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Lymphoblastic lymphoma presenting as soft-tissue swelling – A single-center experience

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Abstract:

BACKGROUND: Lymphoblastic lymphomas (LBL) are a rare, aggressive type of non-Hodgkin lymphomas and constitute 2% of all lymphomas. It is classified as T-lymphoblastic lymphoma (T-LBL) and B lymphoblastic lymphoma (B-LBL) and resembles acute lymphoblastic leukemia (ALL), with no or limited bone-marrow involvement. LBL rarely present as soft-tissue swellings. Soft-tissue involvement is more common in B-LBL than in T-LBL. They occur predominantly in adolescents and young adults and have a prognosis similar to ALL.

OBJECTIVE: The aim was to study the clinical characteristics, treatment response, and survival of patients with lymphoblastic lymphoma presenting with soft-tissue swelling.

SETTINGS AND DESIGN: This was a retrospective study of eight adolescent and adult patients with lymphoblastic lymphoma presenting with soft-tissue swelling conducted in the Department of Medical Oncology at a tertiary cancer center in India.

STATISTICAL ANALYSIS: The baseline patient characteristics, treatment details, and response assessment were analyzed using descriptive statistics. Overall survival (OS) and progression-free survival were obtained by the Kaplan–Meier method, using the SPSS version. 11.

MATERIALS AND METHODS: We present the clinical features, imaging, diagnosis, treatment, and outcome of eight cases of lymphoblastic lymphoma presenting with soft-tissue swellings. Patients above 14 years of age treated over 12 years were included in the study.

RESULTS: There were five males and three females. The median age at diagnosis was 24 years. Common presenting complaints were swelling, pain, and paraparesis. The sites of involvement were the epidural mass, thigh, calf, breast, and anterior chest wall. The diagnosis was confirmed by immunohistochemistry. Seven patients were diagnosed with B-LBL and one with T-LBL. They were treated with intensive chemotherapy (six patients with Berlin–Frankfurt–Munster protocol and two with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone). Three patients received consolidation radiotherapy and one received palliative radiotherapy. Seven patients attained remission after induction chemotherapy and four of them are currently alive at a median follow-up of 48 months. The 2-year OS was 71.4%.

CONCLUSION: Even though rare, lymphoblastic lymphoma should be considered a differential diagnosis in patients presenting with soft-tissue swelling and should be managed with systemic chemotherapy similar to ALL.

Keywords:

Acute lymphoblastic leukemia, B-lymphoblastic lymphoma, soft-tissue swelling, T-lymphoblastic lymphoma

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Introduction

Lymphoblastic lymphomas (LBL) are a rare and aggressive type of non-Hodgkin lymphomas (NHL) and constitute 2% of all lymphomas. It is classified as T-lymphoblastic lymphoma (T-LBL) and B-lymphoblastic lymphoma (B-LBL) and resembles acute lymphoblastic leukemia (ALL), with no or limited bone-marrow involvement.[1] LBL mainly affects children and teenagers. T-LBL is more common among LBL, and B-LBL accounts for only ~10% of cases.[1] LBL presenting as soft-tissue masses are extremely rare. T-LBL commonly presents with a mediastinal mass and precursor B-LBL more often presents with soft-tissue masses involving the skin, head, neck, bone, and lymph nodes.[2] These soft-tissue swellings may be confused with soft-tissue sarcomas; in such cases, diagnosis is established with a biopsy of the swelling. Survival of pediatric patients with LBL is better which exceeds 80% with current therapies, but adult patients and patients with a relapsed disease have a poor prognosis.[3] There is little data on LBL presenting with soft-tissue swelling in adolescents and adults. In this study, we present the clinical characteristics and treatment outcomes of eight patients with LBL who presented with soft-tissue swellings.

Objectives

The objectives were to study the clinical characteristics, treatment response, and survival of patients with LBL presenting as soft-tissue swelling diagnosed and treated at a tertiary care center in India.

Materials and Methods

Ethics

The study was approved by the institutional review board (IRB No. 12/2022/01 dated December 27, 2022). All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Study settings and design

This is a retrospective analysis of eight patients diagnosed with LBL who presented with soft-tissue swellings at our center. The case records of the patients were studied regarding clinical presentation, diagnosis, treatment received, and survival.

Inclusion/exclusion criteria

Patients >14 years with LBL diagnosis presenting as soft-tissue swelling were eligible. Excluded were patients with relapsed LBL or those who received prior treatments.

