Leukemic Phase of Intermediate Non-Hodgkin's Lymphoma with Cells Showing Different Matured Stages in Invaded Various Organs

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A 56-year-old male was admitted to our hospital with lymphocytosis ($16.4 \times 10^9/l$; 79% lymphocytes including 50% small lymphocytes), generalized lymphadenopathy, massive splenomegaly, and heavily infiltrated bone marrow. Immunophenotype analysis of the neoplastic cells in the bone marrow revealed that they were B cells (CD20+CD19+Ia1+sIgM+) positive for CD10. By contrast, the cells in the lymph node were CD20+CD19+Ia1+sIgM+ but negative for CD10. The patient was tentatively diagnosed as having lymphosarcoma cell lymphoma, however, the final diagnosis was leukemic phase of intermediate lymphocytic lymphoma. We concluded that CD10+ neoplastic cells in the bone marrow and peripheral blood had differentiated to CD10- cells.

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Introduction

The disease entity of lymphoproliferative disorders includes chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL) (1-4). The utilization of cell surface marker analysis has made it possible to identify not only cellular ontogeny but also the maturation stage of normal counterparts of lymphocytes (5, 6). In some patients with B cell type lymphoproliferative disorder, the differential diagnosis between CLL and NHL in the leukemic phase is difficult, even when the surface markers of neoplastic cells are analyzed.

We report a case with clinical findings involving central nervous system and cytological features of the circulating cells compatible with so-called lymphosarcoma cell leukemia (LSCL). The maturation level of neoplastic cells in the bone marrow (BM) and peripheral blood (PB) was different from that in the lymph node and cerebrospinal fluid (SCF), indicating that the unusual clinical manifestation was due to the unique characteristics of the neoplastic cells with CD10 antigen.

Case Report

A 56-year-old male complained of lumbago in October 1986 and was admitted to our hospital in December 1986. Physical examination on admission revealed a massive splenomegaly and mild hepatomegaly (20 cm and 2 cm below costal margin). Generalized lymphadenopathy was also noted in the cervical, axillary, and inguinal regions. The leukocyte count was $16.4 \times 10^9/l$, including 79% lymphocytes (Table 1); about 50% of which resembled mature small lymphocytes, but their chromatin patterns were somewhat fine compared to those of normal mature lymphocytes. The remaining 50% had relatively large nuclei with a fine chromatin pattern, and prominent nucleoli (Fig. 1A). The nuclear contour of the later cells was occasionally clefted and folded, and they had irregular cytoplasmic projections. Bone marrow examination revealed a nucleated cell count of $284 \times 10^9/l$, including 78.8% lymphocytes without prominent nucleoli, but some of them had indented nuclei (Fig. 1B). The neoplastic cells in the BM were CD20+CD19+Ia1+sIgM+CD10+ by flowcytometric analysis (Table 2). Biopsy of the inguinal lymph node

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Table 1. Hematological Findings on Admission

Peripheral blood		Bone marrow	
Leukocytes	$16.4 \times 10^9/l$	Nucleated cell counts	$284 \times 10^9/l$
Stab cells	4%	Megakaryocytes	$18.75 \times 10^6/l$
Segmental cells	12%	ME ratio	2.8:1
Eosinophils	2%	Myelogram	
Monocytes	3%	Myeloid cells	12.8%
Lymphocytes	71%	Erythroid cells	5.2%
Atypical lymph.	8%	Lymphoid cells	81.6%
Red blood cells	$3.66 \times 10^{12}/l$	Mature lymphocytes	78.8%
Hemoglobin	115 g/l	Blastoid lymphocytes	2.8%
Hematocrit	34.0%		
Platelets	$126 \times 10^9/l$		

demonstrated a diffuse infiltration composed of small lymphocytic cells (Fig. 2). The pathological diagnosis was diffuse and small cleaved NHL, according to the working formulation of the Non-Hodgkin's Lymphoma Pathologic Classification. The neoplastic cells in the excised lymph node had CD20+CD19+Ia1+sIgM+ (lambda chain) but were negative for CD10 (Table 2). Monoclonal gammopathy was not detected.

The patient was given four courses of CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone). In May 1987, splenomegaly and lymphadenopathy had disappeared, however, the BM was still heavily

Table 2. Surface Marker Analysis (Percent Positive) on Admission

	CD	Peripheral blood	Bone marrow	Lymph node	Cerebrospinal fluid
OKT3	CD3	15.0	17.1	15.6	2.1
OKT4	CD4	11.8	8.8	12.0	<1.0
OKT8	CD8	5.4	5.9	15.0	2.9
OKT10	CD38	68.4	86.6	29.8	ND
Ia1		88.4	88.6	75.5	99.5
B1	CD20	83.2	83.0	62.5	98.1
B2	CD21	17.5	12.6	49.5	8.6
B4	CD19	84.0	85.6	60.3	97.9
HLA-DR		85.4	ND	87.9	ND
J5	CD10	23.0	76.8	5.2	15.6
sIg (total)		85.4	87.0	85.0	96.4
IgG		1.0	ND	11.6	66.9
IgA		1.5	ND	7.0	52.9
IgM		82.9	ND	81.5	97.3
IgD		23.4	ND	11.4	36.4
Igκ		2.3	ND	5.7	25.5
Igλ		79.6	ND	82.8	80.7

CD: cluster designation, ND: not done.

infiltrated with small lymphocytes (75.6%) and the circulating lymphocytes count remained high. Because the patient's status was generally improved and the hematologic conditions were not progressive, he was followed

Fig. 1. A) Photomicrogram obtained from the peripheral blood on admission. The circulating cells were similar to mature small lymphocyte in size, and contained large nuclei with irregular cytoplasmic contours. They have a relatively fine chromatin pattern and prominent nucleoli (May-Grünwald-Giemsa stain, $\times 800$). B) A representative photomicrogram of the infiltrated cells in the bone marrow. The neoplastic cells did not have apparent nucleoli; some cells had indented nuclei (May-Grünwald-Giemsa stain, $\times 800$).

