

## Multiple osteolytic lesions due to Double-Expressor Primary non-Hodgkin Lymphoma of the Bone

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### ABSTRACT

Primary non-Hodgkin lymphoma of the bone (PLB) is a rare type of non-Hodgkin's lymphoma (NHL) that affects the skeletal system with or without regional lymph node involvement. We present the case of a 74-year-old female patient with pain due to multifocal osteolytic lesions. The diagnosis of diffuse large B-cells (non-GCB) phenotype was made by clinical, laboratory, histopathological examination accompanied by an extensive immunohistochemical profile of one of the skeletal lesions.

### Keywords

Lymphoma, Non-Hodgkin; Osteolysis; Positron Emission Tomography Computed Tomography, Immunohistochemistry

### INTRODUCTION

Primary non-Hodgkin lymphoma of the bone (PLB) is a rare type of non-Hodgkin's lymphoma (NHL) that predominantly affects the skeletal system. PLB accounts for 5% of NHLs and 3% of all malignant bone diseases.<sup>1,2</sup> In 80% of PLB, the histological type is diffuse large B-cell lymphoma (DLBCL). PLB predominantly affects males, during the 5<sup>th</sup> and 6<sup>th</sup> decades of life. Diagnosis is based on relevant clinical features as well as imaging studies. The former includes local bone pain, soft tissue swelling, a mass, or a pathologic fracture predominantly in the long bones, followed by the pelvis and spine. Definite diagnosis is based on histopathological examination with immunohistochemical study. The current treatment options include a combination

of immunochemotherapy and radiation.<sup>3,4</sup> However, due to the rarity of the disease, there is no consensus on the best therapeutic management. Here, we report the case of a 74 years-old female patient with PLB and multiple osteolytic lesions.

### CASE REPORT

A 74-year-old woman was admitted because of right ankle pain swelling and gait impairment over the past month. She denied fever, weight loss, or night sweats. Her medical history was otherwise unremarkable. The ankle plain radiography disclosed an osteolytic lesion.

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On physical examination, she was in good performance status (PS), and except for a minor swelling of the right ankle, the remaining physical signs were unremarkable. The hemogram was within normal limits, but the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 61 mm/h and 7.45 mg/dL (reference range RR; <0-5 mg/dL) respectively. Serum calcium was 13.2 mg/dL (RR; 8.5-10.5 mg/dL) and lactate dehydrogenase was of (LDH) 683 U/L (RR; 230-460 U/L). Plain radiography of the right ankle revealed disruption of fibula's architectural structure, compatible with an osteolytic lesion (Figure 1).

Further imaging with Magnetic Resonance Imaging (MRI) demonstrated complete distortion of the architecture of distal fibular metaphysis by a pathological tissue that infiltrates the bone cortex and marrow and extends to the surrounding soft tissue. Other findings included multiple lesions, possibly attributed to metastatic neoplastic disease, on the lower half of the right tibia, fibula, talus, and metatarsal bones (Figure 2).

Bone marrow (BM) biopsy, as well as neck, chest, and abdominal computed tomography, were free of disease.

Moreover, the patient underwent whole-body imaging with positron emission tomography/computed tomography (PET/CT) scan that revealed pathological uptake of 18-FDG by the whole skeleton, particularly cranial and long bones (Figure 3). Many of these lesions' sites were accompanied by soft tissue masses, particularly in the lower extremities and the maxilla (SUV max: 15). Increased 18-FDG uptake was also noted in the nasal and zygomatic bones, bilaterally (SUV max: 20), as well as in the cervical, iliac and inguinal lymph nodes (SUV max: 5.5) and regionally in BM (findings consistent with infiltrating disease).

