Cutaneous Precursor B-Cell Lymphoblastic Lymphoma in 2 Adult Patients

Clinicopathologic and Molecular Cytogenetic Studies With a Review of the Literature

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Background: Precursor B-cell lymphoblastic lymphoma (B-LBL) is an uncommon high-grade neoplasm of immature B cells. In contrast to the more common lymphoblastic lymphoma of T-cell lineage, B-LBL can be an extranodal disease, with a propensity to involve skin and bone. Most reported cases of B-LBL in the skin, a rarity in adults, are manifestations of existing systemic disease.

Observations: We report 2 unusual cases of primary cutaneous B-LBL in adults. Fluorescence in situ hybridization studies, not previously reported in primary cutaneous B-LBL to our knowledge, demonstrated rearrangement of the MLL gene in one patient and possible hyperdiploidy in the other, both reported in precursor acute lymphoblastic leukemia.

Conclusions: Review of the literature identified 13 reported cases of B-LBL occurring primarily in the skin, in addition to our 2 cases. Precursor B-cell lymphoblastic lymphoma is more common in children and in young adults, with a tropism for the head and neck region. Histologically, B-LBL must be differentiated from other high-grade lymphoid tumors and small “blue round cell” tumors. Because of the common absence of mature B-cell markers in immunohistochemical studies and the frequent expression of CD99, B-LBL may present a diagnostic challenge. Although there is a suggestion in a limited number of patients that abbreviated therapy may provide long-term disease control, the risk of relapse remains significant, particularly if a patient’s condition is misdiagnosed and the patient is treated as having mature B-cell lymphoma. In the absence of prospective studies for this population, patients with B-LBL are treated currently with intensive acute lymphoblastic leukemia regimens.
cases. In accord with clinical approaches to T-cell lymphoma, although differences in prognostic factors cannot be accounted for because of the small number of cases, including the skin and bone. In addition, there has been a suggestion of improved survival in patients with B-LBL compared with patients with T-cell lymphoblastic leukemia (ALL), patients with B-LBL are generally treated with ALL regimens, but it is unclear if abbreviated therapy may be appropriate in selected cases.

We report 2 unusual cases of adults having primary cutaneous B-LBL with detailed clinical, morphologic, and immunophenotypic studies. We also report fluorescence in situ hybridization (FISH) studies with previously unreported results. In addition, we reviewed the available English-language literature describing cases that can be classified as primary cutaneous B-LBL in an attempt to identify distinct clinical and pathologic features of this entity. B-cell lymphoblastic lymphoma can present a diagnostic challenge to dermatopathologists and should be included in the histologic differential diagnosis for diffuse lymphomas and other small “blue round cell” tumors involving the skin. Because of the unclear natural history and controversial relationship to ALL, we propose that at present primary cutaneous B-LBL may be considered as an entity separate from but related to ALL.

We believe that it should be incorporated as such in future cutaneous lymphoma classifications to facilitate its recognition by dermatologists and dermatopathologists.

**REPORT OF CASES**

**CASE 1**

A 66-year-old white man was initially seen in our hematology clinic for evaluation of progressive suborbital swelling and truncal skin nodules. Four months earlier, he had been seen by his primary care physician for the skin lesions and was treated with a combination of antihistamines and antibiotics without response. A lesion on the right temple was biopsied by a dermatologist, and the initial pathologic diagnosis at a dermatopathologic laboratory was probable diffuse large B-cell lymphoma. Histologic analysis of a biopsy specimen from a lesion on the patient’s back 1 month later at a referring institution suggested the diagnosis of B-LBL. On physical examination, the patient had significant facial swelling with induration of the peri-orbital skin. A 2.5-cm nodule was on his scalp with central crusting (Figure 1A). Multiple erythematous nodules were present on his trunk (Figure 1B). No lymphadenopathy was identified on physical examination. A second biopsy specimen of a lesion on the patient’s back was obtained at our institution.

