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Primary lymphoma of bones

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Abstract Primary malignant lymphoma of bone (PLB) is an uncommon tumour. A survey of 278 primary malignant cases in our clinic showed that 20 cases of PLB were registered between 1986 and 1997. Fourteen of the 20 cases underwent surgical excision. The mean follow-up time was 36.3 months. The rate of response to treatment was 65% with a rate of complete recovery of 55%. The clinical stage of tumours correlated well with the prognosis. Our results seem worse than most of the series in the literature. A high proportion of stage IV disease and pathological fractures at presentation may be a factor.

Résumé Le lymphosarcome primaire de l'os est une tumeur rare. Parmi 278 cas de tumeurs malignes primitives traitées entre 1986 et 1997 nous avons 20 cas de lymphosarcome. Quatorze des 20 sujets ont été opérés. La durée médiane de suivi était 36.3 mois. Le pourcentage de réponse était 65% avec un pourcentage de réponse complète de 55%. Le stade clinique des tumeurs était bien corrélé avec le pronostic. Nos résultats sont inférieurs à ceux de la littérature, peut-être à cause de la haute incidence des fractures pathologiques et des stades IV de la maladie.

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Introduction

Primary malignant lymphoma of bone (PLB) constitutes approximately 3–15% of all extra-nodal non-Hodgkin's lymphoma (NHL) [6, 13, 14, 18, 19] and approximately 3–7% of primary bone tumours [8, 11, 15, 18]. The true incidence of PLB is difficult to assess, as the site of origin is unclear in patients with disseminated lymphoma and bony involvement [10]. In patients who have a single osseous focus without other involvement, the diagnosis of PLB is easier to make. Although primary lymphoma is potentially curable, lymphomas involving bone secondarily are usually fatal. Surgical treatment is not required in the treatment of disseminated lymphoma other than for pathological fractures, but in PLB chemotherapy and radiotherapy should be combined with surgery.

In this study we describe the clinico-pathological characteristics of 20 patients with PLB treated over an 11-year period (1986–1997) and assess the role of surgery in its treatment.

Patients and methods

Twenty patients with PLB presented to the Department of Orthopaedics of Ankara University at Ibn-i Sina Hospital between November 1986 and December 1997. The details of the patients are shown in Table 1.

In this study a primary site in bone was determined by the following criteria: presentation in a single bone or multifocal osseous sites with or without invasion into surrounding tissue, and with no evidence of visceral or lymph node involvement at the time of initial diagnosis. In all patients the histological diagnosis of NHL was made on open biopsy or from tissue obtained at surgery and was classified according to the Working Formulation [9]. The pathological diagnosis was supported by immuno-histochemical studies using antibodies to leukocyte common antigen (CD 45); and using the B-lineage marked CD 20 in five patients with previous other histological diagnoses.

Treatment Initially all patients received an anthracycline containing combination therapy (CT) regime. Of these, 13 also received radiotherapy (RT) to the primary site after completing CT. In seven patients surgery was performed in combination with CT, and in seven it was combined with both CT and RT. Chemotherapeutic agent and radiation doses and the type of surgery performed

Table 1 Patient characteristics (*ORIF* open reduction internal fixation, *IST* interscapulothoracic disarticulation, *AD* anterior decompression, *AI* anterior instrumentation, *PMMA* polymethylmethacrylate, *LFU* lost to follow-up, *NED* no evidence of disease, *AWD* alive with disease)

