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ORIGINAL ARTICLE

PRIMARY LEIOMYOSARCOMA OF BONE: CLINICOPATHOLOGIC AND PROGNOSTIC FACTORS ANALYSIS IN A SINGLE INSTITUTION

LEIOMIOSSARCOMA PRIMÁRIO ÓSSEO: ANÁLISE CLINICOPATOLÓGICA E DOS FATORES DE PROGNÓSTICO EM UMA ÚNICA INSTITUIÇÃO

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ABSTRACT

Objective: Primary leiomyosarcoma of bone (PLB) is a rare type of malignant bone tumor considered as a variant of the spindle cell sarcomas (SCS). The objective of this study was to analyze the clinicopathologic and the prognostic factors of patients with PLB treated at a single institution. Methods: We retrospectively reviewed the records of 22 patients with pathologically confirmed PLB. The data collected were: age, sex, tumor size and location, grade and stage of the disease and histopathologic features. Mean age was 45.5 years (range, 17 to 73 y). Location was: upper limb (27.3%), lower limb (68.2%) and pelvis (4.5%). Patients had high grade in 90.9% of the reports. Margins were negative in 77.3% of the cases. Histological reports describe spindly sarcomatous cells arranged in fascicles with increased vascular formation without osteoid or chondroid matrix production. On immunohistochemistry, smooth muscle actin and desmin where positive in all cases. Results: Mean follow-up time was 73.5 months (range, 5.3 to 331.1 m). We found 22.7% of local recurrence (LR). Distant metastasis (DM) was reported in 9 (40.9%) patients. Lung metastasis was the only DM affected site. Overall survival (OS) rate in 5 years was 59.1%. Predictors of OS were LR and DM. Conclusions: PLB is an extremely rare malignant bone tumor that has a higher rate of DM and similar OS prognosis compared with other bone sarcomas. ***Level of Evidence IV, Case Series.***

Keywords: Sarcoma. Leiomyosarcoma. Surgical margins. Recurrence. Neoplasm metastasis.

RESUMO

Objetivos: O leiomiossarcoma primário do osso (LPO) é um tumor ósseo maligno raro, considerado uma variante do sarcoma de células fusiformes (SCF). O objetivo deste estudo foi fazer uma análise clínico-patológica e dos fatores de prognóstico dos pacientes diagnosticados com LPO tratados em uma instituição única. Métodos: Foram analisados retrospectivamente os prontuários de 22 pacientes com diagnóstico confirmado de LPO. Os dados coletados foram: idade, sexo, tamanho e localização do tumor, grau histológico, estádio da doença e as características histopatológicas. A média de idade foi 45,5 anos (de 17 a 73 a). A localização foi: membro superior (27,3%), membro inferior (68,2%) e pelve (4,5%). Os pacientes apresentaram alto grau em 90,9% dos relatos. As margens foram livres em 77,3% dos casos. Os relatos histológicos descrevem células sarcomatosas finas e compridas, arranjadas em fascículos, com aumento da vascularização e sem produção de matriz osteoide ou condral. No estudo imuno-histoquímico, a actina do músculo liso e a desmina foram positivas em todos os casos. Resultados: O tempo médio de seguimento foi 73,5 meses (de 5,3 a 331,1 m). Dos pacientes, 22,7% apresentaram recorrência local (RL). Metástase à distância (MD) foi reportada em 9 (40,9%) pacientes. O único local de MD foi o pulmão. O tempo médio de sobrevida em 5 anos foi de 59,1%. Os fatores preditivos de sobrevida global foram: RL e MD. Conclusão: O LPO é um tumor ósseo maligno extremamente raro que tem uma taxa maior de MD, com uma sobrevida global similar aos outros sarcomas ósseos. ***Nível de Evidencia IV, Série de Casos.***

Descritores: *Sarcoma. Leiomiossarcoma. Margens de Excisão. Recorrência. Metástase neoplásica.*

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INTRODUCTION

Leiomyosarcoma (LMS) is a rare tumor that usually affects middle-age persons. Some authors have described cases of LMS in young adults and even in children. It has predilection for female rather than male.[1] The World Health Organization (WHO) defines it as a malignant tumor with distinct features of smooth muscle cells.[2] The most common location of LMS is the retroperitoneum (including the pelvis). It is also predominant in

