10 and this examination may established objective criteria for the diagnosis of this disease, but the expression of CD10 was not detected in the peripheral lymphoblasts of our case. C Lome-Maldonado et al reported
a different subtype of AITL, which was associated with more than 25% of large B-cells. EBV infection to large B cells and clonal rearrangement of TCR genes were detected in these cases, which were denominated as AITL rich in large B-cells. Hawley RC et al reported AITL in which diffuse large B-cell lymphoma, who survived for 9 years after the initial diagnosis of AITL. Therefore, it was not B cell lymphoma and differed from our case. Similarly, EBV proliferation was demonstrated by immunohistochemistry and in situ hybridization in two reports about development of aggressive B cell lymphoma with AITL, suggesting that the infection of EBV was directly involved in the development of B cell lymphoma. Although monoclonal proliferation of B cells was showed in these cases, atypical cells were stained positive with UCHL-1 but negative with L-26. Similarly, the expanded monoclonal B-cell population was pointed out in a minority of patients, however the author considered that it is an EBV-driven lymphoproliferation, too. In our case, immunohistochemical staining revealed positive staining of atypical cells with L-26 and negative staining with UCHL-1, oppositely, and in situ hybridization of EBV RNA showed negative. Several other reports have indicated that the disease-related immunosuppression in patients with AITL may lead to EBV-associated B-cell lymphoproliferation and EBV-associated B-cell lymphoma, but there has been no report, to the author’s knowledge, about EBV-negative B-cell lymphoma showing typical features of AILD/IBL, which has so far been recognized as AITL. In addition, biclonal hypergammaglobulinemia due to B-cell clonal disorders was showed in this case, which was different from any patients with AITL previously. Our investigation of the origins of tumor cells in our case was supportive of a diagnosis of B-cell-derived lymphoma showing typical features of AITL. This observation will be useful to clarify which type of B-cell lymphoma is diagnosed.

Acknowledgment

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References

7) Takagi N, Nakamura S, Ueda R et al. Phenotypic and genotypic study of node-based, low-grade, pe-
B-cell Lymphoma showing AITL


B細胞起源と診断した血管免疫芽球性リンパ腫

森政樹*1,2 古川雄祐*1,3 高徳正昭*1
永井正*1 室井一男*1,2 小澤敬也*1,2

要約

52歳男性。全身性表在リンパ節腫脹の経過観察中、発熱及び末梢血芽球、高ガンマグロブリ
ン血症を認め入院。画像診断で、縦隔、傍大動
脈にも多数のリンパ節腫脹を認めた。常規部リ
ンパ節に、樹枝状の小血管増生や明瞭な核小体
を有する大型のリンパ球浸潤を認め、血管免疫
芽球性T細胞リンパ腫の像を示したが、腫瘍
細胞はL-26抗体陽性、EBV in situ hybridization
陰性であり、免疫グロブリン重鎖遺伝子再構成
陽性、TCR遺伝子再構成陰性であった。更に、
末梢血芽球はCD19、20陽性かつκ/λ比14.4とB
細胞のモノクローナルな増殖を示したため、B
細胞起源の血管免疫芽球性リンパ腫と診断し
た。本症はT細胞性との疾患概念が確立され
ているが、近年T、B両リンパ球の異常クロー
ンの出現の報告もあり、CD20陽性B細胞起源
との診断は治療選択上も重要であると考えた。

*1 自治医科大学内科学講座血液学部門
*2 自治医科大学輸血・細胞移植部
*3 自治医科大学幹細胞制御研究部