A Novel Translocation, t(2;5)(p23;q35), in Childhood Phagocytic Large T-Cell Lymphoma Mimicking Malignant Histiocytosis

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We report a novel chromosome translocation—t(2;5)(p23;q35) or its variant, t(2;5;13)(p23;q35;q12)—in 3 patients with peripheral T-cell lymphoma. All 3 were female children who had peripheral lymphadenopathy without organomegaly and underwent complete remission with or without chemotherapy. Their tumors were characterized histologically by predominant large cells, at times showing phagocytosis, and immunologically by peripheral T-cell phenotype and expression of Ki-1 antigen and epithelial membrane antigen (EMA). Since the same translocation has been reported in the literature in 4 patients with malignant histiocytosis (MH), and our patients had histologic features suggestive of that disease, it is likely that many tumors previously interpreted as MH are actually phagocytic large T-cell lymphoma carrying this translocation.

CASE REPORT

Chromosomes from 149 Japanese patients with non-Hodgkin’s lymphoma were successfully studied at Saitama Cancer Center between March 1978 and May 1988. Of the 29 children (younger than 18 years old) in the group, 19 were classified as lymphoblastic lymphoma, 4 as Burkitt’s lymphoma, and 6 as peripheral T-cell lymphoma. Three of the last 6 patients were the subjects of this report. No adult patients had the 2;5 translocation in their lymphoma cells. The 3 patients were admitted to one of three hospitals mentioned with the authors’ affiliation, which are located in areas nonendemic for adult T-cell leukemia (ATL); anti-HTLV-1 antibody was negative in all of them. Clinical and laboratory data on the 3 patients are summarized in Table 1.

Patient no. 1. A 12-year-old girl was admitted on September 4, 1987, with fever, skin rash, and right axillary lymphadenopathy; there was no hepatosplenomegaly. A chest x-ray film revealed pleural and pericardial effusions, but no mediastinal mass. Computed tomography (CT) scanning revealed no lymphadenopathy in the thorax or abdomen. No malignant cells were found in the bone marrow (BM) or spinal fluid. An acute lymphadenitis was suspected, and a biopsy of an axillary lymph node (LN) was done on the third hospital day. Since fever, skin rash, lymphadenopathy, and the effusions began to resolve, she was followed without chemotherapy. These signs and symptoms completely disappeared on the 16th day and have not recurred to the date of last follow-up (June 30, 1988).

Patient no. 2. An 8-year-old girl was admitted with bilateral cervical lymphadenopathy on January 29, 1987. CT scanning revealed no lymphadenopathy in the thorax or abdomen. No malignant cells were found in the BM or spinal fluid. Biopsy of the right cervical node was diagnostic for malignant lymphoma (ML). After one course of chemotherapy with vincristine (VCR), doxorubicin (DXR), cyclophosphamide (CPA), and prednisolone (PSL), her lymphadenopathy resolved completely, to recur with fever on March 17. She was given etoposide and obtained a brief remission.
After that, fever, enlargement of the right cervical LN waxed and waned. She is in good condition without any clinical symptoms or signs of ML at last follow-up (June 30, 1988).

**Patient no. 3.** A 9-year-old girl was admitted with bilateral cervical lymphadenopathy, without other signs or symptoms, on December 3, 1987. CT scanning revealed no lymphadenopathy in the thorax or abdomen. No malignant cells were found in the BM or spinal fluid. Biopsy of the right cervical LN was interpreted as reactive lymphadenitis. On December 25, 1987, the right cervical lymphadenopathy recurred, and a second biopsy was done, which was diagnostic for ML. After one course of chemotherapy with VCR, DXR, CPA, and PSL, her lymphadenopathy completely resolved. She has been in complete remission (June 30, 1988).

