Primary Bone Leiomyosarcoma in the Distal Femur with Clavicle Metastasis. A Case Report

Leiomiosarcoma primario de hueso en fémur distal metastásico a clavícula. Reporte de un caso

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Abstract

Leiomyosarcoma (LMS) is a type of spindle-cell tumor of very low incidence that tumor has an aggressive behavior, with high mortality rates; therefore, its management must be surgical, with a wide resection of the lesion. The role of radio and chemotherapy in its management is not clear. We present the case of a 28-year-old female patient who consulted for pain lasting 2 months in the right knee. Radiographically, it was characterized as a pure osteolytic lesion in the distal femur. Contrast magnetic resonance imaging (MRI) showed hypervascular areas within the tumor. The scintigraphy showed a marked increase in radiotracer uptake. A biopsy was taken, with a pathology report of well-differentiated osseous LMS. It was treated with 3 cycles of preoperative neoadjuvant chemotherapy with ifosfamide 1,000 mg/m^2 in the first 3 days, as well as doxorubicin 70 mg/m^2, and surgical resection of the lesion and limb salvage with knee endoprosthesis. Once the lesion was resected, the patient underwent adjuvant chemotherapy, with 4 cycles of gencitabine 1,000 mg/m^2 between days 1 and 8, and doxetacel 70 mg/m^2 on day 1. During the 2-month follow-up, the patient presented a fracture in the middle third of the clavicle, which was compatible with a pathological lesion on radiographs and positron-emission tomography (PET) scans. The biopsy showed a metastatic lesion of bone LMS, which was treated by surgical resection of the clavicle. This is a unique case, given that, during the follow-up, the patient underwent adjuvant treatment with chemotherapy, and was evaluated with a PET scan, with a satisfactory clinical evolution and no evidence of new lesions.

Level of evidence IV.

Keywords
- bone tumor
- leiomyosarcoma
- bone metastasis

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Resumen

El leiomiosarcoma (LMS) es un tipo de tumor de células fusiformes de muy baja incidencia, que tiene un comportamiento agresivo, con alta tasa de mortalidad, por lo que el manejo debe ser quirúrgico, con una resección amplia de la lesión. No está claro el papel de la radio ni de la quimioterapia en su manejo. Presentamos a una paciente de 28 años que consultó por dolor de 2 meses en la rodilla derecha. Radiográficamente, se caracterizó como una lesión osteolítica pura en el fémur distal. La resonancia nuclear magnética (RNM) contrastada mostró áreas hipervasculares dentro del tumor. La gammagrafía mostró un marcado aumento en la captación de radiotrazadores. Se tomó una biopsia, con un informe de patología de LMS óseo bien diferenciado. Se trató con 3 ciclos de quimioterapia neoadyuvante preoperatoria con ifosfamida 1.000 mg/m^2 en los días 1 a 3, además de doxorrubicina 70 mg/m^2, y resección quirúrgica de la lesión y salvamento de la extremidad con endoprótesis de rodilla. Una vez que se resecó la lesión, la paciente recibió quimioterapia adyuvante con 4 ciclos de gencitabina 1.000 mg/m^2 entre los días 1 y 8, y doxetacel 70 mg/m^2 el día 1. Durante los dos meses de seguimiento, la paciente presenóa una fractura en el tercio medio de la clavícula, compatible con una lesión patológica en radiografías y tomografía por emisión de positrones (TEP). La biopsia reveló una lesión metastásica de LMS óseo que fue tratada mediante resección quirúrgica de la clavícula. Este es un caso único, dado que, durante el seguimiento, recibió tratamiento adyuvante con quimioterapia y se evaluó con una TEP, con una evolución clínica satisfactoria y sin evidencia de nuevas lesiones.

Nivel de evidencia IV.

Palabras clave
- tumor óseo
- leiomiosarcoma
- metástasis ósea

Introduction

Leiomyosarcoma (LMS) is a type of spindle-cell tumor characterized by smooth muscle markers that does not produce an osteoid matrix and behaves like a malignant tumor. Leiomyosarcomas usually occur at the retroperitoneum and gastrointestinal tract, and[1–3] the presentation in bone is rare. Information regarding intraosseous LMS is scarce in the literature, mostly consisting of case reports.[1–14] We present the case of a female patient with a primary bone LMS at the left distal femur submitted to surgical treatment and chemotherapy who later presented a metastatic lesion at the clavicle with a pathological fracture, which was managed with surgical resection.

