Clinicopathologic Features and Treatment Outcome of Children With Large-Cell Lymphoma and the t(2;5)(p23;q35)

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The t(2;5)(p23;q35) was detected in 9 of the 18 cases of large-cell lymphoma with an abnormal karyotype among 115 children with large-cell lymphoma treated at St Jude Children's Research Hospital from 1975 to 1993. When the cases containing the t(2;5) were classified according to the National Cancer Institute Working Formulation, 7 were large-cell, immunoblastic and 2 were diffuse large cell; according to the Kiel classification system, 6 were anaplastic large cell, 2 immunoblastic, and 1 centroblastic. CD30 expression was documented in 6 of 8 cases tested. All patients had nodal disease and 6 had extranodal involvement (bone in 4 cases and skin in 3). Eight of nine had advanced disease at diagnosis (stage III in 7 and stage IV in 1). Complete remission (CR) was attained in all patients and 6 remain in first CR for 19+ to 97+ months. Three relapsed, but successfully obtained second remissions; 2 are 58+ and 80+ months after retrieval therapy for local recurrences, and 1 patient died of recurrent disease. The t(2;5)(p23;q35) is associated with, but not limited to, anaplastic histology, a CD30$^+$ T-cell phenotype, advanced stage disease with nodal (±extranodal) involvement, and chemosensitivity at diagnosis and relapse.

THE t(2;5)(p23;q35) chromosomal rearrangement has been observed in cases of large-cell non-Hodgkin lymphoma (NHL) defined by the National Cancer Institute (NCI) Working Formulation as large-cell, immunoblastic (polymorphous subtype) and by the Kiel classification system as anaplastic (coherent sheets of cells containing abundant cytoplasm, indented lobulated nuclei, and prominent nucleoli, invading lymph node sinuses).[1-10] Among patients with large-cell NHL, there exists an association between the presence of the (2;5) translocation and expression of CD30, an activation antigen first identified in Reed-Sternberg cells.[4-7,11,12] CD30 is expressed in approximately 40% of pediatric large-cell NHL cases as defined by the NCI Working Formulation and in about 90% of those with anaplastic features (Kiel)[13,14]; however, the frequency of CD30 expression among large-cell NHL cases with the t(2;5) has yet to be determined. Phenotypically, the majority of CD30$^+$ large-cell NHLs exhibit T-cell antigens, although usually in an incomplete or aberrant fashion; the tumor cells also express epithelial membrane antigen and leukocyte common antigen.[15]

CD30$^+$ large-cell NHLs exhibit a bimodal age distribution (resembling that of Hodgkin's disease) and frequent involvement of extranodal disease sites, including skin, lung, bone, soft tissue, and the gastrointestinal tract.[13,14,16-20] Preliminary data suggest that for children with large-cell NHL, CD30 expression does not influence event-free survival, but may be associated with a better overall survival for patients with advanced-stage disease.[13,14,21] Less is known about the prognostic significance of the t(2;5) among children with large-cell NHL.

The partially overlapping nature of CD30$^+$ large-cell NHLs (NCI Working Formulation), anaplastic large-cell NHLs (Kiel), and large-cell NHLs containing the t(2;5) has created some confusion as to the distinction between these entities. Do they, in fact, represent one disease or a spectrum of one disease type? To address this issue, we have studied the histologic features, frequency of CD30 expression, clinical features, and treatment outcome of 9 children with t(2;5) containing large-cell NHLs treated at St Jude Children's Research Hospital, in addition to a review of the literature.

PATIENTS AND METHODS

Patient characteristics. One hundred fifteen children with biopsy-proven large-cell NHL (NCI Working Formulation) were evaluated at St Jude Children's Research Hospital from 1975 through 1993. Of these, 57 did not have tissue submitted for cytogenetics, 21 had insufficient quantity of tissue submitted, 18 had morphologically noninvolved bone marrow (BM) samples evaluated in which no chromosomal abnormality was identified, and 18 had tissue submitted (4 in BM and 14 in tumor samples) in which a karyotypic abnormality was found. The t(2;5)(p23;q35) chromosomal abnormality was identified in 9 of the 18 cases with abnormal karyotypes (50%). The six boys and three girls had a median age at diagnosis of 10 years (range, 2 to 16 years). Their lymphomas were staged and classified according to the St Jude system as previously described.[22,23]

Immunophenotyping. Antibodies were used to detect the CD30 antigen (Ber H2; Dako, Santa Barbara, CA), and the T- and B-cell associated antigens, which included CD45 (leucocyte common antigen; Dako), CD3 (Dako), CD43 (M-1; Biotest, Danville, NJ), CD45Ro (UCHL-1; Dako), CD20 (L26; Dako), MB-2 (Biotest), and CD45Ra (4KB5; Dako).

