CASE REPORT

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Evaluation of primary bone lymphoma and the importance of positron emission tomography

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Primary lymphoma of the bone is an extremely rare tumor in the form of non-Hodgkin lymphoma or Hodgkin lymphoma. The majority of primary bone lymphomas are non-Hodgkin lymphoma, of which the most common subtype is diffuse large cell lymphoma. Patients can present with pain, swelling or pathologic fracture. Definitive diagnosis is made after biopsy examination. Treatment consists of chemotherapy, radiotherapy and surgery. We report 3 male patients who presented with pain and swelling. Involvement was in the distal femur, proximal fibula and iliac crest in all patients. Patients were diagnosed with non-Hodgkin lymphoma in biopsy examination and underwent chemotherapy. The patient with distal femoral involvement underwent distal femoral resection prosthesis. Another patient with involvement of the fibular head experienced foot drop and delayed wound healing. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography revealed complete response to the treatment. Patients are in remission and continue schooling.

Key words: Bone; lymphoma; positron emission tomography.

Lymphoma ranks third among childhood tumors in terms of incidence after leukemia and central nervous system tumors. Lymphomas can be divided into two sub-groups: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Both can involve the bone. In the USA, HL comprised 40% and NHL 60% of childhood lymphomas.[1] The prognosis of HL is much better, particularly in the early stages, and has a tendency to be localized when found in the bone. Non-Hodgkin lymphoma may be encountered as systemic disease including bone involvement or as a limited disease only involving the bone.

Primary bone lymphoma is defined as a bone or bone marrow type of limited lymphoma with no systemic disease findings on first presentation. The vast majority of primary bone lymphomas are NHL and the most common subtype is diffuse large cell lymphoma (DLCL).[2,3] This is an extremely rare group among lymphoid malignancies and it is difficult to determine the true incidence. Primary bone lymphoma is seen at a rate of less than 1% within NHL and comprises 7% of all primary bone malignancies and 4 to 5% of extranodal lymphomas.[4]

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We present 3 cases of NHL that showed a full metabolic response to treatment.

Case report

Case 1– A 16-year-old male presented with complaints of pain and swelling in the left knee after having struck his knee approximately one month previously. In the physical examination, there was swelling in the left knee and sensitivity on palpation and movement. Laboratory test results were as follows: C-reactive protein (CRP) of 11.7 mg/L (normal range: 0 to 3.5), sedimentation (Sed) of 37 mm/hr (normal range: 0 to 10), lactate dehydrogenase (LDH) of 462 U/L (normal range: 0 to 200) and alkaline phosphatase (ALP) of 326 U/L (normal range: 0 to 390). Other tests were normal.

A lytic permeative lesion and swelling in the surrounding soft tissue were observed on the distal metaphysis of the left femur on direct radiograph (Fig. 1a).

T1-weighted magnetic resonance imaging (MRI) showed a hypointense lesion of approximately 6x5x4.5 cm which thinned the cortex and caused intensity changes consistent with edema in the soft tissue. T2-weighted images revealed a heterogeneous lesion on hyperintense and contrast images and widespread bone marrow edema.

Upon initial diagnosis of osteosarcoma, a Jamshidi biopsy was taken. As sufficient pathology samples could not be obtained, an open biopsy was performed. Due to regional malignancy, bone cement was applied (Fig. 1b). Pathology results showed DLCL. The Pediatrics Department was consulted. Positron emission tomography (PET), bone scintigraphy, abdominal-pelvic ultrasonography (USG) and thoracic computed tomography (CT) were applied for staging of the disease.

Pre-chemotherapy fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-PET/CT) revealed activity (SUV max: 23.68) in a destructive lesion, showing cortical and pericortical spread (Fig. 2a-d).

Increased peripheral expansive osteoblastic activity with a photopenic center was observed in the distal epiphysis and metadiaphyseal area in technetium 99m (Tc-99m) methylene diphosphonate (MDP) bone scintigraphy.

