

# Primary intraosseous smooth muscle tumor of uncertain malignant potential: original report and molecular characterization

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## Abstract

We report the first case of primary intraosseous smooth muscle tumor of uncertain malignant potential (STUMP) which is analogous to borderline malignant uterine smooth muscle tumors so designated. The tumor presented in the femur of an otherwise healthy 30-year-old woman. Over a 3-year period, the patient underwent 11 biopsies or resections and 2 cytologic procedures. Multiple pathologists reviewed the histologic material including musculoskeletal pathologists but could not reach a definitive diagnosis. However, metastases eventually developed and were rapidly progressive and responsive to gemcitabine and docetaxel. Molecular characterization and ultrastructural analysis was consistent with smooth muscle origin, and amplification of unmutated chromosome 12p and 12q segments appears to be the major genomic driver of this tumor. Primary intraosseous STUMP is thought to be genetically related to leiomyosarcoma of bone, but likely representing an earlier stage of carcinogenesis. Wide excision and aggressive follow-up is warranted for this potentially life-threatening neoplasm.

## Introduction

Leiomyosarcoma (LMS) is a malignant neoplasm possessing histologic, immunophenotypic and ultrastructural evidence of smooth muscle differentiation. Common sites include the uterus, retroperitoneum and extremities. LMS can rarely present as a primary tumor of bone with only 147 reported cases, where it is

thought to arise from smooth muscle of intraosseous blood vessels, pluripotent mesenchymal stem cells, or intermediate cellular forms such as myofibroblasts.<sup>1,2</sup> The differential diagnosis includes primary intraosseous leiomyoma, which is an exceedingly rare tumor with about two dozen cases reported.<sup>3,4</sup>

Smooth muscle tumor of uncertain malignant potential (STUMP) is a term first used by Stanford investigators after studying 213 cases of problematic uterine smooth muscle tumors.<sup>5-7</sup> According to the World Health Organization classification, a uterine smooth muscle tumor which cannot be diagnosed unequivocally as benign or malignant should be designated as STUMP.<sup>5</sup> Although most STUMPs are of uterine origin, they have also been described arising in non-visceral soft tissues and the urinary bladder.<sup>8,9</sup> Atypical leiomyoma (ALM) is a second *borderline* tumor described in the uterus with histologic features overlapping with STUMP and LMS.<sup>6</sup> A thorough English-language literature review failed to identify any cases of primary intraosseous atypical leiomyoma or STUMP. We present to our knowledge the first reported case of a primary intraosseous smooth muscle tumor of uncertain malignant potential highlighting the challenges of diagnosis and management of these rare neoplasms.

## Case Report

A 30-year-old Caucasian female, with no significant past medical history, presented with progressive left distal femur pain. Conventional radiographs and computed tomography (CT) images of the left femur demonstrated a cortically based lytic lesion in the distal femoral metaphysis with an extraosseous soft tissue component (Figure 1). Initial needle biopsy revealed rare atypical spindle cells immunoreactive with anti-vimentin antibodies but nonreactive with anti-broad spectrum cytokeratin, S100 protein and CD 45. A second series of needle biopsies one week later demonstrated a fibroblastic proliferative process that infiltrated fat and was associated with osteoclast-like giant cells, hemorrhage, pigment deposition, chronic inflammatory cells and rare atypical histiocytes (Figure 2A). The pathologist noted that if it was intramedullary, this constellation of findings would be most consistent with a benign fibrous histiocytoma of bone, but its cortical location made an unequivocal diagnosis impossible. Two weeks later, she underwent femur-preserving, fragmentary resection showing a spindle cell lesion with alternating zones of hypercellularity and relatively acellular foci. Atypical mitotic figures were noted along with focal areas of mineralization. Smooth muscle actin (SMA) and caldesmon

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were focally positive in tumor cells, while CK, S100 protein, and EMA were negative and tumor osteoid was absent. A diagnosis of atypical fibrous histiocytoma was made.

