

Primary Bone Non-Hodgkin's Lymphoma: A Literature Review

Dary Gunawan¹, Anak Agung Ngurah Ronny Kesuma², I Komang Mahendra Laksana M³

¹Intern of Orthopedic and Traumatology Department in Wangaya Regional Hospital, Denpasar, Bali, Indonesia
gunawandary[at]gmail.com

^{2,3}Orthopedic Surgeon of Orthopedic and Traumatology Department in Wangaya Regional Hospital, Denpasar, Bali, Indonesia

Abstract: *Primary Bone Lymphoma (PBL) according to the World Health Organization (WHO) is a single skeletal lymphoma with or without lymph node involvement and multiple bone lesions without visceral or lymph node involvement. The etiopathogenesis of this disease remains unclear and requires further research. Literature search was done using search engines from Pubmed, Google Scholar, Cochrane Library, Web of Science, popular premier orthopedic journals (JBJS, BJJ, CORR, INJURY, ABJS, ActaOrthopædica, IJO) and general medical journals (JAMA, NEJM, Lancet) in the last 5 year, but relevant older articles were included. The diagnosis of PBL is confirmed by clinical examination, radiological support and biopsy. Standard management to date includes immunochemotherapy with or without radiotherapy, while operative measures are limited to biopsy sampling and stabilization of pathologic fractures or impending fractures with risks above intermediate. A good prognosis is found in PBL patients with Diffuse Large B Cell Lymphoma. Until now, due to the rarity of the disease, there are very few studies that discuss PBL and its associated management as guidelines in determining therapy and prognosis. This study describes the related PBL, especially PBL with Non-Hodgkin's lymphoma.*

Keywords: Diffuse Large B Cell Lymphoma, Malignancy, Pathological Fracture, Lymphoma of Bone

1. Introduction

Among the bone tumors, one of which can be caused by primary hematopoietic cancers and by the World Health Organization (WHO) are myelomas and lymphomas. (1) Primary Bone Lymphoma (PBL) was first discovered in 1928 as a type of malignant lymphoma with a malignant lesion that affects the bone as the primary site. (2,3) Until now, PBL was found in only <5% of all cases of extranodal lymphomas and amounted to <10% of the total bone tumors. (1,4–11) Meanwhile, in children, PBL is found in 3-9% of cases. (3)

PBL is found mostly in the type of Non-Hodgkin Lymphoma (NHL). (7) This is confirmed by case findings where as many as 70-80% of patients diagnosed with PBL have a pathological type in the form of Diffuse Large B-Cell lymphoma (DLBCL). (3,6,10,12,13) Even though the number is mentioned at the most, the characterization of the DLBCL subtype is still developing and will probably continue to grow. (10) The etiopathogenesis of PBL which is included in Primary Extranodal Lymphoma (PEL) has different nosological entities than lymphoma in lymph nodes. (14)

To date, there is no literature that describes in detail the etiopathogenesis of PBL, and more cases have been reported in the retrospective case series. (10)

Patients with suspected PBL generally have complaints in the form of pain that is localized in one part of the bone and can provide a picture according to Complex Regional Pain Syndrome (CRPS) type I. (1) Complaints of pain are found in about 82-92% of patients, while symptoms of soft tissue swelling are found in 34-45% of patients. (9) Palpable lump may be found on the side of the lesion. Most patients with bone pain complain that the pain does not improve with rest

and some complain of a decreased range of motion. (3,12) What makes the diagnosis more difficult is finding that most of the patients complain of pain with intensity and varying duration with insidious and slow onset. (1)

This literature review will discuss more about Primary Bone Non-Hodgkin's Lymphoma, especially recent management of the disease.

2. Material and Methods

This literature study not only describes the epidemiology of primary bone Hodgkin's Lymphoma but also recent management of the disease. Literature search was done using four search engines from Pubmed, Google Scholar, Cochrane Library, Web of Science, popular premier orthopedic journals (JBJS, BJJ, CORR, INJURY, ABJS, ActaOrthopædica, IJO) and general medical journals (JAMA, NEJM, Lancet) in the last 5 year, but relevant older articles were included. The search was conducted with keywords: "treatment" and "primary bone non-hodgkin's lymphoma" or "primary bone lymphoma".

