

Primary Lymphoma of Bone -Survival and Prognosis-

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Background: Primary lymphoma of bone is a rare disease. There is yet no systematical evaluation of primary lymphoma of bone in Korea. Here we report our experience of sixteen cases with primary lymphoma of bone focusing on the survival.

Methods: Sixteen cases, collected for 13 years, were evaluated on the clinical presentation, histologic subtype, stage and treatment outcomes of the primary bone lymphoma.

Results: The most common presenting complaint was bone pain. Malignant lymphoma of bone involved a wide variety of sites, the most prevalent site of which in this study was the spine. Most of the cases were in the diffuse large B-cell category. The clinical stage of lymphoma was IEA in two cases, IIEA in three cases, IVEA in five cases and IVEB in three cases. All treated cases received systemic chemotherapy and ten cases among them were treated with combined modality therapy. Median overall survival was not reached after median follow-up period of 28 months and five-year overall survival rate was 54%.

Conclusion: More promising therapeutic strategies are needed for survival improvement on more accumulated cases.

Key Words : Bone and Bones, Lymphoma, Survival, Prognosis

INTRODUCTION

Primary lymphoma of bone (PLB) was previously called reticulum cell sarcoma. It accounts for only 5% of the primary bone tumor and constitutes approximately 3~15% of all extranodal non-Hodgkin's lymphoma (NHL)^{1, 2}. Although the diagnosis of primary lymphoma of bone was first suggested by Oberling in 1928, the disease was established as an entity in 1939 by Parker and Jackson³, who reported 17 cases. In general, lymphoma presenting in bone is a sign of disseminated (stage IV) disease, but it may be a true solitary lesion, defined as involvement of single extralymphatic organ or site (stage IE).

There is yet no systematical evaluation of PLB in

Korea. Here we report our experience of 16 cases with PLB focusing on the survival.

MATERIALS and METHODS

Sixteen cases with PLB at Yonsei Medical Center between January 1988 and July 2001 were retrospectively evaluated.

Four cases presented with the solitary lymphoma of bone which was defined as lymphoma presenting in an osseous site with no evidence of disease elsewhere for at least 6 months after diagnosis. Nine cases presented with multifocal bone involvement, that is, lymphoma in two or more osseous sites only, without evidence of soft tissue or nodal involvement. And three cases presented with simultaneous bone and nodal or soft tissue involvement.

The histopathological classification was done according to the WHO classification.

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Patients were retrospectively staged according to the Ann Arbor staging system. The work-up for staging included complete physical examination, complete blood count, chemistry panel, computerized tomographic scan of neck, chest and abdomen, whole body bone scan, gallium scan, PET scan and bone marrow aspiration and biopsy. A skeletal magnetic resonance image was obtained in five cases. CT scan was also performed in the abdomino-pelvic area in 13 cases, the chest in 13, the neck in 13 and the brain in 10. Whole body bone scan was done in 13 cases and gallium scan was done in 10. Bone marrow study was done in 15 cases.

Response to treatment was recorded as complete remission (CR), partial remission (PR) or no response (NR). CR was defined as a complete disappearance of all clinical evidence of lymphoma by physical examination and imaging studies; PR as a reduction of more than 50% in the sum of the products of perpendicular diameters of all measurable masses with no new lesion; NR as stable or progressive disease except CR or PR.

The overall survival time was calculated from the date of diagnosis until the date of the last follow-up or death. The disease-free survival time was calculated from the date of documentation of CR until the date of the last follow-up in a disease-free state. Survival curves were calculated according to the Kaplan-Meier method and comparison of survival was performed using the log-rank test.

RESULTS

Age and sex

Of the 16 cases studied, ten were male and six were female with a ratio of 1:0.6 (Table 1). The median age was 44 years (range, 1~71 years).

Clinical manifestation

The most common presenting complaints were bone pain (Table 2). Three cases presented with B symptoms. Neurologic symptom (voiding difficulty) was present in two cases. Pathologic fracture was present in one case.

Site of involvement

PLB involved a wide variety of sites (Figure 1). Femur and thoracic spine, which appeared in 6 cases, were the most commonly involved sites at diagnosis. The PLB most often presented in the irregular bone (T spine, femur, L spine, ileum and C spine in order).