The patient underwent a biopsy of the fibula. The histopathological examination showed diffuse infiltration of large-sized cells. Neoplastic cells expressed the B-cell associated antigens CD20, CD79a, PAX5, BCL-6, MUM-1, BCL-2 (80%) [BCL-2(124) Mouse Monoclonal Antibody -Cell Marque], SIg/CIgM(k) and C-MYC (> 40%) [c-MYC(Y69) Rabbit Monoclonal Primary Antibody-Roche]. The expression of CD3, CD4, CD8, CD5, CD23, CD30, CD10, CyclinD1 was negative. Additionally, in situ, hybridization for EBER was negative. The proliferation fraction, as detected by Ki-67 (MIB-1 antigen), was 90%. Fluorescence in situ



**Figure 1.** Plain X-Ray of the right foot. Fibula's infiltrative bone destruction.

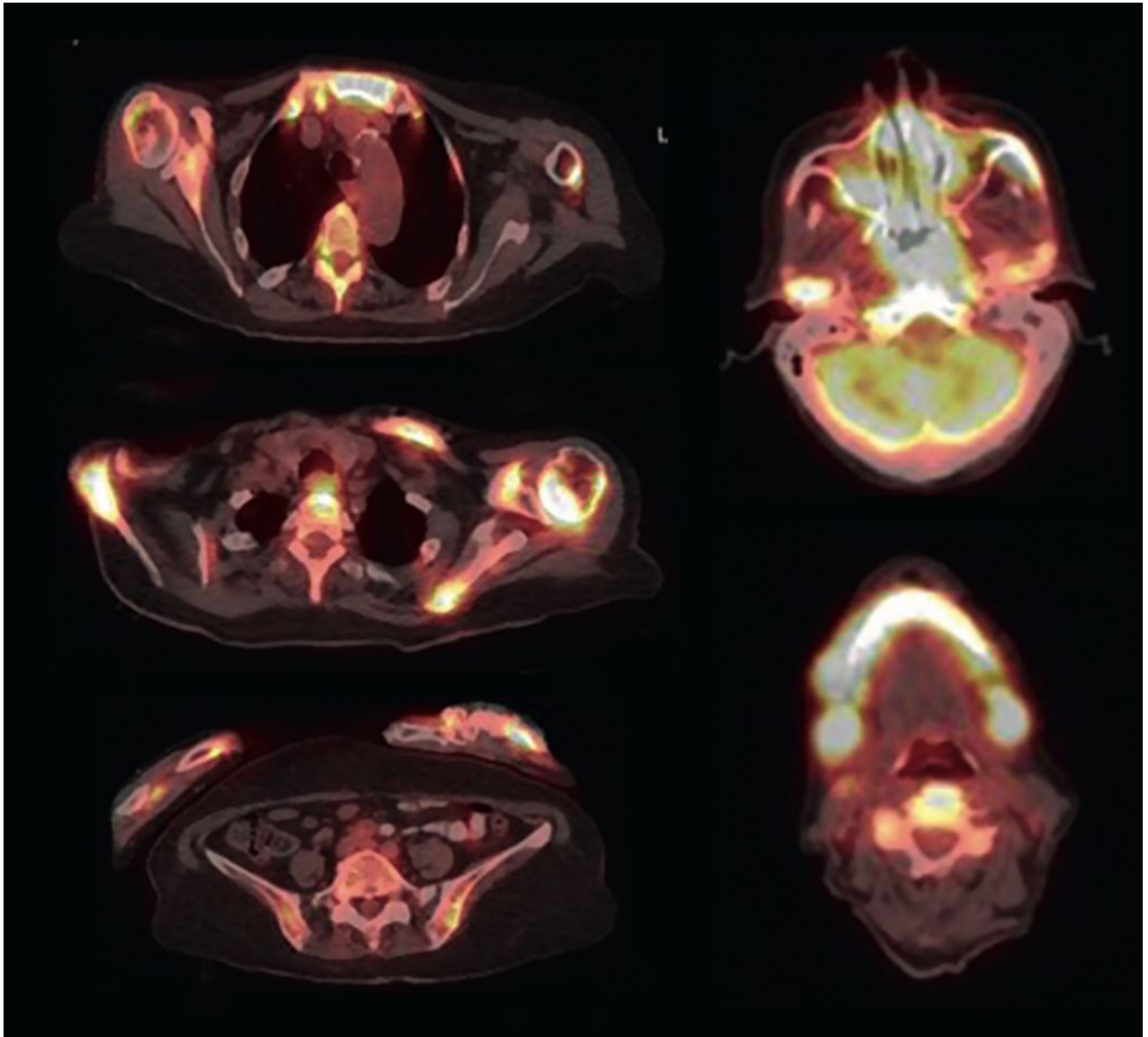


**Figure 2.** MRI of the right foot. T2-weighted images showing abnormal signals involving tibia, fibula, talus and metatarsal bones.

