RESEARCH ARTICLE

Stage IE Primary Bone Lymphoma:Limb Salvage for Local Recurrence

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Received: 2 November 2014 *Accepted: 6 December 2014*

Abstract

Background: Primary bone lymphoma or non-Hodgkin lymphoma of bone is a rare disease. There are only a few case series of stage IE of this condition in medical literature. The aim of this study is to determine the rate of survival for stage IE after combined modality treatment, the rate of local recurrence, and the results of limb salvage in cases of local recurrence.

Methods: We collected data from 61 patients with histologically confirmed PBL treated at the Musculoskeletal Oncology Department of our hospital from 2000 to 2010. Retrospective evaluation included demographics, symptoms, tumor locations, outcomes of surgical treatment for local recurrence and survival rates.

Results: All patients received Combined Modality Therapy. Overall,five year survival was 89% and five year disease free survival rate was 78%. Local recurrence occurred in 6 patients during follow up period, which was treated surgically by wide excision and reconstruction. The mean follow-up for the local recurrence group was 36(24-54) months and mortality rate in this group was 17%.

Conclusions: Combined Modality Therapy for stage IE primary bone lymphomaresults in good survival rate. In case of local recurrence, wide excision and reconstruction improves the outcomes.

Key words: Bone, Limb salvage, Local recurrence, Lymphoma

Introduction

Primary Bone Lymphoma (PBL) is an uncommon entity that accounts for 3% of all primary bone malignancies and 5% of extra nodal lymphomas (1). PBL also referred to as primary Non-Hodgkin's lymphomas (NHL) of the bone, is constituted of several subtypes, the most common of which is the diffuse large B cell lymphoma (DLBCL) (2).

Stage IE PBL is a rare subset of this disease that involves only a single bone. After staging evaluations, only one third of PBL are classified as stage IE. Patients with stage IE PBL experience bone pain, which is not usually dependent on exertion. Sometimes, a tender and warm mass is detected on physical examination (3). Rarely, systemic symptoms (malaise, fever and weight loss) are also accompanied by the bone mass. These are some symptoms that may mislead the physician to a diagnosis of osteomyelitis.Pathologic fracture is not uncommon (4).

The standard treatment of stage IE PBL isgenerally based on chemotherapy accompanied by radiotherapy of the involved bone (5). There are a few case series with long-term follow-up of stage IE PBL. While some studies stated that the survival rate was markedly better in patients after chemo-radiotherapy, others reported its poor results (6,7).

In this study, we present our clinical experience confined to stage IEof PBL to make an expressive contribution to the understanding of the presentation, treatment results as well as the outcomes of this tumor. Additionally, we focus on the results of limb salvage surgical approach for cases withlocal recurrence.

Materials & Methods

The Institutional Review Board of our institution approved this study. We reviewedthe medical records of patients who presented to the Musculoskeletal Oncology Department of Shafa Yahyaian Hospital, Iran University of Medical Science, Tehran, Iran, with an initial diagnosis of bone tumor. Sixty-seven patients were identified with

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Table1. Pre treatment patient's characteristics with primary bone lymphoma stage IE

Characteristics	Mean ± SD (%)
Total cases	61(100)
Gender	
Male	35 (57.4)
Female	26 (42.6)
Age (years)	33.4±16.5
Anatomical site of disease	
Femur	21 (32.8)
Distal	14 (66.6)
Proximal	7 (33.4)
Pelvis	13 (20.3)
Ileum	7 (53.8)
Pubis	3 (23.0)
Sacrum	2 (15.3)
Ischium	1 (7.6)
Humeurs	12 (19.6)
Tibia	11 (17.2)
Scapula	3 (4.7)
Fibula	1 (1.6)
Pathology (n=57)	
DLBCL	46(80.7)
DMCL	5(8.7)
SNCL	3(5.25)
IBCL	2(3.5)
Unclassified	2(3.5)
Overall delay to diagnose time (months)	17.88±2.1

DLBCL: diffuse large B cell lymphoma, DMCL: diffuse mixed cell lymphoma, SNCL: small noncleaved cell lymphoma, IBCL: immunoblastic B cell lymphoma, RT: radiotherapy,

the primary diagnosis of PBL from 2000 to 2010. The diagnosis was made by core needle and open incisional biopsies and confirmed by pathological morphology and immunohistochemistry studies. All patients underwent extensive workup including chest radiography (poster-anterior and lateral), CT scanning of the chest, abdomen, and pelvis, abdominal and pelvic ultrasound, MRI of the affected area and whole bodyTechnetium (99mTc) bone scan. Bone marrow aspirate (BMA) was done for all patients (8).

