Occurrence of the t(2;5)(p23;q35) in Non-Hodgkin’s Lymphoma

By Dennis D. Weisenburger, Bruce G. Gordon, Julie M. Vose, Martin A. Bast, Wing C. Chan, Timothy C. Greiner, James R. Anderson, and Warren G. Sanger

Primary CD30(Ki-1)-positive anaplastic large-cell lymphoma (ALCL) is considered a distinct clinicopathologic entity by some investigators. Clinically, patients with ALCL reportedly have a bimodal age distribution and characteristically present with peripheral lymphadenopathy and frequent extranodal disease, particularly involving the skin. Most patients have advanced disease at the time of diagnosis, but bone marrow involvement is infrequent. The lymphoma is a high-grade process clinically, but recent studies have shown that children and adults with ALCL have survival rates similar to those with other diffuse aggressive lymphoma subtypes if treated with curative therapy.

Histologically, CD30+ ALCL was originally described as a pleomorphic large-cell process that infiltrates the nodal sinuses and paracortical areas as sheets of anaplastic cells, sometimes forming seemingly cohesive tumor nodules with associated fibrosis. However, more recently, the morphologic and immunophenotypic criteria for a diagnosis of ALCL have become less clearly defined. Cases of ALCL lacking CD30 antigen expression have been reported, raising a question regarding the specificity of the t(2;5) for ALCL. More recently, molecular detection has also been reported, raising further doubt regarding the specificity of the t(2;5) for ALCL. Therefore, we performed a detailed analysis of all cases of non-Hodgkin’s lymphoma with t(2;5)(p23;q35) results in the Nebraska Lymphoma Study Group registry, as well as all other cases of non-Hodgkin’s lymphoma with t(2;5) in the registry. We found the t(2;5) in only five of 10 cases of ALCL, four of whom were young patients. However, we also found the t(2;5) in 11 other cases of nonanaplastic lymphoma, including eight children with typical peripheral T-cell lymphomas of various types. The t(2;5) was also found in three older adults with B-cell lymphomas of various types. Thus, the t(2;5) was not specific for CD30+ ALCL. However, t(2;5) may define a clinicopathologic entity in children and young adults characterized by variable morphologies with a T-cell or indeterminate phenotype, CD30-positivity, nodal disease with frequent extranodal involvement, advanced stage, and an excellent response to therapy, including bone marrow transplantation for relapsed disease. The clinical relevance of the t(2;5) in older patients requires further study.

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SUBJECTS AND METHODS

The cases were selected from the files of the Nebraska Lymphoma Study Group registry as follows. First, all cases previously classified as ALCL were included, but further, all cases of non-Hodgkin’s lymphoma with t(2;5)(p23;q35) were also included. The slides of all cases were then reviewed. Ten cases were classified as

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ALCL using the criteria of Stein1 and Pileri et al.,15 and 11 nonanaplastic cases were classified according to the Working Formulation.” Additional studies were performed, if necessary, to elucidate the phenotype of neoplastic cells using a variety of methods. All cases were studied by paraffin and/or frozen-section immunohistochemistry with a variety of antibodies to B-cell antigens (CD19, CD20, CD22, and surface Ig) and T-cell antigens (CD2, CD3, CD4, CD5, CD7, CD8, CD43, and CD45RO) using the avidin-biotin-peroxidase technique.24 Immunostains for CD30 antigen using the Ki-1 or Ber-H2 antibodies (Dako, Carpinteria, CA) were also performed on all cases. Molecular analysis for rearrangements of the Ig heavy-chain, T-cell β and/or T-cell γ receptor genes was also performed on paraffin or frozen tissues of some cases using previously published polymerase chain reaction (PCR) and Southern blot techniques.15,17

Cytogenetic studies were performed in all cases at the time of initial diagnosis using a standard method.18 Briefly, fresh tissue was minced finely and processed within 1 hour of biopsy. A 24-hour unstimulated culture was always initiated and, if tissue was sufficient, a 48-hour unstimulated culture was also performed. Twenty cells were analyzed when possible, and karyotypes were arranged and reported according to the International System for Human Cytogenetic Nomenclature.9 An abnormal clone was defined when the same extra chromosome or the same structural abnormality was present in two or more cells, or the same missing chromosome occurred in three or more cells. Analysis for the fusion transcript resulting from t(2;5) was also performed on cases with available frozen tumor tissue using a reverse transcriptase-(RT)-PCR assay, as previously described.

Clinical information at the time of diagnosis and follow-up evaluation was obtained in all cases. The Ann Arbor system was used to stage the disease. Eight patients were referred to the University of Nebraska Medical Center for bone marrow transplantation following a relapse of lymphoma. The curve of overall survival was drawn using the Kaplan-Meier method.

