Precursor B-Cell Lymphoblastic Lymphoma

A Study of Nine Cases Lacking Blood and Bone Marrow Involvement and Review of the Literature

Anirban Maitra, MD, Robert W. McKenna, MD, Arthur G. Weinberg, MD, Nancy R. Schneider, MD, PhD, and Steven H. Kroft, MD

Key Words: Lymphoblastic lymphoma; Precursor B-cell lymphoma, Precursor B-cell ALL; Acute lymphoblastic leukemia

Abstract

We describe 9 cases of precursor B-cell lymphoblastic lymphoma (LYL) without evidence of marrow or blood involvement. Four patients had superficial nodal disease, 2 cutaneous involvement, and 1 each ovarian, retroperitoneal, or tonsillar primary tumor. Six patients had limited disease; 3 patients were stage III. Immunophenotyping revealed a terminal deoxynucleotidyl transferase (TdT)-positive, immature B-cell population with variable expression of CD10, CD20, and CD45. All patients are in complete clinical remission (median follow-up, 14 months). A literature review yielded 105 patients with a diagnosis of precursor B-cell LYL based on less than 25% marrow involvement. Of these, 64% were younger than 18 years. Skin, lymph nodes, and bone were the most common sites of disease. Mediastinal involvement was uncommon. TdT, CD19, CD79a, CD10, and HLA-DR were the most frequently expressed antigens, while CD45 and CD20 were expressed in only two thirds of the cases. Cytogenetic analysis showed additional 21q material as a recurring karyotypic abnormality. At a median follow-up of 26 months, 74% of patients were alive; the median survival was 19 months for patients dying of disease. Comparison with precursor B-cell acute lymphoblastic leukemia showed several overlapping features, although distinct differences were identified.

Lymphoblastic lymphoma (LYL) is a neoplasm of immature lymphoid cells. The cells are morphologically identical to the lymphoblasts of acute lymphoblastic leukemia (ALL). Commonly used criteria to distinguish LYL from ALL are as follows: (1) manifestation as bulky masses in solid organs; (2) focal (<25%) or absent bone marrow involvement; and (3) absence of peripheral blood involvement.[1] Unlike ALL, in which 85% of tumors are of B-cell lineage,[2] no more than 10% of LYLs express B-cell markers.[3] There are approximately 100 immunophenotyped cases of precursor B-cell LYLs reported in the literature; most are single case reports or very small series.[4-26] Several cases reported as LYL do not conform to the diagnostic criteria for this disease.[27,28] The proposed Revised European-American classification system of lymphoid neoplasms (REAL) has merged the categories of precursor B-cell ALL and LYL into a single entity,[29] but the existing data on LYL are insufficient to validate this proposal. In this report, we describe 9 cases of precursor B-cell LYL and comprehensively review the literature to better characterize this uncommon neoplasm. All 9 cases selected for the present study lacked evidence of blood and bone marrow involvement.

Materials and Methods

A retrospective search of the hematopathology archives of Parkland Memorial Hospital and Children's Medical Center (affiliate hospitals of University of Texas Southwestern Medical Center, Dallas) from November 10, 1989, through May 10, 2000, yielded 9 cases of precursor B-cell LYL lacking evidence of blood and bone marrow involvement. Clinical data were retrieved from the patient charts. Histologic sections were available for review in all cases.

Fresh specimens of tissue or blood were processed according to a variety of protocols depending on the source of the specimen and the period during which it was obtained. The method of tissue preparation for flow cytometry from fresh tumor samples has been described previously.[30] All specimens analyzed at the University of Texas Southwestern Medical Center were studied on a FACSort (3-color) or a FACSCalibur (4-color) flow cytometer (Becton Dickinson [BD] Immunocytometry Systems, San Jose, CA), and data were analyzed with Paint-A-Gate software (Verity House, Topsham, ME). All normal and neoplastic populations within a given sample were characterized. Antigen expression on abnormal populations was compared with appropriate isotypic controls and negative and positive populations in a given tube. *Antigen positivity* was defined as a discrete population shift relative to the same population in the isotypic control tube. Assessments of intensity of antigen expression were qualitative and based on accumulated laboratory experience with individual antibodies in normal and neoplastic cell populations.

