Peripheral artery leiomyosarcoma

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Vascular leiomyosarcomas are extremely rare tumors and represent only 0.001% of all malignancies. Venous leiomyosarcomas occur five times more often than arterial ones, with 50% of them originating in the inferior vena cava (IVC). Arterial leiomyosarcomas are most commonly encountered in the great vessels with less than 50% of them occurring in the peripheral circulation. A total of only seven cases of arterial leiomyosarcomas involving the femoral artery have been reported in literature to date. We report a case of an arterial leiomyosarcoma involving the profunda femoris artery, and provide a comprehensive review on peripheral arterial leiomyosarcomas—distribution, clinical presentation, radiological and histological diagnosis, staging, and treatment. (J Vasc Surg 2009;49:217-21.)

CASE REPORT

A 65-year-old male presented with progressive left anterolateral thigh pain, numbness, and tingling. Worsening pain unrelieved by analgesics, gradually and significantly began to reduce the patient's ability to ambulate and perform activities of daily living. His extensive medical comorbidities included hypertension, diabetes mellitus, hypercholesterolemia, and ischemic cardiomyopathy with a myocardial infarction in the remote past. He admitted to a history of cigarette smoking and alcohol consumption but quit both 7 years ago. His family history was significant for lethal coronary artery disease in his father.

On physical examination, vital signs were normal and pertinent findings were decreased flexional strength at the left knee joint and loss of sensation over the left anterolateral thigh without tenderness. He had bilateral ankle edema with palpable pedal pulses. Lab tests were normal except for hemoglobin of 11.1 g/dl. A lower extremity venous duplex scan revealed a deep venous thrombosis (DVT) involving a small distal portion of his left peroneal vein (treated with enoxaparin) and a mass in his left thigh. A magnetic resonance imaging (MRI) study of his left thigh (Fig 1) was performed which revealed a well-circumscribed, lobulated, enhancing mass measuring 6.5×3.2 cm^2. The mass appeared to involve the femoral nerve and was positioned immediately posterior to the femoral artery and vein with no evidence of muscle or bone infiltration. These findings suggested a benign nerve sheath tumor arising from the femoral nerve.

Neurosurgery consultation was obtained, and the decision was made by the neurosurgeon to take the patient for operative exploration rather than initial core biopsy. A left anterior thigh incision revealed an oval-shaped tumor in the vertical axis. The mass was identified and felt to be of non-neural etiology, and application of a neural stimulator evoked no response. A small incisional biopsy was obtained, which revealed a high-grade soft tissue sarcoma on frozen section, and further excision of the tumor was not attempted until a work-up was completed.

At this point, the patient was referred to a surgical oncologist and metastatic work-up was negative. He underwent re-exploration with planned en bloc resection. A plane was created between the vastus medialis and the quadriceps femoris muscles, and the superficial femoral artery, vein, and nerve were retracted medially revealing an expansile mass in association with the profunda femoris artery. Large thigh collaterals arising from the profunda proximal to the tumor were identified. An en bloc excision of the tumor together with the profunda femoris artery was performed, with proximal and distal arterial ligation. The length of the resected profunda femoris artery was 5.6 cm and contained a fusiform tumor mass (2.3 cm transversely) (Fig 2, *A*) distal to the large thigh collaterals. Longitudinal cross-section of the specimen revealed a fleshy, grey-tan, nodular, well-circumscribed, myxoid mass (measuring 2.3 cm in greatest dimension) growing within the arterial wall and protruding into the lumen (Fig 2, *B*). Transverse cross-section of the specimen showed the gelatinous, myxoid tumor within the arterial media, external to the intima and internal to the serosa.

Histopathological examination of the mass revealed a high nuclear grade with closely packed interlacing bundles of multinucleated, giant spindle cells; elongated cigar-shaped hyperchromatic nuclei embedded within an abundant granular, eosinophilic cytoplasm; atypical mitoses (>5 mitoses/10 hpf); and areas of necrosis and fibrosis within the tissue (Fig 3, *A*). These findings were diagnostic for a high-grade soft tissue sarcoma consistent with an arterial leiomyosarcoma. Longitudinally, the proximal and distal margin of the profunda femoris artery was free of tumor involvement, however, the tumor extended through the serosa into the surrounding adipose tissue. The tumor was stage IIB according to the American Joint Commission on Cancer staging system for soft-tissue sarcomas (see Table I), and stage IIb according to the surgical staging system of the Musculoskeletal Tumor Society for bone and soft tissue sarcomas (see Table II). Immunohistochemical staining of the tumor cells revealed strong positivity for smooth muscle specific markers actin (Fig 3, *B*) and vimentin confirming a leiomyosarcoma, and negativity for S-100 (tumor marker for melanomas, malignant peripheral nerve sheath tumors and clear cell sarcomas), CD 34 (tumor marker for dermatofibrosarcomas, gastrointestinal stromal tumors, and malignant peripheral nerve sheath tumors), and CD 68 (hematopoietic differentiation marker