Methodology

Medical records of patients were studied for demographic details, clinical history, physical examination, and baseline investigations such as complete hemogram, serum chemistry, and serum lactate dehydrogenase (LDH). The histopathology report, bone-marrow study, cerebrospinal fluid analysis, and imaging studies were noted. Patients received treatment based on institutional protocols either with the Berlin–Frankfurt–Munster protocol (BFM) or with the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) regimen. The treatment response at the end of induction and on completion of treatment was obtained. Clinical response was classified as complete remission (CR), partial remission, stable disease, and progressive disease based on Modified Cheson lymphoma response evaluation criteria.[4]

Statistical methods

The baseline patient characteristics, diagnosis, treatment details, and outcome were analyzed using descriptive statistics including frequency, percentage, median, range, and mean. Overall survival (OS) was calculated from the date of initial diagnosis to the date of death from any cause or last follow-up visit. OS was obtained by the Kaplan–Meier method, using IBM SPSS version. 11 (Chicago, IL, USA).

Results

The clinical details of the eight cases are summarized in Table 1. In our series, the median age was 24 years (range 15–51 years), with five males and three females (M: F 1.67:1). Six patients presented with swelling and pain of the involved site, and two patients presented with paraparesis. The sites of involvement were thigh in two patients, leg in two, epidural mass in two, and one each with breast and anterior chest wall swelling [Figure 1]. Patient #1 presented

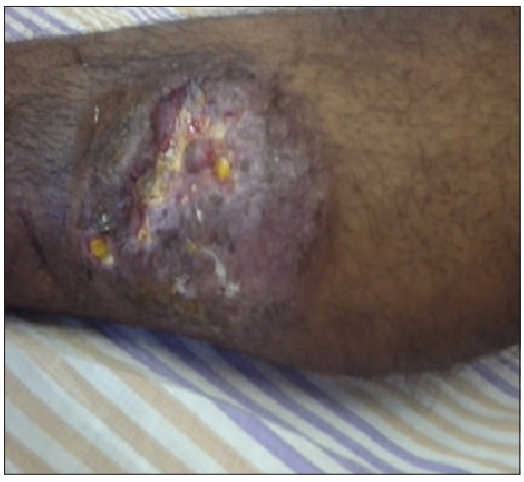

Figure 1: Image showing soft-tissue lesion with ulceration in the right leg of patient #7 with ulceration

Table 1: Summary of clinical presentation and treatment of eight patients with lymphoblastic lymphoma presenting as soft tissue masses

Serial No#	Age/Sex/ subtype	Clinical presentation	Site	MRI scan	IHC	Treatment protocol	RT	Follow up status
1**	19/M (B-LBL)	Lower limb weakness	Epidural soft tissue mass D5-D10 + bone involvement	MRI – Diffuse elongated epidural soft tissue from the level of D5 to D10 with a craniocaudal length of 8.5cm with moderate to severe canal compromise	Tdt + PAX5 + CD34 + CD20 - CD5 - CD3 - MPO - LCA -CD99 -	Hyper-CVAD	Nil	Alive with no evidence of disease (NED) at 95 months
2	19/F (B-LBL)	Lower limb weakness	Epidural soft tissue D10-L1	MRI – Large epidural soft tissue lesion 10cm length extending from D10 to L1 with cord compression at D12	CD10 + CD34 + BCL2 + Tdt + PAX5 + CD5 - CD20 - BCL6 - Cmyc - CD3 -	BFM 95 + RT	18Gy in 10#	Alive NED at 52 months
3**	23/M (B-LBL)	Swelling and pain	Right thigh	MRI - large 3.1 × 5.4 × 7.7 cm T1 isointense and T2 hyperintense lesion in the posterior compartment of the right thigh. Right pelvic nodal mass measuring 7.4 × 5.7cm	Tdt + PAX 5 + CD10 + CD 20 + CD79a + CD3 - CD7 - CD138 - LCA - CK -	BFM 95	Nil	Alive NED at 28 months
4	15/F (B-LBL)	Swelling and pain	Left breast	MR Mammogram – Large 13 × 10 × 9 cm ulceroproliferative growth from the left breast with heterogenous contrast enhancement	Tdt + CD10 + PAX5 + CD20 + CD3 - CD5 - CD7 - MPO -	BFM 95	Nil	Relapsed at 15 months and died at 17 months
5	25/M (B-LBL)	Swelling and pain	Right Thigh+bone involvement	MRI – 8.1 × 6.5cm soft tissue lesion distal meta-diaphysis of the right femur with underlying bone involvement	Tdt + MIC1 + CD20 + CD79a + CD43 + LCA - CD3 - CD5 -	Hyper-CVAD + RT	40Gy in 20 #	Died due to disease progression at 7 months
6`	30/F (B-LBL)	Swelling and pain	Right leg + bone involvement	MRI – A 2 × 1.6 × 7.8 cm T1 isointense lesion in the middle third of the right tibia with lytic bone lesion. Similar lesions in the left tibia	MIC2 + Tdt + CD34 + Pax 5 + CD43 + CD3 - CD7 - CD20 - CD33 -	BFM 95	Nil	Defaulted and died due to relapse at 42 months
7	32/M (B-LBL)	Swelling and ulcer	Right leg + right inguinal nodes	Not available	Tdt + CD3 - CD20 -	BFM 95 + RT	45Gy in 25 #	Defaulted after induction at 2 months
8	51/M (T-LBL)	Swelling and pain	The right side of the chest wall with bone involvement	MRI Heterogeneously enhancing soft tissue lesion anterior chest wall with associated right 10th rib destruction and moderate pleural effusion	CD5 + Tdt + Cd79a -	BFM 95	8Gy/1#	Alive NED at 166 months