Four-color flow cytometric analysis of fresh tumor tissue was performed in 5 cases (1, 3-5, and 7) and 3-color analysis in 1 (case 8); for case 2, diagnosed in 1989, 1-color flow cytometric analysis was performed at a centralized POG (Pediatric Oncology Group) institution (POG protocol 8719). Various combinations of tissue panels were used with the following antibodies: CD2 (55.2), CD3 (SK7), CD4 (SK3), CD5 (L17F12), CD7 (4H9), CD8 (SK1), CD10 (W8E7), CD11b (D12), CD11c (S-HCL-2), CD14 (MϕP9), CD19 (SJ25C1), CD20 (L27), CD22 (S-HCL-1), CD34 (MY10), CD38 (HB7), CD45 (2D1), CD45RO (UCHL-1), CD56 (MY31), monoclonal kappa (TB28-2), and monoclonal lambda (I-155-2), all from BD Immunocytometry Systems; CD23 (B6), CD45RA (2H4LDH11LDB9), FMC7 (FMC7), polyclonal kappa (polyclonal goat IgG), and polyclonal lambda (polyclonal goat IgG), all from Coulter-Immunotech, Hialeah, FL; CD33 (4D3, Caltag, Burlingame, CA); CD30 (BerH2, DAKO, Carpinteria, CA); and terminal deoxynucleotidyl transferase (TdT; HT-1, HT-3, HT-4, DAKO). Immunophenotyping of the bone marrow aspirate at diagnosis was performed with 4-color analysis in cases 1, 3-7, and 9; 3-color analysis in case 8; and 1-color analysis in case 2.

In 2 cases (6 and 9), fresh tumor tissue was unavailable, and immunohistochemical analysis was performed on paraffin sections using various antibodies from the following panel (dilutions are in parentheses): TdT (1:20), CD79a (1:10), CD3 (1:200), CD5 (1:40), CD8 (1:80), and bcl-2 (1:10), all from DAKO; CD10 (1:20), Vector, Burlingame, CA; CD20 (L26; 1:40) and CD45 (1:40) from Signet, Dedham, MA; CD43 (1:320), BD, Franklin Lakes, NJ; CD56 (1:20), Monosan, Burlingame, CA; TIA-1 (1:1,000) and MIB-1 (1:40) from Immunotech, Fullerton, CA; and lysozyme (1:100) and cyclin D1 (1:40) from Zymed, San Francisco, CA. Immunohistochemical analysis was performed using the Ventana BioTek automated immunostainer (Ventana, Tucson, AZ), preceded by microwave antigen retrieval in citrate buffer. A standard streptavidin-biotin–labeled automated detection kit (Signet) was used according to the manufacturer's guidelines. Fresh tumor tissue from 5 cases (1, 3, 5, 7, and 8) was submitted for conventional cytogenetic analysis. Dividing cells from overnight, 48-hour and 7-day cultures were examined using standard G-banding technique.

Results

Clinical Manifestations and Staging

Table 1 summarizes the clinical and radiologic features for 9 patients with LYL. The M/F ratio was 1.25:1. The

Table 1
Clinical Features in Nine Cases of Precursor B-Cell Lymphoblastic Lymphoma

Case No./Sex/ Age at Diagnosis (y)	History	Radiologic Findings
1/M/4	Palpable mass left cheek, 2 y; rapid increase for 3 mo	Multiple nodes left supraclavicular region; normal chest and abdomen
2/F/5	Nontender mass, midline posterior neck, 4-6 wk	Multiple bilateral enlarged cervical and left supraclavicular nodes; normal chest and abdomen on CT
3/M/6	Painless left inguinal adenopathy, 3-4 wk	Extensive retroperitoneal disease
4/F/7	Abdominal mass, 2 mo	Large ovarian mass
5/M/10	Left anterior cervical adenopathy, 2-3 mo	Multiple nodes, left cervical chain; normal chest and abdomen on CT
6/F/10	Erythematous forehead lesion, 5 mo	No evidence of lymphadenopathy
7/M/11	"Neuroblastoma" diagnosed and treated overseas, 15 mo; radiologic recurrence detected in pancreas, 2 mo before surgery	Extensive retroperitoneal disease, including pancreatic involvement
8/M/28	Right cervical adenopathy, 2 mo	Hepatosplenomegaly and inguinal adenopathy
9/F/71	Dysphagia and weight loss, 2 mo	Right tonsillar mass and cervical adenopathy

CT, computed axial tomography scan.

mean and median ages at diagnosis were 17 and 10 years, respectively (range, 4-71 years). The sites of presentation were superficial nodal disease (4 cases); cutaneous lesions (2 cases); and ovarian, retroperitoneal, and tonsillar primary (1 case each). The head and neck region was the initial site of diagnosis in 6 of 9 cases. According to the St Jude classification for non-Hodgkin lymphomas in children,[31] 6 of 9 had limited stage disease (stage I or II), while 3 had stage III disease (Table 1). **Table 2** summarizes the hematologic findings. None of the patients had cytopenias at the time of diagnosis. Morphologically evident bone marrow and peripheral blood involvement was absent in all cases, and cerebrospinal fluid examination was negative in 8 cases. In case 3, mildly "suspicious" cells were observed in the initial lumbar puncture fluid but were not believed to be diagnostic of lymphoma involvement.