3. Discussion

3.1 Definition

According to the WHO classification, PBL is a single skeletal lymphoma with or without lymph node involvement and multiple bone lesions without visceral or lymph node involvement. (1–4,9,12,15) Bindal, et al in their study stated that there were no definitive criteria related to it regarding the outline of malignancy from WHO classification. However, supporting the WHO's previous definition, the International Extranodal Lymphoma Study Group (IELSG) states that only cases with clear bone origin are classified as PBL, such as a single bone lesion, with or without

involvement of regional lymph nodes or multiple bone lesions with or without involvement of nodal or visceral disease, which is referred to as "multifocal osseous lymphoma" or "polyostotic lymphoma".(9)

3.2 Epidemiology

The number of PBL cases itself is quite rare and is commonly found in patients aged 20 to 50 years. PBL is more common in men and has a higher morbidity ratio than in female patients. Moreover, the highest number of PBL was found in the long bones such as the femur (29%), followed by other parts such as pelvis, humerus, skull, neck and tibia.(6,12,16–18) In accordance with the findings above, lymphoma is usually found on the bone with a persistent red marrow and very rarely on small bones on the hands and feet.(1) These findings are similar with a study by Batia, et al in which the statistical analysis according to the IELSG-14 study showed a low incidence of primary DLBCL bone lymphoma affecting the forearm in 5.6% of patients with PBL.(12) In addition, PBL was also found to include the spread of lymph nodes and bone marrow which was found in 28 and 35% of cases. Unfortunately, the data that reports on racial and geographical distribution is still inadequate. (9)

The second is Anaplastic Large-Cell Lymphoma (ALCL) which is a subtype of peripheral T-Cell lymphomas. ALCL is found in 3-5% of PBL cases and is more common in male patients with a young age (<60 years). It affects mostly on the axial bones such as the pelvis and vertebrae.(4,19) ALCL positive ALK is the second type of pathology that is more often found after DLBCL, while Negative ALK is less common and more prevalent in older patients aged 55-60 years with a less satisfactory prognosis than positive ALK at ages 25-35 years.(19) T cell leukemia / lymphoma (ATL) is called a refractory disorder caused by Human T-lymphotropic virus type 1 (HTLV-1) which is epidemic in Japan, the Caribbean, Melanesia, Brazil and parts of Africa.(13,20) Until now, H Kato, et al stated that there were only 5 case reports related to ATL in bones.(13) In addition to the above subtypes, indolent lymphoma is also found in 5% of cases.(10) Other subtypes such as follicular, lymphoplasmacytic, NK / T-Cell, Burkitt and others are even less common.(1)

3.3 Etiology

The etiology of PBL is still unknown at this time.(6,12) Until date, no one has explained the risk factors associated with the occurrence of PBL.(9)

3.4 Pathogenesis

A postulate put forward by Lin, et al mentions in their study on a clinical and biological basis, that most PBL with the DLBCL type originates from centrocytes, where lymphoid follicles on the bone or marrow arise in reaction to anemia, autoimmune disease, as a forerunner or similar neoplastic features. It is like a malignant lymphoma which is subsequently mimic germinal cells. Naive B cells on bone marrow enter the follicle and IgH somatic undergo hypermutation in the 'dark zone' as centroblasts) and form

antibodies with altered affinity for the antigen. Subsequently, the somatic IgH hypermutation moves to the 'light zone' (as centrocytes) and is surrounded by follicular dendritic cells to initiate DLBCL. Alternatively, it is possible that the centrocytes in the germ cells leave the lymph node and move to the bone where the DLBCL occurs. (21)

In PBL patients with ATL, hypercalcemia can be found due to excess PTHrP production associated with osteoclastic activation. This may be due to Humoral Hypercalcemia of Malignancy (HHM) and/ or Local Osteolytic Hypercalcemia (LOH). Apart from HHM and LOH, unsuppressed 1,25OH₂D which occurs due to overexpressing 1-alpha hydroxylase in ATL cells also causes hypercalcemia. However, osteolytic infiltration of ATL cells can also be found in normal PTHrP. Humoral factors produced by ATL cells such as Macrophage Inflammatory Protein 1 (MIP-1) are said to play a role in osteoclastic activation.(13,20)

3.5 Clinical Manifestations

Batia, et al said that almost 50% of cases in patients with PBL were accompanied by palpable mass due to soft tissue extension of the bony disease.(12) In addition, other findings such as pathological fractures and cord compression can also be found. Although rare, patients with PBL may show B symptoms such as fever, weight loss and night sweats.(1,12) Because the symptoms are not very specific, patients often complain of similar symptoms months before seeking medical treatment to get anti-inflammatory and analgetics. (5, 6, 12)