Primary antibodies were detected using biotinylated secondary antibodies (Vector Laboratories, Burlingame, CA), followed by alkaline phosphatase-conjugated Streptaviden (Biogenix, San Ramon, CA). The chromogen was developed with Fast Red TR and tissues were counterstained with hematoxylin. Trypsin digests were performed before CD3 and CD30 analysis. After deparaffinization, mercury pigment was removed from B-5–fixed tissue; this step was omitted for Ber H2 reactions. All procedures were performed on an automated stainer (Code-On; Instrumentation Labs, Lexington, MA).

Samples were interpreted as CD30$^+$ if the majority of the tumor

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Table 1. Chromosome Analysis in 9 Children With Large-Cell NHL and the t(2;5)

Case No.	Karyotype
1*	46,XX,t(2;5)(p23;q35),t(4;12)(q25;q22)[16]/49,XX,t(2;5)(p23;q35),+9,+12,+?21[3]/46,XX[2]
2	46,XX,t(2;5)(p23;q35),t(10;14)(q23;q32)[15]/46,idem,t(11;19)(q21;p13)[6]
3	49,XY,+del(1)(p22),t(2;5)(p23;q35),del(6)(q15q21),+del(6)(q15q21),+7,der(8)t(8;?)(q24;?)[12]/49,idem,der(19)t(19;?)(q13;?)[1]/46,XY[1]
4	66,XXY,+der(1)t(1;3)(p22;q?29)x2,t(2;5)(p23;q35),+der(2)t(2;5)(p23;q35),+der(3)t(1;3)(p22;q?29),+der(5)t(2;5)(p23;q35),+6,+7,+8, +12,+12,+13,+14,+16,+19,+20,+21,+3mar[cp6]
5	45,XY,dic(1;11)(p11;p11),t(2;5)(p23;q35)[3]/87,idemx2,−6,del(8)(q13q22)x2,−10,−17[1]/46,XY[10]
6	79-83,XX,+del(X)(q22)x2,t(1;20)(q11;p13)x2,t(2;5)(p23;q35)x2,der(16)t(16;?)(q22;?)x2,der(16)t(16;?)(q24;?)x2,inc[cp4]/46,XX[4]
7	88-93,XYY,der(X)t(X;?)(q2?6;?),t(2;5)(p23;q35),der(2)t(?;2;?)(?;p23→q23;?),der(3)t(3;?)(q29;?),der(3)t(3;?)(q27;?), der(4)t(4;?)(q22;?),del(6)(q21q23)x2,der(9)t(9;?)(p24;?),der(11)t(11;?)(q23;?)x2,der(15)t(1;15)(q21;p13),der(15)t(15;1;1)(p13;q21→q42; q32→q44),der(17)t(17;?)(p13;?),+mar,inc[cp10]/46,XY[10]
8	47,XY,t(2;5)(p23;q35),+5,dup(6)(p11p25),der(18)t(?1;18)(q2?3;p11),der(19)t(19;?)(p13;?),i(22q)[15]/94,idemx2,i(17q)[5]/46,XY[1]
9	46,XY,der(1)t(1;?)(q44;?),t(2;5)(p23;q35)[24]/46,XY[1]

* Karyotyping was performed in a relapse sample.

cells in adequately fixed portions of the specimen displayed a membrane and/or Golgi pattern of staining. Cases were determined to be either T-cell NHL if one or more T-cell–associated antibodies (UCHL-1, CD3, or MT-1) reacted and B-cell antibodies did not, or, conversely, were determined to be B-cell if one or more B-cell–associated antibodies (L26, 4KB5, or MB-2) reacted and antibodies to T-cell markers did not. In rare instances, MB-2 reacted with samples showing otherwise strong T-cell marking; these cases were considered to be T-cell NHL.

