CONCISE REPORT

Significance of Extra 18q- Chromosome in Japanese t(14;18)-Positive Lymphoma

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Karyotype evolution of t(14;18)-positive lymphoma was studied in 13 Japanese patients. The extra 18q- chromosome, found in six of ten patients with complex karyotypes, was the most common change subsequent to a t(14;18)(q32;q21) chromosome translocation. The additional change was interpreted as being a deletion of an 18q- derived from a t(14;18). The six patients had transformed histology of follicular small cleaved cell lymphoma or diffuse large cell lymphoma, and five of them had extranodal expansion associated with a poor prognosis. These findings indicate that the extra 18q-, together with other chromosome abnormalities, is closely associated with the advanced grade disease of t(14;18)-positive lymphoma, and the extra chromosome is evolutionary comparable with the second Philadelphia (Ph') chromosome often found in the blastic phase of chronic myelocytic leukemia carrying a t(9;22)(q34;q11). In addition, since the extra 18q- is rarely found in American patients with t(14;18)-positive lymphoma, there appears to be a difference in the karyotype evolution between Japanese and American patients.

MATERIALS AND METHODS

The patient population in this study consisted of 13 Japanese patients with malignant lymphoma, whose tumor cells had a t(14;18)(q32;q21) chromosome translocation. The initial pathologic diagnosis was based on the pretreatment biopsy of the lymph node (LN) or involved tumor in all patients; the histologic classification used was that proposed by the International Working Formulation. Except for one patient with stage I disease, all patients were diagnosed as having stage III or IV disease. Chromosome study in nine patients was performed in the same LN sample used for the initial histologic diagnosis, and in the three patients without analyzable LN cells, tumor cells from the pleural or peritoneal fluid involved were studied before treatment. Two patients had chromosome study in the LN biopsied at the time of relapse after receiving chemotherapy. The histology of each was identical to that of the pretreatment node. In two others, tumor cells from pleural or peritoneal effusion were studied when the patients' condition became rapidly less responsive to chemotherapy. Cells from these tissues were cultured for 24 hours with no mitogens and the chromosomes were analyzed as previously described. Chromosomes were analyzed by trypsin-Giemsa and/or the quinacrine banding method. Karyotypes were described according to the short system for designating structural chromosome aberrations in an International System for Human Cytogenetic Nomenclature (1985). An abnormality was regarded as being clonal when at least three cells from a given patient had the same defect.

RESULTS

The clinicopathologic and cytogenetic findings are summarized in Table 1. The initial lymph node biopsy revealed follicular small cleaved cell lymphoma (FSC) in seven patients, diffuse mixed small and large cell lymphoma (DM) in one and diffuse large cell lymphoma (DL) in five. FSC was completely follicular (C-FSC) in two patients and partially follicular (P-FSC) in five; two patients with P-FSC had diffuse areas comprised of mixed small and large cells (P-FSC + DM). All 13 patients were treated with combination chemotherapy. Of the five survivors, one patient with C-FSC and a second patient with DM had a t(14;18) as the single chromosome abnormality, and another with C-FSC...
had a simple hyperdiploid karyotype. However, hyperdiploid karyotypes in a patient with P-FSC and a second patient with DL were complex. The eight patients who died of the disease also had complex karyotypes; they included two patients with P-FSC, two with P-FSC + DM, two with DL, who had hyperdiploidy, and two with DL who had hypotetraploidy.

Recurrence chromosome abnormalities subsequent to a t(14;18) were found. A complete trisomy 12 (+12) was noted in five of nine hyperdiploid patients, including two who had chromosome 12 involved in translocations, and a partial trisomy 12 in one patient. An extra X chromosome was observed in five patients, including one who had a derivative X chromosome. Other common extra chromosomes were +7, +11, +18, and +21 in two patients each, and a complete tetrasomy 7 in one patient. Structural rearrangements involving chromosome 8 were found in six hyperdiploid patients, and the rearrangements occurred at band 8q22 in two patients. However, breakpoints in the others appeared to be different. Together with these chromosome abnormalities, except for +18, one or two extra 18q- chromosomes were observed in four hyperdiploid patients (no. 5, 6, 7, and 9), and the extra 18q- had the same banding pattern as that of an 18q- derived from a t(14;18) (Fig 1). Two hypotetraploid patients (no. 12 and 13) also had the extra 18q- chromosome in addition to the t(14;18) in duplication. Patient five with stage I disease had received chemotherapy four years after the indolent course, when he was in the advanced phase of stage IV; chromosomes of metastatic cells from the pleural or peritoneal fluid were studied before treatment, and chromosome analysis in patients no. 9 and 12 with stage III disease was performed in the same lymph node used for the pretreatment diagnosis. Histologically, patient no. 5 who survived for 90 months exhibited conversion from P-FSC to DL, patients no. 6 and 7 had P-FSC + DM, and patients no. 9, 12, and 13 had DL. The clinical features of these patients having the extra chromosome, except for patient no. 9 who was in complete remission, were characterized by extranodal expansion including sarcomatous pleuritis or peritonitis associated with a poor prognosis. A deletion 6q, a duplication 12q, and a 17q isochromosome were found in two patients each. Other chromosomes that were often involved in structural rearrangements included 1, 3, 13, and 15; however, they had variable breakpoints.

