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Case Report

Hairy B-Cell Lymphoproliferative Disorder and its Differential Diagnosis: a Case with Long-Term Follow-Up

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Abstract. Hairy B-cell lymphoproliferative disorder (HBLD) is one of chronic polyclonal B-cell lymphocytosis. We report a 47-year-old female Japanese patient diagnosed as having HBLD based on lymphocytosis with hairy cell appearance and characteristic phenotypes including CD11c+ and without B-cell monoclonality. She was a non-smoker and possessed HLA-DR4. She has been closely followed up without treatment and lymphoma development for over five years. Although this disease is quite rare and has been reported, to our knowledge, in only 13 Japanese cases, an accurate diagnosis, particularly differential diagnosis from persistent polyclonal B-cell lymphocytosis or hairy cell leukemia-Japanese variant is essential for the prevention of unnecessary treatments.

Keywords: Hairy B-Cell Lymphoproliferative Disorder, Polyclonal B-Cell Lymphocytosis, Hypergammaglobulinemia, CD11c, HLA-DR4.

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Introduction. Primary lymphocytosis is defined as a set of conditions associated with an increase in the absolute number of lymphocytes secondary to an intrinsic defect in the expanded lymphocyte population.[1] These conditions include monoclonal lymphocytic malignancies and polyclonal B-cell lymphocytosis. A representative form of the latter is persistent polyclonal B-cell lymphocytosis (PPBL), with more than 100 cases having been reported in western countries.[2-6] Another form of polyclonal B-cell lymphocytosis is hairy B-cell lymphoproliferative disorder (HBLD), which is extremely rare with, to the best of our knowledge, only 13 cases reported, all of them in Japanese people.[7-14]

For a right diagnosis of HBLD, distinguishing this disease from hairy cell leukemia-Japanese variant (HCL-Jv), an accurate workup is needed

because of their morphological similarities including hairy cell appearance and a characteristic immunophenotype.[8] The essential difference is whether B-cell monoclonality is detected or not.

This report concerns a female patient with HBLD. The absence of B-cell clonalities was confirmed regarding the lack of light chain restriction verified both using flow cytometric analysis and clonal immunoglobulin (Ig) gene rearrangement determined using Southern blotting analysis and multiplex polymerase chain reaction (PCR).

Clinical Presentation. A 47-year-old non-smoking Japanese woman visited the University Hospital Kyoto Prefectural University of Medicine in June 2012 because of blurred vision, exertional dyspnea, and an uncomfortable feeling in the throat. Her past medical history was not remarkable. Physical examination and positron emission tomography/computed tomography detected hepatomegaly (2 cm below the right costal margin) and splenomegaly (4cm below the left costal margin), but no definite signs of lymphadenopathy. Small retinal bilateral hemorrhages were detected. Hematological examination showed 10.5 g/dl Hb, 175 x 10^9 /l platelets, and 23.0 x 10^9 /l WBC with 67.0% atypical lymphocytes. Peripheral blood smears and electron microscopic examination found that these atypical lymphocytes had irregularly shaped abundant cytoplasms with partially hairy projections (**Figure 1**).

No ribosome-lamella complex (RLC) was found, but rouleau formation was detected. The serum level of IgG was 6278 mg/dl, of IgA 359 mg/dl, and of IgM 283 mg/dl. Fractionation of serum protein showed no M-peak, and urine and serum immunoelectrophoretic studies showed no M-protein. Flow cytometric (FCM) analysis of the peripheral blood immunophenotype showed positivity for CD11c (38.9%), CD19 (64.3%), CD20 (62.5%), and CD22 (50.5%), and negativity for CD5 (16.6%), CD10 (0.9%), CD23 (0.1%), CD25 (1.0%), FMC-7 (3.7%), and ZAP-70 (4.4%). No light chain restriction was detected (κ:λ=33.9%:13.6%). Southern blotting analysis of peripheral blood cells showed no rearrangement band for either the clonal immunoglobulin heavy chain (IGH) gene (JH, Cμ) or the light chain gene (Jκ, Cκ, Cλ). Multiplex PCR analysis using the three sets of VH primers and one JH consensus primer as specified for the BIOMED-2 primer sets[15] showed no monoclonal peak of IGH gene recombination (**Figure 2**). Cytogenetic analysis of bone marrow cells using G-banding revealed 46, XX [11/11]. Direct DNA sequencing showed no BRAF V600E mutation.[16] Our patient possessed the HLA-DR4/DR5 histocompatibility complex. She was diagnosed as having HBLD based on the finding of a polyclonal proliferation of hairy B-cells with phenotypes such as CD5-, CD11c+, CD20+, and CD25-. Although she has been closely followed up without treatment, her WBC count has been stable (8.9 x 10^9/l) (atypical lymphocytes 31.0%), and her general status has remained fair over five years.