Cytogenetics. The lymph node or tumor mass suspensions were processed immediately or after culture for 24 to 48 hours. Briefly, the cell suspensions were exposed to colcemid for 45 minutes, to hypotonic solution for 7 to 10 minutes, and to two or more changes of fixative for 15 minutes each, and then G-banded by trypsin and Wright's stain. The chromosome abnormalities are described according to the International System for Human Cytogenetic Nomenclature (ISCN, 1991).[24] Adequate lymph node material for cytogenetic analysis was obtained at diagnosis from 7 patients (cases no. 2 through 7 and 9) and at relapse from 1 patient (case no. 1). The abnormal karyotype in 1 patient (case no. 8) was identified in BM cells; no lymphoid tissue was available for study. Two patients (cases no. 3 and 9) had karyotypic analysis performed in morphologically normal BM in addition to lymph node samples.

Treatment. The 9 children with NHL and the t(2;5)(p23;q35) received a variety of treatment regimens (see Table 2) reflecting the time of their diagnosis. Two patients were treated with CHOP therapy[25] (cyclophosphamide, doxorubicin, vincristine, and prednisone): three courses for the child with stage II disease (case no. 5) and six for the patient with stage III (case no. 4). Four children (cases no. 1, 2, 3, and 6) were treated with the MACOP-B regimen,[26,27] which features rapidly rotating cycles of drug pairs (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) administered over a 12-week period. Three patients (cases no. 7 through 9) were treated with the DAC protocol (a multiagent regimen including dexamethasone, cytarabine, carboplatin, doxorubicin, 6-mercaptopurine, methotrexate, cyclophosphamide, and L-asparaginase) over a 10-month period.

RESULTS

The complete karyotypes of these patient's tumor samples are listed in Table 1. Each patient shared an identical reciprocal translocation involving the short arm of chromosome 2 band p23 and the long arm of chromosome 5 band q35. The modal chromosome number for these cases was diverse; 3 were diploid (46), 2 near tetraploid, and modal numbers of 45, 47, 49, and 66 were found in the other cases. The karyotypes of BM samples taken from patients no. 3 and 9 were normal. In most cases, the karyotypes were very complex and the only discernable common features among them other than the t(2;5) were breakpoints at 1p22, 3q29, and 19p13 identified in two cases each.

Table 2 summarizes the clinical features and the heterogeneous histopathologic and immunophenotypic features of these cases. According to the NCI Working Formulation, 2 were diffuse large-cell and 7 large-cell, immunoblastic. According to the Kiel classification, 6 were anaplastic large-cell, 2 immunoblastic large-cell, and 1 centroblastic. Expression of CD30 was present in 6 of 8 cases tested; CD30 expression in 1 case was focally positive. One patient (case no. 1) was not studied for CD30 expression because of an insufficient quantity of tumor sample. Sites of disease included lymph node (n = 9), bone (n = 4), spleen (n = 3), skin (n = 3), mediastinum (n = 1), testicle (n = 1), and BM (n = 1). None had involvement of the central nervous system. The mean serum lactic dehydrogenase (LDH) level at the time of diagnosis was 240 U/L (range, 118 to 478 U/L).

Treatment outcome. Complete remission was achieved in all patients, although case no. 5 failed to respond completely to CHOP therapy and required involved-field radiation and the DHAP regimen (dexamethasone–cisplatin–high-dose cytarabine) to attain complete remission (CR). Although 3 children suffered a relapse, 2 remain alive in second remission for 58+ and 80+ months after DHAP and autologous BM transplantation (BMT); 1 achieved a short second complete remission with methotrexate, VP-16, and ifosfamide followed by autologous BMT, but subsequently died of recurrent disease.

DISCUSSION

The 9 cases reported expand the previously observed association between the (2;5)(p23;q35) translocation and large-cell NHL and suggest that the disease in children shares striking similarity to that observed in young adults.[2-8] We found that, although the t(2;5) was associated with anaplastic morphology, it was not restricted to a specific histologic

Table 2. Clinical and Laboratory Findings in 20 Children With Large-Cell NHL and the t(2;5)(p23;q35)