She did well for 6 months until she presented with left distal femur pain similar to her initial presentation. Radiographs were non-revealing. Her symptoms persisted, and CT scan 3 months later demonstrated a 3.4×1.8 cm soft tissue component along the posterior cortical margin of resection, which demonstrated stability on follow-up imaging 4 months later. Biopsy confirmed recurrent disease, and a more extensive immunohistochemical panel highlighted smooth muscle differentiation based upon increased reactivity to SMA, muscle specific actin and caldesmon (Figure 2B). Criteria for malignancy were not reached due to a low proliferation rate with Ki-67 staining fewer than 10% of cells and rare mitotic figures. The tumor was again resected, and ultrastructural examination demonstrated scattered arrays of actin filaments with occasional

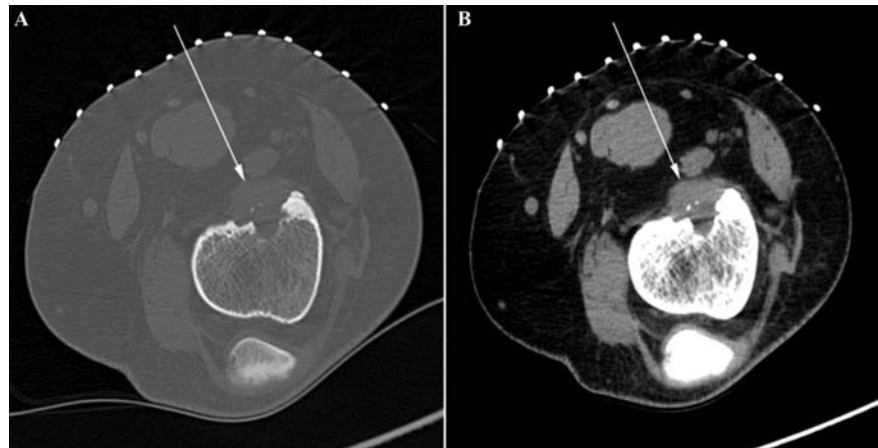
fusiform dense bodies and variable numbers of pinocytotic vesicles along with rudimentary basement membranes consistent with tumor cells of smooth muscle origin (Figure 2C). The tumor was thus reclassified as a STUMP.

The tumor again recurred locally in the left distal femur slightly less than 2 years after the initial biopsy, and repeat biopsy showed more prominent smooth muscle differentiation, a slightly higher Ki-67 staining of 10-15% of cells and a mitotic index of 3/10 hpf, still not fulfilling criteria for malignancy. Comprehensive genomic profiling was performed (Foundation Medicine, Inc., Cambridge, MA) interrogating 405 genes that are validated therapeutic targets or known to be somatically altered in human sarcomas, pediatric cancers and hematologic malignancies. Notably, the tumor contained a number of gene copy number amplifications from chromosome 12. The largest amplicon was a 34 megabase segment of chromosome 12 (chr 12:1-34,300,000) containing a number of genes including *CCND2*, *ETV6*, *FGF6*, *FGF23*, *KRAS*, and *KDM5A*, that was present in an estimated level of 9 copies in the tumor position of the specimen. Another amplicon containing *CDK4* was present in 14 copies (chr 12:58,000,000-58,900,000), an amplicon containing *MDM2* was present in 17 copies (chr 12:66,800,000-76,500,000) and a final amplicon containing *LRRK2* (chr 12:40,200,000-41,300,000) was present in 27 copies. This pattern of gene copy number amplification is similar to previous observations of amplification of segments of chromosome 12 in sarcoma occurring either as ring chromosomes or scattered over the genome as a result of complex structural rearrangements.<sup>10-13</sup> It was also noteworthy that zero somatic base substitution and indel mutations were observed in this specimen, and no amplifications were detected aside from those involving chromosome 12. There was no *ALK* gene rearrangement commonly seen in inflammatory myofibroblastic tumors. These data support the idea that amplification of genes on chromosome 12 is the major genomic driver of this tumor.