Case Description

A 28-year-old female patient complaining of pain in the right knee and functional limitation for 2.5 months, predominantly at night and with limb support. On physical examination, she presented mild pain with limb support and during knee mobilization, with no other important findings and no limitation to knee mobility.

A radiograph of the right knee showed a lytic lesion at the distal femoral metaphysis, with no cortical compromise. Magnetic resonance imaging (MRI) and computed tomography (CT) scans of the knee revealed findings consistent with giant cell tumor due to a lytic lesion at the distal femur, with a potential differential diagnosis of telangiectatic osteosarcoma. Bone scintigraphy showed marked uptake at the distal femur, with no other bone lesions (**figures 1**-**3**).

An open biopsy of the distal femur was performed at the operating room. Pathology reported the presence of spindle cells with blunt ends, pink cytoplasm with vacuolated areas organized in fascicles, moderately pleomorphic tumoral nuclei, variable mitotic activity ranging from 0 to 5, and 5% of necrotic areas. Immunohistochemistry revealed a strong, diffuse positivity for muscle actin, h-caldesmon and myosin.

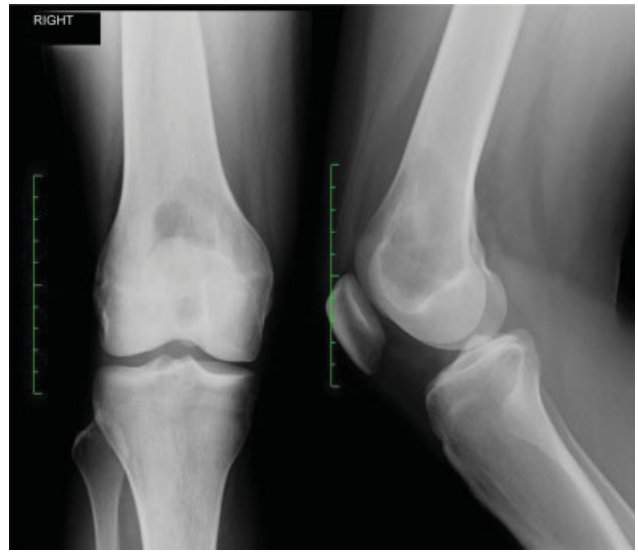

Fig. 1 Anteroposterior and lateral right-knee radiographs showing a lytic lesion in the distal metaphysis of the femur.

