CONCISE REPORT

A New Translocation, t(10;14)(q24;q11), in T Cell Neoplasia

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Four cases of T cell neoplasia are reported: three presenting as T cell acute lymphoblastic leukemia and one presenting in the leukemic phase of a T cell lymphoma. In all cases, the cells of the leukemic clone were characterized by an identical cytogenetic abnormality. This abnormality was a unique reciprocal translocation involving chromosomes 10 and 14. The breakpoint in chromosome 14 was in band q11, coincident with the assigned locus of the α-chain gene of the T cell antigen receptor. The breakpoint in chromosome 10 was in band q24, a region reported to include the locus of the terminal deoxynucleotidyltransferase (TdT) gene.

Our observations suggest that translocation t(10;14)(q24;q11) is specific for T cell neoplasia and that a gene in chromosomal band 10q24, possibly the TdT gene, plays an important role in T cell neoplasia when its expression or coding sequence is altered by aberrant recombination involving a T cell antigen receptor gene.

EARLY CYTOGENETIC STUDIES in human cancer resulted in the identification of chromosomal changes that were specific for certain abnormal clonal proliferations (eg, Ph' in CML).1 With the advent of improved cytogenetic techniques and better characterization of malignant cells, it became apparent that some cytogenetic changes were clearly diagnostic2 and more recently, prognostic3 value. When molecular genetic techniques were used to investigate the basis of these cytogenetic changes, proto-oncogenes and “hotspots” for recombination were discovered at several of the nonrandomly involved chromosomal regions.4

In those cancers characterized by specific reciprocal translocations, a general pattern has emerged in which the expression or coding sequence of a proto-oncogene near one of the translocation breakpoints is altered as a result of its juxtaposition to a sequence of actively transcribed DNA from the other breakpoint. Knowledge of this pattern has been utilized in the cloning and characterization of putative oncogenes when only one sequence (that of the actively transcribed DNA) was known.5,6

Recently, T cell antigen receptor genes have been characterized.7,8 It is now evident that T cell antigen receptor diversity is facilitated by the recombination of subunits in different parts of the genome.9 The α-chain gene of the T cell antigen receptor has been assigned to a region of chromosome band 14q11 to q13.10 This region is considered to be a hotspot for genetic recombination in differentiating T cells and has been observed to be nonrandomly involved in chromosomal abnormalities in T cell neoplasia.11,12 A fragile site has been observed at chromosomal band 10q25,13 and the gene for human terminal deoxynucleotidyltransferase (TdT) has recently been localized to the region 10q23-q25.14

We have observed four cases of T cell neoplasia in which the cells of the leukemic clones had in common a specific translocation involving chromosome 10 in band q24 and chromosome 14 in band q11. Our observations suggest that a gene, or genes, important in T cell proliferation and/or differentiation resides in 10q24 and can play an important role in T cell neoplasia. We speculate that the TdT gene may be involved in these translocations, becoming deregulated or mutated when juxtaposed to the α-chain gene of the T cell antigen receptor.

MATERIALS AND METHODS

Patients. Four patients with t(10;14)(q24;q11) were identified in a collaborative study that included 136 cases from Memphis, 28 from Toronto, and 52 from Vancouver. The translocation was observed at diagnosis in two of 164 cases of childhood acute lymphoblastic leukemia (ALL), at relapse in one of 52 cases of adult ALL, and at bone marrow relapse in one case of adult T cell lymphoma from a series of sporadically studied lymphomas. Of the 164 cases of childhood ALL, 22 were T cell ALL. (Routine immunophenotyping was not performed on the adult cases during the period of this study.) All four patients presented acutely without a history of prior hematological disorder. In cases 1, 2, and 3, the diagnosis of ALL was made on the basis of morphology and cytochemical staining of cells from peripheral blood and marrow. In case 4, the initial diagnosis of lymphoblastic lymphoma was made on the histopathology of a lymph node biopsy. Leukemic marrow cells from cases 1, 2, and 3 were tested for receptors to a host of immunologic markers. All patients were treated with intensive combined chemotherapeutic protocols. All patients were given CNS prophylaxis that included intrathecal methotrexate and received from five to seven chemotherapeutic agents intermittently for maintenance therapy. Informed consent for all biopsy specimens was obtained.

Cyto genetic studies. Marrow cells were obtained from heparinized posterior iliac crest aspirates, and the specimens were processed within 30 minutes of aspiration. Both direct and 24-hour cultures were done in all cases, except case 3 in which the marrow was processed by direct methods only. Cells in cases 1, 2, and 4 were studied using routine cytogenetic techniques.15 Case 3 was studied by the method of Williams et al.16 G-banded metaphase chromosomes were obtained according to routine techniques.17 In all cases, a minimum of 25 metaphases were examined.

RESULTS

Patients. Partial clinical data on all patients are included in Table 1. Complete remission was achieved in all patients. Case 4 relapsed after eight months and died. Case 2 relapsed after four months, was successfully reinuced, but died shortly thereafter. Cases 1 and 3 have both been in
complete and continuous hematologic remission for eight months.

Cytogenetic and morphological findings. Leukemic marrow cells in all four cases showed typical L1 morphology and negative staining with Sudan black. Cases 1, 2, and 4 showed positive staining with periodic acid-Schiff and with acid phosphatase, while in case 3, staining was negative with periodic acid-Schiff and acid phosphatase was not done. TdT expression was studied only in case 3 where it was found to be expressed in 60% of marrow cells. This value was not significantly different from that observed in other childhood cases of T cell ALL (median, 62%, n = 21) or in childhood cases of non-T cell ALL (median, 63%, n = 115). Sections of the lymph node from case 4 revealed a diffuse infiltration of neoplastic lymphoid cells with a high nuclear to cytoplasmic ratio, convoluted nuclei, indistinct nucleoli, and a fine chromatin pattern. These findings were compatible with a T cell lymphoma.