Two biopsy specimens from lesions on the patient’s back several months apart showed similar changes of an atypical superficial and deep infiltrate in the dermis, with a grenz zone in the papillary dermis. The infiltrate was diffuse and bandlike in the upper dermis and was longitudinally arranged along vascular plexuses and skin adnexal structures in the reticular dermis, accompanied by infiltrative strands and aggregates among dermal collagen fibers (Figure 2A). The cells exhibited striking uniformity in their morphologic structure, being medium to large with scant cytoplasm, round nuclei, fine nuclear chromatin, and occasional small inconspicuous nucleoli (Figure 2B). Scattered mitoses were present. On immunohistochemical staining, the cells were uniformly and strongly positive for terminal deoxynucleotidyl transferase (TdT) (Figure 2C) and CD43 (Figure 2D), positive for CD99, weakly positive for CD79a, and negative for CD117, CD34, CD20, and CD56. Flow cytometry of the skin biopsy specimen showed that the cells were dimly positive for CD45; positive for CD19, TdT, and HLA-DR; and negative for CD20, CD10, myeloid markers, T-cell markers, and surface immunoglobulin light chains (Figure 2E). These changes were consistent with early precursor B phenotype.

FISH was performed on sections of paraffin-embedded formalin-fixed tissue using dual-color break-apart probes for the IGH (14q32.3), MYC (8q24), and MLL (11q23) genes and dual-color dual-fusion BCR-ABL for t(9;22) (Abbott Molecular Inc, Des Plaines, Illinois). Forty-one percent of cells had a rearrangement of the IGH (14q32.3), MYC (8q24), and MLL (11q23) genes and dual-color dual-fusion BCR-ABL for t(9;22) (Abbott Molecular Inc, Des Plaines, Illinois). Forty-one percent of cells had a rearrangement of the IGH (14q32.3), MYC (8q24), and MLL (11q23) genes and dual-color dual-fusion BCR-ABL for t(9;22) (Abbott Molecular Inc, Des Plaines, Illinois).
A computed tomographic (CT) scan and a staging bone marrow biopsy specimen with immunophenotyping by immunohistochemical stains did not demonstrate any other sites of lymphoma involvement. Flow cytometry analyses of the peripheral blood did not show lymphoma or leukemia. Cytologic examination of the cerebral spinal fluid showed no malignant cells. The patient began induction chemotherapy with a combination of prednisone, daunorubicin hydrochloride, vincristine sulfate, and L-asparaginase as per the ALL-type regimen used in Eastern Cooperative Oncology Group 2993 trial. Although he had an excellent initial response to induction therapy with near resolution of most lesions, the patient died of complications related to his treatment during induction.

**CASE 2**

A 27-year-old man was initially seen in our hematology clinic with a nodule on his scalp that had been present for 1 year. After the first 6 months, the nodule began to increase in size to approximately 3 cm. An excisional biopsy was attempted, but the margins were reportedly indistinct. Within several weeks, the previously excised area began to enlarge. On physical examination, 3 coalescent firm erythematous nodules measuring 1 cm, 2 cm, and 3 cm in diameter were noted. No other adenopathy or organomegaly was evident on physical examination.

A biopsy specimen from the scalp demonstrated a diffuse infiltrate of atypical lymphoid cells in the entire der-
mis, with a grenz zone in the papillary dermis and invasion of the arrector pili muscle (Figure 4A). The medium to large cells were uniform in morphologic appearance, with scant cytoplasm, irregular nuclear contour, stippled chromatin, and no prominent nucleoli. Scattered mitoses and interspersed small lymphocytes were also present (Figure 4B). Immunohistochemical stains showed that the cells were faintly positive for CD79a (Figure 4D), focally positive for CD20, and positive for TdT (Figure 4C), CD10, and CD34. Ki-67 stained most of the tumor cells. A myeloperoxidase stain was mostly negative, and CD99 was negative.

FISH analyses were performed on formalin-fixed paraffin-embedded sections using dual-color break-apart probes for IGH (14q32.3), MYC (8q24), and MLL (11q23) and dual-color dual-fusion BCR-ABL for t(9;22). The abnormalities observed (case 2 in Figure 3) were an extra copy of IGH (59.5% of cells), MLL (85% of cells), and BCR-ABL (78% of cells). There were 2 copies of MYC. These findings suggest a probable hyperdiploid to near-triploid karyotype.

An initial staging CT scan of the chest, abdomen, and pelvis did not demonstrate any other sites of disease. The findings of a staging bone marrow biopsy specimen with flow cytometry did not reveal any lymphoma involvement, with a normal 46,XY karyotype. Flow cytometry analysis of the peripheral blood did not reveal lymphoma or leukemia. Cytologic examination of the cerebrospinal fluid showed no malignant cells. A CT scan of the chest performed 2 months later before the initiation of chemotherapy revealed a new soft-tissue mass in the anterior mediastinum. Induction, intensification, and consolidation chemotherapy was initiated as per Eastern Cooperative Oncology Group 2993 trial with multiple agents. The patient had an excellent response and continues maintenance therapy at 34 months after his initial diagnosis without any evidence of recurrent disease.

