

CASE REPORT

ALK-positive anaplastic large-cell lymphoma with primary bone involvement: A rare case and review of the literature

Byeong-Joo NOH¹, Chung Soo HAN², Ji Seon PARK³, Juhie LEE⁴, Youn Wha KIM⁴ and Yong-Koo PARK⁴

¹Department of Pathology, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung, 25440, Korea, ²Orthopedic Surgery, and ³Radiology, Kyung Hee University Medical Center, Seoul 02447, Korea and ⁴Department of Pathology, School of Medicine, Kyung Hee University, Seoul 02447, Korea.

Abstract

Primary bone lymphoma (PBL) is an uncommon type of extranodal lymphoma involvement. An anaplastic large-cell lymphoma (ALCL) is an extremely rare type of PBL, and it remains unclear whether ALCLs that primarily involve the bone exhibit favourable or unfavourable biological behaviour, and whether they are similar to ALCLs in general, or not. We reported a case of ALK-positive ALCL with primary bone involvement, and reviewed the clinicopathological features of 22 previously reported cases. An ALCL with primary bone involvement mostly affects younger patients with a preponderant towards the involvement of axial-bone. The prognosis of an ALCL that primarily involves bone is unfavourable, compared with PBL generally. The ALK-positive ALCLs in PBLs had less decedents than the ALK-negative ALCLs with a statistical non-significance ($p=0.198$).

Keywords: Anaplastic large-cell lymphoma, primary-bone lymphoma, ALK

INTRODUCTION

Anaplastic large-cell lymphoma (ALCL) is a distinct clinicopathological type of non-Hodgkin lymphoma. According to the World Health Organization (WHO) classification (2008, 4th edition), the diagnosis is confined to those of the T- or null-cell type, showing pleomorphic lymphoid cells with frequent horseshoe-shaped nuclei, abundant cytoplasm, and the expression of CD30. Anaplastic lymphoma kinase (ALK) expression has been considered as an important favourable prognostic factor for ALCL.¹

Primary bone lymphoma (PBL) is an uncommon type of the extranodal involvement of lymphoma, and most PBLs are diffuse large-B-cell lymphomas (DLBCLs). The ALCL type of PBL is extremely rare and it therefore remains unclear whether an ALCL involving one and more primary bony sites exhibits favourable or unfavourable biological behaviour, and whether they are similar to ALCL in general, or not. In addition, the clinical significance of ALK expression in an ALCL with primary bone lesion requires further investigation.

Herein, we report a case of ALK-positive ALCL with primary bone involvement and describe the clinicopathological characteristics of this entity. We also discuss the prognostic significance of ALK expression in the ALCLs with primary bone involvement.

CASE REPORT

A 34-year-old male patient presented with right hip pain and was admitted. He was bed-ridden condition owing to hip-joint immobility. A physical examination revealed a joint contracture and immobility of the right hip, and there was no evidence of splenomegaly or lymphadenopathy. The initial laboratory studies showed mild leukocytosis with predominant neutrophils and mild anaemia (WBC: $11.7 \times 10^3/\mu\text{L}$, RBC: $4.9 \times 10^6/\mu\text{L}$, Hb: 13.9 g/dL, Platelet: $4.1 \times 10^5/\mu\text{L}$), and other laboratory results were as follows: the C-reactive protein (3.8 mg/dL) was elevated and the liver function tests such as GOT (13 U/L) and GPT (8 U/L) were within normal range.

An initial pelvis anteroposterior view revealed an ill-defined osteolytic lesion with a mild

