Del(7)(q32) Is Associated With a Subset of Small Lymphocytic Lymphoma With Plasmacytoid Features


Deletions of the long arm of chromosome 7, previously documented in myelodysplasias and myeloid leukemias, have also been noted in lymphoid malignancies. Of 558 karyotypically abnormal specimens of non-Hodgkin's lymphoma (NHL), 12 were identified over an 8-year period, 24 cases, of which were of the small lymphocytic (sm lym) subtype. Del(7q) was the third most common karyotypic abnormality among the cohort of 61 sm lym cases in this ascertainment. Mapping of the deletions identified a region of common deletion affecting 7q32, which was the sole karyotypic abnormality in 2 cases. Eight of the ten sm lym cases were characterized by plasmacytoid features in histologic sections of lymphoma tumors or circulating cells in the peripheral blood. The del(7)(q32) was accompanied by 14q32-associated translocations in 11 of 14 cases with histologies other than sm lym, compared with 2 of the sm lym cases. Extranodal involvement was more frequent in the del(7)(q32) sm lym NHLs, although median survival was typical of other low-grade lymphomas. These results suggest that loss or inactivation of a putative tumor-suppressor gene at 7q32 may play a role in the progression of lymphomas as well as constitute an early event in the pathogenesis of lymphoplasmacytoid tumors.

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Comparisons of cases with differing cytogenetic abnormalities were made using the method of differences from proportions based on x^2 analysis. Differences in actuarial survival curves were made using the logrank test.

RESULTS

Cytogenetic and histologic associations. Deletions of 7q were found in 24 (4.3%) of the 558 karyotypically abnormal cases in this ascertainment. Mapping of the deletions identified a region of common deletion (RCD) encompassing 7q32. In a single tumor (no. 1394) the deletion spanned the region 7q11-q22. In 8 of the 24 cases, a recurring deletion, del(7)(q22q32), was noted (Fig 1 and 2). In this ascertainment, a del(7q) was observed in 10 of 61 sm lym NHLs compared with 14 of 497 NHL with other histologies (P < .05). Of the 14 non-sm lym cases, 9 were follicular NHLs and 5 were diffuse large-cell NHLs. In 9 of the 14 cases, the del(7q) was accompanied by a t(14;18)(q32;q21); a t(11;14)(q13;q32) was observed in 1 case and a t(8;14)(q24;q32) was observed in 1 case. In contrast, the 10 sm lym NHLs with del(7)(q32), none was accompanied by t(14;18) or t(8;14), whereas t(11;14) was observed in 2 cases (P < .05). The full karyotypes of the 10 sm lym NHLs with del(7q) are shown in Table 1. The
del(7q) was associated with additional numerical or structural chromosomal abnormalities in all 14 non-sm lym NHLs. In contrast, the del(7)(q32) was the sole karyotypic abnormality in 2 cases of sm lym NHL (Fig 2).

Del(7q) was the third most commonly observed cytogenetic aberration in sm lym NHLs, behind del(6q) and trisomy 18, which were observed in 23% and 18% of cases, respectively.

Morphologic and immunophenotypic features. None of the 10 cases of del(7q) NHLs showed distinct proliferation centers. Lymph node architecture was effaced by infiltrates of small lymphocytes with varying degrees of nuclear irregularity and amounts of cytoplasm (Figs 3 and 4). Of the 10 sm lym NHLs, 5 showed plasmacytoid differentiation in histologic sections; in 2 of these cases, intranuclear Ig inclusions (Dutcher bodies) were identified. Extensive necrosis in 1 case (no. 937) precluded definitive histologic classification. In 4 cases with circulating tumor cells, plasmacytoid features were observed. These features included irregular shape of the cells, abundant cytoplasm, and occasional nucleoli (Fig 5). Thus, in 8 of the 10 cases of sm lym NHLs with del(7q), plasmacytoid features were evident in histologic section and/or circulating cells.

At least 1 case (no. 1327) of the 10 sm lym NHLs was suggestive of monocytoid B-cell lymphoma, with most of the cells showing ovoid or indented nuclei, moderate amount of clear cytoplasm, and distinct cytoplasmic borders (Fig 4). Another case (no. 1296) showed features of a mantle cell lymphoma with a mantle zone growth pattern and a t(11;14)(q13;q32).