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some large blood vessels, specially the inferior vena cava and the pulmonary arteries. When the tumor is in the upper portion of the inferior vena cava, it obstructs the hepatic veins producing the Budd-Chiari syndrome. It is less common but it can also arise from subcutaneous, intramuscular and bone tissues.[2,3] The last one is known as PLB and was first described by Evans and Sanerkin in 1965. The origin of LMS (all types) still remains unclear or partially unknown. Some authors believe that there is some kind of hormonal influence, based on the predilection of the tumor for female when compared with male.[4] All LMSs usually presents the same initial clinical feature: a mass lesion that produces moderate pain. The other clinical symptoms depend on the location of the tumor rather than in the group.[4,5] The classic histological pattern is: compactly cellular with fibrous and myxoid changes, observing marginal spindle cell groups with focal storiform, palisaded or haemangiopericytoma-like arrangement. Also, larger tumors present hypocellular zones with coagulative necroses.[6] Differential diagnoses of PLB are made especially with Dermatofibrosarcoma, Fibrosarcoma of Bone and Myxofibrosarcoma.[2,7] Surgery continues to be the gold standard treatment for PLB. Chemotherapy (CT) can be used, as adjuvant or neoadjuvant setting, but the definitive role is not totally defined. They can be also used as a palliative therapy for metastatic patients.[6-8] Given the lack of randomized trials for the creation of treatment guidelines, the outcomes and prognostic factors for PLB, remain uncertain.They exhibit a relatively better OS rate than the other bone sarcomas, even though publications show that DM is higher.[8] No large publications have yet totally investigated or defined PLB, then, in an effort to improve the understanding of the clinical outcomes and the prognosis, we conducted a retrospective study, evaluating a series of patients, with the purpose of understanding better this bone tumor.

Table 1. List of patients included in the study.

Case	Diagnosis	Grade	Local	Follow-up*	Surgery
1	PLB	III	proximal tibia	42.1	resection
2	PLB	III	pelvis	62.5	resection
3	PLB	III	proximal tibia	48	resection
4	PLB	III	proximal femur	331.1	amputation
5	PLB	III	proximal femur	37.4	resection
6	PLB	III	distal femur	56.8	resection
7	PLB	III	distal femur	217.3	amputation
8	PLB	III	proximal femur	191.4	resection
9	PLB	III	proximal humerus	48.9	resection
10	PLB	III	distal femur	67.7	resection
11	PLB	III	distal femur	66.6	amputation
12	PLB	III	distal ulna	136.1	resection
13	PLB	III	proximal humerus	120.3	resection
14	PLB	I	proximal femur	24.7	resection
15	PLB	III	proximal humerus	28.8	resection
16	PLB	I	proximal femur	29.1	resection
17	PLB	III	distal ulna	31	amputation
18	PLB	III	distal ulna	30.6	resection
19	PLB	III	distal femur	16.9	amputation
20	PLB	III	proximal femur	18.1	resection
21	PLB	III	distal femur	6.4	resection
22	PLB	III	distal femur	5.3	resection

* follow-up time in months.