Address for correspondence: Yong-Koo Park, MD, Department of Pathology, School of Medicine, Kyung Hee University, #23 Kyungheedaero, Dongdaemun-gu, Seoul 02447, Korea Tel: +82-2-958-8742; Fax: +82-2-958-8730; email: ykpark0204@gmail.com

cortical thinning of the superior acetabular rim (Fig. 1A). In a follow-up radiograph taken 1 week later, the extent of the osteolytic lesion was increased and the cortical thickness of the acetabular rim was more thinned (Fig. 1B). In a follow-up radiograph taken 3 weeks after the first radiograph, the inner rim of the pelvis was broken with soft-tissue bulging (Fig. 1C). An axial CT image demonstrated a relatively well-defined, expansile, osteolytic lesion with a non-uniform and non-continuous periosteal reaction at the right ileum (Fig. 1D). A reformatted coronal CT image also revealed a heterogenous osteolytic lesion and cortical discontinuity regarding an extraosseous mass protruding into the pelvic cavity (Fig. 1E). On a PET CT image, the osteolytic lesion (the medial aspect of the iliac lesion) was identified as a hypermetabolic lesion with a maximum SUV of 5.68, whereas the osseous remodelling with cortical thickening (the lateral aspect of the lesion) showed no significant uptake. Another lesion with a mild uptake of FDG was noted in the inguinal region, suggesting regional lymphadenopathy (Fig. 1F-G). No specific lesion was identified except the pelvic bone considered as a primary site on the PET CT image.

A CT-guided bone biopsy was inadequate for diagnosis because the main lesion was not included, and a bone-marrow biopsy was insufficient for diagnosis. As the clinical impression was highly suggestive of a malignant tumour such as osteosarcoma, chondrosarcoma, and lymphoma, the patient underwent a right hemipelvectomy.

Gross examination of pelvic bone showed an ill-defined, whitish infiltrative lesion of the periacetabular area with irregular thickening, fusion of the cancellous bone trabeculae and myxoid change (Fig. 2A).

Microscopic examination showed large atypical pleomorphic cells that were mainly clustered around vessels with a variable admixture of plasma cells, lymphocytes, histiocytes, and neutrophils. The large atypical cells revealed abundant levels of eosinophilic cytoplasm and eccentric nuclei with multiple small nucleoli, as well as occasionally large nucleoli (Reed-Sternberg cell-like feature); the characteristic hallmark cells (horseshoe-shaped or doughnut cell) were also noted (Fig. 2B).

In terms of immunohistochemistry, the large atypical cells showed a membranous immunostaining for CD30, a positive cytoplasmic and nuclear pattern for ALK, a weak positive for CD3, and a focal positive for EMA (Fig.

2C-F); however, a negative immunoreactivity was shown for CD20, CD79 α , CD138, and EBV, respectively. The proliferative index (Ki-67) is approximately 80%. The cytogenetic rearrangement of the monoclonal T-cell receptor-gamma was not identified. The ALK rearrangement at chromosome 2p23 was performed by fluorescence *in situ* hybridisation (FISH) analysis using a dual-colour break-apart probe; however, adequate signalling was not obtained owing to the decalcified tissue.

Taking into consideration the morphological, immunohistochemical, and radiological findings, the diagnosis was consistent with ALK-positive, anaplastic large-cell lymphoma. Pre- or post-operative chemotherapy was not performed due to his poor general condition; 3 months after the surgery, the patient died from postoperative infection.

DISCUSSION

The definition of PBL requires further elucidation. According to the previous version of the WHO classification, the fundamental concept is by exclusion with a definite bone origin should be regarded as PBL. PBL is defined as: 1) a single bone lesion, with or without the involvement of regional lymph nodes; 2) multiple bone lesions without lymph-nodal or visceral diseases.¹

PBLs are not common, as they constitute approximately 5% of extranodal lymphomas and 3% to 7% of all malignant bone tumours.² The most common histopathological PBL subtype is the DLBCL, accounting for 78% to 85% of PBLs; further, ALCLs of PBLs (3% to 5%) are extremely rare.³⁻⁶ To our knowledge, ALCLs with primary bone involvement—those fulfilling the previously mentioned PBL definition, as well as showing typical immunohistochemical and molecular findings in the available English-language literature—are present in only 22 cases including our present case, and these findings are summarised in Table 1. Most reports with large cases of PBLs revealed a slight male prevalence (male/female ratio = 1.3 to 1.6) and a median age at diagnosis ranging between 42 years old and 63 years old.^{3,4,6,7} Based on the overall cases of PBLs, ALCLs with one and more primary bone lesions showed a tendency toward the male sex (male/female ratio = 6.0) and younger patients (median age = 34 years; average age = 39.1 years). The most frequently involved sites for ALCL are axial bones such as the pelvic bone and vertebrae, and this is similar to PBL generally (Table 1).^{4,6,7}