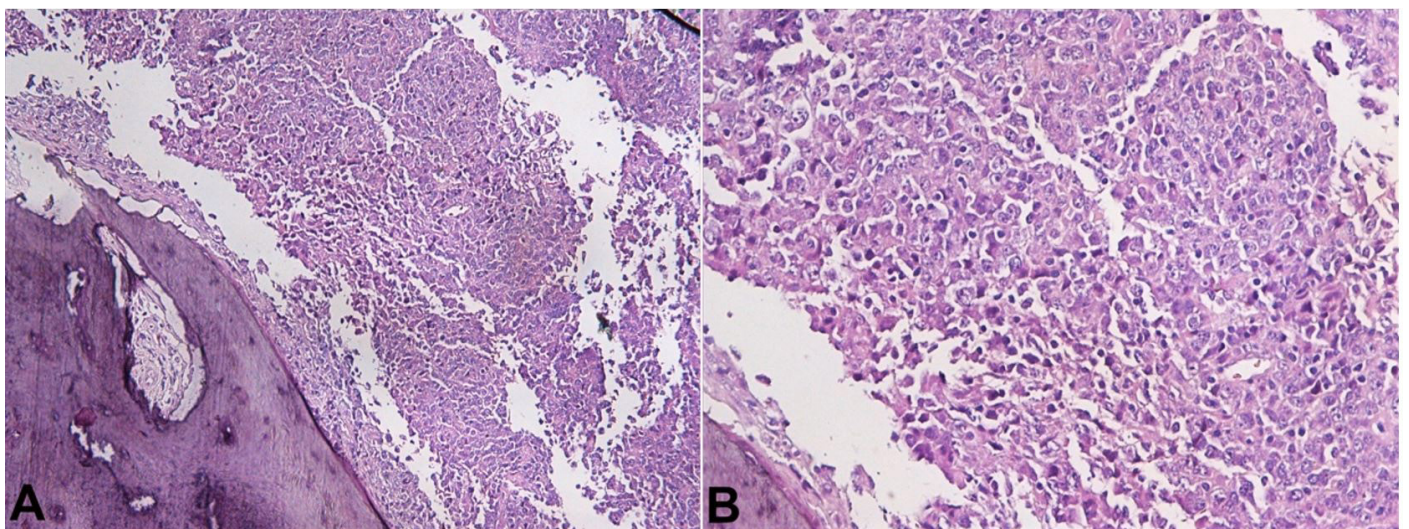
hybridization (FISH) tests did not reveal rearrangement for *C-MYC* and *BCL2* genes. The above histological findings were compatible with the diagnosis of DLBCL not otherwise specified, DLBCL-NOS with no germinal center B-cells (non-GCB) phenotype, and double expression of *C-MYC* and *BCL-2* (Figure 4, 5, 6, and 7).

Thus, the patient was diagnosed with a multifocal double expressor DE-PLB, stage IVEA according to Ann Arbor classification<sup>5</sup> with International Prognostic Index<sup>6</sup> (IPI) score: 5, age-adjusted IPI score: 3, and NCCN-IPI<sup>7</sup> [International Prognostic Index for patients with diffuse large B-cell lymphoma) score: 7 (high risk).