Histologic Features

Lymph node examination in 5 cases (including retroperitoneal nodes in case 7) and tonsillar and ovarian tissue in 1 case each showed diffuse effacement of architecture. Pericapsular extension was seen in lymph nodes. The architectural pattern of involvement by neoplastic cells was different in the 2 cases manifesting in the skin. In case 1, there was replacement of the papillary and reticular dermis by a strikingly nodular infiltrate that splayed the adnexal structures without effacing them. A well-demarcated grenz zone was seen, and the overlying epidermis was not ulcerated or infiltrated. While most of the cells constituting the infiltrate had lymphoblastic morphologic features, a minor component of mature lymphocytes was present. In case 6, a perivascular and periadnexal lymphoid infiltrate was observed that generally spared the papillary dermis and was more prominent in the deep dermis. In contrast with case 1, the majority of cells in the superficial areas of the biopsy specimen were mature lymphocytes; the lymphoblastic component was restricted to the subcutaneous fat.

The neoplastic population in all cases consisted of a monotonous population of medium-sized lymphoid cells, with high nuclear/cytoplasmic ratios, immature chromatin, and inconspicuous nucleoli **Image 1**. The nuclear contours were round to slightly irregular in 1 case, mildly irregular in 7, and markedly irregular in 1. Moderate to marked mitotic activity was seen in all cases.

Immunophenotypic and Immunohistochemical Analysis

Table 3 summarizes the immunophenotypic and immunohistochemical analyses performed on the primary tumor tissues from the 9 patients. All cases expressed either TdT or CD34. Of the 7 cases examined by flow cytometry, TdT was expressed in 6. Partial CD34 expression was observed in 4 of 6 cases; the pan B-cell antigen CD19 was present in all 7. CD22 was positive in 6 of 6 cases, while CD20 was either partially positive (5 of 7) or negative (2 of 7). CD10 (CALLA [common acute lymphoblastic leukemia antigen]) expression was observed in 5 of 7 cases. HLA-DR and CD38 reactivity were present in 5 of 5 and 6 of 6 cases, respectively. CD23, FMC7, and surface light chain expression were absent in all cases. The T-cell antigens CD2, CD3, CD5, CD7, CD45RO, CD4, and CD8, as well as the myeloid antigens CD15 and CD33, were negative in all cases.

Immunohistochemical analysis in case 6 showed expression of TdT, CD45, CD79a, CD10, and CD43 and lack of CD20, CD3, CD5, CD8, CD56, TIA-1, and cyclin D1 expression. The neoplastic cells were bcl-2 positive and had a high proliferative index by MIB-1 labeling. Case 9 also was analyzed using a panel of immunohistochemical markers and demonstrated reactivity for TdT, CD45, and CD20, with lack of CD5, CD3, and cyclin D1 expression.

Cytogenetic Analysis

Fresh tumor tissue was submitted for cytogenetic analysis in 5 cases (1, 3, 5, 7, and 8). In cases 1, 3, and 7, no growth was observed after 7-day cultures. In case 5,

Table 2
Hematologic Findings in Nine Cases of Precursor B-Cell Lymphoblastic Lymphoma

Case No.	WBC Count, /μL (× 10^9/L)	Hemoglobin, g/dL (g/L)	Platelet Count, × 10^3/μL (× 10^9/L)	Bone Marrow (at Diagnosis)	Cerebrospinal Fluid (at Diagnosis)
1	5,200 (5.2)	12.0 (120)	341 (341)	Negative	Negative
2	7,300 (7.3)	12.0 (120)	188 (188)	Negative	Negative
3	5,100 (5.1)	12.4 (124)	293 (293)	Negative	Mildly "suspicious" cells observed
4	6,200 (6.2)	11.8 (118)	225 (225)	Negative	Negative
5	7,000 (7.0)	13.4 (134)	260 (260)	Negative	Negative
6	5,100 (5.1)	13.4 (134)	260 (260)	Negative	Negative
7	7,100 (7.1)	11.7 (117)	255 (255)	Negative	Negative
8	6,300 (6.3)	12.6 (126)	318 (318)	Negative	Negative
9	11,900 (11.9)	10.9 (109)	155 (155)	Negative	Negative

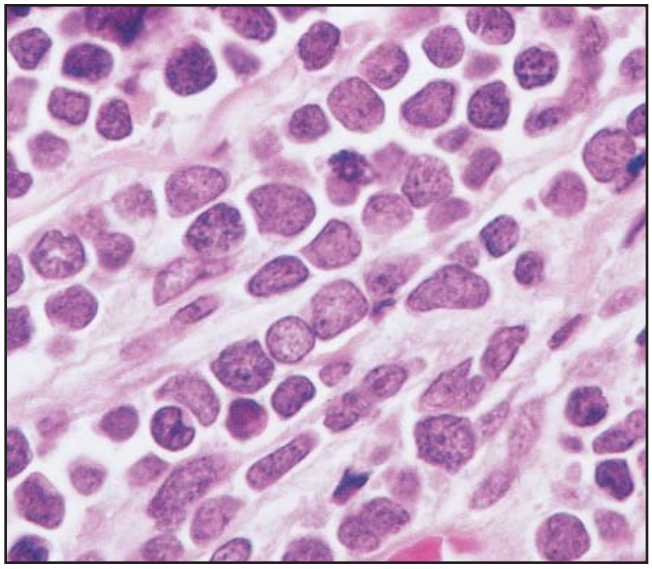

Image 1 (Case 1) Cheek mass. Uniform, medium-sized lymphoblasts with round to mildly irregular nuclei, fine chromatin, and inconspicuous nucleoli (H&E, ×330).

metaphase spreads yielded a 45XY,del3(q21q27),add(9)(p11),–20 karyotype in the neoplastic cells, while in case 8 a 46XY,add(7)(p22),add(21)(q22) clone was isolated.