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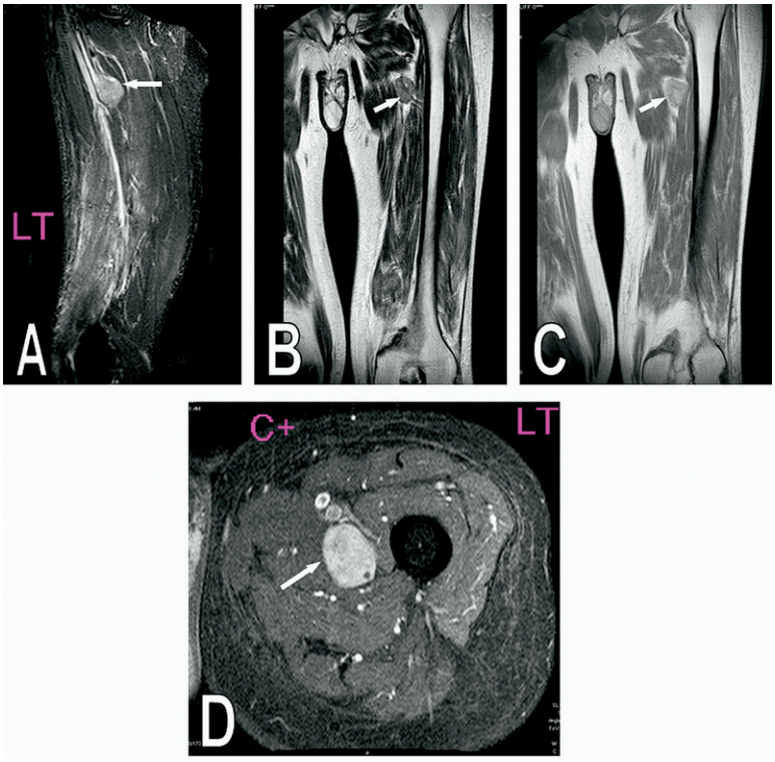

Fig 1. Magnetic resonance imaging (MRI) of the left thigh revealed a well-circumscribed, oval mass (*white arrow*, **A** to **D**) in the anteromedial thigh compartment and in close proximity to the femoral neurovascular bundle. Images (**A**) (*left lateral sagittal view*) and (**D**) (*axial view*) depict the T-1 weighted contrast-enhanced images of the tumor medial to the femur and immediately posterior to the femoral neurovascular bundle. Images (**B**) (*T-2 weighted*) and (**C**) (*T-1 weighted*) present the mass in a coronal plane.

of monocyte-macrophage lineage expressed in myeloid leukemias) excluding a metastatic lesion.

Postoperatively, the patient had an uneventful recovery and was discharged home on hospital day 3. Treatment for DVT continued with enoxaparin and adjuvant radiation therapy was initiated.

DISCUSSION

Leiomyosarcomas are aggressive soft tissue sarcomas arising from smooth muscle cells typically of uterine, gastrointestinal, or soft tissue origin. Embryologically soft tissues originate from the mesoderm, and soft tissue sarcomas are malignant tumors that arise from mesenchymal cells. Primary tumors originating in the blood vessels are extremely rare, and vascular leiomyosarcomas are even rarer. Vascular leiomyosarcomas arise from smooth muscle cells lining blood vessels and may present with signs and symptoms of vascular compromise and/or neurologic symptoms from compression of adjacent nerves. While soft tissue sarcomas account for 0.7% of all malignancies, leiomyosarcomas represent only 5% to 7 % of soft tissue sarcomas, and only 2% of these are of vascular origin.[1] Vascular leiomyosarcomas occur most commonly in the adult population (age range 37-80 years) and with no gender preference.[2]

Vascular leiomyosarcomas involving veins are five times more common than those involving arteries. In a review of 86 cases, vascular leiomyosarcomas involved veins 79% of the times (68 cases) with a majority (33/68 cases) involving the inferior vena cava (IVC).[3] Arterial leiomyosarcomas were seen 21% (18/86 cases) of the time with a majority of them occurring in the pulmonary artery (56%, 10/18 cases). In addition to arterial leiomyosarcomas of the pulmonary artery, other reported sites include the aorta,[4-6] renal,[7] popliteal,[1] splenic,[8] subclavian,[9] carotid,[10] iliac,[11] and common femoral[12] and superficial femoral[2,13] arteries. Arterial leiomyosarcomas originating in the femoral artery are extremely rare, and only seven cases have been reported in the literature to date (Table III).