Case No.	Age (yr)	Sites of Disease	Stage St Jude	Histologic Classification: NCI Working Formula	Histologic Classification: Kiel	Phenotype	Primary Chemotherapy	Time to Relapse (mo)	Survival From Diagnosis (mo)	Ref
1*	7	Node (cervical, axillary) Bone Skin	III	LC, immunoblastic	ALCL	T-cell CD30 (ND)	MACOP-B	7	65+	Present study
2	13	Node (cervical, supraclavicular, paraaortic) Skin	III	LC, immunoblastic	Immunoblastic	T-cell CD30⁺	MACOP-B	7	87+	
3	7	Node (cervical, supraclavicular, retroperitoneal) Bone Pleural effusion, mediastinum Spleen	III	Diffuse LC	Centroblastic	B-cell† CD30⁻	MACOP-B		73+	
4	12	Bone Node (cervical, axillary, supraclavicular, inguinal, femoral) Skin	III	LC, immunoblastic	ALCL	T-cell CD30⁺	CHOP		99+	
5	10	Nodes (cervical)	II	LC, immunoblastic	Immunoblastic	Null-cell CD30⁻	CHOP → DHAP + IFRT		55+	
6	2	Mediastinum, pleural effusion Nodes (axillary, supraclavicular)	III	LC, immunoblastic	ALCL	T-cell CD30⁺	MACOP-B	25	Died‡	
7	10	Nodes (inguinal, iliac); pelvic mass	III	LC, immunoblastic	ALCL	Null-cell CD30⁺	DAC		28+	
8	16	Nodes (para-aortic inguinal); pelvic mass, bone, spleen, bone marrow	IV	Diffuse LC	ALCL	T-cell CD30⁺	DAC		21+	
9	11	Nodes (cervical, hilar, axillary, inguinal), spleen	III	LC, immunoblastic	ALCL	Null-cell CD30⁺	DAC		21+	
10	12	Nodes, pleural effusion	I	NR	ALCL	T-cell CD30⁺	None		10+	3
11	8	Nodes	II	LC, immunoblastic	NR	T-cell CD30⁺	CHOP	2	17+	3
12	9	Nodes	II	LC, pleomorphic	NR	T-cell CD30⁺	CHOP		7+	3
13	18	Nodes	I	NR	ALCL	T-cell CD30⁺	Chemotherapy		NR	5
14	18	Nodes	III	NR	ALCL	T-cell CD30⁺	ProMACE/ MOPP		11+	4, 7
15	21	Nodes	III	NR	ALCL	CD30⁺	M-BACOD		11+	4, 7
16	NR	Nodes	NR	Diffuse LC	NR	T-cell CD30, NR	NR	NR	NR	8
17	NR	Nodes	NR	NR	ALCL	T-cell CD30⁺	NR	NR	NR	8
18	NR	Nodes	NR	Diffuse mixed	NR	T-cell CD30⁺	NR	NR	NR	8
19	8	Nodes, ascites	IV	Diffuse LC	NR	B-cell CD30, NR	NR	NR	48+	9
20	12	Soft tissue	NR	Diffuse mixed	NR	T-cell CD30⁺	NR	NR	NR	10

Abbreviations: IFRT, involved field radiation therapy; DHAP, dexamethasone-cytarabine-cisplatin; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; DAC, dexamethasone, cytarabine, carboplatin, doxorubicin, 6-mercaptopurine, methotrexate, cyclophosphamide, and L-asparaginase, NR, not reported; LC, large-cell; ALCL, anaplastic large-cell lymphoma.

* Translocation was identified at relapse.

† MB2⁺, CD20⁻.

‡ Died with recurrent disease 40 months from initial diagnosis.

subtype of large-cell NHL as defined by either the NCI Working Formulation or the Kiel classification. A review of the literature suggests that our observation is supported by the findings of 11 previously reported cases that included a spectrum of NHL histotypes in which the t(2;5) was identified (cases no. 10 through 20, Table 2); however, these case reports did not include both NCI Working Formulation and Kiel classification terminology, making direct comparison difficult.

Interest in CD30 expression has heightened since its recent identification as a new member of the nerve growth factor receptor family, suggesting a potential mechanism for the growth advantage of $CD30^+$ malignant lymphoid cells.[28] CD30 is expressed in approximately 40% of pediatric large-cell NHLs (NCI Working Formulation) and about 90% of pediatric anaplastic NHLs (Kiel). When genetic subtypes of large-cell NHL are considered, CD30 expression is prominent among cases with the t(2;5). CD30 expression was documented in 6 of our 8 cases and in all 9 previously reported cases of large-cell NHL with the t(2;5) for which CD30 expression was determined (Table 2).[3-6,9,10] Although this finding suggests a tight association (about 90%) between CD30 expression and presence of t(2;5), the actual frequency is difficult to define when the small number of cases tested for both features is considered. Interestingly, all the $CD30^+$ cases were either T- or null-cell phenotypes, and the 2 $CD30^-$ cases were non–T-cell phenotype (1 $MB2^+$, $CD20^-$, suggesting B-cell; 1 null-cell). CD30 expression was not restricted to any histologic subtype of large-cell NHL as defined by the NCI Working Formulation. According to the Kiel classification, 5 of 6 $CD30^+$ cases had anaplastic morphologies, suggesting an association between CD30 expression and anaplastic morphology among large-cell NHL cases with the t(2;5).

