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Extramedullary B lymphoblastic leukemia/lymphoma (B-ALL/LBL): A diagnostic challenge

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Keywords

extramedullary; B lymphoblastic leukemia/lymphoma

Introduction

B lymphoblastic leukemia/lymphoma (B-ALL/LBL) accounts for 2% of lymphoid neoplasms diagnosed in the United States. The incidence appears to be rising in both children and adults. B-cell acute lymphoproliferative disease manifest 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 may be morphologically evident or may require detection by 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. 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).[4, 5] Current 2008 WHO criteria continue to classify B-ALL and B-LBL as a spectrum disorder, with B-LBL defined by the presence of extramedullary lesions with fewer than 25% marrow blasts. [6, 7]

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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 male with no significant past medical history underwent resection of a left post-auricular mass at an outside institution in October 2011 that was interpreted as *"myeloid sarcoma"*. A whole-body positron emission tomograph (PET/CT) scan in January 2012 revealed abnormal fluorodeoxyglucose (FDG) uptake in multiple bones including the cervical, thoracic and lumbar spine, bilateral humerii, 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 on April 2012 with a dental abscess, which was drained, and pathology revealed diffuse intertrabecular infiltration by a proliferative clone that was CD34+, BCL2+, CD2 (weak), CD43+ and TdT+ with a Ki-67 proliferation rate of 80%. The pathologic diagnosis was "*T-cell lymphoblastic lymphoma"*. 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 (LDH) 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 Tcell receptor beta or gamma rearrangements were identified on 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), HLA-DR and TdT. Blast cells were negative for cyto-CD3, CD5, CD11c, CD13, CD14, CD20 (<5%), CD23, CD33, CD56, CD64, CD117, FMC-7, MPO and surface kappa and lambda light chains. This analysis was consistent with B-LBL (Figure 1).

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

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.[8-17] 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.

The natural history of B-LBL is poorly defined and the bulk of known data emanates from case reports and small series. Extramedullary leukemia's are usually T-cell in origin. B-LBL comprises only 10-15% of lymphoblastic leukemia/lymphoma's and frequently involves lymph nodes and extra-nodal sites including skin, bone and soft tissue. Mediastinal masses that characterize T-LBL are much less common in B-LBL. B-LBL may involve miscellaneous sites including head and neck (parotid gland, Waldeyer ring), retroperitoneum, mediastinum, pleura, breast, ovary, GI tract, kidneys, brain and soft tissue. B-LBL demonstrates a higher incidence of skin involvement (33%) compared to ALL (1%).[12, 13, 15, 18, 19]

On immunohistochemistry, LBL blasts show positive periodic acid Schiff (PAS) staining, variable positivity for non-specific 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 CD10 (common acute lymphocytic leukemia antigen, CALLA), CD24, PAX5, TdT and variably 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+). Co-expression 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 to ALL (Table 1).[1, 20]

The differential diagnosis of extramedullary LBL includes aggressive mature B-cell lymphomas (blastoid mantle cell lymphoma, Burkitt lymphoma, double-hit and other gray zone lymphomas), Ewing family tumors and myeloid leukemias. T-ALL/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 MPO differentiating them from acute myeloid leukemia and granulocytic sarcoma. The expression of TdT and lack of surface Ig 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, 6]

The pathophysiology of extramedullary involvement in ALL is not fully discerned but may in part depend on CXCR4/SDF-1 signaling. Signaling involving chemokine receptor CXCR4 and its ligand stromal derived factor-1(SDF-1)/CXCL12 may mediate chemotaxis

and trans-endothelial migration of pre-B cells to extramedullary tissues.[21] CXCR4 over expression has been demonstrated in lymphoblasts from patients with extramedullary involvement and SDF-1 expression is not restricted to 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”.[22] Another molecule of interest is the vascular endothelial growth factor receptor-1 (VEGFR-1 or FLT-1), which regulates the localization of ALL cells to the bone marrow and their survival and exodus to systemic circulation. FLT-1 neutralization impedes the mobilization of leukemic cells and results in apoptosis.[23]

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. The majority of B-LBL's have clonal rearrangements of the immunoglobulin heavy chain, with occasional rearrangement of the light chain genes. [1, 12, 13]

LBL is highly aggressive with an inferior prognosis to ALL. Three year disease free survival rates are 73-90% for children and 45-72 % for adults. [1, 24-27] A number of prognostic factors impact the outcome of LBL. For example, B-LBL has a better prognosis than T-LBL.[1, 6] A pediatric series identified advanced stage as a significant adverse prognostic factor.[20] A higher International Prognostic Index (IPI) for NHL was associated with poor survival in adult LBL but not childhood LBL.[24] CNS involvement at diagnosis was associated with poor outcome in both B and T-LBL reported by Thomas et al.[27]