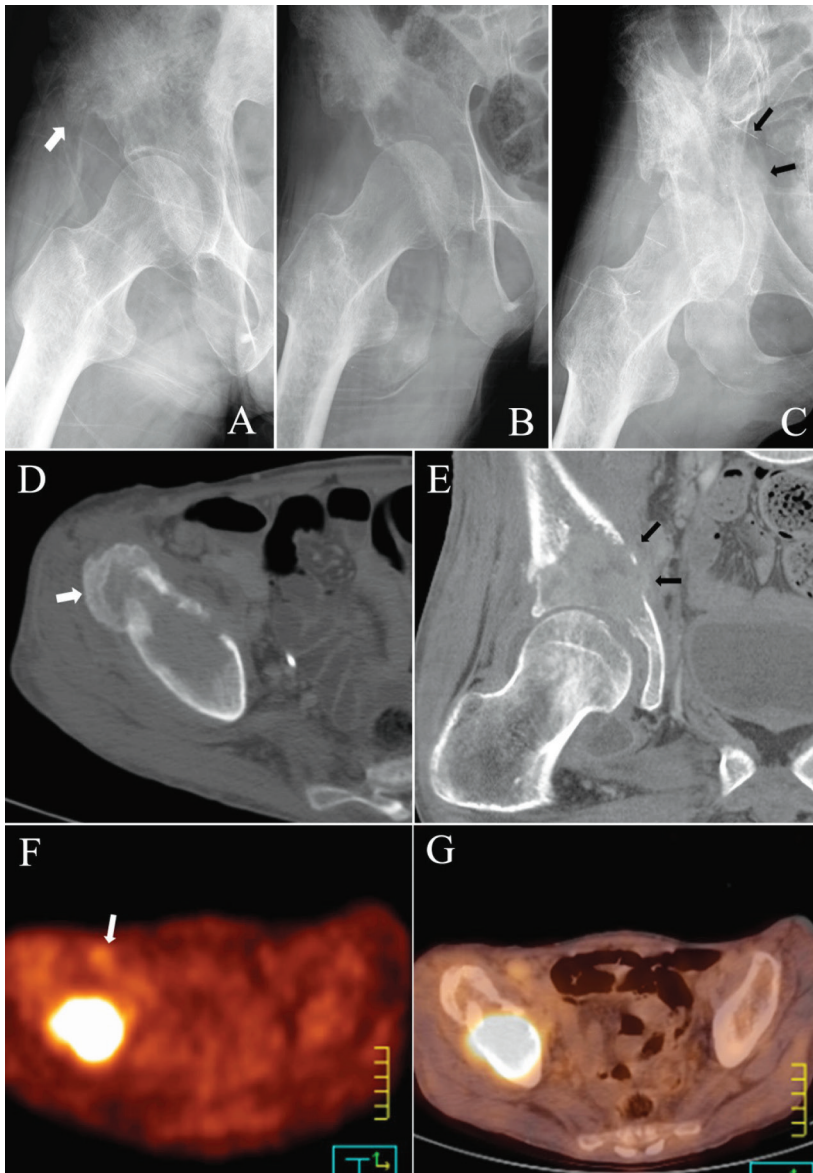


FIG. 1: Radiologic findings. (A) Initial pelvis anteroposterior view revealed an ill-defined osteolytic lesion with a mild cortical thinning of the superior acetabular rim and a sclerotic lesion with a cortical buttress (white arrow) involving the right lower ilium. (B) On the follow-up radiograph taken 1 week later, the extent of the osteolytic lesion was increased and the cortical thickness of the acetabular rim was more thinned. (C) On the follow-up radiograph taken 3 weeks after the first radiograph was taken, the inner rim of the pelvis was broken with soft-tissue bulging (black arrows). (D) The axial CT image displays a relatively well-defined, expansile, osteolytic lesion with a non-uniform and non-continuous periosteal reaction at the right ilium; note the osseous remodelling and cortical thickening with a new bone formation (white arrow) at the lateral aspect of the lesion. (E) The reformatted coronal CT image also reveals a heterogeneous osteolytic lesion and a cortical discontinuity with an extraosseous mass (black arrows) protruding into the pelvic cavity. (F-G) On a PET CT image, the osteolytic lesion (the medial aspect of the iliac lesion) was identified as a hypermetabolic lesion with a maximum SUV of 5.68, whereas the osseous remodelling with cortical thickening (the lateral aspect of the lesion) showed no significant uptake. Another lesion with a mild uptake of FDG was noted in the inguinal region, suggesting regional lymphadenopathy.