Patients enrolled in this study had stage IE according to the Ann Arbor system of staging (involvement of a singleosseous site; i.e., localized disease without regional lymph node involvement) (9). Patients were excluded if they had evidence of systemic involvement, positive bone marrow aspiration or other osseous site involvement, regional lymph node involvement or if they had less than two years of follow-up. Of 68 identified patients, 61 were included in this study. Three patients were excluded because they had positive BMA results and two patients were excluded because they had multiple osseous sites involved. Two other patients were also excluded because they had less than two years of follow up.

Clinical data was obtained from patients' medical records. Pathology slides of 57 patients were available for histological review and were reexamined by abone pathologist at our hospital. All patients received combined modality therapy (CMT) consisting CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) chemotherapy andradiotherapy. Radiotherapy consisted 35 grays in 20 fractions that was given to the whole length of the affected bone and started 2 weeks after completion of chemotherapy (5).

Patients were examined every three months in the first year after completion of CMT and every six months afterwards. At each visit,patientswere checked for any signs or symptoms oflocal recurrence including recurrent or continuing pain, or any evidence of recurrence in x-ray or MRI (in patients who did not have orthopedic fixation).

Statistical methods

Continuous variables were presented as mean ± SD, while categorical variables were summarized by absolute frequencies and percentages. Mann-Whitney U tests was used whenever the data did not appear to have normal distributions. Categorical variables were compared using chi-square test. The disease free survivalwas measured from the date of diagnosis to the date of recurrence or last follow-up and the overall survival was measured from the date of diagnosis to the date of last follow-up or death. Overall and disease free survival were calculated using Kaplan-Meier actuarial method. To determine the predictor factors of survival, Cox-Regression multivariable analysis was performed.

Results

In total, 57% of patients were male. The male to female ratio was 1.3:1. The mean age of patients at admission was 34±15 years (18 to 84 years). Diffuse large B cell subtype was the most common histological subtype occurring in 81% of patients [Table 1].

The distal part of femur was the most common affected site (67%). All patients presented with pain at the involved site, and 18 patients (30%) presented with a concomitant palpable mass. Patients had no constitutional symptoms. Pathological fracture was the initial presentation in ninepatients (15%) out of which five were in femur, two in humerus, and two in pubis. One patient had an impending fracture of the proximal third of the femur according to Mirel's criteria (10). Femoral fractures or impending fractures were fixed using either cephalomedullary nail or interlocking nail and bone cement depending on the location of the fracture. Humerus fractures were fixed using locking plate or

Table2. Laboratory indices at admission time

Laboratory Test	mean ± SE (range)
ESR (mm/hr)	46.2±25.4 (5-85)
CRP (+)	0.79±0.9
Alk-Phos (mg/dl)	345.7±23.5 (100-865)
LDH (IU/L)	501±31.5 (219-1290)
CPK (IU/L)	67.2±4.7 (30-152)
WBC	6945.9±355.2
Lymph (%)	25.3±10.7
Hb (mg/dl)	13.02±1.7 (9.9-16)
Serum Calcium (mg/dl)	8.9±0.0 (7.9-10.5)

dynamic compression plate and bone cement depending on the location. The biopsies were performed at the same time as the internal fixation was done.For two patients presented with fracture of the pubis, CT guided core needle biopsy was done. The overall mean delay from the onset of symptoms until the final diagnosis was 18±2.1 months (1-72 months). Laboratory findings of patients are presented in Table 2.