In the biopsy, a tumor consisting of atypical lymphoid cells of different sizes, sporadically rich in chromatin and with vesicular nucleus was observed to have completely infiltrated the soft tissue samples. In the immunohistochemical examinations, the tumor cells showed strong positive staining with LCA, CD20 and CD79a. Evaluation results of the patient were accepted as Risk Group 3. Two cycles of the Berlin-Frankfurt-Münster (BFM) group protocol AA-BB-CC were applied. The medications in the protocol, doses, means of application and days are shown in Table 1.[5]

Fluorine-18-fluorodeoxyglucose distribution at the pathological level, consistent with full metabolic response was not observed in the post-chemotherapy ^{18}F-PET/CT (Fig. 2e-h).

Tests showed that the patient was in remission and surgical resection was performed to prevent the risk of fracture. Distal femoral resection prosthesis was applied (Fig. 3a). In the histopathological examination, the tested material did not contain any residual tumor and the patient did not develop any complications throughout the 17-month follow-up period. The patient was in remission and continued to attend school.

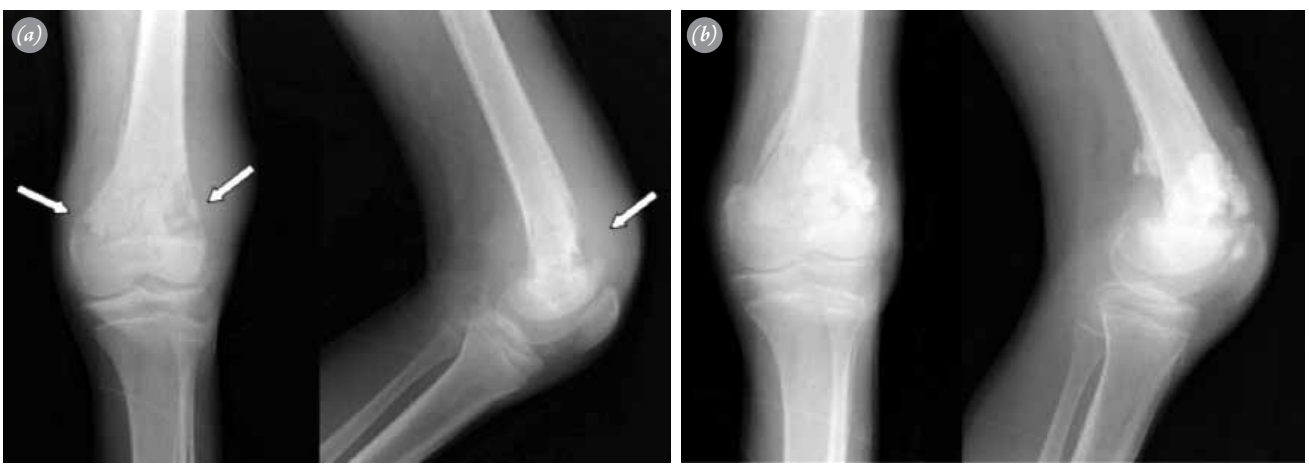

Fig. 1. **(a)** Lytic permeative appearance in the left femur distal metaphysis on direct radiograph (Case 1). **(b)** Image of the distal femur with bone cement after open biopsy (Case 1).