Sex	Age (years)	Location	Histology [9]	Stage [3]	Symptoms	Combination therapy (regimen; no. of courses)	Radiotherapy (cGy/no. of fractions)	Surgery	Status
F	35	Humerus	IG-DLC	I-EA	Pain, pathological fracture	CHOP (6)	–	Curettage + ORIF	LFU at 37 months
F	53	Femur	IG-DLC	I-EA	Pain, mass	CHOP (6)	–	High femoral amputation	LFU at 42 months
F	72	Ulna	IG-ML&SC	IV	Pain, pathological fracture	CHOP (6)	4000/20	–	Dead at 17 months
M	50	Femur	LG-lymphoma	IV	Pain, pathological fracture	COPBleo (5)	–	Curettage + ORIF	Dead at 6 months
F	15	Femur, pelvis	HG-DLC	IV	Pain, mass	CHOP (6)	4000/20	–	Dead at 15 months
F	27	Humerus	HG-DLC	I-EA	Pain, mass	CHOP (4)	3500/15	–	Dead at 6 months
F	32	Femur	HG-DLC	I-EA	Pain, pathological fracture	CHOP (6)	4000/20	Curettage + ORIF	NED at 80 months
F	21	Acetabulum	IG-DLC	I-EA	Pain	CHOP (6)	4200/20	Curettage + PMMA	NED at 72 months
M	19	Humerus	IG-DLC	I-EA	Pain, mass	CHOP (6)	–	IST disarticulation	NED at 65 months
F	48	T12, L1–2	HG-DLC	I-EA	Pain, pathological fracture	CHOP (6)	3000/10	Total laminectomy + posterior instrumentation	NED at 58 months
F	68	T12, L4	IG-lymphoma	I-EA	Pain	CHOP (6)	3000/15	–	Dead at 15 months
M	52	Ileum	IG-DLC	I-EA	Pain, mass	CHOP (8)	–	Curettage	NED at 106 months
M	21	Ileum	IG-ML&SC	I-EA	Pain, mass	CHOP (4)	4200/20	Curettage + PMMA	NED at 66 months
F	58	Femur, T5–7	IG-DLC	IV	Pain, mass	CHOP (6)	3000/20	Enbloc resection + endoprosthesis	Dead at 14 months
M	63	Humerus	IG-DLC	I-EA	Pain, mass	CHOP (6)	4200/20	Resection arthroplasty	NED at 41 months
M	48	Sacrum	HG-DLC	I-EA	Pain	CHOP (6)	4000/20	–	NED at 29 months
F	17	Femur	HG-lymphoma	I-EA	Pain, pathological fracture	CHOP (6)	5040/28	Enbloc resection + endoprosthesis	Dead at 20 months
M	25	Tibia	IG-DLC	I-EA	Pain, mass	CEOP (6)	6000/20	–	NED at 12 months
M	56	L1, tibia	IG-DLC	IV	Pain	CHOP (6)	–	ORIF + AD + PMMA + AI	Dead at 12 months
F	76	T9–10	IG-DLC	IV	Pain	CEOP (6)	–	AD + PMMA + AI	AWD at 12 months

are seen in Table 1. The X-ray and computerised tomography findings of a patient who presented with hip pain and a mass in the ilium and was treated by curettage and reconstruction using polymethyl methacrylate can be seen in Figs. 1, 2, 3.

Cases were restaged approximately 1 month after completion of treatment. Each patient's best response after the completion of an initial therapeutic intervention was assessed. Complete recovery was defined as no radiological or clinical evidence of tumour at follow-up. If there were persistent radiological abnormalities consistent with normal bone reformation, and there was no further evidence of disease, patients were still considered to be in complete remission. Partial recovery was defined as >50% reduction in tumour without complete symptomatic remission after the completion of treatment. No response was defined as <50% reduction in tumour after treatment. Finally, progressive disease was defined

as an increase in the size of the tumour, or the development of the disease at a new site.

Results

The status of the patients at their last visit can be seen in Table 1. Two patients were lost to follow-up at 37 and 42 months, respectively, and had no evidence of disease at their last visit. The latter underwent interscapulothoracic disarticulation with an initial histological misdiagnosis of Ewing's sarcoma after open biopsy. Another pa-

Fig. 1 Twenty-one-year-old man who presented with hip pain and mass in the ileum. Anteroposterior view of the pelvis

Fig. 2 Computerised tomography of the same patient as in Fig. 1

Fig. 3 No evidence of disease after 66 months. Anteroposterior view of the pelvis of the same patient as in Fig. 1 after curettage + cementing with PMMA + open reduction with Steinman pin

tient underwent high femoral amputation with an initial misdiagnosis of osteosarcoma after open biopsy.

The overall recovery rate was 65% with a 55% complete recovery rate and a 10% partial recovery rate. The mean survival for all patients was 60%. The clinical stage of tumours correlated with the prognosis, but this correlation was not statistically significant, which might be due to the small number of patients. The overall survival rate in cases with stage I disease (78%) was significantly more favourable than with stage IV disease (16%).