During the hospitalization, the patient experienced a pathological fracture in the lower third of the right



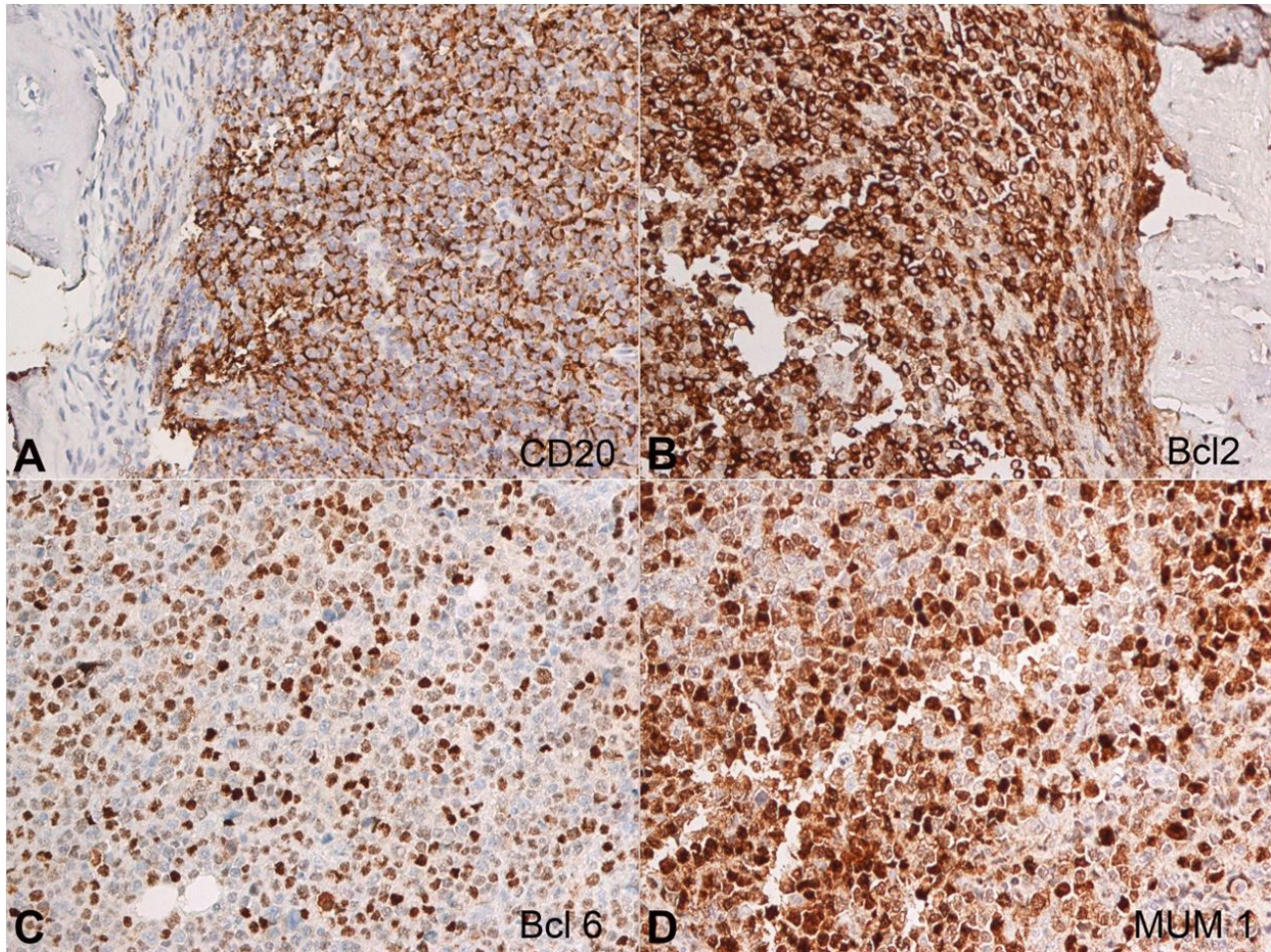
**Figure 3.** 18F-FDG PET/CT imaging demonstrating high FDG uptake in the majority of scanned bones. Cranial and long bones of arms and legs are more severely affected, with soft tissue masses accompanying the bone lesions.