Fig. 2. Photomicrogram of the excised lymph node. Histological findings of the right inguinal lymph node biopsy specimen demonstrated a diffuse neoplastic lesion composed of small lymphocytic cells (hematoxylin-eosin stain, $\times 400$).

up as an out-patient and treated with intermittent oral cyclophosphamide (100 mg/day).

In May 1988, the patient again manifested splenomegaly (10 cm below the costal margin) with generalized lymphadenopathy and was readmitted. Bone marrow aspiration revealed lymphocytic infiltration and an ultrasonogram demonstrated intra-abdominal lymphadenopathy. Thus, the patient was again treated with CHOP therapy and this regimen was effective. However, the patient complained of neurologic symptoms, including a tingling sensation in both lower extremities, headache, and nausea. A spinal tap revealed lymphocytic infiltration of more than $1 \times 10^9/l$: the neoplastic cells were CD20+CD19+Ia1+sIgM+CD10- (Table 2). Although the patient was treated with intrathecal methotrexate injection (15 mg, 8 times), cytosine arabinoside (20 mg, 6 times), and skull irradiation with generalized chemotherapy, optic and facial nerve palsy appeared. These treatments were partially effective in cytoreduction, however, the patient died of sepsis on February 6, 1989.

Discussion

Chronic lymphocytic leukemia and NHL in the leukemic phase are included in lymphoproliferative disorders, and patients with these two neoplastic forms sometimes exhibit similar clinical features (1-4). Therefore, the differential diagnosis of these two neoplasias remains controversial. On the other hand, LSCL has been frequently used and encompasses a variant form of CLL in European and American reports (7-9), presenting clinically without lymphoma with a poorer prognosis than those with typical CLL (8). Recently, however, the trend has been to abolish this diagnosis in the classification of lymphoma to avoid confusion, and the entity of leukemic manifestation of NHL currently includes

LSCL (10).

We first thought that the patient suffered from CLL or NHL in the leukemic phase. However, the morphology of the neoplastic cells led us to consider the diagnosis of LSCL. First, the count of circulating lymphocytes on admission was very high ($13 \times 10^9/l$), but they had CD10 antigen with heterogeneous morphologies. Second, the course of disease was relatively progressive with invasive nature. His general condition, including lymphadenopathy and splenomegaly, improved after chemotherapy, although the neoplastic cells remained in the BM and PB with high occurrence rates. Finally, the morphology of neoplastic cells in the PB was different from those of typical CLL and those of leukemic manifestation of follicular lymphoma (10, 11): some of the neoplastic cells in this case had nucleoli and clefted nuclei, but the clefts were not very narrow as those seen in the leukemic phase of follicular lymphoma. These clinical and cytologic features suggest the presence of the spectrum of chronic lymphoid leukemia consisting of CLL and leukemic NHL. Currently, the diagnosis of LSCL is considered to be included as the leukemic phase of intermediate or mantle zone (centrocytic) NHL (12, 13). The reason, however, that we hesitated to diagnose it as the leukemic phase of intermediate lymphocytic lymphoma is that the main lesion in this patient seemed to be BM and/or PB, since after the first chemotherapy lymphadenopathy and splenomegaly disappeared, whereas the BM infiltration abnormal cells in the PB remained.

Pombo de Oliveira et al (14) reported 16 patients with leukemic phase of mantle zone (intermediate) lymphoma, including 5 suspected cases, and none of the 16 cases manifested the massive splenomegaly likely in this case (20 cm): most of them had splenomegaly less than 10 cm below costal margin (14). Nevertheless, the circulating lymphocytes reported by them resembled those presented here, therefore, the clinical viewpoint alone is insufficient to rule out the possible diagnosis of the leukemic phase of intermediate NHL; the most possible diagnosis for this patient might be the leukemic phase of intermediate NHL at this time.

In the present case, the neoplastic cells found in the BM, PB, LN, and CSF might have originated from the same clone. The neoplastic cells in the LN expressing sIg, CD19, and CD20 without CD10 are considered to be more mature cells than those of BM (sIg+CD19+CD20+CD10+). Thus, it is possible to consider that the CD10- cells in the PB migrated and expanded in the LN. The expression of CD10 in the neoplastic cells in the leukemic phase of intermediate NHL is controversial; the most likely interpretation is that the neoplastic cells in the PB have CD10 antigen by flowcytometric study (12, 13, 15), however Weisenburger et al (11) failed to demonstrate CD10 reactivity by immunocytochemistry on frozen sections of LN. Pombo de Oliveira et al (14) described that circulating lymphocytes of all 16 cases had

CD5 antigen and 8 of 14 cases examined had CD10 antigen. Thus, it is uncertain whether the variety of CD10 expression in the neoplastic cells of leukemic phase of intermediate NHL that was reported previously might be attributable to the difference of techniques (12, 14) or it represents the nature of the disease (14), since the current case also showed the dissociation of CD10 expression between BM and LN. Therefore, detailed investigations of patients with B-cell lymphoproliferative disease are needed to clarify their biological and hematological significance in the spectrum of B-cell type neoplasias.

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