**MATERIALS AND METHODS**

**Pathologic studies.** All patients had LN or lymphoid tissue biopsy and examination of peripheral blood (PB), and bone marrow aspiration was obtained before chemotherapy. LN or lymphoid tissues were fixed in formalin and embedded in paraffin for routine histologic examination of peripheral blood (PB), and bone marrow biopsy.

**Immunophenotyping of cell suspensions.** Immunophenotypes of mononuclear cells separated from LN or lymphoid tissues of the 3 patients were evaluated before chemotherapy. The cells were examined by a direct immunofluorescence method for surface immunoglobulin and an indirect immunofluorescence method using several monoclonal antibodies: T6(CD1), T11(CD2), T3/anti-Leu4(CD3), T4/anti-Leu3(CD4), anti-Leu2(CD8), and MT-1 against T-cell antigens; B4(CD19), B1(CD20), B2(CD21), LN-2, and MB-1 against B-cell antigens; anti-Tac(CD25), anti-Ki-1 or Ber-H2(CD30), and anti-HLA-DR(LN-3) against cellular activation antigens; and anti-EMA. Anti-human lysozyme and anti-α-1 antitrypsin antibodies produced in rabbit (Dakopatts) were also used.

**Immunophenotyping of tissue sections.** Immunophenotypes of lymphoid tissues of the 3 patients were fixed in formalin and embedded in paraffin for routine histologic examination of peripheral blood (PB), and bone marrow biopsy.

**Table 1. Clinical and Laboratory Findings in 3 Patients With t(2;5) Associated Phagocytic Lymphoma**

<table>
<thead>
<tr>
<th>Age (yr)/Sex</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>IB</td>
<td>IIA</td>
<td>IIA</td>
</tr>
<tr>
<td>Primary site</td>
<td>r-axillary LN</td>
<td>r-cervical LN</td>
<td>r-cervical LN</td>
</tr>
</tbody>
</table>

**Hb (g/dl)** 12.7 12.6 13.5

**PLT (x 10^11/µL)** 451 418 259

**WBC (x 10^9/µL)** 14.6 9.6 5.9

**Anti-HTLV-I antibody** Negative Negative Negative

**Anti-human globulin** Positive Positive Positive

**Response to therapy** Spontaneous remission Partial remission Complete remission

**Survival from diagnosis (months)** 10+ 17+ 7+

Hb, hemoglobin; PLT, platelets; WBC, white blood cells; BM, bone marrow; F, female; r, right; LN, lymph node. + after survival indicates that the patient is alive.

**RESULTS**

**Pathologic findings (Tables 1 and 2).** Patient no. 1. The sections showed lymphomatous tissue only, with no evidence of LN structures. The tumor was composed of a highly vascularized uniform sheet of medium to large cells, interrupted by round cells containing phagocytosed nuclear debris, red blood cells (RBC), and, rarely, white blood cells (WBCs) (“starry-sky” pattern) (Fig 1). The neoplastic cells were densely packed, their abundant pale amphiphilic cytoplasm showing sharp, interlocking borders. Most of the cells had round to oval, only slightly atypical nuclei, with stippled chromatin and one or few small nucleoli. Other cells had a larger nucleus with a horse-shoe or doughnut shape, and, due to the contracted cytoplasm in the paranuclear position, were reminiscent of the “lacunar” variant of Reed-Sternberg cells. The round cells with phagocytosed debris appeared to be mostly reactive histiocytes, but at times the nuclei were indistinguishable from those of the neoplastic cells (Fig 1, inset). Several large multinucleated cells were present. The mitotic rate was very high (6.5/high-power field [hpf]) (40x, objective; 15x, eyepiece). The cytology of this area was one of a high-grade lymphoma of peripheral T-cell origin, with the features of a large anaplastic cell type.14 Surrounding the tumor was a less cellular neoplastic tissue composed mainly of small to medium lymphocytes with abundant, pale, eosinophilic, sharply delimited cytoplasm. Their nuclei had open chromatin and most often were regularly round or minimally atypical. Large neoplastic cells were sparsely distributed. Normal lymphocytes were present as well, and there were rare plasma cells, isolated or in small foci. In these areas the mitotic activity was low (2/hpf). This area might be interpreted as either a low-grade lymphoma from which the large anaplastic cell tumor has arisen or a manifestation of regressive changes developing in it.