In their case study, Kato, et al stated that PBL patients with ATL had clinical features showing generalized lymphadenopathy, hepatosplenomegaly, skin lesions, leukemia, lytic bone lesions and hypercalcemia. However, almost similar to others, these clinical symptoms are not found in the early stages of the disease. Generally, patients only complain of pain in the bones in the early stages of the disease.(13) In patients with T-cell lymphoma, the lesions that are found can present with primary bone lesions so that it deserves more attention because of the risk of misdiagnosis. Although rare and the mechanism is still unknown, lymphoma can also be found appearing in the area around prosthetic devices and other implants with complaints of pain, erythema and swelling at surgical sites several years after surgery.(19) Symptoms that are not very specific often lead to a late diagnosis of up to approximately 8 months, where in pediatric patients usually appear healthy with few complaints.(10) In pediatric patients, PBL has better clinical manifestations where the clinical manifestations are more indolent and more curable although it often includes extensive osseous involvement. (22,23)

3.6 Supporting Investigation

Laboratory results are often non-specific, so they are not very helpful in diagnosing PBL.(9)

From the radiological results, the lesions on the bone appear osteolytic and can be multifocal without specific aspects of the picture. Alas, it can also be found with multiple destructive bone lesions.(1,3,5,13) The radiological features

that appear can be a large number of small, elongated rarefactions which are usually uniform in size or mouth-eaten, with moderate to large radiolucent areas depicted indecisive and not always showing the appearance of a periosteal reaction.(1) Lesions of osteolytic or osteoblastic that appear on x-rays usually showing involvement of the cortex and reactive periosteal change.(9) If there is a suspicion of more than an unclear picture on plain radiologic, then an examination should be carried out to perform with more advanced modality.(24)

Computed Tomography (CT) scans and Positron Emission Tomography (PET)/ CT can be used for staging and excluding solid cancer or lymphadenopathy. Meanwhile, bone marrow aspiration and biopsy can be used to rule out multiple myeloma.(6,13) In addition, CT scans will also be useful for determining tumor boundaries and expansion outside the bone such as cortical breaks and pathological fractures that are less visible on plain radiologic.(9,25) On CT images, a sequestrum-like appearance of osteomyelitis can be seen as shown by intraosseous sclerosis due to reactive osteoid.(26) According to Steffner et al, PBL infiltrates the bone marrow to form spaces in the trabeculae and intermixing with fibrotic areas.(10)

PET / CT using Fluorine-18-Fluorodeoxyglucose (F-18 FDG) is determined the standard for lymphoma staging. (7,14) Even though it is a standard, negative results do not rule out PBL. (7) Meta-analysis study by Pakos et al stated that the sensitivity of F-18 FDG PET/ CT to determine bone marrow infiltration ranges from 0-100% and specificity between 72-100%.(27,28) However, the sensitivity, specificity and accuracy for staging using PET/ CT are proven to be better than conventional CT.(9) This is because PET/ CT is able to show involvement of extraskelatal soft tissue and detect additional bone lesions.(27) Therapeutic response can also be seen using PET/ CT in adult patients using the help of Lugano criteria. Decreased FDG activity indicates a response to therapy. Unfortunately, the false positive rate is quite high and these results can also appear if the patient is treated with Granulocyte Colony Stimulating Factor (G-CSF) while on recovery. In children, this evaluation has not been carried out due to the lack of data available.(8) Despite of the false positive rates, Luigi, et al In their study stated that the use of the Deauville Criteria can help reduce the number of false positives that are obtained.(29)

Next is the use of Magnetic Resonance Imaging (MRI). On the MRI image, a decreased signal intensity can be found on T1-weighted images in the fatty marrow image caused by cellular element replacement. In contrast, on T2-weighted images, the focal area of the infiltrating tumor shows only a slight increase in signal intensity or even hypointensity.(1,7) In pediatric patients the use of MRI is more favorable considering radiation exposure. However, MRI can give abnormal results even 2 years after resolution occurs with relapse frequently occurring during this time.(8) On MRI, stress fractures, osteonecrosis and red marrow conversion can resemble the picture of lymphoma. However, this can be distinguished from the T1-weighted image which tends to be normal.(22) MRI has also been shown to be as effective as PET/ CT scan in determining response to therapy.(9)

Reassessment using plain radiographs and PET can be used to detect relapses in patients with recurrent symptoms. (6) Even so, biopsy is a determinant for the reassessment. (6, 8)