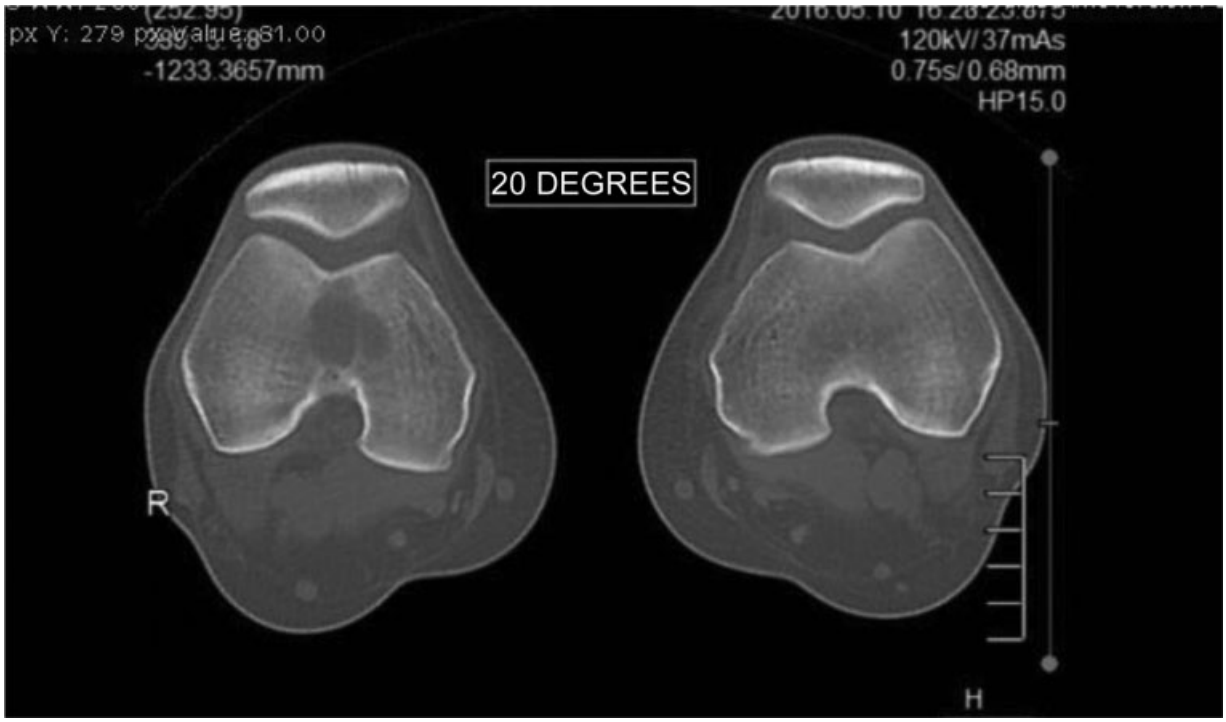

Fig. 2 Comparative knee computed tomography scan. Note the lytic lesion within the right femur.

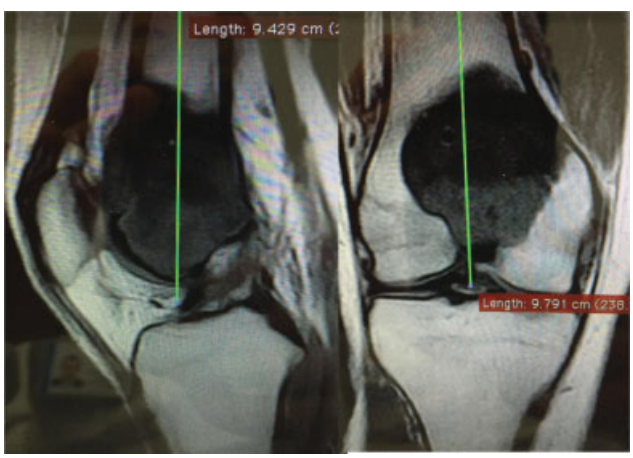

Fig. 3 Right-knee magnetic resonance imaging scan showing extensive involvement of the distal femoral metaphysis, with no extraosseous compromise.

The Ki67 proliferation index was of 60%. There was no positivity for cytokeratin AE1/Ae3, desmin, protein S-100, monoclonal antibiody HMB458, cluster of differentiation 99 (CD99), or for estrogen receptors, resulting in a diagnosis of well-differentiated bone LMS. The treatment started with 3 cycles of preoperative neoadjuvant chemotherapy with ifosfamide 1,000 mg/m^2 from days 1 to 3, and doxorubicin 70 mg/m^2.

A second surgery was carried out for extended tumor resection and limb salvage with a knee endoprosthesis (**figure 4**), with no complications. Pathology confirmed the diagnosis of a well-differentiated primary bone LMS with negative margins and 20% of necrosis (**figures 5** and **6**). Next, the patient received adjuvant chemotherapy, with 4 cycles of

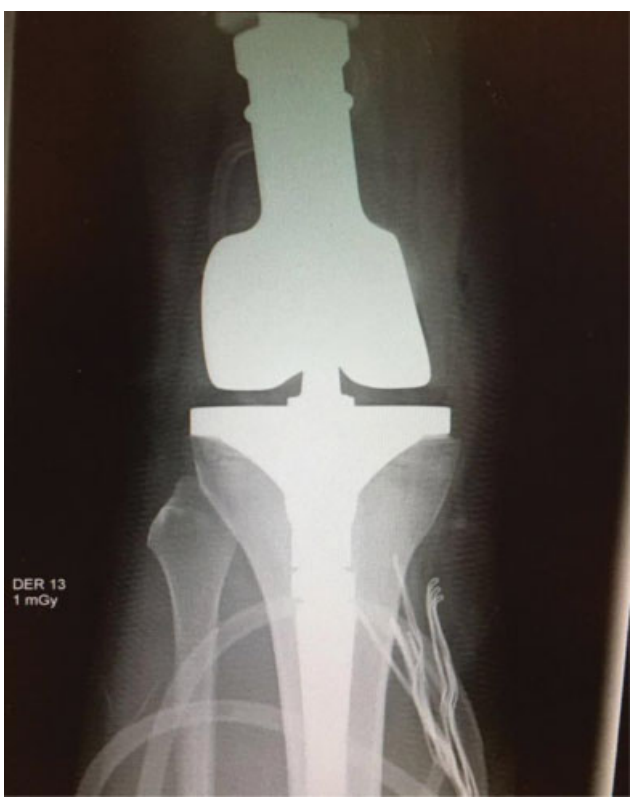

Fig. 4 Postsurgical follow-up right-knee radiograph.

gemcitabine 1,000 mg/m^2 between days 1 to 8, and docetaxel 70 mg/m^2 on day 1.