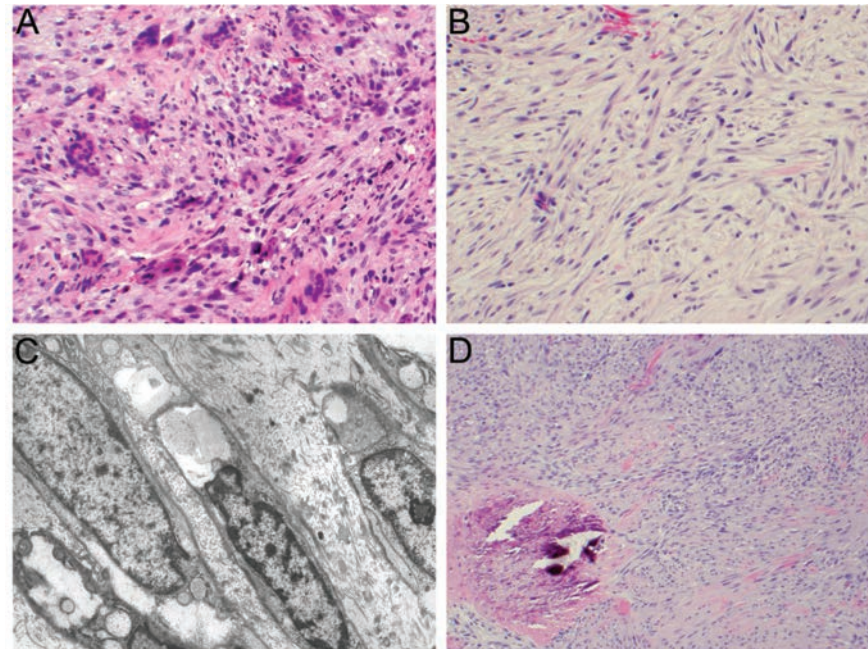
At the time of her third local recurrence, preoperative CT scan showed a 2.3×1.9 cm aggressive appearing lytic distal femur lesion with cortical destruction and peripheral soft tissue enhancement. Chest CT showed no concerning findings. *En bloc* resection was performed with a positive soft tissue margin. Interestingly, the muscle markers other than SMA disappeared on repeat immunohistochemistry, which has been suggested to be a poor prognostic sign. She received adjuvant radiotherapy with 50 Gy delivered to regions at risk for microscopic tumor infiltration with an additional 10 Gy boost to the postoperative bed. Within 3 months of her surgery, subcutaneous nodules were palpated in the left proximal

thigh and left gluteal region. A positron emission tomography (PET)/CT scan showed hypermetabolic foci with standardized uptake values up to 13 within enlarged pelvic lymph nodes, the fourth lumbar vertebra and at multiple subcutaneous sites consistent with metastases. Biopsy of the L4 lesion and excision of the left gluteal subcutaneous nodule revealed metas-

tases with histologic features of smooth muscle and myofibroblastic differentiation. She received radiosurgery to the L4 lesion (20 Gy in a single fraction), which was followed by systemic therapy with gemcitabine and docetaxel at standard doses for LMS. After four cycles, PET/CT showed resolution of all hypermetabolic activity consistent with response to



**Figure 1.** Axial computed tomography images of the left knee in the prone position prior to percutaneous needle biopsy with bone window (A) and soft-tissue window (B). Images show an eccentric, destructive osseous lesion in the posterior distal femoral metaphysis with an associated soft-tissue component that contains scattered calcifications (white arrows).



**Figure 2.** A) Photomicrograph of the original biopsy specimen demonstrating a fibroblastic proliferative process with prominent osteoclast like giant cells, chronic inflammatory cells and hemorrhage [hematoxylin and eosin (H&E), 200×]; B) photomicrograph of the first recurrence featuring an atypical spindle cell lesion with smooth muscle differentiation (H&E, 200×); C) ultrastructural image of the tumor at a recurrence four months later demonstrating prominent actin filaments, occasional dense bodies and pinocytotic vesicles consistent with cells of smooth muscle origin; D) photomicrograph of a subcutaneous metastasis forty-six months after initial biopsy featuring spindle cell sarcoma-like features (H&E, 100×).