To determine the possibility of a tumor caused by PBL, clinical and radiological confirmation should be carried out with surgical sampling and immunohistochemical tests. (9, 12) Bone biopsy can be taken by avoiding excisional biopsy and reducing the amount of resected tissue in order to reduce the risk of pathological fractures. (9) Besides being easy to reach anatomical areas that are difficult to reach, taking biopsy using a core needle is preferred because it is less invasive and cheaper. (10) Taking a biopsy using a new drill core needle provides better tissue sample results and is able to reduce time and pain during the procedure. (30) Meanwhile, sampling using the open biopsy technique provides advantages in the form of a larger sample image and frozen section delivery can also be done to confirm lesion tissue. Unfortunately, this technique put the patients at higher risk for fractures. (10) It should be noted that lymphomatous processes in bone are often accompanied by dense fibrosis which causes the formation of cytologic artifacts while decalcification can cause cytologic and immunohistochemical stains.(1) In the morphological picture, tumor cells are usually found to be large and consistent with follicle center or centroblastic cells. (9)

Suspected tumor cells in patients with PBL can be found immunoreactive on B-cell markers such as CD20, CD21, CD45 and CD79a with variable immunoreactivity for CD75 and CD10.(9,12) Staining for the Ki67, BCL6, IRF4, CD10 and BCL2 protein markers can be used to determine biological aggressive processes.(1)

In ALCL, the diagnosis is determined by the presence of T- or null-cell type with pleomorphic lymphoid cells with frequent horseshoe-shaped nuclei, abundant cytoplasm and expression of CD3.(4) Negative ALK in PBL is less common than positive ALK, but this does not rule out a diagnosis of PBL. (19)

Staging was determined using the Lugano Classification System, where stage IE describes diseases confined to extranodal sites such as solitary bone lesions. Stage II E is determined if there is a feature of regional lymph node involvement. Stage IV is enforced when the multifocal disease is strictly limited to the skeletal system.(9) Staging can be seen in **Table 1**. Patients with PBL with stage IE or IIE are found in 80% of cases.(17)

Table 1: International Extranodal Lymphoma Study Group Staging System. (10)

Stage	Disease Location
IE	Single site in bone with no regional lymph-node involvement
IIE	Single bone site with contiguous regional lymph-node involvement
IVE	Multifocal bone involvement, no other sites
IV	Disseminated disease, at least 1 bone lesion

3.7 Diagnosis

The diagnosis is made using a biopsy which should be done after radiological imaging is complete. This is done in order to reduce the possibility of changes in the radiological image after the biopsy. (10)

3.8 Differential Diagnosis

Batia, et al in their study stated that patients who were found to have symptoms were not so specific that made PBL was difficult to be distinguished from other primary bone tumors such as Ewings sarcoma, osteogenic sarcoma and chondrosarcoma.(12)The radiological features of a single bone lesion in PBL patients are also difficult to be distinguished from osteomyelitis.(10) In osteolytic lesions with the discovery of hypercalcemia, differential diagnosis can be secondary bone involvement from excessive PTHrP production due to malignant tumors, bone metastases, multiple myeloma, malignant lymphoma and granulomatous disorders such as tuberculosis and sarcoidosis.(13)In pediatric patients, solitaire bone lesions can represent a stress fracture, osteonecrosis, Langerhans cell histiocytosis, osteosarcoma and Ewing's sarcoma. Meanwhile, multifocal bone lesions can resemble the features of acute hematogenous osteomyelitis, chronic relapsing multifocal osteomyelitis, SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis), mastocytosis and bone metastases. (10)

3.8 Treatment

Until now, the therapy of choice in PBL patients includes chemotherapy and radiotherapy. (2, 3, 6, 12) The two combined therapies in the form of chemotherapy and radiotherapy have been mostly carried out to date because of the large number of relapses that occur including systemically in nearly 50% of patients. (12)

3.8.1 Medication

In adult patients with PBL, chemotherapy with or without radiotherapy is still an option, assuming that the majority of PBL patients present with aggressive B cell lymphomas. (3, 12) First-line therapy that can be given such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (4,12), and can be given additional anti-CD20 antibody Rituximab.(12) The addition of Rituximab to chemotherapy regimens (R-CHOP) in several studies reported satisfactory results in patients.(1,6) Until now, R-CHOP therapy with radiotherapy has been called a standard (level of evidence III, B).(1)

The use of radiotherapy is still controversial although several studies have stated satisfactory results with the combination of the above therapies.(4–6,9,12) However, patients with unifocal disease may be given consolidative involved field radiotherapy.(5,9,12)A large tumor with size $\geq 5-7.5$ cm is an indication for starting radiotherapy. It shows an increase in event-free survival and overall survival.(31–33)Although controversial, there are studies that suggest that radiotherapy can provide local control so as to provide a complete response to immunochemotherapy in patients with early stage PBL.(10,34) PBL patients who give partial responses are also reported to be at risk of experiencing local relapse and giving better results after receiving radiotherapy.(10,35)