Immunohistochemical and flow cytometric analysis of the tissue or bone marrow specimens of the del(7q) sm lym NHLs showed light chain clonal restriction in 9 cases (5κ and 4λ). Ig gene rearrangement studies confirmed B-cell lineage in 4 cases studied; in 1 plasmacytoid NHL (no. 831), no tissue was available for lineage assessment. All 7 cases analyzed showed expression of CD20. CD5 was expressed in 3 cases (no. 1327, 1356, and 1462) and absent in 2 cases analyzed (no. 1239 and 1296).
Table 1. Clinical, Histologic, and Karyotypic Features of 10 Cases of sm lym Lymphoma With del(7q)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Histology*</th>
<th>Stage†/BM/Paraprotein</th>
<th>Circulating Cells</th>
<th>Extranodal Disease</th>
<th>WBC at Dx</th>
<th>Rx/Survival</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>683</td>
<td>F/56</td>
<td>sm lym-p (LP)</td>
<td>IV/-/IgM</td>
<td>+</td>
<td>B</td>
<td>5.7</td>
<td>A</td>
<td>47,XX,del(7)(q22q32),del(13)(q14q22),+18[15]/46,XX[20]</td>
</tr>
<tr>
<td>831</td>
<td>F/66</td>
<td>sm lym-p (LP)</td>
<td>IV/-</td>
<td>+</td>
<td>L</td>
<td>6.2</td>
<td>S</td>
<td>47,XX,+7,del(7)(q22)/3/46,XX[20]</td>
</tr>
<tr>
<td>937</td>
<td>F/17</td>
<td>sm lym-p (LP)</td>
<td>I/-</td>
<td>+</td>
<td>-</td>
<td>5.7</td>
<td>I</td>
<td>46,XX,t(1;17)(p36;q21),t(12;10)(p13;q22),add(7)(q32)[3]/46,XX[11]</td>
</tr>
<tr>
<td>1239</td>
<td>M/61</td>
<td>sm lym-p (LP)</td>
<td>IV/+</td>
<td>+PF</td>
<td>Li</td>
<td>15.0</td>
<td>A, S</td>
<td>47,Y,Y,del(7)(q22q32),+12[15]/63e,add(10)(q22)(2)/46,XX[11]</td>
</tr>
<tr>
<td>1296</td>
<td>F/85</td>
<td>sm lym (MCL)</td>
<td>IVS/+</td>
<td>-</td>
<td>C</td>
<td>4.6</td>
<td>PrM</td>
<td>39e,add(10)(q22)[2]/46,XX[11]</td>
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<tr>
<td>1302</td>
<td>M/37</td>
<td>sm lym-p (LP)</td>
<td>I/-</td>
<td>+</td>
<td>-</td>
<td>6.0</td>
<td>RT, BMT</td>
<td>46,XY,add(1)(p22),add(7)(q22),-add(10)(q24),der(11)(add11)(p13)add(11)(q13)t(12;19)(q13;q13),der(14)(t11;14;q13;q32)[20]</td>
</tr>
<tr>
<td>1327</td>
<td>F/69</td>
<td>sm lym (MZL)</td>
<td>IVS/+</td>
<td>+</td>
<td>L</td>
<td>8.9</td>
<td>A</td>
<td>47,XX,t(22)(p21;p11),-del(7)(q22),+12,-13,add(14)(q24),add(14)(q32),-21,mar1,mar2[cp13]/46,XX[7]</td>
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<tr>
<td>1356</td>
<td>F/46</td>
<td>sm lym (CLL/SLL)</td>
<td>IV/-/IgM</td>
<td>+PF</td>
<td>P</td>
<td>43.0</td>
<td>A</td>
<td>46,XX[19]/46,XX,del(7)(q32)[11]</td>
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<tr>
<td>1462</td>
<td>F/59</td>
<td>sm lym (CLL/SLL)</td>
<td>IVS/-</td>
<td>+PF</td>
<td>Li</td>
<td>4.6</td>
<td>S</td>
<td>46,XX,del(7)(q32)[2]/46,XX[17]</td>
</tr>
</tbody>
</table>

Abbreviations: p, plasmacytoid; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma subtype with circulating plasmacytoid forms and absence of proliferation centers (see text); LP, lymphoplasmacytoid lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; BM, bone marrow involvement at diagnosis; IgM, IgM paraprotein detected; LN, lymph node enlargement at diagnosis; PF, plasmacytoid forms present; L, lung lesions; Li, liver; B, breast; P, pleura; C, colon; WBC at Dx, leukocyte count (10⁹/L) at diagnosis; Rx, treatment; A, alkylating agents; S, surgery; PrM, cyclophosphamide, vincristine, procarbazine, prednisone, daunorubicin, prednisone, etoposide, nitrogen mustard; I, interferon; RT, radiation therapy; BMT, allogeneic bone marrow transplantation; e, expired; survival, survival in months from diagnosis.

* Diagnosis by International Working Formulation¹⁰ and revised European-American Classification (in parentheses).¹¹
† Stage determined at time of diagnosis.
‡ Alive at last follow-up.

Fig 3. Section of a splenic lymphoma in a case with del(7)(q32) as the solitary karyotypic abnormality (case no. 1462). Paraimmunoblasts are scattered among the small lymphocytes.
Clinical features. The clinical features at the time of diagnosis of the 10 cases with sm lym NHLs and del(7q) are shown in Table 1. A circulating IgM paraprotein was observed in 2 cases. In 6 cases, cytogenetic analysis was performed at the time of initial presentation, whereas 4 were studied at relapse. Advanced stage disease was observed at initial presentation in 7 of the 10 cases. Bone marrow was involved in 4 cases. Although clinical involvement of spleen and peripheral lymph nodes was common, extranodal sites were also frequently involved (Table 1). In 8 cases there was involvement of extralymphatic sites, compared with 31 of 52 cases of sm lym NHL with karyotypic abnormalities other than del(7q) (P < .05). The mean age (54.2 years), mean leukocyte count at presentation (11.1 x 10^9/L), and median survival (84 months) of the del(7q) sm lym NHLs were similar to those of sm lym with other karyotypic abnormalities. There was no prognostic impact of del(7q) in the cohorts of patients with either follicular NHL or diffuse large-cell NHL (P > .2). None of the 5 cases with del(7q) large-cell lymphoma showed a clinical history of prior low-grade NHL.