**Published as case reports[5,6]. M=Male, F=Female, B-LBL=B Lymphoblastic Lymphoma, T-LBL=T lymphoblastic lymphoma, MRI=Magnetic resonance imaging, IHC=Immunohistochemistry, Hyper CVAD=Hyperfractionated cyclophosphamide, vincristine, adriamycin and dexamethasone, BFM=Berlin Frankfurt Munster, RT=Radiotherapy, NED=No evidence of disease

after spinal decompression and fixation and patient # 4 presented to our center after a simple mastectomy. Routine blood investigations were done in all patients. The mean hemoglobin was 11.9 g/dL, the mean total white blood cell count was 8028/mm^3 and the mean platelet count was 359,000/mm^3. All the patients had normal renal function. Patient #5 had altered liver function (elevated aspartate and alanine transaminases). The mean serum LDH was 373 units/L. Three patients had elevated LDH (patients #1, 2, and 5). Viral markers were negative in all the patients.

Magnetic resonance imaging details were available for seven patients [Figure 2]. Two patients (patients #3 and #7) had lymphadenopathy and four patients had underlying bone involvement. None of the patients had bone-marrow or cerebrospinal fluid involvement. Patient #8 had pleural effusion, but the pleural fluid cytology was negative for malignant cells.[5,6]

Histopathological examination of the biopsy specimen in these patients showed atypical cells with round nuclei,

finely dispersed chromatin, inconspicuous nucleoli, and scanty cytoplasm. On immunohistochemistry (IHC), seven patients had B-LBL and one patient had T-LBL. Patients with B-LBL stained positive for CD20, CD79a, PAX5, CD99, CD34, CD10, and Tdt. The patient with T-LBL had positive staining for Tdt and CD5 [Figure 3].

Out of the eight patients, six were treated with BFM protocol (five patients with B-LBL and one patient with T-LBL). All six patients on the BFM regimen attained CR after induction chemotherapy. Currently, two patients have completed maintenance treatment on follow-up and one patient is on maintenance chemotherapy. Two patients relapsed and later died due to disease progression and one patient defaulted to treatment after induction chemotherapy. Two patients were treated with the Hyper-CVAD regimen (patients #1 and 5). Patient #1 attained remission and is on regular follow-up and patient #5 did not attain remission after induction and died due to disease progression and sepsis. Three patients received radiotherapy at the local site as consolidation and patient #8 received single-fraction radiation for pain relief. In our study group, the 2-year OS was 71.4% with a standard error of 17.1%.

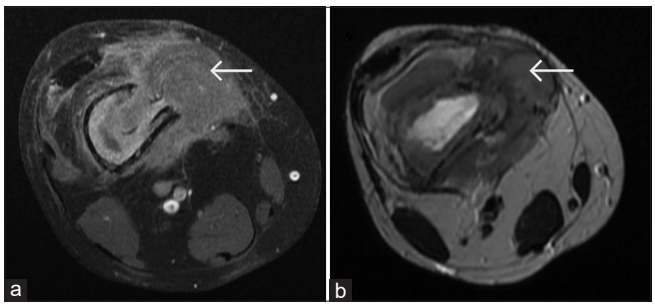

Figure 2: (a) Magnetic resonance imaging (MRI) of the right thigh axial view T1 contrast showing heterogeneously enhancing soft tissue 8.1 cm × 6.5 cm and adjacent distal femur showing altered marrow signal intensity. (b) MRI axial view with T2 contrast shows hyperintense soft tissue lesion. The lesion is pointed with white arrow.