Unfortunately, giving radiotherapy to the pelvis and other parts containing marrow cells needs to be considered carefully regarding the matter of side effects caused by radiotherapy.(9,12) In addition, the side effects of radiation such as post-treatment fractures, abnormal healing and physal injuries in children as well as delayed union, malunion and nonunion fractures also still need to be considered especially when giving high doses of radiotherapy.(6)

A dose of 30-36 Gy can be given to patients who provide a complete response to chemotherapy. Meanwhile, higher doses such as 40 Gy can be considered in patients who provide an intermediate response such as in patients with positive PET which can represent active tumor or healing bone.(9,12) Several studies have also stated that giving high doses of radiation (above 40 Gy) as well as chemotherapy and complete remission are associated with more satisfying results. However, radiotherapy alone does not show a better prognosis, so that the therapy given should be in the form of a combination therapy.(4) It should be noted that the cumulative provision of radiotherapy reaching 40 Gy can cause bone recovery disorders.(10) Ibrahim, et al in their study stated that 5 out of 24 patients with an average radiotherapy dose of 39 Gy experienced fractures.(6)Besides that, Loco-regional Radiotherapy (LRT) can also be done if there are the right indications.(5) In general, the provision of consolidative radiotherapy provides satisfactory results for patients with localized disease to prevent local treatment failure and can also be given to patients with advanced disease if the primary site of the disease is extensive.(1,6)

In PBL patients with ATL as the cause, apart from chemotherapy, bisphosphonate administration is said to be useful for reducing pain and recalcifying bone lesions.(13)Patients with PBL stage IE or IIE are given radiotherapy only at a dose of 25-45 Gy. Most of the patients reported by Govi et al gave a complete response to this therapy.(36) However, the subtype of PBL must still be considered where the risk of dissemination of lymphoplasmacytic and follicular indolent lymphoma may require systemic therapy. (36, 37)

Meanwhile, patients with a higher stage can be given chemotherapy with or without radiotherapy. This was reported by Messina et al with 5-year survival in 76% of patients. (38) In asymptomatic patients with good prognostic factors, the patient can be closely observed. Whereas those with a poor prognosis are generally given Rituximab chemotherapy with Bendamustine. (39) Most patients give a good initial response although some can show eventual relapse with several subtypes that can be at risk of becoming more severe disease.(36)

3.8.2 Operative/ Surgical

Operative action is limited to diagnostic biopsy and stabilization of pathological fractures. (2, 6) If a patient is suspected of having PBL, taking a biopsy needs to be done carefully because the tissue can be fragile and can lose its normal cell architecture and morphology. This is said to be caused by bone spicules which cause mechanical scraping. (10) Chisholm, et al in their study stated that nearly 30% of

patients require repeated biopsy due to inadequate samples. (40) Biopsy samples taken should be stored in sterile containers and formalin-fixed tissue specimens for flow cytometry analysis and cytogenetics if needed.(10)

However, orthopedic management is still an important thing to do because of the possibility of fracture in patients with PBL. Patients with lesions on weight-bearing bones may require internal stabilization or bracing until bone healing occurs.(4,9,12) Orthopedic reconstruction surgery can also be performed if there are strong indications.(5) In isolated lesions, bone removal or amputation can also be done.(3) It is in accordance to the case of PBL with ATL that have a complete remission which was achieved by amputating the affected limb when ATL was found in the limb bones.(13) Operative management in patients with a good prognosis can be postponed by prioritizing chemotherapy unless the lesion is on the weight-bearing area with an intermediate risk or even a high risk of impending fracture. Meanwhile, in patients with a poor prognosis, therapy is usually palliative and should avoid repeated surgeries. (10, 12)

3.9 Prognosis

The prognosis in PBL is determined by age, gender, race, tumor site, staging and given therapies.(2) PBL patients with DLBCL are mostly treated with chemotherapy and radiotherapy with a 5-year survival rate reaching 70% in adult patients and tend to have a good prognosis.(12,13) In other studies according to Jadidi, et al Survival rate 3 years even higher, reaching 63-84%. (3) Patients with DLBCL have a better prognosis, especially in Murphy's stage I or II.(8)

An analytical study from Surveillance, Epidemiology and End Results (SEER) involving 1500 adult PBL patients diagnosed from 1973-2005 obtained survival rates for 5 and 10 years of 58% and 45%. Meanwhile, in the multivariate analysis conducted, only patients with young age and localized disease were independent predictors of survival, with a 5-year survival rate decreasing at older age by 87% in patients diagnosed with age <30 years, 74% at the age of 30-59 years and 45% at the age > 60 years.(12)