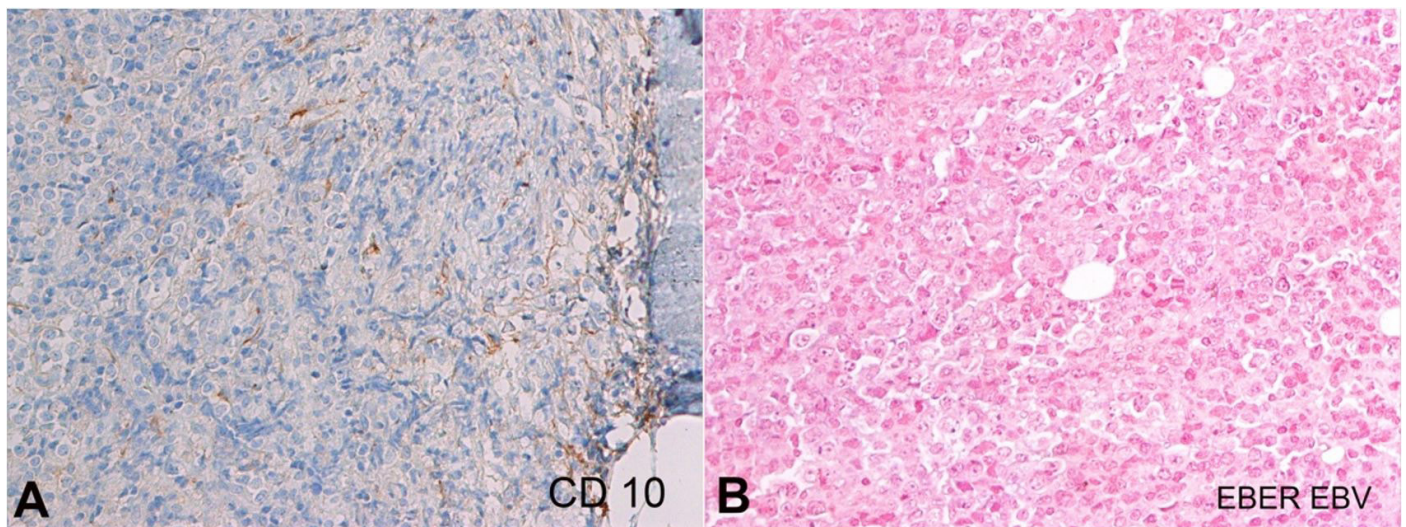
**Figure 4.** Photomicrographs of the bone biopsy. **A** – Diffuse infiltration of bone by a large cell lymphoma (H&E, X100); **B** – Higher magnification of the cell infiltrate (H&E, X200).

femur, which was treated surgically. However, it has aggravated her PS to 4, according to ECOG.<sup>8</sup> Subsequently, the patient received prophylactic local radiotherapy (RT) with a total dose of 36cGy, in the lower third of both legs and was treated with 2 cycles