On frozen sections, approximately 25% of both large and small neoplastic cells were CD3 and CD8 positive, while these cells appeared unreactive with CD4 and CD20. Strong positivity was elicited in the large cells with CD25 (anti-Tac) and CD30 (Ki-1) (Fig 2). On paraffin sections, all large cells...
were positive with Ber-H2 (CD30), but only a few were positive with anti-EMA antibodies.

**Patient no. 2** The sections showed lymphomatous tissue, which infiltrated the soft tissues and was supported by a relatively rich vascular network. There was no evidence of LN structures. The tumor featured a solid cellular proliferation, with two components (Fig 3). The predominant cells, at times closely clustered, at times dispersed, were large cells, with oval to round slightly irregular nuclei, one on several nucleoli, and a moderate amount of pale, basophilic cytoplasm. Some of them contained phagocytosed erythrocytes, lymphocytes, or cellular debris (Figs 3 and 4, insets). The second component consisted of small to medium lymphocytes, with somewhat irregular nuclei and clumped chromatin. Mitotic activity was high (4/hpf). No multinucleated giant cells were found. All these features characterized a peripheral T-cell lymphoma, of immunoblastic type. In addition, there were a few nests of neoplastic cells in some areas, which showed cytologic features similar to the large cells of patient 1. In paraffin sections, all the large neoplastic cells reacted strongly with MT-1 (Fig 4), Ber-H2 (CD30), and anti-HLA DR antibodies (LN-3), but only approximately half of them were positive with anti-EMA antibodies. All neoplastic cells were negative with anti-lysozyme and anti-α1 antitrypsin antibodies.

**Patient no. 3** In the section, the nodal architecture was extensively obliterated by lymphomatous infiltration, mainly involving the interfollicular areas and, focally, the peripheral sinuses, but sparing the follicles (Fig 5). The neoplastic proliferation was associated with abundant small blood vessels, a profusion of tingible-body macrophages ("starry-sky" pattern), and RBC extravasation. It consisted predominantly of large cells with abundant, pale eosinophilic or amphophilic cytoplasm and vesicular nuclei, which had irregular contours, coarse reticulated chromatin, and one or a few small nucleoli. In addition, a wide range of smaller cells with prominent nuclear irregularities were seen: they varied from small elements with dark, convoluted nuclei to medium-sized cells with progressively lighter chromatin and a larger amount of cytoplasm. A few giant cells with bizarre multiple nuclei were also seen. Of the numerous large cells containing phagocytosed nuclear debris, erythrocytes, and rarely lymphocytes, most resembled macrophages, due to their regular, round, or oval vesicular nuclei; some, however, had nuclear features indistinguishable from those of the neoplastic cells.
lymphadenopathy without organ involvement. Two of the

loss of some pan-T antigens. In patient 2, almost all the
mononuclear cells expressed CD2, CD8, and HLA-DR, but
only 28% expressed CD3. Thus, they had a cytotoxic/
suppressor T-cell type,13 with loss of a pan-T marker. In
patient 3, 64% and 66% of mononuclear cells expressed CD2
and CD7, but only 42% CD3. CD8+ cells (40%) predominated
over CD4+ cells (29%). There were about 30% cells
expressing surface immunoglobulin (Slg), CD19, CD20, and
CD21, presumably corresponding to the uninvolved B-cell
areas of the LN. The immunophenotype of this tumor was
therefore that of mature T cells, probably of the cytotoxic/
suppressor type.15

