Extramedullary B Lymphoblastic Leukemia/Lymphoma (B-ALL/B-LBL): A Diagnostic Challenge

Praveen Ramakrishnan Geethakumari,1 Marc S. Hoffmann,2 Naveen Pemmaraju,2 Shimin Hu,3 Jeffrey L. Jorgensen,3 Susan O’Brien,2 Naval Daver2

Clinical Practice Points

- Aggressive precursor B-cell neoplasms comprise B-cell acute lymphoblastic leukemia (B-ALL) and B-cell lymphoblastic lymphoma (B-LBL).
- B-cell lymphoblastic lymphomas account for only 10% to 20% of cases of these aggressive B-neoplasms and by definition have fewer than 25% bone marrow blasts. B-LBL and B-ALL share immunophenotypic properties and are traditionally classified together.
- Precursor B-LBL frequently involves lymph nodes and extranodal sites including the skin, soft tissue, and cortical bone. It rarely presents with an isolated mediastinal mass, which is typically pathognomonic of T-cell lymphoblastic lymphoma.
- Extramedullary lymphoid neoplasms require comprehensive pathologic review including flow cytometry, immunohistochemistry, cytogenetics, and molecular analysis to ensure diagnostic accuracy.
- Herein we describe a unique presentation of isolated extramedullary B-ALL/B-LBL with no bone marrow involvement. Furthermore, we will review pertinent albeit limited published literature, which might guide diagnosis and management of this entity.

Introduction

B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/B-LBL) accounts for 2% of lymphoid neoplasms diagnosed in the United States. The incidence appears to be increasing in children and adults. B-cell acute lymphoproliferative disease manifests as pure leukemia (B-ALL) in 80% of cases, isolated extramedullary disease (B-LBL) in 10%, and mixed B-ALL/B-LBL in 10% of cases. Extramedullary presentations frequently have marrow involvement at diagnosis that might be morphologically evident or might require detection using high-resolution flow cytometry.1-3

Sternberg et al first recognized the correlation between nodal and leukemic presentations of pre-B-cell neoplasms in 1905.5 He described a patient with mediastinal lymphoma that subsequently progressed to acute leukemia. Nathwani and colleagues established the current morphologic description of “lymphoblastic lymphoma (LBL)” presenting with extramedullary mass lesions comprised of cells indistinguishable from acute lymphoblastic leukemia (ALL).5,6 Current 2008 World Health Organization criteria continue to classify B-ALL and B-LBL as a spectrum disorder, with B-LBL defined according to the presence of extramedullary lesions with fewer than 25% marrow blasts.7,8

Herein we describe a case of isolated extramedullary B-LBL and review the pertinent literature regarding diagnosis and management.

Case Report

A 45-year-old Hispanic man with no significant medical history underwent resection of a left postauricular mass at an outside institution in October 2011 that was interpreted as “myeloid sarcoma.” A whole-body positron emission tomography (PET)/computed tomography (CT) scan in January 2012 revealed abnormal fluorodeoxyglucose (FDG) uptake in multiple bones...
including the cervical, thoracic, and lumbar spine, bilateral humeri, femora, tibiae, and fibulae. Bone marrow aspiration/biopsy in February 2012 revealed no evidence of systemic myeloproliferative, lymphoproliferative, or metastatic disease and the patient was placed on observation. He returned in April 2012 with a dental abscess, which was drained, and pathology revealed diffuse inter trabecular infiltration by a proliferative clone that was CD34-positive (CD34+), BCL2 (B-cell lymphoma 2)-positive, CD2 (weak), CD43+, and TdT+ (Terminal deoxynucleotidyl transferase) with a Ki-67 proliferation rate of 80%. The pathologic diagnosis was “T-cell LBL.” In May 2012, he was referred to M.D. Anderson Cancer Center.