**COMMENT**

Precursor B-cell lymphoblastic lymphoma is an uncommon form of lymphoblastic lymphoma that accounts for less than 10% of all lymphoblastic lymphoma cases. This contrasts with ALL, in which precursor B is the more common subtype. Although the survival rates for B-cell ALL (B-ALL) in the pediatric population have reached 60% to 70%, survival in adults has lagged behind and approaches 20% to 40%. Patients with B-LBL often present with extranodal disease. In one of the largest B-LBL case series, Lin et al10 suggest that patients with B-LBL have more favorable complete remission rates and duration of remissions than reported for adult patients with B-ALL treated with similar regimens. Primary cutaneous B-LBL is rare, with only case reports in the literature.10-12,16-18 Several documented cases are reported in the literature describing B-LBL manifesting as a solitary bone tumor.19-21 Our cases, in addition to those already in the literature, provide additional support for primary cutaneous B-LBL as a clinicopathologic entity. In our review of the literature (Table 1), there were 13 cases of B-LBL with only skin involvement at the time of presentation. Excluding our 2 patients, most patients were young (median age, 10 years) and female (10 of 13). The lesions are usually red to purple nodules. Nine patients had involvement of the head and neck area, suggesting a tropism for that particular region. Most patients were treated with ALL-type regimens, often per pediatric protocols. Two
patients (cases 8 and 9) treated with only local therapy ultimately relapsed and died of their disease.

B-cell lymphoblastic lymphoma can present a diagnostic challenge to dermatopathologists. The differential diagnosis of B-LBL (Table 2) includes other lymphoid malignant neoplasms, as well as small blue round cell tumors involving the skin such as Ewing sarcoma. The immature lymphocytes in B-LBL typically express TdT, CD43, and HLA-DR and may express B-cell markers such as CD79a, CD19, CD22, and CD20 (less common). CD10 is typically positive but is often negative in cases with translocation involving MLL on chromosome 11, as seen in patient 1. Cytoplasmic μ heavy chains may be present, but surface immunoglobulin is usually absent. The most striking appearance of our 2 cases is the uniformity of the cytomorphologic features. This tends to set the cases apart from usual lymphomas. However, there are caveats that may lead to misdiagnosis. Cutaneous B-LBL is an uncommon occurrence in the skin; therefore, it may not enter into the differential consideration by dermatopathologists. In skin biopsy specimens, the blastic cytologic nature of the cells may not be apparent owing to compression of the fragile neoplastic cells by dense dermal collagen fibers. This is especially true on thicker and less ideal histologic sections. Immunophenotypically, B-LBL is often negative for the mature B-cell antigen CD20, the most commonly used B-cell marker for immunohistochemistry. CD79a, a marker of early B-cell differentiation, may be useful because most B-LBL cases express CD79a. However, in our patients, CD79a stains were weak in intensity. CD45 (leukocyte common antigen), a marker often used to confirm the hematopoietic nature of tumors, is negative in some B-LBL cases and, if positive, only dimly. This feature, coupled with frequent expression of CD99 in B-LBL, can cause confusion with Ewing sarcoma or primitive neuroectodermal tumors. IGH rearrangement may provide additional support for a diagnosis of lymphoid neoplasm.19 In differential diagnosis with myeloid or myelomonocytic leukemia cutis, it is important to recognize that rare B-LBL cases express myeloid markers. A comprehensive evaluation of B-cell markers is important in differentiating B-LBL from CD4+/CD56+ hematodermic tumors because rare B-LBL cases may express CD56 and, conversely, some cases of CD4+/CD56+ hematodermic tumors are positive for TdT or CD34. In summary, the key to recognizing these rare cases of B-LBL is to perform a complete immunophenotypic study that includes TdT, CD34, CD79a, CD43, CD99, and CD10. Flow cytometry will facilitate the diagnosis because of the wider