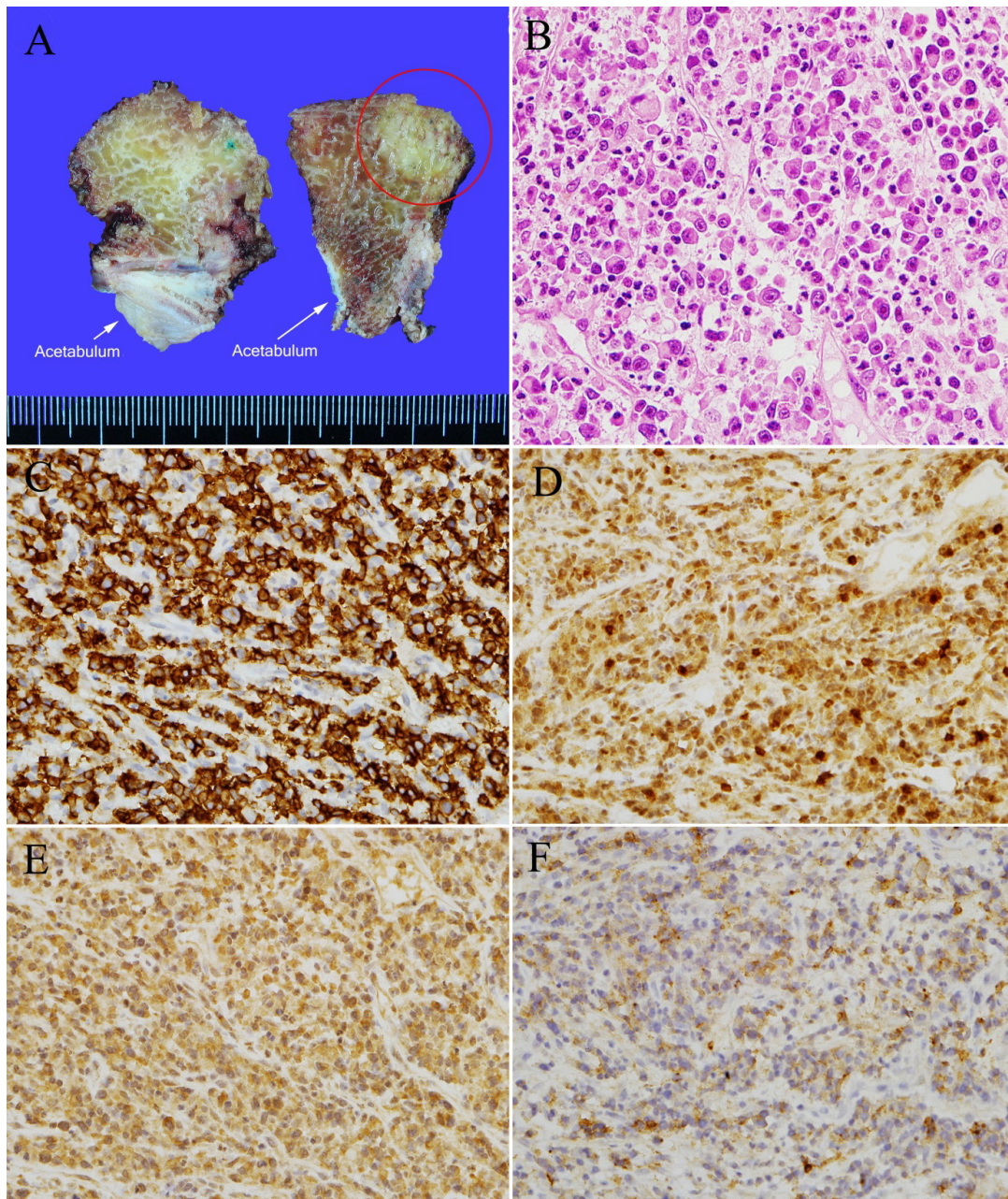


FIG. 2: Gross and histopathologic findings. (A) The gross pathologic examination of the pelvic bone showed an ill-defined, whitish infiltrating lesion (red circle) of the periacetabular area in the background of the irregular thickening and fusion of the cancellous bony trabeculae with a myxoid change. (B) Under microscopy (haematoxylin eosin staining, x400), there were large atypical pleomorphic cells in the infiltrative lesion that are mainly clustered around the vessels with a variable admixture of plasma cells, lymphocytes, histiocytes, and neutrophils. The large atypical cells revealed abundant levels of eosinophilic cytoplasm and eccentric nuclei with multiple small nucleoli, as well as occasionally large nucleoli (Reed-Sternberg cell-like feature). Characteristic hallmark cells (horseshoe-shaped or doughnut cells) were also noted. On immunohistochemistry, the large atypical cells showed a positive membranous immunoreactivity for CD30 (C), a cytoplasmic and nuclear immunohistochemical pattern for anaplastic lymphoma kinase (ALK) (D), a weak positive for CD3 (E), and a focal positive for EMA (F) (C-F magnifications, x400).

TABLE 1: Review of reported cases of anaplastic large-cell lymphomas with primary bone involvement

Age	Sex	Sites	Multiplicity	Staging	Cell type	ALK	Treatment	Prognosis	Ref.