At referral, he had no specific complaints and denied “B” symptoms. Physical exam was notable for absence of lymphadenopathy or hepatosplenomegaly. Laboratory investigations showed normal hemogram, liver, and renal function tests. Lactate dehydrogenase and beta-2 microglobulin were elevated at 902 IU/L (normal, 313-618 U/L) and 3.7 mg/L (normal, 0.7-1.8 mg/L), respectively. Bone marrow biopsy showed 40% cellularity, trilineage hematopoiesis, and diploid cytogenetics with no morphologic evidence of lymphoma/leukemia. No monoclonal T-cell receptor beta or gamma rearrangements were identified in polymerase chain reaction analysis. High-sensitivity multiplanar flow cytometry revealed no evidence of aberrant B cells. A repeat PET/CT scan showed heterogeneous increased FDG uptake in multiple axial bones, retrosternal tissue, and spleen.

Percutaneous CT image-guided surgical biopsy of the PET-avid retrosternal tissue revealed diffuse effacement by sheets of monotonous small- to medium-sized mononuclear blasts with scant cytoplasm, fine chromatin, and small nucleoli. Flow cytometry demonstrated a population of blasts that comprised 80% of the aspirate and positive for CD10, CD19 (100%), CD22 (>90%), CD34, CD38 (bright), CD43, CD44, CD45 (dim), CD123 (dim), CD200 (variable), human leukocyte antigen-DR, and TdT. Blast cells were negative for cyto-CD3, CD5, CD11c, CD13, CD14, CD20 (<5%), CD23, CD33, CD56, CD64, CD117, FMC-7, myeloperoxidase and surface kappa and lambda light chains. This analysis was consistent with B-LBL (Fig. 1).

In June 2012, R-HyperCVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) chemoimmunotherapy was initiated. Our patient received intrathecal prophylaxis per protocol. He attained a complete radiological remission according to PET/CT scans performed after 3 cycles of R-HyperCVAD (Fig. 1). He completed the scheduled 8 cycles of R-HyperCVAD and remained in radiological remission. He is currently on POMP (prednisone, methotrexate, vincristine, and mercaptopurine) maintenance therapy.

**Discussion**

Purely extramedullary ALL is rare. Interestingly, recent reports of isolated extramedullary ALL seem to focus on extramedullary presentations involving the B-cell phenotype, namely B-LBL.9-18 Evolution of B-LBL with sequential involvement of different extramedullary sites including the skin, dental tissue, and bone is unique to our case and hitherto has been poorly described. Furthermore, our case highlights the diagnostic challenges posed by extramedullary presentations of lymphoid leukemias, more specifically the need for complete immunophenotyping in accurate diagnosis.

**Figure 1** Morphology and Immunophenotype of B-LBL and Whole Body PET/CT Images. (A) and (B) Histology and Cytology of B-LBL (Magnification ×1000). (C) and (D) Lymphoma Cells are Positive for CD19 and Negative for CD3 (Magnification ×500). (E) and (F) Lymphoma Cells are Positive for TDT, CD19, CD34, and CD38 Using Flow Cytometry. (G) PET/CT Image Showing Heterogeneous Increased FDG Uptake in Multiple Long Bones and Axial Skeleton. (H) PET/CT Image Showing Radiologic Remission After R-HyperCVAD Chemoimmunotherapy.
The natural history of B-LBL is poorly defined and the bulk of known data emanate from case reports and small series. Extramedullary leukemias are usually T-cell in origin. B-LBL comprises only 10% to 15% of lymphoblastic leukemia/lymphomas and frequently involves lymph nodes and extranodal sites including skin, bone, and soft tissue. Mediastinal masses that characterize T-LBL are much less common in B-LBL. B-LBL might involve miscellaneous sites including head and neck (parotid gland, Waldeyer ring), retroperitoneum, mediastinum, pleura, breast, ovary, gastrointestinal tract, kidneys, brain, and soft tissue. B-LBL demonstrates a higher incidence of skin involvement (33%) compared with ALL (1%),13,14,16,19,20