All patients received CMT. Eleven patients developed febrile neutropenia, which required hospitalization and parenteral antibiotics.Steroid induced diabetes mellitus developed on therapy in three patients and four patients travailed from herpes zoster infection. However, there were no life threatening complications and none of the patients required any major modifications in their dosages or schedule. The five-yearoverall survival rate was 89%and the five-yeardisease free survival rate was 78% [Figure 1]. Cox-Regression analysis demonstrated that age (without cut-off point) was the only predictor of overall survival (OR=1.05, 95% CI: 1.0-1.1, *P*-value=0.04) in our group. Other factors that were analyzed and didn't have any impact on survival were gender (*P*-value= 0.33), elevated serum calcium level (*P*-value=0.77), and serum LDH level (*P*-value=0.39).

Local recurrenceLocal recurrence occurred in 6 (9.8%) patients: two in the proximal femur, two in the proximal humerus, one in the distal femur, and one in the proximal tibia. Mean time to local recurrence was 27 (6-60) months from completion of CMT [Table 3].

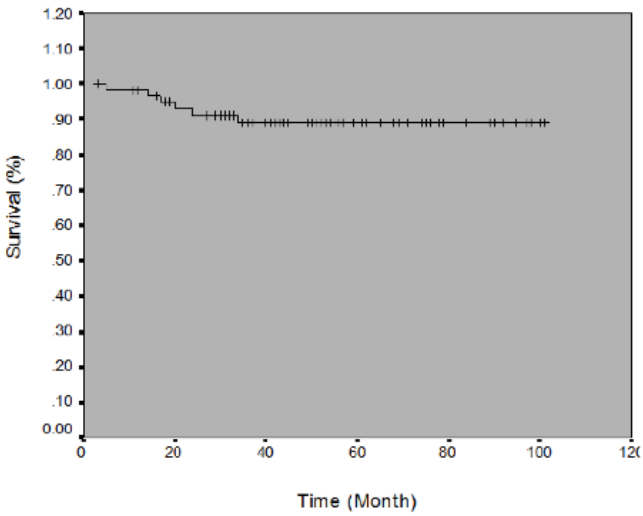

Figure 1. It shows overall survival of patients with stage IE primary bone lymphoma.

Before surgery, re-staging was performed for all patients including CT scanning of the chest, abdomen and pelvis, bone marrow aspirate (BMA), and whole body 99m Tcbone scan.

With extension of the biopsy incision, appropriate length of the involved bone, soft tissue componentand also the biopsy tractswere excised. All patients had intraoperative frozen section to ensure adequate margin has obtained. Howmedica modular replacement prosthesis (HMRS, Stryker Orthopedics USA) was applied for those who had tumor involvement in the proximal femur [Figure 2], distal femur, and proximal tibia.Wide excision and fresh frozen osteoarticular allograft was used for those who had proximal humerus involvement. Osteoarticular allografts were obtained from our hospital bone bank [Figure 3].

The specimen has been sent for histological examination. Tumor cells were found in all six cases. Two weeks after surgery, patients received chemotherapy as the initial treatment. These patients were followedperiodically the same as the initial follow-up. The mean follow–up for this group was 36 (54-24) months. One out of six died 30 months after treatment because of multi-organ involvement while other patients were still alive at the

Table 3. Treatment protocols and follow-up results of recurrence cases with stage IE primary bone lymphoma after combined modality therapy

Cases	Age	Site of tumor involvement	Recurrence (months)	Therapeutic methods	Patients Status
1	55	Proximal of femur	24	Wide excision & HMRS application	Alive
2	62	Proximal of femur	12	Wide excision & HMRS application	Alive
3	65	Distal of femur	6	Wide excision & HMRS application	Dead
4	58	Proximal of tibia	18	Wide excision & HMRS application	Alive
5	55	Proximal of humerus	42	Wide excision& allograft application	Alive
6	67	Proximal of humerus	60	Wide excision& allograft application	Alive