3	M	Sacrum, vertebrae	Poly.	IVB,M	T	Pos.	CThx	AED, 15 ms	¹⁰
9	M	Femur	Mono.	IE	T	Pos.	CRThx	DOD, 1 yr	¹⁰
14	M	Rib	Mono.	IE	T	Pos.	CThx after surgery	NED, 11 yrs	¹⁰
71	M	Rib	Mono.	IE	T	Pos.	CThx after surgery	NED, 3 yrs	¹¹
NA	NA	Skull	Mono.	IE	NA	Pos.	CThx	NED, 12 ms	¹²
27	F	Ileum	Mono.	IE	T	Pos.	CRThx	NED, 8 ms	⁹
63	M	Vertebrae	Mono.	IE	T	Pos.	CThx	DOD, 3 ms	⁹
21	M	Vertabrae, rib, ileum, skull	Poly.	IVB	Null	Pos.	CRThx after surgery	DOD, 8 m	⁸
37	M	Ileum	Mono.	IE	T	Pos.	CRThx	DOD, 23 m	¹³
29	M	Ileum	Mono.	IE	T	Pos.	CThx and BMT	DOD, 18 m	¹³
14	M	Pelvis	Mono.	IE	NA	Pos.	NA	NED, 11 ms	⁷
24	F	Ileum	Mono.	IE	Null	Neg.	CThx	DOD, 1 yr	⁹
30	M	Ileum, rib	Poly.	IVB	Null	Neg.	CThx and MBT	AED, 2 yrs	⁹
50	M	Vertabrae (T6, L2, L3, S1)	Poly.	IVB	Null	Neg.	CRThx	AED, 2 yrs	⁹
60	F	Sternum	Mono.	IVM	T	Neg.	CThx	Died of other cause, 8 ms	¹⁴
60	M	NA	NA	IVM	T	Neg.	CThx	DOD	¹⁵
32	M	Pelvis, maxilla	Poly.	IVE	T	Neg.	CRThx	LTF	⁷
80	M	Rib	Mono.	IE	T	Neg.	CRThx	DOD, 5 ms	⁷
48	M	Pelvis, spine, femur, rib	Poly.	IVE	T	Neg.	RThx	DOD, 2 ms	⁷
69	M	Spine, BM	Poly.	IVE	T	Neg.	CRThx	DOD, 3 ms	⁷
46	M	Pelvis, spine	Poly.	IVE	T	Neg.	CRThx	DOD, 2 ms	⁷
34	M	Pelvis	Mono.	IE	T	Pos.	Surgery	Died of other cause	Our case
Aver.: 39.1	M: 18 F: 3	Pelvis: 12 Vertabrae: 7	Mono.: 13 Poly.: 8	I: 12 IV: 10	T: 16 Null: 4	Pos.: 12 Neg.: 10		Five-year OS: Less than 42.1%	
Median: 34		Rib: 6 Femur: 2 Others: 4							