In immunohistochemistry, LBL blasts show positive periodic acid Schiff staining, variable positivity for nonspecific esterase, and Sudan Black B, and negativity for myeloperoxidase. In B-LBL, tumor cells are positive for B-cell markers like CD19, CD79a, and CD22, frequently express CD20, CD34, CD45, and CD99. The following antigen set is used to define stages of differentiation: ‘pro-B’ stage (CD10+, CD19+, CD79a+, CD22+, nuclear TdT+), ‘common’ stage (CD10-), and ‘late pre-B’ stage (CD20+, cytoplasmic heavy chain-positive). Coexpression of myeloid antigens, mostly CD13 and CD33 can occur in up to 30% of the cases. Some studies have shown that LBL demonstrates a more “mature immunophenotype (mostly pre-B)” compared with ALL (Table 1).1,5,6,10,12,14,15,21

The differential diagnosis of extramedullary LBL includes aggressive mature B-cell lymphomas (blastoïd mantle cell lymphoma, Burkitt lymphoma, double-hit, and other gray zone lymphomas), Ewing family tumors, and myeloid leukemias. T-ALL/ B-LBL is morphologically indistinguishable from B-ALL/LBL, but can often be distinguished by its expression of T-cell markers including CD1a, CD2, CD3, CD4, CD5, CD7, and CD8. Most cases of B-LBL express TdT and lack myeloperoxidase differentiating them from acute myeloid leukemia and granulocytic sarcoma. The expression of TdT and lack of surface immunoglobulin helps differentiate B-LBL from more mature B-cell neoplasms. The negativity of cyclin D1 and CD5 with TdT expression differentiates it from mantle cell lymphoma. Expression of TdT, CD34, CD43, and CD79a help differentiate B-LBL from Ewing family tumors that also express CD99.1,7

The pathophysiology of extramedullary involvement in ALL is not fully discerned but might in part depend on CXCR4 (C-X-C chemokine receptor type 4)/stromal derived factor-1 (SDF-1) signaling. Signaling involving chemokine receptor CXCR4 and its ligand, SDF-1/CXCL12 (C-X-C motif chemokine 12) might mediate chemotaxis and transendothelial migration of pre-B cells to extramedullary tissues.22 CXCR4 overexpression has been demonstrated in lymphoblasts from patients with extramedullary involvement and SDF-1 expression is not restricted to the bone marrow microenvironment but has also been identified in the brain, lymph nodes, liver, and spleen. Similarly, CXCR4 antagonists mobilize leukemic blasts to the peripheral blood and inhibit “extramedullary homing.”23 Another molecule of interest is the vascular endothelial growth factor receptor-1 (VEGFR1 or FLT-1), which regulates the localization of ALL cells to the bone marrow and their survival and egress to systemic circulation. FLT-1 neutralization impedes the mobilization of leukemic cells and results in apoptosis.24

Karyotyping shows differences in cytogenetic profiles between B-LBL and B-ALL (Table 1). For example, additional chromosome 21q material including trisomy, tetrasomy, intrachromosomal amplification of AML1 gene (21q22) have been reported in B-LBL but the cytogenetic aberrations typically associated with medullary ALL including hyperdiploidy, t(12;21), t(1;19), t(9;22), and t(4;11) are less frequent. Most of B-LBLs have clonal rearrangements of the immunoglobulin heavy chain, with occasional rearrangement of the light chain genes.1,13,14

