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CASE REPORT

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Primary bone leiomyosarcoma of distal femur: case report and literature review

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Abstract

We present the case of a 58-year-old patient presented with a spontaneous right supracondylar fracture. The initial bone biopsy, highlighted the defining histopathological (HP) elements for a leiomyosarcoma (LMS), initially considered a metastasis. The complex imaging examinations did not reveal another tumor, so the final diagnosis was primary bone LMS. Final treatment was a wide tumor resection and reconstruction with a knee tumor prosthesis, preceded and followed by three cytostatic cycles (Doxorubicin 75 mg/m^2). The HP examination has confirmed the previous diagnosis. The key microscopic features for the diagnosis of bone LMS was: malignant mesenchymal proliferation composed of intersecting fascicles of cells with eosinophilic, fibrillary cytoplasm and pleomorphic, elongated, blunt-ended, cigar-shaped nuclei of variable sizes; variable mitotic count; presence of tumor necrosis and stroma with changes that include hyalinization, myxoid change, with absence of chondroid or osteoid matrix; diffuse positivity for smooth muscle immunohistochemical markers: smooth muscle actin, desmin, h-caldesmon. At 12 months after the tumor resection, the patient is in good condition without any sign of local recurrence or metastatic disease. LMS represents a type of soft tissue sarcoma (STS), a variant of the spindle cell sarcomas, accounting for about 7% to 10% of all STS. Bone LMS can be primary or secondary; the primary variant is very rare, representing a very small percentage (around 0.7%) of all primary malignant bone tumors, according to the literature data. Very few cases are presented in the literature; the management of this kind of tumor is controversial, especially regarding the chemo- and radiotherapy.

Keywords: primary bone leiomyosarcoma, fascicles of spindle cells, smooth muscle differentiation, absence of malignant osteoid.

Introduction

Soft tissue sarcomas (STS) represent a rare form of cancer (approximately 1% of all adult cancers), which have as starting point the mesenchymal tissue and it consist of more than 50 subtypes [1]. STS are aggressive tumors, with the overall survival rate of five years between 52% and 70%, with an average of 64% [2, 3]. STS may develop at any age, having a peak above 50 years of age, and theoretically in all anatomic sites. Most common involved sites are the limbs (40%), abdomen (35%), trunk (10%), head and neck (5%), and other (10%) [4, 5].

Leiomyosarcoma (LMS) represent a type of STS, a variant of the spindle cell sarcomas, accounting for about 7% to 10% of all STS [5].

It can be present at the level of different areas, especially the retroperitoneum, the urinary tract, gastrointestinal tract, soft tissues of the extremities, and can metastasize to the lung, liver, kidney, brain, skin, and bone. LMS can be detected in the bone more frequent as secondary (metastatic) tumor, but as primary tumor as well; the most common site is the metaphysis of the long bones, especially around the knee joint. Primary bone LMS is a rare tumor, representing less than 0.7% of all primary malignant bone tumors [5].

The bone and soft tissue LMS have similar histological characteristics, but the clinical aspects and the prognosis are different.

Due to the low frequency of this type of tumor, the clinical reports are very few, the diagnostic is difficult and therapeutic approach is still debatable.

Aim

The aim of our paper was to present our diagnostic and therapeutic algorithm in this case, as well as the literature review on a bone tumor very rarely discovered in daily practice.

Case presentation

A 58-year-old patient, without any previous significant medical conditions, has had spontaneous moderate pain in her right thigh and knee for about two months; after a

minor trauma, she felt intense pain at this level in February 2020. Clinical and classical radiological examinations show the presence of a femoral supracondylar fracture, on pathological bone, diagnosis confirmed by magnetic resonance imaging (MRI) examination. The laboratory tests were in the normal range. Three days after hospital admission in an orthopedic department, surgical treatment was performed, practicing stabilization of the fracture with an external fixator that bridges the knee and the biopsy of the fracture site in the same surgical time.

Histopathological (HP) examination of the tissue fragments obtained from surgical biopsy highlighted the following aspects: (*i*) macroscopically, multiple gray tissue fragments, with elastic consistency and hemorrhagic suffusion; (*ii*) microscopically, multiple fragments represented by bone tissue with a malignant mesenchymal tumor cell proliferation, with fascicles of neoplastic cells intersecting at 90°, with vague storiform foci; tumor cells show marked cytonuclear pleomorphism, fine fusiform with imprecise cell boundaries, cytoplasm in moderate amounts, pale eosinophilic, fibrillar; oval or elongated nuclei, vesicular and obvious nucleoli; increased mitotic activity with atypical mitoses [10–15 mitoses/10 high-power fields (HPFs)], areas with myxoid stroma and large areas of tumor necrosis (less than 50%) and recent intratumorally bleeding. Scant intra- and peri-tumoral lymphocytic infiltrate was present. These aspects oriented the diagnosis towards bone metastasis of moderately differentiated LMS.