### RESULTS

ALCL and t(2;5). The features of 10 cases of ALCL with abnormal cytogenetics results are shown in Table 1. All cases consisted of large cells with oval, irregular, indented, or multilobated vesicular nuclei and one or more prominent nucleoli. The nuclei were typically eccentric, and the cells had abundant cytoplasm of variable color. Bizarre tumor giant cells, Reed-Sternberg-like cells, and cells with wreath- or embryo-like nuclei were usually present (Fig 1A). The tumor cells infiltrated the nodal sinuses and paracortical areas as monotonous sheets of cells, sometimes forming seemingly cohesive tumor nodules. Capsular and parenchymal fibrosis was present in some cases. Four cases had a T-cell phenotype and three had a B-cell phenotype; the phenotype was indeterminate in three cases. However, all 10 cases strongly expressed the CD30 antigen on a majority (>70%) of the large cells (Fig 1B).

The t(2;5)(p23;q35) was present in only five of 10 cases, with four of these five cases (no. 1 to 4) being young patients (aged 7 to 23 years). The older patient with the t(2;5) had an ALCL of B-cell type. In contrast, four of five patients without the t(2;5) were older (aged 61 to 86 years). However, distribution of the phenotypes was similar in both groups. Karyotypes of the 10 cases were complex and characterized by hyperdiploidy, including two pseudotriplet and five pseudotetraploid cases. Additionally, all five patients with ALCL without the t(2;5) had structural abnormalities of chromosome 1, although the breakpoints were different in each case. Two of these five cases (cases no. 8 and 9) also had a del(7)(p13) and three (cases no. 6, 9, and 10) had an

### Table 1. Patients With ALCL With and Without the t(2;5)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Phenotype/Genotype (methods)</th>
<th>CD30</th>
<th>Karyotype</th>
<th>NPM/ALK RT-PCR</th>
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<td>1</td>
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<td>I (PI, PM)</td>
<td>+</td>
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</tr>
<tr>
<td>2</td>
<td>18</td>
<td>T (FI, FM)</td>
<td>+</td>
<td>91,XXX,Y,(1q),-t(2;5)(p23;q35),t(2;5)(p23;q35),-4,+5,+6,-7,-11,add(15)(p11),-17, -21, +mar1, +mar2, +mar3, +mar4/46,XY</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>I (PI, FI, FM)</td>
<td>+</td>
<td>46,XX,t(2;5)(p23;q35)/92,XXX,t(2;5)(p23;q35)x2</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>T (FI, FM)</td>
<td>+</td>
<td>91,XXXX,+i(1q),t(2;5)(p23;q35),t(2;5)(p23;q35),-6,-9,-10,-11,-13,del(17)(p11),add(19) (13), +add(20)(p13), +del(20)(q12), -21, -22, -2mar/46,X</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>B (PI, PM)</td>
<td>+</td>
<td>83,X,add(X)(p22),-Y,-Y,add(11)(p11),del(11)(p22),-2,-2,del(17)(q11), -3, -4, -4, -6/46</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
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<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>B (PI)</td>
<td>+</td>
<td>94,XX,-Y,add(1)(p12)x1, -2add(3)(q28)x2, +42, +6,(6)(p10)x2, -7add(7)(q32),del(7) (p13), -8,-9, +10,-12, -13, -15, -16, +18, +20, -22, +mar1x3, +mar2/46,XY</td>
<td>ND</td>
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<td>+</td>
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<td>10</td>
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<td>-</td>
</tr>
</tbody>
</table>

**Abbreviations:** NPM/ALK RT-PCR, nucleophosmin/anaplastic lymphoma kinase fusion gene transcript analysis by RT-PCR; ND, not determined; I, indeterminate phenotype; T, T-cell phenotype; B, B-cell phenotype; PI, paraffin tissue immunohistochemistry; PM, paraffin tissue molecular techniques; FI, frozen tissue immunohistochemistry; FM, frozen tissue molecular techniques.
add (13)(p11), which may represent primary abnormalities in these non-t(2;5) cases. Results of the RT-PCR assay correlated well with the cytogenetic findings. However, one patient (case no. 5) with B-lineage ALCL and the t(2;5) lacked a detectable chimeric gene transcript.