Table 1. Clinical, histological and therapeutic parameters of the patients

	Number of cases	Percentage (%)
Sex		
Male	10	62
Female	6	37
Age		
> 60 years		25
≤ 60 years	12	75
Stage		
I	2	12
II	3	19
III	0	0
IV	8	50
Uncertain	3	19
Histology (WHO classification)		
Diffuse follicular center	1	6
T cell rich B cell	1	6
Diffuse large cell	10	62
Precursor B lymphoblastic leukemia/lymphoma	1	6
Hodgkin's disease (mixed cellularity)	1	6
Peripheral T cell, not otherwise specified	1	6
Unspecified	1	6
Cell type		
T cell	1	6
B cell	14	88
Unspecified	1	6
International Prognostic Index score		
Low (0-1)	4	25
Low intermediate (2)	5	31
High intermediate (3)	0	0
High (4-5)	4	25
Unknown	3	18
Therapy		
Chemotherapy only	3	18
Radiotherapy and chemotherapy	8	50
Radiotherapy only	0	0
Surgery, radiotherapy and chemotherapy	2	12
No treatment	3	18
Response to therapy		
Complete remission	7	53
Partial remission	3	23
No response	3	23

Table 2. Presenting signs and symptoms

Symptom and sign	Number of cases
Pain of bone	10
Mass	3
Fever	2
Voiding difficulty	2
Fracture	1
Swelling	1

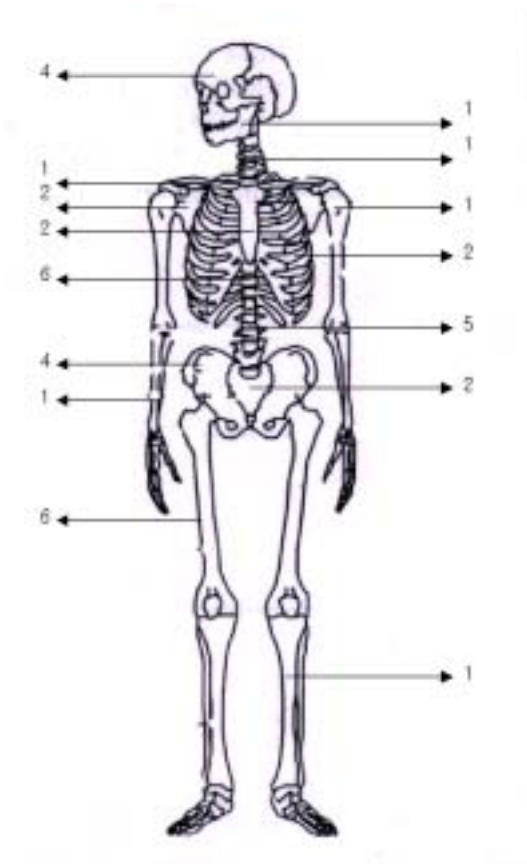


Figure 1. Site of involvement. The sites of involvement are included in the figure; femur 6 cases; thoracic spine 6 cases; lumbar spine 5 cases; skull 4 cases; ileum 4 cases; rib 2 cases; sacrum 2 cases; scapula 2 cases; sternum 2 cases; clavicle 1 case; humerus 1 case; mandible 1 case; cervical spine 1 case; tibia 1 case; ulna 1 case

Histological classification

Using the WHO classification, most of the cases were

in the diffuse large B-cell category (Table 1). One case was classified as Hodgkin’s disease. T-cell immunophenotype was noted in one case.

Clinical staging

The clinical stage of lymphoma was IEA in two cases, IIEA in three cases, IVEA in five cases and IVEB in three cases (Table 1). Stage II diseases had lymph node involvement near the site of the bone localization.

Response to treatment, survival and prognostic factors

Among treated thirteen cases, three cases were treated with only chemotherapy, eight cases with radiotherapy and chemotherapy and two cases with surgery, radiotherapy and chemotherapy. Radiotherapy was delivered by either linear accelerator or cobalt-60. Radiation dose ranged from 30 to 60 Gy with a median dose of 45 Gy.

Seven cases (54%) of all treated cases achieved CR, three cases (23%) PR and three cases (23%) NR (Table 1). The median follow-up period was 28 months (range, 2~108 months). The median disease-free survival of seven cases which achieved CR was not reached (range, 15~97 months) and five-year disease-free survival rate was 85%. The median overall survival of all treated cases was not reached (range, 2~108 months) and five-year overall survival rate was 54% (Figure 2).

There was no significant difference of overall survival according to stage, performance, LDH and IPI (International Prognostic Index) scores (Figure 3).