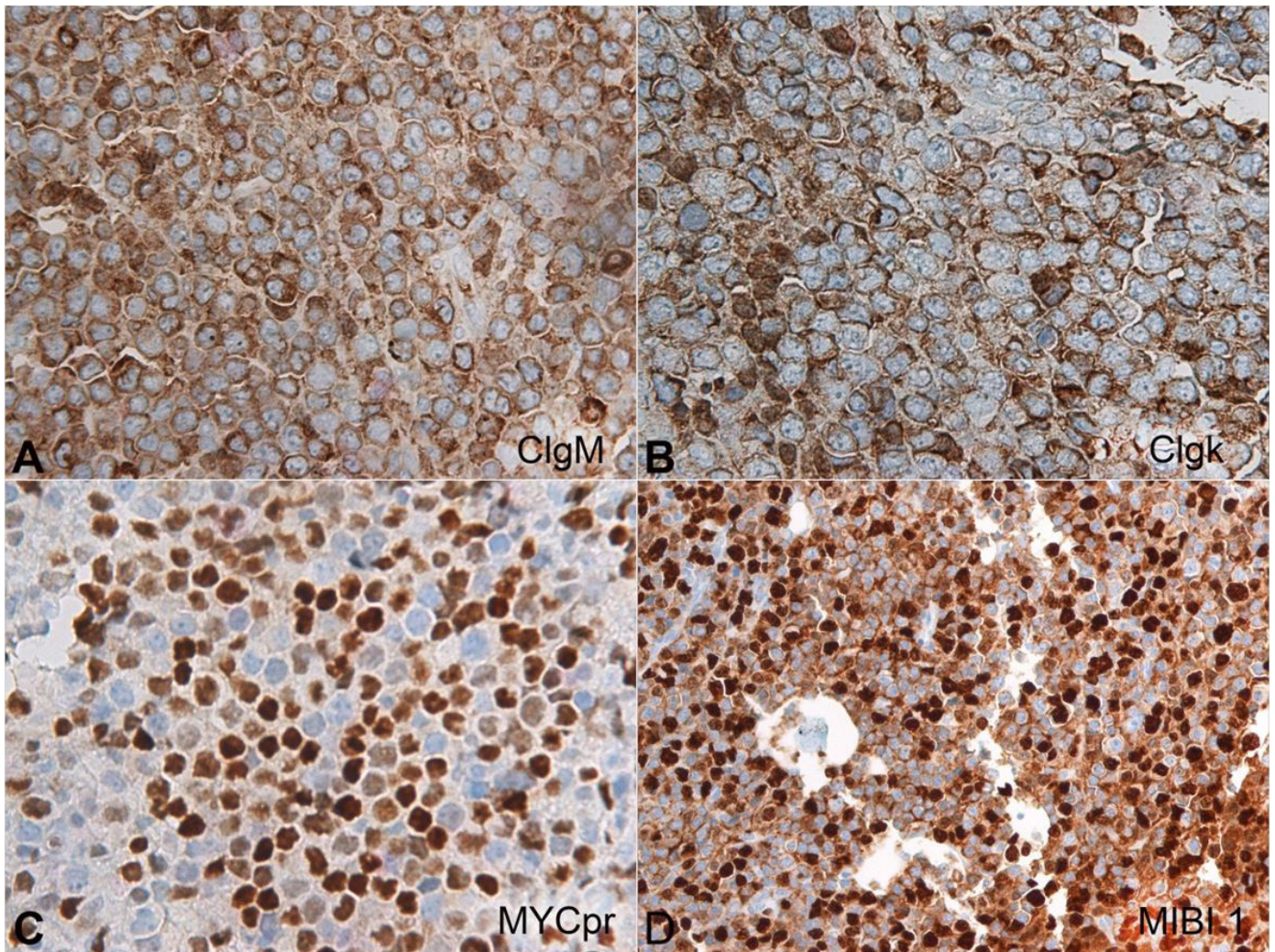
R-CNOP (Rituximab- Cyclophosphamide, Mitoxantrone, Vincristine, and Prednisone). Unfortunately, she experienced septic shock during the neutropenic phase after the 2nd cycle of R-CNOP and succumbed to multiorgan failure.



**Figure 5.** Photomicrographs of the bone biopsy. **A** – CD20 (X200) expressed by lymphoma cells; **B** – BCL2(X200) positive expression; **C** – BCL-6 (X200) positive; **D** – MUM1 (X200) positive.



**Figure 6.** Photomicrographs of the bone biopsy. **A** – CD10(X200) negative; **B** – In situ hybridization (EBER) for EBV (X200), negative.



**Figure 7.** Photomicrographs of the bone biopsy. **A** – ClgM(X400) positive; **B** – Clgκ (X400) positive; **C** – MYC (X400) > 40%; **D** – High rate of proliferation MIB1 (X200) overall ~90%.

## DISCUSSION

PLB is a rare bone malignancy that, according to the World Health Organization (WHO-2016) classification<sup>9</sup>, affects the skeletal system disregarding regional lymph node involvement, and multiple bone lesions without visceral or lymph node involvement.