Similar to the data above, Noh, et al Stated that the survival rate improves with age or pathological fractures that improve with combination chemotherapy.(4) This suggests that a better prognosis is associated with younger age, localized disease, lower IPI score, type of DLBCL and a good response to therapy.(41-43) Meanwhile, old age > 60 years, higher IPI score, poor therapeutic response, multifocal bone involvement and non-germinal center subtypes have a prognosis that tends to be worse.(44,45)

In contrast to DLBCL, PBL with ALCL type has a worse prognosis, reaching <43.1% 5-year survival rate. Noh, et al in their study stated that prognostic factor for ALCL can be determined by calculating Anaplastic Lymphoma Kinase (ALK).(4) ALCL patients with positive ALK are mentioned to have a better prognosis than patients with negative ALK, with the 5-year survival rate for positive ALK being 70-86% versus 30-49% respectively.(19) Several reports state that the prognosis of PBL with ATL is almost similar to that of ATL

in general, and it is better if surgical removal of the affected part is performed.(13)

3.10 Complications

The worst complication of PBL is spinal cord compression, which occurs in nearly 16% of cases of PBL, followed by osteolysis and resultant hypercalcemia in 5-10% of initial presentation of patients.(9)

4. Conclusions

PBL is a rare case and is dominated by the histopathology of DLBCL. The difficulty found in diagnosing patients with PBL is that the symptoms are not very specific in that the patient often complains of bone pain and can find complaints of swelling in the affected lesions. Also, although rare, other complaints such as B symptoms can appear in the patient. This causes the diagnosis of primary bone lymphoma to be a challenge in itself both in determining the clinical and supporting examination results.

Until now, the standard of support carried out is in the form of FDG PET / CT examination which can be used to determine the diagnosis, staging, and also the prognosis of the disease. However, the use of the first line of investigation is a plain radiograph. The standard therapies are R-CHOP and radiotherapy, with biopsy being the standard in determining the diagnosis based on the histopathology of the disease.

Operative action is limited to biopsy and fracture stabilization / prophylaxis is required. However, surgery can be prioritized for isolated lesions, but it is still necessary to consider non-invasive therapy first.

To prevent a worse prognosis and complications, early diagnosis should be made immediately. Because PBL is classified as a rare disease, there are still no randomized trials that show alternative therapies for patients who suffer from it. Most retrospective studies report a variety of therapies given to patients with PBL. Therefore, it requires further study.

5. Acknowledgments

The Authors are responsible for this study and also reports there is no conflicts of interest in this work.

6. Declarations

Conflict of Interest: The author reports no conflicts of interest in this work.

Funding Source: None

Author Contribution: All authors contribute in concepting, designing, conduct the study, prepare the manuscript and agree for this final version of manuscript to be submitted to this journal.

