Diffuse Large B-Cell Lymphoma Carrying both t(3 ; 7)(q27 ; p12) and t(8 ; 14)(q24 ; q32)

Yukitaka Katsura¹, Ikuyo Ohta¹, Chikashi Yoshida¹, Haruo Ohtani² and Takuya Komeno³

Abstract

We report a 60-year-old man with diffuse large B-cell lymphoma harboring both t(3 ; 7)(q27 ; p12) and t(8 ; 14)(q24 ; q32). Although he received six courses of conventional combination chemotherapy plus rituximab, early relapse occurred. Four courses of an intensive salvage regimen and high-dose chemotherapy with autologous peripheral blood stem cell transplantation were performed. The patient has remained in complete remission for over 24 months. This case is noteworthy because both genetic abnormalities are implicated in lymphomagenesis.

Key words: diffuse large B-cell lymphoma, t(3 ; 7)(q27 ; p12), t(8 ; 14)(q24 ; q32), MYC, autologous stem cell transplantation

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Introduction

Genetic alteration of IKZF1, located at 7p12, is frequently seen in acute lymphoblastic leukemia (ALL) and is associated with a poor prognosis (1-3). However, involvement of the gene in lymphoma has not been clearly elucidated. Only a few cases of lymphoma with t(3 ; 7)(q27 ; p12), which results in the fusion of IKZF1 and BCL6, have been reported to date (4, 5). However, a genetic change of MYC, located at 8q24, has been associated with a variety of hematopoietic tumors, leukemias and lymphomas. Translocation or rearrangement of MYC is detected in some cases of diffuse large B-cell lymphoma (DLBCL), and it is associated with a poor prognosis.

Here we present the first reported case of DLBCL harboring t(3 ; 7)(q27 ; p12) and t(8 ; 14)(q24 ; q32), which are both genetic abnormalities implicated in the pathogenesis of lymphoma. Although an early relapse was observed after the initial conventional chemotherapy, the patient was successfully treated with regimens that included high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCCT) and he has remained in complete remission for over two years to date.

Case Report

A 60-year-old man presented to our hospital with neck swelling. He had not noted any B symptoms, systemic symptoms such as fever, night sweats and weight loss. His past history was unremarkable. Physical examination revealed marked bilateral cervical lymphadenopathy. Laboratory data (Table 1) showed elevated levels of serum LDH and soluble interleukin-2 (IL-2) receptor. A CT scan showed multiple enlarged lymph nodes in the bilateral cervical and mesentery regions. Biopsy of the cervical lymph node was performed. The tumor was composed mainly of large lymphoid cells with a starry sky appearance and a high Ki67 labeling index (about 80%) (Fig. 1). Small-sized tumor cells are infrequent (Fig. 1), and CD3+ reactive small lymphocytes were also admixed (not shown). The immunophenotype of tumor cells was CD20+, CD79a+, bcl2-, bcl6+, MUM1+, CD10- and EBER-. Cytogenetic analysis by G-banding demonstrated the following (Fig. 2): 46, XY, del(1)(p?), t(3 ; 7)(q27 ; p12), der(8) add(8)(p21) t(8 ; 14)(q24 ; q32), der(14)(8 ; 14)(q24 ; q32) [16]/46, XY [4]. Fluorescence in situ hybridization study showed MYC/IgH fusion signal in the tumor cells. Careful attention was necessary for

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the differential diagnosis between DLBCL and “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma” (6). We diagnosed the present case as DLBCL because the vast majority of tumor cells were large cells (6, 7). There was no evidence of bone marrow invasion. The clinical stage was defined as IIIA. The patient received six courses of conventional R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy and achieved complete remission.

One month after the final therapy session, the patient noticed a subcutaneous tumor in his anterior chest wall. He also began to feel severe pain and weakness in his left arm. A CT scan showed multiple subcutaneous tumors and enlarged lymph nodes in the bilateral axillary region. Biopsy of the subcutaneous tumor revealed relapse of DLBCL. As salvage therapy, he received two cycles of R-hyper-CVAD/R-MA (rituximab plus cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with rituximab plus methotrexate-cytarabine) regimen (8). This regimen was very effective and led to complete remission. Consolidation therapy with high-dose chemotherapy [LEED regimen (9)] supported by autologous PBSCT was performed. The patient has been in complete remission for over 24 months to date.