Figure 4. A, A punch biopsy specimen of a scalp lesion in patient 2 revealed a diffuse infiltrate in the dermis. Well-preserved areas showed uniform medium-sized cells with interspersed small lymphocytes. Compared with patient 1 (Figure 2), the cells showed irregular nuclear contour (B). The cells are diffusely positive for terminal deoxynucleotidyl transferase (TdT) (C); some cells stained positively for CD79a (D). Original magnification ×20 (A), ×400 (C and D), and ×600 (B).
range of B-cell markers that can be analyzed. A routine punch biopsy specimen can yield sufficient cells for this analysis.22

A biopsy specimen from one of our patients showed a clonal rearrangement of MLL on chromosome 11q23, a gene abnormality typically seen in ALL and in chemotherapy-induced leukemia. To our knowledge, this is the first reported case of B-LBL with the MLL abnormality. Because B-LBL is a rare disease, there is limited information about cytogenetic abnormalities and the implications for prognosis and treatment. Our patient with the MLL rearrangement, a known poor prognostic marker in infant ALL, also expressed markers of the early precursor B phenotype, known to be associated with a poor prognosis. Moorman et al23 recently reported on the cytogenetic data from 1552 adult patients with ALL enrolled in the Medical Research Council United Kingdom Acute Lymphoblastic Leukemia XII–Eastern Cooperative Oncology Group 2993 trial. Fifty-four of 69 patients without the Philadelphia chromosome (Ph−) had an abnormality.

In the pediatric population. Similarly, Moorman et al23 reported that high hyperdiploidy (51-65 chromosomes) in the Ph− patients was associated with significantly improved event-free survival and overall survival. The karyotype and immunophenotype in both of our patients seemed to correlate with the natural history of the disease. Patient 1 with the early precursor B phenotype and the MLL abnormality had more rapid clinical progression and dissemination of his lesions. Patient 2 with the hyperdiploid abnormality had a prolonged natural history with localized disease for almost 1 year. Using a panel of FISH probes for common pediatric and adult B-ALL genetic abnormalities, we can accumulate molecular cytogenetic data for B-LBL. It is probable that patients with B-LBL may be segregated into prognostic categories similar to those of B-ALL.

In light of the histologic, biologic, and immunophenotypic similarities between lymphoblastic lymphoma and ALL, B-LBL is often treated with ALL-type regimens consisting of intensive induction, consolidation, and maintenance. Prospective data to guide the treatment of patients with primary cutaneous B-LBL are limited. However, review of the literature suggests that patients treated with localized therapy appropriate for primary cutaneous mature B-cell lymphomas are at very high risk of systemic relapse.10 Furthermore, there is evidence to suggest that abbreviated chemotherapy such as that used for more mature B-cell neoplasms is insufficient. Neth et al14 reviewed 27 pediatric and adolescent cases of B-LBL treated in 2 multicenter trials of the Berlin-Frankfurt-Munster group in Germany. Twenty-one of these patients were treated according to the ALL-type regimen, with only 2 relapses. Six patients' conditions were initially errone-

Table 1. Clinical, Pathologic, and Cytogenetic Characteristics and Treatment of Primary Precursor Cutaneous B-Cell Lymphoblastic Lymphoma