Cytogenetic data. Two of the five banded cells of patient
1 had a karyotype of 48,XX,+7,+9,t(2;5)(p23;q35), and the
other three had a normal female karyotype. All 10 banded
cells of patient 2 had abnormal karyotypes; 50 had
46,XX,t(2;5)(p23;q35)(Fig. 6), 2 had 47,XX,+7,t(2;5), and
the other 3 had 47,XX,t(2;5),+min. Thus, patients 1 and 2
had the same 2;5 translocation. Patient 3 had six abnormal
metaphase cells and 20 normal cells. All the six abnormal
cells had a three-way translocation involving 2p23, 5q35, and
13q12 without additional abnormalities (Fig 7). The karyo-
type was 46,XX,t(2;5;13)(p23;q35;q12), which we consider
to be a variant translocation of the t(2;5)(p23q35).

Southern hybridization analysis of TCRB, TCRG, and
JH genes in LN cells. Using an enzyme BamHI and the
Cβ1 probe, no rearranged bands were shown in the DNA of
patient 1. A combination of BamHI and the TCRG probe
and of BamHI and the JH probe also showed no rearranged
bands. In patient 3, with the use of BamHI and the Cβ1
probe, one Jβ1 or Jβ2 allele was shown to be rearranged. One
rearranged band of TCRG was shown in BamHI-digested
DNA. No rearranged bands of immunoglobulin heavy-chain
genes were shown in BamHI-digested DNA.

DISCUSSION
In our ongoing chromosome analysis of malignant lymphomas, we found a novel translocation—t(2;5)(p23q35) or
its variant, t(2;5;13)(p23q35;q12)—in three patients. All
three were female children and presented with peripheral
lymphadenopathy without organ involvement. Two of the
Table 3. Immunophenotypic and Immunohistochemical Findings in 3 Patients with t(2;5)-Associated Phagocytic Large T-Cell Lymphoma

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS(%) FS PS</td>
<td>CS(%) PS</td>
<td>CS(%) PS</td>
</tr>
<tr>
<td>CD2</td>
<td>36</td>
<td>98</td>
<td>64</td>
</tr>
<tr>
<td>CD3</td>
<td>74</td>
<td>L+,S+</td>
<td>28</td>
</tr>
<tr>
<td>CD4</td>
<td>45</td>
<td>L-,S-</td>
<td>4</td>
</tr>
<tr>
<td>CD7</td>
<td>59</td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>CD8</td>
<td>26</td>
<td>L+,S+</td>
<td>97</td>
</tr>
<tr>
<td>Pan-T*</td>
<td>L++,S++++</td>
<td>L++,S+++</td>
<td></td>
</tr>
<tr>
<td>CD19</td>
<td>1</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>CD20</td>
<td>2</td>
<td>L-,S-</td>
<td>1</td>
</tr>
<tr>
<td>CD21</td>
<td>0</td>
<td></td>
<td>2</td>
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<tr>
<td>Pan-B†</td>
<td>L-/±,S</td>
<td></td>
<td>L-/±,S</td>
</tr>
<tr>
<td>CD25</td>
<td>5</td>
<td>L++,S+,S+</td>
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<tr>
<td>CD30</td>
<td>L++,S+,S+</td>
<td>L++,S+</td>
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<tr>
<td>HLA-DR</td>
<td>21</td>
<td>L-,S+</td>
<td>93</td>
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<tr>
<td>EMA</td>
<td>L+,S,S+</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>Lysozme</td>
<td>L-,S-,S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1 anti-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trypsin</td>
<td>L-,S-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CS: cell suspension (% of positive cells); FS, frozen sections; PS, paraffin sections
*MT-1
†MB-1/LN-2
L, large cells; S, small cells; ±: occasional positive cells, +: 5-25%, ++: 25-50%, +++: 50-75%, ++++: 75-100% positive cells.