**Table 1. Laboratory Data on Admission**

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Blood chemistry</th>
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<tbody>
<tr>
<td>RBC 527×10^6 /μL</td>
<td>TP 8.0 g/dL</td>
</tr>
<tr>
<td>Hb 14.6 g/dL</td>
<td>ALB 4.7 g/dL</td>
</tr>
<tr>
<td>WBC 6100 /μL</td>
<td>AST 46 IU/L</td>
</tr>
<tr>
<td>seg 71%</td>
<td>ALT 20 IU/L</td>
</tr>
<tr>
<td>baso 1%</td>
<td>LDH 250 IU/L</td>
</tr>
<tr>
<td>eos 2%</td>
<td>ALP 194 IU/L</td>
</tr>
<tr>
<td>mono 7%</td>
<td>γ-GTP 51 IU/L</td>
</tr>
<tr>
<td>Lym 19%</td>
<td>T-bil 0.7 mg/dL</td>
</tr>
<tr>
<td>PLT 21.7×10^4 /μL</td>
<td>BUN 15.5 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Cre 1.06 mg/dL</td>
</tr>
<tr>
<td></td>
<td>CRP 0.04 mg/dL</td>
</tr>
<tr>
<td></td>
<td>sIL2R 1060 U/mL</td>
</tr>
</tbody>
</table>

**Discussion**

The *IKZF1*, located at 7p12, encodes the transcription factor Ikaros, a zinc-finger nuclear protein, which is required for normal lymphoid development. Recent studies showed that *IKZF1* alterations occur in 63-84% of *BCR-ABL1*-positive ALL and in 28% of *BCR-ABL1*-negative B-cell ALL, and are associated with a poor prognosis (1-3). The *IKZF1* deletions have been demonstrated to result in haploinsufficiency or expression of a dominant-negative Ikaros...
isoform. However, involvement of $IKZF1$ in lymphoma has only been reported in a limited number of cases. $IKZF1$ was shown to fuse to $BCL6$ as a result of t(3; 7)(q27; p12) in two DLBCL cases (4, 10). The 5-prime regulatory region of $BCL6$ was replaced by the 5-prime regulatory region of the $IKZF1$ gene, which seems to lead to deregulated expression of the $BCL6$ gene and appears to be related to lymphomagenesis. Irradiation and chemotherapy for these patients provided survival for only 16 and 17 months, respectively (4). This suggests that DLBCL with t(3; 7)(q27; p12) represents a distinct subgroup of DLBCL with a poor prognosis. One case of lymphoma with the same translocation was also previously reported but the details of the histological data and clinical course were not available (5).

It is noteworthy that the present case had t(8; 14)(q24; q32) in addition to t(3; 7)(q27; p12). Approximately 5 to 10% of DLBCLs demonstrate a $MYC$ rearrangement (7). DLBCLs with $MYC$ rearrangement are associated with a shorter survival even in the era of R-CHOP treatment: the optimal treatment for these patients has not yet been established (7, 11). Approximately 20% of cases with a $MYC$ rearrangement have a concurrent $BCL2$ or $BCL6$ translocation (double hit lymphoma) (7). B-cell lymphomas with concurrent $MYC$ and $IGH$-$BCL2$ rearrangements are characterized by highly aggressive clinical behavior and a poor clinical outcome. Less frequently, some cases of DLBCL have both $MYC$ and $BCL6$ rearrangement similar to the present case, and seemed to have a better prognosis than DLBCL cases with $MYC$ and $BCL2$ translocation (6, 12, 13). However, the present patient relapsed early after conventional chemotherapy, which suggests that the partner gene to $BCL6$ has a great impact on determining the prognosis in these DLBCL. R-hyper-CVAD/R-MA regimen followed by high-dose chemotherapy with autologous PBSCT could be an effective treatment option for a portion of DLBCL cases demonstrating these characteristic gene rearrangements. Further studies are necessary to clarify the clinical features and prognosis, and to establish the optimal treatment strategy for these characteristic DLBCLs.

The authors state that they have no Conflict of Interest (COI).

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References