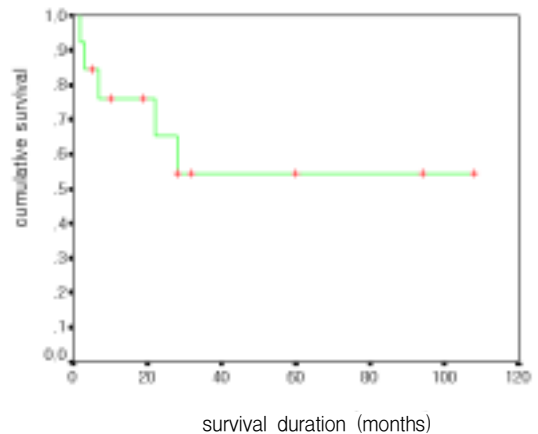


Figure 2. Overall survival (months) of treated patients (N=13)

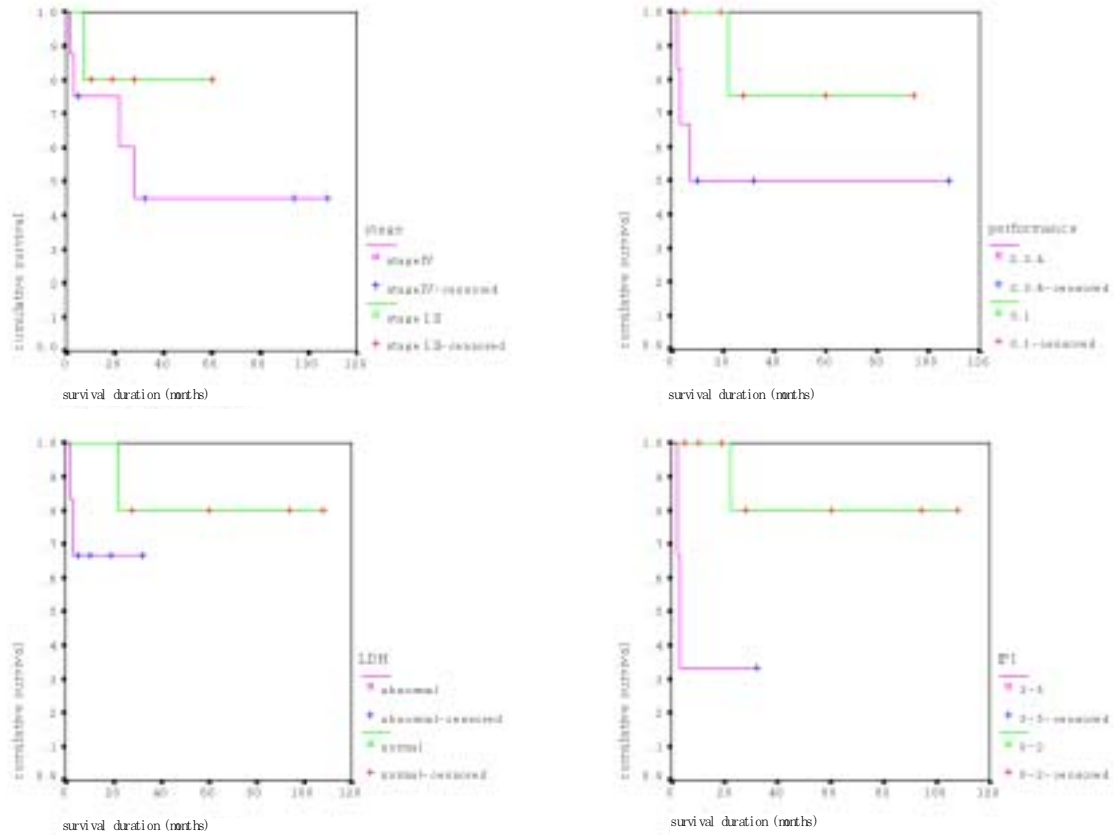


Figure 3. Comparison of overall survival according to stage (stage I, II vs. stage IV, $p=0.392$), performance (ECOG 0, 1 vs. 2-4, $p=0.1974$), LDH (normal vs. abnormal, $p=0.3235$) and IPI score (0-2 vs. 3-5, $p=0.0537$)

DISCUSSION

PLB (previously called reticulum cell sarcoma) is a rare lymphoid malignancy and accounts for approximately 3~15% of all extranodal non-Hodgkin's lymphoma^{2, 4}. The true incidence of PLB is difficult to assess, as the site of origin is unclear in patients with disseminated lymphoma and bony involvement. In Korea, PLB accounts for about 1.3~1.6% of all malignant lymphoma, 1.4~1.8% of non-Hodgkin's lymphoma and 3.7% of extranodal non-Hodgkin's lymphoma^{5, 6}, while there was no report of primary lymphoma of bone in Hodgkin's disease. Song et al.⁷ reported the first case of primary bone lymphoma associated with acquired immunodeficiency syndrome in Korea. During this study, primary lymphoma of bone accounted for 1% (16/1,600 cases) of malignant lymphoma, 1% (15/1,448 cases) of non-Hodgkin's lymphoma and 0.65% (1/152 cases) of

Hodgkin's disease in Severance Hospital.