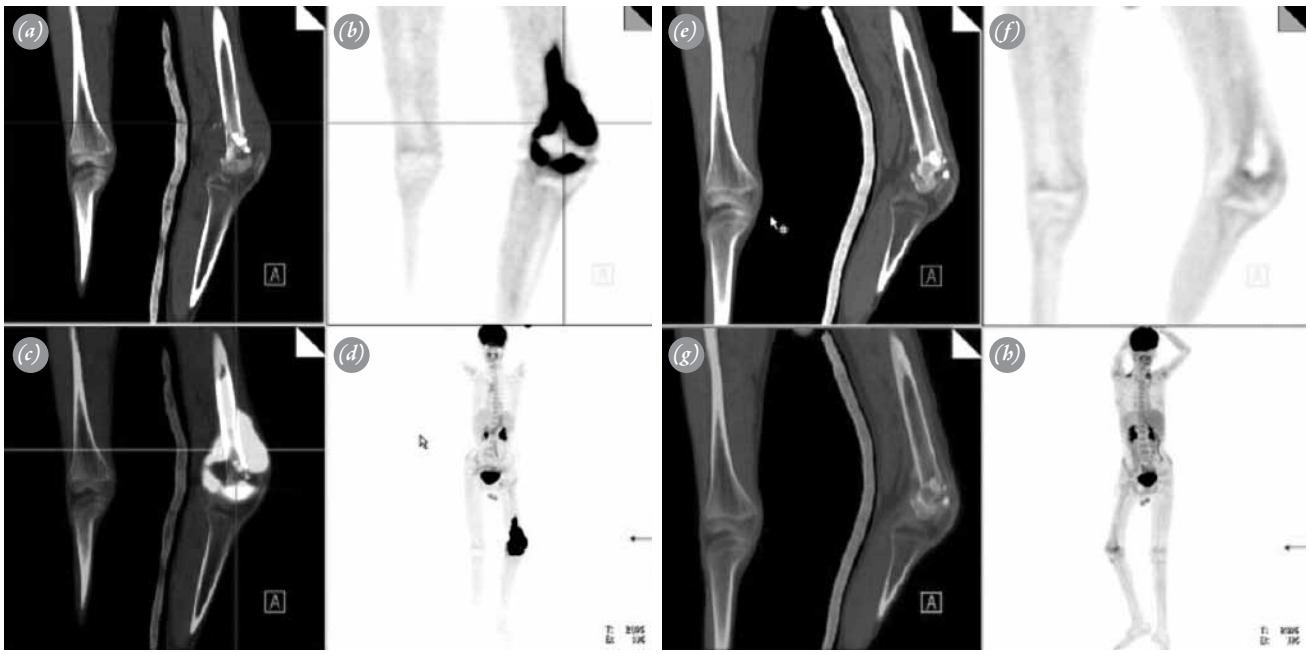

Fig. 2. **(a)** CT, **(b)** PET, **(c)** ^{18}F-PET/CT and **(d)** maximum intensity projection (MIP) images of Case 1. Severe hypermetabolic lesion was observed in the soft tissue of the distal femur (SUV max: 23.68). **(e)** CT, **(f)** PET, **(g)** ^{18}F-PET/CT and **(h)** maximum intensity projection (MIP) images of Case 1. Fluorodeoxyglucose distribution was consistent with full metabolic response following chemotherapy.

Case 2– A 6-year-old male patient presented at our clinic with complaints of swelling in the lateral right knee. Swelling was present in the physical examination. LDH levels were 232 U/L while other test results were within normal ranges.

In the proximal right fibula, a lytic permeative appearance and swelling in the surrounding soft tissue was observed on radiographs (Fig. 3b).

A mass approximately 2.5x2x4.5 cm in size with periosteal boundaries, characterized by cortical destruction was observed on MRI. Different images showing heterogeneous contrast were reported as the appearance of a mass with malignant properties.

A Tru-cut biopsy was performed. The pathology result reported a small round cellular tumor (primarily Ewing's sarcoma or lymphoma) but no clear differentiation could be made. An open biopsy was then performed (Fig. 3c) and the pathology result was reported as high degree B-cell lymphoma (NHL). The Pediatrics Department was consulted and bone scintigraphy and thoracic CT were applied for staging of the disease.

Technetium 99m MDP bone scintigraphy showed increased osteoblastic activity and bleeding consistent with primary bone tumor.

T(8:14) was detected in chromosome analysis.