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B-LBL</th>
<th>B-ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>10% of LBL</td>
<td>85% of ALL</td>
</tr>
<tr>
<td>Patients Aged Younger Than 18 Years</td>
<td>64%</td>
<td>75%</td>
</tr>
<tr>
<td>Definition (WHO)</td>
<td>Presence of mass lesions and &lt;25% marrow blasts</td>
<td>&gt;25% Bone marrow involvement</td>
</tr>
<tr>
<td>Skin Involvement</td>
<td>33%</td>
<td>1%</td>
</tr>
<tr>
<td>Mediastinal Involvement</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>CNS Disease</td>
<td>5%</td>
<td>1%-3%</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Mature “pre-B” common</td>
<td>Immature phenotype</td>
</tr>
<tr>
<td>TdT+</td>
<td>92%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>CD10+</td>
<td>89%</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Cytogenetic Abnormalities</td>
<td>Additional chromosome 21q material in form of trisomy, tetrasomy, additional 21q22, clonal Ig heavy chain rearrangement</td>
<td>Hyperdiploidy, characteristic translocations seen in ALL including (12;21), t(1;19), t(9;22), and t(4;11) (rare in B-LBL)</td>
</tr>
<tr>
<td>Prognostic Indices</td>
<td>No validated prognostic model for adult LBL. Poor prognostic markers: (1) higher IPI (2) advanced stage</td>
<td>Poor prognostic markers: (1) age &gt; 35 years (2) leucocytosis &gt; 30 × 10⁹/L (3) karyotype: t(9;22), t(4;11), complex or hypodiploid (4) therapy-related: time to morphologic CR &gt; 4 weeks, persistent MRD</td>
</tr>
</tbody>
</table>

Abbreviations: ALL = acute lymphoblastic leukemia; B-ALL = B-cell acute lymphoblastic leukemia; B-LBL = B-cell lymphoblastic lymphoma; CNS = central nervous system; Ig = immunoglobulin; IPI = International Prognostic Index; LBL = lymphoblastic lymphoma; MRD = minimal residual disease; TdT = Terminal deoxynucleotidyl transferase; WHO = World Health Organization.
Lymphoblastic lymphoma is highly aggressive with an inferior prognosis to ALL. Three-year disease-free survival rates are 73% to 90% for children and 45% to 72% for adults. A number of prognostic factors affect the outcome of LBL. For example, B-LBL has a better prognosis than T-LBL. A pediatric series identified advanced stage as a significant adverse prognostic factor. A higher International Prognostic Index for non-Hodgkin lymphoma was associated with poor survival in adult LBL but not childhood LBL. Central nervous system (CNS) involvement at diagnosis was associated with poor outcome in both B- and T-LBL, reported by Thomas et al. Multiagent chemotherapy regimens traditionally used in B-ALL remain the standard therapy for B-LBL. The addition of rituximab to the modified HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) regimen as front-line therapy has improved 3-year overall survival from 35% to 68% compared with HyperCVAD alone for adolescents and young adults with B-ALL/LBL. Intensive intrathecal chemotherapy prophylaxis is effective in preventing CNS relapses and might obviate the need for cranial irradiation. Medialateral irradiation for patients with large mediastinal masses at diagnosis might reduce mediastinal relapses, especially in T-LBLs. Patients with adverse prognostic features at diagnosis should be considered for autologous or allogeneic stem cell transplantation (SCT). Monitoring for minimal residual disease in LBL patients in first complete remission in bone marrow analysis and PET/CT imaging might help to identify subsets of patients who will benefit from SCT in the future.

**Conclusion**

B-cell lymphoblastic leukemia/lymphoma can present with varied extramedullary manifestations without bone marrow involvement as demonstrated in our case. Identification and treatment of such diagnostically challenging cases requires interdisciplinary effort, incorporating leukemia specialists, radiologists, and pathologists. Unraveling the biology of extramedullary disease might reveal novel therapeutic targets that could be exploited in the future.

**Disclosure**

The authors have stated that they have no conflicts of interest.

**References**

7. Solow RA, Baeumgen RN, Wanjie RA. B-lineage lymphoblastic lymphoma is a clinicopathologic entity distinct from other histologically similar aggressive lymphomas with blastic morphology. Cancer 1999; 85:2648-54.