At six weeks postoperatively, a chest–abdomen–pelvis computed tomography (CT) scan was performed and does not show the presence of primitive tumors or secondary metastatic determinations. After one month, the CT examination was repeated, adding the examination of the lower limbs which confirms the absence of other primitive or metastatic tumors in the examined areas; note the absence of inguinal tumor lymphadenopathy corresponding to the affected limb.

At six weeks after the mentioned surgery, neoadjuvant chemotherapy with Doxorubicin 150 mg (75 mg/m^2) was instituted for three cycles at three weeks interval, without any significant side effects. After three months, the external fixator was removed, clinical and radiological consolidation of the fracture being achieved (Figure 1, A and B).

The multidisciplinary consult establishes the necessity of tumor resection after those three cycles. For the final preoperative evaluation, another chest–abdomen–pelvis CT scan was performed, completed with right thigh MRI scan, right tight angio-CT scan, and bone scintigraphy.

Chest–abdomen–pelvis CT examination did not show the presence of metastasis.

Contrast-enhanced MRI of right tight examination showed: circumferential tissue mass developed in the distal metaphysis of the right femur with inhomogeneous structure in T2 hypersignal, T1 hyposignal, with diffusion restriction areas and inhomogeneous and intense contrast intakes in T1 + Gadolinium (Gd) sequence. The tumor has an extra-cortical expansion; important extension in the medial, intermediate, and lateral vastus muscles with significant muscular edema and a fluid collection in the extended T2 hypersignal in the articular, retrocondylar space of the knee. The tumor formation has a clear but bumpy contour and dimensions of 60/42/53 mm; two small extracortical areas at the metaphyseal–diaphyseal junction of the right femur, 34 mm above the tumor, with annular appearance, with peripheral contrast socket and diameter of 2 mm, suggesting changes due to orthopedic treatment were noted. There are no primary or secondary lesions in the left femur (skip metastasis) and left thigh (Figure 2).

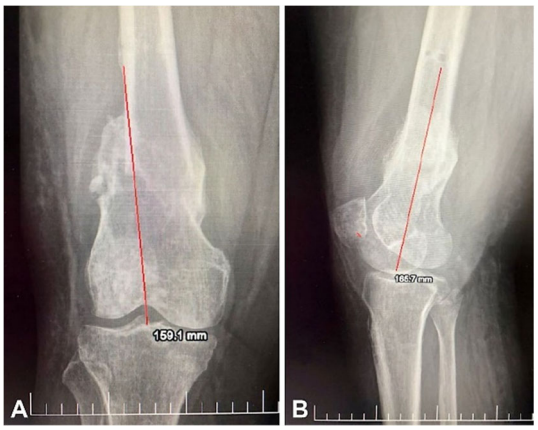

Figure 1 – ***(A and B) Right femur X-rays (three months after the spontaneous fracture), after external fixator removal showed fracture consolidation.***

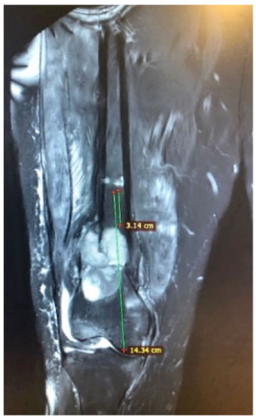

Figure 2 – ***MRI aspect of the left tight with lateral extracortical expansion and extension in the surrounding muscles. MRI: Magnetic resonance imaging.***

Angio-CT of the right thigh did not show signs of tumor invasion in popliteal space, the vessels are free of tumor, and no vascular thrombosis is noted.

Bone scintigraphy did not show other bone tumoral determinations.

According to tumor, node and metastasis (TNM)–G classification system, the tumor can be staged III A (T2, N0, M0, G2).

The surgery consisted of resection of the distal extremity of the right femur (15 cm proximal from the femoral articular surface) and adjacent soft tissues; resection of the biopsy tract from the lateral aspect of the tight; reconstruction with a knee tumoral prosthesis with good muscular coverage to obtain a painless functional result (Figure 3, A and B). HP examination of the bone marrow from the resection level was performed and did not show the presence of tumor cells at this level.

Macroscopic examination of resected bone segment showed the following details: 15/8/6 cm, size of the resected segment; 60/42/53 mm size of the tumor with firm consistence, tan-white color and infiltrative pattern of growth replacing marrow.