Immunologic markers. The immunologic markers that characterized the respective leukemic clones were as follows: case 1, T4+, T10+, T11+, Leu 1+, AET+, CALLA+, Ia+, Ba-2+; case 2, Leu 1+, Leu 2+, Leu 6+, AET+, SLgα; and case 3, T4+, T8+, T11+, Ba-1+, AET+, CALLA-, Ia-, Pan T+, Pan B-, SLgα. These findings confirmed that the leukemic clones in these patients represented T lineage clonal expansions.

Cytogenetic studies. Cytogenetic analysis of leukemic marrow revealed the following karyotypes: case 1, 46,XY (1 cell); 46,XY,t(10;14)(q24;q11),del(22)(q13) (24 cells); case 2, 46,XY (9 cells)/46,XY,−4,−17,+mar,+der(4)t(4;17)(q31;q21),t(10;14)(q24;q11) (8 cells)/45,XY,−4,−17,+der(4)t(4;17)(q31;q21),+der(4)t(4;17)(q31;q21),t(10;14)(q24;q11) (8 cells); case 3, 46,XY,t(10;14)(q24;q11) and case 4, 46,XY,t(10;14)(q24;q11). The consistent cytogenetic abnormality was t(10;14)(q24;q11). Partial karyotypes from cases 1, 3, and 4 are shown in Fig 1.

TABLE 1. Partial Clinical and Hematologic Features in the Four Cases

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Case</th>
<th>Clinical Status</th>
<th>Age/Sex (yr)</th>
<th>Hgb (g/dL)</th>
<th>WBC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>% Blasts</th>
<th>Marrow</th>
<th>Splenomegaly</th>
<th>Lymphadenopathy</th>
<th>CNS Involvement</th>
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<tbody>
<tr>
<td>T cell ALL</td>
<td>1</td>
<td>Dx</td>
<td>5/M</td>
<td>5.4</td>
<td>180</td>
<td>15</td>
<td>80</td>
<td>80</td>
<td>+/+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Dx</td>
<td>30/M</td>
<td>7.9</td>
<td>172</td>
<td>39</td>
<td>88</td>
<td>89</td>
<td>+/+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>Rel</td>
<td>10.7</td>
<td>129</td>
<td>48</td>
<td>92</td>
<td>−/−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>T cell lymphoma</td>
<td>4</td>
<td>Dx</td>
<td>12/F</td>
<td>10.0</td>
<td>97</td>
<td>30</td>
<td>64</td>
<td>88</td>
<td>+/+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>Rel</td>
<td>10.6</td>
<td>427</td>
<td>89</td>
<td>96</td>
<td>97</td>
<td>−/−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

Abbreviations: Dx, diagnosis; Rel, relapse; M, male; F, female; Hgb, hemoglobin.

DISCUSSION

We have presented four cases of T cell leukemia/lymphoma that have in common the following translocation in the leukemic clone; t(10;14)(q24;q11). While translocations involving the proximal long arm of 14 and the long arm of 10 have been reported in T cell neoplasia, breakpoints in chromosome 10 were either not defined or assigned to a band other than 10q24;18,19 (Of particular interest is a cell line with a t(10;14)(q23;11.2) established from a patient with T cell lymphoma in relapse.20) Our report is thus the first report of this translocation occurring as a nonrandom cytogenetic abnormality in any human cancer. The translocation was found in both the pediatric and adult age groups. Except for the T cell immunophenotype and marked leukocytosis, there were no other clinical or laboratory features in this series that correlated with the presence of the t(10;14).
The breakpoints observed in this translocation are intriguing. The one on chromosome 14 (q11) is in the region of the α-chain gene of the T cell antigen receptor and is commonly involved in chromosomal rearrangements seen in T cell neoplasia. Based on the frequent observations in B cell neoplasia of translocations resulting in the juxtaposition, and subsequent deregulation, of the c-myc proto-oncogene with an immunoglobulin gene, it has been suggested that in T cell neoplasia, the T cell antigen receptor genes can assume the role played by the immunoglobulin genes in B cell neoplasia. In support of this, Erikson et al have shown that the α-chain gene of the T cell receptor is split by a chromosomal translocation in two T cell leukemias.

Several genes have been assigned to the distal long arm of chromosome 10, including TdT. The function of the TdT gene is not fully understood, but its expression is elevated in pre-B and pre-T cells. It is also expressed at greatly elevated levels in lymphoblastic malignancies. A common fragile site has been observed at 10q25, and it has been suggested that fragile sites are predisposed to chromosomal mutation. It is possible that the basis for the involvement of 10q24 in these four translocations lies simply in the generalized fragility of this region. It seems more likely, however, that a gene or genes important in T cell differentiation reside in 10q24. TdT may be such a gene and is a good candidate for playing a major role in T cell oncogenesis when its expression or coding sequence is altered as a result of juxtaposition to part or all of the α-chain gene of the T cell antigen receptor through aberrant recombination. Such an altered TdT that aberrantly or constitutively inserted nucleotides could be a potent carcinogen. Further studies are required to determine if TdT is different in cases of T cell neoplasia with the translocation compared to those without the t(10;14)(q24;q11).

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