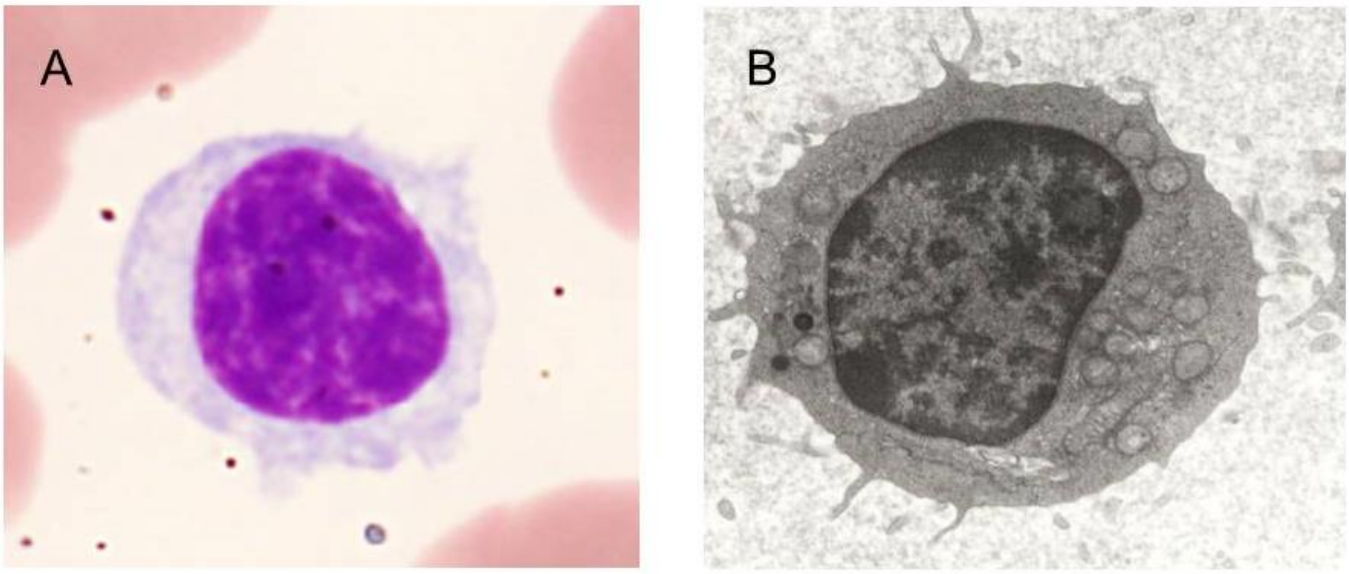

Figure 1. Peripheral blood smears (A) and electron microscopic examination (B) show atypical lymphocytes with partially hairy projections and abundant irregularly shaped cytoplasms. No ribosome-lamella complex was found.

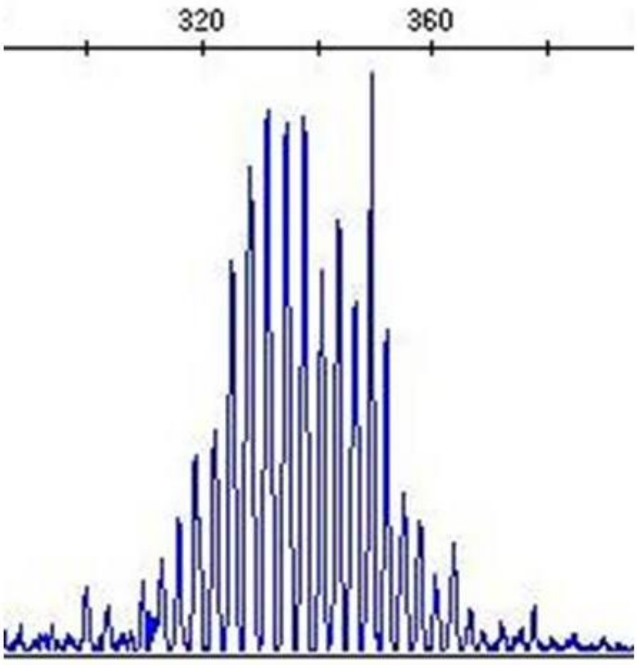

Figure 2. Detection of immunoglobulin heavy chain (IGH) gene recombinations using multiplex polymerase chain reaction (PCR) using a tube A primers set (VH FR1) and one consensus primer (JH) in accordance with the BIOMED-2 protocol.[15] Many different IGH PCR products without a monoclonal peak were detected.

Discussion. The subject of this report is a 47-year-old female Japanese patient with HBLD, which is a very rare disorder so that an accurate diagnosis is important but difficult. To establish the diagnosis of this case, we had to exclude PPBL and HCL-Jv. A comparison between the features of our case, HBLD reported cases, PPBL and HCL-Jv is shown in **Table 1**.