References

- [1] Annibali O, Fabbriani G, Tafuri M, Massarotti M, Sedati P, Tomarchio V, et al. Primary bone lymphoma of the talus: A challenging diagnosis. *Tumori*. 2017;103(Suppl 1):S62–5.
- [2] Wang HH, Dai KN, Li AB. A Nomogram Predicting Overall and Cancer-Specific Survival of Patients with Primary Bone Lymphoma: A Large Population-Based Study. *Biomed Res Int*. 2020;2020.
- [3] Jadidi J, Behzadi F, Sighary M, Alshal M, Kolla S, Lehto SA. Primary bone lymphoma of patella: A case report and review of literature. *Radiol Case Reports*. 2019;14(12):1561–5.
- [4] Noh BJ, Han CS, Park JS, Lee J, Kim YW, Park YK. ALK-positive anaplastic large-cell lymphoma with primary bone involvement: A rare case and review of the literature. *Malays J Pathol*. 2018;40(2):161–7.
- [5] Ben Ayed C, Laabidi S, Said N, Afrif M, Ahmed S Ben, Boussen H. Primary bone lymphoma: Tunisian multicentric retrospective study about 32 cases. *TunisieMedicale*. 2018;96(5):269–72.
- [6] Ibrahim I, Haughom BD, Fillingham Y, Gitelis S. Is Radiation Necessary for Treatment of Non-Hodgkin's Lymphoma of Bone? Clinical Results With Contemporary Therapy. *ClinOrthopRelat Res*. 2016;474(3):719–30.
- [7] Li L, Liu G, Zhu L, Li T. Primary bone lymphoma of the thoracic vertebra in a patient with metastatic lung cancer. *Clin Imaging*. 2020;64(1):119–23.
- [8] Paul MR, Kuo DJ. Challenges of assessing response to therapy in non-Hodgkin's lymphoma of the bone. *BMJ Case Rep*. 2018;2018:1–4.
- [9] Bindal P, Desai A, Delasos L, Mulay S, Vredenburgh J. Primary Bone Lymphoma: A Case Series and Review of Literature. *Case Rep Hematol*. 2020;2020:1–6.
- [10] Steffner RJ, Jang ES, Danford NC. Lymphoma of bone. *JBJS Rev*. 2018;6(1):1–11.
- [11] Shabbir S. Epidemiological features of Lymphoma in Pakistan. *Pure Appl Biol*. 2019;8(1):977–94.
- [12] Batia T, Yassin MA, Mudawi DS, Hamid OA, Abdalhadhi AMA. Primary Bone Lymphoma in Axial Skeleton in a Middle-Aged Female Presented as Recurrent Anemia. *Case Rep Oncol*. 2020;13(1):276–80.
- [13] Kato H, Koga M, Kobayashi H, Maki H, Ikemura M, Kurokawa M, et al. Primary bone adult T cell lymphoma with multiple skeletal lesions and debilitating painful osteolysis: a case report. *Osteoporos Int*. 2020;6–10.
- [14] Okuyucu K, Ozaydin S, Alagoz E, Ozgur G, Ince S, Oysul FG, et al. Prognosis estimation under the light of metabolic tumor parameters on initial FDG-PET/CT in patients with primary extranodal lymphoma. *RadiolOncol*. 2016;50(4):360–9.
- [15] Rosenberg AE. WHO classification of soft tissue and bone, fourth edition: Summary and commentary. *CurrOpinOncol*. 2013;25(5):571–3.
- [16] Kanaya M, Endo T, Hashimoto D, Endo S, Takemura R, Okada K, et al. Diffuse large B-cell lymphoma with a bulky mass in the cranial vault. *Int J Hematol*. 2017;106(2):147–8.
- [17] Beal K, Allen L, Yahalom J. Primary bone lymphoma: Treatment results and prognostic factors with long-term follow-up of 82 patients. *Cancer*. 2006;106(12):2652–6.
- [18] Demircay E, Hornicek FJ, Mankin HJ, Degroot H. Malignant lymphoma of bone: A review of 119 patients tumor. *ClinOrthopRelat Res*. 2013;471(8):2684–90.
- [19] Tuck M, Lim J, Lucar J, Benator D. Anaplastic large cell lymphoma masquerading as osteomyelitis of the shoulder: An uncommon presentation. *BMJ Case Rep*. 2016;2016:1–4.
- [20] Kuriyama T, Kawano N, Yamashita K, Kikuchi I. Two cases of primary adult T-cell leukemia/lymphoma of bone: case reports and a review of the literature. *Int J Hematol*. 2016;104(3):392–5.
- [21] Li X, Xu-Monette ZY, Yi S, Dabaja BS, Manyam GC, Westin J, 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 SurgPathol*. 2017;41(10):1309–21.
- [22] Milks KS, McLean TW, Anthony EY. Imaging of primary pediatric lymphoma of bone. *PediatrRadiol*. 2016;46(8):1150–7.
- [23] Alexandra J. Borst, MD, 1 Lisa J. States, MD, 2 Anne F. Reilly, MD, 1 and Susan R. Rheingold M, 1*. Determining Response and Recurrence in Pediatric B-Cell Lymphomas of the Bone. *Pediatr Blood Cancer*. 2013;60:1281–6.
- [24] Jamshidi K, Jabalameli M, Hoseini MG, Bagherifard A. Stage IE Primary Bone Lymphoma: Limb Salvage. *Arch Bone Jt Surg*. 2015;3(1):39–44.
- [25] Warren, C. Phillips MD, Susan, Kattapuram V, M.D., Daniel, et al. Primary Lymphoma of Bone: Relationship of Radiographic Appearance and Prognosis. 1982;285–90.
- [26] Murphey MD, Kransdorf MJ. Primary Musculoskeletal Lymphoma. *RadiolClin North Am* [Internet]. 2016;54(4):785–95. Available from: <http://dx.doi.org/10.1016/j.rcl.2016.03.008>
- [27] Liu Y. The role of 18F-FDG PET/CT in staging and restaging primary bone lymphoma. *Nucl Med Commun*. 2017;38(4):319–24.
- [28] Pakos EE, Fotopoulos AD, Ioannidis JPA. PET for Evaluation of Bone Marrow Infiltration in Staging of Lymphoma: *J Nucl Med*. 2005;46(6):958–63.
- [29] Luigi Rigacci, Sofia Kovalchuk VB, Puccini B, Lara Mannelli, Gemma Benelli CD, Pupi1, Alberto AB. The use of Deauville 5-point score could reduce the risk of false-positive fluorodeoxyglucose-positron emission tomography in the posttherapy evaluation of patients with primary bone lymphomas. 2018;17.
- [30] Swords RT, Anguita J, Higgins RA, Yunes AC, Naski M, Padmanabhan S, et al. A prospective rAnDomised study of a rotary powered device (OnControl) for Bone marrow aspiration and biopsy. *J ClinPathol*. 2011;64(9):809–13.
- [31] Held G, Zeynalova S, Murawski N, Ziepert M, Kempf B, Viardot A, et al. Impact of rituximab and radiotherapy on outcome of patients with aggressive B-cell lymphoma and skeletal involvement. *J ClinOncol*. 2013;31(32):4115–22.
- [32] Pfreundschuh M, Kuhnt E, Trümper L, Österborg A, Trneny M, Shepherd L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results

