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Case Report

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Primary Diffuse Large B-Cell Lymphoma of the Bone

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Abstract

Primary lymphoma of the bone (PLB) is a rare lymphoproliferative neoplasm that can present either as solitary or multiple bone lesions. We report four patients with PLB who were successfully treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by consolidative radiotherapy. All patients achieved a complete remission and had excellent long-term outcomes. PLB has a favorable response to combined modality treatment with chemoimmunotherapy and radiation. Long-term outcomes of PLB tend to be better than those of non-osseous diffuse large B-cell lymphoma.

Keywords: Primary bone lymphoma; Chemoimmunotherapy; Radiotherapy

Introduction

Primary lymphoma of the bone (PLB) is a rare lymphoproliferative disorder that comprises 5% of primary bone tumors and 5-7% of extranodal lymphomas [1, 2]. Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype, accounting for up to 90% of cases [3, 4]. PLB more frequently affects the axial skeleton than the appendicular skeleton and is more commonly seen in men than in women [5]. As per the World Health Organization (WHO) classification, PLB is defined as a malignant lymphoid neoplasm affecting a solitary bone or multiple skeletal sites without visceral or nodal involvement (except regional lymph nodes) [6]. Patients with PLB tend to be younger than those with other non-osseous DLBCLs [7]. PLB in the pediatric population is considered to be a different disease entity. PLB usually affects the metadiaphyseal junction of the bone [8]. It usually arises from the femur (29%), pelvis (19%), humerus (13%), skull (11%), or tibia (10%) [5, 9]. Here we report a series of four cases of PLB.

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Case Reports

Case 1

A 32-year-old woman presented with a 1-month history of bilateral lower extremity weakness, pain, and difficulty with ambulation. She also reported numbness in the left leg. She denied loss of bowel or bladder control, fevers, chills, night sweats, or weight loss. Initial computed tomography (CT) of the chest, abdomen, and pelvis done in June 2021 demonstrated heterogeneous sclerotic and lucent lytic changes involving the sacrum, particularly the S1 segment and left sacral ala. Magnetic resonance imaging (MRI) of the spine for evaluation of the patient's symptoms revealed a sacral mass. MRI of the pelvis revealed multiple bone lesions within the pelvis, the largest of which was within the sacrum and right supra-acetabular region. Epidural extension of up to 6 mm of the tumor was noted posterior to S1 - S2, resulting in spinal and foraminal stenosis. Positron emission tomography (PET)-CT showed a multifocal uptake at the pelvis, with the maximum standard uptake (SUVmax) at the right acetabulum with an SUVmax of 15.2. Uptake at the sacrum had an SUVmax of 9.7). There was a fluorodeoxyglucose (FDG)-avid lesion in the left humerus as well. Prominent enlarged external iliac nodes were noted. Additional lesions were noted on the right pubic body, right subtrochanteric region, and left intertrochanteric region. The patient underwent laminectomy and decompression of her sacral mass. Pathology demonstrated DLBCL with a high Ki-67 proliferation index of 75-80%. Fluorescence *in situ* hybridization (FISH) was negative for MYC, BCL2, and BCL6 rearrangements. There was no evidence of bone marrow involvement. The patient received radiotherapy at a dose of 30 Gy that was delivered in 10 fractions, and she completed six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). A post-treatment PET-CT showed complete metabolic response (CMR). She remains in complete remission (CR) after 60 months' follow-up.

Case 2

A 34-year-old woman presented with right thigh pain and swelling for 5 - 6 months. She initially had X-rays that were apparently inconclusive, and she was started on symptom management with analgesics, without improvement. Pain and swelling worsened, and the patient eventually had an MRI of the right femur both with and without contrast in July 2017 that showed complete bone marrow replacement involving up

Table 1. Patient Characteristics

Patient	Age/sex	Diagnosis	Site of bone involvement	Stage	Chemoimmunotherapy	Radiotherapy	Follow-up	Outcome
1	32/F	DLBCL, NOS	Sacrum, pelvis, and humerus	IV	R-CHOP × 6 cycles	30 Gy	60 months	Alive and remains in CR
2	34/F	DLBCL, NOS	Proximal femur	IIE	R-CHOP × 6 cycles	39.6 Gy in 22 fractions	50 months	Alive and remains in CR
3	83/M	DLBCL, NOS	Humerus	IIE	R-CEOP × 6 cycles	36 Gy in 18 fractions	32 months	Alive and remains in CR
4	64/F	DLBCL, NOS	Distal femur	IIE	R-CHOP × 6 cycles	30 Gy in 15 fractions	40 months	Alive and remains in CR

