Aggressive B-Cell Lymphoma with Dual Surface Immunoglobulin Light-Chain Expression

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Abstract

Dual surface immunoglobulin light-chain expression in B-cell malignant neoplasm is a rare event, and has been predominantly reported in chronic lymphocytic leukemia. Herein, we report a case of aggressive B-cell lymphoma with κ/λ -dual surface immunoglobulin light-chain expression of a 69-year-old woman. The lymphoma cells were positive for CD5, CD19, CD20, HLA-DR, Ig κ and Ig λ . Southern blot analysis confirmed rearranged bands for both light chains with a monoclonal heavy chain rearrangement. She was treated with a combination of rituximab and CHOP regimen, but died of the progressive disease. To our knowledge, this is the first case of aggressive B-cell lymphoma showing dual κ/λ expression; the possible mechanisms of abnormal light chain expression are discussed.

Key words: aggressive B-cell lymphoma, κ/λ dual expression, gene rearrangement

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Introduction

Mature B lymphocytes typically express either κ or λ light-chain, a restriction known as allelic exclusion. Whereas 99.99% of B cells have allelic exclusion at the IgH locus in mice (1), there are few data to draw from to estimate the extent of allelic exclusion at the IgL locus. Indeed, there have been several examples that report on light-chain double producers in normal peripheral B cells as well as in B-cell malignant neoplasms including chronic lymphocytic leukemia (CLL) (2). However, probably because of the limited number of reports available to date, the cellular and molecular mechanisms of dual light-chain expression have not been completely elucidated. Herein, we report a case of B-cell lymphoma with dual surface immunoglobulin light-chain expression, which pursued a clinically aggressive course.

Case Report

A 69-year-old Japanese woman was admitted to our hospital in July 2006 because of high fever and chills persisting for 4 weeks. She had a past history of cerebral infarction.

She had massive splenomegaly with no obvious lymphadenopathy. Hematological data was as follows: hemoglobin 7.2 g/dL, platelets $95 \times 10^9/L$ and white blood cells (WBC) $12.1 \times 10^9/L$ with 94% neutrophils, 5% lymphocytes, 1% myeloblast. Serum levels of lactate dehydrogenase (LDH), C-reactive protein, soluble interleukin-2 receptor (sIL-2R) and ferritin were 1680 IU/L, 2.1 mg/dL, 9882 U/mL and 2977 ng/mL, respectively. Serum antibody titers did not indicate the presence of autoimmune disease as well as any primary or continuing infection with cytomegalovirus and Epstein-Barr virus. Bone marrow examination disclosed infiltration of abnormal lymphoid cells (15.8% of all nucleated cells) with a high degree of nuclear atypia and distinct nucleoli. Mature histiocytes phagocytosing various hematopoietic cells were also observed. Surface marker analysis of bone marrow mononuclear cells revealed that they were positive for CD5 (55%), CD19 (68%), CD20 (74%) and HLA-DR (72%). Notably, the lymphoma cells were positive for both Ig κ (97%) and Ig λ (89%) based on a CD19+ gate strategy (Fig. 1A). Rearrangement bands for immunoglobulin heavy chain (JH) and both light-chain genes (J κ , C λ) were detected by Southern blot analyses, while only a germline band with decreased intensity was observed when C κ

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Figure 1. Flow cytometric and genetic analyses of the dual κ/λ -positive lymphoma cells. (A) (a) Bone marrow cells were sorted by a CD45⁺ gate procedure using Cytomics FC 500 (BECKMAN COULTER, Tokyo, Japan) and an abnormal cell population, which showed positivity for CD5 and CD20, was detected (arrow). (b, c) Among them, the CD19⁺ fraction was examined for the expression of Ig κ and Ig λ . Antibodies recognizing human kappa F(ab')₂ and lambda F(ab')₂ were purchased from BD Biosciences (San Jose, CA, USA). (B) Southern blot analyses of bone marrow cells using probes for immunoglobulin heavy chain (a; JH) and both light-chain genes (b; J κ , c; C κ and d; C λ) are shown. Arrow indicates the rearranged bands. N; normal sample, P; patient sample, B/H; BamHI/HindIII, H; HindIII, B; BamHI, E/H; EcoRI/HindIII.