Clinically, PLB usually presents as a localized bone pain that may be followed by tissue swelling and, in some cases, a palpable lump. The most frequently involved bone is the femur, accounting for 29% of all cases, followed by the pelvis, humerus, skull, and tibia.<sup>10,11</sup> Males are predominantly affected with a higher morbidity rate slightly higher compared with females.<sup>3</sup>

Imaging findings include osteolytic or osteoblastic lesions depicted in X-ray that may even coexist in the same bone.<sup>12</sup> Contrast-enhanced CT is the standard modality for original staging and follow-up

of lymphoma patients, while MRI may be useful in revealing the details of bone lesions and their extent to surrounding soft tissues. More recently, PET/CT scan has been recommended by the Lugano Classification<sup>13</sup> for the initial evaluation, and follow up of lymphomas; however, its diagnostic value for PLB is not yet well-confirmed.<sup>14</sup> The definite diagnosis of PLB largely depends on the acquisition of adequate tissue samples and extensive immunohistochemical study.<sup>15</sup> DLBCL is the most common pathological type, accounting for up to 70-80% of all cases, and the majority of cases is of the germinal center (GCB) subtype.<sup>15</sup> Based on the 2016 revised WHO classification for lymphoid neoplasms, a new diagnostic entity coined double-hit (DH) lymphoma - defined as a dual rearrangement of *MYC* and *B-cell CLL/lymphoma 2 (BCL2)* and/or *B-cell CLL/lymphoma 6 (BCL6)* genes is an uncommon subset accounting for 5% to 7% of all DLBCLs, which presents an aggressive behavior. Furthermore, the

co-expression of MYC and BCL2 proteins without underlying rearrangements is considered a new adverse prognostic indicator termed double-expressor (DE) lymphoma and accounted for 20% to 30% of DLBCL cases.<sup>9,16</sup> Our patient was diagnosed with non-GCB (DE), but the exact incidence and the impact of this type in the outcome has not been adequately studied in PLB, to date.

Current therapeutic modalities include immunochemotherapy with or without local radiotherapy (RT), mainly for the early-stage disease. The addition of anti-CD20 monoclonal antibody (Rituximab) to chemotherapy seems to improve the outcome with a 3-year progression-free survival of 88% compared to 52% for patients who received only chemotherapy.<sup>17</sup> The role of complementary RT in the Rituximab era should be further investigated. Surgical treatment is required mainly for diagnostic purposes and stabilization of a pathological fracture. The prognosis of PLB is generally good, and relapse or refractory disease is uncommon. However, age over 60 years and high IPI score are adverse prognostic factors for extended survival.<sup>17</sup> Moreover, the histologic subtype of DH or/ and DE may worsen the prognosis.

Our patient initially presented with lower limb pain and swelling, with an osteolytic lesion of right lower fibula depicted by the plain X-Ray. The differential diagnosis of such findings is broad. It includes PLB, multiple myeloma (MM), and other primary malignant bone tumors, such as Ewing's sarcoma, osteogenic sarcoma, and chondrosarcoma, as well as, metastatic neoplasms. The age, poor PS, high IPI score, multifocality, and histological subtype of DE DLBCL, as well as the delay in initiation of immunochemotherapy with R-CHOP due to the occurrence of the pathological fracture, may be related to the poor outcome of our patient.

## REFERENCES

1. Chisholm KM, Ohgami RS, Tan B, Hasserjian RP, Weinberg OK. Primary lymphoma of bone in the pediatric and young adult population. *Hum Pathol.* 2017;60:1-10. <http://dx.doi.org/10.1016/j.humpath.2016.07.028>. PMID:27554207.
2. Huan Y, Qi Y, Zhang W, Chu J. Primary bone lymphoma of radius and tibia: a case report and review of literature. *Medicine.* 2017;96(15):e6603. <http://dx.doi.org/10.1097/MD.0000000000006603>. PMID:28403103.