During the postoperative follow-up, the patient presented adequate clinical evolution, with good rehabilitation and recovery of the mobility and functionality of the

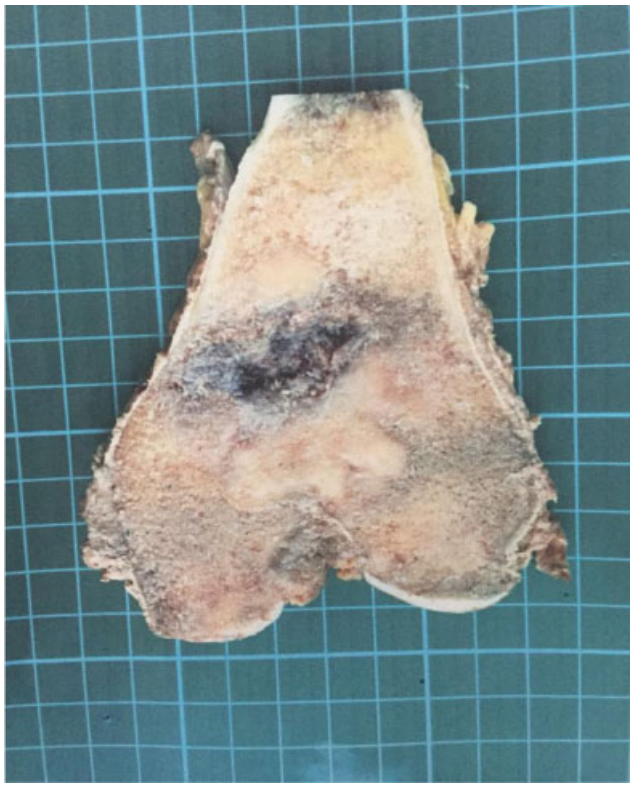

Fig. 5 Gross appearance of the pathology specimen.

right knee. Two months after the surgery, the patient complained of pain in the right clavicle. A radiograph revealed a fracture in the middle third of the clavicle with pathological characteristics (**figure 7**). A positron emission tomography (PET) scan was requested, and it showed a lesion in the middle third of the right clavicle

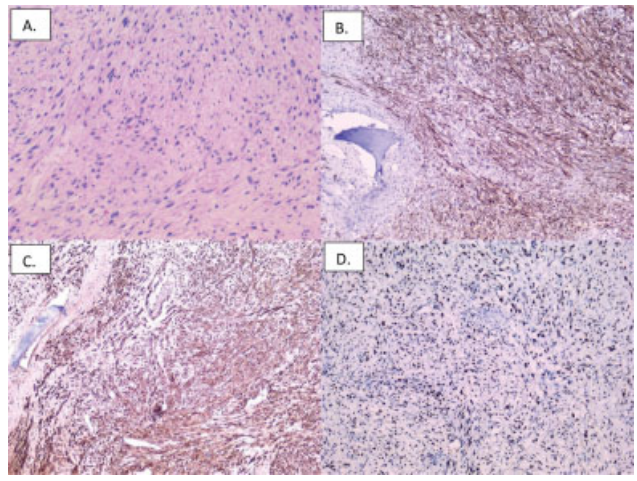

Fig. 6 (**A**) Elongated tumor cells with atypia and mitosis. Hematoxylin-eosin staining, 20x magnification. (**B**) Positive tumor (brown stain) for h-caldesmon. Immunohistochemical technique, 20x magnification. (**C**) Desmin-positive tumor (brown stain). Special immunohistochemical technique, 20x magnification. (**D**) Study of Ki67 proliferation index at 30%. Immunohistochemical technique, 20X magnification. Note: This marker indicates the percentage of dividing cells within a tumor.

consistent with a pathological lesion. A biopsy was taken, and it revealed a metastatic bone LMS lesion, which was surgically resected. Eighteen months after the surgery, the patient was evaluated with a PET scan, which showed no new metastasis (**figura 8**), no infection, and good general conditions. The rehabilitation was adequate, and follow-up radiographs revealed no new lesions, but showed an osteoblastic reaction in the femur and tibia due to the use of a cementless prosthesis.