Clinical Outcome

Table 4 summarizes the therapy instituted and the most recent follow-up for the 9 patients. Six of the 7 children were treated with the DFW (Dallas-Fort Worth) II ALL protocol with induction by dexamethasone, vincristine, daunorubicin, and asparaginase over a 4-week period, followed by a consolidation phase using methotrexate and mercaptopurine.[33] The seventh pediatric patient was treated with the POG 8719 protocol that preceded DFW II at our institution. (See footnote to Table 4; detailed information on past and current POG protocols is present on the POG Web site at http://www.pog.ufl.edu/.) One adult patient (case 8) completed therapy, including 2 years of maintenance chemotherapy, and the second adult (case 9) is currently on a hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) protocol[32] alternating with methotrexate and cytarabine. The median follow-up was 14 months (range, 2-129 months), and all patients are in complete remission.

Discussion

Although precursor B-cell LYL and ALL have been merged as a single entity in the new REAL classification,[29] the data on precursor B-cell LYL are limited to small series or isolated case reports. We report 9 cases of precursor B-cell LYL lacking blood and bone marrow involvement and a review of the literature. Inclusion criteria for the literature review were based on the Murphy criteria for diagnosis of LYL (<25% bone marrow involvement by lymphoma cells), because it often was impossible to distinguish cases with or without bone marrow involvement. We excluded single case reports[27,28] and individual cases from larger series[4,6,9,18] in which the extent of marrow involvement was not defined or was greater than 25%, as well as cases in which immunophenotyping of the neoplastic cells had not been performed.[34,35] By these criteria, 105 cases including 9 from the present study were reviewed.

Age at diagnosis was available for 98 patients, of whom 63 (64%) were younger than 18 years **Table 5**. Precursor B-cell LYL, like precursor B-cell ALL,[2,36] seems to be a disease of young people. The primary site was available for 103 cases. Approximately three fourths of the patients had disease in the skin (with or without adjacent nodal involvement), lymph nodes, or bone. The mediastinum was an uncommon site of presentation. Miscellaneous sites such as head and neck (parotid gland, Waldeyer ring), retroperitoneum, breast, ovary, brain, and soft tissues were the sites in

Table 3
Immunophenotyping in Nine Cases of Precursor B-Cell Lymphoblastic Lymphoma*

Case No.	CD34	CD10	HLA–DR	TdT	CD45	CD38	CD19	CD20	CD22	kappa	lambda	Other
1	–	–	+	+†	Dim +	+	+	–	+	–	–	
2	ND	–	ND	+	ND	ND	+	Partial +	ND	–	–	
3	Partial +	+	+	+	Dim +	+	+	Partial +	+	–	–	
4	Partial dim +	+	+	+	Dim +	+	+	–	+	–	–	CD79a+
5	–	Partial +	+	+	ND	+	+	Partial dim +	+	–	–	
6	ND	+	ND	+	ND	ND	ND	–	ND	ND	ND	CD43+
7	Partial dim +	+	ND	+	–	+	+	Partial dim +	+	–	–	
8	Partial +	+	+	+	Dim +	+	+	Partial +	+	–	–	
9	ND	ND	ND	+	+	ND	ND	+	ND	ND	ND	Cyclin D1–

ND, not done; TdT, terminal deoxynucleotidyl transferase.
* For cases 6 and 9, fresh tissue was not available for immunophenotyping, and results are from immunohistochemical analysis of paraffin-embedded tissue.
† TdT on paraffin-embedded tissue only.

Table 4
Therapy and Follow-up in Eight Cases of Precursor B-Cell Lymphoblastic Lymphoma

Case No.	Therapy	Current Status*
1	Dallas-Fort Worth (DFW) II†	13
2	Pediatric Oncology Group (POG) 8719‡	117
3	DFW II	14
4	DFW II	3
5	DFW II	14
6	DFW II	16
7	DFW II	2
8	Induction: CHOP consolidation: 25 cycles of Stanford high-risk chemotherapy (vincristine, asparaginase); maintenance: mercaptopurine, methotrexate for total therapy of 104 wk	41
9	Hyper-CVAD alternating with methotrexate and cytarabine[32]	3

CHOP, cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone; CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone.
* Months in continuous clinical remission.
† DFW II (standard arm); see text for details.
‡ POG 8719 includes vincristine, prednisone, cyclophosphamide, methotrexate, mercaptopurine, and doxorubicin.

the remaining cases. All patients had less than 25% bone marrow involvement on pathologic staging; 50 (47.6%) of 105 had no marrow disease. Five (4.8%) of 105 patients had central nervous system involvement (including 1 patient with primary LYL of the brain).