MATERIALS AND METHODS

A retrospective study was performed after we obtained the approval from the ethical committee review board from our institute. We identify the clinical records from every patient diagnosed with PLB that underwent surgery, in the division of orthopedic oncology, in the last 10 years. A total of 22 patients with PLB were included in this study (Table 1). All the patients with incomplete data in the medical files and that didn't received surgery as treatment, were excluded from our investigation. Diagnoses were performed by the pathology division of our institute, based on the WHO classification of Soft Tissue Sarcomas (STS). Demographic data including: sex, age, tumor location, surgery and number of surgeries, surgical margins, histologic grade, adjuvant or neoadjuvant therapy, LR and time to develop LR, DM and time to develop DM, follow up and oncologic status were collected. Histologic grade was determined based on French Federation of Cancer Centers (FNCLCC). The decision on using CT for each patient was studied in multidisciplinary meetings. Of these patients, 10 (45.4%) were female and 12(54.6%) were male, with a mean age of 45.5 (range, 17-73years). Most of the tumors, in 12 (54.6%) patients, appeared on the left side of the body. The distal femur was the most affected anatomical location with 7(31.7%) cases, followed by the proximal femur with 6 (27.3%) cases, proximal humerus and distal ulna with 3(13.7%) cases each, proximal tibia 2 (9.1%) cases and pelvis 1 (4.5%) case. The size of the tumor was divided in four groups in accordance with the American Joint Committee on Cancer(AJCC) staging system. Group II had 12 (54.6%) patients, group I and IV had 3 (13.7%) patients each and group III had 4 (18%) patients. Seventeen (77.2%) patients received tumor wide resection surgery, while 5 (22.8%) patients underwent limb amputation. Margins were microscopically positive in 5 (22.8%) cases and negative in 17 (77.2%) cases. Most cases, 20 (90.9%), had grade 3 (FNCLCC) tumor report. LR was found in 5 (22.8%) cases, all of these patients underwent multiple surgical procedures (MSP). Also, we had 9 (40.9%) reports of DM, being the lungs the affected organ in every case. Fifteen (68.1%) patients received neoadjuvantCT. Mean follow up in this study was 73.5 months (range, 5.3 to 331.1 m). The OS rate in 5 years was 59.1%. All the demographic data is summarized in Table 2. Pathology reports of surgical margins, LR and OS were considered the principal objectives of this study. Time for LR, single or multiple, was calculated from the first surgical procedure. OS was estimated using the Kaplan-Meier method. The relation between single surgical procedure (SSP), LR, DM and oncologic status were investigated using the log-rank test for categorical variables. Differences of the $p < 0.05$ were considered statistically significant. Also, we calculated the OS, time to LR and disease free overall survival (DFOS) using Kaplan-Meier functions and log-rank tests to compare the outcomes of the qualitative variables. The influence of age on the outcomes of the patients was tested using the Cox bivariate regression. The not adjusted HR with their respective confidence interval of 95%, were calculated using the Cox bivariate regression. All the variables, that in the bivariate tests presented significant level of 0.10 ($p < 0.1$) with the use of multiple Cox regression, were tested in multiple models. The selected variables that when together presented significant level of 5% in the final model, were tested in multiple models also. For all the statistical analyses, we used the IBM-SPSS software for Windows version 20.0. For tables and charts, we used the Microsoft Excel 2008 version software. All the tests were realized with a significant level of 5%.

Table 2. Patient demographics and clinical characteristics.

Variable	Description (n=22)
Age	
mean	45.5(range 17-73years)
Sex	
female	10(45.4%)
male	12(54.6%)
Follow up (months)	
mean	68.4 (range 5.3-331.1 months)
Grade, n (%)	
I	2(9.1%)
II	0 (00%)
III	20(90.9%)
Local, n(%)	
distal femur	7 (31.7%)
proximal femur	6 (27.3%)
proximal humerus	3 (13.7%)
distal ulna	3 (13.7%)
proximal tibia	2 (9.1%)
pelvis	1 (4.5%)
Size, n(%)	
< 5cm	3(13.7%)
5cm to 9.99cm	12(54.6%)
10cm to 14.99cm	4(18%)
>15cm	3(13.7%)
Side, n(%)	
right	10(45.4%)
left	12(54.6%)
Surgery, n(%)	
resection	17(77.2%)
amputation	5(22.8%)
Margins, n(%)	
negative	17(77.2%)
positive	5 (22.8%)
Adjuvance, n(%)	
yes	15(68.1%)
no	7(31.9%)
Local Recurrence, n(%)	
yes	5(22.8%)
no	17(77.2%)
Multiple Surgeries, n(%)	
yes	6(27.3%)
no	16(72.7%)
Distant Metastasis, n(%)	
yes	9 (40.9%)
no	13 (59.1%)
Local for Distant Metastasis, n(%)*	
lung	9 (100%)
Overall Survival, n(%)**	
mean	59.1% in 5 years

*For the 9 patients with distant metastasis.

