Clinicopathologic and Cytogenetic Analyses of Three Cases of Primary Uterine Non-Hodgkin’s Lymphoma

Hiroto Kaneko, Yuri Kita, Masafumi Taniwaki*, Kei Kashima* and Yasuo Ohkawara

Abstract

Primary uterine non-Hodgkin’s lymphoma (NHL) is an extremely rare disease. To accumulate more information on clinical data, we report three cases of primary uterine NHL with apparently the first demonstration of karyotypic analysis. Histological diagnosis was diffuse large B cell type in all patients. Two of them with advanced stage showed chemoresistance and a short survival. The remaining case with early stage showed an uneventful course following operation. No common chromosomal abnormality was detected. The therapeutic strategy for uterine NHL might therefore be similar to that for other types of aggressive NHL, although a larger study is needed.

Key words: NHL, uterus, karyotype

Case Reports

Case 1
On March 10, 1999, a 72-year-old woman visited our department complaining of abdominal pain that had developed one month earlier. Physical examination revealed left cervical lymph node swelling (2 cm in diameter) and a fist-sized hard tumor on her lower abdomen. A swollen uterus was observed on pelvic magnetic resonance imaging (MRI) (Fig. 1A). Increased serum lactate dehydrogenase (LDH) at 5,478 IU/l and soluble interleukin 2 receptor (sIL-2R) at 2,590 U/ml were seen. Diffuse large B cell NHL (DLBCL) was diagnosed pathologically in the biopsied cervical lymph node (Fig. 2A) with immunohistochemical positivity for leukocyte common antigen (LCA) and L26 and a negative result for UCHL-1. Results of cluster of differentiation (CD) 45 gated flow cytometry were positive for CD19, 20, and human leukocyte antigen (HLA)-DR that were consistent with B cell characteristics. Tumor cells also possessed surface IgM. Chromosomal analysis of the tumor cells showed a complex abnormality with more than three aberrations (Table 1). It is noteworthy that chromosome band 14q32.3, the locus of the IgH gene and most frequently involved region by various translocations in B cell NHL (9), was rearranged. She was classified as high risk according to the International Prognostic Index (IPI) (10). Standard combined chemotherapy regimen of CHOP (11) was not effective. Meningeal invasion that generated diplopia occurred on the 30th hospital day. Salvage intravenous chemotherapies, one consisting of mitoxantrone, etoposide, carboplatin, and prednisolone (12), and the other dexamethasone, high-dose cytosine arabinoside (Ara-C), and cisplatin (13), were ineffective. She died of the disease progression three months after the initial presentation.

From the Department of Hematology, Aiseikai Yamashina Hospital, Kyoto and *the Third Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto

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Reprint requests should be addressed to Dr. Hiroto Kaneko, the Department of Hematology, Aiseikai Yamashina Hospital, 19-4 Takehana Shichouno-cho, Yamashina-ku, Kyoto 607-8086

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Figure 1. A) Pelvic MRI that shows a markedly swollen uterus in Case 1. B) Abdominal CT scan of Case 2, depicting a swelling of uterus and paracorpal lymph nodes.

**Case 2**
A 65-year-old woman was admitted to our hospital on September 4, 1998, with a one-third decrease in urine volume that had continued for two weeks. She also had fever elevation of more than 38°C. Several bilateral cervical lymph nodes (3 cm in diameter) and a lower abdominal hard tumor (10 cm) were palpated. Abdominal computed tomography (CT) imaging showed swelling of the uterus and paracorpal lymph nodes (Fig. 1B). Renal dysfunction with oliguria was also present that was caused by ureteral compression by the tumor. Serum LDH was elevated at 5,239 IU/l and sIL-2R at 14,000 U/ml. Histological diagnosis of the biopsied specimen from left cervical lymph node was DLBCL (Fig. 2B). Findings of flow cytometry and surface immunoglobulin were the same as in Case 1. Complex abnormal karyotype was disclosed, including rearrangement of chromosome 19q13, where the BCL3 gene is located (14) (Table 1). The findings of IPI parameters defined her as high-intermediate risk. She was treated with standard CHOP that resulted in a minimal response. Bone marrow invasion and leukemic change appeared one month after the initial chemotherapy. Her disease was refractory to the second-line chemotherapies delivered similarly to those in Case 1. She died of sepsis six months after the diagnosis.