All cases were immunophenotyped for at least one early B-cell antigen, in addition to other lineage-associated and activation markers. Since the cases spanned almost 2 decades, a variety of different B- and T-cell antibodies were used, including different clones directed against the same antigen. Lineage determination was performed on fresh frozen tissue, archival material, and cell suspensions; the results are tempered by methods, the sensitivity and specificity of different antibodies, and the tissues on which they were applied. **Table 6** summarizes the 9 most commonly examined antigens and the proportion of reactivity in LYL. Among the B-cell antigens, CD 19, CD79a, and CD10 were commonly expressed, while CD20 was expressed in almost two thirds of the cases. Ninety-two percent of cases expressed TdT, while 64% expressed CD34. Two important caveats emerged from the immunophenotyping data: CD45 (leukocyte common antigen [LCA]) was present in 62% of the cases, and in most instances it was dimly expressed; and CD 99 expression, presumed at one time to be specific for the Ewing family of tumors (EFTs), was seen in 75% of cases. The importance of these findings in the differential diagnosis of precursor B-cell LYL is discussed in the subsequent text.

The data on cytogenetic aberrations in precursor B-cell LYL are rudimentary, with only 8 karyotyped cases to the best of our knowledge **Table 7**. Although the number of cases is small, hyperdiploidy does not seem to be as commonly observed as in precursor B-cell ALL.[2] Moreover, some of the characteristic structural cytogenetic changes such as the translocations (9;22), (1;19), and (4;11) seen in precursor B-cell ALLs were not found. Significantly, 3 of the

Table 5
Literature Review of Clinical Features in Precursor B-Cell Lymphoblastic Lymphoma*

Feature	Findings
Age distribution (n = 98)	
<18 y	63 (64)
>18 y	35 (36)
Site (n = 103)	
Skin	34 (33)
Lymph node	23 (22)
Bone	20 (19)
Mediastinum	5 (5)
Miscellaneous (parotid gland, tonsils, breast, ovary, brain, retroperitoneum, soft tissues)	21 (20)
Follow-up available (n = 105)	81 (77)
Patients surviving (n = 81)	60 (74)
Patients dead of disease (n = 81)	21 (26)
Follow-up (mo)	
Median	26
Range	2-144
Follow-up in surviving patients (mo)	
Median	28
Range	2-144
Survival in patients dying of disease (mo)	
Median	19
Range	2-72

* Data are given as number (percentage) unless otherwise indicated.

Table 6
Immunophenotype of Precursor B-Cell Lymphoblastic Lymphoma[4-24,26,37]

Antigen	Percentage Expressed*
TdT	92 (61/66)
HLA-DR	100 (58/58)
CD19	97 (38/39)
CD20	62 (30/48)
CD10 (CALLA)	89 (56/63)
CD79a	96 (22/23)
CD34	64 (14/22)
CD45	62 (16/26)
CD99	75 (6/8)

CALLA, common acute lymphoblastic leukemia antigen; TdT, terminal deoxynucleotidyl transferase.
* Data in parentheses are the number of cases/total number.

Table 7
Cytogenetics in Precursor B-Cell Lymphoblastic Lymphoma

Case No.*	Tissue Karyotyped	Karyotype
1	Skin	46,XX
2	Lymph node	54,XXY,+4,+6,+14,+15,+17,+21,+21
3	Marrow	47,XX,der(1),add(7)(p?),der(14),+21
4	Marrow	46,XX
5	Marrow	46,XY,del(6)(q?)
6	Marrow, skin	46,XX
7	Lymph node	45,XY,del3(q21q27),add(9)(p11),–20
8	Lymph node	46,XY,add(7)(p22),add(21)(q22)

* Cases 1 through 6 are from Millot et al,[23] and cases 7 and 8 are from the present study.

8 cases had additional chromosome 21 material, one as a trisomy, one as a tetrasomy, and the third as an add(21)(q22).[23] Trisomy and polysomy of chromosome 21 are well-characterized, nonrandom changes seen in ALLs.[38] The 21q22 region is involved in the (12;21) translocation, resulting in the *TEL/AML1* fusion gene, and trisomy 21 has been reported to be the most common secondary aberration in TEL/AML1-positive ALL.[38] Presently, the incidence of t(12;21) rearrangement in precursor B-cell LYL is unknown.