probe was used for the analysis (Fig. 1B). Cytogenetic analysis of bone marrow cells showed the complex abnormality, with representative karyotype of 46,XX, -1, -1, -2, -3, add (4) (p14), del (7) (q34), -8, add (9) (p13), add (11) (p11), -14, -14, del (15) (q22), +mar1, +mar2, +mar3, +mar4, +mar5, +mar6, +mar7 (Fig. 2). Thus, she was diagnosed as having B-cell non-Hodgkin's lymphoma associated with hemophagocytic syndrome (HPS). The sites of involvement, clinical features and pathological findings suggested that the lymphoma cell might be categorized into either diffuse large B-cell lymphoma or intravascular large B-cell lymphoma according to the World Health Organization Classification. She was treated with R-CHOP regimen, which initially showed a

good clinical response. However, she had the complication of acute cholangitis in September 2006, which was the obstacle in conducting further chemotherapy. In December 2006, the patient relapsed and died of progressive disease.

Discussion

We report a unique case of B-cell lymphoma showing κ/λ -dual expression on the cell surface, with rearrangements in both light chain genes on Southern blot analysis. Although the underlying molecular mechanisms for the generation of κ/λ -positive clones have not been completely elucidated, three assumptions have been suggested to date (2); 1)

Figure 2. G-banded karyotype of lymphoma cells: 46,XX, -1, -1, -2, -3, add(4)(p14), del(7)(q34), -8, add(9)(p13), add(11)(p11), -14, -14, del(15)(q22), +mar1, +mar2, +mar3, +mar4, +mar5, +mar6, +mar7 [1], 47, idem, +mar [1], 46, idem, +8, -add(11), -mar7, +mar [2], 47, idem, -add(9), -13, +14, add(18)(q23), -mar7, +mar3 [1], 47, idem, -add(9), +add(9)(q34), +14, -16, add(18)(q23), -mar7, +2mar [1], 47, idem, -X, -add(9), +add(9)(q34), +14, add(18)(q23), -mar6, -mar7, +3mar [1], 46, XX [3]. Metaphases were G-banded by a trypsin-treated Giemsa stain. Abberant chromosomes are indicated by arrows.

a failure to destroy expression of the original L gene during a secondary light-chain rearrangement [receptor editing (3)] , 2) a clonal progression from a single rearranged light-chain into dual light-chain expressing cells, 3) simultaneous rearrangements at both light-chain loci. Among them, we speculated that a failure of receptor editing might underlie the generation of dual κ/λ positive clones in the present case, although the data available were too limited. In general, κ rearrangements are favored over λ rearrangements, and κ loci in λ producers are often rearranged and inactivated by rearrangements of the kappa-deletion element (KDE) (3, 4). However, it has also been reported that such processes occasionally fail to destroy the original κ light-chain gene (2, 3). Thus, it might be possible to consider that a moderately decreased germline band detected by C κ probe (Fig. 1B-c) might imply the presence of rearrangement involving KDE to heptamer-nonamer recombination signal sequences, which causes the deletion of C κ locus as well as Ig κ enhancer (5). However, in the present case, this rear-

angement might not be sufficient to inactivate the transcription of Ig κ gene, thereby creating dual κ/λ light-chain positive clones. This point warrants further investigation.

Of interest is that the present case displayed a clinically aggressive course, whereas the previous case reports of κ/λ -dual expression in B-cell neoplasm were predominantly observed in indolent cases comprising CLL (2, 6-8). Unfortunately, there has been no evidence available demonstrating the biological properties of dual κ/λ producers, which would support our observations. In addition, we could not exclude the possibility that the clinical aggressiveness in the present case might be related to the underlying pathological features (aggressive B-cell lymphoma), and the coexistence of B-cell lymphoma-associated HPS, rather than dual κ/λ rearrangement/expression. Therefore, further investigations into similar cases would be necessary to clarify the molecular mechanism and the clinical significance of double light-chain producers.

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