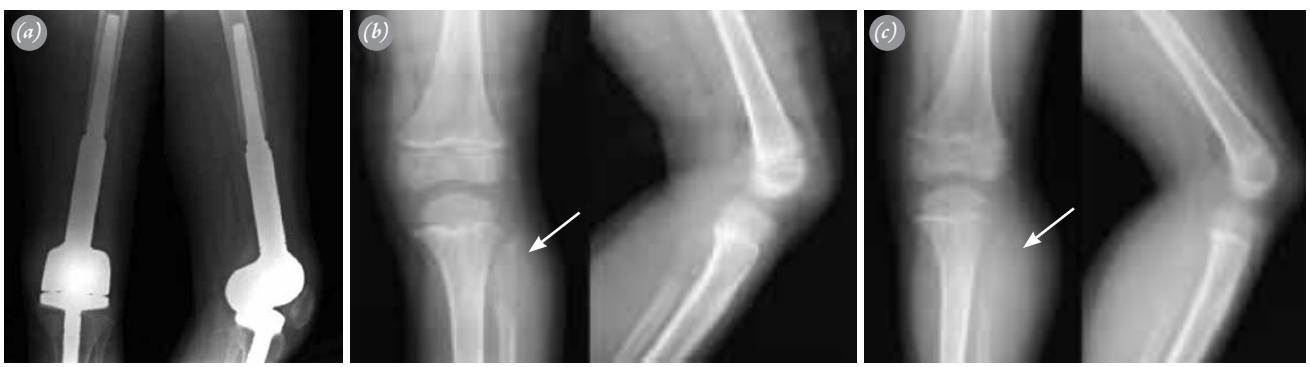

Fig. 3. **(a)** Distal femur resection prosthesis in Case 1. **(b)** Lytic permeative appearance in the proximal right fibula on direct radiograph (Case 2). **(c)** Direct radiograph image of the lesion following open biopsy (Case 2).

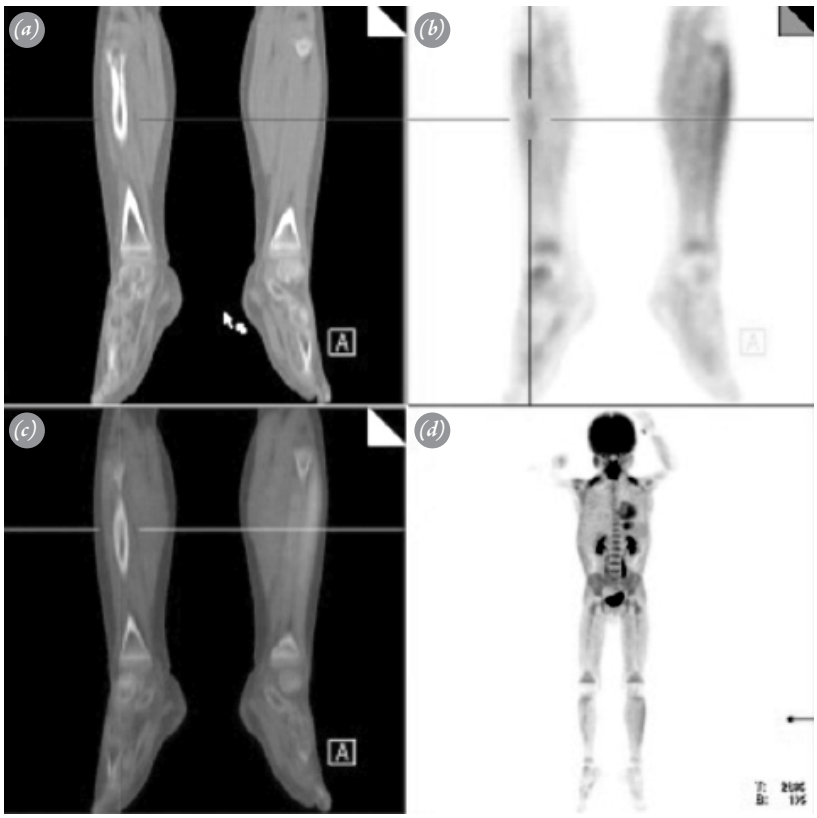

Fig. 4. **(a)** CT, **(b)** PET, **(c)** ^{18}F-PET/CT and **(d)** maximum intensity projection (MIP) images of Case 2. Fluorodeoxyglucose distribution was consistent with full metabolic response following chemotherapy.