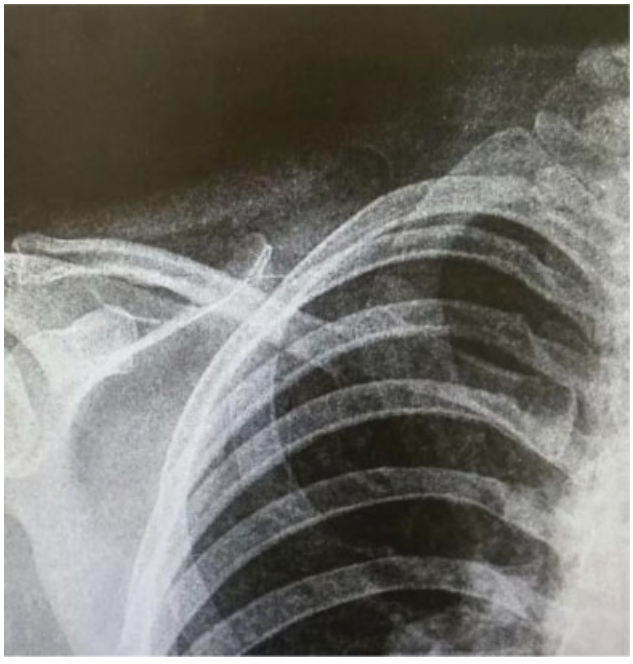

Fig. 7 Right-clavicle radiograph revealing a pathological fracture in the middle third of the bone.

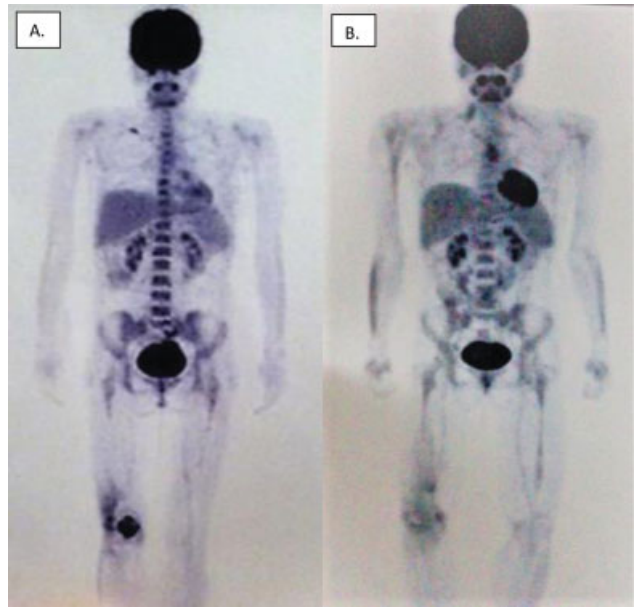

Fig. 8 (**A**) Positron emission tomography (PET) scan revealing a metastatic lesion in the right clavicle two months after salvage surgery. (**B**) Follow-up PET scan 18 months after the resection of the femoral lesion.

Discussion

Bone LMS was first described in 1965 by Evans and Sanerkin.[15] It has a wide presentation according to age and gender,[5–9,14] but it is a very infrequent condition, accounting for less than 0.7% of all bone tumors.[4,5,7,9] It may be primary or metastatic in onset.[16] In recent years, this rate might have increased due to the improvement in immunohistochemical diagnostic techniques.[3,12] According to a 2009 review by Adelani et al.,[17] based on 107 cases reported in English, LMS is more frequent in 40-year-old males (age range: 9 to 87 years); however, the present case report is that of a young female patient.

There are several hypotheses on the origin of primary bone LMS, which probably arises from smooth muscle vascular cells or from fibroblasts capable of differentiating into smooth muscle.[4,18] Some reports[19] have associated LMS with the Epstein-Barr virus (EBV) infection in the context of severe immunosuppression (patients with acquired immunodeficiency syndrome [AIDS] and those submitted to kidney, heart or liver transplantations).[19] Other known factors for the development of sarcomas, such as radiation therapy, were not related to LMS. It occurs mainly in long bones, such as the distal femur (42–45% of the cases), as in the present clinical case, the proximal tibia (25–38% of the cases), and the proximal humerus (15% of the cases), predominantly at the epiphysial-metaphyseal region. Although it is not very frequent, cases of LMS have been reported in the craniofacial bones, the radius, the clavicle, the fibula, the pelvis, the phalanges, the metatarsals, and the vertebrae.[1,5,8–11,14] Symptoms are usually nonspecific and insidious, although some studies[5,8,11] have identified pain as the main symptom, which is consistent with the case herein described.