According to a review of previous reports concerning 13 cases of HBLD, the median age for onset of HBLD was 57 years (range 29-80 years) and the male: female ratio was 3:10. These cases generally possessed HLA-DR4.[8,12,14] Cases of PPBL, on the other hand, usually are also young to middle-aged women, often smokers and HLA-DR7 positive.[5,6] HBLD and HCL-Jv[17,18] are more prevalent in the elderly than PPBL.[6]

As to the clinical features of our case, they showed splenomegaly but no definite signs of lymphadenopathy as mentioned in previous reports of HBLD,[8-11,13,14] PPBL[6] and HCL-Jv.[17,18] Laboratory findings of the peripheral blood showed lymphocytosis and elevated serum IgG level without M-protein. The retinal hemorrhages of our case were thought to be due to hyperviscosity associated with her hypergammaglobulinemia. All the reported HBLD cases[7-14] and some of the HCL-Jv cases[18] had elevated serum IgG levels with a polyclonal pattern but without M-protein. On the other hand, PPBL cases reportedly had elevated serum IgM levels.[6] Although this IgM elevation is mostly polyclonal, Cornet et al. reported that 2 of 111 cases had IgM monoclonal gammopathy of undetermined significance at the time of PPBL diagnosis.[6]

Table 1. Comparison of previously reported cases of hairy B-cell lymphoproliferative disorder (HBLD), persistent polyclonal B-cell lymphocytosis (PPBL), and hairy cell leukemia-Japanese variant (HCL-Jv).

	HBLD	PPBL	HCL-Jv
Male/female	3/10	20/91	21/15
Median age (range)	57 (29-80)	Male 40.9 (28-57) Female 40 (19-66)	56# (32-86)
Clonality	polyclonal	polyclonal	monoclonal
History of smoking	8%	98%	NR
Splenomegaly	85%	10%	94.4%
Lymphoadenopathy	20%	16-24%##	22.9%
Hypergammaglobulinemia	IgG	IgM	IgG
Hairy cell appearance	+	-	+
CD11c	+	-	+
Chromosomal abnormality	-	+###	NR
HLA-DR	DR4	DR7	NR
Malignant transformation	NR	possible	+
References	[7-14]	[6]	[17]

NR, not reported; HBLD, hairy B-cell lymphoproliferative disorder; PPBL, persistent polyclonal B-cell lymphocytosis; HCL-Jv; hairy cell leukemia-Japanese variant; # Mean age; ## reference [4,5]; ### +i(3q), t(14;18) or aneuploidy etc.

Morphologically, the atypical lymphocytes of our case had a hairy cell appearance and a round nucleus, but HBLD cases, including our case, did not have RLC. Although RLC is a specific electron microscopic finding of hairy cell leukemia, it had been found in only 4 of 26 (15%) HCL-Jv cases.[17] The immunophenotype of our case was CD5-, CD11c+, CD20+, and CD25-, which corresponds to previously reported findings of HBLD as well as of HCL-Jv.[8,18] For these reasons, it might be impossible to distinguish HBLD from HCL-Jv regarding morphology and immunophenotype. Moreover, among the PPBL features the atypical lymphocytes are morphologically binucleated and not villous, and immunophenotypically CD11c-.[3]

For these reasons, the clonality analyses are essential for distinguishing HBLD from HCL-Jv and morphology and immunophenotype from PPBL. No B-cell clonalities were detected in our case by FCM analysis for light chains, by Southern blotting and multiplex PCR for the rearrangements of Ig genes, by cytogenetic analysis using G-banding, and by immunoelectrophoretic studies for M-protein. Although proliferated B-cells of both HBLD and PPBL cases are polyclonal, some of the latter may have small numbers of clonal B-cells. In fact, PPBL can be associated with recurrent chromosomal abnormalities such as +i(3q)[4,6] or t(14;18)[19] etc. and clonal Ig gene rearrangements.[3,6,20] Furthermore, while there have been no reports on the clonal evolution of HBLD, cases of PPBL can develop B-cell lymphoma.[5,6]

In conclusion, we reached the diagnosis of HBLD for our case on the basis of hairy cell appearance, the presence of a characteristic immunophenotype (CD5-, CD11c+, CD20+, and CD25-), and the absence of B-cell monoclonality. All previously reported cases of HBLD also satisfied these features. These findings are useful for the correct diagnosis of HBLD and for differentiating this disease from PPBL and HCL-Jv. Of the 14 reported HBLD cases including our case, 7 cases were from Osaka University,[8,9] and 2 from our Institute.[14]

Until now and without therapy, our case has not shown any B-cell clonality nor any malignant development of HBLD. A wait-and-see approach without treatment can, therefore, be considered a potentially useful strategy for HBLD. Our case demonstrates that accurate diagnosis of this disease is essential for the prevention of unnecessary treatments.

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