DISCUSSION

Although rare in lymphoid malignancies, deletions of the long arm of chromosome 7 are frequently observed in acute myeloid leukemias and preleukemias.2-8 Whereas the breakpoints in the myeloid leukemias and preleukemias varied, cytogenetic and molecular mapping of regions of deletion have localized this region to band 7q22.4 The region of common deletion reported in this series of NHL, 7q32, overlaps with that described for solid tumors, including malignancies of the breast, prostate, bladder, testis, and uterine...
leukemia.\textsuperscript{15} In these tumors, the del(7q) was observed as one of numerous cytogenetic aberrations or in the setting of clinically aggressive disease.\textsuperscript{13} In the majority of NHLs in this series, including all of the cases with histologies other than sm lym NHL, there were multiple karyotypic abnormalities other than del(7q). This finding suggests a secondary, progression-related role for a tumor-suppressor gene at 7q32 in these cases. This observation is also consistent with the statistical correlation in this report of del(7q32) with t(14;18) and other translocations in NHLs of follicular and diffuse large-cell histologies and the clinical association of del(7)(q32) sm lym NHL and extranodal involvement.

The sm lym lymphomas have recently been divided into distinct clino-pathologic subsets,\textsuperscript{11} not all of which are reflected in the International Working Formulation.\textsuperscript{10} These subsets include B-cell CLL/prolymphocytic leukemia/sm lym lymphoma, lymphoplasmacytoid lymphoma (including immunocytomas), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL; including monocyto B-cell NHL), and hairy cell leukemia (HCL). Whereas the histology and immunophenotype of the del(7q) NHLs did not fulfill all criteria for one of these subsets, half of the cases showed features of the lymphoplasmacytoid variant described in the revised European-American classification.\textsuperscript{11} None of the cases showed proliferation centers, a characteristic feature of the CLL subtype of sm lym NHL.\textsuperscript{11} Three cases of del(7)(q32) sm lym NHL fulfilled some of the criteria for CLL/sm lym by the revised European-American classification,\textsuperscript{11} although the cases did not show proliferation centers and had plasmacytoid circulating cells.

Extranodal involvement, common in the del(7q) cases, is less frequently observed in lymphoplasmacytoid NHL.\textsuperscript{11} Whereas the immunophenotype of the del(7q) sm lym cases was consistent with that of lymphoplasmacytoid lymphomas, 2 of the cases with plasmacytoid features also expressed CD5, as did the solitary case with features of a monocytoid B-cell lymphoma (MZL). These are atypical immunophenotypic findings for these subsets.\textsuperscript{11} Similarly, case no. 1296, an MCL with t(11;14), lacked expression of CD5. Although none of the cases in this series showed features of HCL or splenic MZL with villous lymphocytes, del(7)(q32) has previously been documented in 1 case of splenic MZL with villous lymphocytes, 1 case of HCL, as well as 1 case of acute lymphoblastic leukemia.\textsuperscript{4-10} The features of the large lymphoid cells seen in the peripheral blood were not of HCL or splenic MZL with villous lymphocytes but resembled those of t(9;14)(p13;q32)-associated plasmacytoid lymphomas\textsuperscript{12} or variant forms observed in sm lym NHL with del(6)(q21q23).\textsuperscript{13} Trisomy 3, previously reported in a high proportion of sm lym NHL\textsuperscript{9} and recently associated with a subset of lymphomas of mucosa-associated lymphoid tissue,\textsuperscript{19} was not observed in any of the del(7)(q32) sm lym cases.

Although the del(7)(q32) NHL in this series comprised several categories by the revised European-American classification,\textsuperscript{11} the majority of the cases were low-grade lymphomas with tumor cells or circulating cells showing plasmacytoid features. In this way, del(7)(q32) may be similar to the recurring translocations t(8;14) and t(14;18), which are observed in all grades of NHL but are seen as solitary aberrations predominantly in distinct histologic subsets of high- and low-grade NHL, respectively.\textsuperscript{1} The association of del(7)(q32) with a subset of lymphoplasmacytoid NHL and the observation of del(7)(q32) as a solitary cytogenetic aberration in two of these tumors suggests a pathogenetic role of this aberration in these low-grade lymphocytic neoplasms. The molecular characterization of each of these classes of cytogenetic aberrations will identify novel genes associated with the pathogenesis of these tumors and may serve to provide additional diagnostic criteria for the recently described clino-pathologic subsets of peripheral B-cell neoplasms.\textsuperscript{11}

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Del (7)(q32) is associated with a subset of small lymphocytic lymphoma with plasmacytoid features

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