The BFM protocol was then applied (Table 1).[5] Post-chemotherapy ^{18}F-PET/CT was consistent with a full metabolic response (Fig. 4). During the follow-up period, wound healing was delayed and drop-foot developed. A splint was applied to hold the ankle in a neutral position for the drop-foot. Throughout the 10-month follow-up, the patient remained in remission and continued to attend school.

Case 3– A 6-year-old male presented with complaints of pain in the right leg starting approximately 6 weeks previously and subsequent limp. In the physical examination, there was swelling, minimally increased heat and hyperemia in the right iliac wing. Results of laboratory testing were as follows: CRP: 92 mg/L, Sed: 77 mm/hrs, LDH: 478 U/L and ALP: 157 U/L. Other test results were normal.

Radiographs revealed increased irregular opacity, destruction and swelling in the surrounding soft tissue in the right iliac wing (Fig. 5).

Signal changes extending to the level of the acetabulum, leading to the periosteal reaction in the bone extending to the adjacent sacroiliac joint and the fat planes between the iliacus and gluteus medius muscles and in the soft tissue component were observed on T1-weighted hypointense and T2-weighted hyperintense MRI. These findings were interpreted as Ewing's sarcoma.

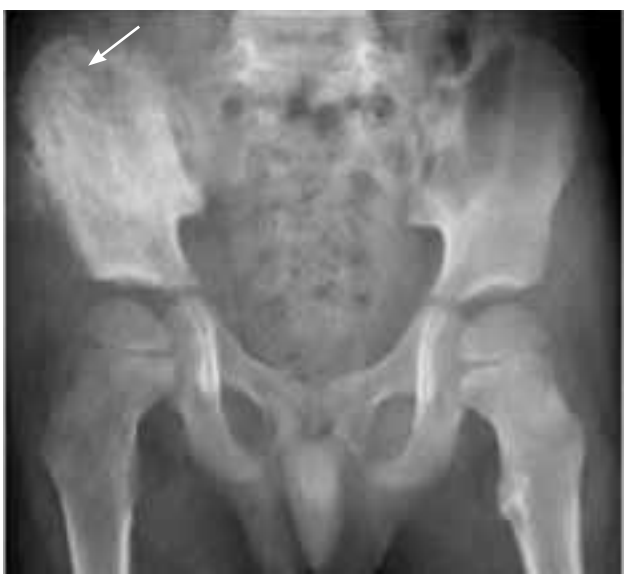

Fig. 5. Heterogeneous appearance in the right iliac wing on direct radiograph (Case 3).

An open biopsy was performed and the pathology result was reported as B-cell malignant NHL. The Pediatrics Department was consulted. PET, bone scintigraphy, thoracic CT and abdominal USG were applied for staging of the disease.

Pre-chemotherapy ^{18}F-PET/CT revealed activity (SUV max: 14.75) in the lesion mass, consistent with a primary bone tumor leading to destruction in the acetabulum and iliac bone surrounding the right iliac wing (Fig. 6a, b).

There was increased heterogeneous MDP and bleeding in the lesion mass contained in the peripheral soft tissue component on Tc-99m MDP bone scintigraphy. This was consistent with a primary malignant bone tumor in the tissue and bone phase.