Multi-agent chemotherapy regimens traditionally used in B-ALL remain the standard therapy for B-LBL. The addition of rituximab to the modified hyper-CVAD regimen as frontline therapy has improved 3-year overall survival from 35% to 68% compared with hyper-CVAD alone for adolescents and young adults with B-ALL/LBL. Intensive intrathecal chemotherapy prophylaxis is effective in preventing CNS relapses and may obviate the need for cranial irradiation. Mediastinal irradiation for patients with large mediastinal masses at diagnosis may 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 (MRD) in LBL patients in CR1 by BM analysis and PET/CT imaging may help to identify patient subsets who will benefit from SCT in the future.[19, 20, 24-27]

Conclusion

B 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 needs requires interdisciplinary effort incorporating leukemia specialists, radiologists and pathologists. Unraveling the biology of extramedullary disease may reveal novel therapeutic targets that could be exploited in the future.

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Clinical practice points

- Aggressive precursor B-cell neoplasms comprise B-cell acute lymphoblastic leukemia (B-ALL) and B-cell lymphoblastic lymphoma (B-LBL).
- B-LBLs accounts for only 10-20% 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 pathognomic of T cell-LBL.
- 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/LBL with no bone marrow involvement. Furthermore, we will review pertinent albeit limited published literature, which may guide diagnosis and management of this entity.

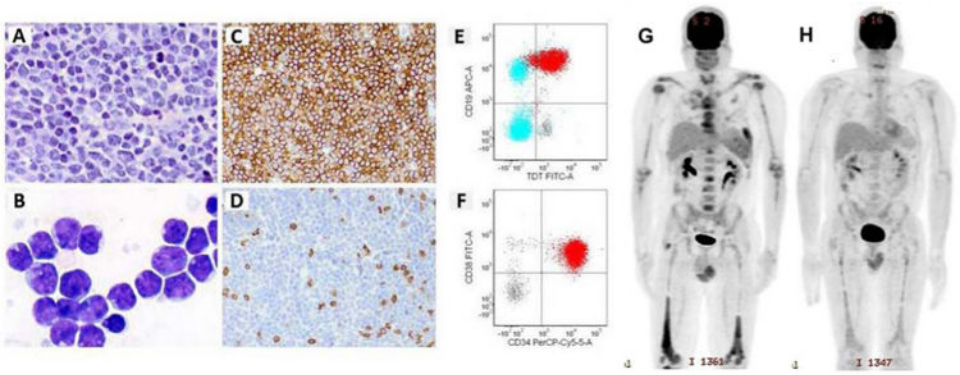

Figure 1.

A-F: Morphology and immunophenotype of B-LBL, G-H: Whole body PET/CT images.

A-B: Histology and cytology of B-LBL (original magnification: 1000×).

C-D: Lymphoma cells are positive for CD19 and negative for CD3 (original magnification: 500×).

E-F: Lymphoma cells are positive for TdT, CD19, CD34, and CD38 by 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 chemo-immunotherapy.

Table 1

Comparison of clinical manifestations, immunophenotype and cytogenetic features of B-LBL and B-ALL[4, 5, 9, 11, 13, 14]

Parameter	B-LBL	B-ALL
Frequency	10% of LBL	85% of ALL
Patients of age < 18 yrs	64%	75%
Definition (WHO)	Presence of mass lesions and <25% marrow blasts	>25% bone marrow involvement
Skin involvement	33%	1%
Mediastinal involvement	4%	1%
CNS disease	5%	1-3%
Immunophenotype	Mature “pre-B” common	Immature phenotype
TdT positive	92%	>90%
CD 10+	89%	80-90%
Cytogenetic abnormalities	Additional chromosome 21q material in form of trisomy, tetrasomy, additional 21q22, clonal Ig heavy chain rearrangement	Hyperdiploidy, Chracteristic translocations seen in ALL including (12;21), t(1;19), t(9;22) and t(4;11) [rare in B-LBL]
Prognostic indices	No validated prognostic model for adult LBL currently. Poor Prognostic markers: **a.** *Higher IPI*, and **b.** Advanced stage	Poor prognostic markers: **a.** *Age*> 35yrs, **b.** *Leucocytosis* > 30×10^9/L, **c.** *Karyotype*: t(9;22), t(4;11), complex or hypodiploid, and **d.** *Therapy related*: Time tomorphologic CR>4wks, Persistent MRD