Successful Allogeneic Hematopoietic Stem Cell Transplantation in a Young Patient with Richter Syndrome Presenting with Chronic Lymphocytic Leukemia and Diffuse Large B-Cell Lymphoma with Different Cell Origins

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Abstract

A 32-year-old woman was referred to our hospital due to systemic lymphadenopathy. The patient’s peripheral blood showed expansion of CD5⁺CD20⁺CD38⁺CD23⁻ mature lymphocytes. However, the axillary lymph nodes were infiltrated by both CD23⁺ large lymphocytes and CD23⁻ small lymphocytes. Because the pattern of the rearranged immunoglobulin heavy chain gene was different between the peripheral blood and lymph node samples in a Southern blot analysis, the patient was diagnosed with Richter syndrome, in which diffuse large B-cell lymphoma develops from a clone distinct from B-cell chronic lymphocytic leukemia. After undergoing rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) therapy, the patient was successfully treated with allogeneic hematopoietic transplantation, and no relapse was observed for three years.

Key words: Richter syndrome, diffuse large B-cell lymphoma (DLBCL), B-cell chronic lymphocytic leukemia (B-CLL)

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Introduction

B-cell chronic lymphocytic leukemia (B-CLL) is the most common leukemia in Western countries and accounts for -30% of all cases of leukemia. In contrast, it comprises only 7% of all types of leukemia in Japan. B-CLL occurs primarily in older patients with a median age of approximately 70 years, and only approximately one-third of patients are under 60 years of age at diagnosis (1). B-CLL is characterized by clonal expansion of B-CLL cells positive for CD5, CD19, CD20, CD23 and monoclonal surface immunoglobulin (Ig) light chains (2). Additionally, B-CLL cells show an appearance similar to that of mature B-lymphocytes and usually do not proliferate in vitro. In accord with these findings, B-CLL patients can often survive without developing clinical symptoms for several years, even if they are observed without treatment.

Richter syndrome (RS) represents the clinicopathologic transformation of B-CLL into aggressive lymphoma, most commonly presenting with the pathologic characteristics of diffuse large B-cell lymphoma (DLBCL). The clinical definition of RS is ambiguous and encompasses at least two molecularly different conditions based on the origin of the lymphoma cells: (i) transformation of a B-CLL clone into DLBCL most likely due to additional genetic abnormalities (this form accounts for approximately 80% of cases); (ii) development of DLBCL from a novel clone distinct from the initial B-CLL clone (3-5). RS has been reported to occur in 2-8% of patients with...
B-CLL, primarily in elderly individuals, during their clinical courses. The clinical outcomes of RS are generally poor with a median survival time of less than one year, even when intensive chemotherapies effective for high-grade non-Hodgkin’s lymphoma or acute lymphoblastic leukemia (ALL) are applied (3-5). Additionally, as most RS patients are elderly, allogeneic hematopoietic stem cell transplantation (alloHSCT) is applicable in limited cases only (6).

We herein report a rare case of a young patient with RS who presented with concomitant B-CLL and DLBCL with different cell origins. In this patient, myeloablative allogeneic hematopoietic transplantation was useful in eliminating both B-CLL and DLBCL clones for at least three years.