Nonanaplastic lymphoma with t(2;5). Eleven cases of nonanaplastic lymphoma with the t(2;5)(p23;q35) were also identified (Table 2). Nine of these cases (cases no. 11 to 19) occurred in children, and all but one of these had a T-cell phenotype. Seven of these nine patients presented with diffuse mixed-cell lymphomas typical of peripheral T-cell lymphoma. The mixed-cell lymphomas consisted of a polymorphous population of atypical small, medium, and large cells in varying proportions, with large cells numbering less than 30 per high-power field. The spectrum of cells suggested a continuum of lymphocyte transformation (Fig 2A). In five of these seven cases, evolution from a mixed-cell lymphoma to a nonanaplastic diffuse large-cell lymphoma or immunoblastic lymphoma of the clear-cell type occurred (Fig 2B). The other two children (cases no. 16 and 17) presented with nonanaplastic diffuse large-cell lymphomas, one with a T-cell phenotype (Fig 2C) and the other with an indeterminate phenotype. However, a majority of the large cells in all nine childhood cases expressed the CD30 antigen, although these cells were a minor population in the mixed-cell tumors (Fig 2D). In some of the mixed-cell tumors, a subpopulation of small- and medium-sized tumor cells also expressed CD30. However, there was no difference in the pattern (ie, membrane, Golgi, or cytoplasmic) or intensity of CD30 staining between ALCL cases and nonanaplastic cases (Fig 2D, E, and F). In all nine childhood cases, the karyotypes were less complex than those seen in ALCL, being diploid or near diploid, with the t(2;5) being an apparent primary abnormality. However, the t(2;5) was more complex than usual in two cases (cases no. 15 and 18). Results of the RT-PCR assay correlated well with the cytogenetics findings in four cases tested (cases no. 12, 13, 16, and 19).

The two remaining cases (cases no. 20 and 21) were adults with B-cell lymphomas, one of which was a typical follicular mixed-cell lymphoma (Fig 3A) and the other a diffuse large-cell lymphoma of the noncleaved cell type (Fig 3B). In the follicular lymphoma, scattered large tumor cells were CD30', whereas the tumor cells were entirely negative in

Table 2. Patients With Nonanaplastic Lymphoma and the t(2;5)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Histology</th>
<th>Phenotype/Genotype (methods)</th>
<th>CD30</th>
<th>Karyotype</th>
<th>NPM/ALK RT-PCR</th>
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<tbody>
<tr>
<td>11</td>
<td>1.5</td>
<td>DM</td>
<td>T (PI, FI)</td>
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<td>46,XX,der(2)inv(2)(p21q13),t(2;5)(p23;q35)/46,XX</td>
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<tr>
<td>12</td>
<td>2.5</td>
<td>DM → DL</td>
<td>T (PI, FM)</td>
<td>+</td>
<td>46,XY,t(2;5)(p23;q35)/46,XY,Y,t(2;5)(p23;q35)</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>DM → IBL</td>
<td>T (PI, FI)</td>
<td>+</td>
<td>47,XY,+X,t(2;5)(p23;q35)/46,XY</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>6</td>
<td>DM → IBL</td>
<td>T (PI, FI)</td>
<td>+</td>
<td>46,XX,t(2;5)(p23;q35)</td>
<td>ND</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td>DM</td>
<td>T (PI, FI, FM)</td>
<td>+</td>
<td>46,XX,t(2;5)(p13)(p23;q14)/46,XX</td>
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<tr>
<td>16</td>
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<td>ND</td>
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<tr>
<td>19</td>
<td>15</td>
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<td>T (PI, FI, FM)</td>
<td>+</td>
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<td>20</td>
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<td>B (PI, PM)</td>
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<td>ND</td>
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<tr>
<td>21</td>
<td>73</td>
<td>DL</td>
<td>B (FI)</td>
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<td>87,XX−Y,Y−,−1,del(1)(p21q25),+2,t(2;5)(p23;q35)</td>
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Abbreviations: NPM/ALK RT-PCR, nucleophosmin/anaplastic lymphoma kinase fusion gene transcript analysis by RT-PCR; ND, not determined; DM, diffuse mixed-cell type; DL, diffuse large-cell type; IBL, immunoblastic type; FL, follicular mixed-cell type; I, indeterminate phenotype; T, T-cell phenotype; B, B-cell phenotype; PI, paraffin tissue immunohistochemistry; PM, paraffin tissue molecular techniques; FI, frozen tissue immunohistochemistry; FM, frozen tissue molecular techniques; −/+ , scattered CD30' large cells.
the other case. Karyotypes in both these cases were complex, and the follicular lymphoma lacked the typical t(14;18). Molecular analysis of the follicular lymphoma for t(14;18) using paraffin tissue and the PCR also failed to detect a rearrangement in the major breakpoint region. Molecular analysis of the diffuse large-cell lymphoma by RT-PCR assay failed to detect the chimeric gene transcript.