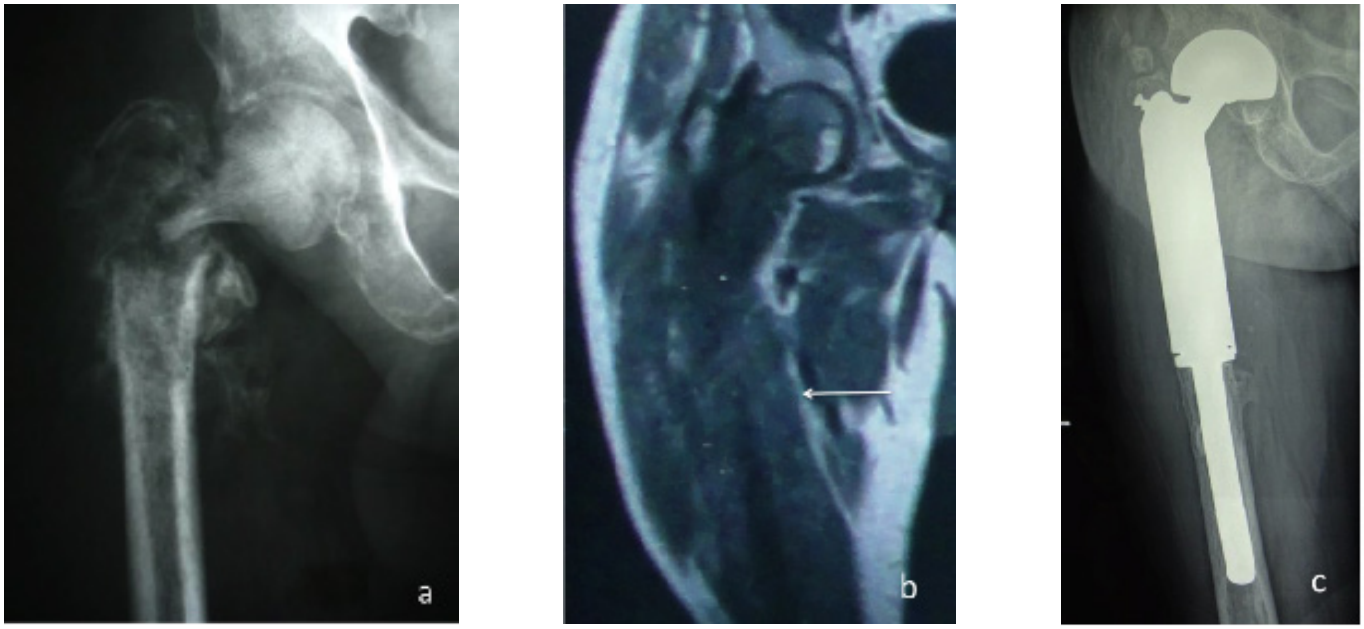

Figure 2a,b,c. A 48 year-old male with PBLof the proximal of the right femur, one yearafter completion of combined modality therapy.

a. Antero-posterior radiograph of the hip and proximal of the right femur showing pathologic fracture and bone destruction due to local recurrence of PBL.

b. Coronal T1 weighted MRI of the right hip and the proximal of the right femur showing soft tissue component (white arrow) due to local recurrence.

c. Antero-Posterior radiograph of the right hip and the femur after 2 years post wide excision and HMRS application.

time of latest follow-up [Table 3]. The mean MSTS score for lower limbs was 87% (80–93) and for upper limbs was 80% (70-80) at the time of latest follow-up visit (11).

Discussion

PBL occurs in almost every bone. But long bones of the lower limb, especially the femur, are the most common site according to literature. The second most common site is spine (5,12). In our study femur involvement was seen in 21 (33%) patients and the second most common site was pelvis in 13 (20%) patients because spinal lesions are not referred to our department. The most common symptom of PBL is local pain and complaints of persistent mild and intermittent dull pain. Other presenting symptoms such as palpable mass, constitutional systemic symptomsand pathologic fractures were demonstrated in several series (13,14). In our study,pain was present in 100% of our patients, and a palpable mass on physical examination was seen in 30%.