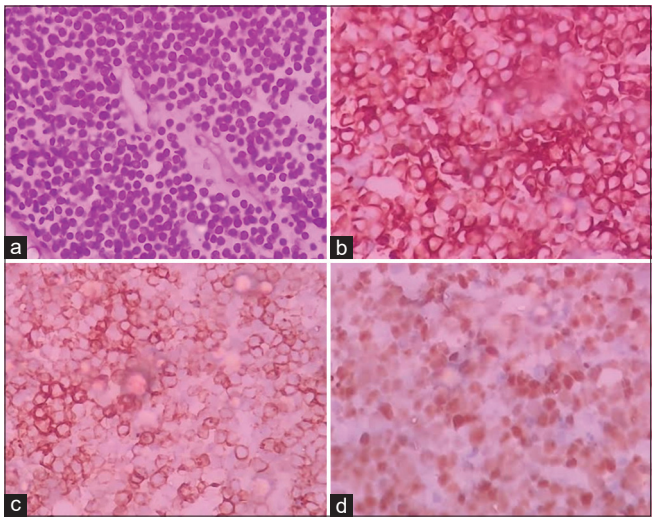

Figure 3: (a) Microscopy section showing a linear core of fibro collagenous tissue infiltrated by atypical cells with round nuclei, finely dispersed chromatin, inconspicuous nucleoli, and scanty cytoplasm. (b) Atypical cells showing CD10 positivity, (c) CD34 positivity, and (d) Tdt positivity (×400)

Discussion

Lymphoblastic lymphoma is a rare and highly aggressive NHL that is virtually indistinguishable from ALL. LBLs predominantly occur in adolescent and young adult patients with a median age at diagnosis of 20 years.[7] It has a slight male predominance. In our series, the median age was 24 years. There were five males and three females. It is rare for LBL to present as soft-tissue swellings. The common sites involved in LBL are lymph nodes, bone, and skin.[2] Other less common sites include the head and neck, retroperitoneum, breast, ovary, brain, and soft tissue. Soft-tissue involvement is relatively more common in B-LBL than in T-LBL. In our study, seven patients were diagnosed with B-LBL and only one patient had T-LBL and the common sites of involvement were epidural mass in two patients, thigh in two patients, calf in two patients, and breast lump in one patient and the patient with T-LBL presented with soft-tissue swelling in the anterior chest wall.

The imaging features of these soft-tissue swellings in LBL are nonspecific and usually overlap with those of other soft-tissue sarcomas. A biopsy with IHC is required to confirm the diagnosis. LBLs are characterized by neoplastic cells which are small to medium size with scanty cytoplasm, fine chromatin, round or convoluted nuclei, inconspicuous nucleoli, and a high-mitotic rate with background mature lymphocytes and plasma cells. The histopathological features overlap with other tumors such as Ewing sarcoma, neuroblastoma, blastoid variant of mantle cell lymphoma, Burkitt lymphoma, rhabdomyosarcoma, and myeloid sarcoma.[8] IHC and molecular studies are the keys to differentiating between these tumors. LBL stain is positive for periodic acid Schiff. B-LBL stain for B cell markers such as CD19, CD79a, and CD22 and frequently express CD10, CD24, PAX5, and TdT.[9] CD99, CD45, CD20, and CD34 are variably expressed. T-LBL may express CD3, CD4, CD8, Tdt, and CD34. Among our cases, IHC details were available in seven patients and all were Tdt positive.

LBLs have immunoglobulin heavy chain (IgH) or T cell receptor gamma chain gene rearrangements. IgH rearrangement is present in 90% of B-LBL and 25% of T-LBL. Similarly, T cell receptor gamma chain rearrangement is present in 90% of T-LBL cases and 50% of B-LBL. This can be demonstrated by polymerase chain reaction in 90% of cases.

In adults, age <40 years, female gender, low international prognostic index score, B cell phenotype, and absence of bone-marrow and central nervous system involvement have been associated with a favorable prognosis.[10]

Two patients with B-LBL presenting as epidural mass were described in the literature and both patients achieved remission after treatment and are on regular follow-up now.[10,11] Two women with bilateral breast lumps diagnosed as LBL were treated with intensive chemotherapy and both patients had a systemic relapse.[12,13] A case series of six patients with B-LBL presenting with soft-tissue swellings was described by Lin *et al*.[14] A 45-year-old woman with T-LBL presenting with postauricular mass was treated with a hyper-CVAD regimen.[15]

Most of the treatment protocols for LBL are derived from regimens for children with ALL. This includes intensive induction, consolidation, and maintenance chemotherapy with cranial prophylaxis.[16] The abbreviated chemotherapy protocols recommended for other NHL are inadequate in these patients. LBLs have a high rate of CR and favorable outcomes. In our series, six patients were treated with the BFM regimen and two received the hyper-CVAD regimen. Both of these regimens are commonly used in ALL. Out of eight patients, four are currently alive, with three patients on follow-up after maintenance and one patient on maintenance chemotherapy. The 5-year OS in children with LBL is 80%–90% and 45%–55% in adults.[16] In our series, the 2-year OS was 71.4%.

Conclusion

Even though rare, LBL should be considered a differential diagnosis in patients presenting with soft-tissue swelling and should be managed with systemic chemotherapy similar to ALL with a 2-year DFS and OS of 71.4%.

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Conflicts of interest
There are no conflicts of interest.

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