Discussion

The peak incidence for the presentation of PLB is in the fifth and sixth decades, with a mean age at presentation of 44 years. There is a male predominance in the literature in a ratio of 1.3–1.8:1. Our series confirms the mean age at presentation (42.8 years). All patients presented with pain at the primary site and nine had a palpable mass, which is similar to that in other series [5, 15, 18]. Our series differs in that there is a female preponderance with a female/male ratio of 1.5:1. Bimodal distribution with reversal of the sex ratio between the peak of age-specific incidence has been shown [7], but in our series the female/male ratio was 2:1 below the age of 40 years and about 1.2:1 above the age of 40 years.

The diagnosis of lymphoma of bone may be difficult because of the mixed cell nature of the infiltrate in malignant lymphoma [12, 18]. If the tumour involves bone without destroying trabeculae, the diagnosis of malignant lymphoma should be favoured. In lesions with carcinomatous features, immunoperoxidase studies of common leukocyte and epithelial membrane antigens are helpful. In small biopsy specimens, malignant lymphoma may be impossible to differentiate from Ewing's sarcoma and undifferentiated small cell carcinoma. In our early two cases this mistake was made and a high femoral amputation and interscapulothoracic disarticulation were performed with a histological misdiagnosis of Ewing's sarcoma and osteosarcoma, respectively. The surgeon must ensure that sufficient biopsy specimen is taken in lesions with carcinomatous features, bearing in mind that malignant lymphoma of bone must be considered in the differential diagnosis.

The staging classification of PLB follows the Ann Arbor classification [3] originally described for Hodgkin's disease. A solitary osseous lymphoma lesion without additional disease is clinical stage I (stage I with extranodal disease is called stage IE), while lymphoma of bone affecting more than one skeletal site is stage IV. In our series six patients had multifocal osseous disease with no evidence of extraosseous involvement. This has been reported in some studies [4, 10, 17] and described as "homing" of tumour cells to bone. A feature of PLB is the discrepancy between the presence of a bulky lesion and the body's tolerance [19], which can further delay the diagnostic process and lead to the development of

multifocal osseous lesions. Ostrowski et al. [10] showed that the stage of the disease is the single most important prognostic indicator in malignant lymphoma of bone. A 5-year survival rate was 58% for patients with PLB and 42% for patients with multifocal osseous disease in Ostrowski's study [10]. In our series the 5-year survival rate of stage I patients was 67%, but five of six patients with stage IV disease died during treatment between 6 and 17 months, and the last was alive with disease at 12 months follow-up.

There are no X-ray features which are pathognomonic for lymphoma of bone. The lesions present as lytic or "moth-eaten" radiolucent areas with a wide transitional zone between the tumour and normal bone, but sclerotic or mixed sclerotic and lytic lesions may also be encountered [2, 16]. In our series plain X-rays of 12 patients revealed an osteolytic lesion of the involved bone. Five patients had a pathological fracture and in one of the five with spinal involvement there was pathological compression. One patient developed a pathological fracture during treatment.

In some patients skeletal X-rays may show no abnormalities [1, 10]. Skeletal scintigraphy with ^{99m}Tc -diphosphonate is more sensitive. Sensitivity and specificity has been found to be >0.96 with an overall accuracy by site of 98% [1]. In Ostrowski's series the multifocality of osseous lymphoma lesions could only be detected in 9% of cases by bone scan when other staging studies including X-rays were normal [10].

The treatment of PLB combines local RT and CT and if necessary surgery. The consensus now favours radiation for control of the primary lesions; surgical ablation becomes necessary if radiation either results in local necrosis that is disabling, or fails to halt the growth of the tumour. Surgical treatment is also required in patients with pathological fractures, and in those with neurological complications caused by vertebral involvement. Surgical procedures other than open biopsies were common in our series, but this can be explained by the incidence of pathological fracture (six at initial diagnosis and one during treatment) and of spinal involvement with neurological symptoms.

The assessment of the response to therapy in PLB remains an enigma. It was emphasised by Ostrowski et al. that the possibility of long-term survival following aggressive treatment was high [10]. In our series the response to treatment was worse than previously reported. This may be due to the incidence of stage IV disease at presentation, which is higher than in other series.

In conclusion, PLB, while rare, will often present to the orthopaedic surgeon in the first instance. It is a po-

tentially curable malignancy, and although it usually presents as a localised bony lesion, no formal guidelines exist for its treatment. Treatment should be undertaken and performed with close collaboration between the orthopaedic surgeon, radiotherapist and oncologist.

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