Clinical features. Clinical features of the 13 young patients with the t(2;5) are summarized in Table 3. This group consisted of five males and eight females and varied in age from 1.5 to 23 years, with a median of 8 years. Nine of the patients presented with advanced-stage disease, and all but one (case no. 18) had nodal disease. Extranodal sites were involved by lymphoma in six patients. All patients received multiagent chemotherapy of various types, and all achieved a complete response, except for one (case no. 17) who received suboptimal primary therapy. However, nine of 12 patients who achieved a complete response subsequently relapsed at a median of 6 months. Eight of these then underwent bone marrow transplantation, and seven are currently alive without disease with a median follow-up period of 54 months. Only two of 13 patients have died of the disease. The overall
Fig 3. (A) Follicular mixed-cell lymphoma. (B) Diffuse large B-cell lymphoma of the noncleaved type. (hematoxylin and eosin stains, original magnification × 100).

Fig 4. Overall survival of 13 young patients with t(2;5)-associated lymphoma. The survival of these patients is shown in Fig 4. The predicted 5-year actuarial survival of the group is approximately 80%. Clinical features of the other eight patients are listed in Table 4. These cases are more heterogenous than the previous group. Except for one child (case no. 6), all were over the age of 60 years, and five of eight had B-cell lymphomas. Of six patients with ALCL (cases no. 5 to 10), five have died of the disease. However, two of three patients (cases no. 5, 20, and 21) with the t(2;5) are currently in complete remission.

DISCUSSION

In our study, we found that the t(2;5)(p23;q35) was not specific for CD30+ ALCL. The t(2;5) was present in only

Table 3. Clinical Features of Young Patients With the t(2;5)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Stage</th>
<th>Nodal Sites</th>
<th>Extranodal Sites</th>
<th>Primary Therapy</th>
<th>Time to Relapse (mo)</th>
<th>Survival From Diagnosis (mo)</th>
<th>Current Status</th>
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<td>7</td>
<td>F</td>
<td>IVB</td>
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<td>MACOP-B</td>
<td>CR</td>
<td>6</td>
<td>DhAP, AlloBMT</td>
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<tr>
<td>2</td>
<td>18</td>
<td>M</td>
<td>IIA</td>
<td>2</td>
<td>0</td>
<td>CNOB, CMT, BMT</td>
<td>CR</td>
<td>18</td>
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<tr>
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<td>F</td>
<td>IA</td>
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<tr>
<td>4</td>
<td>23</td>
<td>F</td>
<td>IIIA</td>
<td>4</td>
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<td>COMP, A, VP</td>
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<td>Orange regimen</td>
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<td>4</td>
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<td>CAPBOP</td>
<td>CR</td>
<td>8</td>
<td>ICE, DECAL</td>
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Abbreviations: F, female; M, male; BM, bone marrow; O, bone; S, skin; T, soft tissue; B, blood; C, central nervous system; CR, complete response; NR, no response; A-, alive without disease; A+, alive with disease; D-, dead with disease; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; DhAP, cisplatinum, cytosine arabinoside, dexamethasone; AlloBMT, allogeneic bone marrow transplantation; AutoBMT, autologous bone marrow transplantation; CNOB, cyclophosphamide, mitoxantrone, vincristine, prednisone; CAPBOP, cyclophosphamide, doxorubicin, procarbazine, bleomycin, vincristine, prednisone; XRT, irradiation; VP, etoposide; C, cyclophosphamide; A, doxorubicin; AC, cytosine arabinoside; COMP, cyclophosphamide, vincristine, methotrexate, prednisone; D, daunorubicin; CCG213, etoposide, daunorubicin, cytosine arabinoside, thioguanine, dexamethasone; IE, ifosfamide, etoposide; V, vincristine; M, methotrexate; orange regimen, cyclophosphamide, doxorubicin, prednisone, methotrexate, etoposide, ifosfamide, DECAL, CARBO, carboplatinum; ICE, ifosfamide, carboplatinum, etoposide; DECAL, dexamethasone, etoposide, cisplatinum, cytosine arabinoside, asparaginase.
five of 10 cases of ALCL in our series (Table 1). However, it was present in four of five young patients (aged 7 to 23 years) with ALCL, but in only one of five older patients (aged 61 to 86 years). Recent molecular studies have demonstrated evidence of the t(2;5) in only a minority of cases of CD30+ ALCL. However, most of the reported cases of CD30+ ALCL with the t(2;5) have been children or young adults, and almost all of these have had a T-cell or indeterminate phenotype. Similarly, our four young patients with CD30+ ALCL and the t(2;5) all had either a T-cell or indeterminate phenotype. The cytogenetic features of our cases of ALCL appeared to correlate with the anaplastic morphology in that the karyotypes were complex and seven of 10 cases were hyperdiploid, a finding also reported by others.