The clinical presentation of our 9 cases was characterized by nodal and extranodal involvement, similar to that of other cases of immunoblastic large-cell lymphomas with the t(2;5)(p23;q35).[16] The limited number of documented $t(2;5)^-$ large-cell NHL cases in our review precluded a meaningful statistical analysis between them and $t(2;5)^+$ cases. However, in our recent study of $CD30^-$ versus $CD30^-$ cases of large-cell NHL, there was a significantly higher incidence of skin involvement in the $CD30^+$ group.[13] That the presence of t(2;5) was associated with skin involvement in one-third of our cases is not surprising in light of the apparent association between the presence of the t(2;5) and CD30 expression. Also of note was the wide range of tumor burden at presentation. Our experience suggests that a large proportion of patients have widespread disease. One of our patients presented with stage II disease (head and neck region), whereas the remaining 8 had more advanced stages, including BM involvement in 1 case. Among the 7 case reports for which stage was reported, 4 were limited (stage I or II) and 3 advanced stage (stage III or IV, Table 2). Thus, it appears that the t(2;5) is associated with advanced stage of disease at presentation in children.

The prognostic significance of the t(2;5)(p23;q35) in childhood large-cell lymphomas has yet to be defined.[16] In one review of 10 cases of $CD30^+$ lymphomas, those lacking the t(2;5) had a poorer treatment response.[7] Of the three cases reported by Kaneko et al,[3] one resolved spontaneously, one achieved a partial response, and one had a complete response to chemotherapy (Table 2). In our study, 1 child did not attain a CR with CHOP therapy and 3 patients with stage III disease developed recurrences after completion of therapy. It is noteworthy that 3 of these 4 failures were successfully treated. This suggests that, despite initial treatment failure, children with large-cell NHL containing the t(2;5) remain chemosensitive and potentially salvagable.

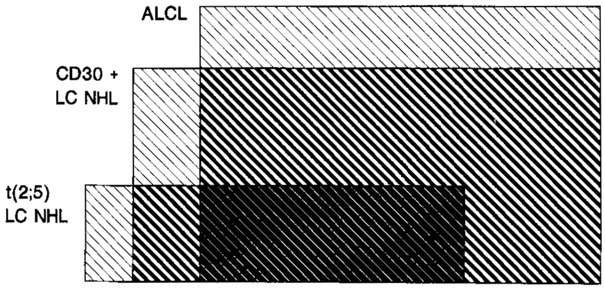

Fig 1. Schematic concept of our current understanding of the partially overlapping nature of anaplastic large-cell lymphomas (ALCL), $CD30^+$ large-cell non-Hodgkin lymphomas (LC NHL), and t(2;5)(p23;q35) containing LC NHLs.

In summary, t(2;5) is associated with but not limited to anaplastic histology, a $CD30^+$ T-cell phenotype, advanced stage disease, and nodal (±extranodal) involvement that is responsive to chemotherapy at initial presentation and in relapse. A conceptual schema of our current understanding of the degree of overlap between $CD30^+$ large-cell NHL, anaplastic large-cell NHL, and t(2;5) containing large-cell NHL, as suggested by our cases and those in the literature, is depicted in Fig 1. Recently, Morris et al[29] have cloned the breakpoint of the t(2;5)(p23;q35) and found that the rearrangement results in a fusion of the NPM nucleolar phosphoprotein gene on chromosome 5 at q35 to a previously unidentified putative protein-tyrosine kinase gene, termed ALK, that is mapped to chromosome 2 at p23. With probes for these genes now available, polymerase chain reaction screening of tumor samples will facilitate both the identification of t(2;5) containing large-cell NHL cases and our understanding of their relationship to CD30 expression and histopathology.

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