Symptoms related to arterial leiomyosarcomas vary widely according to the location of the tumor. Peripheral arterial leiomyosarcomas have a predilection for the lower limb arteries with a majority of them occurring in the popliteal arteries,[1] and they most commonly present with symptoms of claudication. Arterial leiomyosarcomas are slow growing and usually present due to symptoms related to luminal narrowing[7,12,14] or peripheral embolization.[5] This accounts for the fact that they are frequently misdiagnosed as atherosclerotic chronic occlusive disease[12,13] or even as aneurysms if they present as pulsatile masses.[2] These

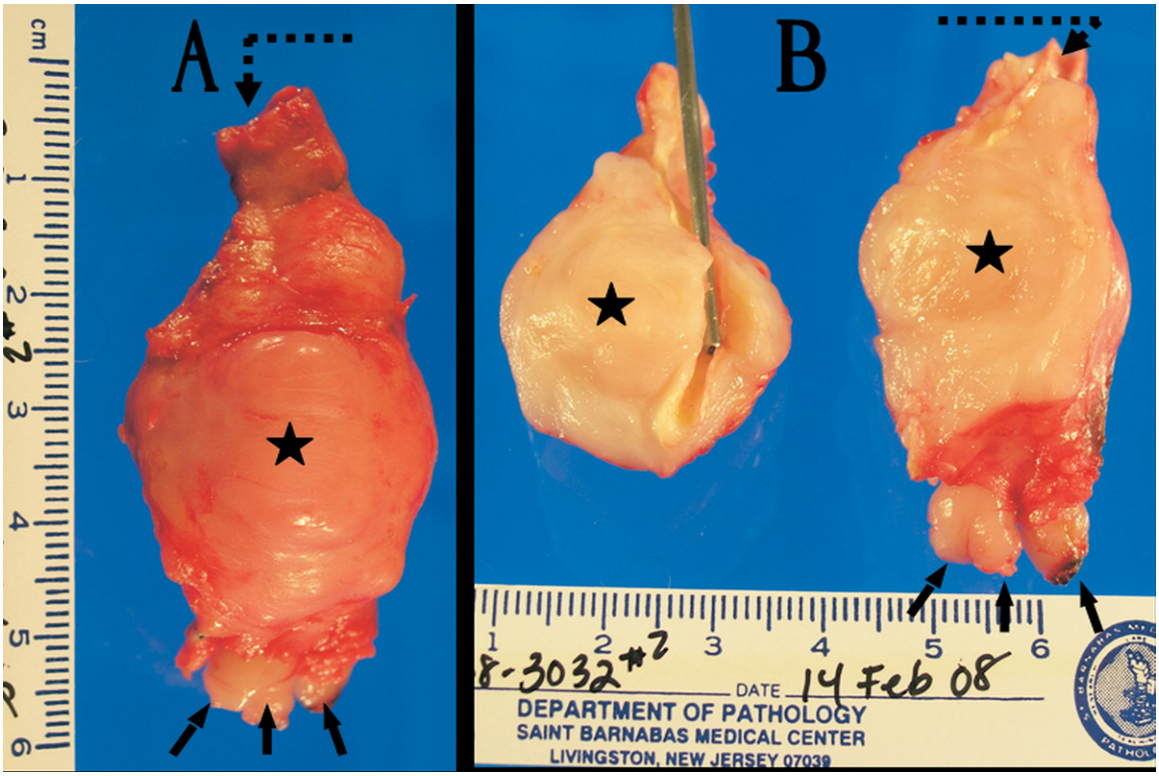

Fig 2. Gross specimen exhibits the proximal end of the resected profunda femoris artery (*dotted arrow*, **A** and **B**), the tumor within the vessel wall (*star*, **A** and **B**), and extension of the tumor into the distal arterial trifurcation (*solid arrows*, **A** and **B**). Longitudinal cross-section of the specimen (**B**) revealed an intact intima lined arterial lumen (*metal pointer*) encased by the tumor (*stars*).