**Case 3**
A 45-year-old woman, whose uterine cervical polyp (1 cm in diameter) was found by a routine medical check without any subjective symptoms, was diagnosed as DLBCL in the biopsied specimen (Fig. 2C). She underwent a total hysterectomy on April 7, 1996. She was then introduced to our department for the purpose of adjuvant chemotherapy. No swelling of lymph nodes or other organs was detected by physical or radiological examinations. The pre-operative serum levels of LDH at 272 IU/l and sIL-2R at 216 U/ml were within the normal limits. The karyotype of the resected tumor was normal (Table 1). Flow cytometry was not available due to insufficient material. She was classified as low risk group according to the IPI. She received six courses of CHOP and has had an uneventful course for 59 months since the operation.

**Discussion**
Uterine lesions with stage III or IV NHL were considered by Vang et al (15) to be secondary involvement of systemic disease. However, uterine tumor size and the subsequent clinical manifestations in the present Cases 1 and 2 indicate that their uterine lesions were primary. The histological diagnosis of all three patients in the present study was DLBCL similarly to the previously reported cases (4, 5). The mechanisms of development of primary uterine NHL remain unclear since the data remains insufficient. In the current study, we conducted chromosomal analyses of the lymphoma cells to elucidate cy-
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Figure 2. Diffuse proliferation of large-sized lymphoma cells is observed in the biopsied lymph node specimen of Cases 1 (A) and 2 (B) and in the resected uterine cervical polyp of Case 3 (C) (HE stain, x400).

Table 1. Clinicopathologic and Cytogenetic Characteristics of Patients

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age</th>
<th>Histology</th>
<th>Stage</th>
<th>IPI</th>
<th>Chromosome</th>
<th>Positive surface markers</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>DLBCL</td>
<td>III_E</td>
<td>H</td>
<td>47, X, -X, -3, +12, add (14) (q32.3), -22, +mar</td>
<td>CD19, 20, HLA-DR IgM</td>
<td>Died of disease 3Mo after the diagnosis</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>DLBCL</td>
<td>III_E</td>
<td>H-I</td>
<td>47, XX, +3, add (6) (q13), add (10) (q26), add (15) (p11), -19, add (19) (q13), -20, -21, +3mar</td>
<td>CD19, 20, HLA-DR IgM</td>
<td>Died of sepsis 6Mo after the diagnosis</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>DLBCL</td>
<td>I_E</td>
<td>L</td>
<td>46, XX</td>
<td>Not available</td>
<td>Disease free for 59Mo after operation</td>
</tr>
</tbody>
</table>

DLBCL: Diffuse large B cell lymphoma. 'H indicates high risk, H-I high-intermediate risk, and L low risk according to International Prognostic Index (IPI).

togenetic aberrations. Cases 1 and 2 showed unbalanced complex chromosome abnormalities that are preferentially seen in NHL. It is notable that rearrangement of chromosome band 14q32.3 was seen in Case 1. IgH gene, rearranged by translocations in a greater part of patients with B cell NHL (9), usually enhances the expression of proto-oncogene, cell-cycle regulator, or apoptosis suppressor in the pathogenesis of NHL. Although Case 1 did not show a known translocation but an addi-
Finally, primary uterine NHL as an intrapelvic tumor is not symptomatic till it extensively grows or metastasizes. It results in the initial diagnosis made in the advanced stages, as in Cases 1 and 2. Unfortunately, routine medical check, that incidentally found early stage NHL in Case 3, has hardly detected asymptomatic uterine NHL to date (18). The routine medical check for uterine tumors must therefore be more refined and its importance should be more strongly emphasized.

References