<table>
<thead>
<tr>
<th>Patient No./Sex/Age</th>
<th>Source</th>
<th>Site/Lesions</th>
<th>CD34</th>
<th>TdT</th>
<th>CD10</th>
<th>CD19</th>
<th>CD20</th>
<th>Cytogenetics</th>
<th>Treatment</th>
<th>Status/Follow-up Period</th>
</tr>
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<tbody>
<tr>
<td>1/M/8 wk</td>
<td>Trupiano et al16 2002</td>
<td>Buttocks, trunk/multiple erythematous nodules</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Rare</td>
<td>Normal</td>
<td>Chemotherapy</td>
<td>CR/13 mo</td>
</tr>
<tr>
<td>2/F/10 y</td>
<td>Maitra et al,12 2001</td>
<td>Forehead/erythematous lesion</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>-</td>
<td>ND</td>
<td>Chemotherapy</td>
<td>CR/16 mo</td>
</tr>
<tr>
<td>3/M/27 y</td>
<td>Lin et al,19 2000</td>
<td>Scalp/erythematous, violaceous tumor, 8 cm</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>Chemotherapy</td>
<td>CR/12 mo</td>
<td></td>
</tr>
<tr>
<td>4/F/11 y</td>
<td>Lin et al,19 2000</td>
<td>Forehead/erythematous, violaceous tumor, 7 cm</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>Weak</td>
<td>Chemotherapy</td>
<td>CR/84 mo</td>
<td></td>
</tr>
<tr>
<td>5/F/6 y</td>
<td>Lin et al,19 2000</td>
<td>External auditory canal</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>ND</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>6/F/9 y</td>
<td>Lin et al,19 2000</td>
<td>Preauricular/erythematous, violaceous tumor, 4 cm</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>Weak</td>
<td>Chemotherapy</td>
<td>Died/60 mo</td>
<td></td>
</tr>
<tr>
<td>7/F/10 y</td>
<td>Lin et al,19 2000</td>
<td>Right scapula/erythematous, violaceous tumor, 10 cm</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>-</td>
<td>ND</td>
<td>Chemotherapy</td>
<td>Died/60 mo</td>
<td></td>
</tr>
<tr>
<td>8/M/24 y</td>
<td>Lin et al,19 2000</td>
<td>Left lumbar/erythematous, violaceous tumor, 5 cm</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Chemotherapy</td>
<td>Died/72 mo</td>
<td></td>
</tr>
<tr>
<td>9/F/5 y</td>
<td>Kahwash and Qualman,11 2002</td>
<td>Scalp/4 cm</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>NA</td>
<td>Radiation, mercaptopurine Chemotherapy</td>
<td>Died/6 mo</td>
</tr>
<tr>
<td>10/F/13 y</td>
<td>Kahwash and Qualman,11 2002</td>
<td>Scalp</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>NA</td>
<td>Chemotherapy</td>
<td>Relapse, CR/8 y</td>
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<tr>
<td>11/F/11 y</td>
<td>Kahwash and Qualman,11 2002</td>
<td>Scalp/7 cm</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>NA</td>
<td>Chemotherapy</td>
<td>CR/6 y</td>
</tr>
<tr>
<td>12/F/3 y and 9 mo</td>
<td>Link et al,11 1983</td>
<td>Scalp</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Chemotherapy</td>
<td>CR/11 mo, relapse and died/2 y</td>
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<tr>
<td>13/F/14 mo</td>
<td>Biasotti et al,14 2001</td>
<td>Buttocks, arm, leg</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>NA</td>
<td>Chemotherapy</td>
<td>CR/18 mo</td>
</tr>
<tr>
<td>14/M/66 y</td>
<td>Present study</td>
<td>Trunk, scalp/largest 2.5 cm</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Dim</td>
<td>-</td>
<td>MLL (11q23)</td>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>15/M/67 y</td>
<td>Present study</td>
<td>Scalp/largest 3 cm</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>Focal</td>
<td>Hyperdiploid to triploid</td>
<td>Chemotherapy</td>
<td>CR/54 mo</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; NA, not specified in the citation; ND, not determined; TdT, terminal deoxynucleotidyl transferase; +, positive; −, negative.
B-LBL was first recognized as a separate entity from ALL, a sufficient number of well-documented cases manifesting primarily cutaneous involvement of B-LBL are generally treated with systemic ALL-type regimens because they are at significant risk for local or systemic relapse with localized therapy or limited chemotherapy regimens. Because of the rarity of the disease, it is difficult to prospectively study whether somewhat less aggressive therapy, particularly shortening or omitting maintenance, may be appropriate in selected patients. Because of the well-documented cases of B-LBL manifesting primarily in the skin and the importance of avoiding misdiagnosis as mature B-cell lymphoma, we propose that this entity should be considered in the future skin lymphoma classification to raise awareness among dermatologists and dermatopathologists. If B-LBL is recognized as a separate entity from ALL, a sufficient number of cases may be collected internationally, permitting better understanding of the natural history of B-LBL.

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Author Contributions: Dr Wu had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Shafer, Wu, Al-Saleem, and Smith. Acquisition of data: Shafer, Wu, Al-Saleem, Reddy, Borgiaei, Lessin, and Smith. Analysis and interpretation of data: Shafer, Wu, Al-Saleem, and Smith. Drafting of the manuscript: Shafer and Wu. Critical revision of the manuscript for important intellectual content: Shafer, Wu, Al-Saleem, Reddy, Borgiaei, Lessin, and Smith. Obtaining funding: Wu. Administrative, technical, and material support: Wu, Al-Saleem, Reddy, Borgiaei, Lessin, and Smith. Study supervision: Wu and Al-Saleem.

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