**Case Report**

A 32-year-old woman was referred to our hospital with a chief complaint of systemic lymph node swelling in June 2009. She had been free from fever, body weight loss and night sweats. A physical examination revealed mild splenomegaly and multiple painless lymphadenopathies in the neck, axillary and inguinal regions. The laboratory findings were as follows: Hb: 10.4 g/dL (normal: 13.9-17.0); WBC: 8,200/mm$^3$ (normal: 3,900-9,300) with neutrophils: 24.5%, lymphocytes: 64.0% (total number: 5,248/mm$^3$), monocytes: 5.0%, basophils: 4.5% and eosinophils: 2.0%; platelet (Plt): 27×10$^4$/mm$^3$ (normal: 16.7-36.2×10$^4$); serum albumin: 4.3 g/dL (normal: 3.6-5.5 g/dL); C-reactive protein: 0.24 mg/dL (normal: <0.3 mg/dL); lactate dehydrogenase (LDH): 409 IU/L (normal: <225 IU/L). The soluble IL-2 receptor (sIL-2R) level was elevated to 3,212 U/mL. Bone marrow (BM) aspirate demonstrated infiltration of small lymphocytes in 51.4% of the total BM cells. Chromosomal analyses using the G-banding technique showed that the BM cells had a normal karyotype. Under the diagnosis of RS, the patient was treated with six courses of combination chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). After the administration of chemotherapy, complete remission of the DLBCL was confirmed on FDG-PET imaging. However, the rearranged band of the IgH gene was still detected on a polymerase chain reaction (PCR) analysis of the samples obtained from the PB and BM aspirate (data not shown). Therefore, we performed alloHSCT from an human leukocyte antigen (HLA)-matched sibling donor with PB as a stem cell source using a myeloablative conditioning regimen consisting of cyclophosphamide and total body irradiation in December 2009. Acute graft-versus-host disease (GVHD) was observed in the patient’s skin (grade 1) on day 100, both resolved spontaneously without the administration of additional treatment. After alloHSCT, the clonal IgH gene rearrangement disappeared from the PB and BM cells for approximately three years.
addition, conducting analyses of the somatic mutation of the...tion. In accord with these reports, we found that the phenotype of the DLBCL cells was different from that of the B-CLL cells in our patient. At first, we supposed that the B-CLL cells had changed their phenotype during the transformation to RS. However, because we detected an additional band in the LN sample on a Southern blot analysis, we concluded that the DLBCL originated from a novel clone distinct from the initial B-CLL clone. In this regard, conducting Southern blot analyses is particularly important for determining the origin of DLBCL cells among CD23-negative lymphocytes, ×600. (D) The large lymphoid cells also expressed CD5, ×200 (E) but not cyclinD1, ×200 (F).

Discussion

We herein report a rare case of RS in a young Japanese patient who presented with concomitant B-CLL and DLBCL. As transformation into RS is a critical event in B-CLL patients, close monitoring is required for patients harboring clinical and/or biological risk factors for RS development. Conventional risk factors present at the time of B-CLL diagnosis include: (i) the expression of CD38; (ii) an absence of del13q14 and (iii) lymph node size ≥3 cm, all of which were detected in this case (5). Other reported risk factors for RS development include the CD38 genotype and use of specific Ig variable genes (7-9). It has been reported that B-CLL cells change their phenotype when they transform into DLBCL cells, such as occurs during the loss of CD5 and CD23. In accord with these reports, we found that the phenotype of the DLBCL cells was different from that of the B-CLL cells in our patient. At first, we supposed that the B-CLL cells had changed their phenotype during the transformation to RS. However, because we detected an additional band in the LN sample on a Southern blot analysis, we concluded that the DLBCL originated from a novel clone distinct from the initial B-CLL clone. In this regard, conducting Southern blot analyses is particularly important for determining the origin of DLBCL cells to achieve a better understanding of the molecular pathology of RS (10). In addition, conducting analyses of the somatic mutation of the IgH gene is considered to be useful not only for predicting the prognosis, but also for determining the origin of DLBCL and B-CLL (7, 8), although we missed the chance to analyze this status in our case. Furthermore, the significance of prognostic factors predicting the transformation to RS, as described above, should be reevaluated in cases involving other type of RS, as observed in our patient, in whom DLBCL developed from a clone distinct from the B-CLL clone.

As for the pathogenesis of B-CLL, it has been shown that virtually all patients with B-CLL experience a precursor phase called monoclonal B lymphocytosis (MBL), that is, asymptomatic monoclonal or oligoclonal B-cell proliferation (11). This finding suggests a stepwise transformation to B-CLL from MBL. Furthermore, Kikushige et al. recently reported that, when hematopoietic stem cell (HSC) fractions isolated from B-CLL patients are transplanted into immunodeficient mice, these cells cause monoclonal or oligoclonal B-cell proliferation with different cell origins in each recipient mouse. This result suggests that some genetic abnormality that promotes B-cell proliferation occurs at the most immature HSC level in B-CLL patients (12). A similar scenario was very recently described in multiple myeloma, indicating that an overexpression of the (MafB) oncogene at the hematopoietic stem/progenitor cell level causes a hematoologic malignancy resembling human plasma cell neoplasm in transgenic mice (13). During the last few years, several genetic abnormalities underlying myeloid malignancies have been identified, including mutations of (TET2), (ASXL1), (EZH2) and (DNMT3A) (14). Although similar abnormalities that promote B-cell malignancies have not been found in clinical samples as yet, future studies using genome-wide screening may identify novel abnormalities preceding the development of B-CLL and multiple myeloma. Additionally, such studies will be useful in molecularly discriminating between the two types of RS, which are different in terms of...
The authors state that they have no Conflict of Interest (COI).

References


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