

Case Report

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

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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 with 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 lymphadenopathy with dysproteinemia (AILD)¹ or” immunoblastic lymphadenopathy (IBL)². Shimoyama et al first indicated³ 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

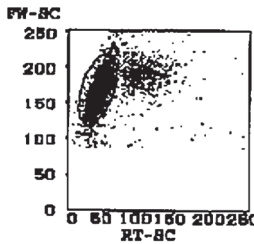
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Table I Laboratory findings

< Peripheral blood >		< Serological study >		< Bone marrow (sternum) >		< Surface markers of peripheral lymphoblasts >	
WBC	15.7 × 10 ⁹ /L	CRP	1.2mg/dL	NCC	200 × 10 ⁹ /L	CD2	7.8%
blast	25.0%	IgG	3,462mg/dL	MgK	0.111 × 10 ⁹ /L	CD3	23.9%
seg	29.5%	IgA	162mg/dL	M/E	1.7	CD4	7.7%
lymph	42.5%	IgM	510mg/dL	blast	69.0%	CD5	13.6%
mono	1.5%	Ferritin	142.3ng/mL	pro	2.8%	CD7	6.5%
eosino	1.5%	RA	(-)	mye	1.4%	CD8	2.1%
RBC	4230 × 10 ⁹ /L	HBsAg	(-)	meta	0.8%	CD8	2.1%
Hb	13.0g/dL	HCV Ab	(-)	stab	4.4%	TCRα/β	5.5%
Ht	39.6%	Cold agglutination	×2,048	seg	7.6%	TCRγ/δ	0.3%
Pt	169 × 10 ⁹ /L	EBV VCA IgM	<10	eos	1.2%	CD10	0.7%
< Blood chemistry >		EBV VCA IgG	×80	lymph	0.6%	CD19	90.5%
TP	9.1g/dL	EBV EBNA	<10	mono	0.8%	CD20	93.5%
Alb	3.1g/dL	Immunoelectrophoresis		plasma	0.4%	CD23	88.0%
T-Bil	0.32mg/dL	M-protein (+)		erythrobl	11.0%	CD25	77.9%
GOT	35mU/mL	IgM (k) + IgG (k) type		Karyotype	46,XY	Smlg (H)	96.8%
GPT	33mU/mL	< Coagulation study >				Smlg (κ)	94.8%
ALP	144mU/mL	PT	12.5sec			Smlg (λ)	6.6%
γGTP	30mU/mL	APTT	29.2sec			CD33	8.8%
LDH	376mU/mL	Fib	459mg/dL			CD34	0.5%
BUN	11mg/dL	AT-III	85.4%			CD38	82.9%
Cre	0.61mg/dL	FDP	6.6mg/mL			HLA-DR	90.9%
UA	4.6mg/dL					CD11b	92.2%
Na	137mEq/L					CD11c	15.8%
K	4.1mEq/L					CD14	69.3%
Cl	106mEq/L					CD15	9.0%
FBS	87mg/dL					CD56	3.7%



Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues issued in 1999⁴, AITL was classified into mature (peripheral) T-cell neoplasms. On the other hand, recently, JL Smith et al revealed⁵ that functional T cell receptor (TCR) and/or immunoglobulin heavy chain (IgH) oligoclones 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 lymphoma. 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-

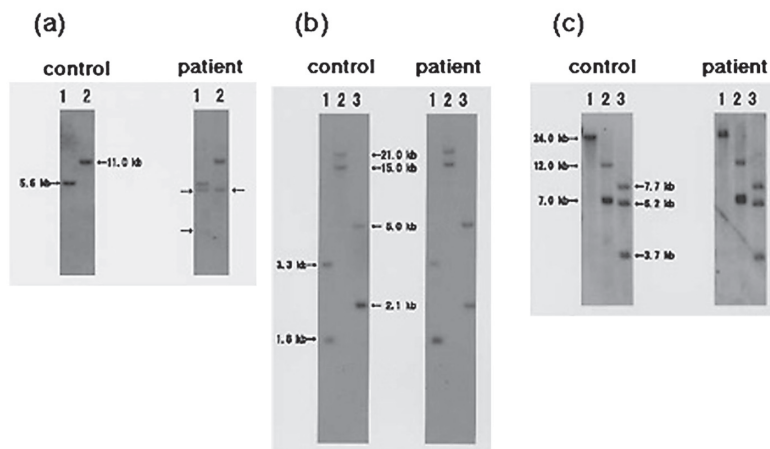


Figure 1. Southern blotting analysis of patient's peripheral blood samples. (a) Ig-H JH rearrangement. Restriction enzymes: 1; Bam HI+Hind III, 2;Hind III. (arrows: bands showing IgH clonal rearrangement) (b) TCR J rearrangement. Restriction enzymes: 1; Eco RI, 2; Bam HI, 3; Hind III. (c) TCR C rearrangement. Restriction enzymes: 1; Bam HI, 2; Eco RV, 3; Hind III.