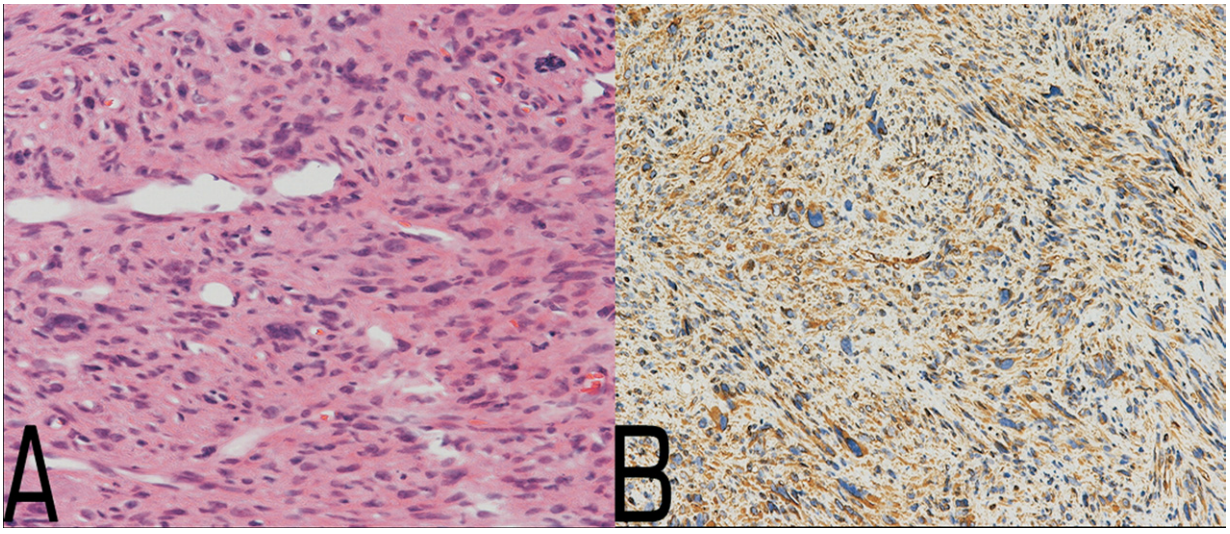

Fig 3. A, Histology of the tumor (hematoxylin-eosin stain, ×40) revealed spindle-shaped, pleomorphic neoplastic cells with hyperchromatic, atypical, elongated nuclei and fibrillary eosinophilic cytoplasm. **B,** The neoplastic cells exhibited strong and diffuse cytoplasmic immunoreactivity for actin (hematoxylin-eosin stain, ×20). Both, (**A**) and (**B**) depicted characteristic features of a leiomyosarcoma.

Table I. The American Joint Committee on Cancer (AJCC) staging system for soft- tissue sarcomas

Stage	*Histologic grade*	*Size*	*Location (Relative to fascia)*	*Metastases*
IA	Low	<5 cm	Superficial or deep	No
IB	Low	≥5 cm	Superficial	No
IIA	Low	≥5 cm	Deep	No
IIB	**High**	**<5 cm**	**Superficial or deep**	**No**
IIC	High	≥5 cm	Superficial	No
III	High	≥5 cm	Deep	No
IV	Any	Any	Any	Yes

The tumor features of the current case are bolded in the table.

Table II. The surgical staging system of the Musculoskeletal Tumor Society (MSTS) is used for bone and soft tissue sarcomas, including leiomyosarcomas

Stage	*Histologic grade*	*Local extent of disease*	*Metastases*
Ia	Low	Confined	No
Ib	Low	Unconfined	No
IIa	High	Confined	No
IIb	**High**	**Unconfined**	**No**
III	Any	Any	Yes

The tumor features of the current case are bolded in the table.

tumors may also compress adjacent nerves causing neurologic symptoms[1,7,13] as was reported in our patient. Overall, arterial leiomyosarcomas tend to behave more aggressively than their venous counterparts,[1,6] and those arising within the intima are typically poorly differentiated with a higher metastatic potential due to direct arterial seeding. Whereas arterial leiomyosarcomas arising within the media tend to be better differentiated, and direct arterial seeding is not their feature until the tumor invades through the intima.[6]

Vascular imaging such as duplex ultrasonography,[13] computed tomography (CT) angiography,[1,4,13,15] and conventional arteriography[2,12] can reveal an intravascular filling defect, but they cannot differentiate between a sarcoma and a thromboembolic process causing it, with invasive arteriography carrying the risk of precipitating tumor embolization.[16] If suspected, the diagnostic evaluation for a vascular leiomyosarcoma should begin with a MRI of the lesion and a CT scan of the chest, abdomen, and pelvis. MRI evaluates the anatomic extent of the tumor and involvement of the adjacent bone, nerves, or vascular structures. In addition, it provides a multiplanar image of the lesion that can differentiate a tumor from atheromatous material through enhancement of the tumor on T-1 weighted and T-2 weighted images without the risk of embolization.[16] CT scan of the chest, abdomen, and pelvis can detect metastases in the lungs and liver, the two most common sites of metastases of vascular leiomyosarcomas. A biopsy is essential to establish a definitive diagnosis, and while both a core needle biopsy under radiological guidance and an open procedure can be performed, the former technique is favored due to less morbidity.