F: female; M: male; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CEOP: cyclophosphamide, etoposide, prednisone, vincristine, and rituximab; CR: complete remission.

to 15.6 cm of the proximal right femur with areas of cortical permeation involving the femoral neck and intertrochanteric regions. In addition, the femoral neck and subtrochanteric regions were enveloped with a large soft tissue mass encompassing the femur measuring 7.3 × 8.7 cm in transverse diameter with invasion of the adjacent vastus intermedius, medialis, and lateralis muscles. CT of the chest demonstrated no thoracic lymphadenopathy and no pulmonary metastasis. CT of the abdomen and pelvis was largely unremarkable. A PET-CT in August 2017 redemonstrated the large FDG-avid mass in the right upper thigh and FDG uptake in the right external iliac nodes. The patient underwent biopsy that showed a germinal center-subtype DLBCL with immunohistochemistry showing positivity for CD20, CD10, BCL6, Pax5, and negativity for CD3, CD5, BLC2, cyclin D1, and vimentin with Ki-67 positivity of 90%. The patient was diagnosed with a stage IIE PLB. She received two cycles of R-CHOP and a total prescribed radiotherapy dose of 39.6 Gy in 22 fractions. Interim PET scan showed a CMR. The patient completed a total of six cycles of R-CHOP in December 2017. Her post-treatment restaging PET-CT scan also showed a CMR. She continues to be in CR after a follow-up of 50 months.

Case 3

An 83-year-old man with chronic kidney disease and coronary artery disease presented with a 4-month history of right arm pain; an X-ray showed a pathologic fracture. MRI of the humerus with and without contrast in December 2019 showed a large multilobulated, irregularly shaped enhancing mass in the right humeral shaft and right arm musculature with associated pathologic fracture. The mass was seen as complex in shape and poorly marginated, measuring 8.5 × 0.5 × 20 cm in length and with tumoral necrosis within the proximal triceps muscle with partial encasement of the brachial neurovascular bundle and large axillary lymphadenopathy measuring 4 cm in dimension. A PET-CT showed a markedly FDG-avid mass in the right humerus and a smaller area of FDG-avid axillary lymphadenopathy with a Deauville score of 5. Biopsy of the right midshaft humerus showed DLBCL with cells positive for CD20, PAX5, CD30, BCL2, BCL6, and MUM 1 with a Ki-67 proliferation marker of approximately 60%. He underwent fixation of pathologic fracture of his right humerus. Given his advanced age and extensive cardiac history, anthracyclines were omitted. The patient was treated with systemic chemotherapy with R-CEOP (cyclophosphamide, etoposide, prednisone, vincristine, and rituximab) for six cycles. An interim PET/CT done after four cycles showed a favorable response to therapy with resolution of involved lymph nodes in right axilla and in right humerus. However, a persistent active FDG uptake in soft tissue surrounding the right humerus was noted (Deauville score 5).

He received radiotherapy with a total dose of 36 Gy in 18 fractions. A post-treatment PET scan showed a CMR. He remains in CR after a follow-up of 32 months.

Case 4

A 64-year-old woman with a history of diabetes and coronary artery disease presented with a progressively enlarging left distal thigh mass. She also reported left hip pain radiating to the left knee and was unable to walk. She denied any fever, weight loss, night sweats, malaise, fatigue, or dizziness. PET-CT showed an FDG-avid mass in the left distal femur. Biopsy of the distal femur and lateral thigh done in March 2019 demonstrated DLBCL of germinal center type that was Epstein-Barr virus encoded RNA (EBER) negative with left inguinal lymph node involvement. The Ki-67 proliferation index was 50-70%. She had no bone marrow involvement. The patient received two courses of R-CHOP and interim PET/CT showed a partial response (Deauville score of 4). She completed four more cycles of R-CHOP and consolidative radiation of 30 Gy in 15 fractions. A post-treatment PET scan showed a partial response with a Deauville score of 4. The patient had some residual FDG avidity at the left distal femur that persisted for 1 year but was stable. A restaging PET/CT done 18 months after completion of therapy showed CMR. She remains in CR at a follow-up of 40 months.

A summary of the four cases is provided in Table 1.