Three underwent remission with chemotherapy, and the other is presently in remission without any treatment. Histologically, the three cases were characterized by a predominant population of large cells with sparse phagocytosis, associated with abundant vascularity and high mitotic activity. The immunophenotype of all three tumors was that of peripheral T cells, and in two of the three patients, it could be subclassified as of cytotoxic/suppressor T-cell type. In addition, the large neoplastic cells of the three patients expressed CD30(Ki-1) antigen and, less strongly, EMA.

The rearrangements of TCRB and TCRG shown in the DNA of patient 3 were consistent with the T-cell phenotype and a clonal chromosome abnormality seen in the LN cells. However, no rearrangements were shown in the TCRB and TCRG alleles of patient 1. We suspect that the abnormal T-cell clone with t(2;5) may have been too small to exhibit clonal TCR gene rearrangements, or that an uninvolved region of the tumor tissue may have been used for the molecular study. It is also possible that the clone with t(2;5) may not have undergone clonal TCR gene rearrangements as reported in some lymphomas.

The same 2;5 translocation we describe here was reported...
in four patients diagnosed as having MH, a disease considered to represent a neoplastic proliferation of histiocytes: one of the four patients was a 1-year-old boy who had been in complete remission for 24 months after chemotherapy; no clinical and histologic data were provided for the other three. The main pathologic characteristics attributed to MH (proliferation of large cells, infiltration of sinuses, and phagocytosis) were also seen in our cases. In addition, even though most patients with MH are affected by disseminated clinical disease with a fatal outcome, two large series included substantial numbers of patients with only peripheral lymphadenopathy and relatively favorable prognosis with chemotherapy, features quite similar to those of our patients. On both pathologic and clinical groups, therefore, it is quite possible that many tumors previously described as MH are actually phagocytic large T-cell lymphoma carrying the 2;5 translocation.

Other evidence supports this hypothesis. Many tumors classified morphologically as MH or true histiocytic lymphoma have been shown to be of a T-cell phenotype. Hemophagocytosis is a feature of many of these lesions: while in some of them it has been attributed to reactive histiocytes activated by the neoplastic T cells, it has also been seen as a characteristic of the neoplastic cells in several unusual forms of lymphomas recently characterized. A comparison of the clinicopathologic features of these lymphomas and our cases is shown in Table 4. The young age of the patients, the presence of peripheral lymphadenopathy without organomegaly, the lack of involvement of BM and PB by lymphoma cells, the relatively favorable prognosis, as well as the pattern of nodal involvement and the expression of Ki-1 and EMA observed in our three cases are similar to the findings of the cases of childhood Ki-1 lymphoma reported by Kadin et al and other investigators. Ki-1 positivity, however, is a feature of large-cell lymphomas of different phenotypes (B cells; T cells; mixed, B and T cells; true