The BFM protocol was applied (Table 1).[5] Post-chemotherapy ^{18}F-PET/CT was consistent with a full metabolic response (Fig. 6c, d). The Radiation Oncology Department was consulted and radiotherapy was not recommended for the patient. The patient was in remission and continued to attend school throughout the 16-month follow-up.

Discussion

Primary bone lymphoma is defined as a lymphoma restricted to the bone or bone marrow without any findings of systemic disease on first presentation and a period of at least 4 to 6 months between the start of skeletal findings and development of systemic disease. Parker and Jackson[6] defined the lesion as 'reticulum cell sarcoma of the bone' in 1939. The frequency at which it is seen reaches a peak in the 5th and 6th decades of life (mean age: 44 years) and the male/female ratio is approximately 1.5:1.[7] The cases presented here are much younger than the average age (two patients were 6 years old and one 16) and all were male. Primary bone lymphoma is defined as malignant lymphoid infiltration of the bone regardless of whether there is bone cortex and/or surrounding soft tissue involvement and there should be no infiltration of distant organ structures or regional lymph glands.[8,9]

Patients often present with localized bone pain, swelling, pathological fractures. Lesion masses are rare. In patients with spinal involvement, there may be nerve root and cord compression. Symptoms may be mild or

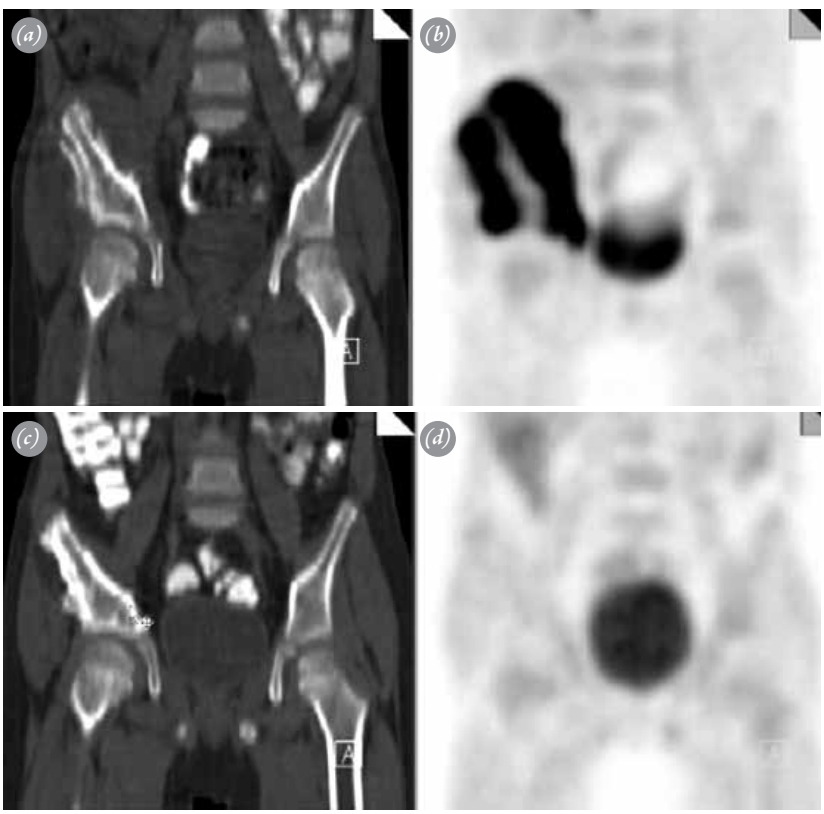

Fig. 6. Images of the right iliac wing of Case 3 before chemotherapy. **(a)** Lesion showing widespread increased sclerosis on CT and **(b)** severe hypermetabolic activity observed on ^{18}F-PET/CT. Images of the right iliac wing of Case 3 after chemotherapy. **(c)** Continued intense sclerotic distribution on CT and **(d)** no observation of FDG distribution at the pathological level on ^{18}F-PET/CT.

Table 1. The Berlin-Frankfurt-Münster chemotherapy protocol.