treatment. She received a total of seven cycles, and response was maintained for 6 additional months until PET/CT demonstrated multiple widely disseminated hypermetabolic subcutaneous nodules (Figure 3). She then received pazopanib for 6 months before experiencing clinical, histopathologic, and radiographic progression in the lungs and subcutaneous nodules. Karyotype analysis was performed on a subcutaneous metastasis resected for palliation of pain and only normal 46, XX metaphase cells were found. Histology showed features of spindle cell sarcoma 46 months after initial biopsy (Figure 2D). Microarray comparative genomic hybridization performed at the University of Alabama at Birmingham on fresh tissue obtained from a distant subcutaneous metastasis resected for palliation revealed extensive amplification of the entire short arm of chromosome 12 and four interstitial amplifications of 12q collectively representing 20.7 megabases similar to results of genomic profiling described above. Notable deletions of the *CDKN2A* gene on chromosome 9p and the *RBI* gene on 13q were detected with no amplifications identified aside from those on chromosome 12. At this stage of clonal evolution, the pattern of copy number changes was suggestive of an intermediate complexity sarcoma.<sup>14</sup> At the time of this report, she is maintaining a good performance status with prolonged stabilization of disease for 5+ months on a Phase I dose escalation trial of a fibroblast growth factor (FGF) inhibitor selected on the basis of amplification of *FGF* genes on chromosome 12p.

## Discussion

Primary LMS of bone most often arises from the appendicular skeleton with the femur being the most common primary site.<sup>1,2,14</sup> The median age at diagnosis is during the fifth decade, and males and females are equally affected. It is typically an aggressive malignancy with a 5-year overall survival rate of 59%, similar to conventional osteosarcoma.<sup>1,15</sup> Metastases most often affect the lungs and axial skeleton. In the largest published series reporting 33 patients, Antonescu and colleagues found no significant differences in disease-free or overall survival between low and high grade LMS of bone.<sup>15</sup> Therefore, the treatment of choice regardless of histologic grade is *en bloc* resection with wide margins.<sup>1,2,15</sup> The value of adjuvant chemotherapy or radiotherapy has not been established.

Uterine STUMP is most often diagnosed early in the fifth decade and may be a precursor to uterine LMS typically diagnosed later. Recurrence occurs in 10-20% of patients following margin negative resection most often

by hysterectomy and is often delayed for years.<sup>5,16</sup> Recurrence may remain histologically *borderline* or frankly transform to low grade LMS, but they should all be regarded as low grade LMS biologically.<sup>5,6,16</sup>

Recent molecular analysis revealed that ALM, STUMP and LMS share similar genetic mutations involving *p53*, *MED12* and *PTEN* as well as similar microRNA fingerprints that are distinct from fully benign leiomyomas, suggesting benign leiomyomas are not malignant precursors.<sup>6</sup> ALM, STUMP and LMS are therefore proposed to have a similar genetic origin and may represent different stages of tumorigenesis.<sup>6</sup> Molecular pathways involved in LMS includes TP53; MDM2; cyclins A, D and E; CDK2 and CDK4; and KRAS activation.<sup>17</sup> Alterations in the Rb/cyclin D pathway appear to constitute early events in LMS, whereas p53 changes seem to occur later in the course of tumor progression and correlate with high tumor grade and relatively poor prognosis.<sup>17</sup> The case of primary intraosseous STUMP presented here is consistent with this paradigm, possessing multiple alterations of the Rb/cyclin D pathway, but lacking p53 mutation. The prominent myofibroblastic features initially observed in this case coupled with amplification of genes encoding fibroblast growth factors and the *ETV6* oncogene associated with fibrosarcoma support potential evolution of LMS of bone from intermediate cellular forms

such as myofibroblasts.<sup>12</sup> Amplification of the 12q 13-15 region including MDM2 and CDK4 seen in this case has been often reported in bone and soft tissue sarcomas.<sup>12,13</sup> Amplification of regions of 12p including CCND2, KRAS and ETV6 also found in this case has been much less frequently reported in myofibroblastic sarcoma and osteosarcoma, but appears to correlate with increased aggressiveness.<sup>10,11</sup>

Bone and soft tissue LMSs typically have complex karyotypes whereas leiomyomas generally have a normal karyotype.<sup>16,17</sup> A subcutaneous metastasis from the case presented here revealed a normal karyotype. This could represent correct characterization of the tumor or a false negative due to poor proliferation of neoplastic cells in culture with resultant karyotyping of normal bystander cells. Either explanation supports the borderline malignancy of this entity.

