Primary Leiomyosarcoma of the Proximal Tibia

Case Report and Review of the Literature

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Leiomyosarcoma is a malignant entity that commonly affects the soft tissues of the body, such as the uterus, gastrointestinal system, and the soft tissues of the extremities. Primary leiomyosarcoma of the bone is a very rare tumor that affects the metaphysis of long bones, especially the distal femur and proximal tibia. Leiomyosarcoma has a radiologic aggressive pattern. The diagnosis is based on microscopic features (elongate and spindled tumor cells) and immumohistochemical and ultrastructural study.

Case Report

A 42-year-old female presented with a five-month history of pain and mild swelling in the left proximal leg. The pain initially occurred solely at night and kept the patient awake. Gradually, she experienced more pain during the day that was exacerbated by walking. The pain was relieved with nonsteroidal anti-inflammatory drugs (NSAIDs). The patient did not complain of any numbness or tingling in the lower extremity nor of any fevers, night sweats, or weight loss. There was no previous history of cancer, benign tumors, prior surgeries, allergies, or infections. Her father had a history of renal cell carcinoma. The patient never smoked or drank alcohol socially. She had traveled to Jamaica one year prior to presentation.

Physical examination revealed mild, localized swelling of the proximal medial left leg that was associated with minor tenderness. The patient had full range of motion about her left knee, hip, foot, and ankle. Motor and sensation evaluations were normal in all of her extremities. She walked with a minor antalgic gait. The pulses were normal in the lower extremity, and she had no palpable lymph nodes in her left groin, popliteal fossa, axilla, or neck. A complete blood count, chemistries, coagulation analysis, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were normal. Radiographic studies were performed that included plain films (Fig. 1), magnetic resonance (MR) images (Fig. 2), and computed tomography (CT) scans. Radiographic evaluation with plain films revealed a permeative, moth-eaten lesion of the left proximal tibia. The lesion was not associated with a periosteal reaction. It appeared to be associated with reactive sclerosis or ossification (Fig. 1). Magnetic resonance images demonstrated a minor degree of extraosseous extension. The lesion was iso-intense to muscle (intermediate signal intensity) on T1-weighted images and hyper-intense on T2-weighted images (Fig. 2). Axial T1-weighted images demonstrated cortical erosion and total marrow replacement by the lesion. Marrow fat was completely replaced. Computed tomography images demonstrated reactive sclerosis and confirmed other radiological findings, such as cortical destruction, total replacement of marrow fat by the lesion and absence of a periosteal reaction. There was increased uptake in the left proximal one-third of the tibia on the bone scan. There were no other areas of abnormal uptake.

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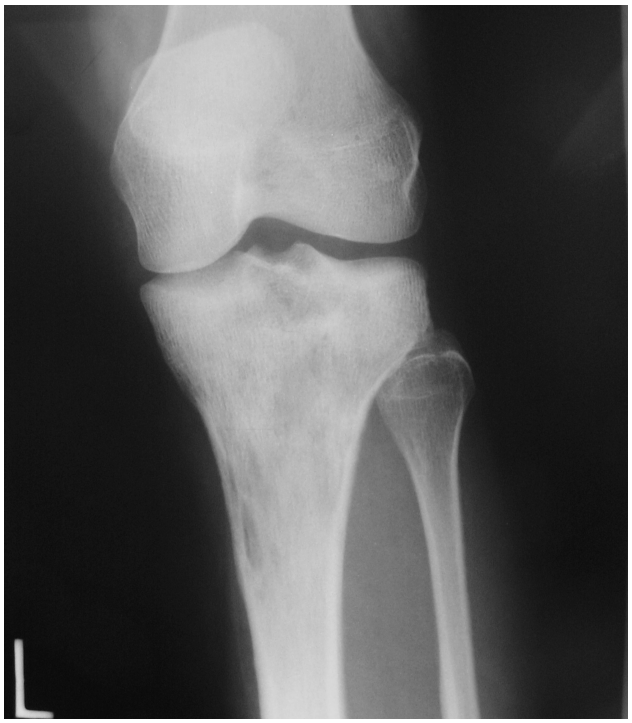

Figure 1 Plain film demonstrating a permeative, moth-eaten lesion of the left proximal tibia with reactive sclerosis or ossification.

Contrast enhanced CT of the abdomen and pelvis were normal. There was an intra-uterine device (IUD) identified within the uterus. Chest CT revealed a nonspecific 5 mm pulmonary nodule in the lower left lobe and borderline enlarged axillary lymphadenopathy. Based on the initial radiographic evaluation, the case was interpreted as a malignant-appearing, permeative mixed sclerotic and lytic lesion in the left proximal tibia. Malignant and metastatic processes, infections, and metabolic processes were all considered as part of the differential diagnosis.