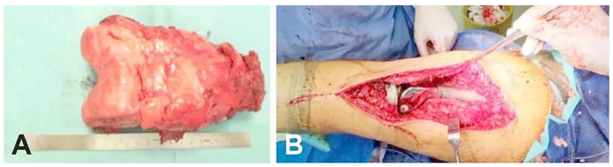

Figure 3 – ***(A) Resection specimen: the distal 15 cm of the right femur surrounded by muscular layer; (B) Reconstruction with modular tumoral knee prosthesis; note the good muscular coverage of the prosthesis.***

All tissue fragments harvested from resected bone were fixed in 10% neutral buffered formalin (pH 7.4) for up to 24 hours, processed using the paraffin-embedding technique for microscopy analysis. All slides were stained with Hematoxylin–Eosin (HE) and examined with Olympus CX41 microscope.

HP mesenchymal tumoral proliferation composed of intersecting fascicles with variable thickness, of big sized, spindle cells with eosinophilic, fibrillary cytoplasm and elongated, blunt-ended nuclei of variable sizes with irregular nuclear contour and clumped chromatin (cigar-shaped nuclei) (Figure 4A). Some nuclei present eosinophilic intranuclear inclusions and mitotic count of 16 mitotic figures/10 HPFs. Myxoid and storiform zones were present (Figure 4, B and C). Limited coagulative tumor necrosis (<50% in nuclei of tumor cells) and frequent nuclear atypia were present as well; the tumor stroma was fibrovascular, in low quantity and with hyalinized zones (Figure 4D). Focally, the tumor breaches the cortex, with minimal involvement of the periosteum. Resections margins were not infiltrated.

According to all these aspects, the final HP diagnosis was grade 2 LMS [total score – 5 in *French Federation of Cancer Centers Sarcoma Group* (*Fédération Nationale des Centres de Lutte Contre le Cancer* – FNCLCC) grading system; tumor differentiation: score 2, mitotic count: score 1, histological grade: score 2].

Immunohistochemical (IHC) analysis was performed on 4 μm sections prepared from formalin-fixed paraffin-embedded tissue using manual technique: anti-smooth muscle actin (SMA) antibody (clone: mouse HHF35, Cell Marque), anti-desmin antibody (clone: mouse D33, Cell Marque), anti-Ki67 antibody (clone: rabbit SP6, Cell Marque), anti-estrogen receptor (ER) antibody (clone: rabbit EP1, Cell Marque). SMA and desmin were diffuse, strong positive in tumor cells (Figure 5, A and B). Ki67 was positive in 50% of malignant cells in the most active areas (Figure 5C) and ER was negative in tumoral cells (Figure 5D).

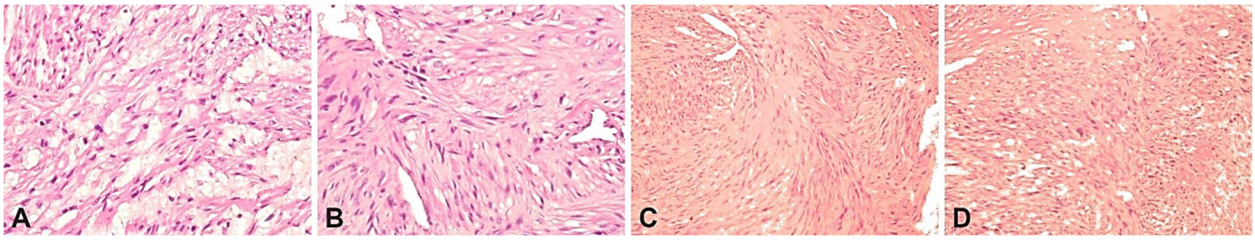

Figure 4 – ***(A) Fascicles of spindle mesenchymal cells with blunt-ended atypical nuclei; (B) Vague storiform zones; (C) Myxoid zones; (D) LMS: atypical, stromal hyalinization and necrosis. HE staining: (A and C) ×400; (B and D) ×200. HE: Hematoxylin–Eosin; LMS: Leiomyosarcoma.***