The present case arising from the femur during the fourth decade is consistent with a borderline precursor to LMS of bone. It overlaps cytologically with low grade LMS but histologic criteria for malignancy, better defined for uterine or gastrointestinal primaries, were never observed despite generous tissue from the primary site obtained on multiple occasions over a span of three years. This case is also distinct from benign metastasizing leiomyoma because no uterine tumor was

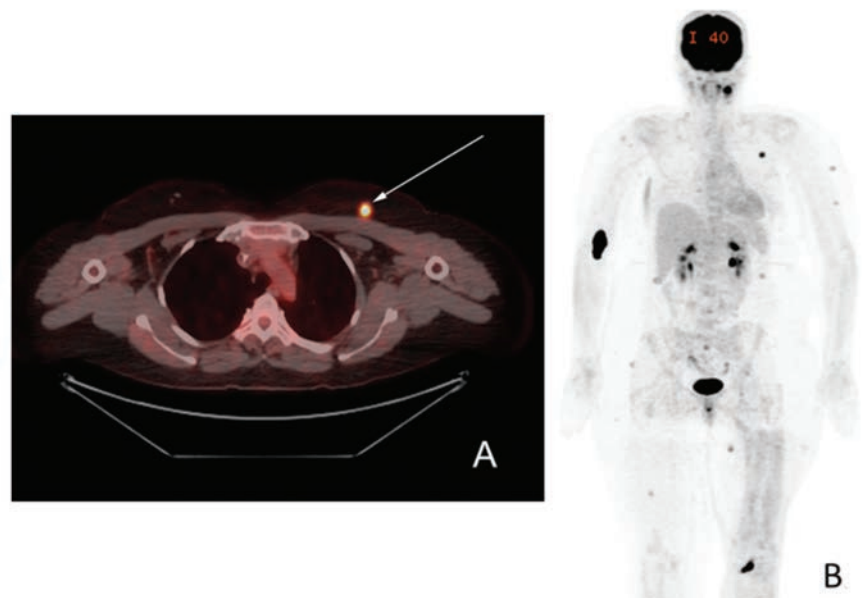


Figure 3. A) 18-FDG positron emission tomography-computed tomography fused image at the level of the upper thorax demonstrates a hypermetabolic lesion in the left anterior chest wall superficial to the pectoralis major (white arrow). This lesion had a maximum SUV of 13.0 and was suspected to represent a subcutaneous metastasis; B) coronal whole body maximum intensity projection image demonstrates multiple hypermetabolic subcutaneous nodules throughout the body consistent with metastases. The hypermetabolic focus in the left knee near the original surgical resection site was compatible with recurrent disease.

detected by PET/CT or pelvic magnetic resonance imaging and metastases were hypermetabolic, rapidly progressive and quite responsive to chemotherapy.<sup>17,18</sup>

Among primary intraosseous tumors of smooth muscle origin, more than 85% of reported cases have been malignant, although benign intraosseous leiomyomas are likely relatively underreported.<sup>1-3</sup> The present case establishes the existence of *borderline* malignant neoplasms within this family. Therefore, wide local excision using oncologic technique appears warranted for most of these tumors. If less aggressive surgical approaches are contemplated, molecular analysis should be strongly considered to provide further evidence of benignity. Otherwise, histologically benign or borderline tumors with more advanced genetic features may be allowed to persist and evolve metastatic potential. Additional research is warranted to molecularly define the spectrum of benign, borderline and malignant smooth muscle tumors of bone to better inform local therapy decisions and identify potential therapeutic targets.

## Conclusions

To our knowledge, this is the first reported case of primary intraosseous STUMP. Histologic criteria for malignancy were at best equivocal over multiple years. Yet, hematogenous metastases were rapidly progressive and sensitive to chemotherapy. Molecular characterization was consistent with a genetic origin similar to LMS, but likely representing an earlier stage of carcinogenesis. Amplification of unmutated chromosome 12p and 12q segments appears to be the major genomic driver of this tumor. Wide local excision using oncologic technique is recommended.

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