An open biopsy was performed and analyzed (Fig. 3A). Light microscopic examination revealed a low to intermediate grade malignant spindle cell neoplasm infiltrating the marrow and permeating the preexisting bone trabeculae (Fig. 3B). The tumor cells were elongated and spindled, with cigar-shaped nuclei having blunt ending and eosinophilic cytoplasm (Figs. 3C and D). The cells were arranged in bundles with fascicles frequently intersecting at right angles. The tumor cells were pleomorphic with hyperchromatic, atypical nuclei and three to four mitoses per high power field (Fig. 3D).

Immunohistochemical studies demonstrated the expression of vimentin, smooth muscle actin (SMA), actin (HHF-35), and caldesmon. The tumor cells did not stain for keratin, S-100, desmin, CD-34, CD-31 or CD 68. Estrogen and progesterone receptors were negative. The final diagnosis was primary leiomyosarcoma of bone of low to intermediate grade.

Treatment and Discussion

Leiomyosarcoma is a malignant, smooth muscle neoplasm that most commonly arises in the soft tissues of the body. The uterus, gastrointestinal tract, retroperitoneum, and extremity soft tissues are the most common sites. Primary leiomyosarcoma of bone is an extremely rare entity; it accounts for less than 0.1% of primary bone tumors analyzed by biopsy.[1] Only approximately 100 cases have been reported up to 2005.[2-4] The number of reported cases has increased recently as diagnostic techniques using immunohistochemical examination have improved.[5] The disease affects males and females equally over a wide age distribution. Patients have ranged from 9 years to 80 years of age.[6] Most patients with leiomyosarcoma of bone present with pain, swelling and, occasionally, a palpable mass.[7] Approximately 50%

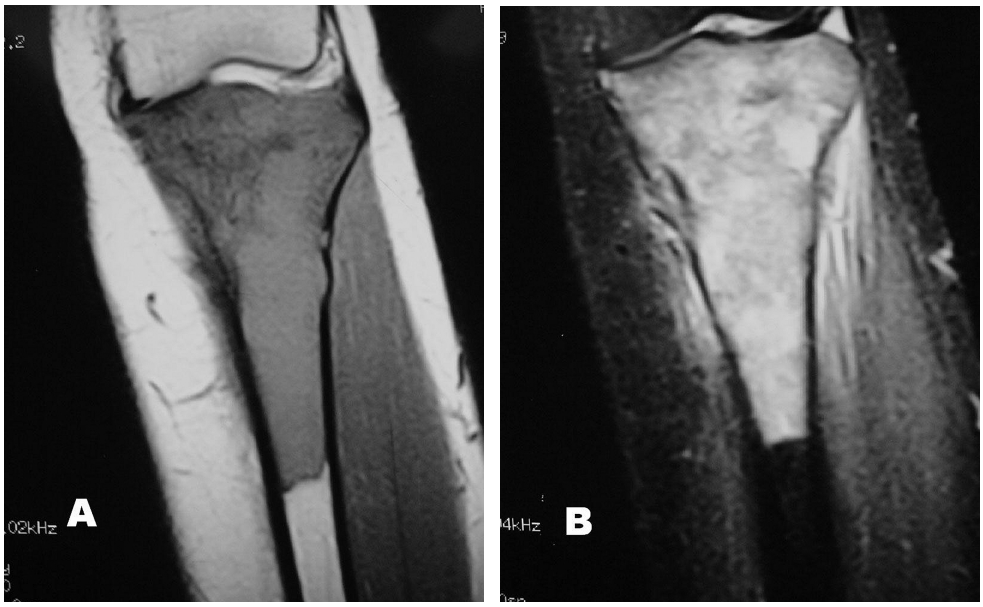

Figure 2 **A**, MRI, Axial T1-weighted MRI demonstrating a cortical erosion and minimal extraosseous extension. The marrow bone is entirely replaced by lesion. **B**, Axial T2-weighted MRI demonstrating a permeative lesion of high signal intensity with surrounding soft tissue edema.

of cases have occurred around the knee, originating from the distal femur or proximal tibia.[4] Less common anatomic sites of origin have included the proximal humerus, pelvis, spine, jaw, facial bones, talus, sternum, ribs, scapula, and fibula.[1-4,7,8]