The differential diagnosis of precursor B-cell LYL includes T-cell LYL and the blastoid variant of mantle cell lymphoma, as well as malignant neoplasms of the small blue cell category, such as EFTs. Although the mean ages for precursor B-cell LYL and T-cell LYL are virtually identical, T-cell LYL has a much higher proportion of cases occurring in the mediastinum, 50% to 65%, compared with 4% for precursor B-cell LYL.[25,39] Most T-cell LYLs also express TdT and CD99,[24-26] while up to a third express CD10.[2] However, reactivity for at least 1 pan T-cell marker (CD2, CD3, CD5, CD7) is present in all cases of T-cell LYL. The blastoid variant of mantle cell lymphoma is also in the differential diagnosis of a "lymphoblastoid" malignant neoplasm. Histologic sections from a blastoid variant of mantle cell lymphoma may look virtually identical to B- or T-cell LYL.[20,25] The blastoid variant of mantle cell lymphoma manifests in older people in their sixth or seventh decades of life, with a strong male predominance.[40] The neoplastic cells express CD5, FMC7, cyclin D1, and surface immunoglobulin light chains but do not express the immature markers such as TdT and CD34.[41,42] Rarely, follicular lymphomas have been reported to undergo blastic/blastoid transformation, with histologic features resembling LYL.[43] The history of previously diagnosed follicular lymphoma, presence of a (14;18) translocation, and lack of expression of immature antigens distinguish this rare entity from LYL.

Precursor B-cell LYLs can manifest as a primary bone lesion,[24,26,37] and EFTs need to be excluded because of overlapping patient populations. Both precursor B- and T-cell LYL express CD99, which at one time was thought to be unique to EFTs.[44] Moreover, only two thirds of precursor B-cell LYLs express CD45 (LCA), and, thus, a CD99+, LCA-negative tumor should not be equated with a diagnosis of EFT. Additional immunohistochemical stains such as TdT, CD34, or CD79a, which are negative in EFTs, are needed to exclude precursor B-cell LYL.[42] CD43 is another commonly expressed antigen found in both B- and T-cell LYLs that is not present in EFTs.[24] The demonstration of an (11;22) translocation or the EWS-FLI1 fusion product characteristic of EFTs is helpful in establishing the correct diagnosis.

The mode of therapy was available for 99 (94.3%) of 105 patients. All except 2 received combination chemotherapy with or without radiation therapy; 2 patients received local radiotherapy without chemotherapy. Thirty-eight (38%) of 99 patients were treated with pediatric or adult non-Hodgkin lymphoma chemotherapy regimens and 29 (29%) of 99 by a variety of ALL protocols; details of multiagent chemotherapy were not available for the remaining 32 patients.

The median follow-up period was 26 months (range, 2-144 months) for the 81 (77.1%) of 105 patients for whom information was available (Table 5). Sixty of the 81 (74%) were alive with no evidence of disease at a median of 28 months (range, 2-144 months); 21 (26%) of 81 were dead of disease, with a median survival of 19 months (range, 2-72 months). Of the patients who died, 13 (62%) of 21 were adults, and 8 (38%) were children. Considering that adults represented a minority of cases, the disease seems to be more aggressive in older people, similar to precursor B-cell ALL.[45] To our knowledge, there have been no multicenter studies to evaluate survival in precursor B-cell LYL using consensus risk stratification or standard treatment protocols. However, based on the present cases and review of the literature, most patients with precursor B-cell LYL have a high rate of complete remission and favorable outcome (74% survival at a median follow-up of 26 months), similar to what has been reported for precursor B-cell ALL.[36,46] Larger studies would be useful to define high-risk criteria in precursor B-cell LYL and to determine the most appropriate therapy.

A comparison of the common clinicopathologic features of precursor B-cell LYL and ALL are given in **Table 8**. Discordant features between the two entities included incidence and frequency of skin involvement. Although very few cases of precursor B-cell LYL have been karyotyped, additional 21q material may possibly emerge as a recurring cytogenetic anomaly, while hyperdiploidy and translocations observed in ALL (12;21, 1;19, 9;22) may be less frequent. There were several similarities between precursor B-cell LYL and ALL, such as the high proportion of cases in childhood, low frequency of mediastinal involvement, similar

Table 8
Precursor B-Cell Lymphoblastic Lymphoma (LYL) and Precursor B-Cell Acute Lymphoblastic Leukemia (ALL)

	LYL	ALL
Frequency	10% of LYL[3]	85% of ALL[47]
Patients younger than 18 y	64%	75%[47]
Mediastinal involvement	4%	1%[47]
Skin involvement	33%	1%[23*]
Central nervous system disease	5%	1%-3%[36]
TdT positive	92%	>90%[2]
CD10+	89%	80%-90%[2]
Common cytogenetic abnormalities	?21q22 +	Hyperdiploidy t(12;21) TEL/AML1t(1;19) E2A/PBX1t(9;22) Ph1t(4;11) MLL[38]

Ph1, Philadelphia chromosome; TdT, terminal deoxynucleotidyl transferase.
* Twelve (1.09%) of 1,101 patients with B-lineage ALL in Children's Leukemia Cooperative Group of the European Organization of Research and Treatment of Cancer trial 58881.[23]

incidence of central nervous system disease at diagnosis, and common immunophenotypic profile.

We report the clinical, pathologic, immunophenotypic, and cytogenetic features in 9 cases of precursor B-cell LYL with no evidence of bone marrow or peripheral blood involvement, and we describe our review of the literature. Our findings indicate that precursor B-cell LYL is an uncommon disease that has many clinicopathologic features similar to precursor B-cell ALL, including some that are distinct. While the unification of precursor B-cell LYL and ALL into a single entity in the REAL classification seems appropriate at present, a multicenter collaborative study to confirm this conclusion may be warranted in the future.