lowed 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 para-aortic 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 25.0% lymphoblasts and bone marrow involvement of 69.0% 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, high-titer of cold agglutination, and positive EBV-viral capsid antigen (VCA)-IgG antibody, but negative EBV-EB nuclear antigen (EBNA) antibody (Table I). We next analyzed the origin of peripheral lymphoblasts by flowcytometry. Surprisingly, these cells expressed CD19, CD20 and high kappa/lambda ratio (14.4) (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 (Figure1). We reanalyzed the former lymph node samples by immunohistochemical staining, revealing that atypical large cells were positively stained with L-26 but negatively with UCHL-1 (Figure2), 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.

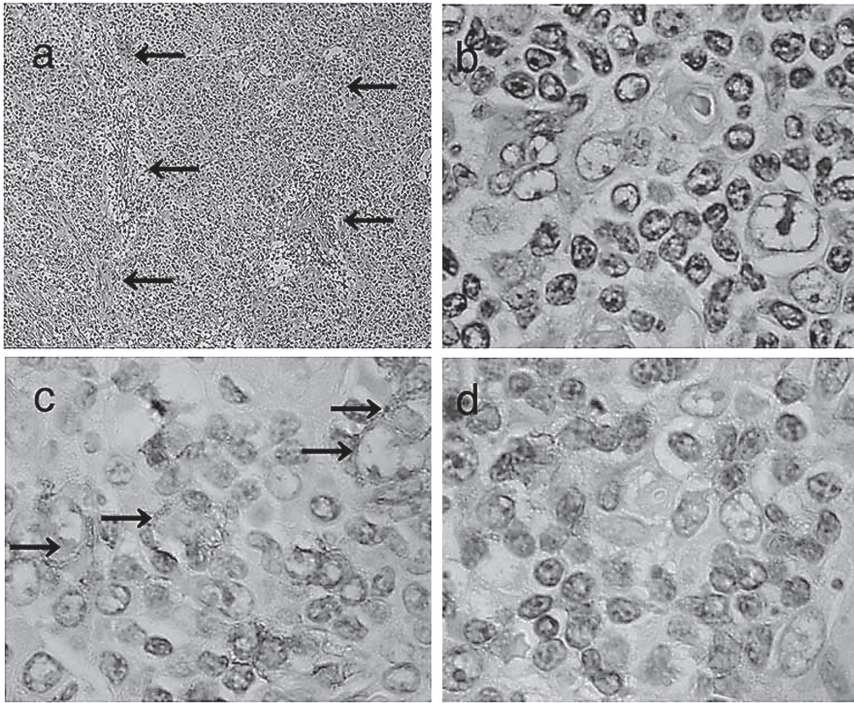


Figure 2. Histological examination of inguinal lymph node. (a) The architecture of lymph node was effaced by polymorphic cellular infiltrate and proliferation of arborizing small vessels (arrows). (HE stain, 100X) (b) Large and medium sized lymphoid cells with prominent nuclei were seen in lymph node. (HE stain, 1000X) (c) Membranes of large cells were immunostained with L26 monoclonal antibody (arrows). (1000X) (d) Large atypical cells were not immunostained with UCHL-1 monoclonal antibody, but small lymphoid cells around them were positive. (1000X).

Discussion

Systemic lymphoproliferative disorders, which are characterized by independent clinical findings including generalized lymphadenopathy, hepatosplenomegaly, fever, skin rash, polyclonal hypergammaglobulinemia, and Coombs-positive hemolytic leukemia, have been recognized and described as AILD¹, IBL², 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^{3,6,7} 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 disease⁸, but the expression of CD10 was not detected in the peripheral lymphoblasts of our case. C Lome-Maldonado et al reported⁹

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 reported¹⁰ 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 lymphoma¹¹. 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, too¹². 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 lymphoma¹³⁻¹⁷, 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

We thank Division of Pathological Diagnosis, Jichi Medical University Hospital for the support of pathological diagnosis.

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B細胞起源と診断した血管免疫芽球性リンパ腫

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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。単径部リンパ節に、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。

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