Pathologically, a leiomyosarcoma can be identified under light microscopy on hematoxylin-eosin (H&E) staining. Specific features include a highly cellular field with abundant pink to red cytoplasm and centrally located classic cigar-shaped nuclei, as well as the presence of myofibrils that run longitudinally along the cell's length. A malignant leiomyosarcoma can be differentiated from a benign smooth muscle tumor based on features such as size, cellularity, atypia, necrosis, and mitoses per high power field. Specifically, increased cellular mitoses along side atypia and/or focal necrosis should raise the suspicion of a malignant process. Additionally, immunohistochemical staining supports the diagnosis of a leiomyosarcoma by demonstrating muscle specific markers such as desmin, actin, and vimentin. Metastatic vascular lesions can be excluded by the absence of immunohistochemical staining for S-100 protein and HMB-45 (melanoma); chromogranin, synaptophysin, and neuron specific enolase (neuroendocrine tumors); carcinoembryonic and epithelial membrane antigens (epithelial tumors); and CD 20, CD 30, CD 43, and CD 99 (hematolymphoid tumors).[16] Electron microscopy can further illustrate the classic nuclear morphology of leiomyosarcomas.

The tumor's local anatomic extent and its metastatic status derived from imaging modalities (MRI and CT) in combination with its histological grade can be utilized to stage the disease (see Tables I and II) and suggest appropriate therapy.

Treatment of vascular leiomyosarcomas typically involves surgical resection of the involved vascular segment with negative margins. In the absence of collaterals, vascular reconstruction with interposition grafts is often required. Many of these tumors may involve or are adjacent to vital structures making wide surgical margins not feasible. In such cases, radiation is a vital neoadjuvant therapeutic tool, especially in high-grade sarcomas, to provide local control. Radiation therapy can also be utilized as an adjuvant after resection of the primary tumor, or for palliation in patients with extensive metastases. Chemotherapy may be beneficial as an adjuvant in localized disease[1] and should be considered for large high-grade or recurrent sarcomas.

In summary, leiomyosarcomas of vascular origin are rare malignant tumors. Prognosis is related to stage at presentation and surgical resectability. Delay in diagnosis often makes en bloc surgical resection difficult if not impossible. Metastatic disease to the lungs, liver, and lymph nodes occurs in 60% of patients with these tumors.[3] The 5-year survival rate with vascular leiomyosarcomas is 36%, with an average survival of 16 months.[1,3] Though early diagnosis of vascular leiomyosarcomas is uncommon, these tumors should be on the differential diagnoses in any vasculopathy with atypical features, or when neurologic symptoms thought to be caused by a mass in close proximity to vascular structures is identified, or when an isolated intraluminal filling defect is identified on arteriography.[12] Both MRI and CT are vital in evaluating local and systemic extent of the disease, respectively. Management of vascular leiomyosarcomas should involve early imaging and his-

Table III. Published reports of leiomyosarcomas of the femoral artery

Reference	*Age (y)/ gender*	*Site of primary tumor*	*Symptomatology*	*Metastasis*	*Treatment*	*Outcome*
Kevorkian[3]	71/m	L Distal femoral artery	L posterior thigh mass	Metastatic, distant (lung)	Surgery & radiation	Recurrence with death at 16 mo
	66/m	Femoral artery	Not available	Not available	Not available	Not available
	70/f	Femoral artery	Not available	Metastatic, locally (bone)	Not available	Alive with disease
	60/f	Femoral artery	Not available	Metastatic, distant (lung)	Surgery	Alive with disease
Porcellini[12]	31/f	L Common femoral artery	Left-sided claudication	No metastasis known	Surgery	Alive at 30 mo without recurrence
Gramith[13]	80/f	R Superficial femoral artery	R thigh pain	No metastasis known	Surgery	Not available
Meulman[2]	79/m	L Superficial femoral artery	L leg painful edema with motor and sensory loss	Metastatic, locally	Surgery	Died at 7 mo
Current case	65/m	L Profunda femoris artery	L thigh pain with motor and sensory loss	No metastasis known	Surgery & radiation	Asymptomatic at 3 mo postop

topathological tissue examination, with subsequent staging of the disease. Surgical treatment aimed at achieving a R_0 resection followed, when appropriate, by adjuvant radiation and/or chemotherapy should then be initiated.

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