

Case Report

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Primary Bone Diffuse Large B-cell Lymphoma with Multifocal Osteolytic Lesions: A Rare Entity

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Abstract

Bone lymphomas can be classified as primary (PBL), or secondary (SBL). PBL is a rare entity, accounting for approximately 7% of malignant bone tumors, 5% of extra nodal lymphomas and <1% of all non-Hodgkin lymphomas. We present here a case of multifocal bone lymphoma in a 72-year old female patient, who was admitted to our clinic for further investigation of persistent back pain, anorexia, weight loss and fatigue. There were no palpable lymph nodes, no hepatosplenomegaly or neurological signs. Her laboratory tests showed a moderate elevation of LDH, ESR and beta-2 microglobulin. In CT and MRI scan a complete fracture of the left hip and multiple vertebral lesions were revealed. Bone biopsy of the left hip showed a Diffuse Large B-cell Lymphoma. She was treated with combined chemotherapy (R-CHOP regimen) plus radiation, followed by bracing with cervical immobilization and cimentoplasty of lumbar vertebrae. She achieved complete response and she is alive at last follow-up.

Keywords: Bone lymphoma; Primary bone lymphoma; Diffuse Large B-cell lymphoma; Chemotherapy; Radiation; Cimentoplasty.

Case Report

A 72-year-old female patient, without any notable medical or family history presented to her general practitioner with persistent middle back pain and failure of common analgesics to ease the pain. Anorexia, weight loss of about 6 kg in the last 3 months and fatigue were also reported. An outpatient MRI of thoracic and lumbar spine revealed a complete fracture of the T10 vertebra and multiple, high signal vertebral lesions indicative of secondary origin (Figures 1 and 2). Then she was referred to our department for further investigation.

Physical examination was notable for back pain at the level of T₁₀, reproducible by palpation. There were no palpable lymph nodes, no hepatosplenomegaly or neurological signs. Blood tests showed a normal full blood count, with mild hypercalcemia, moderate LDH and beta-2 microglobulin elevation and no paraprotein on the electrophoresis. In detail her hematological profile was as follows: Hct: 39%, Hb: 12.7 g/dl, MCV: 92 fl, MCH: 30 pg, MCHC: 33.3 g/dl, reticulocytes: 1.6%; WBC: 8.6×10^9 cells/L (neutrophils 65% - lymphocytes: 30% - monocytes: 5%); PLT: 349×10^9 /L, ESR: 60 mm, and CRP: 0.5 mg/dl (normal range: 0-0.8 mg/dl). Serum biochemistry showed a moderate elevation of LDH: 380 U/L (normal range: 135-214 U/L), normal total proteins: 7.1 g/L (normal range: 6.6- 8.7 g/L), elevated calcium: 11.8 mg/dl (normal range: 8.2-10.6 mg/dl), and elevated beta-2 microglobulin: 4.1 mg/L (normal range: 1.42-3.21 mg/L). HBV, HCV, HIV, EBV and other serologic and immunologic investigations were negative.



Figure 1: T2 Spine MRI showing complete T10 fracture and multiple vertebral lesions.



Figure 2: T1 Spine MRI showing complete T10 fracture and multiple vertebral lesions.

Thoraco-abdominal-pelvis CT revealed multiple osteolytic lesions of the spine (T3, T5, T6, T8, T10, L1, L2, L3, L5), sacrum, iliac crests and pubic symphysis, both iliopubic branches and a complete pathological T10 fracture (Figures 3 and 4). Otherwise no lymphadenopathy or hepatosplenomegaly were detected. Furthermore a PET-CT confirmed hypermetabolic osteolytic bone lesions (SUV max at 10), without any image suggestive of primitive cancer.

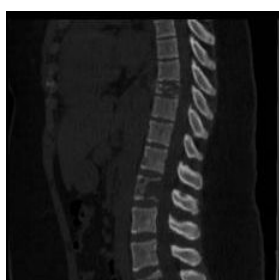


Figure 3: CT images showing osteolytic lesions of the spine.

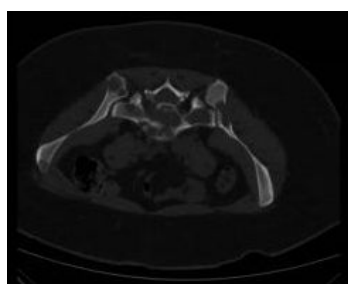


Figure 4: CT images showing osteolytic lesions of the sacrum and iliac crests.