**DISCUSSION**

Recently, Kristoffersson et al suggested that survival in non-Hodgkin’s lymphoma was significantly shorter for patients with ten or more clonal aberrations than for patients with zero to eight aberrations. When the present series of 13 Japanese patients with t(14;18)-positive lymphoma is similarly divided, definite differences in survival are observed: three patients with simple abnormal karyotypes (no. 1, 2, and 8) are still alive, while eight of the ten with complex karyotypes died. An extra 18q- chromosome, found in six patients with complex karyotypes, was the most common additional change, and had the same banding pattern as that of an 18q- chromosome derived from a t(14;18)(q32;q21) chromosome translocation. This was interpreted as being

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**Table 1. Clinicopathologic and Chromosomal Findings in 13 Japanese Patients With t(14;18)-Positive Lymphoma**

<table>
<thead>
<tr>
<th>Patient No.*</th>
<th>Sex/Age</th>
<th>Stage at Diagnosis</th>
<th>From Diagnosis</th>
<th>Chromosome Study</th>
<th>Source of Cells</th>
<th>Survival (mo)†</th>
<th>Mode of Karyotype‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(F/43)</td>
<td>IV M+</td>
<td>39+</td>
<td>39+</td>
<td>LN</td>
<td>46,XX,t(14;18)(q32.3;21.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2(M/40)</td>
<td>III</td>
<td>30+</td>
<td>30+</td>
<td>LN</td>
<td>47,XY,+18,t(14;18)(q32.3;q21.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3(M/67)</td>
<td>III</td>
<td>48</td>
<td>1</td>
<td>P</td>
<td>49,XY,t(14;18), other abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4(M/74)</td>
<td>IV M+</td>
<td>27+</td>
<td>5+</td>
<td>LN</td>
<td>48,XY,t(14;18), other abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5(M/60)</td>
<td>t D+</td>
<td>90</td>
<td>1</td>
<td>A</td>
<td>49,XY,t(14;18), +i(18q-), other abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6(M/67)</td>
<td>IV P+</td>
<td>3</td>
<td>3</td>
<td>P</td>
<td>50,XY,t(14;18), +2x18q-, other abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7(F/73)</td>
<td>IV P+</td>
<td>4</td>
<td>4</td>
<td>A</td>
<td>47,XX,t(14;18), +18q-, other abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8(M/39)</td>
<td>III</td>
<td>115+</td>
<td>62+</td>
<td>LN</td>
<td>46,XY,t(14;18)(q32.3;q21.3)</td>
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<td></td>
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<tr>
<td>9(F/74)</td>
<td>III</td>
<td>48</td>
<td>48+</td>
<td>LN</td>
<td>53,XX,t(14;18), +2x18q-, other abnormalities</td>
<td></td>
<td></td>
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<tr>
<td>10(M/34)</td>
<td>III</td>
<td>7</td>
<td>7</td>
<td>LN</td>
<td>50,X,-Y,t(14;18), other abnormalities</td>
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<td></td>
</tr>
<tr>
<td>11(M/72)</td>
<td>IV</td>
<td>4</td>
<td>4</td>
<td>LN</td>
<td>48,XY,t(14;18), other abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12(M/65)</td>
<td>III</td>
<td>26</td>
<td>26</td>
<td>LN</td>
<td>87,XXYY,2x(t14;18), +18q-, other abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13(F/53)</td>
<td>IV P+</td>
<td>11</td>
<td>11</td>
<td>P</td>
<td>88,-X,-Y,2x(t14;18), +2x18q-, other abnormalities</td>
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</table>

Abbreviations: M+ , bone marrow involvement; D+, dermal involvement; P+, pleural or peritoneal involvement; LN, lymph node; P, pleural effusion; A, ascites.