Abbreviations: AED: alive with disease; ALK: anaplastic lymphoma kinase; Aver.: average age; BMT: bone marrow transplantation; CThx: Chemotherapy; CRThx: Chemoradiation therapy; DOD: Died of disease; F: female; LTF: loss to follow-up; M: male; Mono.: monostotic; NA: not available; NED: no evidence of disease; Neg.: negative; Null: null-cell type; OS: overall survival; ms: months; Poly.: polyostotic; Pos.: positive; Ref.: reference; T: T-cell type; yrs: years

Some studies with large series of PBLs have demonstrated that the most important prognostic factor regarding PBL is the international prognostic index (IPI), while a high radiation dose (more than 40 Gy), chemotherapy, and complete remission are also associated with favourable outcomes^{4,6}; however, the overall survival rate has rapidly improved independently of age, IPI score, or pathological fracture by virtue of the introduction of the existing combinational chemotherapy treatments.⁵ The prognosis of ALCLs in PBLs, however, has been

shown as contradictory.^{8,9} From reviewing only the previously reported PBL cases with primary bone involvement (Table 1), the ALCL type showed poor biological behaviour because the 5-year overall survival (OS) of the ALCL type of PBL is suggestive of less than 43.1%, as shown in Table 1, compared with a 62% to 76% 5-year OS for PBL.^{3,4,6} In an evaluation of the prognostic behaviour of the ALCL, *ALK* rearrangement or expression is the most substantial factor, and *ALK* expression in a conventional ALCL has been considered as one of the favourable

TABLE 2: Clinicopathological factors according to survival rate for 22 cases of anaplastic large-cell lymphoma with primary bone involvement as reported in the literature

Clinicopathological factors		Alive (%)	Dead (%)	P-value
Age	< 60	7 (50.0)	7 (50.0)	0.243
	> 60	1 (20.0)	4 (80.0)	
Sex	Male	6 (37.5)	10 (62.5)	0.735
	Female	1 (50.0)	1 (50.0)	
Multiplicity	Monostotic	5 (45.5)	6 (54.5)	0.914
	Polyostotic	3 (42.9)	4 (57.1)	
Staging	I	5 (45.5)	6 (54.5)	0.729
	IV	3 (37.5)	5 (62.5)	
Cell subtype	T-cell type	4 (30.8)	9 (69.2)	0.482
	Null-cell type	2 (50.0)	2 (50.0)	
ALK	Negative	2 (25.0)	6 (75.0)	0.198
	Positive	6 (54.5)	5 (45.5)	

ALK: anaplastic lymphoma kinase

*Pearson’s Chi-square tests were conducted to analyse the relationship between the clinicopathological factors and survival rates. Three cases with a loss of follow-up or other causes of death were abbreviated for the analysis.

prognostic factors.¹ We conducted statistical analyses (Pearson’s Chi-square tests) to examine the relationship between the clinicopathological parameters and the survival of previously reported ALCLs with primary bone involvement in Table 2. The ALK-positive ALCLs in PBLs had less decedents than the ALK-negative ALCLs with a statistical non-significance ($p=0.198$). The other clinicopathological factors such as age, sex, multiplicity, staging, and cell subtype do not affect the ALCL survival rate (Table 2).