BFM	Medication	Dose	1st day	2nd day	3rd day	4th day	5th day
AA	Dexamethasone, oral/iv	10 mg/m^2	+	+	+	+	+
	Ifosfamide, iv	800 mg/m^2	+	+	+	+	+
	Methotrexate, iv	5 mg/m^2	+				+
	Methotrexate, it	6 mg	+				+
	Cytarabine, it	15 mg	+				+
	Prednisolone, it	5 mg	+				+
	Vincristine, iv (maximum 2 mg)	1.5 mg/m^2	+				
	Cytarabine, iv (at 12 hr intervals)	150 mg/m^2				+	+
	Etoposide, iv	100 mg/m^2				+	+
BB	Dexamethasone, oral/ iv	10 mg/m^2	+	+	+	+	+
	Cyclophosphamide, iv	200 mg/m^2	+	+	+	+	+
	Methotrexate, iv	5 mg/m^2	+				
	Methotrexate, it	6 mg	+				+
	Cytarabine, it	15 mg	+				+
	Prednisolone, it	5 mg	+				+
	Vincristine, iv (maximum 2 mg.)	1.5 mg/m^2	+				
	Doxorubicin, iv	25 mg/m^2				+	+
CC	Dexamethasone, oral/ iv	20 mg/m^2	+	+	+	+	+
	Vindesine, iv (maximum 5 mg/m^2)	3 mg/m^2	+				
	Cytarabine, iv (at 12 hr intervals)	2 mg/m^2	+	+			
	Etoposide, iv	150 mg/m^2			+	+	+
	Methotrexate, it	12 mg					+
	Cytarabine, it	30 mg					+
	Prednisolone, it	10 mg					+

It: intrathecal, iv: intravenous

Table 2. Patient data.

	Case 1	Case 2	Case 3
Age	16	6	6
Location	Distal femur	Fibular head	Iliac wing
Gender	Male	Male	Male
Pathological diagnosis	Non-Hodgkin lymphoma Large cell	Non-Hodgkin lymphoma Large cell	Non-Hodgkin lymphoma Large cell
LDH (U/L) (normal range: 0-200)	462	232	478
Manner of diagnosis	Open biopsy after Jamshidi biopsy	Open biopsy after Tru-cut biopsy	Open biopsy
SUV max value			
Pre-treatment	23.68	–	14.75
Post-treatment*	Negative	Negative	Negative

*Lesion SUV max values post-treatment were found to be at the physiological level

severe. The cases reported here presented with pain and swelling. The disease involves the pelvis, spine, ribs and the long bones, primarily the femur (the most common extremity), tibia and humerus. Involvement of more than one bone is seen in approximately 10 to 40% of cases.[10] All areas of the bone may be involved but central involvement is most common. Associated with bone marrow distribution, the metaphysis is the area primarily affected.[11-13] In the cases presented here, involvement of the iliac wing was observed in 1 case, the proximal

fibula in 1 and the distal femur in one.

Radiographic findings comprise widespread lytic permeation in the cortical bone (70%) or sclerotic bone response accompanying lytic permeation (28%).[14] The cortex may thicken but periosteal reaction is rarely seen.[7] Lesions may be better defined in radiological and nuclear medicine examinations with the visualization of bone marrow and/or soft tissue involvement. While lesion dimensions can be better observed on bone scintigraphy, it is important that diagnosis is based on a whole body evaluation which allows for the determination of potential distant bone metastasis. Lesion dimensions can be more accurately defined on MR evaluation of bone marrow and soft tissue distribution. In the cases presented here, soft tissue involvement was revealed on MRI.

In staging studies, full blood count and serum biochemistry, thoracic, abdominal and pelvic CT, whole body bone scintigraphy and bone marrow biopsy with ^{18}F-PET/CT can be used.