The radiographic presentation of primary leiomyosarcoma of bone is most commonly that of a nonspecific malignant bone lesion. Plain radiographs usually demonstrate a permeative or moth-eaten pattern of bone destruction although geographic patterns have been reported mostly in association with low grade, less aggressive lesions.[7] The tumor is usually associated with an indistinct margin, and penetration of the cortex may be observed (Fig. 1). Periosteal reaction is absent in most cases. There are no intra-lesional calcifications or ossifications. In the patient reported here, there was significant reactive sclerosis associated with the lesion. This feature has not been typically reported in association with this entity. Reactive sclerosis is often seen with lymphoma, metastatic carcinoma, osteosclerotic myeloma, Ewing's sarcoma, and osteomyelitis. Pathological fractures occur in approximately 20% of patients.[7]

Based on the patient's age and clinical and plain radiographic presentation, it was believed that the most likely differential diagnoses included lymphoma, metastatic carcinoma of unknown primary origin, and osteosclerotic myeloma. Osteosarcoma was thought to be unlikely when given the age of the patient and the absence of any predisposing factors, such as a history of radiation or Paget's disease.[9]

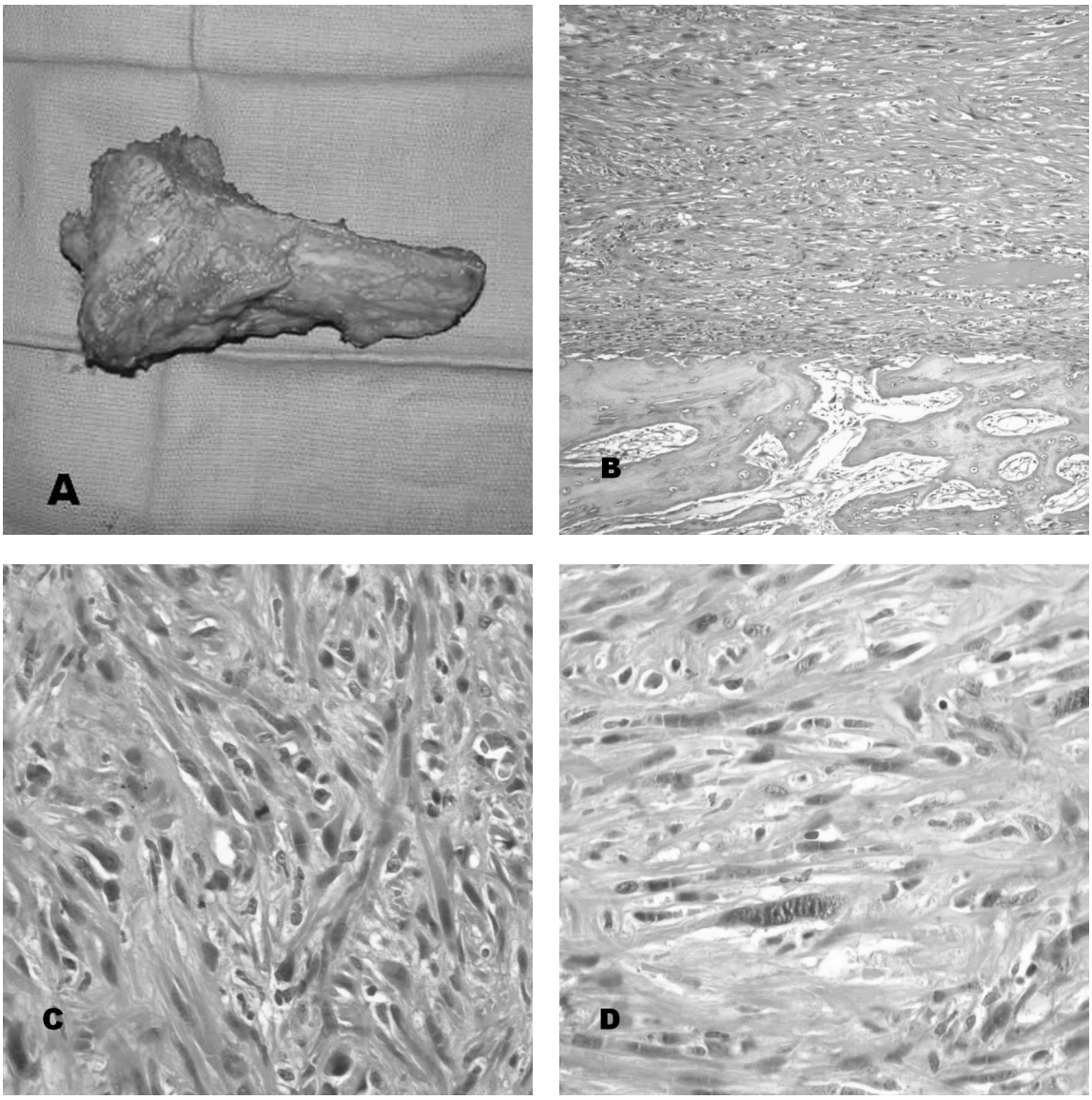

Figure 3 **A**, Gross specimen, proximal tibia. **B**, Spindle shaped tumor cells arranged in interlacing fascicles with moderate nuclear atypia and is permeating the preexisting bone. **C**, The tumor cells are spindle shaped with cigar shaped, blunt ended nuclei and eosinophilic cytoplasm. One mitotic figure in the center. **D**, Tumor giant cells with multiple bizarre nuclei and eosinophilic cytoplasm, with cigar-shaped nuclei in the center.

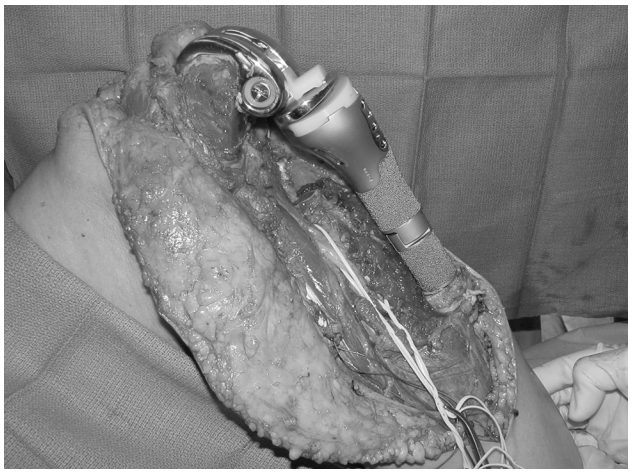

Figure 4 Intraoperative photograph of modular segmental proximal tibia endoprosthesis, courtesy of Howmedica, Inc., Mahwah, New Jersey.

Also, the neoplasm did not demonstrate any ossification on the CT scan. Fibrosarcoma and malignant fibrous histiocytoma (MFH) usually occur in patients older than 50 years of age. These conditions present as permeative, moth-eaten lesions and have a predilection for the distal femur and proximal tibia. They are not typically associated with extensive reactive sclerosis.[10]