RESULTS

LR was statistically influenced by tumor margins, MSP and DM ($p < 0.001$). DFOS was statistically influenced by tumor grade (FNCLCC), tumor margins, MSP and DM ($p < 0.05$). LR suffered statistical influence by MSP alone or by tumor margins and DM together. Patients with MSP had 21.06 times a higher risk of LR than patients that had a single procedure. Positive microscopically margins with DM had 3.73 times a higher risk of LR than negative microscopically margins. Patients with DM had 8.34 times a higher risk of LR than patients without metastasis. DFOS was statistically influenced by MSP and DM. Patients with MSP had 2.64 times a higher risk of diminished DFOS, and patients with reports of DM had 7.93 times a higher risk of diminished DFOS. OS was statistically influenced by tumor grade (FNCLCC), LR, MSP and DM ($p < 0.05$). DM is probably the most important prognostic factor to explain OS in patients with PLB, but we were not able to use this variable since none of the patients without metastasis died.Histological reports describe spindly sarcomatous cells arranged in fascicles with increased vascular formation without osteoid or chondroid matrix production in every case. On immunohistochemistry, smooth muscle actin and desmin where positive in all the reports.

DISCUSSION

PLB is a rare malignant bone tumor, considered most frequent in middle age patients. It is usually reported as a high-grade tumor, with an important potential of DM.[9] The reasons of the high rates of DM are not completely understood. Some authors believe that PLB cause an extensive invasion on the neighbor tissues, fact that is not visible during surgery.[4-10] Some facts, described in few studies, can be considered to be important for the prognosis of PLB: tumor grade, surgical inadequate or positive margins, LR and DM.[7-11,12] To our knowledge, this is the first study that describes PLB as a unique entity, in a Latin American hospital, and the casuistry in this case series, is among the largest found in the investigated literature. In our study, 22 patients with pathologically confirmed diagnosis of PLB, and a mean follow up of 73.5 months presented: 28.8% had positive surgical margins, 90.9 % had high grade tumors, 28.8 % had reports of LR and 40.9% presented DM. This study had a number of limitations. First, the lack of studies describing the disease as a unique entity and the publications focused on specific subjects instead of describing general information were a major difficulty on the research for information on PLB. Second, there are limitations for the applicability of this retrospective study. The information represents those of a single institution, and although it's the only documented paper of PLB in Latin America, we found a limited capacity of describing prognostic factor with narrow confidence intervals. And third, the information on the medical files is not always complete or understandable, which makes the number of cases included less representative. Clinically, PLB tend to have higher rates of DM when compared with other bone sarcomas.[13] The present study reports a DM rate of 40.9%, corresponding to the reports of other papers. It seems that DM has a direct relation with tumor grade, surgical margins and LR.[6,14] Most of the pathological reports for PLB are high grade tumors (FNCLCC).[2,8,15] In a series of three different studies, we found that high grade PLB was predominant.[7,12,14] In our study, high grade tumors were also predominant, but with 90.9%, which is a much higher percentage when compared to the reported in other studies. As for DM, most of the studies report high rates with a range varying from 20% to 25%. The most common affected organ is the lung.[2,15] Not in accordance to the findings in literature, our rate of DM was 40.9%, again, a considerable

higher percentage. Nevertheless, and in accordance with the publications, we also have the lung as the predominant affected organ for DM. Although, the prognostic factors for PLB haven't been totally defined, there are some facts about the disease that have a direct connection with OS.[3-5,16] Authors agree that tumor grade and surgical margins have a close relation with LR, being grade III tumors and reports of positive or not adequate margins, important factors for increasing the rates of LR.[9,14]Another important fact is that the LR also increases the potential for DM, which has a direct effect on follow up time and consequently OS.[16,17] In our study, we identified that high grade tumors and positive margins, alone or together, directly increase the rates of LR. Also, we observed that LR has a principal role on the DM appearance. Interestingly, these facts separately don't seem to affect directly the OS of the patient with PLB. Anyhow, future studies are needed, to see whether these results are similar or not to the new information obtained.

CONCLUSION

In this institutional series we conclude that PLB is an extremely rare malignant bone tumor that has a higher rate of DM and a similar OS prognosis when compared with other bone sarcomas.

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