Discussion

PLB, also known as reticulum cell sarcoma, is a distinct clin-

Table 2. Studies of PBL

Author	Study	N	DLBCL, n	Treatment			Outcome
				CMT, n	RT only, n	Chemotherapy only, n	
Catlett et al, 2008 [22]	Single-center retrospective	30	26	21	3	5	OS favored CMT over either modality alone (P = 0.02)
Tao et al, 2015 [23]	Single-center retrospective	102	102	67	NA	NA	5-year PFS (63% without vs. 88% with RT) and OS (68% vs. 91%) P = 0.0064
Fidias et al, 1999 [24]	Case-control	37	24	35		37 (doxorubicin containing regimen in 33)	5-year DFS with CMT: 78% vs. 42% with RT alone (P = 0.0008); 5-year OS (91% vs. 50%), P = 0.0001
Rathmell et al, 1992 [17]	Single-center retrospective	27	NA	9	15	NA	5-year RFS (89% with CMT vs. 27% with RT alone), P = 0.01
Beal et al, 2006 [19]	Single-center retrospective	101	80	57	14	30	5-year OS for CMT vs. single modality therapy (95% vs. 78%), P = 0.013
Cai et al, 2012 [25]	Multicenter retrospective	116		87	13	14	Lymphoma-specific survival superior with CMT vs. those without RT (P = 0.01)

PBL: primary bone lymphoma; CMT: combined modality therapy; DFS: disease-free survival; RFS: relapse-free survival; RT: radiotherapy; DLBCL: diffuse large B-cell lymphoma; NA: not available; PFS: progression-free survival; OS: overall survival.

icopathologic entity that was first reported by Oberling in 1928 [10]. Patients with PLB usually have a subacute presentation with swelling, palpable tumor, and bone pain lasting for weeks to months [7]. Soft tissue extension is relatively common in PLB [8]. Patients with severe bony destruction involving the weight-bearing bones may present with pathologic fracture [11]. The bony lesions can be multifocal, and patients can have regional lymphadenopathy as well.

The overwhelming majority of patients with PLB have germinal center B-cell (GCB) type DLBCL [2, 5]. The gene expression profile of PLB resembles centrocyte-origin subtype of DLBCL-GCB [12]. PLB exhibits rearrangement of the *c-MYC* or *BCL2* gene without *BCL6* rearrangement [13]. Other pathologic types such as lymphoblastic lymphoma, Burkitt lymphoma, and anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma have rarely been reported in association with PLB [5, 14].

Patients with PLB require a comprehensive staging workup prior to the initiation of systemic chemoimmunotherapy. CT scanning can show the pattern and extend of bony destruction, and MRI can identify the extent of soft tissue involvement [15]. PET-CT shows the metabolic activity of the tumor and is an effective tool for staging extranodal disease and identifying distant metastasis [16].

Staging

PLB staging is similar to that of other non-Hodgkin lymphoma (NHL) types and is as follows: 1) Stage IE: PLB that is limited to a single bony lesion; 2) Stage IIE: regional lymph node involvement in addition to solitary bone lesion [3, 17]; 3) Stage IV: multifocal disease is categorized as stage IV [18].

Treatment

Newly diagnosed patients

Given the rarity of PLB, there is a paucity of high-quality data from prospective randomized controlled trials to guide therapy. Hence, most of the available evidence is from retrospective studies. There is no role for surgery, except for diagnostic biopsy and stabilization of a pathologic fracture. Multiagent chemoimmunotherapy with or without radiotherapy is the preferred treatment modality. Given that most cases of PLB tend to be DLBCL, anthracycline-based chemotherapy in combination with rituximab is preferred (R-CHOP) [19, 20]. In patients with contraindication for anthracycline use, an etoposide-containing regimen (R-COEP (rituximab with cyclophosphamide, vincristine, etoposide, prednisone)) can be used as a good alternative with equivalent curative potential [21]. Patient 3 had contraindication for anthracyclines and hence was treated with R-COEP, achieving durable CR. The addition of rituximab to standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy has shown to improve survival compared with chemotherapy alone [20]. The role of radiotherapy is controversial with conflicting results from multiple studies. Multiple single-center studies have shown that radiotherapy when added to standard chemoimmunotherapy improves progression-free survival (PFS) and overall survival (OS). A summary of the studies is provided in Table 2 [17, 19, 22-25]. Population-based

studies have shown that the greatest survival benefit of radiotherapy is seen in patients with early-stage disease [26].