Primary leiomyosarcoma of bone was thought to be less likely, because it is an extremely rare entity and has not been reported to be associated with reactive sclerosis. Osteomyelitis can be associated with reactive sclerosis although bone infections usually demonstrate some preservation of marrow fat on MR images. In this case, there was complete replacement of marrow fat, an observation that is most consistent with neoplastic growth. Lymphoma may appear quite similar to leiomyosarcoma on plains films although it more frequently manifests with a pathological fracture. It is typically associated with a larger soft tissue component.[11] Lymphoma also tends to have low signal intensity on T1-weighted MR images, as opposed to intermediate attenuation of the lesion in this case.[6] Paget's disease affects the pelvis and is associated with trabecular thickening, not reactive sclerosis. The marrow is not replaced with this entity.

Computed tomography and MRI analysis were useful in this case to establish the degree of cortical penetration, soft tissue extension, and intramedullary extent. These features are often poorly visualized on plain radiographs but provide important information for surgical planning and prognosis. In this patient, permeative destruction of the cortex and a small soft tissue component was identified. Computed tomography was also useful to confirm the presence of reactive sclerosis, as well as the absence of internal mineralization (calcification and ossification) that are typically seen in other neoplasms, such as chondrosarcoma and osteosarcoma, respectively.

Magnetic resonance images are nonspecific for leiomyosarcoma of bone (Fig. 2). Similar to other types of sarcomas and neoplasms involving bone, T1-weighted images usually demonstrate a lesion that appears iso-intense to muscle. T2-weighted images show heterogeneous areas of high and low signal intensity.[5] As with this lesion, the marrow fat is replaced by tumor, and there is minimal soft tissue edema. These are features that generally help to distinguish neoplasm from osteomyelitis.[9] Bacterial osteomyelitis, may present as a permeative lesion on MRI, due to associated extensive edema; however, there is usually preservation of marrow fat in the area of permeation (reflecting bony edema) and more significant soft tissue edema. Since the radiographic studies are nonspecific, the definitive diagnosis, ultimately, requires histological and immunohistochemical analysis.