From the Department of Pathology, University of Texas Southwestern Medical Center, Dallas.

Address reprint requests to Dr Kroft: Dept of Pathology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75235.

Acknowledgment: We are grateful to Nita Raidy, Tumor Registrar at Children's Medical Center, Dallas, TX, for data retrieval.

References

1. Murphy SB. Childhood non-Hodgkin's lymphoma. *N Engl J Med*. 1978;299:1446-1448.
2. Brunning RD, McKenna RW. Acute leukemias. *Tumors of the Bone Marrow*. Washington, DC: Armed Forces Institute of Pathology; 1994:100-135. *Atlas of Tumor Pathology*, Third Series, Fascicle 9.
3. Head DR, Behm FG. Acute lymphoblastic leukemia and the lymphoblastic lymphomas of childhood. *Semin Diagn Pathol*. 1995;12:325-334.
4. Bernard A, Murphy SB, Melvin S, et al. Non-T, non-B lymphomas are rare in childhood and associated with cutaneous tumor. *Blood*. 1982;59:549-554.
5. Castella A, Neuberg RW, Kurec AS, et al. Non-Hodgkin's lymphoma with immunologic phenotype similar to non-T, non-B acute lymphocytic leukemia. *Hum Pathol*. 1982;13:777-779.
6. Link MP, Roper M, Dorfman RF, et al. Cutaneous lymphoblastic lymphoma with pre-B markers. *Blood*. 1983;61:838-841.
7. Cossman J, Chused TM, Fisher RI, et al. Diversity of immunological phenotypes of lymphoblastic lymphoma. *Cancer Res*. 1983;43:4486-4490.
8. Borowitz MJ, Croker BP, Metzgar RS. Lymphoblastic lymphoma with the phenotype of common acute lymphoblastic leukemia. *Am J Clin Pathol*. 1983;79:387-391.
9. Knowles DMD, Dodson L, Burke JS, et al. SIg-E- ("null-cell") non-Hodgkin's lymphomas: multiparametric determination of their B- or T-cell lineage. *Am J Pathol*. 1985;120:356-370.
10. Smith RG. Parosteal lymphoblastic lymphoma: a human counterpart of Abelson virus–induced lymphosarcoma of mice. *Cancer*. 1984;54:471-476.
11. Weiss LM, Bindl JM, Picozzi VJ, et al. Lymphoblastic lymphoma: an immunophenotype study of 26 cases with comparison to T cell acute lymphoblastic leukemia. *Blood*. 1986;67:474-478.
12. Kamps WA, Poppema S. Pre-B-cell non-Hodgkin's lymphoma in childhood: report of a case and review of the literature. *Am J Clin Pathol*. 1988;90:103-107.
13. Sheibani K, Nathwani BN, Winberg CD, et al. Antigenically defined subgroups of lymphoblastic lymphoma: relationship to clinical presentation and biologic behavior. *Cancer*. 1987;60:183-190.
14. Grumayer ER, Ladenstein RL, Slavc I, et al. B-cell differentiation pattern of cutaneous lymphomas in infancy and childhood. *Cancer*. 1988;61:303-308.
15. Schwob VS, Weiner L, Hudes G, et al. Extranodal non–T-cell lymphoblastic lymphoma in adults: a report of two cases. *Am J Clin Pathol*. 1988;90:602-605.
16. Nakamura N, Tominaga K, Abe M, et al. A case of lymphoblastic lymphoma with pre-B cell phenotype [letter]. *Acta Haematol*. 1991;86:53-54.
17. Lands R, Karnad A. Non-T-cell lymphoblastic lymphoma with extensive osteolytic lesions and hypercalcemia. *South Med J*. 1991;84:1405-1406.
18. Sander CA, Medeiros LJ, Abruzzo LV, et al. Lymphoblastic lymphoma presenting in cutaneous sites: a clinicopathologic analysis of six cases. *J Am Acad Dermatol*. 1991;25(6 pt 1):1023-1031.
19. Sander CA, Jaffe ES, Gebhardt FC, et al. Mediastinal lymphoblastic lymphoma with an immature B-cell immunophenotype. *Am J Surg Pathol*. 1992;16:300-305.