In general, lymphoma presenting in bone is a sign of disseminated (stage IV) disease. But, occasionally, it may be a true solitary lesion, defined as involvement of single extralymphatic organ or site (stage E)⁸⁻¹⁰. Reimer et al.⁸ reported that only one of twelve presenting with bone lymphomas had a true solitary lesion. Sweet et al.⁹ reported that 50% of so called solitary lesions were associated with disease elsewhere. He emphasized that all cases with a presumed solitary lymphoma of bone should undergo a thorough evaluation for other involvement. Many studies on primary lymphoma of bone excluded patients with stage IV disease in an effort to eliminate malignancies in which bone involvement is secondary^{11, 12}. In our study, three cases (19%) presented with simultaneous bone and nodal or soft tissue involvement and nine cases (56%) presented with multifocal bone involvement.

Table 3. Summary of clinical characteristics of 16 cases

No	Age /Sex	Site of involvement	Symptom	Symptom duration (months)	Histology (WHO classification)	Stage	Operation	Chemotherapy	Radiation dose (cGy)	Response to induction	Overall survival (months)	Disease-free survival (months)	Current status (cause of death)
1	M/49	Mandible, femur	submandibular mass	3	diffuse follicular center	IVEA		CHOP	4500	CR	94	87	alive
2	M/24	T8, L5, S1 spine, femur, ilium, skull	back pain	1	diffuse mixed small and large B cell (Working formulation)	IVEA		MACOP-B IMVP-16 DHAP Steroid pulse	4000	CR	28	20	death (marrow failure, pneumonia, brain hemorrhage)
3	M/49	Fib, C spine, T spine, L spine, skull	fever	2	T cell rich B cell (large B cell, variant)	IVEB		M-BACOP, IMVP-16, HOAP-Bleo	none	CR	108	97	alive
4	M/20	Clavicle, skull, femur, L1	back pain	4	precursor B lymphoblastic leukemia/lymphoma	IVEB		MACOP-B	none	NR	3		death (parapneumonitis)
5	M/27	T spine, L spine	back pain	10 days	diffuse large B cell	IVEA	laminectomy	CHOP HOAP-Bleo IMVP-16	3550	CR	32	15	alive
6	M/40	ilium	pelvic pain	6	diffuse large B cell	uncertain		none	none		12		death
7	M/47	Humerus, femur, skull, TLS spine, ilium	back pain, voiding difficulty	2	diffuse large B cell	IVEA		CVP	3000	NR	2		death (pneumonia)
8	M/64	Sacrum, sternum	coccyx pain, voiding difficulty	1	diffuse large B cell	uncertain		none	none		15		death (pneumonia)
9	M/29	Sternum, T spine	sternal pain, back pain	3	diffuse large B cell	IVEA		M-BACOP	6000	PR	22		death (PCP pneumonia, AIDS)
10	M/21	Fib, T spine, sacrum, ilium	Fever	1.5	Hodgkins disease (mixed cellularity)	IVEB		ABVD	2520	PR	5		alive
11	F/59	Tibia	tibia pain	1	diffuse large B cell	IIEA	amputation	VCR+ADR+ Eribexin+ Daclizumab	6000	NR	7		death (brain hemorrhage)
12	F/63	Femur	fracture	1 day	diffuse large B cell	uncertain		none	none		3		death (liver cirrhosis, HCC, pneumonia)
13	F/63	Scapula	shoulder mass	4	diffuse large B cell	IIEA		CEOP	4500	CR	19	12	alive
14	F/71	Ulna	elbow pain	12	diffuse large B cell	IIEA		M-BACOP	5040	CR	28	20	alive
15	F/44	Femur	knee pain, swelling	5	diffuse large B cell	IEA		M-BACOP	6000	CR	60	53	alive
16	F/1	Scapula	scapular mass	20 days	peripheral T cell, unspecified	IEA		BECOP	none	PR	10		alive