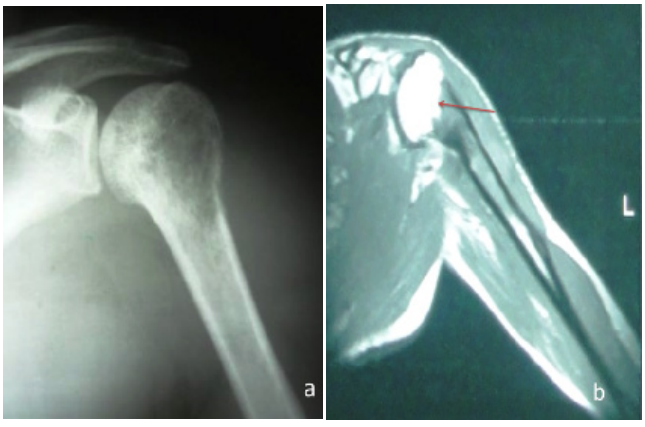

Figure 3 a,b. A 24 year old male. Local recurrence of PBL 2 years after completion of combined modality therapy.

a. Anteroposterior radiograph of the left shoulder and the proximal humerus showed lytic lesion within the head and neck due to local recurrence.

b. Coronal image of T2 weighted MRI showed hyper intense signal within the head (red arrow) due to local recurrence.

Immunohistochemistry (IHC) staining shows that bone lymphoma cells could generate cytokines including IL-21, IL-6, and TNF to enhance the osteoclastic activity (15). When tumor cells penetratethrough cortical bone to the surrounding soft tissues, pathological fractures can easily occur (16). In this study, eight (13%) patients presented with a pathological fracture.

PBL is rare in clinical practice and difficult to diagnose because mischievous and atypical local symptomsare the major complaint. In younger patients, the differential diagnosis of PBL mainly includes Ewing's sarcoma,langerhans cell histocytosis, osteomyelitis, and leukemia. For adult patients, osteolytic osteosarcoma, myeloma and secondary lymphoma of bone should be considered (16,17).

In our study the mean interval between the beginning of

symptoms and final diagnosis (overall delay to diagnose) was about 18 months. This was due tothe delay of patients seekingtreatment, which was the result ofhaving mild pain together with false negative radiographs.This delay was present ineightpatients of our series being misdiagnosed initially: 3 with osteomyelitis, 2 with eosinophilic granuloma, 2 with Ewing sarcoma, and one with osteosarcoma. The misdiagnoseswere done at the pathological units.

In 1994 Fairbanks et al evaluated the results of 63 patients with stage IE PBL They reported an improved 5-year disease-free survival for patients treated with chemotherapy and radiation vs. radiation alone (90% vs. 57% respectively) showing thatthe addition of chemotherapy to the radiation may decrease the local recurrence rate (6).

In recent years, combined radiochemotherapy has often been applied for localized stages as well as for advanced stages of PBL (18-20). Multiple studies have shown that the addition of rituximab to chemotherapy regimens improves outcomes in patients with aggressive non-osseous NHL (21,22). Rituximab is a monoclonal antibody directed against the CD20 antigen expressed on lymphocytes. For PBL addition of rituximab to CHOP did not significantly affect either OS or progression-free survival (21). Historically, before the introduction of chemotherapy as an effective treatment, PBL was treated using radiation or surgery. However, nowadays the role of surgery in PBL has been limited to biopsies, and bone fracture repair.

Maruyama etaldescribed28 patients of PBL in 2007. In their study, six patients (21%) had recurrences of the disease. Three patients with bone relapses received chemotherapy followed by radiotherapy as the initial treatment (23). In our study, the recurrence rate was 9.8 % (six patients) while the mean recurrence time was 28months.New surgical therapeutic approaches were applied in these patients. In patients wherethe recurrence site was the proximal femur, distal femur and proximal tibia, wide excision and HMRS was used. For those with involvement of proximal humerus, wide excision and osteoarticular allograft reconstruction was applied which was followed by three courses of CHOP chemotherapy. These patients were followed up for about 24 months and only one of them died while the others were still alive with high functionality. To our knowledge, this is the first time that wide excision and reconstruction is used for local recurrence of stage IE PBL. We had good results in this manner and we recommend this technique, although we suggest complete investigation and prospective studies with more patients.

In conclusion, our series of PBL supports the application of CMT (stage IE), and showed favorable overall survival for patients who presented with a single osseous focus of lymphoma without other sites of involvement. We recommend internal fixation for those with pathologic fracture whether the fracture occurs before or after CMT. We also suggest the application of wide excision and reconstruction as a new therapeutic method for local recurrences. Although the results of our patients were satisfactory, future studies with additional patients should be pursued.

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