A functional imaging method based on glucose metabolism, ^{18}F-PET/CT plays an important role in grading at the diagnosis stage of lymphomas, the evaluation of response to treatment and prognosis, and the determination of residual disease and recurrence.[15,16] The method is based on the principle that tumors have increased involvement of glucose and its metabolism.

Treatment depends on the stage of the disease at the time of diagnosis, making the accuracy of the imaging method used for staging of great importance.[17] Previous studies have shown ^{18}F-PET/CT to be effective in the staging of lymphomas and treatment.[18,19] When evaluating the role of ^{18}F-PET/CT on staging, Partridge et al.[20] determined a change in the disease stage in 21 of 44 patients (47%) and Naumann et al.[21] reported a change in 18 of 88 patients (20%). Wirth et al. determined an increase in disease stage in 14% of cases after a ^{18}F-PET/CT scan and a change of treatment in 18%.[22]

The timing of treatment response and prognosis evaluation with ^{18}F-PET/CT is important.[23] While evaluation is generally made after treatment completion, Kostakoglu et al.[24] determined that the results of ^{18}F-PET/CT in 13 patients after one cycle of chemotherapy were correlated to the findings after treatment completion. In both HL and NHL, ^{18}F-PET/CT applied after one cycle of chemotherapy has a high prognostic significance in terms of defining the treatment. It has been reported that the observation of continuing high FDG involvement after one cycle of chemotherapy indicates a high possibility of relapse, while negative results are an indicator of long-term remission.[23]

The determination of recurrence before clinical indicators become evident offers the patient the possibility of early treatment. However, false-positive and false-negative results are possible. Tissues in new bone formation following treatment may lead to false-positive findings on ^{18}F-PET/CT and should be confirmed with other imaging methods.[25] In an analysis of 5 studies, Reinhardt et al. reported recurrence rates of 81.5% in ^{18}F-PET/CT positive HL, 10% in negative HL, 100% in positive NHL and 16.5% in negative NHL.[26]

Due to the mixed cell structure of the lesion, the diagnosis of lymphoma is pathologically difficult. However, the possibility of malignant lymphoma is high in tumors involving the bone without trabecular destruction. Generally, the cytoplasm of the cells is narrow. Diagnosis is made histologically from nuclei with a folded appearance and indentation and nucleoli evidently stained pink. As a histological subtype, diffuse B-cell lymphoma has been determined to have a better prognosis at an early age. Cell type can be defined with immunohistochemical investigations in the form of positive reticulin stain, negative keratin and negative PAS. The cases presented here were all diagnosed with NHL. The diagnosis was made with open biopsy in 2 cases (as a clear diagnosis could not be made after Tru-cut biopsy in one and Jamshidi biopsy in another case) and with Jamshidi biopsy in 1 case. All round cell lesions of the bone were included in the differential diagnosis and differentiation must be made with Ewing's sarcoma as the most important of these.

Treatment consists of a multidisciplinary approach including radiotherapy, chemotherapy and surgery. Patients with a primary bone lymphoma (with approximately 55% chance of 5-year survival) have a better prognosis than those with systemic disease (with less than 25% chance of 5-year survival).[7] The primary treatment for lymphoma is chemotherapy, which was applied to all cases presented here. Compared to adult cases, very good survival rates are obtained with chemotherapy in childhood. Localized control is generally provided by radiotherapy. Surgical intervention is very important for diagnosis, but rarely required in treatment. However, it is necessary for the treatment of actual or possible pathological fractures.[11] A tumor resection prosthesis was applied in one of the presented cases because of the risk of fracture and for local control. Patient data are shown in Table 2.

In conclusion, for patients with complaints of mild pain, normal radiograph findings together with abnormal MR and scintigraphy findings, lymphoma should be

considered in the differential diagnosis. In primary bone lymphomas, ^{18}F-PET/CT is a modality which can be used for increased accuracy in the decision making process at both diagnosis staging and treatment evaluation.

Conflicts of Interest: No conflicts declared.

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