We also found the t(2;5) in 11 cases of nonanaplastic lymphomas, including eight children with typical peripheral T-cell lymphomas of various types and one with a large-cell lymphoma of indeterminate phenotype (Table 2). In all nine childhood cases, CD30 antigen was expressed on a majority of the large cells, although these cells were a minor population in the mixed-cell tumors, and there was no difference in the pattern or intensity of CD30 staining when compared with the ALCL cases. Thus, it appears that the t(2;5) and CD30 antigen expression are common features in peripheral T-cell lymphoma of childhood, including ALCL of T-cell type. Interestingly, karyotypes of the nonanaplastic childhood cases were less complex than those in ALCL, being diploid or near diploid in all cases. These findings indicate that the t(2;5) occurs across the morphologic spectrum of peripheral T-cell disease in children and young adults, and may itself define a clinicopathologic entity.

Therefore, we analyzed the clinical features of all 13 young patients with the t(2;5) (Table 3). The majority of patients presented with advanced-stage disease, and all but one had nodal disease. Six patients also had extranodal disease at the time of diagnosis, including two with bone marrow and two with skin involvement. Ten of 13 cases had peripheral T-cell disease, whereas three had an indeterminate phenotype despite extensive studies. Our findings are similar to those of Sandlund et al., who recently reported nine children with large-cell lymphoma and the t(2;5), including one case with a B-cell phenotype. All 12 of our patients who received curative multiagent chemotherapy achieved a complete response, but nine relapsed. The high relapse rate in our series is worse than expected, due to the referral nature of our cases. Eight of these nine patients were referred to us in relapse for bone marrow transplantation, and seven of eight patients were salvaged with transplantation and are alive with a median follow-up period of 4.5 years. Thus, it appears that bone marrow transplantation is a successful salvage therapy for such patients, as reported by others.

Also, the predicted 5-year survival of approximately 80% for our patients is similar to that reported for such cases by others, and is not different from the survival of children with other types of non-Hodgkin's lymphoma. Since the CD30 antigen and t(2;5) are not specific markers of ALCL, the question of whether ALCL is a distinct clinicopathologic entity needs to be reexamined. Also, the original morphologic criteria for a diagnosis of ALCL have been broadened to include a number of variants. However, the monomorphic and Hodgkin's-related variants of ALCL are not well-defined pathologic entities and appear to overlap with other forms of lymphoma, whereas most lymphohistiocytic and small-cell-predominant variants of ALCL appear to be forms of peripheral T-cell lymphoma with variable numbers of CD30+ positive large cells. Although one of our nonanaplastic cases (case no. 17) might be considered a monomorphic variant of ALCL by some hematopathologists, all the rest of the nonanaplastic T-cell cases (cases no. 11 to 16, 18, and 19) had the typical features of peripheral T-cell lymphoma of the mixed-cell type in one or more biopsy specimens. We consider these latter cases to be peripheral T-cell lymphomas even though some CD30+ large cells were present, since they do not differ morphologically from peripheral T-cell lymphomas occurring in children or adults.
without the t(2;5). In practice, we prefer to use the diagnosis of ALCL as originally intended, since the entity is easily recognized and it is important for pathologists to distinguish it from other similar-appearing processes, such as metastatic carcinoma, malignant melanoma, malignant fibrous histiocytoma, etc.

Clinically, ALCL in children or adults seems to have the same prognosis as other diffuse aggressive lymphoma subtypes if treated with curative therapy. Also, the clinical presentation of ALCL of T-cell or indeterminate phenotype is similar to that of other peripheral T-cell lymphomas, and ALCL of B-cell type does not appear to be clinically different from its nonanaplastic large-cell counterparts. Two studies have suggested that ALCL of T-cell or indeterminate phenotype may have a better prognosis than other high-grade peripheral T-cell lymphomas. However, this effect may have been due to the younger age and/or lower disease stage of those with ALCL rather than to the anaplastic phenotype.

In conclusion, we believe that cases of ALCL should be phenotyped and grouped accordingly for therapeutic purposes. However, large studies of uniformly staged and treated patients are clearly needed to determine whether ALCL in children or adults seems to have the same prognosis as other diffuse aggressive lymphoma subtypes if treated with curative therapy.

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Occurrence of the t(2;5)(p23;q35) in non-Hodgkin's lymphoma

DD Weisenburger, BG Gordon, JM Vose, MA Bast, WC Chan, TC Greiner, JR Anderson and WG Sanger