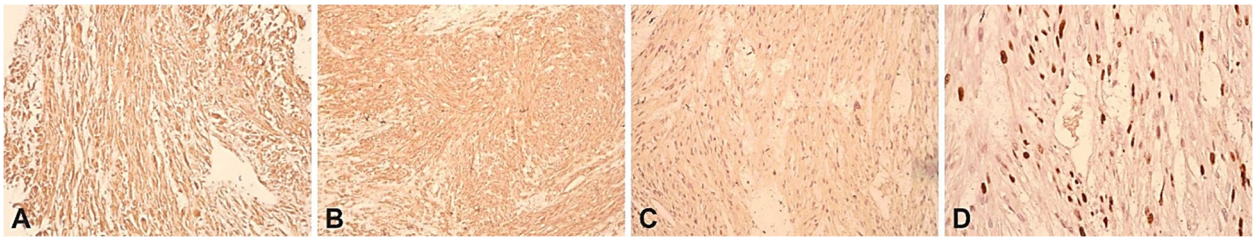

Figure 5 – ***(A) SMA positive, diffuse in tumoral cells; (B) Desmin positive, diffuse in tumoral cells; (C) Ki67 positive in nuclei of tumoral cells; (D) ER negative in tumoral cells. Anti-SMA antibody immunomarking: (A) ×100. Anti-desmin antibody immunomarking: (B) ×100. Anti-Ki67 antibody immunomarking: (C) ×100. Anti-ER antibody immunomarking: (D) ×200. ER: Estrogen receptor; SMA: Smooth muscle actin.***

The morphological aspects correlated with the IHC results establish the diagnosis of moderately differentiated LMS (metastatic or primary).

Correlations of clinical, imagistic and IHC aspects and absence of osteoid or chondroid matrix as well diagnose a primary bone LMS and rule out osteosarcoma or chondrosarcoma.

The postoperative evolution was favorable, with immediate postoperative mobilization and primary healing of the surgical wound.

After six weeks, the adjuvant chemotherapy was resumed with the same agent (Doxorubicin 75 mg/m^2) and time frame (three cycles at three weeks interval).

At nine months the patient was in a good condition, without any sign of local or general recurrence of the disease. The functionality of the replaced joint was normal (100° of flexion, full extension), which permits ambulation without any kind of additional support (crutches or cane).

Discussions

Actually, there are two theories regarding the origin of primary bone LMS: the first suggests that vascular smooth muscle cells from the bone are involved; the second theory sustained the origin from intermediate cells, especially fibroblasts, who are able to differentiate in smooth muscle cells who synthesize connective tissue matrix, and myofilaments [6–8]. These second theory is sustained by the

fact that many studies demonstrate the presence of fibroblasts in different differentiation states in this type of tumor.

The most common symptoms are pain, regional swelling, and if the tumor is big enough and evolves outside the bone, a tumor mass can be palpated. Due to the osteolytic character, which lead to the cortical destruction as well, in 15% of cases, patients present a pathological fracture [9].

The diagnostic is oriented by clinical and imagistic aspects but is established by the HP examination.

The macroscopic features of bone LMS are: (*i*) the diameter usually more than 5 cm, (*ii*) firm consistency, (*iii*) tan-white color, (*iv*) areas of hemorrhage and necrosis (frequent in high grade tumors) and an infiltrative growth pattern, with the tumor replacing the marrow and the surrounding bony trabeculae [1, 10–12].

Bone LMS has the same HP aspects as the LMS from other sites, with long, intersecting at 90° fascicles of cells with eosinophilic, abundant, fibrillary cytoplasm, with occasional vacuoles and blunt-ended, cigar-shaped, elongated, pleomorphic nuclei; the fascicles infiltrate diffusely the stroma [1, 10–16]. Mitotic activity is observed, including atypical forms in high-grade tumors [10, 13, 14]. In the stroma, there can be identified hyalinized areas, coagulative tumor necrosis and myxoid areas; chronic inflammation can be present, usually focally occasionally there can be "hemangiopericytomas" vessels [7, 10, 13, 14].

Regarding the immunophenotype, the cells present with smooth muscle differentiation: positive, diffuse staining with desmin, h-caldesmon, SMA [1]. The immunohistochemistry is required for an accurate diagnosis, especially when the tumor is poorly differentiated or undifferentiated [12, 17].

Differential diagnosis is made with the following tumors [1, 7, 8, 10, 12, 17]: (*i*) undifferentiated pleomorphic sarcoma: epithelioid or spindle tumoral cells, with high-grade and bizarre cytology, frequent mitotic figures and areas of necrosis; it can associate stroma with myxoid changes, areas of inflammation and giant cells, but despite all these aspects, it can still present with an ambiguous morphology and IHC profile; (*ii*) myofibroblastic sarcoma: tumoral cells have amphophilic cytoplasm, short and tapered nuclei, IHC staining for muscle markers is patchy not diffuse; (*iii*) fibrosarcoma: presence of elongated-ended fusiform nuclei not with blunted edges; (*iv*) osteosarcoma: focal osteoid formation and lack of myogenic markers; (*v*) chondrosarcoma: chondroid formation; (*vi*) malignant fibrous histiocytoma: evident storiform pattern and bland nuclei; (*vii*) metastatic sarcomatoid carcinoma: negative muscle markers in immunohistochemistry; (*viii*) leiomyoma of bone: no mitotic activity and no cytological atypia is present.