3. Liu J, Fan S, Wang J, Song B. A rare case report of primary bone lymphoma and a brief review of the literature. *OncoTargets Ther.* 2016;9:4923-8. <http://dx.doi.org/10.2147/OTT.S108000>. PMID:27563248.
4. Santos TMD, Zumárraga JP, Reaes FM, Maçaneiro CH Jr, Baptista AM, Camargo OP. Primary bone lymphomas: retrospective analysis of 42 consecutive cases. *Acta Ortop Bras.* 2018;26(2):103-7. <http://dx.doi.org/10.1590/1413-785220182602185549>. PMID:29983626.
5. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. *Cancer Res.* 1971;31(11):1860-1. PMID:5121694.
6. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphomas. *N Engl J Med.* 1993;329(14):987-94. <http://dx.doi.org/10.1056/NEJM199309303291402>. PMID:8141877.
7. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood.* 2014;123(6):837-42. <http://dx.doi.org/10.1182/blood-2013-09-524108>. PMID:24264230.
8. Oken MM, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-55. <http://dx.doi.org/10.1097/00000421-198212000-00014>. PMID:7165009.
9. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-90. <http://dx.doi.org/10.1182/blood-2016-01-643569>. PMID:26980727.
10. Messina C, Christie D, Zucca E, Gospodarowicz M, Ferreri AJ. Primary and secondary bone lymphomas. *Cancer Treat Rev.* 2015;41(3):235-46. <http://dx.doi.org/10.1016/j.ctrv.2015.02.001>. PMID:25698636.
11. Bruno Ventre M, Ferreri AJ, Gospodarowicz M, et al. Clinical features, management, and prognosis of an international series of 161 patients with limited-stage diffuse large B-cell lymphoma of the bone (the IELSG-14 study). *Oncologist.* 2014;19(3):291-8. <http://dx.doi.org/10.1634/theoncologist.2013-0249>. PMID:24567283.
12. Shoji H, Miller TR. Primary reticulum cell sarcoma of bone: significance of clinical features upon the prognosis. *Cancer.* 1971;28(5):1234-44. [http://dx.doi.org/10.1002/1097-0142\(1971\)28:5<1234::AID-CNCR2820280522>3.0.CO;2-L](http://dx.doi.org/10.1002/1097-0142(1971)28:5<1234::AID-CNCR2820280522>3.0.CO;2-L). PMID:4942244.
13. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano

- classification. *J Clin Oncol*. 2014;32(27):3059-68. <http://dx.doi.org/10.1200/JCO.2013.54.8800>. PMID:25113753.
14. Cıraklı A, Elli M, Dabak N, Canbaz Tosun F, Dağdemir A, Cıraklı S. Evaluation of primary bone lymphoma and the importance of positron emission tomography. *Acta Orthop Traumatol Turc*. 2014;48(3):371-8. <http://dx.doi.org/10.3944/AOTT.2014.3014>. PMID:24901932.
15. Li X, Xu-Monette ZY, Yi S, et al. Primary bone lymphoma exhibits a favorable prognosis and distinct gene expression signatures resembling diffuse large B-cell lymphoma derived from centrocytes in the germinal center. *Am J Surg Pathol*. 2017;41(10):1309-21. <http://dx.doi.org/10.1097/PAS.0000000000000923>. PMID:28817403.
16. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: definition and treatment. *Cancer*. 2018;124(24):4622-32. <http://dx.doi.org/10.1002/cncr.31646>. PMID:30252929.
17. Ramadan KM, Shenkier T, Sehn LH, Gascoyne RD, Connors JM. A clinicopathological retrospective study of 131 patients with primary bone lymphoma: a population-based study of successively treated cohorts from the British Columbia Cancer Agency. *Ann Oncol*. 2007;18(1):129-35. <http://dx.doi.org/10.1093/annonc/mdl329>. PMID:17018705.

**Authors' contributions:** Katsikas T, Vrettos I, Voukelatou P and Kalliakmanis A were responsible for the initial patient's medical care. Papanikolaou A was the pathologist in charge of the case, provided the microscopic images and wrote this topic of the article. Papageorgiou S, Bouchla A, and Pappa V were the hematologists in charge of the post-diagnosis treatment. Katsikas T, Vrettos I and Voukelatou P. performed the initial workup of the case under the supervision of Kalliakmanis A, Papageorgiou S and Katsikas T wrote the manuscript. All authors collectively proofread and approved the final version for publication.

The authors retain informed consent signed by the patient's next-of-kin authorizing the publication of the data, and the manuscript is by the Institutional Ethics committee.

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