Bone LMS has no pathognomonic radiographic appearance, and it can be similar to any other primary or secondary disorder.[10] It is an osteolytic lesion with aggressive behavior, periosteal reaction, endosteal erosion, a permeative pattern, poorly-defined borders, medullary and cortical compromise, and no sclerosis.[7,10,11,14] It presents with pathological fracture in 15% to 20% of the cases.[4,14] In 20% of the cases, areas of calcification are identified, complicating its differentiation with an osteosarcoma.[9] The MRI scans reveal low signal intensity on T1-weighted images, similar to that of muscle, and a high signal intensity on T2-weighted images, usually with areas of greater compromise compared to plain radiographs.[5,7,16] However, MRI enables the clear identification of the tumor and surrounding tissues, which contributes to the correct evaluation of the adjacent structures.[14] Differential diagnoses are gastrointestinal-tract or soft-tissue LMS metastases, low-grade intramedullary osteosarcoma, bone fibrosarcoma, dedifferentiated chondrosarcoma, metastatic spindle-cell carcinoma, malignant hemangiopericytoma, epithelioid angiosarcoma, epithelioid hemangioendothelioma, and osteomyelitis.[1,5,7,8,11]

The most common site of metastasis is the lung, followed by the lumbar spine and liver.[1,16] Other common sites of metastasis include the adrenal glands, the kidney, the mediastinum, the inguinal lymph nodes, and the supraclavicular lymph nodes;[14] herein, we report a distant bone metastasis located at the right clavicle.

Macroscopically, bone LMS is a grayish-white fleshy lesion with necrotic areas.[18] Histologically, it is characterized by the absence of chondral or osteoid matrices, with trabecular-bone infiltration, areas of necrosis or hemorrhage, and the presence of spindle cells, usually arranged in disorganized fascicles with intersections at perpendicular angles, cellular atypia, nuclear pleomorphism with cigar-shaped nuclei, abundant eosinophilic and fibrillar cytoplasm, in addition to an immunohistochemical profile positive for actin, smooth muscle, and tumor markers, including actin, desmin, alpha-smooth muscle actin, h-caldesmon, and vimentin.[1,2,5,6,9–12] Our patient presented spindle cells with blunt ends, pink cytoplasm with vacuolated areas organized in fascicles, moderately pleomorphic tumor nuclei, variable mitotic activity (ranging from 0 to 5), 5% of necrotic areas, and positivity for muscle actin, h-caldesmon, and myosin, which is consistent with descriptions in the literature.[1,2,5,6,9–12]

Surgical excision with wide margins is considered the gold standard in LMS management, ensuring curative treatment. Amputation must be reserved for cases with compromise of the neurovascular bundle or extensive soft-tissue involvement.[1,16] Although the role of preoperative and postoperative chemotherapy and radiation therapy remains debatable, they were used as neoadjuvant therapy in our patient.[1,3,4,6,12]

The prognosis of LMS is difficult to determine because of the limited number of reports.[2,3,5–8,10–15,17] However, most studies report an aggressive behavior associated with an unfavorable prognosis. The prognostic factors that have been related to a lower survival in bone LMS include age >40 years, size >8 cm, the presence of a pathological fracture, amputation, affected margins, the presence of metastasis, delay or absence of surgical management, and poor response to preoperative chemotherapy.[3,20] In a study, Brewer et al.[16] showed that the prognosis is based on the stage at diagnosis. In cases with stages 1b or 2a on the Enneking classification, survival reached 100%; in stage 2b, the 5-year survival was of 60% and the 10 and 15-year survivals were of 43%.[16] A multicenter study[3] in Japan with 48 patients with primary LMS showed an overall 5-year survival rate of 78.3%, and a tumor-free survival of 44.9%. However, neoadjuvant chemotherapy was used in 18 patients, with no clear benefits. The presence of metastases in the first visit and the lack of definitive surgery were significantly correlated with a poor overall survival, and the surgical margin was a significant prognostic factor for disease-free survival.[3] In a case series[20] of 8 patients with bone LMS, all subjects developed metastases within 12 months of the primary diagnosis, regardless of the tumor grade; in the patient herein described, the metastasis appeared 2 months after the initial procedure.

Conclusions

Primary bone LMSs are rare, aggressive tumors that must be treated vigorously. Today, radical surgical management with negative margins represents the only curative option; adjuvant treatment with chemotherapy and radiation therapy

have not been shown to be effective. During follow-up, it is essential to evaluate the possibility of metastatic lesions to treat them in a timely manner. Further studies with long-term case series are required to establish treatment protocols and prognosis for this type of injury.

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Conflict of Interests
The authors have no conflict of interests to declare.

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