Histologically, primary leiomyosarcoma of bone is characterized as a spindle cell sarcoma. The elongated cells are arranged in interlacing bundles or fascicles, with acidophilic cytoplasm and "cigar-shaped," blunt-ended nuclei (Fig. 3D). Most primary leiomyosarcomas of bone are high grade lesions. In a review of 33 cases, Antonescu and colleagues[4] reported an incidence of 66% high grade cases, 21% intermediate cases, and 12% low grade cases. The study also reported an average of five to six mitotic figures per 10 high powered fields. This patient's histological samples demonstrated a low to intermediate grade spindle cell sarcoma with three to four mitotic figures per 10 high powered fields.

Three other diseases in the differential diagnosis also fall into the category of spindle cell sarcomas: malignant fibrous histiocytoma, fibrosarcoma, and osteosarcoma. Although radiographically and histologically similar to the other spindle cell sarcomas, leiomyosarcoma is immunohistochemically distinct.[11,12] This rare neoplasm always demonstrates expression of smooth muscle actin and vimentin. It usually stains positive for common muscle actin (HHF-35) and caldesmon, as was the case for our patient. Only 50% of tumors are positive for desmin.[5] Our patient lacked desmin expression. Also, there was no osteoid production as seen in osteosarcoma.

The patient's characteristic immunohistochemical staining pattern confirmed the diagnosis of leiomyosarcoma, but further tests were necessary to determine if the bone neoplasm was primary or metastatic. In general, whenever a diagnosis of leiomyosarcoma is made, further investigation is important because extraosseous leiomyosarcoma from the uterus or gastrointestinal tract may metastasize to bone. In this case, CT scans of the abdomen and pelvis were negative for other disease sites.

The surgical treatment of this rare neoplasm, in most cases, has been surgical resection with wide, tumor-free margins although some patients with low grade lesions have been successfully managed with curettage and cryosurgery.[4] This tumor's sensitivity to radiation is limited. Radiation may be useful as an adjuvant for eradication of microscopic disease, particularly in anatomic areas, such as the spine, where it is difficult to remove the entire lesion.[13] Pre- and

postoperative chemotherapy have been recommended for high grade tumors although the survival rate of patients with and without chemotherapy and radiation treatment has not differed significantly.[4] Antonescu and associates[4] reported a 51% metastatic rate and 60% survival rate at 5 years for patients with intermediate to high grade lesions. There was 100% survival at 5 years for patients with low grade lesions.

Treatment entailed a radical resection of the left proximal tibia, followed by reconstruction with a special modular segmental proximal tibia endoprosthesis that included a hinged total knee component (Fig. 4). A medial gastrocnemius rotational flap was utilized to reconstruct the extensor mechanism of the knee. The flap aids with soft tissue reconstruction, and the coverage it provides for the prosthesis helps to protect against infection. Routine use of gastrocnemius flaps has drastically improved results, reducing acute infection rates and amputations following resection to less than 10%.[14,15]

Postoperative analysis of the resected specimen confirmed the diagnosis of leiomyosarcoma diffusely permeating bone and bone marrow in the patient. The tumor extended to the subchondral end plate and infiltrated the cortex focally. Some of the bone trabeculae were necrotic but, overall, there was minimal necrosis. The tumor cells were pleomorphic with hyperchromatic, atypical nuclei and three to four mitoses in 10 high power fields (Fig. 3D). The histology was consistent with a low grade spindle cell sarcoma, and, as such, no chemotherapy was recommended at that point in time.

There were no postoperative complications. The patient was followed with chest CT scans. Four months following the resection, the pulmonary nodule present on initial scans appeared to increase in size. An additional pulmonary nodule in the lingula was also noted. The patient subsequently underwent a thoracotomy and pulmonary metastasectomy. The pulmonary nodules were consistent with metastatic leiomyosarcoma. The pulmonary nodules were analyzed and compared with the original specimens. The tumor was reclassified as an intermediate grade tumor. The patient was treated with Doxil® (reformulated version of doxorubicin) every 3 weeks for 6 cycles although there is no standard approach for the chemotherapy treatment of metastatic leiomyosarcoma. In addition, there is no definitive evidence as to the efficacy of chemotherapy to treat this disease.[4] There has been no local or systemic recurrence over a period of 29 months after resection of the pulmonary metastases. The patient is pain free. She has full flexion and extension of her knee, with grade 5 motor strength in extension. There are no activity limitations.

Overall, the functional objective of surgical resection and reconstruction to treat tumors in the proximal tibia is to achieve extensor strength. A study of 55 patients, who underwent the same type of endoprosthetic reconstruction, reported good to excellent results in 87% of patients, characterized by less than or equal to 20º extension lag.[14] Five- and ten-year survival rates for modular segmental proximal tibia endoprostheses have been reported to be 85% and 69%, respectively. Most revisions have been secondary to aseptic loosening or infection.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed in the manuscript, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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