By contrast, more recent studies question the role of radiation in the era of highly effective chemoimmunotherapy. Because most relapses in PLB tend to be distant, the benefit of consolidation radiotherapy is unclear. Also, radiotherapy to the bone can cause significant early and long-term toxicity depending on the location. Myelosuppression remains a concern while radiating marrow-rich areas such as the pelvis. In addition, secondary malignancies have been reported in patients receiving radiotherapy for PLB. Alencar et al reported a single-center study and observed that there was no difference in PFS of patients treated with chemotherapy alone compared with combined modality therapy (CMT) [27]. Ramadan et al reported that in patients with advanced stage PLB, the use of CMT can be detrimental, as those patients had significantly worse outcomes than those treated with chemotherapy alone [20]. Reyes et al published a randomized study of chemotherapy versus CMT in patients with localized aggressive lymphoma and noted that patients treated with chemotherapy alone had superior outcomes over CMT with a 5-year OS of 90% vs. 81% (P = 0.001) [28]. Bonnet et al did a large prospective study comparing CHOP with CHOP plus radiotherapy in elderly patients with localized aggressive lymphoma and noted no advantage with the addition of radiotherapy [29]. The IELSG-14 study evaluated the outcomes of PLB patients treated with different modalities and observed no benefit with the addition of consolidative radiotherapy [7]. Ibrahim et al observed that radiotherapy in PLB can cause higher orthopedic complication without a clear survival advantage [30]. Studies from the pediatric oncology group also showed no benefit with the addition of radiotherapy to chemotherapy [31]. Also, given that lymphoma is a systemic disease, patients are likely to benefit the most from systemic chemoimmunotherapy therapy rather than local therapy. Based on the current evidence, it is difficult to justify consolidation radiotherapy in every patient with PLB. Hence, in the midst of controversy, we feel that it is reasonable to consider consolidation radiotherapy of 30 - 36 Gy in patients with unifocal disease. In our series, CMT was used in all four patients with good tolerability and achieving durable CR; however, more robust prospective randomized trials are crucial to evaluate the benefit of consolidation radiotherapy in PLB.

A post-treatment PET-CT should be obtained 6 - 8 weeks after completing chemoimmunotherapy to assess the response. Relapses can be either local or at distant sites [24]. If there is residual metabolic activity on post-treatment imaging, it may be nonspecific and may reflect inflammatory changes or remodeling of the bone. In patients with high clinical suspicion for relapse or residual disease, a tissue biopsy is essential to confirm the diagnosis prior to initiation of salvage regimens. Patient 4 had residual FDG avidity in the distal femur that persisted beyond a year. However, eventually, 18 months after completion of therapy, she achieved CMR.

Prognostic factors

Clinical outcomes of PLB tend to be better than those of nonosseous lymphomas, and it is believed to have the best survival of all malignant bone tumors. Demircay et al did a retrospective review of 119 patients with lymphoma involving the bones, and outcomes were compared between PLB (90% DLBCL) and systemic lymphoma with secondary bone involvement (68% DLBCL). The 5-year disease-free survival in patients with PLB was 84% compared to 44% in patients with secondary lymphoma of the bone [32]. Li et al evaluated clinicopathological features of PLB (DLBCL = 160) and noted that the 5-year PFS (90%) and OS (93%) were markedly better than those of nonosseus DLBCL (P < 0.0001) [12]. Treatment deescalation is an important consideration, given the favorable outcome for PLB. The phase 3 FLYER study showed that in DLBCL patients without high-risk International Prognostic Index features and bulky disease, four cycles of R-CHOP is not inferior to six cycles [33].

The Surveillance, Epidemiology and End Results (SEER) data base (1973 - 2005) studies have shown a 5-year survival of 58% and 10-year survival of 48% in PLB patients [5]. The inferior outcomes reported by Jawad et al [5] are likely secondary to a different chemotherapy backbone (non-R-CHOP) being used in that era. A more recent SEER data base study (1973 - 2016) by Liu et al [34] showed better outcomes with a 5-year OS of 65% and 10-year OS of 54%. The clinical outcomes could also vary vastly from the community setting to large academic centers, with the latter having significantly better survival [35]. Single-center studies from centers of excellence have reported significantly better outcomes in recent times. Beal et al reported a retrospective study from Memorial Sloan-Kettering showing a 5-year OS of 95% with CMT [19]. Similarly, Alencar et al published data from the University of Miami that showed an excellent 4-year PFS of 83% [27]. A summary of studies showing long-term outcomes in PLB is provided in Table 3 [5, 7, 12, 19, 20, 25, 27, 32, 34-38].