A guided bone biopsy of the left hip revealed a diffuse infiltration of medium to large -sized lymphoid cells, mainly centroblasts with scattered immunoblasts, with focal atypia. The immunohistochemical investigation showed the following tumor-cell immunophenotype: CD20⁺, CD5⁻, CD10⁻, Bcl2⁺, MUM1⁺, CD30⁻, EBER⁻, Ki67: 75%. Cytogenetics by FISH analysis showed BCL6 rearrangement, BCL2 and MYC normal gene status. Based on morphological, immunohistochemical, and molecular data the diagnosis of Diffuse Large B-cell lymphoma, not other specified (DLBCL-NOS) of non-germinal-centre phenotype was made. Bone marrow biopsy showed no evidence of lymphoma involvement.

According to the clinical and imaging examination the patient was classified as stage IVE (IELSG), IV (Ann Arbor), risk group 4 (IPI) (LDH 380, Stage IV, >1 extranodal site). She was treated with combined chemotherapy, 4 cycles of R-CHOP regimen (every 3 weeks) plus radiation of the thoracic spine (2000 cGy in 4 courses), followed by bracing with cervical immobilization and cimentoplasty of lumbar vertebrae. She achieved complete response and she is alive at last follow-up, after 2 years.

Discussion

Bone lymphomas can be classified as primary bone lymphomas (PBL), consisting of unifocal lymphoma (with or without regional

lymphadenopathies) and multifocal- polyostotic lymphoma (with multifocal disease exclusively involving the skeleton; without affecting lymph nodes or other integral organ and secondary (disseminated) lymphomas (SBL) with secondary infiltration of the skeleton [1]. The criteria for the diagnosis of primary bone lymphoma are described by Coley et al. (see ref) (Coley's criteria) and includes: (a): A primary focus in a single bone, (b) unequivocal histologic proof from the bone lesion, and (c) no evidence of distant soft tissue or distant lymph node involvement.

Nevertheless it is difficult in many cases to distinguish the primary site of lymphoma and to categorize it as primary or secondary [2]. PBL account for about 5% of extranodal lymphomas, <1% of all non-Hodgkin lymphomas (NHL) and 3-7% of all malignant bone tumours [3]. Median age at diagnosis ranges between 45 and 60 years old with a male prevalence, while paediatric cases have been also reported [4]. The main patient characteristics are: pain (80-95%) and pathological fracture (15-20%). Pelvic bones and spinal cord are commonly affected, while hypercalcemia and osteolysis can be observed [5]. Diagnosis must be confirmed by histopathological examination of a biopsy (Table 1), obtained by surgical procedure, limited in size due to the risk of pathological fracture [6].

Diffuse Large B-cell lymphoma (DLBCL) accounts for the majority of cases (70-80% of all bone lymphomas) [7]. Primary bone DLBCL has usually specific molecular characteristics in comparison with other extranodal B-cell lymphomas (MUM1 positivity, BCL6 mutations) [8].

Classification	uPBL	mPBL	SBL
DLBCL, n (%)	37(80.4)	23(66.7)	23(50.0)
Follicular lymphoma, n (%)	4(8.7)	3(8.6)	9(19.6)
Small lymphocytic lymphoma, n (%)	1(2.2)	1(2.9)	0(0)
Marginal zone lymphoma, n (%)	1(2.2)	1(2.9)	2(4.3)
Not further subclassified, n (%)	1(2.2)	2(5.7)	1(2.2)
BLUI, n (%)	0	1(2.9)	0(0)
Classical Hodgkin lymphoma, n (%)	1(2.2)	0(0)	10(21.7)
T cell, n (%)	1(2.2) ^b	4(11.4) ^c	1(2.2) ^d
Total, n (%)	46	35	46

Table 1: Histopathological subtypes of patients with bone lymphoma.

Stage of the disease is defined according to the Ann Arbor and the IELSG staging system (Table 2) [2]. The survival of patients with primary bone DLBCL is related to disease stage, while it is independently associated with age, performance status and serum LDH levels [9]. Prognosis seems to be better in patients with multifocal DLBCL compared to disseminated nodal lymphoma; MUM 1 expression >10%, low CD10 expression and a nongerminal centre signature are associated with poorer outcome [10]. Relapses are sign of poor prognosis [5], while presentation at the initial onset of the disease with pathological fracture is associated with worst outcome [11]. First-line treatment should be based on R-CHOP regimens followed when indicated by involved-field radiotherapy and CNS prophylaxis in high risk patients. With this strategy the overall response rate (ORR) is over 90% and the 5-year overall survival is 84% [5]. However there still remain several issues with regard the sequence of treatment, the choice

of radiation volume and the role of surgery for fixation of pathological fractures.

IELSG stage	Lymphoma extension	Ann stage	Arbor
IE	Single bony lesion	IE	
II E	Single bony lesion with involvement of regional lymph nodes	II E	
IV E	Multifocal disease in a single bone or lesion in multiple bones in a disease exclusively limited to the skeleton (without lymph nodal or visceral disease)	IV	
IV	Disseminated lymphoma with at least one bony lesion	IV	

Table 2: IELSG staging system for DLBCL of the bone.

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