CR, complete remission; PR, partial remission; NR, no response; PCP, *Pneumocystis carinii* pneumonia; AIDS, acquired immunodeficiency syndrome; HCC, hepatocellular carcinoma; CHOP, cyclophosphamide, adriamycin, vincristine, and prednisolone; MACOP-B, methotrexate, adriamycin, cyclophosphamide, vincristine, prednisolone, and bleomycin; HOAP-Bleo, prednisolone, and bleomycin; IMVP-16: ifosfamide, methotrexate, and etoposide; CVP, cyclophosphamide, vincristine, and prednisolone; CEOP, cyclophosphamide, epirubicin, vincristine, and prednisolone; M-BACOP, methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisolone (dexamethasone); DHAP, dexmethasone, cytarabine, and cisplatin; BECOP, bleomycin, epirubicin, cyclophosphamide, vincristine, prednisolone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine

The peak incidence appears to be in the fifth decade, with a slight preponderance of males over females¹³. In our study, age and sex distribution were similar to other studies (median age at presentation was 44 years and there was a male predominance with a male to female ratio of 1:0⁶). In most of our cases, the initial symptoms were localized bone pain or swelling, as reported by others¹⁴. Pathologic fractures are possible complication of bone lymphoma. Kenan et al.¹⁵ reported 6 cases (30%) with pathologic fracture among 20 cases of primary skeletal lymphoma. In our study there was one case (6.3%) with pathologic fracture.

Malignant lymphoma of bone involved a wide variety of sites as reported by others¹⁵. The most prevalent site in this studies was the irregular bone. In one study, tumor localization within the pelvis or vertebra was associated with a worse prognosis¹⁶, but in our study tumor localization was not a significant prognostic factor.

Although the histomorphologic features of malignant lymphomas of lymph nodes have been extensively studied in relation to prognosis, there are relatively few similar studies of lymphomas of bone^{16, 17}. Most of the lesions were in the diffuse large B-cell category, as other studies¹⁶. Some study revealed that histologic subgroup has no prognostic significance¹⁵, but in one study, immunoblastic lymphoma had a worse prognosis than other large B cell lymphoma subtypes¹⁰. In our study, there was no significant difference in overall survival between histologic grades (data was not shown).

The stage of the disease is the single most important prognostic indicator in malignant lymphoma of bone^{10, 18, 19}. In this study, the 5-year overall survival rate of stage I or II disease was 80% and the 5-year overall survival rate of stage IV disease was 45%. But there was no significant difference between the two groups ($p=0.3920$).

Treatment of bone lymphoma is based on the extent of disease. Stage IE lesions have traditionally been treated with radiotherapy, with which the cure rate is reported up to 90%. Some studies suggested that the outcomes are superior for patients with primary bone lymphoma who are treated with combined modality therapy versus single modality therapy²⁰, while other studies did not detect any difference between treatments²¹. In this study, all treated patients received systemic chemotherapy. And ten cases were treated with combined modality therapy. Of ten cases who were treated with combined modality therapy, six achieved complete remission, but of three cases who were treated with chemotherapy alone one achieved complete remission. But there was

no significant difference in overall survival between treatment modalities ($p=0.66$).

The overall survival of PLB was reported variably by many authors. Bacci et al.²² reported on 30 cases treated for localized PLB over a 10-year period, with overall disease-free survival rate of 88% at a mean follow-up period of 87 months. Mendenhall et al.¹⁸ reported their experience with 11 cases who received combined modality therapy, nine cases who received local radiotherapy alone and one case who received chemotherapy alone. In the study, five-year overall survival rate was 56% and no treatment modality demonstrated any advantage. Susnerwala et al.²³ reported on 39 cases treated for PLB over a 10-year period. In their report, overall and disease-free survival rates at 60 months were 66% and 56%, respectively. Barr et al.²⁴ reported on 17 cases with PLB, overall survival of which was 79%. Heyning et al.¹⁰ reported on 60 cases with PLB which included the disseminated (stageIV) disease. In their report, the five-year overall survival rate was 61%.

The median overall survival in our study was not reached after median follow-up period of 28 months. And our study revealed 54% of five-year overall survival rate. The overall survival of our study was similar or inferior to other studies^{10, 18, 22-24}. Considering that our study included multifocal skeletal lymphomas, the overall survival was considered to be similar to other studies^{10, 18, 22-24}. More promising therapeutic strategies are needed for survival improvement on more accumulated cases.

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