*Chromosome analysis for four patients (no. 3, 4, 5, and 8) was performed at the time of relapse after therapy, when patients no. 3 and 5 were in the advanced phase of stage IV P+; and others were studied before therapy.

†Survival is recorded on August 31, 1987. ‘+’ after survival indicates that the patient is alive.

‡Full descriptions of the complex karyotypes in ten patients (no. 3, 4, 5, 6, 7, 9, 10, 11, 12, and 13) is given in the Appendix.
We demonstrated that in t(8;14)-positive cancer, the "major routes" of the karyotype evolution are composed of a partial trisomy for 1q and that the major routes are absent in African Burkitt’s lymphoma (BL), which carries a t(8;14)(q24;q32).\textsuperscript{14} The observation may be related to the difference in clustering breakage-regions of the c-myc gene involved in the t(8;14) between endemic and sporadic BL.\textsuperscript{11} The follicular lymphoma group of low-grade malignancies, which is prevalent in the United States, is uncommon in Japan.\textsuperscript{16} In a study of 71 American patients with follicular lymphoma, Yunis et al observed that 85% of the patients had a t(14;18); they proposed a model for the general evolution of t(14;18)-positive follicular lymphoma involving ten types of recurrent chromosomal abnormalities.\textsuperscript{7} Most of these types were found in the present series, including seven American patients with t(14;18)-positive lymphoma, only five had an extra 18q-, which has been described as a deletion or a derivative chromosome 18.\textsuperscript{14,18} Therefore, a duplication of an 18q- derived from a t(14;18) constitutes a "major route" of the karyotype evolution in Japanese t(14;18)-positive lymphoma.

APPENDIX

A full description of the modal karyotypes of patients no. 3, 4, 5, 6, 7, 9, 10, 11, 12, and 13 follows. Patient 3: 49, XY, +X, +7, +12, dir ins (13)8 (q14q22q24), (t8;22)(q24.1;q13.1), (t14;18)(q22.3;q12.1). Patient 4: 48, XY, +X, +18, t(1;8)(q25q13), del(6) (q15q21), t(14;18)(q32.3;q21.3). Patient 5: 49, XY, +7, +13, del(2p) (p21p23), del(15) (q13q15), t(14;18) (q32.3;q21.3), +i(18q). Patient 6: 50, XY, +X, −1, −8, −15, −18, +21, +der(13)(1?) (q40q2?), +der(8)(8?) (q22q2?), +dir dup(12) (q13.1−q24), +der(12)(12?) (p12.2?), (t14;18) (q32.3;q21.3), +der(15)(15?) (p12q13), +18q+. Patient 7: 47, XX, +12, −18, del(10) (q23.2q24.3), t(14;18) (q32.3;q21.3), i(17q), +18q+. Patient 8: 48, XX, +9, +11, +12, −18, +21, +der(X)(X?) (q28q?), (t1;12) (q32.1q24.1), (t3;12) (q21.22q1.15q), t(14;18) (q32.2q21.3), i(17q), +18q+, +18q, −mar, HSR. dm. Patient 10: 50, X, +X, −Y, +7, +7, −8, +11, +12, del(1) (p36p31.2), t(8;12) (p21p12.2?), del(9) (p22), t(14;18) (q32.3;q21.3). Patient 11: 48, XY, −X, +10, +12, −13, −14, −18, −19, +22, dup(1) (q22q2?), +der(8)(8?) (q22q2?), +der(14)(14?) (q32.3;q21.3), +der(19)(19?) (q13.3?), +mar. Patient 12: 87, XXXY, (2xdel(6) (q15q21)), 2xt(14;18) (q32.3q21.3), +18q+, +5mar. Patient 13: 88, −X, −Y, der(X)(X?) (q26 or q28q?), 2del(1) (q11), dic(1) (qter→cen→p3.2→p3.1→cen→qter), 2der(3)(3?) (qter→cen→p3.2→p3.1→cen→qter), 3del(7)(7?) (p22?), +dir dup(12) (p13q-p3), dir dup(12) (q13q-q24), 2xt(14;18)(q32.3q21.3), 2x18q+, +6mar.

REFERENCES

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