- of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2011;12(11):1013–22.
- [33] Bonnet C, Fillet G, Mounier N, Ganem G, Molina TJ, Thiéblemont C, et al. CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: A study by the Grouped'Etude des Lymphomes de l'Adulte. *J ClinOncol.* 2007;25(7):787–92.
- [34] Lehnert N, Krämer I, Saadati M, Benner A, Ho AD, Witzens-Harig M. Analysis of prognostic factors in patients with newly diagnosed diffuse large B-cell lymphoma and skeletal involvement. *BMC Cancer.* 2017;17(1):1–7.
- [35] Juweid ME, Cheson BD. Role of positron emission tomography in lymphoma. *J ClinOncol.* 2005;23(21):4577–80.
- [36] Govi S, Christie D, Mappa S, Marturano E, Bruno-Ventre M, Messina C, et al. The clinical features, management and prognosis of primary and secondary indolent lymphoma of the bone: A retrospective study of the International Extranodal Lymphoma Study Group (IELSG #14 study). *Leuk Lymphoma.* 2014;55(8):1796–9.
- [37] Reddy N, Greer JP. Primary bone lymphoma: A set of unique problems in management. *Leuk Lymphoma.* 2010;51(1):1–2.
- [38] Messina C, Ferreri AJM, Govi S, Bruno-Ventre M, Gracia Medina EA, Porter D, et al. Clinical features, management and prognosis of multifocal primary bone lymphoma: A retrospective study of the international extranodal lymphoma study group (the IELSG 14 study). *Br J Haematol.* 2014;164(6):834–40.
- [39] Mondello P, Mian M, Arrigo C, Pitini V. Primary diffuse large B-cell lymphoma of the bone: Bendamustine and rituximab are able to overcome resistant disease. *Springerplus.* 2014;3(1):1–5.
- [40] Chisholm KM, Ohgami RS, Tan B, Hasserjian RP, Weinberg OK. Primary lymphoma of bone in the pediatric and young adult population. *Hum Pathol [Internet].* 2017;60:1–10. Available from: <http://dx.doi.org/10.1016/j.humpath.2016.07.028>
- [41] 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.
- [42] Hayase E, Kurosawa M, Suzuki H, Kasahara K, Yamakawa T, Yonezumi M, et al. Primary Bone Lymphoma: A Clinical Analysis of 17 Patients in a Single Institution. *ActaHaematol.* 2015;134(2):80–5.
- [43] Jawad MU, Schneiderbauer MM, Min ES, Cheung MC, Koniaris LG, Scully SP. Primary lymphoma of bone in adult patients. *Cancer.* 2010;116(4):871–9.
- [44] Wu H, Bui MM, Leston DG, Shao H, Sokol L, Sotomayor EM, et al. Clinical characteristics and prognostic factors of bone lymphomas: Focus on the clinical significance of multifocal bone involvement by primary bone large B-cell lymphomas. *BMC Cancer.* 2014;14(1):1–9.
- [45] Castillo JJ, Beltran BE, Song MK, Ilic I, Leppa S, Nurmi H, et al. The Hans algorithm is not prognostic in patients with diffuse large B-cell lymphoma treated with R-CHOP. *Leuk Res* 2012;36(4):413–7. Available from: <http://dx.doi.org/10.1016/j.leukres.2011.12.012>