The TNM–G classification of STS according to *American Joint Committee on Cancer* (AJCC) take into consideration the dimension of the tumor (T), presence of regional lymph node (N) metastasis, distant metastasis (M) and histological tumor grade (G) [1]. G is based on cellular differentiation, mitotic rate, and extent of necrosis, according to the *FNCLCC* [1, 14]. For STS, staging should be done carefully because there are tissue types excluded in each location of the sarcoma [18].

A tumor is divided into stage I (low grade: grade 1) and stage II or more (high grade: grade 2 or 3) according to the histological grade and to the tumor size; at the same time, the depth of the tumor (superficial or deep from the superficial fascia) is not considered any more as a factor of staging [19].

A number of prognostic factors have been described for the patients suffering from STS. The size (>8 cm) and depth of the tumor, patient age (>40 years), the presence of a pathological fracture and poor response to preoperative chemotherapy represent poor predictive factors for survival [20, 21]. Anatomic location and histological grade seem to have no effect on evolution and survival rate [4]. More recently the role of systemic inflammation for the prognosis in these patients has been described. Thus, interleukin-6 (IL-6) cytokine is a regulator of the pro-oncogenic transcription factors [nuclear factor–*kappa*B (NF-*κ*B), signal transducer and activator of transcription 3 (STAT3)] [22, 23].

The optimal treatment for this rare type of STS is controversial. Surgical resection remains the most efficient treatment modality and for some authors representing the only curative option. The resection needs to be large with free margins; negative microscopic surgical margins offered much better outcome than positive ones [24]. The level and extension of the resection must be established preoperatively on imaging investigations. MRI (with or without contrast, to certify the optimal distance from the tumor, as well as the presence of skip-metastasis) and a chest–abdomen–pelvic CT scan is recommended. Positron emission tomography (PET)/CT may be useful in staging, prognostication, grading and determining response to neoadjuvant therapy. Other imaging studies, such as angiogram, may be warranted in certain circumstances. In the case of extension in the soft parts, spontaneously or following a fracture, the resection level must be re-evaluated.

Radiotherapy is another treatment solution but with controversial results; Antonescu *et al.* showed no differences in terms of survival between patients who received only surgery and patients who received surgery and radiation therapy, due to a possible resistance of this type of tumor to the irradiation [25]. A recent extensive study examined the effects of external beam radiation therapy (EBRT) compared to no EBRT protocol, showed reduced local recurrence and overall survival [26].

The efficiency of chemotherapy for primary bone LMS is another hot topic under investigation and requires further evaluation, in opposition to the treatment of metastatic bone LMS, for which chemotherapy represents the principal approach; Cisplatin, Doxorubicin, Ifosfamide, Mesna and Dacarbazine (if Ifosfamide is not considered appropriate) constitute the first-line treatment for these metastases. The role of these agents against primary bone LMS and the effect on survival rate and time is still unclear [27]. A retrospective trial conducted by Antonescu *et al.* showed no survival rate improvements for patients treated with chemotherapy compared with patients who did not received chemotherapy [25].

Local recurrence after the surgical resection associated with chemotherapy is not very common, but possible. On the other hand, metastases are a very common finding and are developed early, within 12 months of primary

diagnosis, regardless of the initial tumor grade [28]. The most frequent sites of metastasis are the lung and the axial skeleton. Instead, metastases to the liver and lymph are not so common [29].

Conclusions

Primary bone LMS is a rare type of sarcoma, with a potential disastrous evolution, due to his aggressivity and the relatively poor response to the traditional therapy. The most efficient treatment remains large bone resections and reconstruction. The combination of chemotherapy can be effective without clear data in this regard. Several multi-center studies are currently underway that attempt to establish an adjuvant therapeutic protocol with various chemotherapeutic agents (Doxorubicin, Cisplatin, Ifosfamide, Methotrexate, etc.). Despite these developments, the most important factor in terms of patient survival is the time elapsed from the onset of the symptoms to the surgery. Considering this fact, the importance of a diagnosis as soon and as accurate as possible of all forms of STS in general and of LMS in particular is of paramount importance.

Conflict of interests

The authors declare that they have no conflict of interests.

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