Unifocal bone disease is a favorable prognostic factor in PLB, whereas multifocal disease, soft-tissue extension, and higher International Prognostic Index scores are major adverse prognostic factors. Bone marrow or regional lymph node involvement in PLB does not seem to have a negative impact on clinical outcomes [20, 39]. Other favorable prognostic factors in PLB include early-stage disease, younger age (< 60 years), low serum lactate dehydrogenase (LDH) levels, and good Eastern Cooperative Oncology Group (ECOG) performance status [17]. Pediatric PLB tends to have a favorable outcome compared with the disease in adults [40, 41]. Hence, as per the revised international pediatric NHL staging system, bony involvement is not considered stage IV disease [42]. The prognostic value of the presence of pathological fracture is uncertain. Fidias et al reported that patients with pathologic fracture tend to have a worse outcome, presumably from more aggressive disease biology [24]. However, there was no association noted between pathologic fractures and survival in other studies [20, 27]. Patient 3 had pathological fracture of the humerus on presentation, but he had a favorable response to therapy, and he continues to do well.

Conclusions

PLB is a rare manifestation of NHL that accounts for < 5% of all primary bone tumors. Anthracycline-based chemoimmunotherapy (R-CHOP) with or without radiation is the current standard of care. Clinical outcomes of PLB tend to be superior

Table 3. Outcomes in PBL

Study design	Author	Patients (n)	Treatment regimen	Response rate and clinical outcomes
SEER data base study	Jawad et al, 2010 [5]	1,500	NA	5-year OS 58%, 10-year OS 45%
SEER data base study	Liu et al, 2020 [34]	2,558	Chemotherapy (75%), radiation (54%)	5-year OS 65.70%, 10-year OS 54.40%
Single-center retrospective (MSKCC)	Beal et al, 2006 [19]	82	14% with radiation alone, 30% with chemotherapy alone, 57% with combined chemotherapy and radiation	5-year OS, 78% for those treated with single modality, 95% for those with combined modality
Single-center retrospective (University of Miami)	Alencar et al, 2010 [27]	53	Radiation 6 (12%), chemotherapy 10 (21%), combined modality 30 (62%)	CR in 92% of treated patients, 4-year PFS 83%
Single-center retrospective	Demircay et al, 2013 [32]	119	36 patients had chemo-XRT, 15 patients had surgery, chemo-XRT	Disease-free 5-year survival 81%
Single-center retrospective study from China	Zhang et al, 2016 [36]	61	Chemotherapy alone (60%), chemo-XRT (39%)	ORR 87.7%, 56.1% CR, 5-year PFS 47%, OS 53.0%
Study from British Columbia cancer agency	Ramadan et al, 2007 [20]	131	Chemotherapy alone (57%), chemo-XRT (63%)	ORR 84%, 65% CR, 5-year OS 62%, 10-year OS 41%
Single-center retrospective study	Muller et al, 2020 [37]	109	Chemotherapy (81%), radiation (61%), combined chemo-XRT (47%)	5-year OS 66%
Multicenter retrospective review	Li et al, 2017 [12]	160	Chemotherapy (88%) and 55% consolidative radiotherapy	5-year PFS 80%, OS 93%
Multicenter retrospective study	Cai et al, 2012 [25]	116 (early stage)	Chemo-XRT in 87 patients	5-year OS 76%
International data base study	Ventre et al, 2014 [7]	161 (stage I - II)	Chemo-XRT in 125 (78%) patients	5-year PFS 68%, OS 75%
Prospective study	Christie et al, 2011 [38]	33	Three cycles of CHOP and radiation to a dose of 45 Gy	5-year OS 90%, local control 72%

PBL: primary bone lymphoma; SEER: Surveillance, Epidemiology and End Results; chemo-XRT: chemotherapy and radiation therapy; PFS: progression-free survival; OS: overall survival; CR: complete remission; ORR: overall response rate; NA: not available.

to that of extraosseous DLBCL.

Learning points

PLB is rare and can present either as solitary or multiple bone lesions.

Most patients with PLB have GCB DLBCL.

Anthracycline-based chemoimmunotherapy (R-CHOP) with or without consolidative radiotherapy is an effective treatment modality that can achieve durable remission in PLB.

PLB tends to have a favorable prognosis when compared with non-osseous DLBCL.

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Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from patients.

Author Contributions

BY collected data and wrote the initial draft of the manuscript. AR as the treating physician, served as senior author and critically revised the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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