### Table 4. A Clinicopathologic Comparison of Hemophagocytic Lymphomas

<table>
<thead>
<tr>
<th></th>
<th>t(2;5)-associated Large T Lymphoma (3 pts)</th>
<th>Ki-1 Lymphoma&lt;sup&gt;24, 28, 29&lt;/sup&gt; (11 pts)</th>
<th>Erythrophagocytic Ty Lymphoma&lt;sup&gt;25&lt;/sup&gt; (2 pts)</th>
<th>S-100&lt;sup&gt;+&lt;/sup&gt; T Lymphoma&lt;sup&gt;27&lt;/sup&gt; (3 pts)</th>
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<tr>
<td>Age (yrs): range</td>
<td>8, 9, 12</td>
<td>3-19</td>
<td>30, 33</td>
<td>12, 16, 34</td>
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<tr>
<td>Gender:</td>
<td>3F</td>
<td>9M:2F</td>
<td>2M</td>
<td>1M:2F</td>
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<tr>
<td>Symptoms at presentation</td>
<td>1/3</td>
<td>7/11</td>
<td>2/2</td>
<td>2/3</td>
</tr>
<tr>
<td>Signs at presentation</td>
<td>Peripheral adenopathy</td>
<td>Peripheral adenopathy</td>
<td>Minimal peripheral adenopathy</td>
<td>Adenopathy 2/3</td>
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<tr>
<td></td>
<td>Skin lesions 1/3</td>
<td>Skin lesions 7/11</td>
<td>Marked organomegaly</td>
<td></td>
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<tr>
<td></td>
<td>No organomegaly</td>
<td>No organomegaly</td>
<td>BM involvement</td>
<td></td>
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<tr>
<td>Laboratory:</td>
<td>RBC &amp; PLT normal, WBC 1/3</td>
<td>Normal counts</td>
<td>RBC &amp; PLT</td>
<td>RBC / PLT</td>
</tr>
<tr>
<td></td>
<td>No BM and PB involvement</td>
<td>No BM involvement</td>
<td>BM involvement</td>
<td>BM involvement 2/3</td>
</tr>
<tr>
<td>Evolution:</td>
<td>CR obtainable with CT</td>
<td>CR obtainable with CT</td>
<td>NR with CT</td>
<td>NR with CT</td>
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<tr>
<td></td>
<td>All alive</td>
<td>90% survival (Median 15 mos)</td>
<td>0% survival (few mos)</td>
<td>0% survival (3, 5, 7 mos)</td>
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<td>Histology</td>
<td>Paracortical &amp; sinusoidal</td>
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<td>Sinusoidal</td>
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<td></td>
<td>Large cells</td>
<td>Large cells</td>
<td>Red pulp</td>
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<td>Yes</td>
<td>Infrequent</td>
<td>Medium-sized cells</td>
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<td>Erythrophagocytosis</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Immunophenotypes</td>
<td>Pan-T</td>
<td>CD2 5/11</td>
<td>2/2</td>
<td>All</td>
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<td>Subsets</td>
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<td>CD8 2/2</td>
<td>CD4 1, CD8 2</td>
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<tr>
<td></td>
<td>Others</td>
<td>Ki-1, EMA</td>
<td>IgGCr 2/2</td>
<td>S-100&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

RBC, red blood cell; PLT, platelet; WBC, white blood cell; CR, complete remission; CT, chemotherapy; NR, no response; mos, months
histiocytic30,31 and of variable clinical presentations24,28,32 in children and adults. The tumors with t(2;5) which we are reporting may represent an additional group of lymphomas expressing the Ki-1 antigen.

Recently, a cell line expressing Ki-1, EMA, and T-cell antigens and carrying t(2;5) has been established from PB of a 25-year-old man with large-cell lymphoma.33 Some of the large primitive cells in his BM were phagocytic. This case confirms the association of t(2;5) with large phagocytic T-cell lymphoma.

The combination of histologic, immunophenotypic, and cytogenetic findings observed in our cases identifies within the peripheral T-cell lymphomas a subset of tumors that, despite MH-like histologic features, result in a localized and indolent disease. Similar correlative studies are needed to clarify the relationships of this entity with the other unusual forms of lymphomas mentioned above and, more generally, may become essential for a definitive biologic classification of lymphomas.

REFERENCES

antigen Ki-1 in reactive and neoplastic lymphoid tissue; evidence that Reed-Sternberg cells, and histiocytic malignancies are derived from activated lymphoid cells. Blood 66:848, 1985


33. Fischer P, Nacheva E, Mason DY, Sherrington PD, Hoyle C, Hayhoe FGJ, Karpas A: A Ki-1 (CD30)-positive human cell line (Karpas 299) established from a high-grade non-Hodgkin's lymphoma, showing a 2;5 translocation and rearrangement of the T-cell receptor β-chain gene. Blood 72:234, 1988
A novel translocation, t(2;5)(p23;q35), in childhood phagocytic large T-cell lymphoma mimicking malignant histiocytosis

Y Kaneko, G Frizzera, S Edamura, N Maseki, M Sakurai, Y Komada, M Sakurai, H Tanaka, M Sasaki and T Suchi