20. Cheng AL, Su IJ, Tien HF, et al. Characteristic clinicopathologic features of adult B-cell lymphoblastic lymphoma with special emphasis on differential diagnosis with an atypical form probably of blastic lymphocytic lymphoma of intermediate differentiation origin. *Cancer.* 1994;73:706-710.
21. Niemann TH, Thomas PA. Primary lymphoma of bone: diagnosis by fine-needle aspiration biopsy in a pediatric patient. *Diagn Cytopathol.* 1995;12:165-167.
22. Shibata K, Shimamoto Y, Yamada H, et al. Correlation between immunophenotypic diversity and clinical features in B-cell lymphoblastic lymphoma. *Ann Hematol.* 1995;71:319-323.
23. Millot F, Robert A, Bertrand Y, et al, for the Children's Leukemia Cooperative Group of the European Organization of Research and Treatment of Cancer (EORTC). Cutaneous involvement in children with acute lymphoblastic leukemia or lymphoblastic lymphoma. *Pediatrics.* 1997;100:60-64.
24. Ozdemirli M, Fanburg-Smith JC, Hartmann DP, et al. Precursor B-lymphoblastic lymphoma presenting as a solitary bone tumor and mimicking Ewing's sarcoma: a report of four cases and review of the literature. *Am J Surg Pathol.* 1998;22:795-804.
25. Soslow RA, Baergen RN, Warnke RA. B-lineage lymphoblastic lymphoma is a clinicopathologic entity distinct from other histologically similar aggressive lymphomas with blastic morphology. *Cancer.* 1999;85:2648-2654.
26. Iravani S, Singleton TP, Ross CW, et al. Precursor B lymphoblastic lymphoma presenting as lytic bone lesions. *Am J Clin Pathol.* 1999;112:836-843.
27. Meyers L, Hakami N. Pre-B cell cutaneous lymphoma in infancy: a unique clinical entity. *Med Pediatr Oncol.* 1984;12:252-254.
28. Schmitt IM, Manente L, Di Matteo A, et al. Lymphoblastic lymphoma of the pre-B phenotype with cutaneous presentation. *Dermatology.* 1997;195:289-292.
29. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood.* 1994;84:1361-1392.
30. Kroft SH, Howard MS, Picker LJ, et al. De novo CD5+ diffuse large B-cell lymphomas: a heterogeneous group containing an unusual form of splenic lymphoma. *Am J Clin Pathol.* 2000;114:523-533.
31. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol.* 1980;7:332-339.
32. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol.* 2000;18:547-561.
33. Winick NJ, McKenna RW, Shuster JJ, et al. Secondary acute myeloid leukemia in children with acute lymphoblastic leukemia treated with etoposide. *J Clin Oncol.* 1993;11:209-217.
34. Furman WL, Fitch S, Hustu HO, et al. Primary lymphoma of bone in children. *J Clin Oncol.* 1989;7:1275-1280.
35. Vassallo J, Roessner A, Vollmer E, et al. Malignant lymphomas with primary bone manifestation. *Pathol Res Pract.* 1987;182:381-389.
36. Whitlock JA, Gaynon PS. Acute lymphocytic leukemia. In: Lee GR, Foerster J, Lukens J, et al, eds. *Wintrobe's Clinical Hematology.* 10th ed. Baltimore, MD: Williams & Wilkins; 1999:2241-2273.
37. Lin P, Jones D, Dorfman DM, et al. Precursor B-cell lymphoblastic lymphoma. *Am J Surg Pathol.* 2000;24:1480-1490.
38. Gaidano G, Dalla-Favera R. Molecular biology of lymphoid neoplasms. In: Mendelsohn J, Howley P, Israel M, et al, eds. *The Molecular Basis of Cancer.* Philadelphia, PA: Saunders; 1995:251-272.
39. Yeh KH, Cheng AL, Su IJ, et al. Prognostic significance of immunophenotypes in adult lymphoblastic lymphomas. *Anticancer Res.* 1997;17:2269-2272.
40. Argatoff LH, Connors JM, Klasa RJ, et al. Mantle cell lymphoma: a clinicopathologic study of 80 cases. *Blood.* 1997;89:2067-2078.
41. Soslow RA, Zukerberg LR, Harris NL, et al. Bcl-1 (PRAD-1/Cyclin D-1) overexpression distinguishes blastoid variant of mantle cell lymphoma from B-lineage lymphoblastic lymphoma. *Mod Pathol.* 1997;10:810-817.
42. Soslow RA, Bhargava V, Warnke RA. MIC2, TdT, bcl-2 and CD34 expression in paraffin-embedded high grade lymphoma/acute lymphoblastic leukemia distinguishes between distinct clinicopathologic entities. *Hum Pathol.* 1997;28:1158-1165.
43. Natkunam Y, Warnke RA, Zehnder JL, et al. Blastic/blastoid transformation of follicular lymphoma: immunohistologic and molecular analyses of five cases. *Am J Surg Pathol.* 2000;24:525-534.
44. Riopel M, Dickman PS, Link MP, et al. MIC2 analysis in pediatric lymphomas and leukemias. *Hum Pathol.* 1994;25:396-399.
45. Gee TS, Haghbin M, Dowling MD, et al. Acute lymphoblastic leukemia in adults and children: differences in response with similar therapeutic regimens. *Cancer.* 1976;37:1256-1264.
46. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol.* 1996;14:18-24.
47. Reiter A, Schrappe M, Ludwig WD, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients: results and conclusions of the multicenter trial ALL-BFM 86. *Blood.* 1994;84:3122-3133.