To date, the treatment of choice is combinational chemotherapy for early-stage PBLs, whereby CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the first regimen. Surgery is limited only to patients with a destructive weight-bearing bone lesion or a pathological fracture owing to post-surgical complications and delayed chemotherapy. Irradiation therapy on its own, or administered after chemotherapy, has not improved the prognostic outcome^{3,5}, furthermore, post-chemotherapy irradiation has been associated with a better survival outcome only in cases of polyostotic PBL.²

In conclusion, an ALCL with primary bone involvement mostly affects younger patients with a preponderant to the axial-bone sites such as the pelvis and vertebrae. The prognosis of an ALCL that primarily involves bone is unfavorable, compared with PBL generally.

Conflicts of interest: The authors of this paper have no conflicts of interest regarding the corresponding funding sources to declare.

REFERENCES

1. Santini-Araujo E, Kalil RK, Bertoni F, Park Y-K. Tumors and Tumor-Like Lesions of Bone. Verlag, London, United Kingdom: Spinger; 2015. 385-411 p.
2. Messina C, Christie D, Zucca E, Gospodarowicz M, Ferreri AJ. Primary and secondary bone lymphomas. Cancer Treat Rev. 2015; 41: 235-46.
3. Zinzani PL, Carrillo G, Ascani S, Barbieri E, Tani M, Paulli M, *et al.* Primary bone lymphoma: experience with 52 patients. Haematologica. 2003; 88: 280-5.
4. 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: 129-35.
5. Alencar A, Pitcher D, Byrne G, Lossos IS. Primary bone lymphoma--the University of Miami experience. Leuk Lymphoma. 2010; 51: 39-49.
6. Cai L, Stauder MC, Zhang YJ, Poortmans P, Li YX, Constantinou N, *et al.* Early-stage primary bone lymphoma: a retrospective, multicenter Rare Cancer Network (RCN) Study. Int J Radiat Oncol Biol Phys. 2012; 83: 284-91.
7. Gianelli U, Patriarca C, Moro A, Ponzoni M, Giardini R, Massimino M, *et al.* Lymphomas of the bone: a pathological and clinical study of 54 cases. Int J Surg Pathol. 2002; 10: 257-66.
8. Suzukawa K, Kojima H, Mori N, Mukai HY, Hori M, Komeno T, *et al.* Anaplastic large-cell lymphoma

- of null-cell type with multiple bone involvement. *Ann Hematol.* 1998; 77: 287-90.
9. Nagasaka T, Nakamura S, Medeiros LJ, Juco J, Lai R. Anaplastic large cell lymphomas presented as bone lesions: a clinicopathologic study of six cases and review of the literature. *Mod Pathol.* 2000; 13: 1143-9.
 10. Bakshi NA, Ross CW, Finn WG, Valdez R, Ruiz R, Koujok K, *et al.* ALK-positive anaplastic large cell lymphoma with primary bone involvement in children. *Am J Clin Pathol.* 2006; 125: 57-63.
 11. Lones MA, Sanger W, Perkins SL, Medeiros LJ. Anaplastic large cell lymphoma arising in bone: report of a case of the monomorphic variant with the t(2;5)(p23;q35) translocation. *Arch Pathol Lab Med.* 2000; 124: 1339-43.
 12. Parker JR, Lopez-Terrada D, Gresik MV, Vogel H, Baumgartner JE, Finegold MJ. Neutrophil-rich anaplastic large cell lymphoma of the skull presenting after head trauma. *Pediatr Dev Pathol.* 2001; 4: 397-401.
 13. Jones D, Kraus MD, Dorfman DM. Lymphoma presenting as a solitary bone lesion. *Am J Clin Pathol.* 1999; 111: 171-8.
 14. Szomor A, Al Saati T, Delsol G, Kereskai L, Szijarto Z, Losonczy H. Primary bone marrow T-cell anaplastic large cell lymphoma with triple M gradient. *Pathol Oncol Res.* 2007; 13: 260-2.
 15. Gudgin E, Rashbass J, Pulford KJ, Erber WN. Primary and isolated anaplastic large cell lymphoma of the bone marrow. *Leuk Lymphoma.* 2005; 46: 461-3.